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# Rare Cardiovascular Diseases

From classification to clinical examples



edited by Piotr Podolec

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# Rare Cardiovascular Diseases

## From classification to clinical examples

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*This book is dedicated to my family –  
my wife, Małgosia and our kids,  
Jakub, Mati, Natalia, Magda, and Hubuś,  
who have been with me every step along the way.*



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# Abbreviations

**6MWT** – 6-minute walk test

**AcT** – acceleration time

**AF** – atrial fibrillation

**AFL** – atrial flutter

**Ao** – aorta

**Ao Asc** – ascending aorta

**AQoL** – Australian Quality of Life

**APAH** – associated PAH

**ASD** – atrial septal defect

**AV** – aortic valve

**AVNRT** – atrioventricular nodal reentry tachycardia

**Bi-VAD** – biventricular assist device

**BMS** – bare-metal stent

**bpm** – beats per minute

**CABG** – coronary artery bypass grafting

**CAMPHOR** – Cambridge Pulmonary Hypertension Outcome Review

**CHD** – congenital heart disease

**CHF** – chronic heart failure

**CHQ** – Chronic Heart Failure Questionnaire

**CI** – cardiac index

**CMR** – cardiovascular magnetic resonance imaging

**COPD** – chronic obstructive pulmonary disease

**CPET** – cardiopulmonary exercise test

**CRCD** – Centre for Rare Cardiovascular Diseases at the John Paul II Hospital in Krakow, Poland

**CT** – computed tomography

**CTA** – computed tomography angiography

**CTEPH** – chronic thromboembolic pulmonary hypertension

**Cx** – circumflex artery

**ECG** – electrocardiogram

**EQ-5D** – EuroQoL questionnaire

**ESC** – European Society of Cardiology

**FBN1** – fibrillin-1

**FMD** – fibromuscular dysplasia

**HADS** – Hospital Anxiety and Depression Scale

**HFQ** – 16-item Heart Failure Questionnaire

**HR** – heart rate

**HRQoL** – health-related quality of life

**IE** – infective endocarditis

**IM** – intermediate coronary artery

**INR** – international normalized ratio

**IPAH** – idiopathic pulmonary arterial hypertension

**LA** – left atrium

**LAA** – left atrial auricle

**LAD** – left anterior descending coronary artery

**LCA** – left coronary artery

**LHIS** – lipomatous hypertrophy of the interatrial septum

**LM** – left main trunk

**LMWH** – low-molecular-weight-heparin

**LV** – left ventricle

**LVAD** – left ventricular assist device

**LVEF** – left ventricular ejection fraction

**LVM** – left ventricle myocardium

**MAC** – mitral annular calcification

**MLHF** – Minnesota Living with Heart Failure Questionnaire

**MPA** – main pulmonary artery

**mPAP** – mean pulmonary artery pressure

**MSCT** – multislice computed tomography

**NHP** – Nottingham Health Profile

**NT-proBNP** – N-terminal pro-B-type natriuretic peptide

**NO** – nitric oxide

**NYHA** – New York Heart Association

**PA** – pulmonary artery

**PAA** – pulmonary artery aneurysm

**PAH** – pulmonary arterial hypertension

**PAH-CHD** – pulmonary arterial hypertension associated with congenital heart disease

**PAH-CTD** – pulmonary arterial hypertension associated with connective tissue disease

**PAP** – pulmonary artery pressure

**PAPVC** – partial anomalous pulmonary venous connections

**PA<sub>sat</sub>** – oxygen saturation in pulmonary artery

**PAWP** – pulmonary artery wedge pressure

**PD** – posterior descending branch

**PDA** – persistent ductus arteriosus

**PE** – pulmonary embolism

**PEA** – pulmonary endarterectomy

- PFO** – patent foramen ovale  
**PH** – pulmonary hypertension  
**PH-LHD** – pulmonary hypertension associated with left heart disease  
**PR** – pulmonary regurgitation  
**PROs** – patient-reported outcomes  
**PTPA** – percutaneous transluminal pulmonary angioplasty  
**PV** – pulmonary valve  
**PVR** – pulmonary vascular resistance
- QoL** – quality of life  
**Qp/Qs** – pulmonary to systemic flow ratio
- RA** – right atrium  
**RBBB** – right bundle branch block  
**RCA** – right coronary artery  
**RCT** – randomized controlled trial  
**RFA** – radiofrequency ablation  
**RHC** – right heart catheterization  
**RICA** – right internal carotid artery  
**RV** – right ventricle  
**RVH** – right ventricular hypertrophy  
**RVOT** – right ventricle outflow tract  
**RVSD** – right ventricular systolic dysfunction
- SatO<sub>2</sub>** – oxygen saturation
- SB** – septal branches  
**Sci** – scleroderma  
**SF-36** – Medical Outcomes Study 36-item short form  
**SG** – standard gamble  
**SGRQ** – St George’s Respiratory Questionnaire  
**sPAP** – systolic pulmonary artery pressure  
**SVT** – supraventricular tachycardia
- TAPSE** – tricuspid annular plane systolic excursion  
**TCD** – transcranial Doppler  
**TEE** – transesophageal echocardiography  
**TIMI** – Thrombolysis In Myocardial Infarction  
**TMD** – transmitral Doppler  
**TPG** – transpulmonary gradient  
**TPR** – total pulmonary resistance  
**TPS** – transcatheter Potts shunt  
**TTE** – transthoracic echocardiography  
**Tu** – tumor
- VE/VCO<sub>2</sub>** – slope ventilation efficiency  
**VKA** – vitamin K antagonists  
**VO<sub>2</sub> max** – maximal oxygen consumption  
**VSD** – ventricular septal defect
- WHO** – World Health Organization

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## Preface

*When the disease is rare,  
the expertise is scarce as well*  
(EU Commission on Rare Diseases:  
Europe's Challenge)

*Because fear is driven by the lack of knowledge*  
(2012 International Conference  
on Rare Cardiovascular Diseases, Krakow)

*Relatively common symptoms can hide underlying  
rare diseases, leading to misdiagnosis*  
(Rare Diseases Europe: Fact Sheet;  
[www.eurordis.org](http://www.eurordis.org))

The Authors and Editors are extremely happy to be able to deliver at your hands the first Polish textbook of rare cardiovascular disease – “*Rare Cardiovascular Diseases: From Classification to Clinical Examples*”. As you will recognize, this is also –most likely– the first textbook of this specific type in the world.

### Why a textbook on rare cardiovascular diseases?

Rare cardiovascular diseases are becoming a significant burden for patients, physicians, and the health care system. A “rare” disease is a disease seen so rarely that its appropriate diagnosis and treatment require specific, complex endeavors in the hands of appropriately trained and experienced physicians. Rare diseases are estimated to affect 30 million European Union (EU) citizens. These diseases are chronic, progressive, and often life-threatening. Rare cardiovascular diseases are often disabling – the quality of life of the patients is frequently compromised by the lack or loss of autonomy.

The book stems from the growing experience that the Centre for Rare Cardiovascular Diseases at the John Paul II Hospital in Krakow (CRCVD) has gained throughout the years. The Centre, operational from 2006, was formally established in 2011, as a result of our successful application for the EU Project “Establishing a European Network for Orphan

Cardiovascular Diseases”, cofunded by the Małopolska Regional Operational Programme 2007–2013. The book, and the *Journal of Rare Cardiovascular Diseases* alike, are tools in our commitment to establishing a routine dialogue between those who manage and care for patients who have been labeled as “no-one’s” or “orphan”; a dialog that includes patient-specific discussions aimed at patient-specific solutions.

Let us quote from the Editorial by Professor Ségolène Aymé (Director of Research at the French Medical Research Council, Executive Manager of the European Database of Rare Diseases and Orphan Drugs ORPHANET, Editor-in-Chief of the Orphanet Journal of Rare Diseases, and Head of the European Commission Task Force on Rare Diseases) published in the 2012 opening issue of *the Journal of Rare Cardiovascular Diseases*: “The EU Council recommendation on rare diseases, adopted in 2009, supports the adoption of national strategies on improving the recognition and visibility of rare diseases, on encouraging more research into rare diseases, and forging links between centres of expertise and professionals in different countries through the creation of European reference networks in order to share knowledge and expertise and, where necessary, to identify where patients should go when such experience cannot be made available to them. (...) The first action point is to spot the expertise and organize healthcare pathways to reduce the time to diagnosis and ensure appropriate care. Some European centres of expertise have been established.”

Rare cardiovascular disease, as defined in the book, affects also those with rare forms of disease that is not necessarily “rare” *per se*. Examples include some rare forms of pulmonary hypertension and complex congenital heart disease in those who have reached adolescence and, increasingly, adulthood, following, for instance, specific multi-step surgery for congenital disease. Thus, also some patients with so called grown-up congenital heart disease enter the rare cardiovascular disease cohort. This is reflected in the first classification of rare cardiovascular diseases that we propose in this book – The Krakow Rare Cardiovascular Diseases Classification – which is simultaneously published in this book and in the *Journal of Rare Cardiovascular Disease* [5]. The Classification is

aimed at (1) facilitating recognition of often atypical symptoms (and, on the contrary, sometimes the symptoms commonly associated with another, more frequent disease) in the context of cardiovascular pathology, leading to the appropriate diagnosis and guidance on further management, and (2) grouping the expertise in the main fields of rare cardiovascular disease.

The two main parts of the book, rather than being separate, complement each other. The introduced comprehensive classification of rare cardiovascular diseases includes, for the first time, not only the disease entities traditionally considered “rare” (<5:10 000) but also *rare severe forms* of some cardiovascular diseases that are not necessarily, as a group, of “low prevalence”. The classification provides a systemic framework for clinical examples selected from a broad group of patients, who have been consulted in the Krakow Centre on a regular basis by national and international experts during live teleconferences that have occurred on a quarterly basis since 2006.

We do hope that you will not only find the content of this textbook engaging and stimulating, but also that it will be professionally useful in a direct way. We believe that the book will serve as a reference for multi-disciplinary teams that build their expertise in managing patients with rare cardiovascular diseases, and for those who specialize in internal medicine and cardiology. More than that, we are convinced that the book will be valuable for everyone with an interest in rare cardiovascular diseases, including medical students and medical psychology students (the patients with rare cardiovascular diseases and their families frequently require specific psychological support) who wish to broaden their horizons in the field that is not only expanding but is also becoming more and more organized. We do hope you will be coming back to this book for reference in making decisions concerning your “rare” cardiovascular patients.

As pioneers in the field, it is certain that we have not been able to avoid some errors and inconsistencies that will require further correction or clarification. This is where we come to request you, our Reader, to

feel free to express your opinion and comment. More than that, please feel free to tell us where you believe we are wrong or have gone wrong (in case we have). Voice your opinion contacting us directly or through the CRCDD webpage (<http://www.crcdd.eu>; email: [rare-diseases@szpitaljp2.krakow.pl](mailto:rare-diseases@szpitaljp2.krakow.pl)). This will be very much appreciated. Please use this opportunity to have your own input acknowledged in a new field that is being shaped!

Last but not least, let me thank all those who have been instrumental in making this book real. This includes, in particular, my collaborators from the Jagiellonian University Institute of Cardiology and in John Paul II Hospital in Krakow, but also the national and international Partners and Experts of the CRCDD and trusted Friends and Colleagues. Thank you so much for your support, which you have offered since well before the CRCDD became formally established, for our “bizarre” and “unworkable” vision that has now become a reality!

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# Part 1

Centers for rare cardiovascular diseases:  
spotting the expertise, ensuring appropriate  
patient care, and fostering research  
in rare cardiovascular diseases

**Editors: Piotr Podolec, Grzegorz Kopeć, Piotr Musiałek**



# Centers for rare cardiovascular diseases: an unmet need in Europe and worldwide

Lidia Tomkiewicz-Pająk, Jakub Podolec,  
Piotr Musiałek

*Rare diseases are characterized by a broad diversity of disorders and symptoms that vary not only from disease to disease but also from patient to patient suffering from the same disease*

(Rare Diseases Europe: Fact Sheet  
[www.eurordis.org](http://www.eurordis.org))

## Centers for rare cardiovascular diseases: why?

The population of adults with rare cardiovascular diseases (RCDs) is heterogeneous with respect to the type and complexity of the disease as well as clinical manifestations. Recent progress in cardiac surgery and pediatric cardiology has resulted in increasing numbers of adult patients with new cardiovascular disease patterns [1]. The European Union Committee of Experts on Rare Diseases (EUCERD) has been established [2], and several countries have already taken action to adapt their health care system to meet the needs of RCD patients. There are several particular problems and challenges associated with the organization of care for RCD patients, including:

1. The prevalence of RCDs in the grown-up population is not known and the lack of exact numbers makes it difficult to organize specialist [3,4].
2. There are no guidelines regarding care of this group of patients. We have an increasing population of adult patients with RCDs with limited medical experience to attend to their unique needs.
3. Most adults with RCDs have been lost to specialist follow-up. Adult physicians have not been educated about the complexity of RCDs, neither have patients or their families. There are, in general, no specialized centers for these patients [5].
4. The infrastructure for RCD patients is poor. In some countries, patients have no access to centers

with properly trained staff, adequate diagnostic/imaging modalities, and disease-specific treatment.

5. As the RCD population ages, comorbidities become more common, and there is an increasing need for advice from specialists in other fields, including, among others, endocrinologists, neurologists, rheumatologists, orthopedic surgeons, nephrologists, and anesthetists with expertise in managing RCD patients. Therefore, those specialists who already treat or are planning to treat these patients require (and would benefit from) particular training in RCDs. It is striking that most of RCD patients have not been even counseled with regard to contraception and family planning [3,4].
6. Adults with RCDs have higher levels of psychological distress and behavioral problems. These patients are frequently financially dependent on their parents and social welfare. Furthermore, when entering adulthood without adequate preparation, they encounter problems coping with stressful situations such as marriage, job, and others. In many cases, they have no health insurance.

## Centers for rare cardiovascular diseases: how?

A center for RCDs is regarded as a specialist unit where all patients with rare diseases of the cardiovascular system are managed. It should be located in an adult medical environment with the provision of multidisciplinary specialist care. To meet these requirements, the center's staff should consist of [3,4,7]:

- Cardiologist(s) with specialist training including diagnosing and treating different types of RCDs.
- Cardiac surgeon(s) trained and practicing pediatric and adult cardiac surgery
- Electrophysiologist(s)
- Cardiac anesthetist(s)
- Clinical nurse specialist in RCDs
- Medical secretary and assisting staff
- Cardiac pathologist with an interest in RCDs
- Research coordinator for databases

The center should have a close link to other specialist departments including genetics, endocrinology, gynecology, pulmonology, neurology, surgery, general medicine, and others.

Dental advice and dental surgery should also be available along with a connection to a transplant center. Multidisciplinary consultations should be available on regular basis [1].

With a significant improvement in the life expectancy of patients with RCDs, novel medications, and advancement in therapeutic methods, physicians are more likely to come across these rare and difficult cases in their everyday practice. General physicians and family medicine doctors should be educated to provide support in managing RCD patients. As the treatment of rare diseases is, in most cases, very expensive and long-lasting, it should be channeled through the centers of excellence, which can provide an appropriate diagnosis and effective patient follow-up.

In summary, patients with various RCDs face common problems that include [6,8–13]: (1) lack of access to correct diagnosis or significant delays in diagnosis; (2) lack of quality information on the disease; (3) lack of scientific knowledge of the disease; (4) heavy social burden for patients and families; (5) lack of appropriate quality health care; (6) inequities and difficulties in access to treatment and care.

Dedicated centers for RCDs are expected to play an important role in bringing change to the current unacceptable situation by (1) creating and implementing a comprehensive approach to RCDs; (2) pressing for, and participating in, the development of effective public health care policies; (3) increasing international cooperation in scientific research; (4) generating, gaining, and sharing scientific knowledge about RCDs; (5) developing new diagnostic and therapeutic procedures dedicated to RCD patients; (6) raising public awareness; (7) facilitating the networking of RCD physicians and RCD patient groups to share their experience and best practices; (8) providing comprehensive quality information [9–13].

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# Centre for Rare Cardiovascular Diseases at the John Paul II Hospital in Krakow, Poland (CRCD)

Piotr Musiałek, Grzegorz Kopeć,  
Jakub Podolec, Dominika Gryszówka,  
Jakub Stępniewski, Anna Prokop-Staszecka,  
Piotr Podolec

*The key action point is to spot the expertise and organize healthcare pathways to reduce time to diagnosis and ensure appropriate care*

Ségolène Aymé. Rare Diseases:  
a Priority in public health and research.  
*J Rare Cardiovasc Dis.* 2012; 1: 2

## Objectives

The aims of the CRCD are consistent with the identified needs for centers of excellence in rare cardiovascular diseases (RCDs) as indicated by the European Union Commission on Rare Diseases and discussed in “Centres for Rare Cardiovascular Diseases: an unmet need in Europe and Worldwide”. In brief, these have included as follows: (1) providing efficient diagnostic and therapeutic pathways for RCD patients in the Krakow (Małopolska) region and (as needed) from other Polish regions; (2) development of national and international collaboration network in RCDs; (3) establishing a database of RCDs; (4) knowledge dissemination, targeting both physicians and patients/families; (5) psychological and social support to patients and families. As the staff of the CRCD have gradually built experience in the field, the upcoming stage of the CRCD development includes collaboration with the Ministry of Health and National Health Fund in establishing diagnostic and therapeutic algorithms in RCDs and defining funding pathways, and collaboration with the Jagiellonian University Medical College in Krakow, Poland, in creating graduate and postgraduate curriculum in RCDs.

## Establishing the Centre for Rare Cardiovascular Diseases in Krakow

The CRCD was established at the John Paul II Hospital in Krakow, Poland, as a result of our

successful application for the European Union (EU) Project “Establishing a European Network for Orphan Cardiovascular Diseases”, cofunded by the *Małopolska Regional Operational Programme 2007–2013 (MROP), Priority 8. Interregional cooperation, Action 8.2. Strengthen the position of Małopolska in the European cooperation networks*, consistent with one of the top current priorities of the European Commission – Interregional Cooperation. The first two official Partners of the project were the Pauls Stradins Clinical University Hospital in Riga, Latvia, and Lithuanian University of Health Sciences in Kaunas. Soon after the beginning of the project, other centers have been gradually joining the evolving initiative.

Clinical and research activities of the CRCD date back to 2006, when formal quarterly consultations of RCD patients and first RCDs registries began in the Jagiellonian University Institute of Cardiology, Department of Cardiac and Vascular Diseases, John Paul II Hospital in Krakow.

## Structure of the Centre for Rare Cardiovascular Diseases at the John Paul II Hospital in Krakow, Poland

### Role of the John Paul II Hospital in Krakow, Poland

The John Paul II Hospital in Krakow directed by Dr Anna Prokop-Staszecka, serves as a platform for numerous activities of the CRCD. The Hospital houses five cardiovascular departments of the Jagiellonian University Institute of Cardiology, including the Department of Cardiac and Vascular Diseases, Department of Coronary Heart Diseases, Department of Electrophysiology, Department of Hemodynamics and Angiocardiology, and Department of Cardiac and Vascular Surgery and Transplantation. Together with the Department of Thoracic Surgery and Departments of Pulmonology, it represents a specialized cardiopulmonary unit.

The hospital provides inpatient facilities for the CRCD (including beds), outpatient services, and state-of-the-art noninvasive and invasive diagnostic support.

The Research and Development Office of the hospital, directed by Ms. Dominika Gryszówka, MSc, has played an instrumental role in the success of EU grant applications (to formally establish the CRCD) and is always ready to support the further development and activities of the Centre.

## Research and Development Office at the John Paul II Hospital in Krakow

The Research and Development Office at the John Paul II Hospital in Krakow was established in 2005 to develop projects using EU structural funds. The Unit is devoted to the following:

- Assisting in the preparation of grant applications
- Disseminating information about current grant opportunities.
- Building networks of cooperation between the EU health institutions.

The main asset of the Office is its staff, with various educational background, prior training, and work experience, including international relations, project management, finance and finance control, scientific/research information, and information brokering.

At present, the Office manages 16 projects under the Regional Operational EU Program for Małopolska 2007–2013, Program for Central Europe, INTERREG IV C, The National Science Centre, The National Centre for Research and Development, 7th Framework Programme, Marshal Office in Małopolska Province, Swiss Grant, Competitiveness and Innovation Framework Programme. The John Paul II Hospital in Krakow is a leader in the procurement of external funding amounting to 52 million euro.

## IT support and teleconference services

The idea of the CRCD to provide efficient diagnostic and therapeutic pathways for patients with RCDs and to develop a national and international collaboration network between the European centres of excellence in the field of RCDs, would not have come true without the support of the newest technology and people knowing how to tame it. The CRCD houses a professionally tailored media room for up to 50 persons, equipped with the highest standard devices enabling the organization of international, multicenter videoconferences. These include multifunctional TV, digital projector and screen, IP camera, multidimensional scaler, wireless microphones, audio mixer, wizard control panel with remote controllers and portable keypads. A unique software, teleDICOM, that has been implemented facilitates professional consultations of RCD cases on the Internet platform. It is feasible to share all kinds of medical data, including computed tomography or magnetic resonance scans, echocardiographic, electrophysiological, and conventional angiography studies, etc. and evaluate them in the real time. Intuitive operation and compactness of the entire system encourages physicians, specialists, and experts from all national and international centers to join the conferences and discuss difficult RCD cases.

## CRCD Partners and Consulting Centers

The authors of this book would like to thank the authorities and experts of the centers listed in Table 1 for their engagement in diagnosis and treatment of patients with RCDs.

**Table 1. CRCD Partners and Patient Consultation Network Centers**

Center/Institution	City/Country	Leading Physician(s)/Scientist(s)/Executive Officer(s)
<b>International partners and consulting centers</b>		
San Raffaele Hospital	Milan, Italy	Ottavio Alfieri, Antonio Colombo, Francesco Maisano
Academic Hospital IRCCS Foundation Policlinico San Matteo	Pavia, Italy	Eloisa Arbustini
ORPHANET, INSERM SC11	Paris, France	Ségolène Aymé
Henri Mondore Clinic Universitaire Vasculaire	Paris, France	Jean Pierre Becquemin
Department of Cardiology, University of Hull	Hull, United Kingdom	John GF Cleland
University of Southern California	Los Angeles, USA	Uri Elkayam
Research Institute of Cardiology, Pauls Stradins Clinical University Hospital	Riga, Latvia	Andrejs Erglis, Aldis Rozenbergs, Andris Skride
Department of Paediatric Cardiology and Congenital Heart Defects, German Heart Centre	Munich, Germany	Peter Ewert

Center/Institution	City/Country	Leading Physician(s)/Scientist(s)/Executive Officer(s)
Royal Infirmary of Edinburgh	Edinburgh, Scotland	Keith Fox
Pulmonary Hypertension Centre, University of Bologna	Bologna, Italy	Nazzareno Galiè
The Heart Failure Department at I.R.C.C.S. Policlinico San Donato	Milan, Italy	Marco Guazzi
Medical University of Vienna, Internal Medicine II, Division of Cardiology	Vienna, Austria	Irene Lang
Unidad de Cardiopatías Congénitas del Adulto, Hospital Universitario La Paz	Madrid, Spain	José María Oliver Ruiz
Deutsches Herzzentrum, Berlin	Berlin, German	Roland Hetzer, Henryk Siniawski, Robert Hammerschmidt, Diana Kendall
Department of Cardiology, Philipps University of Marburg	Marburg, Germany	Bernhard Maisch, Sabine Pankuweit
Inherited Cardiac Disease Clinic in the Heart Hospital, University College of London	London, UK	William McKenna
Department of Internal Medicine III, Cardiology and Emergency Medicine, Karl Landsteiner Institut zur Erforschung ischaemischer Herzerkrankungen und Rhythmologie, Landeskrankenhaus, St. Poelten, Austria	St. Pölten, Austria	Deddo Moertl
Lithuanian University of Health Sciences	Kaunas, Lithuania	Remigijus Žaliūnas, Egle Ereminiene
<b>National partners</b>		
Narodowy Fundusz Zdrowia, Oddział Małopolski	Krakow, Poland	Barbara Bulanowska
Katedra Ginekologii i Położnictwa, Uniwersytet Jagielloński Collegium Medicum	Krakow, Poland	Antoni Basta, Krzysztof Rytlewski
Śląskie Centrum Chorób Serca	Zabrze, Poland	Jacek Białkowski, Małgorzata Szkutnik
Centrum Kardiologii Allenort	Warszawa, Poland	Andrzej Biederman
Instytut Kardiologii im. Prymasa Tysiąclecia, Stefana Kardynała Wyszyńskiego	Warszawa-Anin, Poland	Elżbieta Biernacka, Zofia Bilińska, Marcin Demkow, Piotr Hoffman, Jacek Różański, Andrzej Rużyłło, Witold Rużyłło Janina Stępińska, Katarzyna Włodarska
Instytut Matki i Dziecka	Warszawa, Poland	Anna Fijałkowska
Górnośląski Ośrodek Kardiologii	Katowice-Ochojec, Poland	Zbigniew Gąsior, Katarzyna Mizia-Stec, Wojciech Wojakowski
Uniwersytet Jagielloński Collegium Medicum	Krakow, Poland	Tomasz Grodzicki, Piotr Laidler, Wojciech Nowak
Uniwersytecki Szpital Dziecięcy w Krakowie-Prokocimiu	Krakow, Poland	Jacek Kolcz, Zbigniew Kordon, Maciej Kowalczyk, Tomasz Mroczek, Andrzej Rudziński, Janusz Skalski
Specjalistyczny Szpital im. Edwarda Szczeklika w Tarnowie	Tarnow, Poland	Marcin Kuta, Dariusz Raich
Szpital Powiatowy w Chrzanowie	Chrzanow, Poland	Krzysztof Kłos, Jacek Nowak
Wojewódzki Szpital Specjalistyczny	Wrocław, Poland	Jerzy Lewczuk, Ewa Mroczek, Michał Furdal
Samodzielny Publiczny Centralny Szpital Kliniczny	Warszawa, Poland	Grzegorz Opolski, Krzysztof Filipiak, Michał Marchel
Górnośląskie Centrum Zdrowia Dziecka	Katowice, Poland	Jacek Pająk, Lesław Szydłowski
Szpital Powiatowy im. dr Tytusa Chałubińskiego w Zakopanem	Zakopane, Poland	Regina Tokarz, Anna Orzechowska
Samodzielny Publiczny Szpital Kliniczny nr 4	Lublin, Poland	Michał Tomaszewski, Andrzej Wysokiński
Europejskie Centrum Zdrowia, Otwock	Otwock, Poland	Adam Torbicki, Marcin Kurzyzna, Maria Wieteska
I Klinika Kardiologii, Uniwersytet Medyczny w Poznaniu	Poznań, Poland	Olga Trojnarzka, Stefan Grajek

## CRCD national and international experts

A multidisciplinary approach to RCD patients requires cooperation of experts in various medical disciplines. The authors of this textbook would like to thank the experts who actively collaborate with the CRCD (Table 2).

## Centre for Rare Cardiovascular Diseases in regular patient care

From 2006 to 2013, the CRCD has been instrumental in providing diagnostic path and making key therapeutic decisions for over 300 patients with RCDs. Examples of RCD cases consulted in the CRCD are listed in the Table 3. Every example is accompanied by appropriate code according to RCD classification (see Part 2) and a corresponding reference.

**Table 2. CRCD national and international experts (in an alphabetical order)**

International experts
Ottavio Alfieri (IT), Ségolène Aymé (FR), Naser M. Ammash (US), Elosia Arbustini (IT), Helmut Baumgartner (DE), Rimantas Benetis (LT), John GF Cleland (GB), Antonio Colombo (IT), Thomas Deneke (DE), Uri Elkayam (US), Egle Ereminiene (LT), Andrejs Erglis (LV), Peter Ewert (DE), Keith Fox (GB), Nazzareno Galié (IT), Christa Gohlke-Bärwolf (DE), Marco Guazzi (IT), Robert Hammerschmidt (DE), Roland Hetzer (DE), Irene Lang (AT), Bernhard Maisch (DE), Francesco Maisano (IT), William McKenna (GB), Skaidrius Miliuskas (LT), Deddo Moertl (AT), Sabine Pankuweit (DE), Mark Petrie (GB), Jolien W. Roos-Hesselink (NL), Aldis Rozenbergs (LV), Jose Maria Oliver Ruiz (SP), Gerald Simonneau (FR), Henryk Siniawski (DE), Nika Skoro-Sajer (AT), Andris Skrde (LV), Remigijus Zaliunas (LT)
National consultants and CRCD physicians
Cardiologists: Stanisław Bartuś, Jacek Białkowski, Elżbieta Katarzyna Biernacka, Zofia T. Bilińska, Piotr Bogacki, Leszek Bryniarski, Grażyna Brzezińska-Rajszyz, Danuta Czarnecka, Marcin Demkow, Jacek S. Dubiel, Dariusz Dudek, Jarosław Drożdż, Artur Dziewierz, Anna Fijałkowska, Krzysztof Filipiak, Andrzej Gackowski, Grzegorz Gajos, Zbigniew Gąsior, Janusz Grodecki, Tomasz Grodzicki, Marta Hlawaty, Piotr Hoffman, Marianna Janion, Ewa Jankowska, Piotr Jankowski, Anna Kabłak-Ziembicka, Zbigniew Kalarus, Jarosław Kasprzak, Anna Klisiewicz, Monika Komar, Grzegorz Kopeć, Marcin Kurzyna, Władysława Kolasieńska-Kloch, Kalina Kawecka-Jaszcz, Janusz Kleinrok, Marek Kłoczek, Ewa Konduracka, Małgorzata Koniecznyńska, Magdalena Kostkiewicz, Artur Kozanecki, Jacek Legutko, Agata Leśniak-Sobelga, Michał Marchel, Ewa Mirek-Bryniarska, Tomasz Miszański-Jamka, Katarzyna Mizia-Stec, Ewa Mroczek, Włodzimierz Musiał, Piotr Musiałek, Jadwiga Nessler, Bogdan Nessler, Maria Olszowska, Grzegorz Opolski, Tomasz Pasierski, Tomasz Pawelec, Paweł Petkow-Dimitrow, Piotr Pieniżek, Artur Pietrucha, Wojciech Płazak, Jakub Podolec, Piotr Podolec, Piotr Ponikowski, Piotr Pruszczyk, Tadeusz Przewłocki, Marek Rajzer, Tomasz Rakowski, Paweł Rubiś, Bożena Sobkowicz, Janina Stępnicka, Jakub Stępniewski, Danuta Sorysz, Katarzyna Stolarz-Skrzypek, Andrzej Surdacki, Małgorzata Szkutnik, Hanna Szwed, Piotr Szymański, Andrzej Tomaszewski, Lidia Tomkiewicz-Pająk, Adam Torbicki, Wiesława Tracz, Olga Trojnarzka, Marcin Waligóra, Piotr Wilkołek, Beata Wożakowska-Kapłon, Andrzej Wysocki, Krzysztof Żmudka
Electrocardiologists: Jacek Bednarek, Piotr Kułakowski, Jacek Lelakowski, Jacek Majewski, Barbara Malecka
Pediatric cardiologists: Wanda Kawalec, Zbigniew Kordon, Jadwiga Moll, Andrzej Rudziński, Aldona Siwińska, Małgorzata Szkutnik, Lesław Szydłowski, Anna Turska-Kmieć, Bożena Werner
Pediatric cardiac surgeons: Jacek Kołcz, Bohdan Maruszewski, Tomasz Mroczek, Jacek Pająk, Janusz Skalski
Cardiac surgeons in adults: Krzysztof Bartuś, Andrzej Biederman, Bogusław Kapelak, Roman Pfitzner, Piotr Przybyłowski, Jacek Różański, Jerzy Sadowski, Robert Sobczyński, Bogdan Suder, Kazimierz Widenka, Jacek Wojarski, Marian Zembala
General surgeons: Andrzej Matyja
Anesthesiologists: Janusz Andres, Rafał Drwiła
Pulmonologists: Anna Prokop-Staszecka
Thoracic surgeons: Krzysztof Bederski, Jarosław Kuźdzał
Neurologists: Agnieszka Słowik, Andrzej Szczudlik
Gynecologists: Antoni Basta, Krzysztof Rytlewski
Nephrologists: Andrzej Kraśniak, Władysław Sułowicz, Tomasz Stompór
Orthopedic surgeons: Piotr Kłosiński, Tadeusz Niedźwiedzki
Hematologists: Aleksander Skotnicki, Zbigniew Walter, Marta Szostek
Immunologists: Janusz Marcinkiewicz, Jacek Musiał
Diabetes specialists and endocrinologists: Alicja Hubalewska-Dydejczyk, Tomasz Klupa, Maciej Malecki, Marta Matyja
Psychologists and psychiatrists: Dominika Dudek, Karolina Tolińska
Basic scientist: Tomasz Brzozowski, Stefan Chłopicki, Aldona Dembińska-Kieć, Tomasz Guzik, Ryszard Korbut, Piotr Laidler, Marcin Majka, Janusz Marcinkiewicz, Marek Sanak, Ewa Stępień, Anetta Undas
Statistician: Andrzej Sokołowski

**Table 3.** List of patients with rare cardiovascular diseases (RCD) consulted within the formal framework of quarterly videoconferences in 2009–2013 (see corresponding RCD classification code and reference)

Class	Examples	RCD code	Reference
I. Rare diseases of systemic circulation	Adult patient with vascular ring.	I-1B.3	www.crcd.eu
	Adult patient with coarctation of the aorta.	I-1B.6	www.crcd.eu
	28-year-old man with anomalous origin of the right coronary artery from the ascending aorta.	I-1C.1	www.crcd.eu
	Acute coronary syndrome in a patient with single coronary ostium.	I-1C.2	RCD textbook (p. 112)
	Patient with myocardial ischemia as a result of multiple coronary artery fistulas to the left ventricle.	I-1C.4	RCD textbook (p. 117) www.crcd.eu
	Pulmonary sequestration from the right coronary artery in a patient with critical left coronary artery disease.	I-1C.0	RCD textbook (p. 109)
	29-year-old woman with suspicion of Marfan syndrome, after ischemic stroke, with patent foramen ovale, and dissection of the descending aorta.	I-2A.1	www.crcd.eu
	23-year-old woman with Marfan syndrome and deformity of the spine.	I-2A.1	www.crcd.eu RCD textbook (p. 120)
	Postpartum aortic dissection: Ehlers–Danlos syndrome.	I-2A.2	www.crcd.eu
	Multiple endovascular procedures for steno-occlusive arterial disease in the course of drug-resistant Takayasu's disease.	I-3A.1	RCD textbook (p. 127)
	71-year-old man with Giant cell aortitis of the ascending aorta, without signs or symptoms of systemic vasculitis.	I-3A.2	J Rare Cardiovasc Dis 2012; 1: 11–13
	19-year-old man with Kawasaki disease.	I-3A.5	www.crcd.eu
	Rare cause of ischemic stroke. Fibromuscular dysplasia.	I-4A	RCD textbook (p. 127)
	Multivessel coronary artery disease in a very young patient with acute myocardial infarction and preexcitation syndrome.	I-6B.0	RCD textbook (p. 134)
	II. Rare diseases of pulmonary circulation	54-year-old man with severe kyphoscoliosis and pulmonary hypertension.	II-1B.2
47-year-old man with pulmonary hypertension, atrial septal defect, and pulmonary thromboembolism.		II-1C.2	www.crcd.eu
Unusual patient with VSD and pulmonary hypertension.		II-1A.4d	www.crcd.eu
69-year-old woman with atrial septal defect, coronary heart disease, and pulmonary arterial hypertension after thyroidectomy.		II-0	www.crcd.eu
62-year-old woman with ostium secundum atrial septal defect (ASD type II) and coexisting pulmonary hypertension.		II-1B.1	www.crcd.eu
Patient with Down syndrome, VSD, Eisenmenger's syndrome, and high pulmonary artery wedge pressure.		II-1C.1	www.crcd.eu
42-year-old woman with chronic thromboembolic pulmonary hypertension.		II-1A.5	www.crcd.eu
Patient with ventricular septal defect and Eisenmenger's syndrome with gynecological complications.		II-1C.0	www.crcd.eu
Pulmonary hypertension in a patient with HIV.		II-1A.4b	www.crcd.eu
Aneurysm of pulmonary artery in a patient with Eisenmenger's syndrome on medical therapy.		II-3B.1	www.crcd.eu
39-year-old woman with atypical variant of Klippel–Trénaunay syndrome and progressive thromboembolic pulmonary hypertension, successfully treated by pulmonary thromboendarterectomy.		II-1A.5	RCD textbook (p. 178)
An elderly patient with patent ductus arteriosus and pulmonary hypertension		II-1A.4d	www.crcd.eu

Class	Examples	RCD code	Reference
III. Rare diseases of the heart (cardiomyopathies)	Left ventricular noncompaction with congenital diaphragmatic hernia causing cardiac dextroposition	III-5A.1.0	www.crcd.eu J Rare Cardiovasc Dis 2012; 1: 11–13 RCD textbook (p. 235)
	Isolated left ventricular noncompaction in an asymptomatic athlete	III-5A.1.0	www.crcd.eu RCD textbook (p. 241)
	Dilated cardiomyopathy in the course of Emery–Dreifuss muscular dystrophy	III-1A.4b	www.crcd.eu RCD textbook (p. 215)
	Left ventricular noncompaction accidentally found in a patient diagnosed with acute coronary syndrome	III-5A.1.0	www.crcd.eu
	Dynamic progression of aortic stenosis in a patient with Fabry disease despite enzyme replacement therapy during 4.5-year follow-up	III-2B.2a	www.crcd.eu
	19-year-old man with Down's syndrome, after correction of ASD, PDA, VSD, with obstructive hypertrophic cardiomyopathy	III-2B.6.0	www.crcd.eu
	Desmin-related restrictive cardiomyopathy	III-3D.0	www.crcd.eu RCD textbook (p. 224)
	24-year-old man with ventricular arrhythmia and family history of dilated cardiomyopathy and sudden cardiac death	III-1A.1	www.crcd.eu
	Patient with postinflammatory heart and kidney failure	III-1B.1.0	www.crcd.eu
	Adult patient with hypertrophic cardiomyopathy in complex with chronic respiratory failure caused by kyphoscoliosis	III-2B.6.0	www.crcd.eu
	Fabry disease: intraventricular systolic gradient induced by enzyme replacement therapy	III-2B.2a	www.crcd.eu
	IV. Rare congenital cardiovascular diseases	29-year-old man with heterotaxy syndrome, dextrocardia, transposition of the great vessels, double-inlet left ventricle (right ventricular hypoplasia), pulmonary artery stenosis, right-sided superior vena cava after the Fontan procedure in childhood.	IV-5B.1
Patient after correction of tetralogy of Fallot and single pulmonary artery.		IV-5A.2	www.crcd.eu
Female patient with PFO after ischemic stroke, meningioma, and left middle cerebral artery aneurysm.		IV-4A	www.crcd.eu
Management of a patient after surgical repair of truncus arteriosus type I.		IV-1C.3b	www.crcd.eu RCD textbook (p. 255)
36-year-old man after multiorgan injury, stent-graft implantation, brain stroke with PFO and left subclavian artery obstruction.		IV-4.0	www.crcd.eu
Female patient after the Fontan procedure, brain stroke with coexisting leukopenia and thrombocytopenia.		IV-5B.1	www.crcd.eu
Female patient after correction of tetralogy of Fallot with severe pulmonary regurgitation and significant left-to-right shunt at the ventricular septal level.		IV-5A.2	www.crcd.eu RCD textbook (p. 263)
Female patient after the Fontan procedure with myocardial bridging of the coronary artery and ventricular tachycardia.		IV-5B.1	www.crcd.eu
Patient with complex valve defects.		IV-3A	www.crcd.eu
Patient with patent foramen ovale and thrombophilia, after ischemic stroke and massive pulmonary thromboembolism.		IV-4.0	www.crcd.eu RCD textbook (p. 271)
Patient after Fallot correction with stenosis of the graft pulmonary artery-right ventricle.		IV-5A.2	www.crcd.eu
Patient after Fallot correction with stenosis of the pulmonary artery.		IV-5A.2	www.crcd.eu
27-year-old woman after the Fontan procedure and tricuspid valve atresia, ASD, and VSD.		IV-3B	www.crcd.eu
Patient with Ebstein's syndrome and bidirectional shunt through an ASD.		IV-3B	www.crcd.eu
57-year-old man with inoperable Fallot syndrome.		IV-2A.1	www.crcd.eu
Patient with complex congenital heart defect.	IV-3B	www.crcd.eu	

Class	Examples	RCD code	Reference
IV. Rare congenital cardiovascular diseases	Patient with TGA, VSD, PS after the Rastelli procedure.	IV-5A.2	www.crcd.eu
	Patient after the operation for Fallot syndrome with significant pulmonary regurgitation.	IV-5A.2	www.crcd.eu
	Patient with Ebstein's anomaly, VSD, and severe heart failure.	IV-3B	www.crcd.eu
	Ventricular septal defect and pulmonary atresia.	IV-2A.3	www.crcd.eu
	Patient with ventricular septal defect, pulmonary atresia, and PV-PA graft stenosis.	IV-5A.2	www.crcd.eu
	Adult patient with Fallot syndrome.	IV-2A.1	www.crcd.eu
	Cor triatriatum.	IV-1B.1a	www.crcd.eu
	Patient after correction of Fallot syndrome with recoarctation of the aorta.	IV-5A.2	www.crcd.eu
	Double-chambered left ventricle in a young previously healthy man presenting for routine echocardiographic study.	IV-6.1	www.crcd.eu RCD textbook (p. 284)
	20-year-old man after surgery of double outlet right ventricle.	IV-5A.2	www.crcd.eu
	Adult patient with common artery truncus and RV-PA conduit stenosis	IV-5A.2	www.crcd.eu
	Patient with endocarditis after the Ross–Konno procedure.	IV-5A.2	www.crcd.eu
	Patient with conduit stenosis after surgery correction of tetralogy of Fallot.	IV-5A.2	www.crcd.eu
	55-year-old patient with complex congenital heart malformation.	IV-3.0	www.crcd.eu
	Adult patient with TGA, VSD, and RVOT stenosis.	IV-3B	www.crcd.eu
	50-year-old patient with uncorrected tetralogy of Fallot and aortic stenosis.	IV-3B	www.crcd.eu
	Patient after pulmonary valve valvulotomy with ASD sinus venosus type.	IV-5A.2	www.crcd.eu
	Patient after surgery of Fallot syndrome with aortic regurgitation.	IV-5A.2	www.crcd.eu
	60-year-old patient with total anomalous pulmonary venous return and atrial septal defect.	IV-3B	www.crcd.eu
	Patient with Taussig–Bing syndrome	IV-2B.3	www.crcd.eu
Patient after correction of tetralogy of Fallot with pulmonary valve regurgitation and left pulmonary branch stenosis.	IV-5A.2	www.crcd.eu	
Tetralogy of Fallot with anomalous left anterior descending coronary artery and multiorgan malformation.	IV-5A.2	www.crcd.eu RCD textbook (p. 263)	
V. Rare arrhythmias	Unusual electrocardiographic findings in a patient with dextrocardia and multiple cardiac arrhythmias.	V- 4.0	RCD textbook (p. 309)
	Cardiac arrhythmias in a patient with cor triatriatum.	V-4.0	RCD textbook (p. 312)
VI. Cardiac tumors and cardiovascular diseases in malignancy	Myxoma of the heart.	VI-1A.1a	RCD textbook (p. 339)
	Fibroma in the intraventricular septum.	VI-1A.2	RCD textbook (p. 343)
	Lipomatous hypertrophy of the interatrial septum.	VI-1A.3a	RCD textbook (p. 346)
	Mitral annular calcifications.	VI-4D.2	RCD textbook (p. 352)
	Cavernous hemangioma of the heart.	VI-1B.4a	RCD textbook (p. 349)

Class	Examples	RCD code	Reference
VII. Cardiovascular diseases in pregnancy	Pregnant woman with Ebstein's anomaly and arterial septal defect.	VII-IV-1D.1b	JRCD 2012;1:14-18 RCD textbook (p. 388)
	Pregnancy in a patient with Turner syndrome, after operation of coarctation of the aorta, with bicuspid aortic valve, and ascending aortic aneurysm.	VII-I-1B.6	RCD textbook (p. 384)
	Pregnant woman with Eisenmenger's syndrome.	VII-II-1A.4d	www.crcd.eu RCD textbook (p. 369)
	Pregnancy in a patient with L-TGA.	VII-IV-1C.3a	www.crcd.eu
	Acute thromboembolic disease complicated with heparin-induced thrombocytopenia type II in a pregnant woman.	VII-VIII-4	www.crcd.eu
	Postpartum aortic dissection: manifestation of vascular Ehlers–Danlos syndrome?	VII-I-2A.2	www.crcd.eu RCD textbook (p. 361)
	Pulmonary hypertension in a pregnant woman.	VII-II-1A	RCD textbook (p. 364)
	Pregnancy in a patient with hypertrophic cardiomyopathy.	VII-III-2	RCD textbook (p. 373)
	Favorable course of peripartum cardiomyopathy.	VII-III-5C	RCD textbook (p. 377)
	Pregnant woman with uncorrected cyanotic congenital heart disease.	VII-IV-2A.1	RCD textbook (p. 381)
	Long QT syndrome diagnosed postpartum.	VII-V-1A.2	RCD textbook (p. 393)
	Ablation procedure of sustained supraventricular tachycardia in a pregnant woman.	VII-V-3A	RCD textbook (p. 398)
	Cardiac tumor in a pregnant woman.	VII-VI-1A.2	RCD textbook (p. 402)
VIII. Unclassified rare cardiovascular diseases	62-year-old woman with Heyde's syndrome.	VIII-1	RCD textbook (p. 411)
	49-year-old patient with factor VII deficiency, chronic heart failure, and thrombus in the left ventricle.	VIII-2	RCD textbook (p. 415)
	24 year-old patient with vein thrombosis and thrombus in the apex of the heart during ascariasis.	VIII-3	RCD textbook (p. 421)
	Acute thromboembolic disease complicated with heparin-induced thrombocytopenia type II in a pregnant woman.	VIII-4	www.crcd.eu
	47-year-old patient with primary severe tricuspid regurgitation.	VIII-5	www.crcd.eu

RCD code – code of the classification of Rare Cardiovascular Diseases, Kraków, 2013 (see Part 2); www.crcd.eu – website of the Centre for Rare Cardiovascular Diseases, where the clinical cases are published; RCD textbook – Rare Cardiovascular Diseases: From Classification to Clinical Examples book and the page where the clinical example can be found. J Rare Cardiovasc Dis – Journal of Rare Cardiovascular Diseases

## Centre for Rare Cardiovascular Diseases and knowledge dissemination

In addition to expert consultations at the national and international level (videoconference patient consultations), the CRCD has played an important role in the dissemination of knowledge on RCDs through symposia and conferences, RCD registries, RCD website (www.crcd.eu), and the *Journal of Rare Cardiovascular Diseases*.

### CRCD symposia and conferences

In 2011–2012, CRCD organized the following symposia and conferences:

- Opening of the Krakow Centre for Rare Cardiovascular Diseases (CRCD) at the John Paul II Hospital in Krakow; June 6, 2011 (Fig. 1–9).

Opening of the Centre for Rare Cardiovascular Diseases at the John Paul II Hospital in Krakow evoked appreciation in numerous cardiological communities in Poland. Support for this initiative came from the most

prominent Polish cardiologists. Their acknowledgement is best characterized by some quotations from their congratulatory letters sent for the Opening:

“... external recognition for your leadership in this project is a reason of pride for Polish cardiology. Inauguration of this project importantly supplements the beginning of Polish Presidency of the Council of the European Union”.

Professor Grzegorz Opolski  
Polish National Consultant in Cardiology

“... let me congratulate on the implementation of such a fundamental project and turning it into the Centre (...) This initiative is bound to be successful ...”

Professor Waldemar Banasiak  
Past President of the Polish Cardiac Society

“... There is no doubt that your experience taken together with joint efforts of the international network of experts that you create will benefit Polish patients and Polish cardiology ...”

Professor Janina Stępińska  
President of the Polish Cardiac Society

“... I am convinced that Polish patients will benefit from the structured collaboration with routine multi-center video-consultations meetings contribute to the improvement of treatment for patients...”

Professor Zbigniew Kalarus  
President Elect of the Polish Cardiac Society

- 1st Symposium on Rare Cardiovascular Diseases – ESC Congress 2011, Paris, France (Fig. 10–23)
- 2nd Symposium on Rare Cardiovascular Diseases – ESC Congress 2012, Munich, Germany

- 2nd Symposium on Rare Cardiovascular Diseases – ESC Congress 2012, Munich, Germany (Fig. 24–40)
- 1st International Conference on Rare Cardiovascular Diseases in Krakow (Fig. 41–66)
- The 3rd (Amsterdam 2013) and 4th (Barcelona 2014) ESC Symposia on RCDs have secured both funding and logistics and are therefore being organized by the CRCD.

## Photo reports of CRCD symposia and conferences



**Fig. 1.** Opening of the Centre for Rare Cardiovascular Diseases, Krakow, June 6, 2011. Prof. Tomasz Grodzicki (Dean of the Jagiellonian University Medical College, Krakow, Poland) congratulating on the establishment of the Centre for Rare Cardiovascular Diseases. In the first row from the right Dr Krzysztof Bederski (Medical Affairs Deputy Director of the John Paul II Hospital in Krakow), Prof. Piotr Podolec (Head of the Centre for Rare Cardiovascular Diseases at the John Paul II Hospital in Krakow)



**Fig. 3.** Opening of the Centre for Rare Cardiovascular Diseases, Krakow, June 6, 2011. Barbara Bulanowska (Head of the National Health Fund, Małopolska Division) declaring a support from the National Health Fund, Małopolska Division for improvement of care of patients with rare cardiovascular diseases. Sitting from the left Stanisław Kracik, Voivode of the Małopolska Province, and Wojciech Kozak, Marshal of the Małopolska Province who signed the agreement between the John Paul II Hospital and Małopolska Marshal Office for the project “Establishment a European Network for Orphan Cardiovascular Diseases”



**Fig. 2.** Opening of the Centre for Rare Cardiovascular Diseases, Krakow, June 6, 2011. Stanisław Kracik (Voivode of Małopolska Province) declaring a support from local government for patients with rare cardiovascular diseases. Sitting in the first row from the left: Barbara Bulanowska (Head of the National Health Fund, Małopolska Division), Wojciech Kozak (Marshal of the Małopolska Province) who signed the agreement between the John Paul II Hospital in Krakow and Małopolska Marshal Office for the project “Establishment a European Network for Orphan Cardiovascular Diseases”



**Fig. 4.** Opening of the Centre for Rare Cardiovascular Diseases, Krakow, June 6, 2011. Prof. Anna Fijałkowska (Institute of Tuberculosis and Lung Disease, Warsaw) presenting a lecture, „Pulmonary hypertension in Polish patients”. In the first row from the left: Barbara Bulanowska (Head of the National Health Fund, Małopolska Division), Prof. Piotr Podolec (Head of the Centre for Rare Cardiovascular Diseases at the John Paul II Hospital in Krakow), Prof. Jerzy Sadowski (Director of the Institute of Cardiology, Jagiellonian University Medical College)



**Fig. 5.** Centre for Rare Cardiovascular Diseases meeting, Krakow, June 6, 2011. Prof. Piotr Podolec (Head of the Centre for Rare Cardiovascular Diseases at the John Paul II Hospital in Krakow) and Dr Grzegorz Kopeć (Deputy Head of the Centre for Rare Cardiovascular Diseases at John Paul II Hospital in Krakow) moderating a discussion concerning a patient with giant-cell aortitis. The case is presented using a video-conference system by Prof. Egle Ereminiene (Lithuanian University of Health Sciences, Kaunas, Lithuania)



**Fig. 8.** Opening of the Centre for Rare Cardiovascular Diseases, Krakow, June 6, 2011. Prof. Piotr Podolec (Head of the Centre for Rare Cardiovascular Diseases at the John Paul II Hospital in Krakow) talking with experts of the Centre. Standing from the left: Prof. Katarzyna Mizia-Stec (Medical University of Silesia, Zabrze, Poland), Prof. Zbigniew Gašior (Medical University of Silesia, Zabrze, Poland), Prof. Piotr Podolec (Head of the Centre for Rare Cardiovascular Diseases at John Paul II Hospital in Krakow), Prof. Krzysztof Rytlewski (Department of Obstetrics and Perinatology, Jagiellonian University Medical College)



**Fig. 6.** Centre for Rare Cardiovascular Diseases meeting, Krakow, June 6, 2011. Dr Monika Komar (Department of Cardiac and Vascular Diseases at John Paul II Hospital in Krakow) presenting a case of a 20-year old patient after common arterial trunk correction



**Fig. 9.** Centre for Rare Cardiovascular Diseases meeting, Krakow, June 6, 2011. Discussion with the participants



**Fig. 7.** Centre for Rare Cardiovascular Diseases meeting, Krakow, June 6, 2011. Prof. Magdalena Kostkiewicz (Department of Cardiac and Vascular Diseases at John Paul II Hospital in Krakow) discussing a case of a professional athlete with left ventricular noncompaction



**Fig. 10.** 1st Symposium on Rare Cardiovascular Diseases. ESC Congress 2011 in Paris, France. Prof. Piotr Podolec (Head of the Centre for Rare Cardiovascular Diseases at the John Paul II Hospital in Krakow) greeting prof. Jolien W. Roos-Hesseling (Erasmus Universiteit Rotterdam) an invited expert for the case "Patient with conduit stenosis after surgical correction of tetralogy of Fallot"



**Fig. 11.** 1st Symposium on Rare Cardiovascular Diseases. ESC Congress 2011 in Paris, France. Dr Paweł Rubiś (Centre for Rare Cardiovascular Diseases at the John Paul II Hospital in Krakow), Prof. John GF Cleland (Univeristy of Hull, United Kingdom, moderator of the session), Prof. Piotr Podolec (Head of the Centre for Rare Cardiovascular Diseases at the John Paul II Hospital in Krakow) and Dr Piotr Musiałek (Department of Cardiac and Vascular Diseases at the John Paul II Hospital in Krakow) discussing organizational issues of the session



**Fig. 14.** 1st Symposium on Rare Cardiovascular Diseases. ESC Congress 2011 in Paris, France. Dr Grzegorz Kopeć (Deputy Head of the Centre for Rare Cardiovascular Diseases at the John Paul II Hospital in Krakow) presenting objectives of the European Union project: “Establishing a European Network for Orphan Cardiovascular Diseases”



**Fig. 12.** 1st Symposium on Rare Cardiovascular Diseases. ESC Congress 2011 in Paris, France. Prof. Piotr Podolec (Head of the Centre for Rare Cardiovascular Diseases at the John Paul II Hospital in Krakow) presenting the concept of the Centre for Rare Cardiovascular Diseases



**Fig. 15.** 1st Symposium on Rare Cardiovascular Diseases. ESC Congress 2011 in Paris, France. Dr Jakub Stępniewski (Centre for Rare Cardiovascular Diseases at the John Paul II Hospital, Krakow, Poland) speaking about the need of a new registries on rare cardiovascular diseases



**Fig. 13.** 1st Symposium on Rare Cardiovascular Diseases. ESC Congress 2011 in Paris, France. Dominika Gryszówka (Head of Research and Development Office at the John Paul II Hospital in Krakow) presenting the structure of the European Union project: “Establishing a European Network for Orphan Cardiovascular Diseases”



**Fig. 16.** 1st Symposium on Rare Cardiovascular Diseases. ESC Congress 2011 in Paris, France. Prof. Egle Ereminiene (Lithuanian University of Health Sciences, Kaunas, Lithuania) presenting a case “Annuloaortic abscess with extension to anterior leaflet of mitral valve and left ventricular myocardium”



**Fig. 17.** 1st Symposium on Rare Cardiovascular Diseases. ESC Congress 2011 in Paris, France. Dr Aldis Rozenbergs (Pauls Stradins Clinical University Hospital, Riga, Latvia) presenting a case: “A 69-year old woman with atrial septal defect, coronary heart disease and pulmonary arterial hypertension”



**Fig. 20.** 1st Symposium on Rare Cardiovascular Diseases. ESC Congress 2011 in Paris, France. Dr Mateusz Podolec (Department of Coronary Heart Disease, John Paul II Hospital, Krakow, Poland) presenting a case: “Patient with pulmonary arterial hypertension, atrial septal defect and pulmonary thromboembolism”



**Fig. 18.** 1st Symposium on Rare Cardiovascular Diseases. ESC Congress 2011 in Paris, France. Dr Michał Marchel (Warsaw Medical University) presenting a case: “Dilated cardiomyopathy with atrioventricular conduction defects in a patient with Emery-Dreifuss muscular dystrophy in the course of laminopathy”



**Fig. 21.** 1st Symposium on Rare Cardiovascular Diseases. ESC Congress 2011 in Paris, France. Prof. Irene Lang (Medical University of Vienna) and Dr Grzegorz Kopeć (Deputy Head of the Centre for Rare Cardiovascular Diseases at John Paul II Hospital in Krakow) discussing a patient with pulmonary arterial hypertension, atrial septal defect and pulmonary thromboembolism



**Fig. 19.** 1st Symposium on Rare Cardiovascular Diseases. ESC Congress 2011 in Paris, France. Dr Paweł Rubiś (Centre for Rare Cardiovascular Diseases at the John Paul II Hospital, Krakow, Poland) presenting a case: “Patient with noncompacted left ventricle with dextrocardia and intestinal hernia”



**Fig. 22.** 1st Symposium on Rare Cardiovascular Diseases. ESC Congress 2011 in Paris, France. Paris. Invited experts. From the left: Prof. Nazzareno Galiè (Pulmonary Hypertension Centre, University of Bologna, Italy), prof. Gerald Simmoneau (Department of Pulmonary Disease and Intensive Care, Hospital Antoine Beclere –Clamart-University Paris XI), Prof. Grzegorz Opolski (National Consultant of Cardiology, Warsaw Medical University), Prof. Jarosław Drożdż (Medical University of Łódź), Prof. Anna Fijałkowska (Institute of Tuberculosis and Lung Disease, Warsaw), Prof. Zbigniew Gąsior (Medical University of Silesia, Zabrze, Poland),

*Continued on page 37 →*



**Fig. 23.** 1st Symposium on Rare Cardiovascular Diseases. ESC Congress 2011 in Paris, France. Participants of the meeting



**Fig. 25.** 2nd Symposium on Rare Cardiovascular Diseases. ESC 2012 Congress, Munich, Germany. Centre for Rare Cardiovascular Diseases Team preparing for the session. From the left: Dr Piotr Musiałek, Dr Jakub Podolec, Dr Lidia Tomkiewicz-Pająk, Prof. Piotr Podolec, Dr Paweł Rubiś, Dr Grzegorz Kopeć



**Fig. 24.** 2nd Symposium on Rare Cardiovascular Diseases. ESC 2012 Congress, Munich, Germany. Centre for Rare Cardiovascular Diseases members arriving at the Congress venue. From the left: Dr Paweł Rubiś, Dr Grzegorz Kopeć, Dr Lidia Tomkiewicz-Pająk, Dr Jakub Stępniewski



**Fig. 26.** 2nd Symposium on Rare Cardiovascular Diseases. ESC 2012 Congress, Munich, Germany. Prof. Eloisa Arbustini (Center for Inherited Cardiovascular Diseases, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy) discussing with the team of Centre for Rare Cardiovascular Diseases the future scientific collaboration in rare cardiovascular diseases

*Continued from page 36*

**Fig. 22.** Prof. Piotr Hoffman (The Cardinal Stefan Wyszyński, Institute of Cardiology), Prof. Tomasz Kukulski (Medical University of Silesia, Zabrze, Poland), Jolien W. Roos-Hesselink (Erasmus Universiteit Rotterdam), Prof. Eloisa Arbustini (Laboratorio di Diagnostica Molecolare, Patologia Cardiovascolare e dei Trapianti, Pavia, Italy)



**Fig. 27.** 2nd Symposium on Rare Cardiovascular Diseases. ESC 2012 Congress, Munich, Germany. Prof. Piotr Podolec (Head of the Centre for Rare Cardiovascular Diseases) describing the role Centre of Rare Cardiovascular Diseases



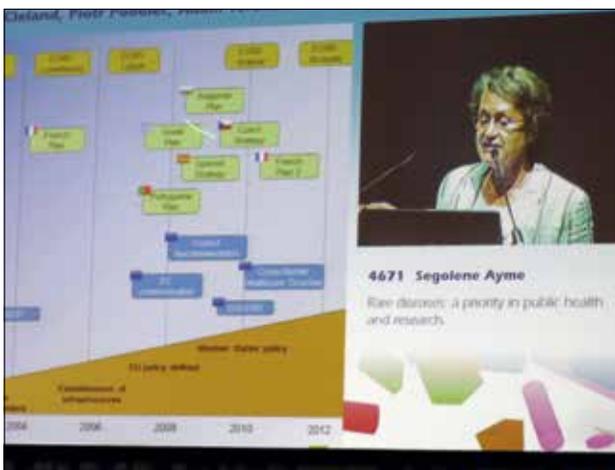
**Fig. 30.** 2nd Symposium on Rare Cardiovascular Diseases. ESC 2012 Congress, Munich, Germany. Dr Lidia Tomkiewicz-Pająk (Centre for Rare Cardiovascular Diseases at the John Paul II Hospital, Krakow, Poland) presenting a case: “Pregnancy in a patient with Turner syndrome, coarctation of aorta, bicuspid aortic valve, and aneurysm of aorta”



**Fig. 28.** 2nd Symposium on Rare Cardiovascular Diseases. ESC 2012 Congress, Munich, Germany. Prof. John GF Cleland (University of Hull, United Kingdom) and Dr Piotr Musialek (Department of Cardiac and Vascular Diseases) moderating the session



**Fig. 31.** 2nd Symposium on Rare Cardiovascular Diseases. ESC 2012 Congress, Munich, Germany. Prof. Piotr Hoffman (The Cardinal Stefan Wyszyński, Institute of Cardiology) giving an expert comment of the case: “Pregnancy in a patient with Turner syndrome, coarctation of aorta, bicuspid aortic valve, and aneurysm of aorta”



**Fig. 29.** 2nd Symposium on Rare Cardiovascular Diseases. ESC 2012 Congress, Munich, Germany. Prof. Ségolène Aymé (Paris, ORPHANET and EUCERD Director) in the symposium’s Keynote Lecture explained why rare diseases have become a top priority in EU public health and research, and acknowledged a leading role of the Krakow CRCD



**Fig. 32.** 2nd Symposium on Rare Cardiovascular Diseases. ESC 2012 Congress, Munich, Germany. Prof. Zbigniew Gašior (Medical University of Silesia, Zabrze, Poland) giving an expert comment on a case: “Pregnancy in a patient with Turner syndrome, coarctation of aorta, bicuspid aortic valve, and aneurysm of aorta”



**Fig. 33.** 2nd Symposium on Rare Cardiovascular Diseases. ESC 2012 Congress, Munich, Germany. Dr Grzegorz Kopeć (Centre for Rare Cardiovascular Diseases at the John Paul II Hospital, Krakow) presenting a case: “Rapid clinical deterioration after first line treatment of a patient with idiopathic pulmonary arterial hypertension”



**Fig. 36.** 2nd Symposium on Rare Cardiovascular Diseases. ESC 2012 Congress, Munich, Germany. Prof. Eloisa Arbustini (Center for Inherited Cardiovascular Diseases, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy) commenting on the presented cases



**Fig. 34.** 2nd Symposium on Rare Cardiovascular Diseases. ESC 2012 Congress, Munich, Germany. Prof. Nazzareno Galiè (Pulmonary Hypertension Centre, University of Bologna) giving an expert comment on a case: “Rapid clinical deterioration after first line treatment of a patient with idiopathic pulmonary arterial hypertension”



**Fig. 37.** 2nd Symposium on Rare Cardiovascular Diseases. ESC 2012 Congress, Munich, Germany. Dr Jakub Podolec speaking about the highlights of the first issue of the *Journal of Rare Cardiovascular Diseases* and presenting the website of the Centre for Rare Cardiovascular Diseases; [www.crkd.eu](http://www.crkd.eu)



**Fig. 35.** 2nd Symposium on Rare Cardiovascular Diseases. ESC 2012 Congress, Munich, Germany. Dr Pawel Rubiś (Centre for Rare Cardiovascular Diseases at the John Paul II Hospital, Krakow) discussing a chance for lung transplantation in the presented patient



**Fig. 38.** 2nd Symposium on Rare Cardiovascular Diseases. ESC 2012 Congress, Munich, Germany. **After the session.** Prof. Nazzareno Galiè (Pulmonary Hypertension Centre, University of Bologna) with his master degree student, Dr Grzegorz Kopeć (Centre for Rare Cardiovascular Diseases at the John Paul II Hospital in Krakow)



**Fig. 39.** 2nd Symposium on Rare Cardiovascular Diseases. ESC 2012 Congress, Munich, Germany. **After the session.** Prof. Piotr Hoffman (The Cardinal Stefan Wyszyński, Institute of Cardiology), Prof. Zbigniew Gąsior (Medical University of Silesia, Zabrze, Poland) and Prof. Piotr Podolec (Head of the Centre for Rare Cardiovascular Diseases)



**Fig. 40.** 2nd Symposium on Rare Cardiovascular Diseases. ESC 2012 Congress, Munich, Germany. The Session was attended by 237 doctors from 19 countries including not only Europe but also Australia, India, South Africa, Brazil, and USA. This high turn-up of participants made the Berlin Hall almost too small to house the Symposium



**Fig. 41.** Announcement of the 1st International Conference on Rare Cardiovascular Diseases, 18–19 October 2012, Kraków, Poland



**Fig. 42.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Prof. Piotr Podolec (Head of the Centre for Rare Cardiovascular Diseases, Krakow) opening the conference and inviting guests



**Fig. 43.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Dr Krzysztof Chlebus (Under-Secretary of State at the Ministry of Health, Poland) declaring a support from Government for further development of the Centre for Rare Cardiovascular Diseases



**Fig. 46.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Dr Anna Prokop-Staszecka (Director of the John Paul II Hospital in Krakow) highlighting the role of multidisciplinary approach in care of patients with rare cardiovascular diseases. Prof. Tomasz Grodzicki (Dean of the Jagiellonian University Medical College, Kraków, Poland) and Prof. Piotr Podolec (Head of the Centre for Rare Cardiovascular Diseases at the John Paul II Hospital in Krakow) moderating the session



**Fig. 44.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Prof. Janina Stępińska (President of the Polish Society of Cardiology, Warsaw) describing the role of Polish Cardiac Society in improvement of care of patients with rare cardiovascular diseases



**Fig. 47.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Prof. Jerzy Sadowski (Director of Institute of Cardiology, Jagiellonian University Medical College) speaking about the need of cooperation between internists, cardiologists and cardiac surgeons in care of patients with cardiovascular diseases



**Fig. 45.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Prof. Grzegorz Opolski (National Consultant in Cardiology, Warsaw) highlighting the importance of specialized centres for patients with rare cardiovascular diseases



**Fig. 48.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Prof. Andrzej Matyja (Head of the Regional Medical Chamber, Kraków) speaking about the need to develop regional network for rare cardiovascular diseases



**Fig. 49.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Dr Jacek Graliński (Chair of the Rare Diseases Committee in the Ministry of Health, Poland) discussing the National Plan for Rare Diseases



**Fig. 52.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Prof. Tomasz Pasierski (Warsaw Medical University, Poland) presenting a lecture: "Ethical problems in financing rare cardiovascular diseases in Poland"



**Fig. 50.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Monika Jezierska-Kazberuk (Deputy Head of the National Health Fund, Małopolska Division) describing financing of rare cardiovascular diseases in Małopolska region



**Fig. 53.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Prof. Tomasz Grodzicki (Dean of the Jagiellonian University Medical College, Kraków, Poland) presenting a lecture: "Do we need centers for rare diseases in Poland?"



**Fig. 51.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Dr Piotr Musiałek (Department of Cardiac and Vascular Diseases) reporting on the 2nd Symposium on Rare Cardiovascular Diseases during European Society of Cardiology 2012 Congress in Munich



**Fig. 54.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Prof. Janusz Skalski (Polish-American Institute of Pediatrics, Jagiellonian University Medical College, Kraków, Poland) presenting a lecture: "The rare diseases: Past or Present?"



**Fig. 55.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Prof. John GF Cleland (University of Hull, United Kingdom) presenting a lecture: “The continuing evolution of cardiovascular diseases: rare, poorly recognized or met need”



**Fig. 58.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Dr Grzegorz Kopeć (Centre for Rare Cardiovascular Diseases at the John Paul Hospital in Krakow, Poland) describing “Pulmonary veno-occlusive diseases: rare in the rare”



**Fig. 56.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Prof. Henryk Siniawski (Deutsches Herzzentrum Berlin, Germany) discussing a problem of “Decision making in rare cardiovascular diseases”



**Fig. 59.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Prof. Adam Torbicki moderating a discussion. Sitting from the left: Prof. Zbigniew Gąsior (Medical University of Silesia, Zabrze, Poland), Prof. Piotr Hoffman (The Cardinal Stefan Wyszyński, Institute of Cardiology), Prof. Adam Torbicki (European Health Centre, Otwock, Poland)



**Fig. 57.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Prof. Nika Skoro-Sajer (Medical University of Vienna, Austria) describing “Non-PAH-current therapeutic options”



**Fig. 60.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Prof. Zofia Bilińska (Warsaw Medical University, Poland) giving a lecture concerning “Family screening in inheritable cardiomyopathies”



**Fig. 61.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Prof. Egle Ereminiene (Lithuanian University of Health Sciences, Kaunas, Lithuania) describing “Tako-Tsubo Cardiomyopathy – underrecognized and misdiagnosed syndrome”



**Fig. 64.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Prof. Maciej Malecki (Department of Metabolic Diseases, Jagiellonian University Medical College, Kraków, Poland) giving a lecture: “Rare forms of diabetes: what cardiologists need to know?”



**Fig. 62.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Dr Pawel Rubis (Centre for Rare Cardiovascular Diseases at the John Paul II Hospital in Krakow) presenting a lecture: “Arrhythmogenic right ventricular cardiomyopathy –rare in the rare”



**Fig. 66.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Dr Wojciech Plazak (Department of Cardiac and Vascular Diseases) presenting a lecture: “Cardiovascular system in connective tissue diseases”



**Fig. 63.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Dr Anna Kablak-Ziembicka (Department of Cardiac and Vascular Diseases) presenting a lecture: “Rare anomalies of systemic arteries”



**Fig. 65.** I International Conference on Rare Cardiovascular Diseases, Krakow 2012. Prof. Anna Fijałkowska (Institute of Tuberculosis and Lung Disease, Warsaw, Poland) presenting a lecture: “Pregnancy in pulmonary hypertension”

## CRCD website: www.crcd.eu

The CRCD website (www.crcd.eu) established in 2010 plays an important role in the achievement of the key goal of the CRCD – dissemination of knowledge (fig. 67). The majority of clinical cases discussed during the quarterly international live videoconferences in 2010–2013 and CRCD Workshops on ESC conferences in Paris in 2011 and Munich in 2012 are available on the website. RCD patient presentations include

a short case description, results of diagnostic procedures, and literature review. All these reports feature expert opinions and conclusions concerning the agreed diagnostic and treatment approach. The news section provides important and up-to-date information about the events and activities of the center. The “easy search” feature based on the new classification of RCDs is a quick way to find relevant information about RCDs. The CRCD website is linked to the website of the *Journal of Rare Cardiovascular Diseases* (www.jrcd.eu).

The screenshot displays the homepage of the Centre for Rare Cardiovascular Diseases (CRCD) website. At the top, there is a navigation bar with icons and labels for 'ABOUT THE CRCD', 'EDUCATION', 'JOURNAL OF RCD', 'PRESS OFFICE', 'CONTACT', and 'LANGUAGE'. Below this is a teal banner featuring a group of medical professionals and the text: 'RARE CARDIOVASCULAR DISEASES also called „orphan“ diseases, occur in less than 5/10000 people, but there are thousands of them all over the world, suffering life threatening situations every day.'

The main content area is divided into several sections:

- NEWS AND PRESS:** Includes a headline 'The next CRCD tele conference meeting' and 'New case presentations of rare cardiovascular diseases'.
- case presentations OF RARE CARDIOVASCULAR DISEASES:** Lists 'MARRIAGE SYNDROME' and 'PULMONARY HYPERTENSION'.
- education FOR PATIENTS AND PHYSICIANS:** Lists topics like 'rare cardiovascular diseases', 'diagnostic methods', 'treatment', 'guidelines', 'science, trials', and 'risk factors of CAC'.
- about us:** Describes the project's goal of establishing a European community for diagnosis and treatment of rare cardiovascular diseases.
- community OF CRCD:** Lists partners such as 'LIDER', 'Kardiológų Taryba Lietuvoje', 'LIETUVOS Sveikatos MOKSLŲ UNIVERSITETAS', and 'Lietuvos širdies ligų asociacija'.
- quick access MOST RELEVANT CONTENT:** Lists 'clinical case reporting', 'download', and 'useful links'.
- meetings AND INITIATIVES:** Promotes the '1st International Conference on Rare Cardiovascular Diseases'.
- don't miss IMPORTANT EVENTS:** Features a graphic with a red silhouette of a person and a heart.

The footer contains logos for 'PROGRAMA REGIONALNY WZROSTOWANIA PRACUJĄCYCH', 'Małopolska', 'European Union', 'LIDER', 'LIETUVOS Sveikatos MOKSLŲ UNIVERSITETAS', and 'LIETUVOS širdies ligų asociacija'.

Fig. 67. CRCD website: www.crcd.eu



Fig. 68. *Journal of Rare Cardiovascular Diseases*. First issue – October 2012. A. Cover. B. Content page

## Establishing the *Journal of Rare Cardiovascular Diseases*

The *Journal of Rare Cardiovascular Diseases* (fig. 68) was established by the CRCDD in 2012 to meet the increasing need for peer-reviewed information on RCDs. The journal is an independent educational initiative and it is registered under European laws. At present, it is published quarterly (simultaneous online and print publication) and it is run by the CRCDD and 'For Heart' Foundation in Krakow. Current sections of the journal include: Review Papers, Original Articles, Case Reports, and Conference/Meeting Reports. Each submission is reviewed by at least one international reviewer and one national reviewer. The journal is expected to receive its first impact factor soon.

## Registries of the Centre for Rare Cardiovascular Diseases

The CRCDD registries of RCDs originate from a large database of patients with a variety of non-rare cardiovascular diseases referred to the departments of the John Paul II Hospital in Krakow. In Tables 4 to 9, we present the registries of RCDs and the registries of non-rare cardiovascular diseases, from which the rare cases originate.

Every disease category is accompanied by a code of RCD classification (see Part 2) and a number of patients recorded in the registry up to May 30, 2013.

**Table 4a. CRCD registry of rare diseases of systemic circulation (Class I)**

Group	Subgroup	Examples/Category/Unit	RCD code	Number of patients
Anatomical malformations of the arteries	Coronary arteries: variants in course and number.	Single coronary artery	I-1D.2	2
		Coronary artery originating from the pulmonary artery	I-1D.3	2
		Others	I-1D.0	3
Connective tissue disorders causing aneurysmal disease	Aneurysmal disease of the aorta	Marfan syndrome	I-2A.1	43
		Ehlers–Danlos syndrome	I-2A.2	1
Autoimmune vascular diseases	Primary systemic vasculitis: predominantly large arteries	Takayasu's arteritis	I-3A.1	21
		Giant-cell arteritis	I-3A.2	2
Intimal hyperplasia	Fibromuscular dysplasia		I-4.A	4
Spontaneous dissection of the artery	Dissection of carotid arteries		I-5.0	8
<b>Total:</b>				<b>86</b>

**Table 4b. CRCD registries of non-rare diseases of the systemic circulation**

Examples	Number of patients
Internal carotid stenosis treated with neuroprotected stent implantation	2085
Symptomatic vertebral stenosis treated with stent implantation	348
Subclavian stenosis treated with percutaneous angioplasty	310
Renal artery stenosis treated with stent implantation	181
<b>Total:</b>	<b>2924</b>

**Table 5. CRCD registry of rare diseases of pulmonary circulation (Class II)**

Group	Subgroup	Examples/Category/Unit	RCD code	Number of patients	
Pulmonary hypertension	Low-prevalence pulmonary hypertension	Idiopathic	II-1A.1	48	
		PAH associated with connective tissue disease	II-1A.4a	12	
		PAH associated with portal hypertension	II-1A.4c	2	
		PAH associated with congenital heart disease	II-1A.4d	80	
		Pulmonary veno-occlusive disease	II-1A.6	1	
		Chronic thromboembolic pulmonary hypertension	II-1A.5	20	
	Non-low-prevalence pulmonary hypertension	Severe pulmonary hypertension due to left heart disease	II-1B.1	38	
		Severe pulmonary hypertension due to lung diseases and/or hypoxia	II-1B.2	15	
	Overlapping pulmonary hypertension		Pulmonary hypertension associated with congenital heart disease overlapping with chronic thromboembolic disease; pulmonary hypertension due to lung fibrosis and chronic thromboembolic diseases; pulmonary hypertension associated with hypoxia due to severe chest deformation overlapping with ventricular septal defect	II-1C	7
	<b>Total:</b>				<b>223</b>
PAH - pulmonary arterial hypertension					

**Table 6a. CRCD registry of rare diseases of the heart (cardiomyopathies) (Class III)**

Group	Subgroup	Examples/Category/Unit	RCD code	Number of patients
1. Dilated cardiomyopathy	A. Genetic	3. Cytoskeletal genes	III-1A.3	4
	B. Nongenetic	1. Inflammatory cardiomyopathy	III-1B.1	20
		2. Due to connective tissue diseases	III-1B.2	3
		4. Due to infiltrative disorders	III-1B.4	4
		5. Medication-induced	III-1B.5	15
		6. Toxin-induced	III-1B.6	8
		7. Tachycardia-induced	III-1B.7	15
		8. End stage of other cardiomyopathies	III-1B.8	16
2. Hypertrophic cardiomyopathy	B. Non-sarcomeric protein mutations	1. Glycogen storage disease	III-2B.1	2
		2. Lysosomal storage disease	III-2B.2	5
		6. Syndromic HCM	III-2B.6	3
3. Restrictive cardiomyopathy	A. Infiltrative	2. Amyloid	III-3A.2	2
		3. Sarcoidosis	III-3A.3	3
	E. Desminopathy	III-3E	1	
	F. Other	III-3.F.0	1	
4. Arrhythmogenic right ventricular cardiomyopathy			III-4	2
5. Unclassified cardiomyopathies	A. Left ventricular noncompaction		III-5A	4
	B. Takotsubo cardiomyopathy		III-5B	2
	C. Peripartum cardiomyopathy		III-5C	4
<b>Total:</b>				<b>114</b>

**Table 6b. CRCD registries of non-rare diseases of the heart (cardiomyopathies)**

Group	Number of patients
Cardiomyopathies (DCM, HCM, RCM)	310 (55%)
Non-cardiomyopathies (most ischemic)	250 (45%)
<b>Total:</b>	<b>560</b>
DCM – dilated cardiomyopathy, HCM – hypertrophic cardiomyopathy, RCM – restrictive cardiomyopathy	

<b>Table 7a. CRCD registry of rare congenital cardiovascular diseases (Class IV)</b>				
<b>Group</b>	<b>Subgroup</b>	<b>Examples/Category/Unit</b>	<b>RCD code</b>	<b>Number of patients</b>
Abnormalities of the position and connection of the heart and vessels	B-Heart chambers	Congenitally corrected transposition of great artery	IV-1B.2a	8
		Ductus arteriosus	IV-2B.4	5
	D-Valves	Ebstein's anomaly	IV-1D.1b	6
		Pulmonary stenosis	IV-1D.1d	30
		Aortic stenosis	IV-1D.2c	39
Shunts	A-Decreased pulmonary flow	Tetralogy of Fallot	IV-2A.1	5
Grown-up Congenital Cardiovascular Diseases	A-After correction	Tetralogy of Fallot after correction	IV-5A	124
		Transposition of the great artery after correction	IV-5A	33
		Pulmonary stenosis after correction	IV-5A	24
		Truncus arteriosus after correction	IV-5A	3
		Common atrioventricular canal after correction	IV-5A	28
		Ductus arteriosus after correction	IV-5A	30
	B-After palliation	After Fontan Procedure	IV-5B.1	36
		Others		50
<b>Total:</b>				<b>421</b>

<b>Table 7b. CRCD registries of non-rare congenital cardiovascular diseases</b>	
<b>Examples/Category/Unit</b>	<b>Number</b>
Ventricular septal defect	21
Atrial septal defect	204
Ventricular septal defect after correction	43
Atrial septal defect after percutaneous closure	420
Atrial septal defect after correction	82
PFO after closure	321
Bicuspid aortic valve	128
<b>Total:</b>	<b>1219</b>

**Table 8. CRCD registry of cardiac tumors and cardiovascular diseases in malignancy (Class VI)**

Group	Subgroup	Examples/Category/Unit	RCD code	Number of patients
1-Primary cardiac tumors	A-Primary benign tumors	1-Myxoma	VI-1A1	32
		2-Fibroma	VI-1A2	5
		3-Lipoma	VI-1A3	11
	B-Primary malignant tumors	1-Rabdomyosarcoma	VI-1B1	0
		2-Angiosarcoma	VI-1B2	4
2-Metastatic cardiac tumors	A-Thorax	1-Lung cancer	VI-2A1	2
	B-Abdomen	3-Prostate cancer	VI-2B3	1
3-Thrombus within the heart chambers			VI-3	115
4-Inflammatory malformations	A.-Vegetations		VI-4A	63
	B-Inflammatory tumors		VI-4B	5
	C-Abscesses		VI-4C	9
	D-Calcifications	1-Pericardium	VI-4D1	11
		2-Valves	VI-4D2	10
5-Cardiovascular complications after oncotherapy	Post-surgery		VI-7A	3
	B- Post-radiotherapy			11
	C- Post-chemotherapy			94
<b>Total:</b>				<b>376</b>

**Table 9a. CRCD registry of rare cardiovascular diseases in pregnancy (Class VII)**

Class	Examples of cardiovascular diseases in pregnancy	Number of patients
VII-I	rare diseases of the systemic circulation	1
VII-II	rare diseases of the pulmonary circulation	3
VII-III	rare diseases of the heart (cardiomyopathies)	4
VII-IV	rare congenital heart diseases	13
VII-V	rare congenital heart diseases	2
VII-VI	cardiac tumors and cardiovascular diseases in malignancy	1
VII-VIII	rare unclassified diseases	1
<b>Total:</b>		<b>25</b>

**Table 9b. CRCD registries of non-rare cardiovascular diseases in pregnancy**

Valvular diseases:	aortic valve diseases	4
	mitral valve diseases	2
	mechanical valve prostheses	5
	bioprostheses	3
Congenital heart diseases:	atrial septal defect	28
	ventricular septal defect	3
	pulmonary stenosis	2
Hypertension		65
Others		5
<b>Total:</b>		<b>117</b>

## Centre for Rare Cardiovascular Diseases Postgraduate Training – international training

International training has included both training of the CRCD physicians in the partner centers abroad,

and visits of physicians from abroad in the CRCD. We present a list of institutions that hosted physicians from the CRCD (Table 10). The authors of this textbook together with all the interns would like to thank the leaders of the institutions and their employees for their hospitality.

**Table 10. CRCD physician training: collaborating institutions**

Centre/Institution	City/Country	Leading Physician(s)/Scientist(s)/Executive Officer(s)
Cardiopatías Congénitas del Adulto Hospital La Paz	Madrid, Spain	José María Oliver Ruiz
Pulmonary Hypertension Centre, University of Bologna	Bologna, Italy	Nazzareno Galiè
Klinik für Innere Medizin und Kardiologie im Philips Universität	Marburg, Germany	B. Maisch, Sabine Pankuweit
Centro per le Malattie Genetiche Cardiovascolari in Fondazione IRCCS Policlinico „San Mateo“ in Pavia, Italy	Pavia, Italy	Eloisa Arbustini
Henri Mondor Clinic Universitaire Vasculaire	Paris, France	Jean Pierre Becquemin
Deutsches Herzzentrum Berlin	Berlin, Germany	Roland Hetzer, Henryk Siniawski, Petra Gehle
Lithuanian University of Health Sciences in Kaunas	Kaunas, Lithuania	Remigijus Zaliunas, Egle Ereminiene
The Heart Failure Department at I.R.C.C.S. Policlinico San Donato	Milano, Italy	Marco Guazzi
Clinic and Polyclinic for Surgery, Department of Vascular Surgery and Endovascular Surgery	Regensburg, Germany	Piotr Kasprzak
Royal Infirmary Hospital	Edinburgh, Scotland	Keith Fox
Inherited Cardiac Disease Clinic in the Heart Hospital, University College of London	London, UK	W. McKenn, P. Eliota.
San Raffaele Hospital	Milan, Italy	Ottavio Alfieri, Aantonio Colombo, Francesco Maisano, Giovanni La Canna
Department of Paediatric Cardiology and Congenital Heart Defects, German Heart Centre	Munich, Germany	Peter Ewert



# Part 2

## Classification of Rare Cardiovascular Diseases

**Editor: Piotr Podolec**



# Classification of Rare Cardiovascular Diseases (RCD Classification), Krakow 2013

Piotr Podolec  
for the RCD Classification Working Group\*

*Worldwide sharing of information, data, and samples to boost research is currently hampered by the absence of an exhaustive rare diseases classification*

Ségolène Aymé  
Rare Diseases: a Priority in Public  
Health and Research  
*J Rare Cardiovasc Dis 2012; 1: 2*

Almost every day brings new reports of a “rare” (“orphan”) disease – a disease that requires multidisciplinary knowledge and particular caution in making diagnostic and therapeutic decisions.

The Classification of Rare Cardiovascular Diseases (RCD) is aimed at (1) facilitating recognition of RCDs, and (2) grouping the expertise in the main fields of RCDs.

The classification provides a systemic framework for clinical examples selected from a broad group of patients who have been consulted in the CRCDD on a regular basis by national and international experts during live videoconferences.

RCD Classification presented in Table 1 and published simultaneously in the *Journal of Rare Cardiovascular Diseases* is based on the CRCDD experience of over 300 patients consulted in the years 2006–2013 (many of whom were diagnosed and treated in the CRCDD) and takes into consideration the majority of publications available through PubMed. RCD Classification encompasses the diseases whose major pathological mechanism affects the cardiovascular system.

RCD Classification accommodates the intensity of clinical symptoms and pathology concerning the systemic and pulmonary circulation (Class I and Class II),

the heart and myocardium (Class III), congenital heart diseases (class IV), and rhythm and conduction disorders (Class V). Cardiovascular diseases in oncological patients (Class VI) and those in pregnant patients are classified separately (Class VI and Class VII, respectively). There are also overlapping syndromes and diseases that cannot be unequivocally classified into any of the Classes I to VII, that is represented by Class VIII.

The main classes of the RCD classification include:

- Class I – rare diseases of systemic circulation
- Class II – rare diseases of pulmonary circulation
- Class III – rare diseases of the heart (cardiomyopathies)
- Class IV – rare congenital cardiovascular diseases
- Class V – rare arrhythmias
- Class VI – cardiac tumors and cardiovascular diseases in malignancy
- Class VII – cardiovascular diseases in pregnancy
- Class VIII – unclassified rare cardiovascular diseases

RCD Classification is presented in Table 1.

It is listed by groups and subgroups as appropriate. It contains RCD Classification code and the code of International Classification of Diseases (ICD-10). The main classes are arranged in order from class I to class VIII. Each entity or group of entities is assigned a unique RCD Classification code. Coding of Class VII is described in a relevant commentary in the Table 1. Consecutive unclassified rare cardiovascular cases included in Class VIII are assigned subsequent code according to the order of publication on the CRCDD webpage – [www.crcdd.eu](http://www.crcdd.eu) or in the *Journal of Rare Cardiovascular Diseases*.

As this classification is regarded the pioneering attempt to systematize rare cardiovascular diseases the authors of this textbook are, indeed, aware of its imperfections and limitations. Therefore, presenting this classification we sincerely encourage the Readers to provide their solid feedback. Constructive contributions will be recognized.

\* Please note that the RCD Classification is currently under the second round of review by the national and international CRCDD experts. For individual author contributions, please see the respective RCD Classes/Sections as per the textbook Parts and Chapters that follow.

**Table 1. Classification of Rare Cardiovascular Diseases, Krakow 2013**

Group	Subgroup	Examples	RCD code	ICD-10 code
<b>Rare diseases of systemic circulation – class I</b>				
1. Anatomical malformations of the arteries	A. Cerebral arteries	1. Anomalies of the circle of Willis	I-1A.1	Q28.3
		2. Intracerebral arteries	I-1A.2	I67.8
		3. Moyamoya disease	I-1A.3	I67.5
		– Others	I-1A.0	
	B. Aorta and aortic arch main branches	1. Right aortic arch	I-1B.1	Q25.4
		2. Double aortic arch	I-1B.2	Q25.4
		3. Aortic rings	I-1B.3	Q25
		4. Interruption of aortic arch	I-1B.4	Q25.4
		5. Variants in aortic arch arteries	I-1B.5	Q25
		6. Coarctation of the aorta	I-1B.6	Q25.1
		– Others	I-1B.0	
		C. Coronary arteries	1. Variants in the course and the number	I-1C.1
	2. Single coronary artery		I-1C.2	Q24.5
	3. Coronary artery originating from the pulmonary artery		I-1C.3	Q24.5
	4. Coronary fistula		I-1C.4	Q24.5
	5. Coronary artery aneurysm		I-1C.5	Q24.5
	– Others		I-1C.0	
	D. Other arteries	1. Abdominal aorta: cephalic trunk, renal, mesenteric, splenic, others	I-1D.1	Q27.2
		2. Iliac and femoral arteries	I-1D.2	Q27.8
		3. Popliteal and below the knee	I-1D.3	Q27.8
4. Upper extremity arteries		I-1D.4	Q27.8	
– Others		I-1D.0		
2. Connective tissue disorders causing aneurysmal disease	A. Aneurysmal disease of the aorta	1. Marfan syndrome	I-2A.1	Q87.4
		2. Ehlers–Danlos syndrome	I-2A.2	I71
		3. Loey–Dietz syndrome	I-2A.3	Q79.6
		4. Familial thoracic aortic aneurysms and dissections	I-2A.4	Q87.4
		– Others	I-2A.0	
	– Others	I-2.0		
3. Autoimmune vascular diseases	A. Primary systemic vasculitis: Predominantly large arteries	1. Takayasu’s arteritis	I-3A.1	M31.4
		2. Giant-cell arteritis	I-3A.2	M31.6
		3. Isolated aortitis	I-3A.3	I77.6
		– Others	I-3A.0	

Group	Subgroup	Examples	RCD code	ICD-10 code
3. Autoimmune vascular diseases	A. Primary systemic vasculitis: Predominantly medium-and small-size arteries	5. Kawasaki disease	I-3A.5	M30.3
		6. Polyarteritis nodosa	I-3A.6	M30
		7. Necrotizing ANCA-associated: a. Churg–Strauss syndrome b. Wegener’s granulomatosis c. Microscopic polyangiitis d. Idiopathic necrotizing crescentic glomerulonephritis	I-3A.7	
			I-3A.7a	M31
			I-3A.7b	M31.3
			I-3A.7c	M31.7
		I-3A.7d	N05.7	
		8. Non-ANCA associated: a. Henoch–Schönlein purpura b. Goodpasture’s disease c. Mixed cryoglobulinemia d. Hypersensitivity vasculitis – others	I-3A.8	
	I-3A.8a		D69	
	I-3A.8b		M31.0	
	I-3A.8c		D89.1	
	I-3A.8d	M31.0		
	I-3A.8.o			
	B. Secondary systemic vasculitis	1. Secondary to infection (unknown) a. Viral b. Bacterial c. Fungal d. Parasitosis	I-3B.1	177.6
			I-3B.1.a	
			I-3B.1.b	
			I-3B.1.c	
		I-3B.1.d		
		2. Secondary to medications	I-3B.2	
	C. Connective tissue disorders causing premature thrombosis / atherosclerosis	1. Systemic lupus erythematosus	I-3C.1	M32
2. Scleroderma		I-3C.2	M34	
3. Antiphospholipid syndrome		I-3C.3	D68.6	
– Others		I-3C.0		
– Others	1. Behçet’s disease	I-30.1	M35.2	
	2. Cogan syndrome	I-30.2	Q30.8	
	3. Others	I-30.0		
4. Intimal hyperplasia	A. Fibromuscular dysplasia	I-4A	177.3	
	- Others	I-40		
5. Spontaneous dissection of the artery	A. Dissection of aortic arch arteries	I-5A	171.0	
	- Others	I-50		
6. Premature atherosclerosis	A. Familial hypercholesterolemia	I-6A.1	E78	
	B. Adult progeria – laminopathies	1. Hutchison–Gilford progeria syndrome	I-6B.1	E34.8
		2. Dunnigan-type partial lipodystrophy	I-6B.2	E88.1
		– Others	I-6B.0	
	C. Secondary	1. Polycystic ovary syndrome	I-6C.1	E28.2
		2. Acquired immunodeficiency syndrome	I-6C.2	B22.2
		– Others	I-6C.0	
– Others		I-0		

Group	Subgroup	Examples	RCD code	ICD-10 code	
<b>Rare diseases of pulmonary circulation – RCD class II</b>					
1. Pulmonary hypertension	A. Low-prevalence pulmonary hypertension	1. Idiopathic PAH	II-1A.1	I27	
		2. Heritable PAH	II-1A.2	I27	
		3. Drug- and toxin-induced PAH	II-1A.3	I27.2	
		4. PAH associated with:			
		a. connective tissue disease	II-1A.4a	I27.2	
		b. HIV infection	II-1A.4b	I27.2	
		c. portal hypertension	II-1A.4c	I27.2	
		d. congenital heart diseases	II-1A.4d	I27.2	
		– others	II-1A.4.o		
		5. Chronic thromboembolic pulmonary hypertension	II-1A.5	I27.2	
	6. Pulmonary veno-occlusive disease	II-1A.6	I27		
	7. Pulmonary hemangiomatosis	II-1A.7	D18		
	8. Persistent pulmonary hypertension of the newborn	II-1A.8	P29		
	– Others	II-1A.0			
	B. Severe forms of non-low-prevalence pulmonary hypertension	1. Severe pulmonary hypertension due to left heart diseases	II-1B.1	I27	
		2. Severe pulmonary hypertension due to lung diseases and/or hypoxia	II-1B.2	I27.2	
		– Others			
C. Overlap pulmonary hypertension	1. Pulmonary hypertension in a patient with congenital shunt and left ventricular dysfunction	II-1C.1	I27		
	2. Pulmonary hypertension associated with congenital heart disease complicated by thromboembolic disease	II-1C.2	I27		
	– Others	II-1C.0			
2. Inborn anomalies of the pulmonary vessels	A. Anomalous morphology	1. Atresia of the pulmonary artery	II-2A.1	Q25.5	
		2. Pulmonary artery coarctation	II-2A.2	Q25.7	
		3. Idiopathic dilatation of the pulmonary trunk	II-2A.3	Q25	
		– Others	II-2A.0		
	B. Anomalous course	1. Pulmonary artery sling	II-2B.1	Q25.6	
		2. Ductal sling	II-2B.2	Q33.2	
		3. Pulmonary sequestration	II-2B.3	E25.7	
		– Others	II-2B.0		
	C. Anomalous connections	1. Inborn pulmonary arteriovenous fistulas	II-2C.1	Q25.7	
		– Others	II-2C.0		
	3. Acquired anomalies of the pulmonary vessels	A. Pulmonary vessel arteritis	1. Takayasu's arteritis	II-3A.1	M31.4
			2. Giant-cell arteritis	II-3A.2	M31.6
3. Behçet's disease			II-3A.3	M35.2	
4. Hughes–Stovin syndrome			II-3A.4	M35.2	
5. Granulomatous vasculitis			II-3A.5	M31.3	
– Others			II-3A.0		
B. Anomalous morphology		1. Pulmonary artery aneurysm	II-3B.1	E25.7	
		– Others	II-3B.0		

Group	Subgroup	Examples	RCD code	ICD-10 code
3. Acquired anomalies of the pulmonary vessels	C. Anomalous connections	1. Pulmonary arteriovenous fistulas	II-3C.1	I77
		2. Bronchial artery–pulmonary artery fistulas	II-3C.2	Q27
		– Others	II-3C.0	
	D. Tumors of the pulmonary vessels	1. Primary	II-3D.1	
		2. Secondary	II-3D.2	
		– Others	II-0	

Group	Subgroup	Examples	RCD code	ICD-10 code
<b>Rare diseases of the heart (cardiomyopathies) – RCD class III</b>				
1. Dilated cardio-myopathy	A. Genetic	1. Sarcomeric protein mutations: β-myosin heavy chain (MYH7; on chromosome 14q12), myosin-binding protein C (MYBPC3; 11p11.2), troponin T (TNNT2; 1q32), troponin C (TNNC1; 3p21.3-p14.3), α-myosin heavy chain (MYH6; 14q12), α-tropomyosin (TPM1; 15q22.1), cardiac actin (ACTC; 15q14), and titin (TTN) – Other	III-1A.1	I42.4
		2. Z-band mutations	III-1A.2	I42.4
		3. Cytoskeletal gene mutations:	III-1A.3	I43
		a. Dystrophin – Duchenne muscular dystrophy	III-1A.3a	G71.0
		b. Dystrophin – Becker’s muscular dystrophy	III-1A.3b	G71.0
		c. Dystrophin – Bethlem myopathy	III-1A.3c	G71.0
		d. Dystrophin – Limb-girdle muscular dystrophy	III-1A.3d	G71.0
		e. Tafazzin – Barth syndrome	III-1A.3e	E71.1
		f. Desmin mutations	III-1A.3f	G71.8
		g. Sarcoglycan complex mutations – Other cytoskeletal gene mutations	III-1A.3g III-1A.3.o	G71.0
		4. Nuclear membrane mutations:	III-1A.4	I42.4
		a. Lamins A/C – DCM + conduction disease	III-1A.4a	G71.0
		b. Lamins A/C – Emery–Dreifuss muscular dystrophy – Other nuclear membrane mutations	III-1A.4b III-1A.4.o	G71.0
	5. Mitochondrial cardiomyopathies	III-1A.5	I43	
	a. Kearns–Sayre syndrome – Other mitochondrial cardiomyopathies	III-1A.5a III-1A.5.o	H49.8	
	B. Nongenetic	1. Inflammatory cardiomyopathy:	III-1B.1	I42.7
		a. Viral inflammatory cardiomyopathy	III-1B.1a	B33.24
		b. Nonviral inflammatory cardiomyopathy	III-1B.1b	I42.7
		c. Autoimmune-induced inflammatory cardiomyopathy – Other inflammatory cardiomyopathies	III-1B.1c III-1B.1.o	I42.7
		2. Due to connective tissue diseases:	III-1B.2	I43
		a. Systemic lupus erythematosus	III-1B.2a	M32
		b. Scleroderma	III-1B.2b	M34
		c. Giant-cell arteritis – Other due to connective tissue diseases	III-1B.2c III-1B.2.o	M31.6
		3. Due to endocrine disorders:	III-1B.3	I43
a. Thyroid hormone excess or deficiency		III-1B.3a	E00-07	
b. Pheochromocytoma		III-1B.3b	C75.5/D35.6	
c. Cushing’s disease – Other due to endocrine disorders	III-1B.3c III-1B.3.o	E24		
4. Due to infiltrative disorders:	III-1B.4	I43		
a. Amyloidosis	III-1B.4a	E85		
b. Sarcoidosis	III-1B.4b	D86		
c. Hemochromatosis – Other due to infiltrative disorders	III-1B.4c III-1B.4.o	E83.1		

Group	Subgroup	Examples	RCD code	ICD-10 code
1. Dilated cardiomyopathy	B. Nongenetic	5. Medication-induced:	III-1B.5	I42.7
		a. Anthracyclines	III-1B.5a	I42.7
		b. Cyclophosphamide	III-1B.5b	I42.7
		c. Trastuzumab	III-1B.5c	I42.7
		d. HAART-HIV: zidovudine, didanosine, zalcitabine	III-1B.5d	I42.7
		– Other	III-1B.5.o	
		6. Toxin-induced:	III-1B.6	I42.7
		a. Ethanol	III-1B.6a	I42.6
		b. Cocaine	III-1B.6b	I42.7
		c. Amphetamines	III-1B.6c	I42.7
		– Other	III-1B.6.o	
		7. Tachycardia-induced:	III-1B.7	I42.8
		a. Uncontrolled atrial fibrillation	III-1B.7a	I48
		b. Atrioventricular nodal reentry	III-1B.7b	I47.1
		c. Preexcitation syndromes	III-1B.7c	I45.6
		– Other	III-1B.7.o	
		8. End stage of other types of cardiomyopathy:	III-1B.8	I42.9
		a. Hypertrophic cardiomyopathy	III-1B.8a	I42.2
		b. Restrictive cardiomyopathy	III-1B.8b	I42.5
c. Peripartum cardiomyopathy	III-1B.8c	O90.3		
d. Takotsubo cardiomyopathy	III-1B.8d	I51.81		
e. Left ventricular noncompaction	III-1B.8e	I42.8		
– Other	III-1B.8.o			
9. Miscellaneous:	III-1B.9	I43		
a. Neoplastic heart disease	III-1B.9a	D15.1		
b. Celiac disease	III-1B.9b	K90		
c. Extensive chest radiation	III-1B.9c	Y84.2		
d. Nutritional (thiamine, selenium, L-carnitine)	III-1B.9d	I43.2		
e. Obstructive sleep apnea	III-1B.9e	G47.3		
– Other	III-1B.9.o			
2. Hypertrophic cardiomyopathy	A. Sarcomeric protein mutations	1. MYH7, MYBPC3, TNNT2, MYH6, TPM1, TNNC1, ACTC, TTN	III-2A.1	I42.2
	B. Nonsarcomeric protein mutations	1. Glycogen storage disease:	III-2B.1	I43.1
		a. Pompe disease	III-2B.1a	E74.0
		b. Danon disease	III-2B.1b	E74.0
		c. Forbes disease	III-2B.1c	E74.0
		– Other	III-2B.1.o	
		2. Lysosomal storage disease:	III-2B.2	I43.1
		a. Fabry disease	III-2B.2a	E75.2
		b. Hurler syndrome	III-2B.2b	E76
		c. Hunter syndrome	III-2B.2c	E76.1
		d. Maroteaux–Lamy disease	III-2B.2d	E76.2
		e. Gangliosidosis	III-2B.2e	E75.1
		f. Gaucher’s diseases	III-2B.2f	E75.2
		g. Niemann–Pick disease	III-2B.2g	E75.2
		– Other	III-2B.2.o	
		3. Metabolic myopathies:	III-2B.3	I43.1
		a. Disorders of fatty metabolism	III-2B.3a	E78
		b. Carnitine deficiency	III-2B.3b	E71.3
		c. Phosphorylase-b kinase deficiency	III-2B.3c	E74
– Other	III-2B.3.o			
4. Systemic diseases:	III-2B.4	I43		
a. Pheochromocytoma	III-2B.4a	C75.5/D35.6		
b. Neurofibromatosis	III-2B.4b	Q85.0		
c. Tuberous sclerosis	III-2B.4c	Q85.1		
– Other	III-2B.4.o			
5. Mitochondrial cardiomyopathies	III-2B.5	I43		

Group	Subgroup	Examples	RCD code	ICD-10 code
2. Hypertrophic cardiomyopathy	B. Nonsarcomeric protein mutations	6. Syndromic HCM:	III-2B.6	I43
		a. Noonan syndrome	III-2B.6a	Q87.1
		b. LEOPARD syndrome	III-2B.6b	Q87.8
		c. Friedreich's ataxia	III-2B.6c	G11.1
		d. Swyer syndrome	III-2B.6d	Q97.3
		e. Costello syndrome	III-2B.6e	Q87.8
		– Other	III-2B.6.o	
3. Restrictive cardiomyopathy	A. Infiltrative	1. Familial amyloidosis	III-3A.1	E85
		a. Transthyretin	III-3A.1a	E85.1
		b. Apolipoprotein	III-3A.1b	E85
		2. Amyloid	III-3A.2	E85.1
		a. AL/prealbumin	III-3A.2a	E85.1
		3. Sarcoidosis	III-3A.3	D86
		4. Gaucher's disease	III-3A.4	E75.2
	5. Hurler syndrome	III-3A.5	E76	
	6. Fatty infiltration	III-3A.6	E78	
	– Other	III-3A.0		
	B. Storage	1. Hemochromatosis	III-3B.1	E83.1
		2. Fabry disease	III-3B.2	E75.2
		3. Glycogen storage disease	III-3B.3	E74
		– Other	III-3B.0	
	C. Noninfiltrative	1. Scleroderma	III-3C.1	M34
		2. Pseudoxanthoma elasticum	III-3C.2	Q82.8
		– Other	III-3C.0	
	D. Sarcomeric protein mutations	Troponin I, essential light chain of myosin	III-3D	I43
	E. Desminopathy		III-3E	G71.8
	F. Endocardial pathology	1. Endomyocardial fibrosis with hypereosinophilia:	III-3F.1	I42.3
		a. Parasitic infection	III-3F.1a	
		b. Drugs – methysergide	III-3F.1b	
		c. Persistent inflammation	III-3F.1c	
		d. Nutritional factors	III-3F.1d	
	2. Endomyocardial disease without hypereosinophilia	III-3F.2	I42.3	
	– Other	III-3F.0		
	4. Arrhythmogenic right ventricular cardiomyopathy	A. Desmosomal ARVC	1. Autosomal dominant inheritance pattern:	III-4A
a. ARVD8 – Desmoplakin mutations			III-4A.1a	
b. ARVD9 – Plakophilin-2 mutations			III-4A.1b	
– Other			III-4A.1.o	
2. Syndromic ARVC (autosomal recessive)			III-4A.2	I42.8
a. Naxos disease – Plakoglobin mutations			III-4A.2a	Q87.8
b. Carvajal syndrome – Desmoplakin mutations			III-4A.2b	I42
c. Alcalai syndrome		III-4A.2c	I42	
– Other		III-4A.2.o		
B. Nondesmosomal ARVC		1. ARVD1 – Transforming growth factor mutations	III-4B.1	I42.8
		2. ARVD2 – Cardiac ryanodine receptor mutations	III-4B.2	
		– Other	III-4B.0	

Group	Subgroup	Examples	RCD code	ICD-10 code
5. Unclassified cardiomyopathies	A. Left ventricular noncompaction	1. Genetic causes of LVNC: a. Tafazzin mutations b. Dystrobrevin mutations – Other	III-5A.1 III-5A.1a III-5A.1b III-5A.1.o	I42.9
		2. Metabolic disorders/genetic syndromes and LVNC a. Barth syndrome b. Beals syndrome c. Becker's muscular dystrophy d. Charcot–Marie–Tooth disease e. Duchenne muscular dystrophy f. Melnick–needles syndrome g. Myotonic dystrophy h. Myoadenylate deaminase deficiency i. Nail–patella syndrome j. Noonan syndrome k. Roifman syndrome l. Trisomy 13 – Other	III-5A.2 III-5A.2a III-5A.2b III-5A.2c III-5A.2d III-5A.2e III-5A.2f III-5A.2g III-5A.2h III-5A.2i III-5A.2j III-5A.2k III-5A.2l III-5A.2.o	I42.9 E71.1 Q87.8 G71 G60 G71 Q77.8 G71.1 E79.8 Q87.2 Q87.1 D81.8 Q90
	B. Takotsubo cardiomyopathy	III-5B	I42.8	
	C. Peripartum cardiomyopathy	III-5C	090.3	

## Rare congenital cardiovascular diseases – RCD class IV

1. Abnormalities of the position and connection of the heart and vessels	A. Heart position	1. Dextrocardia	IV-1A.1	Q24.0	
		2. Mesocardia	IV-1A.2	Q24.8	
		3. Dextroposition	IV-1A.3	Q20.3	
		4. Ectopia cordis	IV-1A.4	Q24.8	
		– Others	IV-1A.0		
	B. Heart chambers	1. Atria a. Cor triatriatum – others	IV-1B.1 IV-1B.1a IV-1B.1.o	Q24.2	
		2. Ventricles a. Congenitally corrected transposition of the great artery – others	IV-1B.2 IV-1B.2a IV-1B.2o	Q20.5	
		C. Veins and arteries	1. Systemic veins a. Left superior vena cava – others	IV-1C.1 IV-1C.1a IV-1C.1.o	Q26.1
			2. Pulmonary veins a. Pulmonary vein stenosis – others	IV-1C.2 IV-1C.2a IV-1C.2.o	Q26.2
			3. Great arteries a. Transposition of the great arteries b. Truncus arteriosus – others	IV-1C.3 IV-1C.3a IV-1C.3b IV-1C.3.o	Q20.3 Q20.0
	D-Valves	1. Right heart valves a. tricuspid atresia b. Ebstein's anomaly c. pulmonary valve atresia d. pulmonary valve stenosis – others	IV-1D.1 IV-1D.1a IV-1D.1b IV-1D.1c IV-1D.1d IV-1D.1o	Q22.4 Q22.5 Q22.0 Q22.1	

Group	Subgroup	Examples	RCD code	ICD-10 code	
1. Abnormalities of the position and connection of the heart and vessels	D-Valves	2. Left heart valves	IV-1D.2		
		a. mitral stenosis	IV-1D.2a	Q23.2	
		b. mitral subvalvular apparatus abnormalities	IV-1D.2b	Q23.8	
		c. aortic stenosis	IV-1D.2c	Q23.0	
		d. aortic regurgitation, – others	IV-1D.2d IV-1D.2o	Q23.1	
2. Shunts	A. Decreased pulmonary flow	1. Tetralogy of Fallot	IV-2A.1	Q21.3	
		2. Pulmonary stenosis and ventricular septal defect	IV-2A.2	Q21.3	
		3. Pulmonary atresia and ventricular septal defect	IV-2A.3	Q25.5	
		– Others	IV-2A.0		
		B. Increased pulmonary flow			
		1. Atrial septum	IV-2B.1	Q21.1	
		2. Atrioventricular junction	IV-2B.2	Q21.2	
		3. Ventricular septum	IV-2B.3	Q21.0	
		4. Aortopulmonary communication	IV-2B.4	Q21.4	
		– Others	IV-2B.0		
	3. Complex congenital cardiovascular diseases	A. Complex abnormalities of the position and connection of the heart and vessels		IV-3A	Q20
		B. Complex abnormalities of position and connection of the heart and vessels with shunts		IV-3B	Q20
		– Others		IV-3.0	
4. Congenital cardiovascular diseases with concomitant organ dysfunction	A. Nervous system		IV-4A	G00-99	
	B. Pulmonary system		IV-4B	J00-99	
	C. Endocrine system		IV-4C	E00-90	
	D. Thrombosis and hemostasis disorders		IV-4D	D65-69	
	– Others		IV-4.0		
5. Grown-up congenital cardiovascular diseases	A. After correction	1. No complication without residual defects	IV-5A.1	Z92.4	
		2. Postprocedural complication and residual defects	IV-5A.2	Z92.4	
		– Others	IV-5A.0		
	B. After palliative procedures	1. Fontan procedure	IV-5B.1	Z92.4	
		2. Systemic-pulmonary anastomosis	IV-5B.2	Z92.4	
		– Others	IV-5B.0		
	C. Uncorrectable		IV-5C		
	6. Others		1. Double-chambered left ventricle	IV-6.1	Q20
			– Others	IV-6.0	

Group	Subgroup	Examples	RCD code	ICD-10 code		
<b>Rare arrhythmias – RCD class V</b>						
1. Arrhythmias due to primary electrical diseases of the heart	A. Channelopathies	1. Brugada syndrome	V-1A.1	I47.2		
		2. Long QT syndrome (LQTS)	V-1A.2	I45.8		
		3. Short QT syndrome (SQTS)	V-1A.3	I45.8		
		4. Catecholaminergic polymorphic ventricular tachycardia	V-1A.4	I45.8		
		– Others	V-1A.0			
	B. Preexcitation syndromes	1. Wolff–Parkinson–White syndrome	V-1B.1	I45.6		
		2. Mahaim syndrome	V-1B.2	I45.6		
		– Others	V-1B.0			
	– Others	V-10				
2. Arrhythmias secondary to rare structural diseases of the heart	A. In the course of cardiomyopathies	1. Arrhythmogenic right ventricular dysplasia/ cardiomyopathy	V-2A.1	I42.8		
		2. Hypertrophic cardiomyopathy	V-2A.2	I42		
		3. Restrictive cardiomyopathy	V-2A.3	I42		
		4. Left ventricular noncompacted cardiomyopathy	V-2A.4	I42.8		
		5. Dilated cardiomyopathy	V-2A.5	I42		
		– Others	V-2A.0			
	B. Due to congenital heart diseases	1. Univentricular heart	V-2B.1	Q20.4		
		2. Shunts	V-2B.2			
		3. Cor triatriatum	V-2B.3	Q24.2		
		4. Persistent left superior vena cava	V-2B.4	Q26.1		
		– Others	V-2B.0			
		3. Arrhythmias of atypical mechanism and ECG presentation	A. Supraventricular	1. Atypical atrioventricular nodal recurrent tachycardia (AVNRT)	V-3A.1	I47.1
				2. Tachycardia with RP interval longer than PR	V-3A.2	I.47.1
3. Antidromic atrioventricular tachycardia in Wolff–Parkinson–White syndrome	V-3A.3			I45.6		
4. Tachycardia in Mahaim syndrome	V-3A.4			I.47.1		
– Others	V-3A.0					
B. Ventricular	1. Bundle branch reentry tachycardia	V-3B.1	I.47.2			
	– Others	V-3B.0				
	– Others	V-30				
4. Arrhythmias in rare and specific clinical settings	A. Iatrogenic	1. Cardiotoxicity of chemotherapy	V-4A.1	Z51.1		
		2. Post heart transplantation	V-4A.2	Z94.1		
		3. Postsurgical correction of congenital heart diseases	V-4A.3	Y83		
		– Others	V-4A.0			
	B. Metabolic disorders	1. Fabry disease	V-4B.1	E75.2		
		2. Niemann–Pick disease	V-4B.2	E75.2		
		– Others	V-4B.0			
	– Others	V-40				

Group	Subgroup	Examples	RCD code	ICD-10 code
<b>Cardiac tumors and cardiovascular diseases in malignancy – RCD class VI</b>				
1. Primary cardiac tumors	A. Primary benign tumors	1. Myxoma	VI-1A.1	D15.1
		2. Fibroma	VI-1A.2	D15.1
		3. Lipoma a. Lipomatous hypertrophy – others	VI-1A.3 VI-1A.3a VI-1A.3.o	D17.0
		4. Rhabdomyoma	VI-1A.4	D21.3
		– Others	VI-1A.0	
	B. Primary malignant tumors	1. Rhabdomyosarcoma	VI-1B.1	C49.3
		2. Angiosarcoma	VI-1B.2	D38.0
		3. Lymphoma	VI-1B.3	C85.9
		4. Hemangioma	VI-1B.4	D18
		– Others	VI-1B.0	
2. Metastatic cardiac tumors	A. Thorax	1. Lung cancer	VI-2A.1	C34.8
		2. Breast cancer	VI-2A.2	C50.8
		– Others	VI-2A.0	
	B. Abdomen	1. Gastrointestinal tract cancer	VI-2B.1	C26.8
		2. Urinary tract and kidney cancer	VI-2B.2	C68.8
		3. Prostate cancer	VI-2B.3	C61
		4. Reproductive system cancer	VI-2B.4	C57.0
		– Others	VI-2B.0	
	C. Hematological system	1. Leukemia	VI-2C.1	C81-96
		2. Lymphoma	VI-2C.2	C81-96
		– Others	VI-2C.0	
	D. Skin cancer		VI-2D	C44
	– Others		VI-20	
3. Thrombus within heart chambers		VI-3	I74.0	
4. Inflammatory malformations	A. Vegetations		VI-4A	I80.9
	B. Inflammatory tumors		VI-4B	R22.6
	C. Abscesses		VI-4C	J85.3
	D. Calcifications	1. Pericardium	VI-4D.1	I32
		2. Valves	VI-4D.2	I39
		– Others	VI-4D.0	
	– Others		VI-40	
5. Cardiovascular complications of oncological therapy	A. Post-surgery		VI-5A	Y83
	B. Post-radiotherapy		VI-5B	Y84.2
	C. Post-chemotherapy		VI-5C	Z51.1
	– Others		VI-50	

Cardiovascular diseases in pregnancy – class VII*					
rare cardiovascular diseases – main classes (table 1–6)	Following characters for subgroups, examples, according to the tables I–VI and VIII			CRCD code	ICD 10
	Group	Subgroup	Example		
rare diseases of systemic circulation (class I)	1...	A...	1...	VII-I-...	099.4
rare diseases of pulmonary circulation (class II)	1...	A...	1...	VII-II-...	099.4
rare diseases of the heart (cardiomyopathies) (class III)	1...	A...	1...	VII-III...	099.4
rare congenital cardiovascular diseases (class IV)	1...	A...	1...	VII-IV...	099.4
rare arrhythmias (class V)	1...	A...	1...	VII-V...	099.4
cardiac tumors and cardiovascular diseases in malignancy (class VI)	1...	A...	1...	VII-VI...	099.4
Unclassified rare cardiovascular diseases (class VIII)	1...	A...	1...	VII-VIII...	

\* The digit VII at the front, indicates class VII and is followed by an appropriate RCD classification code corresponding to a rare cardiovascular entity found in class I to VI. Example: VII-I-1A.1 indicates a pregnant woman with anomaly of the circle of Willis, an entity included in class I of the RCD classification: Class VII – rare cardiovascular diseases in pregnancy, class I – rare diseases of the systemic circulation, group 1 – anatomical malformations of the arteries, subgroup A – cerebral arteries, example 2 – anomalies of the circle of Willis

Unclassified rare cardiovascular diseases – RCD class VIII*	
Examples	RCD code
1. 62-year-old woman with Heyde's syndrome.	VIII-1
2. 49-year-old patient with factor VII deficiency, chronic heart failure, and thrombus in the left ventricle.	VIII-2
3. 24-year-old patient with vein thrombosis and thrombus in the apex of the heart during ascariasis.	VIII-3
4. Acute thromboembolic disease complicated with heparin-induced thrombocytopenia type II in a pregnant woman.	VIII-4
5. 47-year-old patient with primary severe tricuspid regurgitation.	VIII-5

\* Consecutive unclassified rare cardiovascular cases included in Class VIII are assigned subsequent code according to the order of publication on the CRCD webpage – [www.crcd.eu](http://www.crcd.eu) or in the *Journal of Rare Cardiovascular Diseases*.



# Part 3

Rare diseases of systemic circulation  
– RCD class I

**Editor: Anna Kablak-Ziembicka**



# Introduction

Anna Kablak-Ziembicka

Rare diseases of the arteries constitute a heterogeneous group of vascular disorders. The prevalence of these diseases is currently estimated at 1 in 2 000 individuals according to the Orphanet. Considering the rare occurrence and wide variety of clinical symptoms, the disease often remains undiagnosed or many years pass before a specific disease is identified and appropriate treatment initiated.

Because symptoms derive from the organs to which blood is supplied by the diseased or anomalous arteries, these rare arterial diseases, often congenital, attract the attention of specialists in different fields of medicine, including general practitioners, pediatricians, cardiologists, neurologists, nephrologists, pulmonologists, immunologists, geneticists, vascular and endovascular surgeons, and numerous others.

The aim of the present part of the book is not to replace other outstanding publications on rare diseases of the systemic circulation. There is a vast number of studies, textbooks, and classifications that explore, in depth, the arterial variants and malformations (for example, coronary artery anomalies by Paolo Angelini), autoimmune vasculitis (for example, the American College of Rheumatology, The European League Against Rheumatism [EULAR], Chapel Hill criteria, EULAR/PReS consensus criteria, French Vasculitis Study Group), aneurysmal disease of the aorta (Ghent nosology, for example, the Villefranche criteria), and numerous others.

This part of the book is meant to alert physicians to patients with rare diseases of the arterial system because they may come across such patients in their daily practice and be unaware of the true underlying disease and its etiology.

For example, a patient may be ineffectively treated by individual specialists within their area of expertise (e.g., Churg–Strauss disease may present with asthma, renal failure, and cardiac and eye, nose, and throat symptoms). Meanwhile, by combining the efforts of different specialists, it may be easier to identify the underlying cause, establish the diagnosis, achieve remission, and cure or control the disease. Numerous arterial diseases have similar clinical presentation,

although their etiology and prognosis may be strikingly different.

Because these disorders are rare, research is limited and there are no specific clinical practice guidelines.

We hope that, by reading this part of the book, individual physicians will think about their exceptionally difficult cases of patients who do not respond to standard treatment and take into consideration a rare arterial disease as a possible underlying cause. We also hope that this heightened alertness of physicians will facilitate proper decision making in further diagnostic and therapeutic process.

Owing to a wide range of arterial disorders, we focus on five major groups of arterial diseases: malformations of the main arteries, aneurysmal diseases of the aorta, autoimmune vascular diseases, fibromuscular dysplasia, and spontaneous dissection of the aorta.



# Rare diseases of systemic circulation: Perspective of the Centre for Rare Cardiovascular Diseases

## Anatomical malformations of the main arteries

Anna Kabłak-Ziembicka, Tadeusz Przewłocki

**Anomaly of the artery or malformation of arterial vessel(s)** is defined as congenital abnormality in the anatomy, origin, or course of the specific artery [1]. By definition, these abnormalities are variants of anatomy occurring in less than 1% of the general population. They can be found as a single variant or in combination with other congenital defects. Many arterial anomalies do not cause symptoms and are recognized only at the time of autopsy or random angiographic study on different occasions. Although arterial anomalies can occur in all vascular regions, they are most often incidentally identified in cerebral, aortic arch, coronary, pulmonary, or renal circulations.

### Anomalies, variants, and disorders of the cerebral arteries

#### Variants and anomalies of the Willis' circle

The distal portions of the internal carotid arteries (ICA) divide typically into middle (MCA) and anterior (ACA) cerebral arteries, while the basilar artery divides into right and left posterior cerebral arteries (PCA). All middle, anterior, and posterior cerebral arteries form the Willis' circle, which plays an important role in maintaining sufficient cerebral circulation [2].

The complete circle of Willis consists of the proximal portions of both MCAs, ACAs, PCAs, as well as the single anterior communicating artery (ACoA) and two posterior communicating arteries (PCoA) (fig. 1A). Communicating arteries as well as the proximal portions of the ACA (segment A1) and PCA (segment P1) enable transfer of blood flow to hypoperfused regions of the brain in patients with carotid / vertebral arterial occlusive disease.

However, a significant proportion of the population (approximately 60%–80%) has an incomplete circle of Willis, in which one or more elements of the circle

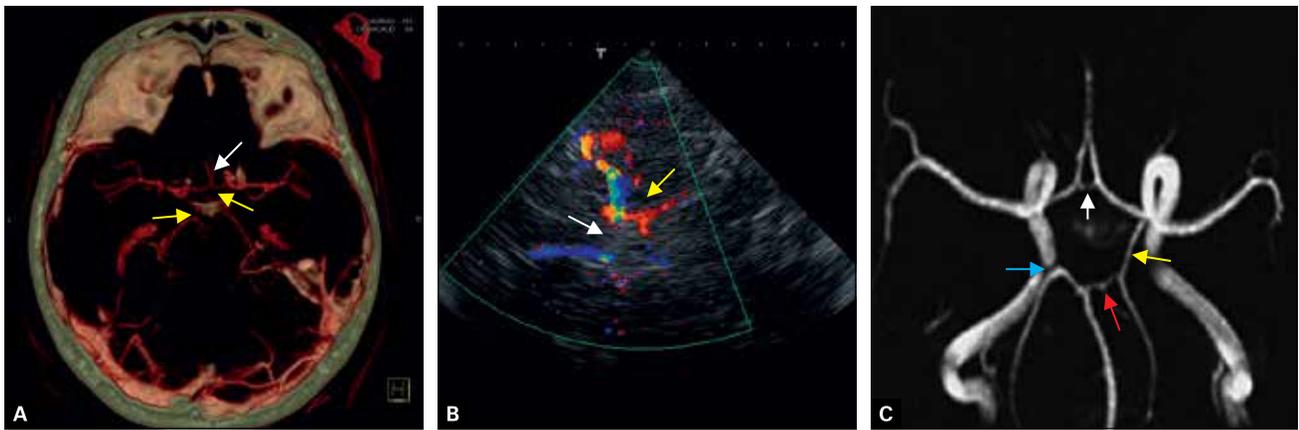
are either missing or are hypoplastic [2–4]. Thus, nonfunctioning ACoA is observed when it is missing, hypoplastic with a diameter of <0.5 mm, or when the A1 segment of the ACA is missing or hypoplastic (fig. 1B). The criteria for a nonfunctioning PCoA are either a diameter of <0.5 mm or a persistent fetal type of PCA circulation associated with an absent or hypoplastic P1 segment (fig. 1C). Occasionally, a duplication or even a triplication of the cerebral artery defined as two (three) distinct arteries with separate origins and no distal arterial convergence can be observed. Duplication of the MCA is observed in 0.2% to 2.9% of the population, while trifurcation is an extremely rare finding and it is thought to be a benign condition; however, the aneurysm formation is described in literature within a duplicate or triplicate vessel [5].

A variant of an incomplete circle of Willis is the lack of or hypoplastic (less than 0.5 mm in diameter) proximal portion of the ACA, which is observed in 1% to 2% and 10% of the general population, respectively. The absence of the ACoA is reported in 5% of surgical dissections. The prevalence of nonexistent or hypoplastic PCoA or both is estimated at 6% to 21% [6].

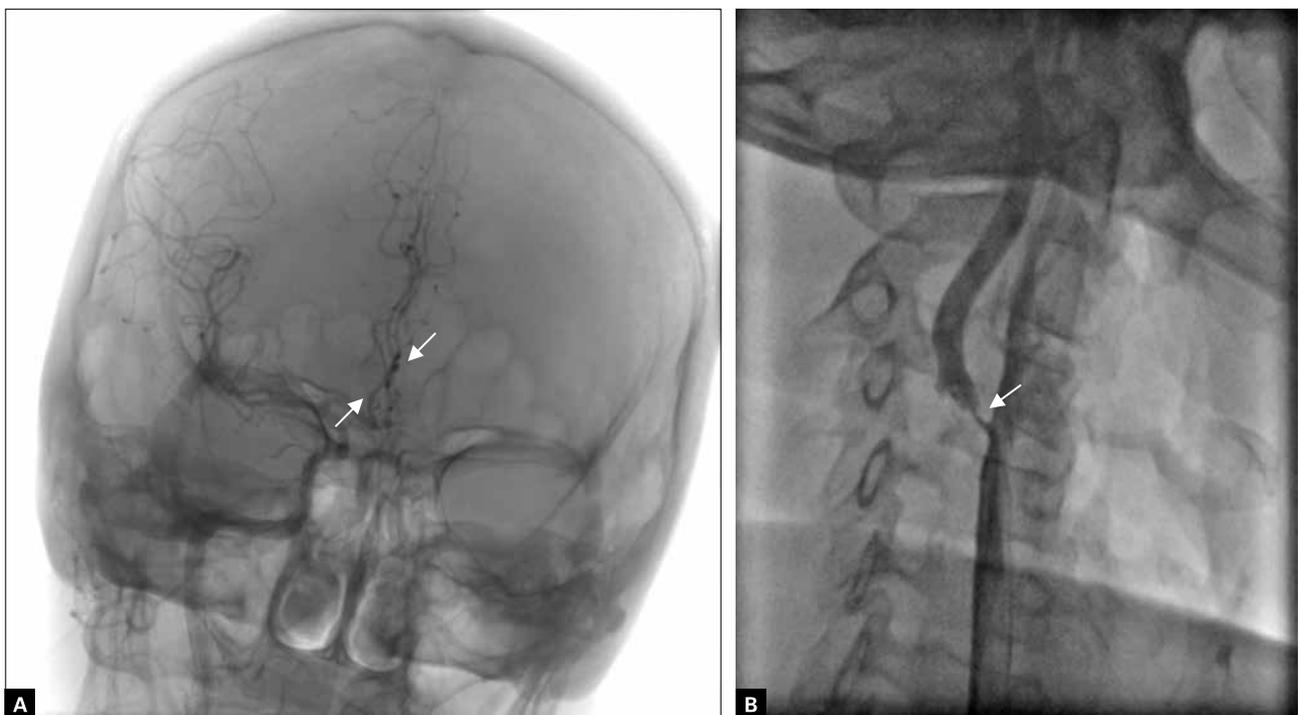
Fetal origin of the PCA occurs when the embryonic posterior cerebral artery fails to regress, resulting in absent proximal segment of the PCA (P1 segment). It may occur on the right side (10% of the general population), left side (10% of the general population), or bilaterally (8% of the general population).

The consequence of the incomplete circle of Willis is higher risk of ischemic strokes in patients with carotid or vertebral arterial occlusive disease [4,7]. In the study of Manninen et al., [7] comprising 92 individuals who suffered from periprocedural fatal ischemic stroke after surgical endarterectomy for carotid arterial occlusive disease, the autopsy material revealed nonfunctioning ACoA in 24% of the subjects, nonfunctioning right PCoA in 60% and nonfunctioning left PCoA in 53%. A totally undeveloped circle of Willis was found in 12% of the subjects, while only 20% had completely developed circle.

An azygos ACA represents persistence of the embryonic median artery of the corpus callosum [5]. Bilaterally, ACA territories are supplied by a single midline A2 trunk. The prevalence of azygos ACA is 0.2% to 4.0%. The anomaly is clinically relevant also



**Fig. 1.** **A.** Computed tomography. Complete circle of Willis. Proximal portions of middle cerebral artery (MCAs), anterior cerebral artery (ACAs), posterior cerebral artery (PCAs) as well as the single anterior communicating artery (ACoA) (white arrow) and two posterior communicating arteries (PCoA) (yellow arrows). **B.** Transcranial Doppler ultrasonography. Missing A1 segment of ACA (white arrow), but present PCoA (yellow arrow). **C.** Computed tomography angiography. Reconstruction. Present ACoA (white arrow), but missing right PCoA (blue arrow), and hypoplastic left P1 segment (red arrow) in association with the present left PCoA (yellow arrow)



**Fig. 2.** Angiography. **A.** Both anterior cerebral arteries (ACAs) (arrows) originating from the right internal carotid artery (ICA). **B.** 90% lumen stenosis (arrow) of the right internal carotid artery (ICA)

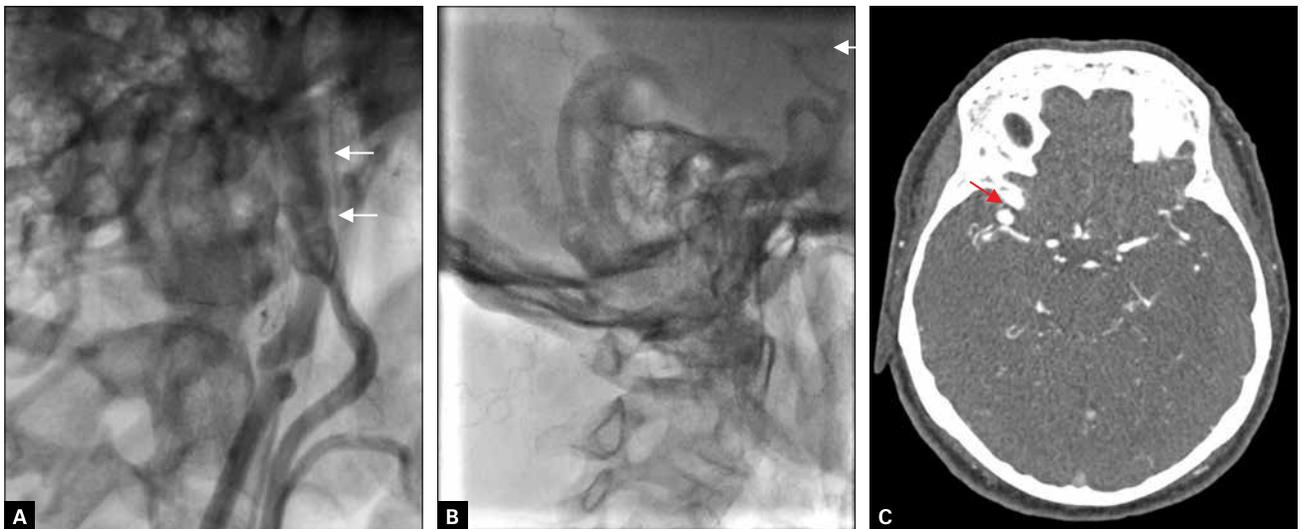
because in the event of ACA occlusion secondary to thromboembolic disease of the carotid artery, the resultant ischemia affects both hemispheres. Both ACAs originating from one ICA as two distinct arteries with separate origins and no ACA on the other side is an extremely rare finding; however, it is clinically relevant in the presence of ICA occlusive disease (fig. 2).

### **Aneurysm of the Willis' circle and intracranial arteries in the course of rare diseases**

Brain aneurysms are common. Their prevalence is estimated at about 5% in the healthy population, with the incidence of rupture and hemorrhagic stroke (subarachnoid

or intracerebral) estimated at 1% per year [8,9]. The later may vary depending on the aneurysm type, size, location, and history of previous aneurysm rupture.

However, compared with the general population, brain aneurysms are found much more often in the course of rare and very rare medical syndromes, including an autosomal-dominant polycystic kidney disease, fibromuscular dysplasia, coarctation of the aorta, and connective tissue diseases, such as Ehlers–Danlos and Marfan syndromes [9–11]. It is currently recommended that patients with autosomal dominant polycystic kidney disease should be screened with magnetic resonance angiography (MRA) for aneurysms [9]. Furthermore, cerebral



**Fig. 3.** **A.** Carotid artery angiography. String of beads lumen stenosis (95%) of the right internal carotid artery due to fibromuscular dysplasia (arrows). **B.** The poorly visible aneurysm due to low blood flow in the distal intracranial segments of the right ICA. **C.** Cerebral arteries computed tomography angiography. Multi-cavity aneurysm in the distal intracranial segments of the right internal carotid artery

aneurysms may be a part of the clinical picture in several primary arterial vasculitides, for example, Kawasaki disease.

Interestingly, although there is an increased risk of brain aneurysm in the offspring if it was present in parents, fewer than 2% of brain aneurysms are familial. Nevertheless, first-degree relatives of those with aneurysms should undergo MRA screening.

Approximately 85% of aneurysms develop in the anterior circulation of the brain, and 15% are found in the posterior circulation. The most common locations are ACoA, PCoA, MCA, basilar tip aneurysm, posterior inferior cerebellar, and ICA.

Typically, patients complain of strong and recurrent migraines for years. Some warning signs that indicate an aneurysm are pain above and behind the eye or headache and neck pain secondary to a leakage of blood from the aneurysm (a sentinel bleed). When the brain aneurysm is located in the ICA (fig. 3), cranial nerve palsy of the III (oculomotor), V (trigeminal), or VI (abducens) cranial nerves may occur.

Headache is also present in patients with giant-cell arteritis or Takayasu's disease, which should be included in a differential diagnosis.

However, most patients have no symptoms or complaints until the aneurysm ruptures. A ruptured aneurysm most frequently presents with subarachnoid hemorrhage.

Diagnosis is based on imaging with computed tomography angiography (CTA), MRA, or conventional angiography.

Treatment options include endovascular aneurysm coiling or combination of stent and coiling, as well as aneurysm clipping by an open surgery [11–13].

### Moyamoya disease

Moyamoya disease is a rare, progressive, noninflammatory arteriopathy of the supraclinoid portion of the ICA of unknown cause, which is found predominantly in East Asia [14].

In the United States and Europe, it is extremely rare, affecting 1 in 1 million children; however, it accounts for 6% of all childhood strokes. It has a bimodal age presentation, the first in childhood (first decade) and the second in adults (fourth decade) [14,15].

When it affects the branches of the both ICAs, the term “moyamoya disease” is used, while for unilateral presentation or in association with systemic disorders the term “moyamoya syndrome” is used. In the medical literature, there are also about 70 cases of moyamoya disease in which abnormalities are also observed in the vertebral arteries, where they are localized mostly bilaterally.

The main pathological finding on autopsy is endothelial thickening, resulting in luminal narrowing, predisposing children to transient ischemic attacks and ischemic stroke, which are the primary presentations in affected patients.

In the adult form, the presenting symptom is intracranial hemorrhage, usually intraparenchymal. This may be explained by collateral net that develops in the presence of intracranial obstruction; however, these vessels are weak and prone to develop aneurysm and/or spontaneous rupture.

Diagnosis is defined by characteristic findings on arteriograms, including stenosis of the branches of the ICA and a pathognomonic spray of small collateral vessels in this region, descriptively likened to a “puff of smoke” (“moyamoya” in Japanese).

The diagnosis of classical moyamoya disease is defined by three angiographic criteria according to the Japanese Ministry of Health and Welfare guidelines [15]:

- stenosis of the distal (intracranial) ICAs, up to and including the bifurcation, along with the segments of the proximal ACA and MCA,
- dilated basal collateral vessels must be present (to varying degrees, depending on stage),
- the findings must be / should be bilateral.

Other diagnostic tools include also [14–16]:

- diffusion-weighted magnetic resonance imaging (MRI), which is useful in evaluating cerebral ischemia
- MRA or CTA of the intracranial and cerebral arteries for identification of steno-occlusive lesions in the terminal portions of the ICAs, as well as occlusion / narrowing of the MCA and ACA.
- in addition, transcranial color-coded Doppler may demonstrate a significant reduction in cerebral artery flow velocities.

The main treatment strategy involves the restoration of cerebral blood flow by surgical revascularization [15,19]. In rare cases, endovascular stenting of stenotic ICA, MCA, or ACA may be considered. Conservative management includes administration of an oral antiplatelet agent (aspirin or clopidogrel). However, the indications and results of both surgery and endovascular treatment are controversial. Recent guidelines from the Japanese Ministry of Health and Welfare regarding indications for surgical treatment of moyamoya disease state the following: “In the cases with (1) repeated clinical symptoms due to apparent cerebral ischemia, or (2) a decreased regional cerebral blood flow, vascular response and perfusion reserve, based on the findings of a cerebral circulation and metabolism study, surgery is indicated [15].

## Main branches of the aorta and aortic arch

The aorta develops during the third week of gestation [20,21]. This complex process is associated with the formation of the endocardial tube, resulting in a variety of congenital variants. Each primitive aorta consists of a ventral and dorsal segments, which are continuous through the first aortic arch. Six paired aortic arches develop between the ventral and dorsal aortas, eventually forming the aortic arch, supraaortic and pulmonary arteries, and ductus arteriosus.

A variability of the aortic arch patterns is commonly observed in clinical practice, with the prevalence of 6% to 15% [20–24]. The majority of them are asymptomatic and recognized incidentally.

The possible classification is as follows:

1. The aberrant anatomy, position, or course of the main aortic arch or arising supraaortic arteries. The possible pathology may be associated with pressure on the esophagus and/or trachea, or more rarely on the bronchi. This group comprises all types of aortic vascular rings and double aortic arch.
2. The abnormal lumen of the aorta resulting in the blockage of the blood stream. This group comprised coarctation of the aorta and all forms of the interrupted aortic arch.

### Aberrant anatomy, position, or course

This pathology may be associated with symptom occurrence that manifests mainly in childhood. The possible symptoms include cough, stridor, dyspnea, breathlessness, cyanosis, swelling problems, and dysphagia. Patients are more prone to recurrent upper and lower respiratory tract infections and pneumonia (also that resulting from choking).

More than 20 different aortic arch configurations have been described. The most common are innominate artery (named also brachiocephalic trunk), left common carotid, and left subclavian artery take-off from the left aortic arch (70%–80% of the population) [25]. The other popular configurations of the arch are bovine arch, separate ostium of the left vertebral artery, and the right subclavian artery lusoria.

**Bovine arch** is defined as the common origin of the innominate artery and left common carotid artery with the main trunk of different length, which constitutes up to 20% of the cases. This anatomical variant is completely asymptomatic; however, a statistically



**Fig. 4.** Computed tomography angiography. **A.** Three-dimensional reconstruction. The separate origin of the left vertebral artery from the aortic arch (arrow). **B.** Two-dimensional subtraction. Variant of the aortic arch arteries origin. Separate origine of the right subclavian artery (lusoria) (arrows). **C.** Three-dimensional reconstruction. Aortic arch ring caused by the right subclavian artery (arrow) that originates from the descending part of the thoracic aorta compressing the bronchi and esophagus

significant connection between the bovine arch and thoracic aorta dissection was confirmed in several studies [20,22].

**The left vertebral artery** originating from the aortic arch is the third most common variant, with the frequency of 4% to 6% (fig. 4A) [20,22]. This variant is asymptomatic. In the case of left subclavian obstruction, upper limb claudication is more probable as there is no collateral flow from the vertebral artery. This variant should be considered before identifying vertebral artery occlusion during subclavian artery angiography.

**Left aortic arch with the aberrant take-off of the right subclavian artery (*arteria lusoria*).** This is the fourth most common aortic arch variant with the reported frequency of 0.5% to 1.2% in the general population (fig. 4B). It is associated with the formation of the incomplete vascular ring (fig. 4C). The right subclavian artery takes off from the aortic arch as the fourth vessel, then it turns to the right, crossing retroesophageally, then it runs typically supplying the right upper extremity. In this situation, the right common carotid artery arises directly from the aortic arch as the first vessel, followed by the left common carotid, left subclavian, and finally the right subclavian artery. This anomaly is usually asymptomatic, apart from cases when the right subclavian artery presses on the esophagus and/or the trachea, which on rare occasions may cause dysphagia and/or dyspnea.

**The right aortic arch**, according to the data of Hastreiter et al. [26], occurs in less than 0.1% of the population. In this anomaly, a part of the distal fetal left fourth arch remains, instead of involute.

This anomaly has two major types:

1. right arch with mirror-image branching
2. right arch with aberrant left subclavian artery or innominate artery or isolation of the left subclavian and innominate arteries.

The right aortic arch with mirror-image branching is associated with other congenital heart diseases, mainly cyanotic, in 98% of the patients [27–29]. Its frequency is estimated at 12.8% to 34% in tetralogy of Fallot, 15% to 60% in truncus arteriosus, 7.7% to 8.8% in tricuspid atresia, 3.7% to 6.7% in transposition, and 2.3% to 2.6% in ventricular septal defect [26].

In the right arch with an aberrant left subclavian artery or innominate artery, they originate as the last artery from the aortic arch, causing pressure on the trachea and esophagus. This type is rarely associated with congenital heart disease. However, symptoms may arise from vascular ring formation. The most common type is the right aortic arch with an aberrant left subclavian artery, in which the vessels originate in the following order: left common carotid, right common carotid, right subclavian, and left subclavian arteries.

**Double aortic arch** is a rare anomaly caused by persistence (to varying degrees) of the fetal double aortic arch system [20,22,23,29]. The ascending aorta divides into two arches that pass to either side of

the esophagus and trachea and reunite to form the descending aorta. Therefore, it is a form of a complete vascular ring, with the sign of four vessels, resulting in noncardiac morbidity (respiratory, gastrointestinal), rarely associated with intracardiac defects.

Congenital heart defects occur in 1 in 120 live births, of which vascular rings account for less than 1% of congenital heart problems, and 45% to 65% of the patients undergoing surgical repair for a vascular ring have a double aortic arch. Thus, its frequency is very rare, approximately 0.004% of the population, that is, 4 cases per 100 000.

They are described in detail in textbooks on pediatric cardiac surgery and radiology of the heart and vessels [24]. In brief, there are several variants of this anomaly with: 1) complete double arch where both arches are patent and of equal or different diameters; 2) one arch is hypoplastic or atretic, 3) including variants with a narrow or atretic left subclavian artery.

Although double aortic arch is rarely associated with cardiovascular anomalies, ventricular septal defect and tetralogy of Fallot are probably the most common defects. Other disorders associated with a double aortic arch may also include truncus arteriosus, transposition of the great arteries, pulmonary atresia, and complex univentricular defects. This makes the surgical treatment even more difficult.

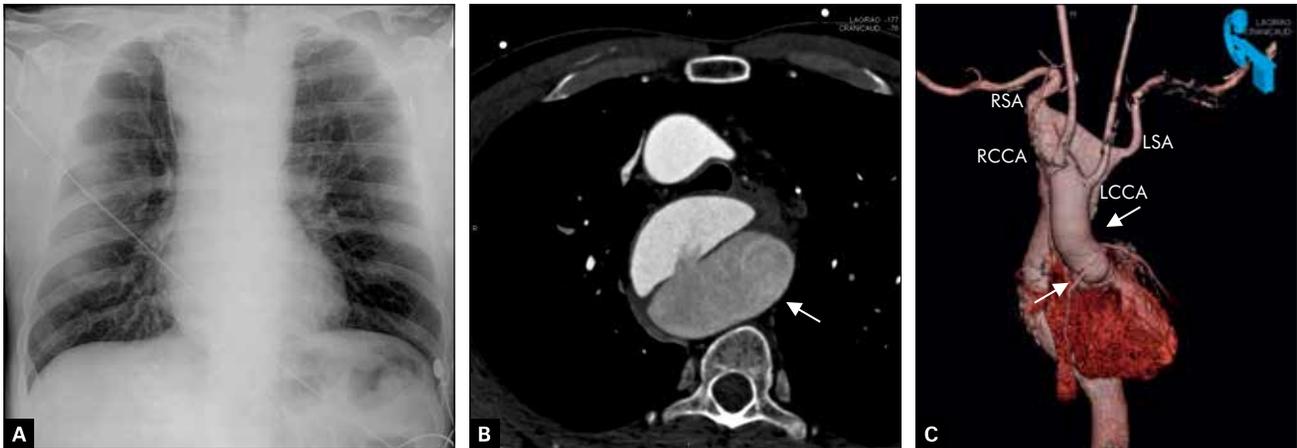
Vascular rings may cause clinical symptoms and may require cardiothoracic surgery. Clinical presentation of symptomatic vascular rings comprises stridor (100% of the cases), chronic cough (75%), dyspnea (75%), reflex apnea (60%), easy fatigue, choking, swallowing problems, and dysphagia (25%) [30]. The stridor noted in aortic vascular rings is usually inspiratory. Patients are prone to severe and recurrent respiratory system infections including pneumonia (56%) [30].

Symptoms of a double aortic arch tend to occur earlier than those of other type of vascular rings. The majority of patients with double aortic arch have surgical correction before 1 year of age, whereas the average age for other congenital vascular ring anomalies is 4 years [33]. Compression of the trachea and esophagus from double aortic arch seems more severe than that associated with other types of vascular rings [30–34].

**Variations in the sequence of branching of the major arch vessels** (fig. 5) are rare (<0.5%). They include, for example, the internal and external carotid arteries directly originating from the aortic arch, or left subclavian branching as a second aortic arch vessel, before the left common carotid artery. Occasionally, this anatomical variant may predispose to aorta dissection and aneurysms.

**Cervical arch** is observed in less than 5% of the population and represents cases where the aortic arch is located abnormally high over the mediastinum or even in the neck.

**ICA hypoplasia or fenestration** of the distal ICA are extremely rare anomalies. There have been only about 25 cases of hypoplasia and less than 10 cases of fenestration reported in the literature. Both hypoplasia and fenestration are often associated with intracranial aneurysm formation.



**Fig. 5.** **A.** Chest X-ray. Posteroanterior view. Abnormally widened upper mediastinum. **B.** Computed tomography angiography. Transverse scan. Aneurysm and dissection of the ascending aorta and aortic arch, with double lumen (false lumen indicated by arrow). **C.** Computed tomography angiography. Three-dimensional reconstruction. Atypical origins and sequence of aortic arch large arteries: high take-off of the left common carotid artery, which originates as first aortic arch artery, followed by the right common carotid artery, right subclavian artery, and finally the left subclavian artery. Note the high origins of the coronary arteries (arrows). LCCA – left common carotid artery, RCCA – right common carotid artery, RSA – right subclavian artery, LSA – left subclavian artery

### Abnormal lumen of the aorta resulting in blockage of the blood stream

#### Interruption of the aortic arch

By definition, interrupted aortic arch is characterized by complete discontinuity of the aortic lumen between the ascending and descending aortas. Its incidence is estimated at 3 in 1 million live births [35,36].

There are two variants of this anomaly: first – interruption of the aorta between the left common carotid and left subclavian arteries; second – interruption between the left subclavian artery and the descending aorta.

Most cases are recognized in early childhood or neonatal period and are surgically corrected. If interrupted aortic arch remains undiagnosed or untreated, most affected infants die of circulatory failure within the first year of life. However, sporadic reports have documented survival into adulthood.

The interrupted aorta usually coexists with the other congenital defects, including ventricular septal defect, patent ductus arteriosus, aortopulmonary window, subaortic stenosis, truncus arteriosus, double outlet right ventricle, and DiGeorge syndrome.

The final diagnosis is based on echocardiography, CTA or MRA, followed by heart and vessel catheterization. CTA and MRA imaging are also important in the evaluation of coexisting congenital cardiac malformations.

Of note, clinical findings in neonates are unremarkable at first or derive from concomitant defects, e.g., systolic or continuous bruit of ventricular septal defect or patent ductus arteriosus, etc. Most importantly, there is a significant difference in pulse and systolic blood pressures between the lower and upper extremities.

With time, the signs of heart failure (tachycardia, tachypnea, and growth impairment) become evident leading to decompensated heart failure and death.

Although outcomes have generally improved, repair of this abnormality is associated with significant mortality and morbidity.

#### Coarctation of the aorta

Coarctation of the aorta constitutes 5% to 7% of all cases with congenital heart disease (4 to 7 cases per 10 000 births) [20]. It is defined as stenosis in the proximal descending thoracic aorta. Because it is not considered rare, it will not be presented in the present section.

#### Hypoplasia of the aorta

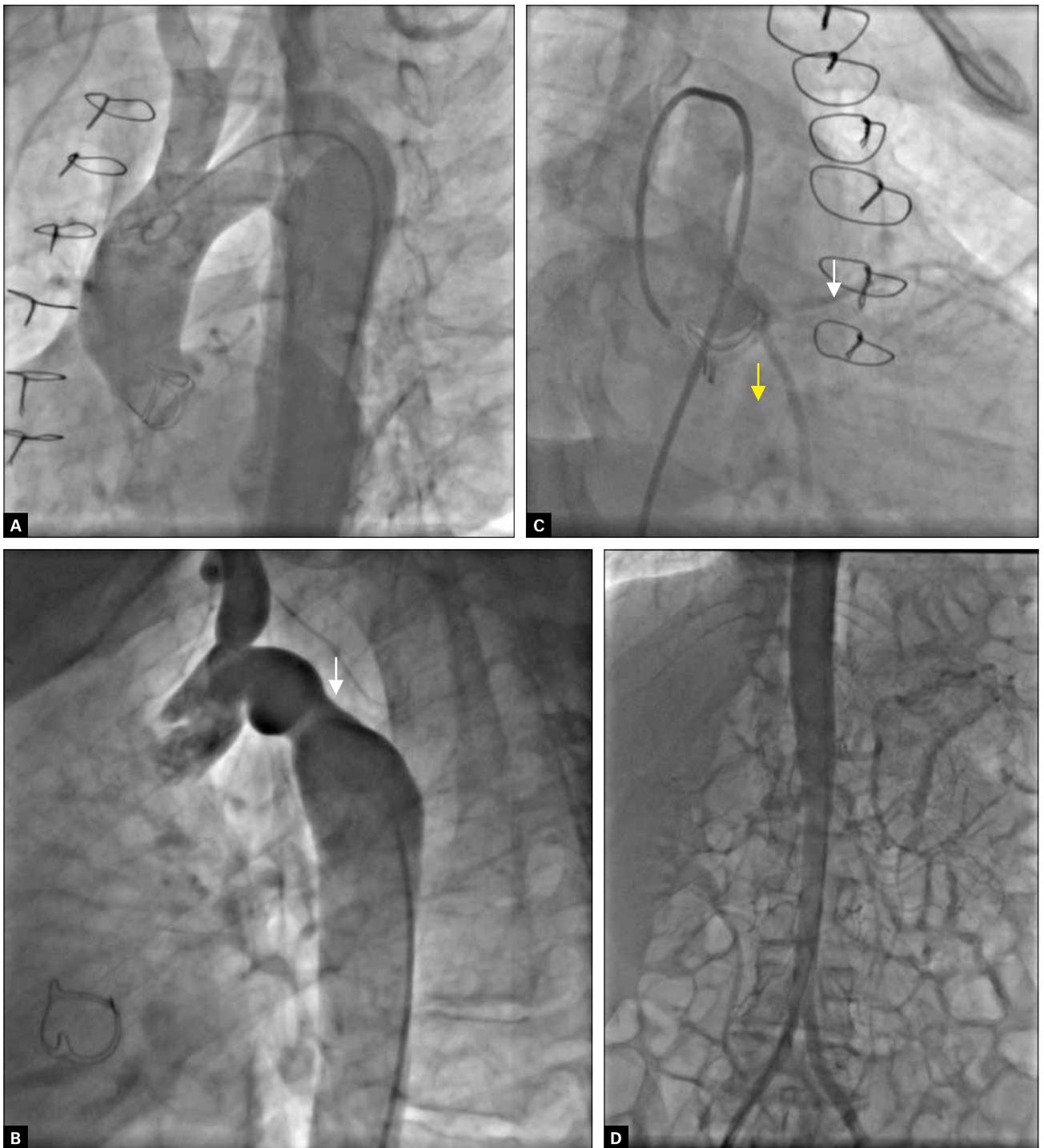
When coarctation of the aorta does not affect a short isolated segment of the aorta but a longer and more diffuse segments of thoracic and /or abdominal aorta, the term “aortic hypoplasia” is used. This is an extremely rare condition, constituting less than 2% of the coarctation cases [37,38]. It usually occurs in association with other congenital vascular anomalies (fig. 6). The most common clinical manifestation of aortic hypoplasia is severe uncontrolled hypertension since childhood and adolescence, claudication, and visceral ischemia. Ischemia may be reduced when well-developed abdominal collaterals are present [38–40].

Surgical bypass grafting is the optimal management strategy to relieve systemic hypertension and restore circulation to the lower extremities, renal arteries, and visceral organs. Terramani et al.[40] described two cases of diffuse thoracic and abdominal aorta hypoplasia, treated with thoracic aorta-to-abdominal aorta bypass.

### Anomalies of the pulmonary arteries

Anomalies of the pulmonary arteries are extremely rare. The most common conditions are described below.

**Atresia of the pulmonary artery (congenital interruption of the pulmonary artery)**, in which one pulmonary artery is missing resulting in small/absent lung and hilum on the side of atresia as well as compensated hyperinflation of the other lung. In the presence of collaterals, some portion of the affected lung can be visible on chest radiography, CT or MRI



**Fig. 6.** Aortic angiography. **A.** Anomaly of the aortic arch: the bovine arch – innominate artery and the left common carotid artery originate from the common trunk. **B.** Coarctation of the aorta distal to the left subclavian artery (ductal type) (arrow). **C.** Coronary angiography shows separate ostia of the left anterior descending artery (white arrow) and circumflex (yellow arrow). **D.** Marked change in caliber of the descending abdominal aorta distal to the celiac trunk and well-developed collaterals (abdominal aortic diameter, 11 mm)

scans [41]. The final diagnosis is based on the confirmation of pulmonary artery atresia with conventional subtraction angiography, CTA, or MRA.

**Pulmonary artery sling** is defined as the left pulmonary artery that arises from the right pulmonary artery, then it crosses over the right bronchus usually making compression on the latter, and it turns posteriorly above the tracheobronchial angle. Before reaching the left lung, the left pulmonary artery passes

backward to the trachea and in front to the esophagus [41,42]. This anomaly may exist in association with complete ring tracheal stenosis.

As the course of the left pulmonary artery is far from normal, it usually causes a number of symptoms in infancy and childhood. However, it is rarely symptomatic in adulthood.

The pressure on the right bronchus and trachea is associated with respiratory symptoms, which usually

occur at or shortly after birth. The stridor is usually expiratory, in contrast to inspiratory stridor noted in aortic vascular rings. Obstruction of the right bronchus or trachea results in hyperinflation of the right lung. When the obstruction is severe, atelectasis may occur. Atelectasis or emphysema of the left lung may be present, although is less frequent. Hypoventilation of the lung may predispose to the respiratory tract infections. Mostly, there is no associated dysphagia.

**Ductal sling (ductus arteriosus sling)** is a very rare anomaly, which may be mistaken for a pulmonary sling. In ductus sling, the ductus arteriosus connects the descending aorta to the right pulmonary artery. This vessel passes between the trachea and esophagus, possibly causing compression on these structures and provoking symptoms.

### **Pulmonary artery coarctation**

Pulmonary artery stenosis at the insertion site of the ductus arteriosus is known as coarctation of the pulmonary artery [41]. This congenital defect usually coexists with the other congenital cardiovascular diseases, occurring in 30% to 40% of the cases with pulmonary atresia, 8.6% to 10% with pulmonary stenosis, 17.2% with tetralogy of Fallot, and 28.3% with right ventricular double outflow tract with pulmonary stenosis.

Surgical correction of coarctation of the pulmonary artery should be performed as early as possible. The correction enables the proper development of the pulmonary tree, favoring the vascularization and maintenance of low resistance in the pulmonary arteries. With the delay of surgical treatment, future procedures may be more complex and have less favorable outcomes because of the underdevelopment of the lung, which receives less blood flow [38].

The correction is usually performed using cardiopulmonary bypass and during the neonatal period, which affects the development of the pulmonary artery and prognosis.

**Pulmonary sequestration** is an uncommon anomaly [20,42]. In pulmonary sequestration, portion of the lung tissue receives its blood supply from an anomalous systemic artery originating from the aorta or one of its branches. There are three main variants: intralobar, extralobar, and communicating bronchopulmonary foregut malformations.

In the intrapulmonary variant, early embryologic development of the accessory lung bud results in the formation of the sequestration within normal lung tissue and is encased within the same pleural covering. In contrast, later development of the accessory lung bud results in the extrapulmonary type. Venous drainage is typically via a systemic vein, although drainage into the pulmonary veins is well documented.

**Anomalous arterial supply** to the normal basal segments of the lower lobe without sequestration is a rare congenital abnormality, and whether it belongs to the broad spectrum of sequestration disorders remains controversial.

### **Diagnostic tools to display aorta, aortic arch branches, and pulmonary vessel aberrations**

Useful diagnostic tools include lateral and anteroposterior chest radiography, esophagography with barium, echocardiography, chest CT or MRI, angiographic imaging with subtraction angiography, CTA or MRA. Bronchoscopy is used to evaluate children with symptoms or airway obstruction or compression.

Currently, the definite diagnosis is mainly based on imaging modalities, such as CT / CTA or MRI / MRA, which reveal aberrant anatomy, origin, course, or steno-occlusive pathology. MRI /MRA is becoming the diagnostic test of choice for evaluating vascular ring anatomy. It provides excellent anatomical reconstructions, showing not only an aberrant artery but also its position and course within the surrounding anatomical structures, which is of utmost value whenever planning surgical repair. MRA is characterized by high sensitivity and specificity.

It seems that cardiac catheterization and aortic angiography are currently limited to cases in which complex congenital cardiac anomalies occur with vascular ring abnormalities.

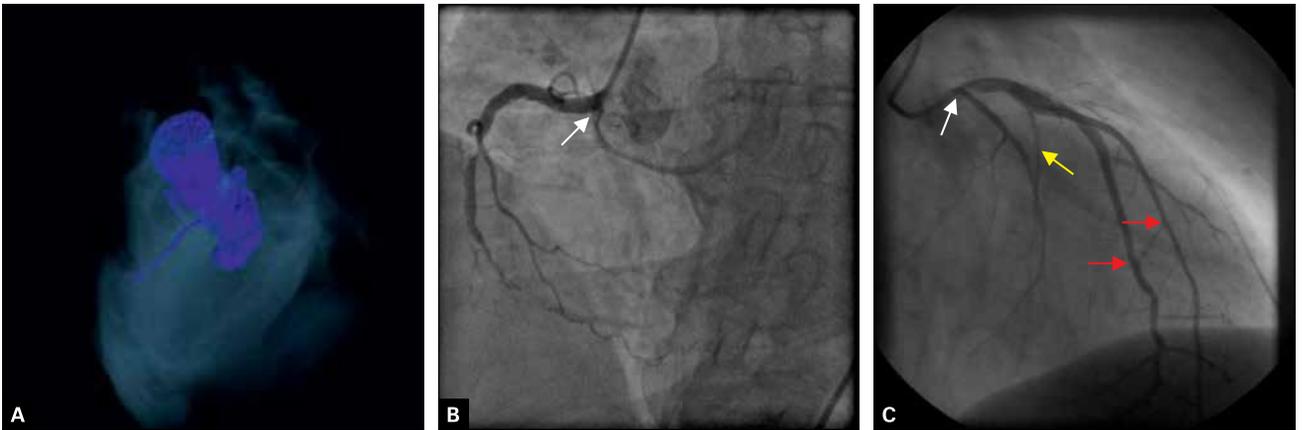
The standard chest radiography, barium esophagography, or echocardiography/ ultrasonography can also aid the initial examination revealing aortic arch or pulmonary artery pathology.

Chest radiography is usually the first and most commonly performed test, broadly used in patients with respiratory problems. On radiogram, the position of the aortic arch can be identified (distinction between the left and right aortic arch), as well as lobar atelectasis or hyperinflation of the right lung associated with an anomalous left pulmonary artery (atresia, sling)

The results of barium esophagography are diagnostic in most cases. Posterior compression of the esophagus is associated with a double aortic arch. Anterior compression of the esophagus is associated with an anomalous left pulmonary artery. It should be noted, however, that the barium study may be normal.

Echocardiography – ultrasonography. Standard echocardiography is helpful in the assessment of aortic root diameter and the proximal portion of the ascending aorta, as well as the dimensions of the pulmonary trunk and proximal portions of the right and left pulmonary artery. It enables the measurement of transvalvular gradients and regurgitation presence and grade. Also, congenital defects in the number and dimensions of the chamber, as well as junctions between the cavities and great vessels are well visualized with echocardiography. Transthoracic echocardiography and ultrasonography with a convex probe enable the assessment of the aortic arch and proximal portion of the descending aorta, which might be useful in the initial diagnosis of the coarctation, anatomical variants, and numbers of aortic arch arteries.

Bronchoscopy is used to evaluate children with symptoms of airway obstruction or compression. Flexible bronchoscopy is the first-line technique to assess neonatal stridor. In cases of an abnormally placed innominate artery, pulsation is observed on



**Fig. 7.** **A.** Multi-sliced computed tomography. Three-dimensional reconstruction. The separate origin of the left anterior descending and the circumflex branches from the left coronary sinus. **B.** Coronary angiography. Circumflex branch arises from the right coronary artery (arrow). **C.** Coronary angiography. Duplication of the circumflex branch. Separate ostium of the first left circumflex branch from the left coronary sinus (white arrow). The left main trunk trifurcates to the second circumflex branch (yellow arrow), the left anterior descending branch and the intermediate coronary artery (red arrows)

the anterior wall of the trachea corresponding to the area of compression.

## Coronary artery anomalies

Coronary anomalies are a group of congenital abnormalities in coronary arteries anatomy including their anomalous origination and course, duplication (*accessory arteries*) or absence of a coronary artery, and finally their abnormal connections with other blood vessels or the heart chambers [43–45].

In the study of Wilkins et al., the major coronary artery anomalies were encountered in 0.88% of cases out of 10,661 consecutive angiographies, including origination of the both coronary arteries from left sinus of Valsalva in 32%; origin of Cx from right sinus of Valsalva or RCA in 40% [46]. Less frequent were: a single coronary artery (7.4%), left coronary trunk originating from pulmonary trunk (3.2%), LAD from pulmonary trunk 4 (4.2%), LAD from RCA (2%), both coronary arteries from right sinus of Valsalva (3.2%) and coronary artery fistulas (8.5%) [46].

### Benign coronary artery anomalies

Origination of a coronary artery above the sinuses of Valsalva is a relatively frequent minor anomaly, observed in around 6% of the patients undergoing coronary angiography [44]. Less common anomalies, encountered in around 0.4% of the coronary angiograms, are the absence of the left main trunk with separate ostia of the LAD and circumflex branches (fig. 7A), and separate origination of the right coronary artery and the conal branch from the aortic root [43,44]. In 0.09% to 0.11% of the patients undergoing coronary angiography left anterior descending or circumflex branch arise from the right coronary artery (fig. 7B). Even more uncommon is a duplication of a coronary artery (fig. 7C).

The aforementioned anomalies have little clinical significance. They do not affect cardiovascular

prognosis, however atypical origin or course of a coronary artery can make it difficult to notice during angiography, thus prevent revascularisation in case of its significant obstruction. The classical coronary angiography enables proper anatomical evaluation only in 53% of cases of coronary anomalies [44].

It is also important to keep in mind that in combination with congenital heart defects (especially complex defects) coronary anomalies can pose both a diagnostic and later a technical challenge during surgical correction [47].

Computed tomography coronary angiography with intravenous contrast injection is a preferred imaging study to apply in the case of suspected coronary anomaly with excellent sensitivity and specificity [44].

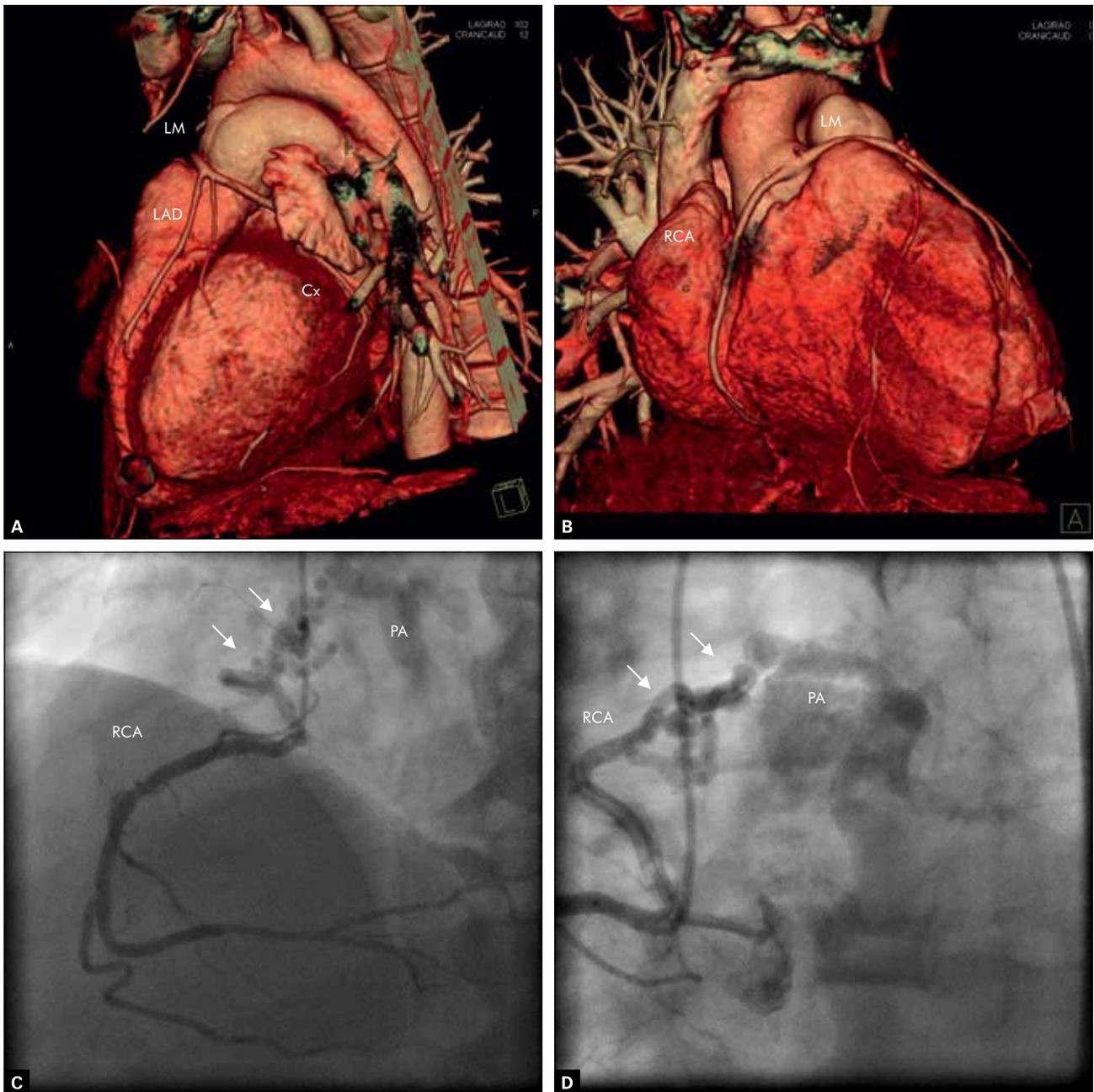
Single coronary artery is a rare anomaly, observed in 0.0024%–0.044% coronary angiograms, a little more common in males. In this anomaly a solitary coronary artery arises from either right or left coronary sinus and then divides into right coronary artery, left anterior descending and circumflex branches (fig. 8AB). Their subsequent course may be more or less typical.

This anomaly is usually observed in combination with complex congenital heart defects, like tetralogy of Fallot, double outlet right ventricle, bicuspid aortic valve, persistent truncus arteriosus, single ventricle defects, ventricular septal defect or heterotaxia [44,46,47].

A serious consequence of this otherwise benign anomaly, is a narrowing of the common coronary trunk, typically atherosclerotic in origin, which leads to widespread ischemia practically of the entire heart, extensive infarct and sudden cardiac death. In cases where the single coronary artery runs between the aorta and the pulmonary artery, there is an increased risk of life threatening arrhythmias [44,47,48].

The absence of one of the coronary arteries is an extremely rare anomaly. In those uncommon instances the remaining artery, usually the left coronary artery, supplies the entire heart.

**Life-threatening coronary anomalies** are a group of conditions that cause coronary perfusion abnormalities resulting in inadequate myocardium blood supply.



**Fig. 8. A, B.** Cardiovascular computed tomography. Three-dimensional reconstruction. A single coronary artery in 20-year-old woman arising from the left coronary sinus dividing into the right coronary artery and the left main, then the circumflex and the left anterior descending branch. **C, D.** Coronary angiography. A large fistula originating from the right coronary artery draining into the pulmonary artery (arrows). RCA – right coronary artery, LM – left main, Cx – circumflex branch, LAD – left anterior descending branch, PA – pulmonary artery

### Myocardial ischemia resulting from coronary anomaly

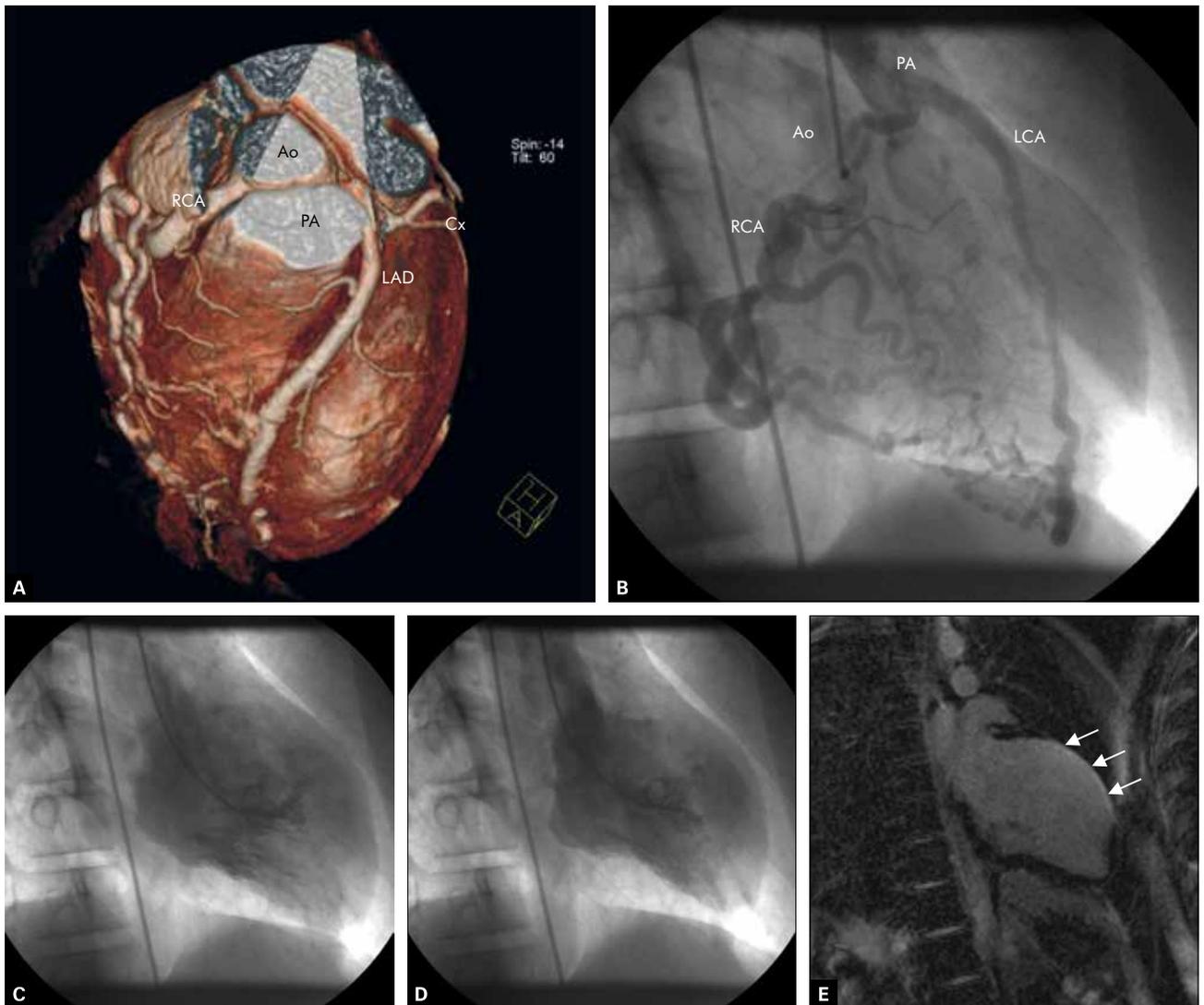
This group of conditions comprise: an anomalous origin of the coronary artery from the pulmonary artery, myocardial bridges, coronary fistulas and coronary aneurysms.

#### Anomalous origin of the coronary artery from the pulmonary artery

This coronary anomaly affects 1: 300 000 of life births, and accounts for less than 0.5% of congenital heart defects [44,47]. It is the most serious coronary anomaly.

In extremely rare instances both coronary arteries arise from the pulmonary artery. In such cases cyanosis, dyspnea and cardiomegaly develops instantly or soon after the birth. Death of the neonate can occur during the first days of life. Longer survival is possible with coexistence of left-to-right intracardiac shunts that cause increased pulmonary artery pressure and blood oxygen saturation.

The most common variant of the anomalous origin of the coronary artery from the pulmonary trunk is Bland–White–Garland syndrome, where it is the left coronary artery that arises abnormally from the pulmonary artery, while the right coronary artery originates correctly from the aorta (fig. 9AB). Variants of Bland–White–Garland syndrome may include



**Fig. 9.** The Bland–White–Garland syndrome in 17-year-old boy. **A.** Multi-sliced computed tomography. Three-dimensional reconstruction. The origin of the left coronary artery from the pulmonary artery and the right coronary artery from the ascending aorta. Widened coronary arteries and a net of collaterals. **B.** Coronary angiography. Posteroanterior view. Contrast agent was injected to the right coronary artery that originates from aorta. Contrast filling left coronary artery branches through the well-developed collaterals, then passes to the trunk of the pulmonary artery. **C, D.** Left ventriculography. Diastole (**C**). Systole (**D**). Apical akinesis, and thrombus formation in apex, as the result of myocardial infarction in the region of the left anterior descending branch vasculature. **E.** Cardiovascular magnetic resonance. Apical late enhancement (arrow) consistent with scarring after myocardial infarction. Ao – ascending aorta, LCA – left coronary artery, RCA – right coronary artery, LAD – left anterior descending branch, Cx – circumflex branch, PA – pulmonary artery

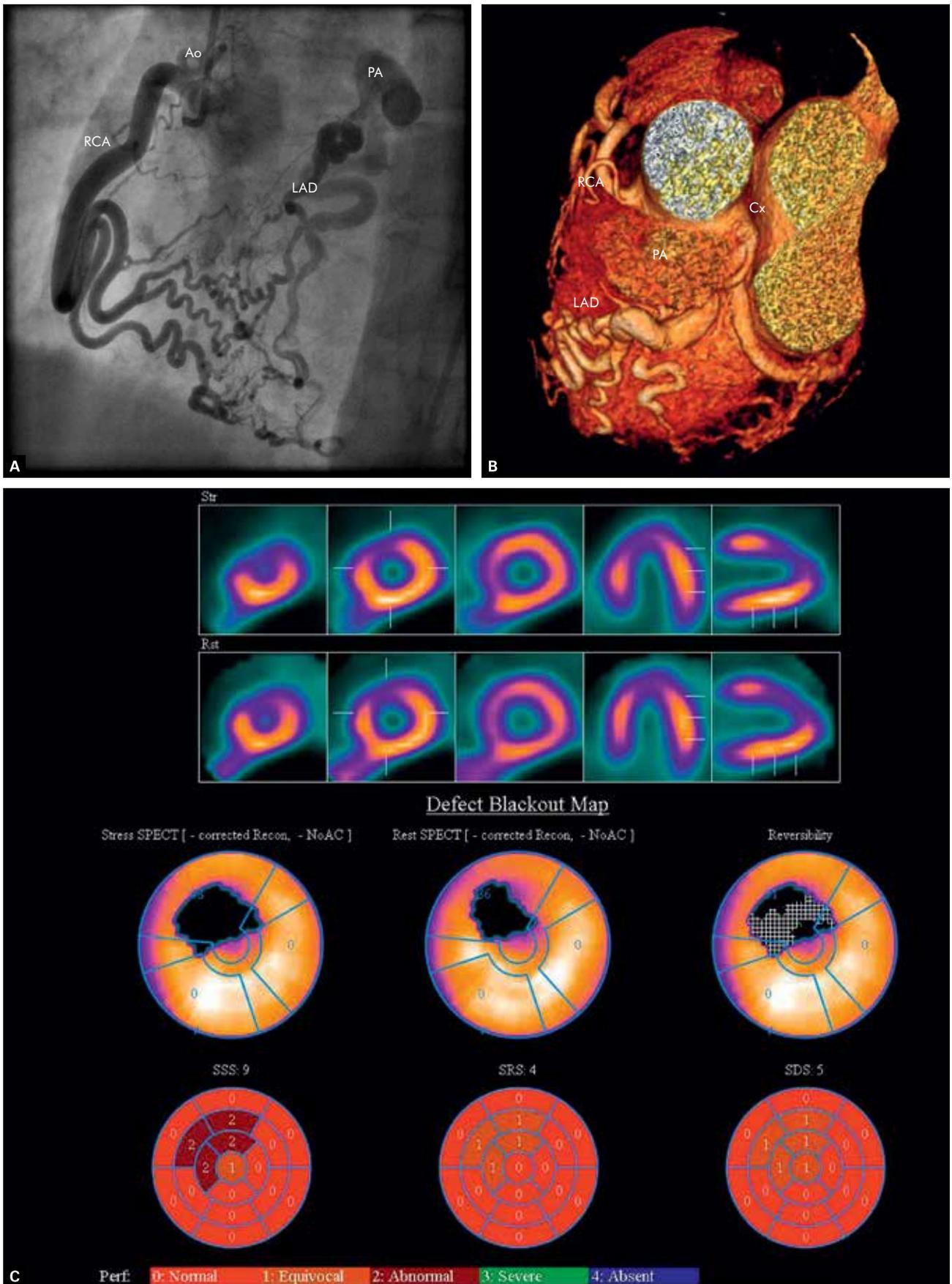
aberrant origination of the left main branches, for example, the left anterior descending artery arising from the pulmonary trunk, while the circumflex and right coronary arteries have a normal origination from the aorta (fig. 10AB).

Without surgical correction, up to 90% of the affected children die during the neonate period, as a result of myocardial ischemia. In our high-volume cardiac surgery center, 8 adult patients with formerly uncorrected Bland–White–Garland syndrome were operated during the period of 10 years.

Survival is possible when a collateral circulation from the correctly originating right coronary artery to the myocardial area supplied by the left coronary artery aberrantly arising from the pulmonary trunk, gradually develops over the first weeks and months of life [47]. After development of efficient collaterals,

the blood flow in the left coronary artery reverses and enters the pulmonary trunk (fig. 9B, 10A). The condition evolves into an adult form with coronary steal from myocardial circulation to the low-pressure pulmonary circulation, with the resultant myocardial underperfusion, left ventricular dysfunction, and mitral valve insufficiency (fig. 10C). This phase of the disease can manifest with the symptoms of heart failure, left ventricle enlargement, systolic heart murmur and cases of exercise induced sudden cardiac death. Myocardial infarction is not a rare associated condition, as well as sustained ventricular arrhythmia requiring implantation of cardioverter-defibrillator or conduction disorders requiring permanent pacemaker (fig. 9CDE).

The diagnostic work-up, apart from medical history and physical examination, consists of: chest X-ray,



**Fig. 10.** A variant of the Bland–White–Garland syndrome, newly recognized in a 48-year-old woman. **A.** Coronary angiography. Posteroanterior view. Contrast agent was injected to the right coronary artery that originates from the aorta. Contrast filling the left anterior descending coronary branch through the well-developed collaterals, then passes to the trunk of the pulmonary artery. Wide right coronary artery. **B.** Multi-sliced computed tomography. Three-dimensional reconstruction. Left anterior descending branch originates from the pulmonary artery, while the circumflex and the right coronary artery from the aorta. **C.** Single-photon emission computed tomography. Myocardial perfusion defect within the anterior wall and the apex. Ao – aorta, RCA – right coronary artery, LAD – left anterior descending branch, Cx – circumflex branch, PA – pulmonary artery

echocardiography, angiography or CTA of the coronary and pulmonary arteries and, if necessary, 24-hour ECG monitoring, myocardial perfusion scintigraphy or MRI perfusion study to evaluate the extension of the ischemia (fig. 9E, 10C) [44,47].

Echocardiography may identify apical and anterior wall motion abnormalities, left ventricular enlargement, and in some instances Doppler color flow imaging can show an accessory jet towards the pulmonary artery [47].

Coronary angiography or CT-angiography demonstrates markedly dilated right coronary artery (3–4 times wider than normal), giving rise to a number of collaterals running to the left coronary artery, from which the contrasted blood flows into the pulmonary artery (fig. 8A).

The definite treatment consists in surgical reconstruction of a two-vessel coronary artery system. The following surgical techniques can be applied [44,47]:

1. Direct reimplantation of the aberrant artery to the aorta (in neonates).
2. Creation of a conduit running from the left coronary artery across the pulmonary trunk to the aortopulmonary window (Takeuchi procedure).
3. Ligation of the left coronary artery at its origin from the pulmonary trunk, with subsequent implantation of the left internal mammary artery or a venous bypass graft to the left main coronary artery.

### Myocardial bridge

Myocardial bridge is the most frequent of the pathologies affecting coronary perfusion. There is much controversy over its actual prognostic significance. Due to a relatively common occurrence, it is not considered a rare pathology. The topic of myocardial bridge is covered in many cardiology textbooks.

### Coronary artery fistula

As a result of a congenital aberrancy, a coronary artery can communicate through a fistula with a heart chamber, the pulmonary artery or an adjacent vein (fig. 8CD). The prevalence of coronary fistulas is 0.07% of coronary angiographies [46].

In 60% of cases, fistulae arise from the right coronary artery, in 32% from the left, in 2% from both and in 7% from an anomalous single coronary artery [44,48].

In 45% to 52% of the cases fistulae drain to the right chamber, in 24% to 25% to the right atrium, in 15% to the pulmonary artery, and in 10% of cases to the left sided heart chambers [44,48,49]. The fistulae are frequently associated with left-to-right shunt with volume overload of the pulmonary circulation and of the left ventricle.

Most patients are asymptomatic, except for a continuous murmur heard over the heart [49,50]. It is believed that about 20% of fistulae close spontaneously [49]. However, the majority grow over time. Commonly the symptoms of myocardial ischemia or congestive heart failure develop in the 5<sup>th</sup>–6<sup>th</sup> decade

of life. Coronary fistula can be associated with accelerated development of atherosclerosis and coronary calcifications, coronary steal phenomenon causing myocardial ischemia, progressive heart failure, dilated cardiomyopathy, occurrence of both benign and life threatening arrhythmias and with sudden cardiac death [49]. Higher incidence of endocarditis, embolization with thrombotic material formed in the fistula, or a coronary aneurysm formation was also observed.

Coronary angiography remains the modality of choice in diagnostic evaluation of coronary fistulae.

According to the American College of Cardiology and the American Heart Association (ACC/AHA) 2008 guidelines for the management of adults with congenital heart disease [50]: large coronary arteriovenous fistula, regardless of symptomatology, should be closed via either a transcatheter or surgical route after delineation of its course and its potential to fully obliterate the fistula. (recommendation class I; level of evidence C), a small to moderate coronary fistula, in the presence of documented myocardial ischemia, arrhythmia, otherwise unexplained ventricular systolic or diastolic dysfunction or enlargement, or endarteritis should be closed via either a transcatheter or surgical approach after delineation of its course and its potential to fully obliterate the fistula. (recommendation class I; level of evidence C), small asymptomatic fistulas should not be closed (recommendation class III; level of evidence C) [50].

Patients with small, asymptomatic fistulas should have clinical follow-up with echocardiography every 3 to 5 years, to exclude development of symptoms or arrhythmias or progression of size or chamber enlargement that might alter management (recommendation class IIa, level of evidence C) [50].

### Coronary artery aneurysm

The incidence of this pathology is extremely low and only one-fifth of cases are a congenital anomaly [44]. These instances can result from aberrancies of the vessel media structure, of the fibrillar connective tissue proteins or both.

Acquired coronary aneurysms are commonly caused by Kawasaki disease (childhood), atherosclerosis, endocarditis, syphilis, polyarteritis nodosa and many other inflammatory disorders. Finally they can result from a congenital coronary artery fistula or from a chest trauma.

Most cases are asymptomatic. In other instances coronary aneurysm can lead to myocardial ischemia symptoms, distal thrombotic embolization, myocardial infarction. Some aneurysms may rupture.

**Proximal narrowing of a single coronary artery** – discussed above.

### Coronary anomalies associated with arrhythmias and sudden cardiac death

Anomalous origination of a coronary artery or its branches from the opposite coronary sinus or from noncoronary (posterior) sinus with subsequent aberrant epicardial course [44,46,51,52].

Possible variants are:

- Aberrant course of the separately arising from the left sinus of Valsalva principal branches of the left main coronary artery or their origination from the right sinus of Valsalva.
- Origination of the left or right coronary artery from the noncoronary sinus.
- Origination of the both coronary arteries from a single sinus of Valsalva.

The right coronary artery arising from the left sinus of Valsalva is seen in 0.03% to 0.17% of coronary angiograms, while the left main coronary artery arising from the right sinus of Valsalva is seen in 0.09%–0.11%. The origin of a coronary artery from the noncoronary sinus is an extremely rare finding.

If they originate from the right or noncoronary sinus, the left coronary artery or the left anterior descending branch may run between the aorta and the pulmonary trunk and be compressed by the flanking great arteries. Similarly compressed may be the right coronary artery, if it arises from the left coronary sinus. Anomalous course of a coronary artery between the aorta and the pulmonary trunk is associated with arrhythmias and sudden cardiac death in 30% to 75% of the affected individuals [44,51,52]. Anomalous circumflex branch arising from the right sinus of Valsalva on the other hand, may be injured during the aortic valve replacement surgery.

**Coronary arterial fistula** – discussed above.

**Proximal narrowing of a single coronary artery** – discussed above.

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## Connective tissue disorders causing aneurysmal disease

Anna Kablak-Ziembicka, Tadeusz Przewłocki

### Aneurysmal disease of the aorta

Systemic connective tissue disorders are caused by mutations in genes coding vascular wall building components, such as fibrillin 1 (Marfan syndrome), collagen III (vascular Ehlers–Danlos syndrome [EDS]), transforming growth factor- $\beta$  receptor genes 1 and 2, *TGFBR1/TGFBR2* (Loeys–Dietz syndrome [LDS]), *TGFBR2*, myosin heavy chain: MYH11, and *ACTA2* (familial thoracic aortic aneurysms and dissections [TAAD]) [1–4].

All the above syndromes are associated with the aortic and large-medium vessel aneurysmal disease. They also affect the organs that are built up of the destructed components [4–6]. They should be differentiated with the other, more frequent, morbidities associated with aortic aneurysm, including bicuspid aortic valve disease (incidence of 1%–2% of the general population), autosomal dominant polycystic kidney disease (1:1000 population), and neurofibromatosis (1:3000 population) [5].

The majority of aortic aneurysms are found incidentally (chest radiography, echocardiography, chest computed tomography [CT] and magnetic resonance imaging [MRI]), because they do not produce any symptoms for years [6]. In the presence of large aneurysms, the symptoms are associated with the effect of mass [6]. The typical clinical symptoms of enlarging aortic aneurysms include upper back pain, coughing and wheezing, hoarse voice, difficulty swallowing, swelling in the neck or arms, Horner's syndrome (constricted pupil, drooping eyelid, and dry skin on one side of the face), deep boring pain or pulsation in the lower back region [6].

Acute aortic aneurysm is an uncommon but potentially catastrophic illness with an incidence of approximately 2.9/100 000 population per year [7]. Aortic dissection symptoms usually develop suddenly and include rapid pulse, sweating, nausea, vomiting, dizziness, fainting, shortness of breath, weak or absent pulse, severe onset of sharp, stabbing, tearing, or ripping pain usually in the chest (front, back, or both) or lower back depending on the site of the dissection, limb weakness, and decreased sensation in the arm or leg.

To avoid aneurysm dissection and choose optimal timing for aortic aneurysm repair, a number of non-invasive imaging modalities are used depending on aneurysm location, such as echocardiography, ultrasonography of the aortic arch and abdominal aorta, CT angiography (CTA) and magnetic resonance angiography (MRA) [5–7]. They are particularly effective in Marfan syndrome, LDS, TAAD, BAV, ADPKD and neurofibromatosis, where the dissection mostly occurs within the aneurysmal portion of the aorta. Caution is

necessary in monitoring patients with EDS and LDS, in whom aortic rupture or dissection frequently occurs in a nondilated aorta [5].

Once an aortic aneurysm or dissection is detected, imaging should be performed more often. The frequency is based on several parameters and is different for individual patients; annual intervals are usually recommended. However, more frequent monitoring (at 3–6-month intervals) is required if the aneurysm continues to increase in size, rapid growth is observed, it approaches the critical size, aortic valve function is compromised, or if an individual's aorta is approaching the size at which there is a family history of aortic dissection or rupture [5,8].

In families with a genetic history of aortic aneurysms or dissections, it is recommended that family members at risk have their aortic root (first part of the ascending aorta) monitored by echocardiography (picture using sound waves to evaluate the size of the root and how the aortic valves are working) and the parts of the aorta further from the heart, specifically the aortic arch and descending aorta monitored by CT or MRI at least once a year.

### Marfan syndrome

Marfan syndrome occurs relatively frequently, with a rate of 2 to 3 persons in 10 000 newborns [9]. It produces changes mostly in the connective fibers of the cardiovascular, musculoskeletal, and ocular systems, but it also affects pulmonary, nervous, and integumentary fibrils [1,9,10].

Cardiovascular manifestations include progressive dilatation of the aortic root, leading to aneurysm formation and aortic dissection or rupture, if not surgically treated [10,11]. The dilatation or dissection of the descending thoracic or abdominal aorta is also often observed. Moreover, the dilatation or aneurysm of the pulmonary artery, cerebral, and renal arteries can be seen. Mitral valve prolapse is diagnosed more often than in the general population. Aortic valve regurgitation should be assessed carefully because it may be the sign of subsequent aortic root and ascending aorta dissection.

Patients with Marfan syndrome are usually strikingly tall and thin. The Ghent diagnostic criteria for clinical diagnosis of Marfan syndrome are presented in Table 1 [12]. The diagnosis requires a major criterion in two systems and involvement of the third system. This should be verified by genetic testing. More than 600 mutations on chromosome 15 in the fibrillin 1 gene (*FBN1*) have been described so far. They are detected in 66% to 93% of the patients who meet Ghent's diagnostic criteria for Marfan syndrome. Of note, the Ghent criteria are unreliable in children because the disease progresses and systemic involvement in childhood may be different from that observed in adulthood.

Pathomorphologically, the Marfan aorta is characterized by elastic fiber fragmentation and disarray, paucity of smooth muscle cells, and deposition of collagen and mucopolysaccharide between the cells of the media (sometimes described as “cystic medial degeneration”) [6].

**Table 1. Characteristics of rare systemic connective tissue disorders associated with aneurysms and dissections of aorta**

	<b>Genetic mutation</b>	<b>Clinical diagnostic criteria</b>	<b>Median survival</b>	<b>Typical cardiovascular presentation</b>	<b>Management</b>
Marfan syndrome Incidence: 2–3: 10 000	FBN1 identified in 66%–93% of cases	<b>Major Ghent criteria:</b> <b>Skeletal:</b> pectus carinatum, pectus excavatum requiring surgery, upper to lower segment ratio <0.86 or span to height ratio >1.05, arachnodactyly: wrist and thumb signs, pes planus, protrusio acetabula, scoliosis >20° or spondylolisthesis, reduced extensions at the elbows (<170°) <b>Ocular:</b> Ectopia lentis (dislocated lens) <b>Cardiovascular:</b> Dilatation of the ascending aorta, aortic root dilatation <b>Dura:</b> Lumbosacral dural ectasia <b>Family/genetic history:</b> Family history, genetic mutations known to cause Marfan syndrome, inheritance of DNA maker haplotype linked to MFS in the family	60–70 years	Dissection occurs in the presence of arterial dilatation	Cardiovascular system assessment: echocardiography follow-up at least at yearly intervals ultrasonography – abdominal, aortic arch aorta assessment selected situations CTA, MRA Different systems assessment: pelvic X-ray, MR, CT, Medications: β-blockers, ACE inhibitors, sartans (?) Surgery: the aortic root at the Sinus of Valsalva >5 cm, pregnancy 4.5cm Endovascular: cerebral aneurysm coiling Avoid: extensive and isometric exercise
Vascular Ehlers–Danlos Syndrome Incidence: 1: 100 000, 1: 200 000	COL3A1	<b>Villefranche criteria</b> <b>Major criteria:</b> Thin, translucent skin Arterial / intestinal / uterine fragility or rupture Extensive bruising Characteristic facial appearance (reduced subcutaneous fat) <b>Minor criteria:</b> Acrogeria Hypermobility of small joints Tendon and muscle rupture Talipes equinovarus Early onset varicose veins Arteriovenous, carotid-cavernous sinus fistula Pneumothorax/ pneumohemothorax Gingival recession Positive family history, sudden death in close relative	40–50 years	Dissection can occur without marked arterial dilatation Spontaneous rupture of aorta and large-middle-size arteries	Cardiovascular system assessment: echocardiography follow-up at least at yearly intervals ultrasonography of vessels and abdomen CT, MR selected situations Medications: celiprolol, ACEI, sartans, Avoid: antiplatelets, anticoagulation, extensive and isometric exercise Surgery: on urgent/emergency bias rather when vascular or organ rupture, or vascular dissection occurs Endovascular: coil embolization of ruptured vessels, fistulas
Loeys–Dietz syndrome Incidence: <1: 100 000	TGFBR1 TGFBR2	<b>Major findings:</b> Widely spaced eyes (orbital hypertelorism) Cleft palate or bifid uvula Aortic and arterial aneurysms/dissections with tortuosity (corkscrew structure) of the arteries. <b>Other findings include:</b> Scoliosis or Kyphosis, Indented or protruding chest wall (pectus excavatum or pectus carinatum), Contractures of fingers and toes (camptodactyly), Long fingers and lax joints, Club foot, Premature fusion of the skull bones (craniosynostosis), Joint hypermobility, Congenital heart problems including patent ductus arteriosus and atrial septal defect, Bicuspid aortic valve, Translucency of the skin with velvety texture, Abnormal junction of the brain and medulla (Arnold-Chiari malformation)	26–37 years	Dissection can occur either without marked arterial dilatation and in the presence of arterial dilatation	Cardiovascular system assessment: echocardiography follow-up at least at yearly intervals, when necessary every 3–6 months ultrasonography of vessels and abdomen CT, MR selected situations Medications: β-blockers, ACE inhibitors, sartans (?) Surgery: aortic repair at 4.0 cm diameter

Thoracic familial aortic aneurysms and dissections syndrome Incidence: <1: 100 000	<i>TGFBR2</i> <i>MYH11</i> <i>ACTA2</i> , <i>MYLK</i> , <i>SMAD3</i> , and others	<b>Major findings:</b> Ascending aorta aneurysm and dissection Familial occurrence Early onset aneurysm (typically 10 years younger patients, as compared to sporadic forms; 54–56-years old vs. 64–66-years old)	60 years	Dissection occurs in the presence of arterial dilatation	Cardiovascular system assessment: echocardiography follow-up at least at yearly intervals ultrasonography of vessels and abdomen CT, MR selected situations Medications: $\beta$ -blockers, ACEIs Surgery: aortic repair at 5.0–5.5 cm diameter
CTA – computed tomography angiography, MRA – magnetic resonance angiography, CT – computed tomography, MRI – magnetic resonance imaging, ACEIs – angiotensin-converting-enzyme inhibitors					

## Management

Pregnancy in women with Marfan syndrome is associated with a 4.5% risk of dissection, and the risk is greater if the aortic root exceeds 4 cm at the start of pregnancy or if it dilates rapidly [5]. If the aortic root dilates to 5 cm during pregnancy, aortic replacement should be considered; otherwise, early delivery or termination of pregnancy must be taken into account [5,6,13]. No increased risk of spontaneous preterm labor, spontaneous miscarriage, or postpartum hemorrhage has been observed in aortic repair procedures [13].

Conservative management includes repeated monitoring of aortic size, routine  $\beta$ -blocker administration to reduce aneurysm / dilatation growth and to decrease the wall stress, systematic control of the blood pressure, and treatment of high blood pressure, preferably with  $\beta$ -blockers and inhibitors of the renin–angiotensin–aldosterone system (angiotensin-converting-enzyme inhibitors [ACEIs]) [14–16]. ACEIs also reduce vascular smooth muscle cell apoptosis, while losartan has been shown in an in-vitro study to reduce the rate of aneurysm growth through reducing signaling on TGFB [17,18].

Contact sports should be avoided to protect the aorta, joints, and the lens of the eye; moreover, scuba diving is not recommended because of the increased risk of pneumothorax.

Surgery / endovascular management. The management of dissected, ruptured, or aneurysmal arteries involves surgical procedures [19]. A prophylactic aortic repair is recommended if an aneurysm exceeds 5 cm (or 4.5 cm in women of childbearing age) [8,13,19]. Endovascular procedures are used for cerebral aneurysm coiling [5].

## Ehlers–Danlos syndrome

EDS is a heterogeneous group of disorders related to mutations in genes coding the collagen tissue that include six different types: classic, joint hypermobility, vascular, kyphoscoliosis, arthrochalasia, and dermatosparaxis [2]. The prevalence of EDS is 1 per 10 000 to 100 000 individuals, with the male-to-female ratio of 1:1 [2].

The vascular type constitutes about 4% to 10% of all cases of EDS, and it is believed to be an autosomal dominant disease that causes arterial spurting, intestinal perforation, uterine rupture, and hemopneumothorax caused by mutations in the alpha 1 type III collagen gene (*COL3A1*), which results in a decreased production of type III collagen [2,20,21]. However, half of the affected patients have no family history of EDS and it is assumed that they develop the disease through newly generated mutations [21].

The clinical diagnosis is based on the Villefranche criteria (Table 1) [20]. The presence of 2 or more major clinical criteria is highly indicative of vascular EDS, while the minor criteria are useful to confirm the diagnosis and their recording is helpful to correlate the results and clinical presentation.

Molecular testing is recommended when two or more major criteria are fulfilled. Most patients with a clinical diagnosis of vascular EDS show an autosomal dominant inheritance pattern associated with mutations in the gene for type III collagen (*COL3A1*).

The molecular diagnosis allows to differentiate EDS from other conditions of blood vessel and organ rupture with a similar course, for example, autosomal dominant polycystic kidney disease and familial arterial aneurysm. Other reasons for molecular testing include the evaluation of status in the relatives of an affected individual for clinical management and genetic counseling, as well as prenatal diagnosis.

The vascular type of EDS is considered to have the most unfavorable prognosis; the first clinical manifestation usually occurs around 20 years of age [2,21,22]. Arterial rupture is usually spontaneous and usually occurs without prodromal symptoms, frequently in previously nonaneurysmal and in nondissected vessels. The sites most prone to rupture or dissection are abdominal aorta and its side-branches, large aortic arch arteries, and iliac and femoral arteries. In the literature, there are several reports describing the rupture or dissection of the splenic artery, presenting with shock, fainting or syncope, and hemoperitoneum, as well as rupture of the renal arteries. Heart muscle rupture with subsequent heart tamponade is also quite common. Mitral valve prolapse is frequent.

Vascular EDS is also associated with a substantial risk of spontaneous rupture of the uterine during pregnancy or gastrointestinal perforation or the rupture of organs that are built up of collagen III. The other common findings in vascular EDS include abdominal wall hernias, spontaneous pneumothoraces, hepatic and splenic ruptures, major and minor joint dislocations, lens dislocations, and miscarriages [23].

These can present as sudden death, ischemic and hemorrhagic stroke, acute abdomen, shock, dyspnea, and uterine rupture at delivery.

A 30-year experience of the Rochester Center described by Oderich et al.[23] and involving a group of 31 patients with vascular EDS showed that survival free of any arterial, intestinal, and uterine complication was 84% at the age of 20 years, 37% at 40 years, and only 4% at 60 years.

## Management

Pregnancy in women with vascular EDS is associated with a 12% risk of death from peripartum arterial rupture or uterine rupture and should be managed as a high-risk obstetric program [2,21].

Although the long-term prognosis is poor, a conservative approach is usually recommended because of high-risk of elective surgical procedures. The 8-year survival rate was 73% in the observational study by Oderich [23]. During follow-up, 33% of the subjects developed new vascular complications.

A recent randomized trial in a group of 53 patients with vascular EDS showed that celiprolol (a  $\beta_1$  receptor antagonist – 25 patients) vs. placebo (28 patients) reduces the relative risk of arterial ruptures by 74% [24]. In the celiprolol group, ruptures were significantly less frequent (20% vs. 50% in the placebo group). Celiprolol has been recently proposed for the prevention of arterial complications.

Inhibitors of the renin–angiotensin system may also be beneficial in EDS because they decrease the wall stress [25].

Patients with concomitant mitral valve prolapse and valvular regurgitation require antibiotic prophylaxis against bacterial endocarditis during invasive procedures [21].

Contraindications in subjects with vascular EDS include [2,21]:

- contact sports or isometric exercises that include weight lifting,
- aspirin and other antiplatelet medications, anticoagulation,
- drugs that interfere with platelet function and anticoagulants
- invasive techniques, e.g., angiography (high risk of severe bleeding or perforation, approximately 23%), elective surgery
- all arterial punctures
- gastrointestinal and uterine endoscopies to prevent perforation complications

Oderich et al. [23] reported serious complications after arteriography in 23% of the patients, including large access site hematomas and carotid artery rupture during attempted embolization of a carotid-cavernous fistula.

**Endovascular procedures** such as arterial and venous coil embolization have shown benefit but they should be limited to coiling ruptured vessels only [25].

Arterial, digestive, or uterine complications require immediate hospitalization and observation in an intensive care unit. The management of dissected, ruptured, or aneurysmal arteries is difficult because owing to collagen defect, there is increased tissue fragility and high risk of perioperative bleed; moreover, wound healing is compromised and complications may recur [2,21,26]. However, **surgery** may be urgently required to treat potentially fatal vascular complications and organ rupture as life-saving interventions. According to recent surgical experience, the majority of patients with EDS could undergo a surgery with minimal complications in specialized centers [26].

Numerous reports emphasize the exceedingly high risk of massive bleeding and anastomotic disruption with attempted operative repair. The reported perioperative death rate was 2/15 procedures, while major

morbidity after surgery was reported at 46%, including mostly excessive bleeding (37%), pulmonary complications (20%), renal failure (10%), cardiac arrest, brachial plexopathy, and prolonged ileus.

Late graft-related complications are frequent, accounting for 40% of the cases. They include graft-anastomotic aneurysms, anastomotic rupture, and graft thrombosis, and require operative repair. Therefore, during surgery, gentle management of the vessels, bowel, and uterine is recommended along with the use of soft, protected arterial clamps, balloon occlusion, or an orthopedic tourniquet and selection of the most expeditious technique of repair. Arterial ligation seems to be the first-choice technique whenever possible without compromising blood supply (e.g., subclavian artery). The use of umbilical tape to prevent sutures from cutting into the arterial wall is recommended. Nevertheless, central arterial complications often require arterial reconstruction with prosthetic grafts. In these cases, use of autologous vein is contraindicated. Anastomosis should be tensionless and buttressed with Teflon felt strips or pledgets.

## Loeys–Dietz Syndrome

LDS was first recognized and described by Loeys and Dietz in 2005; previously, it was known as type 2 of the Marfan syndrome [3]. It is inherited in a dominant autosomal manner. *TGFBR1/TGFBR2* gene mutations lead to an increased signaling of TGF- $\beta$  in blood vessels resulting in increased wall stress [3,27].

LDS is characterized by premature and aggressive aneurysms and dissections, widely spaced in eyes, bifid uvula, or cleft palate, causing generalized arterial tortuosity [3,5]. The other symptoms include skeletal manifestations (pectus excavatum or pectus carinatum, scoliosis, joint laxity, arachnodactyly, and talipes equinovarus). Approximately 75% of the affected individuals have LDS type I with craniofacial manifestations (ocular hypertelorism, bifid uvula/cleft palate, craniosynostosis); approximately 25% have LDS type II with cutaneous manifestations (velvety and translucent skin; easy bruising; widened, atrophic scars). LDSI and LDSII form a clinical continuum. The clinical diagnosis is presented in Table 1.

Most patients with a clinical diagnosis of LDS show an autosomal dominant inheritance pattern associated with mutations in the gene for *TGFBR1* and *TGFBR2*. No differences in the phenotype are observed between individuals with mutations in *TGFBR1* and *TGFBR2*. Approximately 25% of the individuals diagnosed with LDS have an affected parent, while 75% have LDS as the result of a de novo gene mutation. Each child of an individual with LDS has a 50% chance of inheriting the mutation and the disorder [3,27].

The natural history of LDS is characterized by aggressive arterial aneurysms (mean age at death, 26.1 years) and high incidence of pregnancy-related complications including death and uterine rupture. Mortality is mostly from thoracic or abdominal aortic dissection, rupture, or cerebral hemorrhage.

## Management

All individuals with LDS require echocardiography at frequent intervals to monitor the status of the ascending aorta; the frequency of MRA or CTA depends on clinical findings. Individuals with cervical spine instability

and severe or progressive scoliosis should be followed by an orthopedist. Antibiotic prophylaxis is recommended in those undergoing dental work or elective procedures.

$\beta$ -blockers or ACEIs are used to reduce hemodynamic stress. The effect of losartan is currently being investigated.

Patients should avoid:

- contact sports, competitive sports, and isometric exercise;
- agents that stimulate the cardiovascular system including routine use of decongestants;
- activities that cause joint injury or pain.

Mean age for the first vascular surgical procedure is about 20 years. The majority of the patients have aneurysms distal to aortic root. Dissection can occur without marked arterial dilatation (in contrast to Marfan syndrome but similar to EDS). Perioperative vascular surgical mortality is only 1.7% (in contrast to 45% for EDS IV) [5]. Prophylactic repair of adult patients with LDS has been suggested at an aortic diameter of 4.0 cm [28].

### Familial thoracic aortic aneurysms and dissections

Familial TAAD refers to a genetic predisposition to thoracic aortic aneurysm or dissection in the absence of other syndromes such as Marfan syndrome or LDS. The familial aneurysm usually occurs in younger patients, typically at a mean age of 10 years younger than nonfamilial cases (56–57 years vs. 64–66 years) [4]. A detailed analysis by Coady et al., [4] revealed that at least 19% of the patients had a family history of a thoracic aortic aneurysm, which suggests a genetic link [4]. Multiple mutations associated with TAAD have been proposed, the most popular being the *TGFBR2*, *MYH11*, *MYLK*, *SMAD3*, and *ACTA2* genes [29–31]. Pathomorphological studies show a cystic medial degeneration in the aortic wall.

TAAD tends to have a malignant course. A study of the families of 158 patients referred for surgical repair of TAAD revealed that first-degree relatives of probands had a higher risk (risk ratio [RR] 1.8 for fathers and sisters, RR 10.9 for brothers) of thoracic aortic aneurysms or sudden death compared with control subjects [32]. Moreover, Albornoz et al. [33] observed the highest rate of aortic growth in TAAD (0.21 cm/y), intermediate in the sporadic group (0.16 cm/y), and lowest for the Marfan group (0.1 cm/y;  $P < 0.01$ ) [33].

**Bicuspid aortic valve (BAV)** is associated with aortic dilation limited to the aortic root and ascending aorta, whereas it is not present in the descending and abdominal aortas. It is a common condition, affecting 1% to 2% of the population.

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## Autoimmune diseases of the vessels

Anna Kablak-Ziembicka, Tadeusz Przewłocki

### Primary systemic vasculitides

The annual incidence of primary systemic vasculitides is estimated at 100 patients per 1 million population [1]. Some of these vasculitides are associated with high mortality rate, reaching up to 80% in the first year since morbidity onset (polyarteritis nodosa) if not treated correctly [2].

Primary systemic vasculitides constitute a very heterogeneous group of autoimmune disorders [3,4]. By definition, the systemic vasculitis is a consequence of the autoimmune process due to the immune response to a pathogen in which own antigens are identified as hostile, which leads to destruction of the vessel wall, chronic inflammation, and ischemia of the involved organs [1].

These disorders present with a variety of symptoms including general signs of inflammation (fever, body mass loss, easy fatigue, sweats, headaches, myalgia) as well as specific features for an individual vasculitis [1,2,3,4,5,6].

Vasculitides can be divided into primary (no evident pathogen) and secondary vasculitis (in which a well-known pathogen, medication, or other known comorbidity initiate the immune process) [1,3,4]. Once secondary vasculitis is excluded, the identification of primary vasculitis is necessary. Primary vasculitides are classified in relation to the vessel size they affect and the type of cells involved in the proliferation, as well as the specific type of tissue damage occurring in the vein or arterial walls. This classification is essential for appropriate treatment.

Large-vessel vasculitides include adolescent and adulthood Takayasu's disease (TAK), adulthood giant cell arteritis (GCA), and adulthood isolated aortitis (they are nonnecrotizing and not associated with anti-neutrophil cytoplasmic antibodies [ANCA]). Medium-vessel vasculitides (affecting the medium and small blood vessels) comprise a necrotizing primary childhood Kawasaki disease (KD) and a necrotizing adulthood polyarteritis nodosa (PN). Small-vessel necrotizing vasculitides include primary childhood Henoch–Schönlein purpura (HSP) and ANCA-associated adulthood Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), renal limited idiopathic necrotizing crescentic glomerulonephritis, and Churg–Strauss syndrome (CSS). Small-vessel nonnecrotizing vasculitides comprise Goodpasture's disease, mixed cryoglobulinemia, and hypersensitivity vasculitis.

There are two classifications of vasculitides in use, the one of the American College of Rheumatology (ACR) from 1990 and the other of the European League Against Rheumatism (EULAR) from 2010 [4,5]. In 1994, the Chapel Hill Consensus Conference

produced definitions for new vasculitides including MPA [6]. All classifications are based on the vessel size of the affected artery, while, for example, Behçet's disease, Cogan syndrome, or angitides of the central nervous system have no vessel size allocation [7].

### Diagnostic tools

Although exposed to a major criticism, the ACR diagnostic criteria have relatively good sensitivity and specificity for vasculitis identification, estimated at 71% to 95.3% and 78.7% to 99.7%, respectively [4]. The highest diagnostic accuracy is observed in CSS, GCA, and TAK [4].

The diagnostic tools used to identify primary vasculitides include:

- history taking and physical examination (general infection symptoms, pulselessness, claudication, organ ischemia)
- laboratory tests with the assessment of nonspecific infectious markers and specific antibodies and antigens,
- histopathological study – presence of the specific for individual vasculitis proliferative in tissue specimens (cutaneous, vascular, muscular, connective tissue)
- radiological images – intimal hyperplasia, lumen reduction in the affected vessels, location and anatomy of stenotic lesions and occlusions (ultrasonography [US], computed tomography angiography [CTA], magnetic resonance angiography [MRA], angiography)
- assessment of inflammatory activity in the vascular walls (positron emission tomography [PET], PET-CT, magnetic resonance imaging [MRI], PET-MRI, scintigraphy)

The differential diagnosis is also of utmost importance and should include atherosclerosis, connective tissue diseases, and aneurysmal diseases [8].

### Inflammation activity and extent / location and the response to the treatment

**Laboratory tests:** Elevation of inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) is not pathognomonic for the disease but may be a marker of its activity. Similarly, monitoring of ICAM, E-selectin and other more specific markers for a concrete arteritis may be useful in evaluating process activity and response to therapy.

**Imaging tests:** It appears that there is a superiority of FDG-PET and PET/CT over conventional imaging methods (such as US or MRI) in the diagnosis of arteritis, but not in assessing disease activity under immunosuppressive treatment, or in predicting relapse or evaluating vascular complications [10]. The main drawback of PET / PET-CT is the “masking effect” of steroid therapy on the FDG vascular uptake. Moreover, an inverse relationship between the dosage of immunosuppressive drugs and the number of positive FDG-PET scans has been reported.

For the later purpose, MRI and CTA / MRA are more precise in evaluating the response to

immunosuppressive therapy as well as advancing narrowing in the vessels.

It has been postulated that further studies should focus on the comparison of FDG-PET/CT with US and MRI.

### **Therapeutic management and assessment of disease course**

The therapeutic options include medical management (steroids, immunosuppressants, cytotoxic agents, specific antibodies), percutaneous or surgical intervention for large- and medium-sized arteries, as well as new therapeutic targets.

**Primary systemic large vessel vasculitides predominantly affect the large arteries such as aorta, aortic arch large vessels, renal, iliac, mesenteric, and cephalic trunk arteries.**

### **Takayasu disease and giant-cell arteritis**

The incidence of TAK is 1 to 3 per 1 million population, while GCA is quite common accounting for 100 to 250 cases per 1 million population in Europe and United States, and its incidence rate is still increasing [11,12].

Both diseases are more prevalent in women than men, with the female-to-male ratio of 9:1 for TAK and 9:2 for GCA in the European Union countries. This is similar to the prevalence of TAK in Japan (is 8:1), while in America and India female predominance is less evident (3:1 and 6:1, respectively) [12,13]

So far, the division between TAK and GCA has been rather arbitrary, and it is set at 40 years of age according to the ACR classification, and at 50 years of age according to the ARA [4,12]. Thus, patients who present symptoms of primary large artery arteritis before 40 years of age are diagnosed with TAK, while those with disease onset after 50 years of age are diagnosed with GCA. However, according to the EULAR-ACR statement, the role of age in the classification should not be overestimated.

Recently, a difference between antibody profile involved in TAK and GCA has been postulated, which may help in differentiating both types of arteritis based on laboratory findings rather than on age, especially that TAK may remain asymptomatic for a long time despite early onset. In TAK, antibodies directed against aortic endothelial cells are observed in 86% of the cases, while in GCA, monocytes and expression of MCP-1 are present [14,15].

The other difference between TAK and GCA concerns distribution of lesions [16,17]. GCA involves predominantly the side-branches of the external carotid artery – temporal and maxillary, as well as cranial arteries [16]. Moreover, in GCA, the involvement of the axillary artery and thoracic aorta is more frequent than in TAK (40% vs. 10% and 61% vs. 46%, respectively). On the other hand, mesenteric and left carotid lesions are more prevalent in TAK than in GCA (36% vs. 18% and 37% vs. 16%, respectively) [17]. Similar distribution of lesions was found in GCA and TAK with regard to the renal, iliofemoral, abdominal aorta, vertebral, and subclavian arteries [17].

**TAK involves the large arteries, leading to intimal hyperplasia which causes significant lumen stenosis and target organ ischemia.**

Numerous symptoms occurring in TAK are non-specific, resulting from the inflammatory status, including fever, weakness, night sweats, weight loss, and easy fatigue. Some patients may present with anemia or hyperglobulinemia.

Headaches, visual disturbances, retinopathy, tinnitus, vertigo, loss of balance, upper extremity claudication, syncope, or even ischemic stroke may occur as a consequence of progressive narrowing of the supraaortic arteries. If the abdominal aorta is involved, renal failure and/or secondary renovascular hypertension, lower extremity claudication, and postprandial gastrointestinal pain are often observed [18,19].

Cardiac involvement, including coronary artery narrowing, aortic regurgitation, and pericardial effusion, is quite common, accounting for 38% of TAK cases and leading to myocardial infarction, chronic heart failure, or severe aortic valve insufficiency in some patients [20]. Pulmonary artery involvement is also possible although uncommon [20].

In our series of 21 patients with TAK, the supraaortic involvement was present in 43%, abdominal aorta branches in 19%, while 38% of the subjects had lesions in both territories. Cardiac involvement included a significant coronary stenosis in 9 patients (43%), significant mitral/aortic valve disease in 24% of the patients, and pericardial effusion in 1 subject [21].

There are several different **classifications for the diagnosis of TAK.**

The modified Ishikawa's criteria for the clinical diagnosis of TAK include 3 major criteria: 1) left mid subclavian artery lesion; 2) right mid subclavian artery lesion; and 3) characteristic signs and symptoms of at least 1-month duration; and 10 minor criteria: a) high ESR; b) carotid artery tenderness; c) hypertension; d) aortic regurgitation or anuloaortic ectasia; e) pulmonary artery lesion; f) left mid common carotid lesion; g) distal brachiocephalic trunk lesion; h) descending thoracic aortic lesion; i) abdominal aorta lesion; and k) coronary artery lesion. The presence of 2 major, or 1 major and 2 minor, or 4 minor criteria suggests a high probability of TAK [22].

The ACR criteria were developed based on the comparison of 63 patients with TAK with 744 controls with other forms of vasculitis, and 6 criteria were selected for classifying patients as having TAK [13]: 1) age of patient at disease onset <40 years; 2) claudication of the extremities (especially the upper extremity fatigue and discomfort in the muscles); 3) decreased brachial artery pulse, 4) blood pressure difference in systolic blood pressure between the arms >10 mm Hg.; 5) bruit over the subclavian arteries or aorta; 6) arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia, or similar causes; the changes are usually focal or segmental. The sensitivity and specificity of the ACR criteria are 79% and 100%, respectively.

Higher accuracy is observed when hypertension as a diagnostic criterion is added to the ACR criteria (sensitivity of 100%, specificity of 99%), according to the EULAR / PRES consensus from 2005 [23].

The Takayasu Conference in 1994 proposed a classification based on angiographic abnormalities. Type I – classic pulseless type that affects blood vessels of the aortic arch; involving the brachiocephalic trunk, carotid and subclavian arteries. Type II – middle aorta (thoracic and abdominal aorta). Type III – aortic arch and abdominal aorta. Type IV – pulmonary artery in addition to any of the above types. Type V – involvement of the coronary arteries [24].

There are also two radiological classifications of TAK disease, the one by Nasu from 1975 and the other by Numano from 1994, which are used to describe TAK extent based on angiographic findings; however, they are rarely used in clinical practice [25,26].

A long-term prognosis in TAK depends on the disease location, disease activity, as well as response to treatment [10,27,28]. The reported 5-year survival in TAK varies between 65% in the case series of Andrews et al., 70% in Phillip et al., 91% in Maffei et al., and 93% in Luqmani et al. [10,27,28,29]. Maffei et al. reported also a 10-year-survival in TAK of 84% [10].

**Laboratory diagnostic tests** include standard the measurement of standard parameters such as ESR, blood count, and CRP [19,30]. Complete blood count shows normochromic normocytic anemia in 50% of the patients, leukocytosis, and thrombocytosis. CRP and ESR levels poorly correlate with disease activity. Some patients show elevated transaminase levels, hypoalbuminemia, and hypergammaglobulinemia [19,30]. The concentration of von Willebrand factor-related antigen may be elevated. Antiendothelial cell antibodies are often present, and antinuclear antibody is usually negative. Rheumatoid factor is elevated in 15% of the patients [19].

**Histopathological findings** are characterized by T-cell-mediated panarteritis, which starts in the adventitial vasa vasorum and progresses inwards, with the unknown antigen triggering monoclonal T-cell expansion [31,32]. This inflammatory process begins with perivascular cuffing of the vasa vasorum in the early stage of the disease followed by fibrosis and calcification [32]. Destruction and fibrosis coexist with the former, causing aneurysmal formation and the latter leading to the narrowing of the aorta and its branches, resulting in significant stenosis.

Useful **imaging diagnostic tools** in TAK are either CTA, MRA, or digital subtraction angiography (DSA) for the assessment of arterial lesion severity and location [9,19,33,34,35,36,37,38].

DSA provides an accurate assessment of vascular morphology and lumen, thus enabling to precisely plan endovascular or surgical treatment. The disadvantages of DSA include frequent false-negative results in patients at early stages of TAK as well as difficulties in the imaging of vascular segments distal to stenosis [35,36,39].

According to the EULAR-ACR guidelines, CTA and MRA techniques can replace standard angiography in the diagnosis of TAK (level of evidence IIa) [23,29]. According to Khendelwal et al. [34], CTA is characterized by 95% sensitivity, 100% specificity, and 96% accuracy in the diagnosis of TAK.

CTA enables early diagnosis of TAK and identification of critical stenosis of the involved arteries. Moreover, it can reveal early and late inflammatory process in the vessels, such as circumferential vessel wall thickening, thrombosis, stenosis, occlusion, vascular ectasia, aneurysms, and ulcers [35,38,39].

Color Doppler ultrasonography is a widely available noninvasive diagnostic method. This modality allows to identify the presence of stenosis in supraaortic, abdominal aorta and iliofemoral branches as well as to identify typical diffuse hyperechogenic ring-like thickening of the intimal arterial layer in the carotid arteries. Due to the limitation of color Doppler ultrasonography, there are difficulties in the assessment of TAK activity and progression of vascular lesions, which are clearly visible in CTA.

Transesophageal echocardiography is an alternative way of thoracic vessel imaging.

MRA is another modality used to visualize arterial stenosis at multiple levels, mural thrombi, thickening of aortic valve cusps, and pericardial effusions [35,36,37,38].

Both MRA and CTA show the anatomical location, degree, and extent of stenosis and vascular dilation, and patency of collateral vessels and surgical bypass grafts or stents whenever applicable [35,38].

PET alone or hybrid PET-CT may help identify vasculitis in patients referred for whole-body imaging for constitutional symptoms and fever of unknown origin. The increased metabolic activity in the vessel wall is characteristic of the active phase of TAK. FDG-PET has a reported sensitivity of up to 92% and a specificity of 89% to 100% for the detection of large-vessel vasculitis among untreated patients with elevated serum markers. The presence of wall thickening, arterial stenosis, luminal thrombus, and aneurysm cannot be assessed by PET alone; CTA and MRA are complementary to PET for a complete evaluation of the patient with aortitis [35,40,41].

### **Useful tools assessing disease activity and response to therapy**

Tripathy et al. [42] found increased percentages of high tumor necrosis factor (TNF)- $\alpha$  and low interleukin (IL)-2-producing T cells in patients with active TAK compared with those with inactive TAK and controls. Patients with TAK also show higher numbers of T cells than healthy controls [14]. Other studies reported that plasma levels of IL-6, IL-12 and IL-18 as well as metalloproteinases correlate with disease activity [43,44].

Furthermore, the correlation between levels of inflammatory markers and CTA images enables effective evaluation of disease activity. Inflammatory process can be detected at a quite early stage on contrast-enhanced CT. Typically, there is an image of the “double ring” appearance of the thickened aortic wall that corresponds well with a poorly enhanced internal ring of swollen intima and an enhancing outer ring of the inflamed media and adventitia. At milder degrees of inflammation, wall edema may not be apparent on CTA.

MRI and PET-CT are more sensitive modalities for evaluating the degree of inflammation in the aortic

wall. MRI may potentially depict wall abnormalities before luminal changes occur. Gadolinium-enhanced fat-suppressed T1-weighted images are preferred for assessing the thickening and enhancing of the arterial wall and T2-weighted images for showing high signal of the vessel wall representing mural edema. However, according to Pipitone et al. [35], wall edema may not be correlated with disease progression, and some patients showed progression of vascular lesions without accompanying edema.

PET-CT may also be useful for monitoring treatment response, reflected in a decrease of vessel wall metabolic activity. However, the masking effect of steroids must be considered when scheduling the follow-up of patients with TAK by PET.

## Patient management

The two most important aspects of treatment in TAK that affect prognosis are remission of the inflammatory process and control of hypertension. The prognosis also depends on the occurrence of complications such as retinopathy, aneurisms, and aortic insufficiency.

Strict management of traditional cardiovascular risk factors such as dyslipidemia, hypertension, and lifestyle factors that increase the risk of cardiovascular disease is mandatory to minimize secondary cardiovascular complications. These complications are the major cause of death in TAK. Hypertension is treated with antihypertensive agents, preferably calcium channel inhibitors, and aggressive therapy is necessary to prevent complications. Low-dose aspirin may have a therapeutic effect in large-vessel vasculitis. Antiplatelet agents and heparin may prove useful in preventing stroke. Warfarin has also been used.

Pregnancy may exacerbate hypertension and/or cardiovascular complications and can increase the risk for maternal and fetal morbidity and mortality. Diet modification is necessary to manage hypertension or renal failure.

**Anti-inflammatory management** includes administration of corticosteroids, immunosuppression (methotrexate, cyclophosphamide, mycophenolate mofetil, and/or anti-TNF- $\alpha$  monoclonal antibodies (infliximab) [18,30]. Duration of treatment as well as dosage largely depends on the experience of a given center.

The first-choice treatment is usually oral corticosteroid, usually prednisolone/prednisone, with the initial dose of 1 mg/kg/d preferably for 3 months, then on alternate days. The steroid therapy should be continued preferably for 1 year since remission. Then, steroid dose is gradually reduced, and the inflammatory process is monitored thereafter. Subsequently, the corticosteroid treatment can be discontinued. However, the relapse rate of corticosteroids is estimated at 50%–80%.

When steroids are ineffective for 3 months since initiation of treatment, more advanced immunosuppression is indicated with methotrexate, azathioprine, or cyclophosphamide.

Methotrexate was used at a low dose of 0.3 mg/kg/wk (not to exceed 15 mg/wk), increasing every 1 to 2 weeks to 25 mg/wk with prednisolone at 1 mg/kg/d. Combined therapy resulted in remission rates of 81%; of those patients for whom remission of the disease was achieved, 50% had sustained remissions of 4 to 34 months (mean 18 months). This treatment requires supplementation of folic acid.

Cyclophosphamide is used at a dose of 2 mg/kg/d orally for patients with the most severe and refractory disease states. A single-center experience from Turkey suggests that induction with cyclophosphamide and corticosteroids is an effective and safe treatment for children with TAK. In 3 of 4 patients that had received cyclophosphamide (maximum total dose, 150 mg/kg) in combination with prednisolone for 12 to 18 months, disease remission was observed [45]. Intravenous treatment with cyclophosphamide has also been reported to be beneficial. Despite limited therapeutic data, treatment with cyclophosphamide should be considered for patients with life-threatening manifestations.

Mycophenolate mofetil (MMF) is used as an alternative treatment. Shinjo et al. followed 10 consecutive patients with active TAK who received oral treatment with MMF (at a dose of 2 g/d) for a mean duration of 23.3 months together with tapering doses of prednisolone. Clinical activity resolved in all patients, except in 1 who withdrew from the study because of headache, attributed to the medication. Therapy with MMF allowed tapering of the corticosteroid dose in 9 patients and significant reduction of ESR and CRP levels.

Hoffman et al. [46] reported the results of an open-label, multicenter study with infliximab (TNF- $\alpha$  receptor blocker) in 15 patients with TAK who failed to respond to corticosteroids or alternative immunosuppressive therapies. Treatment with infliximab resulted in clinical improvement in 14 and sustained remission in 10 patients, who were able to discontinue glucocorticoid therapy [46]. While the initial results are promising [47,48], the role of TNF inhibition in treating initial disease or relapses of TAK has not yet been established.

Other agents that were examined in a number of patients as alternative therapy include azathioprine and cyclosporine [30].

Recently, there have been some promising reports regarding the blockade of the soluble IL-6 receptor (S-IL-6R) with the humanized monoclonal antibody tocilizumab as well as with a chimeric IgG1 antibody (rituximab) that binds to CD20 expressed on the surface of B cells; however, no large randomized control trials or large multicenter trial have confirmed this finding.

**Endovascular and surgical treatment.** Endovascular revascularization and open surgery with bypass grafting are often used to prevent primary and secondary ischemic events in patients with severe arterial occlusive disease confirmed by CTA, MRA, and / or DSA. Thoracic or abdominal aneurysms, when larger than 5 cm in diameter, should be also treated operatively. Other procedures include aneurysm clipping and revascularization.

The primary success rate of these procedures is high, with an acceptable rate of major and minor complications.

However, the late outcome is mostly determined by the level of disease control and remission of inflammatory process. In the few series of studies, including between 4 and 56 subjects, the occlusion and restenosis rate after angioplasty alone was estimated between 13.5% and 32.7% in a relatively short follow-up period of 1 to 2 years [30,49]. The respective values for stented lesions were between 9% and 42.8% at 1- to 2-year follow-up [49]. On the other hand, the restenosis occlusion rate at 5 years was 67% in a study by Fava et al.[50] In our study of 21 TAK subjects who underwent 39 endovascular procedures, the primary stent patency was 48% during the mean follow-up period of 7 years, while symptomatic lesion progression was observed in 52% of the subjects [21].

In a series involving between 10 and 31 patients with TAK treated with bypass grafting, perioperative mortality rate was between 0% and 7% [49], and the restenosis and occlusion rates were between 5% at 6 months, and 8% to 31% in the time period between 3 and 6.2 years, respectively [49].

**Giant-cell arteritis (Horton disease, temporal artery arteritis)** GCA is the most common form of aortitis in North America, accounting for more than 75% of the cases (incidence, 150–200 / million) [4,11,12,51]. GCA is related to inflammatory cell proliferation in the vessel wall, affecting predominantly the aorta and aortic arch artery, leading to aortic aneurysm and rupture, visual loss, cerebral ischemia, or migraines. The most often involved arteries in GCA include temporal, vertebral, posterior ciliary, and ophthalmic arteries [17,19,51].

Cranial symptoms (tenderness, headache), jaw claudication, visual changes due to an ischemic optic neuropathy (20%–30% of the patients), and neurological changes are commonly observed [12,51]. The main symptoms include blurry vision, new-onset pain in the temporal region with erythema and tenderness, balance disturbances, and general symptoms of systemic inflammation, as well as polymyalgia rheumatica. Visual loss (irreversible, usually monocular blindness) is the most threatening complication. Large artery occlusive disease, including carotid or subclavian arteries, may also occur. Thoracic aortitis with aneurysms occur in approximately 15% of the patients but is generally a late complication of GCA.

GCA is diagnosed based on the 1990 ACR criteria where 3 of 5 criteria are required for diagnosis, with sensitivity of 94% and specificity of 91 %: 1) age older than 50 years; 2) recent-onset localized headache; 3) temporal artery pulse attenuation or tenderness; 4) ESR >50 mm/h; 5) arterial biopsy: necrotizing vasculitis; and 6) no imaging findings are required for diagnosis [12].

The gold standard for the diagnosis of GCA is ultrasound-guided temporal artery biopsy (according to the EULAR-ACR guidelines level of evidence Ia) [29].

CTA or MRA may facilitate the diagnosis [35,36,52,53,54]. Long-segment involvement with

significant wall thickening and smooth tapering proximal and distal to the lesion on CTA and MRA are the classic radiological findings.

CTA and, in particular, MRA can demonstrate vessel wall edema, which reflects disease activity [35,36]. They can also reveal luminal changes similar to TAK, such as stenosis, occlusion, dilatation, aneurysm formation, calcification, and mural thrombi thoracic aortic aneurysm. FDG-PET has been shown to be sensitive for extracranial vasculitis but not for intracranial vasculitis owing to its poor spatial resolution. FDG-PET reveals abnormal uptake in the aortic arch or large thoracic arteries in more than half of the affected patients (sensitivity, 56%; specificity, 98%; positive predictive value, 93%; negative predictive value, 80%) [41,51,52,53].

US is useful in assessing extracranial vessels, showing an increased diffuse, circumferential intima–media complex in transverse sections with the “macaroni sign” reflecting inflammatory edema [51,54].

## Management

GCA is chronic and the clinical course is highly variable. Simultaneous prescription of antiplatelet or anticoagulant therapy was suggested to reduce the occurrence of ischemic events. A standard therapy, high-dose oral steroids (40–60 mg daily) for 1 to 2 years, results in rapid improvement but is associated with high relapse rate [51]. Unlike TAK, additional immunosuppressive therapy does not affect the course of the disease; however, adjunctive immunosuppressive agents, e.g., methotrexate, allow to reduce the use of glucocorticoids. Approximately 50% of the patients experience subsequent disease flares.

The approach to revascularization is similar to that in TAK. Aortic aneurysm complicated by acute dissection or aortic valve insufficiency is associated with decreased survival [55].

**Isolated aortitis** is a term for rare primary inflammatory process limited to the aorta, affecting 5.9 persons per 100 000 population [56]. It is characterized by infectious origin (pyogenic infection, syphilitic, or tuberculous aortitis) or noninfectious origin (TAK, GCA, Marfan syndrome, Behçet’s disease, ankylosing spondylitis, relapsing polychondritis, rheumatoid arthritis, and idiopathic isolated aortitis) [56]. Isolated aortitis accounts for about 4% of all ascending / descending thoracic aorta and/or abdominal aorta aneurysms referred for surgery [57].

Numerous patients are diagnosed postoperatively after histopathological examination of the surgical specimen of aneurysm. In a series of patients reported by Chowdhary et al. [58], 50 of 75 cases of noninfectious aortitis from patients who had undergone surgical repair were classified as idiopathic aortitis [58]. In the remaining patients, GCA/PMR (n = 15), inflammatory arthritis (n = 2), TAK (n = 1), Crohn’s disease (n = 1), bicuspid aortic valve (n = 3), and Marfan syndrome (n = 1) were recognized.

ESR and CRP are usually elevated although insignificantly [56].

Histopathological examination of the aortic wall in idiopathic aortitis reveals a paucity of inflammatory

infiltrate but multiple foci of disruption of elastic lamellae, even in the areas unaffected by inflammation. There is increased expression of matrix metalloproteinase (MMP)-2 in the temporal artery as well as aortic tissue, whereas MMP-9 was found only in temporal artery specimens with active inflammation [56]. Thus, the process of aneurysm formation in systemic inflammatory diseases is complex, multifactorial, and likely involves immune and proteolytic pathways.

Although imaging is rarely used for primary diagnosis of thoracic large-vessel vasculitis, it plays an important role in differentiating between infectious and noninfectious vasculitis, as well as monitoring disease activity or guiding biopsy.

The imaging modalities to show aortic vasculitis are CTA, MRA, and transoesophageal echocardiography [36,51,52,56]. There is also a growing role of PET [9,36,40,41]. Any uptake of FDG in the aortic wall is abnormal because of inflammatory or infectious processes [36], and no specific protocol is needed for assessing vasculitis with PET-CT [36]. Although inflammatory activity is well appreciated on images, morphological assessment is limited because of a relatively low spatial resolution; thus, nuclear imaging studies provide substantial benefit when obtained in conjunction with either CT or MRI, increasing the sensitivity and specificity of this test.

CT is used for the assessment of aortic wall thickness and regularity, aortic diameter, mural calcifications, and aortic branches. CTA can also be used as a follow-up tool to assess treatment response and/or activity of the disease [36].

## Primary systemic vasculitides of the middle- and small-sized arteries

KD and PN account for the necrotizing primary systemic vessel arteritis, which affects predominantly the middle-sized arteries such as the renal and cerebral arteries [1,3–6,59,60].

Small-vessel vasculitis affects intraorgan arteries and comprises HSS, HSP, mixed cryoglobulinemia, Goodpasture's disease, isolated cutaneous leukocytoclastic vasculitis (hypersensitivity vasculitis), and ANCA-associated necrotizing vasculitides such as WG, CSS, MPA and its renal limited form: idiopathic pauci-immune necrotizing crescentic glomerulonephritis (RLV) [6,61–65].

### Kawasaki disease

KD typically affects infants and young children and it is common in Japan and other Asian countries [23,59]. The incidence of KD is 1/270 000 in the United States and 8/100 000 in the United Kingdom, with the highest prevalence in Asia (Japan: 218.6 per 100 000 children <5 years of age). The disease is rare in Caucasians; however, the incidence rate has been increasing over the last few decades. The peak onset of KD is at 9–11 months of age in infants, and 70% of all cases occur in patients younger than 3 years. The female-to-male ratio is 3:1 [23,59].

KD is considered to be a systemic necrotizing vasculitis disease, and it comprises primarily medium-sized arteries: coronary, renal, and cerebral.

The diagnosis of KD is based on the presence of 5 of the 6 major criteria according to the Japan Kawasaki Disease Research Committee: 1) fever persisting for 5 days or more; 2) bilateral conjunctival congestion; 3) changes in the lips and oral cavity: reddening of the lips, strawberry tongue, diffuse injection of the oral and pharyngeal mucosa; 4) polymorphous exanthema; 5) changes in the peripheral extremities (initial stage: reddening of the palms and soles, indurative edema; convalescent stage: membranous desquamation from the fingertips); and 6) acute nonpurulent cervical lymphadenopathy [59]. The EULAR/PRES consensus criteria added perineal desquamation as a diagnostic criterion in children at the Vienna Consensus Conference on the Classification of Childhood Vasculitides [65].

Patients having four of the principal symptoms can be diagnosed as having KD when a coronary aneurysm or dilation is detected by two-dimensional echocardiography or coronary angiography.

Acute cardiac manifestations occur in about 13% to 15% of the cases [59,66]. The mortality rate has markedly decreased to 0.01%. Death in KD is most frequently attributable to ischemic heart disease caused by thrombosed coronary artery aneurysms, secondary to coronary arteritis. Coronary arteritis in KD begins as edematous dissociation of the tunica media 6 to 8 days after the onset of KD, characterized by proliferative granulomatous inflammation that consists of marked accumulation of monocytes/macrophages. On about the 10th day of the disease, lymphocyte and macrophage infiltration into the arterial wall from the luminal and adventitial sides begins, immediately leading to inflammation of all layers of the artery. Structural components of the artery undergo intense damage; the artery then begins to dilate. The aneurysm is easy for thrombosis, and thrombotic occlusion is found in the coronary artery aneurysm on autopsy of numerous patients with advanced stage of KD. Inflammatory cell infiltration continues until about the 25th day of the disease, after which the inflammatory cells gradually decrease in number and almost completely disappear by about the 40th day of the disease. Scar from inflammation remains for a long time thereafter.

Patients should undergo echocardiography initially and every few weeks, and then every 1 or 2 years to screen for progression of cardiac involvement.

Other complications include aortic aneurysm, aneurysm of the axillary, renal, innominate, iliac and femoral arteries, gastrointestinal complications (intestinal obstruction, ischemia, acute abdomen that should be differentiated with HSP), ophthalmologic changes (uveitis, iridocyclitis, conjunctival hemorrhage, optic neuritis, amaurosis, and ocular artery obstruction) [59,65,66]. The neurological complications include meningoencephalitis, subdural effusion, cerebral hypoperfusion, brain ischemia, manifesting with seizures, chorea, hemiplegia, mental confusion,

lethargy, and coma. Other neurological complications from cranial nerve involvement are reported as ataxia, facial palsy, and sensorineural auditory loss. Behavioral changes are thought to be caused by localized cerebral hypoperfusion.

Treatment comprises high-dose intravenous immunoglobulin for acute stage. Currently, immunoglobulin is administered to 85% of children with acute KD, which reduces the incidence of coronary artery disorders and the mortality rate. About 20% of the patients relapse to this treatment and develop coronary complications. Although steroids, neutrophil elastase inhibitors, cyclophosphamide, plasma-exchange and anticytokine antibody therapy (infliximab) have been tried, the additional or alternative management of patients nonresponsive to immunoglobulin remains controversial [66]. Corticosteroid use is associated with an increased risk of coronary artery aneurysm, and it is generally contraindicated. Another treatment may include the use of infliximab (Remicade). Infliximab works by binding TNF- $\alpha$ .

Aspirin therapy is started at high doses until the fever subsides, and then it is continued at a low dose after discharge, usually for 2 months to prevent formation of blood clots (caution Reye's syndrome) [66].

The worst prognosis occurs in children with giant aneurysms. This severe outcome may require further treatment such as percutaneous transluminal angioplasty, coronary artery stenting, bypass grafting, and even cardiac transplantation [66].

### **Polyarteritis nodosa (PN)**

PN is a systemic medium-sized vessel necrotizing multifocal vasculitis, with the incidence of 3/100 000 population, with male predominance. It is more frequently observed in individuals between 40 and 60 years of age.

The ACR criteria for the diagnosis of PN include at least 3 of the following: 1) weight loss >4 kg; 2) livedo reticularis; 3) testicular pain or tenderness; 4) myalgias, weakness or leg tenderness; 5) motor polyneuropathy; 6) hypertension; 7) elevated blood creatinine or blood urea nitrogen; 8) hepatitis B antigen or antibodies in the serum; 9) aneurysm or occlusion of the visceral arteries; and 10) granulocytes in small- or medium-sized arteries on vessel wall biopsy [60].

The EULAR/PRES consensus provided the following diagnostic criteria of PN in children: histological evidence of necrotizing vasculitis in medium- or small-sized arteries or angiographic abnormalities (aneurysms, stenoses, or occlusion) as a mandatory criterion, plus 1 of the following 5: skin involvement, myalgia or muscle tenderness, hypertension, peripheral neuropathy, or renal involvement [65].

Fully symptomatic PN presents with sudden onset arterial hypertension, abdominal pain (50% of the patients) due to pancreatitis, appendicitis, hemorrhage or perforation, and renal function deterioration (renal infarction, minor proteinuria, 60% of the cases) [65,67]. The other clinical manifestations include rapid weight loss, paralysis of the peripheral nerves (50%–70% of the cases), arthralgia (almost 100%), myalgia (50%)

cardiac (30%), less frequently cephalalgia, ocular, and genital (orchitis) manifestations [2,60, 65,66].

In the majority of the cases, there is no known triggering event, although the disease may develop after hepatitis B infection [60]. The diagnosis should be confirmed by muscular, neuromuscular, or subcutaneous nodule biopsy [68].

Angiography may also be performed (except in cases of severe renal failure); it shows the presence of microaneurysms of the digestive and renal arteries.

Treatment is based on hypertensive agents, corticosteroids, and cyclophosphamide in selected severe cases after exclusion of viral infection. Antiviral treatment with plasmapheresis is recommended for patients with viral infection. Treatment is efficient in more than 80% of the patients and remission can be obtained within 1 to 3 years. The prognosis is good when treatment is appropriate. The 5-year survival rate is over 80% [2].

In case of thrombotic and hemorrhagic complications, surgery is recommended. The disease is fatal with a median survival rate of 6 years, when untreated [2]. The main cause of death is hyperuricemia, circulatory insufficiency, cerebral or digestive system hemorrhage, and multiorgan insufficiency.

### **ANCA-Associated Vasculitides (MPO-ANCA and PR3-ANCA)**

ANCA-associated vasculitides are characterized by necrotizing inflammation of the small vessels in conjunction with the presence of ANCA directed either to proteinase 3 (PR3) or myeloperoxidase (MPO).

ANCA are found in the serum of patients with WG in over 90% of the cases, with RLV in 67%, with MPA in 70%, and with CSS in 40%, and they are used as diagnostic markers of these diseases [69,70,71]. PR3-ANCAs are predominant in WG, whereas MPO-ANCAs predominate in MPA, RLV, and CCS.

A biopsy of the affected organs is useful in diagnosis and further management.

A normal angiogram, CTA or MRA, does not exclude this form of vasculitides because the affected vessels are often smaller than the resolution of angiography.

All small-vessel vasculitides may present with symptoms associated with ear, nose, and throat (66% of the cases), respiratory tract (41%), nervous system (30%), gastrointestinal tract (11%), and renal insufficiency. In CCS, cardiac involvement may be observed, which is associated with poor prognosis.

Medical treatment comprises first-line glucocorticosteroids, cyclophosphamide in more advanced and resistant ANCA-associated vasculitides, and MMF for remission induction or in patients who cannot be treated with cyclophosphamide [72,73].

A meta-analysis of studies on systemic vasculitis performed by the EULAR showed that the factors affecting remission, relapse, renal, and overall survival included the type of immunosuppressive therapy used, pattern of organ involvement, presence of ANCA, older age, and male sex [74]. Overall remission rates vary between 30% and 93% in WG, 75% and 89% in MPA,

and 81% and 91% in CSS. The 5-year survival for WG, MPA, and CSS is 74% to 91%, 45% to 76%, and 60% to 97%, respectively [74]. Relapse (variably defined) is common in the first 2 years but the frequency varied: 18% to 60% in WG, 8% in MPA, and 35% in CSS [74].

**CSS** is an antineutrophil cytoplasmic autoantibody-mediated vasculitis, eosinophil-rich, with the estimated incidence of 5 to 8 per 1 million population. CSS is more frequently diagnosed in asthmatic patients (1/15000) [71]. The onset usually occurs between 15 and 70 years of age [71]. For clinical diagnosis, at least 4 of the following criteria must be met: 1) asthma; 2) history of allergy; 3) eosinophilia (>10%); 4) mono- or polyneuropathy; (5) migratory or transitory pulmonary infiltrates; and (6) sinusitis [61].

CSS affects also other organs including the kidneys, skin (two-thirds of the cases), lymph nodes, muscle, heart, and digestive and central nervous systems. Neurological involvement occurs in 62% of the cases, manifesting as stroke and intracerebral hemorrhage, which are significant causes of death. Cardiac involvement may occur as myocarditis, pericardial and endocardial involvement, or dilated cardiomyopathy.

Renal manifestations occur in 25% to 45% of CSS patients and are usually less severe than in the other forms of ANCA-associated vasculitis. Rapidly progressive renal failure is a rare finding in CSS, in contrast to WG and MP. The most typical picture is pauci-immune focal and segmental necrotizing glomerulonephritis, with or without crescents, which usually involve <50% of the glomeruli. Eosinophilic tubulointerstitial nephritis, although not specific to CSS, may be present.

A biopsy of the affected organs, including small arteries, arterioles, or venules, shows a vasculitis with extravascular eosinophils, which confirms the diagnosis, necrotizing vasculitis and sometimes granulomatous inflammation.

Abnormalities on chest radiography are common and include parenchymal abnormalities, pleural effusion, and bronchial wall thickening. Ground-glass opacities and consolidations, pulmonary micronodules, interlobular septal thickening, linear opacities, bronchial wall thickening and/or bronchial dilatation, and pleural effusions can be identified on high-resolution CT (HRCT) [75].

According to the French Vasculitis Study Group, there are 5 factors that are related to a poor outcome (Five-Factor Score [FFS]) in CSS: 1) elevated serum creatinine >140  $\mu\text{mol/L}$  (>1.58 mg/dL); 2) proteinuria (>1 g/d); 3) severe gastrointestinal tract involvement; 4) cardiomyopathy; and 5) central nervous system involvement [71].

The prognosis worsens with the increasing number of the risk factors, and estimated 5-year mortality rate is 26% when one factor is present [71]. Thus, treatment of CSS should be tailored to individual patient needs on the basis of prognosis. In subjects who receive 0 points, a corticosteroid monotherapy should be administered, usually prednisone as initial therapy at an starting dose of 1 mg/kg/d. Other immunosuppressive regimens, such as those using cyclophosphamide, are

used as first-line therapy for patients with aggressive disease (FFS >0). Cyclophosphamide is also added to steroids in cases of steroid-resistant, steroid-dependent, or frequently relapsing diseases. Furthermore, the optimal duration of treatment with cyclophosphamide is disputable; however, a lower relapse rate was observed when patients received cyclophosphamide for 1 year, compared to 4 to 6 months.

The other agents include methotrexate and MMF; in severe cases, infliximab and etanercept may be added for a limited period [76].

**Wegener's granulomatosis (WG).** The incidence of WG is 2 to 3 per 100 000 population with an annual incidence between 2 and 12 cases per million [62]. The typical age of onset is the 5th decade of life [62]. It is a small-vessel necrotizing vasculitis characterized by the association of inflammation of the vessel wall and peri- and extravascular granulomatosis, confirmed by the biopsy of the skin, nose, lungs, or kidneys.

The ACR criteria for the diagnosis of WG include the presence of 2 or more of the following: 1) nasal or oral inflammation (oral ulcers or purulent or bloody nasal discharge); 2) abnormal chest radiograph (nodules, fixed infiltrates or cavities); 3) microhematuria (>5 blood cells in field) or red cell casts in urine sediment; and 4) granulomatous inflammation on biopsy [62].

Typical clinical presentation of WG comprises: 1) ear, nose, and throat manifestations in 70% to 100% of the patients (persistent nasal obstruction, sinusitis, hemorrhagic and/or crust-forming rhinitis, serous otitis media, hearing loss, and/or saddle nose deformity), 2) pulmonary involvement (nodules, infiltration, and alveolar hemorrhage), 3) renal involvement (typically extracapillary rapidly progressive necrotizing glomerulonephritis) [77,78]. Neurological symptoms such as peripheral polyneuropathy occur in 11% to 68%, while cerebral or meningeal involvement in 2% to 8% of the cases (headaches, sensorimotor deficit, hemiplegia, and epilepsy). Cutaneous lesions (purpura, papules, and ulcers) are found in 10% to 50% of the patients. Ocular anomalies account for 14% to 60% of the cases. Cardiac involvement is less common (<10% of the patients) and is often asymptomatic; however, it can present with pericarditis, coronary vasculitis, and valvular lesions [77,78]. General signs such as asthenia, fever, arthralgia, myalgia, and/or weight loss are frequent.

Chest radiographs may show pleural effusion, opacities and consolidations, nodules with or without cavitations, hemorrhage on radiography or HRCT [78]. In renal involvement, color Doppler ultrasonography shows large echogenic kidneys, CT shows reduced nephrogram, rarely pseudotumor due to infiltration, and MRI shows infiltrative lesions [77].

Corticosteroids in combination with intravenous administration of cyclophosphamide, initially every 2 weeks and then every 3 weeks until the patient is in remission, is the first-line treatment. Azathioprine or methotrexate is then used as a maintenance therapy. Rituximab, anti-TNF- $\alpha$ , and abatacept are currently under study with promising results. With treatment, disease remission is achieved in 85% of the cases

but recurrence occurs in half of the patients during 5 years after diagnosis.

**MPA** is an inflammatory, necrotizing, systemic vasculitis that affects predominantly small vessels (i.e., small arteries, arterioles, capillaries, and venules) in multiple organs [3,6]. MPA has an annual incidence of approximately 1/100 000 and a mean age of onset of 50 to 60 years. Pediatric-onset MPA (<10 years of age) is uncommon [65].

There is no agreement as to diagnostic criteria. The ACR, Sørensen, and Chapel Hill criteria did not reliably differentiate WG from MPA [79].

The early clinical manifestations include fever, arthralgias, myalgias, fatigue, and/or loss of appetite. As the disease progresses, 90% of the patients show renal involvement with pauci-immune necrotizing and crescentic glomerulonephritis, which can have a rapidly progressive course if not treated promptly. Pulmonary involvement (alveolar hemorrhage, pleural effusion) is frequent and manifests with symptoms such as dyspnea, cough, or hemoptysis. Gastrointestinal involvement can present with abdominal pain, nausea, or vomiting, and can be life-threatening in case of peritonitis, ischemia, or perforation. Neurological symptoms and signs (mainly mononeuritis multiplex), dermatologic (mainly leukocytoclastic angiitis; see this term) and musculoskeletal (arthralgias, myalgias) involvement, and ocular signs (e.g., episcleritis, retinal vasculitis, uveitis) are also observed. Cardiovascular involvement (e.g., pericarditis, cardiac insufficiency) is rare.

Diagnosis is based on the clinical presentation and specific blood tests, which show MPO-ANCA in 50% of the patients, PR3-ANCA in 40% of the cases, and no ANCA in 10% of the cases. Elevated CRP levels, leukocytosis, and anemia are usually present. Urine tests can show proteinuria, hematuria, and leukocyturia.

Renal, pulmonary, and skin biopsy can support the diagnosis. Pathological findings in MPA are characterized by segmental vascular necrosis with infiltration of neutrophils and monocytes, typically with leukocytoclasia and accumulation of fibrin.

Treatment consists of three phases: induction of remission, maintenance of remission, and treatment of relapse. The first-line induction therapy consists of oral or intravenous administration of high-dose corticosteroids with immunosuppressive treatment (e.g., cyclophosphamide or rituximab). In the case of severe renal disease and major alveolar hemorrhage, plasma exchange is beneficial. Maintenance treatment consists in continuation of cyclophosphamide or rituximab, or substitution with azathioprine. Relapses are treated with increased or reinstated immunosuppression. In the case of renal failure, dialysis and/or renal transplantation are appropriate.

**HSP** is the most common systemic vasculitis of childhood with a reported incidence of 10 to 20 cases per 100 000 children per year, while 1 per million in the adult population [63]. It is most common in children under 5 years of age. The male-to-female ratio is 1.5:1. The prognosis is generally good.

Presenting symptoms at the initial diagnosis include hypertension, palpable purpuric rash

(symmetrical and primarily localized to the buttocks and legs; 100% of the cases), arthralgia (45%), joint swelling (predominantly involving the knees and ankles, 19%), abdominal pain (9%), fever (5%), lethargy (1%), bloody stools (1%), hematuria (1%), scrotal pain (1%), and limp (1%) [80]. Other symptoms involve the gastrointestinal (hepatomegaly, perforation, hemorrhage, enteropathy), pulmonary, renal, or cerebral systems. Patients may be nephrotic, nephritic, or may have abnormal renal function. Renal impairment is the most important determinant of the outcome in HSP. Owing to the asymptomatic course of HSP-associated nephritis, most centers provide a program of regular urine and blood pressure monitoring for up to 12 months [80].

Other manifestations are rare but may include headaches, seizures, paresis, orchepididymitis, urethritis, pancreatitis, myositis, episcleritis, pulmonary bleeding, and myocarditis [80,81,82].

In the pathomechanism of HSP, the increased secretion and polymerization predominantly of immunoglobulin A1 (IgA1) is observed, followed by the deposition of IgA-dominant immune complexes in the capillaries and arterioles of the skin, nervous system, kidneys, and gastrointestinal tract.

Skin and kidney biopsies reveal tissue deposition of IgA with circulating IgA immune complexes [81,82,83].

Diagnostic tests include urinalysis: (isolated proteinuria in 37% of the cases; hematuria in 2%). Persisting proteinuria and progressive chronic renal failure occur in the minority of the patients. Nephritic and/or nephrotic syndromes are more commonly observed at presentation in HSPN. End-stage renal failure caused by HSPN is infrequent in adults, but it reached 5.1% in a large series of children from Necker-Enfants Malades Hospital [80].

The treatment is symptomatic. The use of steroids and/or immunosuppressants is controversial but may be considered in case of severe gastrointestinal or renal manifestations.

## Secondary systemic vasculitides

Secondary vasculitides include systemic lupus erythematosus, rheumatoid arthritis, scleroderma, polymyalgia, Sjögren's syndrome, ulcerative colitis, Crohn's disease, cancer (e.g., lymphoma), viral infections (herpes, hepatitis B, hepatitis C, parvovirus B19), bacterial infections (e.g., *Streptococcus pneumoniae*, *Pneumococcus meningitidis*), and fungal infections (*Aspergillus*) [1]. Among medications include antiviral agents, sulphonamide, vaccinations, sera, selective serotonin reuptake inhibitors, sympathomimetics, anti-epileptic drugs (carbidopa, levodopa), and thiouracil are listed [1]. Also cocaine, heroin, and amphetamine are associated with a higher risk of vasculitis. The differentiation between primary and secondary vasculitis is often problematic.

In conclusion, the current classification, diagnostic algorithms, and management of primary systemic

vasculitides, although useful, have important limitations that affect their validity with respect to clinical research and practice. The ACR criteria were developed before the widespread use of ANCA testing, which facilitates the diagnosis of WG, MPA, and CSS and helps exclude the diagnosis of PAN. No distinction has been made between PAN and MPA.

A currently ongoing study, the Diagnosis and Classification of Vasculitis (DCVAS), aims to reclassify primary systemic vasculitides and optimize their management. The study is supported by grants from the Vasculitis Foundation, ACR, and EULAR.

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## Effect of autoimmunity and systemic inflammation on thromboembolic complications in patients with connective tissue diseases

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### History of research

In 1972, Einstein and Rapaport [1] used the term “lupus anticoagulant” (LA) while describing a coagulation inhibitor found in some patients with systemic lupus erythematosus (SLE). It soon occurred that lupus anticoagulant, acting in vitro as an anticoagulant, may cause thromboembolic complications in vivo. Further studies, including those that discovered anticardiolipin (aCL) antibodies in 1983, threw the light on the connection between the presence of aCL antibodies and thromboembolic events. In 1987, the term “antiphospholipid syndrome” was introduced. Since 2006, the modified criteria for diagnosing the syndrome have been used [2]. In 1990, a protein named  $\beta_2$ -glycoprotein I ( $\beta_2$ GPI) was described. The presence of anti- $\beta_2$ GPI antibodies is also connected with higher thromboembolic risk.

### Antiphospholipid syndrome

The laboratory criteria for the diagnosis of antiphospholipid syndrome include the presence of LA (in 2 measurements at a 12-week interval) and the presence of aCL or anti- $\beta_2$ GPI antibodies.

A precise mechanism of clot formation in patients with antiphospholipid syndrome is unknown. It is postulated that antiphospholipid antibodies may interact

with protein C and components of the complement system, disturb protective anticoagulant action of annexin A5, and activate numerous cells such as platelets, monocytes, and endothelial cells, changing their phenotype into procoagulant [3]. It was proved that in patients with high antiphospholipid antibody titer, endothelial damage causes significantly higher thrombin generation than in people without those antibodies [4].

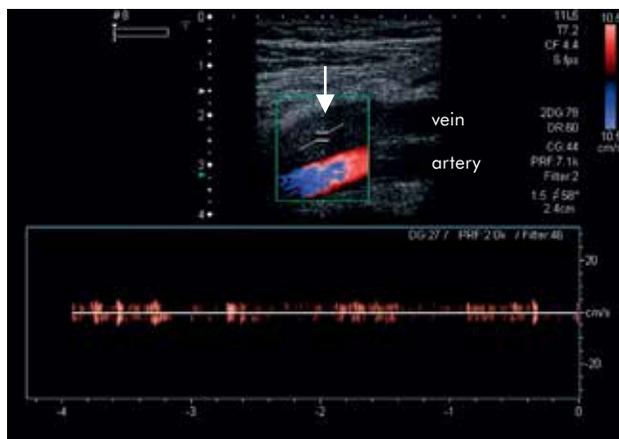
The most common clinic manifestation of antiphospholipid syndrome is venous thrombosis, particularly deep vein thrombosis of the lower limb (fig. 1). Arterial thrombosis, which occurs rarely, is related mainly to the cerebral arteries, and may be present in the coronary or other peripheral arteries [5].

Predicting the risk factors of the next thrombotic event seems particularly relevance in patients with antiphospholipid syndrome. The first meta-analysis of 25 trials revealed that the highest risk concerns patients with LA and medium or high titer of immunoglobulin G (IgG) class aCL antibodies [6]. The recent trials have shown that “multiple positive patients” (that is, “double positive” [LA + aCL IgG or LA + anti- $\beta_2$ GPI IgG] or “triple positive” [LA + aCL IgG + anti- $\beta_2$ GPI IgG]) have a significantly higher risk of recurrent thrombotic complications [7].

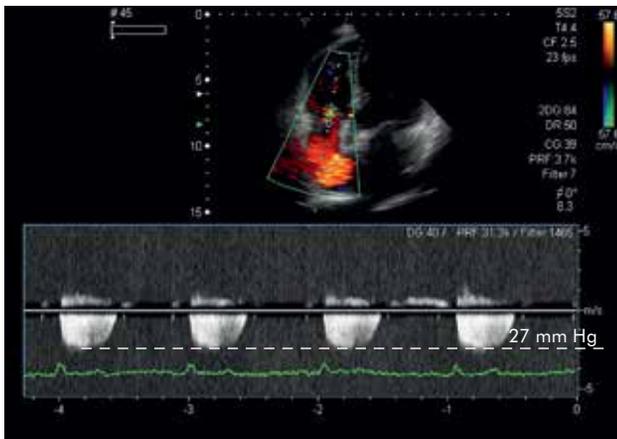
### Systemic lupus erythematosus

An increased risk of thromboembolic events in patients with SLE results from the common presence of antiphospholipid antibodies in these patients. The latest studies have shown that the elevated levels of IgG class aCL and anti- $\beta_2$ GPI cause an increase in systolic right ventricular pressure (fig. 2, 3) [8]. A higher incidence of aCL antibodies was also observed in patients with SLE and pulmonary hypertension compared with patients with normal pulmonary artery pressure [9]. In another study, in patients with mixed connective tissue disease, pulmonary hypertension was connected with a higher level of anti- $\beta_2$ GPI antibodies [10]. High pulmonary artery systolic pressure observed in patients with high titers of aCL antibodies may be a result of microthrombosis/microembolism, leading to the elevation of pulmonary resistance, raised right ventricular systolic pressure, and right ventricular enlargement. It should be emphasized that the relative risk of pulmonary embolic events in patients with SLE in the first year from diagnosis is higher than in the general population and it equals 10.23 [11].

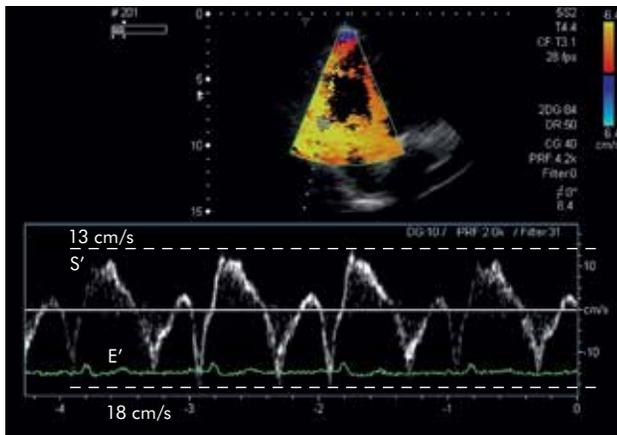
The connection between myocardial perfusion defects (showed in single-photon emission computed tomography [SPECT]) with elevated aCL IgG and anti- $\beta_2$ GPI IgG antibodies has also been described in patients with SLE [8]. It is highly probable that cardiac perfusion disturbances in these patients are caused by small clots in the coronary microcirculation that cannot be detected by noninvasive techniques. Those clots cause persistent (present at rest and during exercise) blood flow disturbances in small myocardial areas. These data are consistent with those from a



**Fig. 1.** Doppler ultrasonography. Thrombosis in the femoral vein in a patient with antiphospholipid syndrome. Thrombus is present in the lumen of the femoral vein (arrow); Doppler ultrasound confirms the lack of flow in the vein and normal, color-coded flow in the artery



**Fig. 2.** Transthoracic echocardiography. Apical view. Elevated right ventricular systolic pressure in a patient with systemic lupus erythematosus (SLE); high titer of aCL IgG (26.11 RU/mL) and anti-b2GPI IgG antibodies (3.66 RU/mL). The risk of pulmonary hypertension is significantly increased in patients with SLE if aCL IgG >20 RU/mL or anti-b2GPI IgG >3 RU/mL (see text and [11]). Tricuspid regurgitant flow gradient is 27 mm Hg; right ventricular systolic pressure is 37 mm Hg



**Fig. 3.** Transthoracic echocardiography. Tissue Doppler imaging. Despite the elevation of the right ventricular systolic pressure in this patient, the right ventricular function is normal. Tissue Doppler imaging shows the maximal systolic velocity of the tricuspid annulus (S') of 13 cm/s and the maximal early-diastolic velocity of the tricuspid annulus (E') of 18 cm/s

large trial involving 380 patients with SLE, which showed that the elevated levels of antiphospholipid antibodies significantly affected the risk of myocardial infarction, and, to a lesser extent, the presence of classic atherosclerotic lesions. Therefore, the incidence of focal myocardial necrosis is observed independently of atherosclerotic lesions and a possible mechanism may be intravascular thrombosis [12].

## Rheumatoid arthritis

An increased mortality in patients with rheumatoid arthritis results from the high rate of cardiovascular events [13]. The traditional risk factors of coronary artery disease are observed slightly more often in

patients with rheumatoid arthritis than in the general population and do not explain a significantly higher occurrence of cardiovascular episodes, including embolic events. The relevant factor increasing the risk in that group is inflammatory process [14]. It was proved that the high level of inflammatory markers is an independent cardiovascular risk factor [15]. Therefore, the guidelines of the European League Against Rheumatism [16] advise the assessment of cardiovascular risk in patients with rheumatoid arthritis with a standard risk indicators multiplied by 1.5, especially when the time from the onset of the disease is longer than 10 years, the patient is positive for rheumatoid factor or anticyclic citrullinated peptide antibodies, or extra-articular manifestations of the disease are present.

The relative risk of pulmonary embolic event in patients with rheumatoid arthritis in the first year from the diagnosis, compared with the general population, equals 5.66 [11].

## Prophylaxis and treatment of thromboembolic complications in connective tissue diseases

It is generally suggested that in patients with antiphospholipid syndrome and without thrombosis, antithrombotic prophylaxis is not required despite the presence of antiphospholipid antibodies. In patients with the symptoms of thrombosis, the standard treatment should be introduced. Continuous antithrombotic prophylaxis is not recommended in patients with SLE or rheumatoid arthritis.

However, it is well known that atherosclerotic lesions in the coronary arteries, perfusion defects in SPECT, and elevated pulmonary artery pressure, which are observed in numerous patients with connective tissue diseases [8,17], are significant risk factors for death [18,19]. A microthrombotic mechanism underlying these factors in patients with autoimmune diseases draws attention to thrombosis prevention in asymptomatic patients with high antiphospholipid antibody titer. It was proved that in asymptomatic patients with aCL antibodies, antithrombotic prophylaxis with the use of aspirin or low-molecular-weight heparin reduced the number of thromboembolic complications in clinical situations of increased risk (surgery procedures, immobilization) [20]. In this group of patients, primary prophylaxis with the use of aspirin and hydroxychloroquine is also effective [21].

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## Fibromuscular dysplasia

Anna Kablak-Ziembicka, Tadeusz Przewłocki

Fibromuscular dysplasia (FMD) is a group of non-atherosclerotic, noninflammatory arterial diseases that affect small- and medium-caliber vessels by causing luminal narrowing.

FMD most commonly involves the renal and carotid arteries; it only rarely affects other arterial territories such as the abdominal and iliac arteries, and, very rarely, the coronary arteries (fig. 1).

The prevalence of symptomatic renal artery FMD is about 4/1000 of the general population and the prevalence of symptomatic cervicocranial FMD is probably half lower. However, in healthy renal donors, renal FMD has been identified quite often – it has been shown in 3.8% to 6.6% of the angiograms [1,2]. In the cervicocranial location, internal carotid artery FMD constitutes 93% of the cases, while the prevalence of vertebral artery FMD is estimated at 7% [3]. Both carotid and vertebral FMD are located in the middle and distal portions of the arteries (carotid at level C1–C2, vertebral segments V3–V4), typically bilaterally. The prevalence of coronary FMD is difficult to determine because only fewer than 30 cases have been reported worldwide [4].

More than 80% of all FMD cases involve women aged between 30 and 50 years. It appears to be familial in 10% of the cases. The etiology of FMD is unknown, although various hormonal, genetic, and mechanical factors have been suggested [5,6]. Subclinical lesions are found at arterial sites distant from the stenotic arteries, and this suggests that FMD is a systemic arterial disease. Some researchers believe that FMD

is a heterogeneous group of arterial diseases with varied etiology but presenting with a similar phenotypic expression.

The symptoms and clinical presentation of FMD depend on its location [3,5,6]. Renal artery FMD, which is the most common, is associated with early onset of hypertension, rarely with renal failure. Stenosis progression in renal artery FMD is slow and rarely leads to ischemic renal failure.

Internal carotid FMD presents with recurrent migraines and headaches for years as well as tinnitus and carotidynia (pain in the neck); nevertheless, it can be complicated by acute dissection with heavy headache, Horner's syndrome, syncope, transient ischemic attack (TIA) or stroke, and cranial nerve palsy (V, VII, VIII), or it can be associated with intracerebral aneurysms (between 20% and 50% of the subjects) with a substantial risk of subarachnoid or intracerebral hemorrhage [7].

Chatzikonstantinou et al., [8] reported that FMD was responsible for ischemic stroke in 1.9% of 104 consecutive patients aged between 19 and 45 years (mean age, 38.4 ± 6.9 years). Among the other identified reasons for ischemic stroke in subjects under the age of 45 years, patent foramen ovale (PFO) accounted for 27.9%, carotid and vertebral artery dissection for 15.4%, carotid / cerebral artery thrombosis for 8.6%, vasculitides or antiphospholipid syndrome for 8.6%, and cardiac emboli for 7.7% of the cases [8]. About 30% of ischemic strokes were of unknown or uncertain etiology; however, a hypoplastic vertebral artery was identified in 20% of these patients.

As evidenced by the above study, the first-choice examinations to determine the etiology of ischemic stroke / TIA that should be performed in young adults are Doppler ultrasonography of the carotid and vertebral arteries (accounting for 46% of ischemic strokes),



**Fig. 1.** Angiography. Different locations of the fibromuscular dysplasia (FMD). **A.** Most common renal FMD. **B.** Intracranial internal carotid FMD. **C.** Left iliac artery FMD

echocardiography, and 24-hour ambulatory electrocardiogram [8]. Further diagnostic tests should be then performed depending on the findings. For precise visualization of the cervicocranial arteries, computed tomography angiography (CTA) and / or magnetic resonance angiography (MRA) can be performed. In subjects with thinning or aneurysm of the intraatrial septum, transesophageal echocardiography should be performed to exclude PFO.

Coronary artery FMD constitutes a rare cause of sudden cardiac death, the mechanism of which has not been fully elucidated. FMD dissection causes heart ischemia and / or nonsustained ventricular arrhythmia [4,9,10].

The iliac external artery or femoral artery FMD manifests itself with claudication, and rarely with acute limb ischemia. Mesenteric FMD may be associated with gastrointestinal symptoms.

Harrison and McCormack proposed a histological classification of FMD in 1971, which differentiates between the three main types, although they may occur concurrently in a single patient [11]:

- intimal fibroplasia (10% of all FMD cases),
- medial dysplasia with three subtypes (medial dysplasia, paramedial dysplasia, and medial hyperplasia – 75%–80% of all FMD cases),
- adventitial fibroplasia (less than 1% of all FMD cases)

Although there are several other classifications, the one mentioned above is used in clinical practice and reflects also the therapeutic success in FMD.

The angiographic classification includes the following types of FMD [3]:

- multifocal, with multiple stenoses and the “string-of-beads” appearance, which is related to medial FMD (“pearl necklace”; 62%)
- tubular, with long, concentric stenosis (14%),
- focal, with a single stenosis of less than 1 cm (7%)
- mix stenosis (21%).

All cases with multifocal stenosis were associated with medial FMD. Tubular and focal types are not clearly related to specific histological lesions.

The gold standard for diagnosis is angiography, which shows multifocal stenoses with the “string-of-beads” appearance in most cases [12]. Noninvasive diagnostic tests include Doppler ultrasonography, which is the most accurate, followed by MRA and CTA [13,14]. As an invasive procedure, angiography is usually used in patients in whom revascularization is planned during the same procedure.

The differential diagnosis includes atherosclerotic stenoses and stenoses associated with vascular Ehlers–Danlos and Williams syndromes as well as type 1 neurofibromatosis [15].

The management of patients with renovascular hypertension includes antihypertensive therapy, percutaneous angioplasty of severe stenoses, and reconstructive surgery in cases with complex FMD that extends to segmental arteries [13,14,15]. The results of endovascular treatment are good, with a high proportion of cured hypertension (70%–80%) and acceptable rate of restenosis.

The therapeutic options for securing ruptured intracerebral aneurysms are microvascular neurosurgical clipping and endovascular coiling [5,6,7,13,14].

Carotid and vertebral FMD is usually treated with percutaneous angioplasty (PTA) alone; however, stent implantation is necessary in complicated cases (dissection) or in the case of suboptimal PTA result [13,14]. PTA is also the method of choice in mesenteric or iliac locations.

Coronary artery FMD is extremely difficult to manage because the majority of symptoms have rapid, unexpected onset, usually with a life-threatening course with ventricular arrhythmia, or acute coronary syndrome due to dissected, ruptured or thrombosed FMD. The literature reports fewer than 30 cases of FMD, of which all but one were fatal, confirmed on autopsy.

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## Spontaneous dissection of the artery

Anna Kablak-Ziembicka, Tadeusz Przewłocki

### Spontaneous carotid and vertebral artery dissection

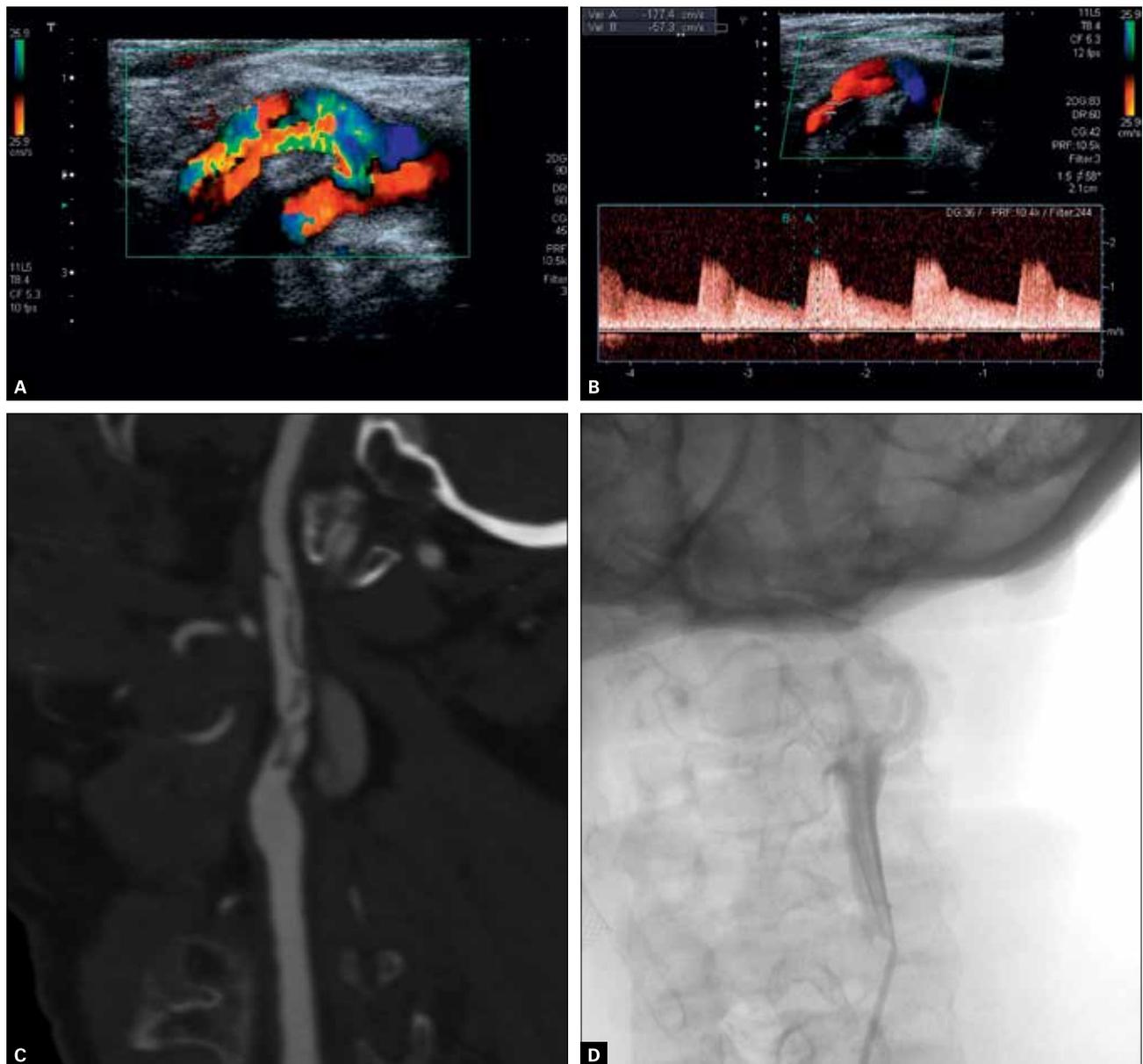
The prevalence of carotid artery dissection is estimated at 1.9 to 2.9 cases per 100 000 population, while that of the vertebral one at 0.48 to 1.52 per 100 000 population [1].

Chatzikonstantinou et al.[2] reported that carotid and vertebral artery dissection is causative in about

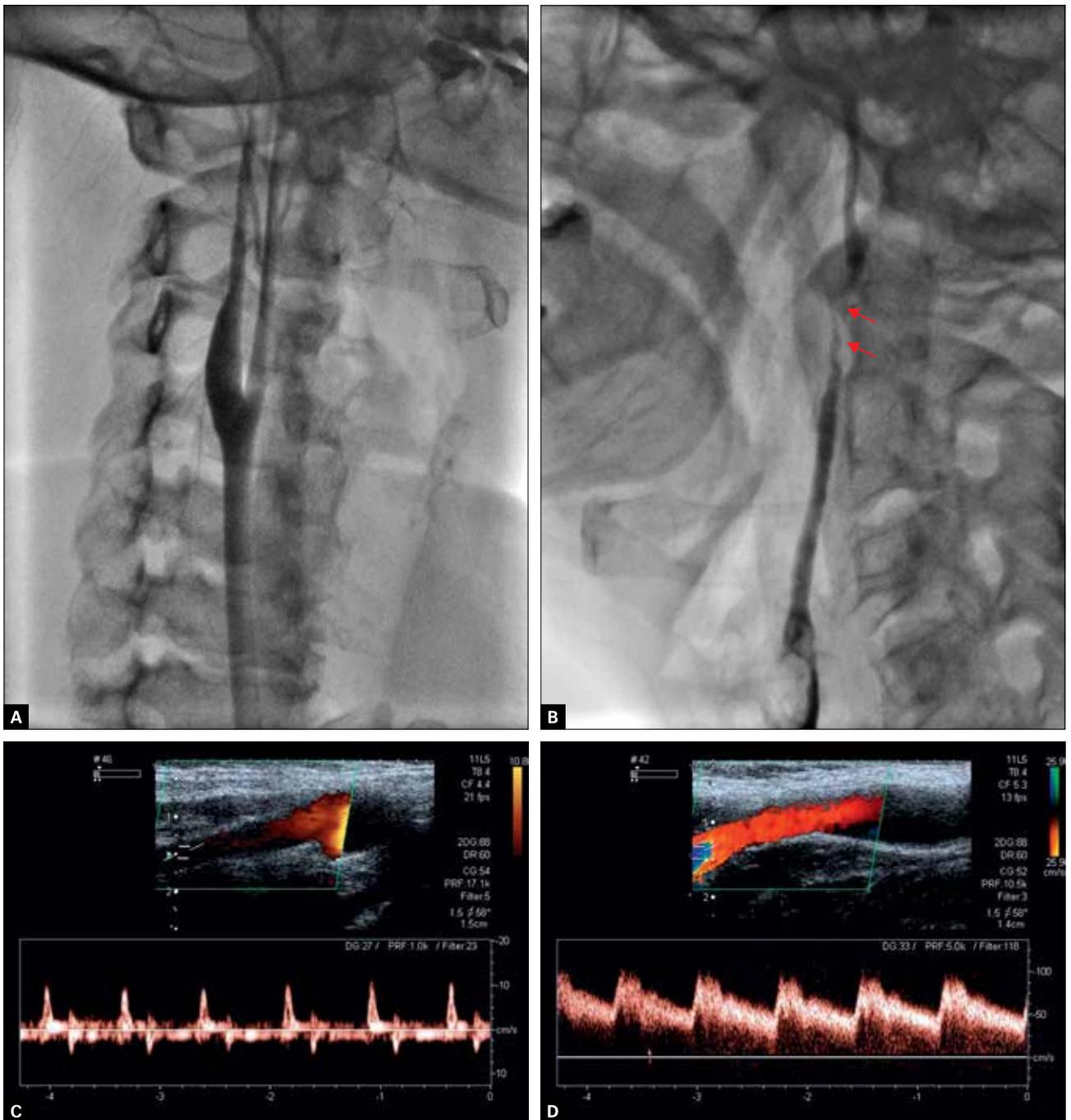
15% of all ischemic strokes in patients under 45 years of age.

In a study by Lee et al.,[1] including 32 patients with acute dissection of the internal carotid artery and 18 with vertebral artery dissection (aged 27–77 years), the presenting symptoms were transient ischemic attack in 29% and 11%, ischemic stroke in 41% and 83%, Horner's syndrome in 25% and 22%, migraine in 41% and 22%, and carotidynia in 97% and 83% of the subjects, respectively. Cranial nerve palsy is also common, with a predominance of XII cranial nerve palsy, followed by nerves IX, X, and XI [3,4]. Only 3% of carotid and 11% of vertebral artery dissections were asymptomatic.

The mechanism of cerebral ischemia is not completely clear; however, according to Lucas et al. [5], the origin is embolic rather than hemodynamic because the majority



**Fig. 1.** A. Color Doppler ultrasonography. Acute cerebral ischemia in the course of long left internal carotid artery dissection. Patent double channels in dissected left internal carotid artery with turbulent flow (arrows). B. Pulsed-wave color Doppler ultrasonography. High peak-systolic and the end diastolic velocities within dissected segment indicate high-stenosis grade of the left internal carotid artery. C. Computed tomography angiography. Long left internal carotid artery dissection. D. Angiography. internal carotid artery dissection



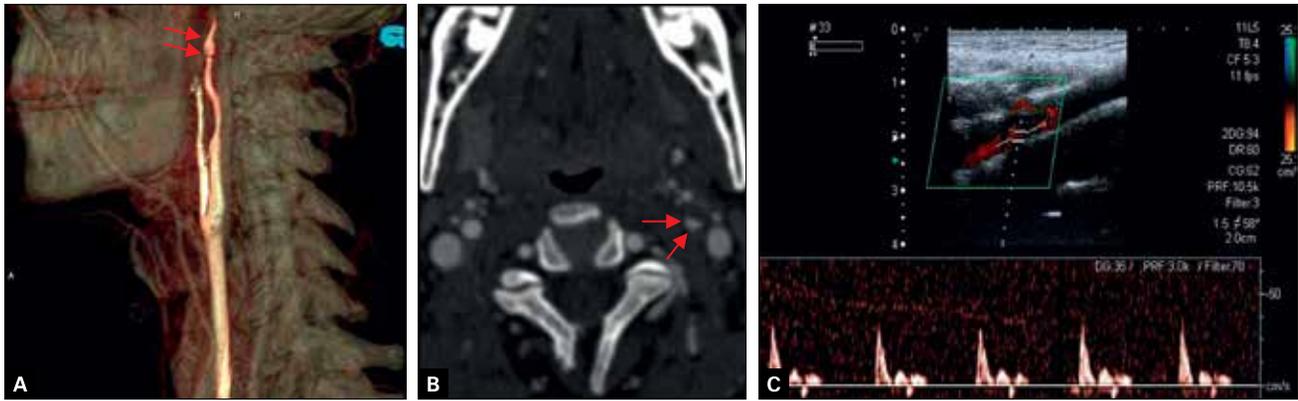
**Fig. 2.** Acute cerebral ischemia in the course of: A. – dissection of the distal portion of the right internal carotid artery (arrows). Angiography. B. – Pulse Doppler ultrasonography shows aberrant high-peak signals in pre-dissected patent portion of ICA consistent in dissecting occlusion of the upper segment of the right internal carotid artery. C. – Pulse Doppler ultrasonography. The normal pattern spectrum flow in the contralateral normal internal carotid artery

of stroke patterns are cortical. Consistent with this mechanism, studies reveal cerebral microembolism on transcranial Doppler in over half of acute carotid dissections, which disappear in 70% of the cases within 24 hours after initiation of anticoagulant therapy [6,7]. However, brain hypoperfusion should also be considered [3].

The diagnosis of dissection is usually reached during angiography, on computed tomography angiography and/or magnetic resonance angiography, because the majority of dissections are located in the intracranial portions of the cervicocranial arteries; it is rarely reached on ultrasonography (fig. 1) [1,3,4,8,9].

Ultrasonography may suggest dissection of the carotid and vertebral arteries when the abnormal Doppler spectrum is recorded in its proximal to dissection portion; however, the dissected segment is rarely visible with a standard linear vascular probe. Occasionally, an intimal flap or double lumen of the artery can be identified (fig. 1).

At the time of diagnosis, the occlusion of the dissected artery is observed in 25% of carotid and 50% of vertebral dissections, stenosis in 56% and 39%, and dissecting aneurysm in 19% and 11%, respectively (fig. 2) [1].



**Fig. 3.** **A.** Multi-sliced computed tomography. Three-dimensional reconstruction. Aneurysmal dissection of the intracranial portion of the left internal carotid artery (arrows). Arrow indicates longitudinal splitting of the arterial wall producing a tear in the intima that establishes communication with the lumen. **B.** Computed tomography angiography. True and false lumen of internal carotid artery distally to aneurysm (arrows). **C.** Pulsed-wave color Doppler ultrasonography. Aberrant high-peak signals in pre-dissected patent portion of internal carotid artery consistent with dissecting occlusion of the upper segment

There is no consistent pharmacological management of this patient group. Antiplatelet or anticoagulant therapy is usually recommended, and probably most patients receive warfarin for 3 to 6 months after the event. According to the various reports, aspirin is administered in 30% to 45% of the patients. Bleeding risk and healing rates seem to be similar with both strategies. However, a number of patients (up to 10%) are left without antiplatelet or anticoagulant treatment.

Tissue plasminogen activator, administered intraarterially or intravenously, or other thrombolytic drugs may be occasionally considered, consistent with prior reports that acute thrombolysis does not appear to increase the risk of wall hematoma extension in dissections [10,11]. Embolectomy may also be considered.

Percutaneous angioplasty, preferably with stent implantation, is used in acute cases, when a well-defined double lumen in the artery is visible, providing identification of the true lumen (optionally with intravascular ultrasound [IVUS]) [12].

The outcome is usually favorable in more than 90% of the subjects; however, in rare cases (2%–3%), dissection may be fatal [1,13]. In 30% to 40% of the patients, spontaneous recovery is observed, with opening of the artery. The recurrence of symptomatic carotid artery dissection has been reported at a rate of 0.3% to 1.0% per year [14,15].

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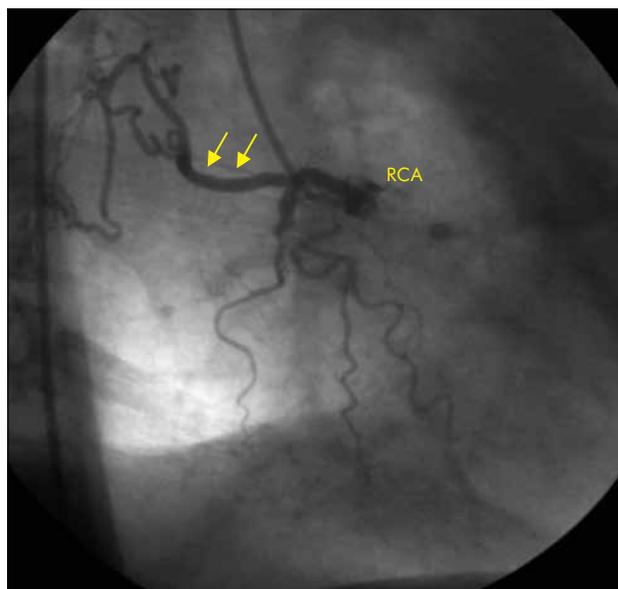
## Rare diseases of systemic circulation: Clinical examples

### **Pulmonary sequestration from the right coronary artery in a patient with critical left coronary artery disease (RCD code: I-1C.0)**

Mieczysław Pasowicz, Anna Kabłak-Ziembicka, Jerzy Sadowski, Tadeusz Przewłocki, Henryk Olechnowicz, Piotr Pieniżek, Zbigniew Moczulski, Piotr Klimeczek, Małgorzata Koniecznyńska, Wiesława Tracz

#### Background

Pulmonary sequestration refers to a situation where a portion of the lung tissue receives its blood supply from an anomalous systemic artery originating from the aorta or one of its branches. This is an extremely rare congenital anomaly, often asymptomatic.



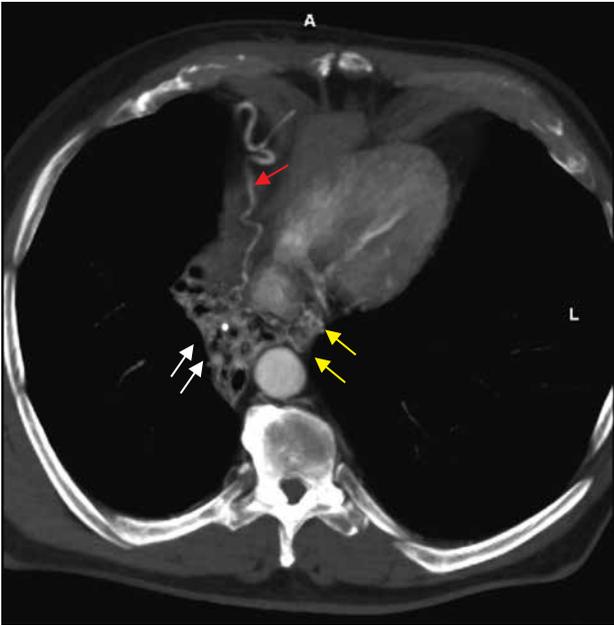
**Fig. 1.** Coronary angiography. Abnormal right coronary artery with a branch (arrows) supplying blood to the right lung. RCA – right coronary artery

#### Case presentation

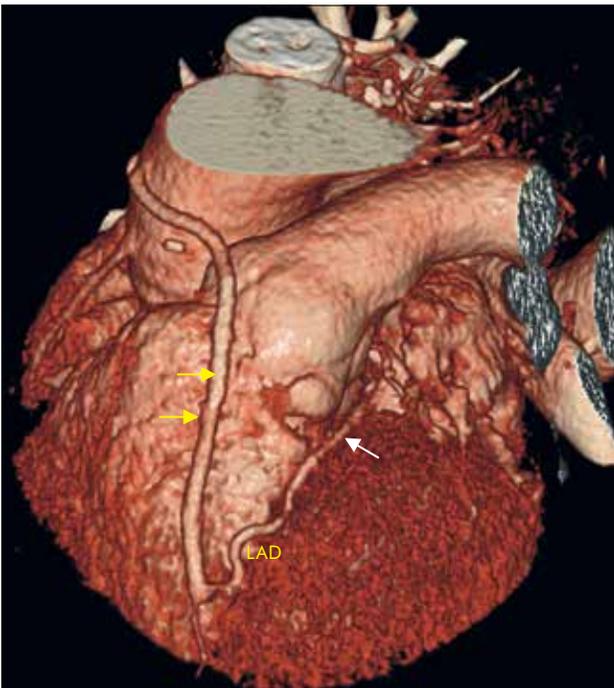
A 67-year-old man with hypertension and non-insulin-dependent diabetes mellitus, a 12-month history of typical exertional chest pain with a positive treadmill test, and frequently recurring acute bronchitis since adolescence was referred to our institute.

He was admitted with normal electrocardiographic findings and mildly elevated blood pressure (150/90 mm Hg). Routine chest X-ray imaging showed a slight increase of hyperdensity in the medium and lower lobes of the right lung. On echocardiography, left ventricular hypertrophy with no abnormalities in segmental contraction was shown (ejection fraction, 60%). Coronary angiography revealed two-vessel coronary artery disease (critical stenosis of the left anterior descending and circumflex arteries). No atherosclerotic lesions were found in the right coronary artery; however, it supplied blood to the lung circulation (fig. 1). A preliminary diagnosis of a coronary–pulmonary fistula was established. Twelve hours later, the patient developed cough and dyspnea with massive hemoptysis. Urgent bronchoscopy revealed multifocal hemorrhage in the right bronchial tree. The patient was given adrenaline solution into the bronchi to stop the bleeding. He then underwent spiral computed tomography (CT) using Somatom Plus 4 (Siemens), with intravenously administered contrast. CT scans revealed a pathological systemic arterial supply from the right coronary and right interior mammary arteries to the lower and medium lobes of the right lung (fig. 2). CT chest scans showed hypoplastic lobes of the right lung. Overall, CT allowed to identify pulmonary sequestration.

Pulmonary sequestration was confirmed during surgical procedure and partial resection of the right lung was performed. A month later, bypass grafting to the left anterior descending and marginal coronary arteries was performed. The patient was discharged in good general condition and was symptom-free at 6 months. The effectiveness of surgical intervention was confirmed by follow-up multislice spiral CT performed with Somatom Plus 4, Volume Zoom, Siemens (4 × 1 collimation; slice thickness, 1.25 mm, with intravenously administered contrast, Ultravist 370, 4 mL/s) (fig. 3).



**Fig. 2.** Cardiovascular computed tomography. Multiple enhancing collateral vessels (white arrows) in the aortopulmonary window. Right internal mammary artery (red arrow); Branch from the right coronary artery to the pulmonary sequestration (yellow arrows)



**Fig. 3.** Cardiovascular computed tomography. Three-dimensional reconstruction. Critical stenosis of the proximal left anterior descending branch (white arrow), venous bypass graft (yellow arrows) to the left anterior descending branch, and patent distal left anterior descending branch supplied from the graft. LAD – left anterior descending branch

## Discussion

Pulmonary sequestration prevalence is estimated between 0.15 and 6.4% of all congenital pulmonary malformations, making it an extremely rare disorder [1]. It can be divided into 2 main types. In the intralobar type, constituting 85% of all sequestrations, the lesion is located within a normal lobe and lacks its own visceral pleura [1]. In an extralobar type, the sequestered lung mass is located outside the normal lung and has its own visceral pleura.

Pulmonary sequestrations typically receive the blood supply from the thoracic or abdominal aorta in 75% of cases. However, the reported other blood supply sources include pulmonary, innominate, subclavian, intercostal, pericardiophrenic, internal mammary, celiac, splenic, or renal arteries.

We describe an extremely rare case of the extralobar sequestration receiving blood supply from the right coronary artery, moreover having an abnormal communication with the tracheobronchial tree. The latter was associated with heavy dyspnea, massive hemoptysis and caught which developed after routine coronary angiography. In the presented case, apart quite unexpected clinical manifestation recurrent frequent respiratory tract infections, periodical productive cough and chest pain was reported by the patient. Otherwise, he was asymptomatic.

Although, the angiographic study is a gold standard in recognition of pulmonary sequestration, in the presented case, the accessory aberrant artery arising from the right coronary artery was initially referred to coronary – pulmonary fistula, which is another rare congenital malformation.

Due to the hemoptysis occurrence in the postprocedural period, other investigations were performed, including urgent bronchoscopy, as well as, computed tomography angiography (CTA) and high-resolution computed tomography (HRCT). This imaging modalities allowed setting correct diagnosis. According to literature, CTA scans and HRCT of lungs have 90% accuracy in the diagnosis of pulmonary sequestration. Also magnetic resonance angiography (MRA) can be useful diagnostic tool.

Pulmonary sequestration usually have a clinical manifestation at birth or during early childhood or adulthood <20 years of age (60-70% of sequestrations). The common symptoms include: productive cough, recurrent pneumonias, hemoptysis, chest pain, and dyspnea.

It can be complicated by the hemorrhage from the respiratory tract, chronic bronco-pulmonary infections and heart failure due to arteriovenous shunts [2]. There are also frequent superimposed infections such as tuberculosis, mycobacterial and fungal infections, or hemoptysis, requiring immediate treatment. A further complications include the aneurysm formation within the aberrant vessels associated with a risk of rupture. Furthermore, cases of malignant tumors arising in intralobar lung sequestrations have been described [3].

Diagnostic delays are common in the adult patients since the symptoms often mimic other common diseases such as pneumonia, emphysema, lung abscess and ischemic heart disease [4].

Pulmonary sequestration can be removed by surgical resection or embolization. Both strategies can be applied as they are effective, with the reported by Brown et al. complication rate of 27% for surgery and of 4.7% for embolization ( $p = 0.1$ ) [2].

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## Acute coronary syndrome in a patient with single coronary ostium (RCD code: I-1C.2)

Andrzej Gackowski, Marcin Misztal, Bogusław Gawęda, Jerzy Sadowski, Jadwiga Nessler

### Background

Abnormal coronary anatomy is observed in less than 1% of the general population; however, in a series of 1950 coronary angiograms, it was identified in 5.64% of the patients. Although several coronary anomalies can cause ischemia or even sudden cardiac death at a young age, most of them remain asymptomatic until significant atherosclerosis develops. Symptoms may begin acutely as presented in the following case. The knowledge of possible coronary variants is important for proper and, in some cases, urgent interpretation of the result of a coronary angiogram.

### Case presentation

A 64-year-old hypertensive man experienced the first episode of chest pain in his life. The pain lasted several minutes and since then, he started to experience chest pain on exertion (Canadian Cardiovascular Society class II). Five days later, at night, he had to call the ambulance because the pain occurred at rest and continued for more than an hour.

On admission, the patient still had moderate chest pain, without dyspnea. His blood pressure was 130/80 mm Hg, and his heart rate was regular, 80 beats/min. No abnormalities were revealed by physical examination. An electrocardiogram showed sinus rhythm, ST-segment depression, and negative T waves in numerous leads (fig. 1). Echocardiography showed normal heart dimensions, akinesia of the anterior wall, and mildly depressed global left ventricular (LV) function (LV ejection fraction, 45%) without other abnormalities.

Acute coronary syndrome was diagnosed and the patient was referred for urgent coronary angiography, which revealed coronary anomaly (fig. 2). No coronary artery ostium could be found in the left sinus of Valsalva. The only coronary artery originated from the right sinus (Table 1). After a short run, the common trunk gave a big branch, which can be named the left main coronary artery, and then followed the normal course of the dominant right coronary artery (RCA), giving the posterior descending and large obtuse marginal branches. Severe stenosis was observed at the third segment and at posterior descending branch of the RCA (fig. 2). The left main artery originating from the main trunk of the single coronary artery was located between the aorta and main pulmonary artery. Moreover, the left main artery was distally subtotally stenosed before branching to the left anterior descending artery (LAD) and another smaller ramus. The distal parts of the poorly perfused vessels were narrow and filled with delay (TIMI II flow).

Immediately after the coronary angiography, the pain aggravated and blood pressure dropped to 90/60 mm Hg, while the sinus rhythm accelerated to

**Table 1.** Simplified classification of coronary anomalies by Angelini (classification of the present case is marked red)

A. Anomalies of the origin and course
1. Absent left main trunk (split origination of LCA)
2. Anomalous location of coronary ostium within aortic root or near proper aortic sinus of Valsalva (for each artery)
a. High
b. Low
c. Commissural
3. Anomalous location of coronary ostium outside normal "coronary" aortic sinuses
a. Right posterior aortic sinus
b. Ascending aorta
c. Left ventricle
d. Right ventricle
e. Pulmonary artery
– LCA that arises from posterior facing sinus
– Cx that arises from posterior facing sinus
– LAD that arises from posterior facing sinus
– RCA that arises from anterior right facing sinus
– Ectopic location (outside facing sinuses) of any coronary artery from pulmonary artery
f. Aortic arch
g. Innominate artery
h. Right carotid artery
i. Internal mammary artery
j. Bronchial artery
k. Subclavian artery
l. Descending thoracic aorta

4. Anomalous location of coronary ostium at improper sinus (which may involve joint origination or “single” coronary pattern)
  - a. RCA that arises from left anterior sinus, with anomalous course
    - Posterior atrioventricular groove or retrocardiac
    - Retroaortic
    - Between aorta and pulmonary artery (intramural)
    - Intraseptal
    - Anterior to pulmonary outflow
    - Posteroanterior interventricular groove (wraparound)
  - b. LAD that arises from right anterior sinus, with anomalous course
    - Between aorta and pulmonary artery (intramural)
    - Intraseptal
    - Anterior to pulmonary outflow
    - Posteroanterior interventricular groove (wraparound)
  - c. Cx that arises from right anterior sinus, with anomalous course
    - Posterior atrioventricular groove
    - Retroaortic
  - d. LCA that arises from right anterior sinus, with anomalous course
    - Posterior atrioventricular groove
    - Retroaortic
    - Between aorta and pulmonary artery
    - Intraseptal
    - Anterior to pulmonary outflow
    - Posteroanterior interventricular groove

#### 5. Single coronary artery

#### B. Anomalies of intrinsic coronary arterial anatomy

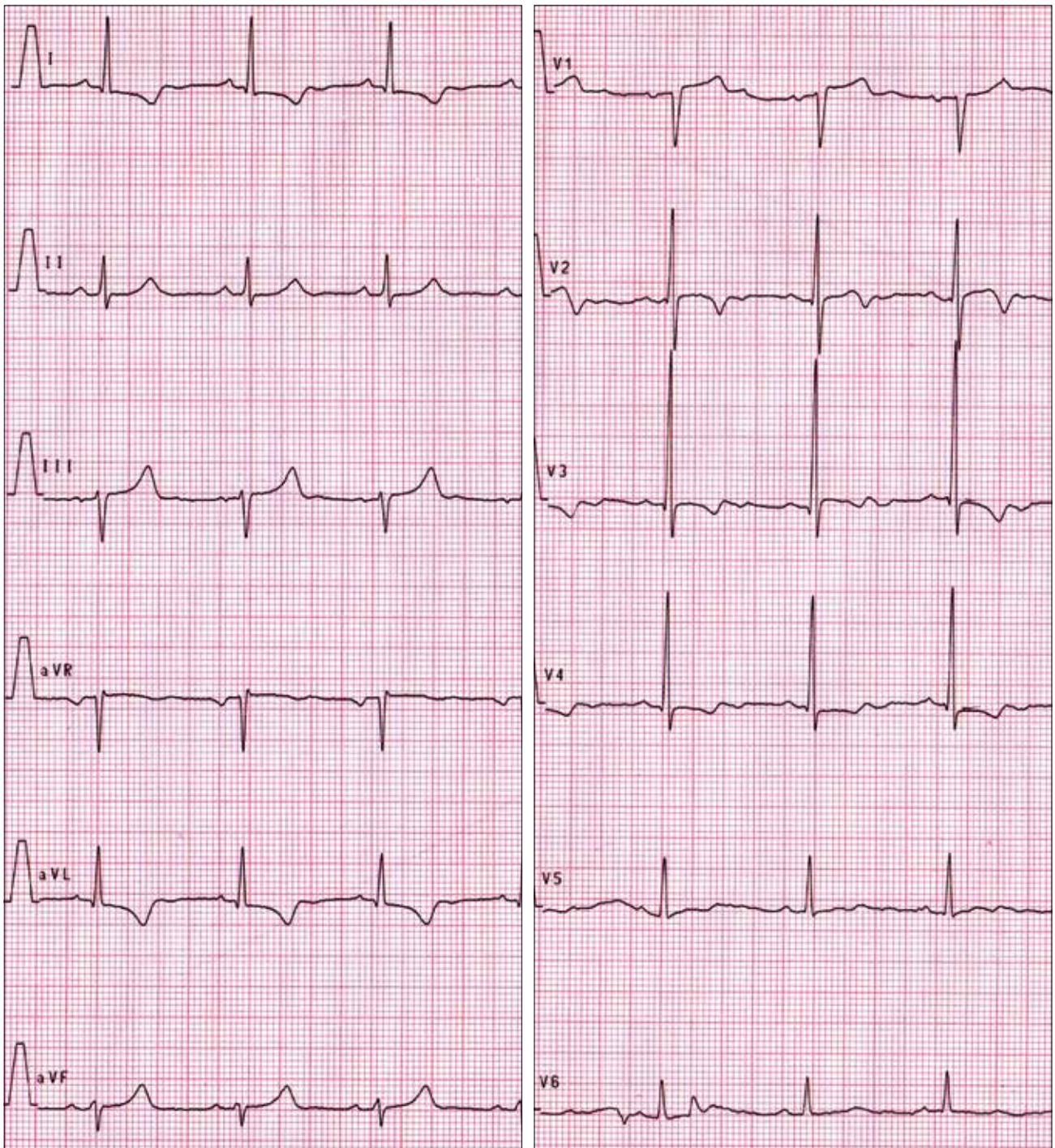
1. Congenital ostial stenosis or atresia (LCA, LAD, RCA, Cx)
2. Coronary ostial dimple
3. Coronary ectasia or aneurysm
4. Absent coronary artery
5. Coronary hypoplasia
6. Intramural coronary artery (muscular bridge)
7. Subendocardial coronary course
8. Coronary crossing
9. Anomalous origination of posterior descending artery from the anterior descending branch or a septal penetrating branch
10. Split RCA
  - a. Proximal + distal PDs that both arise from RCA
  - b. Proximal PD that arises from RCA, distal PD that arises from LAD
  - c. Parallel PDs  $\times 2$  (arising from RCA, Cx) or “codominant”
11. Split LAD
  - a. LAD + first large septal branch
  - b. LAD, double (parallel LADs)
12. Ectopic origination of first septal branch
  - a. RCA
  - b. Right sinus
  - c. Diagonal
  - d. Ramus
  - e. Cx

#### C. Anomalies of coronary termination

1. Inadequate arteriolar/capillary ramifications
2. Fistulas from RCA, LCA, or infundibular artery to:
  - a. Right ventricle
  - b. Right atrium
  - c. Coronary sinus
  - d. Superior vena cava
  - e. Pulmonary artery
  - f. Pulmonary vein
  - g. Left atrium
  - h. Left ventricle
  - i. Multiple, right + left ventricles

#### D. Anomalous anastomotic vessels

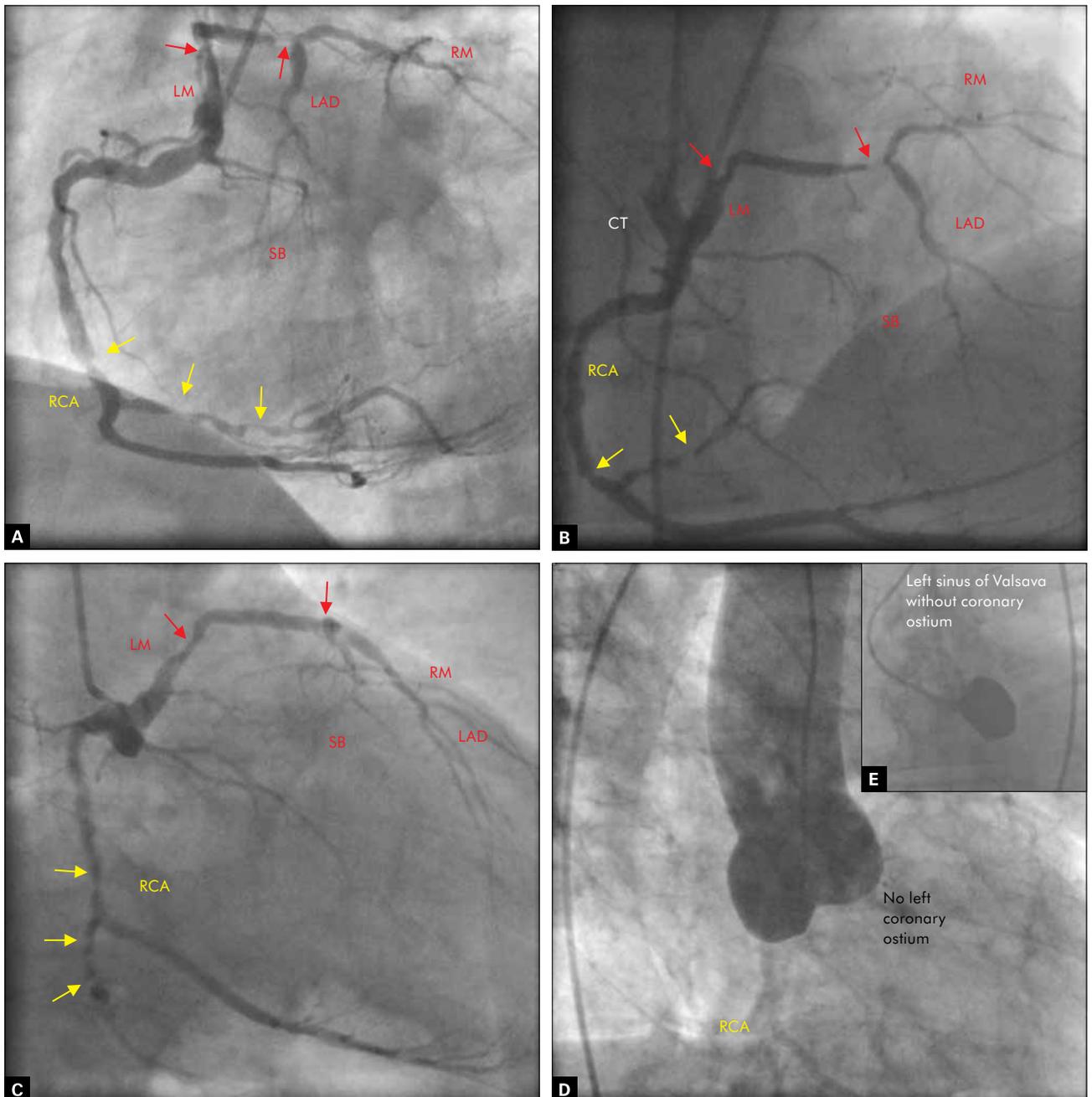
Cx – circumflex artery, LAD – left anterior descending branch, left anterior descending coronary artery, LCA – left coronary artery, PD – posterior descending branch, RCA – right coronary artery



**Fig. 1.** Electrocardiogram.. Sinus rhythm, 60/min. Negative T waves in leads I, aVL, and V<sub>2</sub> through V<sub>4</sub>, and borderline ST-segment depression in leads I, aVL, and V<sub>4</sub>

100 beats/min. Because of the anatomy, percutaneous intervention was contraindicated (diffuse disease of the RCA and bifurcation lesion of the anomalous left main coursing between the aorta and pulmonary trunk and with poor peripheral branches). After a consultation with a cardiac surgeon, we decided to perform urgent coronary artery bypass grafting (CABG). Cardiac necrosis markers were measured on admission, and the results arrived from the laboratory. High-sensitive troponin I was 1.1 ng/mL (normal value, <0.015ng/mL), and the final diagnosis of non-ST-elevation myocardial infarction was made.

The surgery was performed without complications. The left internal mammary artery graft was used to supply the LAD and the venous graft to supply the RCA. The subsequent course was uneventful, and the patient was discharged after 7 days. Control echocardiography showed only mild anterior hypokinesis with preserved LVEF of 58%.



**Fig. 2.** Coronary angiography. **A.** Cranial left anterior oblique view. **B.** Posteroanterior view. **C.** Caudal right anterior oblique view. The whole coronary system is visualized from a single ostium, located at the right sinus. The dominant right coronary artery splits off from a short common trunk, coursing typically and giving posterior descending and obtuse marginal branches. Right coronary artery stenoses are shown (yellow arrows). The left main trunk originates from the common trunk and crosses the aorta and the main pulmonary artery. Two left main stenoses are shown (red arrows). The left coronary artery ends in the left anterior descending and ramus branches. Septal branches can be identified. **D.** Aortography. **E.** Selective left sinus of Valsalva injection. No left coronary ostium. RCA – right coronary artery, CT – common trunk, LM – left main, LAD – left anterior descending branch, RM – ramus branch, SB – septal branches

## Discussion

Coronary angiography, which is a very common procedure nowadays, reveals an increasing number of coronary anomalies. The anomaly described in our patient is extremely rare, with the incidence between 0.0024%–0.044%. Not only the origin of the left main artery was abnormal. The location of the coronary artery between the aorta and pulmonary trunk coincides with acute ischemia, sudden death during exercise, or an increase in blood pressure due to vessel

compression. Our patient had no symptoms of myocardial ischemia in the past history but he became symptomatic at the age of 64 years due to severe atherosclerosis. It is possible that periodical left main artery compression between the great arterial trunks could accelerate the atherosclerotic process. In the present case, critical stenosis of both the anomalous left main artery and the RCA led to an unstable clinical course that might cause rapid deterioration, severe heart failure, and death. Percutaneous coronary intervention was contraindicated not only because of the number

and morphology of stenotic vessels but also because the stent implanted in the left main artery could potentially be compressed in-between the great arteries. Identification of the anatomy allowed us to decide on an immediate and successful CABG procedure, which proved to be the optimal treatment.

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## Patient with acute coronary syndrome and multiple coronary artery fistulas draining into the left ventricle (RCD code: I-1C.4)

Agnieszka Rosławiecka, Tadeusz Przewłocki, Anna Kabłak-Ziembicka

### Background

Acute coronary syndrome due to atherosclerotic lesions is the most common reason of unexpected chest pain, ischemic changes on a resting electrocardiogram, elevated biomarkers of cardiac ischemia, and wall-motion abnormalities on transthoracic echocardiography in adults. However, an emergent coronary angiography occasionally shows normal coronary arteries or other surprising findings concomitant with steno-occlusive coronary disease [1].

One of these unexpected and rare findings is a coronary artery fistula, which is defined as an anomalous connection between a coronary artery and a major vessel or cardiac chamber. Its incidence in the general population is about 0.002% [2,3]. According to Krakow, Rare Cardiovascular Diseases Classification classification, coronary fistula is positioned as an I-1.D4 group [4].

Fistulas represent congenital connections between the coronary system and a cardiac chamber and appear to represent persistence of embryonic intertrabecular spaces and sinusoids (Thebesian veins). About 50% of the fistulas are clinically silent, and in about 20% of the cases self-healing is reported (spontaneous closure) [5,6]. The majority of the fistulas tend to grow with time.

### Case presentation

A 73-year-old woman was admitted to an acute cardiac care unit due to suspicion of acute coronary syndrome. She presented with prolonged chest pain, an electrocardiogram revealed negative T waves in the precordial leads. High-sensitive troponin T level was elevated to 0.922 ng/mL (normal range, 0.0–0.014 ng/mL). A physical examination revealed only a systolic-diastolic bruit located at the apex. Before the present event, she complained of untypical chest discomfort and shortness of breath. Her past history revealed myocardial infarction, ischemic stroke (of unknown origin) in 1996, arterial hypertension, diabetes mellitus, and depression.

An echocardiogram showed hypokinesis of the inferior wall with preserved global left ventricular function and ejection fraction of 58%. No signs of right ventricular overload were observed, and the Qp:Qs (left-to-right shunt) index was 1.0. Moreover, numerous color-flows within the hypertrophic lateral wall of the left ventricle with a typical diastolic coronary artery flow were present (fig. 1).

On coronary angiography, the left main trifurcation was noted. All 3 branches of the left main artery were large and tortuous with no lumen reduction. Surprisingly, a contrast agent injected into the left coronary tree passed directly into the left ventricular cavity via multiple small and 3 large fistulas originating from the mid and distal segments of the intermediate and left anterior descending coronary arteries (fig. 2A,B). The right coronary artery was chronically occluded with a good collateral circulation from the left anterior descending artery (fig. 2C).

### Discussion

The most common complications of coronary artery fistulas include premature atherosclerosis, coronary calcifications, “steal” phenomenon resulting in myocardial ischemia (angina or myocardial infarction), heart failure and dilated cardiomyopathy, ventricular arrhythmias, and sudden cardiac death [5–8]. Hemodynamically significant fistulas can induce pulmonary hypertension. Uncommon complications include endocarditis, aneurysm formation and rupture, embolization with thrombotic material from an aneurysmal fistula, and the rupture of an aneurysm resulting in tamponade.

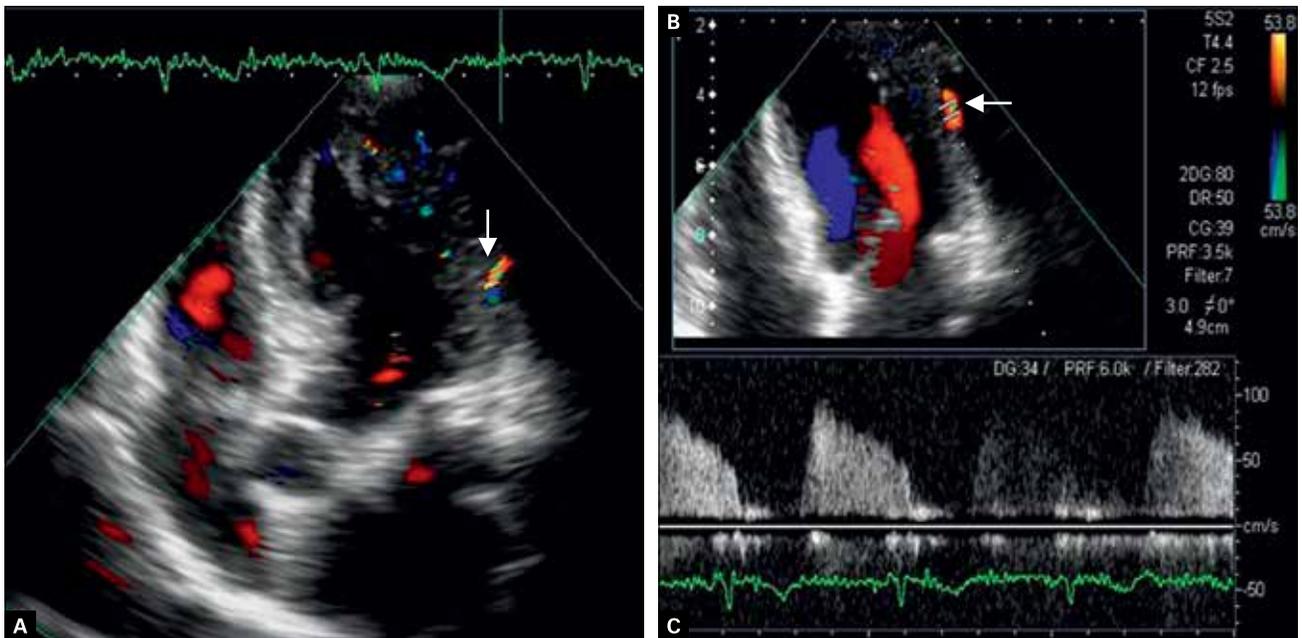
Clinical predictors associated with adverse outcomes are older age at diagnosis ( $p < 0.001$ ), tobacco use ( $p < 0.006$ ), diabetes ( $p < 0.05$ ), systemic hypertension ( $p < 0.001$ ), and hyperlipidemia ( $p < 0.001$ ) [9]. The rate of major complications reaches 17%.

The left coronary artery to left ventricular chamber fistulas are extremely rare. To our knowledge, the coexistence of micro- and macrofistulas has not been previously reported. The previous occlusion of the right coronary artery might have resulted in the activation and growing of collaterals supplying the occluded artery. We postulated that a locally elevated concentration of growth factors might have stimulated the angiogenesis and growing of microfistulas, leading to the formation of macrofistulas.

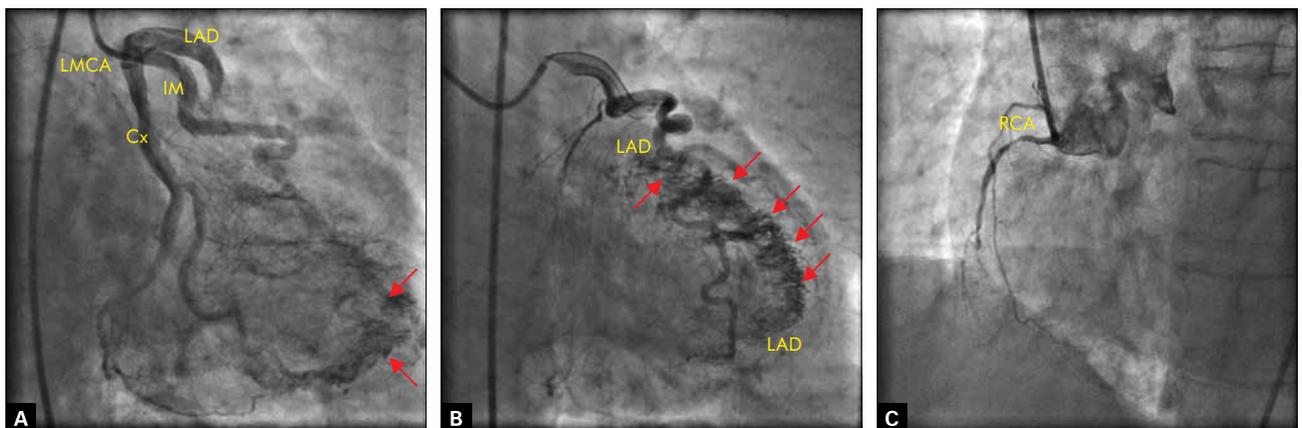
The present acute coronary syndrome might have originated from:

1. the “steal” phenomenon (type 2 myocardial infarction), as suggested by low levels of cardiac necrosis markers.
2. primary thrombotic origin (type 1 myocardial infarction), as suggested by thrombus formation in tortuous left coronary arteries feeding the multiple fistulas, which is consistent with the coexistence of multiple thrombotic risk factors, such as stroke in history or diabetes mellitus.

According to the current guidelines, large arteriovenous fistulas (both symptomatic and asymptomatic) should be closed (class I, level of evidence C) [10]. However, in the case of documented myocardial ischemia, arrhythmia and otherwise unexplained ventricular systolic or diastolic dysfunction or enlargement, or endarteritis, even small fistulas should be closed



**Fig. 1.** Transthoracic echocardiography. **A, B.** Five-chamber view. Numerous color-flows within a hypertrophic lateral wall of the left ventricle (arrows). **C.** Pulsed-wave color Doppler. Typical diastolic coronary artery flow observed in the lateral wall



**Fig. 2.** Coronary angiography. **A.** Contrast agent injected into the left coronary tree passes directly into the left ventricular cavity via multiple small and 3 large fistulas (arrows) originating from the mid and distal segments of the intermediate and the left anterior descending branch. **B.** Numerous microfistulas (arrows). **C.** Chronic occlusion of the right coronary artery with good collateral circulation from the left anterior descending branch. LAD – left anterior descending branch, LMCA – left main coronary artery, Cx – circumflex branch, IM – intermediate branch, RCA – right coronary artery

whenever it is technically feasible (class I, level of evidence C). The choice of treatment depends on the morphology and anatomy of a fistula. Both transcatheter and surgical approaches are accepted on condition that the fistula is completely obliterated.

Our symptomatic patient had numerous fistulas that were not very well-defined, which made it difficult to apply any interventional treatment. In such patients, nitroglycerin and its derivatives (used in optimal therapy to alleviate cardiac ischemic symptoms in most patients with coronary artery disease) are strongly contraindicated because they can aggravate the steal phenomenon and produce angina-like symptoms in cardiac ischemia caused by fistulas.

## Expert opinions

**Bogusław Kapelak:** This type of coronary fistulas (numerous and not well-defined) are not suitable for surgical treatment.

**Zbigniew Kordon:** Fistulas of such morphology are not good candidates for transcatheter treatment. Moreover, the left coronary artery to left ventricular chamber fistulas are extremely rare; there may be another explanation of this clinical picture, for example, LV noncompaction cardiomyopathy.

**Lidia Tomkiewicz-Pająk:** I would consider scintigraphy to make an objective, functional assessment of the extent of myocardial ischemia.

**Piotr Podolec:** I would focus on optimal medical treatment in this particular case. I would continue the therapy of acute coronary syndrome and, additionally, apply calcium channel blockers.

**Piotr Musiałek:** We should remember that in the case of coronary fistulas, nitroglycerin and its derivatives can exaggerate the “steal” phenomenon and produce angina-like symptoms.

**Krzysztof Rytlewski:** I would consider pharmacotherapy to improve the quality of life because depression might increase the patient’s discomfort and symptoms associated with the underlying condition.

## Conclusions

In our opinion, the management of this patient had to involve the functional assessment of myocardial ischemia together with the optimal medical treatment. A correctly diagnosed etiology of myocardial ischemia in this case was crucial for the optimal modification of medical treatment, which included aspirin, clopidogrel for at least 12 months (due to numerous cardiovascular and thrombotic risk factors), statin, angiotensin-converting-enzyme inhibitors,  $\beta$ -blockers, and calcium channel blockers.

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## A 23-year-old woman with Marfan syndrome and spine deformity (RCD code: I-2A.1)

Hanna Dziedzic-Oleksy, Lidia Tomkiewicz-Pająk, Bogdan Suder, Jerzy Sadowski, Piotr Podolec

### Background

Marfan syndrome is one of the most common inherited disorders of the connective tissue, transmitted as an autosomal dominant trait, with the prevalence of 2 to 3 per 10 000 population [1]. It is characterized by clinical variability and pleiotropic manifestations – from isolated features to severe neonatal presentation. It involves abnormalities of the cardiovascular, musculoskeletal, and central nervous systems, eyes, lungs, and skin. [2]

Typical characteristics of Marfan syndrome are associated with various mutations of the fibrillin-1 (FBN1) gene [2]. However, there are also cases of Marfan syndrome, where no mutation in FBN1 is identified (10%) [1]. In some of these patients, mutation in the gene for transforming growth factor- $\beta$  receptor may be responsible [2].

FBN1 gene is located on chromosome 15q-21.1, and it encodes extracellular matrix protein called fibrillin. It is a major component of elastic and nonelastic connective tissues [2]. Mutation of the FBN1 gene leads to widespread fragmentation of usually thin, elastic fibers, causing abnormalities in the formation of collagen, and, consequently, weakening the connective tissue [2]. Other frequent histologic features include cystic medial necrosis, fibrosis, and loss of the smooth muscle cells [3]. All of the above characteristics are not specific for Marfan syndrome; however, they are more commonly found in microscopic examinations in patients operated for ascending aortic aneurysms who have Marfan syndrome than in those with ascending aortic aneurysms and without Marfan syndrome [3].

The cardinal features of Marfan syndrome are aortic root dilatation and ectopia lentis [4]. The various other systemic features support the diagnosis. In 1996, the stringent criteria for the diagnosis of Marfan syndrome (Ghent nosology) were proposed [5]. They were based on the recognition of both “major” and “minor” clinical manifestations involving the skeletal, cardiovascular, and ocular systems, and the dura [5]. The major criteria included ectopia lentis, aortic root dilatation involving the sinuses of Valsalva or aortic dissection, and lumbosacral dural ectasia (found in computed tomography [CT] or magnetic resonance imaging [MRI]), family or genetic history, and 4 of 8 typical skeletal manifestations. However, the criteria had their limitations. The validation of these criteria was insufficient; moreover, they could not be applied to children and required expensive and specialized evaluation [4]. As a result, in 2010, the revised Ghent nosology was introduced (Table 1), underlining

the importance of aortic root aneurysm/dissection and ectopia lentis as the cardinal clinical features of Marfan syndrome and of testing for mutations in FBN1 and other relevant genes [4].

### Multisystemic abnormalities

#### Cardiovascular system

Aortic root dilatation is found on echocardiography in 60% to 80% of the patients with Marfan syndrome [1], and it is often accompanied by aortic regurgitation [1]. In most cases, dilatation affects the root of the aorta, but it may be found in any part of the thoracic or abdominal aorta. It may also include the carotid and intracranial arteries.

Aortic root aneurysm or dissection is the key diagnostic criterion in the new nosology; therefore, it is essential to evaluate it properly. Aortic root aneurysm is an enlargement of the aortic root at the level of the sinuses of Valsalva. The measurements should be done parallel to the plane of the aortic valve and perpendicular to the axis of blood flow. The largest correctly measured root diameter was obtained from at least 3 trans-thoracic images. Because the normal range for aortic diameter varies depending on the body size and age, the measurement should be corrected and interpreted as a Z-score [4,6]. Z-scores are based on the assumption of the linear relationship between the body surface area and aortic root size [6]. However, there are reports which suggest that dilatation is identified in all patients who have an aortic root diameter of 40 mm or more [7].

Because of the abnormal structure of the aortic wall, aortic dissection is a common problem, especially in untreated patients with Marfan syndrome. It is usually due to an intimal tear in the proximal ascending aorta. In most cases, it starts above the coronary arteries and extends the entire length of the aorta (type I dissection in the DeBakey classification or type A in the Dailey scheme). Ten percent of the dissections are type III (DeBakey classification) or type B (Dailey scheme), beginning distally to the left subclavian artery. Clearly, the wider the aortic root diameter, the bigger the risk of dissection, but dissection may occasionally occur even in patients with mild aortic dilation [1].

Mitral valve prolapse, caused by elongated leaflets, is another characteristic cardiac problem in patients with Marfan syndrome, although nonspecific [8]. Mitral valve prolapse in patients with Marfan syndrome may be accompanied by mitral regurgitation. The worsening of mitral regurgitation may occur due to spontaneous rupture of the chordae tendineae or as a result of infective endocarditis. In some of these cases, tricuspid valve prolapse may also occur.

#### Skeletomuscular system

Most patients with Marfan syndrome are tall (but not necessarily) because of excessive linear growth of long bones. They have disproportionately long extremities compared with the length of the trunk. Consequently, the ratio of the upper to the lower segments (US/LS) is decreased and the ratio of the arm span to height

is increased (greater than 1.05). The lower segment is measured from the top of the symphysis pubis to the floor in the standing position, and the upper segment is the height minus the lower segment [4]. Because the measurements may vary with age and ethnicity, a reduced US/LS ratio is <0.85 for white adults and <0.78 for black adults. A typical feature is arachnodactyly with positive thumb and/or wrist signs. Generalized joint hypermobility may also occur, but there are some individuals with Marfan syndrome who have reduced joint mobility of the elbow and digits, for example, reduced elbow extension ( $\leq 170$  degrees with full extension) [4]. Chest deformity may be present: pectus carinatum (thought to be more specific for Marfan syndrome), pectus excavatum, or chest asymmetry [4]. Hindfoot valgus is the result of the abduction of the forefoot and lowering of the midfoot. In some patients, only flat foot without hindfoot valgus is present. Acetabular protrusion is diagnosed by plain radiography, computed tomography (CT), magnetic resonance imaging (MRI) [9]. It is the deformity of the hip joint, in which the femoral head is displaced and the medial wall of the acetabulum invades the pelvic cavity. It causes hip joint stiffness, limited range of motion, and pelvic tilt resulting in hyperlordosis of the spine. The criteria involve loss of the normal oval shape of the pelvic inlet at the level of the acetabulum.

#### Visual problems

Ectopia lentis is a displacement or malposition of the lens caused by dysfunction or disruption of the supporting zonular fibers. It is recognized in 60% of the patients with Marfan syndrome. A common symptom of Marfan syndrome is myopia greater than 3 diopters, which is due to increased axis globe length. There is also an increased risk of retinal detachment, glaucoma, and early cataract formation. [2].

#### Other findings

Dural ectasia follows the enlargement of the spinal canal usually in the lumbosacral part of the spine [10]. It is a nonspecific feature of Marfan syndrome and is commonly observed in patients with Loeys–Dietz syndrome and in the vascular form of Ehlers–Danlos syndrome.

Skin stria are characteristic for Marfan syndrome after exclusion of other causes of stria such as weight changes or pregnancy. They are also usually found in an uncommon location such as the mid back, lumbar region, upper arm, axillary region, or thighs [4].

The differential diagnosis of Marfan syndrome includes evaluation of the characteristic features that may be present in other conditions. Marfan syndrome should be differentiated with regards to cardiac and aortic problems with Loeys–Dietz syndrome, mitral valve prolapse syndrome, MASS phenotype, familial thoracic aortic aneurysm syndrome, Ehlers–Danlos syndrome; with regards to ocular problems with Ectopia lentis syndrome; and with regards to skeletal problems with Shprintzen–Goldberg syndrome, and Ehlers–Danlos syndrome.

**Table 1.** Systemic scoring presented in the revised Ghent nosology includes [4]

Feature	Scoring
Wrist <b>AND</b> thumb sign Wrist <b>OR</b> thumb sign	3 points 1 point
Pectus carinatum deformity Pectus excavatum <b>OR</b> chest asymmetry	2 points 1 point
Hindfoot deformity Plain pes planus	2 points 1 point
Pneumothorax	2 points
Dural ectasia	2 points
Protrusion acetabuli	2 points
Reduced upper segment/lower segment ratio <b>AND</b> increased arm span/height <b>AND</b> no severe scoliosis	1 point
Scoliosis or thoracolumbar kyphosis	1 point
Reduced elbow extension ( $\leq 170$ degrees with full extension)	1 point
Facial features at least 3 of the following 5 features: ■ dolichocephaly (reduced cephalic index or head width/length ratio) ■ enophthalmos ■ downslanting palpebral fissures ■ malar hypoplasia ■ retrognathia	1 point
Skin stria	1 point
Mitral valve prolapse	1 point
A systemic score $\geq 7$ indicates systemic involvement.	

#### Diagnostic criteria

In the absence of family history of Marfan syndrome, the presence of one of any of the following criteria is diagnostic for Marfan syndrome:

- Aortic dilatation (aortic diameter  $Z \geq 2$  or aortic root dissection) and ectopia lentis
- Aortic dilatation (aortic diameter  $Z \geq 2$  or aortic root dissection) and a causal *FBN1* mutation
- Aortic dilatation (aortic diameter  $Z \geq 2$  or aortic root dissection) and a systemic score  $\geq 7$  (Table 1)
- Ectopia lentis and a causal *FBN1* mutation that has been identified in an individual with an aortic aneurysm

In the presence of family history of Marfan syndrome, the presence of one of any of the following criteria is diagnostic for Marfan syndrome:

- Ectopia lentis
- Systemic score  $\geq 7$  points (Table 1)
- Aortic dilatation (aortic diameter  $Z \geq 2$  above 20-years old,  $Z \geq 3$  below 20-years old, or aortic root dissection)



**Fig. 1.** Physical examination. Abnormalities in the skeletomuscular system. Arachnodactyly in a patient with Marfan syndrome



**Fig. 2.** Physical examination. Abnormalities in the skeletomuscular system. **A.** A positive wrist sign: the top of the thumb covers the entire fingernail of the fifth finger when wrapped around the contralateral wrist. **B.** A positive thumb sign indicates that the entire distal phalanx protrudes beyond the ulnar border of the clenched fist with or without the assistance of the patient or examiner to achieve maximum adduction

## Case presentation

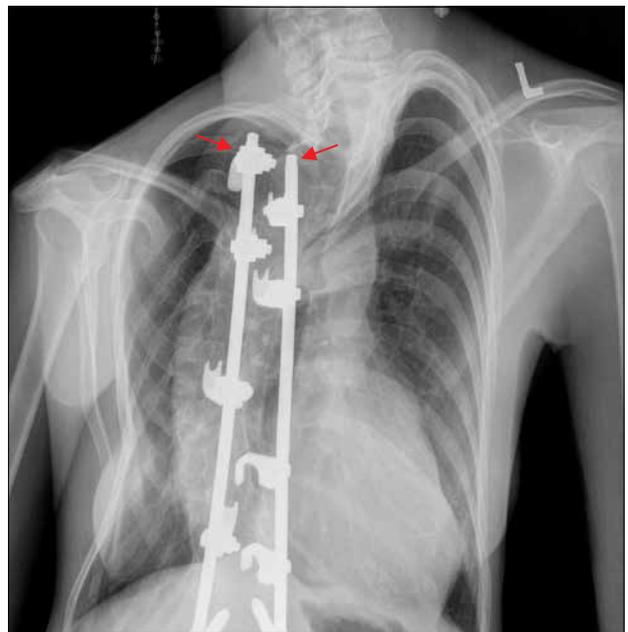
A 23-year-old white woman (height, 169 cm; weight, 48 kg) with the familial history of Marfan syndrome (mother and sister after aortic aneurysm operation) presented for a routine check-up in May 2012. In 2007, at the age of 18 years, she was referred to a cardiac clinic by a pediatrician to continue observation and treatment. In 2000 and 2003, corrective rods were inserted because of severe thoracic scoliosis.

On a physical examination (May 2012) performed according to the revised Ghent nosology [4], she received 10 points: arachnodactyly (fig. 1) with present wrist and thumb sign (fig. 2), severe chest deformity due to thoracic scoliosis (fig. 3, 4), facial features (dolichocephaly, enophthalmos, downslanting palpebral fissures), hindfoot deformity, and plain foot.

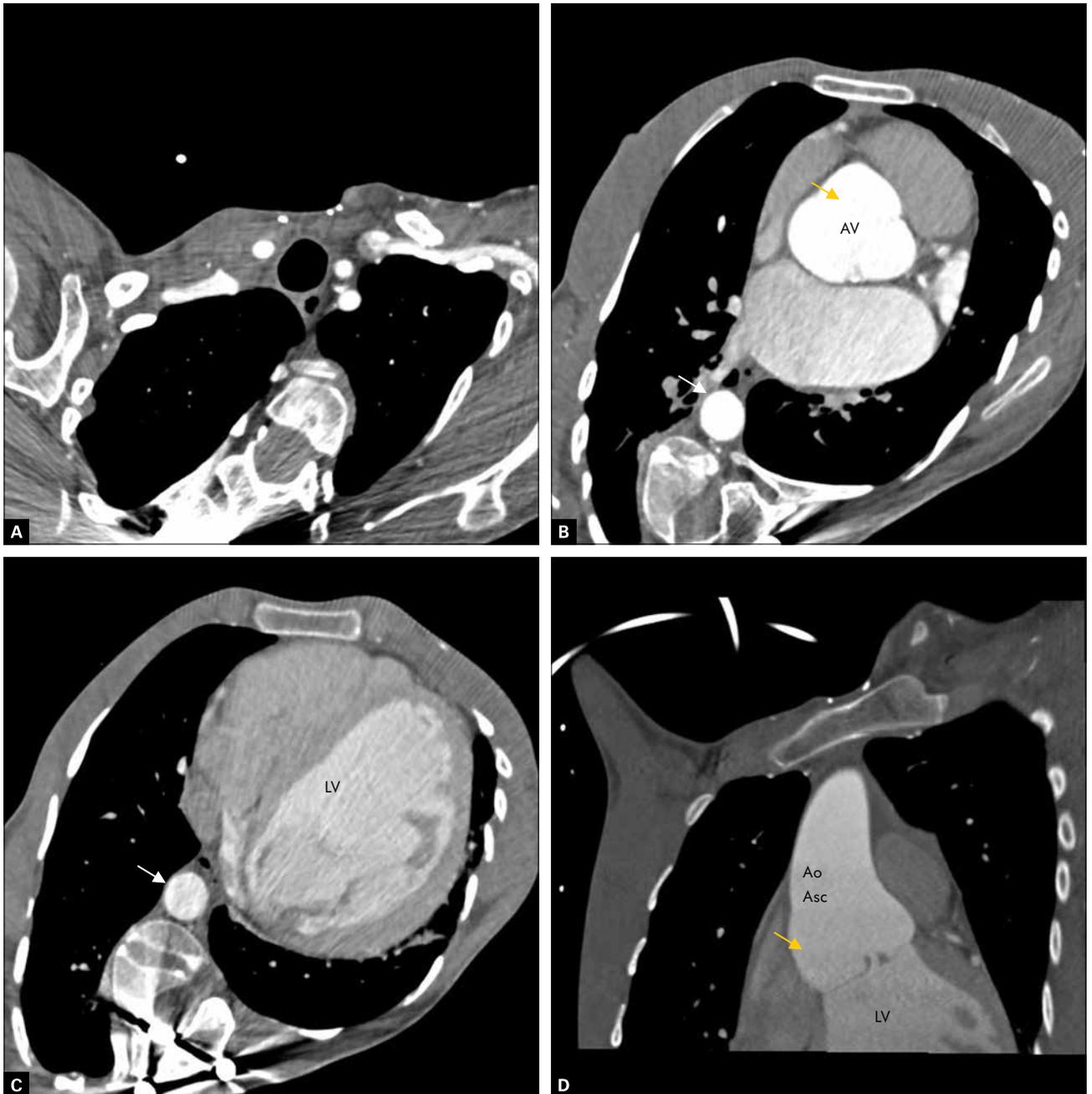
A CT scan performed in 2008 showed widened aortic bulb at the level of coronary sinuses (40 mm) and normal width at the level of the sinotubular junction (32 mm), ascending aorta (26 mm), and descending



**Fig. 3.** Physical examination. Abnormalities in the skeletomuscular system. Patient with Marfan syndrome. Severe scoliosis and chest deformity



**Fig. 4.** Chest X-ray. Patient after implantation of corrective rods (red arrows)



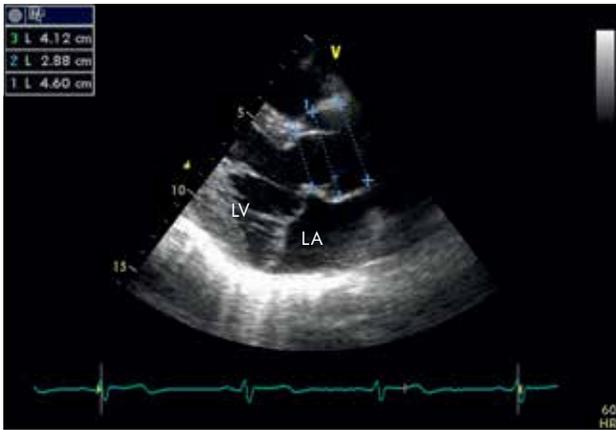
**Fig. 5.** Computed tomography. **A.** Severe chest deformity due to thoracic kyphoscoliosis. **B–D.** Enlargement of the aortic root (yellow arrow). Descending aorta (white arrow). LV – left ventricle, Ao Asc – ascending aorta, AV – aortic valve

aorta (18 mm). Follow-up cardiovascular CT performed in January 2012 showed enlargement of the aortic bulb (48 mm) and mild enlargement at the level of the sinotubular junction (35 mm), ascending aorta (27 mm) (fig. 5). At that time, she remained under observation.

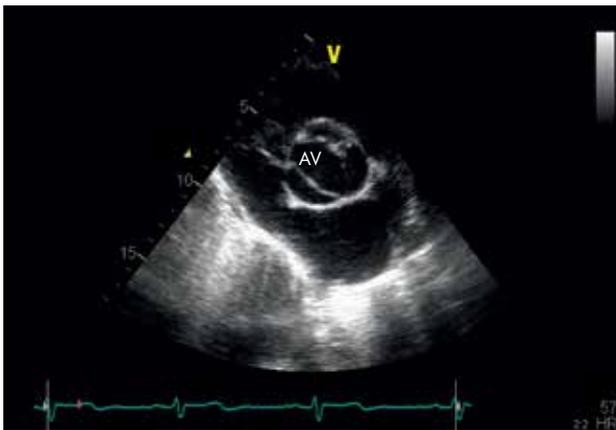
Echocardiography (June 2012) revealed enlarged left ventricle (67×43 mm) and left atrium (43×53×55 mm) with the ejection fraction of 63%; the width of the aortic annulus was 29 mm, aortic bulb – 46 mm, sinotubular junction – 41mm, and ascending aorta – 44 mm (fig. 6). The aortic valve was bicuspid, tricommissural with thick platelets and mild aortic regurgitation towards anterior mitral platelet (fig. 7); the mitral valve were also platelets thick. There was a prolapse of both platelets with moderate mitral regurgitation (fig. 8).

The patients' history and images were presented at the 5th meeting of the Center for Rare Cardiovascular Diseases at the John Paul II Hospital in Krakow. The experts agreed that severe chest deformity was not contraindication for an urgent operation of the aorta, preferably the Bentall procedure.

The patient underwent a surgery in January 2013. It was performed with the use of a cardiopulmonary bypass, hypothermia, and crystalline cardioplegia. During the procedure, the aortic aneurysm (50 mm) and the bicuspid tricommissural aortic valve were observed. They were removed and replaced with the prosthesis of the aortic root and valve (ST. Jude Medical 25 A Masters). Mitral valve was also replaced during the procedure (ST. Jude Medical 33 M Masters).



**Fig. 6.** Transthoracic echocardiography. Parasternal long-axis view. Width of the aortic annulus – 2,88 cm, aortic bulb – 4,6 cm and sinotubular junction – 4,12cm. LV – left ventricle, LA – left atrium



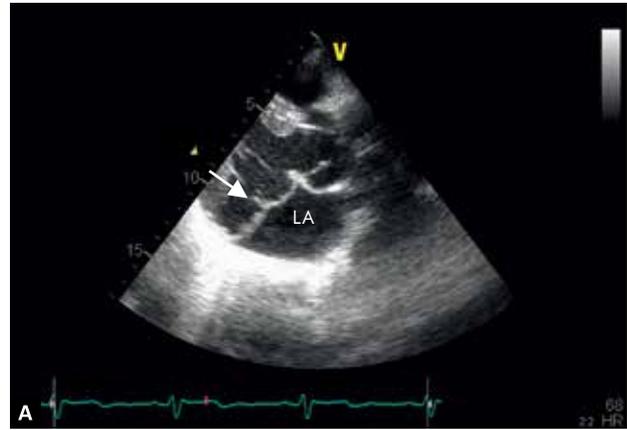
**Fig. 7.** Transthoracic echocardiography. Parasternal short-axis view. Bicuspid tricommissural aortic valve. AV – aortic valve

The postoperative course and wound healing were without complications. The patient was discharged from the cardiac surgery department in good general condition. She is currently symptom-free.

## Discussion

The 2010 American College of Cardiology / American Heart Association / American Association for Thoracic Surgery guidelines for thoracic aortic disease recommend to perform transthoracic echocardiography in patients with Marfan syndrome at the time of diagnosis and 6 months later to determine the aortic root and ascending aortic diameters and their rate of enlargement [11]. If the aortic diameter is stable over time and is less than 45 mm, annual echocardiography should be performed. A more frequent examination is necessary if the aortic diameter is 45 mm or more or grows significantly. At that time, surgery may be indicated [4].

During echocardiography, the assessment of the aortic root should include the measurements at the level of the ring, sinus, sinotubular junction, and distal ascending aorta. The evaluation of the left



**Fig. 8.** Transthoracic echocardiography. **A.** Parasternal long-axis view. The prolapse of both leaflets of the mitral valve (arrow). **B.** Apical 3-chamber view. LA – left atrium

ventricular function, aortic valve, and aortic regurgitation, or mitral valve and/or tricuspid valve prolapse and regurgitation should be performed.

Every patient should undergo imaging of the entire aorta preferably with CT angiography (CTA) or magnetic resonance angiography (MRA) [1]. It was reported that evaluation of aortic elasticity of the thoracic descending aorta MRA, was an independent predictor for progressive descending aortic dilation [12]. MRA should be performed at baseline and, if the size of the aorta beyond the root is normal, it should be repeated every 5 years. If an aneurysm develops, MRA imaging should be repeated at least once a year [1]. CTA or MRA imaging should also be performed if transthoracic echocardiography do not allow precise visualization and measurement of the proximal aorta [4]. CTA should preferably be used for exclusion of coronary artery disease before surgery since catheter manipulation may carry a risk of dissection of the weakened aortic wall [1].

## Medical treatment

Medical therapy includes  $\beta$ -blockers that decrease myocardial contractility and pulse pressure. They may improve the elastic properties of the aorta and reduce the rate of aortic dilation [1,13].

It is important to maintain systolic blood pressure at the level of 120 mm Hg. If the aortic dissection occurs, a rigorous antihypertensive medical treatment should be introduced, aiming at reducing the systolic

blood pressure to 110 mm Hg. The data suggest usefulness of  $\beta$ -blockers and angiotensin receptor blockers or angiotensin-converting-enzyme inhibitors [1].

The angiotensin receptor blocker, losartan, because of antagonism to transforming growth factor- $\beta$ , is also reported to reduce the rate of aortic dilatation. However, its potential usefulness should be supported by presently ongoing clinical trial [13]. Medical treatment should be continued after surgery.

### Surgical treatment

Since the operation of the replacement of the aortic valve and ascending aorta has become a low-risk and a very durable procedure, patients with Marfan syndrome and aortic root aneurysms are recommended to undergo elective operation. Regular diagnostic imaging and early planning of the operation may prevent critical dilatation or the life-threatening outcomes of aortic dissection and emergency repair [14]. The valve may be replaced with the artificial one or with the homogenic aortic graft [15]. Aortic homograft implantation does not require postoperative anticoagulation [15].

The 2010 European Society of Cardiology (ESC) guidelines [1] recommend elective operation for patients with Marfan syndrome if the diameter of the aorta (root [IC] or any other part [IIaC]) is 50 mm or more to avoid acute dissection or rupture. If the diameter is between 46 and 50 mm, the indications for repair include family history of aortic dissection, progression of dilatation (>2 mm/year), severe aortic regurgitation, or desire of pregnancy.

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## Expert comments

**Roland Hetzer:** Severe chest deformity is not contraindication for operation of the aorta. The operation of the aorta, preferably the Bentall procedure, should be performed as soon as possible.

**Bogusław Kapelak:** Severe chest deformity is not contraindication for operation of the aorta. During the operation, mitral valve should also be replaced.

**Wojciech Plazak:** Chest deformity is not a contraindication for operation of the aorta. The Bentall procedure should be performed as soon as possible. Mitral regurgitation should be diagnosed more precisely, and probably replaced.

**Krzysztof Bederski:** Pulmonary involvement in Marfan syndrome and spine deformity. Marfan syndrome is a disorder of the connective tissue, inherited in an autosomal dominant pattern with variable expression, and in, its classical form, it comprises abnormalities in the skeleton, cardiovascular system, and eye.

Disorders of the respiratory system have been noted in some patients with the syndrome in published reports. As no confirmatory biochemical test yet exists, the diagnosis must be made based on the clinical features alone. Some of the clinical features are not specific for Marfan syndrome and are found in other clinical entities, for example, Ehlers–Danlos syndrome.[1] A study and meta-analysis conducted in the Brompton Hospital and the Paediatric Research Unit, Guy's Hospital, London, and described by Wood et al.[1] shows the main pulmonary problems in patients suffering from this disorder. Spontaneous pneumothorax was the most common respiratory abnormality detected in these patients, being present at some time in 11%. A patient with Marfan syndrome is probably several-hundred times more likely to sustain spontaneous pneumothorax than a normal individual. The possibility that Marfan syndrome may be common in patients presenting with spontaneous pneumothorax has been

investigated in a study of patients presenting with this condition, in whom metacarpal index and height-arm span difference were determined and ophthalmological examinations performed.[2] Spontaneous pneumothorax has been reported in association with other inherited disorders of the connective tissue, including Ehlers–Danlos syndrome and the Marfanoid hypermobility syndrome, which has the features of both Marfan and Ehlers–Danlos syndromes.[3] Recurrent pneumothorax, bullae, and emphysema in Marfan syndrome are likely to be due to the generalized connective tissue defect, to which cardiac valve abnormalities, aneurysms, ectopia lentis, and bone changes have been attributed. Several studies have documented abnormal elastic tissue in the lungs of patients with Marfan syndrome.[4–7] Whether the changes in the elastic tissue in the lung are secondary to a collagen defect or represent an additional abnormality remains to be determined. A suggestion that elastic fiber changes result from cyclical tissue stresses in the tissue lacking adequate mechanical support owing to defective collagen seems reasonable. Several reports suggested an increased susceptibility to pulmonary infection in patients with Marfan syndrome. It is possible that this may be related to bronchiectasis resulting from connective tissue weakness [8].

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**Jakub Podolec:** Due to the enlargement of the aortic bulb to 48 mm in women with Marfan syndrome, the risk of developing an aortic dissection is high. The ESC guidelines indicate that women should be surgically treated before pregnancy [1]. There was an increase of 8 mm observed during the 4-year follow-up (2 mm per year). Due to the fact that the measurements had been done 5 months ago, an MRI scan should be considered before the decision regarding the surgical treatment. In case of the enlargement of the aortic bulb above 48 mm, surgery should be performed in the nearest future. If the diameter remains at the level of 48 mm, it might be considered to monitor the status of the patient (echocardiography or MRI). Physical activity should be limited for that period of time. Bentall-de Bono with mitral valve replacement

surgery should be considered. Administration of  $\beta$ -blockers should be considered to slow down aortic enlargement. Factors that will prompt the recommendation for surgery when aorta is 0.5 to 1 cm/year include family history of premature aortic dissection <50 mm and the presence of greater than mild aortic regurgitation. Surgical replacement of the aortic root does not completely normalize the risk because dissection may occur elsewhere in the aorta [2,3]. In the last 20 years, mortality rates after surgical treatment decreased significantly which may favor the decision of early surgery [4]. Gott et al.[5] reported that 30-day mortality after aortic root surgery was 0% in patients treated electively and 5.6% in those undergoing urgent surgery.

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**Piotr Musiałek:** This patient requires urgent surgery of the aortic root, because of the ongoing (documented) aortic root dilatation. The final decision about the mitral valve will be made by the surgeon performing aortic root surgery.

**Anna Kabłak-Ziembicka:** Severe chest deformity is related to an increased risk of cardiothoracic surgery. However, due to a substantial risk of aortic dissection during potential pregnancy and childbearing period, the patient should be referred to cardiac surgery department to undergo the Bentall procedure for aortic aneurysm.

## CONCLUSION

The patient should undergo the operation of the aorta (the Bentall procedure) and the replacement of the mitral valve as soon as possible.

## Multiple endovascular procedures for steno-occlusive arterial disease in the course of drug-resistant Takayasu's disease (RCD code: I-3A.1)

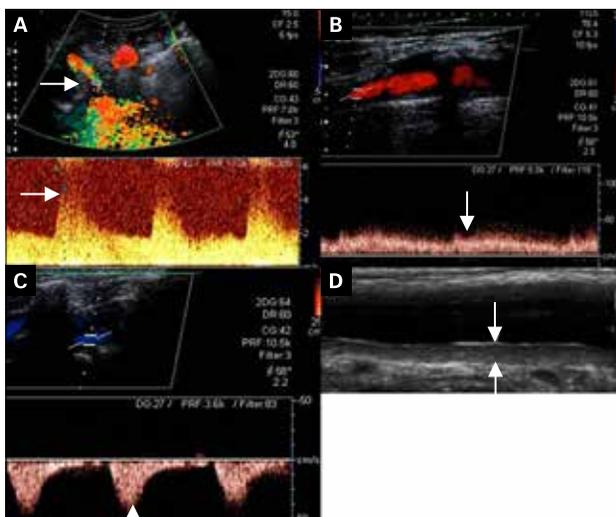
Leszek Wrotniak, Anna Kabtak-Ziembicka, Piotr Pieniżek, Piotr Wilkołek, Łukasz Tekieli, Tadeusz Przewłocki

### Background

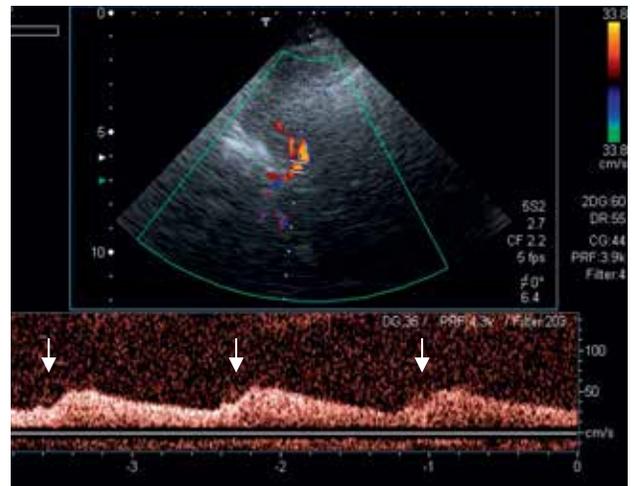
Takayasu's disease is a rare form of arteritis involving the walls of the aorta and its main branches and mainly affecting young women. Its annual incidence was estimated at 1 to 2 million cases per year, in hospital-based studies [1].

The symptoms of Takayasu's arteritis typically includes upper-limb claudication, dizziness or fainting, renovascular hypertension, and, in some cases, ischemic stroke or myocardial infarction. Because the symptoms are often the results of ischemia caused by the narrowing of the affected arteries, these patients are frequently within the scope of interventional cardiology.

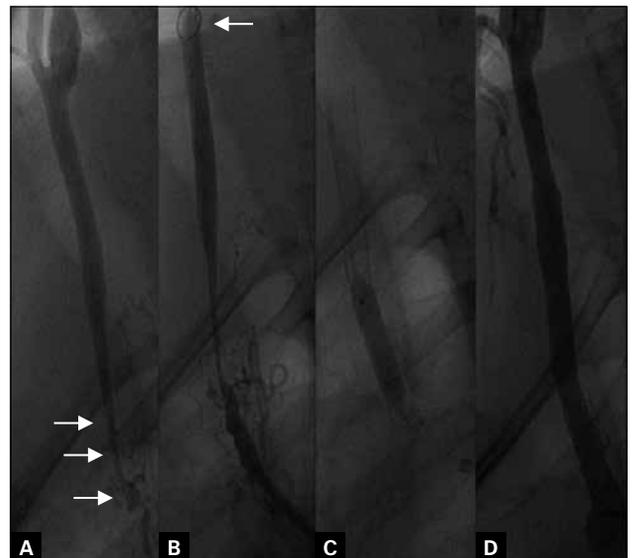
The major drawback of the surgical and endovascular interventions in Takayasu's arteritis is frequent and recurrent stenosis and thrombosis, as well as development of new steno-occlusive lesions that limit the long-term outcome [2].



**Fig. 1.** **A.** Color Doppler (above) and pulsed-wave Doppler ultrasonography. Subtotal long stenosis of the innominate artery and the right common carotid artery causing a significant increase in flow velocity. **B.** Pulsed-wave Doppler ultrasonography. Slow blood flow (steal grade I) in the right internal carotid artery (arrow) due to a tight stenosis of the proximal portions of the common carotid and innominate arteries. **C.** Pulsed-wave Doppler ultrasonography. Retrograde flow (steal grade III) in the right vertebral artery (arrow) consistent with the proximal occlusion of the right subclavian artery. **D.** B-mode presentation. Carotid artery with the “macaroni sign” typical for Takayasu's arteritis (arrow)



**Fig. 2.** Transcranial Doppler ultrasonography. B-mode presentation (above) and pulse-wave Doppler ultrasound (below). The arrow indicates low flow velocities in the right middle cerebral artery

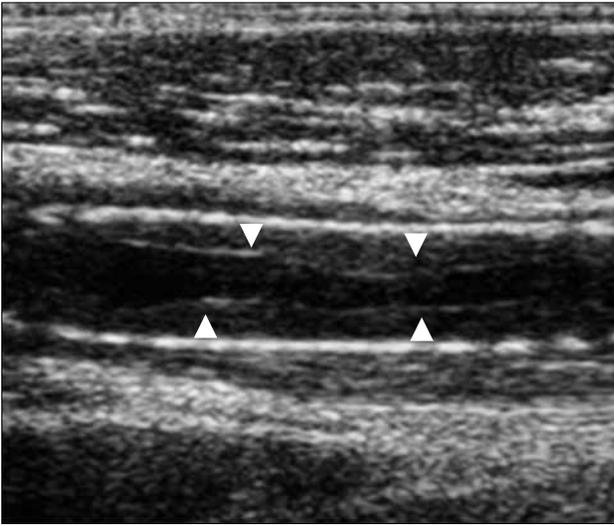


**Fig. 3.** Carotid arteries angiography. Right common and internal carotid artery. **A.** The arrows indicate long-segment, 90% stenosis of the right common carotid artery. **B.** The arrow shows the position of the distal neuroprotection system. **C.** Postdilation of the stent with 5×20 mm balloon. **D.** Final angiographic result

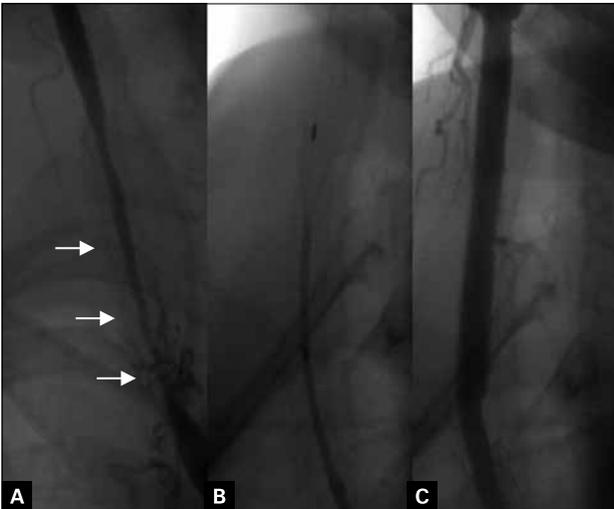
### Case presentation

A 34-year old woman was referred for color Doppler ultrasonography of the carotid and vertebral arteries in the course of diagnostic work-up for her recent ischemic stroke of the right cerebral hemisphere in October 2006.

An ultrasound examination revealed long-segment 90% lumen stenosis of the innominate artery and proximal portion of the right common carotid artery as well as occlusion of the right subclavian artery associated with retrograde blood flow in the right vertebral artery, consistent with subclavian steal syndrome (fig. 1). Both the left common carotid artery and its branches as well as the left vertebral and subclavian arteries were intact, with normal intima-media complex and no evidence of atherosclerosis.



**Fig. 4.** Carotid arteries ultrasonography. B-mode presentation. The arrows show diffuse critical intimal hyperplasia that cause a significant in-stent restenosis in the right common carotid artery



**Fig. 5.** Carotid arteries angiography. Right common carotid artery. **A.** Significant restenosis (arrows). **B.** Stent implantation. **C.** Final angiographic result

The study was complemented by the evaluation of the hemodynamics in the circle of Willis (fig. 2). After consultations with an independent neurologist and endovascular surgeon, the patient was referred for angioplasty and stenting of the right common carotid artery.

On admission, a careful review of the patient's history revealed recurrent syncope in the past few years, episodes of transient weakness in her left arm and leg during the last 5 years, claudication and numbness in the right arm and palm, visual disturbances of the right eye, excruciating headaches since adolescence, and dizziness.

Previous neurological consultations and examinations excluded multiple sclerosis, epilepsy, skeletal deformities, and neurodegenerative brain and spine diseases.



**Fig. 6.** Carotid arteries angiography, December 2007. **A.** Significant restenosis (arrow). **B.** Stent implantation. **C.** Final angiographic result

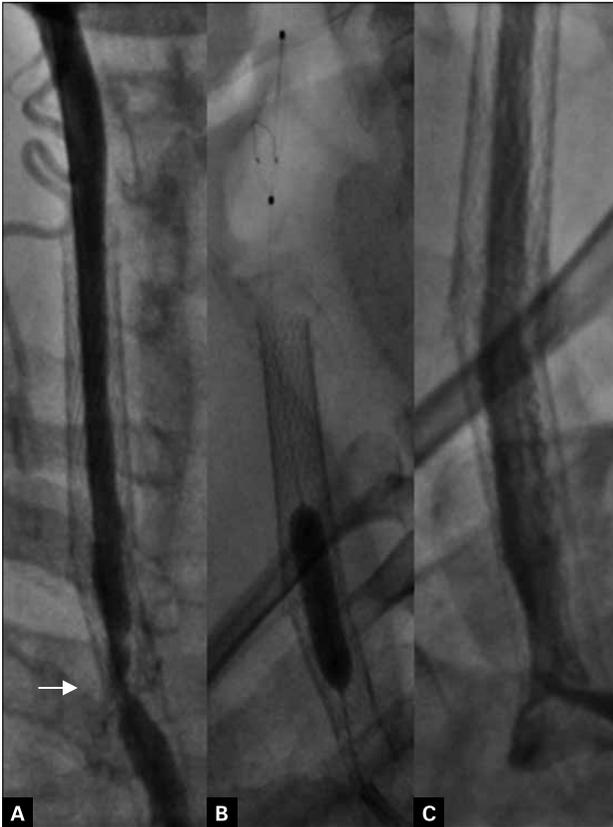
A physical examination revealed a systolic bruit over the right clavicle and weak pulse in the right radial artery. Right and left arm blood pressure was 70/40 mm Hg and 110/70 mm Hg, respectively.

Laboratory blood tests showed mild leukocytosis (14 000), elevated C-reactive protein levels (CRP, 49 mg/L) and erythrocyte sedimentation rate (ESR, 42 mm/h), and hyperlipidemia (low-density lipoprotein [LDL] cholesterol, 3.09 mmol/L).

Subsequent angiography confirmed 90%–95% right common carotid artery stenosis and concurrent occlusion of the right subclavian artery (fig. 3AB). The patient underwent right carotid artery angioplasty with the use of neuroprotection system subsequent stent implantation (CarotidWallstent) with good outcome (fig. 3CD). Periprocedural and postprocedural periods were uneventful.

Considering the multiple factors consistent with the American College of Rheumatology (ACR) criteria for Takayasu arteritis, such as early onset of carotid stenosis (<40 years), right arm claudication, weak pulse on the right radial artery, difference of 40 mm Hg in systolic blood pressure between the arms, systolic bruit, and angiographic findings typical for this disease, the patient was referred to an immunology department for consultation. She was discharged on simvastatin (20 mg once daily), aspirin (75 mg once daily), and clopidogrel for 3 months (75 mg once daily). When Takayasu's disease was confirmed, the patient was given corticosteroid (methylprednisolone, 8 mg daily).

Five months later, a routine follow-up ultrasonography showed evidence of tight stenosis recurrence within



**Fig. 7.** Carotid arteries angiography. August 2008. **A.** Significant restenosis (arrow). **B.** Balloon angioplasty. **C.** Final angiographic result

the previously implanted stent (fig. 4). Restenosis was managed with another stent-supported angioplasty (fig. 5). Blood test results showed evidence of an active inflammatory process (leukocytosis,  $14\,500\text{ mm}^3$ ; CRP,  $133\text{ mg/L}$ ; ESR,  $98\text{ mm/h}$ ). On discharge, aspirin, clopidogrel, and statin were continued, while methylprednisolone was increased to  $24\text{ mg}$  per day.

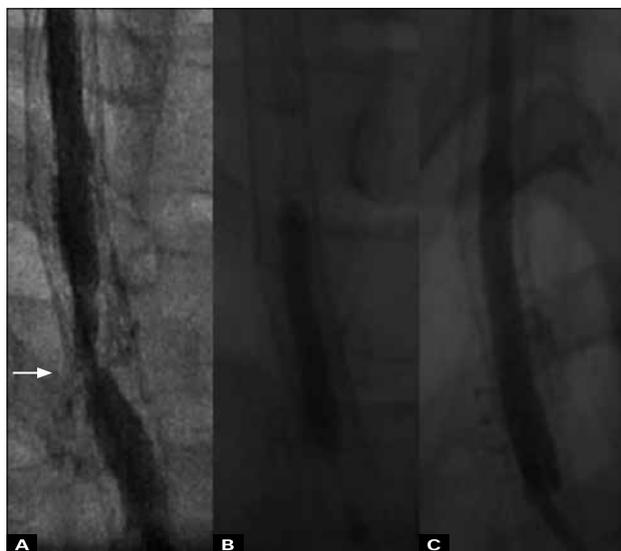
The corticosteroid therapy soon turned out to be ineffective because active inflammation persisted. Furthermore, stenosis recurred after 9 months, in December 2007. It was treated with another stent-supported angioplasty (fig. 6). Aspirin dose was increased to  $150\text{ mg}$ , corticosteroid was stopped, and cyclophosphamide was started.

However, stenosis continued to recur and, because of associated neurological symptoms, the patient underwent balloon angioplasty in August 2008 (8 months) (fig. 7), and stent supported angioplasty in April 2009 (8 months) (fig. 8).

Considering restenosis and persistent high CRP levels, ESR, and white blood cell count, which suggested lack of response to drug treatment of Takayasu's arteritis, cyclophosphamide was replaced with azathioprine ( $100\text{ mg}$  initially and later increased to  $150\text{ mg}$ ), which, in turn, was replaced with hydroxychloroquine ( $200\text{--}400\text{ mg}$ ) per day. The levels of inflammatory markers normalized. However neurological symptoms recurred 28 months later, in August 2011. This time, drug-eluting stent was implanted to the restenosed right common carotid artery, in which stenosis



**Fig. 8.** April 2009. **A.** Computed tomographic angiography. Focal subtotal in-stent restenosis (arrow). **B.** Restenosis in angiography (arrow). **C.** Stent implantation. **D.** Final angiographic result



**Fig. 9.** Carotid arteries angiography. August 2011. **A.** Significant restenosis (arrow). **B.** Stent implantation. **C.** Final angiographic result

recurred (fig. 9). The patient was given infliximab intravenously, at a dose of 5 mg/kg. The dose was repeated 4 and 8 weeks later, and then continued at 8-week intervals.

Currently, the patient is free of symptoms. Her blood tests improved (leukocytosis, 6200 mm<sup>3</sup>; CRP, 1.28 mg/L; ESR, 8 mm/h; LDL cholesterol, 2.0 mmol/L). Ultrasonography does not show any signs of restenosis.

## Discussion

The present case report demonstrates two major clinical problems encountered in young patients with Takayasu's arteritis who had suffered for years from neurological and vascular disorders. The first one is a significant delay in correct diagnosis, and the other is recurrence of arteritis despite pharmacological treatment, which is commonly observed in clinical practice.

The low incidence of Takayasu's arteritis makes physicians less alert to its symptoms when examining patients, which often leads to a delayed diagnosis. In many cases, the patient is not diagnosed until arterial obstruction manifests itself [3, 4]. At this point, the treatment must include revascularization of the affected arteries, combined with the initiation of immunosuppressive treatment to alleviate the inflammatory process and prevent future vascular complications [5]. In our patient, corticosteroids were introduced after endovascular revascularization. However, proved ineffective both with respect to biological disease activity and new clinical manifestations. Glucocorticoid therapy, which plays a pivotal role in Takayasu's arteritis, is associated with disease relapses or steroid dependence in 50% to 80% of the cases [6].

The second-choice treatment in relapsing Takayasu's arteritis is either azathioprine, methotrexate, or cyclophosphamide alone or in addition to steroids. They may improve disease control, prevent

the development of new arterial lesions, and help reduce the cumulative glucocorticoid dose [6]. The pharmacotherapy protocol largely depends on the individual center experience. In the present case, both cyclophosphamide and subsequent azathioprine were ineffective in terms of both control of biological disease activity and prevention of restenosis.

Hydroxychloroquine sulphate, a substance used in malaria prevention, or in the treatment of rheumatoid arthritis and lupus erythematosus, was also reported to be effective in Takayasu's arteritis. However, due to possible eye toxicity, patients receiving hydroxychloroquine sulphate should undergo regular ophthalmological check-up. Our patient required a high dose of hydroxychloroquine sulphate; however, it resulted in good biological and clinical response for almost 2 years.

Restenosis that occurred 2 years later called for another change in the anti-inflammatory regimen. This time, infliximab, the tumor necrosis factor- $\alpha$  specific monoclonal antibody, was introduced. While there are promising reports on infliximab use from many centers, its role in the treatment of Takayasu's disease has not been fully elucidated so far [7,8].

Yet another challenge in the treatment of Takayasu's disease is the assessment of the disease activity because there are no generally recognized indicators. Moreover, clinical disease activity, considered as the intensity of the signs and symptoms on clinical examination or the presence of complications, is not always correlated with the results of routine inflammatory tests [7].

A set of criteria for disease activity used in our center is consistent with those proposed by Mekinian et al [7]. The disease is considered clinically active if the patient presents one of the following features: a new onset of carotidynia, pain over the other large vessels, new ischemic vascular claudication, transient ischemic episodes that cannot be attributed to other factors, and either a new bruit or asymmetry of the pulse or blood pressure.

Biological activity is defined as the presence of at least two of the following features: ESR >30 mm/h, or CRP >10 mg/L, or fibrinogen >3 g/L, and/or leukocyte count >10 000/mm<sup>3</sup> (in the absence of infection) [7]. Radiological activity is defined as the presence of at least two of the following: arterial wall thickening on ultrasonography or multislice computed tomography; or arterial wall thickening with mural enhancement in magnetic resonance imaging; or arterial hypermetabolism on positron emission tomography.

## Conclusion

Considering the significant incidence of drug resistance and relapses of Takayasu's disease, revascularization is inevitable in the long-term treatment of numerous patients, often providing necessary time to stop the disease by pharmacotherapy.

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## Fibromuscular dysplasia: a rare cause of ischemic stroke (RCD code: I-4A)

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### Background

According to Salisbury et al. [1], in women aged from 15 to 45 years who recently had ischemic stroke, other than classical risk factors of stroke should also be taken into account, such as exogenous hormone intake, pregnancy, patent foramen ovale, vascular diseases (fibromuscular dysplasia [FMD], spontaneous dissection), connective tissue diseases (systemic lupus erythematosus, antiphospholipid syndrome), primary vasculitis (Takayasu's arteritis, central nervous system angiitis), moyamoya disease, migraine with aura, Susac's syndrome, sarcoidosis, and Hashimoto's encephalopathy. FMD is a rare noninflammatory disease of unknown etiology that affects mainly the medium-size arteries, predominantly in women (female-to-male ratio of 10 to 1). It occurs usually in young women of childbearing age and, in most cases, renal and carotid arteries are involved. In a large autopsy study, FMD was found in 0.02% of over 20 000 consecutively examined carotid arteries [3,4].

### Case presentation

A 45-year-old woman, who had been unsuccessfully treated for several years for headaches and “swishing” noise in her right ear, presented with a 12-day history of right-hemisphere ischemic stroke (4 points in the National Institute of Health Stroke Scale). A Doppler ultrasound image on admission revealed long, irregular, string-sign right internal carotid artery (RICA) stenosis in its proximal segment, with peak systolic velocity of 5.28 m/s and end-diastolic velocity of 2.53 m/s, which corresponded to lumen stenosis of more than 90%. Subsequent computed tomography angiography confirmed a 5-cm-long 95% RICA stenosis at a level of C1 and C2 vertebra, typical for FMD (fig. 1). After a neurological consultation, the patient was referred for carotid artery angioplasty. Except tight stenosis, the angiography revealed local RICA dissection (fig. 2A). Using the proximal neuroprotection system (Mo.Ma), angioplasty with a 4-mm balloon was performed. Because of a suboptimal effect of the procedure, a self-expanding open-cell stent (Precise 8×30 mm) was implanted and postdilated with a 5×20 mm balloon, and the final result was optimal (fig. 2B–E). The peri- and postprocedural period was uneventful. No signs of FMD lesions were found in other arteries. During the next 42 months of follow-up, the patient did not present any new



**Fig. 1.** Computed tomography angiography. **A.** Two-dimensional reconstruction. **B.** Three-dimensional reconstruction. Subtotal long stenosis (arrows) of the right internal carotid artery

neurological symptoms, and ultrasonography did not reveal restenosis nor any new signs of FMD.

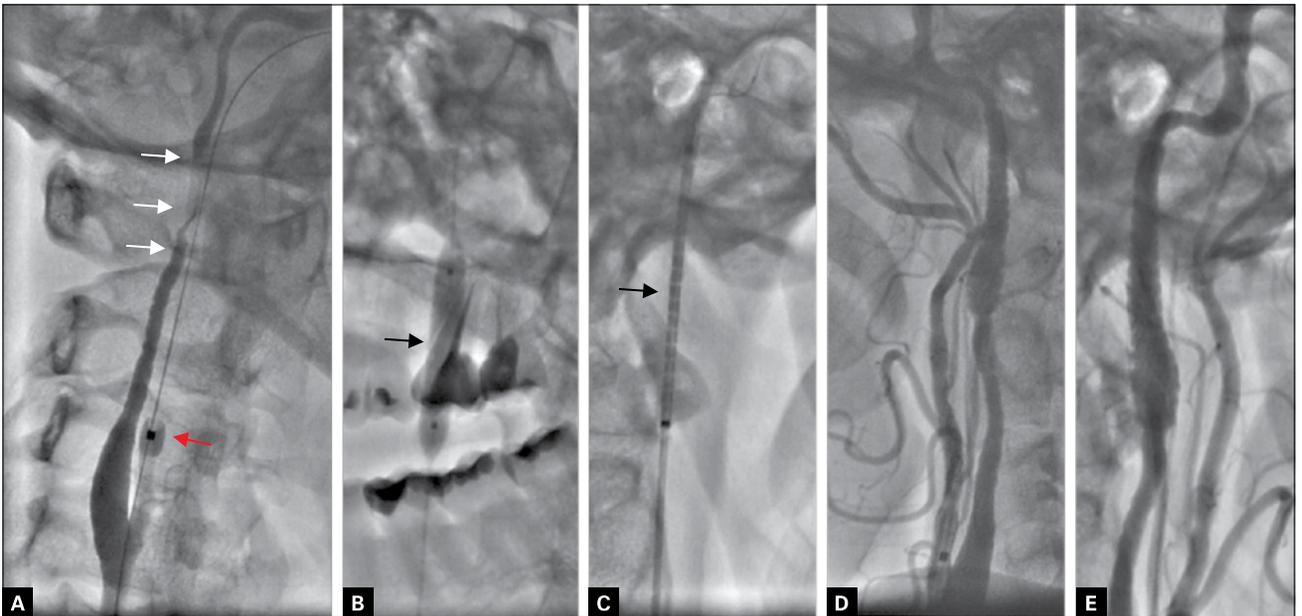
### Discussion

As reported by Chatzikonstantinou et al. [2], FMD is responsible for 1.9% of all ischemic strokes in patients aged between 19 and 45 years. In our center, we have treated 5 patients with FMD of 2500 patients with carotid stenosis undergoing carotid angiography.

In most cases, carotid FMD is asymptomatic; however, the symptoms may occur with the increasing grade of artery stenosis. They typically include severe migraine headaches, noise in the ears, or lightheadedness. Many affected patients usually contact their family doctor and, if they consult a specialist, it is usually a neurologist. Although the incidence of carotid FMD is marginal, we believe that ultrasonography should be recommended in patients with recurrent heavy migraines, also because it may reveal other abnormalities in the extracranial arteries, such as hypoplastic vertebral artery or vasculitis.

Although FMD is considered by some as a benign condition, in fact it may lead to serious complications including transient ischemic attack (TIA) or stroke (19.2%), spontaneous dissection (19.7%), and aneurysm formation (17%) [4]. The reported TIA, ischemic stroke symptoms suggestive of complicated FMD are Horner's syndrome (enophthalmos, ptosis, miosis), carotidynia, cranial nerve palsy (nerves V, VII, and VIII), which may be accompanied by limb weakness, syncope, aphasia. Of note, FMD is commonly associated with aneurysms in the cerebral arteries; thus, intracranial bleeding related to aneurysm rupture may be the first symptom of FMD.

FMD lesions can be usually identified in the middle and distal segments of the extracervical internal carotid artery, sometimes extending to the base



**Fig. 2.** Carotid arteries angiography. Right internal carotid artery. **A.** White arrows indicate string-sign artery stenosis with local dissection; red arrow shows distal balloon of proximal neuroprotection system. **B.** Predilatation with 4×20 mm balloon (arrow). **C.** Precise 8×30 mm stent positioning (arrow). **D, E.** Final angiographic result of angioplasty at left anterior oblique 30 and right anterior oblique 30 projection

of the skull. Typical findings on angiography include multifocal concentric luminal narrowing alternating with the areas of mural dilatation that are wider than the original lumen (the string-of-beads appearance). This finding is present in 80% to 90% of the patients with FMD. Histopathological findings show the accumulation of dysplastic muscle cells forming “fibromuscular hillocks” and disruption of the internal elastic membrane [3,4]. Macroscopically, FMD may lead to aneurysms, dissections, or stenosis.

For screening purposes, careful ultrasound examination is required because FMD may involve more than 1 supraaortic artery. An examiner should keep in mind that carotid FMD lesions, as opposed to atherosclerotic ones, are typically located at the level of the C1-C2 vertebra; thus, they can be easily overlooked. Therefore, it is important to scan the carotid artery as distally as possible, and, if the case is doubtful, further noninvasive evaluation should be considered. According to the authors ultrasound may be successfully use for evaluation of FMD in vertebral arteries.

The management of FMD includes conservative endovascular and surgical treatment. The endovascular treatment of symptomatic carotid stenosis caused by FMD has been reported as an effective and safe procedure [5]. Balloon angioplasty, recommended for symptomatic FMD, should be the first-line treatment. If the result of balloon angioplasty is not satisfactory (>30% of residual stenosis, dissection), stent placement should be considered.

Endovascular FMD treatment requires preload with antiplatelet including aspirin, clopidogrel, and heparin administered during the procedure. It is of key importance to perform angiography of both the extracranial and intracranial arteries to evaluate the risk of endovascular intervention, including the evaluation of bilateral FMD and the risk of periprocedural intracranial bleeding, which is significantly higher in

patient with intracranial aneurysm (that may accompany FMD in the carotid artery).

Although guidelines recommend the long-life use of aspirin in patients after stroke, it is not clear how long it should be administered in the case of treated carotid FMD because the origin of FMD lesion is not atherosclerotic in nature and the prevalence of intracranial aneurysm is higher. However, after percutaneous angioplasty alone, aspirin at a dose of 75 mg once daily and clopidogrel at a dose of 75 mg daily should be administered for at least 4 weeks, followed by aspirin alone (long-life). After stent implantation, aspirin and clopidogrel should be given together at doses of 75 mg for 4 weeks to 3 months, followed by aspirin alone (75 mg daily).

## Conclusions

Carotid FMD is a rare but potentially dangerous condition that may provoke symptoms of brain ischemia. Angioplasty (stent-supported if indicated) is an optimal therapeutic option for patients with severe, symptomatic, or complicated carotid FMD.

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## Multivessel coronary artery disease in a very young patient with acute myocardial infarction and preexcitation syndrome (RCD code: I-6B.0)

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### Background

Although heart and vessel diseases, including acute coronary syndrome (ACS), constitute the major cause of morbidity and mortality worldwide, atherosclerosis causing cardiac ischemia rarely occurs in adults below the age of 30 years [1]. Premature atherosclerosis is mostly attributed to a variety of gene mutations, for example, those encoding endothelial function, low-density lipoprotein (LDL) receptors, and apolipoproteins, which results in premature atherosclerosis [2].

We present a case of a patient previously treated for arrhythmia, who experienced ACS and underwent a cardiac surgery at the age of 29 years, followed by repeated percutaneous coronary interventions (PCI).

### Case presentation

In 2007, a 25-year-old man, a heavy smoker, was admitted to the Department of Cardiology due to atrioventricular reentrant tachycardia (AVRT) with recurrent syncope. A physical examination revealed abdominal obesity, flexion contracture at the elbows, and muscle dystrophy of the upper and lower limbs. Blood pressure was normal (110/70 mm Hg).

In a family history, his father had hypertension and hypercholesterolemia. Moreover, at the age of 56 years, he suffered left hemispheric stroke and underwent right internal carotid artery stenting. His mother suffered from obesity and diabetes and his younger brother had hypertension.

An electrophysiological study revealed concealed left anterior accessory pathway. Radiofrequency ablation using the transaortic retrograde access was performed. After 4 years, arrhythmia reappeared and the ablation procedure was repeated.

In March 2011, he experienced sudden chest pain. An urgent electrocardiogram (ECG) showed horizontal ST-segment depression in leads I, aVL, and V<sub>4</sub> through V<sub>6</sub> and ST-segment elevation in lead aVR. An echocardiogram showed mild left ventricular hypertrophy with normal size and segmental wall motion changes (apical segment akinesis and interventricular septum hypokinesis). The ejection fraction was 51% and the left atrium was slightly enlarged (22 cm<sup>2</sup>).

Laboratory test results showed markedly elevated troponin I levels of 0.68 ng/mL (normal range,

0–0.014 ng/mL), which was consistent with non-ST elevation myocardial infarction. On coronary angiography, multivessel coronary steno-occlusive lesions were found, including ostial occlusion (99%) of the left anterior descending (LAD) coronary artery, 80% lumen reduction of the circumflex artery (Cx), and 99% of the first marginal branch (MgI), while the right coronary artery was recessive but with no evident stenotic lesions. As clinical status of the patient deteriorated with the development of cardiogenic shock, intravenous adrenaline, dopamine, and dobutamine were administered.

The patient was urgently referred for coronary artery bypass grafting (CABG). It was performed with the implantation of the right mammary artery to the LAD, left mammary artery to the MgI, and radial artery to the MgII. The intra-aortic balloon pump was placed during the surgery. After the surgery, the patient's clinical state began to improve gradually, although extremely difficult wound healing was observed.

Laboratory tests showed markedly elevated levels of inflammatory markers (C-reactive protein, 35 mg/L; white blood cell count,  $14\,300 \times 10^6/L$ ; fibrinogen, 5.8 g/L) and atherothrombotic lipid profile (total cholesterol, 5.48 mmol/L; LDL cholesterol, 3.35 mmol/L; high-density lipoprotein [HDL] cholesterol, 0.83 mmol/L; triglycerides, 2.86 mmol/L).

In October 2011, recurrence of chest pain was observed. On ECG, a horizontal ST-segment depression was noted in leads I, aVL, and V<sub>4</sub> through V<sub>6</sub>, negative T wave in leads I, aVL, V<sub>2</sub> through V<sub>5</sub>, ST-segment elevation in leads aVR, V<sub>1</sub>, and V<sub>2</sub>, and QS in lead V<sub>1</sub>. No features of preexcitation were shown (fig. 1). Cardiac markers were negative.

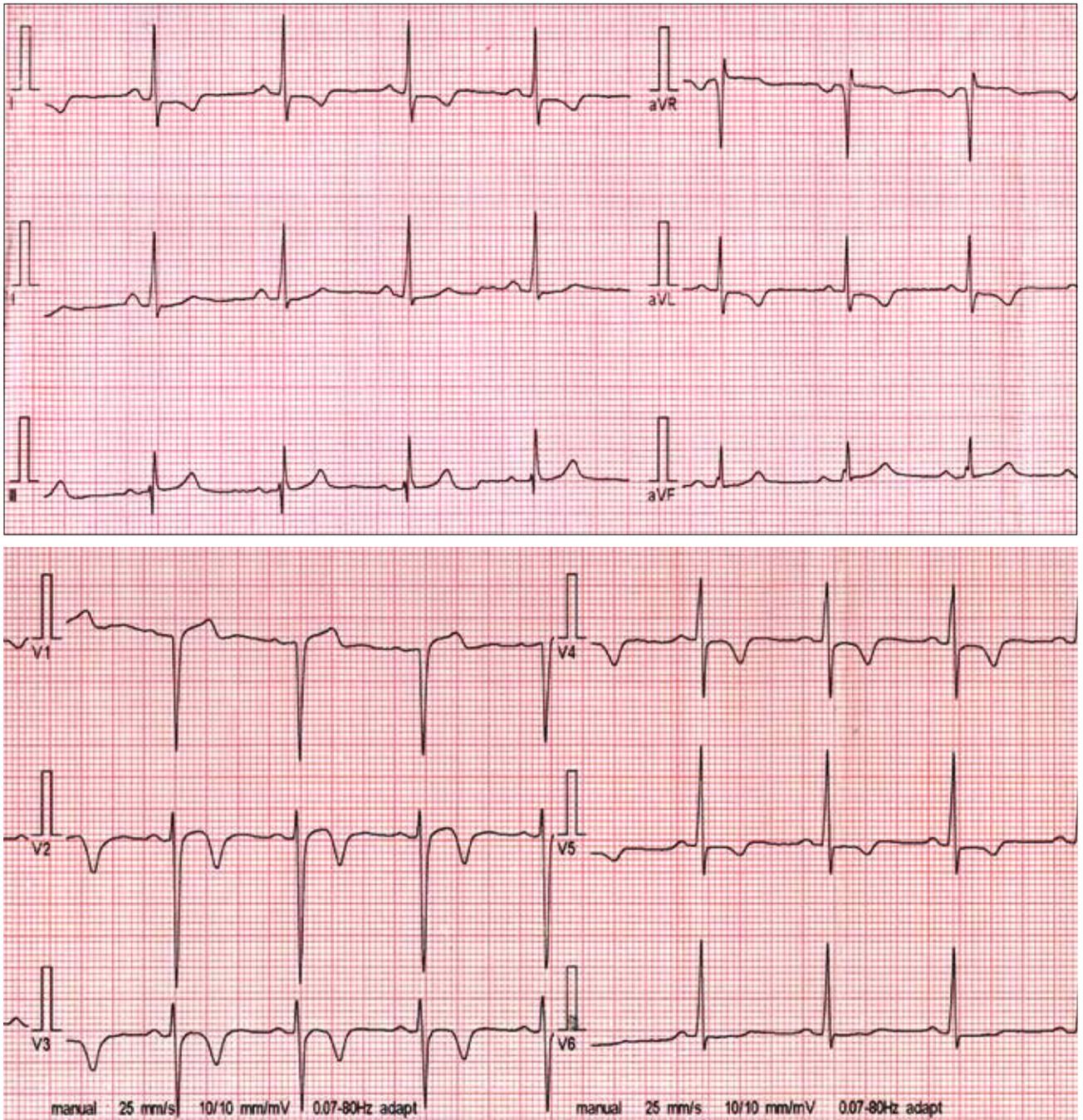
Coronary angiography revealed left main trunk (LM) near occlusion (99% lumen stenosis), 99% Cx stenosis, 80% lumen stenosis of the anastomosis between the right internal mammary artery (RIMA) and LAD. At the same time, PCI (LM/Cx) with drug-eluting stent implantation was performed (fig. 2).

After 3 weeks, using the right transradial approach, RIMA-LAD anastomosis PCI was performed with additional drug-eluting stent implantation (2.75 × 12 mm) (fig. 3A–C). The angiographic result of both procedures was optimal. Computed tomographic angiography 2 years after PCI revealed both stent to be patent.

Currently, AVRT has developed again and evident electrocardiographic preexcitation – Wolf–Parkinson–White syndrome emerged. It indicates the location of the Kent bundle in the left lateral position (fig. 4).

### Discussion

In the presented case, arrhythmia was the first manifestation of the cardiovascular system disorders. It had an atypical course. Initially, the patient presented with symptomatic, recurrent AVRT paroxysms without the features of preexcitation in a resting ECG. The electrophysiological study revealed the concealed form of accessory pathway, which was ablated twice, in August 2007 and in January 2011.



**Fig. 1.** Electrocardiogram. Performed during chest pain. Features of acute ischemia. Sinus rhythm with a heart rate of 75 beats/min, no features of preexcitation (PQ segment duration of 160 ms), normal QT segment duration (340 ms), and ST-segment depression in leads I, aVL, and V<sub>4</sub> through V<sub>6</sub>, negative T-wave in leads I, aVL, V<sub>2</sub> through V<sub>5</sub>, ST-segment elevation in leads aVR, V<sub>1</sub>, and V<sub>2</sub>, and QS in V<sub>1</sub>

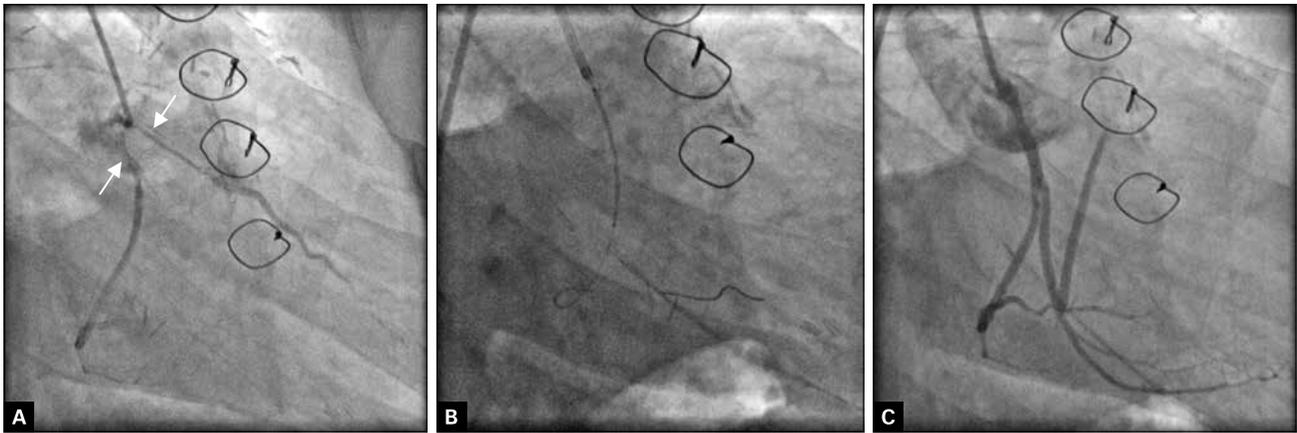
The patient remained asymptomatic for the next 2 years but then he again developed AVRT. Moreover, the typical electrocardiographic features of Wolf-Parkinson-White syndrome emerged on ECG, with the left lateral position of the accessory pathway (Figure 4). The patient was referred for the third ablation using transseptal approach in 2013.

Another problem in the patient was premature multivessel coronary artery atherosclerosis, which manifested with ACS at the age of 29 years.

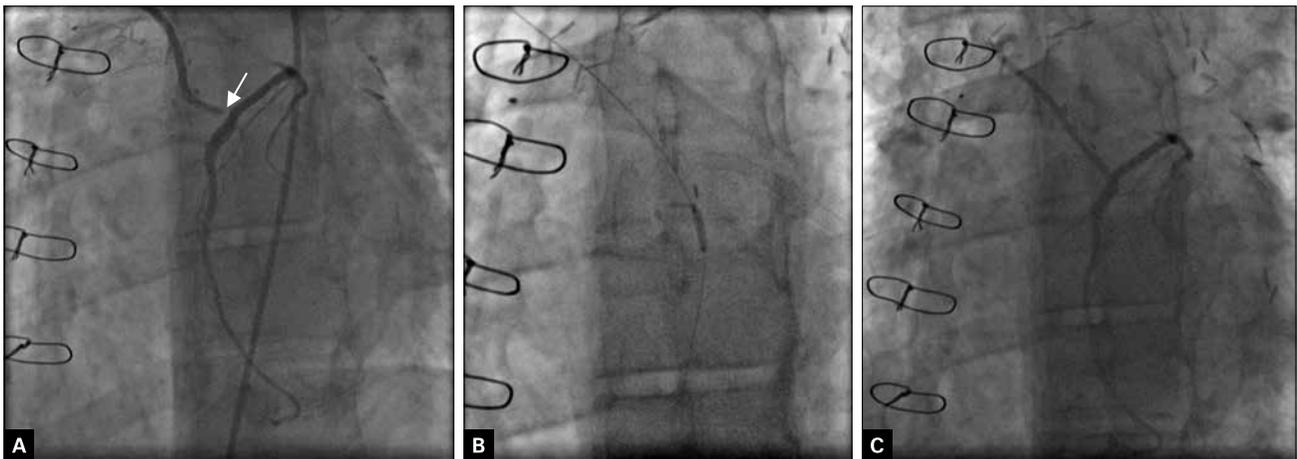
Myocardial infarction in individuals under the age of 45 years constitutes from 6% to 10% of all myocardial infarctions; however, it accounts for less than 1%

of myocardial infarctions in patients under the age of 30 years in Europe and the United States [1].

In this age group, it predominantly affects men. Important risk factors include a family history of myocardial infarction before the age of 55 years, hyperlipidemia, smoking, and obesity [3]. ACS at a young age is commonly characterized by the presence of multiple cardiovascular risk factors and unfavorable prognosis [1,3]. In the present case, after a successful CABG procedure, we faced the problem of progressive atherosclerotic lesions leading to chest pain recurrence and requiring two-vessel angioplasty with stent implantation.



**Fig. 2.** Coronary angiography. A 29-year-old patient after coronary artery bypass grafting admitted with unstable angina. The left main trunk / circumflex artery percutaneous coronary intervention was performed with drug-eluting stent implantation. **A.** Subtotal stenosis of proximal left anterior descending coronary artery and circumflex (arrows). **B.** Drug-eluting stent implantation (3.0×30 mm) **C.** Final angiographic result



**Fig. 3.** Coronary angiography. Second percutaneous coronary intervention in a 29-year-old patient after coronary artery bypass grafting. Right internal mammarian artery – left anterior descending branch (RIMA-LAD) anastomosis percutaneous transluminal angioplasty was performed with drug-eluting stent implantation. **A.** Critical stenosis of RIMA-LAD graft anastomosis (arrow). **B.** Drug-eluting stent implantation (2.75×12 mm). **C.** Final angiographic result

Evidence of a significant disease on coronary angiography suggests the presence of a premature atherosclerotic process. A number of reports have investigated the association between various gene polymorphisms and the phenotypic expression of myocardial infarction [2,4,5].

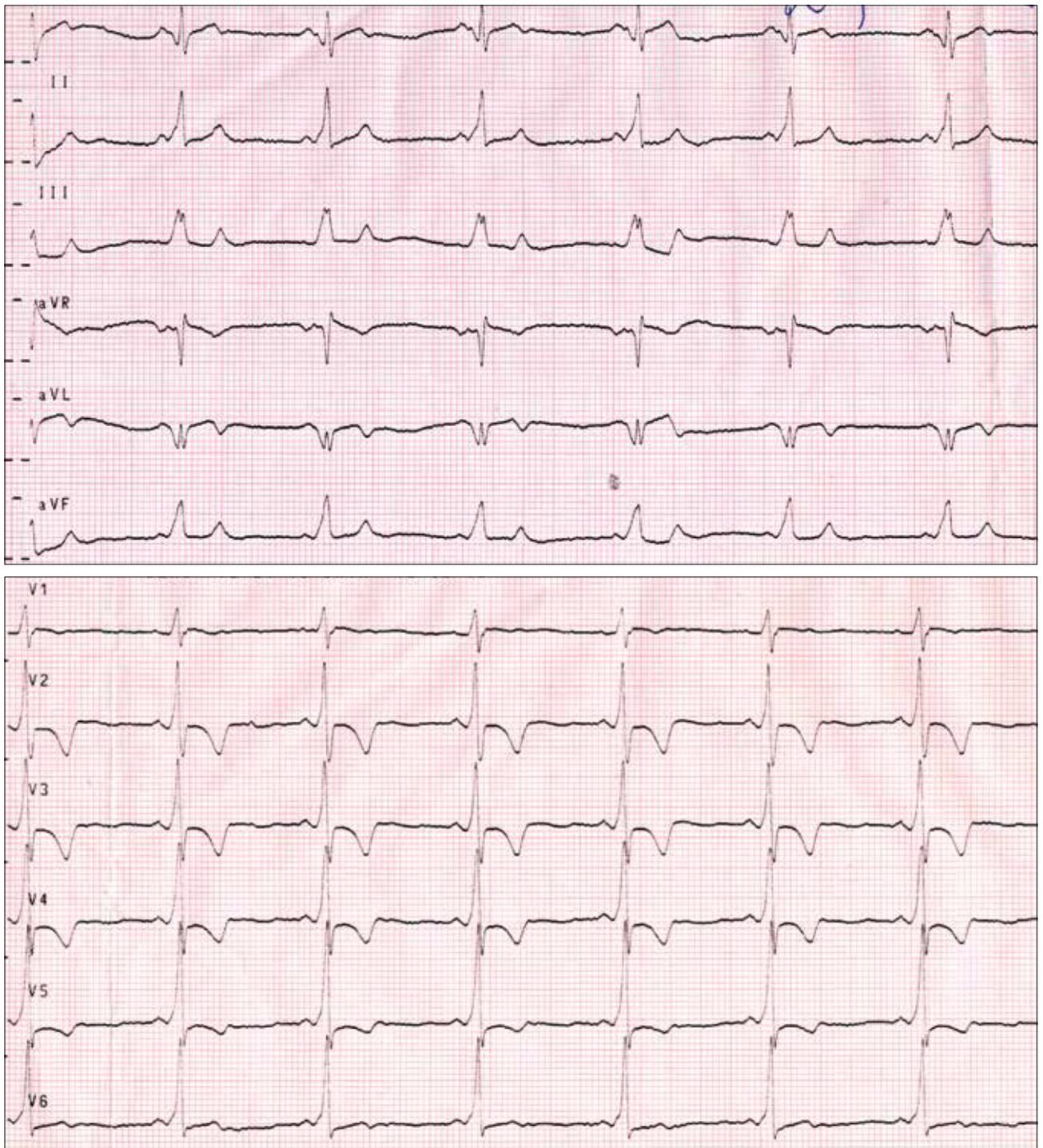
The most frequent cause of ACS and premature atherosclerosis in young adults is familial hypercholesterolemia characterized by the abnormally high level of LDL [4]. The incidence of familial hypercholesterolemia is 1 in 500 patients with coronary artery disease for heterozygotes, and 1 in million patients for homozygotes [4]. Possible mutations include LDL receptor, apolipoprotein B, or proprotein convertase subtilisin/kexin type 9 (*PCSK9*) genes [4].

Brsic et al.[5] suggested that ApoE polymorphism appears to be a strong independent predictor of adverse events, suggesting a significant effect in accelerated coronary artery disease. However, in the presented case, familial hypercholesterolemia was excluded during blood tests. Patient had a typical atherothrombotic pattern of the lipid profile [6].

The levels of triglycerides, total cholesterol, and LDL cholesterol were elevated, with an apparent low level of HDL cholesterol. Inflammatory markers were increased, similarly as in patients with early-onset carotid atherosclerosis [7].

In this case, among gene mutations, laminopathies (progeria syndromes) must be taken into account. The reported incidence of progeria is approximately 1 in every 4 to 8 million newborns [8]. According to the classification proposed by the Universal Mutation Database (UMD-LMNA; [www.umd.be/LMNA/](http://www.umd.be/LMNA/)), our patient revealed the features of Emery–Dreifuss muscular dystrophy (EDMD) and, perhaps, Hutchinson–Gilford progeria syndrome (Table 1).

Among numerous clinical features of EDMD, cardiac symptoms predominate, probably because cardiomyocytes are more sensitive to a nuclear protein defect than myocytes [9,10]. The cardiac symptoms follow a different course in each EDMD group. In emerinopathy, the atrial muscle is affected early, ventricular function is preserved for longer, but the ejection fraction decreases and dilatation of the left atrium



**Fig. 4.** Electrocardiogram. Sinus rate of 60/min with PQ of 0.12 s and QT of 0.39 s. Wide QRs with delta wave visible in all leads. Negative T in leads aVL and V<sub>2</sub> through V<sub>5</sub>. Its morphology and polarity indicates the left lateral Kent bundle position

develops with age. In laminopathy, systolic dysfunction is prevalent, ventricular muscle is affected, and dilatation of the left ventricle appears early leading to a dangerous ventricular arrhythmia. Implantation of a cardioverter-defibrillator is recommended [11–13].

In the present case, after a few years of follow-up, electrocardiographic features typical for Wolf-Parkinson-White syndrome became evident with paroxysms of AVRT. This phenomenon can result from the initial domination of physiological atrioventricular junction over the accessory pathway in atrioventricular

conduction property. The concomitant laminopathy could destroy the structure of atrioventricular junction cells, which could overbalance this domination towards the accessory pathway [12]. However, this theory needs to be confirmed in further investigation.

In Hutchinson–Gilford progeria syndrome, a progressive rapid steno-occlusive atherosclerosis predominates, perhaps with the most apparent predisposition to the coronary artery localization. This results in ACS in adolescents and young adults, with the evidence of multivessel coronary artery atheromas

**Table 1. Classification of the clinical syndromes associated with laminopathies according to the Universal Mutation Database (UMD-LMNA; [www.umd.be/LMNA/](http://www.umd.be/LMNA/))**

1. Emery–Dreifuss muscular dystrophy (EDMD2, EDMD3).
2. Limb-girdle muscular dystrophy type 1B (LGMD1B).
3. Dilated cardiomyopathy with conduction defect (DCM-CD / CMD1A).
4. Autosomal recessive Charcot–Marie–Tooth disease (CMT2B1).
5. Dunningan-type familial partial lipodystrophy (FPLD2).
6. Mandibuloacral dysplasia (MADA).
7. Hutchinson–Gilford progeria syndrome (HGPS).
8. Restrictive dermopathy (DR).
9. Other premature aging syndromes generalized lipodystrophy, insulin-resistant diabetes, disseminated leuko-melanodermic papules, liver steatosis and cardiomyopathy (LIRLLC / LDHCP), atypical Werner syndrome (WRN-like), arthropathy, tendinous calcinosis and progeroid features
10. Variants and overlapping combinations

causing a steno-occlusive disease. The lipid profile is usually within the normal range or LDL cholesterol is only mildly elevated in contrast to familial hypercholesterolemia. Thus, statins and fibrates are probably less effective in preventing atherosclerotic progression, which is independent of the lipoprotein level.

The continuously growing class of laminopathies is characterized by the involvement of several tissues such as striated muscles with partial lipodystrophy, striated muscles and peripheral nerves, striated muscles and lipodystrophy and association of myopathy and progeroid features (Table 1) [8]. In the present case, flexion contracture at the elbows and muscle dystrophy of the upper and lower limbs were present.

In conclusion, ACS is a disease with complex pathogenesis with the involvement of individual gene background, lifestyle, and environmental risk factors. Laminopathies and the other gene mutations responsible for the development of premature atherosclerosis will probably be more frequently described as these patients are more and more systematically investigated. It suggests the existence of an overlapping continuum within the different types of laminopathies.

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# Part 4

Rare diseases of pulmonary circulation  
– RCD class II

**Editor: Grzegorz Kopec**



# Introduction

Grzegorz Kopec

Pulmonary vascular diseases have recently been extensively reviewed by experts in the form of journal articles and textbooks. The most recently published positions are *Guidelines for the diagnosis and treatment of pulmonary hypertension* by Galiè N, Hooper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G; *Textbook of pulmonary vascular diseases* by Yuan J, Garcia J, Hales Ch, Rich S, Archer S, West JB; *Pulmonary circulation. Diseases and their treatment. Third Edition* by Peacock A, Naeije R and Rubin LJ; and *Pulmonary Hypertension* by Humbert M and Lynch JP.

In the current part of this book, we did not aim to review the data already covered by the superb publications. We rather intended to show the problem of pulmonary hypertension from the perspective of the Centre for Rare Cardiovascular Diseases in Krakow, Poland. We also provided the reader with recent epidemiological data on pulmonary hypertension and presented some emerging therapies of this group of diseases.

The introductory chapter is followed by a chapter on arrhythmias in pulmonary hypertension, which emerge as a significant challenge in everyday clinical practice for pulmonary hypertension specialists. Next, we present the current approach to vasoreactivity testing in patients with pulmonary hypertension due to left heart diseases. We believe that this is an especially important issue considering the lack of generally accepted algorithms for vasoreactivity testing in these patients. Afterwards we discuss health-related quality of life in pulmonary arterial hypertension. These chapters are followed by 8 clinical cases from our and other centers. Readers interested in pulmonary artery vasculitis and tumors are especially referred to the above mentioned *Textbook of pulmonary vascular diseases*. Inborn disorders of the pulmonary arteries are described in Part 3 of the current textbook.

And last but not least I would like to express my gratitude to prof. Nazzareno Galiè from the University of Bologna, a Master of Masters in pulmonary vascular diseases. Prof. Galiè consulted the most difficult patients from our centre and taught me the art of care for patients with pulmonary hypertension.



# Rare diseases of pulmonary circulation: Perspective of the Centre for Rare Cardiovascular Diseases

## Pulmonary hypertension as a rare cardiovascular disease

Grzegorz Kopeć

### Definitions

- **Pulmonary hypertension (PH)** – an increase of mean pulmonary artery pressure ( $\geq 25$  mm Hg) at rest as assessed by right heart catheterization (RHC) [1]
- **Pulmonary arterial hypertension (PAH)** – an increase of the mean pulmonary artery pressure ( $\geq 25$  mm Hg) and pulmonary vascular resistance (PVR;  $> 3$  Wood units) at rest as assessed by RHC (World Symposium on Pulmonary Hypertension, Nice 2013)
- **Low-prevalence PH** – types of PH with the prevalence estimated at  $< 1:2000$  citizens
- **Non-low-prevalence PH** – types of PH with the prevalence estimated at  $\geq 1:2000$  citizens
- **Severe PH** – life-threatening or chronically debilitating types of PH with no effective cure
- **Overlapping PH** – types of PH caused by 2 or more etiologic factors.

### Classification

Diseases of the pulmonary circulation constitute class II according to the the Krakow Rare Cardiovascular Diseases (RCD) Classification (see Part 2). Class II is further divided into 3 groups: inborn anomalies of the pulmonary vessels, acquired anomalies of the pulmonary vessels, and PH. Although in most cases, PH is an acquired disease of the pulmonary circulation, it has been distinguished as a separate group because of its complex pathogenesis and pathophysiology.

PH has been recently classified [2] according to clinical characteristics and associated risk factors into five groups.

Table 1 shows the classification of PH established during the 4th World Symposium on Pulmonary Hypertension in Dana Point in 2008. An updated classification has been recently presented at the 5th

World Symposium on Pulmonary Hypertension, Nice 2013.

In Part 1 of this book, the current definition of rare diseases is presented. Importantly, the definition includes not only the low prevalence (less than 1:2000 citizens) but also the debilitating character of these diseases, the lack of effective therapies, and poor prognosis.

Many disorders included in the Dana Point classification of PH have low prevalence. However, not all of them are life-threatening or chronically debilitating. The others can be efficiently cured. An example is PH associated with atrial septal defect with a low estimated prevalence of 0.14:2000 [3,4]. It can usually be cured by surgical or percutaneous closure and cannot be classified as RCD due to its good prognosis. However, some patients with atrial septal defect will develop severe PH, which will be a contraindication to a curative operation, and some will have persistent PH despite closure of the defect, which will chronically debilitate them and will require combined therapeutic efforts. These cases are classified as a low-prevalence PH, group II.1.A according to the RCD classification (see Part 2).

Some diseases listed in the Dana Point classification are quite frequent. For example, chronic obstructive pulmonary disease (COPD) affects about 5% of the European adults [5], and a significant proportion of these individuals may suffer from PH (between 30% and 70%, depending on the severity of COPD) [6]. Most of them will require smoking cessation and specific COPD treatment, and only a small proportion will develop severe PH (1% of the patients with COPD) [5], which will chronically debilitate the affected patients. These cases will be classified as severe form of non-low-prevalence PH (class II.1.B according to the RCD classification).

Other patients with rare forms of PH, requiring combined efforts, are those with two or more overlapping diseases leading to PH, for example, PH with atrial septal defect and venous thromboembolic disease. These cases are classified as overlapping PH (class II.1.C according to the RCD classification).

### Epidemiology of PH

The overall prevalence of PH in adult population has been estimated at 0.3% in a recent retrospective

**Table 1. Clinical classification of pulmonary hypertension – Dana Point 2008 [2]**

<b>1. Pulmonary arterial hypertension</b>
1.1. Idiopathic
1.2. Heritable
1.2.1. BMPR2
1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
1.2.3. Unknown
1.3. Drugs and toxins induced
1.4. Associated with (APAH)
1.4.1. Connective tissue disease
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart disease
1.4.5. Schistosomiasis
1.4.6. Chronic hemolytic anemia
1.5. Persistent pulmonary hypertension of the newborn
<b>1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis</b>
<b>2. Pulmonary hypertension due to left heart disease</b>
2.1. Systolic dysfunction
2.2. Diastolic dysfunction
2.3. Valvular disease
<b>3. Pulmonary hypertension due to lung diseases and/or hypoxia</b>
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental abnormalities
<b>4. Chronic thromboembolic pulmonary hypertension</b>
<b>5. Pulmonary hypertension with unclear and/or multifactorial mechanisms</b>
5.1. Hematological disorders: myeloproliferative disorders, splenectomy
5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK-1 – activin receptor-like kinase 1 gene; APAH – associated pulmonary arterial hypertension; BMPR2 – bone morphogenetic protein receptor type 2, HIV – human immunodeficiency virus

observational cohort study. Strange et al. [7] used a database from a large echocardiography laboratory, to which all patients from the Australian city, Armadale, were referred. Between January 2003 and December 2009, over 10 000 individuals (6.2% of the Armadale population) underwent echocardiography. Based on the obtained data, the prevalence of all forms of PH, defined as systolic pulmonary artery pressure exceeding 40 mm Hg, was estimated at 326 cases per 100 000 population. Clinical and echocardiographic data revealed that the most common cause of PH was left heart disease (250/100 000 population) followed by

PH due to respiratory diseases (37/100 000 population), PAH (15/100 000 population), and idiopathic PAH (IPA; 4.8/100 000 population) (Table 2). The overall prevalence of PH was similar in a prospective study in a random sample of 511 men and women aged 48–76 years (men, 47%) selected from population registers in Krakow. An elevated right ventricular systolic pressure of 36 mm Hg or higher on echocardiography was observed in 3 patients (0.6%) [8].

The main limitation of the population studies in PH is that the echocardiographic estimation of the right ventricular pressure is subject to a significant error [9]; therefore, a definite diagnosis of PH cannot be made using this technique. On the other hand, RHC, which is the gold standard for diagnosing PH, cannot be used as a screening tool in population studies because it is an invasive technique.

RHC has been used to make a definitive diagnosis of PH in registries conducted in the PH reference centers. Recently, Hurdman et al. [10] have presented the results of a registry from a single pulmonary vascular center serving a referral population of about 15 million. Between 2001 and 2010, 1737 consecutive patients were screened, of which 1344 incident patients with PH aged 59 ± 17 years (women, 62%) were enrolled into the study. Most patients were diagnosed with PAH (44%), and the prevalence of other PH groups (according to the Dana Point classification) was as follows: group 2, 12%; group 3, 13%; group 4, 18%; group 5, 2.4%.

Other registries from the referral centers focused on patients with PAH. The prevalence of PAH was estimated at 15 cases per million and its annual incidence at 2.4 cases per million population [11].

The limitation of the studies from the reference centers is the risk of underestimating the true prevalence of the disease in the population because a significant percentage of the patients may die before being evaluated in a tertiary center. Table 3 shows the proportion of different types of PAH diagnosed in the reference centers.

## Prognosis of pulmonary hypertension

PH is associated with poor prognosis. The mean survival of patients with different types of PH was 4.3 ± 0.1 years in the study by Strange et al. [7], which involved over 900 patients with PH, aged 75 ± 15 years. The mean survival was similar in patients with PH due to left heart disease (4.2 years) and in those with PH due to respiratory disease (4.1 years). It was significantly better (about 5 years) in the PAH group, which, however, was 10 years younger than the other PH groups. Additionally, all patients with PAH were treated with PAH-targeted therapies.

In a study conducted in a reference center [10], when compared with PAH (3-year survival, 68%), the mortality rates were lower in patients with group 3 PH (3-year survival, 44%) and better in those with chronic thromboembolic PH (CTEPH; 3-year survival, 71%) even when adjusted for other risk predictors such as

**Table 2.** Distribution of different types of pulmonary hypertension in a population-based echocardiographic study [7]

Etiology of pulmonary hypertension	Proportion
Group 1. Pulmonary arterial hypertension	5%
Group 2. Pulmonary hypertension due to left heart disease	77%
Group 3. Pulmonary hypertension due to lung diseases and/or hypoxia	11%
Group 4. Chronic thromboembolic pulmonary hypertension	2.8%
Group 5. Pulmonary hypertension with unclear and/or multifactorial mechanisms	4.2%

age, cardiac index, and the World Health Organization (WHO) functional class. Patients with interstitial lung disease and COPD with 3-year survival rates of 16% and 41%, respectively, accounted for the poor prognosis in group 3 PH, while good survival rates of patients with operated or mild (too mild changes to be operated) CTEPH (83% and 100%, respectively) accounted for the best prognosis in group 4 PH.

Prognosis in patients with PAH has changed significantly with the introduction of PAH-specific therapy. Table 4 shows 1-, 2-, 3-, and 5- year survival of patients with IPAH from two registries: the US National Institute of Health (NIH) registry [12] (conducted in the years 1981–1988, before PAH-specific therapy was introduced) and United Kingdom and Ireland registry [13] (conducted in the years 2001–2009 when PAH-specific therapy was already available).

Benza et al. [14] used the database from the United States observational Registry to Evaluate Early And Long-Term PAH Disease Management (REVEAL Registry), including 55 centers, to estimate survival in patients with group 1 PAH diagnosed after November 2001, that is, after the first oral drug for the treatment of PAH – bosentan – was approved in the United States. A total of 2635 newly or previously diagnosed patients aged 3 months and older at diagnosis (mean age, 50 ± 17 years; women, 77%) were enrolled to the registry between March 2006 and December 2009. The mean time from the initial symptoms to diagnosis was 31 months. During follow-up, 716 patients died and 67 underwent lung or heart and lung transplantation. The 1-, 3-, 5- and 7-year survival rates from diagnosis for all PAH patients were 85%, 68%, 57%, and 49%, respectively. The highest 7-year survival rate was in patients with PAH associated with congenital heart disease (67%) and the lowest in patients with PAH associated with connective tissue disease (35%) and portopulmonary hypertension (29%). In patients with IPAH, PAH associated with HIV infection, familial PAH, and other forms of PAH, the 7-year survival rates were similar (56.5%, 63.8%, 50.5%; 47%, respectively). In the REVEAL population, the authors identified a subpopulation with IPAH or familial PAH and similar characteristics (based on age, sex, and mean

**Table 3.** Different types of pulmonary arterial hypertension diagnosed in a reference center [10]

Type of PAH	Proportion
Idiopathic PAH	39.2%
PAH associated with connective tissue diseases	15.3%
PAH associated with congenital heart diseases	11.3%
PAH associated with portal hypertension	10.4%
Drug- and toxin-induced PAH	9.5%
PAH associated with HIV infection	6.2%
PAH with more than 1 risk factor	4.3%
Familial PAH	3.9%
PAH – pulmonary arterial hypertension, HIV – human immunodeficiency virus	

pulmonary artery pressure) to the population of the NIH registry to compare the survival rates between the two studies. The rates were better in the REVEAL registry by 22% to 29% respectively.

It is estimated that the median survival time has increased from 2.8 years in the era of conventional treatment to approximately 9 years in the era of PAH-specific therapies. However, considering the relatively young age of patients with PAH, the time from the onset of symptoms to diagnosis is still too long and the prognosis is still poor.

The REVEAL registry [15] identified the following variables that were independently associated with increased mortality in PAH: men aged >60 years, familial PAH, PAH associated with portal hypertension or connective tissue disease, family history of PAH, WHO functional class III or IV, renal insufficiency, resting systolic blood pressure <110 mm Hg, heart rate >92 beats/min, mean right atrial pressure >20 mm Hg, 6-minute walking distance (6MWT) <165 m, brain natriuretic peptide (BNP) levels >180 pg/L, PVR >32 Wood units, percentage of predicted diffusing capacity of lung for carbon monoxide ( $DL_{CO}$ ) ≤32%, and the presence of pericardial effusion on echocardiogram. Additionally, four variables that increased 1-year survival in this group were identified: WHO functional class I, 6MWT ≥440 m, BNP <50 pg/mL, and percentage of predicted  $DL_{CO}$  ≥80%. Based on these data, a risk equation and calculator for predicting 1-year survival in an individual patient with PAH was created and further validated. In the new risk score calculator, two points were assigned to a variable that increased the hazard for mortality at least twice, and one point for the risk factor that had a smaller effect on mortality. For variables that increased the survival rates, points were subtracted from the total score. The total risk score could range from 0 (lowest risk) to 22 (highest risk). The 1-year survival rates for patients with a risk score of 1–7, 8, 9, 10–11, and ≥12 were 95.2%, 91.5%, 88.6%, 71.9%, and 65.9%, respectively. Both the risk calculator and the prognostic equation predicted the 1-year survival similarly well

**Table 4.** Survival in patients with idiopathic pulmonary arterial hypertension before (US 1981–1988) and during (UK, Ireland, 2001–2009) the era of PAH-specific therapy [12,13]

Years of follow-up	Survival (UK, Ireland) 2001–2009	Survival (US) 1981–1988
1	92.7%	68%
2	84%	–
3	73.3%	48%
5	61.1%	34%

in the validation cohort with the c-index equal to 0.726 and 0.724, respectively.

Recently, a group from the Bologna University conducted a survival analysis of patients with different types of PAH associated with congenital heart diseases and compared them with the IPAH population [16]. Their results are shown in Table 5. Interestingly, a 20-year survival was similar in patients with Eisenmenger's syndrome and patients with PH and uncorrected shunt but was much lower in patients with PH and small septal defects or PH after shunt correction.

## Diagnosis of pulmonary hypertension

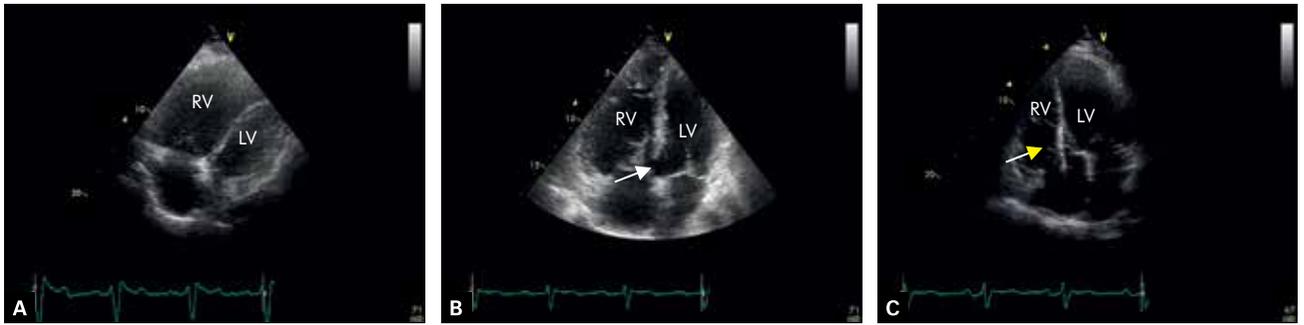
A diagnostic algorithm for PH was suggested and discussed in detail by the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology [1]. According to the current definition, PH can be diagnosed only by RHC. Echocardiography has been shown to be inaccurate for the measurement of pulmonary arterial pressure, cardiac output, or right atrial pressure [9]. In one study, the systolic pulmonary artery pressure measured by echocardiography differed from that obtained during RHC by more than 10 mm Hg in 48% of the patients. Nevertheless, echocardiography is the main screening tool in PH [17]. Additionally, it provides information about the possible etiology of PH. Typical echocardiographic signs for most types of PH include enlarged right ventricle and right atrium, reduced contractility

of the right ventricle, and small left-sided chambers. Other patterns may suggest PH due to left heart disease with enlarged both left- and right-sided chambers of the heart or PH due to congenital heart defect, in which the blood flow through the shunt frequently maintains normal left ventricular volume. Figure 1 shows typical echocardiographic findings in patients with IPAH, PH associated with ventricular septal defect, and PH due to left ventricular systolic dysfunction.

Considering the relatively high prevalence of post-capillary PH, it would be impractical to do invasive studies in all patients suspected of PH; however, differentiation between the pre- and postcapillary PH is crucial to determine further diagnostic and therapeutic procedures. Therefore, Opatowsky et al. [18] developed a practical score based on simple and readily available echocardiographic parameters to differentiate between patients with PH caused primarily by pulmonary vascular disease (PH<sub>PVD</sub>) or PH caused by other conditions (non-PH<sub>PVD</sub>), that is, PH due to left heart disease or high cardiac output. The authors reviewed hemodynamic, echocardiographic, and clinical data of 108 patients with PH aged 61.3 ± 14.8 years (men, 36.1%) of whom 52 (48.1%) were classified as having PH<sub>PVD</sub> (mean pulmonary artery pressure ≥ 25 mm Hg, pulmonary capillary wedge pressure ≤ 15 mm Hg, and PVR > 3 Wood units) and the others as having non-PH<sub>PVD</sub>. After the analysis of 16 different echocardiographic parameters, they selected three (such as E/e' from the lateral mitral annulus, left atrial anteroposterior [LAAP] dimension, and right ventricular outflow tract [RVOT] pulsed-wave midsystolic notch or acceleration time) which together created an echocardiographic score with the best accuracy (area under the curve = 0.921) in differentiating between PH<sub>PVD</sub> and non-PH<sub>PVD</sub>. The parameters were assigned either a positive or a negative point, provided they achieved a specified value as follows: –1 point was assigned for E/e' exceeding 10 and the LAAP dimension exceeding 42 mm, while +1 point was assigned for the LAAP dimension of less than 32 mm and the presence of RVOT pulsed-wave midsystolic notch or the acceleration time of less than 80 ms. Interestingly, a score of 0 and higher had 100% sensitivity and 62.3% specificity, which means that the negative score excluded PH<sub>PVD</sub>. Additionally, the authors observed a positive relationship between the score and PVR; for –2, 0, and +2 points, the mean PVR was 2.5, 4.5, and 8.1 Wood units, respectively. A negative score in conjunction with

**Table 5.** Survival in patients with different types of pulmonary hypertension associated with congenital heart defect as compared with patients with idiopathic pulmonary arterial hypertension [16]

Survival	1 year	5 years	10 years	15 years	20 years
Eisenmenger's syndrome	99%	93%	89%	–	87%
Systemic-to-pulmonary shunt	100%	93%	93%	–	86%
Small defects	100%	88%	88%	–	66%
Congenital shunts after correction	98%	83%	65%	–	36%
Idiopathic pulmonary arterial hypertension	90%	63%	46%	38%	–



**Fig. 1.** Transthoracic echocardiography. Apical views. Typical patterns of different types of pulmonary hypertension. **A.** Idiopathic pulmonary arterial hypertension. **B.** Pulmonary arterial hypertension associated with ventricular septal defect. **C.** Pulmonary hypertension due to left ventricular systolic dysfunction. White arrow – ventricular septal defect, yellow arrow – electrode of the implantable cardioverter-defibrillator, RV – right ventricle, LV – left ventricle

acceleration time exceeding 100 ms and preserved right ventricular function (tricuspid annular plane systolic excursion  $\geq 18$  mm) excluded elevated PVR [18].

Further diagnostic tests used in the differential diagnosis of PH are summarized in Table 6.

Echocardiography, cardiopulmonary exercise stress test, 6-minute walking test, measurement of N-terminal pro-B-type natriuretic peptide (NT pro-BNP) levels, and RHC are routinely used to assess the clinical status and prognosis of a patient with PH. In tertiary centers, cardiovascular magnetic resonance is used and is considered a gold standard to assess right ventricular structure and function [19,20].

## Treatment of pulmonary hypertension

Currently available treatment strategies in PH are presented in Figure 2.

Supportive therapy includes oxygen supplementation, diuretics, and anticoagulation. They are commonly used in clinical practice and are recommended by experts but the level of evidence for their use is low due

to a lack of randomized control trials. The indication for chronic anticoagulation in patients with IPAH has been recently questioned following the introduction of advanced PAH-specific therapy, which relieved many patients from bed rest. Additionally, recent data suggest an increased bleeding risk in patients with IPAH compared with patients chronically using vitamin K antagonists for other reasons [21].

Currently approved PAH-specific therapies belong to three therapeutic groups, namely, endothelin receptor antagonists, phosphodiesterase 5 inhibitors, and prostanoids. The mechanisms of action of PAH-specific drugs that are currently being approved or investigated are presented in Table 7.

Receptors for platelet-derived growth factor have been a target in a recently published IMPRESS trial with imatinib, a drug used to treat chronic myeloid leukemia. Imatinib increased the 6-minute walking distance in patients with PAH with PVR exceeding  $900 \text{ dyne} \times \text{s} \times \text{cm}^{-5}$  treated with at least two PAH-specific drugs [22]. Unfortunately, 38% of the patients stopped the treatment because of side effects (compared with 18% in the placebo group); 8 patients suffered from subdural hematoma. Recently completed but not yet

**Table 6.** Diagnostic tests in the differential diagnosis of pulmonary hypertension

Type of pulmonary hypertension	Diagnostic tests
Pulmonary hypertension due to lung diseases and/or hypoxia	Pulmonary function tests and high resolution computed tomography, arterial blood gas analysis
Pulmonary hypertension due to left heart diseases	Echocardiography, right heart catheterization
Chronic thromboembolic pulmonary hypertension	Ventilation-perfusion lung scan, computed tomography, classical angiography of the pulmonary arteries
Pulmonary arterial hypertension associated with congenital heart disease	Transthoracic echocardiography, transesophageal echocardiography, computed tomography, cardiovascular magnetic resonance, right heart catheterization
Pulmonary hypertension associated with portal hypertension	Liver ultrasonography, liver function tests, pulmonary vein catheterization
Pulmonary hypertension associated with HIV infection	Anti-HIV antibodies
Pulmonary hypertension associated with connective tissue disease	Antinuclear antibodies, anti dsDNA antibodies, other tests specific for particular connective tissue diseases
HIV – human immunodeficiency virus	

Supportive treatment	Specific therapies	Interventional therapy	Regenerative therapy
<ul style="list-style-type: none"> <li>– Oxygen therapy</li> <li>– Diuretics</li> <li>– Anticoagulation</li> </ul>	<ul style="list-style-type: none"> <li>– Prostanoids</li> <li>– Endothelin receptor antagonists</li> <li>– Phosphodiesterase 5 inhibitors</li> <li>– Calcium channel blockers</li> <li>– Imatinib</li> <li>– Riociguat</li> <li>– Selexipag</li> </ul>	<ul style="list-style-type: none"> <li>– Atrial septostomy</li> <li>– Pulmonary endarterectomy</li> <li>– Lung transplantation</li> <li>– Percutaneous Potts'a procedure</li> <li>– Percutaneous transluminal pulmonary angioplasty</li> <li>– Pulmonary artery denervation</li> </ul>	<ul style="list-style-type: none"> <li>– Endothelial progenitor cells</li> <li>– Genetically modified endothelial progenitor cells</li> </ul>

Therapies under investigation and not yet approved for clinical practice are marked with green

Fig. 2. Currently available treatment strategies in adult patients with pulmonary hypertension

published trials tested macitentan (SERAPHIN) in PAH and riociguat (PATENT, CHEST) in PAH and in chronic thromboembolic pulmonary hypertension (CTEPH), respectively. Selexipag, a nonprostanoid agonist of prostanoid receptors, is currently under investigation (GRIPHON). The pivotal trials on currently approved PAH-specific drugs are summarized in Table 8.

Studies on animal models showed that infusion of endothelial progenitor cells (EPC) prevents or reverses PH induced by monocrotaline [41]. In the first human study, 16 patients with IPAH were randomized to conventional therapy and 15 to the combination of conventional therapy and autologous EPC infusion [42]. A significant increase in 6MWT and improvement in hemodynamic parameters were achieved with EPC. A new trial is currently being conducted in Canada, in which genetically modified EPCs are infused to the pulmonary artery of the patients with PAH.

In 1962, Osorio et al. [43] showed that dilation of the pulmonary artery leads to a gradual increase in pulmonary artery pressure. Further studies showed that this pulmo-pulmonary reflex was mediated by the sympathetic fibers (fig. 3).

Interestingly, a pharmacological blockade of the sympathetic nerves or surgical removal of the adventitial and medial layers of the pulmonary arteries were shown to attenuate this reflex. Recently, it has been reported that percutaneous radiofrequency ablation around the bifurcation area of the main pulmonary artery abolishes the hemodynamic effects of pulmonary artery occlusion [44]. The percutaneous catheter-based pulmonary artery denervation (PADN-1) study has been the first to confirm the efficacy and safety of pulmonary artery denervation in humans [45]. In this study, 21 patients with PAH not responding to conventional therapy were randomized to receive standard therapy or to undergo radiofrequency ablation of the pulmonary artery. Three levels of the pulmonary artery were selected for ablation: <2 mm distal to the orifice of the left pulmonary artery; <2 mm proximal to the bifurcation level, and <2 mm distal to the ostial right pulmonary artery. After 3 months, the mean pulmonary artery pressure dropped from 37 ±5 mm Hg to 23 ±2 and the 6MWT increased from 354 m to 455 m in the intervention group. No significant changes were observed in the conventional treatment group. A randomized controlled trial (PADN-2) aiming to estimate the short- and long-term hemodynamic parameters and clinical outcomes of pulmonary artery denervation and pharmacotherapy is currently ongoing (registration number: ChiCTR-TRC-12002097).

Another emerging technique in the treatment of severe cases of PH is the establishment of communication between the descending aorta and left pulmonary artery. It has some potential advantages over atrial septostomy because it does not pose a risk of central nervous system embolization, does not affect arterial blood saturation in the coronary and carotid arteries, and is not dependent on right atrial pressure [46]. Surgical creation of the shunt was first described by Potts in 1946 [47] and has been successfully used in

Table 7. The mechanism of action of pulmonary hypertension – specific drugs currently being approved or under investigation

Group	Endothelin receptor antagonists	Phosphodiesterase 5 inhibitors	Prostanoids and nonprostanoid agonist of prostanoid receptors	Tyrosine-kinase inhibitors	Soluble guanylate cyclase stimulators
Drug	Bosentan Macitentan Ambrisentan	Sildenafil Tadalafil	Epoprostenol Treprostinil Iloprost Selexipag	Imatinib	Riociguat
Mechanism of action	Block endothelin-1 receptors (A or A and B)	Increase the cGMP level by inhibition of its metabolism	Increase the cAMP level	Blocks platelet-derived growth factor receptors	Increases the level of cGMP by direct activation of guanylate cyclase

Abbreviations: cGMP – cyclic guanosine cyclase, cAMP – cyclic adenosine cyclase

**Table 8. Pivotal trials on currently approved pulmonary arterial hypertension specific drugs**

Acronim/Reference	N	Methodology	Type of pulmonary hypertension	WHO functional class	Primary endpoint	Results
<b>Intravenous epoprostenol</b>						
Ann Intern Med. 1990; 112: 485 [23]	24	epoprostenol iv vs. conventional therapy for 8 weeks, open-label study, without placebo	IPAH	II, III, IV	not specified	TPR: -7.9 WU (95% CI, 13.1 to -2.2) in epoprostenol group; no change in conventional treatment group
NEJM. 1996; 334: 296 [24]	81	open-label, prospective, randomized, multicenter study; epoprostenol vs. conventional therapy for 12 weeks	IPAH	III, IV	not specified	6MWT: +47 m (placebo corrected) $P < 0.002$ CI: +0.5 L/min (95% CI, 0.2-0.9) deaths: epoprostenol, 0; conventional treatment, 8 ( $P = 0.003$ )
Ann Intern Med. 2000; 132: 425 [25]	111	open-label, randomized	APAH-Scl	II, III, IV	change in 6MWT	+108 m (95% CI, 55.2-180.0)
<b>Subcutaneous treprostinil</b>						
Am J Respir Crit Care Med. 2002; 165: 800 [26]	470	treprostinil (up to 22 ng/kg/min) sc vs. placebo for 12 weeks	IPAH, 270 (57%); APAH-CTD, 70 (15%); CHD (after correction or Eisenmenger's syndrome), 109 (23%)	II, 53 (11%); III, 362 (77%); IV, 34 (7%)	change in 6MWT	+16 m (95% CI, 4.4-27.6)
<b>Inhaled iloprost</b>						
AIR (NEJM 2002; 347: 322) [27]	203	iloprost (2.5 µg or 5 µg; 6 or 9 times a day) vs. placebo	IPAH, 102; drug-induced PAH, 9; CTD, 25; CTEPH, 57	III, IV	composite: improvement in NYHA class + increase in 6MWT >10%	16.8% vs. 4.9% ( $P = 0.007$ )
STEP (Am J Respir Cit Care Med. 2006; 174: 1257) [28]	67	iloprost (5 µg) vs. placebo for 12 weeks in patients treated with bosentan	IPAH, 37; APAH, 30	II, III, IV	not defined	6MWT +26 m ( $P = 0.051$ ); Borg index -0.5 ( $P = 0.16$ ); change in NYHA ( $P = 0.002$ ); clinical worsening ( $P = 0.02$ )
<b>Sildenafil</b>						
JACC 2004; 43: 1149 [29]	22	sildenafil (according to body weight) vs. placebo for 6 weeks, cross-over design	IPAH	II-III	change in the time of exercise in CPET (Naughton protocol)	+211 s ( $P < 0.0001$ )
SUPER (NEJM 2005; 353: 2148) [30]	278	sildenafil (20, 40, 80 mg 3 times daily) vs. placebo for 12 weeks	IPAH, 175; APAH-CTD, 84; APAH-CHD corrected >5 years before, 18	I, II, III, IV	change in 6MWT	20 mg: +45 m; 40 mg: +46 m; 80 mg: +50 m; ( $P < 0.001$ ); no difference between doses
Am Heart J 2006; 151: 851.e1 [31]	20	sildenafil (100 mg 3 times daily) vs. placebo (cross-over design)	IPAH, 10; Eisenmenger's syndrome, 10	II-IV	change in 6MWT	+96 m ( $P < 0.0001$ )
PACES (Ann Intern Med. 2008; 149: 521) [32]	267	epoprostenol + sildenafil (20-80 mg) vs. placebo	IPAH, 212; APAH-CTD, 45; others, 10	I-IV	change in 6MWT	+28.8 m (95% CI, 13.9-43.8)

**Table 8. Pivotal trials on currently approved pulmonary arterial hypertension specific drugs (continued)**

Acronim/Reference	N	Methodology	Type of pulmonary hypertension	WHO functional class	Primary endpoint	Results
<b>Tadalafil</b>						
PHIRST (Circulation. 2009; 119: 2894) [33]	450	tadalafil (2.5; 10; 20; 40 mg once daily) vs. placebo for 16 weeks; patients, treatment-naive or on bosentan	IPAH, 247; drug-induced PAH, 19; APAH-CTD, 95; APAH-ASD, 32; APAH-VSD, PDA corrected >1 year before, 15	I, II, III, IV	change in 6MWT	+33 m (95% CI, 15 m – 50 m); significant only with 40 mg
<b>Bosentan</b>						
Lancet 2001; 358: 1119 [34]	32	bosentan vs. placebo for 12 weeks	IPAH, 27 (84%); APAH-Scl, 5 (16%)	III	Change in 6MWT	+76 m (95% CI, 12–139)
BREATHE-1 (NEJM 2002; 346: 896) [35]	213	bosentan vs. placebo for 16 weeks	IPAH, 150 (70%); APAH-Scl, SLE, 63 (30%)	III, 195 (92%); IV, 18 (8%)	change in 6MWT	+44 m (95% CI, 21–67)
BREATHE-2 (Eur Respir J 2004; 24: 353) [36]	33	epoprostenol + bosentan vs. placebo (2:1)	IPAH, 27 (84%); APAH-Scl, SLE, 5 (16%)	III, 25 (76%); IV, 8 (24%)	change in TPR	–13.7% ( <i>P</i> = 0.08)
SERAPH (Am J Respir Crit Care Med. 2005; 171: 1292) [37]	26	sildenafil (50 mg twice daily; 50 mg 3 times daily) vs. bosentan for 16 weeks	IPAH, 23 (88%); APAH-Scl, SLE, 3 (12%)	III	change in RV mass (CMR)	–5.8 g (95% CI, –14 to 2.1)
BREATHE – 5 (Circulation 2006; 114: 48) [38]	54	bosentan vs. placebo for 16 weeks	Eisenmenger's syndrome	III	change in PVR	–472.0 dyne · s · cm <sup>-5</sup> ; <i>P</i> = 0.038
EARLY (Lancet 2008; 371: 2093) [39]	185	bosentan vs. placebo for 6 months	IPAH, 112 (61%); CHD, 32 (17%); CTD, 33 (18%); HIV, 7 (4%); others, 1 (1%)	II	change in PVR; change in 6MWT	PVR: –22.6% (95% CI: –33.5 to –10.0); 6MWT: +19.1 m (95% CI, 3.6–41.8)
<b>Ambrisentan</b>						
AIRES 1 (Circulation 2008; 117: 3010) [40]	202	ambrisentan (5 mg or 10 mg once daily) for 12 weeks	IPAH, 126; APAH-CTD, 62; APAH-HIV, 7; drug-induced PAH, 5	I, II, III, IV	change in 6MWT	5 mg +31 m ( <i>P</i> = 0.008) 10 mg +51 m ( <i>P</i> <0.001)
ARIES 2 (Circulation 2008; 117: 3010) [40]	192	ambrisentan (2.5 or 5 mg once daily) for 12 weeks	IPAH, 125; APAH-CTD, 62; APAH-HIV, 4 drug-induced PAH, 1	I, II, III, IV	change in 6MWT	2,5 mg +32 m ( <i>P</i> = 0.02) 5 mg + 59 m ( <i>P</i> <0.001)
APAH – associated pulmonary arterial hypertension, CI – confidence interval, IPAH – idiopathic pulmonary arterial hypertension, ASD – atrial septal defect, CHD – congenital heart disease, CTD – connective tissue disease, CMR – cardiovascular magnetic resonance imaging, CPET – cardiopulmonary exercise test, NYHA – New York Heart Association, PDA – persistent ductus arteriosus, PVR – pulmonary vascular resistance, RV – right ventricle, Scl – scleroderma, TPR – total pulmonary resistance, VSD – ventricular septal defect, 6MWT – 6-minute walk test, SLE – systemic lupus erythematosus, WHO – World Health Organization, WU – wood unit						

children with IPAH [48]. Recently, transcatheter Potts shunt (TPS) creation has been described in 4 severely diseased adult patients with PAH who did not respond to conventional therapy [49]. The procedure was successful in 3 patients but 1 patient died due to massive hemothorax. Another patient died of pneumonia 5

days after TPS procedure. Patients 3 and 4 were alive at a 4 and 10 months follow-up, respectively.

Pulmonary thromboendarterectomy is considered a treatment of choice for CTEPH. However, it is contraindicated in patients with distal lesions or in poor physical condition because of a high risk-to-benefit ratio. It

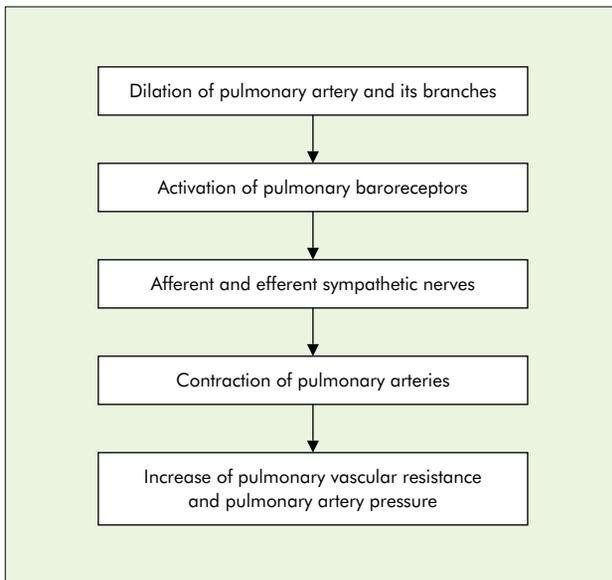


Fig. 3. Pulmo-pulmonary reflex [43]

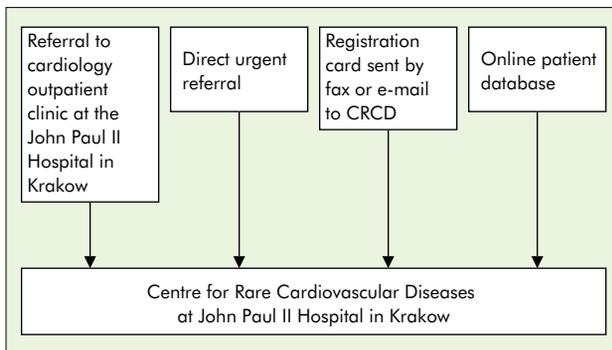


Fig. 4. Referral of patients with suspected pulmonary hypertension in Malopolska

was suggested that balloon dilation may be considered in these patients because it is associated with decreased pulmonary artery pressure and long-term improvement in exercise capacity. In their recent paper, Kataoka et al. [50] described the results of percutaneous transluminal pulmonary angioplasty (PTPA) performed in 29 patients with CTEPH (aged  $62.3 \pm 11.5$  years; women, 79%) with lobar, segmental, and subsegmental lesions who refused thromboendarterectomy or were suggested PTPA because of advanced age or comorbidities. Additionally, the study included patients after thromboendarterectomy with residual PH due to lesions that could not be surgically removed. During each procedure, from 1 to 6 lesions were dilated using 1.5 to 9.0 mm balloon catheters. One patient died 2 days after PTPA because of a wiring perforation; therefore, the mortality rate in this study was 3.4%. Hemodynamic data did not change immediately after the procedure but improved significantly during follow-up ( $6.0 \pm 6.9$  months) as did the functional class and plasma BNP levels. Reperfusion pulmonary edema was the most common complication of PTPA (68% of the patients) and its risk was associated with poor hemodynamic status, higher NYHA class, and higher BNP levels at baseline. Only 1

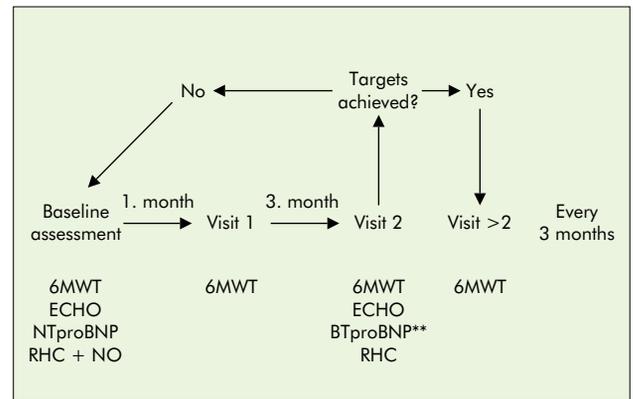


Fig. 5. Follow-up of patients treated with pulmonary arterial hypertension specific therapies in the Centre for Rare Cardiovascular Diseases in Krakow. The follow-up scenario was adapted from the Pulmonary Hypertension Centre, University of Bologna (Head: prof. Nazzareno Galiè) and adapted to local condition. 6MWT – 6-minute walk test, RHC – Right Heart Catheterization, NO – nitric oxide, ECHO – cardiac echo study, NTproBNP – N-terminal pro-brain natriuretic peptide

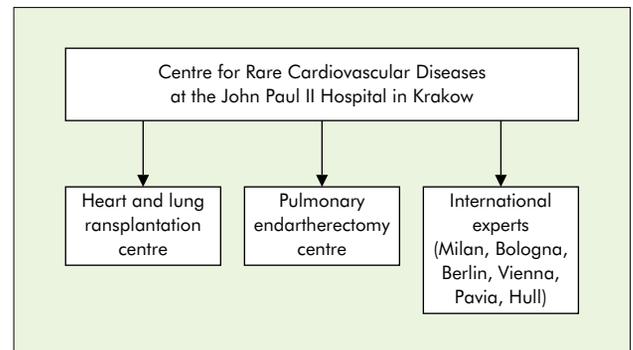


Fig. 6. Centre for Rare Cardiovascular Diseases range of cooperation

patient required intubation and mechanical ventilation due to edema; others were treated with biphasic positive airway pressure with high concentration oxygen inhalation; and yet others with high concentrations of oxygen only. During PTPA, there was 1 wiring perforation of the pulmonary artery, 1 dissection of the pulmonary artery after balloon dilatation, which did not require further management, and 1 extravascular leak, which was stopped by a prolonged low-pressure balloon inflation. The results of the study, although promising, need to be confirmed in larger multicenter studies. As the authors themselves suggest, it will be of major interest to investigate the risk of restenosis and long-term survival after PTPA.

### Organization of care for patients with pulmonary hypertension at the Centre for Rare Cardiovascular Diseases in Krakow

Due to poor prognosis of patients with PH, we aim to facilitate the flow of patients with this disease to our

center. Therefore, different scenarios have been proposed to physicians (namely, cardiologists and pulmonologists) from our region as shown in Figure 4.

Contact data to the Centre for Rare Cardiovascular Diseases (CRCDD) as well as a registration form are available on the center's website at [www.crcdd.eu](http://www.crcdd.eu). Additionally, internet-based registry is available for partner hospitals. Using this virtual tool, patient data can be sent to the CRCDD. Based on the individual case, the patient can further be admitted to the CRCDD for diagnosis, consulted by an expert from the CRCDD or other centers based on the submitted patient's records, or just recorded in the database when no additional tests or treatment decisions are required.

Patients with suspected PH are diagnosed, treated, and followed-up by the PH team at the CRCDD. Following training at the Bologna University, we have adopted the follow-up scenario proposed by Professor Nazzareno Galie, Head of the Pulmonary Hypertension Center at the University of Bologna (fig. 5).

The National Health Fund in Poland currently reimburses PAH-specific therapies only in patients with PAH associated with a congenital heart disease, PAH associated with a connective tissue disease, and IPAH. Patients in the WHO functional class III receive sildenafil (IPAH, PAH associated with connective tissue disease) or bosentan (PAH associated with congenital heart disease). Patients with the WHO functional class IV or patients who do not respond adequately to the first-line treatment can receive subcutaneous or intravenous treprostinil, inhaled iloprost, bosentan, ambrisentan, or the combination of iloprost and sildenafil. Patients whose treatment cannot be reimbursed (patients with other types of PAH, patients with CTEPH), if required, are usually treated with sildenafil because of the lowest costs of this drug.

The CRCDD strictly cooperates with international experts, lung transplantation center in Zabrze, Poland, and pulmonary endarterectomy center in Warsaw, Poland. The most difficult cases are presented during online video conferences with experts from European countries (fig. 6).

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## Rhythm disorders in adult patients with pulmonary arterial hypertension

Marcin Waligóra, Grzegorz Kopeć, Jacek Łach, Piotr Podolec

### Background

The number of studies concerning cardiac arrhythmias in patients with pulmonary arterial hypertension (PAH) is limited. The current evidence on the prevalence and clinical significance of rhythm abnormalities in this group of patients is based mostly on a single-center studies.

### Ventricular arrhythmias, sudden cardiac death, and cardiopulmonary resuscitation in pulmonary arterial hypertension

Despite major advances in the treatment during the last 20 years, PAH is still associated with a high mortality rate. Sudden cardiac death has been reported to account for approximately 30% to 40% of all deaths in patients with PAH [1,2].

The following causes of sudden cardiac deaths in patients with PAH have been proposed: rupture or dissection of the pulmonary trunk [3], compression of the left main coronary artery by dilated pulmonary artery, severe decompensation of heart failure, and arrhythmias [4].

Hoeper et al. [4] assessed the prevalence of cardiac arrest and outcomes after cardiopulmonary resuscitation in a multicenter retrospective study involving 3130 patients with PAH from 17 different centers in Europe and the United States. During follow-up between 1997 and 2000, cardiorespiratory arrest occurred in 513 patients. Cardiopulmonary resuscitation was initiated only in 132 subjects. Cardiorespiratory arrest was associated with significant comorbidity in 54% of the cases, including respiratory tract infection (18%), followed by viral enteritis, inguinal hernia, thrombophlebitis, and gastroenteritis. Electrocardiography performed at the time of collapse showed severe bradycardia (45%), pulseless electrical activity (28%), and asystole (15%). Ventricular fibrillation and tachycardia were observed only in 8% of the patients; therefore, defibrillation or cardioversion was rarely performed. The study also showed 90-day survival after cardiorespiratory arrest, without neurological deficits, only in 6% of the study population. In 80% of the cases, cardiopulmonary resuscitation was unsuccessful, and 14% of the patients died within the next 7 to 90 days because of recurrent cardiac arrest and neurological complications.

Primary prevention of sudden cardiac death in PAH is not currently recommended [1].

### Supraventricular arrhythmias

The most common clinically relevant supraventricular arrhythmias in pulmonary hypertension (PH) are atrial fibrillation (AF) and atrial flutter (AFL) [5].

In a retrospective study of 109 adults with Eisenmenger's syndrome, Cantor et al. [6] showed that clinically relevant supraventricular arrhythmias, which required medical therapy, predicted increased mortality with a hazard ratio of 3.44 in a Cox multivariate survival analysis. The most common cause of death in this group was congestive heart failure in 19 patients, followed by sudden cardiac death in 7 patients. Less common causes included endocarditis, cerebrovascular event, and noncardiac causes.

Tongers et al. [5] assessed the prevalence and incidence rate of AF and AFL as well as their clinical significance. A 6-year retrospective analysis included 231 patients: 204 patients with PAH and 27 patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH). Each patient was monitored and clinically assessed in time periods ranging from 1 to 6 months. During the follow-up period, supraventricular tachycardia (SVT) occurred in 27 patients (31 episodes), most commonly represented by AF (13 episodes in 12 patients) and AFL (15 episodes in 12 patients), followed by significantly less frequent atrioventricular nodal reentry tachycardia (AVNRT) (3 patients). New onset of these arrhythmias resulted in clinical deterioration or right heart failure or both in 84% cases. During the episodes of supraventricular arrhythmias, an interventional approach was usually used as a first-choice treatment. If unsuccessful, it was followed by pharmacological treatment. AFL was terminated by direct electrical cardioversion in 6 patients, overdrive pacing in 2 patients, radiofrequency ablation (RFA) in 3 patients, and pharmacological treatment in 1 patient. AFL recurred only in 2 patients; in both of these patients, a sinus rhythm was successfully restored with overdrive pacing and RFA. In 3 patients with AVNRT, the use of RFA effectively terminated the arrhythmia. AF was successfully ceased by electrical cardioversion only in 2 of 12 patients. Attempts to convert AF to sinus rhythm with drugs were unsuccessful in the remaining 10 patients. One patient after RFA for AVNRT developed persistent AF. Of 11 patients with persistent AF, 9 died during the follow-up. Unfortunately, AF was resistant to any attempted treatment. In contrast, of 16 patients with persistent sinus rhythm after at least 1 episode of SVT, only 1 patient died during the follow-up. In cases in which sinus rhythm was re-established, the risk of death was much lower (cumulative mortality of 6.3% within the follow-up time of 26 ± 23 months) than in patients with persistent AF (cumulative mortality rate of 82% within the follow-up time of 11 ± 8 months). The global annual incidence of new-onset SVT was 2.8% per patient [5]. Despite the observed association between new-onset SVT and clinical deterioration, there is still no strong evidence whether SVTs are the cause or the consequence of right heart failure.

**Table 1.** Criteria for right ventricular hypertrophy according to the AHA/ACCF/HRS recommendations. Amplitudes are given in millimeters, where 1 mm = 0.1 mV [1]

Criterion		Prevalence in IPAH [11]
Tall R in V <sub>1</sub>	>6 mm	35%
Deep S in V <sub>5</sub>	>10 mm	26%
Deep S in V <sub>6</sub>	>3 mm	74%
Tall R in aVR	>4 mm	17%
Small S in V <sub>1</sub>	<2 mm	61%
Small R in V <sub>5,6</sub>	<3 mm	8.7%
(R <sub>1</sub> + S <sub>III</sub> ) – (S <sub>I</sub> + R <sub>III</sub> )	<15 mm	96%
(Max R in V <sub>1 or 2</sub> ) + (max S in I or aVL) – (S in V <sub>1</sub> )	>6 mm	83%
R in V <sub>1</sub> + S in V <sub>5 or 6</sub>	>10.5 mm	74%
Increased R:S ratio in V <sub>1</sub>	>1	67%
Reduced R:S ratio in V <sub>5</sub>	<0.75	39%
Reduced R:S ratio in V <sub>6</sub>	<0.4	4%
Reduced (R:S in V <sub>5</sub> ) to (R:S in V <sub>1</sub> ) ratio	<0.04	6.7%
R peak in V <sub>1</sub> (QRS duration <0.12 s)	>0.035 sec	75%
QR in V <sub>1</sub>	present	61%
<b>Supporting criteria</b>		
RSR V <sub>1</sub> (QRS duration > 0.12s)	present	0%
S > R in I	present	78%
S > R in II	present	22%
S > R in III	present	8.7%
S I and Q in III (S <sub>I</sub> Q <sub>III</sub> )	present	78%
R:S in V <sub>1</sub> > R:S in V <sub>3</sub>	present	67%
R:S in V <sub>1</sub> > R:S in V <sub>4</sub>	present	67%
Negative T-wave V1 through V <sub>3</sub>	present	57%
P amplitude in II (P <sub>II</sub> )	2.5 mm	26%
IPAH – idiopathic pulmonary arterial hypertension		

In a prospective study, Olsson et al. [7] assessed the risk of a new-onset AFL and AF in patients with PH. The study included 239 patients (157 with PAH; 82 with inoperable CTEPH) followed up between the years 2005 and 2010. Each patient was monitored in an out-patient clinic every 3 to 6 months. During the follow-up, at least 1 episode of AFL or AF occurred in 48 patients (24 cases of AF and AFL, each). New-onset AF or AFL was associated with clinical worsening, manifesting as a decreased 6-minute walking distance (362 ±114 m on a routine follow-up visit prior to the event vs. 258 ±147 m at the onset of arrhythmia). After successful restoration of sinus rhythm, 6-minute walking distance was 345 ±137 m. The initial treatment of SVT was

successful in all cases of AFL and in 16 patients (67%) with AF. The most common initial treatment in AFL were drugs (11 patients) followed by electrical cardioversion in 9 patients, RFA in 3 patients, and overdrive pacing in 1 patient. To prevent the recurrence of AFL, 16 patients underwent further RFA. In 5 patients, AFL developed into AF, and in 3 of these patients AF became permanent. In patients with AF, the treatment of choice was electrical cardioversion if the patient presented symptoms of heart failure; otherwise, amiodarone was preferred. In the case of AF (24 episodes), sinus rhythm was successfully restored in 16 patients with electrical cardioversion (within 18 attempts) and in 3 patients with the use of drugs. Although electrical cardioversion had high initial success rate, 5 of 16 patients had their sinus rhythm restored only temporarily and eventually developed a refractory AF. A stable sinus rhythm was sustained during the follow-up in 21 patients (88%) with AFL and 16 patients (67%) with AF. The authors determined the following risk factors for new-onset AF/AFL: etiology of PH (AF/AFL were more frequent in PAH than in CTEPH), hemodynamic parameters (higher right atrial pressure and mean pulmonary arterial pressure, lower cardiac index), and laboratory tests (high bilirubin and N-terminal pro-B-type natriuretic peptide [NT-proBNP] levels). Patients without episodes of AF/AFL had a significantly better survival (5-year survival rate of 68%) compared with patients who developed at least 1 incident of AF/AFL (5-year survival rate of 47%). The incidence of AF/AFL during the follow-up was associated with an increased mortality risk with a hazard ratio of 1.75 [7].

The current guidelines for the diagnosis and treatment of PH emphasize that sustaining a stable sinus rhythm is an important goal of treatment in patients with PAH. Moreover, they recommend that preventive treatment may be considered to achieve this goal by using drugs without negative inotropic effects (for example, amiodarone) [8].

Showkathali et al. [9] evaluated the efficacy, safety, and feasibility of RFA in patients with precapillary PH. They enrolled 22 patients: 10 patients with IPAH, 1 patient with associated PAH, and 11 patients with CTEPH. All patients had previously confirmed isthmus-dependent AFL. Radiofrequency isthmus ablation was successful without complications in all cases. The success rate was high and only 3 patients had recurrence of arrhythmia during a 3-month follow-up. Two patients died during the follow-up for causes that were unrelated to the procedure, namely, pneumonia and pulmonary embolism. Patients underwent clinical assessment 3 months after the procedure. In 9 of 20 patients, the functional class significantly improved, while it did not change in the remaining 11 patients. There was also a significant improvement in the 6-minute walking distance: from 275 ±141 before to 293 ±146 m after the procedure. Echocardiography did not show any changes in the parameters of the right ventricular function [9]. The study confirmed the short-term efficacy and safety of RFA but data are lacking on long-term benefits.

## Electrocardiography in pulmonary arterial hypertension

Typical changes in electrocardiogram (ECG) observed in patients with PH are the signs of the right ventricular and right atrial enlargement and hypertrophy.

Currently, there are 24 criteria for the diagnosis of right ventricular hypertrophy (RVH), as developed by the American College of Cardiology, American Heart Association Task Force, and the European Society of Cardiology Committee [10]. The criteria, together with their estimated prevalence in patients with IPAH, are presented in Table 1 [10,11]. The majority of data that were used to establish the ECG signs of RVH were derived from surgical or postmortem studies including heterogeneous groups of patients [12–19].

We have recently assessed the accuracy of the recommended ECG criteria for predicting RVH and dilation in patients with idiopathic PAH (IPAH). We referred the ECG criteria to the right ventricular mass and volume as evaluated by cardiac magnetic resonance.

In patients with IPAH, only the ECG voltage criteria based on the R-wave amplitude in lead  $V_1$  ( $RV_1 > 6$  mm,  $R:SV_1 > 1$ ,  $R:SV_5$  to  $R:SV_1 < 0.04$ ,  $\max RV_{1,2} + \max SI_{1,aVL} - SV_1 > 6$  mm,  $RV_1 + SV_{5,6} > 10.5$  mm,  $R:SV_1 > R:SV_3$ ,  $R:SV_1 > R:SV_4$ ), R-wave amplitude in lead aVR, P-wave amplitude in lead II, and ventricular activation time in lead  $V_1$  were useful for differentiating between patients with and without RVH. A ventricular activation time in lead  $V_1$  of less than 0.01 s excluded RVH, whereas  $RV_1$  exceeding 6 mm,  $R:SV_1$  exceeding 1,  $RaVR$  exceeding 4 mm,  $R:SV_5$  to  $R:SV_1$  of lower than 0.04, and PII exceeding 2.5 mm confirmed the diagnosis of RVH with a 100% positive predictive value. Dilation of the right ventricle could be diagnosed when the ventricular activation time was more than 0.045 s [11].

Although ECG can be useful in predicting RVH in patients with IPAH, it is not generally useful as a screening tool in PH because it lacks sensitivity and specificity [8].

Recently, Bonderman et al. [20] have shown that ECG might be clinically useful to exclude the presence of precapillary PH. They proposed a two-step algorithm based on the assessment of the right ventricular strain (defined as ST-segment deviation and T-wave inversion in leads  $V_1$  through  $V_3$ ) and NT-proBNP levels. If a patient did not have the right ventricular strain and the levels of NT-proBNP were lower than 80 pg/mL, precapillary PH was excluded.

Right ventricular systolic dysfunction (RVSD) is the major complication of PH and the main predictor of death in patients with PAH [21,22].

Nagai et al. [23] assessed the usefulness of ECG to determine RVSD in patients with PAH and inoperable CTEPH. Cardiac magnetic resonance imaging was used as a reference test for the measurement of the right ventricular ejection fraction. The cut-off point for the presence of RVSD was at the level of 35%. The prevalence of RVSD was high and almost half of the recruited group met the assumed criteria. The R/S

ratio exceeding 1 in lead  $V_1$  or the presence of qR pattern in  $V_1$  were found to be the predictors of RVSD in the whole group.

Interestingly, when only patients with IPAH were analyzed, the combination of these two criteria provided strong evidence for the presence of RVSD (with positive predictive values of 100%) [23].

The usefulness of ECG in monitoring the response to PAH-specific treatment was evaluated by Henkens et al. [24] The study included 81 patients with PAH treated with endothelin receptor antagonists, sildenafil, prostacyclin, or calcium channel blockers. ECG and hemodynamic data were collected and evaluated at baseline and at 1 year. A positive response to treatment was defined as a decrease in pulmonary vascular resistance (PVR) exceeding 25% to an absolute PVR of less than 500 dyne·s·cm<sup>-5</sup>. A number of associations were identified between the T-wave axis, P-wave amplitude, QRS axis, and PVR. Interestingly, the P-wave amplitude in lead II correlated linearly with PVR. The authors concluded that patients with a T-wave axis of less than 25° or patients with a T-wave axis of 25° and more and a P-wave amplitude in lead II of 0.175 mV and less, can be expected to respond positively to treatment.

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## Health-related quality of life in pulmonary arterial hypertension

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### Background

The years of research on pathophysiology and treatment of pulmonary arterial hypertension (PAH) resulted in various therapeutic strategies. This progress expanded treatment goals from increasing survival to improving the quality of life (QoL). Since the World Health Organization (WHO) established a definition of health as not only an absence of disease but also as a state of physical, mental, and social well-being, the investigations on QoL became more important in the clinical setting.

According to the WHO, the QoL represents individual's perception of life position in the context of the culture and value systems. It is influenced by the person's physical health, psychological state, level of independence, social relationships, and personal beliefs [1]. Health-related QoL (HRQoL) can be distinguished from QoL to emphasize the predominant influence of health care providers and health care systems on QoL [2]. HRQoL is defined as "the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient" [3] and is a reflection of one's health on physical, psychological, and social aspects of life.

### Health-related quality of life as an important clinical endpoint in pulmonary arterial hypertension

HRQoL is becoming a valuable tool to define endpoints in PAH clinical trials. Current therapeutic protocols has improved survival in this disease, making QoL a complementary goal in its therapy [4]. Studies have shown that PAH, especially with coexisting systemic sclerosis, is associated with a significantly decreased HRQoL. Pharmacological treatment of PAH often requires frequent dosing and strict monitoring along with the use of specialized drug delivery systems (continuous intravenous or subcutaneous infusion, nebulization) which may lead to major adverse effects. These interventions may affect hemodynamic parameters without improvement in the QoL, especially in mental and emotional aspects [5]. Therefore, the QoL has been recommended as a tool to determine the effects of treatment [4].

### Why do we use patient-reported outcomes?

There is a growing recognition that physiological parameters not completely correlate with patient's personal benefits [6]. Patient-reported outcomes (PROs) are patient-centered measurements of health status that allow to assess treatment effects from the patient's perspective (which may otherwise remain unrecognized). That is why PROs may be used to determine patient's benefits for which no adequate observable or physical measures exist. What is more, PROs are relatively quick and easy to assess [7]. Until now, only a few instruments assessing PROs have been precisely evaluated; however, the use of these measures continues to grow.

### Effect of pulmonary arterial hypertension on patient-reported outcomes

PAH is a condition associated with symptoms that may severely affect patient's QoL. Awareness of having a rare disease of poor prognosis, with limited therapeutic options and symptoms restricting daily activities may cause anxiety, panic, depression, anger, and hopelessness [8]. Shafazand et al. [9] have found moderate or severe levels of anxiety and depression in 20.5% and 7.5% of the patients with PAH, respectively. The Hospital Anxiety and Depression Scale was used in that study. In a Heidelberg cohort, 35% of the patients with pulmonary hypertension suffered from mental disorders. The most common were major depressive disorders (15.9%) and panic disorders (10.4%), most of them were potentially treatable and their prevalence increased as the severity of disease progressed [10]. Current European Society of Cardiology guidelines suggest that psychosocial support should be considered in patients with PAH (with recommendation class IIa and level of evidence C) [2].

PAH frequently affects relatively young, professionally active people, predominantly women. Severity of symptoms, complex treatment, or psychological distress often makes it challenging to tolerate normal work conditions and responsibilities. This may result in job loss, which can lead to loss of economic independence and social isolation [8]. Work ability in PAH is determined by specific job demands, patient's health condition, and mental resources [11]. Qualifying of work ability is crucial for obtaining social security or medical disability benefits; however, many patients with PAH experience problems with qualifying their work ability status by health care providers. The main factors contributing to this situation are rare prevalence and rapid course of PAH, young age of the patients, late or missed diagnosis, and relatively normal physical examination [8].

**Table 1.** Instruments used to assess health-related quality of life in pulmonary arterial hypertension patients (modified from [8])

Questionnaire	Contents of domains
NHP	Physical mobility Pain Sleep Social isolation Emotional reactions Energy
MLHFQ	Physical Emotional
HFQ	Dyspnea Fatigue Emotional function of daily living
SF-36	Physical functioning Social functioning Role limitations due to physical problems Role limitations due to emotional problems Mental health Energy/vitality Pain General health perception
EQ-5D	Mobility Self-care Usual activity Pain/discomfort Anxiety/depression
SGRQ	Symptoms Activity Impact
AQoL	Illness Independent living Physical ability Psychological well-being Social relationships
CAMPHOR	Symptoms (energy, breathlessness, mood) Functioning QoL

AQoL – Australian Quality of Life; EQ-5D – EuroQoL questionnaire; HFQ – 16-item Heart Failure Questionnaire; MLHF – Minnesota Living with Heart Failure Questionnaire; NHP – Nottingham Health Profile; SGRQ – St George’s Respiratory Questionnaire

## Instruments used to assess health-related quality of life in pulmonary arterial hypertension

Instruments used to measure HRQoL are multidimensional tools designed to assess not only the level of impairment but also its impact on individual’s physical, psychological, and social well-being (Table 1) [1]. Therefore they usually contain multiple number of domains to evaluate various aspects of health status. In the last years, a number of studies on HRQoL impairment in PAH has grown but there is still no consensus on the instrument type. The available options for the assessment of HRQoL are generic measurements, designed primarily for broad

spectrum of disorders or condition-specific tools dedicated to particular group of patients.

**Generic measures** such as the Medical Outcome Study 36-item Short Form Health Survey (SF-36) [12] and the Nottingham Health Profile (NHP) [13] may be used in a broad disease spectrum, even in healthy subjects to compare individual’s outcome with population norms. EuroQoL (EQ-5D) [14] and the Australian Assessment of Quality of Life (AQoL) [15] provide a multidimensional assessment of general health in addition to preference-based “utility” scores that can be applied in economic analyses. A specific type of generic instrument is a standard gamble (SG). This tool allows to gather all health state domains into a single measure [9]. SG is expressed as the willingness to die in exchange of perfect health. This value represents the QoL of patients and can be used to determine perception of disability and possible benefits from the treatment. In a recent study evaluating PAH, a mean SG value was 0.71, suggesting that patients were willing to accept 29% risk of death to become completely cured [8].

**Condition-specific measures** are designed for more specified group of patients. They are assessing selected health aspects, and therefore may be more sensitive to treatment changes than generic measures. Cardiac and respiratory-specific instruments are often used in patients with PAH considering the effect of dyspnea and activity limitations on individual’s condition [5]. Measures such as Minnesota Living with Heart Failure Questionnaire (MLHFQ) or Chronic Heart Failure Questionnaire (CHQ) are frequently used in PAH; therefore, they are well evaluated and have been proved to have high internal consistency and good test–retest reproducibility [16].

The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) is currently the only available **PH-specific measure**. CAMPHOR consists of three scales for the assessment of symptoms, functioning, and QoL [17]. This tool has been validated in the United Kingdom and United States, where a study confirmed a good test–retest reliability and internal consistency. CAMPHOR scales correlated with the SF-36 and 6-minute walk test (6MWT), making it a promising instrument. However, its use in the clinical trial setting still has to be determined [18].

## Application of health-related quality of life instruments in the assessment of patient status

Recent studies in PAH have shown that measures of physiological response and exercise capacity, such as 6MWT, account for only a portion of the observed variance in HRQoL [5,16]. A gradual reduction in exercise tolerance in PAH is usually measured by WHO functional class, 6MWT, or cardiopulmonary exercise tests. Taichman et al. [5] showed that better HRQoL scores correlated with greater 6MWT but not with hemodynamic measurements. Furthermore, they

reported significantly depressed physical and mental component scores of the SF-36 in PAH patients. This was similar in patients with other debilitating and life-threatening conditions such as spinal cord injury and metastatic cancer [5]. In a study comparing the MLHFQ with the SF-36 and AqoL [19], the total scores of all three tools correlated well with 6MWT and New York Health Association (NYHA)/WHO class. As in a previous study, a correlation with hemodynamic parameters was poor. What is more, SF-36 and MLHFQ outcomes better reflected changes in 6MWT and NYHA/WHO class than AqoL, which was much less responsive.

## Application of health-related quality of life instruments in clinical trials

The most frequently used generic measure in PAH trials has been the SF-36, alongside with the condition-specific MLHFQ and CHQ. Based on the available data, domains related to physical functioning appear to be the most responsive to change in the trial setting. [7] General improvement of the QoL has been shown in the following PAH-specific drugs: sildenafil [20,21], tadalafil [22], bosentan [23], ambrisentan [24], iloprost [25], treprostinil [26], and epoprostenol [27]. Despite a growing number of conducted studies, they frequently use different instruments to determine the HRQoL, thereby making it difficult to compare the outcomes. Other chronic diseases associated with PAH may also confound the outcomes when generic measures are used. Further investigations involving identification of additional factors modifying treatment responses seem to be essential to understand why some treatments, while efficacious from the physical point of view, may be ineffective from the patient's perspective.

## Conclusions

PAH is a progressive disease, leading to a gradual reduction in exercise tolerance and significantly decreasing the HRQoL. A recent development of PAH-specific therapies has significantly improved patients' survival and rate of clinical deterioration. It may be useful to consider patient's personal outcomes in predicting treatment benefits and decision making. For that reason, PROs are becoming an important endpoint in clinical trials. The HRQoL can be currently assessed with a number of designed instruments. Different instruments are dedicated for different purposes. Generic measures such as the SF-36 are useful in evaluating the general outcome of intervention and in comparing results in various conditions. Condition-specific measures focus on a particular clinical group and can be sensitive tools especially in treatment modifications. CAMPHOR, the PAH-specific measure, is a relatively new instrument that appears to be promising in future clinical trials.

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## Pulmonary hypertension in candidates for cardiac transplantation

Deddo Moertl

### Introduction

Heart transplantation is an effective treatment option for patients with end-stage heart failure, in whom conventional guideline-recommended treatment options like medication and device therapy have failed [1]. However, a considerable proportion of these patients develop pulmonary hypertension of group 2 (due to left heart disease) according to the international guidelines of pulmonary hypertension (Dana Point classification) [2]. It is well accepted that increased pulmonary vascular resistance (PVR) is associated with early and late mortality after heart transplantation due to right heart failure [3–8], which can be explained by the inability of the donor right heart to adapt to pre-existing and remaining elevated pulmonary vascular resistance. Therefore right heart catheterization is a standard procedure in the evaluation for heart transplantation. Since end-stage heart failure is so closely associated with pulmonary hypertension, re-evaluation of the hemodynamic situation of patients on the waiting list for transplantation with right heart catheterization is performed on a regular basis (usually every 3–6 months) [9].

The key hemodynamic parameters to assess pulmonary hypertension in candidates for heart transplantation are:

1. Pulmonary artery systolic pressure (sPAP, mm Hg)
2. Pulmonary vascular resistance (PVR, Wood units)
3. Transpulmonary gradient (TPG, mm Hg)

Although cut-off values of hemodynamic parameters may vary to a certain degree between transplantation centers and networks, pulmonary hypertension represents a relative contraindication for heart transplantation. The current guidelines from the International Society of Heart and Lung Transplantation state that a PVR of >5 Wood units or a TPG exceeding 16 to 20 mm Hg is a relative contraindication for heart transplantation and that, if sPAP exceeds 60 mm Hg in conjunction with any of the preceding variables, the risk of right heart failure and early death is increased [9].

Importantly, these recommendations are based on cut-off values of continuous variables, while the risk of death post transplantation increases steadily with the increase of pulmonary hypertension. Accordingly, in patients with a pre-transplantation PVR of <2 Wood units, 2–3 Wood units and > 3 Wood units 30-day mortality after heart transplantation was 5.1%, 10.6%, and 17.7% [4].

Pulmonary hypertension due to left heart failure is caused by increased back pressure from the left heart

and vasoconstriction. Therefore, in most of these patients pulmonary hypertension is reversible and does not provide a significant problem after transplantation. Several provocative maneuvers can be used to discriminate between reversible and nonreversible pulmonary hypertension in the evaluation for transplantation. The aim of these maneuvers is to demonstrate that the above-mentioned key hemodynamic parameters can be lowered below pre-defined, but again arbitrary cutoff values. Currently, there is no reliable hemodynamic threshold below which right ventricular failure post transplantation can be avoided and at the same time above which it is likely to occur. Although some agreements on these hemodynamic goals have been established among heart transplantation specialists, it is clear that listing a patient for transplantation on the basis of reversibility testing of PH requires an individual decision by the treating physicians in every single case.

### Vasoreactivity testing

As mentioned before pulmonary hypertension is associated with increased mortality after heart transplantation due to right heart failure. However, if pre-existing PH is reversible in vasodilator testing, the risk is much lower and some even reported no differences compared to patients without PH before transplantation [6, 8, 10]. Therefore, patients whose PVR can be acutely reduced by pharmacological measures to a certain level are usually considered candidates for transplantation. A reduction below 4 Wood units is acceptable for heart transplantation in many centers, although a PVR below 2.5 Wood units is the desired goal. In one report, the three-month mortality rate was higher in patients whose PVR was above 2.5 Wood units compared to those with lower values (17.9% versus 6.9%) [3]. However, it is important that this reduction of PVR is not gained at the expense of systemic hypotension: Patients with a drop in systemic systolic blood pressure below 85 mm Hg during vasoreactivity testing remain at high risk for mortality due to right heart failure after heart transplantation, even if PVR can be reduced to <2.5 [3, 9]. Therefore, guidelines recommend a vasodilator challenge when the pulmonary artery systolic pressure is  $\geq 50$  mm Hg and either TPG is  $\geq 15$  or the PVR is >3 Wood units while maintaining a systolic arterial blood pressure >85 mm Hg [9].

### Selected drugs for vasodynamic testing

Currently, there is no consensus, which is the preferred method for vasodynamic testing of reversibility of pulmonary hypertension. This might be due to the scarcity of prospective, comparative studies evaluating vasodynamic testing in transplant candidates with pulmonary hypertension and relating the results to outcome after heart transplantation. Further,

the demonstration of reversibility of PH seems more important than the actual method used. However, while the demonstration of reversibility of PVR to <2.5 Wood units seems desirable, these cut-off values for hemodynamic goals during vasodynamic testing in cardiac transplant candidates are not based on strong evidence from prospective trials. Table 1 shows the most commonly used drugs for vasoreactivity testing before heart transplantation.

## Vasodilators

**Nitroglycerin** can be given sublingual or oral, but generally i.v. is the preferred route of administration for vasodynamic testing. In a small study in candidates for heart transplantation using an i.v. nitroglycerine infusion, PVR and mean PAP values after transplantation could be predicted and nitroglycerine responders showed a drop in pulmonary pressures and PVR immediately after transplantation [11].

**Sodium nitroprusside** is one of the most commonly used drugs in this setting. Started with an infusion rate of 0.5 µg/kg/min, it is usually increased stepwise by 0.5 µg/kg/min until PVR drops or systemic symptomatic hypotension occurs [3]. As mentioned above, the systemic blood pressure is a major parameter for interpretation of results: Using sodium nitroprussid it has been shown that patients with a reduction in PVR below <2.5 Wood units at a stable systemic blood pressure >85 mm Hg had a 3-month mortality of 3.8% after heart transplantation, while patients with a reduction in PVR below <2.5 Wood units at the expense of a drop in systemic blood pressure to <85 mm Hg had a 3-month mortality of 27.5%. Of interest, all patients who died due to right heart failure

after transplantation belonged to the latter group or were no responders at all and none of the patients with reversible pulmonary hypertension at stable systemic blood pressures developed right ventricular failure after transplantation.

**Inhaled nitric oxide (NO)**, the gold standard for vasoreactivity testing in pulmonary arterial hypertension, has also been studied and compared to other vasodilators in candidates for heart transplantation [12–14]. It is a selective pulmonary vasodilator with a short half-time. Therefore, it causes rapid, selective decrease of TPG and PVR with minimal systemic effects. Attempts have been made to use inhaled NO to test for operability in children [8, 15] but caution has to be used in adults: Inhalative NO increases left ventricular filling pressures in left heart failure and thus NO testing in left heart disease comprises the danger of lung edema [16].

Similar to the other nonselective vasodilators, the primary hemodynamic effect of **nesiritide** is to lower left ventricular filling pressures and to increase pulmonary flow rather than lower TPG [17, 18]. Importantly, nesiritide has shown no clinical benefit in acute decompensated heart failure and systemic hypotension and worsening of renal function have been a major concern [19, 20].

## Prostanoids

Prostanoids have potent vasodilating effects on the pulmonary artery smooth muscle cells and are therefore also used as specific treatment for pulmonary arterial hypertension. In a prospective study with vasoreactivity testing using **prostaglandin E1**, the percentage of patients with PVR >2.5 WU was reduced from 44.2%

**Table 1.** The most commonly used drugs for vasoreactivity testing before heart transplantation

Agent	Administration	Dosage	Side effects
Sodium nitroprusside	i.v.	0.5-5 mcg/kg/min	Hypotension
Adenosine	i.v.	100 µg/kg/min	Flush, nausea, AV-block, metallic taste
Nitrates	Sublingual	0.8 mg	Hypotension
	Oral	5 mg	
	i.v.	10–200 µg/kg/min	
Prostacyclin	i.v.	2–10 ng/kg/min	Tremors, flushing, dizziness, hypotension, nausea, vomiting, fever, diarrhea
Prostaglandin E1	i.v.	0.01–0.3 µg/kg/min	Tremors, flushing, dizziness, hypotension, nausea, vomiting, fever, diarrhea
Inhaled nitric oxide	Face mask	10-80 ppm	Methemoglobinemia
	Ventilator circuit		
Milrinone	i.v.	0.375–0.75 µg/kg/min or 50mcg/kg bolus	Hypotension
Nesiritide	i.v.	2 µg/kg bolus followed by 0.01 µg/kg/min infusion	Hypotension, renal insufficiency
Levosimendan	i.v.	0.5-2mcg/kg/min	Hypotension

to 10.5% [21]. PVR decreased in each patient, and only 1% of patients remained ineligible for listing because of a final PVR of >4.0 Wood units. Similarly, in a study using **prostaglandin I<sub>2</sub>**, 62% percent of patients fell in PVR below 2.5 Wood units and in TPG below 15 mm Hg, and none of them remained above 4 Wood units [22]. Furthermore, **prostaglandin E<sub>1</sub>** seems to produce more pronounced hemodynamic effects on TPG and PVR than other drugs used for vasoreactivity testing including nitroglycerin, nitroprusside, and intravenous inotropic agents dobutamine and enoximone [23]. This was confirmed in another study comparing prostaglandin E<sub>1</sub> with nitroglycerin and sodium nitroprusside. None of the patients that were transplanted after reversibility of PH had been shown with prostaglandin E<sub>1</sub> developed donor right heart failure [24].

## Inodilators

The most commonly used inodilator in this setting is **milrinone** [25]. Apart from its positive inotropic effects, milrinone decreases pulmonary arterial pressure, left ventricular filling pressure and systemic vascular resistance [26].

In acute decompensated heart failure, the calcium-sensitizer **levosimendan** led to a significant reduction in PVR and pulmonary arterial pressure that was similar to low dose prostaglandin E<sub>1</sub> [27]. However, no published trial exists on the usage of levosimendan for vasoreactivity testing in PH in candidates for heart transplantation. Since the systolic PAP increases and the PVR decreases as cardiac output increases, inodilators are often questioned as an appropriate tool for testing for reversibility of PH in transplant candidates.

## Management of candidates for heart transplantation with PH

There is considerable clinical experience that PH in transplant candidates that is not acutely reversible can be successfully treated over weeks or months, although this is not supported by multicenter controlled randomized trials. Specific drugs used for pulmonary arterial hypertension are not recommended for chronic treatment in patients with left heart disease [2, 28], although some of them have shown favorable hemodynamic effects. Prostacyclin has been tested in a randomized controlled trial in patients with severe heart failure but increased mortality compared to placebo [29]. Prostaglandin E<sub>1</sub> is used for bridging to heart transplantation in single centers [30], but a placebo-controlled trial has never been performed. Likewise, endothelin receptor antagonists have neutral or unfavorable effects in chronic heart failure [31–33]. Sildenafil has shown favorable effects in a long-term reduction of PVR and sPAP in end-stage heart failure [34, 35]. However, concerns have been raised about a potential increase in

sudden cardiac death rate [36], and a large double-blind placebo-controlled trial in this indication is still lacking.

Other drugs used for vasoreactivity testing should be used with caution as well. Oral milrinone has increased mortality in chronic heart failure [37]. Single administration of levosimendan over 24-hours also increased mortality in those patients with lower initial blood pressures values [38].

Currently there is an increasing use of ventricular assist devices, which can be attributed to the observed dramatic reduction in complication rates, to expanding indications and to the increasing time on waiting list for heart transplantation. Ventricular assist devices have been shown to successfully reduce systolic PAP and PVR and thus can make these patients eligible for transplantation [39, 40]. Combined heart and lung transplantation may also be an option in some centers.

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# Rare diseases of pulmonary circulation: Clinical examples

## Rapid progressive idiopathic pulmonary arterial hypertension (RCD code: II-1A.1)

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### Background

Data from registries confirm that the prevalence of pulmonary arterial hypertension (PAH) is in the range of 15 to 50 cases per million [1,2]. Current clinical classification distinguishes several forms of PAH, namely, idiopathic PAH, heritable, induced by drugs and toxins, associated with other disorders (e.g. connective tissue diseases, HIV infection, portal hypertension, congenital heart disease), and persistent pulmonary hypertension of the newborn [3].

Several anorectic drugs, such as aminorex, fenfluramine, dexfenfluramine, and benfluorex have been shown to be directly related to the development of PAH. Some other drugs and toxins are also suspected to participate in its development, especially those disturbing noradrenergic and serotonergic systems, including selective serotonin uptake inhibitors, cocaine, and methamphetamines [4]. Sibutramine is a serotonin and noradrenaline reuptake inhibitor used in patients with obesity to facilitate weight loss. Short-term observations from several clinical trials did not show an increased risk of pulmonary hypertension in patients taking sibutramine. [5]. However, postmarketing data have shown at least 1 case of pulmonary hypertension that may be attributed to this drug [6].

### Case presentation

A 48-year-old woman was admitted to the Center for Rare Cardiovascular Diseases, Krakow, Poland, on June 18, 2010, with a 2-month history of breathlessness and fatigue at rest (New York Heart Association functional class IV on admission). The patient reported milder symptoms for several months prior to admission.

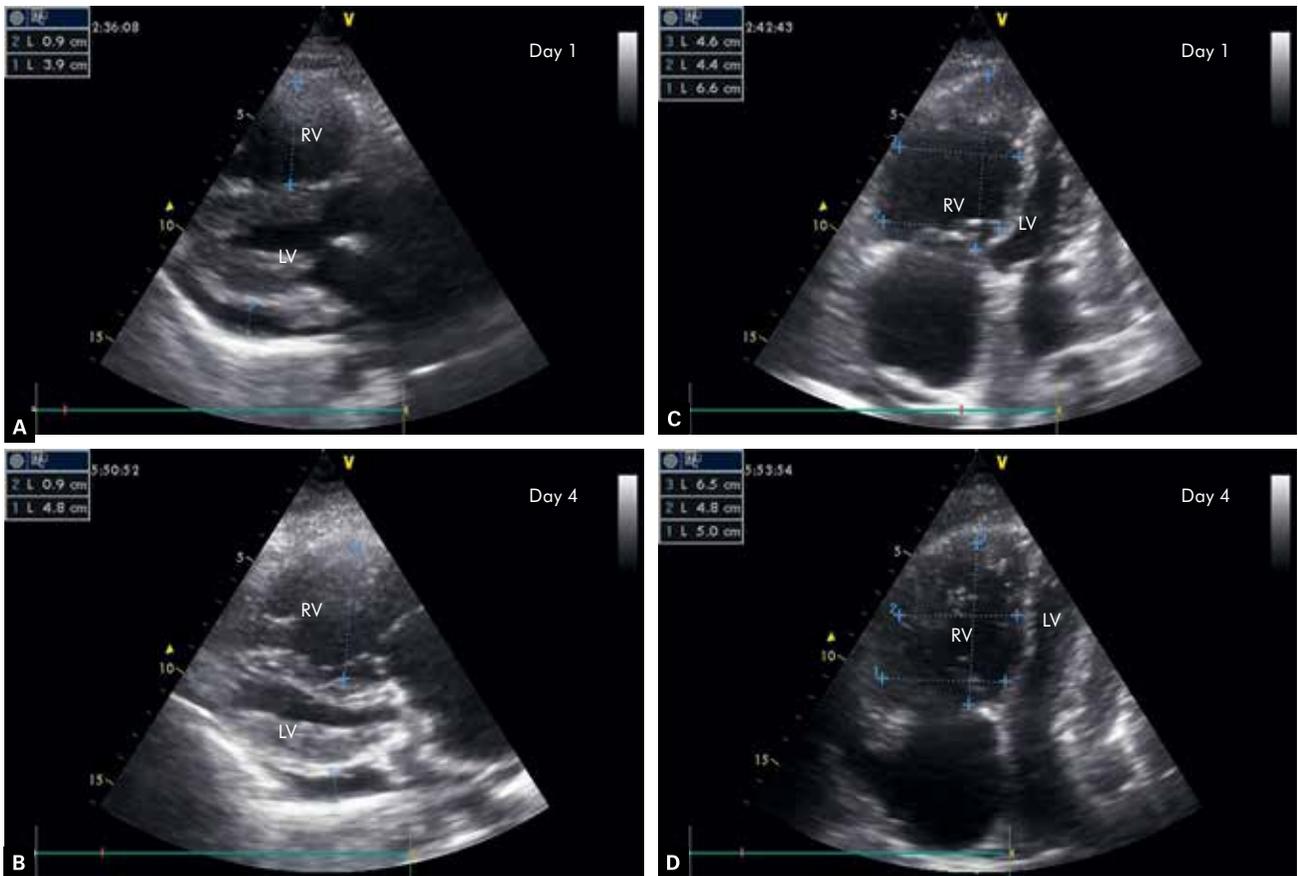
Proximal deep vein thrombosis of the left leg was recognized 2 months before admission. Anticoagulation therapy with heparin intravenously was initiated and subsequently converted to warfarin.

In the past (July and August 2009), the patient had a short episode of sibutramine use to reduce weight. A family history was negative for pulmonary hypertension.

On admission, the patient was in a bad general condition. The signs and symptoms of advanced heart failure were observed. A physical examination revealed low blood pressure (96/58 mm Hg), regular heart rate 88 beats/min, accentuated pulmonary component of the second heart sound, high-pitched pansystolic murmur, most prominent in the fourth intercostal space in the left parasternal region, jugular vein distension, decreased breath sounds at the lung bases, hepatomegaly, central cyanosis, massive peripheral edema, ascites, and obesity (body mass index, 32.8 kg/m<sup>2</sup>). Pulse oximetry showed low SpO<sub>2</sub> of 86%. Routine laboratory tests revealed polycythemia (red blood cells, 5.6×10<sup>3</sup>/μL; hemoglobin 16.7 g/dL, and hematocrit, 50.7%), elevated levels of brain natriuretic peptide (2871 pg/mL; normal values, <100 pg/mL), troponin I (0.16 ng/mL; normal values, <0.1 ng/mL), C-reactive protein (7.6 mg/mL), international normalized ratio of 2.26, and normal levels of D-dimers (<300 ng/mL). HIV and antinuclear and anticentromere antibodies were negative, and so were the blood cultures for bacteria and fungi. Arterial oxygen and carbon dioxide tensions were decreased (PaO<sub>2</sub>, 56 mm Hg; PaCO<sub>2</sub>, 25 mm Hg). A resting electrocardiogram showed right axis deviation and low-voltage R waves in the limb and precordial leads. A Holter examination revealed increased heart rate (mean, 88/min) and single premature ventricular beats. A chest X-ray showed an enlarged cardiac silhouette, mild prominence of the main pulmonary artery, redistribution of pulmonary blood flow, and moderate pleural effusion in the right pleural cavity. Pulmonary function tests and 6-minute walking test could not be performed due to dyspnea at rest. Venous ultrasound examination excluded the recurrence of deep-vein thrombosis.

Transthoracic echocardiography revealed numerous abnormalities (fig. 1–5):

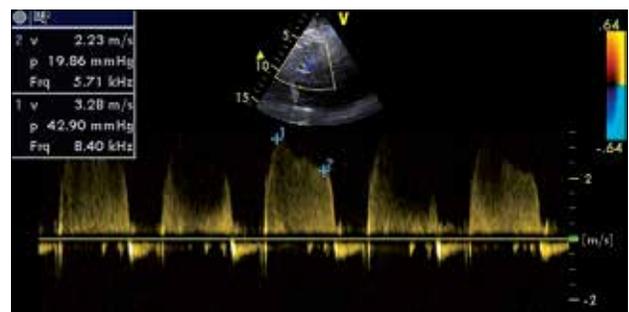
- right ventricular (RV) and right atrial enlargement: RV end-diastolic area was 26 cm<sup>2</sup> (N <25 cm<sup>2</sup>);



**Fig. 1.** Transthoracic echocardiography. **A, B.** Parasternal long-axis view. **C, D.** Apical four-chamber view. Dynamic progression of right chambers dilatation between day 1 (A,C) and day 4 (B,D) of hospitalization. Main abnormalities include enlarged right ventricle (RV), small left ventricle (LV), pericardial effusion. **A,B.** RV end-diastolic diameter measured at proximal portion of RV outflow tract: day 1 – 39 mm, day 4 – 48 mm. **C,D.** RV end-diastolic inflow tract diameter: day 1 – 44 mm, day 4 – 48 mm; RV long-axis: day 1 – 66 mm, day 4 – 65 mm; RV end-diastolic area: day 1 – 24.4 cm<sup>2</sup>, day 4 – 30.9 cm<sup>2</sup>



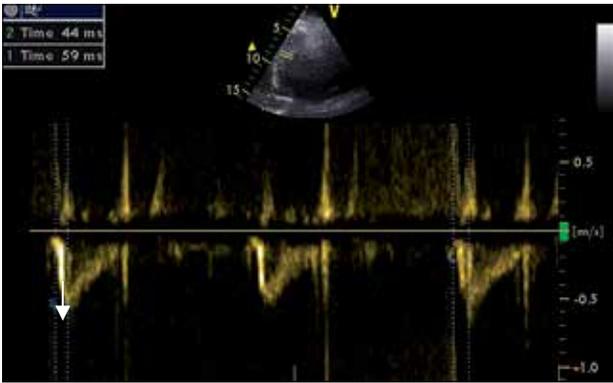
**Fig. 2.** Transthoracic echocardiography. Parasternal short-axis view at the mid-ventricular level. Day 1 enlarged right ventricle (RV); small left ventricle (LV). The interventricular septum is shifted toward the LV cavity. The LV eccentricity index above 1 suggests RV pressure overload (LV eccentricity index = LV anteroposterior diameter / LV septolateral diameter = 33 mm / 16 mm = 2.06)



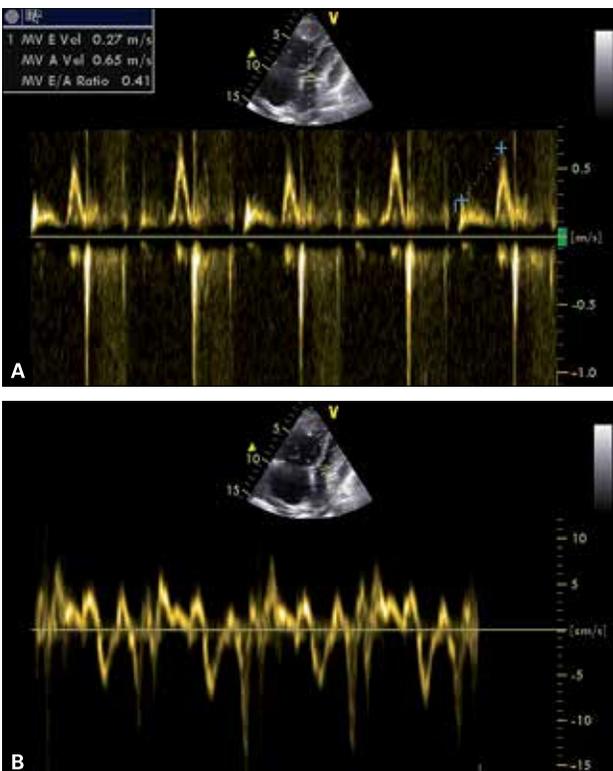
**Fig. 3.** Transthoracic echocardiography. Continuous-wave Doppler. Pulmonary regurgitation flow pattern. Increased peak early-diastolic pulmonary regurgitation gradient (43 mm Hg)

- right atrial area at ventricular end-systole was 23 cm<sup>2</sup> (N <18 cm<sup>2</sup>)
- small left ventricle (left ventricular [LV] end-diastolic diameter, 27 mm; LV eccentricity index, 2.06)
- impaired RV systolic function: RV fractional area change was 23% (N >35%); tricuspid annular plane systolic excursion was 10 mm (N >16 mm)

- paradoxical septal motion
- preserved LV ejection fraction of 70%
- increased trabeculation of the right ventricle
- moderate-to-severe tricuspid regurgitation due to RV and tricuspid annular dilatation: vena contracta width was 6 mm, tricuspid E-wave velocity was 0.7 m/s, and effective regurgitant orifice area was 0.35 cm<sup>2</sup>
- dilated inferior vena cava of 28 mm without any collapse with a sniff
- increased RV systolic pressure estimated at 91 mm Hg as a sum of tricuspid regurgitation peak gradient (76 mm Hg; V<sub>max</sub> 4.3m/s) and right atrial pressure (15 mm Hg)



**Fig. 4.** Transthoracic echocardiography. Pulsed-wave Doppler. Pulmonary flow pattern with short acceleration time of 52 ms (arrow)



**Fig. 5.** Transthoracic echocardiography. **A.** Pulsed-wave Doppler. Mitral flow pattern. E/A = 0.42. **B.** Pulsed tissue Doppler of mitral annulus. E' = 6 cm/s

- increased mean pulmonary artery pressure estimated at 58 mm Hg as a sum of early-diastolic pulmonary regurgitation gradient (43 mm Hg;  $V_{\max}$  3.3 m/s) and right atrial pressure
- dilated pulmonary trunk and branches
- short acceleration time of pulmonary arterial flow (52 ms)
- mild pulmonary regurgitation
- ratio of pulmonary-to-systemic flow of 1:1
- moderate pericardial effusion without features of tamponade

Contrast computed tomography (CT) angiography of the pulmonary artery did not reveal pulmonary embolism. High-resolution CT excluded interstitial lung disease and emphysema but confirmed the presence

**Table 1.** Hemodynamic data at baseline and after 5 minutes of nitric oxide (20 ppm) inhalation

Pressure [mm Hg]	Baseline	After NO
right atrium	26/21/19	–
pulmonary artery	111/47/69	110/46/72
left ventricle	104/10/16	100/5/9
aorta	102/75/85	–
<b>Saturation [%]</b>		
superior vena cava	43.1	–
inferior vena cava	40.7	–
pulmonary artery	36.2	28
aorta	87	83
cardiac output [L/min]	1.78	1.64
cardiac index [L/min/m <sup>2</sup> ]	1.0	0.9
ratio of pulmonary to systemic flow	1:1	1:1
pulmonary vascular resistance [dyne $\times$ s $\times$ cm <sup>-5</sup> ]	3095	3071

of pleural effusion with a 5-cm layer in the right pleural cavity and pericardial effusion (8 mm). Using right-sided thoracentesis, we were able to evacuate 200 mL of transudate.

Coronary angiography revealed no critical lesions in the coronary arteries. Right heart catheterization showed severe pulmonary hypertension (mean pulmonary artery pressure, 69 mm Hg), increased pulmonary vascular resistance (PVR, 3095 dyne  $\times$  s  $\times$  cm<sup>-5</sup>; 38.7 Wood units), borderline pulmonary capillary wedge pressure (15 mm Hg), and very low cardiac output – 1.78 L/min (1.0 L/min/m<sup>2</sup>). The results of a vasoreactivity test with inhaled nitric oxide were negative (Table 1).

The patient's general condition deteriorated despite the initiation of sequential PAH-specific therapy (iloprost, 5 mcg 6 times/day; subsequently, combination therapy with sildenafil, 20 mg t.i.d.) and supportive treatment (warfarin, digoxin, diuretics, inotropic agents, oxygen supplementation). Intravenous epoprostenol was not available at that time. Transthoracic echocardiography revealed progression of ventricular enlargement and dysfunction (fig. 1). The patient died 4 days after admission due to low-output heart failure. A histological examination of specimens obtained during autopsy revealed primary pulmonary arteriopathy and fungal mural endocarditis.

## Discussion

Overall 5-year survival for idiopathic PAH has increased from approximately 30% in the 1980s to approximately 60% at present. This is mainly associated with the introduction of PAH-specific therapy

**Table 2. Etiology of acute right ventricular failure in pulmonary hypertension [40]**

- Myocardial ischemia
- Sepsis
- Infective endocarditis
- Pulmonary embolism
- Atrial and ventricular tachyarrhythmias
- Iatrogenic causes:
  - acute withdrawal of PAH-specific therapy
  - use of
    - negative inotropic agents ( $\beta$ -blockers, calcium channel blockers)
    - sedatives
    - vasodilators (nitroprusside, milrinone)
    - mechanical ventilation with high plateau and high positive end-expiratory pressures

**Table 3. Recommendations for pulmonary arterial hypertension – targeted therapy in patients at functional class IV [7]**

	class* level#
Epoprostenol i.v.	I/A
Ambrisentan, Bosentan, Sildenafil, Tadalafil, Iloprost inhaled, i.v., Treprostinil s.c., i.v., inhaled	IIa/C
Sequential combination therapy ERA $\pm$ PDE-5I $\pm$ prostanoids	IIa/B
Initial combination therapy ERA $\pm$ PDE-5I $\pm$ prostanoids	IIa/C
* Class of recommendation # Level of evidence ERA – endothelin receptor antagonist; PDE-5I – phosphodiesterase type-5 inhibitor	

**Table 4. Recommendations for supportive therapy in pulmonary arterial hypertension [7]**

	class* level#
Diuretic treatment in patients with the signs of RV failure and fluid retention	I/C
Continuous long-term O <sub>2</sub> therapy if arterial blood O <sub>2</sub> pressure is consistently less than 8 kPa (60 mm Hg)	I/C
Oral anticoagulant treatment in patients with idiopathic PAH, heritable PAH, and PAH caused by anorexigens	IIa/C
Oral anticoagulant treatment in patients with PAH due to the use of anorexigens	IIb/C
Digoxin in patients who develop atrial tachyarrhythmias to slow ventricular rate	IIb/C
*Class of recommendation #Level of evidence PAH – pulmonary arterial hypertension, RV – right ventricular	

to clinical practice. RV failure is the leading cause of death in PAH [7]. The management of decompensated RV failure secondary to pulmonary hypertension requires treatment of the underlying cause and hemodynamic support (Table 2–4). The RV function can improve significantly in patients with myocardial infarction who underwent revascularization or in unstable patients with acute pulmonary embolism after thrombolytic therapy or embolectomy [8,9]. Thromboendarterectomy is a treatment option for patients with chronic thromboembolic pulmonary hypertension and RV failure [10]. Treating the reversible underlying cause of the disorder improves prognosis. The effect of hemodynamic support on long-term survival is not clear. Hemodynamic support includes oxygen, intravenous fluids, inotropic agents, pulmonary vasodilators, mechanical assist devices, and surgery. The effect of volume loading on ventricular hemodynamics depends on the degree of RV afterload and volume status. Low preload restricts cardiac output. Fluid administration may improve the condition of patients without increased right-sided preload and LV failure. On the other hand, volume overload may lead to overdistension of the RV, increased wall tension, decreased contractility, interventricular septal shift, and compression of the LV that results in decreased LV filling and reduced systemic cardiac output [11]. Patients with severe RV dysfunction often have high RV filling pressure, and aggressive fluid resuscitation can worsen their condition [12]. Diuretic therapy and restriction of fluid and sodium intake reduces ventricular filling pressures. Intravenous loop diuretics are most efficient in patients with severe congestion and hypoperfusion. Typically, they are used in combination with other diuretics. Hemofiltration is an option if volume overload and renal dysfunction are present [13].

Inotropic agents, such as dobutamine, milrinone, or levosimendan, improve biventricular function but may cause vasodilation and systemic hypotension [14,15]. Combined treatment with inotropes and vasopressors may increase cardiac output without causing hypotension and hyperfusion, but it is associated with an increased risk of proarrhythmic events. In normotensive patients with decreased cardiac output, therapy may be started with inotropic agents. Vasopressors should be added if hypotension develops. In hypotensive patients, vasopressors should be instituted followed by inotropes if cardiac output remains low [16]. The choice of vasopressors and inotropes should be individualized and based on a patient’s response and effects on PVR and cardiac output. Adverse effects limit the use of drugs of both classes. Dobutamine in moderate doses (above 5  $\mu$ g/kg/min) may cause tachycardia and systemic hypotension [17]. Norepinephrine increases PVR and worsens PAH. Beneficial effects include a decrease in the ratio of pulmonary arterial pressure to systemic blood pressure [18]. Dopamine and epinephrine increase PVR and have high proarrhythmic potential [19]. Vasopressin, owing to nonadrenergic mechanism of action, may help avoid exacerbation of tachycardia but, at high doses, may increase PVR [20]. Digoxin

may produce a small increase in cardiac output and is useful for controlling heart rate [21].

Vasodilators may improve RV output by reducing afterload. Systemic vasodilators, such as nitroglycerine and nitroprusside, reduce right ventricular preload and afterload at the cost of decreased systemic vascular resistance, which may cause hypotension, worsen ischemia, and reduce right-sided cardiac output [22]. Pulmonary vasodilators can significantly reduce pulmonary artery pressure, improve ventilation/perfusion matching, and arterial oxygenation. Inhalation route of administration and a short half-life prevents systemic vasodilation [23]. Inhaled nitric oxide improves cardiac output in patients with pulmonary hypertension of varied origin, for example, acute respiratory distress syndrome, pulmonary embolism, and chronic obstructive pulmonary disease [24]. Rapid interruption of nitric oxide administration causes rebound pulmonary hypertension and rapid clinical deterioration. A gradual discontinuation prevents rebound effect [25]. Inhaled iloprost, a prostacyclin analog, appears to induce greater hemodynamic improvement [26]. Other prostacyclin analogs, such as subcutaneous or intravenous treprostinil and intravenous alprostadil, have relatively long half-lives and higher risk of hypotension [27]. Epoprostenol has the highest recommendation (1/A) in the treatment of PAH in the World Health Organization class IV [7]. Pulmonary vasodilators can also increase capillary wedge pressure in patients with concomitant severe LV dysfunction leading to pulmonary edema. Other PAH-specific drugs, including phosphodiesterase-5 inhibitors and endothelin receptor antagonist, are usually introduced after an episode of acute right heart failure (Table 3). Sildenafil, a phosphodiesterase-5 inhibitor, can be used to minimize rebound pulmonary hypertension after inhaled nitric oxide discontinuation [28]. Data on endothelin receptor antagonist use in the setting of acute RV failure are limited. A combination of pulmonary vasodilators and milrinone, a new inotropic and vasodilator agent, has additive effect on pulmonary vasodilation and RV contractility [29].

In selected patients, intraaortic balloon pump may increase coronary artery perfusion and reduce ischemia. RV assist devices and extracorporeal membrane oxygenation may be an option for patients with potentially reversible acute pulmonary hypertension [30]. Other surgical options include atrial septostomy and lung or heart and lung transplantation. However, they are associated with high morbidity and mortality in critically ill patients [31]. Patients with respiratory failure may require mechanical ventilation. A strategy based on reduction of transpulmonary pressure (low tidal volumes) and end-expiratory pressure limits the negative effect of mechanical ventilation on PVR [32]. Treatment with 100% oxygen reduces PVR in patients with PAH [33].

Patients without the signs of RV volume overload should be treated with fluids and, subsequently, with pulmonary vasodilators. Patients with RV volume overload should receive vasopressors, inotropic agents, and pulmonary vasodilators. If unsuccessful, mechanical assist devices, balloon atrial septostomy,

and transplantation should be considered. Invasive hemodynamic monitoring may be helpful in guiding management [8,11,13].

Fungi are responsible for 1% to 6% of the cases of infective endocarditis (IE). The incidence of fungal endocarditis in patients with PAH is unknown. Pierrotti et al., [34] analyzed 152 cases of fungal endocarditis reported in English-language literature between 1995 and 2000. The most common predisposing conditions included underlying anatomical cardiac conditions, prosthetic cardiac devices, central venous catheters, and previous antibiotic use. *Candida* and *Aspergillus* species were identified in 95 and 28 patients, respectively. Patients with *Candida* IE had positive blood culture more often than patients with *Aspergillus* IE (81.2% vs. 30.8%). Transthoracic echocardiography demonstrated vegetations or myocardial abscess in 81% and 5.9% of the cases, respectively. The overall mortality rate was 56.6%. The mortality rate among patients with *Aspergillus* IE exceeded 90% [34]. Amphotericin B remains the drug of choice for antifungal therapy. Successful monotherapy with caspofungin has also been reported. Valve replacement may improve prognosis in selected patients (Table 3) [35,36].

Nonvalvular mural endocarditis is an uncommon condition. Kearney et al. [37] described 52 patients with mural endocarditis in 3 autopsy studies. The majority of these infections were caused by bacteria [37]. The most common symptoms of fungal mural endocarditis include fever, chills, and peripheral embolization. Transthoracic echocardiography or magnetic resonance imaging may reveal nonvalvular mural mass intertwined within the ventricular trabeculae [38,39]. In patients with fungal mural endocarditis, blood cultures are rarely positive (7%–16%). The prognosis for fungal mural endocarditis is poor. IE may exacerbate RV failure in chronic pulmonary hypertension [40]. The death of our patient might have been, at least partially, related to IE.

**Table 5. Recommendations for surgical treatment of right-sided infective endocarditis [35]**

	class* level#
Microorganisms difficult to eradicate (e.g., persistent fungi) or bacteremia for >7 days (e.g., <i>S. aureus</i> , <i>P. aeruginosa</i> ) despite adequate antimicrobial therapy	Ila/C
Persistent tricuspid valve vegetations >20 mm after recurrent pulmonary emboli with or without concomitant right heart failure	Ila/C
Right heart failure secondary to severe tricuspid regurgitation with poor response to diuretic therapy	Ila/C
* Class of recommendation # Level of evidence	

## Management strategy

Our patient suffered from 2 rare disorders: PAH and fungal mural endocarditis. The examinations suggested that the symptoms of RV failure could be attributed to PAH. Fungal mural endocarditis was diagnosed postmortem. It presented in a subtle and unremarkable manner: the patient was afebrile, inflammatory markers were low, blood cultures were negative, and echocardiography revealed only increased trabeculation of the RV. A rapid deterioration of the patient's condition limited the time of diagnosis. Clinical diagnosis of PAH was confirmed by autopsy. The association between PAH and exposure to sibutramine cannot be excluded.

We observed insufficient response to PAH-specific drugs (sildenafil and iloprost) and supportive treatment (warfarin, digoxin, diuretics, inotropic agents, O<sub>2</sub> therapy). We suspect that IE contributed to this poor response.

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## Idiopathic pulmonary arterial hypertension with a positive pulmonary artery reactivity test and pulmonary artery aneurysm (RCD code: II-1A.1)

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### Background

Pulmonary hypertension is a rare disease of unclear etiology and pathogenesis. It is defined as an elevated mean pulmonary artery pressure (mPAP)  $\geq 25$  mm Hg at rest measured by right heart catheterization (RHC) [1].

Idiopathic pulmonary arterial hypertension (IPAH) is diagnosed by the exclusion of other causes of pulmonary hypertension. In patients with IPAH, in diagnostic RHC, the vascular reactivity test should be performed to identify patients who may benefit from long-term therapy with calcium channel blockers (CCBs) [1,2].

A positive response in this test is defined as a decrease in the mPAP  $\geq 10$  mm Hg, reaching an absolute value of the mPAP  $\leq 40$  mm Hg with unchanged or increased cardiac output [1]. Only about 10% of the patients with IPAH meet the above criteria [1,2].

Patients with a positive acute vasoreactivity test are most likely to maintain a long-term response to the prolonged administration of high doses of CCBs and are the only patients who can be safely treated in this way [1,2]. About half of the patients with IPAH reacting positively to the acute vasodilator test also respond well to the long-term treatment with CCBs, and only in such cases, it is reasonable to continue the administration of CCB monotherapy [1,2].

The usefulness of acute vasoreactivity tests and long-term value of CCB treatment is less clear in patients with other types of pulmonary arterial hypertension (PAH) than IPAH, heritable PAH and PAH associated with anorexigen use. There are no data on the long-term effects of CCB therapy in patients with PAH associated with congenital heart disease; therefore, the value of the vasoreactivity test in this group remains controversial. The use of the vasoreactivity tests to identify patients with long-term favorable response to CCB treatment in clinical groups 2, 3, 4, and 5 (Dana Point classification of 2008) of pulmonary hypertension is currently not recommended.

Pulmonary vascular disease of any etiology can lead to an increase in pulmonary vascular resistance and pulmonary arterial pressure. The proximal pulmonary artery (PA) exposed to elevated pressure tends to expand and form an aneurysm [3,4]. Predisposition to form an aneurysm varies between individuals and does not appear to depend directly on the value of the pressure recorded inside the vessel. Pulmonary artery aneurysm (PAA) was defined by some authors as PA dilation

greater than 4 cm; however, according to the classical definition, aneurysm is a localized dilatation of an artery of at least 50% involving all three layers of the vessel, namely, the intima, media, and adventitia [5]. Most PAA are caused by trauma, often iatrogenic, infection, and Behçet's syndrome. Less common causes include pulmonary hypertension, congenital heart disease, neoplasms, and connective tissue disease [4–6].

PA dilatation emerges as an independent risk factor for death unexplained by right ventricular failure or comorbidities in patients with PAH and chronic thromboembolic pulmonary hypertension (CTEPH).

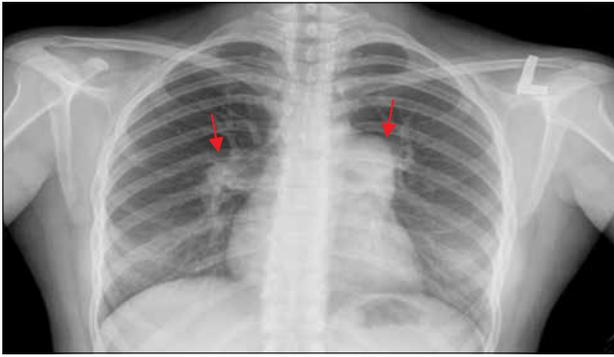
Prognostic significance of PA dilatation has been recently assessed in 264 patients with PAH or CTEPH [7]. PA pulse pressure, younger age, and duration of symptoms were independently but weakly related to the PA diameter. During a follow-up (median, 38 months), 99 patients (37%) died. Of these 99 deaths, 73 (74%) were due to heart failure or comorbidities, and 26 (26%) were unexpected deaths. PA diameter (hazard ratio [HR], 1.06 per 1 mm; 95% confidence interval [CI], 1.03–1.08), heart rate (HR, 1.30 per 10 beats/min; 95% CI, 1.01–1.66), and systolic pulmonary arterial pressure (HR, 1.02 per 1 mm Hg; 95% CI, 1.01–1.04) were the only independent predictors of unexpected death and differed from the usual predictors found in the study group for all-cause mortality. A PA diameter of  $\geq 48$  mm had 95% specificity and 39% sensitivity and carried 7.5-times higher risk of unexpected death during follow-up.

The possible mechanisms of unexpected deaths in patients with PAA include PA compression of the left main coronary artery, PA rupture, or dissection with cardiac tamponade. Proximal PAA occasionally induces some other serious complications, including compression of the bronchus and thrombus of the PA.

### Case presentation

A 23-year-old woman with a history of 7 months of progressive dyspnea in World Health Organization (WHO) functional class II, was admitted to the Centre for Rare Cardiovascular Diseases at the John Paul II Hospital for clinical evaluation. A suspicion of pulmonary hypertension was raised by the referring doctor on the basis of an enlarged PA in chest computed tomography. Patient denied any chest pain. A general physical examination on admission did not show any abnormalities. Auscultation revealed no significant changes. During hospitalization, the patient was in a stable condition, with no clinical signs of heart failure and shortness of breath at rest. The patient's father died at the age of 33 years from an unknown heart disease.

Laboratory test results were normal. An electrocardiogram (ECG) showed regular sinus rhythm of 55 beats/min, with the features of right ventricular overload such as right axis deviation, dominant R wave in lead  $V_1$ , ST depression (0.5 mm), and negative T wave in lead  $V_1$ .



**Fig. 1.** Chest X-ray. Posteroanterior view. Marked dilatation of the right and left pulmonary arteries (arrows)

Holter ECG did not show significant arrhythmias.

A chest X-ray examination revealed marked dilatation of the PAs (fig. 1).

Computed tomography of the lung revealed a dilated pulmonary trunk and PAs, persistent thymus, and a mosaic lung perfusion.

Transthoracic echocardiography showed a borderline dilated right ventricle and right atrium (area, 16 mm), marked dilatation of the pulmonary trunk up to 49 mm, and both PAs (right PA diameter, 26 mm; left PA diameter, 29 mm). Right ventricular systolic pressure was estimated at 53 mm Hg. The left ventricle was normal. Table 1 summarizes the echocardiographic parameters during the follow-up of the patient.

Transesophageal echocardiography revealed a persistent foramen ovale and greatly dilated PAs.

Cardiac magnetic resonance (fig. 2) showed the enlargement of the right ventricle to 34.6 cm<sup>2</sup>, aneurysmal pulmonary trunk (4.9×5.0 cm) dividing into two dilated PAs (right, 3.4×2.5 cm; left, 2.8×2.7 cm). There was no communication between the systemic and pulmonary circulation. Four pulmonary veins drained into the left atrium.

Spirometry results were normal but diffusion capacity for carbon dioxide was reduced to 55%.

In the 6-minute walk test, the distance was 356 m, without significant desaturation (at baseline, at peak exercise). The results of the 6-minute walk test at baseline and at follow-up are shown in Table 2. The peak oxygen consumption in the cardiopulmonary exercise test was as low as 13.7 mL O<sub>2</sub>/kg/min.

**Table 1.** Echocardiographic parameters at baseline and at follow-up

Parameter	November 2009	July 2011
Right ventricle [mm] Reference values [26–43]	41 (4 CH)	40 (4CH)
right atrial area [cm <sup>2</sup> ] Reference values [8.3–19.5]	16	16
RVSP [mm Hg]	53	45
Pulmonary trunk diameter [mm] Reference values [9–26]	49	45
TAPSE [mm] Reference values [17–25]	17	19
RVSP – right ventricular systolic pressure, TAPSE – tricuspid annular plane systolic excursion, 4 CH – apical four-chamber view		

Lung ventilation/perfusion scan excluded pulmonary embolism.

RHC revealed elevated pulmonary artery pressure and resistance in the pulmonary circulation, with a good response to inhaled nitric oxide. Table 3 presents the results of RHC at baseline and at follow-up.

The final diagnosis was IPAH with positive acute vasoreactivity test and PAA. Verapamil was started at a dose of 40 mg three times daily and then uptitrated to 80 mg three times daily. As of June 2013, the patient is in WHO functional class II.

## Discussion

Uncontrolled studies have suggested that long-term administration of high-dose CCBs prolongs survival in patients who respond to the acute vasodilator test. Sitbon et al. [2] performed a retrospective study with long-term use of CCB in 557 patients with IPAH. A total of 155 patients were tested acutely with intravenous epoprostenol and 401 with inhaled NO. Most patients (n = 487) did not respond to acute vasodilator challenge and did not receive CCB therapy. In

**Table 2.** Results of 6-minute walk test at baseline and at follow-up

Parameter	Date			
	November 2009		July 2011	
	Before test	After test	Before test	After test
Blood pressure [mm Hg]	120/70	120/70	110/70	120/85
Heart rate [L/min]	73	105	55	59
Pulse oximetry [%]	98	92	98	99
Walk distance [m]	356		492	
Borg scale	1		1	

**Tabela 3.** Results of right-heart catheterization with acute vasoreactivity test at baseline and at follow-up

Date		November 2009	July 2011
Pulmonary artery pressure [mm Hg]	Baseline	78/43/56	53/36/44
	After no	36/21/27	36/17/26
PAWP [mm Hg]	Baseline	13/12/11	5/6/4
	After no	13/12/11	6/6/4
TPR [mm Hg]	Baseline	1565	852
	After no	723	584
PVR [mm Hg]	Baseline	1257	774
	After no	428	427
CI [L/min/m <sup>2</sup> ]	Baseline	1.7	2.36
	After no	1.8	2.03
CO [L/min]	Baseline	2.86	4.1
	After no	2.98	3.56

CI – cardiac index, CO – cardiac output, PAWP – pulmonary artery wedge pressure, PVR – pulmonary vascular resistance, TPR – total pulmonary resistance

the remaining 70 patients who responded acutely to NO or epoprostenol, mPAP and pulmonary vascular resistance decreased significantly by a mean of 33%  $\pm$ 11% (range, 20%–59%) and 45%  $\pm$ 15% (range, 24%–77%), respectively. In all these patients, mPAP decreased by >10 mm Hg from baseline during acute testing. The mean change in mPAP was similar in acute responders tested with inhaled NO (a decrease by 33%  $\pm$ 12% from baseline) and in those tested with intravenous epoprostenol (32%  $\pm$ 11%). Finally, in the 70 patients who showed acute pulmonary vasoreactivity, long-term treatment with oral CCB was initiated with either diltiazem (n = 53), nifedipine (n = 15), or amlodipine (n = 2). Among patients who were considered acute responders, 38 improved after 1 year on CCB therapy (long-term CCB responders group), and 32 failed to improve (CCB-failure group). Long-term CCB responders represented 54% of acute responders and 6.8% (95% CI, 4.7%–8.9%) of the patient sample. These patients had a less severe disease than patients from the CCB failure group, as indicated by a greater proportion of patients in New York Heart Association (NYHA) functional class II, a longer distance walked, and less compromised hemodynamics.

At the time of the last evaluation, 22 patients were in NYHA functional class I and 16 in class II. Their mean 6-minute walk distance was 467  $\pm$ 101 m, and all displayed a sustained improvement in hemodynamics, with mean right atrial pressure of 5  $\pm$ 3 mm Hg, mPAP of 35  $\pm$ 7 mm Hg, and mean pulmonary wedge pressure of 8  $\pm$ 3 mm Hg.

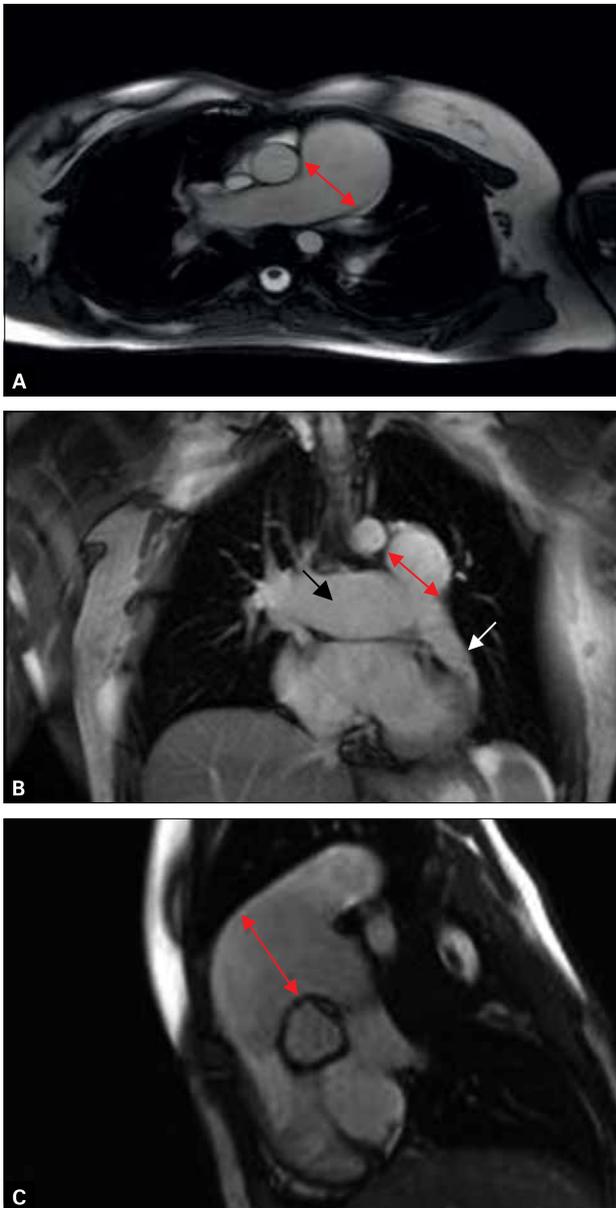
In the CCB failure group, the mean follow-up of patients was 30  $\pm$ 28 months (range, 1–100 months). Twelve patients died (7 on CCB, 4 after transition to intravenous epoprostenol, 1 after transition to iloprost), 7 patients had undergone lung or heart/lung transplantation, 3 were lost to follow-up (on CCB), and 10 remained alive.

The analysis of survival started from 1 year onward on CCB demonstrated a significant difference in mortality between the long-term CCB responders and CCB failure groups.

The study suggests that only a minority of patients with IPAH benefit from long-term treatment with oral CCB. No clinical characteristics or baseline hemodynamic features enabled physicians to distinguish patients who would respond acutely to vasodilators from those who would not.

In published studies, the most frequently used CCBs were nifedipine, diltiazem, and, less commonly, amlodipine [1]. Generally, the choice of CCB is determined by the baseline heart rate. When the heart rate is slow, nifedipine or amlodipine is chosen. It is recommended to initiate treatment with a low dose, for example, 30 mg of nifedipine twice daily, 60 mg of diltiazem 3 times daily, or 2.5 mg of amlodipine once daily. Then, the dose should be carefully increased to the highest well tolerated. The daily doses of drugs effective in IPAH are relatively high: 120 to 240 mg of nifedipine, 240 to 720 mg of diltiazem, and 20 mg of amlodipine. If the patient does not show an adequate response, defined as WHO functional class I or II, and hemodynamic improvement, it is an indication to provide additional treatment of PAH [1].

There are no clear guidelines on PAA treatment; therefore, the approach should be individualized [8,9]. PAA may lead to complications such as extrinsic compression of the left bronchus, left main coronary artery, and left pulmonary vein, thrombus formation, secondary thromboembolic phenomena (such as stroke or lower extremity emboli), and rupture [10,11]. PAA can be treated by surgical correction with resection of the main PA and its two branches and their substitution by allograft tissue; however, some authors have suggested that if the PAA is asymptomatic, it should only be observed [12,13].



**Fig. 3.** Cardiac magnetic resonance. **A.** Transverse view – sine gradient echo. **B.** Coronal view – sine gradient echo. **C.** Long-axis view – sine gradient echo. Dilated pulmonary trunk (red arrow) and right pulmonary artery (black arrow) and left pulmonary artery (white arrow)

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## Pulmonary arterial hypertension after systemic-to-pulmonary shunt correction (RCD code: II-1A.4d)

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### Background

Pulmonary arterial hypertension (PAH) develops in a significant number of patients with congenital heart diseases (CHD). CHD predispose to pulmonary vascular remodeling as a result of increased pulmonary blood flow and increased pulmonary pressure. PAH associated with CHD (PAH-CHD) is a major determinant of functional capacity and survival in this group of patients.

### Case presentation

A 23 year-old woman after surgical closure of atrial and ventricular septal defect was admitted to the hospital due to worsening of dyspnoea. CHD was diagnosed at the age of 4 years. The main clinical symptoms at childhood were recurrent infections of the upper respiratory tract. On echocardiography, atrial septal defect (ostium secundum type) with left-to-right shunt and perimembranous ventricular septal defect with left-to-right shunt were diagnosed. Also a mild enlargement of the right atrium and right ventricle and mild tricuspid and pulmonary regurgitation were observed. On ECG, sinus rhythm of 90 beats/min and right-axis deviation were registered. In laboratory tests, no signs of polycythemia were observed (red blood cell,  $5 \times 10^3$ ; hematocrit, 41.6%; hemoglobin, 14.1 g/dL). The patient underwent corrective cardiac surgery, atrial and ventricular defects were closed. On echocardiography, performed a couple of days after the surgery, no residual shunts through atrial or ventricular septum were observed. Moreover, no tricuspid regurgitation or elevated right ventricular systolic pressure were diagnosed. No right heart catheterization was performed at that time. After discharge, she was routinely monitored in an outpatient clinic at least once a year.

Ten years after the surgery, she started to complain of syncope during exercise. She was admitted to a pediatric cardiac department. On a physical examination, no signs of heart failure were observed, arterial oxygen saturation was between 96% and 100%, and blood pressure was 120/80 mm Hg. An ECG revealed right-axis deviation and right ventricular hypertrophy. A 24-hour ECG showed no abnormalities. On echocardiography, enlargement of the right atrium and right ventricle, elevated right ventricle systolic pressure (110 mm Hg), and elevated diastolic

pulmonary artery pressure (70 mm Hg) were observed. On right heart catheterization pulmonary arterial hypertension was confirmed (mean pulmonary artery pressure, 85 mm Hg; pulmonary capillary wedge pressure, 14 mm Hg; cardiac output, 3.8 L/min; cardiac index, 2.2 L/min/m<sup>2</sup>; pulmonary vascular resistance, 17.4 Wood units). According to the European Society of Cardiology guidelines, she was administered sildenafil at a standard dose of 20 mg three times a day and vitamin K antagonist (VKA).

After 3 months of therapy, the patient reported improvement in exercise capacity. On right heart catheterization, an increase in the cardiac index (2.65 L/min/m<sup>2</sup>) and a decrease in pulmonary vascular resistance (8.8 Wood units) were observed. Sildenafil and VKA were continued.

In 2009, 5 years after the diagnosis of PAH had been established, she was admitted to the Centre for Rare Cardiovascular Diseases at the John Paul II Hospital because of dyspnea, low exercise tolerance, and dizziness. On admission, she was in class III of the World Health Organization functional classification. Brain natriuretic peptide levels was low – 17 pg/mL (normal range, 0–100 pg/mL). A distance in the 6-minute walk test was 411 meters. Echocardiography showed signs of severe pulmonary hypertension, including the enlargement of right heart chambers shortening of the acceleration time, systolic notch of pulmonary flow (fig. 1), severe tricuspid regurgitation with right ventricular systolic pressure of 80 mm Hg, and tricuspid annular plain systolic excursion of 16 mm (fig. 2). Right heart catheterization showed the following parameters: mean pulmonary artery pressure of 91 mm Hg, pulmonary capillary wedge pressure of 15 mm Hg, mixed venous blood saturation of 62%, cardiac index of 2.7 L/min/m<sup>2</sup>, and pulmonary vascular resistance of 16.8 Wood units. Acute vasoreactivity test with inhaled nitric oxide was negative.

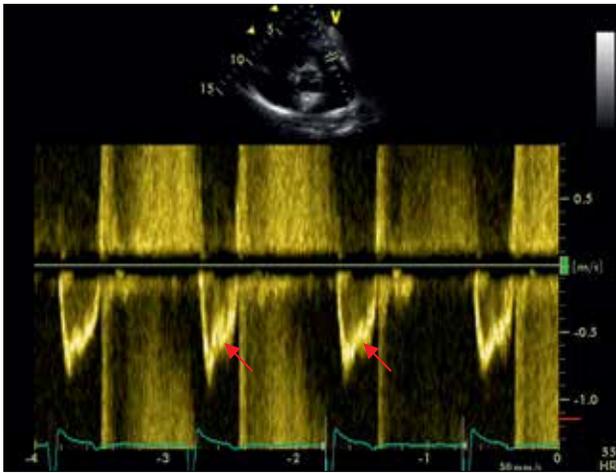
The patient was included in the Study with an Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve cliNical outcome (SERAPHIN), which was a randomized, placebo controlled study to assess the efficacy of a novel endothelin receptor antagonist, macitentan, in patients with PAH. After 3 months of a blinded phase, she was switched to an open-label phase of the trial from that time having been on dual PAH-specific therapy. A significant improvement was observed. Currently, she is in functional class II with the N-terminal pro-B-type natriuretic peptide level of 330 pg/mL (normal range, <125 pg/mL) and a 6-minute walk distance of 542 meters.

### Discussion

#### Epidemiology of PAH-CHD

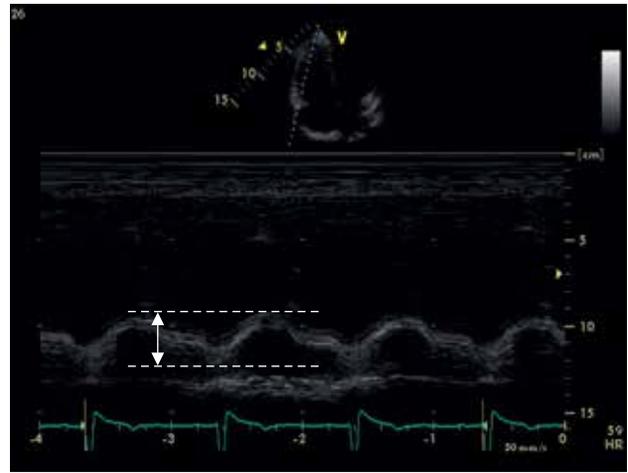
PAH leads to right ventricular failure, decreased functional capacity, and ultimately death.

The prevalence of CHD in adults is increasing, probably because more children survive to adulthood [4]. A significant proportion of the patients with



**Fig. 1.** Transthoracic echocardiography. Parasternal short-axis view. Pulsed wave Doppler through the pulmonary valve. Shortening of the acceleration time to 53 ms, characteristic for pulmonary hypertension systolic notch (red arrows)

CHD develop PAH, especially when left untreated. The prevalence of PAH associated with congenital systemic-to-pulmonary shunts in Europe and North America was estimated at 1.6 to 12.5 per million adults; 25% to 50% of this population had Eisenmenger's syndrome [1]. Among all adults with PAH, 11.3% have PAH-CHD [2]. In 2007, Duffels et al. [3] reported, based on the Dutch registry, that the overall prevalence of PAH among CHD patients was 4.2%. PAH was most frequently found in the aortopulmonary window (100%), atrioventricular septal defect (41%), double outlet right ventricle (17%), univentricular heart (11%), ventricular septal defect (11%), and atrial septal defect



**Fig. 2.** Transthoracic echocardiography. Four-chamber view. M-mode. Tricuspid annular plain systolic excursion (TAPSE) 16 mm (white arrow)

(7.6%). Eisenmenger's syndrome was observed in 58% of the patients with septal defect. It was shown that PAH developed in 3% of the patients with previously closed atrial or ventricular septal defect, which means that closure of the defect does not necessarily prevent the development of PAH.

In many cases, it is not clear whether irreversible pulmonary vascular lesions were already present before the surgical intervention or whether the pulmonary vascular disease has progressed despite successful correction [8].

### Classification of PAH-CHD

PAH-CHD has been classified as belonging to the same broad group of PAH as idiopathic PAH. Classification of PAH-CHD from the Dana Point meeting is shown in Tables 1 and 2. This classification was designed to include clinical as well as anatomical and physiological changes to precisely define the different strategies used in the management and treatment in four PAH-CHD categories [5]. The final group in clinical classification are patients with high pulmonary vascular resistance and pulmonary artery pressure after corrective cardiac surgery, despite normalized heart anatomy.

### Pathophysiology of PAH-CHD

Pathophysiological mechanisms leading to PAH-CHD are similar to those causing idiopathic PAH [6,7]. Left-to-right shunting causes increased pulmonary blood flow and increased pulmonary artery pressures, leading to the damage of the endothelial barrier. Endothelial dysfunction induces vasoconstriction, smooth muscle hypertrophy and proliferation, inflammation, and thrombosis in situ. Endothelial dysfunction shifts the balance between vasoconstrictors and vasodilators in favor of vasoconstrictors. All these changes lead to a progressive increase in pulmonary vascular resistance. Histological classification of pulmonary vascular disease was introduced by Heath and Edwards in 1958. It was suggested, that histological changes

**Table 1.** Clinical classification of congenital systemic-to-pulmonary shunts associated with PAH [5]

#### A. Eisenmenger's syndrome

Eisenmenger's syndrome includes all systemic-to-pulmonary shunts due to large defects leading to a severe increase in PVR and resulting in a reversed (pulmonary-to-systemic) or bidirectional shunt. Cyanosis, erythrocytosis, and multiple organ involvement are present.

#### B. Pulmonary arterial hypertension associated with systemic-to-pulmonary shunts

In these patients with moderate-to-large defects, the increase in PVR is mild to moderate, systemic-to-pulmonary shunt is still largely present, and no cyanosis is present at rest.

#### C. Pulmonary arterial hypertension with small a defects

In cases with small defects (usually ventricular septal defects <1cm and atrial septal defects <2 cm of effective diameter assessed by echocardiography) the clinical picture is very similar to idiopathic PAH.

#### D. Pulmonary arterial hypertension after corrective cardiac surgery

In these cases, congenital heart disease has been corrected but PAH is either still present immediately after surgery or has recurred several months or years after surgery in the absence of significant postoperative residual congenital lesions or defects that originate as a sequela to previous surgery.

<sup>a</sup> The size applies to adult patients.

PAH – pulmonary arterial hypertension; PVR – pulmonary vascular resistance

**Table 2.** Anatomical-pathophysiological classification of congenital systemic-to-pulmonary shunts associated with PAH [5]

<b>1. Type</b>
<b>1.1 Simple pre-tricuspid shunts</b>
1.1.1 Atrial septal defect (ASD)
1.1.1.1 Ostium secundum
1.1.1.2 Sinus venosus
1.1.1.3 Ostium primum
1.1.2 Total or partial unobstructed anomalous pulmonary venous return
<b>1.2 Simple post-tricuspid shunts</b>
1.2.1 Ventricular septal defect (VSD)
1.2.2 Patent ductus arteriosus
<b>1.3 Combined shunts</b>
<b>1.4 Complex congenital heart disease</b>
1.4.1 Complete atrioventricular septal defect
1.4.2 Truncus arteriosus
1.4.3 Single ventricle physiology with unobstructed pulmonary blood flow
1.4.4 Transposition of the great arteries with VSD (without pulmonary stenosis) and/or patent ductus arteriosus
1.4.5 Other
<b>2. Dimension</b>
2.1 Hemodynamic (specify Qp/Qs) <sup>a</sup>
2.1.1 Restrictive (pressure gradient across the defect)
2.1.2 Nonrestrictive
2.2 Anatomic <sup>b</sup>
2.2.1 Small to moderate (ASD ≤2.0 cm and VSD <1.0 cm)
2.2.2 Large (ASD >2.0 cm and VSD >1.0 cm)
<b>3. Direction of shunt</b>
3.1 Predominantly systemic-to-pulmonary
3.2 Predominantly pulmonary-to-systemic
3.3 Bidirectional
<b>4. Associated cardiac and extracardiac abnormalities</b>
<b>5. Repair status</b>
5.1 Unoperated
5.2 Palliated [specify type of operation(s), age at surgery]
5.3 Repaired [specify type of operation(s), age at surgery]
<sup>a</sup> Ratio of pulmonary (Qp) to systemic (Qs) blood flow.
<sup>b</sup> The size applies to adult patients.
ASD – atrial septal defect, VSD – ventricular septal defect

correlate with clinical severity of PAH. This classification involved 6 stages: the early lesions display medial hypertrophy (grade 1), progressing to intimal proliferation (grade 2), lumen occlusion (grade 3), progressive arterial dilatation and plexiform lesions (grade 4), thinning and fibrosis of the media (grade 5), and necrosis (grade 6). Changes in grade 1 to grade 3 were supposed to be reversible. In some patients, severe PAH can be detected after successful corrective cardiac surgery.

## Management strategy

The diagnostic algorithm in PAH-CHD patients is the same as in other types of pulmonary hypertension.

The most common manifestations of PAH of all causes are exercise intolerance, dyspnea, and fatigue.

Clinical symptoms of PAH-CHD may differ according to the underlying defect, severity of PAH, or patient's age [9].

Each patient after corrective cardiac surgery should undergo routine echocardiography examination; right ventricular function and right ventricular systolic pressure should be estimated. Transthoracic echocardiography is a cost-effective, time-efficient, and universal method to evaluate patients after surgery for the presence of PAH. Cardiovascular magnetic resonance imaging (CMR) and computed tomography (CT) can be used to complement echocardiography for the assessment of PAH-CHD. CT scans give information about cardiovascular structures, lung pathology, and the presence of thromboembolism. CMR provides precise assessment of cardiac structures without radiation exposure. However, the gold standard in establishing the diagnosis and severity of PAH is right heart catheterization, similarly to all other types of PAH [5].

Current management with PAH-CHD comprises pharmacological disease-targeted therapy. It should be emphasized that PAH after corrective cardiac surgery is similar to idiopathic PAH and should be treated according to the IPAH treatment algorithm with phosphodiesterase inhibitors, prostacyclin analogues, and endothelin receptor antagonists [5]. The only curative option for end-stage disease is heart and lung transplantation.

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## **A 39-year-old woman with atypical variant of Klippel–Trénaunay syndrome and progressive thromboembolic pulmonary hypertension, successfully treated by pulmonary thromboendarterectomy (RCD code: II-1A.5)**

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### **Background**

Klippel–Trénaunay syndrome is a rare congenital vascular malformation of the veins, capillaries, and lymphatic vessels, which can be associated with thromboembolic events. We report a case involving a woman with Klippel–Trénaunay syndrome and severe complications.

### **Case presentation**

A 39-year-old woman with previously diagnosed Klippel–Trénaunay syndrome affecting her right lower extremity was admitted to our hospital due to a significant deterioration in exercise tolerance and progressive dyspnea. The symptoms had been aggravating slowly for about a week.

Varicose veins in her right lower limb were diagnosed in childhood and the patient underwent a three-staged procedure of varicose vein removal at the age of 17 years. She gave birth to 2 children, without complications, at the age of 19 and 21 years, respectively. At the age of 36 years, she experienced the first episode of pulmonary embolism (PE) treated in a public hospital with unfractionated heparin, and later, she was switched to warfarin therapy.

At the age of 37 years, she gave birth to the third child by cesarean section without complications. The following year, she miscarried at 10 weeks of the next pregnancy. Two months later, despite treatment with oral anticoagulant, she had another episode of PE (international normalized ratio [INR] values were not recorded). Antiphospholipid syndrome and thrombophilia were excluded. An inferior vena cava filter was implanted to prevent recurrent PE and warfarin therapy was continued.

A day before admission, the INR ratio was 1.86. The patient reported that INR levels were not systematically measured during the preceding period.

On admission, the patient was in New York Heart Association (NYHA) functional class IV, with resting

dyspnea, tachypnea (26 breaths/min), tachycardia (heart rate, 102/min), and SaO<sub>2</sub> of 85%. Moreover, we observed central exertional cyanosis and 2 irregular hemangiomas in the sacral region and varicose veins of the lower extremities without the signs of inflammation or thrombosis (fig. 1). The systemic blood pressure was 108/80 mm Hg, but soon after admission the patient developed hypotension of 80/45 mm Hg. On palpation, there was tenderness of the right subcostal region.

Laboratory tests revealed slightly elevated plasma D-dimer levels of 644 µg/L (normal value <486 µg/L). The arterial blood gas analysis showed pO<sub>2</sub> of 59 mm Hg, pCO<sub>2</sub> of 23 mm Hg, pH of 7.47, and SaO<sub>2</sub> of 91.5%. On admission, the electrocardiogram showed sinus tachycardia (115/min), right axis deviation, high P-wave voltage, incomplete right bundle branch block, left posterior fascicular block, and right ventricular (RV) hypertrophy. Chest radiography showed main pulmonary artery enlargement and prominent vascular hili (fig. 2). Colour duplex ultrasonography did not show venous thrombosis in the lower limb. Transthoracic echocardiography (TTE) revealed dilatation of the RV with the proximal RV outflow tract diameter of 40 mm, thickening of the RV free wall of up to 7 mm, flattening and paradoxical motion of the interventricular septum, and reduced RV systolic function with tricuspid annular plane systolic excursion (TAPSE) of 13 mm. An estimated RV systolic pressure was 80 mm Hg and pulmonary flow acceleration time (AcT) was 40 ms (fig. 3, 4: left panels). Computed tomographic (CT) angiography of the chest showed PE (fig. 5). In particular, it showed multiple intraluminal filling defects (emboli) localized in the pulmonary artery of the middle lobe and in the segmental arteries of the middle and lower lobes of the right lung. Based on the clinical course and CT results, the diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) was suggested. Due to a gradual improvement on enoxaparin therapy, the attending physician did not administer thrombolytic treatment. Prior to pulmonary endarterectomy, the patient was referred for right heart catheterization. Due to the presence of the inferior vena cava filter, we used the internal jugular vein access. Before the puncture, color duplex ultrasonography was performed and revealed multiple thrombi in the jugular and subclavian veins so the procedure was aborted due to the risk of thrombus mobilization (fig. 6). As no central PE was found, the consulting cardiac surgeon did not recommend urgent pulmonary thrombectomy. The patient was referred to the Department of Chest Medicine in Warsaw for further evaluation and treatment. The previous findings were confirmed.

Ventilation/perfusion lung scintigraphy showed multiple areas of ventilation/perfusion mismatch at the segmental and subsegmental levels. Right heart catheterization revealed elevated pulmonary artery pressure (56 mm Hg), elevated pulmonary vascular resistance (1636 dyne×s×cm<sup>-5</sup>), and cardiac output of 2.2 L/min. Pulmonary angiography revealed signs of distal chronic thromboembolism (fig. 7). As central



**Fig. 1.** Recurrent lateral varicosity of the right lower extremity due to Klippel-Trenaunay syndrome. Normal size (no hypertrophy) of the leg is present



**Fig. 2.** Chest X-ray image. Main pulmonary artery enlargement and prominent vascular hili

PE was not observed, the patient was discharged in a stable medical condition. The follow-up examinations were repeated after a month. Treatment with nadroparin at a dose of  $2 \times 5700$  IU was continued.

Three weeks later, the patient was admitted to the Department of Cardiac Surgery in Warsaw in critical condition due to the next episode of severe PE. The arterial blood gas analysis revealed  $pO_2$  of 42 mm Hg,  $pCO_2$  of 21.1 mm Hg, pH of 7.49, and  $SaO_2$  of 81%. TTE showed severe right atrial and RV enlargement, severe tricuspid regurgitation, RV systolic pressure of 85 mm Hg, moderate pulmonary regurgitation, TAPSE of 12 mm, AcT of 45 ms, and dilatation of the inferior vena cava without inspiratory collapse. CT pulmonary angiography demonstrated massive thrombi in the branches of the right pulmonary artery

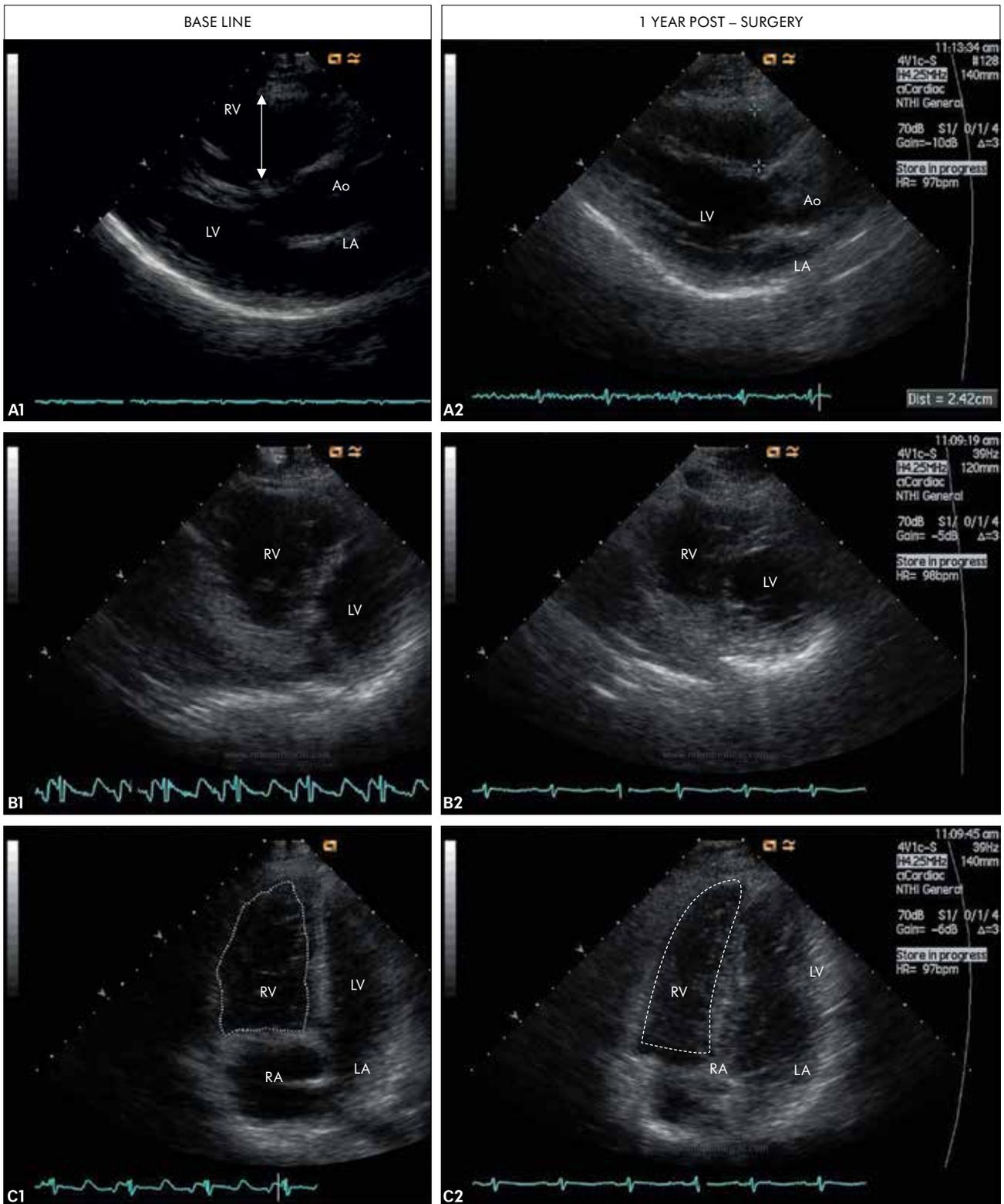
(in the upper lobe pulmonary artery, in the interlobar artery, and in the arteries of the basal segments of the lower lobe). The N-terminal pro-B-type natriuretic peptide (NT-proBNP) level was 6390 pg/mL. Repeated Doppler ultrasound of the lower extremities showed no evidence of deep vein thrombosis.

The patient underwent urgent pulmonary endarterectomy. Extensive amounts of chronic thromboembolic material were removed from both pulmonary arteries. The early postoperative period was complicated by respiratory distress because of the right lung edema; moreover, the patient required dialysis due to acute renal failure. Nine days after pulmonary endarterectomy, a rethoracotomy had to be performed to evacuate a postoperative mediastinal hematoma.

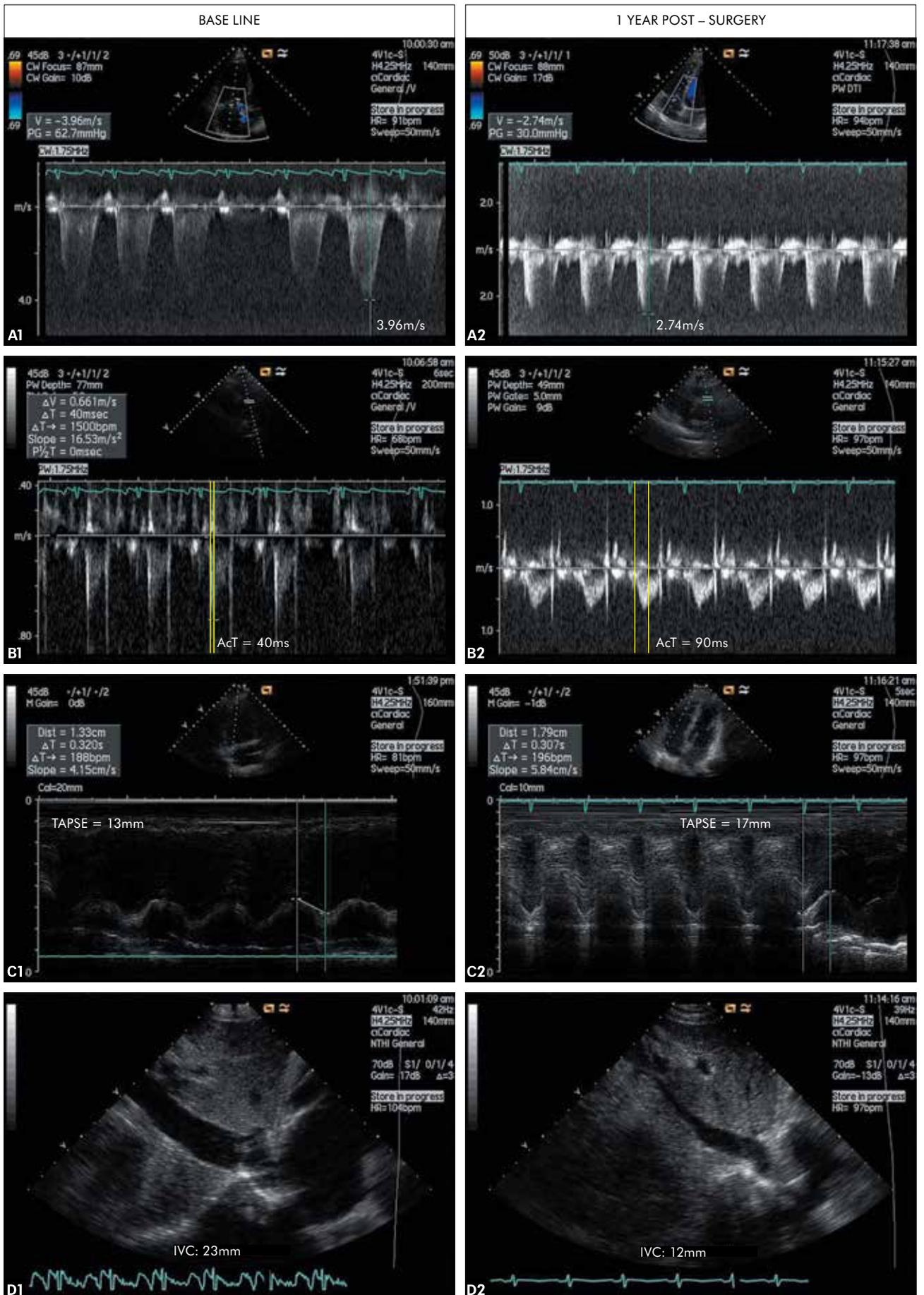
Postoperative TTE demonstrated a significant improvement in the RV function. The NT-proBNP level decreased to 498 pg/mL. The improvement was confirmed by right heart catheterization. The mean pulmonary artery pressure was 12 mm Hg, pulmonary vascular resistance dropped to  $210 \text{ dyne} \times \text{s} \times \text{cm}^{-5}$ , and cardiac output was 4.05 L/min. The patient was discharged on the 45th postoperative day and life-long enoxaparin treatment was recommended. The dose of heparin was adjusted based on anti-Xa levels. The functional status of the patient significantly improved at 1 year of follow-up, and, currently, she is classified as NYHA class I. TTE showed normal diameter and function of right cardiac chambers. An estimated RV systolic pressure was 35 mm Hg (fig. 3, 4 – right panels).

## Discussion

In the literature, there are only a few reports on Klippel-Trénaunay syndrome, which was first described in



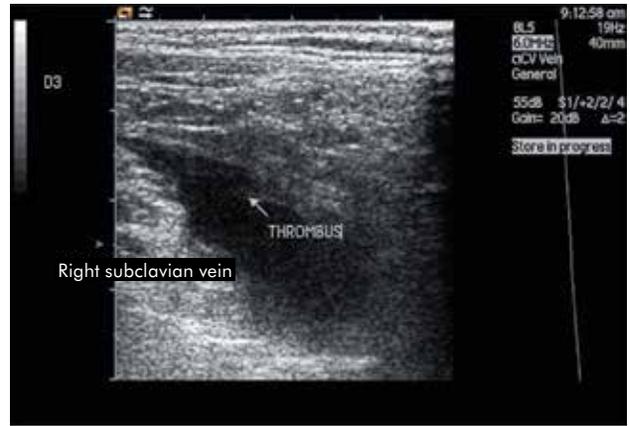
**Fig. 3.** Transthoracic echocardiography. Examination on admission (left panel) and 1 year after the surgery (right panel). **A1, 2.** Parasternal long-axis view. **B1, 2.** Parasternal short-axis view. **C1, 2.** Apical four-chamber view. Significant decrease of the right ventricular (RV) and right atrial (RA) dimensions after the surgery can be observed. LV – left ventricle, LA – left atrium, RVOT prox - proximal part of the right ventricular outflow tract



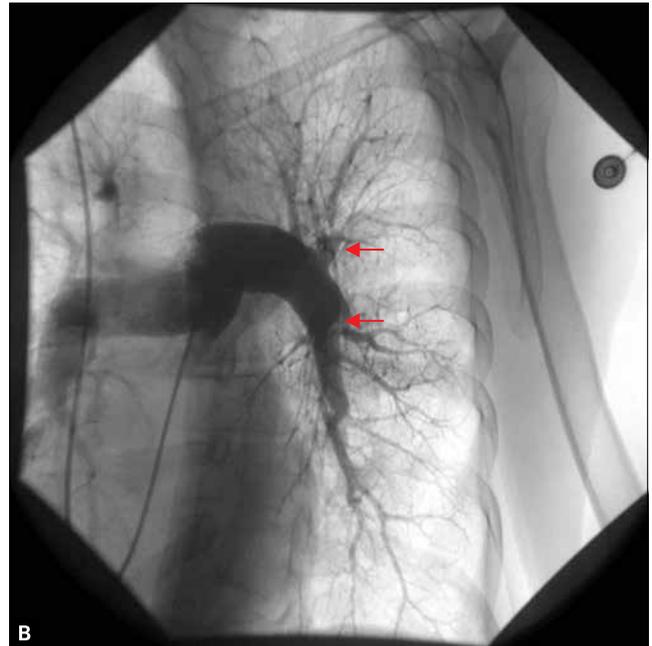
**Fig. 4.** Transthoracic echocardiography. Examination on admission (left panel) and 1 year after the surgery (right panel). **B1,B2.** Significant increase in pulmonary valve acceleration time (AcT). LV – left ventricle, LA – left atrium, RVOT prox – proximal part of the right ventricular outflow tract, TAPSE – tricuspid annular plane systolic excursion, IVC – inferior vena cava



**Fig. 5.** Computed tomography. Thrombotic material in the right lobal pulmonary artery (arrow)



**Fig. 6.** Ultrasonography. Mural thrombus in the subclavian vein



**Fig. 7.** Pulmonary angiography. Examination performed before operation. **A.** Narrowing of the right segmental pulmonary arteries (arrow); area of hypoperfusion (yellow line). **B.** Amputation of left segmental pulmonary arteries (red arrows)

the beginning of the 20th century [9]. It is a rare congenital condition with mixed vascular malformation of the veins, capillaries, and lymphatic vessels. The typical triad of symptoms in Klippel–Trénaunay syndrome consists of capillary malformations (port-wine stains, hemangiomas), atypical, severe lateral varicosity, as well as soft tissue and bone hypertrophy of the limbs [1,2,11–14,38].

A unilateral manifestation in the lower limb is present in about 95% of the cases but the arm, trunk, head, or neck can also be affected [1]. The prevalence of Klippel–Trénaunay syndrome is estimated to be 1/20 000 to 1/100 000.

A review of the literature showed that Klippel–Trénaunay syndrome has been associated with venous thromboembolism in 8% to 22% of the cases [3–9].

The underlying mechanism of hypercoagulability in vascular malformations is still unclear. Inadequate formation of the vascular tree, abnormal vein function, abnormalities in the endothelial structure, and segmental widening of the venous system are likely responsible for stagnation of blood and activation of thrombosis. This combination of factors can lead to thrombi migration and worsening of recurrent PE and CTEPH in this vicious circle of venostasis, thrombosis, and embolism [2,3,34,35].

Chronic presentation and lack of adequate treatment can lead to CTEPH [25–30]. The early diagnosis of recurrent PE is crucial for proper treatment and prevention of CTEPH [3,26]. Another severe complication is recurrent bleeding from vascular malformations [31–33].

Our patient had an atypical manifestation of Klippel-Trénaunay syndrome with only 2 of the 3 components, namely, cutaneous hemangiomas and vein malformation without hypertrophy of the limb. It might have been caused by the removal of abnormal veins at an early stage. After that procedure, the patient was followed-up by her general practitioner and she gradually developed new (recurrent) varicose veins in the area of the lateral marginal vein and presented with shortness of breath. After the second childbirth, she had another episode of PE.

It is still unknown whether hypercoagulability in vascular malformations is the sole cause of thromboembolism in patients with Klippel-Trénaunay syndrome. Our patient did not have any signs of vein thrombosis in the lower limbs on Doppler ultrasound. Interestingly, we identified the signs of deep vein thrombosis in the upper extremity when the patient was prepared for angiography. It can lead to a conclusion that vascular anomalies in Klippel-Trénaunay syndrome may be responsible not only for local but also for general hypercoagulability.

The implantation of vena cava filters could be recommended for patients with Klippel-Trénaunay syndrome and a history of thrombosis [12]. Unfortunately, our patient had recurrent PE despite adequate anticoagulation and implantation of the filter. Awad et al. [35] observed a single case of anomalous venous communication between the lower extremities and the inferior vena cava, which bypassed the filter [35–37]. Currently, magnetic resonance venography seems to be the optimal method to detect such malformations. Another explanation of the recurrent PE may be thrombosis within the veins proximal to the filter or patency of the filter to small emboli [26].

According to the current management of Klippel-Trénaunay syndrome, the absolute indications for surgical treatment of vascular malformations are: hemorrhage, infections, acute thromboembolism, or intractable ulcers. The relative indications include pain, functional impairment, chronic venous insufficiency, limb asymmetry, and other cosmetic defects [12].

It is difficult to diagnose PE because of nonspecific signs and symptoms [15–18,23,24]. CTEPH is rare in the general population, and only from 0.5% to 5% of the patients after acute PE develop pulmonary hypertension [20,21]. CTEPH may be detected in up to 50% of the patients without previous history of clinically symptomatic acute PE or deep vein thrombosis [19,22].

The incidence of chronic venous thromboembolism and CTEPH among patients with Klippel-Trénaunay syndrome is unknown [3]; however, it is certain that without early diagnosis and treatment the prognosis in CTEPH is very poor. It is known that the presence of large phlebectasia in the deep venous system is a risk factor for PE [1,2]; therefore a strict follow-up of patients is recommended. Patients with Klippel-Trénaunay syndrome should possibly undergo CT venography or contrast magnetic resonance imaging of the venous system because duplex ultrasound may not be sensitive enough to identify all venous malformations and thrombosis.

Guidelines for secondary prophylaxis in patients with vascular malformations after the first episode of venous thromboembolism are still under discussion. Mazoyer et al. [36] proved that use of low-molecular-weight heparin and compression therapy might be better than that of unfractionated heparin or vitamin K antagonists. Furthermore, the recommended INR range is still debated; perhaps, higher INR levels (2.5–3.5) should be considered. The role of novel oral anticoagulants has not been tested in this setting.

Another controversial issue is superior vena cava filter implantation in patients with vascular malformations (i.e., those with Klippel-Trénaunay syndrome) after thromboembolic episodes. Surprisingly, in our case, we observed jugular vein thrombosis. Therefore, superior vena cava filter implantation could be beneficial although the precise risk-to-benefit ratio of this therapy it is still unknown [39,40,10]. No prospective studies involving patients with Klippel-Trénaunay syndrome have been published so far.

## Management strategy

The presented case confirms that recurrent thromboembolic events are possible in patients with Klippel-Trénaunay syndrome and may persist despite the implantation of an inferior vena cava filter. Proper anticoagulation and search for additional vascular anomalies and atypical thrombosis sites are necessary. Pulmonary thromboendarterectomy performed by experienced staff may be a safe and effective method of treatment in patients with Klippel-Trénaunay syndrome and CTEPH. To conclude, patients with Klippel-Trénaunay syndrome require a multidisciplinary diagnostic and therapeutic approach to manage this rare disease at a very early stage.

## Acknowledgement

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## A 35-year-old man with dyspnea on exertion, history of acute pulmonary embolism, and ischemic stroke (RCD code: II-1A.5)

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### Background

Chronic thromboembolic pulmonary hypertension (CTEPH) is considered a rare complication of acute pulmonary embolism. It is caused primarily by ineffective recanalization of pulmonary arteries occluded by thromboembolic material [1–7]. The estimated incidence of CTEPH is between 0.5% and 5.0%, and it usually occurs 2 years after an episode of acute pulmonary embolism [8–10]. Undissolved clots adhere to pulmonary artery walls leading to increased pulmonary vascular resistance (PVR). Although commonly believed to be a consequence of thromboembolic disease, Lang et al. showed that up to 63% of the patients with CTEPH have no history of symptomatic acute pulmonary embolism [11]. This may partly be explained by usually unremarkable clinical course of pulmonary embolism but also by the differences in the pathogenesis of CTEPH. Progression of the disease may be related to the occlusion of pulmonary arteries but also to the presence of distal pulmonary vasculopathy in small precapillary vessels in occluded and nonoccluded arteries. Vascular lesions that develop in CTEPH are similar to those observed in idiopathic pulmonary arterial hypertension and consist of endothelial dysfunction, intimal thickening, vascular proliferation and fibrosis, smooth muscle hypertrophy, and plexiform lesions. Some authors suggest that local pulmonary thrombosis (in situ) may contribute to progression of CTEPH [12–13].

### Case presentation

A 35-year old man was admitted to our hospital because of fatigue and dyspnea on exertion. He felt shortness of breath after walking approximately 100 m on flat surface or after climbing half flight of stairs. He had a history of idiopathic acute pulmonary embolism with an intermediate risk of in-hospital death and deep venous thrombosis of his right leg 4 months before the current admission. At that time, he also suffered from ischemic stroke with aphasia and central paresis of the right facial nerve. He was treated with subcutaneous enoxaparin (1 mg/kg, twice daily) for 5 days in the acute phase of pulmonary embolism and, subsequently, with oral anticoagulants with the target international normalized ratio (INR) level between 2.0 and 3.0. After a few weeks of improvement, he started

to complain of shortness of breath and fatigue. One month before the current admission, he had an episode of hemoptysis.

Physical examination revealed a well-developed man in a significant distress with breathlessness when talking. He was considered to be in the New York Heart Association (NYHA) functional class III. His vital signs were as follows: body temperature of 36.6°C, respiratory rate of 22 breaths/min, regular heart rate of 95 beats/min (bpm), blood pressure of 120/80 mm Hg, and oxygen saturation on room air of 88%. Heart auscultation revealed increased second heart sound accentuation and a systolic murmur best audible over the apex. The liver was slightly enlarged, palpable 1 cm below right costal margin in the midclavicular line. Hepatojugular reflux was positive. Pitting edema of the right ankle was present.

Blood tests revealed elevated levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) of up to 1456 pg/mL and troponin T of up to 0.5 ng/mL. Total bilirubin levels of 1.7 mg/dL was mildly elevated. Other biochemical parameters were within the normal range. Coagulation studies revealed an INR of 2.4 and prolonged activated partial thromboplastin time of 42.4 s. A capillary blood gas analysis disclosed alkalosis (pH, 7.48), hypoxemia (pO<sub>2</sub>, 63 mm Hg), and hypocapnia (pCO<sub>2</sub>, 33 mm Hg). Complete blood count, erythrocyte sedimentation rate, C-reactive protein levels, and urinalysis parameters were all within normal limits. Lupus anticoagulant and antiphospholipid antibodies were negative.

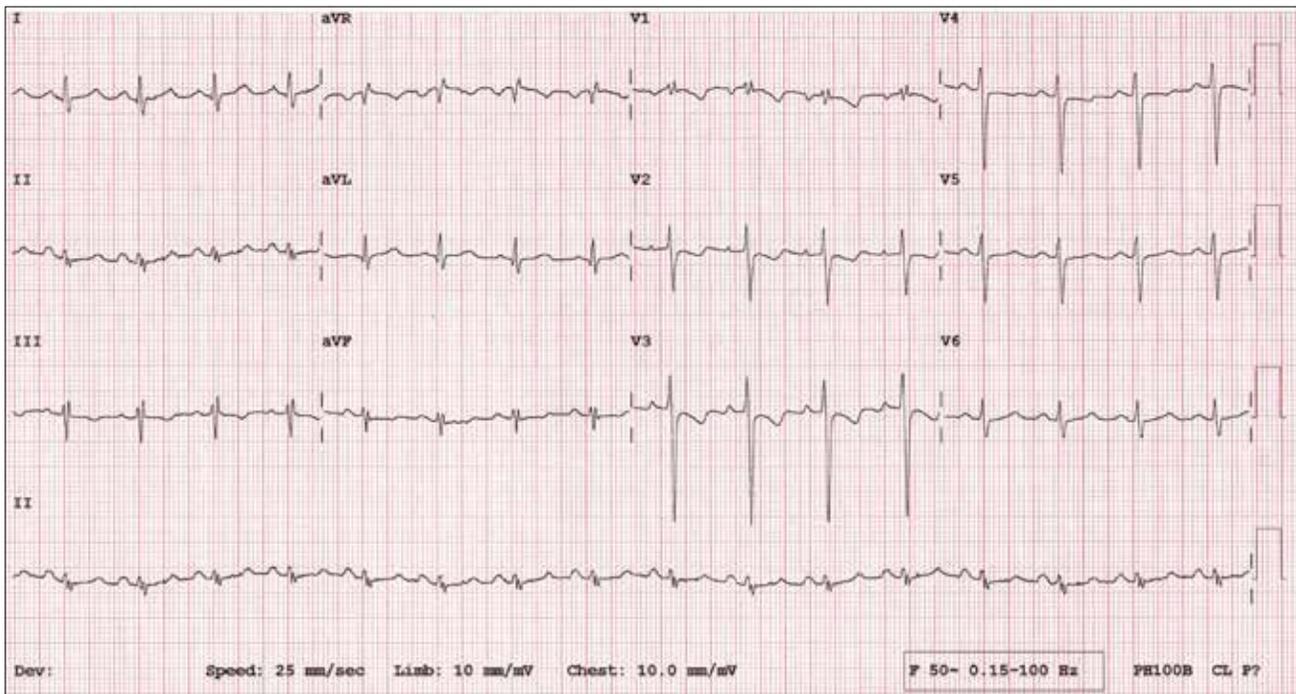
Resting electrocardiogram (ECG) (fig. 1) showed a sinus rhythm of 97 bpm, right axis deviation, incomplete right bundle branch block (RBBB), negative T waves in the precordial leads of V1 to V4.

Transthoracic echocardiography (fig. 2) revealed an enlarged right ventricle (RV) and right atrium with the RV diameter of 47 mm and right atrium area of 35 cm<sup>2</sup> with significant tricuspid insufficiency and signs of pulmonary hypertension (tricuspid valve systolic gradient of 70 mm Hg, acceleration time of 63 ms, pulmonary artery valve insufficiency gradient of 21/14 mm Hg, and tricuspid annular plane systolic excursion of 16 mm). The left ventricle and atrium were small. A small pericardial effusion was present. The left ventricular ejection fraction was normal (80%).

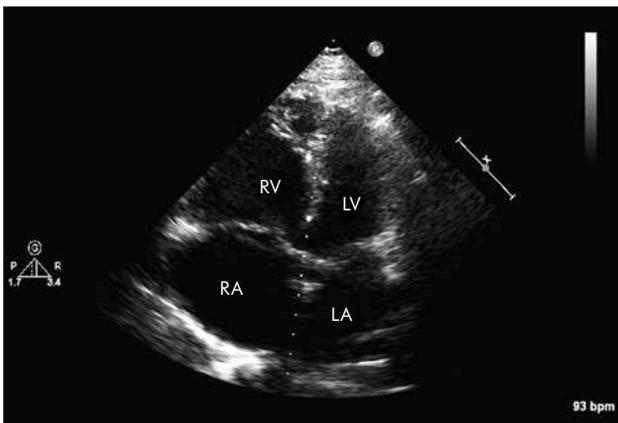
Impaired exercise capacity was confirmed by the 6-minute walking test (6MWT), with a walking distance of only 411 m and significant oxygen desaturation from 93% to 88%. Tachycardia was present during the test (heart rate before the test of 100 bpm and after the test of 127 bpm). Transoesophageal echocardiography showed persistent foramen ovale with a small right-to-left shunt that was not hemodynamically significant.

The venous ultrasound compression test showed organized thrombus narrowing the right popliteal vein by 40%.

A 128-slice spiral computed tomography of the chest (fig. 3) revealed chronic thromboembolic material located in the distal part of the right pulmonary artery spreading into the inferior lobe, medial lobe,



**Fig. 1.** Electrocardiogram. Sinus rhythm of 97 bpm, right axis deviation, incomplete right bundle branch block, negative T waves in the precordial leads (V1–V4)



**Fig. 2.** Transthoracic echocardiography. Apical view. Enlargement right ventricle (RV) and right atrium (RA); small left ventricle (LV) and left atrium (LA)

and segmental arteries 4, 5, 9, 10. Chronic thromboembolic material was also observed on the left side in the inferior lobe and segmental arteries 8, 9, and 10. Mosaic perfusion in the pulmonary parenchyma was present in both lungs. Pulmonary angiography revealed significant narrowing of the proximal pulmonary arteries in both lungs (fig. 4).

In the right heart catheterization, high precapillary pulmonary hypertension was observed with elevated mean pulmonary artery pressure (mPAP) of 54 mm Hg, PVR of  $817 \text{ dyne} \times \text{s} \times \text{cm}^{-5}$ , right atrial pressure of 12 mm Hg, and pulmonary artery wedge pressure (PAWP) of 13 mm Hg, together with a decreased cardiac index of  $2.25 \text{ L/min/m}^2$  and decreased mixed venous saturation of 58%. Based on the above findings, a diagnosis of CTEPH was made.

The patient was referred to a cardiologist, radiologist, and cardiothoracic surgeon, and pulmonary endarterectomy (PEA) was recommended. Because of a history of acute pulmonary embolism and ischemic cerebral stroke, the closure of patent foramen ovale during PEA was scheduled. The patient was treated with an oral anticoagulant (acenocumarol) 4 mg once daily with the target INR level between 2.0 and 3.0 until the operation. Before PEA, a Greenfield vena cava filter was implanted. PEA was performed according to the San Diego protocol. An extracorporeal circulation was used during the procedure. Operation lasted 4 hours with 30 minutes of full cardiac arrest. Chronic thromboembolic material with the intima of the pulmonary arteries was removed on both sides. Based on the classification developed by Jamieson and Kapelansky [14], we diagnosed type 1 CTEPH. During rewarming, patent foramen ovale was closed. The patient was extubated on the second day after the operation and discharged from the cardiothoracic surgery department on the 10th postoperative day.

The patient was admitted to the cardiology department 1 month after PEA. He was classified as NYHA class II. No signs of RV dysfunction were present. The sternum cicatrized without any complication. A physical examination revealed blood pressure of 130/80 mm Hg, heart rate of 64 bpm, normal heart sounds with no murmurs audible, and normal liver size. The NT-proBNP level decreased to 113 pg/mL and troponin T level was 0.0013 ng/mL. A capillary blood gas analysis and other laboratory tests provided normal results. An ECG continued to show incomplete RBBB. On transthoracic echocardiography, the RV diameter was normal, RV hypertrophy was still present, tricuspid valve systolic gradient decreased to 30 mm Hg, and



**Fig. 3.** Cardiovascular computed tomography. Chronic thromboembolic parietal material (arrows) starting in the distal part of the right pulmonary artery and spreading into the inferior lobe artery. No perfusion in the segmental pulmonary arteries in the left inferior lobe



**Fig. 4.** Pulmonary arteriography. Right (A) and left (B) pulmonary arteries. Occlusion of segmental arteries in both lungs and narrowing of the distal part of the right pulmonary artery (arrows)

pericardial effusion was no longer observed. The patient was prescribed oral anticoagulants and was discharged from the hospital in good general condition. A clinical follow-up visit was scheduled at 6 months after hospital discharge.

## Discussion

In the natural history of CTEPH, an increase in pulmonary artery pressure (PAP) leads to progressive right heart failure, low output syndrome, and death [1–6]. The prognosis in CTEPH is poor if no specific

treatment is administered. Most patients with mPAP of 30 mm Hg or higher die within 2 to 3 years after diagnosis [15,16].

The pathogenesis of the disease is still under debate. An association between acute thromboembolic disease, especially idiopathic, and large clots, recurring nature, and young age is well known. Other risk factors for CTEPH include splenectomy, antiphospholipid syndrome, chronic inflammatory conditions such as Crohn's disease or ulcerative colitis, history of malignancy, osteomyelitis, atrioventricular shunts, infected pacemaker, blood group other than O, or substitution of levothyroxine [17,18].

Active screening for CTEPH after acute pulmonary embolism is currently not recommended in asymptomatic patients, but patients with an elevated PAP in transthoracic echocardiography or signs of RV overload should be followed-up by echocardiography 3 to 6 months after acute thromboembolic disease to exclude CTEPH [1]. The symptoms of CTEPH are non-specific. Patients typically complain of exertional dyspnea and reduced exercise tolerance. Other symptoms include palpitation, dizziness, presyncope or syncope on exertion, and chest pain. Resting dyspnea often occurs in the late stage of the disease when the RV is unable to meet metabolic and hemodynamic needs. A physical examination may reveal the signs of RV insufficiency, but it may as well be absent in the earlier phases of the disease. With progression of CTEPH, jugular vein distension, right ventricular S3 gallop, signs of severe tricuspid regurgitation, hepatomegaly, ascites, and peripheral edema may occur [1–6].

Electrocardiographic evaluation may show right axis deviation, signs of RV hypertrophy, right atrial enlargement, RBBB, and T-wave inversion in the anterior and inferior limb leads.

Transthoracic echocardiography with Doppler imaging is often the first-step tool that is noninvasive and reveals the elevation of right ventricular systolic pressure, right heart chamber enlargement, tricuspid regurgitation, or paradoxical interventricular septal motion. Echocardiography can be used to exclude other potential causes of elevated pulmonary pressure and in the follow-up of the patient.

The initial evaluation includes the assessment of functional class according to the NYHA classification and the evaluation of exercise capacity by the 6MWT [1–7].

Plasma NT-proBNP troponin levels may reflect the severity of the disease and have prognostic value, and thus their measurement can be helpful in making therapeutic decision [19–21].

A pulmonary ventilation/perfusion (V/Q) scan is a well-recognized first-line test used to differentiate between CTEPH and pulmonary hypertension indicated by echocardiography. The V/Q scan reveals typical triangle-shaped lacks of perfusion in the lung region with normal ventilation. It is useful in distinguishing proximal and distal disease. However, in most patients with CTEPH, a comprehensive evaluation of pulmonary vasculature requires the use of multiple modalities. These include pulmonary scintigraphy, spiral computed tomography, and pulmonary angiography.

In some cases, nuclear magnetic resonance may also be used [6]. Computed tomography angiography may reveal mosaic perfusion of the lung parenchyma, pulmonary artery dilation, right atrium and RV enlargement, or chronic, organized thrombi in main, lobar, segmental or subsegmental pulmonary vessels. Several signs of CTEPH may be shown on pulmonary angiography, including the enlargement of pulmonary arteries, poststenotic vascular dilations, bends, webs, or irregular thickening of the arterial wall [2–4].

Cardiac catheterization, typically performed with the Swan–Ganz catheter, is used to confirm the diagnosis of pulmonary hypertension. It is used to determine the severity of pulmonary hypertension and RV dysfunction as well as for risk stratification of the patients. Precapillary pulmonary hypertension with an mPAP of 25 mm Hg or higher and normal PAWP (<15 mm Hg) are typical findings in patients with CTEPH [1–7]. Some hemodynamic parameters have been identified for their prognostic value and others are used to identify patients requiring PEA.

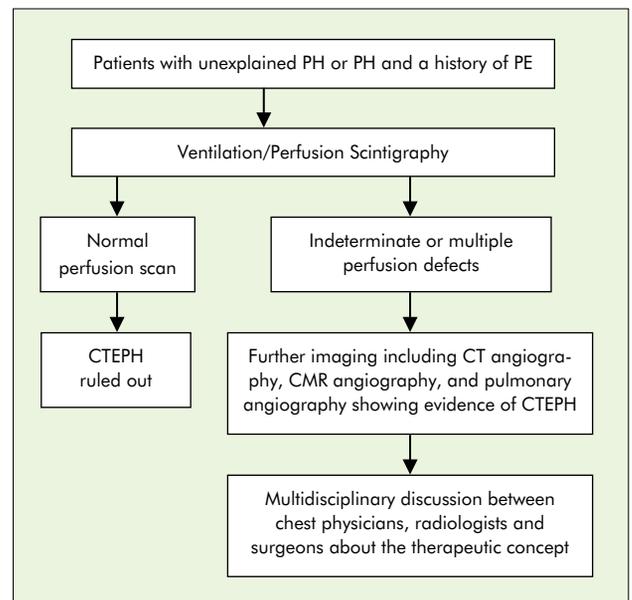
PEA is a treatment of choice for patients CTEPH and proximal lesions (thromboembolic material located in main, lobar, or segmental pulmonary arteries). It is a cardiac surgical procedure, during which thromboembolic material is removed from the pulmonary arteries [14,22,23]. Indications for PEA are as follows: NYHA class III or IV, presence of thromboembolic material in the proximal vessels, PVR of  $\geq 300 \text{ dyne} \times \text{s} \times \text{cm}^{-5}$ , mPAP of  $\geq 40 \text{ mm Hg}$ , and a lack of severe comorbidities [24]. PEA is performed in line with the guidelines developed by the San Diego group [14,23]. Professional anesthetic care is mandatory during the procedure. The body temperature has to be reduced to 17–18°C before a cardiopulmonary bypass is instituted. The cooling-down process generally takes about 45 minutes. In the case of life-threatening rhythm abnormalities, such as ventricular fibrillation, the cannulas are inserted into the superior and inferior vena cava and to the ascending aorta. Additional intermittent episodes of total cardiac arrest are necessary to eliminate bleeding from the bronchial arteries. This improves the visibility of the internal arterial wall, thus enabling to identify the appropriate plane for PEA. A thrombus, together with the medial part of the vessel wall, is then removed (thrombectomy and endarterectomy are performed). Complete PEA usually requires circulatory arrest time of 15 to 20 minutes for each of the artery. After endarterectomy is completed, cardiopulmonary bypass is reinstated and the warming-up process is started. Rewarming takes usually from 90 to 120 minutes. Successful PEA leads to a decrease in the mPAP and PVR and restores normal cardiac output. Moreover, it improves the outcome of the patients with CTEPH, has acceptable perioperative mortality rate, and brings excellent long-term results. A precise assessment of patients requiring PEA is fundamental. According to Jamieson and Kapelansky [14], there are 4 types of pulmonary occlusive disease depending on the thrombus removed. In type 1 (20% of the cases), the main vessels are affected and thrombus is found in the major pulmonary

arteries. These patients are the best candidates for surgery. In type 2 (70% of the cases), no major vessels are affected but thickening of the main lobar or segmental vessels is present and the plane of dissection can be usually identified. These patients are also good candidates for surgery. In type 3 (10% of the cases), only distal disease is present with the thickening of segmental and subsegmental vessels. This group remains the grey zone for experienced centers and surgeons. In type 4, only the signs of distal disease are present [14] and they should not be operated. Hospital discharge can occur by the sixth or seventh postoperative day, if no complications occur [14,22–25]. Perioperative mortality rate in experienced centers is close to 2% [14,22,23]. Possible complications after PEA include lung injury and reperfusion edema, pericardial effusion with cardiac tamponade, persistent pulmonary hypertension, postoperative sternal wound infection, or atrial arrhythmias [26].

Hemodynamic improvement is typically observed directly after surgery. Clinical studies showed a significant improvement of arterial blood gas parameters, exercise tolerance, and functional status within 3 months after surgery. Reverse RV remodeling and normalization of the V/Q scan occur more slowly, approximately 6 to 12 months after the procedure [14,22,23,27]. For the best practice, all cases of CTEPH should be managed in experienced centers. The average of 20% to 40% of the patients cannot be operated because of distal lesions (the most common reason), lack of consent, or comorbidities (especially severe chronic obstructive pulmonary disease, malignancy, and severe hematologic disorders) [28,29]. Several reports suggested that the degree of preoperative PVR correlates with the postoperative mortality rate. Jamieson et al. [22] observed that preoperative PVR of more than  $1000 \text{ dyne} \times \text{s} \times \text{cm}^{-5}$  was associated with a higher mortality rate of 10.1% compared with 1.3% in the subgroup with lower PVR. Up to 20% of the patients who underwent PEA have persistent pulmonary hypertension after intervention. In such cases, lung transplantation, pulmonary artery balloon angioplasty, and specific drug treatment may be considered, which applies also to inoperable patients [1–7].

Lifelong anticoagulation for all patients is recommended with the INR level of 2.0 to 3.0 [14,22,23]. Supportive therapy includes diuretics, digitalis, and oxygen. Medical targeted therapy similar to that approved for pulmonary arterial hypertension is often prescribed. Medical treatment should potentially inhibit or slow down pulmonary artery remodeling and vasculopathy progression, but it does not remove mechanical occlusion. In the group of patients with CTEPH, the best candidates for medical targeted therapy are patients with contraindications to surgery or as a bridge therapy to transplantation or to endarterectomy, as well as patients with pulmonary hypertension that persists after the operation.

There have been only a few clinical trials investigating the effects of prostacyclin analogues (epoprostenol, inhaled iloprost, and beraprost), dual endothelin receptor antagonist (bosentan), or phosphodiesterase-5



**Fig. 5.** Diagnostic algorithm for patients with chronic thromboembolic pulmonary hypertension [6]. CTEPH – chronic thromboembolic pulmonary hypertension, CT – computed tomography, CMR – cardiovascular magnetic resonance imaging. Pulmonary angiography should be performed only if PEA is considered as a potential option † CTEPH, despite a normal or nearly normal perfusion scan, has been reported on rare occasions. Thus, further diagnostic work-up may be warranted if there is high clinical suspicion of CTEPH

inhibitors (sildenafil) in patients with CTEPH [30–33]. A multicenter, randomized, controlled trial in 77 patients with inoperable CTEPH or with CTEPH persistent after the operation demonstrated an improvement in the NYHA class, NT-proBNP levels, and hemodynamic parameters after 16 weeks of treatment with bosentan 125 mg twice daily. However, no significant improvement in the results of the 6MWT was observed [30]. In a multicenter, randomized, placebo-controlled trial with iloprost, on a subgroup of 33 patients with CTEPH, a significant improvement of functional class, 6MWT results, and hemodynamic parameters after 12 weeks of treatment were observed [31]. In a single-center study, Suntharalingam et al. [32] randomized 9 patients with CTEPH into sildenafil or placebo. After 12 weeks of treatment with sildenafil, they observed improved hemodynamic parameters and 6MWT results [32]. However, despite those findings there are still too few data to formally recommend medical targeted therapy in CTEPH patients.

## Management strategy

CTEPH is a rare but severe complication of acute pulmonary embolism. When left untreated, it leads to an increase in PVR, progressive right heart failure, and death. In all cases admitted to the hospital with the suspicion of pulmonary hypertension, CTEPH should be considered as a differential diagnosis. A diagnostic algorithm is presented in Figure 5. Patients with CTEPH should be evaluated in specialized

centers experienced in the diagnosis and surgical treatment of the disease. The treatment of choice in patients with CTEPH and proximal lesions (thromboembolic material located in main, lobar, or segmental pulmonary arteries) is PEA. Compared with medical treatment, successful PEA improves the long-term survival of patients with CTEPH. Moreover, it leads to functional improvement and prevents RV overload and dysfunction. Specific therapy used in pulmonary arterial hypertension appears to be a potentially attractive treatment for CTEPH in patients with distal disease, contraindications to PEA, and pulmonary hypertension persistent after the operation; however, the evidence is still limited to develop official recommendations.

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## Therapy with sildenafil in a patient with pulmonary hypertension associated with end-stage left ventricular failure (RCD code: II-1B.1)

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### Background

In the last decade, a substantial progress in the therapy of pulmonary arterial hypertension (PAH) was made. According to the European Society of Cardiology (ESC) guidelines issued in 2009, there are several types of agents targeted on specific pathophysiological mechanisms of PAH, such as calcium channel blockers, prostanoids, endothelin receptor antagonists, and phosphodiesterase type 5 (PDE5) inhibitors. The treatment of PAH with 1 or more of the above types of agents is well established on the basis of evidence from numerous clinical trials. Unfortunately, there is still a lack of evidence from randomized clinical trials on the so called non-PAH forms of pulmonary hypertension (PH) [1].

PH due to left heart disease (PH-LHD), also called postcapillary PH or “venous” PH, is the most common type of PH. It is defined as a mean pulmonary artery pressure (mPAP) of 25 mm Hg or higher and pulmonary artery wedge pressure (PAWP) exceeding 15 mm Hg with normal or reduced cardiac output. PH-LHD is further classified into passive, if a transpulmonary gradient (TPG = mPAP – PAWP) is 12 mm Hg or less, or reactive (out of proportion), if TPG is higher than 12 mm Hg. PH-LHD is a consequence of various pathologies including left ventricular (LV) systolic dysfunction, LV diastolic dysfunction, or valvular disease [2]. Approximately 60% of the patients with severe left heart failure and low ventricular ejection fraction develop PH-LHD, and this condition is associated with a particularly poor prognosis for these patients [3].

### Case presentation

We describe a case of a 51-year-old Caucasian man with a history of ischemic heart disease after anterolateral myocardial infarction in 2007, with chronic heart failure (CHF) and a markedly reduced LV ejection fraction (LVEF), after implantable cardioverter-defibrillator implantation in 2008. Coronary angiography performed in 2008 showed the proximal occlusion of the left anterior descending artery, with no significant changes in other coronary arteries. The LVEF was estimated at 20% by ventriculography. In 2009, right heart catheterization (RHC) was performed and PH-LHD with high pulmonary vascular resistance (PVR) was diagnosed. An acute vasodilator

test with nitroglycerin showed no significant decrease of mPAP or PVR. Accordingly, the patient was no longer considered for heart transplantation.

In 2011, the patient was admitted to the Center for Rare Cardiovascular Diseases at the John Paul II Hospital in Krakow, Poland, for clinical and hemodynamic assessment.

On admission, he was in New York Heart Association (NYHA) class III and a physical examination showed no signs of heart failure decompensation (normal breath sounds on lung auscultation; regular heart rhythm of 80/min with no heart murmurs on heart auscultation; no peripheral edema, liver enlargement, ascites, or cyanosis). He was on a stable treatment with an angiotensin – converting enzyme inhibitor,  $\beta$ -blocker, furosemide, spironol, digoxin, and acetylsalicylic acid. An electrocardiogram showed sinus rhythm with a heart rate of 80/min, left axis deviation, QRS duration of 110 ms, PQ interval of 200 ms, abnormal Q-wave in I and aVL, low progression of R-wave in V3–V6, and sustained ST-elevation in V2–V6.

To evaluate exercise capacity, the cardiopulmonary exercise test (CPET) and 6-minute walking test (6MWT) were performed. Oxygen consumption (peak  $\text{VO}_2$ ) in CPET was 4 mL/kg/min, and ventilation efficiency ( $\text{VE}/\text{VCO}_2$ ) was 34.3. The distance in 6MWT was 195 m, with the Borg scale of 7 (range, 0–10). No significant desaturation during exercise was observed. Echocardiography revealed the following abnormalities: enlargement of all heart chambers, markedly reduced LVEF (15%), vast dyskinesia of the apex and adjacent segments, moderate tricuspid valve and pulmonary valve regurgitation, mild mitral valve regurgitation, tricuspid annular plane systolic excursion of 11 mm, and estimated right ventricular systolic pressure of 60 mm Hg.

For the hemodynamic assessment of the patient, RHC with the acute vasodilator test was performed. Hemodynamic measurements were noted at baseline, 5 minutes after administration of inhaled nitric oxide (NO) (at a dose of 20 ppm), and 10 minutes after cessation of NO. Next, the patient received 50 mg of sildenafil p.o. and hemodynamic measurements were repeated 30 minutes after sildenafil administration. As shown in Table 1, after NO inhalation, an increase of mPAP, PVR, TPG, and PAWP was observed. Unlike NO, sildenafil decreased mPAP, PVR, PAWP, and LV end-diastolic pressure. Moreover, the vasodilator effects of sildenafil were associated with an increase in cardiac output, cardiac index, and pulmonary artery blood saturation ( $\text{PA}_{\text{Sat}}$ ).

All the results were presented to a team of specialists including a cardiologist, interventional cardiologist, and cardiac surgeon. Considering high mPAP and PVR with an insufficient decrease after the use of vasodilators, the team decided against heart transplantation in the patient and recommended a long-term therapy with sildenafil. After obtaining written informed consent from the patient, a treatment with oral sildenafil (20 mg 3 times/day) was started in an open-label clinical study approved by the local ethics committee. Sildenafil was well-tolerated and the patient did not report any side effects of

**Table 1.** Right heart catheterization at baseline and after 3 months of therapy with sildenafil in a patient with pulmonary hypertension associated with left ventricular systolic dysfunction

Hemodynamic measurements at baseline				Hemodynamic measurements after 3 months of therapy with sildenafil	
parameter	baseline	after NO	after sildenafil	baseline	after NO
mPAP (mm Hg)	40	44	39	35	39
PVR (dyne $\times$ s $\times$ cm <sup>-5</sup> )	309	397	305	209	344
TPG (mm HG)	10	12	8	8	11
CI (L/min/m <sup>2</sup> )	1.4	1.3	1.7	1.6	1.5
PAWP (mm Hg)	30	32	27	27	27
PA <sub>Sat</sub> (%)	49.8	50.2	53.1	56.6	52.4

NO – nitric oxide, mPAP – mean pulmonary artery pressure, PVR – pulmonary vascular resistance, TPG – transpulmonary gradient, CI – cardiac index, PAWP – pulmonary artery wedge pressure, PA<sub>Sat</sub> – blood oxygen saturation in the pulmonary artery

treatment. After 3 months, the clinical and hemodynamic status of the patient was evaluated again. He was still in NYHA class III but he reported subjective improvement in exercise capacity. Compared with baseline, the peak VO<sub>2</sub> measured in CPET increased (from 4 to 7.3 mL/kg/min) and VE/VCO<sub>2</sub> decreased (from 34.3 to 29.6). There was also a significant improvement in the results of the 6MWT (from 195 to 246 m). In RHC performed after 3 months of sildenafil therapy, a decrease of mPAP, PVR, PAPW, and TPG and an increase in cardiac output, cardiac index, and PA<sub>Sat</sub> were observed. The hemodynamic measurements are presented in Table 1.

According to the study protocol, due to clinical and hemodynamic improvement, the continuation of therapy with sildenafil and a clinical follow-up assessment every 6 months were recommended.

## Discussion

### Pathophysiology of PH-LHD

Increased afterload of the LV and high LV end-diastolic pressure are the principal features of CHF with low LVEF. Elevated LV end-diastolic pressure is transmitted passively “backward” to the left atrium and pulmonary vasculature; it leads to pulmonary vascular damage and reactive increase in PVR and pulmonary artery pressure. The right ventricle (RV) is a low-pressure, high-volume pump that allows the blood to flow into a highly compliant pulmonary circulation. The RV can accommodate large changes in volume with minimal pressure changes but if the pulmonary pressure rises, the RV dilates, which leads to maladaptive RV hypertrophy and fibrosis. As a consequence, RV failure develops, with the clinical manifestation of hepatic congestion, peripheral edemas, cachexia, and, ultimately, death.

A number of studies provided evidence that RV performance is an important determinant of exercise capacity [4,5] and, also, an independent predictor of survival in patients with LV heart failure, especially

in the presence of PH-LHD [6,7]. Several studies have also proved that exercise capacity, measured by peak VO<sub>2</sub>, is more closely associated with RVEF than with LVEF in patients with CHF [6].

The process of pulmonary vascular damage and remodeling in PH-LHD is similar, to some extent, to that observed in PAH, with the characteristic features including smooth muscle cell dysfunction, vasoconstriction, endothelial dysfunction and cell proliferation, inflammatory cell activation, and thrombosis.

### Management strategy in PH-LHD

#### Diagnosis

According to the ESC guidelines, the diagnostic approach to PH-LHD is similar to that to PAH [2].

Doppler echocardiography remains the best diagnostic tool used for screening; abnormal LV systolic and diastolic dysfunction as well as valvular diseases are easily detectable by echocardiography [2]. Data on tissue Doppler echocardiography show that the ratio of early mitral flow velocity (E) and early tissue Doppler velocity (E') closely correlates with LV filling pressures: when the E/E' ratio exceeds 15, LV filling pressure is elevated, and when the ratio is lower than 8, LV filling pressure is within the normal range; if the ratio is between 8 and 15, additional noninvasive testing is required. Although increased left-sided filling pressure can be estimated by Doppler echocardiography, invasive measurements of PAWP or LV end-diastolic pressure in RHC are necessary to confirm the diagnosis of PH-LHD [8].

The measurement of plasma brain natriuretic peptide (BNP) levels for the diagnosis of left heart disease in the presence of PH is not very useful because elevated BNP levels are observed in both pathophysiological conditions [2].

An elevated TPG on RHC (>12 mm Hg) suggests fixed changes in the pulmonary circulation. The acute vasodilator test performed during RHC is recommended in heart transplant candidates to identify patients with unresponsive (fixed) pulmonary hypertension

**Table 2.** European Society of Cardiology Guidelines on the management of patients with pulmonary hypertension associated with left heart disease\*

Statement	Class <sup>a</sup>	Level <sup>b</sup>
The optimal treatment of the underlying left heart disease is recommended in patients with PH due to left heart disease	I	C
Patients with “out-of-proportion” PH due to left heart disease should be enrolled in RCTs targeting PH-specific drugs	IIa	C
Increased left-sided filling pressures may be estimated by Doppler echocardiography	IIb	C
Invasive measurements of PAWP or LV end-diastolic pressure may be required to confirm the diagnosis of PH due to left heart disease	IIb	C
RHC may be considered in patients with echocardiographic signs suggesting severe PH in patients with left heart disease	IIb	C
The use of PAH-specific drug therapy is not recommended in patients with PH due to left heart disease	III	C

<sup>a</sup> Class of recommendation  
<sup>b</sup> Level of evidence  
 LV – left ventricular, PAWP – pulmonary artery wedge pressure, PH – pulmonary hypertension, RCT – randomized controlled trial, RHC – right heart catheterization  
 \* Based on the European Society of Cardiology Guidelines for the diagnosis and treatment of pulmonary hypertension [2]

who are at a high risk of acute postoperative RV failure. In heart transplant candidates, a persistent increase in PVR above 2.5 Wood units or of TPG above 15 mm Hg or both is associated with up to a 3-fold increase in the risk of RV failure and early posttransplant mortality [9]. Because there is no standardized protocol for the acute vasodilator test, various agents are used to test the responsiveness of pulmonary hypertension, including inotropic agents, prostanoids, NO, and PDE5 inhibitors [2,10]. Our data have shown that a standard protocol for pulmonary artery reactivity with NO used in patients with idiopathic PAH is not useful for detecting this reactivity in heart transplant candidates with severe PH due to LV systolic dysfunction. Compared with NO, sildenafil is superior in detecting pulmonary artery reactivity; however, further head-to-head studies are needed to indicate the vasodilator of choice for testing pulmonary artery reactivity in this group of patients [11].

### Treatment

Although PH-LHD is the most common type of PH, there is currently no specific treatment for this condition. Therefore, according to the ESC guidelines, the management of PH-LHD should be aimed at the optimal treatment of the underlying disease [1]. No heart failure drugs are contraindicated in PH [12]. A sustained reduction of PH is expected in a few weeks to months in most patients successfully operated for mitral valve disease, even if PH represents a risk factor for surgery [13].

Only a few studies have examined the role of drugs currently recommended in PAH in PH-LHD. Randomized clinical trials (RCTs) evaluating the effects of chronic use of epoprostenol and bosentan in advanced heart failure have been terminated early due to an increased rate of events in the group receiving drug treatment compared with that on conventional treatment. A number of studies suggested that sildenafil (PDE5 inhibitor) may improve exercise capacity and

quality of life in patients with PH-LHD. Thus, the use of PAH-specific drugs is not recommended until robust data from long-term studies are available [1,2].

ESC recommendations for PH-LHD are summarized in the Table 2.

### Clinical trials and small studies on the treatment of PH-LHD due to LV dysfunction

There was a remarkable development in the therapy of PAH over the last decade. The positive results of PAH treatment have led to attempts to treat PH-LHD secondary to CHF with the same groups of vasodilators as used for PAH therapy (Table 3).

#### Prostanoids

In a large-scale randomized controlled trial – Flolan International Randomized Survival Trial (FIRST) [14] – 471 patients with severe left heart failure (NYHA classes III–IV) were randomized to epoprostenol infusion or standard CHF treatment. The primary endpoint was survival and secondary endpoints were clinical events, congestive heart failure symptoms, distance walked in 6 minutes, and quality of life (QoL). Epoprostenol administration resulted in a significant increase in the cardiac index (from 1.81 to 2.61 L/min/m<sup>2</sup>), decrease in pulmonary capillary wedge pressure (from 24.5 to 20.0 mm Hg), and decrease in systemic vascular resistance (from 20.76 to 12.33 Wood units). However, the trial was terminated early because of a strong trend toward decreased survival in patients treated with epoprostenol. Chronic intravenous epoprostenol therapy did not improve the results of the 6MWT or the QoL. Considering the above results, there is a limited role of epoprostenol or other prostacyclin agonists in the therapy of patients with PH-LHD [14].

#### Endothelin receptor antagonists

In a large pilot study, Research on Endothelin Antagonism in Chronic Heart Failure (REACH-1),

**Table 3.** Major clinical trials on the use of pulmonary vasodilators in patients with chronic heart failure

Study name/Reference	Agent	Number of patients randomized	Main clinical outcomes
FIRST [14]	epoprostenol	471	terminated early; hemodynamic and clinical improvement but decrease in survival in the epoprostenol group
REACH-1 [15]	bosentan	377	terminated early; no apparent benefit in the bosentan group
ENABLE [16]	bosentan	1613	early risk of worsening of CHF and the need of hospitalization in the bosentan group
Lewis GD et al. [17]	sildenafil	34	increase of peak $VO_2$ in CPET; improvement in the 6MWT and QoL in the sildenafil group
Guazzi M et al. [18]	sildenafil	45	decrease in sPAP and E/E' ratio; increase in LVEF and E'; improvement of $VO_2$ , VE/ $VCO_2$ , and QoL in the sildenafil group

FIRST – The Flolan International Randomized Survival Trial; a randomized controlled trial of epoprostenol therapy for severe congestive heart failure, REACH – Multicentre, double-blind, placebo-controlled study of long-term endothelin blockade with bosentan in chronic heart failure, ENABLE – Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure, CPET – cardiopulmonary exercise test, LVEF – left ventricular ejection fraction, QoL – quality of life, 6MWT – six-minute walking test, sPAP – systolic pulmonary artery pressure

377 patients with CHF (NYHA classes III–IV) were randomized to receive bosentan (goal doses of 500 mg twice daily) or placebo for 26 weeks. Safety concerns led to an early termination of the trial (increased risk of heart failure in the first month of treatment) when only 174 patients had an opportunity to complete 26 weeks of therapy. Bosentan delivered no apparent benefit when all patients were analyzed, but in the subgroup of patients who were treated for at least 26 weeks, a significant beneficial effect of bosentan was observed [15]. A large randomized trial, Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure (ENABLE), [16] evaluated the effects of bosentan in patients with CHF (NYHA classes III–IV). A total of 1613 patients were randomized to receive either bosentan (125 mg twice daily) or placebo. The primary endpoint of all-cause mortality or hospitalization for heart failure was reached in 321 of 808 patients on placebo and 312 of 805 patients receiving bosentan. Treatment with bosentan demonstrated an early risk of worsening heart failure and the need of hospitalization due to fluid retention. The results from the ENABLE study have shown a doubtful potential benefit of nonspecific endothelin receptor blockade in heart failure.

#### PDE5 inhibitors

As the clinical trials with prostanoids and endothelin receptor antagonists in the treatment of patients with CHF have failed, much attention has been focused recently on PDE5 inhibitors and their potential utility in the treatment of patients with CHF and PH-LHD. The efficacy of PDE5 inhibition in the treatment of PAH is encouraging [17–22]. In CHF due to LV systolic dysfunction, there is an impaired endothelium-dependent NO–cyclic guanosine monophosphate (cGMP)-mediated vasodilatation in the pulmonary and skeletal muscle vasculature. Therefore, inhibition of PDE5, the principle enzyme responsible for cGMP catabolism, has been postulated as a potent mechanism to prevent

pulmonary and systemic vasoconstriction that contributes to increased RV and LV afterload in CHF [23]. Moreover, it has been suggested that PDE5 inhibition blunts  $\beta$ -adrenergic signaling [24] and prevents cardiac hypertrophy and remodeling [25]. Sildenafil is a specific PDE5 inhibitor that increases NO availability and NO-mediated vasodilatation [26]. It has been shown to improve endothelium-dependent, flow-mediated brachial artery dilation in patients with CHF [27].

In a small study performed by Lewis et al. [17], 34 patients with symptomatic CHF (NYHA classes II–IV; LVEF <40%) and PH were randomized to a 12-week treatment with sildenafil (25 to 75 mg orally 3 times/day) or placebo. Compared with placebo, a significant increase in peak  $VO_2$  measured by the CPET was observed in the sildenafil group. Moreover, sildenafil reduced PVR and increased cardiac output with exercise without altering PAWP or mPAP, heart rate, or systemic vascular resistance. It was also associated with improvement in the results of the 6MWT and QoL.

In yet another randomized, placebo-controlled study with sildenafil [18], 45 patients (NYHA classes II–III; LVEF <40%) were assigned either to placebo or sildenafil (50 mg 3 times/day) for 1 year. Although baseline systolic pulmonary artery pressure (sPAP) measured by echocardiography was only slightly elevated in all patients, it was significantly decreased in the sildenafil group after 1 year of follow-up. Moreover, only in the sildenafil group, a significant increase in LVEF and early diastolic tissue Doppler velocity (E') and a decrease in the E/E' ratio were observed. These changes were accompanied by a decrease of the left atrial volume index and LV mass index. Furthermore, sildenafil improved exercise performance (peak  $VO_2$ ), ventilation efficiency (VE/ $VCO_2$ ), and QoL in patients with CHF and slightly elevated PH. The results have provided evidence that chronic PDE5 inhibition has a beneficial effect also on LV diastolic function and cardiac geometry.

The same group of investigators conducted another randomized study to assess the effects of sildenafil treatment in patients with CHF [19]. A total of 46 patients (NYHA classes II–III; LVEF  $\leq$ 45%) were randomly assigned to placebo or sildenafil at a dose of 50 mg twice daily for 6 months. At baseline, sPAP in all patients was within the upper normal range, but it decreased significantly after 6 months in the sildenafil group. Moreover, in an active treatment group, there was a significant increase in brachial artery flow-mediated dilatation as well as reduction in the effect of ergoreflex on ventilation and VE/VCO<sub>2</sub> measured by the CPET.

#### Left ventricular and biventricular assist devices

Elevated PVR unresponsive to pharmacological vasodilatation is a major contraindication for heart transplantation. The postoperative course of patients with CHF and PH-LHD is associated with an increased risk of life-threatening right heart failure [9,27]. Mechanical support using an implantable LV assist device (LVAD) is an efficient approach to treat severe PH in patients with end-stage heart failure before heart transplantation. Data from trials on patients with CHF and severe PH treated with an LVAD suggest that it is associated with a reduction in PH that was resistant to pharmacological treatment with vasodilators [28–30]. However, in a number of patients undergoing the placement of LVAD, acute RV failure occurs because of PH and high PVR, requiring the simultaneous placement of an RVAD [31]. According to the latest ESC guidelines for the diagnosis and treatment of acute and CHF [12], an LVAD or biventricular assist device (BiVAD) is recommended in selected patients with end-stage CHF despite optimal pharmacological and device treatment, and who are otherwise suitable for heart transplantation, to improve symptoms and to reduce the risk of hospitalization for worsening HF and to reduce the risk of death while awaiting transplantation (I, B). A BiVAD rather than LVAD support should be considered as a “bridge to transplantation” in patients with biventricular failure or in those at high risk of developing RV failure after LVAD implantation.

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## Partial anomalous pulmonary venous connection (RCD code: II-3C.0)

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### Background

Partial anomalous pulmonary venous connection (PAPVC) is a rare congenital heart defect where some of the pulmonary veins drain into the right atrium either directly or indirectly through its venous tributaries.

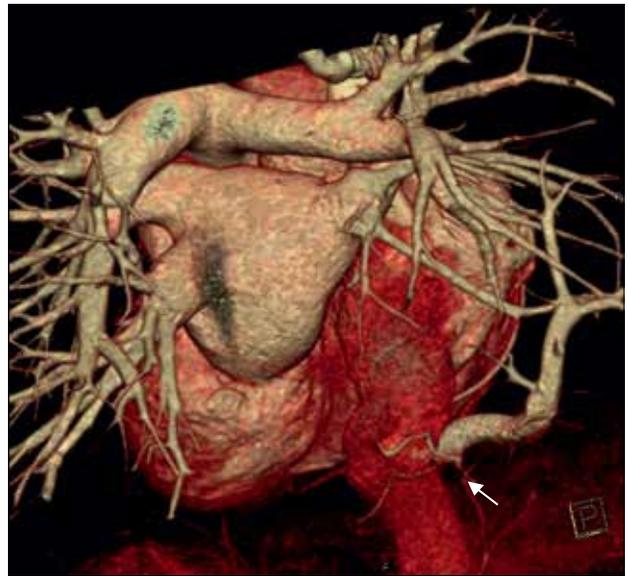
In contrast to total anomalous pulmonary venous connection, not all pulmonary veins in PAPVC show anomalous connection. The exact incidence of PAPVC is unknown. In an autopsy series published in 1952, it was estimated to be 0.4% [1]. In a more recent retrospective analysis of a series of computed tomography (CT) scans performed for other indications, the condition was found in 0.1% to 0.2% of adult patients [2,3]. In a significant proportion of the cases, PAPVC is associated with an atrial septal defect (ASD). Anomalous connected right-sided pulmonary veins can drain into the right atrium, superior vena cava, or, less frequently, into the inferior vena cava. The first two variations often accompany the sinus venosus type of ASD. The possible connections for the left-sided aberrant pulmonary veins include the left brachiocephalic vein, coronary sinus, and hemiazygos vein.

### Case presentation

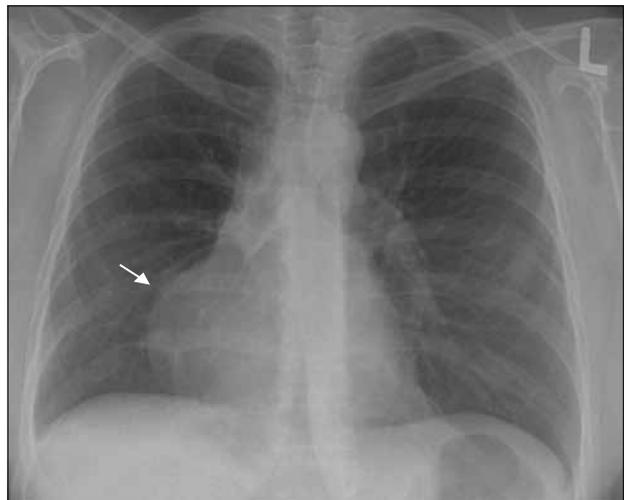
We present a case involving a 48-year-old woman admitted to the Centre for Rare Cardiovascular Diseases, Krakow, Poland, with a year's history of uncharacteristic chest pain episodes and decrease in exercise tolerance. A lung CT scan performed 9 months earlier, as part of the initial diagnostic work-up of the above symptoms, revealed an anomalous vein arising from the right lower pulmonary lobe and draining into the inferior vena cava at the level of hepatic veins (fig. 1). A chest radiogram performed 2 months prior to admission showed a curved shape in the lower right pulmonary field adjacent to the heart (fig. 2).

During admission, an electrocardiogram (ECG) showed right ventricular hypertrophy and overload.

A transthoracic echocardiogram did not confirm right ventricular dilation but it revealed an additional blood vessel with a turbulent flow draining into the inferior vena cava 2.5 cm from the right atrium. Both left ventricular function and size were normal and there was no significant valvular dysfunction. Laboratory studies including complete blood count, electrolytes, liver and kidney function tests were within normal limits. Nevertheless, there were signs of hyperlipidemia. An exercise ECG test with ventilatory gas analysis demonstrated no

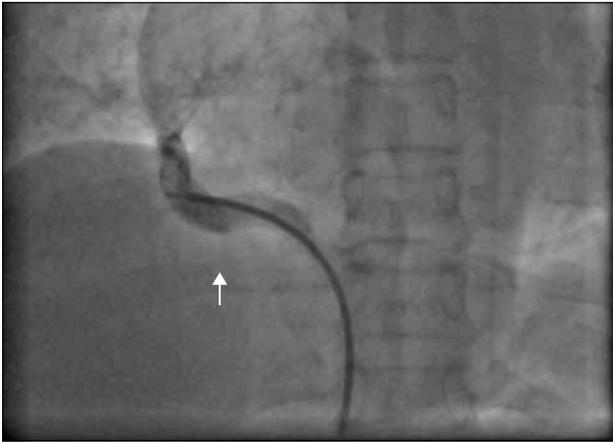


**Fig. 1.** Cardiovascular computed tomography. Reconstruction of heart and great vessels. Anomalous pulmonary vein draining into the inferior vena cava (arrow)



**Fig. 2.** Chest X-ray. Posteroanterior view. Prominent right heart border (arrow)

signs of myocardial ischemia and a peak oxygen uptake at 21.0 mL/kg/min. A transesophageal echocardiogram did not show any pathological connection between the atria, although it did demonstrate only 3 pulmonary vein ostia in the left atrium. Coronary angiography showed no evidence of coronary artery disease. Right heart catheterization was performed, which revealed normal systolic, diastolic, and mean pulmonary artery pressure (19, 5, and 10 mm Hg, respectively) and normal pulmonary resistance (1.6 Wood units). Selective angiography demonstrated an anomalous pulmonary vein draining into the inferior vena cava (fig. 3). A direct catheter measurement revealed a saturation of 98% in the anomalous vein. However, the shunt volume was insignificant, and the pulmonary to systemic blood flow ratio ( $Q_p:Q_s$ ), estimated using the modified Fick equation, was 1:1. Pulmonary artery angiography showed that the aberrant pulmonary vein had an additional



**Fig. 3.** Angiography. Anomalous pulmonary vein (arrow)

connection with the right upper pulmonary vein through an anastomotic vessel (fig. 4). The patient was diagnosed with PAPVC. No associated congenital anomalies were identified.

## Discussion

PAPVC causes a left-to-right shunt, which, if severe enough, can cause right ventricular overload and can lead to the development of pulmonary arterial hypertension. The symptoms depend on the shunt volume and the presence of other congenital anomalies. Possible clinical manifestations involve fatigue, exercise intolerance, and frequent pulmonary infections. Another possible manifestation is palpitations resulting from atrial flutter or atrial fibrillation, caused by long-standing right-sided heart volume overload. A single, isolated anomalous vein rarely produces any symptoms. Scimitar syndrome is a distinct form of PAPVC, in which a pulmonary vein, usually arising from the lower and the middle lobe of the right lung, drain into the inferior vena cava. It has been reported in 3% to 6% of the patients with PAPVC. The syndrome is frequently associated with other congenital abnormalities such as pulmonary sequestration, lung hypoplasia, dextroposition of the heart, abnormal arterial lung supply from the systemic arteries, and ASD [5]. The scimitar vein can often be visible on a plain chest X-ray at the right side of the heart silhouette, as a structure resembling a scimitar in shape – a Turkish sword used in the times of the Ottoman Empire.

## Management strategy

Definitive treatment of PAPVC consists of a surgical redirection of an aberrant pulmonary venous drain into the left atrium [4]. There are no widely accepted indications for surgical repair. The current guidelines of the European Society of Cardiology for the management of grown-up congenital heart disease do not specifically address PAPVC. Indications for surgical repair



**Fig. 4.** Pulmonary artery angiography. Anastomotic vessel (arrow) connecting an anomalous pulmonary vein with the right upper pulmonary vein

are similar to those in ASD [5]. Management generally depends on the magnitude and effects of the left-to-right shunt. Patients with a significant shunt that results in right ventricular volume overload and right-sided heart dilation are candidates for surgical repair. On the other hand, surgery can be avoided in many asymptomatic patients with low shunt fraction and no signs of the right heart overload or pulmonary arterial hypertension. However, given the fact that the age-related changes, mainly a reduction in left ventricular compliance, may increase the size of the shunt later in life, these patients should undergo regular evaluation in a center that specializes in the management of grown-up congenital heart diseases.

Given the fact that we observed only mild symptoms, no echocardiographic signs of the right-sided heart volume overload, insignificant shunt fraction, and normal parameters of pulmonary circulation, the patient was prescribed a conservative treatment and close medical observation in our outpatient clinic was recommended.

## Acknowledgement

This article was previously published in the *Journal of Rare Cardiovascular Diseases*. The authors submitted this article to the current textbook with permission.

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## Enormous dilatation of the pulmonary artery in a patient with mitral stenosis – an aneurysm or natural history? (RCD code: II-2A.0)

Małgorzata Knapp, Anna Lisowska,  
Bożena Sobkowicz, Agnieszka Tycińska,  
Marta Kamińska

### Background

Aneurysm of the pulmonary trunk is extremely rare. It has been reported in 1 per 14 000 autopsy cases [1,2]. It may be found in patients with congenital and acquired cardiovascular diseases, systemic vasculitis, connective tissue diseases, infections, and trauma. Pulmonary hypertension of any cause may induce the development of a pulmonary artery aneurysm (PAA) [1,3,4]. However, the pathogenesis and natural history of PAA are poorly understood [1]. There is no linear correlation between the degree of pulmonary trunk dilatation and pulmonary artery pressure [5]. In some patients with PAA, a sudden death occurs due to aneurysm rupture. Isolated, “idiopathic” PAA is a particularly rare disease (1:100 000 autopsies) [6] with only a few cases described in the literature. If there are no clinical symptoms of PAA, it may be discovered accidentally during a chest X-ray examination [7]. Pulmonary hypertension occurs in the natural history of rheumatic mitral stenosis. Subsequent dilatation of the pulmonary artery is, therefore, a frequent finding.

### Case presentation

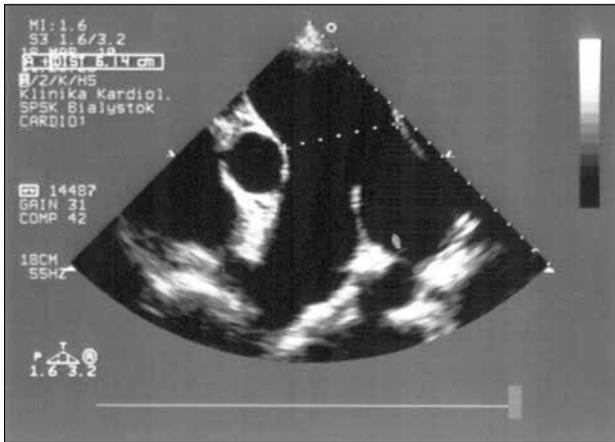
A 62-year-old woman with a history of chronic atrial fibrillation was admitted to the hospital due to the worsening of heart failure symptoms. On admission, the patient presented with dyspnea. Her blood pressure was 90/50 mm Hg. During auscultation, she had complete irregular heart rate of approximately 80 beats/min, the first tone was louder, and a diastolic murmur over the apex was found. She had symptoms of pulmonary congestion, enlarged liver by about 3 cm, and peripheral edema. An electrocardiogram revealed atrial fibrillation and right axis deviation. Chest X-ray showed enlarged hilus of the right lung as well as unusual enlargement of the mediastinum right below the aortic arch. Echocardiography showed mitral valve stenosis with severe calcifications of the leaflets with the mitral valve area of 0.9 cm<sup>2</sup> and the mean transvalvular gradient of 7 mm Hg. The left atrial diameter at the parasternal long-axis view was 51 mm, left ventricular (LV) diastolic diameter was 39 mm, and LV ejection fraction was 45%. The right ventricle was dilated and hypertrophied (11 mm) with impaired contractility; tricuspid

annular plane systolic excursion was 13 mm. Significant tricuspid regurgitation was also observed. The estimated systolic pulmonary artery pressure was 141 mm Hg, and the estimated mean pulmonary artery pressure was 88 mm Hg. The diameter of the pulmonary trunk was 61 mm and the diameters of both the right and left pulmonary arteries were 39 mm each (fig. 1, 2). The pulmonary valve leaflets were flabby with severe regurgitation. Congenital heart diseases were excluded by transesophageal echocardiography. A standard pharmacological treatment of heart failure was introduced and the patient's condition improved. Because of the mitral valve morphology and severe tricuspid valve insufficiency, surgical treatment was considered, but the patient refused. On discharge, she was at New Your Heart Association class III. Computed tomography angiography of the chest was planned as the next diagnostic step, but the patient did not present for further evaluation.

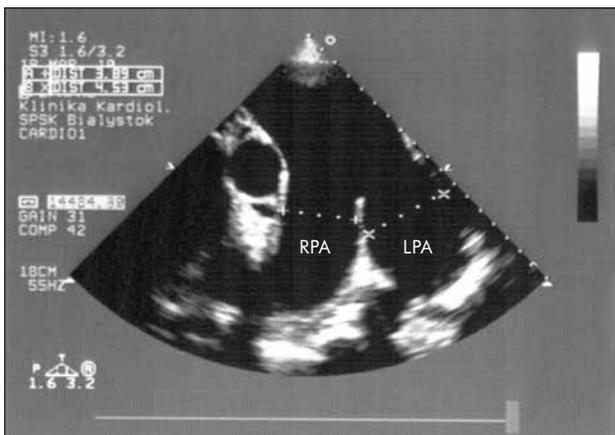
### Discussion

On computer tomography, the diameter of the main pulmonary artery should not exceed 28 mm [7]. According to the guidelines, the upper limit of the pulmonary trunk diameter in echocardiography is 21 mm, and a diameter exceeding 30 mm is considered as severely abnormal [8]. A rapid enlargement of the vessels may occur following changes in right-sided heart hemodynamics and an increase in systolic pulmonary artery pressure. To our knowledge, the available literature data do not specify what diameter of the pulmonary trunk defines PAA [9]. The largest study on PAA was performed by Żyłkowska et al. [5], who investigated 184 patients with pulmonary hypertension. According to their findings, a pulmonary trunk diameter larger than 48 mm was a risk factor for a sudden cardiac death [5]. The authors did not find any associations between the pulmonary artery diameter, right and left heart pressures, demographic data, and clinical variables. They speculated that unknown individual factors related to the histology (morphology) of the vessel wall might have been responsible for the development of PAA. This might have been the case also with our patient: apart from the enlargement of the pulmonary artery, atypical morphology of pulmonary valve leaflets (“flabbiness”) was observed, which resulted in severe valve regurgitation. In our opinion, the presence of severe pulmonary hypertension does not explain such marked dilation of the pulmonary trunk.

Dyspnea, hemoptysis, and atypical chest pain are the most frequent complaints reported by patients with PAA [3,4]. Massive hemoptysis related to pulmonary artery diseases is a common symptom [10] that might suggest the instability of the pulmonary trunk aneurysm resulting in dissection and rupture, which, in turn, is an indication for cardiac surgery [1].



**Fig. 1.** Transthoracic echocardiography. Parasternal short-axis view. Dilated pulmonary trunk (61 mm)



**Fig. 2.** Transthoracic echocardiography. Parasternal short-axis view. Right and left pulmonary artery, both dilated to 39 mm

## Management strategy

Currently, there are no precise guidelines for the timing of the surgery in the case of PAA, as there are, for example, in the case of an ascending aortic aneurysm [3,9]. Some authors suggest that the decision on surgical treatment should be based on the changes in the size and function of the right ventricle [11]. A surgery (prosthesis, reconstruction with pericardium, pulmonary artery plasty) should be considered as a prevention against aneurysm rupture. In the latter case, the surgery should be performed when the diameter of the pulmonary trunk exceeds 6 cm, independently of the clinical symptoms [1,3]. In our patient, the surgical treatment of the aneurysm, apart from mitral and tricuspid valve surgery, could be considered.

## Acknowledgement

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# Part 5

Rare diseases of the heart (cardiomyopathies)  
– RCD class III

**Editor: Paweł Rubiś**



# Introduction

Paweł Rubiś

The complexity of classification, pathology, diagnosis, and optimal management of cardiomyopathies has been extensively reviewed and summarized by leading experts in the field in the form of guidelines, review articles, and reference textbooks. The backbone of contemporary cardiology are rigorously developed evidence-based guidelines. The area of cardiomyopathies has been covered by several guidelines issued and endorsed by scientific societies, including the European Society of Cardiology (ESC), the American College of Cardiology (ACC), and the American Heart Association (AHA). The widely accepted, at least in Europe although not without any doubts, classification of cardiomyopathies has been proposed by the Working Group on Myocardial and Pericardial Disease of the ESC by Elliot P, Anderson B, Arbustini A, Bilińska Z, Cecchi F, Charron P, Dubourg O, Kuhl U, Maisch B, McKenna WJ, Monserrat L, Pankuweit S, Rapezzi C, Seferovic P, Tavazzi L, and Keren A [1]. The discrepancies between the European and American perspectives on the classification of cardiomyopathies are well reflected in the AHA guidelines issued in 2006 and written by Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, and Young JB [2]. An extensively studied hypertrophic cardiomyopathy (HCM) is covered in now a little outdated joint document of the ESC and ACC and developed by Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, Shah PM, Spencer WH 3rd, Spirito P, Ten Cate FJ, and Wigle ED [3]. The more up-to-date guidelines on HCM has been recently published in the joint effort of ACC/AHA and authored by Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW [4]. Because many patients with cardiomyopathies will eventually develop the signs and symptoms of heart failure, some issues related to cardiomyopathies are covered in the ESC guidelines on heart failure developed by McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY,

Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, and Zeiher A [5]. The research on cardiomyopathies is very dynamic, and numerous high-quality papers and studies are published every week. Therefore, it is always a good choice to read well-written reference textbooks to remain up to date. Among numerous books, there are a few particularly valuable ones including *Principles and Practice of Clinical Cardiovascular Genetics* edited by Kumar D and Elliot P, *Inherited Cardiac Disease* edited by Elliot P and Lambiase P, and *Cardiomyopathies – From Basic Research to Clinical Management* edited by Josef Veselka [6–8].

It should be clearly acknowledged that the aim of the present part of the book is not to evaluate or review the accumulated data or guidelines presented by leading experts in the field and published in widely recognized high-impact journals. Rather, we aimed to present the perspective of the Centre for Rare Cardiovascular Diseases (CRCVD) at the John Paul II Hospital, Krakow, on certain aspects of cardiomyopathies, including classification and state-of-the-art management of unique patients with rare cardiomyopathies. Being a referral center for cardiomyopathy in a large area of south-eastern Poland, we routinely see patients with all types of cardiomyopathies and related problems. Therefore, we have already gained considerable experience as well as observed some gaps in the current knowledge. Based on experience, extensive literature search, as well as fruitful and balanced discussions with world-class experts, we developed our working classification of cardiomyopathies, which we find particularly useful in the daily management of patients. Moreover, we constructed some diagnostic algorithms that are routinely used, especially in patients with dilated and restrictive cardiomyopathies. On the other hand, we clearly admit that those algorithms have not been validated in other patient cohorts and their significance is yet to be proved.

This editorial is followed by an introductory chapter on cardiomyopathies, which contains a short description of the main types and subtypes of cardiomyopathies. In the condensed format, we present epidemiology, pathology with particular attention to genetics, and management. Moreover, we included

the state-of-the-art algorithms on dilated and restrictive cardiomyopathies. Finally, we present the place of cardiomyopathies in the aforementioned RCD classification. The introductory chapter is followed by seven exceptional clinical cases that were managed in our as well as in our partner centers. Two more cases on hypertrophic and peripartum cardiomyopathies during pregnancy are included in separate Part 9, entitled “Cardiovascular diseases in pregnancy”. What is of utmost importance is that all of those cases were extensively studied and discussed during meetings with Polish and European experts from the United Kingdom, Italy, Germany, Lithuania, and Latvia in order to find the optimal management strategy. However, we have to admit that, occasionally, we were not able to propose the best strategy owing to the complexity of the case, certain gaps of knowledge, or the need for highly-sophisticated and costly procedures or medicines that were not reimbursed by the National Health Fund. Nevertheless, we have always tried to reach balanced and well-thought conclusions, bearing in mind that the patient’s well-being is of the highest value.

At the end of this editorial, we would like to express our deepest gratitude to our European Partners and Cooperators from whom we learn so much and who are always willing to consult our cases. In particular, we would like to honor **Professor John Cleland** from the Department of Academic Cardiology in the Castle Hill Hospital in Kingston upon Hull, United Kingdom, who is a world expert in the field of heart failure. We would also like to thank **Professors Bernhard Maisch and Sabine Pankuweit** from the Department of Cardiology, Hemodynamics and Cardio-Immunologic Laboratory at the University Hospital, Philipps University in Giessen and Marburg; Marburg, Germany, for their supervision over the optimal management of myocarditis and inflammatory cardiomyopathy. We are grateful to **Professors William McKenna and Perry Elliot** from the Department of Inherited Heart Diseases in the Heart Hospital at the University College of London, United Kingdom, as well as **Professor Eloisa Arbustini** from the Center for Inherited Cardiovascular Disease in San Matteo Hospital in Pavia, Italy, for their supervision over our studies on the genetics of cardiomyopathies. It should be acknowledged that all of our partners are world-class experts and authors of contemporary guidelines on cardiomyopathies.

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# Rare diseases of the heart (cardiomyopathies): Perspective of the Centre for Rare Cardiovascular Diseases

## ■ Cardiomyopathies as rare cardiovascular diseases

Paweł Rubiś, John GF Cleland

According to the definition proposed by the Working Group on Myocardial and Pericardial Diseases of the European Society of Cardiology, cardiomyopathy is “a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular heart disease, and congenital heart disease sufficient to cause the observed myocardial abnormality” [1]. Therefore, whenever cardiomyopathy is suspected in an individual patient, an active and comprehensive exclusion of those four common causes of heart damage and failure should be performed at the beginning of the diagnostic process.

Clinically-oriented classification traditionally distinguishes between four structural and functional cardiomyopathy phenotypes such as dilated (DCM), hypertrophic (HCM), restrictive (RCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC) [1]. Although very useful on the daily basis, it should be acknowledged that cardiomyopathies frequently overlap or mimic one other, for example, end-stage (dilated) HCM or ARVC with predominant left ventricular (LV) involvement. Moreover, cardiomyopathies are further subclassified into familial and nonfamilial forms. To confirm familial cardiomyopathy, it is necessary to diagnose either the same or similar (considerable differences in age and gene penetration) cardiac phenotype in at least two family members. Most familial cardiomyopathies are monogenic disorders. Non-familial cardiomyopathies are defined by the presence of the disease in the index patient and the absence of the disease in other family members [1].

### Dilated cardiomyopathy

The phenotype of DCM is established by means of imaging studies, echocardiography being the most common. DCM is characterized by LV dilatation and

usually severe impairment of systolic function and associated changes in diastolic function.

The most reliable data on the epidemiology of DCM comes from a relatively old study from Olmsted County, Minnesota, conducted between 1975 and 1984, which estimated DCM prevalence at 35.5:100 000 inhabitants (1:2700). The annual incidence of DCM is approximately 5 and 8 per 100 000 of the general population [2]. Although DCM may occur at any age, in the great majority of the cases, it affects adolescents and young adults. Although coronary artery disease is the primary cause of heart failure (HF), DCM has recently become the most common diagnosis in patients referred for heart transplantation.

The etiology of DCM is largely heterogeneous. Despite an enormous progress in the diagnosis and management of cardiovascular diseases, the causes of DCM remain unknown in many patients.

In developed countries, ischemic heart disease (IHD) and myocardial infarction (MI) are the most common causes of HF observed in 50% to 75% of all patients with HF. Even the term “ischemic cardiomyopathy” had been extensively used in the literature but, currently, this terminology is no longer recommended. Nevertheless, potentially reversible ischemia to the heart must always be actively sought because effective therapy (medications and revascularization) can favorably alter the patient's outcome. Obviously, the presence of IHD and MI naturally excludes the diagnosis of cardiomyopathy. However, in the widely cited study by Felker et al., even after careful medical history and noninvasive examinations, the causative role of IHD in the development of HF was confirmed only after coronary angiography in up to 7% of the patients with initially unexplained DCM [3].

Other causes of DCM that should always be considered in the diagnostic process are as follows: the other types of cardiomyopathies, which may either mimic or progress to DCM, connective tissue diseases, endocrine disorders, infiltrative diseases, medications and toxins, tachycardia-induced DCM, and miscellaneous other causes. Most of those diseases may be identified after careful medical history and basic laboratory and imaging studies (electrocardiogram, echocardiography). However, some disorders, especially infiltrative diseases, may require more sophisticated

examinations such as laboratory tests, cardiac magnetic resonance imaging, or histopathological studies.

Once the above causes of DCM have been excluded, the etiology of DCM can be either genetic (familial) or nongenetic. The genetic nature of DCM is increasingly recognized; however, at this stage, only 35% of DCM patients have confirmed causative mutations. Among nongenetic causes, persistent myocardial inflammation as a consequence of myocarditis is probably most common [4]. Figure 1 presents the working CRCD diagnostic algorithm for dilated cardiomyopathy.

## Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is characterized by otherwise unexplained left ventricular hypertrophy (LVH) with nondilated ventricular chambers. Clinically, HCM is recognized by a maximal wall thickness  $\geq 15$  mm [5]. Of note, there is a considerable disagreement between the European and American definitions of HCM. In the European perspective, HCM is a largely heterogeneous group of myocardial disorders that encompasses not only sarcomeric protein diseases but also metabolic, infiltrative, and storage diseases. Such an approach reflects everyday practice, when it is impossible to differentiate LVH caused by hypertrophy and cardiomyocyte disarray, typical for sarcomeric protein mutations, from interstitial (e.g., amyloidosis) or intracellular (e.g., Fabry disease) accumulation of metabolic substrates [1]. On the other hand, the American guidelines endorse the concept that HCM is a disease exclusively caused by the mutations of cardiac sarcomeric genes and, in the case of LVH that results from an infiltrative or metabolic causes, it cannot be termed HCM [6]. The prevalence of LV hypertrophy, which is an essential manifestation of the HCM phenotype, is about 0.2% (i.e., 1:500) in the general population. HCM is a heterogeneous group of rare and very rare conditions [5].

### HCM attributable to sarcomeric protein mutations

HCM is a disease entity caused by autosomal dominant mutations in genes encoding contractile proteins of the cardiac sarcomere. At present, 11 mutant genes are associated with HCM, most commonly  $\beta$ -myosin heavy chain and myosin binding protein C. The remaining nine genes account for far fewer cases of HCM and include troponin T and I, regulatory and essential myosin light chains, titin,  $\alpha$ -myosin heavy chain,  $\alpha$ -actin,  $\alpha$ -tropomyosin, and muscle LIM protein. This genetic diversity is even more complicated by the intragenetic heterogeneity, with over 1400 individual mutations now identified. The majority are missense mutations but insertions, deletions or splice mutations are also commonly observed. As HCM is inherited in an autosomal dominant pattern, the risk that an affected patient transmits disease to each offspring is 50% [5,7,8].

### HCM attributable to nonsarcomeric protein mutations

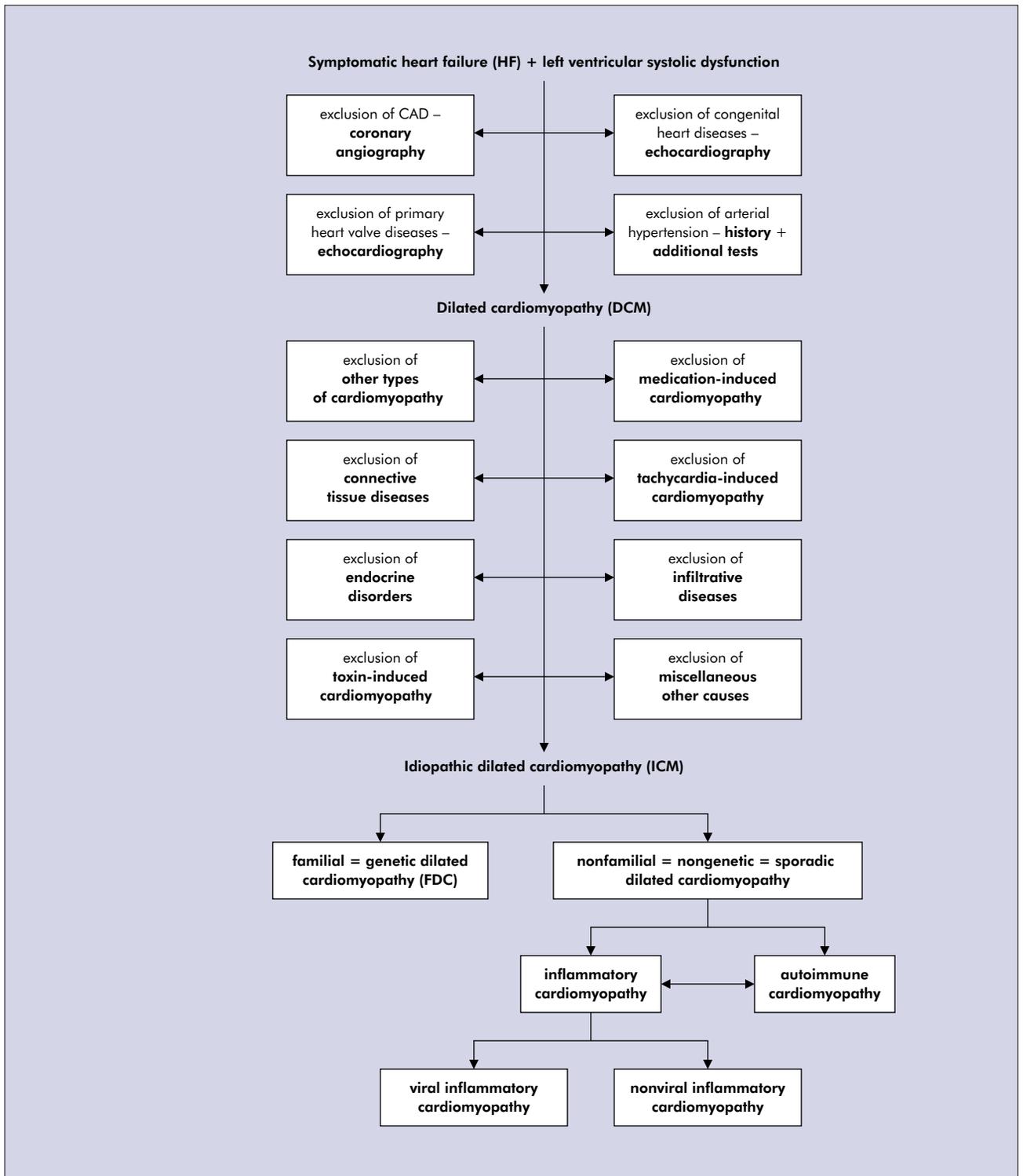
In less than 10% of the patients with echocardiographic phenotype of HCM, the disease is associated with other disorders including infiltrative, metabolic, systemic, mitochondrial, and syndromic disorders [1,8,9].

1. **Infiltrative HCM** can result from:
  - **glycogen storage diseases** such as:
    - **Pompe disease** (caused by deficiency of  $\alpha$ -1,4-glycosidase),
    - mutation of the gene encoding the  $\gamma$ -2-regulatory subunit of the AMP-activated protein kinase (PRKAG2),
    - **Danon disease** (mutation of the gene encoding lysosome-associated membrane protein-2 – LAMP-2),
    - **Forbes disease**
  - **lysosomal storage disease** such as:
    - **Anderson–Fabry disease** (caused by the deficiency of the lysosomal enzyme,  $\alpha$ -galactosidase A)
    - **Hurler’s disease**
2. **Metabolic myopathies**, which are caused by ATP production and utilization defects
  - Disorders of fatty acid metabolism
  - Carnitine deficiency
3. **Systemic diseases** that can cause HCM:
  - Pheochromocytoma
  - Neurofibromatosis
  - Lentiginosis
  - Tuberous sclerosis
4. **Mitochondrial cytopathies**, which include:
  - Mutations encoding mitochondrial DNA – Kearns–Sayre syndrome
  - Mutations of mitochondrial proteins associated with ATP electron transport chain enzyme
5. **Syndromic HCM**, which include:
  - Noonan syndrome
  - LEOPARD syndrome
  - Friedreich’s ataxia
  - Beckwith–Weidemann syndrome
  - Swyer syndrome

Moreover, the two most common conditions, namely, hypertensive heart disease and the physiologic remodeling associated with athletic training (“athlete’s heart”), should always be taken into account. Young age, history of training, and maximal wall thickness in the modest range of 13 to 15 mm strongly suggest “athlete’s heart” [8].

## Restrictive cardiomyopathy

Restrictive cardiomyopathy (RCM) is an uncommon, heterogeneous group of heart muscle disorders characterized by impaired ventricular filling, with normal or even decreased ventricular volumes [1]. This leads to advanced diastolic dysfunction with relative preservation of systolic function. However, it is not true



**Fig. 1.** Proposed etiopathogenetic (causative) diagnostic algorithm of dilated cardiomyopathy

that systolic function is completely normal in RCM as usually only short-axis contractility is preserved, whereas the long axis may be severely depressed. Depending on the underlying etiology, ventricular wall thickness may be normal or increased. The atria are usually severely dilated owing to increased ventricular resistance in each diastole. The precise epidemiology of RCM is unknown but true RCM is a rare disease. Importantly, RCM is a diagnosis of exclusion because restrictive physiology is typically

observed in numerous other cardiac disorders, including end-stage HCM or early stages of DCM. The majority of RCM are secondary to systemic disorders such as amyloidosis, sarcoidosis, scleroderma, hemochromatosis, eosinophilic heart disease, or a result of radiation therapy. The rarest diagnosis of idiopathic RCM is only made after active exclusion of the more common causes of RCM [10].

■ **Infiltrative disorders** such as amyloidosis (familial – transthyretin or apolipoprotein, and nonfamilial

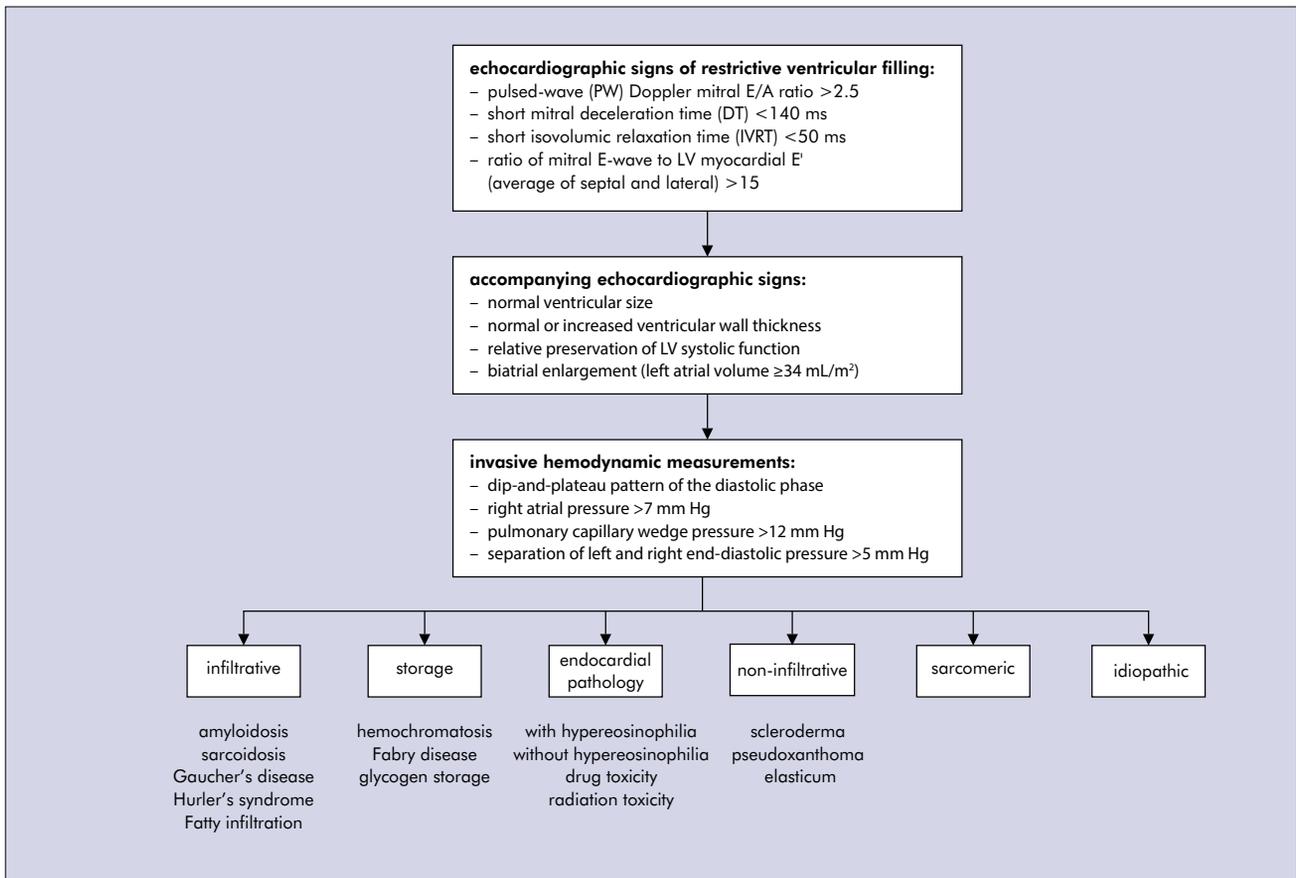


Fig. 2. The proposed diagnostic algorithm of restrictive cardiomyopathy

- AL/prealbumin), sarcoidosis, Gaucher's disease, Hurler's disease, and fatty infiltration.
- **Storage diseases** such as hemochromatosis, Fabry disease, and glycogen storage diseases.
- **Non-infiltrative disorders** such as scleroderma, pseudoxanthoma elasticum.
- **Sarcomere protein gene mutations** – as in other types of cardiomyopathies, some RCM patients have defective contractile proteins caused by mutations.
- Disorders that cause **endocardial pathology** (fibrosis, fibroelastosis, thrombosis) that are subclassified according to the presence of **eosinophilia** into **endomyocardial diseases with hypereosinophilia**, also known as **hypereosinophilic syndromes**, and **endomyocardial diseases without hypereosinophilia** or **endomyocardial fibrosis (EMF)**. Acquired forms of EMF may be caused by parasitic infection, drugs such as methysergide, serotonin, busulfan, nutritional factors, and radiation toxicity.

Moreover, RCM has to be always differentiated from constrictive pericarditis, which presents with similar impairment of diastolic function. Patient's history may be crucial because the most common causes of constrictive pericarditis are open-heart surgery, radiation therapy, and uremia. Computed tomography and cardiac magnetic resonance imaging are useful to determine pericardial thickness and the presence of calcification. However, echocardiography with

Doppler assessment of mitral inflow during the respiratory cycle plays the decisive role. In RCM, there are no changes of transmitral and transtricuspid inflow velocities either during inspiration or expiration. On the contrary, in constrictive pericarditis, the transmitral velocities are reduced while the tricuspid velocities are increased in deep inspiration, while the opposite happens during expiration [11].

### Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare distinct cardiomyopathy that has been described in detail in the following clinical case.

### Unclassified cardiomyopathies

Unclassified cardiomyopathies, including left ventricular noncompaction and peripartum cardiomyopathy, have been presented in great detail in the following chapters.

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# Rare diseases of the heart (cardiomyopathies): Clinical examples

## Severe course of dilated cardiomyopathy associated with Duchenne muscular dystrophy (RCD code: III-1A.3a)

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### Background

Inherited neuromuscular disorders, such as dystrophin-related disorders, Emery–Dreifuss muscular dystrophy, facioscapulohumeral muscular dystrophy, myotonic dystrophy, Friedreich's ataxia, and Barth syndrome, are frequently associated with cardiac involvement, mainly with cardiomyopathies.

Dystrophin-related disorders are caused by the mutation in the dystrophin gene on the X chromosome, which encodes dystrophin, a high-molecular-weight protein localized on the sarcolemmal membrane of the skeletal muscle. Two types of dystrophin-related disorders, namely, Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) have been identified. DMD is a more severe form of muscular dystrophy than BMD and is characterized by the complete or almost complete lack of dystrophin in the skeletal muscles, whereas patients with BMD have an abnormal structure of dystrophin protein. These two types of muscular dystrophies also have different course of the disease. The first clinical manifestation of DMD, namely, muscle weakness, starts between the second and third year of age, whereas BMD develops later in life and its progression is much slower. In contrast, cardiac involvement can be more severe in BMD compared with DMD, which is partly explained by the fact that BMD patients can perform certain exercises, which could be an extra burden on the myocardial cells with already abnormal dystrophin.

Only men develop the full spectrum of DMD symptoms, while women are carriers of dystrophin gene mutation. The cardinal symptoms of DMD are progressive skeletal muscle weakness, which eventually leads to complete loss of walking ability at the age of 10 to 12

years, and respiratory insufficiency due to the weakness of the respiratory muscle, which is the leading cause of premature death. Nowadays, advances in the treatment and rehabilitation of respiratory insufficiency, including mechanical ventilation, nocturnal ventilation, or spinal operation, allow patients to live longer with relatively preserved respiratory function. Owing to the improvement in the general and respiratory care of DMD patients, associated cardiovascular abnormalities, mainly cardiomyopathies, are gradually becoming the main cause of comorbidity and mortality in these patients [1].

This dramatic change in the landscape of muscular dystrophies is well reflected in the current guidelines for the diagnosis, monitoring, and treatment of concomitant cardiac disorders.

### Case presentation

An 18-year-old man with DMD was admitted to the Centre for Rare Cardiovascular Diseases in the John Paul II Hospital in Krakow because of progressive development of heart failure. He was diagnosed with DMD at the age of 2 years. He presented with enlarged calves, delayed walking, and difficulty in stair climbing. A genetic examination revealed deletion of 46–48 exons in the dystrophin gene (rod structure of the dystrophin gene), which confirmed DMD. At the age of 10 years, he became wheelchair-bound. At the age of 12 years, he underwent echocardiography for the first time, which revealed asymptomatic systolic insufficiency of the left ventricle. Treatment with an angiotensin-converting-enzyme inhibitor (ACEI, perindopril) was started. He remained under the care of the Institute of Pediatrics and, subsequently, when he reached the age of 18 years, he became the patient of the Congenital Heart Clinic of the John Paul II Hospital.

At presentation to the Centre, the patient's weight was 62 kg, his height was 156 cm, and the body mass index was 25.5 kg/m<sup>2</sup>. The patient did not report any cardiac symptoms, but he complained of fatigue and sleep disturbances. A physical examination revealed skeletal muscle weakness, a heart rate of 100/min, blood pressure of 110/70 mm Hg, audible third heart sound, and oxygen saturation of 96%. The respiratory

rate was 19/min and the signs of fluid presence were heard in the inferior parts of the lung auscultation. No peripheral swellings or cyanosis were present. A standard 12-lead ECG revealed sinus tachycardia with a heart rate of 100/min, no deviated axis, abnormally tall R waves in leads V<sub>1</sub> through V<sub>3</sub>, and large Q waves in leads II, aVF, V<sub>5</sub>, and V<sub>6</sub> (fig. 1, 2). The levels of biochemical parameters such as hemoglobin, amount of erythrocytes, and liver function enzymes (ASpat, Alat) were normal. A chest X-ray image showed the presence of fluid in the inferior parts of the lungs field and mild enlargement of the cardiopulmonary index (0.53). Echocardiography showed a dilated left ventricle with thinned wall and a significant decrease in the ejection fraction (20%); moderate mitral regurgitation was also observed (fig. 3, 4). So far, the patient has been treated with enalapril (5 mg/d), spironolactone (50 mg every 2 days), and digoxin (50 µg/d).

According to the current guidelines, patients with DMD older than 10 years should undergo echocardiography once a year. It allows to detect the development of a cardiac disorder. Our patient underwent his first echocardiography when he was 12-years old, and asymptomatic systolic insufficiency of the left ventricle was observed. He received perindopril and remained under the care of the Institute of Pediatrics, where he had been systematically monitored and his therapy modified accordingly. When he became the patient of the Congenital Heart Clinic of the John Paul II Hospital at the age of 18 years, he had advanced left ventricular cardiomyopathy.

During the next 6 months, his condition was rather good and he did not report any significant heart failure symptoms. Subsequently, he started to show more severe symptoms of a cardiac disorder, such as tachycardia with a heart rate of 100/min, peripheral swellings, and difficulty in breathing. He was prescribed a β-blocker. Echocardiography revealed a severely dilated left ventricle with pronounced spherical remodeling and secondary mitral regurgitation.

Despite optimal drug therapy, his condition gradually deteriorated until he suffered end-stage heart failure and died.

## Discussion

### Epidemiology

DMD is an X-linked disease that has an incidence of about 1 in 3500 male births, while BMD occurs in about 1 in 19 000 males [2]. The incidence of cardiomyopathy during the course of DMD increases with age. By the age of 6 years, almost one-quarter of DMD patients are diagnosed with cardiomyopathy, whereas in the next 4 years (until 10 years of age), almost two-thirds develop cardiomyopathy. Before reaching adulthood, almost all patients with DMD have concomitant cardiac involvement [3].

### Genetics

Both DMD and BMD result from the mutation of the gene encoding dystrophin protein, which is located within the band Xp21 on the X chromosome. The mode of DMD inheritance is recessive and X-transmitted; thus, the probability of passing the mutation to children is 50%, while the risk of having a sick son is 25%. Furthermore, almost 30% of DMD cases are caused by de-novo spontaneous mutations, which probably occurs during an ovary cell division [4].

Dystrophin is a membrane-associated cytoskeletal protein present in the skeletal and cardiac muscles, which forms a connection with the dystrophin–glycoprotein complex and has a crucial role in signal transduction [5]. In the absence of dystrophin, this connection becomes destabilized, disrupting the integrity of the cellular membrane, and eventually leads to an increase in intracellular calcium content. The higher concentration of intracellular calcium ions activates

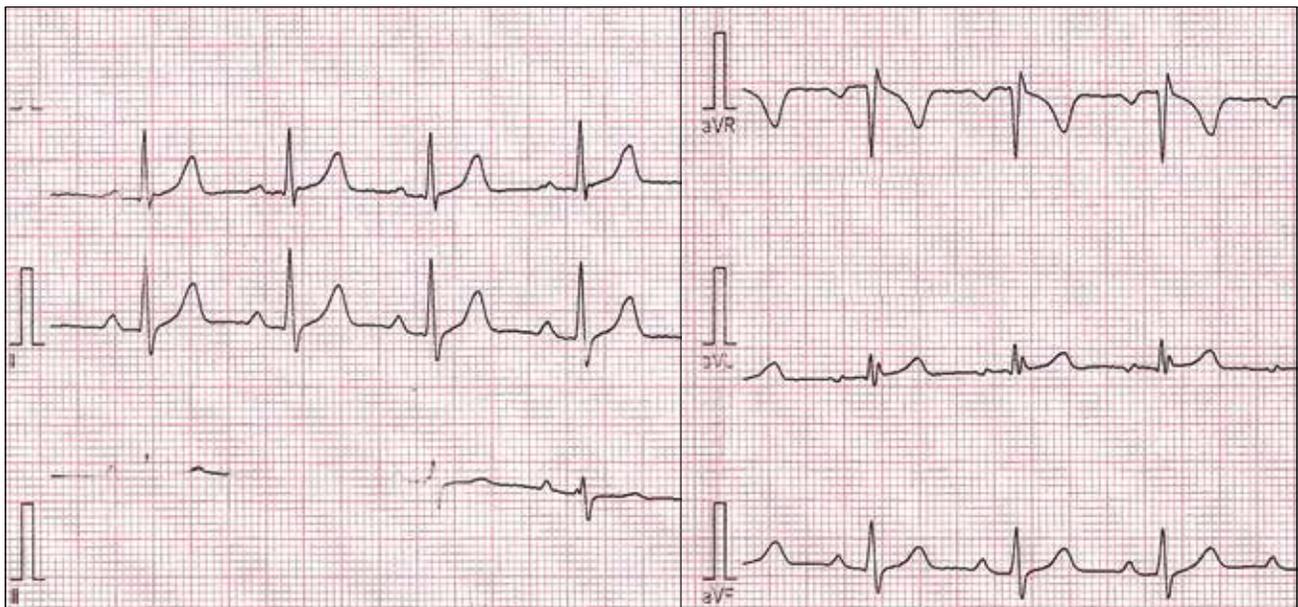


Fig. 1. Electrocardiogram. Sinus rhythm of 80 beats per min. Deep negative T waves in aVR

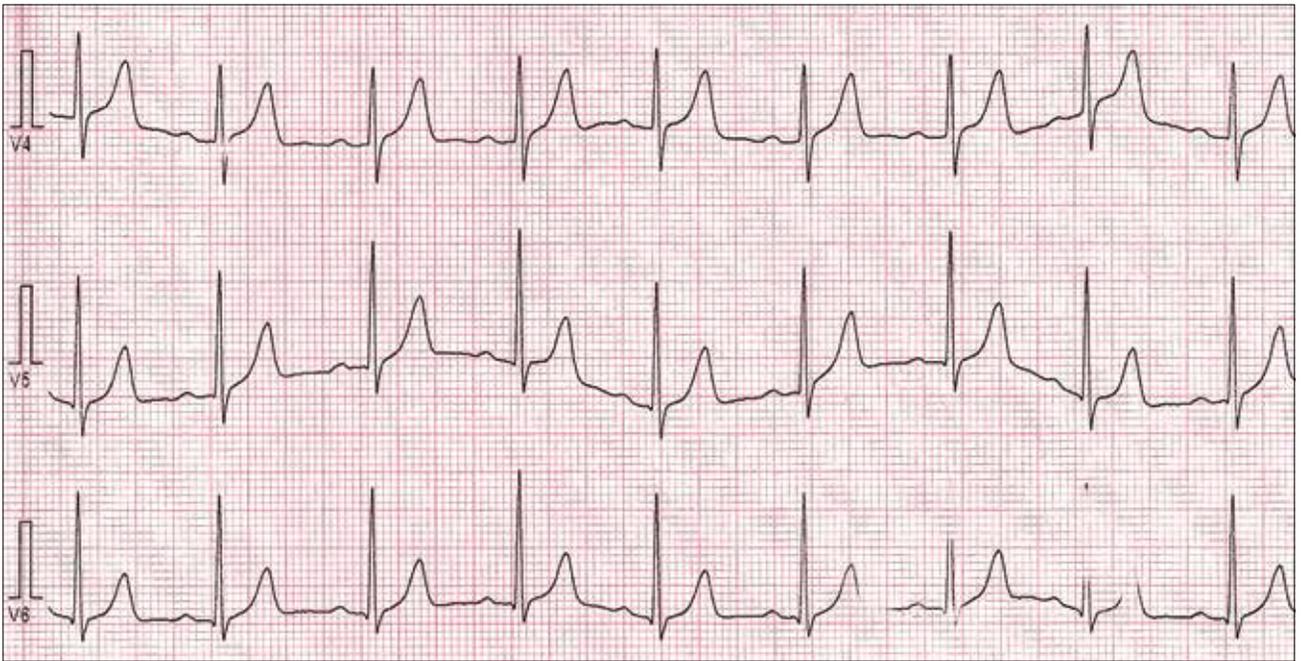


Fig. 2. Electrocardiogram. Abnormally tall T waves in V4–V6

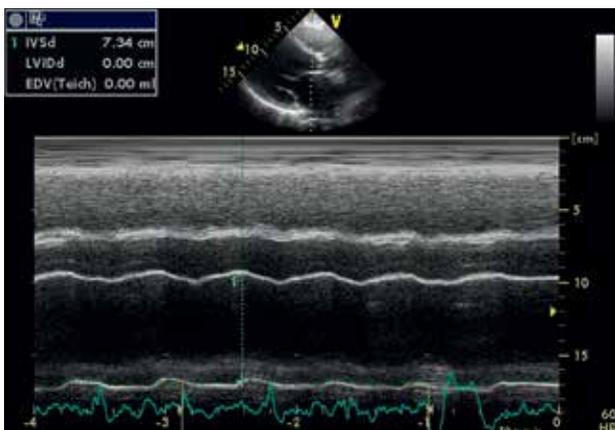


Fig. 3. Transthoracic echocardiography. Severe dilatation of a hypocontractile left ventricle and left atrium

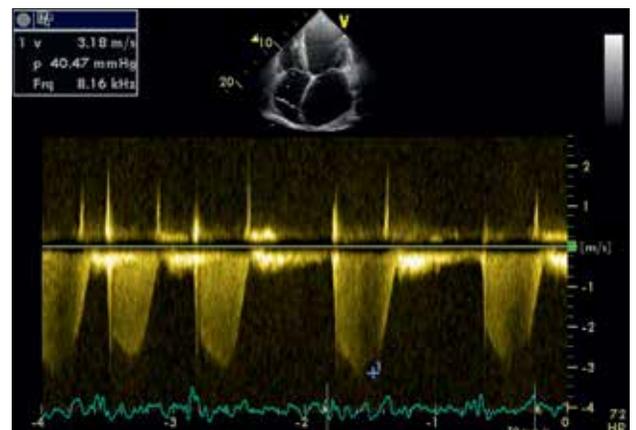


Fig. 4. Transthoracic echocardiography. Moderate tricuspid regurgitation with elevated right ventricle systolic pressure 55 mm Hg

the process of proteolysis causing muscle destruction. Damaged muscles are replaced with interstitial fibrosis and fatty tissue. In the heart, the degeneration of cardiomyocytes leads to fibrosis.

### Clinical manifestations

The intensity of clinical symptoms, course of the disease, and degree of skeletal muscle impairment depend on the type of muscular dystrophy. In DMD, where there is an absence of dystrophin, an early manifestation of disease is frequently observed. These patients show impaired mobility, with delayed walking and difficulty in stair climbing between the age of 2 and 4 years [6]. The enlargement of the calves is usually one of the first symptoms. On the contrary, patients with BMD, who have a reduced amount of dystrophin, have delayed onset of muscular weakness and overt symptoms. There are numerous muscles involved, including the proximal hip and shoulder girdle muscles, anterior

neck, and abdominal muscles. In DMD, full-time use of a wheelchair is usually required between the age of 10 and 12 years. In the second decade of life, the impairment of the thorax muscles, responsible for the mechanism of breathing, becomes apparent, leading to progressive respiratory insufficiency. This severe complication is an ominous sign of the disease, requires highly-specialized medical care, including rehabilitation, passive and active breathing support, and so far has been the leading cause of death in these patients.

### Cardiac involvement

Cardiac involvement during the course of muscular dystrophies encompasses numerous abnormalities including various types of arrhythmias, dilated cardiomyopathy (DCM), intramural thickening of the coronary arteries, and persistent hypotension. The severity of a cardiac disorder may not parallel the severity of skeletal muscle disease. Overt DCM usually develops

by the end of the second and the third decades of life in DMD patients, while the development of DCM in BMD patients is less predictable and may occur at any age. Although the echocardiographic phenotype of DCM is indistinguishable from DCM of other causes, there are certain characteristic features, which should always be considered in muscular dystrophies. First, even the basic assessment of the functional status by means of the New York Heart Association classification, is not feasible and or practical because the majority of patients are wheelchair-bound. Typical symptoms of the left- and right-ventricular congestion are rarely observed, while rather noncharacteristic symptoms of fatigue, weight loss, nausea, cough, heart palpitations, sleep disturbance, chest or abdominal discomfort, loss of appetite, decreased urinary output, or sweating should rise the suspicion of heart failure [6]. The “classic” cardiac symptoms such as chest pain, palpitations, dizziness, or syncope are usually manifestations of arrhythmias rather than heart failure. Unquestionably, a detailed history and examination of the patients and their caregivers play a fundamental role in early diagnosis of cardiac involvement in muscular dystrophies.

### Diagnosis of cardiac involvement

The current guidelines recommend a routine echocardiogram as the “gold standard” for early diagnosis of cardiomyopathy in DMD patients. Every patient should be examined by the age of 6-years old and have subsequent evaluations every 2 years until the age of 10 [7]. Thereafter, the echocardiogram should be repeated once a year. As early as in the second year of age, various cardiac abnormalities such as left ventricular dilatation, wall thinning, impairment of regional contractility, or secondary mitral regurgitation are frequently observed. These pathologies result from fibrosis of the posterior wall of the left chamber and later progress apically and laterally. Although an echocardiogram is an invaluable tool, there are some limitations specific for muscular dystrophies, which include gross kyphoscoliosis, wheelchair confinement, increased chest wall adiposity due to prolonged systemic steroid use. These inconveniences lead to technical difficulties in obtaining proper echocardiographic images. Thus, cardiovascular magnetic resonance imaging has become the additional diagnostic tool, which can be used to provide supplementary information about the structure and malfunctioning of the heart [8]. Moreover, late gadolinium enhancement identifies myocardial fibrosis and nonfunctioning myocardium [9].

### Prognosis

Life expectancy of DMD patients depends primarily on the natural progression of the disease and respiratory insufficiency. However, recent improvements in the treatment of respiratory muscle disorder allow patients to live longer with better respiratory function. The average lifespan is much longer than it has been earlier and, at present, most patients live until the third and even fourth decade of life [10].

### Treatment

According to the 2004 recommendations, the cornerstone of drug therapy in DMD are long-term oral steroids [11]. These recommendations were based on numerous studies which showed the beneficial effects of steroids on the skeletal and respiratory muscle function and progression of heart disease. Moreover, the current guidelines recommend early administration of ACEIs, which delay the progression of LV dysfunction and also decrease cardiac mortality in the long-term follow-up [12]. If ACEIs are not tolerated, alternatively angiotensin receptors blockers can be used. Additionally, adrenergic  $\beta$ -receptor blockade also proved valuable in the improvement of both cardiac symptoms and function. However, there is a paucity of rigorous scientific studies, especially those evaluating major mortality/morbidity endpoints. As in other areas of heart failure, neither diuretics nor digoxin provided any mortality benefits; nevertheless, they are frequently used to alleviate symptoms and eliminate congestion.

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## Dilated cardiomyopathy in a patient with Emery–Dreifuss muscular dystrophy type 2 (laminopathy) (RCD code: III-1A.4b)

Michał Marchel, Agnieszka Madej-Pilarczyk, Irena Hausmanowa-Petrusewicz, Grzegorz Opolski

### Case presentation

A 48-year-old male with a family history of muscular dystrophy and cardiovascular diseases (patient's mother died at the age of 44, presenting dystrophic symptoms, his sister had three ischemic strokes and died suddenly at the age of 46), who actively practices sport as teenager, at the age of 24 was admitted to hospital due to general weakness and a suspicion of myocarditis. At that time, a first-degree atrio-ventricular block was detected.

Eleven years later, at the age of 35, the patient was implanted with an atrioventricular dual-chamber pacemaker because of complete third-degree atrio-ventricular block. Non-sustained supraventricular tachycardia was seen, but no ventricular arrhythmia occurred.

Two years later neurologic examination revealed atrophy and weakness of proximal muscles, spine rigidity, elbow, knee, and ankle contractures; electromyography showed myopathic pattern and morphological analysis of skeletal muscle biopsy was consistent with muscular dystrophy. Clinical presentation, pedigree analysis and diagnostic test justified a suspicion of Emery-Dreifuss muscular dystrophy (EDMD2, autosomal dominant trait of inheritance). Molecular test revealed a heterozygous missense mutation in exon 7 of *LMNA* gene, encoding a nuclear protein lamin A/C, c.1357C>T (p.Arg453Trp), therefore it confirmed the diagnosis of EDMD.

At the age of 40, the atrial standstill phenomenon (concomitant lack of electrical and mechanical activity of the atrial muscle) was found in electrocardiogram. The pacemaker was reprogrammed for the ventricular mode of pacing; the atrial electrode was inactivated (fig. 1). On echocardiography the heart diameters were normal and systolic function was preserved, with left ventricle ejection fraction of 60%. The patient was given anticoagulation treatment with warfarin. Despite electro- and pharmacotherapy one year later the patient experienced ischemic stroke resulted in mild left-sided hemiparesis. Treatment with an ACE-inhibitor, beta-blocker, and statin was introduced.

At the age of 43 the patient was admitted to the hospital because of clinical deterioration with fatigue, mild peripheral edema, and congestion in the lungs.

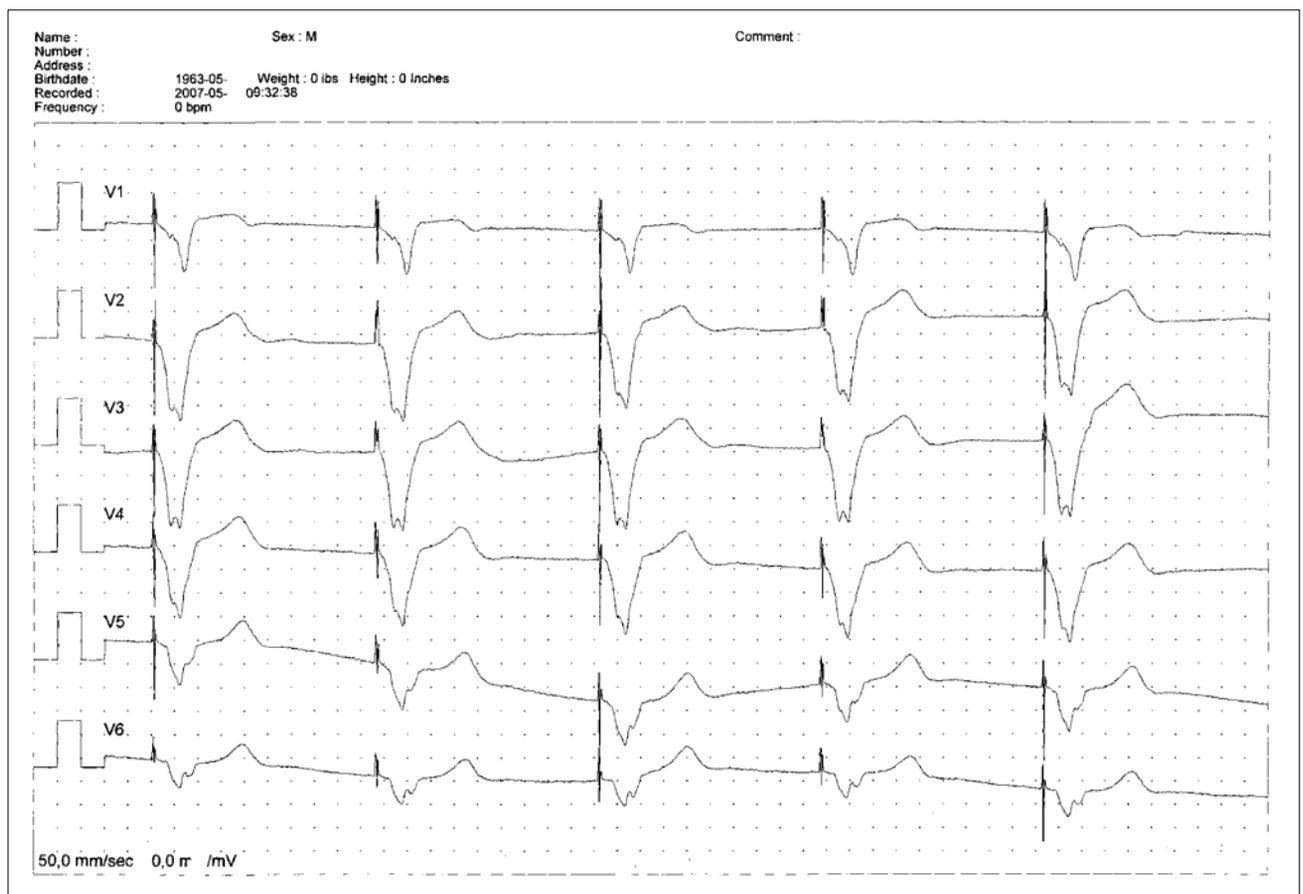


Fig. 1. Electrocardiogram. Ventricular pacing (VVI mode) 60/min, with no P waves (paper speed: 50 mm/s)



**Fig. 2.** Transthoracic echocardiography. Four-chamber apical view. Left ventricular enlargement; pacemaker electrode in the right heart chambers

**Table 1. Cardiac history**

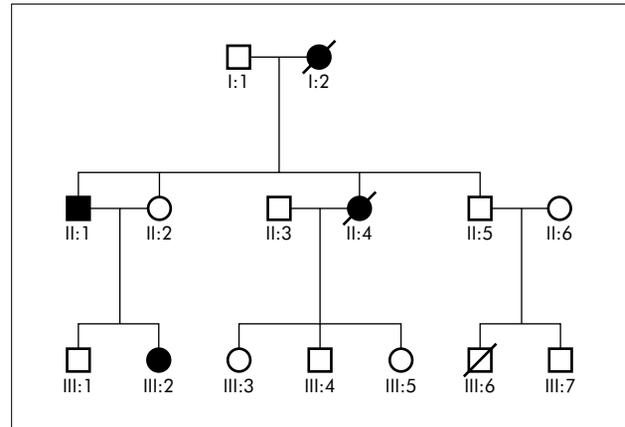
- age 24: AV block (1o) first detected (myocarditis susp.)
- age 35: PM implanted (DDD), complete AVB
- age 40: atrial standstill (VVI), EF 60%
- since 40: anticoagulation
- age 41: ischemic stroke
- age 44: Holter ECG: nsVT, EF 36%
- age 44: CRT-D implanted (no interventions in a 12 month follow-up)
- age 45: CRT-D explanted due to endocarditis (ICD-VR implanted)
- age 46: clinical deterioration, EF 25%, (several adequate interventions of ICD due to VT)

On echocardiography the left ventricle was enlarged (end-diastolic diameter of 63mm) with evidence of significant systolic dysfunction (EF 36%) (fig. 2). Holter monitoring revealed a few episodes of non-sustained ventricular tachycardia. Because of the progression of systolic dysfunction and heart failure symptoms as well as the apparent high risk of sudden cardiac death (laminopathy and positive family history: 2 cases of sudden cardiac death in the patient's first degree relatives: mother and sister), the patient was implanted with a CRT-D device (implantable cardioverter-defibrillator with an option of resynchronization therapy). Unfortunately, the procedure was complicated with left subclavian vein thrombosis and local infection, which required extraction of the device one year later. At that time one chamber ventricular ICD was implanted.

At present, the patient is diagnosed with dilated cardiomyopathy (DCM) in the course of EDMD2, with a complete atrio-ventricular block (AVB). He presents heart failure symptoms, currently NYHA class 3. The patient is pace-dependent (no escape rhythm). He has marked enlargement of the left atrium and of the left ventricle, low EF (25%) and moderate mitral regurgitation. Present pharmacological treatment includes an ACE-inhibitor, beta-blocker, aldosterone antagonist, statin, and warfarin. In this case DCM has a well-defined genetic background, carrying high risk of sudden death.

**Table 2. Family history**

- Patient's mother died suddenly at the age of 44, presenting clinical symptoms of EDMD; unavailable for genetic test
- Patient's sister suffered from 3 ischemic strokes, died at the age of 46; *LMNA* mutation confirmed
- Patient's daughter aged 23 has 1st degree AV block (PR interval 280 ms), no DCM (EF 65%), asymptomatic, already implanted with ICD in primary prevention of sudden cardiac death; *LMNA* mutation confirmed
- Mutation in *LMNA* gene: htz c.1357C>T, p. Arg453Trp (familial)



**Fig. 3.** Pedigree. Autosomal dominant inheritance. Proband (II.1), his mother (I.2), sister (II.4), and daughter (III.2) with confirmed heterozygous mutation in *LMNA* gene, c.1357C>T. Black – affected, white – unaffected, crossed – deceased, circle – female, square – male

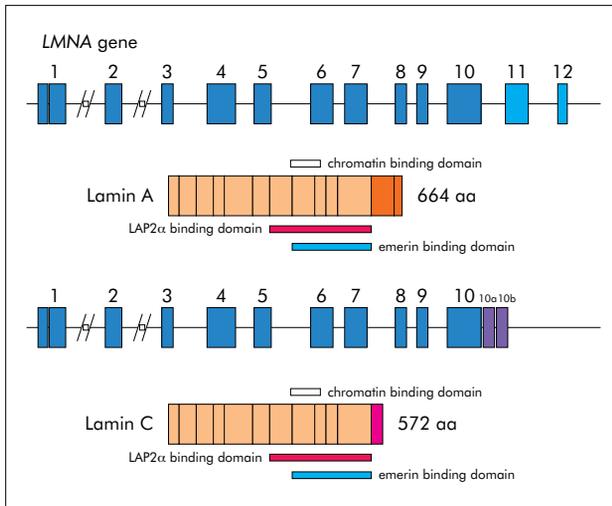
The patient's cardiac history is summarized in Table 1.

Molecular diagnostics confirmed the same mutation in *LMNA* gene, htz c.1357C>T, in the patient's daughter. Cardiological examination at the age of 18 revealed asymptomatic first-degree atrio-ventricular block. She was given perindopril 4 mg. At the age of 23 she was qualified to elective ICD implantation as primary prevention of sudden cardiac death.

The patient's family history is summarized in Table 2, and the pedigree is presented in Figure 3.

## Definition and pathogenesis

Emery-Dreifuss muscular dystrophy (EDMD) is a rare disease, with estimated frequency of below 1:100 000 live births. It is characterized by mild humero-peroneal myopathy, multijoint contractures and cardiac insufficiency with conduction defects. There are at least two types of EDMD: associated with mutation in *EMD* gene encoding emerin (EDMD1), with X-linked recessive trait of inheritance, or with mutations in *LMNA* gene, encoding lamin A/C, with dominant (EDMD2) trait of inheritance. EDMD belongs to a group of so-called laminopathies, rare inherited human diseases, associated with structural/functional defect of genes that encode the nuclear envelope proteins, i.a. lamin A/C (fig. 4). Laminopathies affect tissue of



**Fig. 4.** Lamin A and lamin C are produced by alternative splicing of *LMNA* gene

mesenchymal origin and they include a wide spectrum of clinical phenotypes: Emery-Dreifuss muscular dystrophy [EDMD], limb-girdle muscular dystrophy type 1B [LGMD1b], dilated cardiomyopathy [DCM], familial partial lipodystrophy [FPLD], Hutchinson-Gilford progeria [HGPS], most of them with cardiac involvement (Table 3). Arrhythmias and DCM are the major manifestations of cardiac disease in carriers of *LMNA* mutations. EDMD patients are at high risk of SCD.

## Clinical presentation and prognosis

Emery-Dreifuss dystrophy associated with laminopathy was described at first by Bonne G et al. in 1999 [1]. The first description of a DCM caused by mutations in *LMNA* gene was published in the same year by Fatkin D et al. [2]. The molecular screening included eleven families with dilated cardiomyopathy and atrio-ventricular block; it revealed five novel missense mutations in *LMNA* gene. In natural course of the disease heart failure and sudden deaths were seen. Interestingly DCM in these patients was an isolated disease, as it was not accompanied by skeletal muscle involvement [2]. In a paper by Arbustini E et al. [3] 73 cases of DCM (49 pure, 15 with AVB) were described. Five novel *LMNA* mutations were identified in five families affected by DCM with AVB (5/15: 33%) [3]. The natural history of DCM in laminopathy was presented by Taylor MR et al. in 2003 [4]. After analysis of 49 patients with DCM (40-familial, 9-sporadic) and confirmed laminopathy the authors concluded that overall prognosis was very poor. Event-free survival at the age of 45 was 31% vs. 75% (patients with DCM and laminopathy vs. patients with other DCM, respectively). Four different predictors of possible lamin defect in DCM patients were: skeletal muscle involvement ( $p < 0,001$ ), supraventricular arrhythmia ( $p = 0,003$ ), conduction defects ( $p = 0,01$ ), “mildly DCM, low EF, no LV enlargement” ( $p = 0,006$ ). Sanna T et al. [5] showed in their paper that patients with EDMD2 are at high risk

**Table 3.** Phenotype spectrum in laminopathies

<b>Muscular:</b>
<ul style="list-style-type: none"> <li>■ Emery–Dreifuss muscular dystrophy (EDMD2)</li> <li>■ Dilated cardiomyopathy type 1A (CMD1A)</li> <li>■ Limb-girdle muscular dystrophy type 1B (LGMD1B)</li> <li>■ Congenital muscular dystrophy (L-CMD)</li> </ul>
<b>Peripheral neurogenic:</b>
<ul style="list-style-type: none"> <li>■ Charcot-Marie-Tooth axonal neuropathy type 2B (CMT2B)</li> </ul>
<b>Adiposocytopathies:</b>
<ul style="list-style-type: none"> <li>■ Dunnigan familial partial lipodystrophy (FPLD)</li> <li>■ Metabolic and hormonal disorders with insulin resistance</li> </ul>
<b>Premature ageing syndromes</b>
<ul style="list-style-type: none"> <li>■ Mandibuloacral dysplasia (MAD)</li> <li>■ Atypical Werner syndrome (a-WRN)</li> <li>■ Hutchinson-Gilford progeria (HGPS)</li> <li>■ Restrictive dermopathy (RD)</li> </ul>

of cardiac involvement, which might manifest as supra-ventricular arrhythmias, AVB, ventricular arrhythmias, dilated cardiomyopathy, non-dilated cardiomyopathy, restrictive cardiomyopathy, and sudden death. Pacemaker does not provide full protection [5]. Meta-analysis by van Berlo JH et al. [6], showed that cardiac arrhythmias occurred in 92% of patients over 30 years old, and overt heart failure – in 64% of patients over 50 years old. Forty six percent of patients with DCM and laminopathy died suddenly (SCD). Although 28% of *LMNA* mutation carriers received a pacemaker, the intervention did not alter the rate of SCD [6]. Since the high risk of SCD was already known, Meune C et al. [7] recommend implantation an ICD instead of a classic pacemaker in all patients with laminopathy and AVB or sick sinus syndrome. The authors described 19 patients (mean EF 58%, no VT/VF), 8 of whom (42%) received appropriate ICD therapy (6 VF and 2 VT) and then were observed for approximately 34 months. The authors concluded that an ICD was superior to a pacemaker in patients with cardiac disease associated with mutations in *LMNA* gene [7]. In 2008 the specific risk factors of SCD in cardiomyopathies [8,9] have been described. Passoti M et al. [8] found that asymptomatic carriers of *LMNA* mutations, with no clinical evidence of cardiomyopathy, were at low risk of cardiac events. Multivariable analysis revealed that heart failure in NYHA class III-IV and highly dynamic competitive sports were independent predictors of overall cardiac events. Bivariable Cox model showed that splice site mutations and competitive sports might be a predictors of sudden cardiac death [8]. In 2012 Van Rijsingen IA et al. described risk factors of malignant ventricular arrhythmias in carriers of *LMNA* mutations [9]. In a group of 269 patients with confirmed mutation in *LMNA* gene (median follow-up: 43 months) the authors identified four independent risk factors for malignant ventricular arrhythmias: nsVT, EF <45%, male sex, and non-missense mutations. The probability of cardiac event was increased in patients with at least two risk factors [9].

## Cardiological management in laminopathies

Patients with EDMD or another laminopathy should be carefully observed towards defects of the conduction system, arrhythmias, and systolic or diastolic dysfunction of the left ventricle. Early detection of cardiac conduction abnormalities may be life-saving in patients with cardiomyopathy and confirmed *LMNA* mutation. ACE-inhibitors are recommended in primary prevention of cardiac remodeling before overt cardiac dysfunction occurs. Once cardiomyopathy becomes symptomatic cardiological management follows algorithms of treatment in heart failure. Pharmacotherapy includes ACE-inhibitors, beta-blockers, and aldosterone antagonists. In the primary prevention of SCD, implantation of ICD is recommended, including those patients who require pacing but still do not meet criteria for ICD. The optimal use of ICD in primary prevention of SCD and medical intervention to prevent cardiac damage and to alleviate heart failure symptoms remains unresolved and requires further research.

## Conclusions

Mutations in *LMNA* gene are associated with different types of conduction abnormalities, which occur prior to development of chamber dilatation. Atrial and ventricular arrhythmias are common. Patients with laminopathies should be monitored carefully for atrio-ventricular conduction defects and other arrhythmias [10,11]. The natural course of cardiolaminopathy is aggressive and it often leads to premature death.

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## Cardiac manifestations in a two-generation family with Fabry disease (RCD code: III-2B.2a)

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### Background

Fabry disease (FD), also called angiokeratoma corporis diffusum, ceramide trihexosidosis, and Anderson-Fabry disease, is an X-linked inborn error of metabolism of the glycosphingolipid pathway. It is caused by the deficiency of the lysosomal enzyme, hydrolase  $\alpha$ -galactosidase A, which results in the accumulation and subsequent tissue deposition of globotriaosylceramide, the glycolipid substrate for  $\alpha$ -galactosidase A. The incidence of the disease varies between 1:17 000 to 1:117 000 men in the Caucasian population. The disease is less common among women and, if present, the symptoms are milder. Enzyme replacement therapy of the agalsidase- $\alpha$  or agalsidase- $\beta$  offers a specific treatment for patients with FD.

Clinical manifestation frequently begins in childhood but because it resembles more common diseases, the diagnosis of FD based on symptoms only is challenging. Pediatric patients first show neurological involvement, manifesting as persistent, neuropathic pain of the extremities, (often misdiagnosed as growing pains) and gastrointestinal disorders (diarrhea, nausea, vomiting). In the later stages, other organs are becoming involved causing multiorgan failure, renal insufficiency, cardiovascular impairment, cerebrovascular incidents, cutaneous changes (telangiectasias, angiokeratomas, and lymphedema), malfunction of the sensory organs (cornea verticillata, retinal vascular tortuosity), and other symptom such as anhidrosis, sweating problems, heat collapse, or depression.

### Case Presentation

We report a case of a two-generation family with FD; a 53-year-old man and his 22-year-old daughter who were referred to our department for evaluation and treatment. The father has suffered from severe neuropathic limb pains (precipitated by heat) since childhood. He also had cutaneous changes (angiokeratomas), mostly on the lower back and buttocks, sweating problems (anhidrosis), and visual disturbances. At the age of 28 years, he was diagnosed with hypertrophic cardiomyopathy and, 2 years later, a pacemaker was implanted because of bradycardia. At the age of 47 years, he underwent a cerebrovascular stroke but there were no major neurological consequences and he almost completely recovered. In 2008, he was diagnosed with severe renal insufficiency (proteinuria, hematuria, significantly decreased estimated glomerular filtration rate [eGFR]). Because of suspected amyloidosis, the patient underwent kidney biopsy, which unexpectedly revealed the abnormal deposition of globotriaosylceramide in the glomerular cells. Based on his general symptoms and very low activity of lysosomal  $\alpha$ -galactosidase in leukocytes (0.5 nmol/mg/h), he was diagnosed with FD. In the years 2008–2010, specific treatment with agalsidase- $\alpha$  enzyme was introduced.

The patient's daughter has also suffered from various unspecific symptoms including severe neuropathic limb pain, paresthesia, chronic diarrhea, hearing impairment, and visual disturbances since childhood. She was diagnosed with FD at the age of 19 years when a lower activity of lysosomal  $\alpha$ -galactosidase in leukocytes (2 nmol/mg/h) was confirmed. The genetic tests were performed, which revealed that she was a carrier of c.1118G>A mutation in the *GLA* gene on chromosome Xq22 (reference sequence NM\_000169.2). She has never been on specific enzyme replacement therapy (ERT).

At presentation, the father complained of paroxysmal atrial fibrillation, had gradually increasing dyspnea on exertion, and peripheral edema, while the daughter complained of gradually increasing dyspnea on exertion and palpitations. Apart from mild edema and angiokeratomas on the lower back and buttocks, a physical examination did not reveal any significant abnormalities in the father. There were no pathological findings on a physical examination in the daughter.

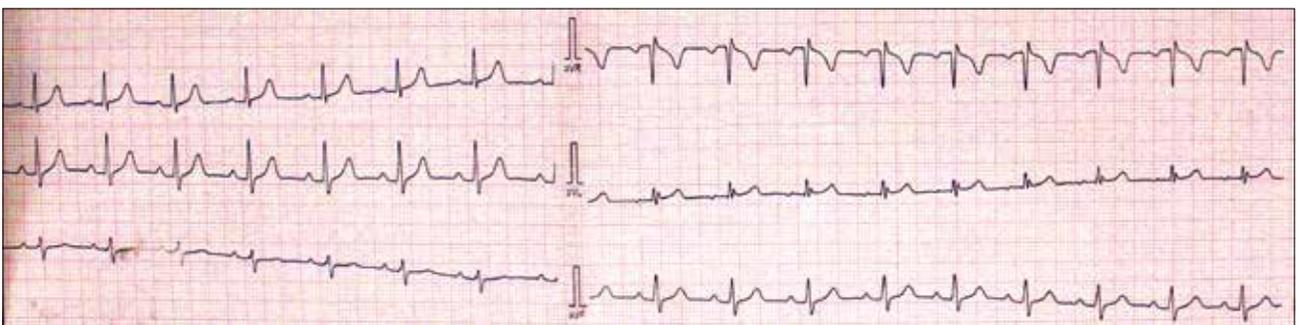
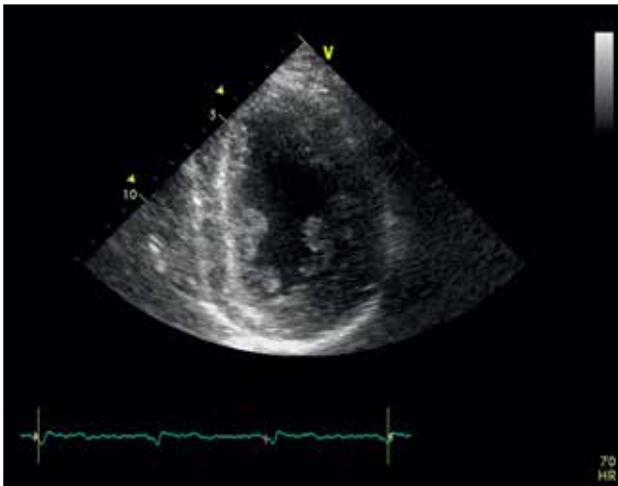


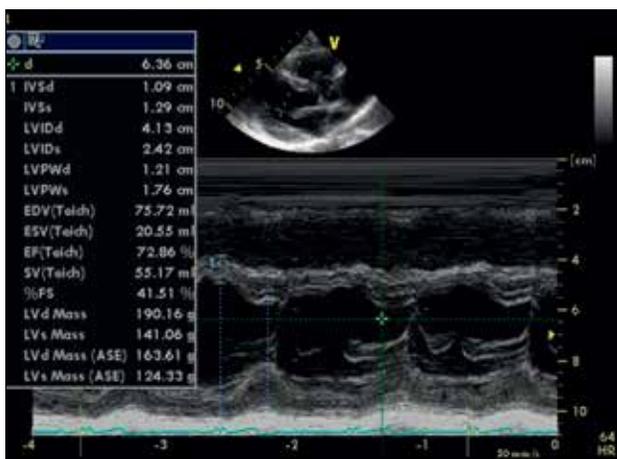
Fig. 1. Electrocardiogram in the patient's daughter. Sinus rhythm with a heart rate of 87/min. No axis deviation



**Fig. 2.** Transthoracic echocardiography of the father. Parasternal long-axis view. Symmetric left ventricular hypertrophy



**Fig. 3.** Transthoracic echocardiography of the father. Parasternal short-axis view. Left ventricle with two-layered structure consisting of the thickened hyperechogenic layer of intracellular glycolipid



**Fig. 4.** Transthoracic echocardiography of the father. Parasternal long-axis view. Mild projection of the left ventricle in the parasternal long axis. Mild hypertrophy of the posterior wall; preserved ejection fraction of the myocardium

A 12-lead electrocardiogram showed a pacemaker rhythm of 60 ppm (the VVIR mode) in the father and no abnormalities in the daughter (fig. 1). Biochemical serum and urine test results were normal in the daughter, while they revealed mild anemia and severe renal insufficiency in the father (creatinine level, 204  $\mu\text{mol/L}$ ; eGFR, 29.9 mL/min). Transthoracic echocardiography in the father revealed significant/severe symmetric left ventricular (LV) hypertrophy (LVH), moderately impaired LV systolic function, as well as characteristic thickened hyperechogenic layer (which may represent intracellular glycolipid deposition in the endocardium and the subendocardial myocardium) and hypoechogenic layer that paralleled the hyperechogenic layer (which may represent either the mildly affected mid-wall myocardium or, possibly, a shadowing artifact due to the intracellular lipid-rich layer) (fig. 2, 3). Transthoracic echocardiography in the daughter revealed mild enlargement of the left atrium, proper LV size with preserved systolic function, and mild thickening of the walls (fig. 4). Cardiac magnetic resonance imaging showed a small area of nonischemic damage of the myocardium on the inferior wall of the heart.

Spirometry revealed mild obstruction in the father. On a neurological examination, the father had normal mental status; he was alert, attentive, and oriented; there was no focal neurological deficit. The ankle reflexes were bilaterally decreased; there were no signs of paresis; sensation was reduced in all 4 extremities (right upper extremity up to two-thirds of the forearm; left upper extremity up to half of the forearm; lower extremities up to half of the thighs). His deep sensation was intact; there were no signs of meningeal irritation.

Therapy with valproic acid (300 mg twice daily) was recommended by a neurologist.

A neurological examination in the daughter revealed that she was aware, alert, and oriented. She complained of the lower back pain. The cranial nerves II through XII and the deep tendon reflexes on the upper extremities were intact. Reflexes in the ankles were absent and sensation was reduced in the right lower extremity (nerve roots, L3–L4). Deep sensation was intact; there were no signs of meningeal irritation. Therapy with carbamazepine (200 mg twice daily) was recommended by a neurologist. An ophthalmology examination revealed the characteristic finding of cornea verticillata (corneal deposits). Visual field deficits were also observed (white and red color). Both the father and daughter presented signs of mild depression.

## Discussion

### Epidemiology

FD belongs to a group of lysosomal storage disorders, which comprises at least 50 genetically distinct diseases. The exact prevalence of FD is unknown and is estimated to range from 1:17 000 to 1:117 000 in Caucasian men.

## Genetics

The basis of FD is the deficiency of the lysosomal enzyme, hydrolase  $\alpha$ -galactosidase A, which is responsible for the cleavage of the galactose from globotriaosylceramide (Gb3). The lack of this enzyme is a consequence of the mutation in the *GLA* gene, mapped to the long arm (Xq22.1) of the X chromosome. More than 500 mutations in this gene have been identified so far, most of which are private mutations. The progressive accumulation of Gb3 in various cells and tissues, especially endothelium, vascular smooth muscles, autonomic ganglia, dorsal root ganglia, renal glomerular, tubular and interstitial cells, and cardiomyocytes, is probably the main cause of the disease's manifestations. However, it is postulated that Gb3 deposition may be only partially responsible for clinical manifestations, and yet unexplained mechanisms likely contribute to the pathology.

## Diagnosis

Considering the effective ERT, although not widely available, the early diagnosis can favorably alter the natural course of the disease. However, the initial clinical manifestation is highly variable, especially in the pediatric setting, which makes early identification of FD difficult. To confirm the clinical suspicion of FD, the measurement of the activity of  $\alpha$ -galactosidase in plasma or leukocytes is regarded as a laboratory reference method. The measurement of plasma Gb3 has also been performed but it is considered inferior owing to difficult and long laboratory procedures. A definitive diagnosis is established on the basis of molecular analysis and sequencing of the *GLA* gene. Considering the small size of the *GLA* gene, a direct molecular analysis is relatively simple and provides information on the type of *GLA* gene mutation.

## Clinical manifestations

As deposition of Gb3 can occur in virtually all cells and tissues, FD is characterized by a wide array of clinical symptoms. This clinical spectrum ranges from highly symptomatic homozygous men, who have no residual  $\alpha$ -galactosidase A activity, to the seemingly asymptomatic heterozygous women.

Kidney involvement is one of the major features of FD and is observed in at least 50% of the men and 20% of the women. The severity of renal pathology usually increases with age. Kidney impairment typically begins in the second or third decade of life and is probably the result of the accumulation of Gb3 in renal cells, including glomerular endothelial, mesangial, and interstitial cells, in podocytes, and in the epithelium of the Henle's loop or in the distal tubules. This leads to the destruction of functional nephrons and, eventually, to progressive chronic kidney disease (CKD). In untreated patients, CKD may progress to end-stage renal failure, which is the main cause of death in patients with FD.

One of the first and most frequent symptoms is an unspecific pain in various areas, particularly in the limbs, which is a consequence of nerve fiber damage of both the systemic and autonomic systems. It is

estimated that 60% to 80% of young boys experience various degrees of pain in their first years of life. Most patients are affected by two different types of pain. The first one is called "Fabry crises"; it is described as episodic and is characterized by burning pain of the extremities, frequently radiating to the other parts of the body. The second type is chronic pain with concomitant paresthesia.

Unspecific gastrointestinal disorders, such as abdominal pain, diarrhea, nausea, vomiting, or irritable bowel syndrome, also occur early in childhood and persist during adolescence. They are probably related to the deposition of Gb3 in the autonomic ganglia of the bowel and mesenteric blood vessels.

The typical skin manifestations are angiokeratomas – small reddish skin lesions commonly found on the buttocks, lower back, umbilicus, and upper thighs or groins. Additionally, telangiectasia and subcutaneous edema can also be observed.

The sensory organs such as the eyes and ears can be affected with the corneal and lenticular changes – "cornea verticillata" (dystrophy of cornea) – causing visual impairment as well as symptoms of tinnitus, vertigo, and even loss of hearing.

Cerebrovascular involvement is characterized by a wide variety of signs and symptoms, including headache, vertigo, dizziness, transient ischemic attack, ischemic stroke, and dementia.

Patients with FD also suffer from respiratory disorders due to airway obstruction and they can present with dyspnea on exertion, chronic cough, and wheezing. The majority of patients have some degree of osteopenia or osteoporosis, which may lead to spontaneous bone fractures. Finally, patients with FD complain about abnormal sweating or overheating during exercise as well as chronic fatigue and difficulty in weight gaining.

## Cardiac involvement

The frequency of cardiac involvement increases with age, and approximately half of the adults with FD have some degree of cardiovascular abnormalities. The hallmark is LVH, followed by conduction disturbances, coronary artery disease, aortic and mitral valve insufficiency, and aortic root dilatation. The degree of LVH correlates with the severity of the disease. Importantly, LVH is usually concentric (symmetric) in contrast to asymmetric LVH, typically observed in hypertrophic cardiomyopathy. However, both systolic and diastolic functions are relatively preserved and overt heart failure symptoms are rarely observed. Although not always present, the echocardiograms typically reveal two-layered LV structure, comprising of a thickened hyperechogenic layer of intracellular glycolipid deposition in the endocardium and epicardium and an inner hypoechogenic layer of deposition-spared myocardium. Moreover, LVH may also result from progressive myocardial fibrosis, which almost always starts in the mid-myocardium of the posterior lateral wall. The intensity of fibrotic process determines the development of diastolic and, at later stages, systolic dysfunction. Arrhythmias

and conduction disturbances are the consequence of lipid deposits in virtually all components of the heart conduction system. Moreover, an imbalance between sympathetic and parasympathetic nervous systems may also increase arrhythmic problems. Apart from the signs of LVH, typical findings on an ECG include a short PR interval and prolonged QRS complex often associated with the right bundle branch block pattern. Although almost half of the patients complain about angina-type chest pain, the results of coronary angiography are normal or near-normal in the majority of the cases. The possible explanation of those symptoms is endothelial dysfunction, which leads to the impairment of coronary micro-circulation. The valvular insufficiency is only modest in most of the cases and results from the accumulation of globotriaosylceramide in the valve tissues. Progressive dilatation of the aortic root may potentially have life-threatening consequences. Furthermore, approximately two-thirds of the patients also have associated changes in right ventricular morphology and function, such as hypertrophy and diastolic dysfunction. The ERT may have a beneficial effect on the heart just as it has on the kidneys and other affected organs. It was observed to reduce LVH, improve cardiac function, and clear endothelial lipid deposits.

## Management

The optimal management of FD involves conventional treatment, ERT, and adjunctive therapies. The cornerstone of the contemporary therapy is a multidisciplinary approach. One of the most bothersome symptoms in FD is pain, which can be managed in several ways. The neuropathic pain is best avoided by eliminating frequent triggers such as physical exertion or temperature shocks. From the wide array of painkillers, nonsteroidal anti-inflammatory drugs should be avoided because they are ineffective and potentially harmful for the kidneys. The widely used drugs in FD are carbamazepine, oxcarbazepine, gabapentin, pregabalin, and phenytoin. Gastrointestinal symptoms are addressed with metoclopramide and histamine receptor type 2 antagonists. Angiotensin-converting-enzyme inhibitors (ACEIs) or, if not tolerated, angiotensin receptor blockers are used in proteinuria and more advanced stages of CKD. Because CKD progresses during the course of FD, many patients require dialysis or even renal transplantation. Use of aspirin or, if not tolerated, clopidogrel is recommended for stroke prevention. In the case of stroke despite antiplatelet therapy, oral vitamin K antagonists are the treatment of choice. B-group vitamins, particularly B<sub>6</sub>, B<sub>9</sub>, and B<sub>12</sub> are also recommended for patients with cerebrovascular involvement. In the case of exertional angina, the first-line therapy is calcium channel blockers, followed by  $\beta$ -blockers. Device cardiac therapy with permanent pacemaker and cardioverter-defibrillator is increasingly popular in patients with severe conduction disturbances to prevent sudden cardiac death

in the case of malignant ventricular arrhythmias. Amiodarone should be avoided because it may interfere with lysosomal metabolism. Although overt heart failure is rare in FD, if present, it should be managed according to the current guidelines with ACEIs and  $\beta$ -blockers as the backbone of therapy.

## Enzyme replacement therapy

Since 2001, specific ERT, using recombinant human  $\alpha$ -galactosidase A, has become the most efficient therapy, which addresses the underlying defect of FD. The guidelines on the ERT vary greatly between individual countries, mainly because of the high cost of treatment. It is generally accepted that patients with renal manifestations of FD should be started with ERT as soon as the diagnosis is confirmed. Moreover, ERT is also recommended in male and female carriers with substantial nonrenal manifestations, particularly cardiac involvement. At present, there are two enzyme preparations available: agalsidase- $\alpha$  (Replagal<sup>®</sup>), registered for use at a dose of 0.2 mg/kg twice a week and agalsidase- $\beta$  (Fabrazyme<sup>®</sup>) with a dose of 1.0 mg/kg twice a week. According to the meta-analyses, treatment with agalsidase- $\alpha$  remarkably slows down the progression of renal insufficiency in patients with mild-to-moderate nephropathy and proteinuria. However, this treatment did not show any significant benefit in patients with more advanced nephropathy. As for cardiac involvement, numerous studies have shown a significant reduction in the LV mass, measured by magnetic resonance imaging after 6 months of therapy with agalsidase- $\alpha$ . Moreover, patients with the highest degree of LVH at baseline had the largest decrease in the LV mass. Similarly, treatment with agalsidase- $\beta$  also improved the regional LV structure and function. However, the effectiveness of ERT on other organs, including the central nervous system, has not yet been established and is still under research.

## Prognosis

Male patients, who are more severely affected, have significantly reduced survival. The life expectancy of FD patients is reduced by approximately 20 years for men and 10 years for women compared with the general population. The median survival is less than 50 years. The main contributors of death in untreated patients are renal failure, cerebrovascular and cardiovascular incidents, including myocardial infarctions, cardiomyopathy, and pulmonary embolism.

## Screening

Screening for FD can be performed by the measurement of plasma  $\alpha$ -galactosidase A levels in patients

with unexplained LVH, particularly in those with binary appearance of the LV endocardial border and in those who are diagnosed with hypertrophic cardiomyopathy or have a family history consistent with X-linked disease.

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## Desmin-related restrictive cardiomyopathy (RCD code: III-3E)

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### Background

Restrictive cardiomyopathy (RCM) is an uncommon form of congestive heart failure (HF) of heterogeneous origin, in which diastolic dysfunction of one or both ventricles is the main pathophysiological feature [1]. Desmin-related myopathy (DRM) is a genetic skeletal and cardiac muscle disorder, caused by a mutation of the desmin gene (DES) [2]. The phenotype of desmin-related cardiomyopathy is characterized by a variable degree of neurological and cardiac involvement [3]. The course of DRM varies but inevitably leads to premature death [4].

### Case presentation

A 33-year-old man with signs of chronic HF and the history of several episodes of severe cardiopulmonary decompensation was admitted to the Centre for Rare Cardiovascular Diseases at the John Paul II Hospital in Krakow, Poland, for cardiac evaluation in March 2012. He was physically active until cardiac disorder was first diagnosed in 2007 after an acute HF episode. RCM was initially suspected on the basis of cardiac echocardiography. Subsequent coronary angiography revealed no abnormalities in the coronary arteries. Holter monitoring showed multiple ventricular and supraventricular extrasystoles and first-degree atrioventricular block. Unremarkable changes on cardiac magnetic resonance imaging (CMR) were found indicating possible myocarditis or arrhythmogenic right ventricular dysplasia. Follow-up CMR was scheduled after 3 months. Two months later, another decompensation occurred with an Adams–Stokes attack due to a newly developed third-degree atrioventricular block. A cardiostimulator was subsequently implanted.

On admission to the Centre in March 2012, he was hemodynamically unstable with signs of pulmonary congestion (class II according to the Killip classification) and peripheral edema with ascites. He required high doses of diuretics. Laboratory work-up showed elevated levels of N-terminal pro-B-type natriuretic peptide, liver enzymes, troponin T, creatine kinase (CK) and CK-MB, and myoglobin (Table 1). An echocardiographic evaluation revealed signs of RCM together with fluid overload and mildly decreased left ventricular ejection fraction of 40% (Table 2) (fig. 1, 2). His exercise capacity was considered poor. He walked a distance of 440 meters in the 6-minute walk test and reached

**Table 1. Biochemical blood analysis**

Parameter	Value
NT-proBNP	4739 pg/mL
Liver function test	AST: 48 U/L, ALT: 41 U/L, albumin: 28.1 g/L [35–52], INR: 1.14
hsTnT	0.305 ng/mL [<0,014]
CK	239 U/L [<190]
CKMB	36 U/L [<24]
Myoglobin	157 [23–72]
NT-proBNP – N-terminal pro-B-type natriuretic peptide, AST – aspartate transaminase; ALT – alanine transaminase, CK – creatinine kinase, CKMB – creatinine kinase MB isoenzyme, hsTnT – high sensitive troponin T	

**Table 2. Echocardiographic parameters**

Parameter	Value
LVdD/LVdS	45/38 mm
IVSdD/IVSdS	8/10 mm
PWdD/PWdS	9/10 mm
RVd/(4ChV)	33/50 mm
LAd/LAa	42 × 43 × 58 mm/28 cm <sup>2</sup>
RAd/RAa	50 mm/32 cm <sup>2</sup>
LVEF	40%
Mitral flow	E: 0.81 m/s A: 0.31 m/s – E/A: 2.6 E': 0.08 m/s – E/E': 16
RVSP	22 mm Hg
IVC	18 mm, no respiratory collapse
LVdD – left ventricular diastolic diameter, LVdS – left ventricular systolic diameter, IVSdD – interventricular septum diastolic diameter, IVSdS – interventricular septum systolic diameter, PWdD – posterior wall diastolic diameter, PWdS – posterior wall systolic diameter, RVd – right ventricle diameter, 4ChV – four-chamber view, LAd – left atrium diameter, LAa – left atrium area, LVEF – left ventricular ejection fraction, RVSP – right ventricular systolic pressure, IVC – inferior vena cava	

9 mL/(kg × min) of oxygen consumption in the cardiopulmonary exercise test. The patient complained of leg weakness; moreover, he had difficulty walking and had elevated levels of muscle enzymes (CK, myoglobin). He was consulted by neurologists, who confirmed the suspicion of myopathy and recommended electromyography with peripheral muscle biopsy. Peripheral muscle biopsy was preferred over endomyocardial biopsy because of cardiac wall thinning. Prior to the biopsy, the patient underwent right heart catheterization, which revealed elevated right atrial, right ventricular, and left ventricular end-diastolic pressures (14 mm Hg, 15 mm Hg, and

19 mm Hg, respectively). A severely decreased cardiac index of 1.35 mL/kg/min was also reported. A pathological examination of the biopsy confirmed the diagnosis of myopathy most probably as a form of myofibrillar myopathy (fig. 3). For a more precise diagnosis, a genetic evaluation was performed, which revealed desmin encoding gene mutation located in exon 3, chromosome 2 (c.735+1G>A).

Medical treatment included high doses of diuretics: furosemide (160 mg once daily), spironolactone (100 mg once daily), torasemide, (15 mg once daily), and hydrochlorothiazide (25 mg once daily). Despite optimal medical treatment, the patient's clinical condition was gradually deteriorating. He was consulted by a heart transplant team which decided against an urgent heart transplantation because of severe peripheral muscle myopathy. He died soon after owing to further cardiopulmonary deterioration.

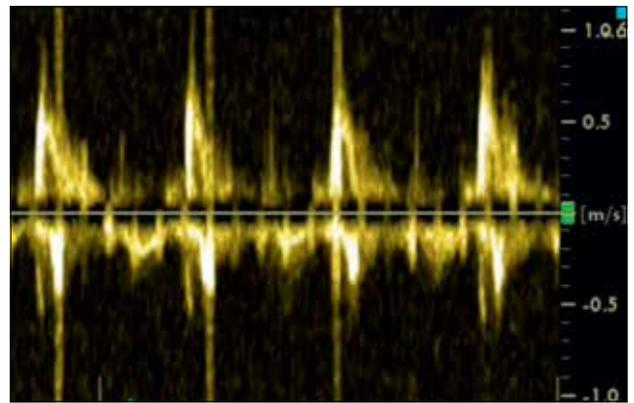
## Discussion

### Classification

RCM is an uncommon form of congestive HF with predominant dysfunction of the cardiac muscle. Diastolic dysfunction of one or both ventricles is the main pathophysiological feature of RCM [5]. Restricted ventricular filling is caused by reduced myocardial compliance, which leads to an increase in ventricular pressure with only a small increase of ventricular volume. Although ventricular systolic performance is usually intact, a mild-to-moderate decrease may be observed in the course of the disease. Wall thickness tends to be normal but in some cases may also be increased [1]. Typically, normal-size ventricles with markedly dilated atria and no signs of pericardial disease are major morphological findings.

Although, RCM represents a heterogeneous condition, it is grouped together with classic forms of cardiomyopathies according to the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases guidelines [6]. At the same time, the American Heart Association recognizes RCM as mixed genetic and nongenetic pathology, reflecting its etiological complexity [7]. Contrary to the other forms of cardiomyopathies classified according to the anatomical criteria, RCM is essentially a functional distinction. Therefore, a correct diagnosis of RCM may often cause difficulties as the restrictive physiology may be exhibited in numerous morphological variants.

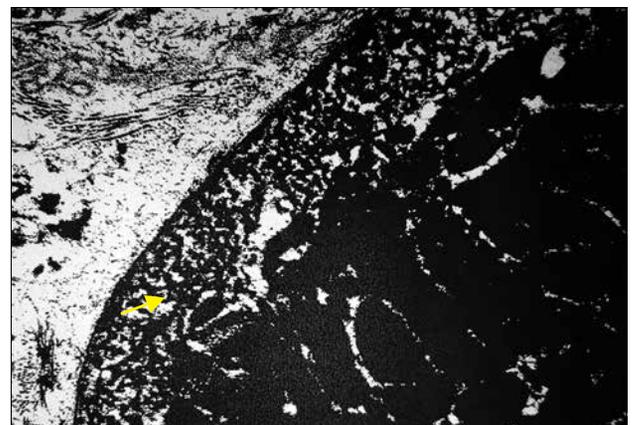
Myocardial inflammation, infiltration, and fibrosis result in the development of restrictive myocardial disease [8]. These may be caused by infiltrative pathologies such as amyloidosis, sarcoidosis, storage diseases (including hemochromatosis or Fabry disease), endomyocardial disorders (including hypereosinophilic syndrome, endomyocardial fibrosis, carcinoid heart disease, or anthracycline toxicity), and noninfiltrative pathologies (including idiopathic cardiomyopathy, scleroderma, or pseudoxanthoma elasticum). By far, RCM is secondary to systemic disorders.



**Fig. 1.** Transthoracic echocardiography. Transmitral Doppler. Restrictive mitral flow



**Fig. 2.** Transthoracic echocardiography. Apical four-chamber view. Enlargement of both atria. LV – left ventricle, RV – right ventricle, LA – left atrium, RA – right atrium; right atrial pacemaker electrode (arrow)



**Fig. 3.** Electron microscopic study. Cross-section of the peripheral muscle biopsy. Subsarcolemmal and intra-myofibrillar electron-dense deposits (arrow)

### Epidemiology

RCM appears to be one of the least common cardiomyopathies. Given the variety of causes, its true prevalence occurs to be vastly diverse. Cardiac amyloidosis accounts for the majority of RCM cases worldwide,

whereas endomyocardial fibrosis predominates in tropical regions [1].

The actual epidemiology of idiopathic RCM is unclear. In a nationwide survey performed in Japanese hospitals, a crude prevalence of 0.2% per 100 000 population was reported [9]. Among 167 recipients of cardiac transplantation from Italy, RCM was diagnosed only in 0.6% [10]. There are several studies available concerning the epidemiology of RCM in pediatric population, which have reported that RCM accounts for 2% to 5% of all pediatric cardiomyopathies with a total annual incidence rate of 0.03 per 100 000 children [11–14].

### Clinical manifestations

Clinically overt RCM may develop at any age. It has been more frequently observed in women than in men with the approximate 1.5:1 ratio [15]. Patients with RCM usually complain of gradual loss of exercise capacity and progressively worsening shortness of breath. In a retrospective study conducted by Mayo Clinic and Mayo Foundation researchers, dyspnea was present in 71% of the patients [15]. Other symptoms included edema (46%), palpitations (33%), fatigue (32%), and chest pain (22%). Jugular venous distension with positive Kussmaul's sign was the most common physical finding (52%) followed by systolic murmur (49%), third heart sound (27%), pulmonary rales (18%), and ascites (15%). As many as one-third of the patients may present with thromboembolic complications [16].

### Diagnosis of restrictive cardiomyopathy

Electrocardiographic abnormalities are unspecific and often depend on the stage of the disease and the underlying cause. Atrial fibrillation is common, affecting up to 74% of the patients [15]. Also, nonspecific ST-T wave changes are frequent (75%). Premature ventricular and supraventricular beats, atrioventricular block, or intraventricular conduction abnormalities are observed in up to 20% of the patients.

Chest radiography reveals enlargement of the heart in most cases, with the cardiothoracic ratio exceeding 55%. Pulmonary congestion, interstitial edema, or pleural effusions are also commonly observed. Pleural calcifications typical for constrictive pericarditis are not usually seen on chest radiography [15].

Echocardiography is an elementary tool for diagnosing restrictive hemodynamics. In many cases, it may be helpful for distinguishing the initial cause of the observed restrictive physiology as well as for differentiation from constrictive pericarditis. The enlargement of both atria along with nondilated, well-contracting ventricles and Doppler signs of diastolic dysfunction are the most characteristic findings [17]. About 80% of the patients have mild-to-moderate mitral and tricuspid regurgitation. Doppler derived indices presenting a restrictive filling pattern include increased early diastolic filling velocity ( $E \geq 1$  m/s), decreased atrial filling velocity ( $A \leq 0.5$  m/s), increased E/A ratio ( $\geq 1.5$ ) invariably during respiration, decreased deceleration time ( $\leq 150$  ms), and decreased isovolumic relaxation time ( $\leq 70$  ms) [18]. The evaluation of the pulmonary vein or hepatic vein flow shows lower systolic than diastolic

forward flow and increased reversal of diastolic flow after atrial contraction. Additionally, tissue Doppler imaging reveals decreased early annular diastolic velocity ( $E' \leq 7$  cm/s) and increased E/E' ratio ( $\geq 15$ ) indicating elevated left ventricular filling pressure [18].

A hemodynamic profile obtained during cardiac catheterization typically presents with deep and rapid early diastolic decline in ventricular pressure with a rapid rise to a plateau, the so called dip-and-plateau pattern or square root sign [1]. End-diastolic equalization or near-equalization of ventricular pressure, together with elevated pulmonary wedge and right atrial pressure, are also characteristic findings in RCM. As a consequence, a decrease in the cardiac index may be observed [15].

To determine the causative factor of observed restrictive myocardial disease, endomyocardial biopsy may be necessary. A pathological evaluation of specimens demonstrates patchy endocardial and interstitial fibrosis with increased collagen deposition and compensatory myocyte hypertrophy [19]. The presence of eosinophilic infiltrates, amyloid, or iron depositions helps establish the final diagnosis. To detect underlying diseases, immunofluorescent staining, immunohistochemical studies, and electron microscopy are often required [20].

Use of magnetic resonance imaging in patients with RCM provides valuable information regarding cardiac morphology and function. It is the gold standard for quantification of heart chambers and hemodynamics with standardized protocols [21,22]. Complementary to echocardiography and invasive studies, cardiac magnetic resonance imaging is a useful tool in assessing restrictive physiology [23–25]. Tissue characterization techniques enable to differentiate between particular types of RCM such as amyloidosis, sarcoidosis, or hemochromatosis as well as to detect signs of inflammation and fibrosis [22,23].

### Desmin-related myopathy

DRM, also called desminopathy (OMIM #601419) belongs to a group of genetically determined myofibrillar myopathies [2]. As a chronic neuromuscular disorder, desminopathy is caused by DES mutation (OMIM \*125660). Desmin, a 53-kDa intermediate filament of the myocardial, skeletal, and smooth muscles, clasps myofibrils and the sarcolemma in the region of Z discs. This makes the contracting apparatus stable and thus enables the normal function of the sarcomere [26]. Over 50 DES mutations have been reported, the majority of which are missense mutations of autosomal dominant inheritance pattern [27]. However, several cases of de novo mutations or autosomal recessive inheritance pattern have also been described [28]. Defect of any of the four main domains results in the accumulation of insoluble subsarcolemmal and intracytoplasmic aggregates leading to myocyte death and consequent fibrotic replacement [29]. Detection of granulo-filamentous material in histopathological, immunohistochemical, or electron microscopic studies of myocardial biopsy samples is considered a morphological hallmark of desminopathy [30].

Detailed epidemiology of DRM is currently unknown. The prevalence of DES mutation in a study of

116 families and 309 additional individuals with dilated cardiomyopathy was around 2% [31]. In another investigation of 35 Spanish families with myofibrillar myopathy, 11 were DES mutation carriers [32].

The age of onset typically varies between the second and fourth decade of life [4]. No major sex differences have been reported; however, male heterozygous mutation carriers might be more prone to develop cardiac manifestations [33]. Clinical manifestations include skeletal myopathy, cardiac abnormalities, conduction disorders, or various types of arrhythmias [4]. Typically, skeletal muscle involvement is most prominent in the distal parts of the lower limbs with slow progression to the proximal and upper limbs, trunk, neck, or facial muscles. The respiratory muscles may also be affected leading to respiratory failure and death [34]. In a meta-analysis conducted by van Spaendonck-Zwarts et al. [4], the signs of skeletal muscle disease were present in 74% of the patients with DES mutation. Distal muscle weakness was reported in 27% of the cases, proximal in 6%, and combined proximal and distal in 67%. The elevated levels of CK in mutation carriers were observed in 57% of the individuals, of whom 91% had less than a 4-fold increase, showing the limited availability of CK as a diagnostic marker. One-third of the patients had normal CK levels. Isolated neurological signs were present in 22% of the carriers and cardiac signs also in 22%. A combination of neurological and cardiac symptoms was observed in 50% of the cases. Cardiomyopathy was detected in half of the patients: dilated cardiomyopathy in 17%, restrictive in 12%, and hypertrophic in 6%. Around 60% of DES mutation carriers had cardiac conduction disease or arrhythmias including atrial fibrillation, premature ventricular beats, or ventricular tachycardia. Atrioventricular block was observed in up to 50% of DRM cases indicating it as an important feature of the disease. A pacemaker was implanted in all patients with conduction disorders, whereas only 4% of all patients had an implantable cardioverter-defibrillator implanted. Death was reported in 26% of the cases at a mean age of 49 years. Documented causes of death in both studies were sudden cardiac death, HF, respiratory insufficiency, chest infection, and iatrogenic complications of cardiac treatment.

Diagnosis of DRM requires a multidisciplinary approach. The presence of neuromuscular signs should prompt neurological investigation including a thorough physical examination, level of muscle-specific enzymes, needle electromyography, and muscle biopsy with subsequent ultrastructural evaluation [34]. Coexistence of cardiac involvement including cardiomyopathy, atrioventricular conduction disorders, or other types of arrhythmia shown on echocardiography or magnetic resonance imaging is often indicative of DRM [35]. The final diagnosis can be established based on detection of DES mutation. No specific therapy is currently available. Symptomatic treatment of HF is required. Cardioverter-defibrillator or pacemaker implantation can be life-saving. In some cases, heart transplantation may be needed although careful consideration is necessary.

## Our management strategy

Since there is no DRM-specific therapy available, the patient was treated symptomatically according to the European Society of Cardiology guidelines for the management of HF [36]. He required high doses of diuretics. An angiotensin-converting-enzyme inhibitor (ramipril, 2.5 mg once daily) and  $\beta$ -blocker (carvedilol, 3.125 mg twice daily) were administered. He was considered for urgent heart transplantation based on a few reports of successful transplantation in patients with inherited myopathies and end-stage cardiomyopathy, but due to severely impaired neuromuscular function he was rejected [37].

## Conclusion

The coexistence of RCM, peripheral muscle weakness, and conduction disorders, especially atrioventricular block, must prompt investigation towards DRM. A thorough multidisciplinary evaluation by a neurologist, cardiologist, surgeon, pathologist, and geneticist, is necessary to determine the proper management of these patients.

## Acknowledgement

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## Long-term follow-up of arrhythmogenic right ventricular cardiomyopathy (RCD code: III-4A)

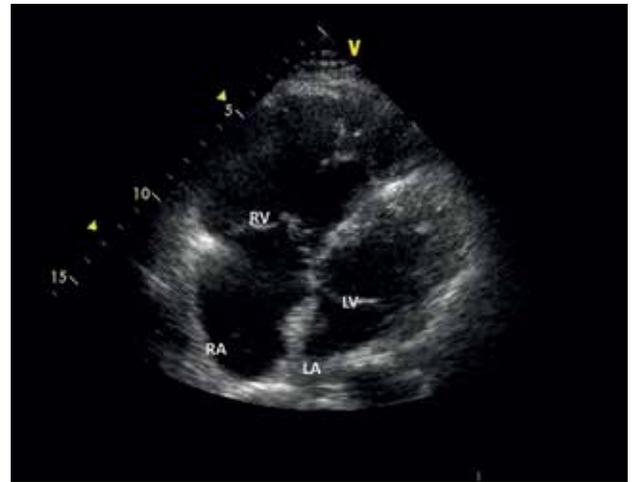
Paweł Rubiś, Jacek Łach, Jacek Bednarek, Jakub Stępniewski, Wiesława Tracz, Piotr Podolec

### Background

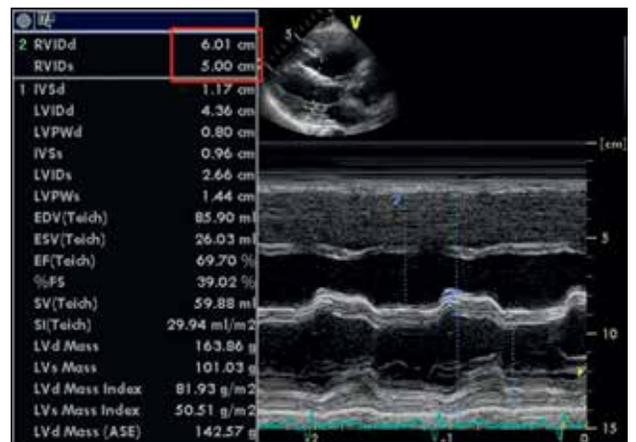
Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare myocardial disease. It results from the replacement of cardiomyocytes by fibrous and fatty tissue, which leads to dilatation and impaired contraction of the right ventricle (RV) and electrical instability. ARVC is a disease of the desmosomes, which serve as cell-to-cell junctions. The cardinal symptoms of ARVC include palpitations, dizziness, and syncope.

### Case presentation

We present long-term follow-up of a 33-year-old man with all typical features of ARVC. The disease first manifested itself at the age of 25 years with fast palpitations and chest discomfort in a previously well and active individual. The patient presented to the emergency department after a few hours of persisting symptoms. An electrocardiogram (ECG) showed ventricular tachycardia (VT, 200/min) of left bundle branch block (LBBB) morphology. Because the patient was hemodynamically stable, pharmacological cardioversion with intravenous amiodarone was attempted but was ineffective. Successful restoration of the sinus rhythm was achieved by electric cardioversion. No abnormalities were detected on echocardiogram and the patient was discharged without further examination. He remained asymptomatic until another episode of palpitation about 1 year later. Arrhythmia was managed in the same way; however, this time slight enlargement of the right ventricle (RV) was noted on echocardiogram. He was discharged on sotalol (40 mg twice daily) and had an outpatient visit scheduled in a reference center; however, he did not show up. A few months later, he started to complain of recurrent palpitations and occasional dizziness. Eventually, he was urgently hospitalized because of cardiogenic shock caused by VT. Urgent electrical cardioversion was performed, which restored the sinus rhythm and stabilized the patient's condition. On echocardiogram, progressive dilation and moderate systolic impairment of the RV was noted. This time, the patient was transported to the tertiary center for extensive cardiac work-up. On ECG, the sinus rhythm with T-wave deep inversion in leads  $V_1$  through  $V_3$  as well as the relative prolongation of QRS duration in leads  $V_1$  through  $V_3$  in comparison with leads  $V_4$  through  $V_6$  ( $(V_1 + V_2 + V_3)/(V_4 + V_5 + V_6)$



**Fig. 1.** Transthoracic echocardiography. Apical four-chamber view. Enlargement of the right ventricle. RV – right ventricle, LV – left ventricle, RA – right atrium, LA – left atrium

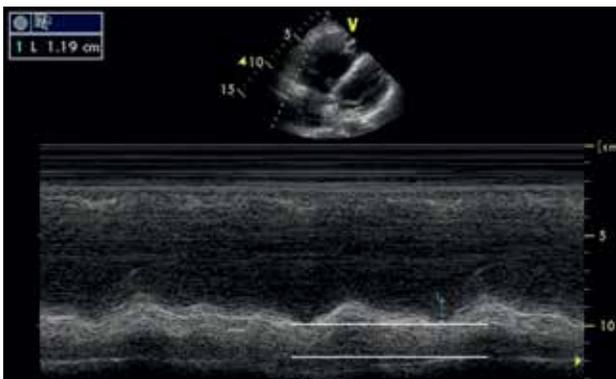


**Fig. 2.** Transthoracic echocardiography. Parasternal long-axis view. Dilatation of the right ventricle. In diastole: 6 cm, in systole: 5 cm. The rest of the measurements within the reference range

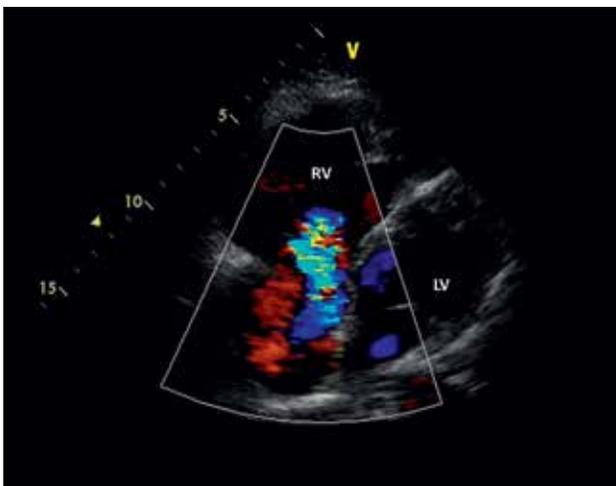
equaled 1.23. On echocardiogram, a severely dilated RV with systolic dysfunction, severe tricuspid regurgitation, but normal RV systolic pressure alongside normal left ventricular (LV) diameter with preserved systolic function, were noted (fig. 1–5). Cardiac magnetic resonance imaging (MRI) confirmed dilated, thinned, and hypocontractile RV with an increased diameter of the RV outflow tract (RVOT) as well as patchy areas of late gadolinium enhancement on the RV free anterior wall. Based on these findings, the diagnosis of ARVC was made and, considering recurrent symptomatic VT (fig. 7, 8), the decision was made to refer the patient for implantable cardioverter-defibrillator (ICD) implantation. Because the patient is left-handed, a single-chamber ICD was implanted on the right side. However, it occurred that the patient did not tolerate ventricular stimulation well and recurrent conduction 1:1 was occasionally detected. Therefore, the device was replaced with a dual-chamber ICD and second lead was placed in the right atrium. The next 2 years were uneventful and the patient remained in a good physical condition. However, almost 2 years after dual-chamber



**Fig. 3.** Transthoracic echocardiography. Parasternal short-axis view. Enlargement of the right ventricle. RV – right ventricle, LV – left ventricle



**Fig. 4.** Transthoracic echocardiography. Apical four-chamber view. M-mode presentation of the tricuspid annular plane systolic excursion



**Fig. 5.** Transthoracic echocardiography. Apical four-chamber view. Enlargement for the right ventricle and moderate tricuspid regurgitation. RV – right ventricle, LV – left ventricle

ICD implantation, the patient was urgently readmitted to the hospital due to acute inflammation of an ICD pocket. No evident pathology was observed on transthoracic and transesophageal echocardiography and repeated blood cultures were negative. The patient was managed conservatively with gentamicin and clarithromycin. Nevertheless, he was scheduled for the removal of ICD and reimplantation on the left side. Both procedures were successful and the patient was discharged on metoprolol succinate (50 mg twice daily) and propafenone (150 mg three times daily). Six months later, he was admitted to the emergency department due to severe symptoms (blood pressure of 90/50 mm Hg, anxiety, cold and pale skin) of recurrent VT (120/min) without any reaction from the ICD. Urgent electrical cardioversion was successful and the ICD was re-checked and reprogrammed. Two months later, he was hospitalized again because of recurrent VT and ICD shocks, and electrical storm was diagnosed. The relative stabilization was achieved with high doses (1200 mg) of intravenous amiodarone. Cryoablation of two arrhythmogenic foci in the LV and RV was performed with the electromechanical mapping of the CARTO system. However, the procedure was ineffective because a few hours later the patient again developed electrical storm. The repeated electromechanical mapping revealed extensive damage to the anterior and posterior RV wall, in which the various forms of VT and late potentials were detected. Late and fragmented potentials were also observed in the RVOT. During the study, thermoablation was performed in all electrically unstable regions. After the procedure, instability was no longer observed and the patient was discharged home on metoprolol succinate (75 mg four times daily) and amiodarone (200 mg four times daily). In the past 8 months, the patient did not experience episodes of arrhythmia but he reported a gradual deterioration of exercise capacity.

## Discussion

### Classification

ARVC is a rare myocardial disease, which results from the replacement of cardiomyocytes by fibrous and fatty tissue. It leads to dilatation and impaired contraction of the RV and electrical instability [1]. By definition, the RV is almost always affected; however, simultaneous LV involvement is commonly observed. Moreover, the LV may occasionally be predominantly involved, and this condition is called left-sided arrhythmogenic cardiomyopathy, left-sided ARVC, or arrhythmogenic left ventricular cardiomyopathy [2].

According to the current European Society of Cardiology Working Group on Myocardial and Pericardial Diseases guidelines, ARVC is regarded as a distinct morphological and functional cardiomyopathy, which can be subclassified into familial (genetic) and nonfamilial types [3]. Similarly, the American Heart Association classified ARVC as a primary genetic cardiomyopathy [1].

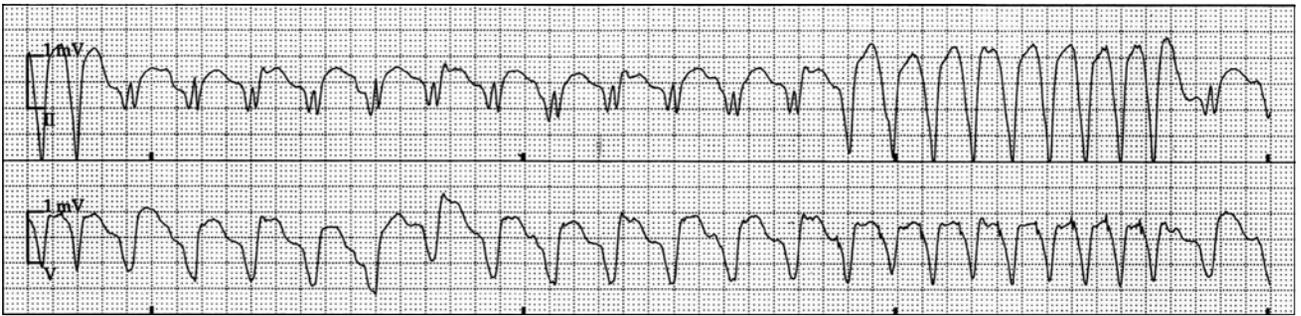


Fig. 7. Holter monitoring. Runs of ventricular tachycardia

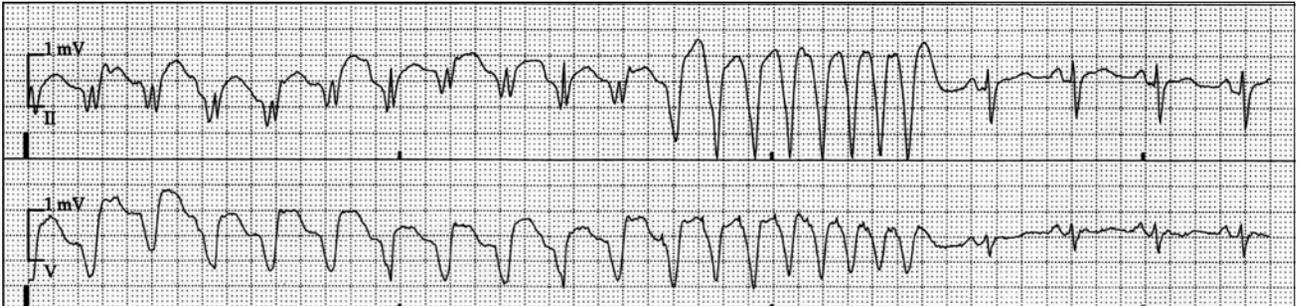


Fig. 8. Holter monitoring. Runs of ventricular tachycardia, spontaneously terminated

## Epidemiology

The prevalence of ARVC is estimated at 1:5000/10000 in the general adult population. It mainly affects men with the male-to-female ratio of approximately 3:1 [4]. ARVC is a frequent cause of unexplained sudden cardiac death (SCD). In two European registries from France and Italy, ARVC was confirmed as the cause of SCD in 10% and 11% of the cases, respectively [5,6]. Furthermore, SCD in ARVC is strongly related to exercise, which is explained by increased stress on the RV and influx of catecholamines. In a recent Italian registry, ARVC was responsible for 22% of SCDs in the cohort of 49 athletes [7].

## Genetics

In at least half of the cases, ARVC runs in families. Typically, ARVC is transmitted in an autosomal dominant pattern with variable penetrance [8]. The majority of causative mutations affect the genes encoding desmosomal proteins (junctions between myocytes), such as plakoglobin, desmoplakin, plakophilin, desmoglein, and desmocolin. Additionally, ARVC pathogenic mutations have been observed in the genes for cardiac ryanodine receptor, which also accounts for catecholaminergic polymorphic VT and transforming growth factor- $\beta$ 3, with a confirmed role in inflammation [9]. Based on the mutation character, at least nine different types of ARVC have been reported with ARVC-9 (mutation of the plakophilin gene) being the most common [9]. Genetic testing is important in ARVC because the identification of a pathogenic mutation is one of the major diagnostic criteria according to the 1994 Task Force guidelines as revised in 2010 [10].

So far several recessive syndromic variants of ARVC have been described, including Naxos syndrome, Carvajal syndrome, and Alcalai syndrome. The affected individuals come from small ethnic groups from isolated geographical areas and have associated palmoplantar keratoderma and wooly hair.

## Pathogenesis

The accumulated data indicate that ARVC is a disease of the desmosomes, which serve as a cell-to-cell junctions. Desmosomes are present particularly in the tissues that are prone to constant mechanical stress, such as epidermis and myocardium. They are built from three major protein families of plakins, armadillo proteins, and cadherins. The most important desmosomal proteins in the myocardium include desmoplakin, plakoglobin, plakophilin-2, desmoglein-2, and desmocolin-2. The consequences of mutations of desmosomal proteins are presented in the diagram (fig. 9).

Fibrofatty replacement of RV myocardium is a reparative mechanism for necrosis and apoptosis of myocytes. In the first place, the regions that are most prone to increased stress are affected, namely, “triangle of dysplasia” that includes the RV inflow and outflow tracts and apex. As the disease progresses, the structural changes encompass the whole RV and, in many cases, the LV. According to the relative content of the fibrous and fatty tissue, based on endomyocardial biopsies, two types of ARVC have been identified – fatty and fibrofatty. A tendency to ventricular arrhythmias is best explained by the micro- and macro-reentry circuits that form in the borders between the normal and altered ventricular wall.

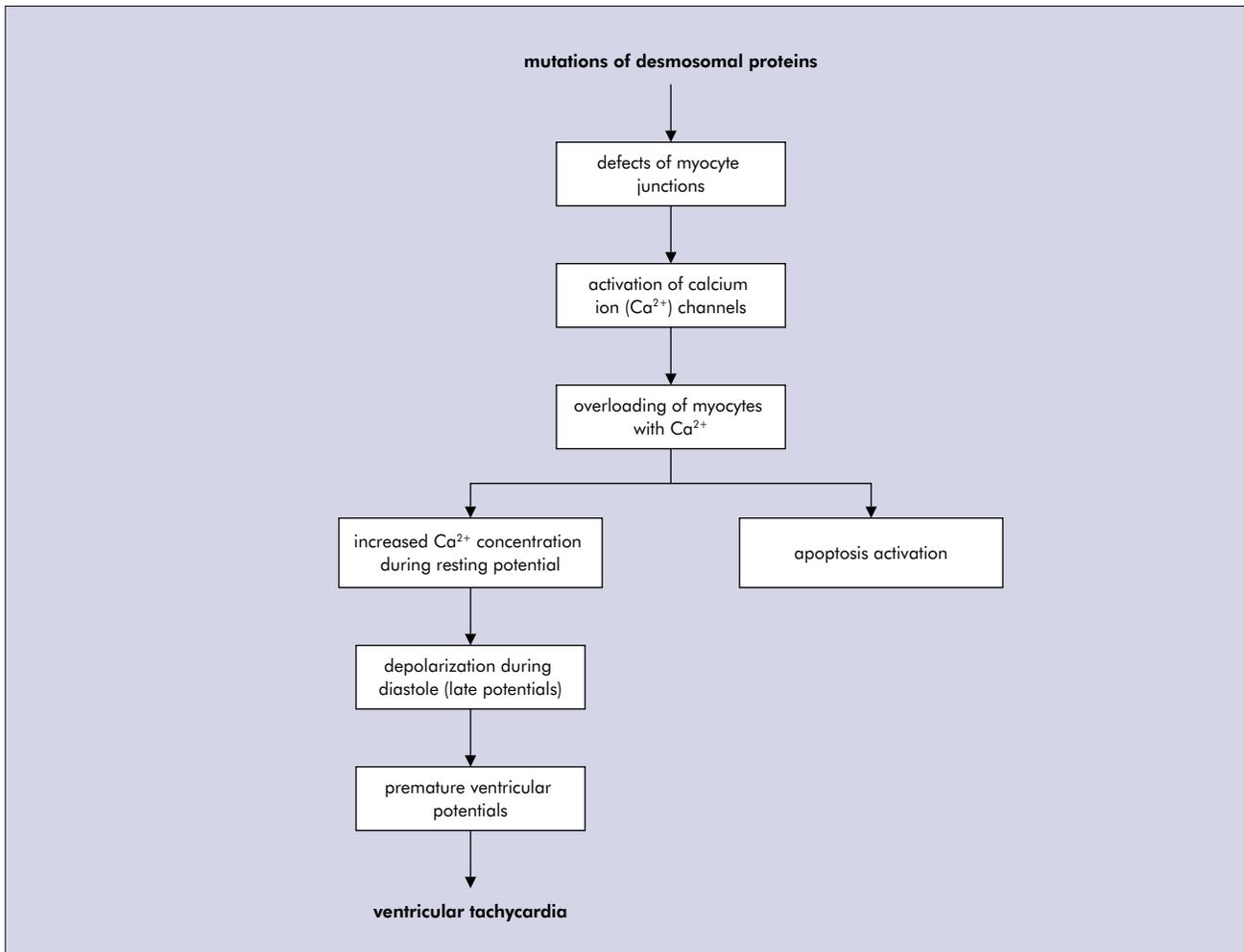


Fig. 9. The consequences of mutations of desmosomal proteins

### Clinical manifestations

The cardinal symptoms of ARVC include palpitations, dizziness, and syncope. In a contemporary registry of consecutive 130 patients with ARVC, two-third reported palpitations, one-third syncope, one-quarter atypical chest pain, and 11% breathlessness. Surprisingly, despite the fact that the RV is almost always dilated and dysfunctional, RV failure is rarely observed. Furthermore, ARVC represents a unique pathology where RV failure is associated with low pulmonary arterial pressure. First manifestation of the disease could be symptomatic ventricular arrhythmia, syncope, or SCD often in previously fit individuals. Recent studies showed that LV involvement in ARVC is not uncommon; in fact, more than 80% of 200 patients with confirmed ARVC had concomitant LV pathology of various degrees. First manifestations of the disease occur in adolescence and early adulthood. When disease develops in more advanced age, RV failure predominates. In most cases, ARVC is a progressive, three-staged disease, consisting of:

- latent phase – discrete morphological changes, normal ECG, absent/asymptomatic arrhythmias
- electrical instability phase – regional RV wall motion abnormalities, symptomatic ventricular arrhythmias

- dilatation phase – RV dilation and failure, frequent LV involvement

### Diagnosis of ARVC

Currently, a comprehensive diagnosis of ARVC is based on the 2010 Task Force criteria developed by the International Task Force of the European Society of Cardiology and International Society and Federation of Cardiology [10]. The 2010 criteria encompass six categories such as: 1) global/regional dysfunction and structural alternations, 2) tissue characterization of the wall, 3) repolarization abnormalities on the ECG, 4) depolarization/conduction abnormalities on the ECG, 5) arrhythmias, and 6) family history. There are major and minor criteria within each category. In order to make a diagnosis of ARVC, it is necessary to confirm the presence of two major criteria or one major plus two minor criteria, or four minor criteria from different categories. The differential diagnosis of ARVC includes idiopathic VT from the RVOT, Uhl anomaly, Brugada syndrome, RV involvement in myocarditis, or sarcoidosis.

### Electrocardiogram

Abnormalities detected on the ECG include both depolarization and repolarization phases:

- QRS prolongation in leads  $V_1$  through  $V_3$   $>100$  ms
- Ratio of QRS duration in  $(V_1 + V_2 + V_3)/(V_4 + V_5 + V_6) \geq 1.2$  has 98% sensitivity for the detection of ARVC
- Brugada syndrome-like incomplete or complete right bundle branch block
- small-amplitude potentials at the end of the QRS complex to onset of the T wave in the right precordial leads (epsilon wave)
- inversion of T waves in right precordial leads ( $VR_1$  through  $VR_3$ )

Typically, in ARVC, nonsustained or sustained VT of LBBB morphology with the superior axis (negative or intermediate QRS in leads II, III, aVF and positive in lead aVL) is observed.

### Signal-averaged electrocardiogram

Signal-averaged ECG is useful in detecting late potentials, which has a diagnostic significance in the absence of a QRS duration  $\geq 100$  ms. The definition of late potentials according to the 2010 Task Force criteria is as follows:

- filtered QRS duration  $\geq 140$  ms
- duration of terminal QRS  $<40$   $\mu\text{V}$  (low-amplitude signal duration)  $\geq 38$  ms
- root-mean-square voltage of the terminal 40 ms  $\leq 20$   $\mu\text{V}$

### Echocardiography

Almost omnipresent echocardiographic signs of ARVC are RV dilation and regional-to-global contractility impairment. According to the 2010 Task Force criteria, the major echocardiographic signs are regional RV akinesia, dyskinesia, or aneurysm and 1 of the following: RVOT  $\geq 32$  mm or  $\geq 36$  mm measured in end-diastole in parasternal long- or short-axis views, respectively, or RV fractional area change  $\leq 33\%$ . Additionally, other echocardiographic abnormalities are quite common, such as RV wall thinning, thickened moderator band, increased trabeculation of the apex region, spontaneous contrasting in right heart chambers, pericardial fluid, dilatation of the inferior vena cava and hepatic veins, low RV systolic pressure, and associated structural and functional changes in the LV.

### Cardiac magnetic resonance imaging

The 2010 Task Force guidelines provided detailed recommendations on the diagnosis of ARVC with cardiac MRI. Similarly to echocardiography, the major criterion is regional RV akinesia, dyskinesia, or dyssynchronous RV contraction and one of the following: increased RV end-diastolic volume ( $\geq 110$  mL/m<sup>2</sup> in men and  $\geq 100$  mL/m<sup>2</sup> in women) or RV ejection fraction  $\leq 40\%$ . Cardiac MRI is particularly useful for monitoring the RV volume and contractility. Additional findings include intramyocardial fat, late gadolinium enhancement, and focal wall thinning.

### Right ventricular angiography

Due to increasing availability of cardiac MRI, RV ventricular angiography is rarely used, mostly as an addition to coronarography or endomyocardial biopsy. Apart from regional RV wall motion abnormalities,

the typical findings include hypertrophic trabeculae separated by deep fissures. RV angiography should be performed in two orthogonal planes to adequately evaluate complex RV geometry.

### Endomyocardial biopsy

Although tissue characterization of the wall is an integral part of the 2010 criteria, endomyocardial biopsy is rarely performed due to relatively low sensitivity and specificity and increased risk of perforation of thinned RV wall. The major criterion is detection, by morphometric analysis, of less than 60% of residual myocytes with fibrous replacement of the RV free wall in  $\geq 1$  sample, regardless of the presence of the fatty replacement of tissue.

### Electrophysiological study and electroanatomical mapping

The main indication for an electrophysiological study is to localize substrate of arrhythmia and guide ablation. Electroanatomical mapping is increasingly popular for arrhythmia mapping, which can be used in precise ablation.

### Management

Considering a strong association between SCD and exercise, patients with ARVC should not be engaged in any professional sports. Furthermore, if any symptoms such as palpitations, dizziness or presyncope appear during recreational physical activity, it should be discontinued.

The main goal in the management of ARVC is to prevent SCD. The current recommendations for the management of ventricular arrhythmias in ARVC are based on the 2006 American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) guidelines. Several randomized controlled trials unequivocally confirmed the benefit of ICD in primary and secondary SCD prevention in ARVC patients. Therefore, the single most effective and proven way to prevent SCD in ARVC is ICD. As for secondary SCD prevention, ICD is indicated for patients who experienced sustained ventricular arrhythmias. ICD is also recommended for primary prevention of SCD in high-risk patients who are defined as those with familial history of SCD, syncope, hemodynamic instability during VT, family history of SCD  $<35$  years of age, severe RV dilation and dysfunction, associated LV involvement, QT dispersion  $\geq 40$  ms, epsilon wave, ARVC types 2 and 5, and Naxos syndrome. Although ICD is a life-saving intervention in numerous patients, it is also associated with some complications specific to ARVC, including perforation of the thin RV wall; on the other hand, prolonged and extensive fibrofatty replacement of RV over the years can reduce effectiveness of ICD shocks.

Although antiarrhythmic medications can decrease the number of ventricular arrhythmias, they do not prevent SCD. Therefore, they cannot be considered as an alternative to ICD but rather as an adjunctive therapy. Sotalol and amiodarone are the most effective drugs in ARVC and are recommended by the 2006 ACC/AHA/ESC guidelines. Similarly, radiofrequency ablation has been shown to be effective in suppressing arrhythmias in patients with frequent VT and electrical storm; nevertheless, it is not an alternative to ICD but rather an adjunctive treatment. A surgical approach, which is no longer popular today, involved total disconnection of the RV free wall, which aimed at the reduction of ventricular mass available for fibrillation and also prevented LV from VT/ventricular fibrillation, which originated in the diseased RV.

Increased awareness of ARVC and advancement in treatment methods, particularly owing to ICD, have led to a decrease in SCDs; however, severe or even end-stage RV heart failure leading to death has been more often observed in recent years.

## Our management strategy

The diagnosis of ARVC may be challenging and requires in-depth understanding of the disease as well as extensive knowledge and skills in cardiology. As in many cases, the diagnosis of ARVC in the present patient was delayed by at least 2 years. Probably the simple rule to be followed is to have a low threshold for ARVC suspicion when confronted with young adults with recurrent VT and some degree of abnormalities in RV. To establish a correct diagnosis of ARVC, it is necessary to follow the current 2010 Task Force criteria. The present case fulfilled three major criteria: 1) RV dilatation and dysfunction detected on echocardiography and confirmed by cardiac MRI, 2) repolarization abnormalities on ECG of inverted T waves in leads V<sub>1</sub> through V<sub>3</sub>, 3) frequently documented symptomatic nonsustained and sustained VT of LBBB morphology. As the guidelines require “only” two major criteria, the diagnosis of ARVC in this patient has been firmly established.

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## Left ventricular noncompaction with congenital diaphragmatic hernia causing cardiac dextroposition (RCD code: III-5A.1.0)

Paweł Rubiś, Tomasz Miszalski-Jamka, John GF Cleland, Eloisa Arbustini, Zbigniew Gąsior, Magdalena Kostkiewicz, Agata Leśniak-Sobelga, Marcin Krupiński, Piotr Podolec

### Background

Left ventricular (LV) noncompaction (LVNC) is a rare congenital cardiomyopathy, which presumably results from the premature arrest of endomyocardial formation during embryogenesis [1]. The hallmark feature of the LVNC is a double-layered LV wall, which is composed of thin, compacted myocardium on the epicardial side and much thicker, trabeculated, noncompacted myocardium on the endocardial side, which forms deep, blood-filled recesses protruding into the LV cavity [1,2].

### Case presentation

A previously fit and well 45-year-old man with a 2-month history of gradually increasing breathlessness, fatigue, and irregular heart rate (HR) was referred from the district hospital after cardiopulmonary decompensation for the exhaustive cardiac work-up. The patient had typical risk factors of cardiovascular diseases, such as hypertension, hyperlipidemia, and nicotine abuse; otherwise, the medical and family history was unremarkable. At presentation, he was stable with an irregular HR of 120 beats/min, arterial blood pressure of 140/90 mm Hg, oxygen saturation of

98%. He was classified as New York Heart Association (NYHA) class II. On a physical examination, he was euvoletic, with normal jugular venous pressure and clear lung fields. Interestingly, the heart sounds were more audible at the right side of the chest. A standard 12-lead electrocardiogram (ECG) showed atrial fibrillation, low R-waves voltage, and deep S-waves with nonspecific ST changes in leads V<sub>1</sub> through V<sub>6</sub> (fig. 1). However, after electrodes were replaced to the right side of the thorax, ECG revealed prominent R waves in precordial leads (fig. 2). A posterior-anterior chest radiograph revealed an enlarged cardiac silhouette, whereas an unusual structure was identified in the thorax cavity on lateral X-ray image (fig. 3). A transthoracic echocardiogram was of poor quality; nevertheless, it revealed enlarged and hypertrophied LV with severe global systolic impairment (ejection fraction of 20%) and biatrial enlargement with right ventricular systolic pressure up to 40 mm Hg. As the results of the examinations were rather inconclusive, the patient was scheduled for more advanced imaging studies. Computed tomography (CT) revealed an intestinal loop in the anterior mediastinum resulting in heart dislocation to the right side. A detailed analysis of a CT scan confirmed the diagnosis of a rare form of congenital diaphragm hernia known as the Morgagni hernia (fig. 4). Apart from heart dislocation, the hernia might have also caused lung compression and impairment of the breathing mechanism; however, no functional abnormalities were detected by spirometry. Cardiac magnetic resonance imaging (MRI) repeatedly demonstrated heart displacement to the right side and confirmed severe systolic dysfunction of the enlarged LV (end-diastolic volume, 197 mL; ejection fraction, 20%). More importantly, a thinned apex (4.5 mm) coupled with increased trabeculation (up to 15 mm) at the apex, posterior, lateral and anterior walls clearly showed a double-layered LV structure (fig. 5A). The thorough measurements of the LV wall thickness and calculation of the ratio of compacted and noncompacted layers, confirmed the diagnosis of LVNC. Moreover, cardiac MRI revealed persistent left superior vena cava draining to the coronary sinus (fig.



Fig. 1. Electrocardiogram. Atrial fibrillation, low R-waves voltage and deep S-waves with nonspecific ST changes in leads V<sub>1</sub> through V<sub>6</sub>

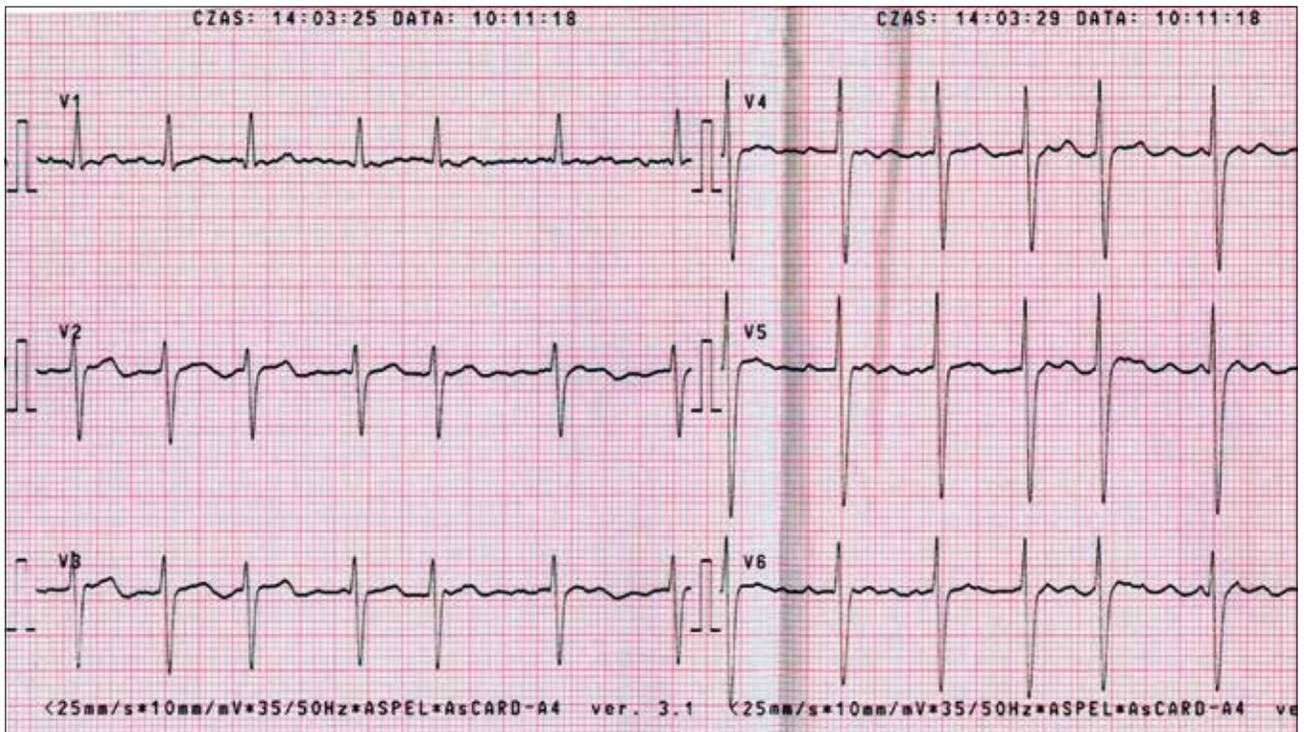


Fig. 2. Electrocardiogram with the electrode replacement to the right side of the thorax. Prominent R waves in precordial leads

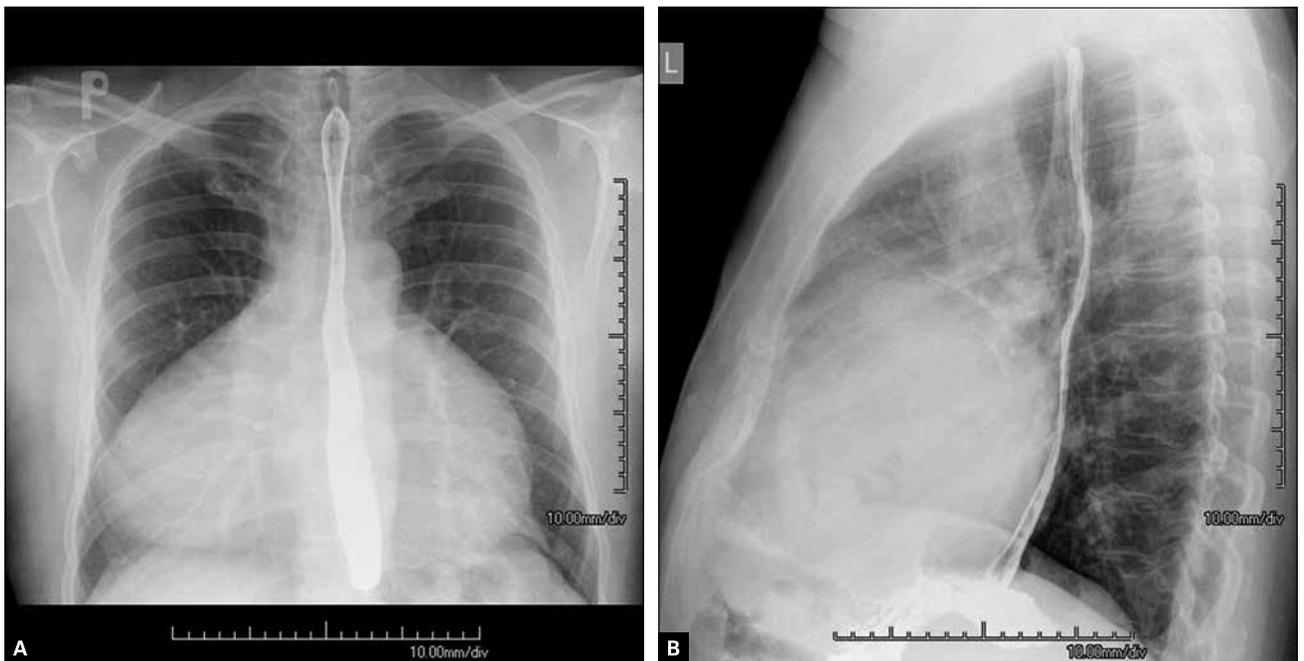
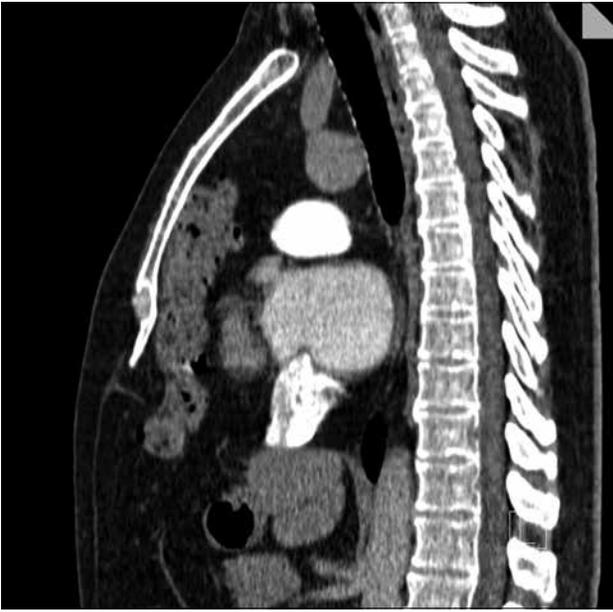


Fig. 3. Chest X-ray. **A.** Posteroanterior view. Enlarged cardiac silhouette. **B.** Lateral view radiograph shows an unusual structure in the anterior mediastinum

5B). The patient underwent the cardiopulmonary exercise test, which revealed moderate exercise capacity impairment with a peak oxygen uptake ( $VO_{2peak}$ ) of 18 mL/kg/min (which represents 54% of the predicted value), and normal ventilatory equivalent for carbon dioxide ( $VE/VCO_2$ ) of 27. On 24-hour ECG monitoring, atrial fibrillation (AF) was observed during the whole time with an inadequately controlled ventricular rate ( $HR_{max}$ , 130/min;  $HR_{min}$ , 78/min;  $HR_{mean}$ , 93/min),

coupled with numerous supraventricular (1500) and ventricular (1200) singular ectopic beats but no serious ventricular arrhythmias. To complete the diagnostic process, the patient underwent invasive studies. Coronary angiography excluded coronary artery disease and other abnormalities in the coronary bed. Left ventriculogram confirmed global LV systolic dysfunction and two-layered LV structure with deep, blood-filled recesses (fig. 6). Right heart catheterization



**Fig. 4.** Computed tomography. Intestinal loop in the anterior mediastinum resulting in heart dislocation to the right side

showed no intracardiac shunts, moderately reduced cardiac output of 3.5 L/min, mean pulmonary artery pressure of 25 mm Hg, pulmonary capillary wedge pressure of 12 mm Hg, and pulmonary vascular resistance of 3 Wood units.

## Discussion

### Classification

The complexity of LVNC is well reflected by the difficulties in classifying this rare condition. According to the current European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Diseases guidelines, LVNC belongs to a heterogeneous group of unclassified cardiomyopathies [3]. However,

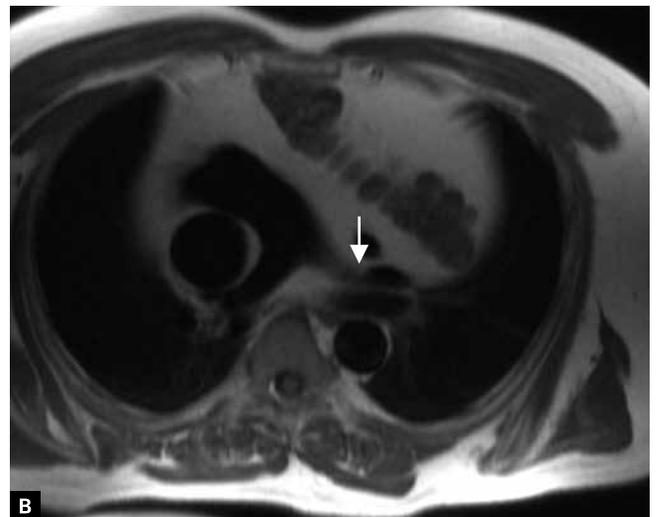
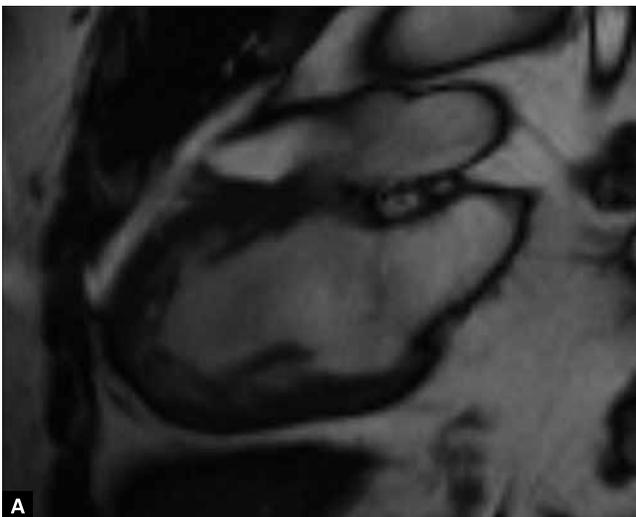
the American Heart Association classified LVNC as primary genetic cardiomyopathy [1]. Although LVNC is recognized as an isolated disease, the noncompaction of the ventricular wall is frequently observed in other conditions such as congenital right or left outflow tract abnormalities, bicuspid aortic valve, Ebstein's anomaly, patent ductus arteriosus, or ventricular and atrial septal defects [4]. Additionally, noncompacted myocardium has been confirmed in other types of cardiomyopathies due to neuromuscular disorders or metabolic diseases [5].

### Epidemiology

The true epidemiology of LVNC in the general population is unknown. There were only 34 diagnosed cases of LVNC in a referral echocardiography laboratory in Sweden (0.014% of all echocardiograms) during 15 years [6]. This is probably underestimated and with the increasing awareness of this rare echocardiographic phenotype, LVNC will be diagnosed more often. In the contemporary registry of systolic heart failure (HF), LVNC was confirmed in 3% of 960 consecutive patients with HF [7].

### Genetics

As any cardiomyopathy, LVNC may be either sporadic or familial. A detailed history and echocardiographic examinations of relatives showed familial occurrence of LVNC in 12% to 50% of the cases [6]. Generally, autosomal dominant inheritance pattern is the most common but X-linked and recessive transmission has also been reported. So far, the causative mutations have been identified in 9 genes encoding the following proteins: tafazzin (TAZ),  $\alpha$ -dystrobrevin (DTNA), LIM-domain-binding protein (LDB3),  $\beta$ -myosin heavy chain (MYH7),  $\alpha$ -cardiac actin (ACTC), lamin A/C (LMNA), cardiac troponin T (TNNT2), tropomyosin 1 (TPM1) [8]. Of note, the same mutations described in LVNC can lead to dilated, hypertrophic, or restrictive cardiomyopathy and the same genotype can produce various phenotypes even within the same family.



**Fig. 5.** Cardiovascular magnetic resonance. **A.** Double-layered left ventricular structure. **B.** Short-axis view revealed persistent left superior vena cava (arrow) draining to the coronary sinus



**Fig. 6.** Left ventriculogram. Global systolic dysfunction and two-layered left ventricular structure with deep, blood-filled recesses

Therefore, from the genetic point of view, the completely different phenotypes of cardiomyopathies can have the same genetic background and this phenomenon is known as “phenotypic heterogeneity”. Therefore, the most exciting and yet unresolved question is to determine why mutations in the same genes can lead to different myocardial disorders.

The increasing understanding of the genetic nature of cardiomyopathies has resulted in the development of the recent European and American guidelines [9,10]. Unlike in the case of other cardiomyopathies which are more often and better studied, the recommendations on the routine genetic evaluation of LVNC are weak and reflect numerous uncertainties and gaps in the understanding of this condition. Nevertheless, a careful, at least three-generation family history and clinical and echocardiographic evaluation is currently recommended [9,10].

### Clinical manifestations

Classically, LVNC is characterized by the triad of 1) HF symptoms such as fatigue, dyspnea on exertion, lung or peripheral congestion, etc., 2) arrhythmias, and 3) consequences of thromboembolic events including stroke [6,11]. In the historical and widely cited Swiss registry, dyspnea was reported in 80% of the patients, 35% of the patients were in NYHA class III or IV, and 25% had AF [6]. Based on the overlapping symptoms and sometimes inconclusive results of the examinations, the differential diagnosis of LVNC should include other types of cardiomyopathies such as dilated, hypertrophic (particularly apical), infiltrative, and a hypertensive heart disease.

### Diagnosis of LVNC

The first-line modality for the diagnosis of LVNC is transthoracic echocardiography. At present, there are

3 distinct echocardiographic criteria of LVNC, established by Stollberger [5], Jenni [12], and Chin [13]. They differ in a number of ways, such as the phase of the cardiac cycle when the measurements are performed, echocardiographic projections, and what cardiac structure is actually being assessed. Generally, the criteria are based on the concept of a two-layered LV wall, where the noncompacted, endocardial layer is much thicker than the compacted, thin, external layer. Although such an approach to LVNC reflects the hallmark feature of the disease, serial echocardiographic and cardiac MRI studies in the large cohorts of patients showed that increased LV trabeculation is more common than previously considered [14]. Therefore, the diagnosis of LVNC on the individual basis may be problematic and it seems that it is rather a continuum between normal echocardiographic images, through various stages of hypertrabeculation, to the phenotype of LVNC. Additionally, there is only a weak correlation between those 3 sets of criteria. In a recently published study, Kohli et al. [15] reported that only one-third of the patients diagnosed with LVNC fulfilled all 3 criteria and 8% of healthy individuals had at least 1 criterion of LVNC, especially people of the African origin.

Because of the frequent overdiagnosis of LVNC by echocardiography, cardiac MRI is becoming increasingly more useful. There are two approaches to confirm LVNC by cardiac MRI. The criteria published by Petersen et al. [16] use the same two-layered LV wall structure as echocardiography. The other, currently validated approach would be to measure the LV mass and, separately, trabecular mass. If the mass of the trabecula exceeds the mass of the LV by 20%, LVNC can be diagnosed.

Newly-developed echocardiographic assessment of LV rotation seems promising as a supportive measurement in LVNC. In healthy subjects and in the majority of cardiac conditions, including dilated cardiomyopathy, the opposite direction of rotation between the heart base and apex is observed, where the base rotates clockwise while the apex counterclockwise. Interestingly, in LVNC both the base and apex rotate in the same direction.

### Prognosis

Historical studies reported very poor prognosis in patients diagnosed with LVNC with 35% mortality in a 4-year follow-up [6]. However, those reports came mostly from the tertiary centers and severely affected patients, who were not treated with modern pharmacotherapy. More recent studies showed that LVNC is not as malignant as previously believed. In a report of 45 patients with LVNC, the 4-year survival was 97% [2].

### Management

Considering low prevalence and challenging diagnosis of LVNC, there are no randomized, controlled

therapeutic trials and the management is mostly based on the analogy with other types of cardiomyopathies and HF. Furthermore, there is no specific therapy for LVNC. Generally, when patients presents with HF symptoms and LV systolic dysfunction (LVSD) is present on echocardiogram, the ESC guidelines on HF should be applied [19]. Similarly, for asymptomatic LVSD, the recent ESC guidelines on pharmacotherapy and devices in HF should be followed. Because of an altered LV structure with deep recesses and blood pooling, LVNC patients have increased risk of thromboembolic events, particularly when associated with AF. Therefore, rather low threshold for oral anticoagulation is widely accepted. Patients with LVNC are particularly prone to life-threatening ventricular arrhythmias. In a case series by Murphy et al. [2] 24-hour Holter monitoring showed either symptomatic or asymptomatic ventricular tachycardia (VT) 20% of the patients. Therefore, regardless of the arrhythmia symptoms, annual Holter monitoring is recommended for all patients with LVNC. Indications for implantable cardioverter-defibrillator (ICD) are not different from standard indications in nonischemic cardiomyopathy. However, as patients with LVNC are probably at a higher risk of sudden cardiac death (SCD), the broader use of ICD may be beneficial. Therefore, the widely accepted criteria for the primary prevention of SCD include syncope, nonsustained VT, severe LVSD (ejection fraction <35%), or family history of SCD. Patients with refractory, end-stage HF are potential candidates for LV assist devices and heart transplantation.

## Cardiac malposition in the thorax cavity

Cardiac dextroposition is defined as a displacement of the heart to the right secondary to extracardiac causes such as right lung hypoplasia, right pneumectomy, or diaphragmatic hernia. Mechanical malposition, as in the case of diaphragmatic hernia, usually causes leftward cardiac axis. In contrast, the broad term “dextrocardia” is a pathological cardiac location in the right hemithorax but is intrinsic to the heart itself and not caused by extracardiac abnormalities. In dextrocardia, the base-to-apex axis is directed rightward. Dextrocardia occurs in approximately 0.01% of life births, while the precise epidemiology of dextroposition is unknown. There are several types of dextrocardia, which will be briefly reviewed below. The most common is dextrocardia with situs inversus, L-loop ventricles, and inverted great arteries, which is termed “mirror-image dextrocardia”. In one-quarter of the cases with mirror-image dextrocardia cases, Kartagener syndrome occurs (primary ciliary dyskinesia), which is characterized by the triad of situs inversus, parasternal sinusitis, and bronchiectasis. Dextrocardia with situs solitus, D-loop ventricles, and normally positioned great arteries is caused by the lack of the final leftward shift of the heart during embryologic development and is

termed “dextroversion”. The great majority of patients with dextroversion have additional cardiac malformations, including septal defects, tetralogy of Fallot, and others. Less common types of dextrocardia include dextrocardia with situs solitus, L-loop ventricles, and congenitally corrected transposition of the great arteries (TGA), dextrocardia with situs inversus, D-loop ventricles, and congenitally corrected TGA, and lastly dextrocardia with the heterotaxy syndromes of asplenia and polysplenia [20,21,22].

In the present case, the extracardiac abnormality causing dextroposition was proofed to be an asymptomatic congenital diaphragmatic hernia. Surprisingly, the base-to-apex axis was rightward, which was probably caused by additional right-sided cardiac rotation along the longitudinal axis during the movement of the heart to the right hemithorax.

Congenital diaphragmatic hernia occurs in 1 of every 2000 to 3000 live births and accounts for 8% of all major congenital anomalies [23]. Anterior Morgagni hernia represents only 2% of all cases with congenital diaphragmatic hernia [23].

So far, very few cases of LVNC associated with cardiac malposition have been published. In those reports, the reason for cardiac malposition was dextroversion, which is the result of an abnormal heart development. Despite extensive search of the literature, no report of LVNC with dextroposition has been identified.

## Our management strategy

This case represents a constellation of rare anomalies of LV noncompaction, persistent left superior vena cava with congenital diaphragm hernia, known as anterior Morgagni hernia, resulting in heart displacement to the right side of the thorax, mimicking dextrocardia but in fact being dextroposition. Therefore, the proper management is based rather on expert’s opinions or anecdotal reports rather than randomized studies.

Considering that the diagnosis of LVNC is challenging, the multimodality imaging with the use of cardiac MRI is strongly recommended, especially when the results of echocardiography are inconclusive.

The mean age of the LVNC diagnosis is usually the third or fourth decade of life, so our patient has been asymptomatic for a long time. The initial hemodynamic compromise was considered to be the result of new-onset AF. Therefore, after reducing ventricular response with a  $\beta$ -blocker to approximately 100 beats/min, the patient’s condition improved. Patients with LVNC have an increased risk of thromboembolic events, especially in the setting of AF. Our patient was initially treated with low-molecular-weight heparin and after all diagnostics tests, including invasive studies, he was switched to prolong oral anticoagulation with warfarin. According to the guidelines on HF, the patient was prescribed a  $\beta$ -blocker (bisoprolol, 7.5 mg twice daily), angiotensin-converting-enzyme inhibitor (ramipril, 5 mg twice daily), and aldosterone antagonists (spironolactone, 25 mg twice daily). The patient

had no major risk factors for SCD except LVSD and no serious ventricular arrhythmias were observed on Holter monitoring. Therefore, we postponed the decision about ICD implantation as primary prevention. The decision to perform invasive studies was made to search for possible abnormalities in the coronary circulation and to verify the presence of pulmonary hypertension because an echocardiogram did not provide conclusive results. After 4 weeks on adequate oral anticoagulant therapy, we performed direct current cardioversion, which restored the sinus rhythm of 62 beats/min; nevertheless, we decided to continue with warfarin. After an interdisciplinary discussion with a lung specialist and a cardiothoracic surgeon, we decided against thoracic reconstructive surgery owing to lack of clear benefits and high risk of the procedure. Drug therapy for HF resulted in the improvement of the functional status, and the patient is not currently considered for heart transplantation. A careful family history did not reveal inherited cardiac diseases. Moreover, we performed clinical and echocardiographic examinations of the patient's pedigree, which showed normal left-sided heart position in the thorax cavity and no abnormalities in the heart. The patient remains under the care of a local HF clinic.

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## Isolated left ventricular noncompaction in an asymptomatic athlete (RCD code: III-5A.1.0)

Izabela Karch, Lidia Tomkiewicz-Pająk, Monika Komar, Maria Olszowska, Paweł Rubiś, Piotr Podolec

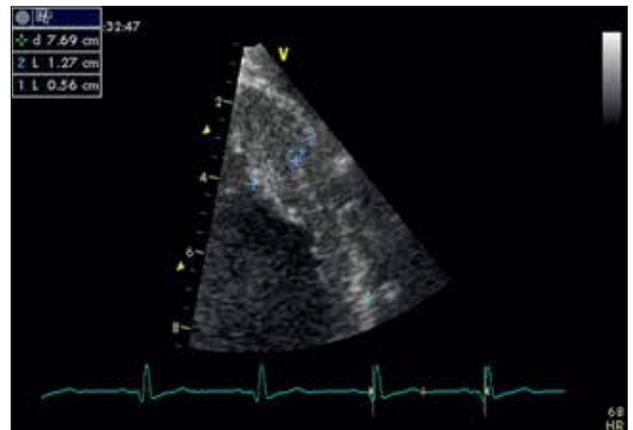
### Background

Left ventricular noncompaction (LVNC) is a rare form of cardiomyopathy due to abnormal morphogenesis of the endocardium and myocardium that occurs in the early stages of fetal life [1]. Given the increased risk of sudden cardiac death (SCD) associated with LVNC, athletes with this diagnosis should be excluded from most competitive sports with the possible exception of those of low intensity (class IA) in selected cases [2]. We report a case of asymptomatic football player with newly diagnosed LVNC.

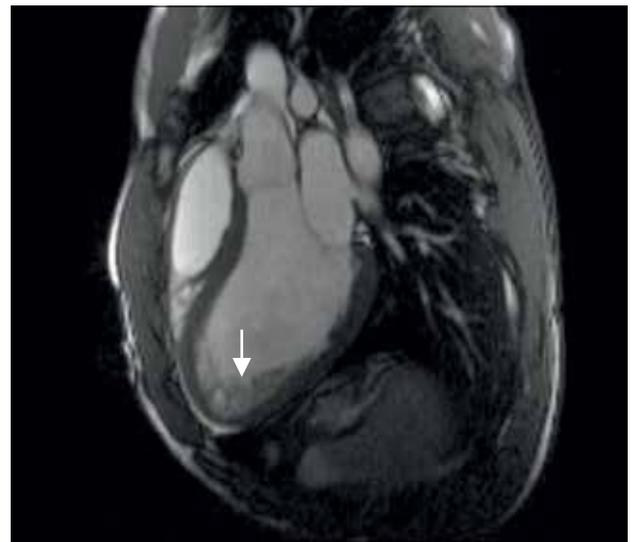
### Case report

A 21-year-old professional football player underwent cardiovascular assessment as part of routine screening. He had no family history of cardiac diseases or sudden deaths. No abnormalities in a physical examination were found. A resting electrocardiogram (ECG) showed sinus bradycardia (50/min) and early repolarization (recording within the normal limits). Wenckebach-type atrioventricular (AV) block and nocturnal sinus pauses (the longest, 2.3 s) were recorded in 24-hour Holter monitoring. Moreover, episodes of atrial ectopic rhythm were reported. The cardiopulmonary exercise test was performed in a protocol designed for professional athletes. Exercise lasted for 17 minutes. The patient achieved 16.2 METs. No ST-segment changes or arrhythmias during the test were recorded. A peak oxygen uptake was 42 mL/kg/min (within the normal range).

Transthoracic echocardiography showed the enlargement of four cardiac chambers and mildly impaired left ventricular function (ejection fraction, 42%) (fig. 1). Periapical thickening of the left ventricular myocardium was noted. The ventricular wall in this region was inhomogeneous in appearance. A compacted, epicardial layer and a thick, noncompacted endocardial zone could be distinguished. The ratio of the thickness of noncompacted-to-compacted myocardial layers was 2.3. No additional abnormalities were observed. On cardiac magnetic resonance imaging, the presence of two-layered structure of the left ventricular wall with a noncompacted-to-compacted ratio of 3.8 was observed, which confirmed the diagnosis of LVNC (fig. 2). The patient's case was discussed during a multidisciplinary consultation. The experts agreed that in asymptomatic patients with diagnosed LVNC



**Fig. 1.** Transthoracic echocardiography. Apical region of the left ventricle. The measurement of the ratio of the thickness of noncompacted-to-compacted myocardial layers



**Fig. 2.** Cardiovascular magnetic resonance. Trabeculations in the left ventricle (arrow)

aspirin for the prevention of thromboembolic complications and an angiotensin-converting-enzyme inhibitor (ACEI) should be considered. Competitive sport was strongly contraindicated. Echocardiographic screening in asymptomatic family members was recommended.

### Discussion

According to the definition, a professional athlete is a person who participates in an organized team or individual sport that requires regular competition against others as a central component, places a high premium on excellence and achievement, and requires some form of systematic (and usually intense) training [2]. Competitive sports activity is associated with a significant increase in the risk of sudden death (2.5-fold in individuals aged between 12 and 35 years) and an annual incidence is estimated at 1 to 2 per 100 000 athletes [3,4]. Sport per se is not the cause of increased mortality but it acts as a trigger of cardiac

arrest in those athletes with previously undetected cardiovascular conditions. The causes of SCD among athletes are strongly correlated with age. In adolescents and young athletes (<35 years), the leading causes are congenital cardiac diseases, particularly hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, congenital coronary artery anomalies, and other forms of cardiomyopathies [5]. By contrast, in older athletes ( $\geq 35$  years), the most common cause of fatal events is coronary artery disease.

LVNC is a rare form of cardiomyopathy caused by abnormal morphogenesis of the endocardium and myocardium, which occurs between the 5th and 8th week of fetal life [1]. It is characterized by prominent myocardial trabeculations accompanied by deep intertrabecular recesses, which communicate with the left ventricular cavity. There are discrepancies in LVNC classification. The American Heart Association classifies LVNC as a primary genetic cardiomyopathy, while the European Society of Cardiology places this pathology in the category of unclassified cardiomyopathies [6,7]. Defects of genes encoding various proteins including tafazzin,  $\alpha$ -dystrobrevin,  $\beta$ -myosin heavy chain, lamin, and calsequestrin have been identified in almost 50% of the patients with LVNC [8].

The phenotype of LVNC frequently resembles typical characteristics of dilated cardiomyopathy and its symptoms are unspecific and include dyspnea, impaired exercise tolerance, syncope, thromboembolic complications, and SCD [9]. LVNC is diagnosed within a wide range of ages. The course and symptoms of the disease differ from case to case. The more advanced symptoms of cardiac insufficiency at the time of diagnosis, the worse prognosis can be expected. The vast majority of patients (87%) with LVNC show abnormal ECG findings [10]. Echocardiography is a primary diagnostic tool in LVNC but because of various diagnostic criteria and suboptimal echocardiography quality, magnetic resonance imaging is recommended in most cases. The final diagnosis of LVNC should be based on the clinical picture and accurate multimodality imaging, typically including echocardiography and cardiac magnetic resonance [11].

LVNC is a rare cardiovascular disease and no specific therapy is currently available. We previously reported a case of LVNC in a patient with congenital diaphragmatic hernia causing cardiac dextroposition [12]. In our opinion, aspirin for the prevention of thromboembolic complications and an ACEI should be considered in asymptomatic patients with diagnosed LVNC and mildly impaired left ventricular function. Considering the asymptomatic course of the disease and some conduction problems (second-degree AV block type I) in our patient, the decision to introduce  $\beta$ -blockers has been postponed. According to the position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases, screening is indicated in first-degree relatives of the patients with LVNC [13]. ECG and echocardiography should be started already in newborns and then systematically repeated until 50 to 60 years of age.

## Management strategy

Currently, only medical history, physical examination, and resting ECG are obligatory in preparticipation screening of competitive athletes [14]. So far, sparse cases of athletes with diagnosed LVNC have been described and all of them were symptomatic [15]. The most common symptom is brief syncope during exercise; thromboembolic events including stroke, transient ischemic stroke and pulmonary embolism have also been described. The athlete described above was asymptomatic, had no family history of cardiac diseases or SCD, and no abnormalities in a resting ECG. The suspicion of LVNC was based on echocardiography, which is the obligatory part of screening of competitive athletes in our department. In our opinion, transthoracic echocardiography performed by cardiologists experienced in sports cardiology should become an indispensable part of the preparticipation screening of competitive athletes.

## Conclusions

Data on the optimal management of LVNC are limited and there is no specific therapy currently available. An athlete with diagnosed LVNC should be excluded from competitive sport. Aspirin for the prevention of thromboembolic complications and an ACEI are recommended in the treatment of asymptomatic patients with LVNC.

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# Part 6

Rare congenital cardiovascular diseases  
– RCD class IV

**Editor: Lidia Tomkiewicz-Pająk**



# Introduction

Lidia Tomkiewicz-Pająk

Recent progress in cardiac surgery and pediatric cardiology has resulted in large numbers of adult patients who have surgically corrected complex congenital heart disease. Congenital heart diseases are characterized by low prevalence and most of them are classified as rare. The pathophysiology, epidemiology, diagnosis, and follow-up of congenital heart disease have been previously described [1,2,3]. The problems of adult patients with congenital heart diseases have been recently extensively reviewed by experts in journal articles and textbooks. The most recently published positions are the “ESC Guidelines for the management of grown-up congenital heart diseases” (2010 update) [4]; “Diagnosis and Management of Adult Congenital Heart Disease” [5], and “Cases in Adult Congenital Heart Disease”. Currently, the management of the majority of rare congenital heart defects is not easy and straight forward although they are frequently described in the literature. Most of them occur only in few patients. In the current part of the book, we did not aim to review the data already covered by the outstanding publications. Our intention was rather to establish a clinical classification of rare congenital heart defects and present the system of care developed in the Centre for Rare Cardiovascular Diseases (CRCD).

The present part includes epidemiological data and reviews on diagnosis and treatment of rare congenital cardiovascular diseases. We aimed to draw the attention of the readers to the assessment of exercise tolerance in patients with these conditions. We also focused on presenting the Rare Cardiovascular Diseases Classification (RCD). Further, we present seven interesting clinical cases with a short preface, in which a given disease is briefly reviewed. Pulmonary hypertension due to rare congenital heart diseases is presented in Part 4 Readers interested in pregnancy in rare congenital heart diseases are especially referred to Part 9 and those interested in arrhythmias to Part 7.

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# Rare congenital cardiovascular diseases: Perspective of the Centre for Rare Cardiovascular Diseases

## ■ Congenital heart diseases as rare diseases

Lidia Tomkiewicz-Pająk, Piotr Podolec

### Definition

Congenital heart disease is the most common developmental anomaly and represents about 1% of all live-born children [1]. Rare diseases are defined as life-threatening or chronic diseases the prevalence of which is so low that special combined efforts are required for their diagnosis and treatment. The term “low prevalence” is later defined as generally meaning fewer than 1 in 2000 people. The majority of congenital heart defects are classified as rare congenital heart diseases. The pathophysiology of congenital cardiovascular disease have been previously described [2–6].

### Epidemiology

The number of patients with grown-up congenital heart diseases patients has increased. It is estimated that about 85% of the newborns with heart defects will reach adulthood. The 32nd Bethesda Conference October 2000 guidelines indicate that the frequency of congenital heart diseases in adults is about 2800 per million subjects, and at least in half of them, the disease is moderate or complex [4,7]. In 1996, in Canada, the number of adult patients with congenital heart diseases was 94 000, and increased to 124 000 in 2006. There are approximately 1 million patients with congenital heart diseases in the United States, and the number increases each year as children become adults [8,9]. Among adults with congenital heart diseases, the number of patients not undergoing any intervention (cardiac surgery) has been decreasing in favor of the growing population of subjects undergoing cardiac procedures or one- or multi-stage cardiac surgery. In Poland, the available data show that the number of patients after corrective cardiac surgery increases by about 3000 patients and of those after cardiac intervention by about 500 patients each year [10].

### Diagnosis

In diagnostic work-up, **clinical examination** plays a major role. The analysis of past history including type of heart defect, methods of treatment, past symptoms, medications, and concomitant diseases is very important.

An **electrocardiogram and pulse oximetry** should be performed alongside a clinical examination at each visit [4].

**Echocardiography** remains the first-line investigation in the diagnosis of patients with grown-up congenital cardiovascular diseases. It has become more useful since three-dimensional echocardiography, Doppler tissue imaging, contrast echocardiography, and perfusion imaging were introduced [4,11]. Echocardiography provides information on cardiac anatomy, morphology of the cardiac chambers and valves, as well as ventricular function. Moreover, it allows to detect and evaluate shunt lesions and provides useful hemodynamic data. However, it also has several limitation. First, it depends on the experience of the examiner in congenital heart diseases and on the quality of the echocardiogram. Second, in many cases, particularly in univentricular hearts and systemic right ventricle (RV), the assessment of ventricular volumes and function may be complicated by chamber geometry. Doppler gradients may sometimes be misleading, particularly in RV outflow tract obstruction and coarctation of the aorta [4].

**Evaluation of arrhythmias**, primarily in symptomatic patients, may require Holter monitoring, event recorders, and, eventually, an electrophysiology study [4].

**Cardiovascular magnetic resonance imaging (CMR) and computed tomography (CT)** have growing significance in the evaluation of patients with grown-up congenital cardiovascular diseases. According to the ESC Guidelines, there are several indications for CMR and CT in clinical practice [4,12]:

1. An alternative to echocardiography, when both techniques can provide similar information but echocardiography cannot be obtained with sufficient quality.
2. A second method when echocardiography measurements are borderline or ambiguous.

3. Indications where cardiac MRI is considered superior to echocardiography and should be regularly used when the information is essential for patient management. These indications include:

- Quantification of the RV volumes and RV ejection fraction
- Evaluation of the RV outlet tract occlusion and RV–pulmonary artery conduits
- Quantification of pulmonary regurgitation
- Evaluation of the pulmonary arteries (stenosis, aneurysms) and the aorta (aneurysm, dissection, coarctation)
- Evaluation of the systemic and pulmonary veins (anomalous connection, obstruction, etc.)
- Collaterals and arteriovenous malformations (CT is superior)
- Coronary anomalies and coronary artery disease (CT is superior)
- Evaluation of intra- and extracardiac masses (CT is superior)
- Quantification of myocardial mass (left ventricle and RV)
- Detection and quantification of myocardial fibrosis/scar (gadolinium late enhancement)
- Tissue characterization (fibrosis, fat, iron, etc.).

Both CT and CMR require expensive equipment and staff experienced in complex congenital heart diseases. Patients with implantable pacemaker, defibrillator, some prosthetic valves, other metallic implants, and claustrophobia should not undergo CMR [12]. In this group of patients, a CT scan may be an alternative diagnostic tool.

**Cardiac catheterization** is indicated to estimate pulmonary vascular resistance, ventricular diastolic function, pressure gradients, shunt quantification, and the evaluation of extracardiac vessels such as aortic pulmonary collateral arteries. Before surgery or invasive intervention, coronary angiography should be performed in men at the age of 40 years, postmenopausal women, and patients with the signs of coronary artery diseases or atherosclerotic risk factors [4].

**The cardiopulmonary exercise test (CPET)** is an objective diagnostic method of exercise tolerance quantification. CPET parameters such as peak oxygen uptake, peak ventilator equivalent for carbon dioxide ( $VE/VCO_2$ ), heart rate reserve, and blood pressure response are strong prognostic markers in patients with congenital heart diseases [13–15]. Therefore, serial CPET should be a part of long-term follow-up and should be considered when an intervention is scheduled [4]. For more details, see chapter 6.2.

## Treatment

The ESC guidelines recommend multidisciplinary care including pediatric specialists (pediatric cardiologists, pediatric cardiac surgeons) and specialists taking care of adults (cardiologists, cardiac surgeons, anesthesiologists, internists, surgeons) [4]. Each patient with

a rare congenital heart disease should be carefully discussed and usually individual decisions making is required. Psychological support and social assistance play an important role in the management of such patients [16,17].

In many patients, congenital heart disease, after corrective surgery in childhood, does not significantly affect their adult life. However, some of these patients require multidisciplinary care and many of them face the prospect of further operation, arrhythmias, increased risk of heart failure, and premature death. These adult patients with moderate and extremely complex congenital heart diseases, despite reaching their adulthood, are unable to function independently in the society [18].

Congenital heart diseases affect everyday life in many different ways. Some patients are inclined to believe that they are “different” from the rest. They are frequently raised by overprotective parents. Such symptoms as cyanosis, changes in their fingernails or scars make them perceive their own body as being far from normal and physically less attractive. Their relationships with friends are frequently dysfunctional, they frequently miss lessons, sometimes pursue individual educational plans, do not participate in elective courses, and experience reduced exercise tolerance. The feeling of being different usually is stronger during puberty. This may lead to developmental, emotional, and social problems in some adolescents and adults with congenital heart disease. These are most frequently memory disorders, attention problems, difficulty in planning, and impaired intellectual and educational development. These problems are partially related to the pressure of the society, thus enhancing psychological difficulties and decreasing self-confidence.

Previous studies showed that adolescents and adults with congenital heart diseases have higher levels of psychological distress and behavioral problems. Possible factors which are related to higher psychological distress are cardiac status, health-related quality of life, and perception of disease severity. Earlier studies also reported lower self-esteem and self-concept in patients with congenital heart diseases and showed that psychological factors such as personality, behavior, emotions, or cognitive processes may affect body responsiveness and modify the course of various diseases including cardiovascular disease [19,20]. Furthermore, physical capacity of patients late after corrective surgery is lower than that of the general population and does not meet the criteria of full recovery. Such patients are afraid of performing physical activity, which hinders participation in social life [13]. They frequently have disability certificates and are financially dependent on their parents or social welfare. When entering adulthood without adequate preparation, they have trouble coping with stressful situations such as deciding to get married or finding a job [20].

## Organization of care at the Centre for Rare Cardiovascular Diseases

One of the main goals of the CRCDD is to facilitate the access to specialist care for patients with rare congenital cardiovascular diseases. All doctors in our region have the CRCDD contact data and a registration form is available at the website: [www.crcdd.eu](http://www.crcdd.eu). Additionally, an internet-based registry is available for partner hospitals. Using this virtual tool, individual patient's data can be sent to the CRCDD. The patient can be further admitted to the CRCDD for diagnosis, consulted by CRCDD and/or other experts based on the submitted data, or just recorded in the database when no additional tests or treatment decisions are required.

## RCD classification of rare congenital cardiovascular diseases

There are several ways to classify congenital cardiovascular diseases [21,22]. A pathophysiological classification, namely, a classification based on the clinical consequences of structural defects impairing the physiology of blood circulation is frequently used [23].

Some congenital cardiovascular diseases may occur on their own, while others may occur as part of various genetic syndromes such as Down's syndrome, Marfan syndrome, Turner's syndrome, and DiGeorge syndrome, or with other concomitant diseases. The classification of congenital cardiovascular diseases has always been challenging. There are two global systems of classification: International Classification of Diseases (ICD-10) created by the World Health Organization [24] and International Pediatric and Congenital Cardiac Code (IPCCC) created by the International Congenital Heart Surgery Nomenclature and Database Project of The European Association for Cardio-Thoracic Surgery and The Society of Thoracic Surgeons with the European Paediatric Cardiac Code of the Association for European Paediatric Cardiology [25]. Houyel and al. [26] proposed his own classification based on the IPCCC regrouping congenital heart diseases into 10 categories. The RCD classification is presented in Part 2.

We believe that comprehensive classification based on the IPCCC will be useful in clinical practice. Apart from anatomical and clinical classes, we created a new category – Grown-up Congenital Cardiovascular Diseases. The population of adults with congenital heart diseases is heterogeneous and requires different levels of expertise: 20%–25% of the cases are complex, rare, and require life-long expert supervision and/or intervention; 35%–40% require access to expert consultation; and the remaining 40% have simple or cured diseases and need little or no specialist care [7]. Patients after the surgery for congenital heart diseases have different type of hemodynamics and its consequences, for example tetralogy of Fallot is classified as a congenital heart disease with decreased

pulmonary flow. After operation, the pulmonary flow is usually normalized but pulmonary valve regurgitation and arrhythmias are the main problems. In some cases, residual ventricular septal defect is detected and such patients may be classified as having congenital heart diseases with increased pulmonary flow. In our classification, the group of grown-up congenital cardiovascular diseases consists of 3 subgroups: patients after correction, those after palliation, and those with uncorrectable disease. The subgroup of congenital heart diseases after correction is divided into patients without late complication and residual defects and those with postprocedural complication and residual defects who require expert supervision and/or intervention. Our classification is easy to use in clinical practice and in the management of patients with rare congenital cardiovascular diseases.

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## Assessment of physical activity in rare congenital heart diseases

Natalia Dłużniewska, Lidia Tomkiewicz-Pająk, Piotr Podolec

There is an increasing number of adolescents and adults after with grown-up congenital heart diseases. In these group of patients, the assessment of exercise capacity and exercise tolerance can be a long-term evaluation of treatment efficacy. Moreover, an objective diagnostic and prognostic tool for the assessment of exercise capacity allows to evaluate the actual physical condition of patients. The standard methods for evaluation are the cardiopulmonary exercise tests (CPET), 6-minute walk test (6MWT), and personal questionnaire.

The CPET allows to precisely evaluate exercise capacity. It directly measures respiratory oxygen uptake ( $VO_{2peak}$ ) and carbon dioxide delivery ( $VCO_{2peak}$ ), which are compared with the norms for age, weight, and gender [1]. A significant value has equivalent to oxygen utilization ( $VE/VO_{2peak}$ ) and carbon dioxide production ( $VE/Vco_{2peak}$ ) occurring in the cell. Electrocardiogram, heart rate, and blood pressure are also analyzed during the CPET. The 6MWT measures the total distance walked, blood pressure, heart rate, and arterial oxygen saturation before, immediately after, and 10 minutes after the physical activity. The quality of life is assessed by the questionnaire consisting of questions about the current lifestyle (physical activity, intensity of exercise). Respondents are asked about their current or previous jobs, use of stimulants (smoking, alcohol), course of education, and participation in physical education classes during school days.

According to Gierat-Haponiuk et al. [2], patients after surgical correction of congenital heart disease have worse exercise capacity compared with healthy individuals, and that their health status does not fulfill the criteria of complete recovery. Numerous studies have shown that reduced  $VO_{2peak}$  in patients with congenital heart diseases strongly correlates with heart failure [3]. A large number of analyses have been conducted comparing the obtained results with the gold standards for healthy population by Jones et al. and others [4]. Diller et al. [5] showed significantly lower  $VO_{2peak}$  values in grown-up patients with congenital heart diseases than in healthy subjects and even supposedly asymptomatic patients (New York Heart Association class I). Distribution of  $VO_{2peak}$  and  $VE/VCO_{2peak}$  slope varies depending on the type of heart disease. The  $VO_{2peak}$  value was the highest in patients with repaired aortic coarctation and in those with transposition of the great arteries after arterial switch operation and the lowest in patients with Eisenmenger's syndrome [3,5]. The  $VE/VCO_{2peak}$  slope reached the highest values in patients with Eisenmenger's syndrome and complex heart disease and the lowest in patients with transposition of the great arteries after arterial switch and corrected aortic coarctation [3,6]. None of the patients with grown-up congenital heart diseases achieved the maximal heart

rate. Lack of heart rate response to exercise, pulmonary arterial hypertension, and impaired pulmonary function are important correlates of exercise capacity and chronic heart failure [6]. An analysis of the respiratory exchange ratio (RER) at peak exercise showed that patients with congenital heart disease do not reach their cardiovascular limit or make an adequate effort (in the healthy group, an RER exceeding 1.00 has been suggested as indicative of good effort). The prognostic power of  $VO_{2peak}$  and heart rate reserve was significantly reduced in patients whose peak RER was lower than 1.00 [7,8].

Patients whose cardiopulmonary system is incapable of supporting normal amounts of exercise are likely to be less resilient, more vulnerable to illnesses, and also likely to be more susceptible to further damage or injury and more predisposed to health complications [7,9]. Inuzuka et al. [10] reported that data on  $VO_{2peak}$  and heart rate reserve can be used to generate estimates of 5-year survival across a wide spectrum of adults with congenital heart disease.

In summary, the exercise capacity and physical activity of young adults with a history of surgical treatment for congenital heart diseases are worse than those observed in healthy people, and their health status does not fulfill the criteria of complete recovery. The CPET results confirm significantly lower maximal oxygen consumption, maximum heart rate at peak exercise, and higher index of the respiratory workload ( $VE/VCO_{2slope}$ ) and forced vital capacity [2]. The lower activity and exercise capacity in patients with grown-up congenital heart diseases may increase the risk of modern cardiovascular diseases.

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# Rare congenital heart diseases: Clinical examples

## Management of a patient after surgical repair of truncus arteriosus type I (RCD code: IV-1C.3b)

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### Background

Truncus arteriosus (TA) is a rare congenital heart disease occurring in 0.034 to 0.56 per 1000 newborns. It affects 1.4% to 2.8% of all congenital heart disease patients [1]. In this anomaly, a single arterial trunk arises from the heart, overrides the interventricular septum, and supplies systemic, pulmonary, and coronary circulations [2,3]. Without surgical treatment, 80% of the patients die within the first year of life, usually in early infancy [4]. Repair of TA during the neonatal and early infant period has become a standard practice in many centers, with good outcomes [5]. We present a case of a patient who underwent a surgery of TA type I.

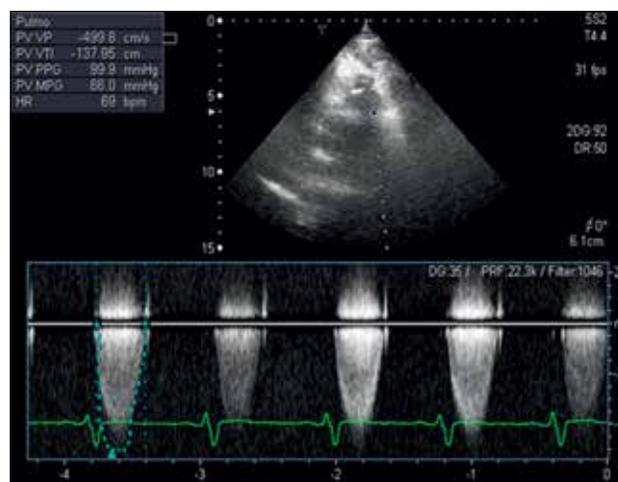
### Case presentation

A 21-year-old Caucasian man with TA type I was referred to the Centre for Rare Cardiovascular Diseases (CRCD) at the John Paul II Hospital in Krakow, Poland, for cardiac evaluation due to gradual loss of exercise capacity and exertional dyspnea. TA was diagnosed in the second day of life by cardiac echocardiography. The patient underwent a surgical repair in August 1990 with implantation of the pulmonary homograft no. 9 and Dacron conduit no. 12. In 1993, reoperation was performed due to stricture of pulmonary homograft. Homograft no. 19 pulmonary and Dacron conduit no. 22 were implanted. No complications were observed during either of the procedures.

The patient was referred to our center by his general practitioner in May 2011 with suspicion of pulmonary

homograft stricture based on echocardiographic examination. On admission, he was hemodynamically stable with no signs of peripheral or pulmonary edema. His heart rate was 75 beats/min and blood pressure was 135/80 mm Hg. He was considered to be in class I according to the New York Heart Association (NYHA) classification. He complained of minor reduction in exercise capacity. Comorbidities included mild bronchial asthma and recurrent migraine headaches. He had no family history of congenital heart defects. No drug, alcohol, or cigarettes use was reported. In 1990, he underwent pyloroplasty due to inborn pylorus stenosis. A physical examination revealed no significant abnormalities. A biochemical blood analysis showed normal values of complete blood count and no signs of kidney or liver dysfunction.

Transthoracic echocardiography revealed calcifications of the homograft and stricture of the pulmonary conduit. The pressure gradient in the right ventricular (RV) outflow track was 99.9/66 mm Hg (fig. 1). During 24-hours Holter ECG monitoring, no abnormalities were detected. A cardiopulmonary exercise test was completed in 15 min and 2 sec and the result was 11.7 METs, which confirmed that exercise capacity was within the reference range. No chest pain, arrhythmia, or ST-segment deviation was observed during the test. Maximal oxygen consumption reached 23.4 mL/kg/min.



**Fig. 1.** Transthoracic echocardiography. Parasternal short-axis view. The pressure gradient in the right ventricular flow tract was 99.9/66 mm Hg



**Fig. 2.** Cardiovascular computed tomography. Two-dimensional reconstruction. Calcification of the homograft (arrow)

Cardiac computed tomography showed calcified homograft and stenotic Dacron pulmonary conduit (fig. 2, 3). Right heart catheterization revealed high systolic pressure in the RV (100 mm Hg) and severely elevated systolic pressure in the pulmonary graft (up to 100 mm Hg) (fig. 4).

## Management strategy

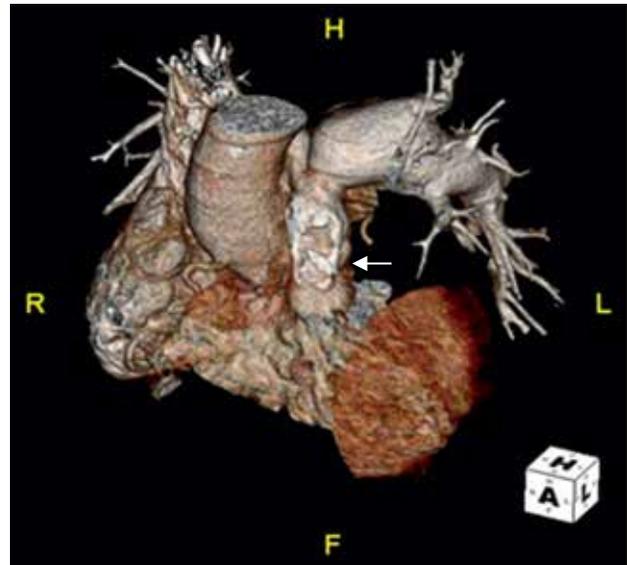
Because the patient is currently asymptomatic and reports only a minor reduction in exercise capacity (NYHA class I), he should be considered for optimal medical therapy. No surgery is indicated at this point.

## Discussion

TA is an uncommon congenital cardiac malformation constituting less than 3% of all congenital heart malformations [1]. TA is characterized by a single great artery arising from the base of the heart, which supplies systemic, coronary, and pulmonary blood flow, together with a ventricular septal defect [2,3]. The two main classification systems used to describe the anatomy of TA are those of Collett and Edwards (1949) and Van Praagh (1965) [6,7]. Without surgical treatment, 80% of the patients die within the first year of life, usually during early infancy [8,9]. The results of physiological repair have improved over the years, but pulmonary hypertensive episodes in the immediate postoperative course are major risk factors [10].

Conduits establish the continuity between the RV and the pulmonary artery in complex defects when the native outflow tract is not amenable to reconstruction.

The types of conduits include valved (pulmonary or aortic homograft, bioprosthetic valves, bovine jugular vein conduits [Contegra]) and nonvalved conduits [11].



**Fig. 3.** Cardiovascular computed tomography. Three-dimensional reconstruction. Calcification of the homograft and stenosis of Dacron conduit (arrow)

There is no ideal conduit. Limited durability implicates early reoperation. Predictors for conduit failure are sterilization/preservation process, smaller conduit, conduit type, younger age at implantation, pulmonary artery stenosis, and diagnosis of transposition.

A 20-year period free from reoperation for conduit failure was reported at the level of 32% to 40% [12]. Complications include outgrowth, progressive obstruction with and without regurgitation, endocarditis, and aneurysms or pseudoaneurysms [13].

Clinical presentation may include exertional dyspnea, palpitations, syncope, and sudden cardiac death [14].

In our patient, no clinical symptoms were observed, and the diagnosis of conduit obstruction was made accidentally.

Echocardiography is the first-line diagnostic tool providing providing the measurement of the size and function of both ventricles, pulmonary and tricuspid regurgitation, and associated lesions. Gradients across the conduit may be difficult to measure and not reliable. The RV pressure derived from tricuspid regurgitation velocity should be used to assess conduit stenosis. Cardiac magnetic resonance imaging and computed tomography may be required to image the conduit (level of stenosis), pulmonary artery, and coronary artery for the assessment of the RV and severity of pulmonary regurgitation.

Catheterization with hemodynamic assessment is always required if intervention is considered. Angiography provides information on the level of stenosis, peripheral pulmonary artery stenosis, and coronary anatomy (anomalies/abnormal course).

In our case, we performed the whole diagnostic algorithm including echocardiography, computed tomography, and cardiac catheterization, which allowed us to confirm the diagnosis of conduit stenosis. Owing to the lack of clinical symptoms, we decided against surgery and recommended regular follow-up.

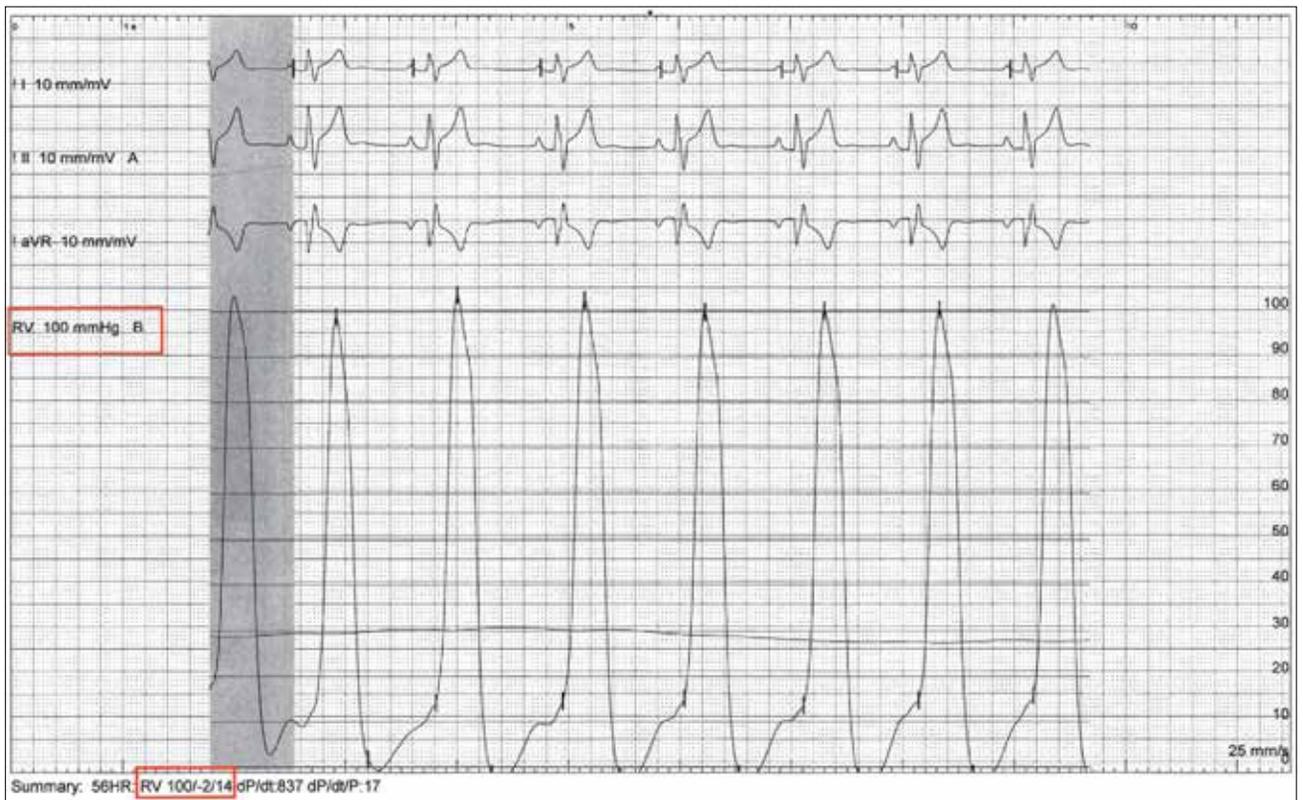


Fig. 4. Right heart catheterization. The right ventricular systolic pressure was 100 mm Hg

Longitudinal monitoring of the homograft and conduit morphology are more important for timing of reintervention than single measurements. Regular follow-up in a center specializing in grown-up congenital heart diseases is recommended at least every 12 months.

In our case, we decided to perform regular follow-up at least every 3 months. Special attention should be given to exercise capacity (cardiopulmonary exercise testing), RV systolic pressure (conduit gradient), RV function, tricuspid regurgitation, and arrhythmias.

## Conclusions

The patient has been scheduled for optimal medical treatment and regular follow-up. Transthoracic echocardiography with careful assessment of the RV function, RV systolic pressure (conduit gradient), and the severity of tricuspid regurgitation is required every 3 months. Periodical cardiopulmonary exercise testing and Holter examination are required. If new symptoms develop and the patient's condition worsens, indications for surgery should be evaluated again.

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## Obese woman with perimembranous ventricular septal defect and concomitant diseases (RCD: IV-2B.3)

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### Background

Pulmonary hypertension (PH) is recognized when the resting mean pulmonary arterial pressure measured during cardiac catheterization is 25 mm Hg or higher [1]. There are various clinical groups of patients with PH. Precapillary PH (pulmonary capillary wedge pressure of 15 mm Hg or lower and normal or decreased cardiac output) comprises pulmonary arterial hypertension (PAH), PH caused by lung diseases, chronic thromboembolic PH, and PH with unclear or multifactorial mechanisms. Postcapillary PH (pulmonary capillary wedge pressure exceeding 15 mm Hg) is caused by left-heart diseases (left ventricular end-systolic or diastolic dysfunction or valvular disease). There are numerous known risk factors for the development of PH, such as left ventricular systolic and diastolic dysfunction, mitral and aortic valve diseases, chronic obstructive pulmonary disease, interstitial lung diseases, pulmonary embolism, obstructive sleep apnea, connective tissue diseases, HIV infection, portal hypertension, and obesity [1].

Ventricular septal defect (VSD) is the most common congenital heart defect when bicuspid aortic valve is not considered. The perimembranous location is most common. It is often diagnosed and corrected in childhood. The prevalence of VSDs in adults is estimated at 0.3:1000 [2]. The hemodynamic significance of VSD depends on the size of the defect, pulmonary vascular resistance, and pressures in the right and left ventricles. In the absence of PAH, the left-to-right shunt is observed. A long-term left-to-right shunt, especially of high volume, may lead to irreversible PAH and, as a result, may reverse the shunt with desaturation and cyanosis.

### Case presentation

A 66-year-old woman with VSD was admitted to our hospital with symptoms of heart failure (functional class III according to the New York Heart Association). The patient had been treated for many concomitant diseases including hypertension, chronic heart failure, chronic obstructive pulmonary disease, permanent atrial fibrillation, type 2 diabetes treated by insulin, hypothyroidism, hyperuricemia, and depression. In 2005, she underwent pacemaker implantation because of tachycardia-bradycardia syndrome. Another serious problem was obesity; her body mass

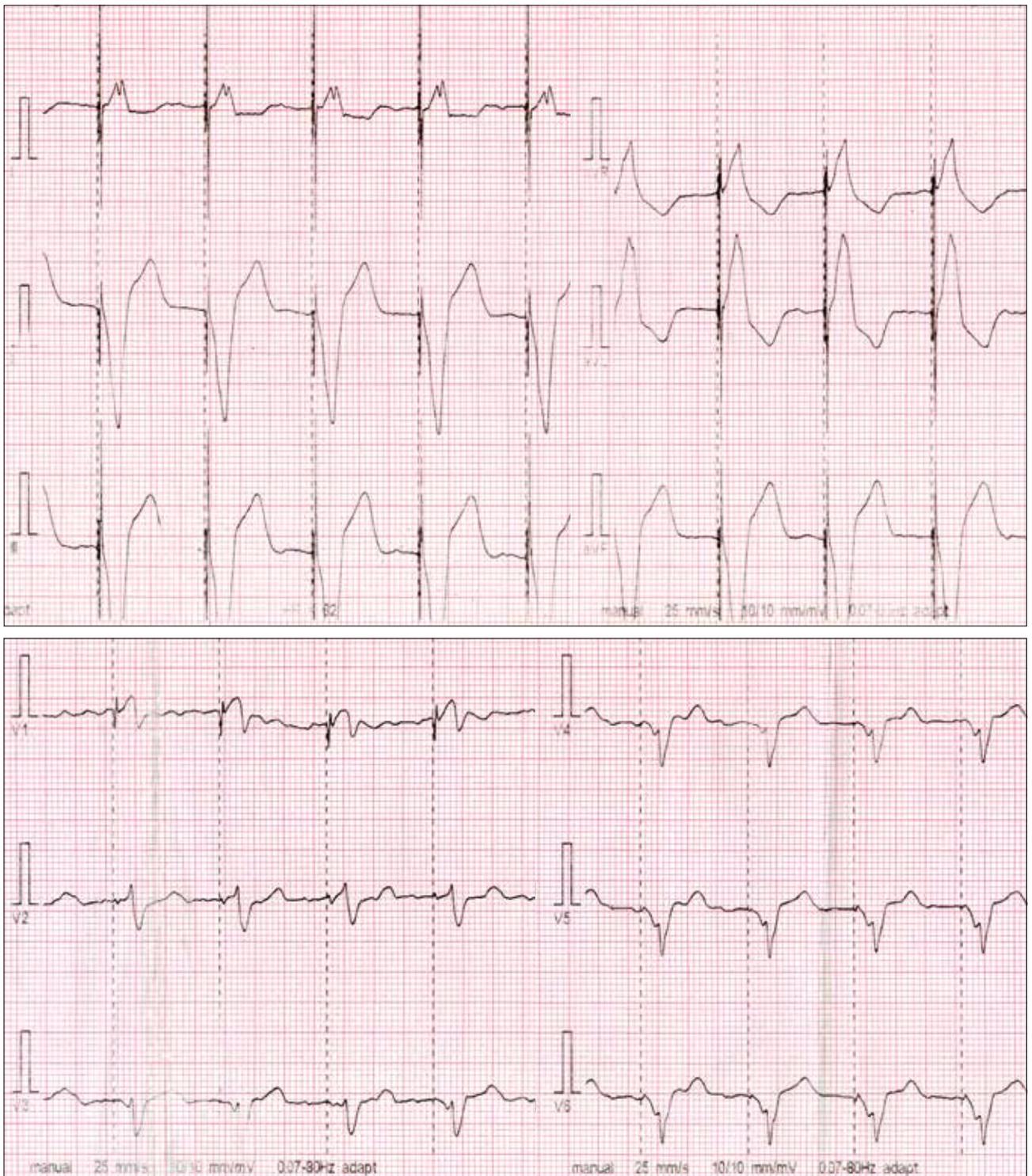
index was 48 kg/m<sup>2</sup> (height, 150 cm; weight, 107 kg). A physical examination revealed holosystolic murmur best heard over the lower left sternal border. Other findings included regular heart rate of 80 beats/min, blood pressure of 110/70 mm Hg, and vesicular breath sounds. The liver edge was not palpable. The patient did not have peripheral edema. Blood saturation in the upright position was 92% with desaturation in the supine position to 88%. Laboratory tests revealed elevated red blood cells,  $5.25 \times 10^3/\mu\text{L}$  (normal range,  $3.7\text{--}5.1 \times 10^6/\text{mm}^3$ ); hemoglobin, 16.4 g/dL (normal range, 12–16 g/dL); hematocrit, 49.0% (normal range, 37%–47%), and glucose, 8.6 mmol/L (normal range, <5.5 mmol/L). White blood cell and platelet counts and the levels of creatinine, high-sensitive C-reactive protein, alanine transaminase, aspartate transaminase, uric acid, and thyroid hormones were within the normal ranges. A 12-lead electrocardiogram showed atrial fibrillation and permanent ventricular pacing of 84 beats/min; QRS duration was 240 ms (fig. 1).

24-hour Holter monitoring revealed atrial fibrillation; about 98% of the QRS complexes were paced. The minimal, maximal, and mean heart rate was 79 beats/min, 115 beats/min, and 81 beats/min, respectively. Transthoracic echocardiography showed enlargement of the right ventricle and both atria, impaired left ventricular systolic function with the ejection fraction of 35%, perimembranous restrictive VSD with the left-to-right shunt and the gradient of 80 mm Hg, mild mitral and tricuspid valve regurgitation, mild aortic stenosis, and right ventricular systolic pressure of 55 mm Hg. There was poor acoustic window due to patient's obesity (Table 1, fig. 2).

Computed tomography excluded pulmonary embolism. The pulmonary trunk was dilated to 39×29 mm (upper normal value, 26 mm); the right and left pulmonary arteries were also dilated to 29×29 mm and 28×27 mm, respectively (fig. 3). Whole-body plethysmography showed restrictive dysfunction of ventilation (Table 2). The cardiopulmonary exercise test was not performed due to lack of consent of the patient. Cardiac catheterization was performed, which revealed irreversible PH with the mean pulmonary artery pressure of 49 mm Hg, pulmonary vascular resistance of  $416 \text{ dyne} \times \text{s} \times \text{cm}^{-5}$  (<2/3 of the systemic values), and pulmonary-to-systemic flow ratio (Qp:Qs) of 1.53. The pulmonary capillary wedge pressure (PCWP) was increased to 25 mm Hg and the cardiac index (CI) was decreased. The transpulmonary pressure gradient was 24 mm Hg (Table 3). Coronary catheterization excluded coronary artery stenosis.

The patient was first treated by carvedilol (12.5 mg twice daily), perindopril (5 mg), eplerenon (50 mg), torasemid (10 mg), acenocumarol, fenofibrate (215 mg), ipratropium, salmeterol, allopurinol (300 mg), levothyroxine (100 µg), metformin (850 mg), and insulin glulisine and isophane.

VSD closure and specific treatment of PAH were contraindicated in our patient because of significant left ventricular systolic and diastolic dysfunction and concomitant chronic obstructive pulmonary disease, which are considered the major clinical factors causing PH. Because of progressive symptoms of heart failure and



**Fig. 1.** 12-lead electrocardiogram. Atrial fibrillation and ventricular pacing of 84 beats/min. QRS complex duration of 240 ms

prolonged QSR duration during right ventricular stimulation, she was scheduled for cardiac resynchronization therapy. Obesity is a significant problem in our patient but invasive treatment is not recommended because of high risk of the surgery. Optimal medical therapy and depression treatment were continued. After a specific diet program, she lost 6 kg of weight in 3 months.

The case of the patient was presented at the Meeting of the Center for Rare Cardiovascular Diseases.

## Discussion

According to the current guidelines, VSD should be closed in symptomatic patients with the left-to-right shunt and without severe pulmonary vascular disease and in asymptomatic patients with left ventricular volume overload [3]. VSD closure should be considered in patients with a history of infectious endocarditis or progressive aortic regurgitation with

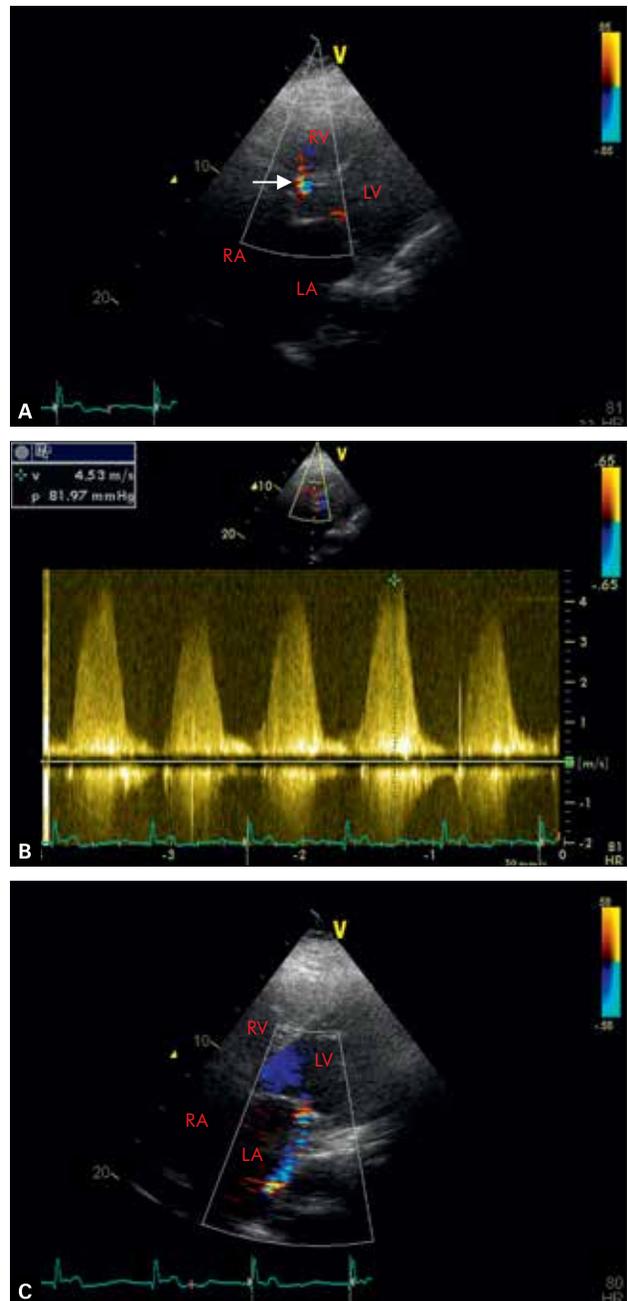
**Table 1.** Transthoracic echocardiography

Left ventricular ejection fraction (LVEF)	35%
LV end-diastolic dimension (LVDD)	55 mm
Right ventricular (RV) dimension	30 mm
Left atrial area	35 cm <sup>2</sup>
Right atrial area	31 cm <sup>2</sup>
Peak aortic valve pressure gradient	20 mm Hg
Mean aortic valve pressure gradient	8 mm Hg
Mitral valve regurgitation	mild
Tricuspid valve regurgitation	mild
Perimembranous ventricular septal defect with the left-to-right shunt, pressure gradient	80 mm Hg
Estimated right ventricular systolic pressure	55 mm Hg

aortic leaflet prolapse. It should also be considered in patients with PAH when the Qp:Qs is higher than 1.5:1 and pulmonary artery pressure or pulmonary vascular resistance is below two-thirds of the systemic values: baseline or after vasodilators or target PAH therapy [3]. Currently, mortality during VSD surgical closure is low (1%–2%), and surgery remains the method of choice [2]. The interventional treatment could be performed in selected patients (muscular or perimembranous location, high risk of surgery).

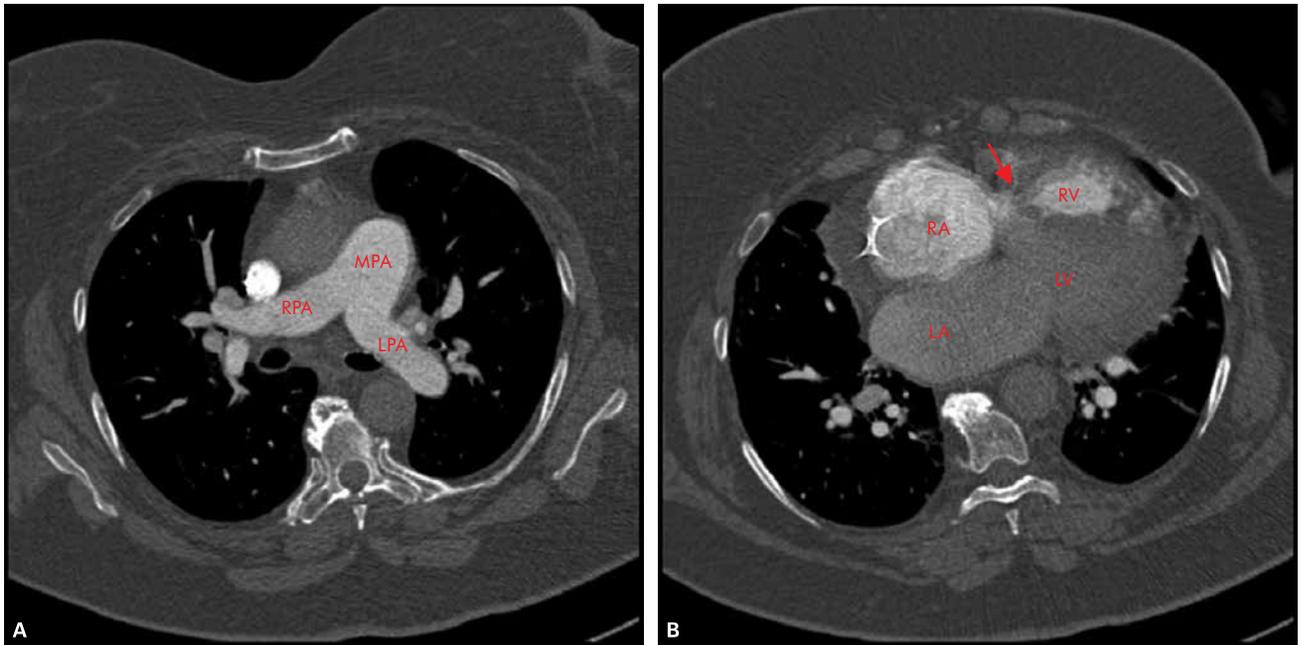
In PH due to left heart disease, the optimal therapy of the underlying disease is essential. In PH caused by lung disease with severe hypoxemia, long-term oxygen therapy is indicated. The European Society of Cardiology recommends bosentan for the treatment of PAH associated with congenital cardiac shunt and Eisenmenger's syndrome [1].

Despite the presence of PH with the pulmonary artery pressure and pulmonary vascular resistance below two-thirds of the systemic values and left-to-right shunt with the Qp:Qs exceeding 1.5, our patient was not referred for VSD closure. First, the perioperative risk was high because of numerous concomitant diseases, of which severe obesity and restrictive dysfunction of ventilation seemed to be the most important. Second, the patient had PH of mixed etiology: due to congenital heart disease, left heart disease and lung disease, and the VSD was probably not the main etiologic factor. Also the symptoms were caused by many coexisting disorders. Moreover, the specific treatment of PH with bosentan was not administered because of the left ventricular systolic and diastolic dysfunction with severely increased PCWP. Obesity was a significant problem in our patient but bariatric surgery was contraindicated due to high risk of the procedure. It was difficult for her to lose weight because of poor exercise tolerability and depression. However, she was informed about the importance of restrictive diet and managed to lose 6 kg.



**Fig. 2.** Transthoracic echocardiography. **A.** Left-to-right shunt through the ventricular septal defect (white arrow). **B.** Gradient between the left and right ventricles. **C.** Mild mitral valve insufficiency (white arrows). Poor acoustic window due to obesity of the patient. LV – left ventricle, RV – right ventricle, LA – left atrium, RA – right atrium

It is known that dyssynchrony occurring during right ventricular pacing deteriorates the left ventricular function, especially when the left ventricular ejection fraction is initially decreased. There are reports suggesting that upgrading from single to biventricular pacing can reduce dyssynchrony and improve the clinical status [4–7]. Our patient was initially referred for cardiac resynchronization therapy; however, because of technical difficulties, the left ventricular electrode was not implanted. The pharmacological therapy is currently continued.



**Fig. 3.** Cardiovascular computed tomography. **A.** Dilatation of the pulmonary trunk and the right and left pulmonary arteries. **B.** Ventricular septal defect (red arrow). MPA – pulmonary trunk, RPA – right pulmonary artery, LPA – left pulmonary artery, RV – right ventricle, LV – left ventricle, RA – right atrium, LA – left atrium

**Table 2.** Whole-body plethysmography revealing restrictive dysfunction of ventilation

	Predicted	Actual
Vital capacity [L]	2.1	0.97
Inspiratory capacity [L]	1.44	0.97
Tidal volume [L]	0.75	0.46
FEV <sub>1</sub> [L]	1.66	0.81
FVC [L]	2.02	0.96
FEV <sub>1</sub> /FVC [%]	86.48	84.87
RV [L]	1.74	1.89
Total lung capacity [L]	4.04	2.86
RV/TLC [%]	41.06	66.1

TLC – total lung capacity, FEV<sub>1</sub> – forced expiratory volume in 1 second, FVC – forced vital capacity, RV – residual volume

**Table 3.** Results of cardiac catheterization

Pressure (mm Hg)	Rest	After NO inhalation
RA	23/21	19/22/20
PA	68/40/49	72/43/51
RV	72/24/28	
PCWP	26/26/25	27/28/27
LV	140/10/27	154/5/27
Aorta	135/89/106	158/87/110
<b>Saturation (%)</b>		
IVC	55.2	
SVC	50.5	
RA	55.4	56.6
RV	60.2	
PA	63.9	65.4
Aorta	88.5	88.3
Cardiac output (L/min)	3.0	3.45
Cardiac index (L/min/m <sup>2</sup> )	1.53	1.76
Qp/Qs	1.53	1.46
VPR (ARU)	416	382
TPR (ARU)	851	812
<b>VSR (mm Hg)</b>		
NO – nitric oxide, RA – right atrium, PA – pulmonary artery, RV – right ventricle, PCWP – pulmonary capillary wedge pressure, LV – left ventricle, IVC – inferior vena cava, SVC – superior vena cava, Qp:Qs – pulmonary-to-systemic flow ratio, PVR – pulmonary vascular resistance, TPR – total pulmonary resistance, VSR – systemic vascular resistance		

## Management algorithm

1. It is essential to check whether the patient is symptomatic.
2. In symptomatic patients, cardiac catheterization should be performed to assess the pulmonary artery pressure.
  - a) Symptomatic patients with no severe PH should be scheduled for VSD closure.
  - b) Patients with PH but when pulmonary artery pressure or pulmonary vascular resistance are below the two-thirds of the systemic values

- (at rest, after vasodilators or PH treatment), VSD closure should be considered.
- c) In patients with desaturation on exertion and with Eisenmenger's syndrome, VSD closure is contraindicated.
3. When the patient is asymptomatic:
- a) It is necessary to check, for example, by echocardiography, whether there is left ventricular overload. If left ventricular overload is caused by VSD, the intervention is indicated.
- b) If there is a history of infective endocarditis, VSD closure should be considered.
- c) If there is progressive aortic insufficiency due to aortic valve cusp prolapse, surgery should be considered.

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## Tetralogy of Fallot with anomalous left anterior descending coronary artery and multiorgan malformations (RCD code: V-A2)

Monika Smaś-Suska, Lidia Tomkiewicz-Pajak, Leszek Drabik, Maria Olszowska, Natalia Dłużniewska, Piotr Podolec

### Background

Tetralogy of Fallot is one of the most common cyanotic congenital heart diseases affecting 10% of newborns with congenital heart failure. This heart malfunction involves ventricular septal defect (VSD), obstruction of the right ventricular (RV) outflow tract (RVOT), which can be valvular, subvalvular, or both, overriding aorta, and RV hypertrophy. About 3% of the patients have anomalous left anterior descending coronary artery [1].

### Case presentation

An 18-year-old man with tetralogy of Fallot and coronary artery abnormality was admitted to the Centre for Rare Cardiovascular Disease (CRCDD) at the John Paul II Hospital in Krakow, Poland. At 13 months of age, he underwent the left Blalock–Taussig shunt. At 4 years of age, total corrective surgery was performed, which included VSD closure and implantation of a valveless conduit between the RV and main pulmonary artery (MPA). After 1 year, the patient required another cardiac intervention. Angioplasty of the MPA with homograft implantation owing to an aneurysm and dilation of the conduit was performed. The patient suffered also from mental regurgitation (no further diagnostic tests including genetic test were performed), bilateral cryptorchidism (he was operated in 1998), chronic gastroesophageal reflux disease, and esophagitis.

For the next 14 years, he remained under the care of the Institute of Pediatrics and, subsequently, when he reached 18 years of age, he became the patient of the Adult Congenital Heart Clinic of the John Paul II Hospital in Cracow. So far, he has been treated with metildigoxin (0.1 mg/d) and omeprazol (40 mg/d).

The patient was admitted to the CRCDD because of chronic fatigue and reduced exercise tolerance. According to his mother's report, he had been in the New York Heart Association (NYHA) class II/III for a few months.

On examination, his weight was 55 kg, height was 152 cm (body mass index, 23.8 kg/m<sup>2</sup>), and dysmorphic facial features were present.

On auscultation, his heart rate was 70 beats/min, blood pressure was 105/70 mm Hg, and systolic murmur was heard in the left second intercostal space (3/6 according to the Levine's scale). The respiratory rate was 17/min and vesicular sound was heard on lung

auscultation. Peripheral swellings were absent and no cyanosis was present.

An electrocardiogram revealed a sinus rhythm of 70 beats/min, right-axis deviation, Q wave in leads III and aVF, inverted T waves in leads I and aVL, and signs of the RV enlargement (fig. 1). Holter monitoring showed sinus rhythm, average heart rate of 79 beats/min, maximum heart rate of 115 beats/min, minimum heart rate of 56 beats/min, PQ of 200 ms, episodes of wandering pacemaker, and episodes of supraventricular rhythm (fig. 2).

The cardiopulmonary exercise test (CPET) was performed and it was finished after 12 minutes and 13 seconds because of fatigue and dyspnea and showed reduced exercise tolerance with maximal oxygen consumption (max VO<sub>2</sub>) of 19.0 mL/kg/min. It was his second CPET. The first one was conducted 6 months earlier; it was finished after 3 minutes and 20 seconds because of fatigue and dyspnea and showed reduced exercise tolerance with max VO<sub>2</sub> of 12.4 mL/kg/min.

#### Echocardiography showed:

- normal size and function of the left ventricle (LV) with residual VSD (fig. 3, 4)
- enlargement of the right atrium, 22 cm<sup>2</sup> (normal range, 10–18 cm<sup>2</sup>), and the RV, 34 mm (normal range, 9–26 mm) with septomarginal trabecula (fig. 5)
- normal systolic function of the RV (fig. 6)
- RVOT, 25 mm (normal range, 17–25 mm) with turbulent flow (fig. 7)
- hypoplastic pulmonic valve with calcification, residual flow, and regurgitation (fig. 8, 9)
- pressure gradient measured in the RVOT was 32/19 mm Hg (fig. 9) and remained stable during 2 years of follow-up (Table 1).
- diameter of the conduit between the RV and MPA of 15 mm with turbulent flow (fig. 10)
- mild tricuspid regurgitation; moderate aortic regurgitation

Diagnostic procedures also included cardiovascular computed tomography, which revealed:

- enlargement of the right atrium (27 cm<sup>2</sup>) and RV (34 cm<sup>2</sup>)
- subvalvular stenosis (the narrowest diameter of 1.7×0.6 cm) (fig. 11),
- hypoplastic pulmonary valve (diameter, 2.0×0.7 cm) (fig. 12),
- MPA, 25×34 mm; right pulmonary artery, 15×9 mm; and left pulmonary artery, 16×10 mm (fig. 12),
- RV and MPA connected by the conduit, with calcification in the middle part of the conduit reducing its lumen to 1.9×1.5 cm
- wide, permeable connection of the conduit with the RV and MPA.

Furthermore, the examination confirmed anomalous coronary arteries (fig. 13): a single artery originated from the left sinus of Valsalva, coursed in the front of the aortic valve, giving the right coronary artery, then coursed in the right atrioventricular groove, encircled the aortic valve, and bifurcated to the anterior descending coronary artery and circumflex artery.

**Cardiovascular magnetic resonance imaging (CMR)** was performed and confirmed the enlargement of the right atrium ( $31.5 \text{ cm}^2$ ), RV ( $37.5 \text{ cm}^2$ ; end-diastolic volume,  $192 \text{ mL}$ ), subvalvular stenosis (diameter  $1.7 \times 0.6 \text{ mm}$ ), and normal systolic function of the RV (ejection fraction,  $62\%$ ). The examination revealed also a wide permeable connection of the conduit between the RV and MPA, the narrowing of the right and left pulmonary arteries, and RV overload (late gadolinium enhancement in the connection of the RV posterior wall and interventricular septum).

Because of the differences between the symptoms reported by the patient's mother and the results of our studies, the case was presented at the Meeting of

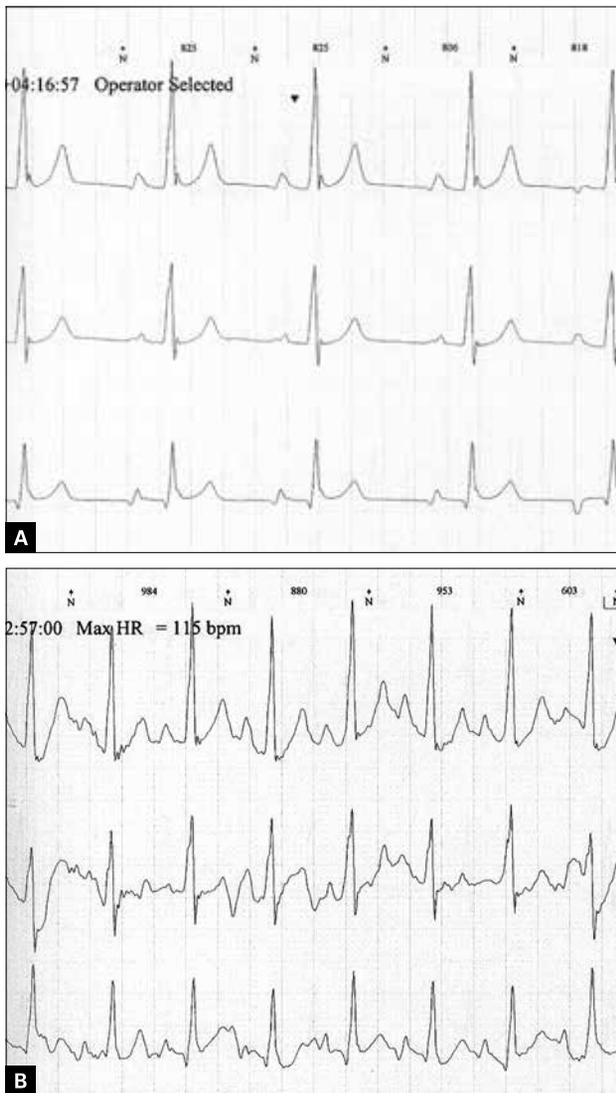
the CRCD to decide on the best method of treatment. As a result, observation and catheterization were recommended but the patient did not agree to undergo right heart catheterization.

## Discussion

About 3% of the patients with tetralogy of Fallot have anomalous left anterior descending coronary artery. An anomalous coronary artery, crossing the RVOT, makes the reconstruction of the RVOT by using a transannular patch impossible and it may



**Fig. 1.** 12-lead electrocardiogram.. Sinus rhythm 70 bpm, right axis deviation, Q wave in III, aVF, inverted waves in I, aVL and signs of RV enlargement



**Fig. 2.** 24-hour Holter electrocardiogram. **A.** Episode of wandering peacemaker. **B.** Episode of supraventricular rhythm – 115 bpm lasting 30 seconds

necessitate a conduit type of repair. Conduits connect the RV and MPA and they enabled to repair previously uncorrectable congenital heart defects. They can be nonvalved or valved (xenograft, bioprosthetic valves, bovine jugular vein [Contegra] pericardial or pulmonary/aortic homografts). The first conduit (nonvalved) was placed in 1964 by Rastelli et al. [2] in a 6-year-old child with pulmonary atresia. After 2 years, Ross and Sommerville [3] used an aortic valve homograft for the correction of pulmonary atresia. However, durability of the conduits is limited by the lack of growth, aneurysmal dilatation, or degeneration and calcification. Conduit can become dysfunctional and it may undergo obstruction and/or regurgitation. It is associated with such effects as RV dilatation and its systolic and diastolic dysfunction, extension of tricuspid annulus, and, in consequence, tricuspid regurgitation. In the long term, it may cause arrhythmias, heart failure, and sudden death [4]. About 40% of the patients with conduit does not require reoperation within the subsequent 20 years, while the rest of the patients are affected by

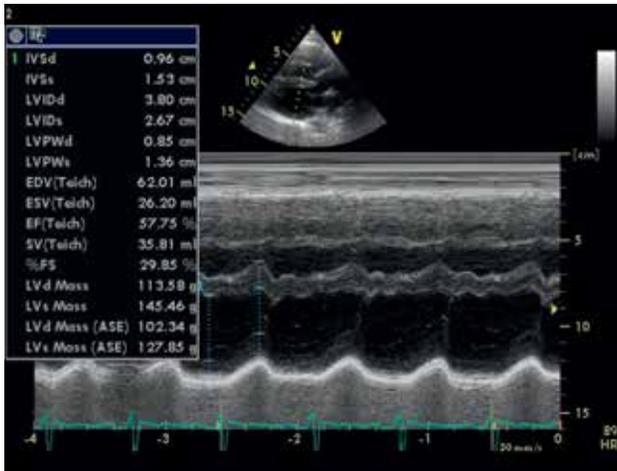
hemodynamic consequences of conduit failure and require surgical procedure [5]. Of note, in some studies, the lifespan of conduits has been reported to be less than 10 years [6–8]. Thus, the majority of the patients with conduits from the RV to MPA undergo multiple surgical operations during their lifetime.

The most common symptoms reported by the patient with conduit failure are dyspnea, palpitations, and syncope. Patients with a comparable degree of conduit failure usually experience the symptoms subjectively and their tolerance varies between individuals. Subjects with mental disorder constitute a substantial group of patients with congenital heart failure. What is more, they pose a specific diagnostic challenge owing to the lack of cooperation with a physician. That is why, it is usually difficult to identify objective symptoms, which is indispensable for diagnosis. In these cases, it is usually insufficient to perform a clinical examination, such as the CPET, including such parameters as time of exercise, peak oxygen uptake, ventilation efficiency ( $VE/VCO_2$  slope), chronotropic and blood pressure response, and exercise-induced arrhythmias, which usually enables to assess the fitness of the patients and may correlate with the mortality and morbidity of the subjects with congenital heart disease [9]. Thus, it is necessary to perform additional examination in these cases. Among the available techniques, CMR enables to examine the morphology and function of the heart. It is considered to be a more valuable technique than transthoracic echocardiography in assessing the RV volume, ejection fraction, and outflow tract, as well as in examining the condition of the RV–MPA conduit and the measurements of regurgitation of the pulmonary valve.

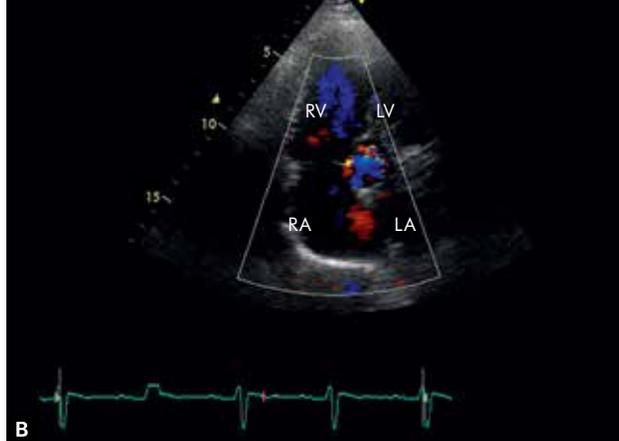
For patients with conduit failure with indications for intervention (see below), a catheter procedure (such as balloon dilatation, stent implantation) should be considered. To reduce the number of repeat cardiac surgeries in the group of patients with progressive obstruction or regurgitation of the conduit, endovascular treatment may be administered in selected cases. Moreover, considering that those patients have already undergone a number of surgical procedures, and will probably suffer from more interventions in the future, a noninvasive approach is always preferable [10].

The available data on endovascular treatment in patients with tetralogy of Fallot and nonvalved conduit are limited.

One of transcatheter treatment options for conduit stenosis is stent implantation. There are studies demonstrating that stenting the obstructed conduits may reduce the pressure gradient across the conduit and RV systolic pressure [11]. According to one study, the reduction of the gradient was more significant in patients with higher base pressure and in those who had not undergone interventions on the branches of the pulmonary artery before [12]. The study included 241 patients with median gradient RV pressure and conduit gradient of 89 mm Hg and 58 mm Hg, respectively. According to the study, conduit stenting enabled to delay repeat cardiac surgery for 3.9 years in the group of children older than 5 years, and for 2.7 years overall. The intervention significantly reduced RV systolic pressure

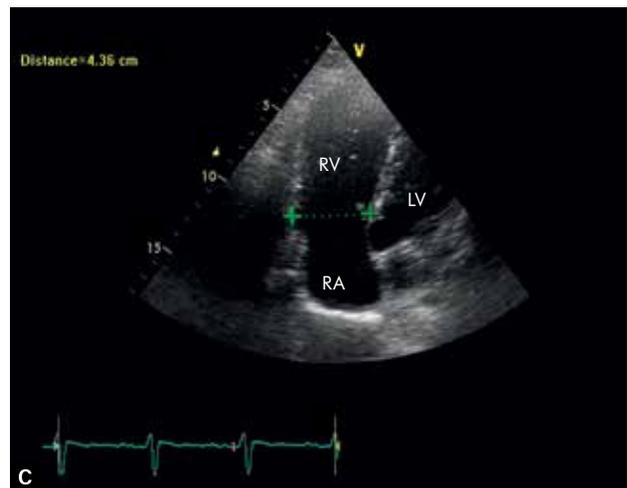
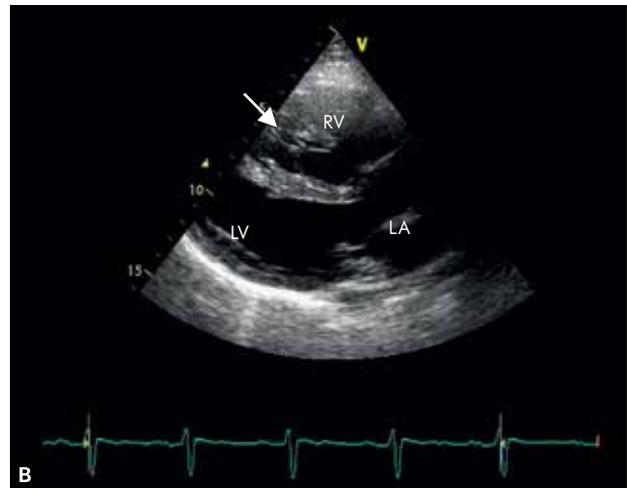
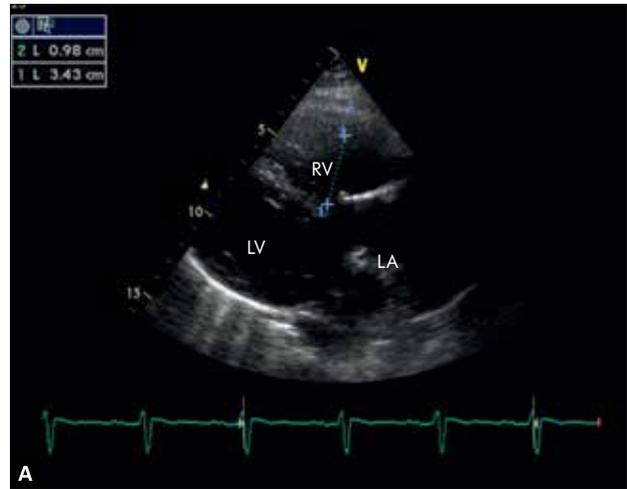


**Fig. 3.** Transthoracic echocardiography. Parasternal long-axis view. M-mode imaging. Normal left ventricle function



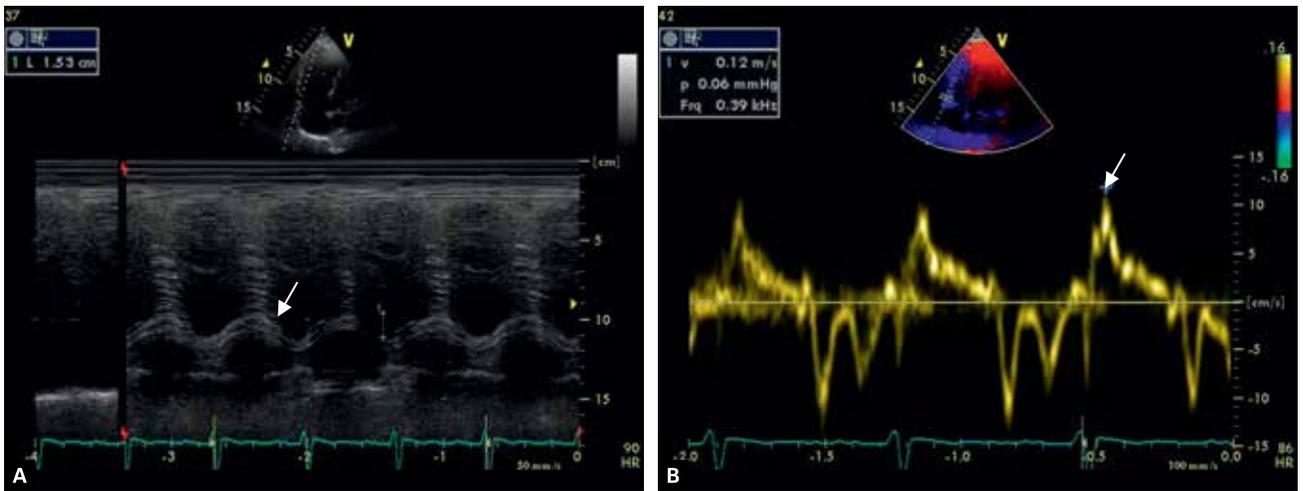
**Fig. 4.** Transthoracic echocardiography. Color Doppler imaging. Residual VSD. **A.** Parasternal long-axis view. **B.** Parasternal short-axis view. RA – right atrium, RV – right ventricle, LA – left atrium, LV – left ventricle

(from  $89 \pm 18$  to  $65 \pm 20$  mm Hg) and the peak RV–MPA gradient (from  $59 \pm 19$  to  $27 \pm 14$  mm Hg). Unfortunately, the commonly observed complication during follow-up was the fracture of the stent without any hemodynamic consequences, diagnosed during catheterization in 40%

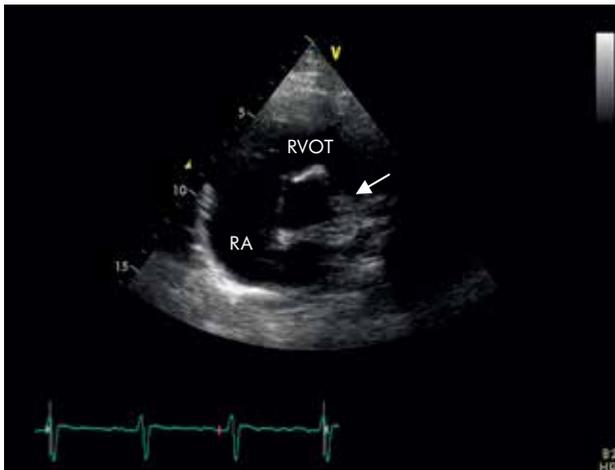


**Fig. 5.** Transthoracic echocardiography. **A.** Parasternal long-axis view. RV enlargement 34 mm (N: 9–26 mm). RV muscle hypertrophy 10 mm (N: 4–5 mm). **B.** Parasternal long-axis view. Septomarginal trabecule (arrow). **C.** Apical four-chamber view. RV enlargement diameter 44 mm (N: 20–35 mm). RA – right atrium, RV – right ventricle, LA – left atrium, LV – left ventricle

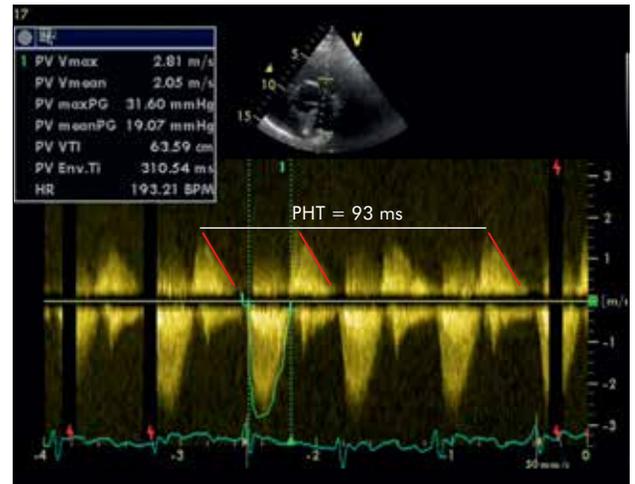
of the patients. However, this intervention has a significant drawback owing to the fact that the relief of stenosis leads to the creation of free pulmonary regurgitation. During stent implantation, the important part of the procedure is predilatation of the stenotic area. It allows to determine the location of the stenosis, eventual compression of the coronary arteries with simultaneous



**Fig. 6.** Transthoracic echocardiography. Apical four-chamber view. **A.** M-mode. Tricuspid annular plane systolic excursion (TAPSE) = 15 mm (white arrow) ( $N: \geq 23$  mm). **B.** Tissue Doppler imaging (TDI),  $S' = 12$  cm/s (white arrow) ( $N: \geq 12$  cm/s)



**Fig. 7.** Transthoracic echocardiography. Parasternal short-axis view. Calcification of hipoplastic pulmonic valve (white arrow). RA – right atrium, RVOT – right ventricle outflow tract



**Fig. 8.** Transthoracic echocardiography. Parasternal short-axis view. Continuous wave Doppler. Gradient in RVOT 32/19 mm Hg. Pulmonic regurgitation, pressure half time (PHT) = 93 ms

coronary angiography, and helps limit the risk of stent malposition.

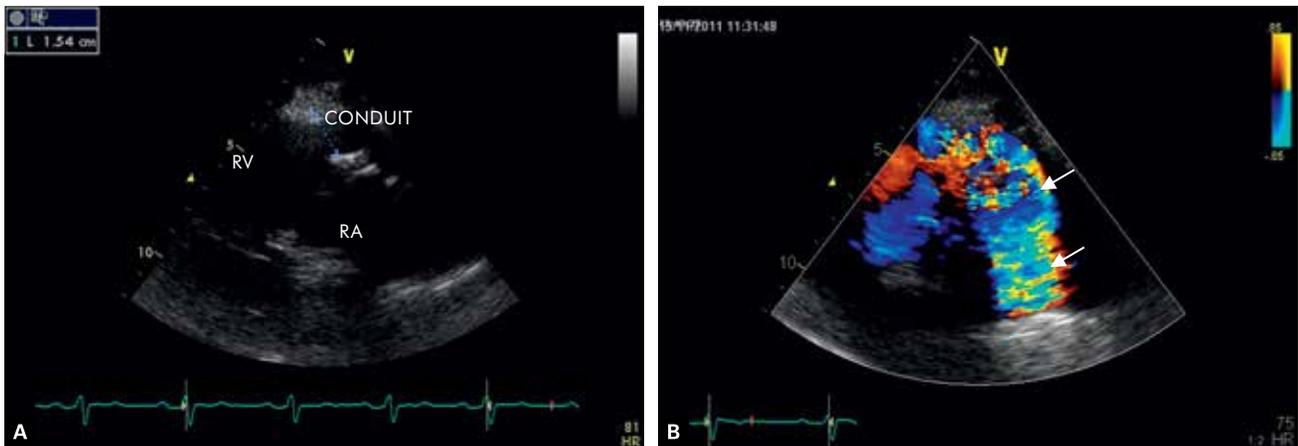
The latest innovation, namely, percutaneous pulmonary valve implantation, is used in patients with dysfunctional conduit or homograft connecting the RV with MPA. It was implanted for the first time in 2000, and since then, more than 1000 procedures have been performed worldwide. Currently, the contraindications for percutaneous pulmonary valve implantation include the occlusions of the central veins, active infection, outflow tract of the native tissue and of unfavorable morphology ( $>22$  mm in diameter), conduit of less than 16 mm, and unfavorable coronary anatomy (compression by the extended implant) [12].

The first results of the studies on the effectiveness of percutaneous pulmonary valve implantation have been published recently. The study included 102 patients classified into 1 of 3 groups: pulmonary valve regurgitation (18 patients), pulmonary stenosis (36 patients), or combined dysfunction of conduit/pulmonary homograft [13]. After 352 days of follow-up, 9% of the patients

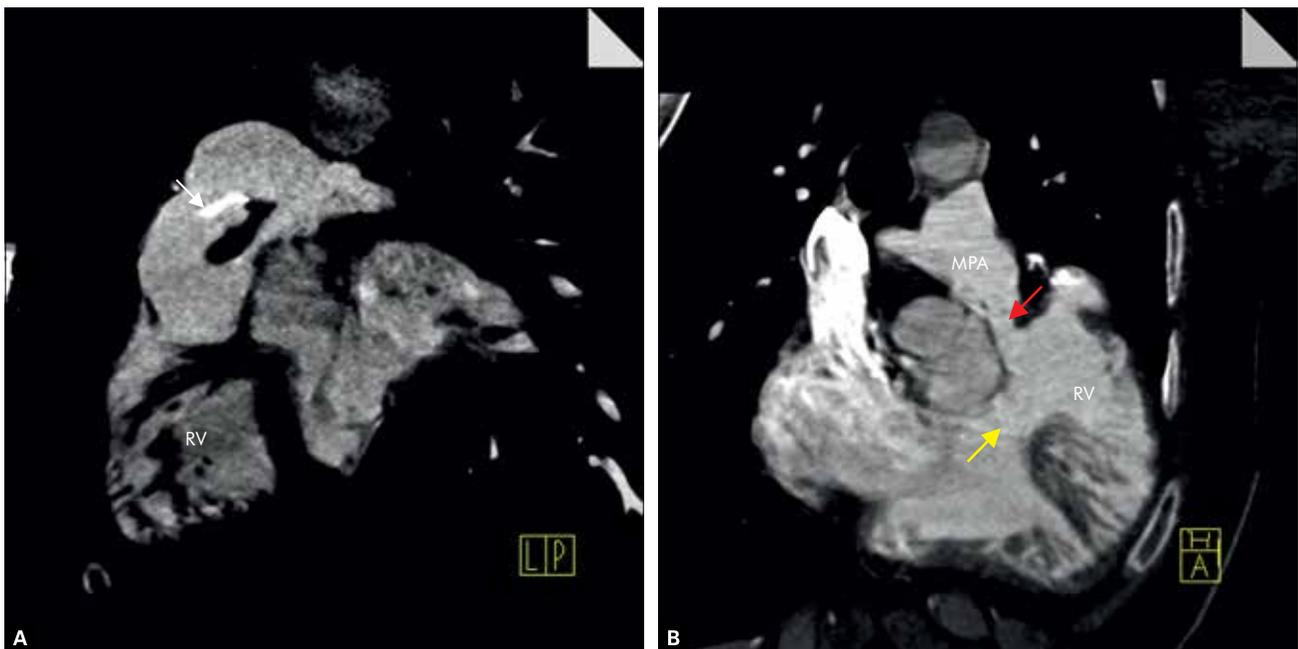
required recatheterization because of peak gradient exceeding 50 mm Hg. In 5% of the patients, the fracture of the stent was observed. One patient was affected by endocarditis and 1 patient died. In the remaining patients, the reduction of the pulmonary pressure gradient, pulmonary regurgitation, and the improvement of the RV function were reported. Maximum oxygen uptake before the intervention was 22.4 mL/kg/min, and it has been stable during follow-up.

Eicken et al. [13] also showed a significant reduction of the pressure gradient in the RVOT and indicated improvement of the RV parameters within 1 to 12 months of the follow-up after percutaneous pulmonary valve implantation. A total of 65 patients were divided into 2 groups: the first one included patients with stenosis, and the second patients with regurgitation. The study also showed that systolic function and maximum oxygen uptake improved significantly only in patients with stenosis.

In 2011, the results of a 6-month prospective study were published. The study included 10 patients with



**Fig. 9.** Transthoracic echocardiography. Conduit between RV and main pulmonary artery. **A.** Connection of the conduit with RV has a diameter of 15 mm. **B.** Turbulent flow in the conduit (white arrows). RA – right atrium, RV – right ventricle



**Fig. 10.** Cardiovascular computed tomography. **A.** Conduit with calcification. (white arrow). **B.** RVOT obstruction (red arrow), VSD (yellow arrow). RV – right ventricle, MPA – main pulmonary artery, RVOT – right ventricle outflow tract, VSD – ventricular septal defect

**Table 1.** Transthoracic echocardiography. Pressure gradient measured in the right ventricular outflow tract at different time points (RVOT)

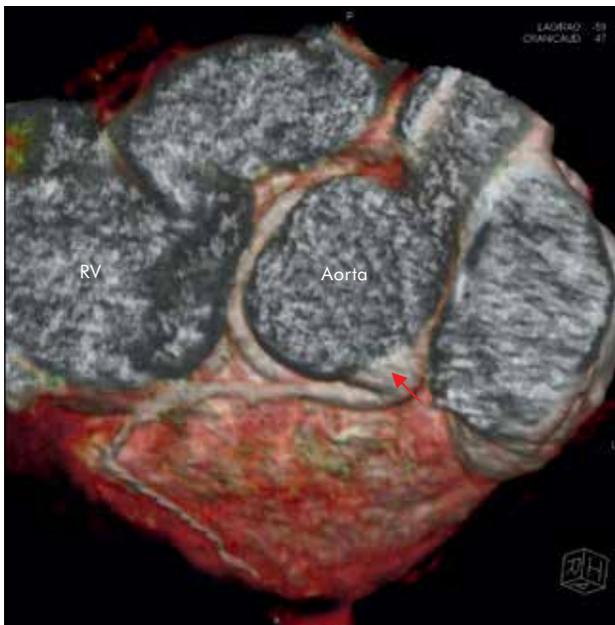
	January, 2011	July, 2011	November, 2011	May, 2012
RVOT (mm Hg)	28.5/17	55/32	30/15	31/19

RVOT, who underwent Melody valve implantation with bare-metal stent (BMS) [14]. Six months after percutaneous pulmonary valve implantation with BMS, the reduction in RVOT obstruction was associated with a significant decrease in RV end-diastolic and end-systolic volumes, improvement in the RV ejection fraction, and a decrease in the NYHA class. Importantly, no stent fractures were observed.

In 2009, a study that compared hemodynamic effects between percutaneous pulmonary valve implantation and treatment of RVOT with BMS implantation was published [15]. Fourteen patients with congenital heart diseases (transposition of the great arteries, tetralogy of Fallot, double-outlet RV), with significant RVOT obstruction, and after various surgical interventions (Rastelli procedure, Ross procedure) underwent BMS implantation followed by percutaneous pulmonary valve implantation. The effects (ventricular volumes and function, great vessel flow, and hemodynamic invasive pressure measurements) of the procedures were assessed by radiography / CMR hybrid laboratory. The measurements were performed before BMS, after BMS, and after percutaneous pulmonary valve implantation. According to the study, BMS significantly reduced the ratio of the RV to systemic pressure with no further change after percutaneous pulmonary valve



**Fig. 11.** Cardiovascular computed tomography. **A.** Hypoplastic pulmonic valve (white arrow), conduit with calcification (red arrow). **B.** RPA – 1,5×0,9 cm (yellow arrow), LPA – 1,6×1,0 cm (green arrow)



**Fig. 12.** Cardiovascular computed tomography. Three-dimensional reconstruction. Single artery origin from left sinus of Valsalva (red arrow). RV – right ventricle

implantation. However, BMS resulted in free pulmonary regurgitation, which was eliminated after percutaneous pulmonary valve implantation. Effective RV stroke volume (RV stroke volume minus pulmonary regurgitant volume) after BMS remained unchanged but was significantly increased after revalvulation with percutaneous pulmonary valve implantation. The improvements after percutaneous pulmonary valve implantation were accompanied by a significant reduction in the heart rate at maintained cardiac output. The study demonstrated superior acute hemodynamic effects of percutaneous pulmonary valve implantation over BMS in patients with RVOT obstruction.

When performing any of the above procedures, it is necessary to exclude a potential possibility of coronary artery damage during stent implantation, which could be the cause of sudden death. Anomaly of the left anterior descending coronary artery arising from the right sinus of Valsalva is frequent in tetralogy of Fallot, affecting 3% of the patients. The right coronary artery originating from the left anterior descending coronary artery, which passes through the aortic root and the MPA, can be compressed by the stent. For that reason, a proper estimation of the coronary artery tracts is necessary. In some cases, the balloon test should be performed, because it can mimic the condition after stenting. The balloon inside the homograft should be first decompressed to a diameter similar to the size of the valve or stent after the implantation to exclude coronary artery compression by the implant. Selective coronarography should be simultaneously performed.

## Management strategy

In line with the 2010 European Society of Cardiology guidelines for the management of adult patients with congenital heart disease, our patient undergoes regular cardiac follow-up in the CRCDC. So far, the patient has been stable and have had no indications for an intervention (Table 2, 3). Medical treatment was modified: metildigoxin was excluded and replaced by  $\beta$ -blocker (metoprolol CR, 25 mg/d). He is scheduled to visit the CRCDC once a year, providing that he remains stable.

Echocardiography and CMR will be performed every year to check for complications including RVOT obstruction, pulmonary regurgitation, RV dilatation and dysfunction, residual VSD, aortic root dilatation with aortic regurgitation, LV dysfunction, and endocarditis. In the case of progressive symptoms, computed tomography will be performed to image the conduit, pulmonary artery, and coronary artery anatomy.

**Table 2.** Indication for intervention in patients after repair of tetralogy of Fallot [11]

Indications	Class	Level
Aortic valve replacement should be performed in patients with severe aortic regurgitation with the signs and symptoms of LV dysfunction	I	C
Reoperations should be performed in symptomatic patients with severe pulmonary regurgitation and/or stenosis (RV systolic pressure >60 mm Hg; tricuspid regurgitation velocity >3.5 m/s)	I	C
Reoperations should be considered in asymptomatic patients with severe pulmonary regurgitation and/or pulmonary stenosis when at least one of the following criteria is present: <ul style="list-style-type: none"> <li>■ Decrease in objective exercise capacity</li> <li>■ Progressive RV dilation</li> <li>■ Progressive RV systolic dysfunction</li> <li>■ Progressive tricuspid regurgitation (at least moderate)</li> <li>■ RVOT obstruction with RV systolic pressure &gt;80 mm Hg (tricuspid regurgitation velocity &gt;4.3 m/s)</li> <li>■ Sustained atrial/ventricular arrhythmias</li> </ul>	II a	C
VSD closure should be considered in patients with residual VSD and significant LV volume overload or if the patient is undergoing repeat pulmonary valve surgery.	II a	C

**Table 3.** Indication for intervention in patients with right ventricular to pulmonary artery conduits [11]

Indications	Class	Level
Symptomatic patients with RV systolic pressure >60 mm Hg (tricuspid regurgitation velocity >3.5 m/s (may be lower in the case of reduced flow) and/or moderate/severe pulmonary regurgitation should undergo surgery.	I	C
Asymptomatic patients with severe RVOT stenosis and/or severe PR should be considered for surgery when at least one of the following criteria is present: <ul style="list-style-type: none"> <li>■ Decrease in exercise capacity (CPET)</li> <li>■ Progressive RV dilatation</li> <li>■ Progressive RV systolic dysfunction</li> <li>■ Progressive tricuspid regurgitation (at least moderate)</li> <li>■ RV systolic pressure &gt;80 mm Hg (tricuspid regurgitation velocity &gt;4, 3 m/s)</li> <li>■ Sustained atrial/ventricular arrhythmias</li> </ul>	II a	C

Moreover, the CPET will be performed to monitor such parameters as time of exercise, peak oxygen uptake, VE/VCO<sub>2</sub> slope, chronotropic and blood pressure response, and exercise-induced arrhythmias.

To indicate supraventricular or ventricular arrhythmias, which could be the cause of sudden cardiac death, electrocardiogram and Holter monitoring will be performed at each visit. In the case of new symptoms such as syncope, presyncope, fatigue, or reduced exercise tolerance, the check-ups will be more frequent and electrophysiological testing will be considered.

Currently there are no contraindications for regular physical activity. To avoid infective endocarditis, a preventive treatment with antibiotics is recommended.

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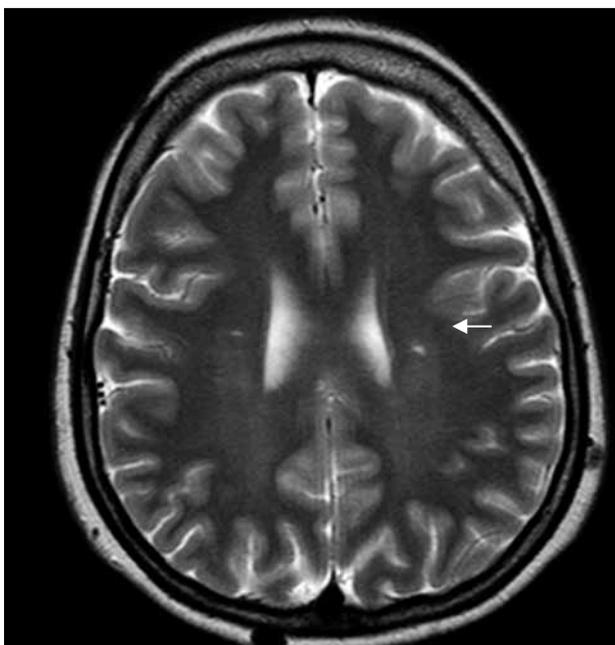
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## Patient with patent foramen ovale and thrombophilia, after ischemic stroke, massive pulmonary thromboembolism, and acute coronary syndrome (RCD code: IV-4D)

Monika Komar, Jakub Stępniewski, Tadeusz Przewłocki, Bartosz Sobień, Hanna Dziedzic, Maria Lelakowska, Piotr Podolec

### Background

Patent foramen ovale (PFO) is a residue of the foramen ovale, an integral part of the normal fetal circulation [1]. It is an oblique, slit-shaped tunnel formed by two septa, primum and secundum [2]. During the intra-uterine period, its role is to lead oxygenated blood from the venal to the arterial part of the circulatory system [2]. In 70% to 75% of the newborns, the septa become fused by the age of 2 years; however, in up to 25% to 30% of the general population, the connection remains patent [3]. The reasons why a PFO fails to close are unknown, but this is likely a multifactorial process [4]. Although most often asymptomatic, several clinical conditions are known to be strongly related to the presence of a PFO. Cryptogenic stroke, migraine, and vascular headache or decompression sickness and air embolism are the most common complications [5–8]. Acute myocardial infarction as well as other forms of paradoxical embolism such as renal infarction, fat embolism, or carcinoid heart disease are less common [9–12].

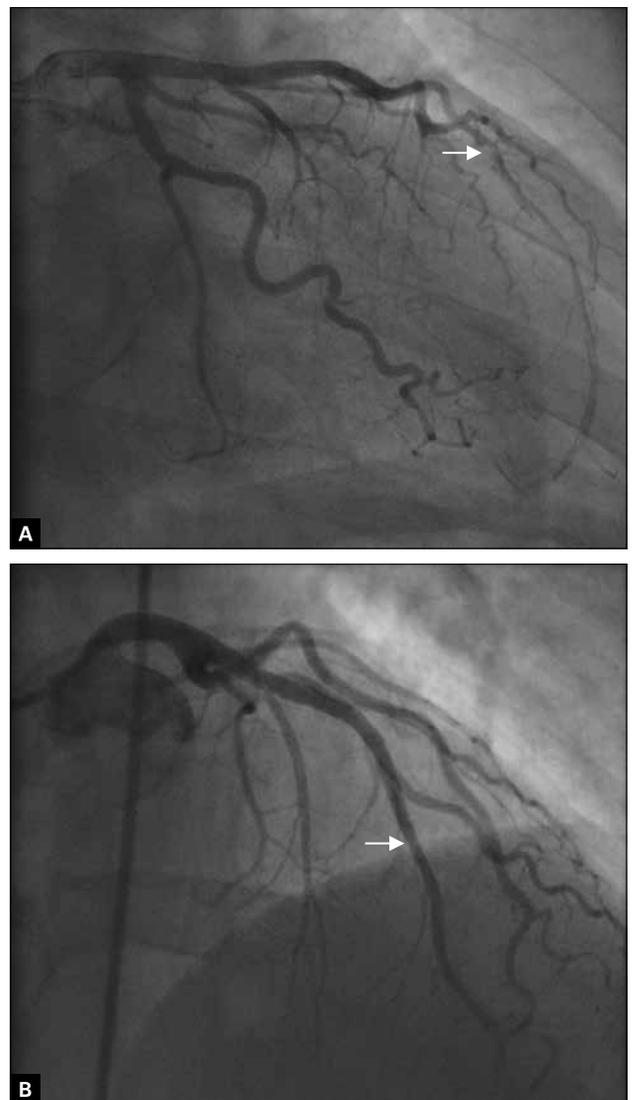


**Fig. 1.** Brain computed tomography. Cerebral ischemia. Ischemic lesion in the left parietal lobe (arrow)

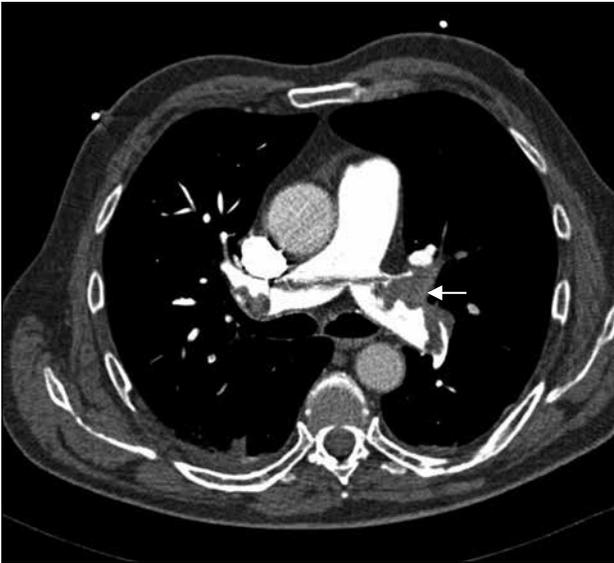
### Case presentation

A 67-year-old Caucasian man after cerebral ischemic episode and massive pulmonary thromboembolism was referred to our center for complete cardiac evaluation.

In May 2011, he was hospitalized in a local hospital due to sudden loss of consciousness accompanied by right-sided hemiparesis and aphasia. An electrocardiogram (ECG) revealed atrial fibrillation and ST-segment elevation in leads V1 through V6. A brain computed tomography (CT) scan, performed at that time, showed an ischemic lesion located in the left parietal lobe (fig. 1). Laboratory and ECG results suggested cardiac ischemia; therefore, coronary angiography was performed, showing a thrombus in the left anterior descending branch (fig. 2A). Subsequent revascularization was performed with a positive effect of thrombectomy (fig. 2B). Additional CT angiography of the pulmonary arteries revealed massive pulmonary thromboembolism (fig. 3). Anticoagulation therapy was initiated and the patient



**Fig. 2.** Coronary angiography. **A.** A thrombus in the left anterior descending branch (LAD) (arrow). **B.** Coronary angiography. Successful thrombectomy (arrow)



**Fig. 3.** Cardiovascular computed tomography. Angiography of the pulmonary arteries. Massive pulmonary thromboembolism (arrow)

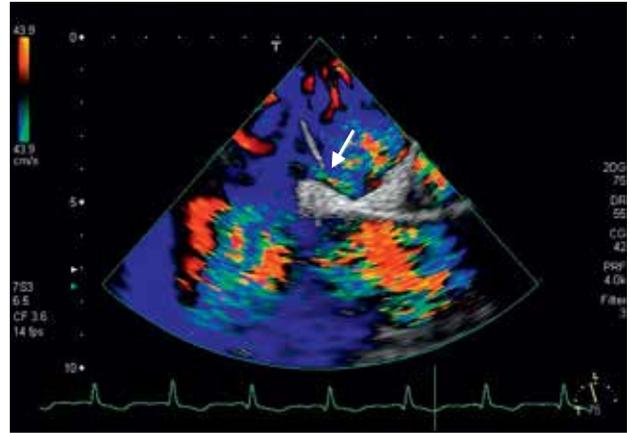


**Fig. 4.** Transesophageal echocardiography. The left upper view. Contrast imaging. Microbubbles passing across the patent foramen ovale (PFO) (arrow)

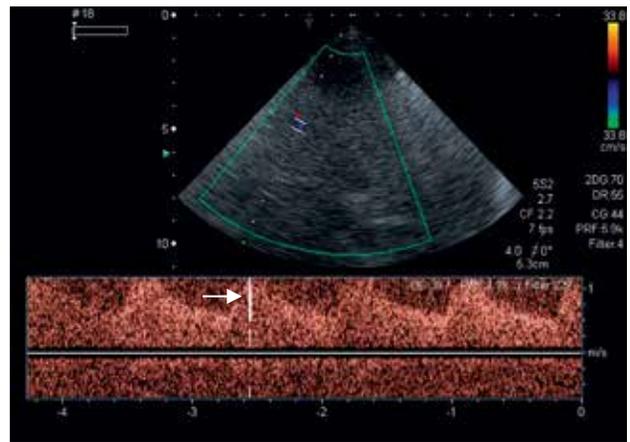
was discharged from the hospital with the diagnosis of transient ischemic attack, acute coronary syndrome, and massive pulmonary thromboembolism.

Based on the clinical findings suspicion of a concomitant hypercoagulable condition was raised. Laboratory evaluation of hemostasis and thrombosis was therefore conducted, which revealed factor V Leiden mutation. The patient was kept on vitamin K antagonists and aspirin.

On admission to our center, the patient was hemodynamically stable with persistent right upper limb dysmetria and ataxia. Holter ECG monitoring, ambulatory blood pressure monitoring, and tilt table test did not reveal any abnormalities. Transesophageal echocardiography (TEE) confirmed the presence of a PFO (fig. 4). An agitated saline contrast injected to the right basilic vein during the Valsalva maneuver proved right-to-left shunting across the PFO (fig. 5). To confirm the hemodynamic significance of PFO shunting, a transcranial Doppler (TCD) study was



**Fig. 5.** Transesophageal echocardiography. The left upper view. Color Doppler. Right-to-left shunting across the patent foramen ovale (PFO) (arrow)



**Fig. 6.** Transcranial Doppler. Microbubble artifact (spike) detected in the middle cerebral artery (arrow)

performed. Microbubble signals were identified and the results were considered positive (fig. 6).

Therefore, considering the past medical history of the patient and thrombophilia related to the factor V Leiden mutation, we discussed whether a PFO closure device was indicated in this patient as secondary stroke prevention.

## Discussion

Recently, there has been a growing interest in PFO in clinical practice. The causal relationship between PFO and ischemic stroke has been evaluated in several studies. About half of the young patients with cryptogenic stroke have PFO, while the coexistence of these two clinical conditions in the general population is rare [13,14].

All patients with paradoxical embolism and those showing the signs of a PFO should be carefully assessed for the presence of the PFO and for a possible relationship between the PFO and the embolic event by excluding other potential causes of thromboembolism and stroke.

A PFO is diagnosed by ultrasonography. Several modalities are used, including transthoracic echocardiography (TTE), TEE, TCD, or transmittal Doppler (TMD). TEE has emerged to be the gold standard method and is most commonly used [15,16]. It has the advantage of visualizing the site of the right-to-left shunt. It allows detailed evaluation of PFO morphology and its hemodynamic significance. TTE is less sensitive in diagnosing a PFO than TEE, although supported by detection of the right-to-left bubble passage after intravenous administration of agitated saline contrast on TMD, it becomes much more useful. [17–19] TCD, as a noninvasive tool, is a potential alternative to TEE; however, it only indicates the presence of the right-to-left shunt without specifying its site [20,21].

There are several controversies regarding the therapeutic possibilities for secondary stroke prevention. Medical therapy with antiplatelet agents or anticoagulation versus surgical or percutaneous closure are the most widely discussed treatment options [22]. The use of aspirin is supported by a few nonrandomized trials suggesting its potential benefit, and it is recommended by the 2012 American College of Chest Physicians and the 2011 American Heart Association/American Stroke Association guidelines [23–26]. These guidelines, however, do not recommend the use of anticoagulants in patients with PFO, unless an additional indication such as a hypercoagulable state is present.

The benefits of surgical PFO closure in patients with a history of stroke have not been fully determined [27–29]. There are no randomized trials comparing surgical closure with medical therapy. An important advancement in this field was the introduction of noninvasive percutaneous closure devices, although their effectiveness in secondary cryptogenic stroke prevention has not yet been established [30]. The available data show the reduction of stroke recurrence rate on one hand and potential risks including periprocedural vascular complications, new-onset arrhythmias, or device failure on the other. Several randomized clinical trials and meta-analyses have not shown clear benefit of this procedure [31–36].

## Management strategy

Considering that the patient had already been on anti-coagulant therapy with VKAs, we consulted a panel of experts about further management strategy during a videoconference of the Centre for Rare Cardiovascular Diseases (CRCDD). The experts recommended against PFO closure. A thorough hematological evaluation was necessary to assess the risk of thromboembolic episodes. VKAs were considered the treatment of choice.

Several months later, the patient was admitted to the hospital for follow-up. On admission, he had no new neurological symptoms or consequent thromboembolic complications. His clinical condition was good. However, he expressed concerns about our decision not to use the closure device. He admitted that he

would feel much safer if the procedure was performed. Therefore, considering his medical history and concomitant conditions, that is, thrombophilia related to the factor V Leiden mutation, we again referred to the experts of the CRCDD for the reevaluation of indications for PFO closure.

## Conclusion

The patient is at a high risk of thromboembolic consequences, including ischemic stroke, because of the hypercoagulable state and the history of thrombosis. The presence of a PFO additionally increases the risk of recurrent strokes. However, PFO closure, which is a potential source of further formation of thromboembolic material, is not recommended. Therefore, life-long anticoagulation therapy is the treatment of choice in this patient.

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## Female patient after correction of tetralogy of Fallot with severe pulmonary regurgitation and significant left-to-right shunt at the ventricular septal level (RCD code: IV-5A2)

Leszek Drabik, Lidia Tomkiewicz-Pająk, Tomasz Miszalski, Jacek Pająk, Bogusław Kapelak, Piotr Podolec

### Background

Tetralogy of Fallot is the most common cyanotic congenital heart disease after 1 year of age. Less than 5% of all patients with uncorrected tetralogy of Fallot live beyond the age of 40 years. Prognosis after surgical correction is good with a 32-year survival of 86% of the cases. Predictors of long-term mortality include older age at operation and postoperative right-to-left ventricular peak systolic pressure ratio of 0.5 or higher [1]. Surgery is performed to close ventricular septal defect (VSD) and relieve right ventricular (RV) outflow tract obstruction. Adult patients with surgical repair of tetralogy of Fallot in history often develop complications, which include severe pulmonary regurgitation (PR), RV outflow tract obstruction, RV dilation and dysfunction, residual VSD, aortic root dilation with aortic regurgitation, left ventricular (LV) dysfunction, endocarditis, atrial and ventricular tachycardia, and sudden cardiac death. We present a case of a female patient with several long-term complications after tetralogy of Fallot repair.

### Case presentation

A 40-year-old woman after surgical correction of tetralogy of Fallot was admitted to the hospital due to deterioration in exercise tolerance (New York Heart Association functional class III). Correction of tetralogy of Fallot was performed in 1974, and surgical closure of residual VSD was performed in 2003. A dual-chamber pacemaker was implanted due to sick sinus syndrome associated with paroxysmal atrial fibrillation in 2005. Current treatment included warfarin and metoprolol CR. A physical examination revealed a holosystolic murmur with a thrill at the fourth left intercostal space. The patient's weight was 47 kg, height 159 cm, body mass index 18.6 kg/m<sup>2</sup>, blood pressure 120/80 mm Hg, and heart rate 60 bpm. Regular normal breath sounds were heard and no cyanosis or peripheral edema was observed. The results of routine laboratory tests were within the normal limits except for elevated natriuretic peptide level (1300 pg/mL; normal range, <125 pg/mL).

A resting electrocardiogram showed sequential atrial and ventricular pacing. Holter monitoring did

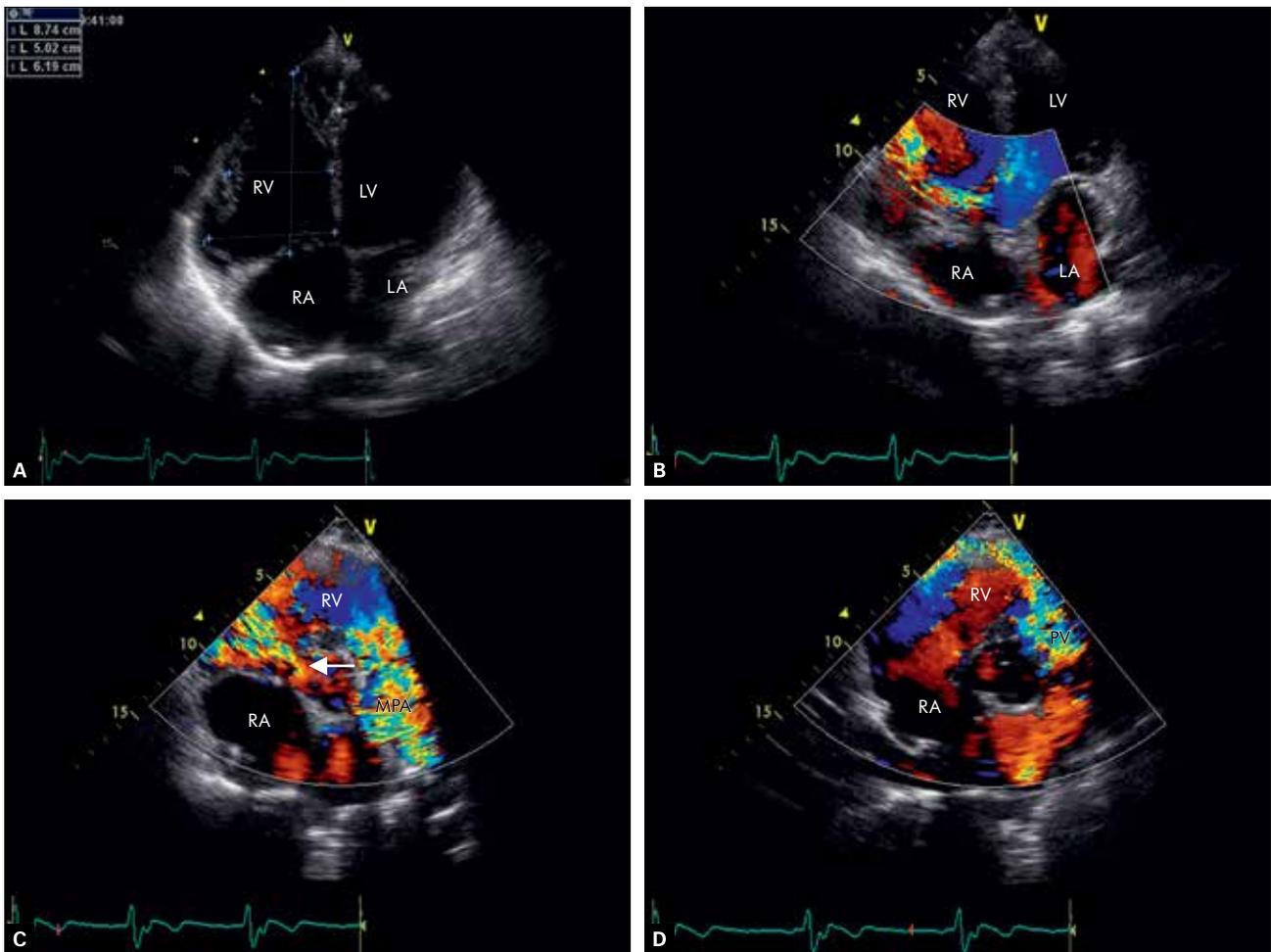
not reveal cardiac arrhythmias or pacing disturbances. Cardiopulmonary exercise testing showed reduced exercise tolerance (workload of 8.4 metabolic equivalents) and maximal oxygen consumption (15.2 mL/kg/min; normal range, >43.1 mL/kg/min). The values of maximal oxygen consumption were significantly lower compared with the previous measurements (February 2011, 22 mL/kg/min and October 2010, 23 mL/kg/min).

Transthoracic echocardiography revealed numerous abnormalities (fig. 1):

- enlargement of all heart chambers:
  - RV basal diameter, 62 mm (normal range, <42 mm); mid-cavity diameter, 50 mm (<35mm); longitudinal diameter, 88 mm (<86 mm), end-diastolic area, 48 cm<sup>2</sup> (<25 cm<sup>2</sup>)
  - LV end-diastolic diameter, 58 mm; 36 mm/m<sup>2</sup> (<31 mm/m<sup>2</sup>)
  - left atrial area at ventricular end-systole, 24 cm<sup>2</sup> (<20 cm<sup>2</sup>), right atrial area at ventricular end-systole, 32 cm<sup>2</sup> (<18 cm<sup>2</sup>)
- impaired RV systolic function: fractional area change, 31% (normal range, >35%), tricuspid annular plane systolic excursion, 14 mm (>16 mm)
- preserved LV ejection fraction, 62% (normal range, >55%)
- paradoxical septal motion
- residual perimembranous VSD with left-to-right shunting
- severe PR assessed by dense/steep jet deceleration, early termination of diastolic flow, shortened pressure half-time of 68 ms, and wide origin of regurgitation jet exceeding 50% annular width
- dilated pulmonary trunk and branches of the pulmonary artery
- mild aortic regurgitation
- moderate-to-severe tricuspid regurgitation assessed by vena contracta width (6 mm); tricuspid early diastolic wave velocity (0.9 m/s)
- dilated tricuspid annulus: four-chamber diameter (56 mm; normal range, 20–40 mm)
- elevated RV systolic pressure (normal range, <31mm Hg) estimated by:
  - the difference between LV peak systolic pressure and interventricular pressure gradient through residual VSD (120 – 60 = 60 mm Hg) tricuspid regurgitation gradient (40 mm Hg, V<sub>max</sub> 3.2m/s) and right atrial pressure (40 + 15 = 55 mm Hg)

Considering that cardiovascular magnetic resonance imaging (CMR) is not suitable for patients with pacemakers, we performed computed tomography (CT) as an alternative. A CT scan confirmed the following: RV enlargement, impaired RV systolic function, residual VSD situated below the right cusp of the aortic valve (the defect size was 12×15 mm), and dilation of the main pulmonary artery and branch pulmonary arteries (fig. 2).

Coronary angiography revealed no critical lesions in the coronary arteries. The findings of left ventriculography and pulmonary angiography were



**Fig. 1.** Transthoracic echocardiography. **A.** Apical four-chamber view, diastole. Enlarged right ventricle (basal diameter, 62 mm; mid-cavity diameter, 50 mm; longitudinal diameter, 88 mm; end-diastolic area,  $48 \text{ cm}^2$ ). Dilated tricuspid valve annulus, 56 mm. **B.** Apical five-chamber view. Residual perimembranous VSD with left-to-right shunt. **C.** Parasternal short-axis view at the base of the heart. Residual perimembranous VSD with left-to-right shunt (white arrow). Turbulent flow pattern in pulmonary trunk. **D.** Parasternal short-axis view at the base of the heart. Severe PR, a regurgitant jet width is  $>50\%$  annular width. VSD – ventricular septal defect, PR – pulmonary regurgitation, RA – right atrium

consistent with those of echocardiography and CT. Right heart catheterization confirmed the presence of residual VSD with left-to-right shunt (the ratio of pulmonary-to-systemic flow was 2:1). Other findings included mild pulmonary hypertension (mean pulmonary artery pressure, 29 mm Hg; pulmonary hypertension  $\geq 25$  mm Hg), increased pulmonary vascular resistance ( $203.9 \text{ dyne} \times \text{s} \times \text{cm}^{-5}$ ;  $<130 \text{ dyne} \times \text{s} \times \text{cm}^{-5}$ ), and increased pulmonary capillary wedge pressure (16 mm Hg;  $<12$  mm Hg). An increase in the pulmonary pressure and resistance had been observed since 2007 (Table 1).

## Discussion

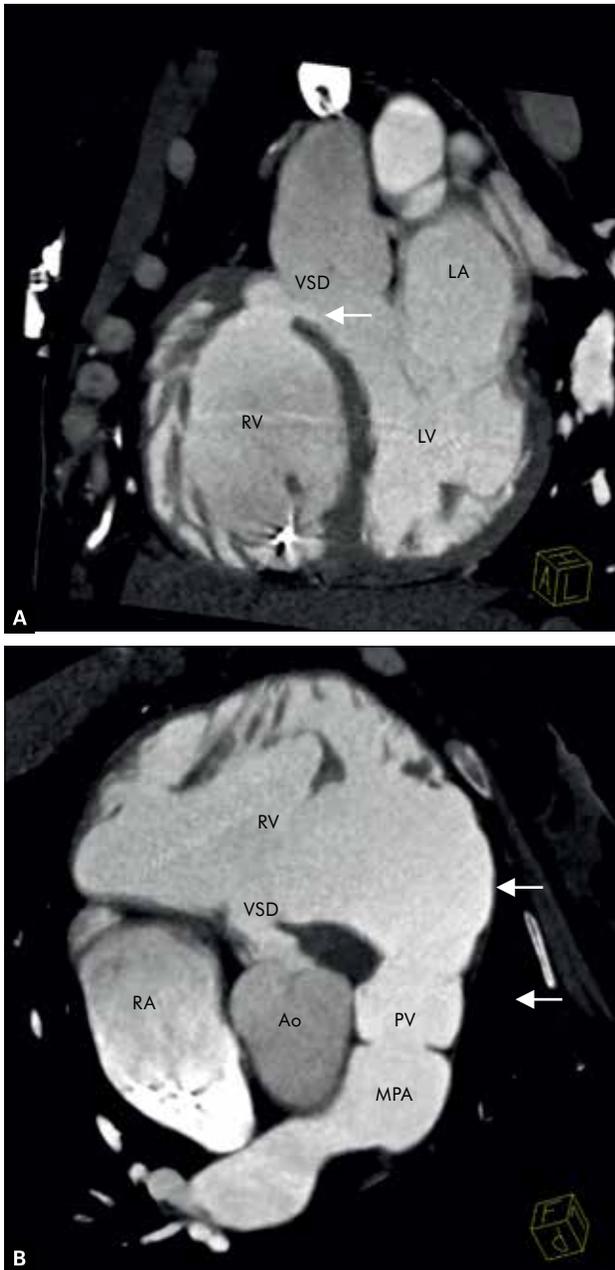
We described a case of a patient after repair of tetralogy of Fallot with severe pulmonary valve regurgitation and significant left-to-right shunting through the residual VSD.

Patients after transannular patch repair of the RV outflow tract obstruction have higher degree of PR

compared with patients with subvalvular resection or repair without a patch [2]. PR may be well-tolerated for decades before any symptoms develop but, in some patients, it can lead to progressive RV dilatation, onset of tricuspid regurgitation, and the need for surgery. It is also known as a risk factor for ventricular arrhythmias and sudden cardiac death [3]. Long-term consequences of PR are augmented by coexisting distal pulmonary stenosis and pulmonary arterial hypertension.

CMR is the gold standard to measure the RV function and severity of PR. A regurgitation fraction of 20% to 40% assessed with cardiac MRI is regarded as severe regurgitation [4]. Cardiac MRI cannot be performed in the presence of pacemakers, implantable cardioverter-defibrillators, cochlear implants, and clips for aneurysms in the brain.

The measurement of PR severity by echocardiography is less validated than that of mitral and aortic regurgitation degree. The European Association of Echocardiography recommends several parameters for grading the severity of PR: pulmonary valve morphology, color-flow jet width, continuous-wave



**Fig. 2.** Cardiovascular computed tomography. **A.** Modified three-chamber view. Residual perimembranous VSD (white arrow). **B.** Right ventricular outflow tract (arrows). Residual perimembranous VSD. RA – right atrium, PV – pulmonary valve, MPA – main pulmonary artery, Ao – aorta, VSD – ventricular septal defect

signal of the PR jet, and pulmonary-to-aortic flow by pulsed-wave Doppler. The cut-off values for the vena contracta width, effective regurgitant orifice area, and regurgitant volume have not been established for routine use in the clinical setting [5]. Silversides et al. [4] reported a pressure half time of less than 100 ms to be highly sensitive and specific for identifying severe PR in patients after repair of tetralogy of Fallot or after pulmonary valvulotomy [4]. Puchalski et al. [6] reported that jet/annulus width exceeding 50% identified patients with severe PR (Table 2).

Timing for pulmonary valve replacement is the most challenging aspect of treatment. Possible beneficial effects should be weighed against the risk

**Table 1.** Hemodynamic data

Pressure [mm Hg]	2007	2011
RA	14/16/12	16/19/14
RV	51/3/11	61/8/17
pulmonary artery	49/11/23	59/12/29
pulmonary capillary wedge pressure	13/12/12	20/9/16
aorta	116/65/84	126/74/95
Saturation [%]		
superior vena cava	53.8	50.3
inferior vena cava	60.6	62.8
pulmonary artery	72.6	77.9
aorta	91	97.1
cardiac output [L/min]	5.3	5.1
ratio of pulmonary-to-systemic flow	2.16:1	2.00:1
pulmonary vascular resistance [dyne $\times$ s $\times$ cm <sup>-5</sup> ]	175	203.9
total peripheral resistance [dyne $\times$ s $\times$ cm <sup>-5</sup> ]	1940	1490

of reoperation due to graft dysfunction. Perioperative mortality in patients without heart failure is low (<1%) [7]. Pulmonary valve replacement results in improvement in exercise capacity, reduction of the RV size, and decrease in QRS duration [8]. A positive effect of pulmonary valve replacement on the RV function is unlikely as soon as the end-diastolic volume exceeds 160 mL/m<sup>2</sup>. Delaying pulmonary valve replacement until the patient becomes symptomatic may increase the risk of high preoperative RV volume [9]. Achieving normalization in the RV volume may improve long-term outcome but there are very limited data on long-term mortality. The development of complications that require a surgery, for example, significant residual VSD, severe tricuspid regurgitation, or pulmonary stenosis may affect the timing of pulmonary valve replacement. Another factors include the development of sustained atrial or ventricular arrhythmias, QRS duration, and the presence of myocardial fibrosis on CMR [6,7].

There are a number of different pulmonary valve prostheses, such as allografts, xenografts, and mechanical prostheses. Allografts are most common but approximately 50% of the patients will require reoperation due to graft dysfunction 10 years after the surgery [10]. Compared with bioprosthesis, mechanical valve prosthesis shows a lower initial gradient and no substantial increase in the gradient or regurgitation with time. The advantages are reduced by the risk of valve thrombosis and pannus-related dysfunction, leading to similar reoperation rates [11]. Percutaneous pulmonary valve implantation (Melody, Medtronic, Inc.) may be an option for selected patients with pulmonary homograft dysfunction. Patients after repair

**Table 2. Grading the severity of pulmonary regurgitation (PR) [5]**

Parameters	Mild PR	Severe PR
pulmonary valve morphology	normal	abnormal
color-flow jet width	small, <10 mm in length with narrow origin	large, with wide origin; may be brief in duration
continuous-wave Doppler signal of PR jet	faint/slow deceleration	dense/steep deceleration, early termination of diastolic flow
pulmonary vs. aortic flow by pulsed-wave Doppler ultrasound	normal or slightly increased	greatly increased

of tetralogy of Fallot involving valvotomy or valvec-tomy may not provide secure anchorage to the stented valve. Early after percutaneous pulmonary valve im-plantation, a significant decrease in the RV end-dia-stolic volume is observed [12]. The rate of complica-tions in short-term follow-up is low but the longevity of the valve is unknown [13].

According to the current guidelines, pulmonary valve replacement is the standard treatment in symp-tomatic patients with severe PR. It should be consid-ered in asymptomatic patients with progressive RV dilation or systolic dysfunction, progressive tricuspid regurgitation, and sustained atrial or ventricular ar-rhythmias [7].

**Table 3. Indications for surgical VSD closure [7]**

	class* level#
Patients with symptoms that can be attributed to left-to-right shunting through (residual) VSD and who have no severe pulmonary vascular disease	I/C
Asymptomatic patients with evidence of LV volume overload attributable to VSD	I/C
Patients with a history of infective endocarditis	IIa/C
Patients with VSD-associated prolapse of an aortic valve cusp causing progressive aortic regurgitation	IIa/C
Patients with VSD and pulmonary arterial hypertension when there is still net left-to-right shunt ( $Q_p:Q_s > 1.5$ ) present and pulmonary artery pressure or pulmonary vascular resistance are below 2/3 of systemic values (baseline or when challenged with vasodilators, preferably nitric oxide, or after targeted pulmonary arterial hypertension therapy)	IIa/C
Contraindications for surgical VSD closure:	
Eisenmenger's VSD and when exercise-induced desaturation is present	III/C
If the VSD is small, not subarterial, does not lead to LV volume overload or pulmonary hypertension, and if there is no history of infective endocarditis	III/C
* class of recommendation # level of evidence LV – left ventricular, VSD – ventricular septal defect	

Tricuspid regurgitation occurs mainly from RV and tricuspid annular dilatation. It results in progressive RV enlargement. Tricuspid valve repair is indicated in patients with moderate and severe dilation of the an-nulus (diameters, >40 mm or >21 mm/m<sup>2</sup>) undergoing cardiac surgery. Tricuspid valve repair using an an-nuloplasty ring is the preferred surgical approach for tricuspid regurgitation [14].

Residual VSD requiring reintervention after pri-mary surgical repair of Tetralogy of Fallot is rare [15]. Significant left-to-right shunting through VSD leads to LV volume overload, pulmonary hyperten-sion, resulting in shunt reversal and Eisenmenger's syndrome. Patients with symptoms that can be attrib-uted to left-to-right shunting through VSD who have no severe pulmonary vascular disease as well as pa-tients with VSD and pulmonary arterial hypertension

**Table 4. Indications for intervention after repair of tetralogy of Fallot**

	class* level#
Aortic valve replacement in patients with severe aortic regurgitation with symptoms or signs of LV dysfunction	I/C
PR in symptomatic patients with severe pulmonary regurgitation and/or stenosis (RV systolic pressure >60 mm Hg, tricuspid regurgitation velocity >3.5m/s)	I/C
PR in asymptomatic patients with severe pulmonary regurgitation and/or stenosis when at least one of the following criteria is present:	IIa/C
– Decrease in objective exercise capacity	
– Progressive RV dilation or systolic dysfunction	
– Progressive tricuspid regurgitation (at least moderate)	
– RV outflow tract obstruction with RV systolic pressure >80 mm Hg (tricuspid regurgitation velocity >4.3 m/s)	
– Sustained atrial/ventricular arrhythmias	
VSD closure in patients with residual VSD and significant left ventricular volume overload or if the patient is undergoing pulmonary valve surgery	IIa/C
* class of recommendation # level of evidence LV – left ventricular, PR – pulmonary regurgitation, RV – right ventricular, VSD – ventricular septal defect	

with left-to-right shunt ( $Q_p:Q_s >1.5$ ) and pulmonary artery pressure or pulmonary vascular resistance below 2/3 of systemic baseline values or when challenged with vasodilators are candidates for surgery (Table 3). Moreover, residual VSD closure is recommended if the patient is undergoing pulmonary valve surgery (Table 4).

## Experts' opinions of CRCD

**Jacek Pająk:** The patient has significant left-to-right shunt at the ventricular level that should be closed. Severe pulmonary and tricuspid regurgitation is also a strong indication for surgical pulmonary valve replacement and tricuspid valve annuloplasty.

**Bogusław Kapelak:** High-risk surgery. Correction of residual VSD is technically difficult. PVR is indicated. Tricuspid valve repair should be taken into account.

## Management strategy

Echocardiography and right heart catheterization confirmed that symptoms can be attributed to left-to-right shunting through residual VSD, pulmonary and tricuspid regurgitation. There are several strong indications for complex surgery according to the European Society of Cardiology guidelines for the management of grown-up congenital heart disease and guidelines on the management of valvular heart disease (Table 3). Our patient was scheduled for surgical closure of residual ventricular septal defect, pulmonary valve replacement, and tricuspid valve annuloplasty.

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## Adult patient with tricuspid valve atresia (RCD code: IV-2A.0)

Danuta Sorysz, Barbara Zawiałak, Jacek Dubiel

### Background

Tricuspid atresia is a complex congenital heart disease, in which one of the ventricles is underdeveloped or not completely formed and as a result the patient has only one functional ventricle and frequently the hypoplastic pulmonary artery and stenosis of the pulmonary valve [1]. To facilitate survival, it is necessary to enable the venous blood flow from the right atrium to the lungs. That is why, tricuspid atresia is combined with atrial septal defect (ASD) and ventricular septal defect (VSD).

For many years, surgical treatment for patients with tricuspid atresia has been the Fontan procedure. It was first described in 1971. This particular procedure is performed to restore the pulmonary circulation and connection between the right atrium and the main pulmonary artery [1]. It is typically performed in two stages. First, hemi-Fontan or Glenn procedure is performed followed by complete Fontan circulation. There are several clinical conditions which are a contraindication for the procedure. These conditions include, in particular, low pulmonary resistance, mean pulmonary artery pressure (PAP) of less than 15 mm Hg, sufficient pulmonary artery dimension, good univentricular function, small atrioventricular valve regurgitation, and undisturbed systemic circulation [2,3].

### Case presentation

The 47-year-old woman was diagnosed shortly after birth with atresia of the tricuspid valve and main pulmonary artery combined with hypoplasia of the right ventricle and with ASD II and VSD. The diagnosis of this complex congenital heart disease was based on cardiac catheterization, which was performed in early childhood. The patient was consulted by Professor Fontan and, based on the hemodynamic measurements obtained by catheterization, the patient was scheduled to conservative treatment.

A moderate decrease in cyanosis was observed during the first years of life as well as a satisfactory improvement in the child's motor development. In subsequent years, the patient led a normal life because she remained almost asymptomatic and presented only with mild decrease of exercise capacity. However, a notable progression of scoliosis was observed.

The patient's parents did not agree for further diagnostic procedures, particularly the invasive ones, either in Poland or at Professor Fontan's Institute. That is why, the patient was not under specialist care for

the subsequent 11 years. Fortunately, during that period, there was no significant deterioration in her general condition and she continued to develop relatively normally except for progression of scoliosis.

At the age of 26 years, the patient started to suffer from shortness of breath, persistent cough, and occasional anxiety. However, because the symptoms were not very severe and annoying, the patient failed to present for regular check-ups. At the age of 32 years, she was admitted to the hospital with the symptoms of profound hypovolemic shock. The main reason of this acute deterioration was excessive blood loss due to massive bleeding from the respiratory tract. The patient required blood transfusion. Fortunately, the restoration of the blood volume allowed to stabilize her condition. Despite serious complications and deterioration of the general state, the patient again refused to undergo cardiac catheterization. Since that particular episode, the patient remained in New York Heart Association (NYHA) class II and complained of mild, temporary hemoptysis. During the next 10 years, she suffered twice from transient ischemic attack.

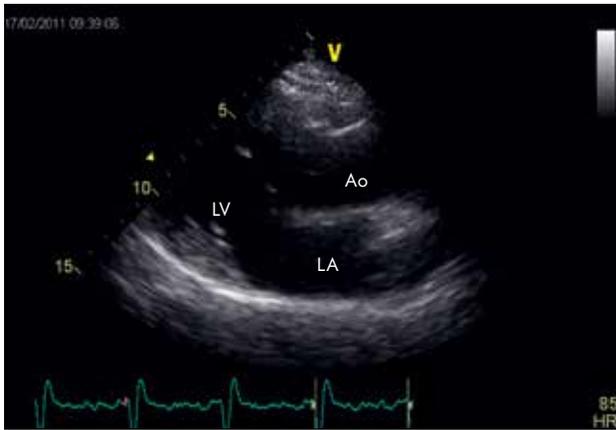
The patient was scheduled for therapeutic phlebotomy when the level of hematocrit reached 60.7%. She was also recommended antithrombotic therapy with vitamin K antagonists, but did not consent to such treatment. Instead, enoxaparin was introduced.

Currently, the patient is 47 years old and is classified in NYHA class III. She complains of occasional palpitations and dizziness. On a physical examination, several abnormalities can be detected, particularly, central cyanosis and clubbed / cardiac fingers. Auscultation reveals an absence of the second heart sound of the pulmonary valve, but without pathological murmurs. The pulse on the superficial arteries is well palpable and strong. There are no signs of peripheral edema.

An electrocardiogram revealed the left bundle branch block. Laboratory test results showed the elevated levels of red blood cells,  $6.9 \times 10^6/\text{mm}^3$  (normal range,  $3.7\text{--}5.1 \times 10^6/\text{mm}^3$ ), hematocrit, 54% (37%–47%), and hemoglobin, 17.9 g/dL (12–16 g/dL). An arterial blood gas analysis revealed severe hypoxemia,  $\text{pO}_2$ , 32.9 mm Hg (75–100 mm Hg) and significantly decreased oxygen saturation, 63.6% (95%–99%).

Echocardiography was performed to assess the current state and to confirm the primary disorders diagnosed in childhood as well as any additional cardiac abnormalities. It showed situs solitus, atresia of tricuspid valve, hypoplastic right ventricle with small VSD and large ASD II, and dilatation of the ascending aorta. It was not possible to distinguish the pulmonary valve, main pulmonary artery, and pulmonary branches (fig. 1,2,3), but 2 atypical vessels with accelerated and turbulent flow, branching off the descending aorta could be seen. The narrowing of the left vessel was also diagnosed (fig. 4).

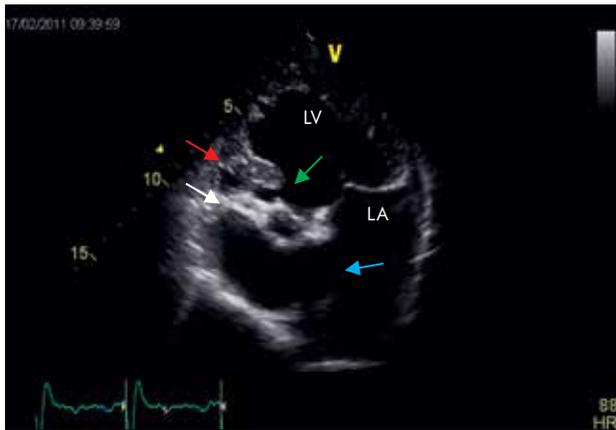
The patient still refuses to undergo invasive diagnostic procedures; therefore, computed tomography was performed to confirm the results obtained by echocardiography. The hypoplastic right ventricle and dilated left ventricle were observed. ASD and dilation of



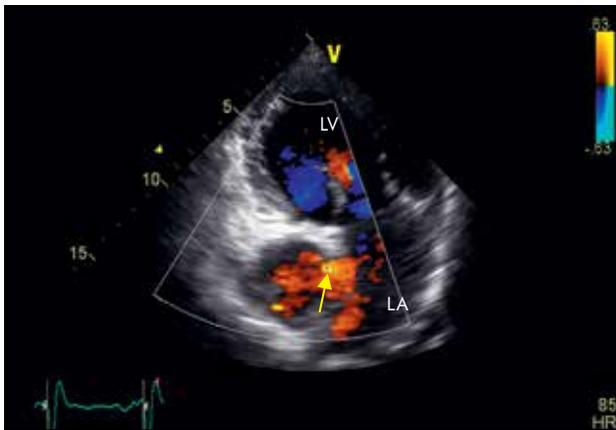
**Fig. 1.** Transthoracic echocardiography. Parasternal long-axis view. Hypoplastic right ventricle, dilatation of left ventricle and ascending aorta. LA – left atrium, LV – left ventricle, Ao – aorta



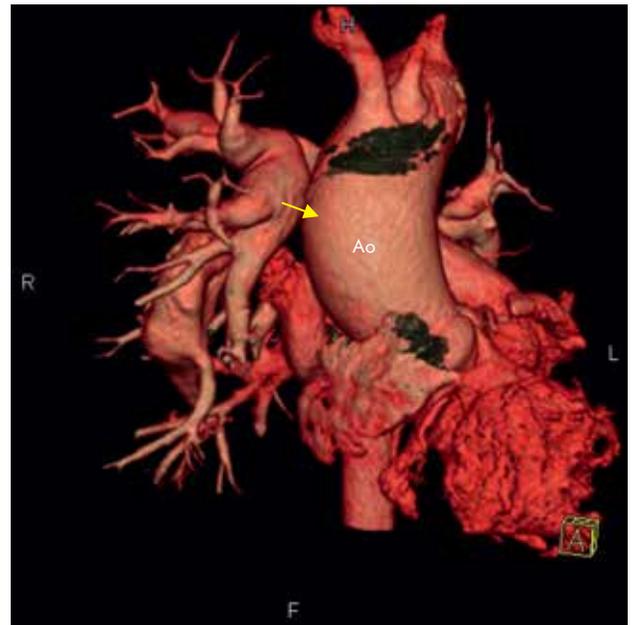
**Fig. 4.** Transthoracic echocardiography. Apical view. Left main aorto-pulmonary collateral (yellow arrow) from descending aorta (red arrow), flow acceleration (green arrow)



**Fig. 2.** Transthoracic echocardiography. Four-chamber view. Tricuspid atresia (yellow arrow), right ventricle (RV) (red arrow) VSD (green arrow), ASD II (blue arrow) LA – left atrium, LV – left ventricle



**Fig. 3.** Transthoracic echocardiography. Four-chamber view. Color Doppler imaging. Atrial septal defect (ASD) type II. ASD II flow (yellow arrow). LA – left atrium, LV – left ventricle

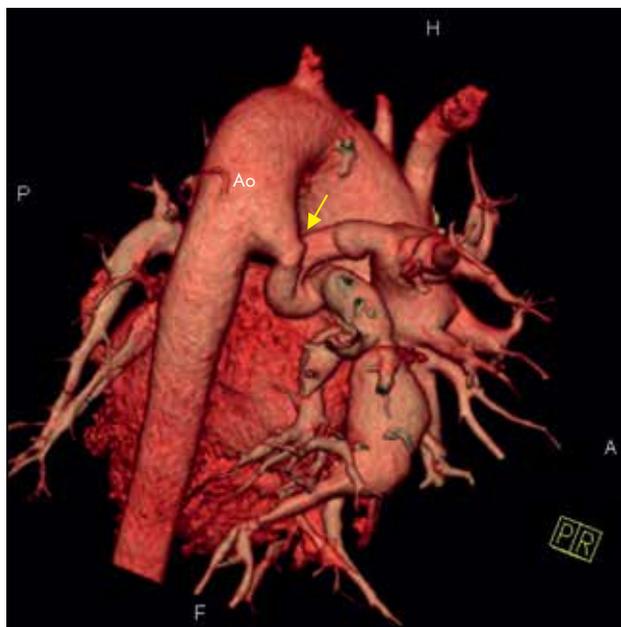


**Fig. 5.** Cardiovascular computed tomography. Three-dimensional reconstruction. Dilatation of ascending aorta (yellow arrow). Ao – aorta

the ascending aorta (48×48 mm) were also confirmed. Moreover, it confirmed the presence of the pulmonary vessels branching off the descending aorta. The right vessel was slightly higher than the left one; they were previously detected in echocardiography and may

be considered as major aortic pulmonary collaterals. The right pulmonary vessel at the site where it branches off the aorta has the lumen of approximately 11 mm and is notably curved. Its distal part and the branches are significantly dilated with multiple loss of contrast and additive calcifications, which may constitute the parietal thrombi. The left vessel is also significantly curved. The proximal lumen is 12 mm with stenosis in the curve of about 2.5 to 3 mm. There is no loss in contrast in the main vessel and its branches. The pulmonary veins flow into the left atrium, whereas no pulmonary arteries and branches in the typical location were identified (fig. 5, 6, 7).

On the basis of the available clinical and imaging data, the patient has recently been initially scheduled for heart and lung transplantation by the experts of the Centre for Rare Cardiovascular Diseases at the John Paul II Hospital, Krakow, Poland.

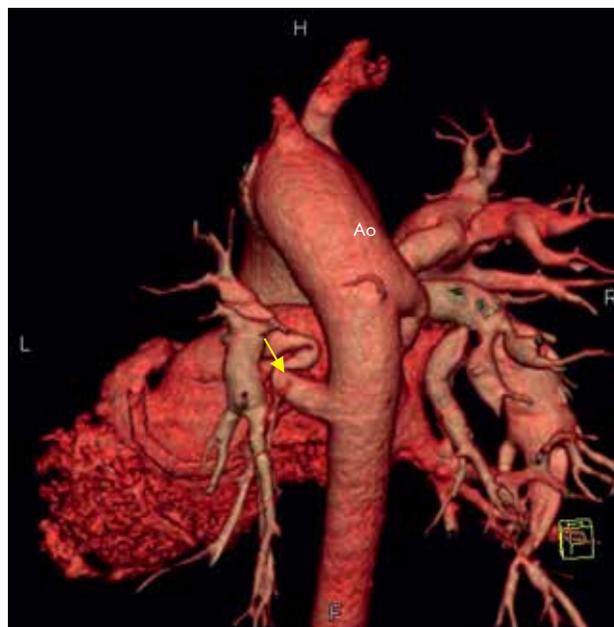


**Fig. 6.** Cardiovascular computed tomography. Three-dimensional reconstruction. Right main aorto-pulmonary collateral (yellow arrow). Ao – aorta

Stenting of the narrowed pulmonary vessels and, in the next step, percutaneous occlusion of pulmonary fistulas were considered as palliative treatment or as a bridge to transplantation. However, the patient did not give her consent. The final decision on heart or heart and lung transplantation will be possible after cardiac catheterization. However, because pulmonary vascular disease and pulmonary hypertension are already suspected, treatment with a phosphodiesterase type 5 inhibitor, sildenafil, has been introduced. After a short period of good results and clinical improvement, there was further deterioration of the patient's general condition and progression to NYHA class III/IV. Modification of pharmacological treatment is currently being considered. The patient is awaiting transplantation of heart and lungs in Silesian Center of Heart Diseases, Zabrze, Poland and begins to accept and understand the necessity of catheterization.

## Discussion

The present case is a rare example of a complex congenital heart malformation, which basically involves the univentricular heart. Nowadays, the primary and sufficient diagnostic technique is transthoracic echocardiography, which can be supported by transesophageal echocardiography if necessary. To obtain extracardiac anatomy, cardiac magnetic resonance imaging and computed tomography are recommended. When invasive treatment is planned, cardiac catheterization is recommended to obtain hemodynamic measurements, particularly PAP, vasoreactivity, and transpulmonary gradient, and to reveal vascular abnormalities. Based on the current guidelines of the European Society of



**Fig. 7.** Cardiovascular computed tomography. Three-dimensional reconstruction. Left pulmonary vessel – double kinking (yellow arrow). Ao – aorta

Cardiology for the management of grown-up congenital heart disease, the only surgical treatment in patients with such complex disorders and at this clinical stage (without previous surgical correction) is heart or heart and lung transplantation. However, considering the shortage of donors, alternative therapeutic options should also be considered. One of the options is extending stenotic parts of the pulmonary vessels to maintain pulmonary blood flow and to prevent severe cyanosis. On the other hand, this may aggravate pulmonary hypertension, which is usually present at this stage.

Of note, even after surgical corrections, which are mostly palliative, those patients remain at a very high risk of morbidity and mortality. Therefore, depending on the clinical situation, the high risk of any type of surgical intervention should be weighed very carefully against the possible benefit. Our patient is currently considered as a no-option patient, and only palliative and symptom-reducing treatment may be recommended.

## Management strategy

### Management of cyanosis

Anatomical communication between the systemic and pulmonary circulation at atrial, ventricular, or arterial levels results in cyanosis. The severity of cyanosis depends on the pulmonary blood flow. Several adaptive processes to maintain the proper delivery of oxygen to the tissues have been described. The most important is erythrocytosis, which leads to elevation of red blood cell count as well as hematocrit and hemoglobin levels [4]. This may be the cause of severe

thromboembolic complications due to increased blood velocity [5]. Moreover, the accelerated red blood cell turnover may result in hyperuricemia and hyperbilirubinemia [1]. On the other hand, patients with reduced arterial oxygen saturation have abnormal hemostasis, including thrombocytopenia, and hence they are at risk for bleeding and thrombosis [6]. It should be highlighted that hemostatic abnormalities do not protect against thrombotic complications but routine anticoagulation is not currently recommended [7]. Cyanosis-related multiorgan impairment may be the main challenge in the management of patients with cyanosis. Therefore, risk reduction strategies in patients with cyanotic congenital heart disease should be implemented. Pregnancy, iron deficiency and anemia, dehydration, infectious disease, cigarette smoking, and recreational drug abuse including alcohol should be avoided [8].

### Management of pulmonary arterial hypertension

Another important consequence of the abnormal hemodynamics in patients with congenital heart disease is the development of pulmonary arterial hypertension due to pulmonary overflow and endothelial dysfunction. It is defined as an increase in the mean PAP over 25 mm Hg at rest as assessed by right heart catheterization. Right heart catheterization is necessary not only for diagnostic reasons but also to assess vasoreactivity, which determines treatment options. Most commonly, vasoreactivity testing is performed with nitric oxide. Calcium channel blockers are recommended for patients with positive acute response defined as a reduction of the mean PAP of more than 10 mm Hg to reach an absolute value of the mean PAP of less than 40 mm Hg with an increased or unchanged cardiac output [8,9].

In terms of the management of nonvasoreactive pulmonary arterial hypertension, 3 classes of drugs targeted at the modification of endothelial dysfunction are currently available: prostanoids (epoprostenol), endothelin receptor antagonists (bosentan), and phosphodiesterase type 5 inhibitors (sildenafil). However, the efficacy of this pharmacological treatment is not well established and based mainly on small nonrandomized trials [5,7,8]. The management of this particular condition is complex and survival of subjects with pulmonary hypertension is reduced compared with the general population. It inevitably leads to heart failure and progressive deterioration of exercise capacity. Heart and lung transplantations is an alternative option for patients not responding to the above treatment strategies [7].

### Conclusions

Treatment strategies in this particular case were mostly dependent on the patient's decisions; however, it should be emphasized that therapeutic options were significantly limited because of anatomical conditions

and were focused mainly on controlling the distressing symptoms. Adult patients with congenital heart disease require a multidisciplinary approach and should be managed in centers that specialize in grown-up congenital heart diseases and can ensure comprehensive care.

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## Double-chambered left ventricle in a young previously healthy man presenting for a routine echocardiographic study (RCD code: IV-6.1)

Katarzyna Mizia-Stec, Tomasz Bochenek, Magdalena Mizia

### Background

A double-chambered left ventricle constitutes a rare congenital malformation. It is usually diagnosed at a neonatal or pediatric age, and often shows mixed criteria for diverticula and aneurysms. This anomaly is characterized by the subdivision of the left ventricle (LV) into 2 chambers by an abnormal septum or muscle band.

### Case presentation

We present a case involving a 30-year-old patient who was admitted to our outpatient clinic for a routine echocardiographic study that was required for his employment health check. He was asymptomatic and had no history of cardiac diseases or any other chronic diseases. He reported no symptoms of heart failure, dyspnea, or chest pain. A physical examination did not reveal any abnormalities. Sinus rhythm was observed on an electrocardiogram, and no rhythm disturbances were seen.

Transthoracic echocardiography revealed normal LV function (fig. 1). No valvular dysfunction or hypertrophy was observed. However, an additional cavity lying within the LV was visualized in two-chamber (fig. 2) and modified two-chamber (fig. 3) apical long-axis views. The additional cavity of the LV was located in the posteroinferior LV wall. It was not clearly visible in the traditional parasternal long-axis 2D view, and no pathology could be definitely determined on the images in the apical four-chamber view (fig. 1). The global LV systolic function was normal. The muscle of the additional LV cavity thickened during systole; however, the myocardium was nonhomogenous with small lacunae. The ratio of spongy / compacted layers was about 1. No thrombus was observed. There was a septum dividing both cavities, which was rich in fenestrations and lacunae that enabled free flow between the two of them (fig. 3). Turbulent systolic inflow and diastolic outflow with high velocities were present in the pulse and color Doppler imaging. Cardiac magnetic resonance imaging showed the dimensions of the additional LV cavity to be 77×60×39 mm; moreover, it revealed reduced ejection fraction (20%). Narrow neck of the cavity was observed (17×20 mm). The cavity consisted of fibrous membrane (thickness of 3–4 mm) with some fenestrations (max. 4 mm). At the same



Fig. 1. Transthoracic echocardiography. Apical four-chamber view.

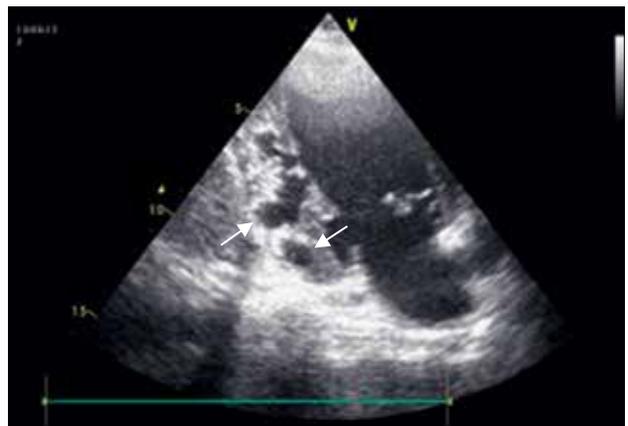


Fig. 2. Transthoracic echocardiography. Apical two-chamber view. Additional cavity within the left ventricle – subdivision of the left ventricular cavity by an abnormal septum into 2 chambers; fenestrations and lacunae within the pathology (arrows)

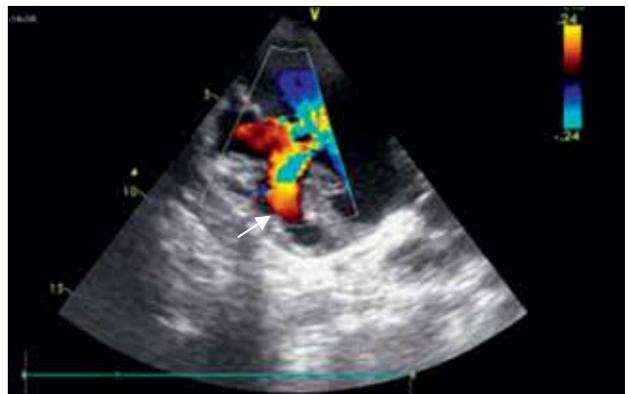
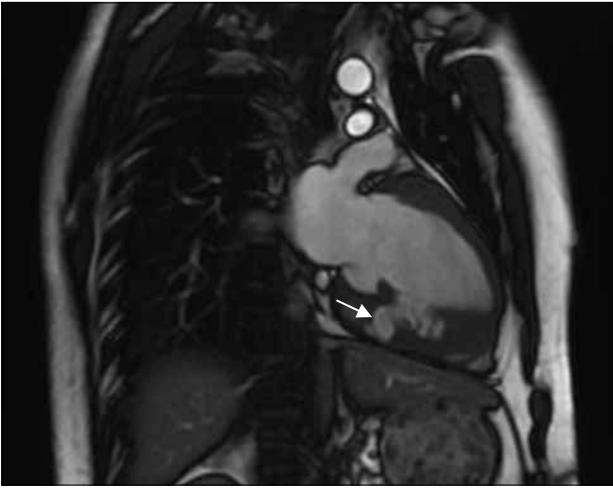


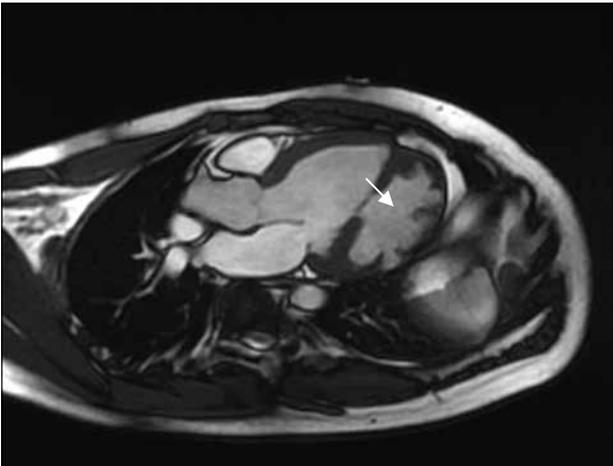
Fig. 3. Transthoracic echocardiography. Apical two-chamber view, modified. Color Doppler imaging. Turbulent flow between the two cavities is observed (arrow)

time, the main LV cavity had preserved ejection fraction of 58% as well as end-diastolic volume of 168 mL and end-systolic volume of 71 mL (fig. 4, 5). The final diagnosis was a double-chambered LV.

The patient was evaluated by a cardiac team and the decision was made to administer conservative



**Fig. 4.** Cardiovascular magnetic resonance. Fiesta imaging. The additional cavity is seen (arrow)



**Fig. 5.** Cardiovascular magnetic resonance. Fiesta imaging. A large additional cavity (arrow) consisting of fibrous membrane with some fenestrations and a narrow neck

treatment. He was advised to take anticoagulants to prevent thrombotic complications of the pathology (which are possible but not frequent). He was also advised to undergo regular echocardiographic check-ups.

## Discussion

In the literature, only a few case reports of a double-chambered LV have been described to date. When the PubMed database was searched for “Double-chambered left ventricle” (DCLV), only 19 citations were found. The majority of the papers focused on single cases. Thus, this pathology may be rightly named an “orphan disease”, according to the classifications of the Centre for Rare Cardiovascular Diseases.

A double right ventricle (RV) is a much more common pathology. This is probably because the RV is normally partially divided into the inlet and outlet portions by the muscular ridge of the supraventricular crest and the septomarginal trabecula. Abnormalities

of the various muscle bands in this region are the most frequent cause of a two-chambered RV.[1]

A rare congenital disorder diagnosed in our patient is best classified as double-chambered LV, a term which has been used to describe the subdivision of the LV cavity into 2 chambers by an abnormal septum or muscle bundle. The etiology of this disorder is not well-known, but the anomaly is generally thought to be congenital if it is diagnosed late and is nonprogressive. Only a few cases with variable morphologies have been reported in the literature, mostly with either a diverticular appearance or small contracting chambers attached to the LV lateral wall or within the apex.[2] The exact mechanism of a double apex.[2] The exact mechanism of a double ventricle is unknown; however, cardiomyopathy is often an underlying pathology.

Gerlis et al.[1] reported 3 cases with endomyocardial fibroelastosis and cardiomyopathy. All 3 patients had double-chambered ventricles. All of those patients died in the first year of life from cardiomyopathy. A double-chambered ventricle coexisting with tetralogy of Fallot has also been described.[3] Our patient, in contrast to some other cases shown in the literature, had no echocardiographic evidence of cardiomyopathy and was diagnosed relatively late in life, as no symptoms had been previously reported.

The differential diagnosis is extremely important in trying to define the pathology. Echocardiography and computed tomography can aid in the detection of double-chambered ventricles. Magnetic resonance imaging will characterize the condition better because of its higher spatial resolution and the ability for tissue characterization, especially with the differentiation between fibrosis and normal myocardium.[4]

Detection of an accessory chamber in communication with the LV cavity needs special consideration, because an LV aneurysm or diverticulum can sometimes mimic a double-chambered LV. Therefore, a precise evaluation of their wall motion during systole and diastole as well as the width of their communication with the main LV cavity would help to differentiate between these entities [5]. Even more importantly, the treatment modalities are different for each of these pathologies. The diagnosis with the worst prognosis is an LV pseudoaneurysm, which is a contained rupture of the LV free wall. However, this disease follows chest trauma, myocardial infarction, or endocarditis. An aneurysm of the LV is described as a wall that is thinner than the adjacent myocardial segments, while a diverticulum is an outpouching containing the endocardium, myocardium, and pericardium. Both an aneurysm and a diverticulum need to be resected when symptomatic [6].

Another diagnosis that should be taken into consideration is LV noncompaction. In our patient, the ratio between the spongy and compact layers (about 1 in the systole phase) did not fulfill the criteria for this cardiomyopathy.

Accessory cavities sequestered by aberrant muscular ridges are not well recognized. Surgically, they may be resolved by a resection of the aberrant tissue [4]. Indications for surgery must be made for each

individual case as there have only been few reports on this pathology. We decided on a conservative treatment for the patient. Our decision was based on the fact that the patient was totally asymptomatic, had no history of thromboembolism, and there seemed to be a low probability of developing thrombus in the additional LV cavity. Another point that we considered important was that the condition did not affect the overall function of the LV.

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# Part 7

Rare arrhythmias – RCD class V

**Editor: Jacek Majewski**



# Introduction

Jacek Majewski

Rare arrhythmias and conduction disorders represent a vast group of diseases, which management often requires individual approach. Making a right diagnosis involve thorough evaluation of patient's symptoms, concomitant conditions, family history and detailed analysis of available additional studies such as electrocardiography, cardiac electrophysiology, echocardiography, magnetic resonance etc. Genetic evaluation is increasingly becoming useful for verifying a diagnosis and therefore it may support stratification of the risk of fatal arrhythmias or sudden cardiac death. The role of genetic testing in diagnosis, risk stratification and management of patients with inherited primary arrhythmia syndromes is discussed in recent position statements of world's heart rhythm societies: *Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes* an *Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies*. Alongside with the above mentioned papers concerning primary arrhythmias, heart rhythm societies including Heart Rhythm Society, European Heart Rhythm Association, Asia and Pacific Heart Rhythm Society, American Heart Association etc. regularly publish updated guidelines which represent the reference for all physicians engaged in managing patients with all sorts of arrhythmias and conduction disorders.

This part presents our experience in managing patients with rare arrhythmia syndromes. We describe patients with rare primary electrical heart disease such as: Brugada syndrome, Long QT syndrome, Short QT syndrome, Catecholaminergic Polymorphic Ventricular Tachycardia. Additionally, we focus on various rhythm abnormalities observed in uncommon cardiovascular disorders like congenital heart diseases, cardiomyopathies, rare abnormalities of pulmonary and systemic circulation or cardiac tumors. We discuss custom approach for diagnosing and treating patients with uncommon presentations of common arrhythmias or rhythm abnormalities occurring in particular conditions like malignancy or pregnancy.

Multitude of rare arrhythmias and their vast diversity requires exceptional approach and combined effort of various specialists like cardiologists, electrocardiologists, cardiac surgeons, anesthesiologists, pulmonologists, neurologists, gynecologists, endocrinologists, geneticists, immunologists, basic scientists, etc. Their cooperation is often crucial to elaborate the most appropriate management for patients with uncommon rhythm abnormalities. Therefore, we propose a new classification of rare arrhythmias. It has been designed to facilitate recognition of rare arrhythmias, to enhance knowledge development and dissemination, to promote research and foremost to group the expertise on particular forms of rare arrhythmias and arrhythmias occurring in uncommon clinical settings.



# Rare arrhythmias: Perspective of the Centre for Rare Cardiovascular Diseases

## ■ Arrhythmias as rare cardiovascular diseases

Jacek Majewski

### Definition

The term “rare arrhythmias” is used to describe:

1. Heart rhythm abnormalities resulting from rare diseases of the heart, such as congenital anatomical anomalies or inherited disorders of the electrical function of the heart.
2. Arrhythmias occurring in specific clinical situations and requiring complex diagnostic procedures and often necessitating the use of advanced non-pharmacological treatment modalities, i.e., modern electric therapy, involving the use of implantable devices such as implantable cardioverter-defibrillator devices, cardiac resynchronization therapy devices, or ablation procedures.
3. Arrhythmias with atypical electrophysiological mechanisms and rare electrocardiographic features

### Epidemiology

1. Arrhythmias in rare diseases of the heart.
  - A. Congenital anatomical anomalies.
    - *Clinically significant congenital diseases of the heart* occur in approximately 1% to 2% of live births. Arrhythmias are the principal cause of hospital admission and sudden cardiac death (SCD) in the adult population with congenital diseases of the heart. Types of arrhythmias observed in individual congenital diseases of the heart have been discussed below.
    - *Atrial septal defect (ASD)*. Atrial arrhythmias are observed in approximately 20% of the patients with nonsurgically treated ASD. These include macro-reentry atrial tachycardia, typical atrial flutter,

and atrial fibrillation. After surgical correction of ASD, atypical atrial flutter (independent of the cavotricuspid isthmus) may occur; most commonly, the reentry circuit is located along the right atrial lateral wall and along a figure-of-eight double loop within the right atrium.

- *Ventricular septal defect (VSD)*. Ventricular arrhythmias often occur in patients with non-operated VSD in the form of polymorphous ventricular beats, and approximately 6% of the patients demonstrate sustained or nonsustained ventricular tachycardia (VT). There is a positive relationship between the magnitude of pulmonary hypertension and the severity of ventricular arrhythmia in this patient group. After surgical correction of VSD, ventricular arrhythmias continue to be a significant clinical problem. Late SCD after surgery occurs in 4% of the patients. Atrioventricular block develops in 3% to 4% of the patients after catheter correction of VSD.
- *Congenitally corrected transposition of the great arteries (L-TGA)*. The primary problem in this patient group are conduction abnormalities with a risk of complete atrioventricular block of 2%/year. The block is most commonly located above or within the His bundle. Fibrosis has been noted to be the primary pathology on histology. Patients commonly have competent nodal escape rhythms. Surgical correction of coexistent VSD is associated with a relatively high risk of atrioventricular block (25%).
- *Ebstein's anomaly*. Accessory atrioventricular conduction pathways are present in approximately 25% of the patients; these pathways are most commonly right-sided and multiple in relation to patients without Ebstein's anomaly.
- *Heart after the Fontana procedure*. The main cause of late postoperative mortality is SCD due to arrhythmia. Atrial arrhythmias are also observed after the Fontana procedure, including primarily macro-reentry atrial tachycardia; atrial fibrillation is less commonly observed.
- *Tetralogy of Fallot*. Arrhythmias are a significant problem in patients operated for tetralogy of Fallot. Typical (isthmus-dependent) atrial flutter is the predominant abnormality in the group of atrial arrhythmias. Other abnormalities may include

atypical atrial flutter and focal atrial tachycardias. The main cause of late postoperative mortality is SCD reported in 8% of the patients in a 35-year postoperative follow-up. Monomorphic VT is observed in 10% of patients in a 20-year postoperative follow-up. Risk factors for VT and SCD in this patient group include: QRS duration >180 ms, QT dispersion, nonsustained VT, electrophysiology study-induced VT, age, and the presence of a patch in the right ventricular outflow tract.

- *Dextro-transposition of the great arteries (D-TGA), surgically corrected with the Mustard/Senning procedure.* In a 20-year postoperative follow-up, sinus node dysfunction develops in approximately 60% and atrial tachyarrhythmias in 24% of the patients. Risk factors of SCD include ventricular arrhythmias, circulatory failure, and documented atrial flutter and fibrillation.
  - *Left ventricular outflow tract obstruction.* The occurrence of ventricular arrhythmias correlates with the severity of obstruction, left ventricular hypertrophy, and systolic function impairment. The risk of SCD persists despite surgical treatment. The incidence of SCD is estimated to be 3% at 10 years and 20% at 30 years after surgery.
  - *Atrioventricular canal defect.* Isolated ventricular ectopic beats are observed in 30% of the patients, whereas complex ventricular arrhythmias occur primarily in patients with impaired left ventricular function. The most common surgical complication is complete atrioventricular block in 1% to 7% of the patients immediately after surgery, and in approximately 2% in the late postoperative period. Atrial flutter or fibrillation occurs in 5% of the surgically treated patients.
  - *Arrhythmogenic right ventricular dysplasia (ARVD)* is a genetic cardiomyopathy with the incidence of 1/2500 to 1/5000. The underlying pathology is replacement of the myocardial tissue by fatty and fibrous tissues. The consequence is impairment of the right ventricular systolic function but changes may involve the left ventricle as well. The disease is typically inherited by autosomal dominant pattern. Mutations are found in genes encoding desmosomal proteins, that is, proteins found in the filaments connecting the neighboring cells. A significant role in the ARVD process is played by apoptosis. The signs and symptoms include palpitations and syncope caused by ventricular arrhythmias and circulatory failure. Ventricular arrhythmias originate most commonly from the right ventricle and include premature ventricular contractions, VT or ventricular fibrillation (VF). SCD may be the first symptom of the disease. Predisposing factors of SCD in patients with ARVD include: right ventricular dilation, abnormal repolarization in precordial electrocardiographic (ECG) leads, left ventricular involvement, and family history of SCD.
- B. Genetic electric heart function abnormalities. These include the so called primary electric heart diseases: Brugada syndrome, long QT syndrome,

short QT syndrome, and catecholaminergic polymorphic VT. It is estimated that these rare genetic diseases are responsible for approximately 5% to 10% of all SCDs.

- *Brugada syndrome.* This clinical syndrome is characterized by typical ECG changes in the form of ST elevation in leads V<sub>1</sub> through V<sub>3</sub> with co-existent features of the right bundle branch block. Patients are at risk of an SCD in the mechanism of VT, evolving to VF. The pathogenesis includes abnormal function of sodium channels encoded by the *SCN5A* gene, resulting in shortened phase 2 of action potential and abnormal repolarization predisposing to the reentry phenomenon. The inheritance pattern is autosomal dominant. The incidence of Brugada syndrome is in the range of 5/1000 (Caucasian race) to 14/1000 (Japan and other Asian countries). It mainly affects men (up to 90% of cases). The onset of symptoms is usually in the 3rd to 4th decade of life and cardiac arrest is the first presenting symptom in 30% of the subjects. Other symptoms include syncope. Paroxysmal atrial fibrillation occurs in approximately 20% of the patients. It is estimated that up to 50% of SCDs in patients without structural abnormalities of the heart is caused by Brugada syndrome.
- *Congenital long QT syndrome (LQTS).* The syndrome is characterized by genetically mediated QT-segment elongation in ECG (QTc corrected for heart rate is >450 ms) and a risk of life-threatening ventricular arrhythmias. Clinically, the syndrome manifests with syncope or SCD, resulting from polymorphic *torsade-de-pointes* VT, often evolving into VF. The disease incidence is estimated to be 1/2500, with the predominance of women (60%–70%). Currently, 10 genes have been identified as responsible for mutations causing individual LQTS types (LQT1–LQT10). The most prevalent types are LQT1, LQT2, and LQT3. In the LQT1 type, the mutation is located in the *KCNQ1* gene, encoding potassium channels. This type is responsible for approximately 50% of the LQTS cases. The autosomal recessive Jervell–Lang–Nielsen syndrome associated with deafness and syndactyly are other diseases in this class. In the LQT2 type, the mutation is located in the *KCNH2* gene, also encoding potassium channels. The third most prevalent LQT3 syndrome (approximately 10% to 15% of all LQTS cases) involves mutation of the *SCN5A* gene encoding sodium channels. Less prevalent mutations pertain to the following genes: *ANK2* (LQT4), *KCNE1* (LQT5 includes Romano–Ward syndrome and type 2 Jervell–Lang–Nielsen syndrome), *KCNE2* (LQT6), *KCNJ2* (LQT7 includes Andersen–Tawil syndrome with intermittent paralysis responding to Kalium, VT, dysmorphies: low stature, hypertelorism, broad nose base, defects of the soft and hard palate), *CACNA1c* (LQT8, referred to as the Timothy syndrome), *CAV3* (LQT9), and *SCN4B* (LQT10).
- *Short QT syndrome (SQTS)* was described relatively recently, in 2000, by Gussak et al. It is

characterized by short QTc and a risk of SCD due to ventricular arrhythmias. It is usually accepted that for diagnosis of SQTS, the QTc interval should not exceed 300 ms. The longest QTc reported in a patient with SQTS and tachyarrhythmias is 315 ms. Atrial fibrillation can be observed in some patients. The incidence of the syndrome has not been well studied. SQTS is genetically mediated and is associated with a mutation of genes encoding sodium channels. Abnormal ion transport affects the repolarization process, leading to electrical instability and ventricular and atrial arrhythmias. Five types of SQTS have been described to date based on the mutation type. In types SQT1–SQT3, mutations are located in genes encoding potassium channels: *KCNH2* – SQT1, *KCNQ1* – SQT2, and *KCNJ2* – SQT3. Genes encoding calcium ion transport, *CACNA1C* and *CACNB2B* are responsible for types SQT4 and SQT5, respectively.

- *Catecholaminergic polymorphic ventricular tachycardia (CPVT)*. Clinical signs and symptoms include syncope on exercise or emotions in subjects without structural diseases of the heart. The underlying cause is fast VT. These arrhythmias can evolve to VF and, consequently, lead to SCD. Two genes have been identified the mutations of which lead to CPVT. These are *RYR2* and *CASQ2*. The *RYR2* gene encodes the ryanodine receptor, while the *CASQ2* gene

encodes calsequestrin – a sarcoplasmic reticulum protein capable of buffering calcium ions. The true prevalence of CPVT in the population is unknown. It is estimated to be 1/10 000.

- *Wolff–Parkinson–White (WPW) syndrome* is a congenital anomaly involving an accessory conduction pathway connecting the atria with the ventricles. This pathway results in arrhythmias. The most common locations of the accessory pathway are left lateral (50%–60%) and posteroseptal (20%–30%). The presence of multiple accessory pathways is observed in approximately 5% to 20% of the patients with WPW syndrome. The syndrome is observed in approximately 0.1% to 0.3% of the general population and is twice more common in men. The incidence is estimated to be 0.004% to 0.1%/year. A slightly higher prevalence (0.55%) is observed in first-degree relatives of the patients with WPW syndrome. Approximately 50% of the subjects with an accessory pathway remain asymptomatic. The remaining patients demonstrate paroxysmal atrioventricular reentrant tachycardia. Another 20% to 30% of the patients experience atrial arrhythmias (atrial fibrillation, atrial flutter, and atrial tachycardia). There is a subgroup of patients with WPW syndrome (approximately 0.15%/year) at risk of SCD. The mechanism of SCD in these patients involves atrial tachyarrhythmia with fast conduction



**Fig. 1.** Electrocardiogram. Atrioventricular node reentrant tachycardia (AVNRT) initially conducted with atrioventricular block 2:1. After a ventricular extrasystole (third QRS complex), AVNRT continues with atrioventricular conduction 1:1 and the left bundle branch block. Conduction abnormalities are functional

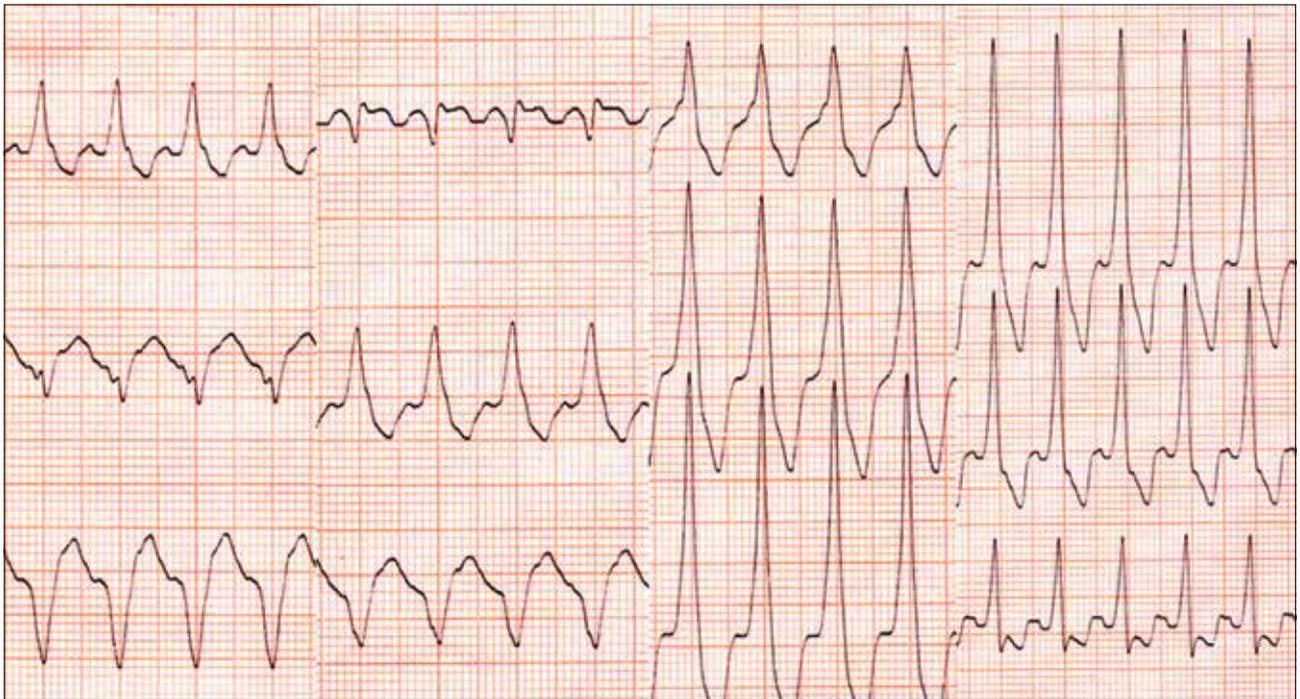


Fig. 2. Electrocardiogram. Antidromic tachycardia in a patient with Wolff–Parkinson–White syndrome

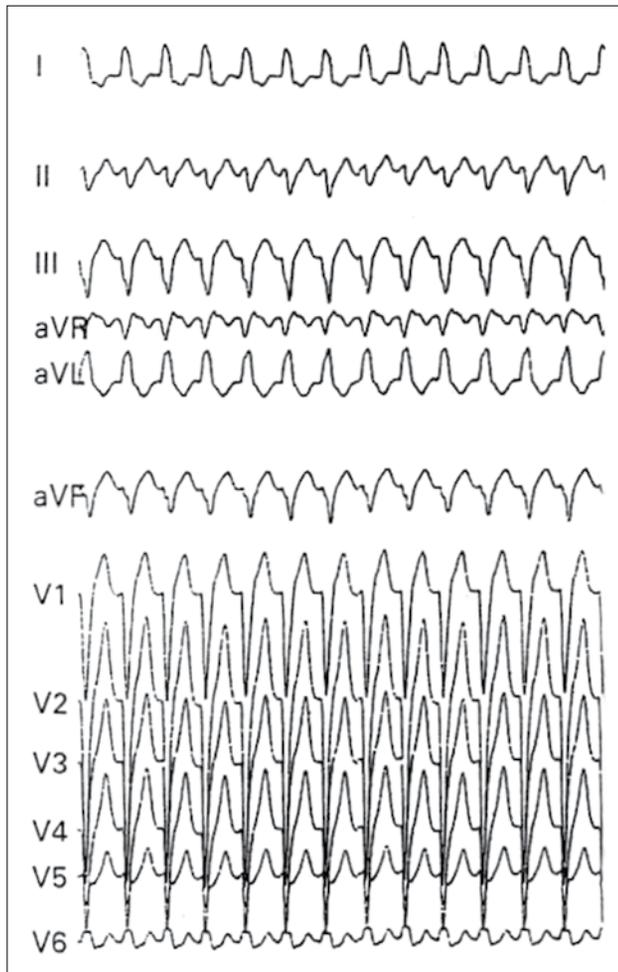


Fig. 3. Electrocardiogram. Antidromic tachycardia in a patient with Mahaim syndrome

through the accessory pathway, potentially triggering VF. The identified risk factors for SCD in this patient group include short RR cycle (<250 ms) during an atrial fibrillation episode, short refraction time of the accessory pathway (<270 ms), the presence of multiple accessory pathways, and postero-septal location.

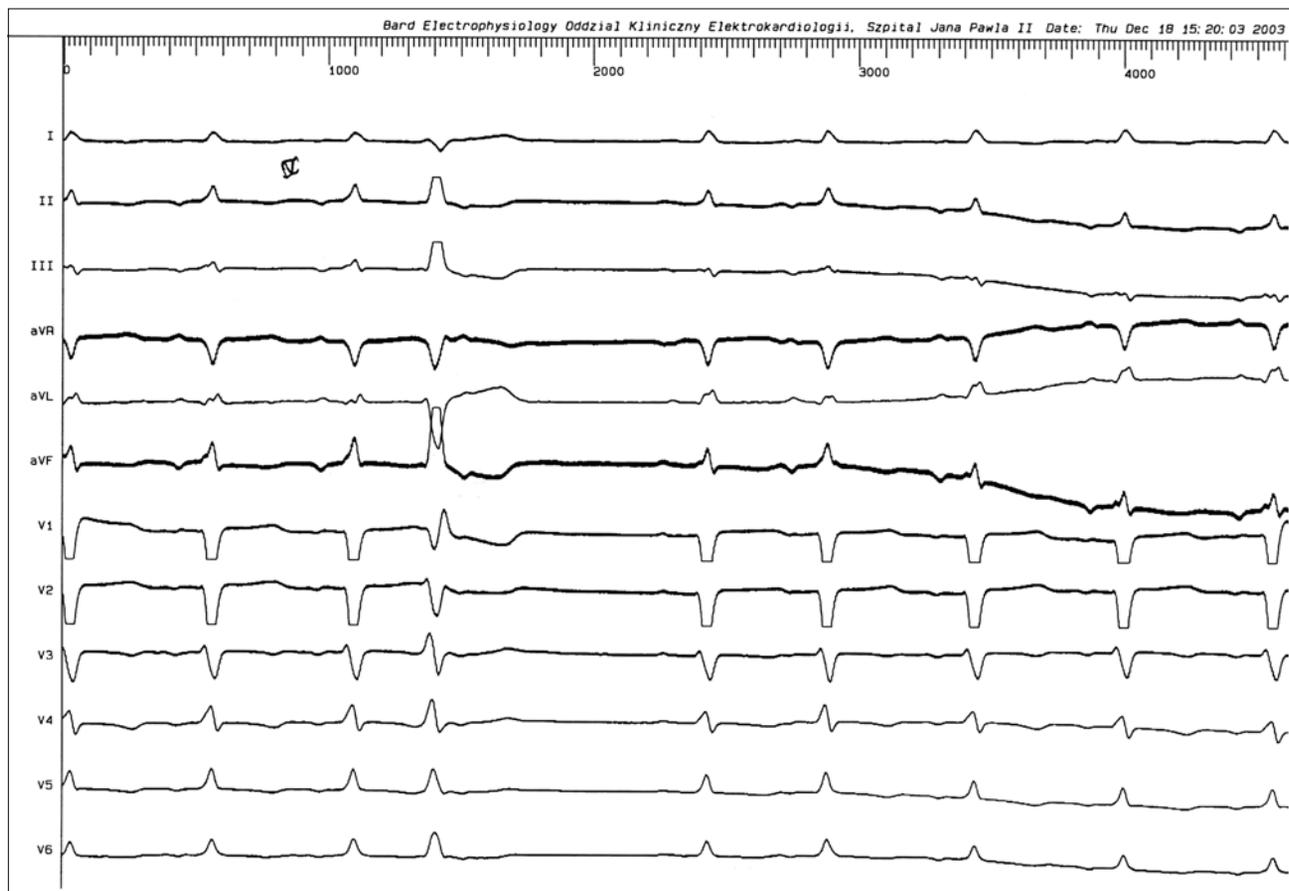
II. Arrhythmias occurring in specific clinical situations

A. Arrhythmias in pregnancy.

Cardiovascular diseases affect approximately 0.2% to 4% of pregnant women. Depending on the geographical location, congenital heart diseases (75%–82% of circulatory diseases in the pregnant woman in the Western world) or valvular heart disorders resulting from rheumatic fever (56%–89% of circulatory diseases in the pregnant woman in the rest of the world) may predominate. In pregnancy, supraventricular tachycardias worsen in approximately 20% to 44% of the women who suffered from this type of arrhythmia before pregnancy. Paroxysmal supraventricular or ventricular tachycardias requiring treatment occur in 5% of the pregnant women with congenital heart diseases.

B. Arrhythmias after cardiothoracic surgery

Postoperative arrhythmias may occur early or late after cardiothoracic surgical procedures. They are a significant risk factor for morbidity and mortality after surgical correction of congenital heart diseases. Factors favoring early postoperative arrhythmia include injury to the conductive system and myocardium, metabolic and electrolyte abnormalities, increased



**Fig. 4.** Electrocardiogram. Persistent reentrant atrioventricular tachycardia in a patient with the Coumel's pathway. The ventricular ectopic beat (the fourth QRS complex) stops the tachycardia. The arrhythmia restarts after a single sinus impulse

adrenergic activity due to surgical stress, and inotropic drugs. Late postoperative arrhythmias are promoted by surgical scars (incisional arrhythmias), sutures and patches, and hemodynamic abnormalities resulting from the surgery. Arrhythmias occurring after surgical correction of congenital diseases have been discussed previously in this book in the section on congenital anatomical anomalies. Arrhythmias are also observed in heart transplant recipients. The mechanism of atrial arrhythmias after heart transplantation has not yet been fully elucidated. It is considered that they may result from focal tachycardias originating in the donor's heart, atrial fibrillation in the donor's heart, reentry foci in the surgical scar or in the valves, reentrant arrhythmias involving the atrioatrial junction, and arrhythmias generated in the recipient's heart, activating the donor heart atria. The reported prevalence of post-transplant atrial arrhythmias ranges from 18% to 65% of the patients, and it is associated with an elevated risk of death. The patient population is markedly heterogeneous with respect to indications for transplantation, age, and the used surgical technique.

### C. Arrhythmias complicating chemotherapy

The proarrhythmic effects of drugs used in cancer chemotherapy are one of the most common reasons for cardiology consults in oncology patients. Administration of anthracyclines is associated with new-onset atrial fibrillation in 2% to 10% of

the patients. Less commonly, the use of drugs in this class results in VT or VF associated with increased QT interval. An undesirable effect of 5-fluorouracil are ischemia-related ventricular arrhythmias due to coronary artery spasm. Intrapericardial cisplatin relatively commonly induces atrial fibrillation (approximately 12%–32% of the patients). Use of this drug was also associated with VT (8% of the patients). Melphalan induces atrial fibrillation in 7% to 12% of the patients.

### III. Arrhythmias with atypical electrophysiological mechanism and rare electrocardiographic features

The exact prevalence of these types of arrhythmia is unknown. These are rhythm abnormalities rarely encountered in clinical practice and their appropriate diagnosis usually requires an invasive electrophysiology study. The examples of these arrhythmias are presented below.

- A. Atypical atrioventricular node reentrant tachycardia (AVNRT) (fast–slow, slow–slow, coexistent aberration, atrioventricular block). A sample ECG is presented in Figure 1.
- B. Antidromic tachycardia in a patient with WPW syndrome is a significantly less common type of reentrant tachycardia than orthodromic tachycardia and constitutes approximately 5% to 10% of all tachycardias in patients with WPW syndrome. During antidromic tachycardia, the ventricles are depolarized

by the accessory pathway resulting in wide QRS complexes (fig. 2), whereas retrograde conduction (the ventricles to the atria) occurs through the atrioventricular node. During orthodromic tachycardia with narrow QRS complexes, the direction of reentry loop depolarization is opposite.

#### C. Tachycardia in a patient with Mahaim syndrome.

Accessory pathways described by Mahaim and Winston are a connection between the atrioventricular node and the distal portion of the right bundle branch block or the adjacent myocardium. They are therefore classified as nodofascicular or nodoventricular pathways, respectively. These pathways conduct only towards the ventricles and with decrement, i.e., increased atrioventricular conduction time with increasing atrial rate. The Mahaim pathways are the anatomical background of reentrant antidromic atrioventricular tachycardia with QRS appearance typical for the left bundle branch block (fig. 3). In most patients with Mahaim fibers, there is double physiology of the atrioventricular junction, potentially resulting in AVNRT.

#### D. Bundle branch reentrant ventricular tachycardia.

This is a rare form of reentrant ventricular tachycardia resulting from the presence of reentry loop within the His-Purkinje system. It is most commonly observed in patients with nonischemic cardiomyopathy (up to 40%) and, less frequently, in ischemic cardiomyopathy (6%).

E. Tachycardia with RP longer than PR. This electrocardiography feature can be seen in atrial tachycardia, atypical nodal tachycardia (fast-slow) where retrograde conduction occurs through the slow pathway of the atrioventricular junction or during atrioventricular orthodromic tachycardia, conducted in a retrograde direction through the accessory pathway of Coumel. The Coumel's pathway is located in the posteroseptal region; it is characterized by slow and solely retrograde conduction (fig. 4). Tachycardias with RP>PR are often sustained and may result in the development of tachyarrhythmic cardiomyopathy.

## Diagnosics

Diagnostic work-up in patients with rare arrhythmias includes:

- History and physical examination
- ECG and 24-hour Holter monitoring
- Imaging studies of the heart (plain radiography, echocardiography, computed tomography (CT, CT angiography), and magnetic resonance imaging.
- Invasive electrophysiology study.

The objective of these studies is diagnosing the underlying disease as well as coexistent arrhythmias. Assessment of SCD risk is important.

## Treatment

- Pharmacology: antiarrhythmic and other drugs used in the treatment of primary disease;
- Nonpharmacological modalities of treatment of arrhythmias (electrical therapy modalities), including:
  - Percutaneous radiofrequency ablation; cryoablation.
  - Implantation of cardioverter-defibrillator, cardiac pacemaker or resynchronization device (cardiac resynchronization therapy).

Treatment in patients with rare arrhythmias focuses on the treatment of the underlying disease, quality-of-life improvement, and prevention of SCD. It should be conducted in accordance with the current recommendations/standards of care for individual diseases. An in-depth description of the diagnostic and treatment methods lies outside the scope of this brief introduction.

Cases of patients with selected rare arrhythmias are presented in the following chapter. Case descriptions are provided with detailed discussion of the diagnostic and management algorithms.

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## Rare arrhythmias: Clinical examples

### Overlapping syndrome of arrhythmogenic right ventricular cardiomyopathy with left ventricular involvement and Brugada syndrome – differential diagnosis (RCD code: V-1A.1)

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#### Case report

A 32-year-old man presented with monomorphic ventricular arrhythmia with the morphology of the left bundle branch block (LBBB). He reported two episodes of situational syncope (post-micturition). There was a family history of sudden cardiac death – the patient's father died suddenly in his sleep at the age of 49 years. A resting electrocardiogram (ECG) demonstrated J-point elevation in right ventricular (RV) precordial leads  $V_2$  through  $V_3$ . Baseline echocardiography showed normal left and RV systolic function. After several months, a resting ECG demonstrated ventricular arrhythmia with LBBB morphology with J-point elevation of 2 to 3 mm with concomitant coved downsloping ST elevation in lead  $V_1$  and saddle ST elevation in lead  $V_2$ , resembling the features of Brugada syndrome (BrS) (fig. 1). These abnormalities were observed only in sinus beats immediately preceding the premature ventricular contractions (PVC). BrS was suspected. Due to unavailability of ajmaline, a propafenone test was performed, which showed J-point elevation, failing to meet the diagnostic criteria for BrS. Interestingly, the propafenone test revealed an abnormality, which was difficult to interpret, namely, J-point elevation in precordial leads  $V_1$  through  $V_6$  with altered morphology of the ST segment and T wave, initially completely normal to saddle ST elevation in all precordial leads  $V_1$  through  $V_6$  (fig. 2).

At 3 months, the patient's clinical condition was unchanged. The ajmaline test was performed but the results failed to fulfill the diagnostic criteria for

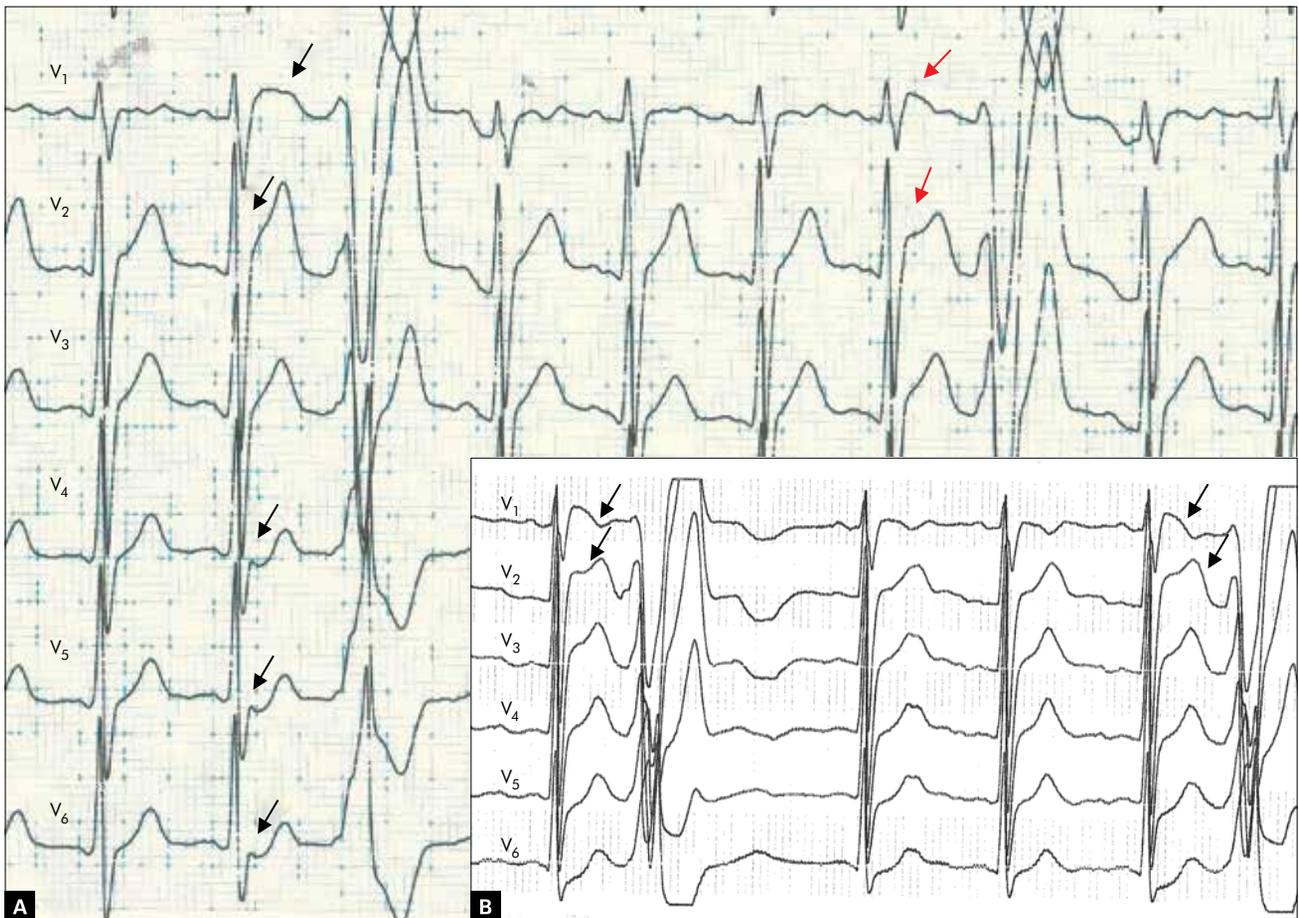
BrS (fig. 3). However, due to spontaneous and dynamic ST-segment changes preceding the PVC in leads  $V_1$  through  $V_2$  typical for BrS and the ambiguous results of the ajmaline test, the patient was closely followed for BrS symptoms. Cardiac magnetic resonance imaging (MRI) was scheduled to exclude or confirm structural myocardial abnormalities.

MRI revealed borderline left ventricular (LV) systolic function (LV ejection fraction [LVEF], 51%) and RV systolic function (RVEF, 40%). LV weight was 131 g, LV weight index was 98.6 mL/m<sup>2</sup>, and RV weight index was 108.5 mL/m<sup>2</sup>. Dilated LV cavity was 64 mm and LV wall thickness was normal. Moreover, it showed normal LV segmental contractility, dilated RV cavity with borderline global contractility, and akinesia of the intermediate segment of the anterior portion of the RV free wall. After administration of contrast, no late-enhancing segments were visualized (fig. 4).

A follow-up echocardiogram at 2 months showed dilated LV cavity of up to 58 mm, borderline RV size, and an enlarged right atrium. Generalized abnormal contractility of the LV with impaired LV systolic function was visualized – LVEF of 40% with akinesia of the RV free wall. Coronary angiography did not show any abnormalities in the coronary arteries. A transesophageal echocardiogram at 3 months revealed a dilated LV cavity of up to 59 mm, dilated RV cavity of up to 44 mm in the 4-chamber view and 39 mm in the parasternal longitudinal view, with akinesia of the RV free wall. The patient denies symptoms of cardiac failure or syncope. Holter monitoring showed monomorphic ventricular arrhythmia (with LBBB morphology) with 200 to 2000 PVCs in 24 hours, without complex forms of ventricular or supraventricular arrhythmia. No conduction abnormalities were shown. Only dynamic changes of the ST/J point were observed in leads  $V_1$  through  $V_2$  and aVL (fig. 5). A  $\beta$ -blocker and an angiotensin-converting-enzyme inhibitor (ACEI) were started. Implantation of a cardioverter-defibrillator device is considered if any indications are observed during follow-up.

#### Discussion

BrS was first described in 1992 by brothers Josep and Pedro Brugada; it is characterized by three distinct



**Fig. 1.** Electrocardiogram. **A.** Precordial leads V<sub>1</sub> through V<sub>6</sub>. Covered ST elevation in lead V<sub>1</sub> (arrows) and saddle-type in lead V<sub>2</sub> in sinus beats preceding the premature ventricular contractions (arrows). In leads V<sub>4</sub> through V<sub>6</sub>, concomitant ST-segment depressions in sinus beats preceding the premature ventricular contractions (arrows). **B.** Precordial leads V<sub>1</sub> through V<sub>6</sub>. Study conducted on a different day with a different device to exclude possible artifacts. Covered ST elevation in lead V<sub>1</sub> (arrows) and saddle-type in lead V<sub>2</sub> in sinus beats preceding the premature ventricular contractions (arrows)

morphological types of ST-segment elevation in RV leads V<sub>1</sub> through V<sub>3</sub> [1]. However, only the coved pattern (initial ST-segment elevation of  $\geq 2$  mm, slowly descending and concave or rectilinear with respect to the isoelectric baseline, with negative symmetric T wave) is diagnostic for BrS. According to the diagnostic consensus, the following features are required for the diagnosis of BrS [2, 3]:

1. electrocardiography:  $\geq 2$  mm covered ST-segment elevation in  $>1$  precordial RV leads V<sub>1</sub> through V<sub>3</sub>, spontaneous or induced by a sodium channel blocker
2. documented episode of ventricular fibrillation and/or polymorphous ventricular tachycardia; a family history of sudden cardiac death (at  $<45$  years), coved ST elevation in ECG in family members, induced arrhythmia in an electrophysiology study, syncope, or death during sleep.

The presence of the above ECG features without clinical symptoms is sufficient to (descriptively) diagnose the idiopathic Brugada sign, but not the Brugada syndrome.

Patients who fail to fulfill the proposed criteria (and present with coved ST elevation on ECG with J-point elevation of, for example, 1 to 1.5 mm), but

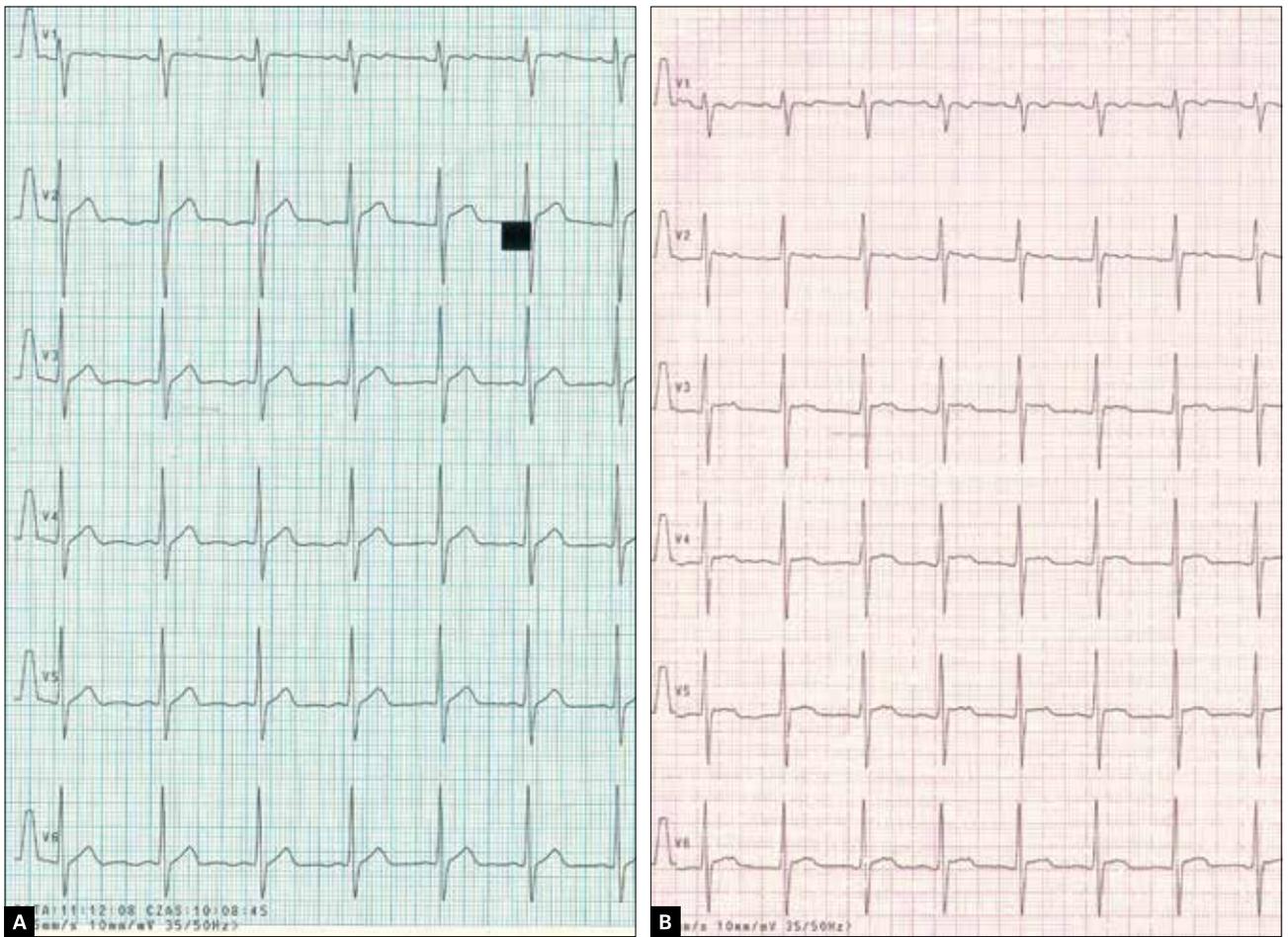
present with clinical symptoms, require further diagnostic tests such as an electrophysiology study, cardiac MRI, genetic screening, and careful follow-up.

Challenge tests with sodium channel blockers are used for confirmation or provocation of latent BrS. To date, the following drugs are recommended in clinical practice [4]:

- Ajmaline, 1 mg/kg of body weight IV over 10 minutes
- Flecainide, 2 mg/kg of body weight IV over 10 minutes (max. 150 mg)
- Procainamide, 10 mg/kg of body weight IV over 10 minutes (100 mg/min)

The recommended sodium channel blocker is ajmaline owing to its short half-life and electrophysiological properties. When directly compared, ajmaline is superior to flecainide in visualization of electrocardiographic features of BrS [4]. Procainamide has the lowest sensitivity. However, the results of recent studies indicate that no test is 100% reproducible. The Priori group have demonstrated that flecainide sensitivity in revealing carriers of occult gene BrS mutations is only 35%; this was evidenced in genetic studies [5,6].

The test is considered positive when ST elevation of 2 mm and more in leads V<sub>1</sub> through V<sub>3</sub> leads is observed, independent from right bundle branch block.



**Fig. 2.** Electrocardiogram. Precordial leads  $V_1$  through  $V_6$ . IV propafenone challenge test. **A.** Before propafenone challenge. **B.** After propafenone challenge

The increase of J-point elevation above 2 mm without electrocardiographic features of type 1 (coved) ST elevation is also considered a positive result.

Of note, structural myocardial damage must be excluded to diagnose BrS.

In our patient, the initial electrocardiographic features of atypical ST-segment elevation in sinus beats preceding the PVC fulfilled BrS diagnostic criteria. A family history of sudden cardiac death in the father was a strong clinical predictor of BrS. Ambiguity and controversies result from the spontaneous ST elevation preceding the PVC, not included in the electrocardiographic definition consensus of BrS. Furthermore, the ajmaline and propafenone test results did not fulfill the diagnostic criteria for BrS. The patient was followed up regularly by cardiology service in accordance with the recommendations. The baseline echocardiogram did not demonstrate structural damage to the myocardium.

In regular follow-up, in consecutive echocardiograms, there was reduced global contractility of the LV and dilated RV cavity.

Cardiac MRI confirmed enlarged RV cavity with segmental contractility abnormalities of akinesia type and impaired RV systolic function (RVEF of 40%). Arrhythmogenic RV cardiomyopathy (ARVC) with LV involvement was then suspected due to segmental contractility disorders in the lateral wall and a moderate reduction in global LV contractility to 40%–45%.

In 2010, Sen-Chowdhry et al.[7] proposed new diagnostic criteria of ARVC. Certain diagnosis is made if 2 major criteria are present or 1 major and 2 minor criteria, or alternatively 4 minor criteria of different categories.

Borderline diagnosis is made if 1 major and 1 minor criteria or 3 minor criteria from different categories are present. According to the 2010 ARVC criteria, our patient was assessed as follows:

#### 1. Imaging studies

Echocardiography: segmental akinesia and RV size in the long parasternal RV outflow tract view >32 mm (39 mm in our patient) (**major criterion**).

Cardiac MRI: RV free akinesia with the RVEF of 40% (**major criterion**).

#### 2. Abnormal depolarization

ECG: widening of the terminal activation in the QRS complex >55 ms in leads  $V_1$  through  $V_3$  (80 ms in our patient, fig. 5) (**minor criterion**)

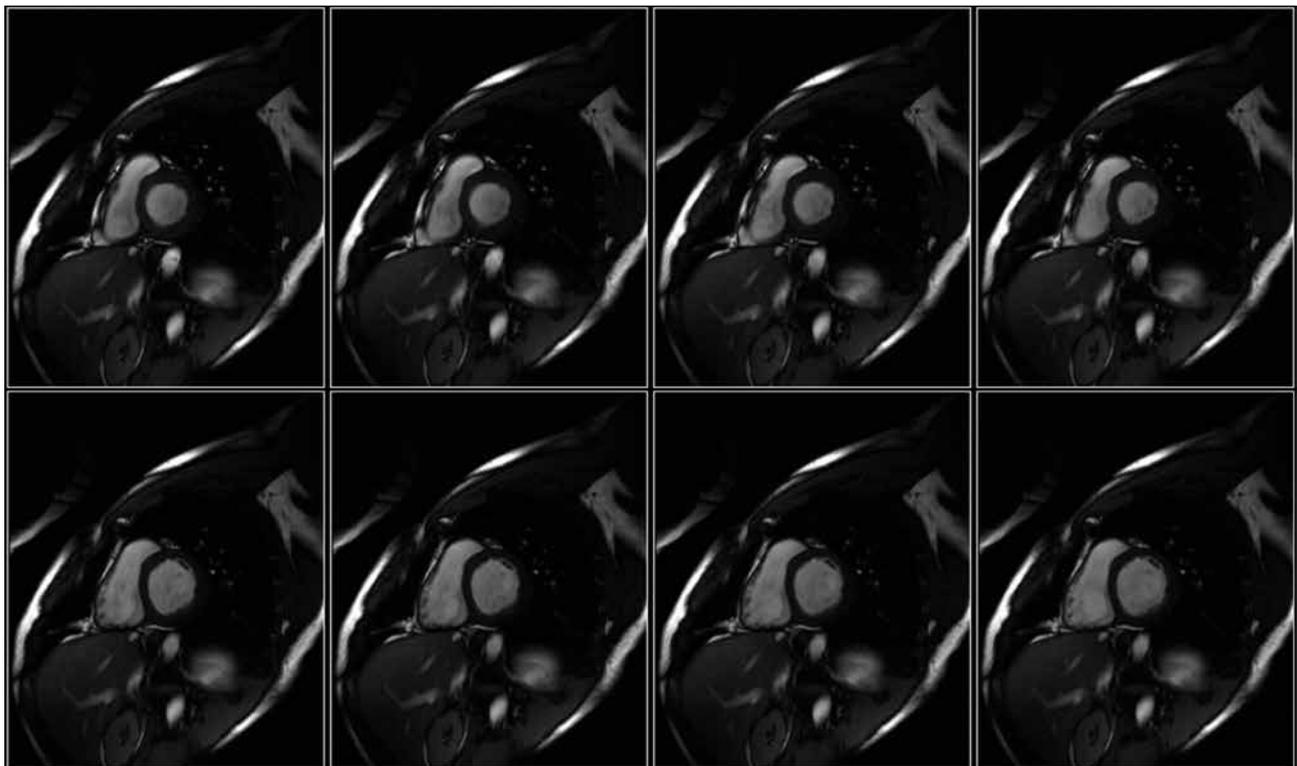
#### 3. Arrhythmia

Ventricular arrhythmia of LBBB morphology >500 PVC in 24 hours (**minor criterion**).

Based on the above criteria, 1 major and 2 minor, a working diagnosis of ARVC with LV involvement was made.



**Fig. 3.** Electrocardiogram. Ajmaline test. **A.** After the ajmaline challenge test. Visible epsilon wave in lead V2 (arrow). Coved ST-segment elevation in lead V2; J-point elevation +1.5 mm in lead V3. SI–SII–SIII complex, wide R wave in aVR – most likely abnormal conduction in the right ventricular outflow tract. **B.** Vignette with enlarged V2 lead – arrow pointing to the epsilon wave



**Fig. 4.** Cardiovascular magnetic resonance. In systole and diastole. For description see the text. Akinesis of the right ventricular free wall



**Fig. 5.** 12-lead Holter monitoring. **A.** Dynamics of changes of the J point and ST segment in leads V1, V2, and aVL (arrows). Alternating ST (variable morphology) in lead V2 (arrows). Variable QRS morphology in lead V1 (asterisks), with widened terminal QRS portion >55 ms. **B.** Enlarged V1 and V2 trace

## Differential diagnosis of arrhythmogenic right ventricular cardiomyopathy and the Brugada syndrome

Our case clearly indicates that some cardiac diseases with genetically mediated arrhythmias and sudden cardiac death may be symptomatically extremely similar to others and, at some disease stages, even mimic each other (overlapping syndromes). In 1988, Martini and Nava, Italian investigators from Padova, reported on ARVC which, on electrocardiography, was identical in phenotype with BrS first described in 1992 [8].

Differential diagnosis of ARVC and BrS may be difficult at times, notably in cases with minimal RV involvement. ARVC often mimics BrS and definitive diagnosis can only be made on autopsy. ARVC must be excluded before the diagnosis of BrS is made. In electrocardiography, ARVC presents with the epsilon wave in approximately 30% of the patients [9]. The epsilon wave is observed in 13% of BrS patients; it can be induced by the ajmaline test [10]. Recently, it has been stressed that fragmentation of the QRS and the starting portion of ST segment mimicking the epsilon wave can be seen in 40% of BrS patients, notably in those with a history of ventricular fibrillation [11,12]. These fragmentations mirror the local conduction disorders within the RV outflow tract in the surface ECG [12].

Furthermore, ARVC features include late ventricular potentials (91%) (minor diagnostic criterion), but these are increasingly observed in BrS patients (80%) depending on the method used for detection [13].

The problem is further complicated by the positive ajmaline test result as this can be positive also in ARVC patients. Peters et al. reported a positive ajmaline test result typical for BrS in 16% of ARVC patients [14]. Such case was first reported as an “overlapping syndrome” (ARVC and BrS) in the Polish literature by Włodarska et al. [15] and by the German investigators, Schmidt et al. [16].

## Management

Owing to ventricular arrhythmias and moderate RV systolic function impairment, a  $\beta$ -blocker was started. Ventricular arrhythmia remains asymptomatic.

An ACEI was started because of moderate LV systolic function (LVEF, 40% to 45%).

The patient remains asymptomatic with respect to cardiac failure. He is regularly followed up by ECG, 24-hour Holter monitoring, and echocardiography. Because of the family history of sudden cardiac death in the father, he is evaluated with the criteria for implantable cardioverter-defibrillator at each visit as primary prevention.

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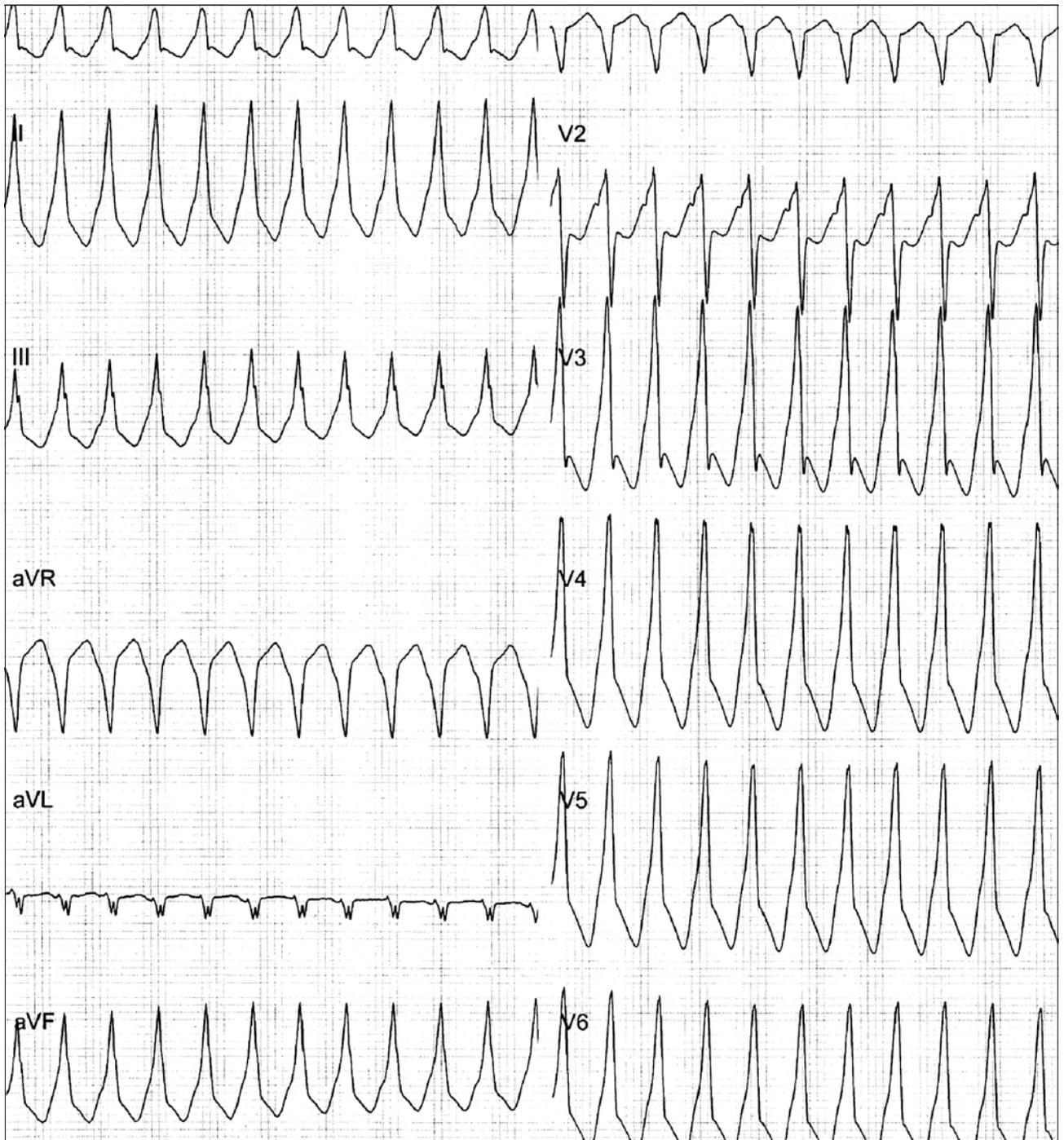
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## Arrhythmia in a patient with muscular dystrophy (RCD code:V-4A.0)

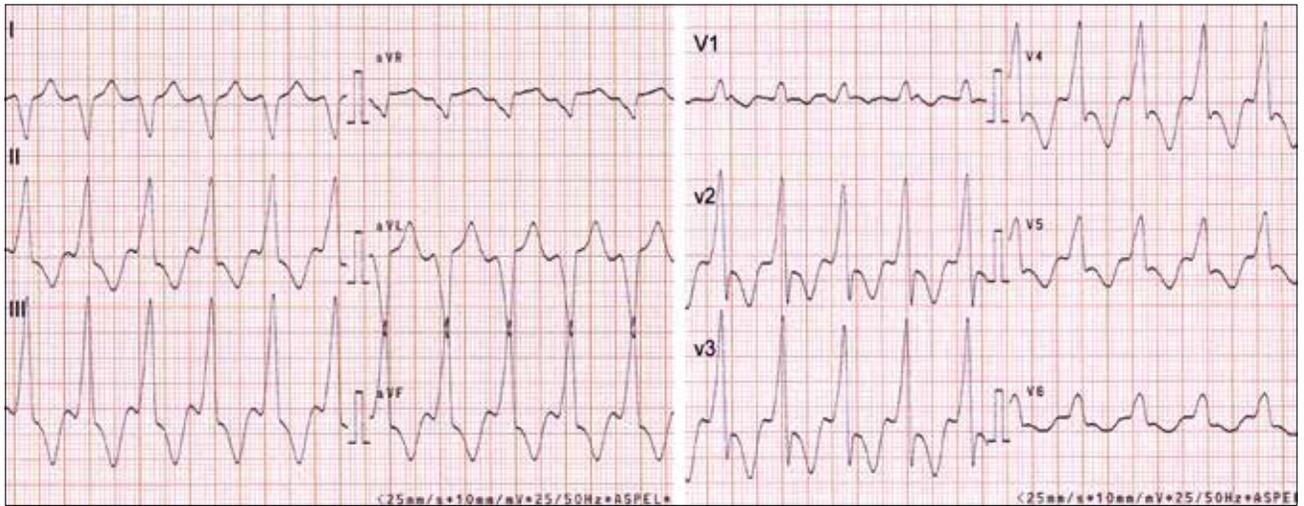
Marek Jastrzębski

Muscular dystrophies are a group of rare neuromuscular diseases, manifesting as reduced muscle power and muscular atrophy. Different forms of muscular

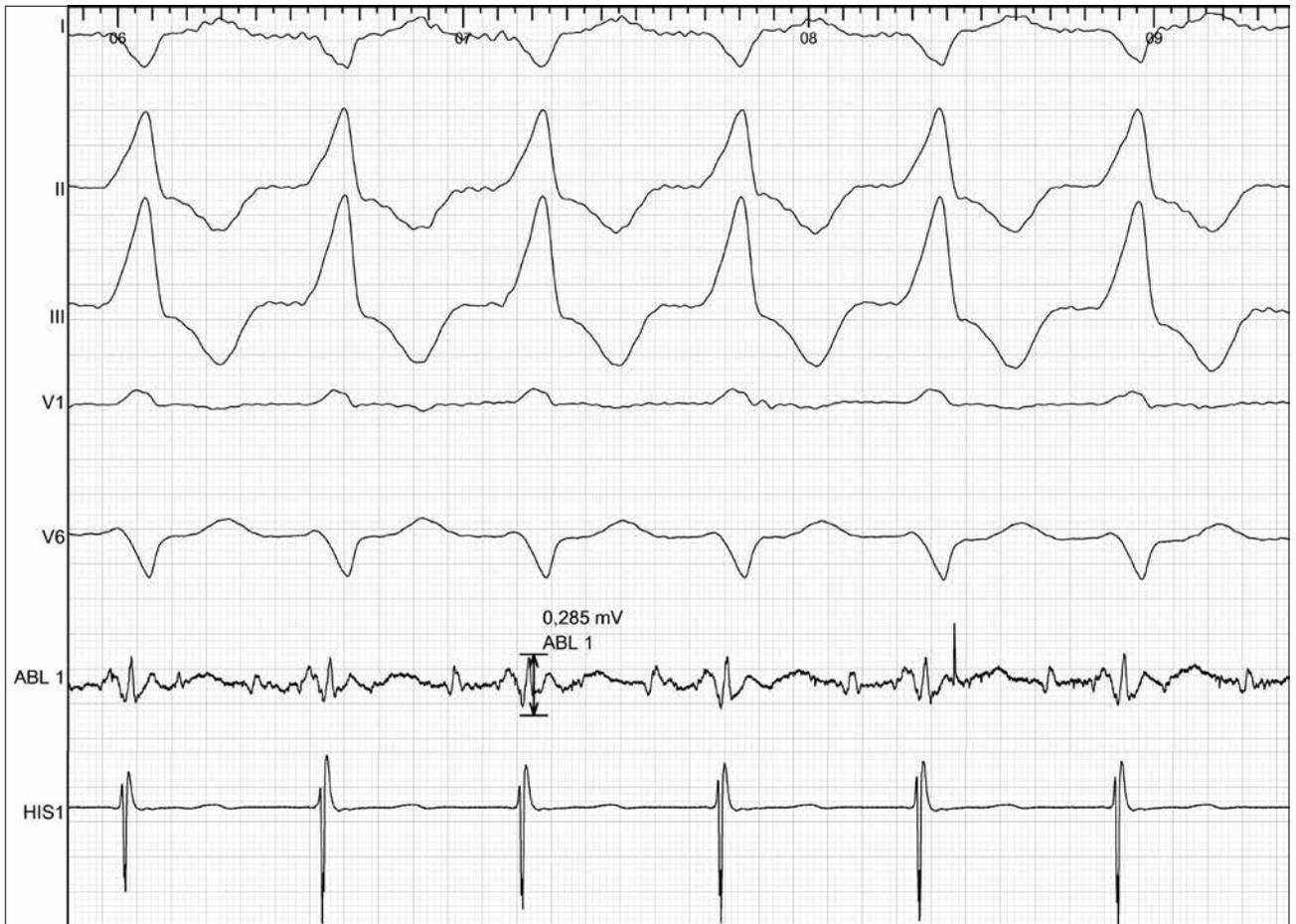
dystrophy have been described, including Becker, Duchenne, and myotonic dystrophies, calpainopathy (limb-girdle muscular dystrophy type 2A) and laminopathy (limb-girdle muscular dystrophy type 1B or Emery–Dreifuss muscular dystrophy), and others. The etiology of these diseases is associated with several gene mutations, many of which have not yet been elucidated. Cardiomyopathy is observed in a high percentage of the patients with muscular dystrophies and cardiac symptoms are primarily associated with tachy- and bradyarrhythmia and, less often, with cardiac failure [1–3].



**Fig. 1.** Electrocardiogram. Tachycardia recorded before implantation of the defibrillator at the onset of cardiac complaints. This rapid ventricular tachycardia was the cause of syncope. The relatively narrow QRS complexes suggest arrhythmic trigger location within the paraseptal (basal) region or within the septum; a role of Purkinje fibers in reentry loop cannot be excluded here



**Fig. 2.** Electrocardiogram. Tachycardia registered 5 years after ICD implantation during amiodarone treatment. This tachycardia usually stopped with „burst” stimulation however, occasionally was resistant to antiarrhythmic stimulation. This arrhythmia was the cause of ICD discharges and an electric storm. Note the same deflection of QRS complexes in precordial leads indicating tachycardia exist site was in the basal area of the left ventricle. The electrical axis is directed inferiorly (positive QRS complexes in leads II, III, and aVF) indicating an exit site high on the anterior wall of the left ventricle



**Fig. 3.** Electrophysiological study. Endocavitary trace during tachycardia from the site of successful ablation (ABL 1). Note the very low-amplitude potentials at this site (0.285 mV) indicating an area of deep scar, and the mid-diastolic potential typical for a protected isthmus of a reentrant circuit. Paper speed 50 mm/s

## Case report

A 38-year-old woman with no prior history of circulatory problems was admitted with recurrent syncope due to rapid ventricular tachycardia with a rate of 240 beats/min. She had a history of muscular dystrophy diagnosed at the age of 7 years based on muscle biopsy. Genetic typing was scheduled but not conducted because of insufficient diagnostic facilities at the neurological unit; therefore, no exact type of myopathy was diagnosed. The course of the disease since childhood was relatively benign and manifested as fatigability on ambulation and reduced limb muscle power. A family history was negative for cardiac and neurological diseases and no abnormalities were detected on biochemical tests.

On admission and confirmation of ventricular tachycardia with an electrophysiology study (fig. 1), a dual-chamber cardioverter-defibrillator device was implanted. Mild atrioventricular conduction abnormalities at the atrioventricular node level were seen (first-degree block in an electrocardiogram [ECG]; PQ interval, 320 ms; AH interval [atrium-His bundle], 226 ms). An echocardiogram showed discrete features of cardiomyopathy: slightly enlarged thickness of the interventricular septum (14 mm) and left ventricular posterior wall (12 mm) despite normal arterial pressure; additionally, nonuniform echogenicity of the myocardium was observed. The size of the cardiac chambers and left ventricular ejection fraction (LVEF, 62%) were normal.

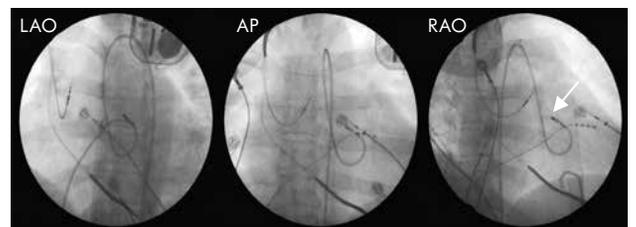
Numerous interventions of the cardioverter-defibrillator owing to episodes of ventricular tachycardia were observed in the follow-up. In the first years, interventions were mostly pain-free (antiarrhythmic stimulation), but with time the device increasingly failed to stop the tachycardia episodes with stimulation and the patient periodically experienced high-energy discharges. Paroxysmal atrial fibrillation occurred along with inappropriate implantable cardioverter-defibrillator (ICD) interventions. The patient received sotalol (2 × 160 mg) at this time; later amiodarone was started owing to inadequate effects of sotalol. Unfortunately, amiodarone failed to prevent arrhythmia; furthermore, amiodarone reduced the rate of ventricular tachycardia to 125–145 beats/min (**Figure 2**), causing the overlapping of the tachycardia rate on the sinus tachycardia, preventing the detection of arrhythmia and adequate interventions of the defibrillator device. After 5 years from defibrillator implantation, the patient returned to the hospital in a serious condition with cardiogenic shock caused by an electric storm with numerous discharges (on faster tachycardias) and incessant slow ventricular tachycardia with a rate below the detection threshold of the defibrillator. The device memory contained over 300 interventions due to ventricular tachycardia. Progression of cardiac involvement was also observed: perpetuation of atrial flutter/fibrillation, occurrence of new advanced atrioventricular block (second- and third-degree) and reduction of the LVEF to 30% without dilation of heart

chambers. Areas of hypokinesia and akinesia were most evident in the basal segments of the left ventricle.

After stabilizing the patient's condition by partial suppression of the arrhythmia with combined antiarrhythmic treatment (amiodarone and propafenone), an electrophysiology study was conducted. Very slow (100–110 beats/min) ventricular tachycardia was induced during the study in a reproducible manner, with every attempt of incremental ventricular stimulation. Classic electrophysiology mapping was carried out (entrainment and activation mapping) locating the critical isthmus of the reentry loop in the basal segment of the anterior wall (**Figure 3**). Tachycardia was stopped with a single radiofrequency application at that site (**Figure 4**); several consolidating applications were then performed in the same area; from that moment, ventricular arrhythmias were noninducible. Amiodarone and propafenone were stopped after the procedure, reducing the treatment to a moderate  $\beta$ -blocker dose (metoprolol, 50 mg). No ventricular arrhythmia episodes or defibrillator interventions were observed during subsequent follow-up of over 2 years.

## Discussion

Cardiac involvement is observed in a high percentage of patients with muscular dystrophies, even in their subclinical forms.<sup>4–8</sup> Based on the clinical picture with dominant tachy- and bradyarrhythmia, it can be suspected that the present patient had laminopathy (limb-girdle dystrophy type 1B or Emery-Dreifuss dystrophy) rather than dystrophinopathy; however, considering the broad and variable spectrum of the cardiac involvement in these disorders, similar symptomatology may be present in other forms of muscular dystrophy. Even in X-linked disorders (Duchenne and Becker muscular dystrophy), in which women are generally considered carriers of the gene mutation, several percent of women present with cardiac symptoms.<sup>9,10</sup> In some cases of muscular dystrophy, such as in our patient, cardiac symptoms can dominate the clinical picture. Furthermore, cardiac sequelae of the disease may result in premature and sometimes sudden death in these patients.<sup>11,12</sup> Modern technologies (implanted cardioverter-defibrillator device and ablation procedure) certainly have helped prevent cardiac death in our patient.



**Fig. 4.** Fluoroscopy. Ablation electrode introduced in the left ventricle through a transaortic approach. Site of successful RF ablation on anterior wall of the left ventricle, parabolal (white arrow)

Cardiac involvement usually manifests in ECG as various forms of atrioventricular block and supraventricular as well as ventricular tachyarrhythmias. For example, approximately 30% of the patients with myotonic dystrophy present with first-degree atrioventricular block, usually caused by the His-Purkinje system abnormalities and burdened with high risk of death due to asystole. Prophylactic implantation of a pacemaker is therefore indicated in many of these patients. It should be considered when prolonged HV interval (His bundle–ventricle) exceeding 70 ms is detected by an electrophysiology study.<sup>13,14</sup> Patients with different types of dystrophy require regular follow-up with ECG and periodic echocardiography.<sup>15</sup> Similarly to myotonic dystrophy or laminopathies and in Becker dystrophy, a large number of the patients show ECG abnormalities mainly in the form of intraventricular and atrioventricular conduction disorders.<sup>5</sup> In the present patient, atrioventricular conduction disturbances on ECG preceded cardiac complaints and there was a relatively rapid progression of the atrioventricular block from mild to advanced.

A hazardous sequela of Purkinje fiber damage in patients with muscular dystrophies is reentrant ventricular tachycardia involving the conductive fibers. These tachycardias, similarly to arrhythmia observed in our patient on presentation, are characterized by relatively narrow QRS complexes (Figure 1).<sup>16</sup> The involvement of the working myocardium in patients with cardiomyopathy leads to development of regions of akinesis and hypokinesis on the basis of degeneration and fibrosis. This creates a substrate for reentrant ventricular tachycardias similarly to as in patients with myocardial infarction. Certainly this was the pathophysiological basis for arrhythmias which triggered numerous ICD discharges and the electrical storm in our patient.

Implantation of a cardioverter-defibrillator device is a recognized treatment method for patients with hemodynamically unstable ventricular tachycardia. It should be noted that this treatment modality is only useful in occasional arrhythmia. Frequent high-energy discharges severely affect the quality of life, while an electric storm is life-threatening. Therefore, when arrhythmia is refractory to drug treatment, ablation is the best choice. Several studies have demonstrated high efficacy of radiofrequency ablation in the prevention of electric storm episodes and significant reduction of ventricular tachycardia attacks.<sup>17, 18</sup>

## Summary

Cardiac disorders are a significant problem in muscular dystrophy, which is a neuromuscular disease. Therefore, patients should be regularly followed up both by cardiologists and neurologists; and in the case of new arrhythmia onset in the form of brady- or tachyarrhythmia – by an electrophysiology cardiologist. Patients without cardiac symptoms should be periodically followed up with a 12-lead ECG and Holter

24-hour ECG monitoring. The onset of unexplained syncope/presyncope is a red flag for extending cardiac diagnostic work-up.

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## Unusual electrocardiographic findings in a patient with dextrocardia and multiple cardiac arrhythmias (RCD code: V-2D.0)

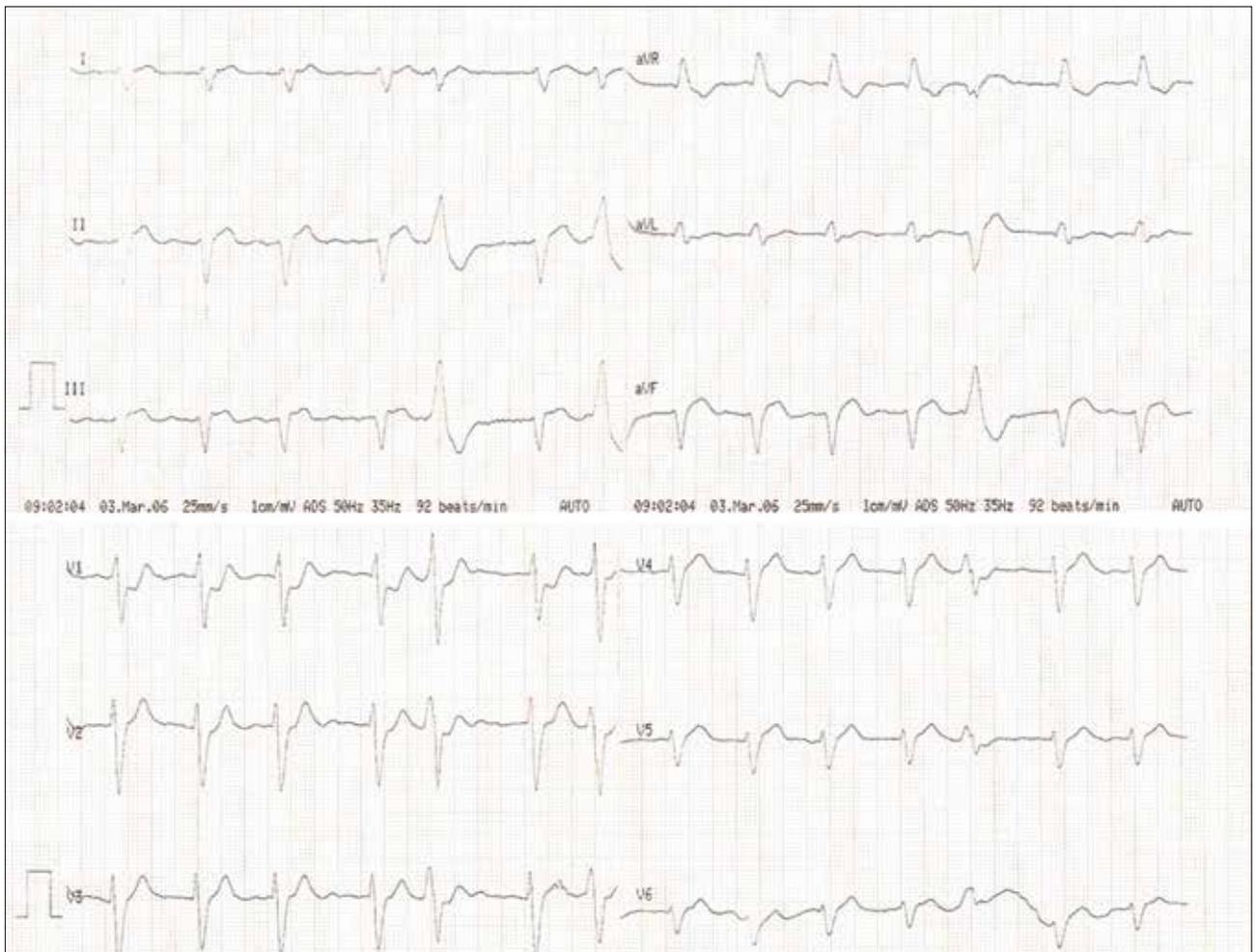
Jacek Majewski, Katarzyna Holcman, Renata Pacholczak, Jacek Lelakowski

We present a case of an 82-year-old man with a ventricular pacemaker implanted 6 years earlier in a different hospital due to permanent atrial fibrillation and episodes of complete atrioventricular block. In addition, the patient was diagnosed with arterial hypertension and chronic obstructive pulmonary disease. He had a history of prostate resection due to cancer. He was admitted to the hospital for pacemaker reimplantation (box change). The procedure was performed without complications. An electrocardiogram on admission showed typical features of dextrocardia, which was confirmed by chest radiography (fig. 1–4) and echocardiography. In our patient, dextrocardia occurred in the configuration of

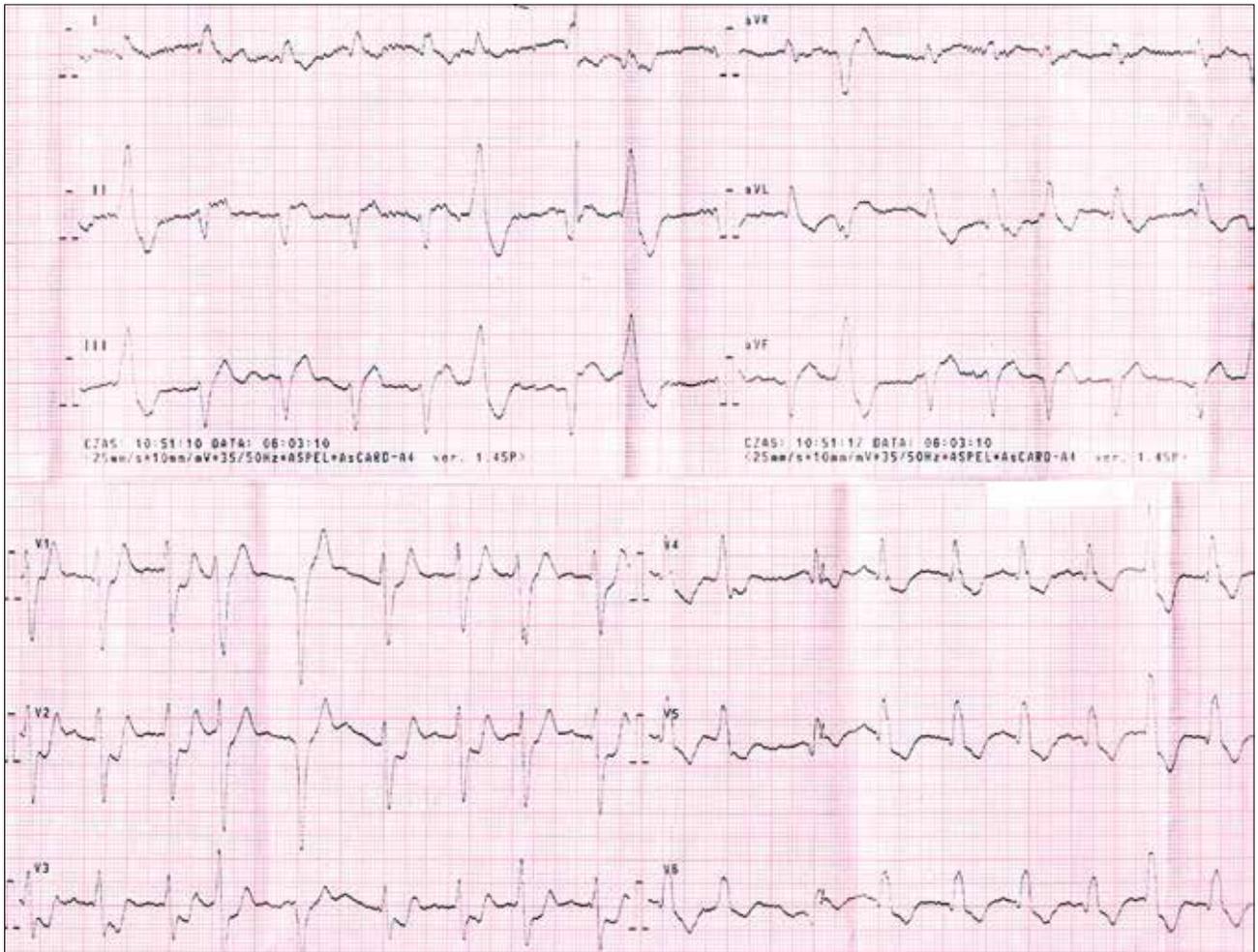
L-loop ventricles, congenitally corrected transposition of the great arteries (cTGA), and situs solitus. The stomach and spleen were on the left and the larger lobe of the liver was on the right side of the body.

## Discussion

Dextrocardia is a congenital condition in which the heart is located in the right hemithorax with its base-to-apex axis directed to the right and caudal [1]. The exact incidence of dextrocardia is unknown. According to the population-based studies, it is estimated at 1/12 000 [2]. Dextrocardia is caused by abnormalities in cardiac looping during gastrulation (a period in embryonic development that occurs in the third week of gestation). It may occur with situs solitus (normal configuration of asymmetric organs) or it may be associated with abdominal situs inversus, a rare congenital condition in which the major organs are transposed. Dextrocardia may also be accompanied by situs ambiguus (heterotaxy syndrome), in which the arrangement of the organs is abnormal, that is, the spleen may be completely missing or may



**Fig. 1.** Electrocardiogram. Performed after pacemaker reimplantation (box change) shows atrial fibrillation and features typical for dextrocardia. Lead I: negative QRS. Lead II corresponds to lead III in normal individuals, and vice versa. Lead aVL corresponds to lead aVR in normal individuals, and vice versa. Precordial leads show R-wave regression from V1 to V6



**Fig. 2.** Electrocardiogram. Performed after transposition of the electrodes to the right side. Atrial fibrillation, left bundle branch block, and premature ventricular complexes originating from the right ventricular outflow tract can be seen

be multiple. The two primary subtypes of situs ambiguous include right isomerism, or asplenia syndrome, and left isomerism, or polysplenia syndrome [3,4].

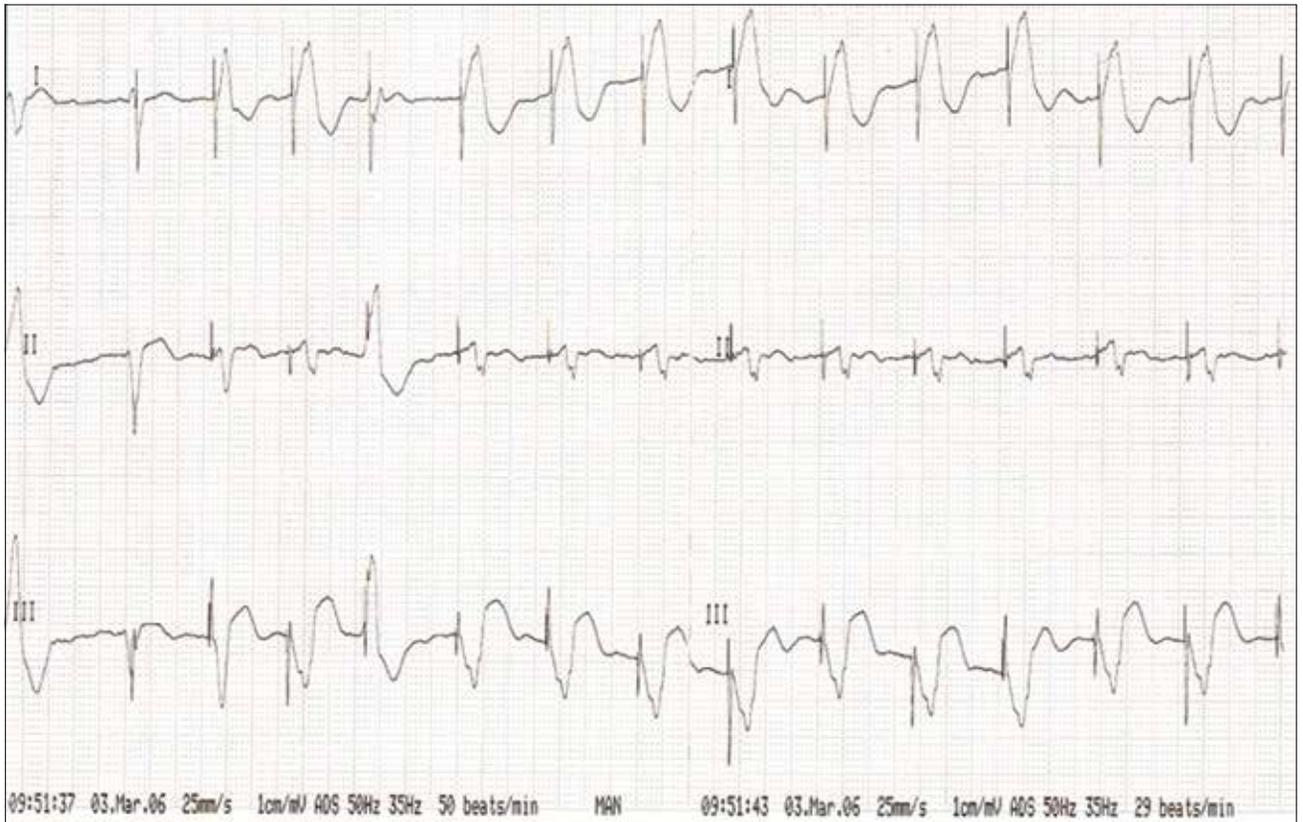
There may be other clinical conditions in which the heart is right-sided. Dextroversion means a rotation of the ventricular portion of the heart to the right with the atria remaining in the normal position. Furthermore, dextrocardia should be differentiated from cardiac dextroposition, which is defined as displacement of the heart to the right, secondary to extracardiac causes, such as right lung hypoplasia, right pneumonectomy, or diaphragmatic hernia. Dextrocardia may be associated with other congenital heart malformations, including cTGA, as was the case in our patient [5]. Arrhythmias are also commonly associated with dextrocardia and cTGA [1]. Moreover, the anatomy of the conduction system is affected. The sinus node and the proximal part of the atrioventricular node are located in morphologic right atrium, while the His bundle and bundle branches rotate with the bulboventricular loop [6]. Complete atrioventricular block occurs in up to 30% of the patients with dextrocardia [7]. The risk of developing atrioventricular block increases with age (2%/year). Most of the patients with this complication require pacemaker implantation, which may be challenging due to abnormal anatomy [8,9].

## Dextrocardia – diagnostic algorithm

Situs abnormalities might be initially suspected on the basis of the physical examination and confirmed by radiography and ultrasonography. Computed tomography could be useful for the definitive diagnosis because it allows to confirm the anatomical position of the visceral organ and apex of the heart as well as great vessel branching. Magnetic resonance imaging may be useful in difficult cases or in patients with associated cardiac anomalies [1].

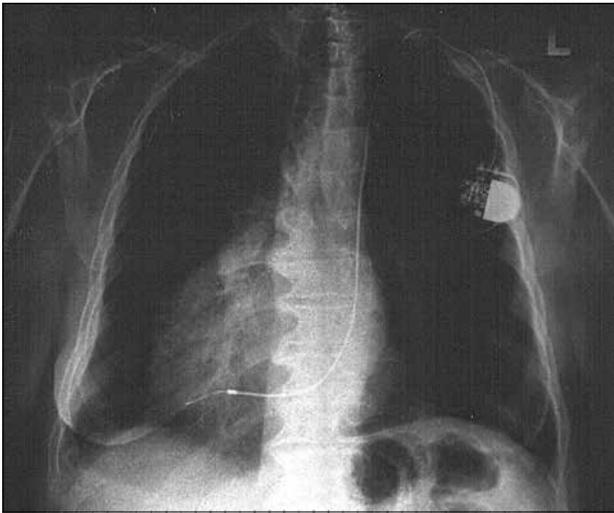
The case of our patient shows that dextrocardia can be sufficiently diagnosed by electrocardiography. The typical features of dextrocardia on electrocardiography are as follows [10]:

- Lead I: inversion of all complexes, “global negativity” (inverted P-wave, negative QRS, inverted T-wave)
- Lead II corresponds to lead III in normal individuals, and vice versa
- Lead aVL corresponds to normal lead aVR in normal individuals, and vice versa
- Leads V1-VC6: right axis deviation, R-wave regression from V1 (Rs or qR), V2 (RS) to V6 (rS) [5]



**Fig. 3.** The magnet was applied to evaluate the pacemaker function. Ventricular spikes followed by paced QRS complexes are shown

In order to obtain normal record, both limb leads and precordial leads should be placed in reversed positions.



**Fig. 4.** Chest X-ray. Primary electrocardiographic diagnosis of dextrocardia. Right-sided cardiac silhouette with left-sided gastric bubble. The cardiac apex is pointed to the right side. The pacemaker with a lead placed in the morphologic right ventricle is present

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## Arrhythmia in a patient with cor triatriatum sinistrum (RCD code: V-2B.3)

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### Case report

A 37-year-old woman was referred to the Department of Electrophysiology at the John Paul II Hospital in Krakow for ablation of atrial fibrillation. The patient had a 14-year history of spontaneous paroxysmal atrial fibrillation and had experienced exacerbation in the last few months before hospitalization.

Atrial fibrillation in our patient was diagnosed at the age of 23 years. Despite antiarrhythmic treatment, the episodes did not resolve but increased in frequency and duration. Her symptoms were classified as the European Heart Rhythm Association score III (severe symptoms affecting daily activities) [1]. The patient experienced palpitations, chest pain, dyspnea, and impaired exercise tolerance several times a week. She did not respond to any pharmacological agents, and electrical cardioversion had an efficacy rate of 50%. Most frequently, atrial fibrillation resolved spontaneously after a few hours.

Transthoracic echocardiography was performed to assess the size of cardiac cavities; it revealed a structure within the left atrium, which appeared to be a septum in the longitudinal heart axis. Other standard tests performed before CARTO ablation include computed tomography to assess the number and diameter of the pulmonary veins and the size of the left atrial auricle and transesophageal echocardiography (TEE). Computed tomography is necessary for the exact function of the electroanatomical mapping system. It is also required to elucidate echocardiographic findings. TEE

allows to assess atrial hemodynamics, the presence of flow through the interatrial septum, and the presence of thrombus in the left atrium.

Computed tomography revealed that the left atrium was not completely divided by the membranous septum, which divides the atrial cavity into the anterior and posterior parts. All pulmonary veins terminated in the posterior part of the left atrium, whereas the auricle communicated with the anterior part. Both cavities communicated through a large defect in the membranous septum.

TEE showed normal confluence from the right and left pulmonary veins, all of which had normal diameters. Inside the atrial cavity, a defect of the flaccid septum was shown in the superior portion (21–25 mm) with nonrestrictive flow in the area. In addition, TEE demonstrated an enlarged interatrial septum resembling an aneurysm without the left-to-right shunt. The valvular apparatus and the remaining cardiac cavities did not show any abnormalities.

We consulted a cardiothoracic surgeon and decided to perform radiofrequency ablation with the CARTO system, despite the structural abnormality of the left atrium. Circumferential pulmonary vein isolation according to Pappone was performed together with mitral isthmus and left atrial ceiling ablation. The procedure was supplemented by IVC-TA veno-tricuspid isthmus and fragmented atrial potentials right atrium ablation.

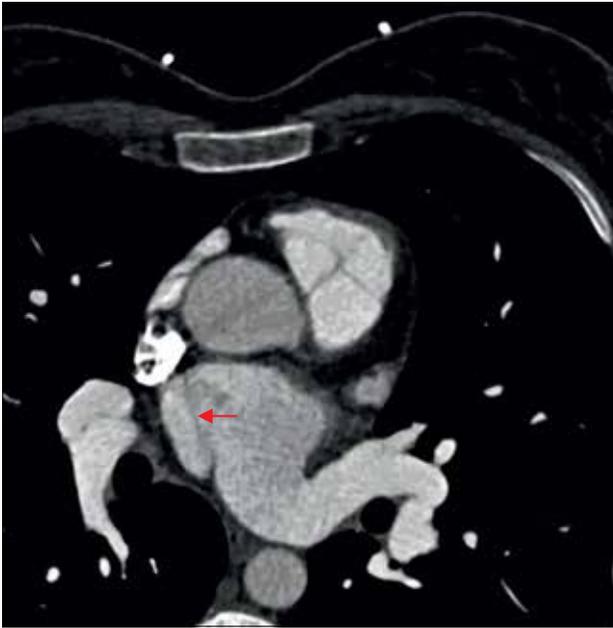
The patient remained asymptomatic and free from atrial fibrillation episodes throughout the 6-month follow-up period; there were only a few episodes of momentary palpitation.

### Discussion

Cor triatriatum sinistrum is the least common congenital heart disease; it is observed in approximately 0.1% to 0.4% of the general population [2]. In this disease, a fibromuscular membrane divides the left atrium into two cavities: a posterosuperior portion, communicating



Fig. 1. Electrocardiogram. Before before radiofrequency ablation with the CARTO system



**Fig. 2.** Cardiovascular computed tomography. Left atrium with a visible portion of the septum on the right side (red arrow)

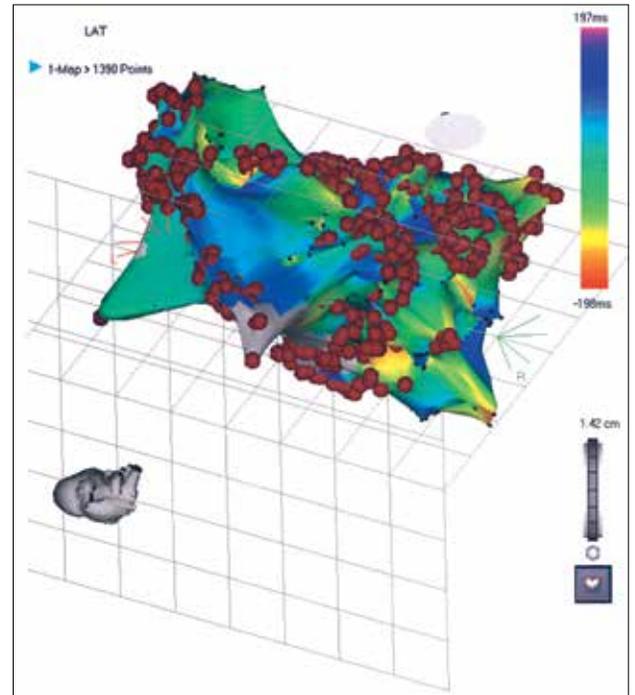


**Fig. 3.** Cardiovascular computed tomography. Three-dimensional reconstruction. Visible space in the superior portion of the atrium demonstrates different blood flow (arrow)

with the pulmonary veins, and an anteroinferior portion communicating with the left atrial auricle (commonly atrophic) and the mitral valve ring [3,4].

The symptoms most often occur in young patients and can mimic mitral stenosis with dyspnea, orthopnea, hemoptysis, and the development of secondary pulmonary hypertension caused by a high pressure gradient between the cavities of the left atrium. Therefore, patients with exacerbation of symptoms are scheduled for a cardiothoracic surgery involving septum resection, which eliminates the symptoms [5,6].

The severity of symptoms depends on the number and size of septal defects. With increasing size of the defect, the intensity of symptoms is reduced and they occur later in life [4].



**Fig. 4.** Mapping of RF application with the CARTO XP system. Circumferential pulmonary veins isolation

It is unclear why our patient experienced symptoms of atrial fibrillation rather than those of mitral stenosis and pulmonary hypertension. The most likely cause was atrial wall distention during increased left atrial filling, which triggered atrial fibrillation.

This hypothesis is further supported by the effectiveness of atrial fibrillation ablation procedure.

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## Arrhythmias in chemotherapy patients (RCD code: V-4A.1)

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### Case 1

A 48-year-old woman was referred to our center with stinging chest pain, palpitations, and dyspnea. The symptoms persisted for the past 3 weeks, were of short duration, and subsided spontaneously; on admission, they persisted for over 6 hours without subsiding. The patient also had a history of impaired exercise tolerance for approximately 1 month (New York Heart Association [NYHA] class II).

Four and a half years prior to admission, the patient was treated for breast cancer with surgery, radiotherapy, and chemotherapy (cyclophosphamide and adriamycin). Moreover, a history revealed arterial hypertension treated for 2 years with ramipril and chronic nicotine use.

On admission, a physical examination revealed stable hemodynamics, arterial blood pressure of 120/80 mm Hg, slight peripheral pitting edema, and no other pathology of significance.

A baseline electrocardiogram (ECG) showed abnormal left-axis deviation and broad QRS atrial flutter

at a rate of 150 beats/min (fig. 1). After arrhythmia resolved (by intravenous amiodarone), an ECG showed abnormal left-axis deviation, normal sinus rhythm at a rate of 80 beats/min, PQ of 0.24 s, QT of 0.40 s, and left bundle branch block (not previously observed) (fig. 2).

Laboratory studies demonstrated normal levels of electrolytes, complete blood count, and thyroid-stimulating hormone, negative cardiac necrosis markers, and no other significant abnormalities.

Chest radiography showed an enlarged cardiac silhouette and features of pulmonary circulation stasis. An echocardiogram revealed features of dilated cardiomyopathy with significantly low (30%) left ventricular ejection fraction (LVEF), with features of intra- and interventricular asynchrony and moderate mitral valve insufficiency.

Considering the presence of dilated cardiomyopathy of unknown etiology, coronary angiography was conducted and no significant abnormalities of the pericardial vessels were observed.

A Holter ECG trace demonstrated normal sinus rhythm with intraventricular conduction abnormalities and second-degree atrioventricular block with one episode of nonsustained ventricular tachycardia and numerous (nearly 5000 episodes) of ventricular extrasystoles including pairs, bigeminy, and triplets.

Considering the full clinical picture, the patient was diagnosed with dilated cardiomyopathy of toxic etiology secondary to oncology treatment; a cardiac resynchronization device (CRT-D) was implanted



Fig. 1. Electrocardiogram. Wide QRS 150 beats/min (atrial flutter)

without complications. Directly after the procedure, ECG demonstrated narrowing of stimulated QRS complexes (fig. 3). At 6 months following the procedure, improved exercise tolerance was noted (confirmed in the 6-minute walk test). The CRT-D telemetry follow-up did not reveal episodes of ventricular fibrillation, ventricular tachycardia, or device interventions.

## Case 2

A 26-year-old man was admitted to the intensive care unit at the Department of Hematology following a cardiac arrest in the mechanism of ventricular fibrillation.

Two years earlier, the patient was treated for testicular and epididymal neoplasm (surgery and chemotherapy with etoposide and cisplatin); the current hospitalization was for chemotherapy for acute myelocytic leukemia (AML M5, second treatment cycle), most likely associated with the previous oncology treatment. During current hospitalization, the following drugs were used: cytarabine, mitoxantrone, methotrexate, ondansetron, vancomycin, amikacin, nystatin, fluconazole, and others.

On admission, the patient was unconscious, intubated, ventilator-assisted respiration, receiving three pressure support amines (dopamine, dobutamine, and adrenaline); blood pressure was 100/60 mm Hg.

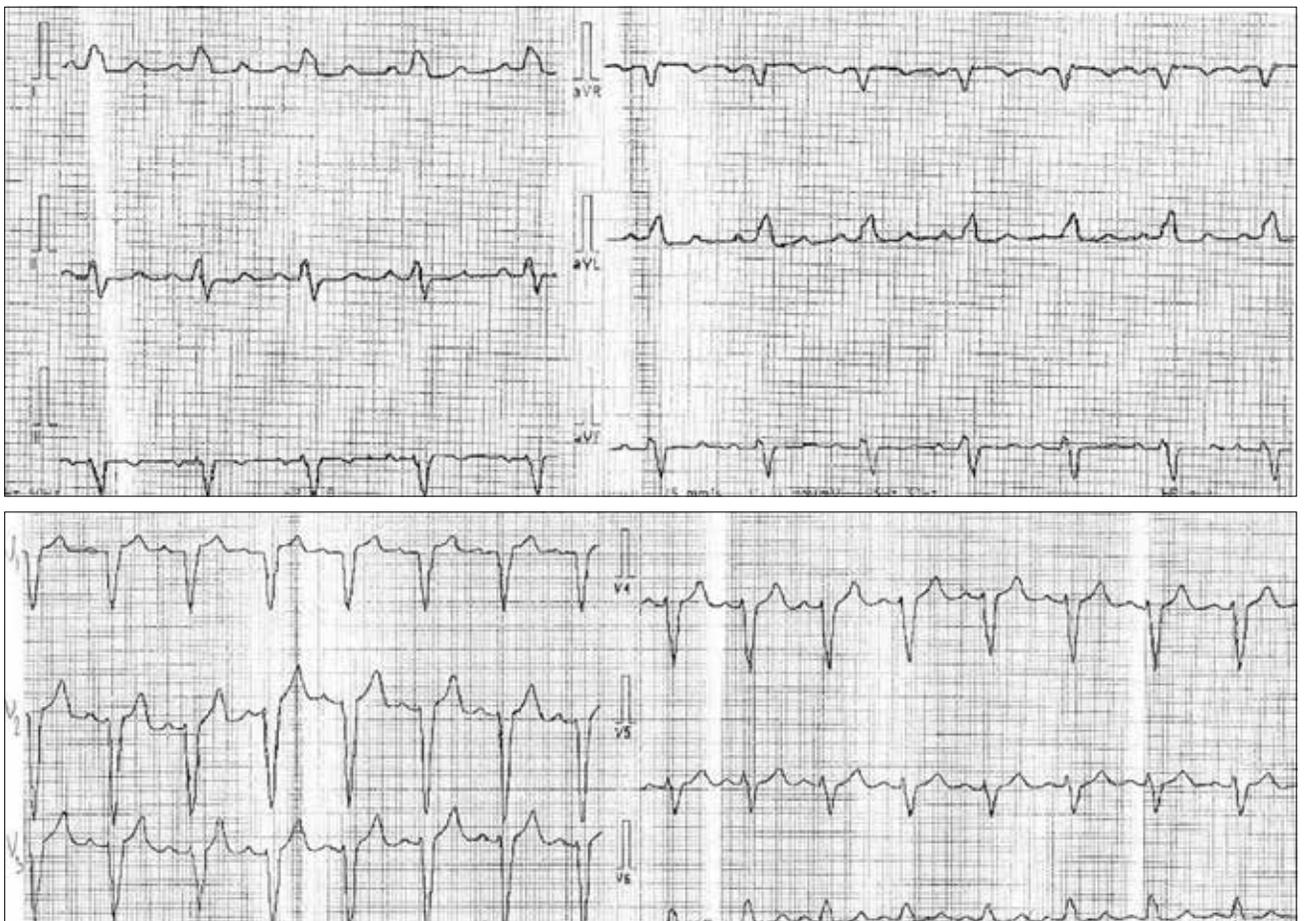
An ECG on admission showed sinus rhythm of 85 beats/min, left-axis deviation, PQ of 0.14 s, QTc (Bazett's formula) of 0.58 s. Numerous R-on-T ventricular extrasystoles could be noted (fig. 4). A bedside echocardiogram was conducted, demonstrating no segmental contractility abnormalities; LVEF was 50% with no significant pathology. Laboratory studies demonstrated serum potassium of 2.8 mmol/L, anemia (red blood cells,  $2.72 \times 10^6$ ; hematocrit, 22.3%; and hemoglobin, 8.1 g/dL), leukopenia (white blood cells,  $0.54 \times 10^3$ ), with no other significant abnormalities.

The treatment included potassium supplementation and a  $\beta$ -blocker. Overdrive endocavitary stimulation was started. Despite the treatment, polymorphic ventricular tachycardias recurred. After 3 days of hospitalization, the patient died.

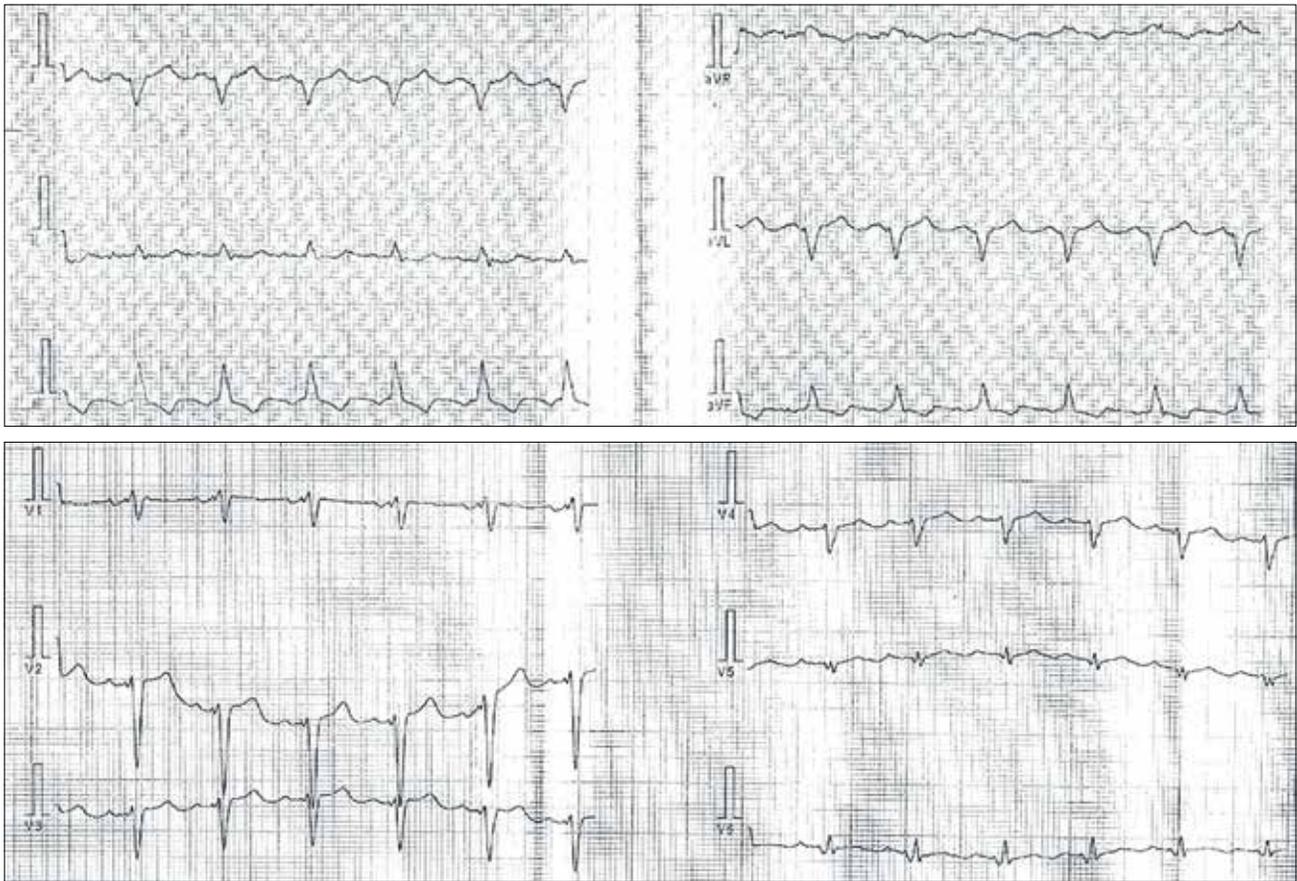
## Discussion

Cancer chemotherapy is associated with significant adverse effects, including the relatively well-known and frequently reported cardiotoxicity. Chemotherapy-related cardiomyopathy is estimated to constitute approximately 1% of all cases of cardiomyopathy [1].

Cardiotoxic drugs include: anthracyclines, alkylating agents, antimetabolites, mitosis inhibitors, monoclonal



**Fig. 2.** Electrocardiogram. The same patient after pharmacological cardioversion: normal sinus rhythm, rate 80 beats/min; left bundle branch block



**Fig. 3.** Electrocardiogram. Biventricular stimulation; controlled by sinus rhythm; rate, 90 beats/min. Note the narrow stimulated QRS complexes and the change in the electrical axis when compared with the previous trace

antibodies, proteasome inhibitors, and small-molecule tyrosine kinase inhibitors [2,3]. The drugs most commonly producing cardiotoxic effects are anthracyclines. The cardiotoxicity of anthracyclines can be acute (<1% of the cases) or chronic with early (1.6%–2.1%) or late onset (1.6%–5%), respectively [2].

Several explanations exist for the cardiotoxicity of anthracyclines. The main hypothesis is the effect of free radicals; however, there are other theories of the effect of this drug class on intracellular metabolism, apoptosis, intracellular ATP transcription in myocytes, or abnormal sodium-potassium exchange in cardiomyocytes [2,4]. It is thought that a significant role in the cardiac response to anthracyclines is played by the angiotensin II receptor type 1, participating in cardiac muscle remodeling after myocardial infarction. Studies are being conducted on the protective effect of angiotensin-converting-enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) in patients undergoing chemotherapy [5].

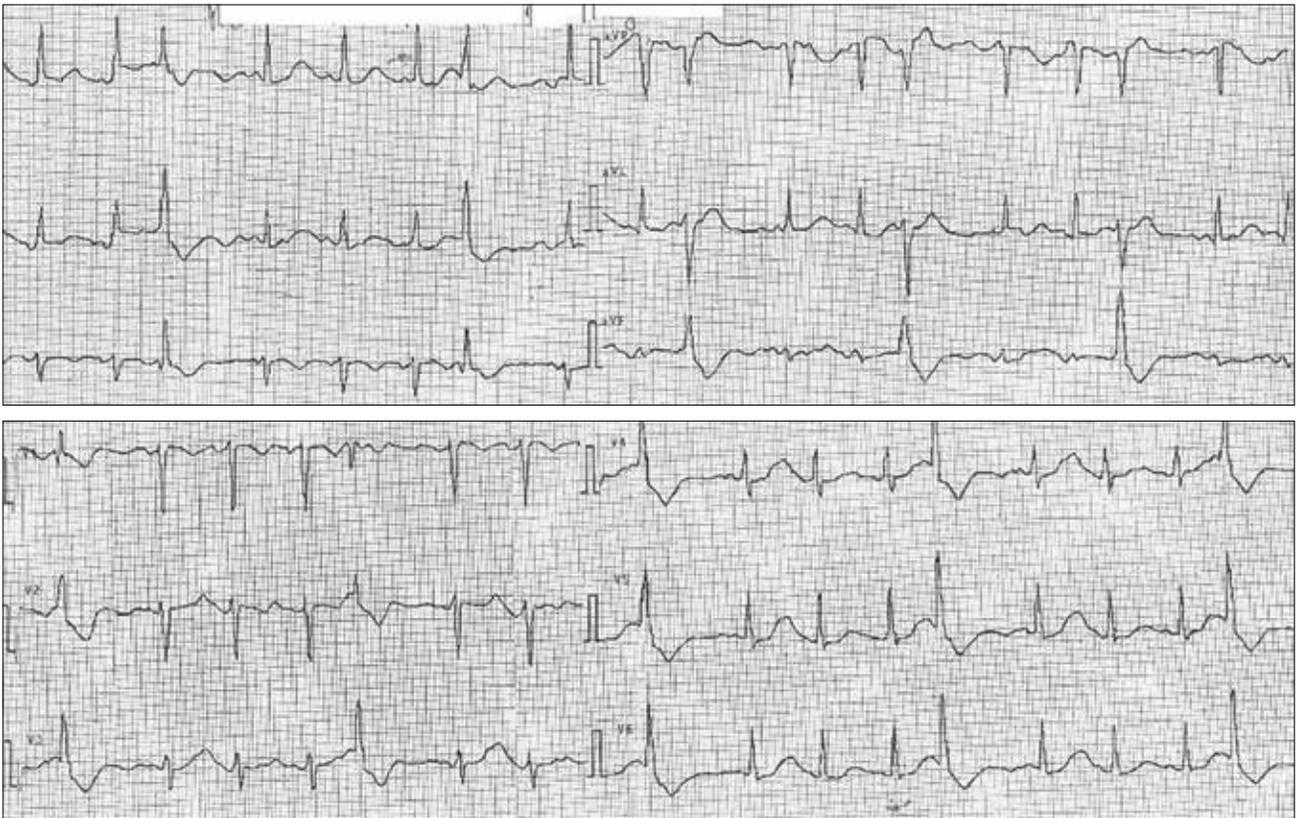
Risk factors of myocardial injury during chemotherapy include higher cumulative dose, bolus intravenous administration, higher single doses, earlier radiotherapy, concomitant use of other cardiotoxic agents (such as cyclophosphamide, bleomycin, cisplatin, and methotrexate), female sex, concomitant cardiac disease, age (both the very young and the elderly), and tobacco use [2, 4, 6].

The first of the reported cases had relatively numerous cardiotoxicity risk factors: sex, earlier

radiotherapy, type of chemotherapy, and nicotine use. Despite the fact that the patient was previously treated for arterial hypertension with an ACEI, she developed circulatory failure. This was possibly caused by the fact that the treatment was started approximately 2 years after chemotherapy was stopped. Cardinale et al.[1] reported that the greatest effect on the successful response rate in oncology patients with low LVEF is dependent on the time since treatment initiation. This large study showed that already after 6 months since the reduction of the ejection fraction had been observed, the percentage of cured patients in the group of asymptomatic individuals significantly decreased and there was basically no improvement in individuals in NYHA classes III and IV.

Chemotherapy-related cardiac injury can manifest as circulatory failure, myocardial ischemia, arterial hypertension, thromboembolic complications, or arrhythmia. The most typical clinical manifestation of anthracycline-associated cardiac injury is, as described in the first reported case, delayed-onset progressive dilated cardiomyopathy becoming overt after many years after treatment completion [2]. There are reports of pediatric patients where up to 65% demonstrated abnormal systolic and diastolic left ventricular function [7].

Chemotherapy-associated cardiotoxicity can, in rare cases, manifest as myocardial ischemia, pulmonary embolism, or arrhythmia [2]. Arrhythmia in



**Fig. 4.** Electrocardiogram. Significant elongation of the QT interval (QTc, 0.58 s) and multiple R-on-T ventricular extrasystoles

chemotherapy is rare. Most commonly, it is transient and asymptomatic, and includes isolated ventricular and supraventricular beats [4]. Atrial fibrillation was reported in 2% to 10% of the cases on anthracycline treatment and in up to 12% to 32% of those on cisplatin. The use of 5-fluorouracil commonly caused ischemic-type arrhythmias including ventricular tachycardia. Taxanes are associated with sinus bradycardia and atrioventricular conduction abnormalities [8].

There are reports of long QT interval and polymorphic ventricular tachycardia associated with chemotherapy. The long QT interval is statistically most commonly associated with arsenic trioxide; such cases have also been reported with anthracycline use. Oncology patients are at an increased risk of arrhythmia associated with increased QT interval, not only due to chemotherapy but also to the other drug classes (antimycotics, antibiotics, antiemetics) and electrolyte disturbances (caused by vomiting, diarrhea, and malnutrition). This type of coincidence of arrhythmogenic factors was observed in the second reported case, who apart from hematologic, antiemetic, and antibiotic treatment, experienced hypokalemia; this resulted in long QT interval and ventricular fibrillation [2,8].

Rudziński et al. [9] reported a case of a woman treated with anthracyclines with no therapeutic alternative available, who presented with recurrent symptomatic sustained ventricular tachycardia. An implantable cardioverter-defibrillator was implanted in the patient with good outcome. In the present case, the poor general condition of the patient precluded ICD implantation.

Radiotherapy most commonly causes delayed-onset chronic pericarditis but can also cause injury to the conductive system, valvular apparatus, and coronary vessels. The reported arrhythmias and conduction disorders include various grades of atrioventricular blocks, abnormal repolarization, ventricular extrasystoles, and bundle branch blocks. The right bundle branch block has been most commonly observed, although not in our patient [10].

Nearly all available publications stress the problem of close cardiologic monitoring in chemotherapy patients. It should include echocardiography with the assessment of LVEF at baseline and its monitoring throughout the treatment and after its completion. Ho et al. [6] reported that in all patients at 6 years after chemotherapy in breast cancer, at least subclinical changes in the systolic and diastolic left ventricular function were present. It is considered that the first signal of cardiac injury in the course of chemotherapy is impairment of the diastolic function; an indication for treatment discontinuation is LVEF reduction by >10% from baseline or <50%, increased end-diastolic left ventricular diameter of >60mm, or end-systolic diameter >40 mm [11]. The diagnostic work-up of patients with cardiac injury includes laboratory studies: B-type natriuretic peptide and troponin I [2,3,11,12].

Treatment includes (most commonly combined) ACEIs and  $\beta$ -blockers. Enalapril and carvedilol have been most commonly used in studies to date. There are reports on efficacy of early treatment with these drugs used as prophylaxis, possibly immediately after

a decrease in LVEF [1,2]. When symptomatic circulatory failure develops, as was in the case of our patient, the treatment is only symptomatic.

## Proposed management algorithm in chemotherapy patients

1. Echocardiogram and ECG before chemotherapy initiation, before every treatment cycle, and after its completion (at 3, 6, and 12 months, then every 1 to 2 years). Follow-up Holter ECG every 2 years.
2. Oncology treatment: reduce peak dose; give anthracycline analogues; use alternative methods of administration (slow continuous infusion, liposomal anthracyclines); use cardioprotective drugs (antioxidants, iron-chelating agents).
3. In patients receiving cardiotoxic drugs, prophylactic ACEI or ARB. If LVEF drop observed <45% – add a  $\beta$ -blocker [1,11].

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## Niemann–Pick disease with aortic valve insufficiency and neurogenic myocardial stunning (RCD code: V-4B.2)

Piotr Kukla, Marek Jastrzębski, Leszek Bryniarski

### Case report

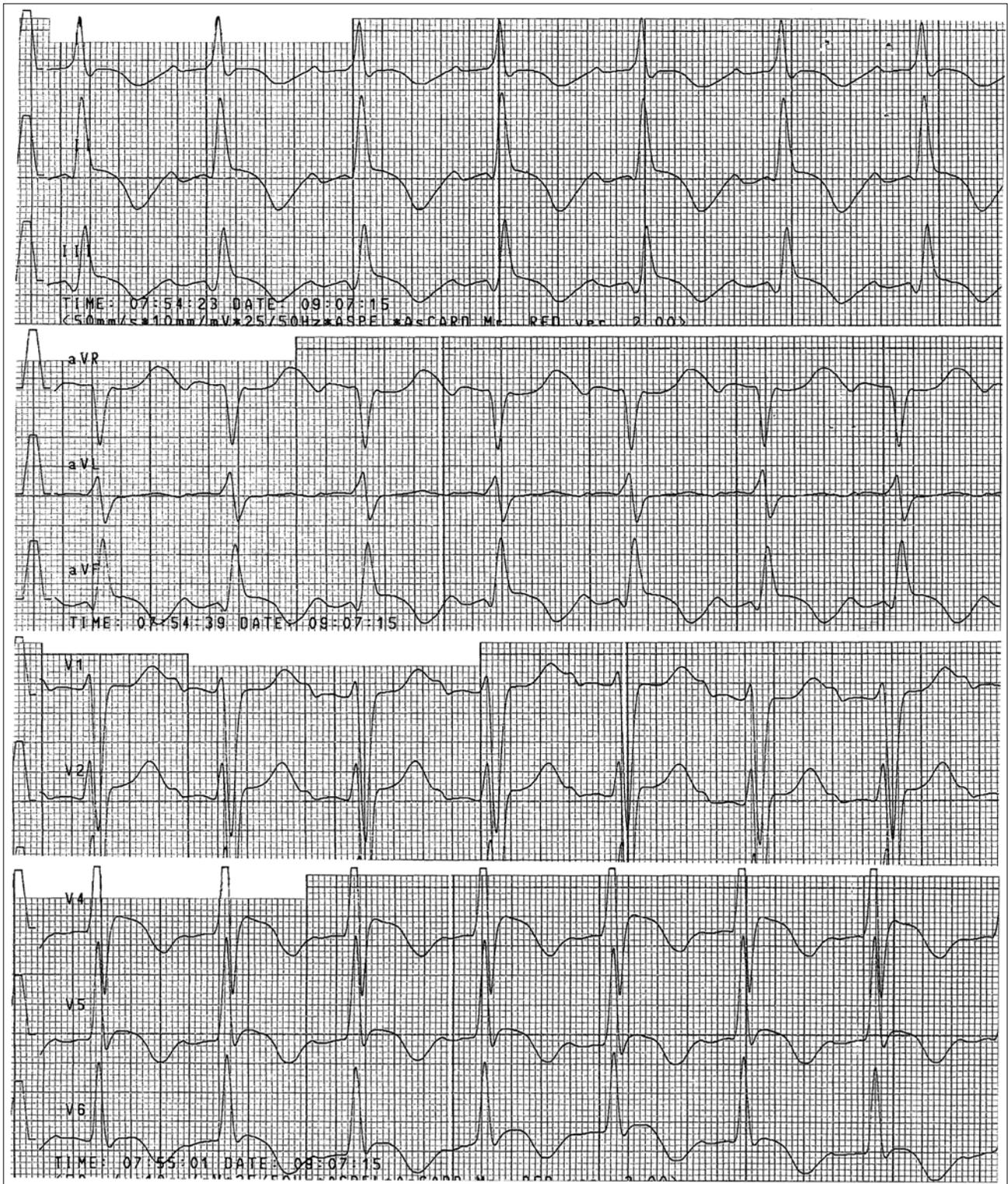
A 20-year-old woman, previously described in a report published elsewhere [1], with a history of Niemann–Pick (NP) disease diagnosed at the age of 6 years, was admitted to the internal medicine department following a seizure episode with suspected Wolff–Parkinson–White syndrome. Hepatomegaly and splenomegaly were observed in the patient at the age of 6 years on abdominal ultrasound, while scintigraphy showed a homogeneous uptake in the enlarged organs. Initially, Gaucher's disease was suggested based on significant hepatomegaly and splenomegaly. The  $\beta$ -glucosidase level was 12.7 nmol/mg of protein/hour, which excluded Gaucher's disease. NP disease was considered in further differential diagnosis. An ultrastructure study of a conjunctival sample was conducted – the epithelial cells contained a small number of storage vacuoles with morphology typical for NP disease. Similar structures were observed in the endothelial cells, in pericytes and fibroblasts. NP disease was diagnosed based on hepato- and splenomegaly and the electron microscopy results in the conjunctival sample, which simultaneously excluded Gaucher's disease.

The patient had been previously treated for epilepsy. On admission, blood pressure was 130/80 mm Hg and heart rate was 76 beats/min. On auscultation, the chest was clear and no peripheral edema was observed. The patient showed no cardiovascular signs or symptoms. An electrocardiogram (ECG) performed in the neurology department following a series of seizure attacks showed normal sinus rhythm (96 beats/min), normal electrical axis, ST-segment elevations in leads II, III, and aVF of up to 1.5 mm and in leads  $V_2$  through  $V_6$  (max.  $V_4$ , 3 mm) with inverted T waves in leads I, II, III, aVF, and  $V_3$  through  $V_6$ . Increased QTc interval was noted (512 ms) (fig. 1). Considering these changes, the patient was transferred to the internal medicine department. An ECG performed on the third day of hospitalization revealed progression of inverted T-wave amplitude in leads  $V_2$  through  $V_4$  of up to 12 mm and long QTc interval of 469 ms (fig. 2). Throughout the hospital stay, the patient had no cardiovascular complaints. An echocardiogram showed an enlarged left ventricular (LV) chamber of up to 68 mm in diastole and 44 mm in systole; left atrium of 32 mm, and right ventricle of 16 mm. Mitral valve cusps were thin. Aortic valve cusps were thickened, unstable, prolapsing into the LV outflow tract. Diffuse contractility abnormalities included akinesis of the apex, hypokinesis of the periapical segments of the septum and of the anterior and inferior walls. LV

ejection fraction was slightly decreased (35%–40%). Mitral valve insufficiency was classified as grade 2, aortic valve insufficiency as grade 2/3, regurgitation area was 2.7 cm<sup>2</sup>, and vena contracta was 5 mm. On chest radiography, the lung fields were normal and heart silhouette widened. An abdominal ultrasound demonstrated hepatomegaly (anteroposterior size, 155 mm; reduced echogenicity) and significantly enlarged spleen (over 250 mm in the long axis; reduced echogenicity; uniform). Laboratory tests showed normal complete blood count and electrolyte levels; C-reactive protein level was 0.2 mg/L; creatine kinase, 14 u/L; creatine kinase MB, 3.1 ng/mL; and troponin T, 0.1 ng/mL (upper limit of normal range, 0.03 ng/mL). No features of Wolff–Parkinson–White syndrome were observed in ECG; the patient did not complain of palpitations or episodes of tachycardia; Holter ECG monitoring did not demonstrate rhythm or conduction disorders. The diagnosis of Wolff–Parkinson–White syndrome suggested before the transfer to our department was not confirmed. Treatment included: bisoprolol, 2.5 mg/d; perindopril, 2.5 mg/d; trimetazidine MR twice daily; and valproic acid, 600 mg/d. An ECG at 4 weeks showed normal sinus rhythm (76 beats/min), normal electrical axis (PQ 160 ms), QT of 460 ms, and normal ST-T wave (fig. 3). An echocardiogram at 4 weeks no longer showed contractility abnormalities reported in the previous study (akinesis of the tip and hypokinesis of periapical segments of the septum, anterior, and inferior walls). The LV ejection fraction was 63%. The LV chamber size reduced to 61 mm in diastole (fig. 4). The remaining parameters were the same as in the previous study. For the next 2 years, the patient had normal circulatory function; the  $\beta$ -blocker, angiotensin-converting-enzyme inhibitor, trimetazidine, and valproic acid were continued. At 2 years, right ventricular failure exacerbated and was refractory to drug treatment, which resulted in multiorgan failure and eventually death.

### Discussion

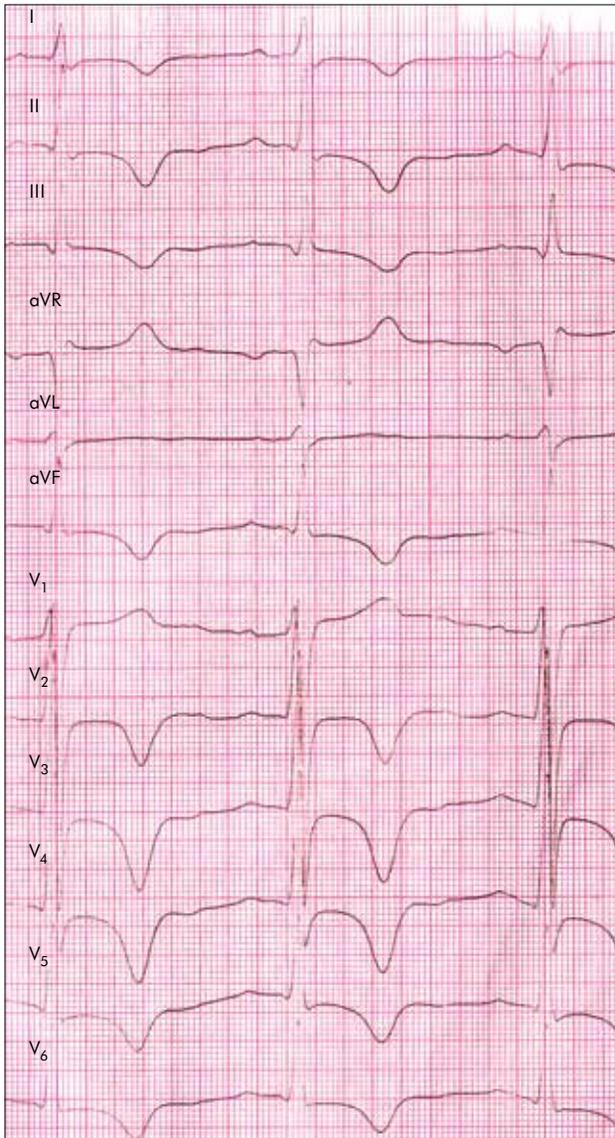
Storage diseases are congenital metabolic defects resulting from the absence or insufficient activity of various enzymes. The disease symptoms appear due to damage to specific organs by stored substances that in a healthy individual are metabolized and eliminated. Depending on the type of the stored substance, storage diseases are termed glycogenoses, mucopolysaccharidoses, sphingolipidoses, etc. Abnormalities in glycogenoses (Pompe disease, Cori's disease) are often related to the heart. Apart from the signs and symptoms resultant from the involvement of other organs such as skeletal muscles, there is myocardial hypertrophy and enlargement [2]. Lipidoses such as NP disease cause injury to the central nervous system. In our report, we describe NP disease with cardiac manifestations such as aortic and mitral insufficiency and with neurogenic myocardial stunning of the LV apical area following epileptic episodes.



**Fig. 1.** Electrocardiogram. After trace after a seizure episode in the neurology department. See the text for description. Reprint with permission of *Kardiologia Polska* Editorial Board and Via Medica Publishing House, Gdańsk, Poland

NP disease is a lipidosis affecting mainly the central nervous system. The most common forms of NP are A, B and C types. NP disease types A and B (NPA and NPB) are caused by deficiency of acidic sphingomyelinase (ASM), an enzyme necessary for the metabolism of a protein called sphingomyelin. Patients with NPA produce very little or no ASM (less than 1% of the normal level), whereas patients with NPB

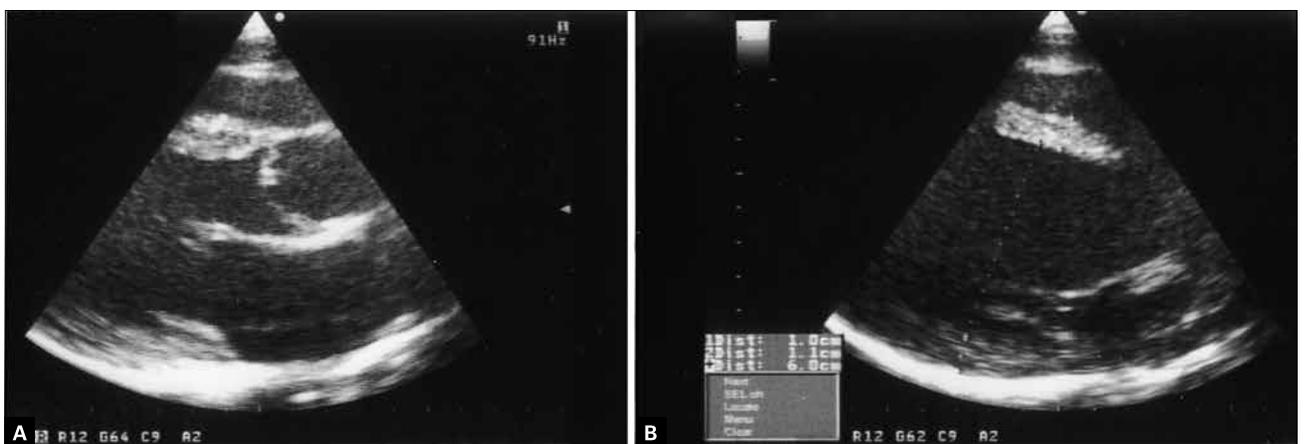
usually have 10% of the normal ASM level. The clinical prognosis in NPA and NPB patients is variable. NPA is a severe neurological disease leading to death before the age of 2 to 4 years. In contrast, patients with NPB have a few or no neurological signs or symptoms, and survive until late childhood or adulthood. Patients with type B disease usually have hepatomegaly and splenomegaly and often complain of respiratory



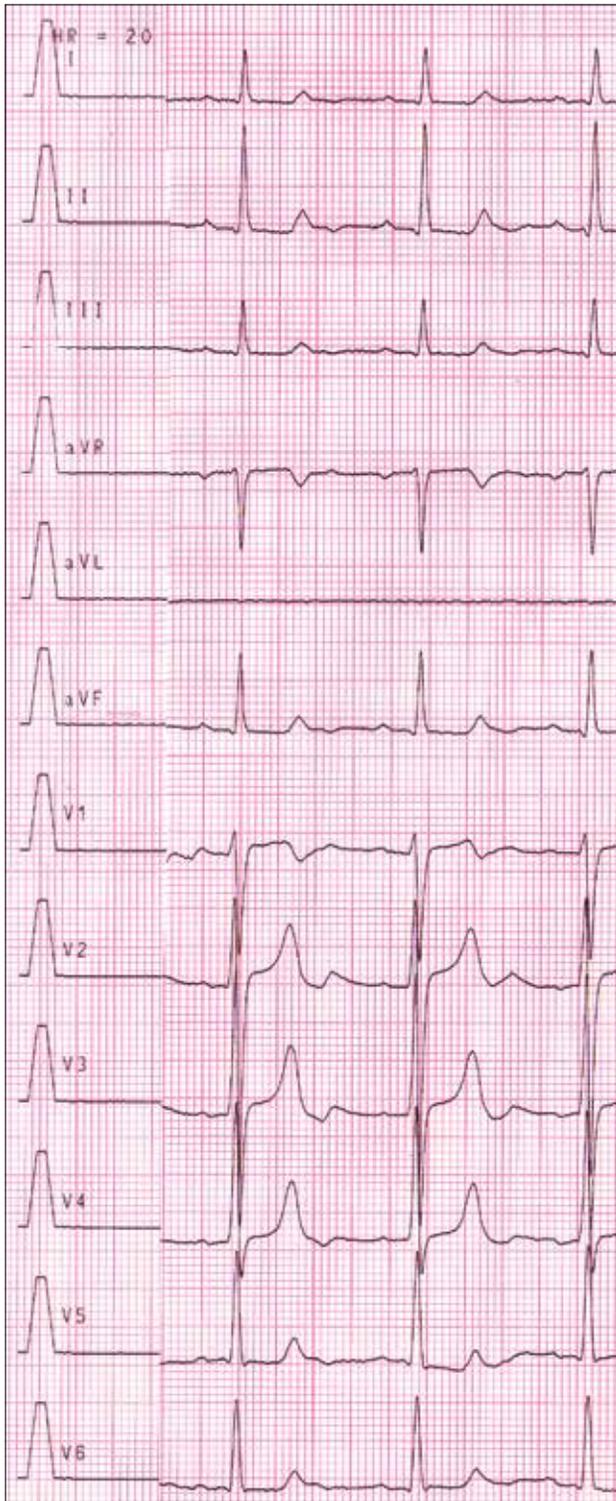
**Fig. 2.** Electrocardiogram. Trace on the third day of hospitalization. Sinus rhythm, 71 beats/min; deep inverted T waves in leads V<sub>3</sub> and V<sub>4</sub>; inverted T waves in leads I, II, III, aVF, V<sub>2</sub>, V<sub>5</sub>, and V<sub>6</sub>; long QTc interval, 469 ms. Reprint with permission of *Kardiologia Polska* Editorial Board and Via Medica Publishing House, Gdańsk, Poland

problems. There are fewer than 1200 patients with NPA and NPB. Our patient had NPB because this disease type is characterized by longer survival, epilepsy as the sign of the central nervous system involvement, and hepato- and splenomegaly. Cardiac involvement is characteristic for other storage diseases such as Pompe or Fabry disease. In these diseases, patients are commonly referred to a cardiologist with suspected hypertrophic cardiomyopathy and an ECG shows LV hypertrophy along with typical features of preexcitation such as short PQ interval.

Cardiac involvement is not a typical complication of NP disease and there have only been a few reports of such complications in the course of NP disease. Lever and Ryder [3] reported a patient with cor pulmonale secondary to pulmonary disease. Ishii et al. [4] described NP disease in two sisters, of whom one died due to LV dysfunction. An anatomopathological report indicated significant stenosis in the distal portions of the coronary arteries due to smooth muscle edema. Fotoulaki et al. [5] described a case of a patient with NPB diagnosed with grade mitral valve insufficiency at the age of 4 years and heart failure at the age of 5 years [5]. The largest registry published to date pertaining to the clinical course of NPB reported cardiovascular abnormalities [6]. Abnormal ECG results were reported in 28% of the patients, bradycardia in 10%, conduction abnormalities in 10%, and LV hypertrophy in 7% [6]. Half of the patients showed abnormalities on echocardiography [6]. The most commonly observed abnormality was mild mitral insufficiency. Mild and severe aortic insufficiency was observed in 2 patients [6]. Our patient was also diagnosed with a cardiac disorder, most likely secondary to degenerative valvular changes: aortic valve and mitral valve insufficiency. Reversible LV systolic dysfunction, diffuse contractility abnormalities of the LV apex and periapical segments, and the LV ejection fraction returned to normal within 4 weeks, while ST-segment elevations in multiple leads and deep T waves regressed and subsequently completely returned to normal. Electro- and echocardiogram results are typically restored to normal in the course



**Fig. 4.** Transthoracic echocardiography. Parasternal long-axis view. **A.** Prolapse of aortic valve cusps into the left ventricular outflow tract. Aortic valve cusps with abnormal morphology. **B.** Enlarged left ventricular chamber with normal left ventricular wall thickness in diastole. Reprint with permission of *Kardiologia Polska* Editorial Board and Via Medica Publishing House, Gdańsk, Poland



**Fig. 4.** Electrocardiogram. At 4 weeks. Sinus rhythm, 68 beats/min. Repolarization disorder subsided – positive T waves in leads I, II, III, aVF, and V2 through V6. QTc interval of 469 ms. Reprint with permission of *Kardiologia Polska* Editorial Board and *Via Medica* Publishing House, Gdańsk, Poland

of neurogenic myocardial stunning and transient LV apical ballooning (TLVAB) syndrome. We considered the epileptic episodes to be the inducing factor of neurogenic myocardial stunning in our patient. Similarly to TLVAB syndrome, neurogenic myocardial stunning is a reversible cardiac dysfunction. It may be observed

in such disorders as Guillain–Barré syndrome [7], subarachnoid hemorrhage [8], or cerebral metastases [9]. There are several reports of TLVAB syndrome after epileptic seizures [10,11]. Shimizu et al. [12] reported a case of neurogenic myocardial stunning that was similar to ours. A 75-year-old patient experienced recurrent epileptic seizures within 2 hours [12]. After the seizures were relieved, a decrease in systolic blood pressure to 80 mm Hg was observed along with the following changes on an ECG: ST-segment elevation in leads II, III, aVF, and V<sub>2</sub> through V<sub>5</sub>. Follow-up ECG traces showed inverted T waves (amplitude up to 12 mm) in leads V<sub>3</sub> through V<sub>5</sub> and inverted T waves in leads I, II, III, aVF, V<sub>2</sub>, and V<sub>6</sub>. These abnormalities on an ECG were identical to those observed in our case (fig. 1, 2).

Neurogenic myocardial stunning is caused by excessive sympathetic activation resulting from excessive catecholamines secretion following, for example, seizure episodes [13]. Simon et al. [14] reported sudden increases in noradrenaline and adrenaline levels within 30 minutes after seizure episodes and subsequent rapid reduction. Cardiotoxicity resulting from excessive catecholamine levels, apart from neurogenic myocardial stunning, has been postulated as one of the mechanism underlying takotsubo cardiomyopathy [15]. The greatest density of catecholamine receptors is observed in the cardiac apex; therefore, abnormalities typically affect this area. It is known that the distribution of sympathetic system receptors and local noradrenaline levels is greater in the LV apex than in the remaining parts of the myocardium [16]. It is interesting that the LV apex, contrary to other regions of the LV, does not consist of three layers of myocardium but serves as the so called border zone notably in the presence of impaired coronary blood flow. The apical region easily loses its elasticity on increased functional load such as adrenergic stimulation [17]. Takotsubo cardiomyopathy and neurogenic myocardial stunning share many similarities but should be considered as separate entities. The Mayo Clinic group proposed diagnostic criteria for takotsubo cardiomyopathy, stressing that the diagnosis of TLVAB syndrome requires the exclusion of other possible causes of abnormal contractility. These include neurological problems such as head injury, subarachnoid hemorrhage, stroke, or brain tumor [18].

## Treatment

There is no causal treatment in storage diseases; only treatment modalities aiming at partial or complete improvement of the sequelae are available. In general, causal treatment can be classified into enzymatic and nonenzymatic methods. NP disease is lethal. Currently no effective treatment method exists for patients with NPA. Several patients with NPB have been subjected to bone marrow transplant and the results are encouraging. Patients with NPB might benefit from the development of enzyme replacement

therapy and gene therapy because first attempts to use these methods in this patient group have already been made. Currently, bone marrow transplant from healthy donors is thought to be the most promising treatment modality. Experimental studies conducted in patients with NPB have now entered the evaluation phase. Studies involving drug therapy with histone deacetylase inhibitors are currently being conducted in patients with NPC. One of the treatment modalities is low-fat diet (notably low in cholesterol), but the obtained results do not sufficiently support any efficacy of the method.

Considering a concomitant cardiac disease in our patient (aortic valve disorder and enlarged LV cavity), the administered treatment included a  $\beta$ -blocker and an angiotensin-converting-enzyme inhibitor.

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## Electrocardiogram in a heart transplant recipient (RCD code: V-4A.2)

Jacek Majewski, Jacek Lelakowski

According to the current definition, atrial fibrillation is diagnosed based on complete irregularity of RR intervals and the absence of P waves on electrocardiogram (ECG). In some leads (notably V<sub>1</sub>), the trace may demonstrate organized atrial electrical activity with a rate exceeding 300 beats/min [1]. Figure 1 demonstrates an ECG trace with a completely irregular QRS rate with fast atrial rate exceeding 300 beats/min in leads V<sub>1</sub> and V<sub>2</sub>. There are P waves (arrows) fulfilling the sinus rhythm criteria (positive in leads I and II; negative in aVR) with a rate of 100 beats/min. There is no temporal relationship between the P waves and QRS complexes. The visible T waves in leads I, aVL, and V<sub>2</sub> through V<sub>4</sub> result from temporary ventricular pacing (so called repolarization electric memory). The presented atypical ECG was obtained in a heart transplant (HTx) recipient. The evident sinus rhythm is generated in the remnant

of the recipient's right atrium, whereas AF developed in the donor's atria. This phenomenon is possible with the biatrial HTx technique when the donor's atrium is completely electrically isolated from the recipient's atrial remnant [2]. Atrial fibrillation in a HTx recipient has an unfavorable prognostic effect and results in increased mortality. This arrhythmia may develop in the course of transplant rejection [3,4].

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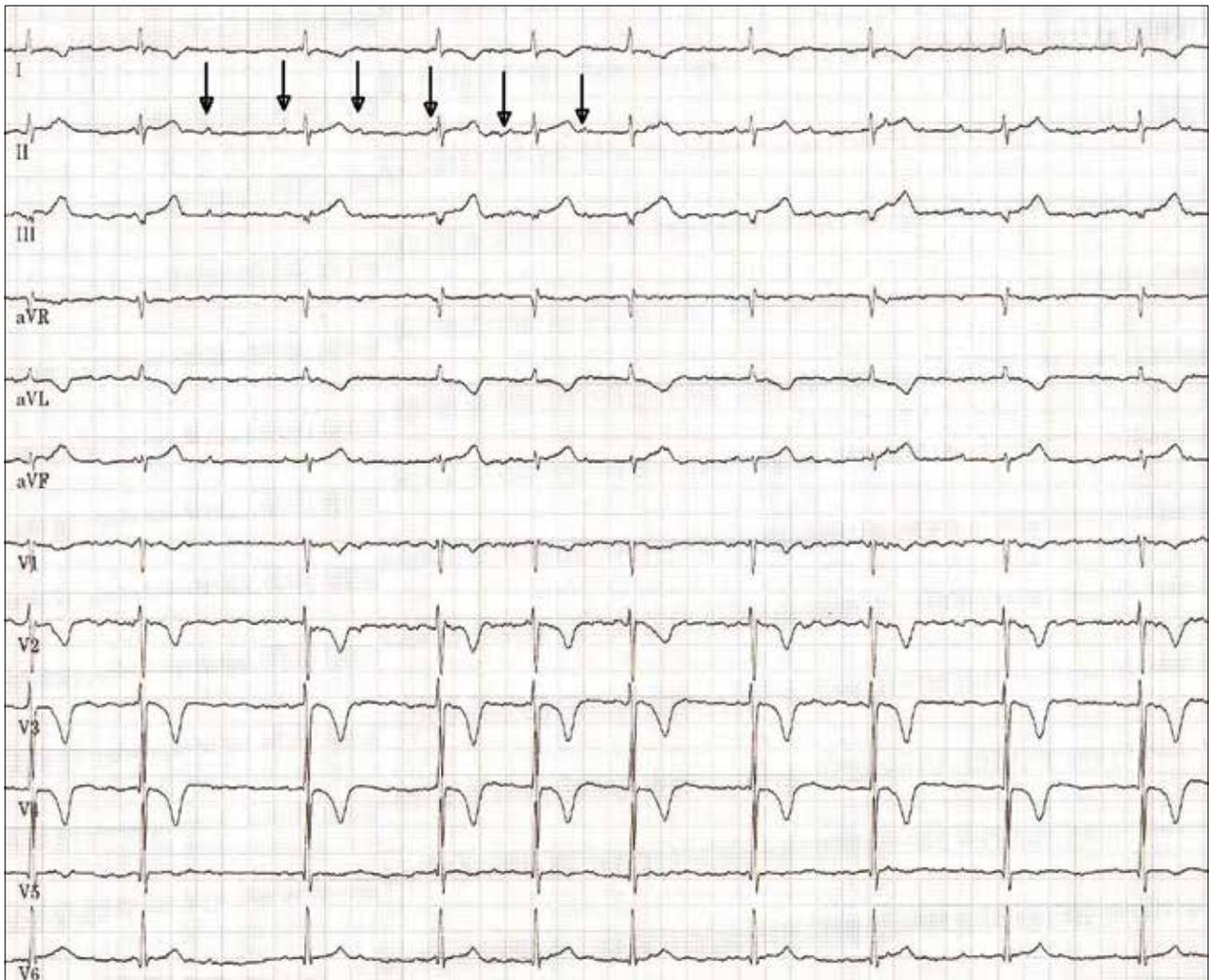


Fig. 1. Electrocardiogram. Heart transplant recipient. See the text for description

## Repolarization changes in the electrocardiogram of patients with pectus excavatum and a history of syncope (RCD code: V-4A.0)

Marcin Kuniewicz, Anna Rydlewska, Jacek Lelakowski, Jacek Majewski

### Case report

Three young men, aged 17, 21, and 35 years, respectively, were referred to the Department of Electrophysiology at the John Paul II Hospital within the last year. All patients were physically active and all reported repeated syncope of unknown etiology. The working diagnosis was Brugada syndrome, based on the changes on electrocardiogram (ECG), i.e., J-point elevation in lead V<sub>2</sub>. Other factors supporting the working diagnosis were age and sex. None of the patients underwent a neurological examination before admission.

All 3 patients were referred for an electrophysiology study (EPS) and for the ajmaline (Gilurytmal) test, and underwent Holter monitoring, echocardiography, and an exercise tolerance test. The expected duration of hospital stay was 3 days. All noninvasive tests were scheduled on day 1; the EPS was planned for day 2; the analysis of the results, dressing changes, and discharge were scheduled for day 3.

To minimize the risk of potentially life-threatening arrhythmias during diagnostic procedures, our unit has developed a diagnostic protocol as detailed below.

1. echocardiogram (on admission day);
2. exercise tolerance test (on admission day after confirming normal echocardiogram);
3. ajmaline (Gilurytmal) test (2–3 h following the exercise tolerance test);
4. 24-hour Holter monitoring (after the ajmaline test);
5. electrophysiology study (on the second day of hospitalization).

The ajmaline test was conducted according to the relevant protocol [1]. Patients received 1 mg of Gilurytmal/kg of body weight over 10 minutes – an IV injection of 10% of total dose every minute. The test was carried out in the electrophysiology room and the ECG trace was recorded in the BARD system, where a computer analysis of ST-segment changes and the QT-interval length was performed. The study conditions aimed to establish maximum patient safety with 2 peripheral IV lines and a cardioverter-defibrillator device on standby in the case of life-threatening arrhythmia.

On the following day, patients underwent the EPS, where the Wenckebach point, sinus node recovery time, ventriculoatrial conduction, and programmed ventricular stimulation for arrhythmia induction were assessed. Patients received 0.5 mg of IV salbutamol during the EPS study.

The EPS study was aimed to exclude any other possible causes of syncope such as idiopathic ventricular fibrillation [2]. To exclude catecholaminergic polymorphic ventricular tachycardia, patients underwent a treadmill exercise-tolerance test.

Despite the changes on ECG, none of the tests performed in all 3 patients supported Brugada syndrome as the cause of syncope.



**Fig. 1.** Electrocardiogram. Leads V<sub>1</sub> through V<sub>3</sub> with electrocardiographic changes, which were the basis for the suspicion of Brugada syndrome and referral to the Department of Electrophysiology





**Fig. 4.** Physical examination. Subtle chest deformity; depressed-sternum chest

Carotid sinus hypersensitivity was diagnosed as the cause of syncope in 1 of the patients; the second patient had a focus of ventricular extrasystolia in the right ventricular outflow tract, becoming overt at a maximum exercise load; no causes of syncope were identified in the third patient. A decision was made to implant an implantable loop recorder and to perform detailed neurological examination.

## Discussion

To understand why all 3 patients were referred to our department with their working diagnosis, their history and physical examination rather than the ECG traces should be considered.

All 3 patients were tall and of slender build; they had a characteristic chest deformity. Two of the patients had a typical pectus excavatum, whereas the third one had an anatomic variation of the sternum resulting in its depressed appearance in the anterior midline. Furthermore, all patients were active amateur athletes and engaged in swimming, basketball, and mountaineering.

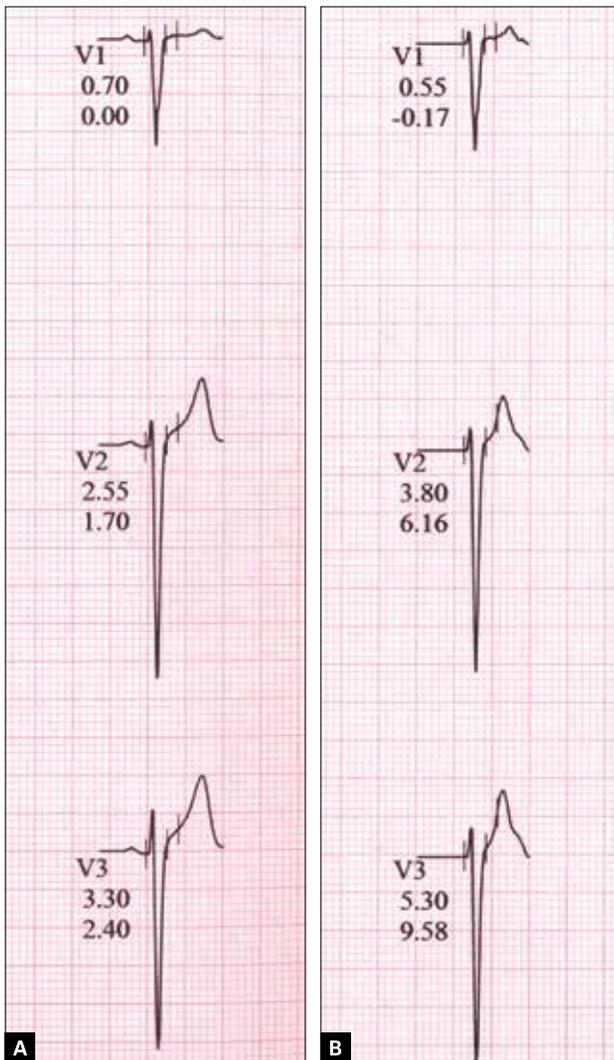
An interesting observation during the EPS study was the variability in the ECG trace in precordial leads  $V_1$  and  $V_2$  on deep respiration.

Brugada syndrome usually becomes clinically overt in patients aged between 20 and 40 years and is 8 times more prevalent in men; characteristic ECG changes are the main diagnostic criterion.

To exclude or confirm the disease, a test with ajmaline or another sodium channel blocker is required, e.g., flecainide, with the endpoint of J-point and ST-segment elevation of over 0.2 mV in leads  $V_1$  through  $V_3$  and T-wave inversion: this is called type 1 abnormality. The J-point elevation of less than 0.2 mV, a saddle ST elevation of more than 0.1 mV with a positive or biphasic T wave are termed type 2 abnormality;



**Fig. 5.** Electrophysiological study. Deep respiration mimics the J-point and ST-segment elevation in leads  $V_1$  and  $V_2$



**Fig. 6.** Electrocardiogram. Variability of the J-point. **A.** Resting  $V_1$  to  $V_3$  trace. **B.** J and ST depression on maximum exercise load

a J-point elevation exceeding 0.2mV with an ST elevation of less than 0.1 mV are called type 3 abnormality, respectively. Other possibilities include elevations in inferior-wall leads, long PQ segment, and a wide or biphasic P wave [3].

Syncope or cardiac arrest in Brugada syndrome are caused by a rapid polymorphic ventricular tachycardia (often spontaneously subsiding), resulting from shortened duration of the action potential (reduced phase 2 of the action potential) selectively in the sub-epicardial layer of the right ventricle, leading to intramural dispersion of repolarization and creating conditions for a reentrant arrhythmia. Brugada syndrome is potentially lethal; 30% of the patients with this ion channel disease will have cardiac arrest before the age of 60 years [4].

The most likely cause of ECG changes in our patients was chest wall deformity, resulting in altered surface location of precordial electrodes  $V_1$  and  $V_2$  and possibly abnormal heart position in the inferior mediastinum. Apparent ECG abnormalities might have resulted from conformation of myocardial depolarization and repolarization vectors; this hypothesis is best

supported by the significant ECG changes accompanying deep respiration.

Furthermore, ECG abnormalities can be demonstrated in 80% of athletes compared with the general population. The most common abnormalities include sinus bradycardia, first-degree atrioventricular block, incomplete right bundle branch block, QRS complexes with features of left ventricular hypertrophy, and early repolarization resulting from adaptive changes in the autonomous nervous system of the heart in response to exercise [5,6].

Such abnormalities as incomplete right bundle branch block are observed in approximately 35% to 50% of young athletes (versus 10% of the general young population) and are associated primarily with elite athletic levels in swimming, cycling, long-distance running, and mountaineering; these abnormalities result from right ventricular myocardial hypertrophy [7].

Early repolarization is observed in 50% to 80% of young athletes and is evidenced by elevated J-point and ST segment by at least 0.1 mV, often with indentation of variable morphology following a QRS complex. The J-point elevation is most commonly observed in leads  $V_3$  and  $V_4$  but may be evident in any lead. These elevations result from the autonomous system activity and are variable dependent on the heart rate. The elevations are increased with decreasing heart rate and are reduced or disappear on exercise or administration of isoprenaline [8]; this is evident in the exercise tolerance test trace presented on Figure 6.

However, the above abnormalities may mask a life-threatening arrhythmia including Brugada syndrome or other idiopathic ventricular tachycardia; therefore, any patient with syncope or cardiac arrest of unknown origin should undergo detailed cardiac evaluation [9].

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# Part 8

Cardiac tumors and cardiovascular diseases  
in malignancy – RCD class VI

**Editors: Monika Komar, Piotr Podolec**



# Introduction

Monika Komar

Cardiovascular disease is common in patients with cancer. The coexistence of heart disease and cancer often complicates the management of a patient because treatment of one disease may negatively affect the outcome of the other.

There is extensive literature on the diagnosis and treatment of heart disease and cancer [1–10]. However, little data exist on the management of patients who carry the diagnosis of both cardiovascular disease and cancer.

Cardiovascular disease and cancer are frequently found in the same patient owing to the high prevalence of both diseases. Moreover, some forms of cardiovascular disease are caused by cancer or its treatment. However, the guidelines for the treatment of cardiovascular disease are often based on the studies that exclude patients with cancer. Therefore, the generally accepted strategies for the diagnosis and therapy of cardiovascular disease may not always apply to patients with cancer.

In the current section of the book, we did not aim to review the data on cardiovascular disease and cancer that have already been covered by numerous outstanding publications. We rather intended to show the perspective of the Centre for Rare Cardiovascular Diseases (CRCVD), the classification of cardiac tumors and malignant diseases and to present our approach to the management of patients with complications related to cardiovascular disease and cancer. We also reported some recent epidemiological data and described some future directions in the treatment of this group of diseases.

Cardiac tumors are rare tumors that originate in the heart. Since there is no generally recognized classification, the CRCVD proposed its own classification of this heterogeneous group of tumors.

The introductory chapter is followed by a chapter on cardiac tumors, in which we review the available data and attempt to summarize the current knowledge. The chapter is followed by seven reports of clinical cases from our and other centers.

We would like to express special thanks to all radiologists, surgeons, and immunologists who cooperated with us on the project. We are especially grateful to a cardiac team from the San Raffaele Hospital in Milan, Italy, and, in particular, to Mrs. Halina Liberek and Professor Giovanni La Canna.

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# Cardiac tumors and cardiovascular diseases in malignancy: Perspective of the Centre for Rare Cardiovascular Diseases

Monika Komar, Giovanni La Canina,  
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Maria Olszowska, Piotr Podolec

## Introduction

Cardiac tumor is an additional structure within the heart chambers, myocardium, or endocardium.

Malignant rhabdomyoma was the first cardiac tumor described by von Recklinghausen in 1862 [1]. Subsequent reports, mostly on isolated cases diagnosed on autopsy, were collected and analyzed by Mahaima in 1945 [2], followed by Prichard and Bigelow [3,4]. Initially, cardiac tumors were treated solely as a pathological curiosity. Along with the advancement in the diagnosis and treatment of congenital heart diseases, it became possible to save patients suffering from tumors of the heart. The first successful surgical removal of a cardiac tumor in adult patient was performed in 1954 [5].

Cardiac tumors are extremely rare and histologically heterogeneous. Therefore, there are no established diagnostic schemes that would allow to distinguish cardiac tumors from metastatic tumors, intracardiac thrombi, vegetations on the valves in infective endocarditis or in connective tissue diseases or thrombotic changes of the valves in metastatic disease (called *endocarditis marantica*).

Cardiac tumors may be symptomatic or found incidentally during evaluation for a seemingly unrelated problem or a physical finding. In symptomatic patients, a mass can be detected by echocardiography, magnetic resonance imaging (MRI) and/or computed tomography (CT). Because symptoms may mimic other cardiac conditions, the clinical challenge is to consider the possibility of a cardiac tumor so that the appropriate diagnostic tests can be conducted.

There are very few studies assessing the results of cardiac surgery in the individual centers. There is also lack of a set of standards in the chemotherapy of malignant cardiac tumors.

## Epidemiology and etiology

The prevalence of cardiac tumors is 0.021% (1 in 5000 individuals). These data are based on a meta-analysis of pathological studies from the early decades of the 20th century. It is likely that nowadays the incidence of cardiac tumors and primary tumors of the heart is greater.

Primary malignant cardiac tumors are rare, regardless of the age of the patients. Based on the results of a large number of dissections, Straus and Merliss [6] reported the incidence rate of 0.0017%.

In children, the tumors of the heart occur slightly more frequently. Simcha reported that the incidence of cardiac tumors in children is 0.08% [7]. He based his conclusion on an over 20-year follow-up of the patients hospitalized in his facility. Nadas and Ellison [8] evaluated the prevalence of cardiac tumors among 11 000 children undergoing postmortem examination at 0.027%.

The pathophysiology of cardiac tumors is heterogeneous and depends on the type of the tumor.

Heart tumors are divided into two groups:

- primary heart tumors – deriving from the heart
- secondary heart tumors – most commonly metastatic malignancies of other organs.

The primary heart tumors may be benign (75%) or malignant (25%).

In some cases, a genetic background has been confirmed. For example, 10% of the cases of atrial myxomas are familial, as part of the Carney syndrome (mutation in the *PRKARIA* gene on chromosome 17, encoding a regulatory subunit of protein kinase).

Primary cardiac lymphoma raises the suspicion of acquired immune deficiency syndrome.

## Clinical symptoms

At the beginning, heart tumors are usually asymptomatic and therefore are detected incidentally. The clinical manifestations largely depend on the size of the tumor, its localization, mobility, and the degree of malignancy (infiltration, mass effect). Specific signs and symptoms are generally determined by the location of the tumor in the heart and not by its histopathology.

The most common symptoms are:

- shortness of breath (including paroxysmal nocturnal dyspnea)
- impaired heart contractility, arrhythmias, heart block, pericardial effusion with or without tamponade due to the direct invasion of the myocardium
- valve regurgitation or stenosis
- embolic events
- systemic features of inflammation
- obstruction of the coronary arteries with symptoms of angina, myocardial infarction, or heart failure.

Mechanisms by which cardiac tumors may cause symptoms include:

- Obstruction in the blood flow in the heart or through the heart valves, producing symptoms of heart failure
- Interference with the heart valves, causing regurgitation
- Direct invasion of the myocardium, resulting in impaired contractility, arrhythmias, heart block, or pericardial effusion with or without tamponade
- Invasion of the adjacent lung may cause pulmonary symptoms and may mimic bronchogenic carcinoma
- Embolization, usually systemic but may be pulmonary
- Constitutional or systemic symptoms

Risk factors for embolization were evaluated in a report of 323 patients treated surgically [9]. Eighty patients presented an embolic event (cerebrovascular accident, 31 [10%]; transient ischemic attack, 30 [9%]; and other systemic or pulmonary event, 19 [6%]). The data showed that:

- Aortic valve and left atrial tumors were associated with greatest risk of embolization.
- Patients with smaller tumors (<13.3 cm<sup>2</sup>), minimal cardiac symptoms, and no evidence of mitral regurgitation had higher risk of embolization.
- Operative mortality was similar in patients with and without embolism (1% vs. 3%). No recurrent embolic events were observed postoperatively at a mean of 6 years of follow-up.

## Diagnosics

Considering the likelihood of cardiac tumors, the diagnostic procedures should be performed in all patients with unexplained cardiac murmurs, congestive heart failure, arrhythmias, which are accompanied by fever, anemia, and weight loss of unknown cause. In such cases, the basic laboratory tests should include tumor markers.

Cardiac diagnostic procedures should be extensive with particular emphasis on imaging methods.

An electrocardiogram may not indicate any change, and some features found in patients with a cardiac tumor on an electrocardiogram are usually nonspecific. It has been reported that tumors of the heart are associated with shortening of the PR interval, the right or left bundle branch block, or complete heart block [8]. Recurrent tachycardia may also occur [9].

Standard chest radiography may not reveal any changes. Uncharacteristic enlarged heart contour may be a consequence of heart failure. Asymmetrical enlargement of the heart may occur when the tumor is located within the anterolateral wall of the left ventricle. Calcifications are rare, usually in the case of rhabdomyoma and lipoma. Pericardial effusion as the only radiological indicator of a cardiac tumor has been described in the case of the rhabdomyoma associated heart failure [10,11].

Modern echocardiography often provides sufficient data about the presence of cardiac tumor, its location, size, mobility, and communication with other anatomical structures of the heart. Echocardiography shows both the myocardium and the cardiac chambers and can usually identify the presence of a mass and its mobility. In addition, echocardiography may provide information about blood flow disturbances as well as the possibility that the tumor could be a source of the emboli. Fetal echocardiography allows early diagnosis of cardiac embryonic tumor [12]. Although transthoracic echocardiography is simpler and usually can identify a tumor, transesophageal echocardiography may be more informative. The superior diagnostic utility of transesophageal echocardiography is due to the proximity of the esophagus to the heart, the lack of intervening lung and bone, and the ability to use high-frequency imaging transducers, which afford superior spatial resolution [13].

CT and MRI are performed especially in cases where tumor infiltration of other structures of the mediastinum requires clarification [14]. Although both cardiac MRI [15,16] and ultrafast CT [14,17] provide noninvasive, high-resolution images of the heart, MRI is generally preferred. In addition to furnishing detailed anatomic images, the T<sub>1</sub>- and T<sub>2</sub>-weighted sequences reflect the chemical microenvironment within a tumor, thereby offering clues as to the type of the tumor that is present [18]. However, CT scanning is still useful when MRI is not immediately available or is contraindicated. An excellent pictorial review of many cardiac tumors and comparison of MRI and CT scanning has been published by Hoey et al. [19].

Positron emission tomography is useful in identifying cardiac involvement in patients with metastatic tumors, atrial myxoma, or lipomatous septal hypertrophy [20,21].

Coronary angiography is performed to assess the vascularity of the tumor and its infiltration of the coronary arteries. This is of particular importance in making the decision about surgery and the choice of a surgical method.

Cardiac catheterization provides additional information about the hemodynamic consequences of the cardiac tumor [22].

Limited data are available on the risks and benefits of transvenous biopsy of suspected cardiac tumors. Because myxomas may embolize, transvenous biopsy is not generally justified if the appearance is typical on noninvasive imaging. Biopsy is considered reasonable for other cardiac tumors if potential benefits are deemed sufficient to outweigh potential risks.

## Characteristic of selected cardiac tumors

**Benign tumors (RCD code: VI-1A)** – Over 75% of primary cardiac tumors are benign [23,24]. In adults, the majority of benign lesions are myxomas; other common benign lesions include papillary fibroelastomas and lipomas. In children, rhabdomyomas and fibromas are the most common.

**Myxomas** are the most common primary cardiac neoplasms in adults, rarely found in children. Histologically, these tumors are composed of scattered cells within a *mucopolysaccharide stroma*. The cells originate from a multipotent mesenchyme that is capable of neural and endothelial differentiation [25]. Myxomas produce vascular endothelial growth factor, which probably contributes to the induction of angiogenesis and the early stages of tumor growth [25,26].

Macroscopically, typical myxomas are pedunculated and gelatinous in consistency; the surface may be smooth, villous, or friable. Tumors vary widely in size, ranging from 1 to 15 cm in diameter, and weigh between 15 and 180 g [27]. About 35% of myxomas are friable or villous, and these tend to present with emboli. Larger tumors are more likely to have a smooth surface and to be associated with cardiovascular symptoms.

The cardiovascular manifestations depend upon the anatomic location of the tumor. Approximately 80% of myxomas originate in the left atrium, and most of the remainder is found in the right atrium [7,27–29].

In addition to their cardiovascular effects, patients with myxomas frequently have constitutional symptoms (e.g., weight loss, fever) and laboratory abnormalities that suggest the presence of a connective tissue disease [30]. Although the etiology of these symptoms is not fully understood, the production of various cytokines and growth factors by the tumor may contribute to these clinical and laboratory abnormalities [30,31].

The relative frequencies of different signs and symptoms associated with left atrial myxomas are illustrated by a series of 112 patients, 72 of whom were women [27]:

- Cardiovascular symptoms were present in 67% of the patients. Most commonly, they resembled symptoms of mitral valve obstruction and were frequently associated with electrocardiographic evidence of left atrial hypertrophy. Although auscultatory abnormalities were found in 64% of the patients, the classic tumor “plop” was identified only in 15%.
- Evidence of systemic embolization was present in 29% of the patients, and 20% had neurological deficits. Despite the greater frequency of myxomas in women, men were more likely to have evidence of embolization.
- Constitutional symptoms (e.g., fever, weight loss) were reported in 34% of the patients. Laboratory abnormalities (e.g., anemia and elevations in the erythrocyte sedimentation rate, C-reactive protein, or globulin levels) were present in 37% of the patients, usually those with systemic symptoms.

Other large series of patients with myxomas have also included mostly women (60% to 70%), and have reported similar incidence rates of cardiovascular, embolic, and constitutional symptoms [32,33].

**Treatment and prognosis** – Once a presumptive diagnosis of myxoma has been made on imaging studies, prompt resection is required because of the risk of embolization or cardiovascular complications, including sudden death [30,31]. The results of surgical resection are generally very good, with most series reporting an operative mortality rate under 5% [32–34]. Cardiac autotransplantation (with atrial reconstruction) or transplantation are potential options for treatment of recurrent atrial myxoma [33,34].

Postoperative recovery is generally rapid. However, atrial arrhythmias or atrioventricular conduction abnormalities were present postoperatively in 26% of the patients in one series [27]. In addition, patients are at risk for recurrence of the myxoma, which may occur in 2% to 5% of the cases, or the development of additional lesions [27,34]. Development of a second primary myxoma may be more common in patients with a family history of myxoma [35].

**Carney complex** – The Carney complex is an inherited, autosomal dominant disorder characterized by multiple tumors, including atrial and extracardiac myxomas, schwannomas, and various endocrine tumors. The cardiac myxomas are generally diagnosed at an earlier age than sporadic myxomas and have a higher tendency to recur [36]. The Carney complex should be distinguished from other syndromes associated with Carney, with which it may be confused. Prominent among them are the Carney–Stratakis syndrome and the Carney triad, neither of which include cardiac tumors [36,37].

Patients with the Carney complex also have a variety of pigmentation abnormalities, including pigmented lentiginos and blue nevi on the face, neck, and trunk. The Carney complex is discussed elsewhere.

**Rhabdomyomas** are very rare in adults, but in children they develop often, mostly before 1 year of age. These are predominately found in the ventricular walls or intraventricular septum. Most rhabdomyomas regress spontaneously, and resection is usually not required unless a child is symptomatic.

**Fibromas** are the second most common pediatric cardiac tumors but can also occur in adults. The most common location is the left ventricular muscle (walls or intraventricular septum). Histologically, they are similar to fibromas arising elsewhere in the body (e.g., fibromas of the uterine). The tumor is usually single, while the structure has well-defined boundaries.

**Lipomas** are benign tumors, which are found incidentally and usually are clinically insignificant. They are built of fatty cells. They usually arise in the sub-endocardial region

**Angiomas** may localize in every cavity of the heart, but may also arise on the surface of the heart, leading to a bloody pericardial effusion. Angiomas may also sometimes attack the heart conduction system, causing arrhythmia.

**Teratoma** – There have only been a few cases of this tumor. Generally, it is mainly found in the left ventricle or surrounding of the atrioventricular node. The histological studies of excised teratomas showed that the tumor may contain the nervous tissue, smooth

muscle, bone, and cartilage as well as the thyroid and pancreatic cells.

**Fibroelastomas** are the second most common primary cardiac tumors in adults. They are mainly found on the heart valves, usually on the left side of the heart. They may cause angina, myocardial infarction, and sudden death due to valve stenosis or closure of the coronary arteries.

**Primary malignant tumors (RCD code: VI-1B)**

– Malignant tumors constitute approximately 15% of the primary cardiac tumors [23]. Sarcomas are the most common, although other tumor types have been reported.

**Sarcomas** – Virtually all types of sarcomas have been reported in the heart [38]. Cardiac sarcomas are extremely rare, and for most types, only isolated case reports have been described.

As with benign lesions, the clinical presentation is largely determined by the location of the tumor rather than its histopathology. The diagnostic approach relies upon echocardiography, MRI, and CT to define the presence of a tumor and its anatomic relationship to normal structures.

The most frequently described sarcomas include:

- **Angiosarcomas** – Angiosarcomas are composed of malignant cells that form vascular channels. The pathology of angiosarcomas may overlap with Kaposi's sarcoma, which can also involve the myocardium. Angiosarcomas arise predominantly in the right atrium. Epithelioid hemangioendothelioma, another sarcoma of the vascular origin, has also been reported [39].
- **Rhabdomyosarcomas** – Rhabdomyosarcomas constitute as many as 20% of all primary cardiac sarcomas. These tumors are most commonly found in adults, although they have also been described in children. Multiple sites of myocardial involvement are common, and there is no predominant localization within any area of the heart [40].
- **Fibrosarcomas** – Fibrosarcomas and malignant fibrous histiocytomas are white fleshy (“fish flesh”) tumors that are composed of spindle cells, and may have extensive areas of necrosis and hemorrhage. These tumors tend to extensively infiltrate the myocardium [41].
- **Leiomyosarcomas** – Leiomyosarcomas are spindle-celled, high-grade tumors that most frequently arise in the left atrium. These sarcomas have both a high rate of local recurrence and systemic spread. Other types include liposarcoma, synovial sarcoma, and undifferentiated sarcoma [42].

**Treatment and prognosis** – In general, sarcomas proliferate rapidly, and cause death through widespread infiltration of the myocardium, obstruction of blood flow through the heart, and/or distant metastases. Although complete resection is the treatment of choice, most patients develop recurrent disease and die of their malignancy even if their tumor can be completely resected. The median survival is typically 6 to 12 months, although long-term survival has been reported with complete resection. Patients with low-grade sarcomas may have a better prognosis [40–43].

Adjuvant chemotherapy has been used in an effort to improve on the poor results with resection alone. However, most of the published experience consists of anecdotal case reports, and no randomized trials have been conducted. Radiation has been used infrequently, and primarily as a treatment of metastases [44].

The largest series consists of 34 patients treated at the Mayo Clinic over a 32-year period [45]. The median survival was significantly longer when a complete surgical resection was possible (17 vs. 6 months when complete resection was not possible). Similarly, the median survival was longer in those who did not have metastases on presentation (15 vs. 5 months in those with detectable metastases at diagnosis).

The poor results with surgical resection have led to occasional attempts to treat patients with cardiac transplantation, if extracardiac disease is not present [46,47]. Most of these patients have undergone chemotherapy and radiation prior to transplantation. In the largest series, results of cardiac transplantation in patients with malignant tumors (most of which were sarcomas) were evaluated in a review of 21 cases [47]. Although mean survival was only 12 months, 7 patients were free of recurrent malignancy at a mean follow-up of 27 months.

An alternative treatment, cardiac autotransplantation, seems promising. In these cases, the heart is excised, the tumor is resected *ex vivo*, and the heart is reconstructed before being reimplanted. The advantage of this procedure is the increased ease with which major resection and reconstruction can be performed, while at the same time avoiding the need for antirejection treatment [48].

Rhabdomyosarcomas may have a better outcome with chemotherapy.

**Other primary cardiac tumors** – Primary lymphomas arising in the myocardium have been reported. In a review of 40 cases identified from the literature between 1995 and 2002, the outcome was generally poor [49]. However, 38% of the cases achieved a complete response with systemic therapy. At least some of these responses may be durable [49].

Other tumors may also arise in the heart, including paragangliomas [50] and extramedullary plasmacytomas [51].

**Metastatic cardiac tumors (RCD code: VI-2)**

– In contrast to primary malignant cardiac tumors, metastatic involvement of the heart is relatively common. As an example, in one of the largest autopsy series of over 1900 patients dying of cancer, 8% had metastatic disease involving the heart [5]. Cardiac involvement may arise from hematogenous metastases, direct invasion from the mediastinum, or tumor growth into the vena cava and extension into the right atrium [52].

Malignant melanomas are particularly likely to metastasize to the heart. Other solid tumors commonly associated with cardiac involvement include lung cancer, breast cancer, soft tissue sarcomas, renal carcinoma, esophageal cancer, hepatocellular carcinoma, and thyroid cancer. There is also a high prevalence of secondary cardiac involvement with leukemia and lymphoma.

Cardiac or pericardial metastasis should be considered whenever a patient with known malignancy develops cardiovascular symptoms, particularly if this occurs in conjunction with cardiomegaly, a new or changing heart murmur, electrocardiographic conduction delay, or arrhythmia. Emboli thought to originate in the heart should also raise the possibility of cardiac involvement with tumor. Cardiac metastases rarely may be the first manifestation of malignant disease [53].

The specific symptoms will reflect the site of cardiac involvement, in a manner analogous to primary cardiac tumors. The diagnostic evaluation is the same as that for primary cardiac tumors and relies upon echocardiography, MRI, and CT to assess the extent of cardiac involvement. In very carefully selected patients, resection of cardiac metastases has been used to provide symptom palliation and prolong life [53,54].

Other causes of cardiac symptoms must also be considered. In particular, metastatic disease must be distinguished from cardiotoxicity that may be associated with chemotherapeutic agents, particularly anthracyclines.

## CRCD perspective

Cardiovascular disease and cancer are frequently found in the same patient because of the high prevalence of both diseases, and because some forms of cardiovascular disease are caused by cancer or its therapies. The coexistence of heart disease and cancer in a patient often complicates treatment, because therapy for one disease may negatively affect the outcome of the other disease.

Cardiac tumors and other cardiooncology complications are a heterogeneous group of rare diseases; furthermore, there is no clear classification or division of these pathologies. The CRCD proposed its own cardiac tumor classification. We distinguished five main groups of **Cardiac Tumors and Malignant Diseases**: primary cardiac tumors (benign and malignant – **group 1**), metastatic cardiac tumors (**group 2**), thrombus within the heart chambers (**group 3**), inflammatory malformations (**group 4**), and cardiovascular malformations after oncotherapy (**group 5**). The subgroups within group 2 (thorax, abdomen, and so on) is due to the need to choose the appropriate expert teams for an individual patient. For instance, patients with metastatic tumor from subgroup B (abdomen) should have gastroenterologist consultation. The CRCD distinguished also a group of inflammatory malformations (group 4: vegetations, inflammatory tumors, abscesses, calcifications) so that these patients are managed by multidisciplinary expert teams dealing with systemic inflammatory disease (immunologists, infectious diseases doctors). By this classification, we aimed to look at cardiac tumors and related cardiooncology issues in terms of their implications for clinical practice.

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# Cardiac tumors and cardiovascular diseases in malignancy: Clinical examples

## Myxoma of the heart (RCD code: VI-1A.1)

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### Background

Myxomas are the most common primary benign cardiac tumors. They most commonly occur in the fourth decade of life. They are typically located in the left and right atria [1]. The tumors are smooth, pedunculated, and are gelatinous in consistency. Their size varies from 1 to 15 cm in diameter, and their weight is between 15 and 180 g [2]. Histologically, myxomas are composed of multipotent mesenchymal cells. The mesenchyme is capable of neural and endothelial differentiation [3].

The clinical manifestation of a myxoma depends on the anatomical location of the tumor. Myxomas in the left atrium may cause symptoms similar to mitral stenosis [1], and they are frequently associated with electrocardiographic evidence of left atrial hypertrophy

[2]. Patients with myxomas in the right atrium present with features of right heart failure [1]. There is evidence that myxomas may cause systemic embolization [1,2].

### Case presentation 1: myxoma of the heart in a 49-year-old woman identified by echocardiography

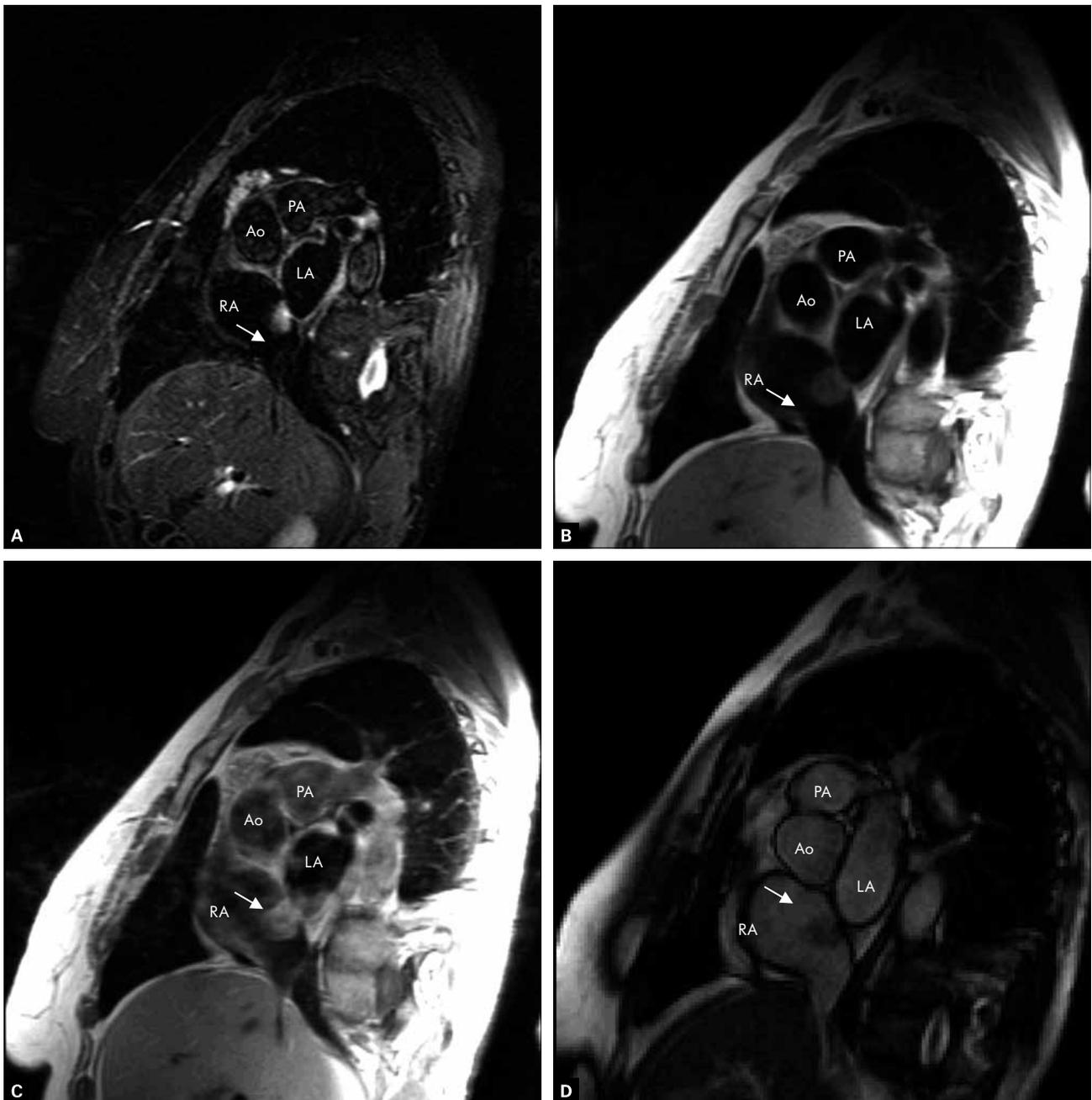
A 49-year-old woman with persistent atrial fibrillation in the course of Graves' disease was admitted electively (November 2004) to the cardiac department to undergo electrical cardioversion. During the previous hospitalization (October 2004) in the same department due to chest pain, echocardiography was performed. It revealed an enlarged left ventricle with impaired contractility and reduced ejection fraction to about 38%. Coronary angiography was performed and no significant changes in the coronary arteries were observed.

Laboratory tests showed that the level of the international normalized ratio was not in the therapeutic range.

During current hospitalization, transthoracic and transesophageal echocardiography revealed the presence of a round, movable tumor of about 20×21 mm in size in the right atrium (fig. 1). The tumor was evenly



**Fig. 1.** Transthoracic echocardiography. **A.** Parasternal short-axis view. **B.** Apical view. The tumor in the right atrium (black arrows). RV – right ventricle, LV – left ventricle



**Fig. 2.** Cardiovascular magnetic resonance. **A.** STIR sequence. T1-weighted images. **B.** Spin echo sequence. T1-weighted images. Precontrast. **C.** Spin echo sequence. T1-weighted images. Postcontrast. **D.** Sine gradient echo. Short axis view. Atrial projection. The tumor in the right atrium (white arrows). Ao – aorta, PA – pulmonary artery, RA – right atrium, LA – left atrium

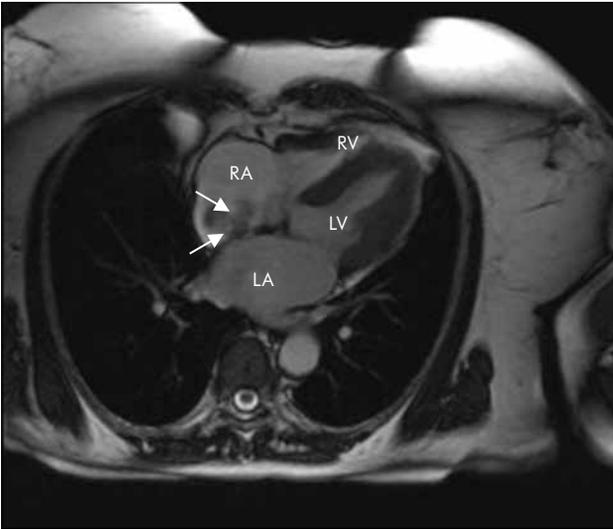
saturated; the saturation was similar to the structures of the heart. In addition, transesophageal echocardiography showed no thrombus within the left atrial appendage.

Cardiac magnetic resonance confirmed the presence of an abnormal oval structure in the right atrial cavity, approximately 23×19 mm in size. Its middle part was connected to the intra-atrial septum. The structure was movable and showed an intermediate signal on T1 images. Moreover, it was hyperintense on STIR sequences and enhanced after contrast administration. The image corresponded to a myxoma but did not exclude blood clots (fig. 2).

The patient received heparin but there was no change in the tumor's size after 10 days of therapy.

Therefore, she was scheduled for urgent cardiac surgery.

The surgery was performed with the use of cardiopulmonary bypass, normothermia, and cold crystalloid cardioplegia. During the procedure, a tumor (myxoma) was shown (30×30 mm in size) after the opening of the right atrium, located at the base of the atrial septum. The entire lesion was removed, including the fragments of the intra-atrial septum. After the procedure, low-output syndrome developed, which was treated medically. There were no complications during the postoperative course and wound healing process. The patient was discharged from the cardiac surgery department in good general condition.



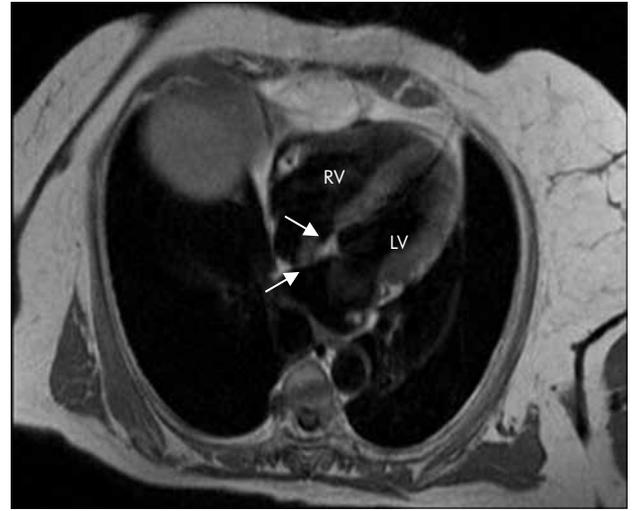
**Fig. 3.** Cardiovascular magnetic resonance. Four-chamber long-axis view. Sine gradient echo. The tumor in the right atrium (arrows). RV – right ventricle, LV – left ventricle, LA – left atrium, PA – pulmonary artery



**Fig. 4.** Cardiovascular magnetic resonance. Two-chamber view. Right ventricular projection. Sine gradient echo. The tumor in the right atrium (arrows). RV – right ventricle, RA – right atrium, Ao – aorta, PA – pulmonary artery

### Case presentation 2: myxoma of the heart in a 57-year-old woman identified by echocardiography and magnetic resonance imaging

A 57-year-old woman was admitted to the cardiac department to undergo diagnostic procedures of the tumor in the right atrium.



**Fig. 5.** Cardiovascular magnetic resonance. Four-chamber long-axis view. Spin echo T1-weighted images. The tumor in the right atrium (arrows). RV – right ventricle, LV – left ventricle

The tumor was recognized on transthoracic echocardiography in an outpatient clinic. For 2 months before admission, she complained of a nonspecific stabbing chest pain and high blood pressure.

In the cardiac department, the transesophageal echocardiography was performed. It revealed the presence of a lesion in the right atrium that was attached from one side to the atrial septum. The size of the lesion was 23×27 mm. Its distal portion was irregular and had polycyclic contours. The image was not typical for a myxoma.

Cardiac magnetic resonance imaging confirmed the presence of an abnormal tissue in the right atrial cavity, approximately 32×23×31 mm in size. Its middle part was connected to the intra-atrial septum. The structure was movable, hyperintensive on STIR sequences, hypointensive on T1 and heterogeneous on T2 scans, and enhanced after contrast administration. There were no features of malignancy or infiltration of the surrounding parts of the heart. The image corresponded to a myxoma and, less likely, to a clot (fig. 3, 4, 5).

An abdominal ultrasound examination and a chest X-ray image did not show significant changes. Coronarography did not reveal coronary stenosis.

The patient underwent surgery in 2011 with the use of cardiopulmonary bypass, normothermia, and crystalline cardioplegia. During the procedure, after the opening of the right atrium, a myxoma was showed, 20×15 mm in size, located at the base of the atrial septum. The tumor was completely removed.

There were no complications during the postoperative course and wound healing process. The patient was discharged from the cardiac surgery department in good general condition.

## Management strategy

Two-dimensional echocardiography is the most valuable tool for the assessment of myxomas [1]. It clearly shows the site, size, shape, attachment, mobility, prolapse into the ventricle, and surface characteristics of myxomas [4].

As soon as the diagnosis of a myxoma has been made, prompt surgical resection of the myxoma is required to avoid the risk of cardiovascular complications and embolization [5]. An appropriate surgical intervention is recognized as a definitive, curative therapy [6]. Postoperative recovery is rapid. However, atrial arrhythmias or atrioventricular conduction abnormalities may be present [2]. Patients after the operation are at risk of recurrence (2%–5% of the cases) [2].

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## Fibroma in the intraventricular septum (RCD code: VI-1A.2)

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### Background

Primary cardiac tumors are usually benign [1,2].

Cardiac fibromas are most commonly found in children and young people with the same frequency in both sexes. The mean patient age at diagnosis is 13 years. In children, it is the second most common primary benign tumor. Sometimes, fibromas are associated with Gorlin syndrome, an inherited autosomal dominant disease characterized by the presence of pigmented moles and basal cell carcinoma of the skin.

Morphologically, cardiac fibromas are similar to other fibromas – they are usually single, have calcification in the central part, are not surrounded by a capsule, and do not form metastases but may invade the myocardium. They typically occur in the septum and the anterior wall of the left ventricle. Microscopically, they are composed of fibroblasts and extensive extracellular matrix consisting mainly of collagen and elastin [3].

### Case presentation

An 18-year-old patient with a 3-year history of recurrent noncharacteristic chest pain, with radiation to the left arm and intensifying during breathing, was admitted to the hospital for further cardiac evaluation. He was often hospitalized due to chest pain in the past.

In 2009, cardiac magnetic resonance imaging was performed due to chest pain and revealed a cardiac tumor. The tumor was located in the myocardium in the lower part of the interventricular septum and on the left ventricular wall. It measured  $4.5 \times 3.1 \times 3.9$  mm,



**Fig. 1.** Cardiovascular magnetic resonance. Two-chamber view. Sine gradient echo. Fibroma in the interventricular septum (arrow)

causing the bulge of the muscle in the lumen of the left ventricle, a little more in the lumen of the right ventricle, and the outer bottom wall of the pericardium (fig. 1, 2, 3).

The patient did not report episodes of fainting, dizziness, presyncope, or palpitations. He described his exercise tolerance as good.

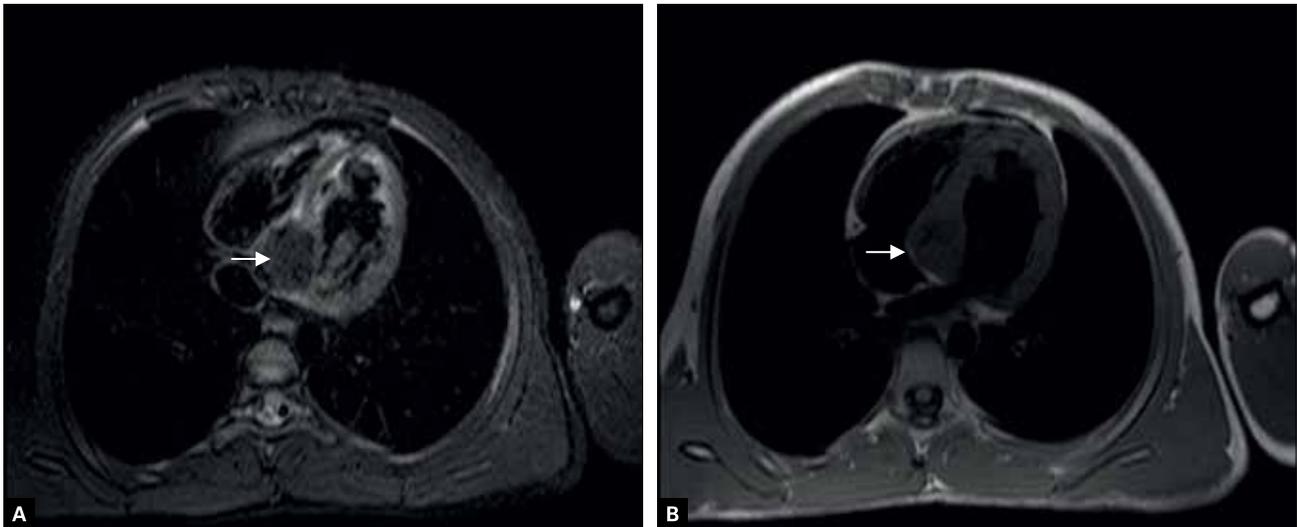
On admission to the local hospital, his condition was stable, his circulatory and respiratory systems were efficient, and pain was not reported.

An electrocardiogram showed normal sinus rhythm; the rate was 60/min with features of intraventricular conduction disturbances; also, higher elevation of the J point in V1-V3 was noted.

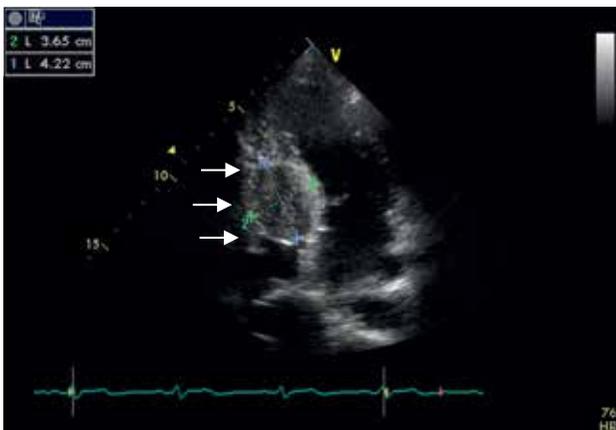
In laboratory tests, there were no deviations from the normal values.



**Fig. 2.** Cardiovascular magnetic resonance. **A.** Short axis view, T1-SE. **B.** Short axis view, STIR sequence. **C.** Short axis view, T2-SE. Fibroma of the heart: the main mass of the tumor occupying the interventricular septum – hypoechogenic area (arrows)



**Fig. 3.** Cardiovascular magnetic resonance. **A.** Four-chamber view, STIR sequence. **B.** Four-chamber view, T1-SE. Cardiac fibroma (arrows)



**Fig. 4.** Transthoracic echocardiography. Apical four-chamber view. Lesion in the interventricular septum (arrows)



**Fig. 5.** Transthoracic echocardiography. Apical four-chamber view. Fibroma in the interventricular septum (arrow)

Transthoracic echocardiography revealed a heterogeneous, well-demarcated intramural tumor measuring 34×41 mm in the bottom wall and the bottom of the septum; moreover, it showed the normal size of the heart chambers and normal global and segmental contractility of the left ventricle with an ejection fraction of about 58% (fig. 4, 5). Holter monitoring did not show significant arrhythmias.

Cardiac magnetic resonance imaging was performed again and the findings were the same as in 2009. Considering the changes in signals and the young age of the patient, we established a preliminary diagnosis of a cardiac fibroma (fig. 1, 2, 3).

### Management strategy

The case of the patient was consulted with cardiac surgeons. Based on their opinion, our findings, and asymptomatic course, we decided against the surgery and recommended further observation of the tumor.

### Discussion

Cardiac fibromas are typically seen in children and adolescents, but they can also occur in adults. The clinical presentation can vary widely. Up to one-third of the patients are asymptomatic when the tumor is discovered incidentally. Another 23% of the cases can present with sudden death from ventricular arrhythmia [4]. The clinical course of cardiac fibromas depends on the location and size of the tumor. Patients typically complain of noncharacteristic chest pain, shortness of breath, decreased exercise tolerance, as well as palpitations, presyncope, and syncope [4]. Transthoracic echocardiography is the most common initial diagnostic test to identify a cardiac mass. It can also provide information on the valvular function. It is important to examine the mitral valve, which can be distorted by the tumor. Cardiac magnetic resonance imaging helps delineate the mass anatomically and reveal its interaction with mitral valve function [5]. When fibromas are adjacent to the coronary arteries, the possibility of arterial

displacement or occlusion warrants cardiac catheterization and coronary arteriography.

There are a number of modalities to choose from to manage patients with cardiac fibromas [6,7]. In symptomatic patients, surgery is usually recommended. In the absence of symptoms or if they are not severe, as in our case, conservative (nonsurgical) treatment and close observation of the patient are suggested. It is also reasonable to resect asymptomatic fibromas that are large or growing, because there have been reports of sudden cardiac death with no previous symptoms and no significant arrhythmias [8]. Tumor resection can be complicated by the large size and the anatomical location of fibromas, which may encroach upon the coronary arteries or the ventricular cavity. Distortion or involvement of the papillary muscles can lead to mitral regurgitation at any time before or after resection. When cardiac fibromas are too extensive for complete local excision, orthotopic cardiac transplantation can be successfully performed.

The recurrence of cardiac fibromas is highly unusual, and long-term survival rates after resection are excellent. However, surgery carries a risk of complications, and there is still no consensus as to the management [7,9,10]. Therefore, each case should be carefully analysed and individual approach is recommended.

## Conclusions

Cardiac fibromas represent the second most common benign cardiac tumor observed in the pediatric population. They are rarely observed in adults. Given their large size and unpredictable location within the heart, patients may present with varying symptoms, and, in many cases, the initial presentation is sudden death. Both echocardiography and magnetic resonance imaging are critical to the early diagnosis and prompt treatment of these potentially dangerous primary tumors. Cardiac transplantation has been suggested as a preferable treatment option; however, most ventricular fibromas, although extensive, can be completely resected with excellent early and late results. For patients with tumors extending into critical locations, subtotal excision can be performed that also gives excellent long-term outcomes [10].

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## Lipomatous hypertrophy of the interatrial septum (RCD code: VI-1A.3a)

Izabela Karch, Monika Komar, Hanna Dziedzic-Oleksy, Małgorzata Urbańczyk-Zawadzka, Maria Olszowska, Piotr Podolec

### Background

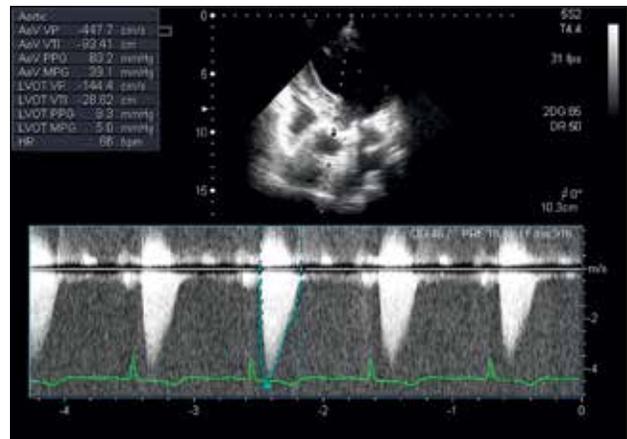
Lipomatous hypertrophy of the interatrial septum (LHIS) is a benign disorder caused by the excessive deposition of the adipose tissue in the interatrial septum. In most cases, LHIS is asymptomatic and does not require treatment. It is usually diagnosed incidentally by echocardiography. Advanced noninvasive imaging techniques make it possible to avoid misdiagnosis and unnecessary intervention. It should always be considered in the differential diagnosis of benign and malignant atrial tumors.

### Case presentation

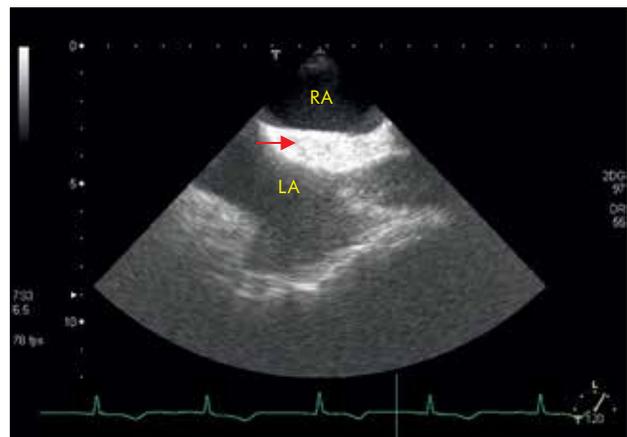
A 52-year-old woman with severe aortic stenosis and right atrial tumor was referred to our hospital for cardiac surgery. She had a history of arterial hypertension, hyperlipidemia, smoking, and rheumatoid arthritis treated with corticosteroids. In 1997, she underwent total thyroidectomy and radiotherapy because of cancer. The patient had a single episode of syncope within the last 3 months and dyspnea on exertion (class II according to the New York Heart Association). On a physical examination, she was slightly overweight but her general health was good. Her blood pressure was 145/70 mm Hg and her heart rate was 82 beats/min.

A grade 3/6 systolic ejection murmur was heard over the entire heart. An electrocardiogram showed sinus rhythm, left ventricular enlargement, and nonspecific ST-segment and T-wave abnormalities. Transthoracic echocardiography confirmed severe aortic stenosis with an effective orifice area of 0.6 cm<sup>2</sup>, a mean gradient of 39 mm Hg (fig. 1). The aortic leaflets were thickened with calcifications. The left ventricular ejection fraction was normal. The interatrial septum was thick and hyperechogenic (fig. 2). Echocardiography revealed also the presence of a mobile, pedunculated structure in the right atrium (fig. 3). The length of the pedunculus was 5.8 cm; the size of the structure was 6.8×9.7 mm.

Computed tomography showed thickened interatrial septum (up to 16 mm) (fig. 4). Its negative values in Hounsfield units suggested the fat tissue and lipomatous hypertrophy. The fat tissue was also present in the posterior wall of the right atrium. Between the orifice of the inferior and superior vena cava, there was a linear structure of 6 mm in size, which was connected to the posterior wall of the right atrium and extended to its lumen. The structure also included



**Fig. 1.** Transthoracic echocardiography. Apical five-chamber view. Measurement of the pressure gradient across the aortic valve



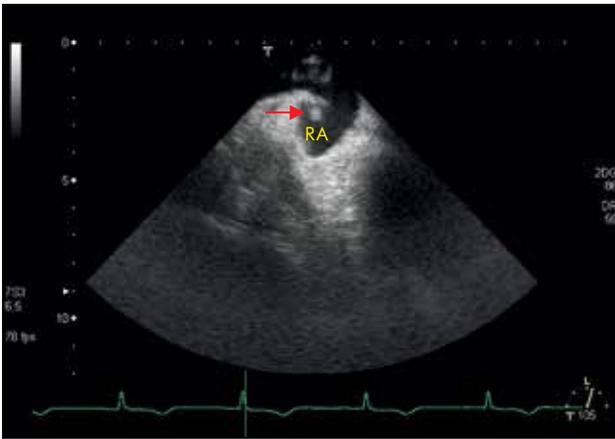
**Fig. 2.** Transesophageal echocardiography. Bicaval view. Thick atrial septum proximal to the fossa ovalis (arrow). LA – left atrium, RA – right atrium

the fat tissue and it was probably the enlarged crista terminalis. An intraoperative evaluation confirmed the preoperative imaging findings. The patient underwent an aortic valve replacement surgery.

### Discussion

LHIS, also called “massive fatty deposits” or “lipomatous hamartoma,” is a rare benign disorder caused by the excessive deposition of the adipose tissue in the interatrial septum [1]. It was first described in 1964 by Prior [2]. Normally, the atrial septum, both cephalad and caudal to the fossa ovalis, is less than 1 cm thick. LHIS is defined as a deposition of fat in the atrial septum that is more than 2 cm thick in the transverse diameter. LHIS typically spares the fossa ovalis and membranous atrioventricular septum; however, the fatty infiltration may extend into the free wall of the left atrium, the wall of the right ventricle, and interventricular septum.

LHIS is not a neoplastic process but rather a developmental aberrancy. It is a nonencapsulated lesion,



**Fig. 3.** Transesophageal echocardiography. Modified upper left view. Tumor in the right atrium (arrow). RA – right atrium



**Fig. 4.** Cardiovascular computed tomography. Four-chamber view. Lipomatous hypertrophy of the interatrial septum (arrow). LA – left atrium, LV – left ventricle, RV – right ventricle, RA – right atrium, IAS – interatrial septum

histologically composed of mature adipocytes and brown fat cells with multiple small vacuoles and central nucleus [3]. Interspersed cardiomyocytes may be present and they often show hypertrophic and degenerative changes. Typically, epicardial structures such as nerve ganglion, areas of fibrosis, and focal collections of chronic inflammatory cells may also be observed in these lesions. There is a theory that LHIS originates from embryonic mesenchymal cells, which differentiate into adipocytes by unknown stimuli [4]. During embryogenesis, the right and left atria are divided by progressive in-folding of the roof and the upper anterior and posterior walls of the rudimentary common chamber along the midline [3]. Mesodermal tissues are drawn into the wall of the primitive atrial septum during this process, and pockets of entrapped adipose tissue remain in the septum after the heart is fully formed.

The exact prevalence of LHIS is unknown. The reported incidence of LHIS at autopsy varies from 1% to 2.2% [5,6], while according to transthoracic echocardiographic studies, it is present in about 8% of the patients [7]. LHIS is typically associated with obesity and aging [5], and it is more common in women [8]. It is rarely observed in younger patients and, in these cases, a more extensive investigation to exclude a malignant process is necessary. LHIS can be associated with rare metabolic disorders such as cerebrotendinous xanthomatosis [9] or mediastino-abdominal lipomatosis [10]. Another risk factor for developing LHIS is long-term parenteral nutrition [11]. LHIS is most often asymptomatic and its diagnosis is made incidentally. However, in rare cases, it may be implicated in supraventricular tachycardia [12] or may cause obstruction of the superior vena cava [13]. Malignant cardiac arrhythmias may occur as a result of extensive bleeding into the lesion and cause sudden cardiac death [15].

Echocardiography, magnetic resonance imaging, and computed tomography are the most common imaging techniques used to visualize LHIS. In echocardiography, LHIS is brightly echogenic and has a characteristic hourglass shape [15]. It is typical that the thickness of the atrial septum proximal to the fossa ovalis is greater than that of the distal one [1]. In some cases, transesophageal echocardiography is more useful owing to obesity of the majority of patients with LHIS. The first patient was diagnosed with LHIS using computed tomography scanning in 1982 [16]. Cardiac computed tomography shows nonenhancing homogeneous thickening of the septum with typical fat tissue signal characteristics [17]. In cardiac magnetic resonance image, the fat in the septum is hypointense on  $T_1$  imaging, without enhancement, and has the expected tissue characteristics on fat suppression sequences [17]. Recent studies have proved the usefulness of positron emission tomography (PET) and PET-CT in the diagnosis of LHIS [18,19].

LHIS should be considered as part of the differential diagnosis for any atrial cardiac tumor [20]. Lipomas, unlike lipomatous hypertrophy, are distinctly encapsulated and are more common in young patients.

In most cases, LHIS does not require any specific treatment. Surgical management is necessary in patients with the symptoms of superior vena cava syndrome or right atrial obstruction as well as intractable rhythm disturbances [21]. When complete excision of the tumor is necessary, reconstruction of the interatrial septum with autologous pericardium or Dacron must be performed [22].

## Management strategy

LHIS, with possible simultaneous presence of the fat tissue in the free wall of the left atrium, the right ventricular wall, and interventricular septum, should always be considered as part of the differential diagnosis

of any cardiac tumor. It has characteristic features in echocardiography, computed tomography, and magnetic resonance imaging and, when associated with advanced age, female sex, and obesity, it does not require any further investigation. It is rarely observed in younger patients and, in these cases, more extensive investigation to exclude a malignant process is necessary. In most cases, LHS is asymptomatic and does not require treatment. In these patients, we consider periodic echocardiographic follow-up because of possible lesion enlargement. In rare cases, this benign condition may show the symptoms of malignancy associated with supraventricular arrhythmia and obstruction of the superior vena cava. Surgical management may be necessary in these symptomatic patients.

## Conclusion

In summary, LHS should be included in the differential diagnosis of patients in whom echocardiography reveals brightly echogenic masses in the interventricular septum. Computed tomography and magnetic resonance imaging provide additional information about the features of tissue components. When asymptomatic, LHS does not require any treatment and only clinical and echocardiographic follow-up is necessary.

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## Cavernous hemangioma of the heart (RCD code: VI-1B.4)

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### Background

Cardiac hemangiomas are extremely rare tumors, which constitute only 2.8% to 5% of all benign cardiac tumors [1,2]. Cardiac hemangiomas are nonmalignant vascular tumors consisting of blood vessels and are identical to hemangiomas observed in other parts of

the body. They can be histologically classified as a cavernous hemangioma, capillary hemangioma, and arteriovenous hemangioma or cricoid aneurysm. Among them, cavernous and capillary types are the most frequent. The epicardium is the most common location for cardiac hemangiomas, but they may also be found in the myocardium and endocardium. A cavernous hemangioma is a spongy mass of wide blood-filled spaces, which are pleomorphic in shape and dimension [3].

### Case presentation

A 37-year-old man with a 6-month history of atypical nonexertional chest pain and markedly limited exercise capacity was referred to our department for evaluation. He had no previous medical history. He worked as a carpenter. Of risk factors, only hypercholesterolemia was present. There were no abnormalities in the physical examination and laboratory tests.

A standard electrocardiogram revealed inverse T-waves in leads I and aVL, and first-degree atrioventricular block. A chest X-ray image showed a tumor-like structure on the left cardiac contour.

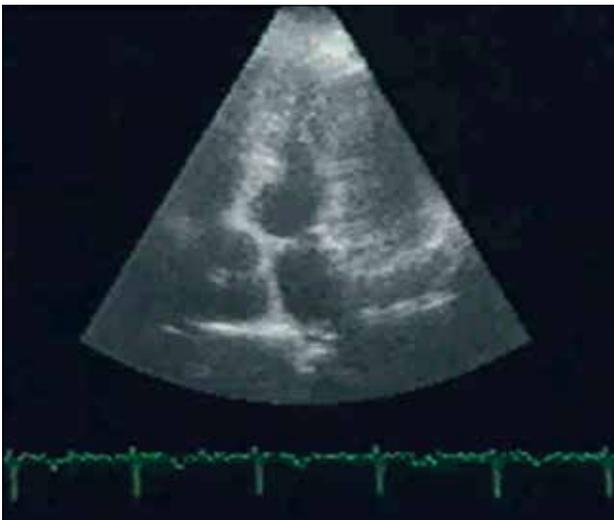
Echocardiography revealed a large echolucent tumor adjacent to the lateral wall of the left ventricle (fig. 1). Multislice computed tomography (CT) with intravenous contrast medium was performed using Somatom Plus 4 Volume Zoom Siemens (Heart View Software) with 3-mm collimation. A chest CT scan showed a large oval tumor on the left demarcation of the heart (fig. 2). Contrast-enhanced coronary angiography showed a cystic tumor (75×80×80 mm) located in the epicardium of the left ventricle and separated from the myocardium. The mid portion of the left anterior descending coronary artery (LAD) was located well within the tumor (fig. 3, 4). Coronary angiography showed no coronary artery disease but significant modeling of a large portion of the LAD on the tumor mass.

Surgical resection of the mass was performed and the LAD was grafted. A histopathological examination revealed cavernous hemangioma, a rare primary heart tumor. The patient was discharged in good condition, with normal electrocardiographic results, and was symptom-free 6 months later.

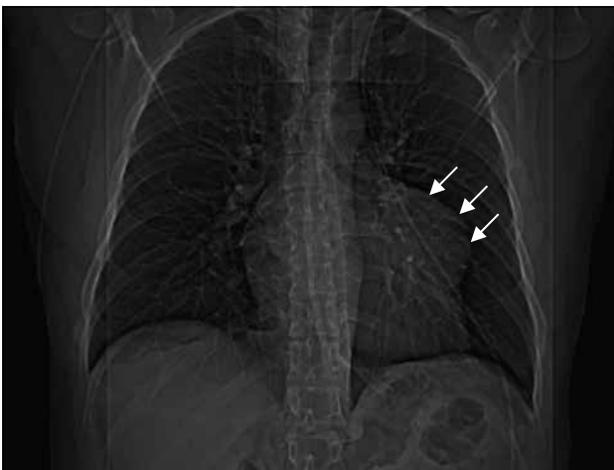
### Discussion

The clinical presentation (dyspnea, palpitations, atypical chest pain, arrhythmia) varies according to the tumor's location, size, and its relationship to the surrounding structures. In some patients, cardiac hemangiomas may cause conduction disturbances, pericardial effusions, congestive heart failure, right ventricular outflow obstruction, coronary insufficiency or embolization, and even sudden death.

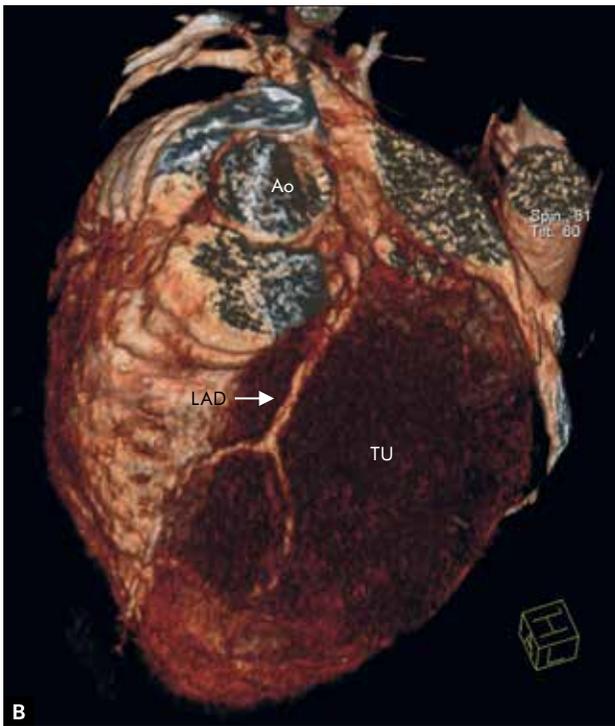
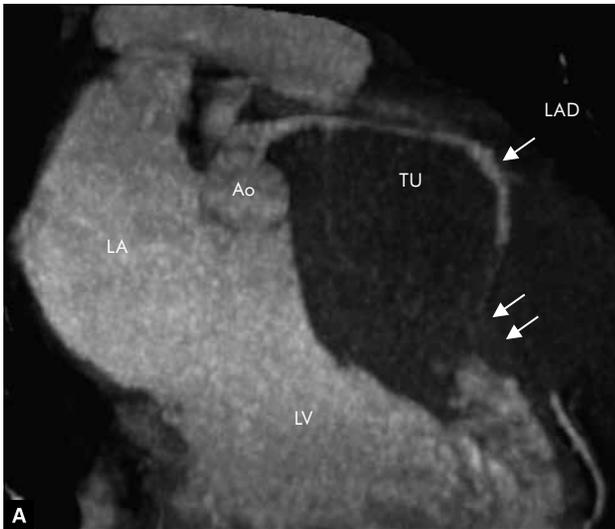
Successful treatment usually requires timely surgery. In most cases, prognosis is reportedly satisfactory



**Fig. 1.** Transthoracic echocardiography. Apical four-chamber view. Tumor adjacent to the lateral wall of the left ventricle. LA – left atrium, LV – left ventricle, RA – right atrium, RV – right ventricle, Tu – tumor



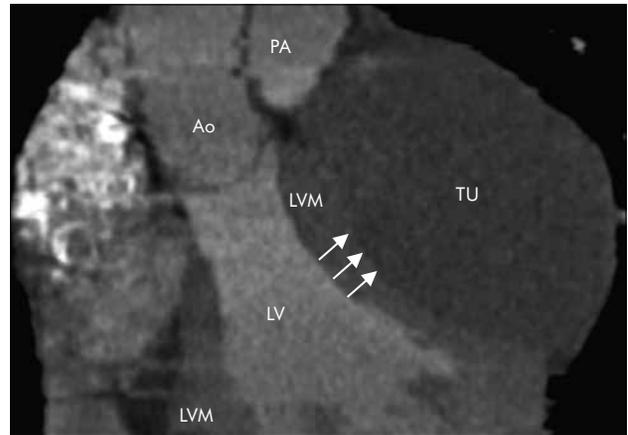
**Fig. 2.** Computed tomography. Chest scan. Left contour of the heart irregularly enlarged (arrows)



**Fig. 3. A.** Cardiovascular computed tomography. Medial part of the left anterior descending branch (LAD) is located within the tumor mass (arrows). LA – left atrium, Ao – aorta, LV – left ventricle, Tu – tumor, LAD – left anterior descending coronary artery. **B.** Cardiovascular computed tomography. Three-dimensional reconstruction. Left anterior descending branch (LAD) is located within tumor mass. Ao – aorta, LAD – left anterior descending coronary artery, Tu – tumor

following simple resection, if multiple lesions do not recur. Spontaneous tumor resolution during a 2-year follow-up has also been reported [4,5]. However, since this tumor may cause sudden death, surgical treatment seems to be recommended in cases with clinical symptoms.

There has been at least 1 case of recurrence and subsequent progression of the neoplasm. In particular, one of the papers described a benign lesion treated surgically that transformed into a malignant neoplasm, angiosarcoma, 7 years after surgery [6].



**Fig. 4.** Cardiovascular computed tomography. Two-dimensional reconstruction. Tumor located on the wall of the left ventricle. The border line between the left ventricular wall and the tumor mass is well visible (arrows). LVM – left ventricle myocardium, LV – left ventricle, Ao – aorta, PA – pulmonary artery, Tu – tumor

## Management strategy

Most cardiac masses (including hemangiomas) are asymptomatic and are discovered incidentally by imaging techniques, such as chest radiography, echocardiography, CT, or cardiac magnetic resonance imaging (MRI) [7,8]. Therefore, noninvasive cardiac imaging plays an important role in the diagnosis and subsequent management of the patients with cardiac tumors.

The diagnosis of cardiac tumors is aided by imaging techniques. Periodic examinations and echocardiography are recommended [9]. Echocardiography is a sensitive and noninvasive modality for detecting hemangiomas [9,10]. Multislice CT may be useful when a more precise evaluation of the tumor extent is required. It allows to specify the relationship of the mass with the coronary vessels. Intense central contrast enhancement on CT suggests the diagnosis and can assist in preoperative surgical planning. Cardiac catheterization and cardiac MRI are superior in the qualitative diagnosis of a cardiac tumor. Cardiac MRI can demonstrate the extent of intramural development more accurately as well as reveal the hypervascular nature of the hemangioma [2].

## Conclusion

Due to the potential risks of a cardiac hemangioma, surgical resection is recommended when possible. Postoperative follow-up is necessary to monitor potential recurrence [8].

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## Mitral annular calcification (RCD code: VI-4D.2)

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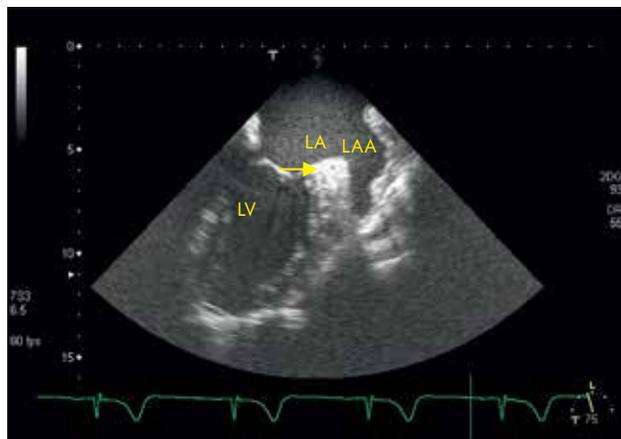
### Background

The differential diagnosis of cardiac tumors should include malignant and benign neoplasms but also benign conditions such as mitral annular calcification (MAC). MAC is a common echocardiographic finding in older patients [1]. It is formed as a result of a degenerative process involving the fibrous annulus of the mitral valve [2]. Although MAC is a benign disorder, in some cases, it can show clinical malignancy associated with the dysfunction of the mitral valve, conduction system disease, endocarditis, or thromboembolic complications [3–6].

### Case presentation

A 69-year-old woman with hypertension, hyperlipidemia, coronary artery disease, after myocardial infarction in 2009, was admitted to the cardiac department to undergo diagnostic tests for cardiac tumor. The tumor was recognized during earlier hospitalization in the surgery department, where she underwent abdominal operation due to mesenteric emboli. It was suggested that the tumor might have been the cause of the emboli.

On transthoracic and transesophageal echocardiogram massive calcifications of mitral annulus were shown. The atrial wall between the left atrial appendage and mitral annulus was thick (up to 22 mm) and contained calcifications that were connected to



**Fig. 1.** Transesophageal echocardiography. The upper left view. Calcifications between the left atrial appendage and mitral annulus (arrow). LA – left atrium, LV – left ventricle, LAA – left atrium appendage

the mitral annulus (fig. 1). There was no significant stenosis or regurgitation of the mitral valve.

Magnetic resonance imaging excluded other cardiac pathologies (fig. 2) and computed tomography confirmed the diagnosis of MAC (fig. 3).

Holter monitoring revealed no significant rhythm or conduction abnormalities.

The patient's case was presented during the meeting of a heart team. It was agreed that there were no indications for cardiac surgery.

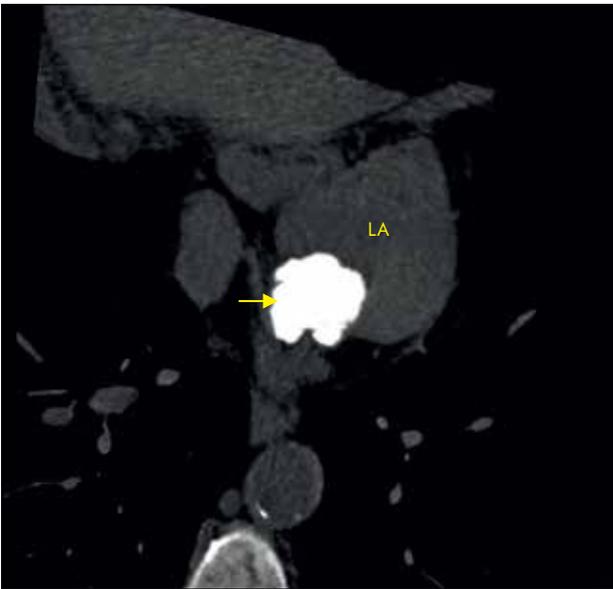
MAC was recognized as the most probable cause of peripheral arterial embolization. Oral anticoagulant therapy and regular cardiac evaluation were recommended.

### Discussion

MAC is a degenerative process causing progressive calcium deposition in the fibrous annulus of the mitral valve [2]. Its rare caseous variant is a periannular mass consisting of calcium, fatty acids, and cholesterol [7]. The precise incidence of MAC is unknown. According to various authors, its prevalence is estimated at 3% to 9% of the adult population [8,9]. In patients undergoing an echocardiogram, MAC has been reported to occur in 10.6%, and the caseous variant only in 0.06% to 0.07% [1]. The prevalence of MAC increases



**Fig. 2.** Cardiovascular magnetic resonance. Short-axis view after contrast (gadolinium) injection. Late enhancement. Tumor in the left atrium hypointensive compared with the myocardium (arrow). LA – left atrium



**Fig. 3.** Cardiovascular computed tomography Axis scan. Calcification of the mitral annulus (arrow). LA – left atrium

with age and some data suggest higher frequency in women [10,11]. Most of the risk factors for MAC and its pathophysiology are similar to atherosclerosis [12]. It has also been shown that calcification may be accelerated in patients with chronic renal disease – a condition associated with altered mineral metabolism [13]. The development of MAC in adolescence or young adulthood has been recognized in patients with genetic abnormalities of the fibrous tissue, (for example, Marfan syndrome [14]) and with chronic inflammatory disorders (for example, systemic lupus erythematosus [15]). The specific factors that lead to caseous degeneration of the mitral annulus are unknown.

The presence of MAC may lead to the dysfunction of the mitral valve, causing either its functional stenosis or regurgitation [3]. MAC is also related to other cardiac conditions such as atrial fibrillation (because of left atrial enlargement as a result of mitral valve dysfunction) [16], conduction system disease (because of calcifications localized near the AV node and His bundle) [4], and coronary artery disease (similar risk factors and pathogenesis) [17]. MAC is associated with an increased risk of ischemic stroke, the potential causes of which include atrial fibrillation and vascular atherosclerotic disease. In rare cases, thrombi adherent to MAC were recognized as the source of peripheral thromboembolism [6]. Endocarditis in patients with MAC has also been reported [5].

The most commonly used diagnostic procedure to identify MAC is echocardiography. It reveals a well-defined, irregular, bright echodense structure involving the mitral valve annulus beneath the posterior leaflet, yielding posterior acoustic shadowing. The involvement of the basis of the mitral valve posterior leaflet is possible, whereas the anterior mitral leaflet, commissures, and chordae tendineae are generally not involved [18]. On echocardiography, caseous MAC appears as round or semilunar echodense mass with

smooth borders, central areas of echolucency without posterior acoustic shadowing [19]. MAC can be also easily identified by X-ray imaging such as chest radiography, fluoroscopy, and computed tomography [20]. Magnetic resonance imaging is not commonly used to diagnose MAC, because calcium is hypointensive compared with the myocardium [21].

The differential diagnosis of MAC should include benign and malignant cardiac tumors localized near the mitral valve and containing calcium deposits. The involvement of the leaflet commissures and anterior leaflet, usually absent in MAC, is characteristic for rheumatic mitral disease. Caseous MAC can be misdiagnosed as a cardiac tumor, thrombus, or abscess [22–24].

There is no established therapy for the prevention or treatment of MAC. However, the presence of MAC is a sign of potential risk factors and cardiovascular conditions that may require treatment. Since MAC may be associated with ischemic stroke and systemic embolism, it may require specific antithrombotic treatment [25]. The routine prophylaxis of endocarditis is not recommended [26]. The development of MAC in patients who undergo mitral valve replacement may complicate the surgical procedure and is associated with higher surgical mortality rate [27].

## Management strategy

There are no specific recommendations on the optimal management of patients with MAC coexisting with systemic embolism. Other possible sources of emboli should be excluded. In our patient, MAC was recognized as the most probable cause of peripheral arterial embolization; therefore, oral anticoagulant therapy was administered. There was no severe mitral stenosis or mitral regurgitation so no indications for mitral valve replacement were identified. Regular cardiac evaluation was recommended because MAC is a dynamic process and may lead to mitral valve dysfunction. When mitral valve surgery is indicated in patients with MAC, a careful assessment of potential risks and benefits should be performed. In all patients with MAC, modifiable cardiovascular risk factors such as hypertension and dyslipidemia should be evaluated and treated.

## Conclusion

MAC is a common echocardiographic finding in elderly population. It should be considered as a part of the differential diagnosis for benign and malignant cardiac tumors localized near the mitral valve and containing calcium deposits. It should also be considered as a risk factor for stroke or systemic embolism.

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# Part 9

Cardiovascular diseases in pregnancy  
– RCD class VII

**Editors: Agata Leśniak-Sobelga, Piotr Podolec**



# Introduction

Agata Leśniak-Sobelga

Cardiovascular diseases in pregnancy are rare, affecting from 0.2% to 4% of all pregnant patients. Because of advances in the treatment of congenital heart diseases, an increasing number of women with heart disease reach childbearing age. Heart disease is the main cause of maternal death during pregnancy in Western countries.

The counseling and management of young women with cardiac disease should be started before pregnancy is planned. These patients should be managed by interdisciplinary teams including a cardiologist, gynecologist, obstetrician, neonatologist, anesthesiologist, and genetic specialist). Safe and effective methods of contraception, maternal and fetal risks during pregnancy, potential long-term maternal morbidity and mortality as well as the time, mode, and place of delivery should be discussed. High-risk patients should be treated in specialized centers with experience in the management of pregnant women with heart disease [1].

In counseling, the underlying cardiac lesion, maternal functional status, the possibility of further palliative or corrective surgery, additional associated risk factors, maternal life expectancy and ability to care for a child, and the risk of congenital heart disease in the offspring should be considered [2].

Major hemodynamic alterations occur during pregnancy, labor and delivery, and the postpartum period. They begin during the first weeks of pregnancy (5 to 8 weeks) and reach the peak in the late second trimester. The main physiological changes in the circulatory system during pregnancy involve an increase in the volume of the circulating blood (increased preload), increased heart rate and cardiac output, and a decrease in vascular resistance (decreased afterload) [3]. These changes can impose a hemodynamic stress on the heart and affect the course of pregnancy. Furthermore, the changes in hemostatic system prevent hemorrhage but, on the other hand, predispose to thrombosis [4]. Treatment of venous thromboembolism in pregnancy constitutes a challenge in daily clinical practice, because of possible hemorrhagic and teratogenic complications for the mother and fetus [5].

Knowledge of the risk factors associated with cardiovascular diseases during pregnancy and their

management is crucial. The goal of the management is the optimal treatment, effectively protecting not only the mother but also the child/fetus. In clinical practice, the World Health Organization (WHO) classification is used, according to recent guidelines [1]. Patients with rare cardiovascular diseases are usually classified as WHO class III or IV.

There are numerous publications on cardiovascular diseases in pregnancy. A couple of examples are as follows: Elkayam U, Norbert G. *Cardiac Problems in Pregnancy: Diagnosis and Management of Maternal and Fetal Heart Disease*. John Wiley & Sons, 1998; Elkayam U, Bitar F. *Valvular heart disease and pregnancy*. *J Am Coll Cardiol* 2005; Oakley C, Warnes CA. *Heart disease in pregnancy*. Blackwell Publishing, 2nd ed. 2007; Briggs GG, Freeman RK, Yaffe SJ. *Drugs in pregnancy and lactation*. 6th edition. Baltimore, MD: Lippincott Williams and Wilkins, 2002; Pieper PG. *The pregnant woman with heart disease: management of pregnancy and delivery*. *Neth Heart J*. 2012; Pieper PG, Hoendermis ES, Drijver YN. *Cardiac surgery and percutaneous intervention in pregnant women with heart disease*. *Neth Heart J*. 2012; Drenthen W, Boersma E, Balci A, et al. *Predictors of pregnancy complications in women with congenital heart disease*. *Eur Heart J* 2010; Leśniak-Sobelga A, Tracz W, Kostkiewicz M, et al. *Clinical and echocardiographic assessment of pregnant women with valvular heart diseases – maternal and fetal outcome*. *Int J Cardiol* 2004; Oleg M. Eliseev. *Cardiovascular Diseases and Pregnancy*. Springer-Verlag, 2011; Silversides CK, Coleman JM, Sermaer M, et al. *Early and intermediate-term outcomes of pregnancy with congenital aortic stenosis*. *Am J Cardiol* 2003; Gelson E, Johnson M. *Pregnancy Outcomes: Effect of Maternal Heart Disease: Effect of Heart Disease on Pregnancy Outcomes*. Expert Review of Obstetrics & Gynecology. 2010; Yap SC, Drenthen W, Pieper PG, et al.; ZAHARA investigators. *Risk of complications during pregnancy in women with congenital aortic stenosis*. *Int J Cardiol* 2008; Kuppuswamy S, Balla S. *Cardiac diseases in pregnancy*. 2nd Edition 2011; Regitz-Zagrosek V, Lundqvist CB, Borghi C, et al. *ESC Guidelines on the management of cardiovascular diseases during pregnancy*. The Task Force on the Management of Cardiovascular Diseases during

Pregnancy of the European Society of Cardiology (ESC) (European Heart Journal 2011) [1,6–18].

Recent European and American guidelines on the management of pregnant women with cardiac diseases [1, 19] contain important practical information on how to treat patients with cardiovascular pathology during pregnancy, labor, and postpartum.

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# Cardiovascular diseases in pregnancy: Perspective of the Centre for Rare Cardiovascular Diseases

## Cardiovascular diseases in pregnancy as rare diseases

Agata Leśniak-Sobelga, Piotr Podolec

The management of pregnant women in the Centre for Rare Cardiovascular Diseases (CRCD) is provided mainly by an outpatient clinic and the Department of Cardiac and Vascular Diseases. Precounseling of women with underlying cardiovascular diseases includes an adequate assessment of disease severity by clinical evaluation, laboratory tests, electrocardiogram (ECG), echocardiography, spirometry, and computed tomography/magnetic resonance imaging.

Potential risks in pregnancy for the mother and fetus should be discussed and use of teratogenic drugs should potentially be discontinued.

The risk of congenital heart disease in the offspring should also be discussed because it is significantly higher compared with that in the offspring of parents without congenital heart disease (about 1%). The risk depends on whether only the mother or the father or both of them have hereditary cardiac defects, and is higher if the mother is affected. The recurrence risk varies between 3% and 50%, depending on the type of maternal heart disease [1,2]. Fetal echocardiography is performed between the 18th and 20th week of pregnancy.

The follow-up visits are scheduled according to the WHO class indications: from 1 visit during pregnancy in WHO class I to 1 visit per week in WHO class IV, and after delivery. Clinical evaluation, ECG, echocardiography, and 24-hour Holter monitoring are performed once in each trimester of pregnancy; in some indications, they are performed more often. Because echocardiography is not associated with radiation exposure and is easy to perform, it might be repeated as often as needed. Holter monitoring is performed in patients with previously documented paroxysmal or persistent arrhythmia or those with the symptoms of palpitations. Serial monitoring of brain natriuretic peptide levels is essential in the management of patients with heart failure. Other diagnostic procedures such as transesophageal echocardiography, radiography,

computed tomography, and magnetic resonance imaging are justified only in life-threatening clinical situations, for example, when pulmonary embolism is suspected.

The patients in our center are managed by a multidisciplinary team including a cardiologist, cardiac surgeon, gynecologist, obstetrician, neonatologist, and anesthesiologist. We closely cooperate with the Clinic of Coagulation Disorders. The optimal timing, mode (vaginally or cesarean section), and the exact choice of the place of delivery are discussed at the end of the second trimester. According to the recent guidelines, the preferred mode of delivery is vaginal, with an individualized delivery plan: spontaneous or induced, method of induction, analgesia/regional anesthesia, and hemodynamic monitoring required. A cesarean section is generally performed in cases with obstetric indications but should also be considered in women taking oral anticoagulants when the labor is preterm, for women with Marfan syndrome and an aortic diameter exceeding 45 mm, women with acute or chronic aortic dissection, and those with acute refractory heart failure. In all high-risk cases, delivery should take place in a tertiary center with the involvement of a multidisciplinary specialist team [1].

In the RCD classification, we attempted to systematize rare cardiovascular diseases into 8 groups and to several subgroups.

To facilitate the understanding of the classification of cardiovascular diseases in pregnancy, we used the same classification of rare cardiovascular diseases for groups I–VI and VIII, the same subgroups, and codes. An example of the code of idiopathic pulmonary hypertension in a pregnant woman is as follows: VII–II1A.1. It should be read as: group VII – rare cardiovascular diseases in pregnancy, I – rare diseases of the pulmonary circulation, 1 – pulmonary hypertension, A – low-prevalence pulmonary hypertension, 1 – idiopathic pulmonary hypertension.

During the last 2 years since the foundation of the CRCD, we have managed 142 pregnant women (they are listed in Part 2 of the book). The current section of the book contains the reports of the most rare and interesting clinical cases, for example, Ehlers–Danlos syndrome and its complications, peripartum cardiomyopathy, fibroma.

A number of preexisting cardiac conditions carry an extremely high maternal risk. For example, pulmonary arterial hypertension is associated with high mortality of the mother and child; therefore, pregnancy is strongly contraindicated in these patients.

The management strategy of the patients with complex forms of congenital heart diseases during pregnancy, delivery, and the postpartum period is presented.

Cardiomyopathies during pregnancy are rare but are a serious cause of cardiovascular complications. Hypertrophic cardiomyopathy with outflow obstruction increases the risk of clinical deterioration. Peripartum cardiomyopathy is a rare disorder ranging from 1/1485 to 1/15 000 live births, and is the most common cause of left ventricular function and clinical status deterioration [3].

The optional treatment of severe life-threatening arrhythmias in pregnancy is discussed below.

In conclusion, although the classification that we propose (presented in Part 1 of the book) may be a helpful reference, we should remember that the management of pregnant women with rare cardiovascular diseases requires a highly individualized approach.

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# Cardiovascular diseases in pregnancy: Clinical examples

## Postpartum aortic dissection: a manifestation of vascular Ehlers–Danlos syndrome? (RCD code: VII-I-2A.2)

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### Background

Aneurysmal disease of the aortic and large-medium vessels can be driven by the mutation in genes encoding the building material of the vascular wall [1]. Thus, the Marfan syndrome, which is most common among these rare diseases, develops as a result of gene mutation that is responsible for fibrillin 1 synthesis; vascular Ehlers–Danlos syndrome results from collagen III mutation; and Loeys–Dietz syndrome is caused by the mutation of the transforming growth factor  $\beta$  receptor genes 1 and 2. Familial thoracic aortic aneurysm and dissection syndrome is associated with the mutations in the genes of myosin heavy chain (*MYH11*) and *ACTA2* [1,2,3].

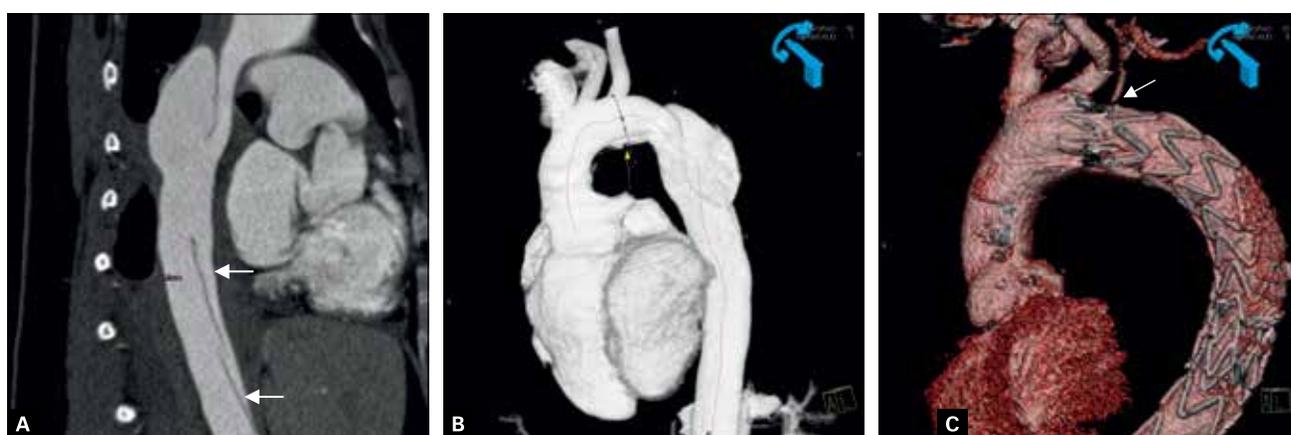
These mutations not only cause aneurysmal syndromes but also affect the organs that contain fibrillin, collagen, or myosin, such as the eye, intestine, heart, uterus, skin, spleen, joints, and numerous others.

Subjects affected by these diseases often present with a variety of multiorgan dysfunction and disorders since childhood. They are managed by specialists in different medical fields. However, sudden premature dissection or rupture of the aorta, which is a life-threatening clinical manifestation, is a turning point for the diagnosis [2,3].

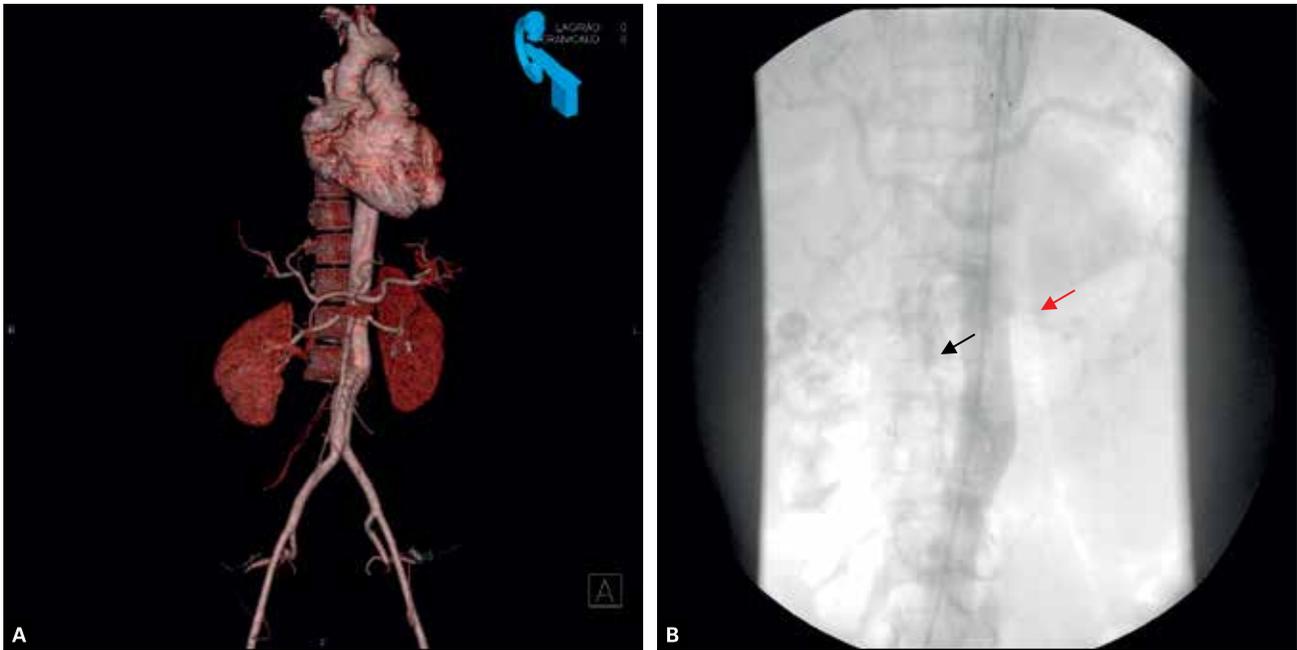
### Case presentation

In December 2008, a 28-year-old woman was admitted to the cardiac emergency unit with chest pain and syncope and with symptoms of developing cardiogenic shock. It was on the 10th day postpartum after previous uneventful delivery of a healthy girl.

On admission, she presented with sweat, pallor, and clumsy skin and she was hypotonic (blood pressure of 80/40 mm Hg). Laboratory test results were within the normal ranges; obstetric and hemorrhagic issues were excluded. Urgent computed tomographic angiography (CTA) revealed acute dissection of the thoracic aorta (fig. 1A), which was successfully treated with endovascular implantation of stent-graft prosthesis (fig. 1C).



**Fig. 1.** Computed tomography angiography. Images show the primary event in December 2008. **A.** Long spiral dissection of the thoracic descending aorta (white arrows). **B.** The dissection is localized primarily in the normal-sized aorta. **C.** The optimal result of stent-graft implantation in the proximal part of the descending aorta. No leaks can be seen. The left subclavian artery ostium is jailed by the stent graft (white arrow)



**Fig. 2. A.** Computed tomography angiography. The descending thoracic and abdominal aorta. Note the dissection of the normal-sized abdominal aorta extending towards the right common iliac artery. **B.** Classic aortography of the abdominal aorta during transcatheter treatment of organ ischemia caused by abdominal aortic dissection. Black arrow indicates the stent in the superior mesenteric artery. The left renal artery (red arrow) is not contrasted due to dissection on unselective angiography

During the hospital stay, progressive dissection (fig. 2) was observed from the distal portion of the stent graft to the right common iliac artery, which was managed by the second stent-graft implantation in the suprarenal part of the descending aorta, followed by the palliative fenestration procedure and stent implantation to the superior mesenteric and the left renal arteries (to reduce organ ischemia). The patient's clinical status gradually improved, and she was discharged after 10 days. Routine follow-up visits with occasional CTA of the thoracic and abdominal aorta were scheduled.

The clinical course was uneventful until November 2011, when the Doppler ultrasonography of the extracranial arteries revealed an aneurysm of the right subclavian artery, which was not present on former examinations in 2010. The finding was confirmed by CTA and followed for 12 months with repeated CTA examinations. The aneurysm grew in diameter from 17 mm in November 2011 to 24 mm in October 2012 (fig. 3A). The patient was scheduled for surgical repair with prosthesis implantation, followed by the implantation of the right vertebral artery to the right subclavian prosthesis to prevent ischemic stroke in the posterior circulation (the patient already has the left subclavian artery closed with proximal stent graft resulting in the subclavian steal syndrome).

Furthermore, on repeated CTA of the stent grafts and aorta, the enlargement of the abdominal aorta was observed with a maximum diameter of 45 mm (28 mm in 2008). The management strategy was changed because the abdominal aortic aneurysm was an urgent indication for repair (fig. 3C).

Meanwhile, the patient was assessed for genetic mutations because of recurrent spontaneous arterial

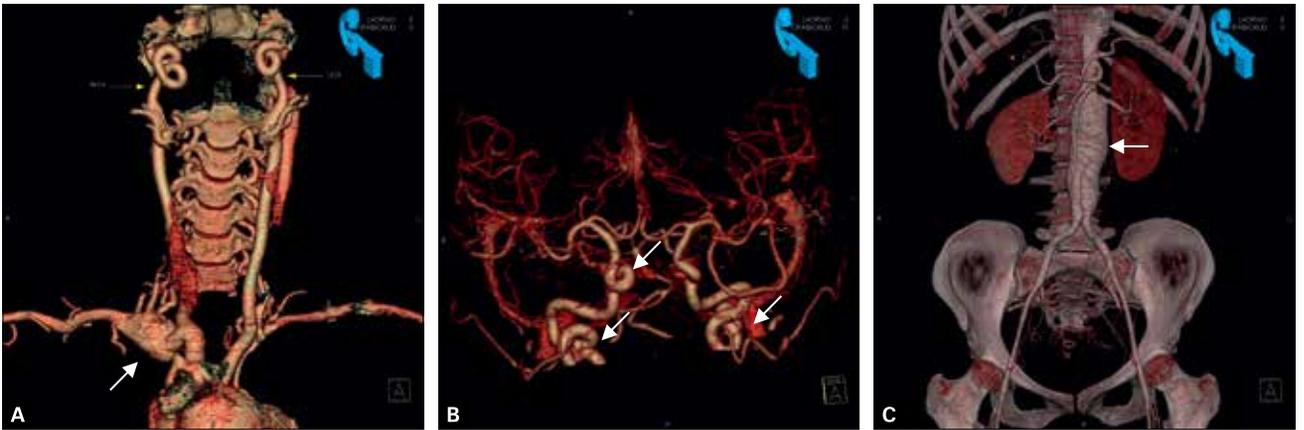
dissections and progressive dilatation of the large and middle sized arteries. Marfan syndrome was excluded. However, numerous symptoms that were revealed during detailed examination led to a suspicion of vascular Ehlers–Danlos syndrome (type IV).

There were numerous findings consistent with Ehlers–Danlos syndrome according to the Villefranche classification. Among the major criteria, the patient had thin and translucent skin, former arterial rupture, and extensive bruising since childhood [4]. She also scored 8 points for the minor criteria (laser coagulation of the retina of the right eye owing to bilateral retinal degeneration in January 2012; deformities of the spine and advanced S-curve scoliosis, overflexibility and hypermobility of the joints, very loose joints, abnormal wound healing, widened atrophic scars, and translucent skin) [4].

Considering the patient's clinical history, genetic counseling was performed with the assessment of collagen mutation (COL3A1). However, the result was negative. Thus, the more rare diseases were considered, including Loeys–Dietz and thoracic familial aortic aneurysm and dissection syndromes [2,3,5].

## Discussion

In adults, symptoms of vascular Ehlers–Danlos syndrome are present mainly in the cardiovascular and respiratory systems and digestive organs, where the gene is expressed, and are often observed during pregnancy and childbirth [2,3,6,7]. In the present case, thoracic aorta dissection and aneurysm syndrome was identified 10 days after uneventful delivery. The symptoms



**Fig. 3.** Computed tomography angiography. **A.** A new right subclavian artery aneurysm of 24 mm in diameter (white arrow) diagnosed in October 2012. Small yellow arrows indicate arterial loops caused by the elongation of both internal carotid arteries. **B.** Arrows indicate arterial loops caused by the elongation of both intracranial portions of the internal carotid arteries. **C.** The most recent finding (March 2013) – a new descending aorta aneurysm (45 mm in diameter)

from the cardiovascular system are reported in 77% of the patients with vascular Ehlers–Danlos syndrome.

Approximately 98% of the cases with vascular Ehlers–Danlos syndrome are caused by a mutation in the *COL3A1* gene. *COL3A1* consists of 52 exons and is expressed in the arteries, intestines, lungs, and uterus [8,9]. Mutations of this gene cause aortic aneurysms, aortic dissection and rupture, gastrointestinal hemorrhage and perforation, uterine rupture, pneumothorax, hemothorax, and, eventually, sudden death. In most cases, the synthesis of the normal type III collagen is impossible because glycine present in the *COL3A1* gene is substituted for other amino acids because of the mutation.

During follow-up visits, we faced the problem of new aneurysmal formations in new arterial territories, namely, in the right subclavian artery and the abdominal aorta. We believe that the operation is necessary to prevent further rupture and/or dissection, especially that vascular Ehlers–Danlos syndrome had not been confirmed in the genetic tests.

Interestingly, celiprolol, a  $\beta_1$ -receptor antagonist, has been recently proposed for the prevention of arterial complications [10]. In a report on 53 patients with vascular Ehlers–Danlos randomized to celiprolol (25 patients) or placebo (28 patients), the incidence of arterial ruptures caused by aortic dissection was significantly lower (20%) in the celiprolol group compared with 50% in the placebo group.

Because our patient has a 5-year-old daughter, genetic counseling and psychological support are of crucial importance. We conducted a genetic test for vascular Ehlers–Danlos syndrome also for this reason. In the present patient, no mutation in the *COL3A1* gene was identified; however, this does not entirely exclude the clinical diagnosis because other rare mutations, which were not tested in this sample, could be present.

## Conclusion

Our case report shows the complexity of the problems encountered in patients with multisystemic disorders and complications, which finally presented as an acute life-threatening manifestation from the vascular system. We believe that our data will facilitate the diagnosis of patients with vascular Ehlers–Danlos or Loeys–Dietz syndrome in the future and will help look at those patients in a more broad-based way.

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## Pulmonary hypertension in a pregnant woman (RCD code: VII-II-1A)

Magdalena Kaźnica-Wiatr, Piotr Podolec

### Background

Pregnancy in a woman with pulmonary arterial hypertension (PAH) is reported to be associated with high mortality both for the mother and child. The highest death rates are observed in the perinatal and postnatal periods. Therefore, it has recently been suggested that pregnancy is absolutely contraindicated in patients with PAH [1].

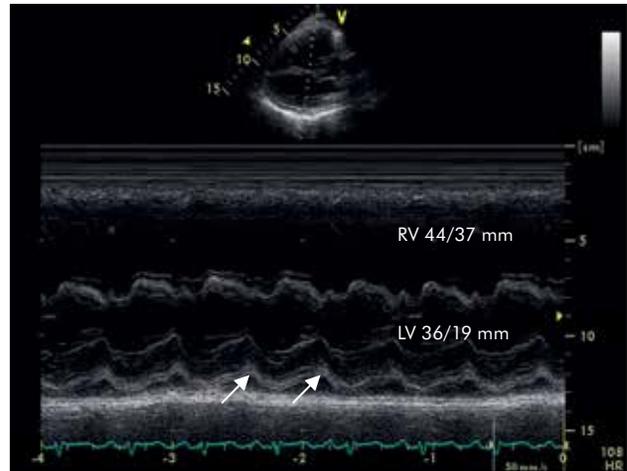
### Case presentation

A 32-year-old woman in the 24th week of her second pregnancy was referred to the Department of Cardiac and Vascular Diseases at the John Paul II Hospital in Krakow for cardiac consultation because of increasing dyspnea.

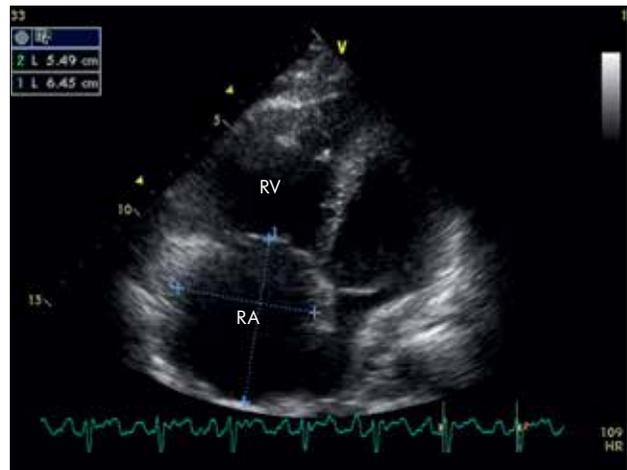
The patient's medical history included shortness of breath, reduced exercise capacity, leg edema, and palpitations escalating since the 22nd week of gestation. She had not been treated for any chronic disease or received specialist cardiac care before. Her first pregnancy was 12 years earlier; it was without complications and ended in a spontaneous labor in the 40th week of gestation.

The patient was admitted to the hospital in severe condition with dyspnea at rest. Lung auscultation revealed vesicular sounds. On a physical examination, she had tachycardia (100/min) and low systemic blood pressure of 90/60 mm Hg. An electrocardiogram showed regular sinus rhythm (100/min), right-axis deviation, and incomplete right bundle branch block. Echocardiography revealed the enlargement of the right ventricle, small left cardiac cavities, and trace of fluid in the pericardium (fig. 1, 2). The vascular projection showed dilatation of the pulmonary trunk to 30 mm and moderate pulmonary regurgitation. The acceleration time of the pulmonary flow was reduced to 44 ms and typical systolic notch on Doppler waveform was observed (fig. 3). The area of the right atrium was 31 cm<sup>2</sup>. Tricuspid regurgitation was moderate and the right ventricular systolic pressure was estimated at 110 mm Hg (fig. 4). Laboratory tests did not reveal any significant deviations from the standard values; the D-Dimer level was normal. Verapamil at a dose of 120 mg/d was started and electrolyte supplementation was ordered since no PAH-specific drugs were available at that time in Poland.

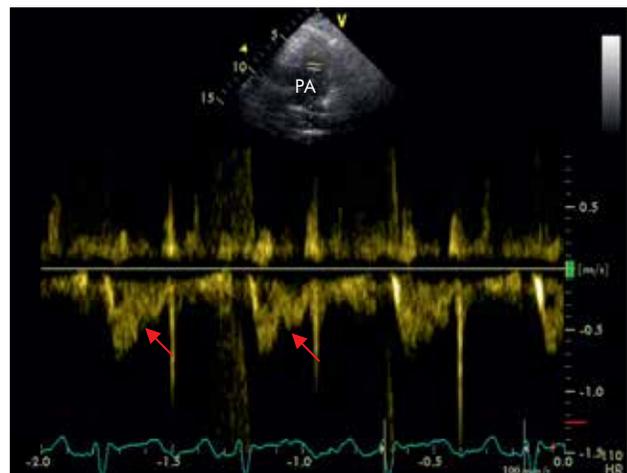
In the 32nd week of gestation the patient delivered prematurely in a spontaneous labor. After the delivery she was readmitted to our department owing to symptoms of severe right heart failure with massive



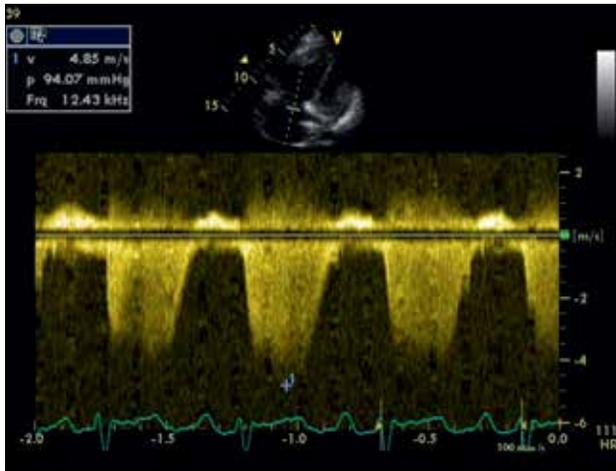
**Fig. 1.** Echocardiography. Parasternal long-axis view. M-mode visualization. Enlargement of the right ventricle (RV) 44/37 mm, small left ventricle (LV), pericardial effusion (arrow)



**Fig. 2.** Echocardiography. Four-chamber view. Enlargement of right ventricle (RV) and right atrium (RA). Small left heart cavities. RA: 65×55 mm, area 31 cm<sup>2</sup>



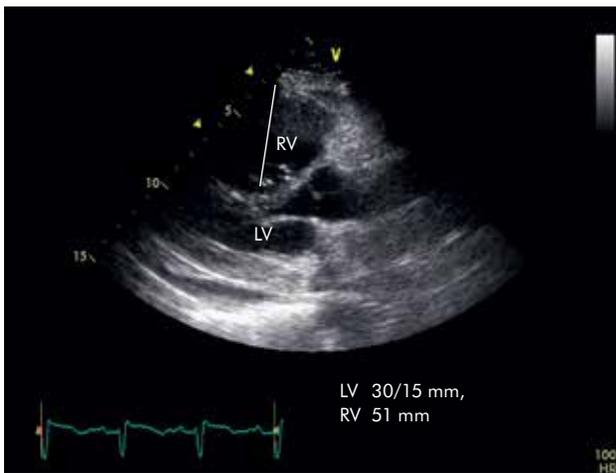
**Fig. 3.** Echocardiography. Shortening of the acceleration time to 44 ms, characteristic for pulmonary hypertension systolic notch (red arrows)



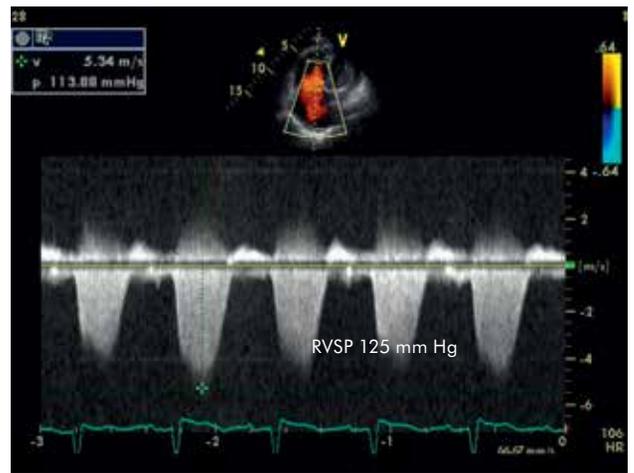
**Fig. 4.** Echocardiography. Measurement of tricuspid regurgitation wave velocity to estimate right ventricular systolic pressure



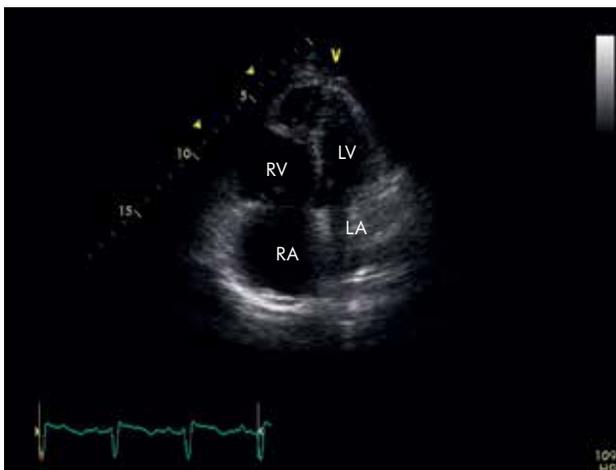
**Fig. 7.** Echocardiography. Four-chamber view. Severe tricuspid regurgitation to enlarged right atrium (RA)



**Fig. 5.** Echocardiography. Enlargement of the right ventricle (RV) 51 mm – red arrow. Small left heart cavities. RV – right ventricle, LV – left ventricle



**Fig. 8.** Echocardiography. Four-chamber view. Measurement of tricuspid regurgitation wave velocity to estimate right ventricular systolic pressure (RVSP)



**Fig. 6.** Echocardiography. Four-chamber view. Further enlargement of right ventricle and right atrium. Small left atrium and left ventricle. LV – left ventricle, RV – right ventricle, LA – left atrium, RA – right atrium

swelling of the lower limbs up to the thighs, massive dyspnea, and tachycardia. A physical examination confirmed respiratory and circulatory failure with a heart rate of about 105/min, systemic blood pressure of 80/50 mm Hg, and massive swelling of the lower limbs. Echocardiography revealed further dilatation of the right heart cavities (fig. 5, 6), severe tricuspid regurgitation (fig. 7), and the estimated right ventricular systolic pressure of 125 mm Hg (fig. 8). Dopamine, furosemide in a continuous intravenous infusion, spironolactone and oxygen were administered.

With diuretic treatment, a gradual but insignificant improvement in the patient's clinical condition was observed. On the 26th day after the delivery, the patient reported a deterioration of her general physical and mental state and increased dyspnea. A decrease in the systemic blood pressure was observed, after which further pressure drop and bradycardia were recorded. Asystolic circulatory arrest occurred in the afternoon, and successive attempts to resuscitate the patient were unsuccessful.

## Discussion

### Pathophysiology of the circulatory system of pregnant patients with pulmonary arterial hypertension

Physiological changes in the circulatory system of pregnant women involve an increase of circulating blood volume (increased preload), a decrease of vascular resistance (decreased afterload), and an increased heart rate. These changes result in increased cardiac output [2].

Circulating blood volume increases from the 6th week of pregnancy onwards, peaking around the 32nd week; no further significant growth is observed until the delivery. The volume increases between 45% and 50% compared with the prepregnancy period. The central venous pressure does not rise during pregnancy, unlike the end-diastolic dimensions of the cardiac cavities.

The heart rate increases throughout pregnancy; the largest increase is observed during the second and third trimesters. The increase of an average heart rate in the third trimester is between 10 and 20 beats more than before pregnancy. Cardiac output increases physiologically to about 6 L/min. The largest increase is observed between 28 and 32 Hbd; towards the end of the pregnancy, the cardiac output is larger by 30% to 50% compared with the prepregnancy period.

An extreme challenge for a pregnant woman with PAH is the increased blood volume, increased heart rate, and fluid shifts after the delivery.

Normally, the pulmonary blood vessels dilate during gestation. As a consequence, physiologically increased blood volume does not significantly load the low-pressure pulmonary bed. In patients with PAH, a decrease in the diameter of the small pulmonary vessels, resulting from the remodeling of the vascular wall and impaired vascular relaxation, leads to right ventricular pressure overload and consequent right ventricular failure.

Apart from the right ventricular afterload, a decreased blood flow through the pulmonary bed leads to a decrease of the heart rate, hypotonia, and disturbed perfusion of other organs and, above all, of the fetus. A physiological decrease in vascular resistance is observed during gestation. For pregnant women with Eisenmenger's syndrome, the above condition results in an enhanced right-to-left shunt and increased hypoxemia, which causes secondary contraction of the vessels. Above that, hypercoagulability observed during gestation may contribute to clotting in the pulmonary bed, a further increase pulmonary pressure, and lung infarction.

For pregnant women with PAH, the delivery carries the greater risk. Tachycardia and hypovolemia make the already present hypotonia and right ventricular ischemia even more severe, which may lead to ventricular arrhythmias or right ventricular infarction and death. Metabolic acidosis that occurs during the second stage of labor enhances vascular contraction and increases vascular resistance.

### Epidemiology of pulmonary arterial hypertension in pregnant women

Data concerning the frequency and clinical course of gestation of patients with PAH are rather scarce and come from the few retrospective analyses. Two most important studies have been published by Weiss et al. in 1998 [3] and Bedard et al. in 2009 [4].

Weiss et al. [3] analysed 125 pregnant patients with PAH (beyond the 22nd week of pregnancy) published between 1978 and 1996. The etiology of PAH was as follows: Eisenmenger's syndrome in 73 patients, idiopathic PAH in 27 patients, and other in 25 patients. Maternal mortality was 36% among patients with Eisenmenger's syndrome, 30% among patients with idiopathic PAH, and 56% among those with other conditions leading to the development of PAH. Three deaths were recorded among patients in the prenatal period (in the group with Eisenmenger's syndrome), while other patients died within less than 35 days following the delivery. It was established that late diagnosis of pulmonary hypertension and too late hospitalization of the patients are independent risk factors for maternal mortality. The risk of death is higher among primiparas and is connected with the severity of pulmonary hypertension and operative delivery.

The results published by Bedard et al. [4] are much more optimistic. They analyzed all cases of pregnancies with PAH described in the years 1997–2007. During this period, there was a major breakthrough in the treatment of PAH associated with the introduction of PAH-specific therapies. Maternal mortality among patients with idiopathic PAH was 17%; among those with PAH related to a congenital heart disease it was 28%; and among patients with PAH of other etiologies – 33%. The majority of deaths occurred within the first month after delivery, while none was observed during gestation or labor. The deaths were mostly caused by treatment-resistant right ventricular failure and cardiogenic shock, ventricular arrhythmia, pulmonary embolism, cerebral embolisms, and dissection or rupture of the pulmonary artery. Death risk factors included general anesthesia and first gestation.

In the published studies, infant survival rate oscillated between 87% and 89%. It was established that neonatal mortality was not connected with the etiology of PAH. Of note, 59% to 85% of the deliveries were premature and, moreover, higher frequency of intrauterine fetal retardation was observed.

### Clinical symptoms and diagnosis of pulmonary hypertension during gestation

Usually deterioration during pregnancy is observed between 20 and 24 weeks of gestation [5]. The most frequent symptoms include fatigue, worsening of dyspnea, syncope and chest pain. Dyspnea, swollen lower extremities, and increased body weight may delay the de novo diagnosis of PAH, as the above symptoms can be observed in physiological gestation [6].

Transthoracic echocardiography is the screening method to diagnose pulmonary hypertension but cardiac catheterization still remains the gold standard in PAH diagnosis; it is required to assess the severity

of the disease and to decide about further procedure, whether to modify the pharmacological treatment and whether to terminate pregnancy.

## Medical therapy in pregnancy with pulmonary arterial hypertension

### Conventional treatment

Considering the high mortality rate and the progression of the disease during gestation, treatment must be introduced at an early stage even despite insufficient scientific evidence.

Patients are advised to reduce physical activity, and bed rest in a lateral position is recommended to facilitate decompression of the inferior vena cava and the blood flow to the heart. Diuretics must be avoided during gestation but if the patient develops right ventricular failure, they must be administered to decrease overload; furosemide and torasemide are loop diuretics of choice. Patients with hypoxemia are subjected to oxygen therapy to block the progress of vasoconstriction and further increase of pulmonary vascular resistance.

Anticoagulation is recommended for pregnant patients with idiopathic PAH to reduce in situ thrombosis and thromboembolism.

### Pulmonary arterial hypertension-specific therapy in pregnancy

Calcium channel blockers (high doses) are recommended only for patients with positive results of the acute vasoreactivity testing [7]. Diltiazem and nifedipine are recommended during gestation, although it has been reported that diltiazem applied during the first trimester has a negative effects on the fetus.

There have been cases of the intravenous epoprostenol use during gestation described in the literature. The treatment was effective for the majority of patients, and the fetuses did not develop complications. The effectiveness of treatment is determined by early introduction of the prostanoid therapy [8].

In some centers, another prostacyclin analogue, iloprost, was administered during the second and the third trimesters [9]. It did not cause any inborn defects of the fetuses and there was no postpartum maternal or neonatal mortality.

A positive effect of sildenafil on pregnant patients with PAH has also been reported without any adverse fetal outcomes [10].

Endothelin receptor antagonists have a teratogenic effect and are contraindicated during gestation [11]. Contraception is recommended during the treatment with any of the drug from this group.

The cases of inhaled nitrogen oxide administration during gestation and in the perinatal period have been described as well [12].

### Delivery

The timing and mode of delivery are still under debate [4,5]. Vaginal delivery is connected with less blood loss

and less severe hemodynamic changes, and it implies a lower risk of thromboembolic complications and infections. Analgesia and the shortening of the second stage of labor are particularly important during the delivery.

Cesarean section is advisable in the case of maternal hemodynamic deterioration or fetal distress, when urgent delivery is required. Considering the very high rate of premature deliveries, most of the pregnancies are ended through cesarean section (about 57.9%). The period between 32 and 34 weeks of gestation is considered to be the optimum time for planned delivery. Oxygenation, normovolemia, and normotension must be maintained throughout the anesthetization. General anesthesia has a depressive effect on cardiac contractility and causes an increase of pulmonary vascular resistance and pressure in the pulmonary artery during intubation. Patients subjected to general anesthesia died more frequently; hence, it is the recommended to apply epidural anesthesia. Some of the authors prefer combined spinal-epidural anesthesia.

### Postpartum period

The highest maternal mortality was observed within 30 days following the delivery [4,5]. Many patients were diagnosed with acute right ventricular failure in that period. During 72 hours following the delivery, patients should be monitored in an intensive care unit. Hypotonia and hypoxia may suggest the worsening of the right ventricular failure. If the patient's condition deteriorates, inhaled nitric oxide, epoprostenol, and iloprost should be administered. Anticoagulants should be applied during the postpartum period; low-molecular-weight heparin must be reintroduced about 12 hours after the delivery, depending on the hemostasis.

### Management strategy

Considering the invariably high mortality rate among pregnant women with PAH despite the PAH-specific treatment, pregnancy is unconditionally contraindicated in this group of patients [13]. Women of child-bearing age must use effective contraceptives; the recommended methods include progesterone-based drugs (medroxyprogesterone acetate, etonogestrel), levonorgestrel-releasing intrauterine systems (Mirena), or the combination of these two methods. It must be remembered that bosentan reduces the effectiveness of oral contraceptives.

If a pregnancy occurs in a patient with PAH, termination should be considered. It should be carried out as early as possible, not later than before the 22nd week of gestation.

Patients who decide to continue their pregnancy should be put under medical care in a specialist center with a multidisciplinary approach. Their clinical condition should be assessed and echocardiography performed at least once every 4 weeks. The development of the fetus should be monitored on a regular basis.

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## Pregnant woman with Eisenmenger's syndrome (RCD code: VII-II-1A.4d)

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### Background

Pregnancy in women with pulmonary arterial hypertension (PAH) due to congenital heart disease (CHD-PAH) is associated with significant morbidity and mortality both in the mother and fetus. Data from the years 1978 to 1996 showed a maternal mortality rate of 36% [1]. Historically, neonatal survival was 86% [1]; however, if oxygen saturation was less than 85%, a live birth was unlikely (<12%) [2].

### Case presentation

A 25-year-old woman with PAH associated with an aortopulmonary window was admitted to the Centre for Rare Cardiovascular Disease at the John Paul II Hospital in June 2011 because of worsening dyspnea. She worked as a hairdresser. She had a partner but still lived with her parents. On admission, she was classified as class III according to the World Health Organization (WHO) functional classification.

The aortopulmonary window was diagnosed when she was 6-months old. At the age of 3 years, she underwent the first right heart catheterization, which revealed right-to-left flow through the aortopulmonary window.

Prior to admission she was not taking any drugs. A physical examination on admission revealed central cyanosis and clubbing without peripheral edema. Her vital signs were as follows: body temperature of 36.6°C, respiratory rate of 14 breaths/min, heart rate regular of 95 beats/min, blood pressure of 120/80 mm Hg, and oxygen saturation on room air of 88%. Heart auscultation revealed increased accentuation of the second heart sound. Breath sounds were normal. The liver was not enlarged.

Chest radiography revealed thoracic scoliosis and an electrocardiogram showed regular sinus rhythm of 90 beats/min with a high R in lead V<sub>1</sub> (10 mm). The results of pulmonary function tests were normal. A lung ventilation/perfusion scan showed no segmental perfusion defects. Angiographic computed tomography did not reveal signs of pulmonary thromboembolism. In laboratory tests, the N-terminal pro-B-type natriuretic peptide (NT-proBNP) level was 93 pg/mL and the hemoglobin level was 16 g/dL. She walked a distance of 429 m in the 6-minute walking test (6MWT); arterial oxygen saturation decreased from 90% to 79% at the end of the test.

Echocardiography showed normal left heart dimensions and valves, left ventricular ejection fraction of 70%, right ventricular hypertrophy, and benign tricuspid valve regurgitation with estimated right ventricular systolic pressure of 110 mm Hg.

In cardiac catheterization, systolic, diastolic, and mean pulmonary artery pressures were 96, 42, and 67 mm Hg, respectively; right atrial pressure was 5 mm Hg, cardiac output was 2.89 L/min, cardiac index was 2.26 L/min/m<sup>2</sup>, and pulmonary vascular resistance was 1816 (dyne × s × cm<sup>-5</sup>). Additionally, there was a decrease in oxygen saturation of 10% between the ascending (98%) and descending aortas (88%). The patient received bosentan at a standard dose.

On routine follow-up in November 2011, the patient was still in WHO class III. In the 6MWT, she walked a distance of 429 m with desaturation from 85% to 70% at the end of the test. During the hospital stay, she experienced the first pulmonary hemorrhage. In bronchoscopy, blood flow to right segmental bronchi 1 and 3 was revealed. The results of the bronchopulmonary lavage were as follows: cultures for bacteria and fungi – negative, cytology – normal, and the test for *Pneumocystis jiroveci* – negative. Owing to low resting oxygen saturation, the patient received home oxygen therapy.

During a follow-up visit in February 2012, the patient reported to have been pregnant for 8 weeks. She stopped bosentan therapy about 7 weeks before the visit because she suspected to be pregnant. She suffered from more severe dyspnea. In the 6MWT, she walked a distance of 369 m with desaturation from 72% at rest to 62% at the end of the test. The NT-proBNP level was 200 pg/mL and the hemoglobin level was 12.8 g/dL. She was urgently admitted to the hospital. Bosentan was replaced with sildenafil. The patient, her mother, and her partner were informed about the high risk of pregnancy to the mother and the child. However, they refused to stop pregnancy, and they signed a written statement.

During hospital stay, the patient developed the symptoms of stroke. Urgent diffusion magnetic resonance imaging of the brain revealed the area of acute ischemic stroke. She was transported to a stroke unit. Despite the early phase of stroke, thrombolytic therapy was contraindicated because of severe neurological condition. She received 25 points on the National Institute of Health Stroke Scale. The symptoms of stroke resolved during the next 48 hours. Based on an ultrasound examination, deep vein thrombosis was excluded. Acetylsalicylic acid (75 mg) was introduced as secondary prevention of stroke, and the patient was sent back to the cardiac ward. A gynecological examination was normal and ultrasonography revealed normal fetal growth. The case of the patient was consulted by a local multidisciplinary team, including a cardiologist and neurologist, as well as by international experts, including Professor Nazzareno Galiè (Bologna, Italy), Professor Uri Elkayam (Los Angeles, United States), and Professor Adam Torbicki (Otwock, Poland).

Further management plan included:

- hospitalization of the patient in the department of high-risk and pathological pregnancy from the 26th week of gestation

- switch from aspirin to low-molecular-weight heparin with anti-Xa monitoring in the third trimester of pregnancy to prevent premature closure of patent ductus arteriosus in the fetus
- continuation of sildenafil
- treatment with intravenous epoprostenol in case of clinical deterioration
- use of nitric oxide in case of a decrease in arterial oxygen saturation during delivery, combined with milrinone or dobutamine in case of hemodynamic compromise
- slow withdrawal of epoprostenol after delivery with simultaneous introduction of oral therapy of PAH
- supportive management with diuretics during pregnancy, if needed, with higher doses expected in the postpartum period
- digoxin
- iron supplementation for anemia
- embolization of the bronchial arteries after the first trimester in case of recurrent hemoptysis
- planned vaginal delivery in the 34th week of gestation.

The patient was discharged from the hospital 3 weeks after stroke in a relatively good clinical condition (WHO class II). She was prescribed the following drugs: sildenafil, iron supplementation, oxygen, aspirin (75 mg/d), and folic acid. In the 26th week of gestation, she was admitted to the ward, as previously scheduled. Aspirin was switched to enoxaparin at a dose adjusted to the level of anti-Xa activity. The delivery started spontaneously in the 33rd week of gestation and was terminated by a cesarean section with epidural anesthesia. The child was alive (5/6 points in the Apgar scale; weight 1050 g). After delivery, the mother was referred to the intensive care unit for infusion of milrinone owing to low blood pressure. The infusion dose was gradually reduced and stopped after 5 days. She did not require mechanical ventilation and her pressure was maintained at about 110/80 mm Hg. She was then treated in the cardiac ward for the next 4 weeks. Lactation was suppressed pharmacologically and bosentan was added to sildenafil. The patient was discharged from the hospital in stable condition (WHO class II). Currently, after a year from the delivery, both the mother and child are in good condition.

## Discussion

### Changes in the cardiovascular system during pregnancy in patients with Eisenmenger's syndrome

In normal pregnancy, the increase in blood volume is accompanied by a reduction in systemic and pulmonary vascular resistance to maintain the systemic and pulmonary artery pressure within the normal limits [3]. The total blood volume rises above the prepregnant level by 10%, 30%, and 45% over the first, second, and third trimester, respectively [4]. During and immediately after the delivery, the uterine contractions and aortocaval decompression lead to an additional

increase in the blood volume of up to 1.5 L. In patients with pulmonary hypertension, the increased blood volume in the presence of the reduced total area of the pulmonary vasculature and reduced ability of the pulmonary arteries to dilate results in excessive afterload in the right ventricle and ultimately right ventricular failure [5]. Additionally, in mothers with Eisenmenger's syndrome, a decrease in systemic vascular resistance may increase the right-to-left shunt, which reduces the pulmonary blood flow and worsens hypoxemia [6]. Pulmonary hemorrhage and paradoxical embolism pose an additional risk.

During the past decades, novel advanced therapies have been developed and the management of high-risk pregnancies has improved. In a recent systematic review of the publications from 1997 to 2007, the maternal and fetal/neonatal mortality in CHD-PAH was estimated at 28% and 7%, respectively [7]. A premature delivery occurred in 86% of the women and intrauterine growth retardation was reported in 24% of the newborns. All maternal deaths occurred after delivery (median time postpartum, 6 days), with the majority of cases due to severe right heart failure, followed by pulmonary thromboembolism, sudden cardiac death, pulmonary hypertension crisis, or bacterial endocarditis. A half of the women received advanced PAH therapy and only about 30% received antithrombotic treatment. The main risk factors for unfavorable outcome was general anesthesia as compared with regional anesthesia (odds ratio [OR], 4.37; 95% confidence interval [CI], 1.28–16.5). Additionally, women in their first pregnancies were at a higher mortality risk compared with those with previous pregnancies (OR, 3.7; 95% CI, 1.15–12.5). In a systemic overview of reports published between 1978 and 1996 [1], the following indications for hospital admission were listed in patients with Eisenmenger's syndrome: worsening of dyspnea and cyanosis, hemoptysis, cerebrovascular incident, syncope, chest pain, atrial fibrillation, or premature uterine contractions. Of 73 women, 3 died during pregnancy, 33 delivered at term, 23 delivered between the 32nd and 36th gestation weeks, and 14 delivered before the 31st gestation week.

### Prevention of pregnancy

Any type of pulmonary hypertension belongs to class IV of the modified WHO classification of maternal cardiovascular risk. This means that pulmonary hypertension is associated with an extremely high risk of maternal mortality or severe morbidity and, therefore, pregnancy in pulmonary hypertension is contraindicated (Class I, Level of Evidence C) [8]. Currently, there is no consensus relating to the most appropriate method of birth control in patients with pulmonary hypertension. It is important to educate on and discuss the methods of birth control with the patient [9]. The contraceptive methods recommended by experts and their potential drawbacks are presented in Table 1. Usually, the use of at least two effective forms of birth control are recommended [10], especially in patients treated with bosentan, which may reduce the effectiveness of hormonal birth control. It

**Table 1. Methods of birth control in patients with pulmonary hypertension**

Type of contraception	Comment
Combined (estrogen and progesterone) oral contraceptive pills; EVRA®, skin patch; NuvaRing®, vaginal ring	Increased risk of arterious and venous thrombosis posed by the estrogen component. Contraindicated in patients with the right-to-left shunt owing to the risk of stroke
Standard progesterone-only pills	No additional thrombotic risk Less effective than combined; therefore, not advised in patients with Eisenmenger's syndrome where maximum effect is needed. Interaction with warfarin; strict monitoring of the international normalized ratio is advised Bosentan reduces the efficacy of this method; therefore, progesterone-only preparations should not be used in patients on bosentan.
Cerazette® (desogestrel, 75 µg)	A new progesterone-only pill with similar effectiveness to combined oral contraceptives. Can be used in patients with pulmonary hypertension. At increased doses, it can be used in patients taking bosentan
Mirena®, intrauterine system (progestagen – levonorgestrel)	Risk of infection during insertion. The insertion should be covered with antibiotics in patients with Eisenmenger's syndrome Risk of vasovagal reaction during insertion; rare (5%) but hazardous in pulmonary hypertension; therefore, generally contraindicated in patients with pulmonary hypertension but acceptable if no other methods are suitable and risk of pregnancy outweighs risk of insertion As effective as sterilization
Implanon®, subdermal implant (progestagen – etonogestrel)	As effective as sterilization. Safe for patients with pulmonary hypertension. Subdermal implant needs replacing every 3 years
Depo-Provera (progestagen – medroxyprogesterone)	Highly effective. Safe in patients with pulmonary hypertension. Deep intramuscular injection every 12 weeks; risk of hematoma in anticoagulated patients
Barrier methods (condoms, condoms with spermicidal foam)	Safer than other methods but less effective
Tubal ligation	Risk of operation and anesthesia
Levonelle®, emergency contraception (levonorgestrel)	Safe and effective if initiated within 72 hours of sexual exposure. In patients on bosentan, the dose should be increased by 50% to 100%

Adapted from: Thorne S, Nelson-Piercy C, MacGregor A, et al. Pregnancy and contraception in heart disease and pulmonary arterial hypertension. *J Fam Plann Reprod Health Care* 2006; 32(2): 75–81.

is our practice to refer every patient with pulmonary hypertension to a gynecologist with experience in the management of such patients. Our patient was advised against pregnancy and after discussing the possible methods of birth control, she declared to use condoms with spermicide. Unfortunately, the risk of pregnancy in this method, even in compliant users, is 3% per year.

### Pregnancy outcome

If pregnancy occurs in a patient with pulmonary hypertension, it is recommended to discuss with the patient early termination in the first trimester [10]. However, this procedure is associated with a significant risk [10].

In patients with Eisenmenger's syndrome, spontaneous abortion occurs in up to 40% of the cases, premature delivery in 50%, and term delivery only in 25% of the pregnancies [11,12].

The optimal mode of delivery is a matter of debate. Vaginal delivery is associated with smaller shifts in blood volume, fewer thrombotic and bleeding complications, and a lower risk of infection [13]. However, a recent review showed a decrease in the number of vaginal deliveries in the last decades [7]. Generally

planned elective delivery in a tertiary center conducted by a specialist multidisciplinary team is recommended [10]. A scheduled cesarean section has the advantage over an urgent delivery of occurring during the day and in stable hemodynamic conditions. If the maternal or fetal condition deteriorates, an early cesarean delivery should be planned [2,8].

If vaginal delivery is chosen, low-dose epidural analgesia is recommended because it has no significant deleterious hemodynamic effect by itself [14] and it considerably decreases the adverse hemodynamic effects of labor [15]. General anesthesia is associated with worse outcomes, which is explained by negative inotropic effects of volatile agents and also by increased pulmonary pressure due to positive pressure ventilation [7].

### Specific therapies for pulmonary arterial hypertension in pregnancy

Generally, no PAH-specific drugs are currently registered for use in pregnant women because they have not been tested in this population. However, several case reports described a beneficial effect of PAH-specific

**Table 2. Pregnancy categories according to the Food and Drug Administration**

Category	Description
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

drugs during pregnancy. Most authors reported positive outcomes with the use of epoprostenol [16-20]. Less data is available for nitric oxide [21], sildenafil [22,23], iloprost [24], and nebulized iloprost combined with epoprostenol [16,25]. A recent study has shown that 52% of pregnant women with CHD-PAH received PAH-specific therapy [7]. The Food and Drug Administration assigned the following risk categories to the currently used PAH-specific drugs:

- Revatio (sildenafil) – category B
- Adcirca (tadalafil) – category B
- Flolan (epoprostenol) – category B
- Remodulin (treprostinil) – category B
- Ventavis (iloprost) – category C
- Tracleer (bosentan) – category X
- Letairis (ambrisentan) – category X.

The definitions of the different pregnancy categories are summarized in Table 2.

## Management strategy

In pregnant women with Eisenmenger's syndrome, the risk of complications should be discussed and a termination of pregnancy should be recommended. If the patient decides to continue pregnancy, she should be treated in a specialized (preferably tertiary) unit. The use of PAH-specific drugs should be considered. Supportive treatment should be based on an individual clinical status. The delivery should be planned (not urgent). Regional anesthesia is preferred over general

anesthesia. If the maternal and fetal condition deteriorates, an early cesarean section should be scheduled.

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## Pregnancy in a patient with hypertrophic cardiomyopathy (RCD code: VII-III-2)

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### Background

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiovascular disease, occurring in approximately 0.2% of the general population, and the most common primary cardiomyopathy in pregnant women. In most women with HCM, pregnancy is usually well-tolerated; complications are rare and occur mainly in women symptomatic before pregnancy. Risk is increased in women with heart failure, significant outflow tract gradient, massive hypertrophy, and complex ventricular arrhythmia.

### Case presentation

We present a case of a 35-year-old woman with HCM diagnosed 9 years earlier after an episode of a syncope. Fifteen years earlier, the patient had vaginal delivery at term. Pregnancy, labor, and postpartum period were uneventful. A family history of HCM was negative. Before second pregnancy, the severity of HCM was evaluated. Echocardiography revealed asymmetrical cardiac hypertrophy mainly involving the anterior part of the interventricular septum reaching the apex of the left ventricle (LV) with no hemodynamically significant outflow tract gradient (fig. 1). Electrocardiogram revealed sinus bradycardia and signs of left ventricular hypertrophy with deep T-wave inversion in anterolateral leads (fig. 2). A 24-hour Holter electrocardiogram showed single ventricular ectopy (3 ventricular extra beats per day) and

supraventricular ectopy (2 supraventricular extra beats per day). The cardiopulmonary exercise test showed good exercise tolerance (12.2 METS) with appropriate blood pressure response during the test, with the peak  $\text{VO}_2$  reaching 27.7 mL/kg/min (85% of the predicted value). The patient was treated with  $\beta$ -blockers (25 mg of metoprolol twice daily).

An echocardiographic examination performed at 18 and 37 weeks of the second pregnancy revealed a significant increase in the thickness of the anterior part of the interventricular septum from the initial 27 mm to 30 mm and 46 mm, respectively (fig. 3).

Initially, normal thickness of the LV posterior wall did not change remarkably during pregnancy. Simultaneously, relative wall thickness (RWT) index increased from 1.0 at baseline to 1.11 at 18 and 1.41 at 37 weeks of pregnancy due to solid LV end-diastolic diameter. Despite preserved LV ejection fraction (70%–75%) before and during second pregnancy, a precise analysis of systolic function in Doppler myocardial imaging showed the worsening of regional and global function. At 37 weeks of pregnancy, mean mitral annular systolic velocities derived from four sites around the mitral annulus (interventricular septum, lateral, anterior and inferior wall) decreased from 13.25 cm/s to 10.25 cm/s and the Sa value derived from the interventricular septal part of the mitral annulus decreased from 12 cm/s to 9 cm/s. A profound worsening of regional myocardial deformation was observed especially in three segments (basal, medium, and apical) of the anterior part of the interventricular septum, which was most hypertrophied (fig. 3). A 24-hour Holter electrocardiogram performed at 20 weeks of pregnancy did not differ remarkably compared with the previous examination (29 ventricular extra beats per day). The patient remained asymptomatic throughout the rest of pregnancy. A healthy female infant, Apgar score of 8, was delivered in a planned cesarean section under general anesthesia at 40 weeks of pregnancy.

Echocardiographic examination was performed 2 months postpartum. A significant increase in the LV end-diastolic diameter from 39 mm to 45 mm and a decrease in interventricular septum thickness from 46 mm to 35 mm resulted in a decrease in the RWT index to 0.96. This parameter increased again 2 years postpartum when LV wall thickness and end-diastolic diameter

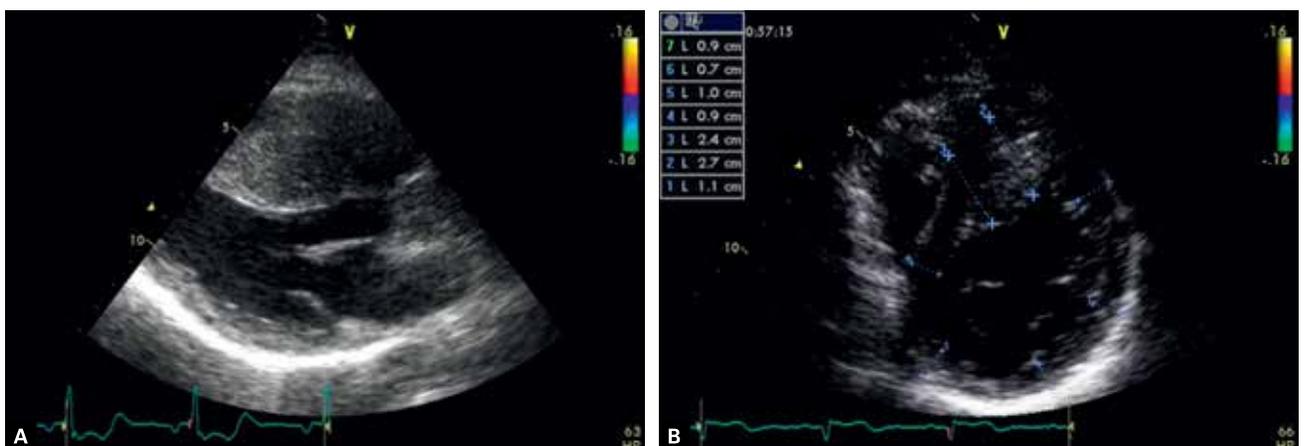
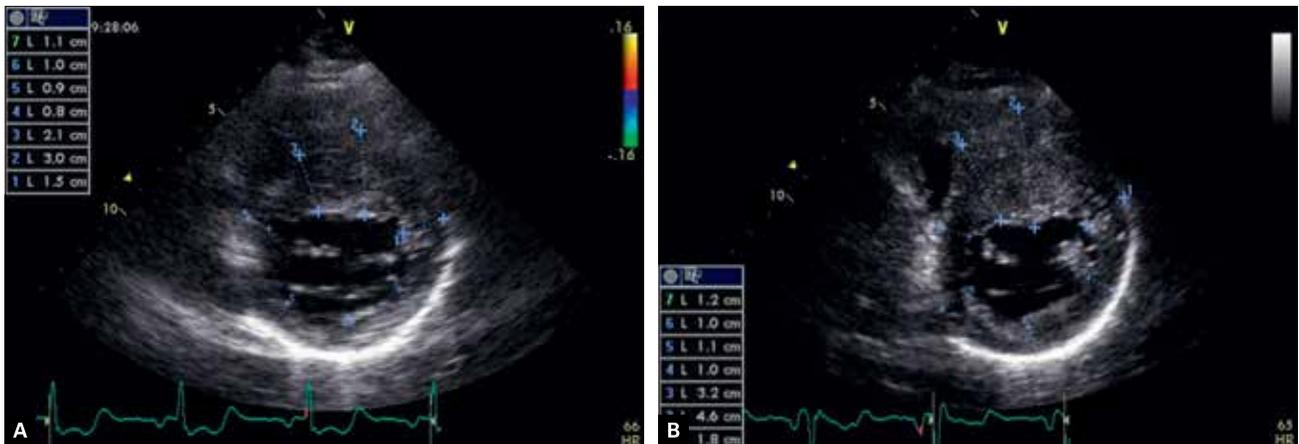
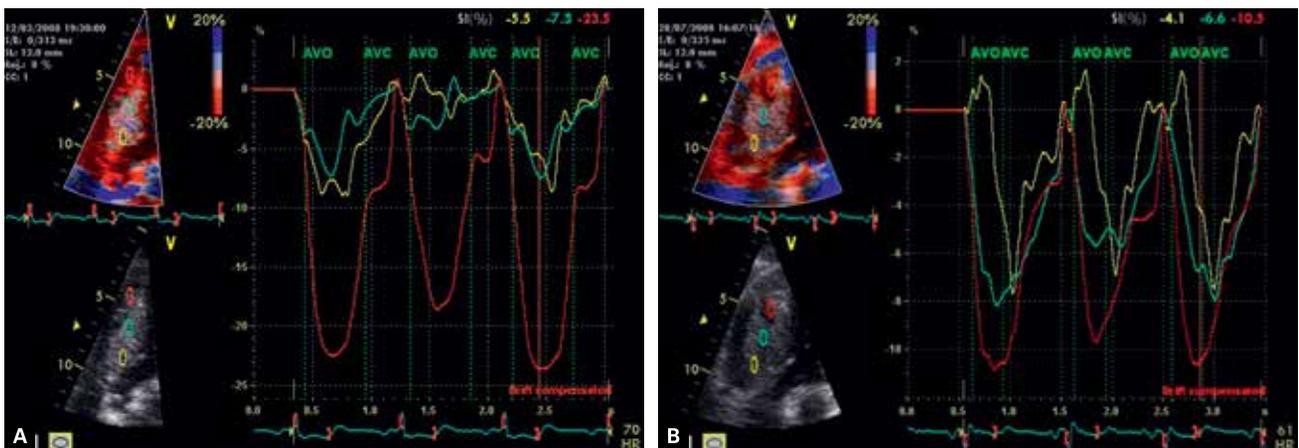


Fig. 1. Echocardiography. A. Parasternal long-axis view. B. Parasternal short-axis view at the level of the mitral valve



**Fig. 2.** Echocardiography. Parasternal short-axis view of the left ventricle at the level of the mitral valve at 18 (A) and 37 (B) weeks of pregnancy.



**Fig. 3.** Echocardiography. Myocardial deformation curves of 3 segments of the anterior part of the interventricular septum: basal (yellow color), medium (green color), and apical (red color) at 18 (A) and 37 (B) weeks of pregnancy

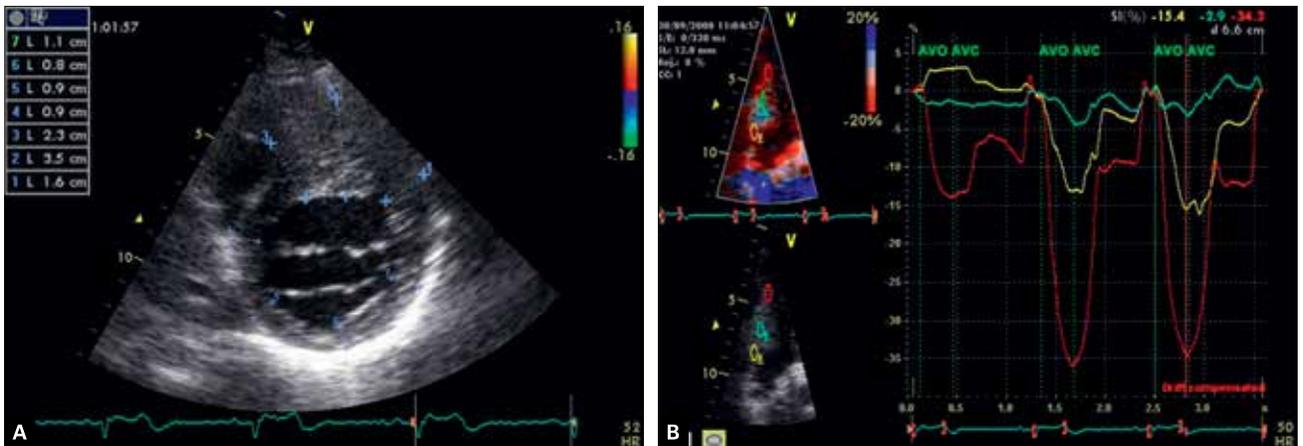
returned to baseline values. An echocardiogram performed 2 months postpartum showed a decrease in interventricular septum thickness accompanied by improvement of myocardial deformation of basal and especially apical segments of the intraventricular septum as well as an increase in mean LV myocardial deformation from (–10.2%) to (–17.5%) (fig. 4). This improvement appeared to be only temporary. A decrease in longitudinal myocardial deformation of all interventricular septum segments as well as a decrease in the mean strain of all the remaining 15 LV segments to (–7.7%) was observed in an echocardiographic examination 2 years postpartum (fig. 5). Despite this deterioration, the patient felt well and had no symptoms of heart failure. Holter monitoring showed only single ventricular extra beats (7 per day).

## Discussion

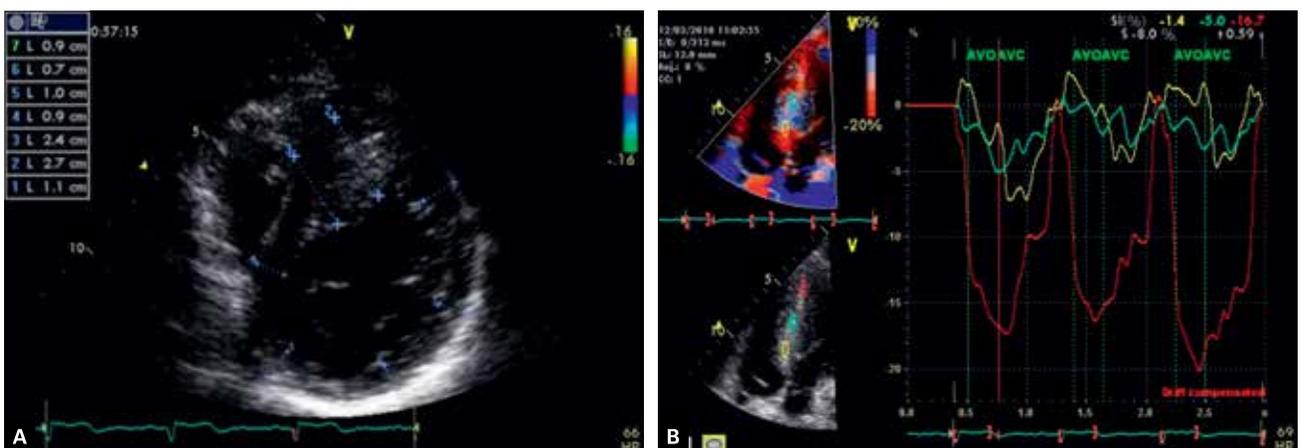
HCM is the most common genetic cardiovascular disease, occurring in approximately 0.2% of the general population, and the most common primary cardiomyopathy in pregnant women [1–3]. Mutations of genes encoding sarcomere protein components are inherited in an autosomal dominant way with incomplete penetration. It

means that the probability of mutation transfer, according to the Mendel's law, is almost 50%. However, the inheritance of the disease without phenotypic manifestation is possible. So far, mutations in 12 genes encoding the protein components of the sarcomere have been described, of which the mutations of  $\beta$ -myosin heavy chain, cardiac troponin T, myosin binding protein C constitute over 50% [1,3,4]. HCM demonstrates a remarkable diversity in disease clinical manifestations from asymptomatic patients to symptoms such as syncope, chest pain, arrhythmia, heart failure, or sudden cardiac death. A positive family history of HCM, decrease of blood pressure during exercise, extensive cardiac hypertrophy ( $\geq 3$ cm), and nonsustained ventricular tachycardia recorded in Holter monitoring are the main risk factors for sudden cardiac death [1,2,4,5].

Pregnancies in patients with HCM have been investigated in several retrospective and prospective studies, with relatively small study groups (from 9 to 40 women) [3]. Case reports and case series were also available but they focused mainly on the mode of delivery (vaginal labor or cesarean section), mode of analgesia (general, epidural, spinal), or pharmacological treatment [6–12]. All authors agree that pregnancy in women with HCM is usually well-tolerated; complications are rare and occur mainly in women symptomatic before pregnancy.



**Fig. 4.** Echocardiography. Parasternal short-axis view at the level of the mitral valve, myocardial deformation curves of 3 segments of the anterior part of the interventricular septum: basal (yellow color), medium (green color), and apical (red color) 2 months postpartum



**Fig. 5.** Echocardiography. Parasternal short-axis view at the level of the mitral valve; myocardial deformation curves of 3 segments of the anterior part of the interventricular septum: basal (yellow color), medium (green color), and apical (red color) 2 years postpartum

Risk is increased in women with heart failure, significant outflow tract gradient, massive hypertrophy, and complex ventricular arrhythmia [3,8,10,12,13].

The presented patient was almost asymptomatic (history of one episode of syncope without loss of consciousness 10 years earlier), hemodynamically stable, with no significant outflow tract gradient (8 mm Hg) during  $\beta$ -blocker treatment, with no significant ventricular arrhythmia in repeated 24-hour Holter monitoring. There were no complications during her first pregnancy. The second pregnancy, described in this report, was also uneventful.

During pregnancy, there are significant hemodynamic changes in the cardiovascular system. Gradual plasma volume expansion throughout pregnancy reaching a peak of 40% and elevated heart rate result in increased cardiac output. This high-output state is accompanied by vasodilatation and reduction of peripheral vascular resistance. These physiological adaptations to pregnancy lead to an increase in LV end-diastolic and left atrial diameters and decrease in the RWT index [14–16].

In the presented case, we observed increasing asymmetrical hypertrophy of the interventricular septum, mainly during the third trimester. Thickness of the anterior part of the intraventricular septum expanded

from 20 mm to 46 mm at 37 weeks of pregnancy with insignificant widening of the LV end-diastolic diameter (from 35 mm to 37 mm) and a remarkable increase in the left atrial diameter (from 26 mm to 36 mm). The RWT index should decrease but, paradoxically, it increased reaching an extremely high value (1.41) at 37 weeks of pregnancy. We did not find similar results in the available literature. Moreover, we did not find a precise analysis of the LV systolic function during pregnancy using Doppler myocardial imaging. Our analysis of myocardial deformation curves showed increasing regional and global deterioration of that function during the second and third trimester. In our opinion, the worsening of LV systolic function was an effect of significantly increased cardiac output putting a strain on an extremely hypertrophied myocardium, which was initially affected by myocardial disarray typical for HCM [1,4,5]. This is confirmed by the improvement of systolic function in the postpartum period.

Of note, abnormal myocardial deformation curves did not depend on myocardial hypertrophy. This observation, already described in several reports using tissue Doppler and magnetic resonance imaging, indicates extensive and heterogeneous character of myocardial structure in patients with HCM [17–22].

The mode of delivery is another important issue concerning patients with HCM. The majority of authors agree that pregnancy in this population of patients is mostly uneventful [3,10,12]. In low-risk patients, vaginal delivery with analgesia is recommended because it reduces labor-related stress and pain reaction. Spinal anesthesia and combined epidural analgesia are the most commonly used methods. Careful monitoring of blood pressure is extremely important because of a risk of systemic hypotension, especially in patients with a small LV diameter and outflow tract obstruction [9,11]. However, if hypotension occurs, careful intravenous fluid infusion and phenylephrine administration are the methods of choice. Catecholamines should be avoided because they can exacerbate outflow tract gradient and ventricular arrhythmia. Oxytocin, which induces uterus contractions, can be potentially hazardous and for that reason lower dosages (5 IU) in approximately 10-minute intravenous infusion are recommended. Administration of full oxytocin dose (15 IU) may result in hypotension, tachycardia, and even ventricular arrhythmia, which are potentially dangerous for patients with HCM [7,10,11,23].

A cesarean section, which is associated with more blood loss compared with vaginal delivery, should be applied in high-risk patients (heart failure, significant outflow tract gradient, extreme hypertrophy) or for obstetric indications [12]. In our patient, we decided to perform a cesarean section under general anesthesia because of extreme LV hypertrophy and low values of regional and global strain, indicating hidden systolic dysfunction of the LV. Labor was uneventful with normal blood pressure values and without arrhythmias. In line with the guidelines, the patient was given oxytocin intravenously in a reduced dose (5 IU) directly after delivery of the fetus to increase the contractility of the uterus.

### Pregnant woman with hypertrophic cardiomyopathy: management algorithm

1. Stratification for mother's risk before pregnancy (recommended) and/or during the first trimester. Precise stratification for sudden cardiac death (main risk factors).
2. Evaluation of familial inheritance and genetic counseling is recommended.
3. Multidisciplinary medical care throughout the pregnancy, labor, and postpartum period (cardiologist, obstetrician, anesthesiologist, neonatologist).
4. Schedule of follow-up visits according to mother and fetus risk (cardiologist, obstetrician).
5. Pharmacological therapy during pregnancy:  $\beta$ -blockers are recommended or verapamil if  $\beta$ -blockers contraindicated in women with at least intermediate LV outflow tract obstruction or LV wall thickness  $>15$  mm – IIaC [12].
6. Decision concerning the mode of delivery and mode of analgesia (cardiologist, anesthesiologist).
7. Anticoagulation in case of atrial fibrillation: low-molecular-weight heparin or vitamin K antagonists depending on the pregnancy period – IA [12].
8. Electrical cardioversion in case of persistent atrial fibrillation – IIaC [12].
9. Breastfeeding (cardiologist, obstetrician), allowed during therapy with  $\beta$ -blockers or verapamil.
10. Planning of medical care for the offspring (pediatric cardiologist).

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## Favorable course of peripartum cardiomyopathy (RCD code: VII-III-5C)

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### Background

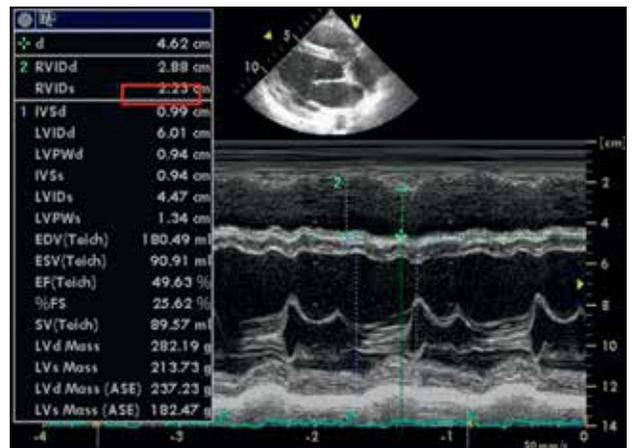
Peripartum cardiomyopathy (PPCM) has been variably defined over the years. The most recent definition, issued in 2010 by the Heart Failure Association of the European Society of Cardiology, states that it is an idiopathic cardiomyopathy, presenting with heart failure (HF) secondary to left ventricular (LV) systolic dysfunction at the end of pregnancy or in the early months after delivery. Importantly, there should be no other identifiable cause of HF. The main difference between the European and American perspectives is that the European experts no longer use the specific time frames of 1 month prior to and 5 months after delivery when PPCM can be diagnosed [1].

### Case description

Previously fit and well, a nulliparous 25-year-old Caucasian woman, gradually developed dyspnea on exertion and fatigue 2 months after successful vaginal twin delivery. The patient did not have any typical risk factors for cardiovascular diseases, her family history was unremarkable, and the whole pregnancy period was uneventful. Eventually, she was urgently admitted because of resting dyspnea and massive peripheral edemas. At presentation, she was clearly decompensated with a heart rate of 130 beats/min, arterial blood pressure of 90/60 mm Hg, oxygen saturation of 90% (on air), respiratory rate of 20 per minute; she was classified as New York Heart Association (NYHA) class IV. Physical examination revealed lung congestion (Killip class 2/3), massive lower-limb edema up to the thighs, raised jugular venous pressure, and possible ascites. On an electrocardiogram, she was in sinus tachycardia with right-axis deviation and with signs of left atrial enlargement. Echocardiography revealed dilatation of the LV (LV end-diastolic diameter, 71 mm), severe global contractility impairment with the ejection fraction of 8% calculated by the Simpson's method, with accompanying severe pulmonary and tricuspid regurgitation but without the features of pulmonary hypertension (right ventricular systolic pressure of 30 mm Hg and pulmonary acceleration time of 138 ms) (fig. 1–3). Laboratory test results showed slight anemia (hemoglobin levels, 13.3 g/dL; hematocrit, 38.8%), significantly increased levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP, 6910 pg/mL), and no



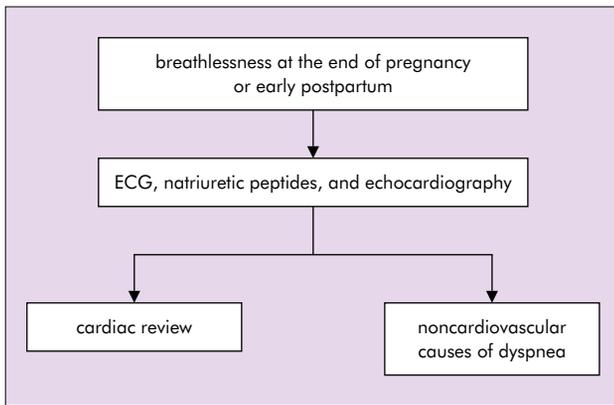
**Fig. 1.** Echocardiography. Apical four-chamber view shows marked dilatation of the left ventricle (LV); normal size right ventricle (RV) and both atria. LA – left atrium, RA – right atrium



**Fig. 2.** Echocardiography. Parasternal long-axis view shows marked dilatation of the left ventricle (LV); normal size right ventricle (RV)



**Fig. 3.** Echocardiography. Parasternal short-axis view shows marked dilatation of the left ventricle (LV); normal size right ventricle (RV) and both atria. LA – left atrium, RA – right atrium



**Fig. 4.** Simple diagnostic algorithm for peripartum cardiomyopathy, endorsed by the Working Group of the HF Association

signs of systemic infection (white blood count, 7.56; high-sensitive C-reactive protein, 1.4 mg/L; procalcitonin, 0.06 ng/mL). Because the patient's clinical status deteriorated rapidly, pharmacologic circulatory support with catecholamines (dopamine and dobutamine) and small doses of intravenous diuretics were started. After a few days, her hemodynamic status greatly improved and catecholamines were safely withdrawn. Subsequently, a low dose of prolactin inhibitor (bromocriptine) and  $\beta$ -blocker (carvedilol, 3.125 mg twice daily) were introduced. Unfortunately, the combination of a  $\beta$ -blocker and angiotensin-converting-enzyme inhibitor (ACEI) resulted in pronounced hypotension; therefore, we continued only with a  $\beta$ -blocker. After a week of progressive clinical improvement, echocardiography showed a significant increase in the LV ejection fraction (LVEF, about 20%), which was associated with a decrease in NT-proBNP levels (1833 pg/mL). After another week, the patient was able to walk a distance of 100 meters and climb one flight of stairs and was discharged home. At the follow-up visits 2 and 4 weeks later, we observed clinical and echocardiographic improvement. At present, she is in NYHA class II with significant reverse remodeling (LV end-diastolic diameter, 58 mm; LV end-systolic diameter, 48 mm). At present, she is no longer on bromocriptine and we could introduce an ACEI (ramipril, 2.5 mg twice daily).

## Discussion

### Epidemiology

The precise epidemiology of PPCM in the general population is unknown [2–4]. A few studies, performed in various geographic locations, particularly in the United States, Haiti, South Africa, and Nigeria, provide conflicting data. The incidence of PPCM is about 1:2500–4000 pregnancies in the United States, 1:1000 in South Africa, 1:300 in Haiti, and it is unprecedentedly high in Nigeria – 1:100. Unfortunately, there is lack of epidemiological studies from the European region.

The course of the disease is largely unpredictable with roughly two-thirds of the cases showing spontaneous

improvement, while the remaining one-third of the cases showing severe or even end-stage HF.

### Pathophysiology

The pathophysiology of PPCM is not fully understood and is probably multifactorial. Apart from hormonal imbalance, particularly in the prolactin cascade, other potential mechanisms may be implicated in the disease pathology, such as myocardial inflammation, abnormal immune response to fetal antigen, and hemodynamic factors. Moreover, familiar and geographical clustering of PPCM suggests that the genetic background and environmental factors may be significant contributors.

Although not completely understood, new data are emerging on the possible role of oxidative stress, nursing-hormone prolactin, and the prolactin-cleaving protease, cathepsin D, in the pathology of PPCM. In the late pregnancy and early postpartum, cellular oxidation is particularly high and activates cathepsin D in cardiomyocytes, which eventually transforms prolactin into angiostatic and proapoptotic subfragments. In an experimental mouse model of PPCM, the 16 kDa fragment of prolactin was responsible for various detrimental effects on the cardiovascular system, such as endothelial cell apoptosis, vasoconstriction, and impairment of cardiomyocytes function and metabolism. Although not definitively confirmed in humans, it seems that the damaging complex of oxidative stress–cathepsin D–16kDa prolactin can be broken by the suppression of prolactin production by dopamine  $D_2$  receptor agonist, bromocriptine, which favorably alters the course of PPCM.

A number of risk factors have been associated with increased risk of PPCM, including age over 30 years, multiparity, African descent, pregnancy with multiple fetuses, a history of preeclampsia, eclampsia, or postpartum hypertension, maternal cocaine abuse, more than 4 weeks of oral tocolytic therapy with  $\beta$ -adrenergic agonists [1].

### Clinical manifestations

Most of the symptoms are related to systolic dysfunction of the LV and are similar to those observed in other forms of systolic HF. Symptoms range from mild to very severe. Severe symptoms may result in death. PPCM is characterized by dyspnea on exertion in mild cases or dyspnea at rest in more severe stages, orthopnea, lower-limb edema, and persistent cough. Additional symptoms include abdominal discomfort, which is secondary to hepatic and gastrointestinal congestion, as well as palpitations, and dizziness. Patients and clinicians often attribute the symptoms either to gravidity or general weakness as well as associated anemia, which often results in misdiagnosis. Therefore, the most frequent initial presentation is associated with the symptoms of NYHA class III or IV [1,5]. Importantly, delays in diagnosis and treatment are associated with increased mortality. In order to promptly make the diagnosis of PPCM, the Working Group on peripartum cardiomyopathy of the HF Association developed a simple algorithm (fig. 4).

### Diagnosis of peripartum cardiomyopathy

PPCM is a diagnosis of exclusion, where both cardiac and noncardiac symptoms should be carefully evaluated. In patients who are clinically suspected of having PPCM, electrocardiogram, echocardiography, and the measurement of brain natriuretic peptide levels (BNP or NT-proBNP) should always be performed [1].

### Electrocardiogram

The most common findings on electrocardiogram include sinus tachycardia or, rarely, atrial fibrillation, signs of LV hypertrophy, unspecific ST-T-wave abnormalities, and, occasionally, Q waves in anterior precordial leads, PR interval, and the QRS complex may be prolonged [1].

### Echocardiography

Echocardiography is the most important and widely used diagnostic method to confirm the diagnosis and to monitor the effectiveness of ongoing treatment. The examination typically reveals LV dilatation with or without hypertrophy and a global reduction of contractility. The cut-off values of LV dilatation and systolic dysfunction to diagnose PPCM have not been precisely defined. In daily practice, LV end-systolic dimension exceeding 27 mm/m<sup>2</sup> and the LVEF of less than 45% is considered as indicative of PPCM. Other abnormalities such as left atrial enlargement, secondary mitral and tricuspid regurgitation, or small pericardial effusion are frequently observed in PPCM. Apart from the initial examination, echocardiogram should be repeated before discharge, at 6 weeks, 6 months, and once a year to evaluate cardiac recovery or disease relapse. Predictors of poor LV function recovery are the baseline LVEF of less than 30% and LV end-diastolic diameter exceeding 60 mm [6,7].

### Brain natriuretic peptides

As in virtually any severe form of HF, the levels of BNP are significantly elevated during the course of PPCM as a result of systolic dysfunction and elevated end-diastolic pressure [1].

### Chest radiography

Although chest radiography has limited diagnostic accuracy, it is frequently performed to assess the status of pulmonary congestion but, even more importantly, to search for other causes of breathlessness.

### Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (MRI) is definitively less often used than echocardiography but it provides a more accurate measurement of chamber volumes, wall thickness, and regional and global systolic functions, and has higher sensitivity for the detection of thrombus. Moreover, a few studies showed that the presence of late gadolinium enhancement was associated with poor recovery of cardiac function. Finally, cardiac MRI has better diagnostic accuracy for myocarditis, which should also be considered in the diagnostic pathway. According to the European Society of Radiology, gadolinium contrast should be

avoided until delivery but breast-feeding does not have to be interrupted [8].

It is important to distinguish PPCM from other preexisting cardiomyopathies, such as dilated cardiomyopathy unmasked by pregnancy, HIV/AIDS cardiomyopathy, and other prior cardiac disorders including valvular heart disease, hypertensive heart disease, unrecognized congenital heart disease, pregnancy-associated myocardial infarction, or pulmonary embolus.

## Management

The principles of treatment of patients with PPCM, either in acute or chronic state of HF is not very different from the other types of HF.

### Acute heart failure

In the acute setting, there are three goals, namely, optimization of hemodynamics, relief of symptoms, and initiation of chronic therapies approved for HF. This is usually achieved by appropriate oxygen therapy, intravenous diuretics, and, depending on hemodynamic status (hyper- or hypotensive), by vasodilators (e.g., nitroglycerin) or inotropic agents. In rare cases, more advanced mechanical circulatory support may be needed to stabilize the patient until recovery or as a bridge to heart transplantation.

### Stable heart failure

Treatment depends on whether the patient is still pregnant or in the postpartum period because some of the drugs may have a negative effect on the fetus. It is generally believed that the treatment of stable HF after delivery should not be different from the current HF guidelines of the European Society of Cardiology [9]. In case of ongoing pregnancy, ACEIs and angiotensin receptor blockers (ARB) are contraindicated because of serious renal and fetal toxicity [10,11].  $\beta$ -blockers are generally safe during pregnancy; however, caution is advised. As a rule,  $\beta_1$ -selective antagonists are preferred over  $\beta_2$  as the latter may show antitokolytic action. Diuretics are the basis for symptomatic treatment [12]. Aldosterone antagonists, both spironolactone and eplerenon, should be avoided during pregnancy because of the unknown interactions with hormonal pathways. On the other hand, less frequently used hydralazine and long-acting nitrates are valuable replacements for ACEIs and ARBs [13]. Finally, antithrombotic therapy should be considered in patients with seriously depressed LVEF, especially in the setting of atrial fibrillation. Vitamin K antagonists should rather be avoided owing to potential fetotoxicity as well as difficulties in the management of patients on this therapy. Generally safe and much easier to manage are unfractionated or low-molecular-weight heparins. Implantable cardioverter-defibrillators and cardiac resynchronization therapy devices, which have an important and proven role in the management of systolic HF, are occasionally implanted in women with persistent severe symptoms and lack of LV function

recovery. However, the final decision of whether to implant an ICD or not is usually difficult and a natural course of PPCM (which is favorable in many patients) should also be considered in addition to numerous other factors.

### Novel therapies

The rationale behind the treatment of PPCM with bromocriptine comes from an experimental study on mice, in which PPCM was prevented with this agent via prolactin blockade. In a randomized open-label study of newly-diagnosed PPCM in South African women, an addition of 2.5 mg bromocriptine twice daily for 8 weeks to standard HF treatment resulted in a significant improvement of HF symptoms and LVEF. Although bromocriptine seems to be a promising “tailored” adjunctive therapy of PPCM, its safety and efficacy needs to be verified in larger randomized trials before it can be widely recommended in the guidelines [1].

Immunosuppressive agents have been anecdotally used in women with PPCM and biopsy-proven myocarditis with good results. However, its routine use is currently not recommended. Similarly, intravenous immunoglobulin has also been tried in concurrent PPCM and myocarditis but is not a standard of care.

### Prognosis

The data on the PPCM prognosis are sparse. Although initial reports suggested that mortality in PPCM vary geographically, the more recent reports suggest similar rates of survival in women from the United States, Haiti, and South Africa. Unfortunately, there are no mortality studies in European women. The largest series of 123 women with PPCM showed a mortality rate of approximately 10% at follow-up of 2 years. A slightly worse outcome was observed in women from South Africa with the mortality of 10% and 28% in 6-month and 2-year follow-up, respectively. The mode of death is typically progressive pump failure, sudden cardiac arrest, or thromboembolic events. The negative prognostic factors are as follows: worse NYHA class, Blacks, and multiparity. Fortunately, the functional status and cardiac function of the majority of patients improve with treatment, and over 50% of the patients experience complete recovery of heart function (LVEF of 55% or greater). Although the risk of PPCM relapse in subsequent pregnancies is not completely defined, it is generally believed that it is significantly increased compared with women without prior PPCM. Women who had not fully recovered from PPCM, have a particularly high risk of disease recurrence or exaggeration of symptoms. Though it is not formally supported by the guidelines and it is difficult to give individual counseling, women with a history of PPCM who have persistent LV dysfunction should be best advised to avoid pregnancy owing to the high risk of HF progression and death.

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## Pregnant woman with uncorrected cyanotic congenital heart disease (RCD code: VII-IV-2A.1)

Olga Trojnarska

### Background

There are not many patients with primary cyanotic congenital heart disease who had not been operated in childhood. Moreover, because of their clinical condition, they are rarely pregnant [1,2]. Therefore, we decided to present a case of a pregnant woman with tetralogy of Fallot manifesting as pulmonary valve atresia, left pulmonary branch stenosis, and well-developed collateral circulation between the descending aorta and the right pulmonary artery (major aortopulmonary collateral arteries). She reached adulthood owing to hemodynamic balance between the pulmonary and ventricular septal defect flow.

### Case presentation

A 32-year-old woman was admitted to an outpatient clinic of adult congenital heart diseases at the 1st Department of Cardiology, Poznan University of Medical Sciences, at 24 weeks of gestation. Her first pregnancy was tolerated well and ended by natural childbirth in the 38th week. Unfortunately, the child died in the postoperative period due to shortage of oxygen after umbilical cord complications. Her second

pregnancy was planned. During the first visit, her clinical condition was stable and she only presented mild symptoms of heart failure. She did not receive any pharmacological treatment. A physical examination revealed cyanosis (oxygen saturation, 78%), heart blood pressure of 110/70 mm Hg, and normal heart rate (86 beats/min). On auscultation, there was no second heart tone over the pulmonary artery, systolic murmur grade 3/6 best heard over the second right intercostal space. An electrocardiogram showed normal sinus rhythm (82 beats/min), right-axis deviation, Q wave in leads II, III, and aVF, and inferior T wave in lead III (fig. 1).

Echocardiography showed enlarged ventricles (left, 45 mm; right, 44 mm) and normal ejection fraction. Moreover, we observed a malalignment type of ventricular septal defect. No blood flow between the right ventricle and pulmonary trunk and mild tricuspid valve insufficiency were observed (fig. 2).

Laboratory test results were as follow: hemoglobin, 14.1 g/dL; red blood cell count,  $4.7 \times 10 \times 12/L$  (normal range,  $3.7\text{--}5.1 \times 10 \times 12/L$ ); hematocrit, 42% (37%–47%); serum iron levels, 29  $\mu\text{g/dL}$  (60–170  $\mu\text{g/dL}$ ); total iron binding capacity, 439  $\mu\text{g/dL}$  (223–446  $\mu\text{g/dL}$ ); and blood ferritin levels, 5  $\mu\text{g/dL}$  (10–200  $\mu\text{g/dL}$ ). Other blood test results were normal.

At 32 weeks of gestation, just before admission to the clinic, the patient was consulted twice by an experienced cardiologist. Following admission, she was treated with unfractionated heparin (enoxaparin,  $2 \times 40$  mg/d). Compression stockings were recommended. During hospital stay, her clinical condition improved and she showed no symptoms of heart failure, arrhythmia, venous stasis, or thromboembolism. After consulting an obstetrician, a decision was made to end pregnancy at 35 weeks by cesarean section. To stimulate fetal lung maturation, the patient received 12 mg

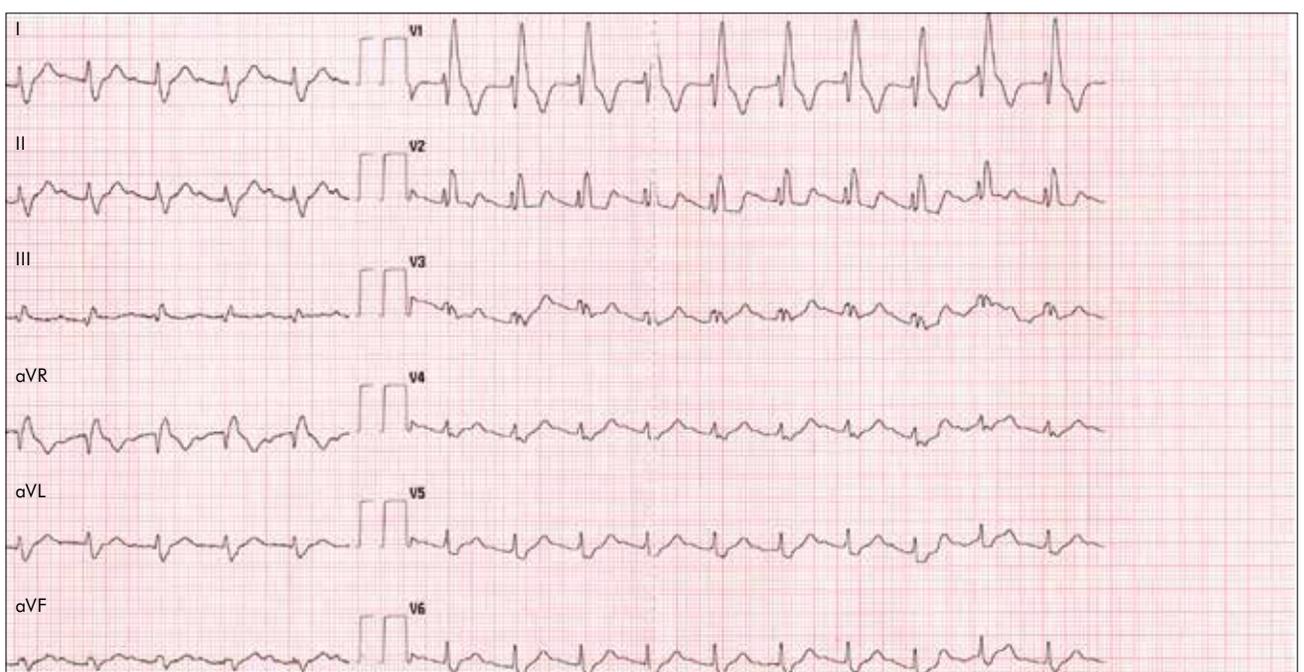
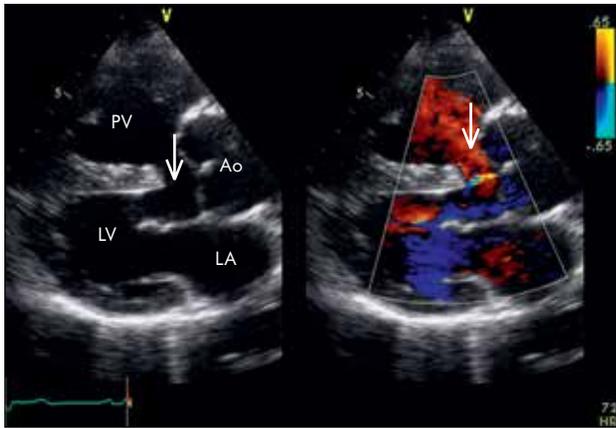


Fig. 1. Electrocardiogram – tetralogy of Fallot. Sinus rhythm, 100 beats/min. Right-axis deviation. Right bundle branch block



**Fig. 2.** Transthoracic echocardiography. Parasternal long-axis view. **A.** Aorta arises from the left and right ventricles. Ventricular septal defect (white arrow) **B.** Color Doppler imaging. Ventricular septal defect flow (white arrow)

of dexamethasone for 10 days. Twelve hours before cesarean delivery, heparin administration was stopped and, 1 hour before the delivery, 1 g of first-generation cephalosporin was administered. The cesarean section was performed in a cardiac surgery unit. The newborn female child received 10 points in the Apgar scale at 1 and 5 minutes after birth, and heart disease was not confirmed. The patient spent the postpartum period in a cardiac intensive care unit. Because of low hemoglobin levels (12.2 g/dL), red blood cell transfusion was performed. Anticoagulation therapy with low-molecular-weight heparin was restarted after 12 hours. Bromocriptine at a dose of 2.5 mg twice daily for 14 days was used to suppress lactation. The patient was discharged in good general condition with the recommendation of iron intake (325 mg) and regular control visits at an outpatient clinic of adult congenital heart diseases. Another pregnancy is strongly contraindicated.

## Discussion

Cardiac death in pregnant women with congenital heart diseases that had not been corrected in childhood occurs in 4% to 15% of the cases and depends on the anatomy of the disease [4–8]. Experts from the European Society of Cardiology (ESC) classify patients with heart disease as a high-risk group (World Health Organization risk class III). One-third of these patients have arrhythmias, thromboembolism, advanced stages of heart failure, and risk of hemorrhage [4,8]. Therefore, these patients should be managed by interdisciplinary teams in specialized centers with experts in hemodynamic alterations during pregnancy [9]. Heart failure is caused by active vasodilatation, raised heart rate, and increased cardiac output, which lead to insufficiency of fibrotic cardiac muscle. Vasodilatation is related to decreased preload and causes increased right left shunt and decreased saturation. Heart insufficiency and cyanosis stimulate arrhythmogenesis. Pregnant women should avoid

physical exercises and immobilization, which is associated with thromboembolic episodes. Pregnancy is associated with increased indices of hypercoagulability, and patients with cyanosis who have increased levels of coagulation factors and dysfunction of platelets are at risk of life-threatening events [3]. Graduated compression stockings are recommended [9]. According to the ESC guidelines, heparin is the drug of choice [9] but, on the other hand, it is associated with a higher risk of bleeding [4]. ESC experts [9] recommend oxygen therapy to elevate saturation. Perloff et al. [3] suggested that oxygen therapy may induce cough that may lead to severe and potentially lethal hemoptysis of pulmonary arterial origin.

## Management strategy

Timing and type of delivery are individualized according to fetal maturity and the clinical status of the mother. Vaginal delivery was reported as preferable by numerous authors [5,8,9] but, nowadays, obstetric and anesthetic techniques allow to perform cesarean section [4,10]. Cesarean delivery is associated with twice higher blood loss as well as an increased risk of infection, venous thrombosis, and thromboembolism [11,12]. On the other hand, it allows to control the hemodynamic parameters and to avoid catecholamine-dependent tachycardia and vascular resistance. In our case, we used general anesthesia, which, if safely administered, causes minor systemic hypotension compared with lumbar epidural analgesia. This type of delivery requires the involvement of skilled experts including a cardiologist, cardiac surgeon, obstetrician, and anesthesiologist. Our center have performed this procedure for years with good outcomes [13].

Endocarditis prophylaxis was recommended because of the type of heart disease and desaturation [9]. Studies in women with structural heart disease have shown that delivery is associated with a high risk of death in the first few days after delivery and that it may induce right ventricular failure and thromboembolism [8]. Therefore, hemodynamic monitoring should be continued for 10 days after delivery [8,9]. If no significant bleeding occurs, postpartum heparin treatment should be restarted 12 hours after a cesarean delivery [9]. Breastfeeding is potentially dangerous because the hypotensive effect of prolactin can increase cyanosis. Lactation is associated with a high risk of bacteremia and should be suppressed by bromocriptine [11].

Maternal cyanosis and heart failure are the main threats to the fetus because they may lead to intrauterine growth retardation [14]. About 43% of the babies born to mothers with congenital heart disease are small-for-gestational age and have lower birth weights and about 37% of the babies are prematurely born [4]. Congenital heart disease in a mother is also associated with a significantly higher abortion rate (31%–50% of the cases) [15,16].

Hypoxia and increased hemoglobin levels in a mother are the two most important risk factors for

mortality of live-born infants [3,4,8]. Presbitero et al. [4] studied the outcome of 96 pregnancies in 44 patients with cyanotic congenital heart disease and revealed that arterial oxygen saturation of 85% was associated with high incidence of miscarriage and small chance of a live birth (12%). Our patient who had oxygen saturation of 78% was in the high-risk group. The risk of inherited congenital heart disease is 5% and is 10-fold higher than in the general population.

## Conclusion

Pregnancy and delivery in patients with cyanotic congenital heart disease is rare. Nonetheless, these high-risk patients should be treated by interdisciplinary teams including skilled cardiologists and obstetricians.

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## Pregnancy in a patient with Turner syndrome, after operation of aortic coarctation, with bicuspid aortic valve, and ascending aortic aneurysm (RCD code: VII-I-1B.6)

Lidia Tomkiewicz-Pajak, Agata Leśniak-Sobelga, Tomasz Pawelec, Bogdan Kapelak, Piotr Wilkołek, Piotr Podolec

### Background

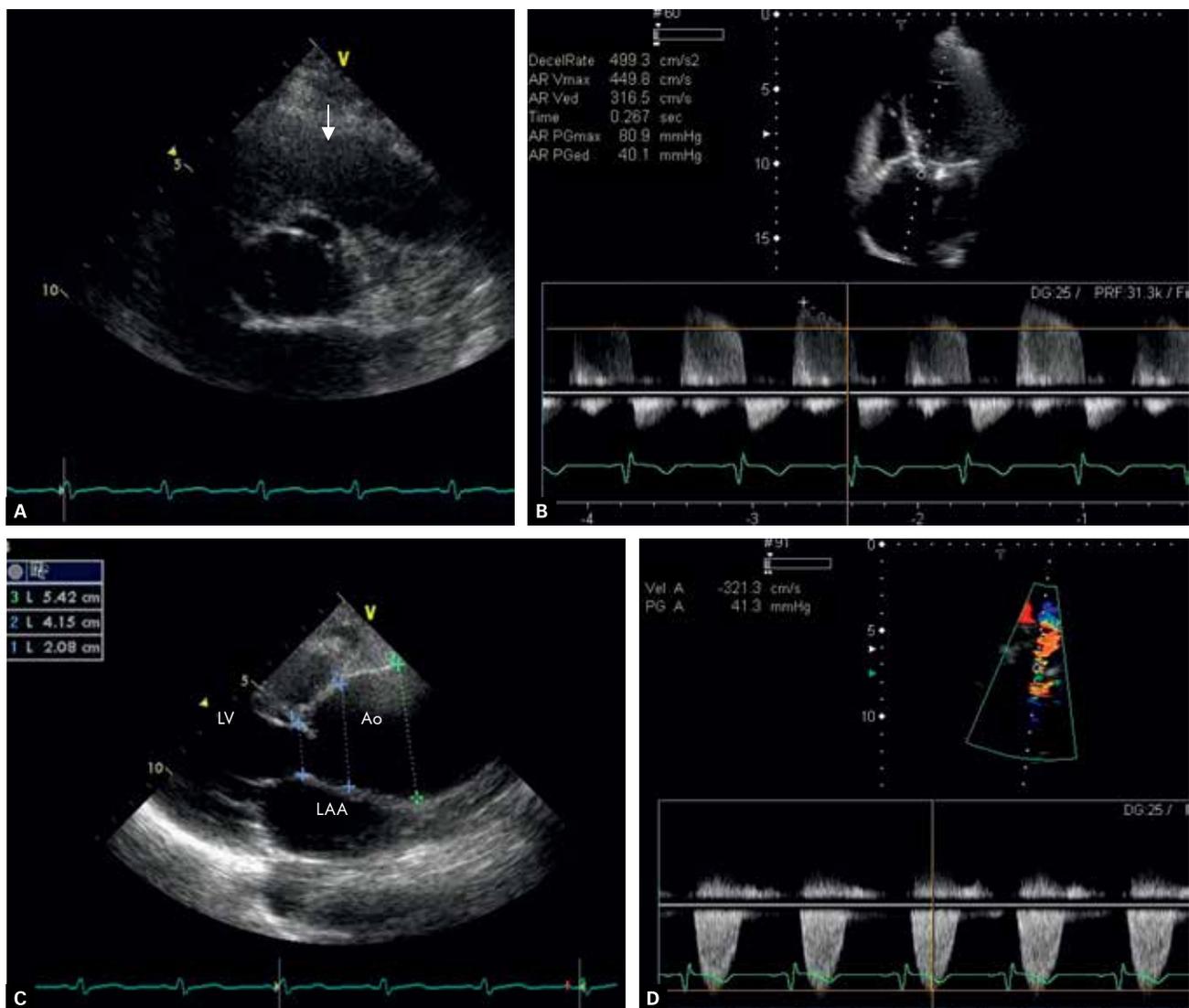
Turner syndrome, also known as gonadal dysgenesis, is a rare chromosomal abnormality, in which all or part of one of the sex chromosomes is absent. It occurs in 1 in 5000 live births [1]. Congenital heart diseases, such as aortic coarctation or bicuspid aortic valve,

are also frequently present in patients with Turner syndrome. Other congenital cardiovascular malformations, such as partial anomalous venous drainage and aortic valve stenosis or aortic regurgitation, are also more common in patients with Turner syndrome than in the general population. Systemic hypertension has been reported in 50% of the patients with Turner syndrome [2,3].

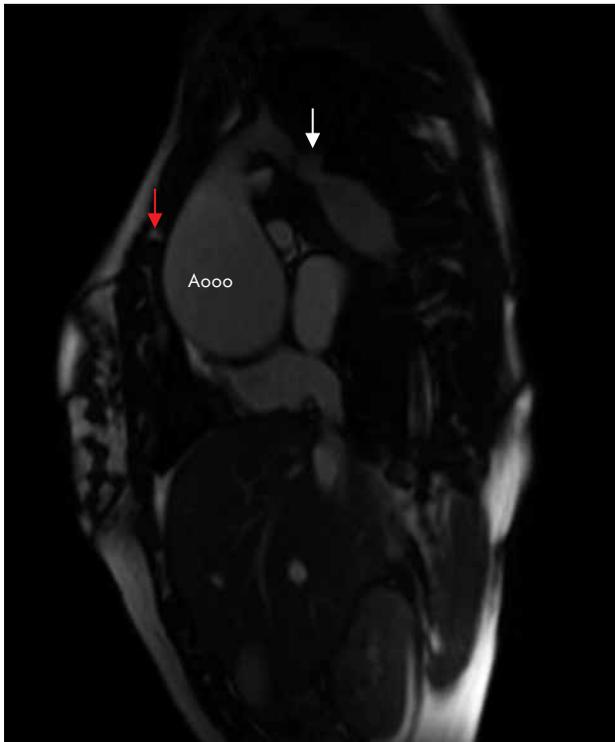
### Case presentation

A 30-year-old woman with Turner syndrome (karyotype 80% 45, X0, 15% 46, XX, 5% 47, XXX) with aortic coarctation, bicuspid aortic valve, and ascending aortic aneurysm was admitted to the hospital at 12 weeks of pregnancy. The patient's height was 139 cm, weight – 46 kg, body mass index – 23.5, and body surface area – 1.3 m<sup>2</sup>.

The surgical correction of aortic coarctation was performed at the age of 2 years (end-to-end).

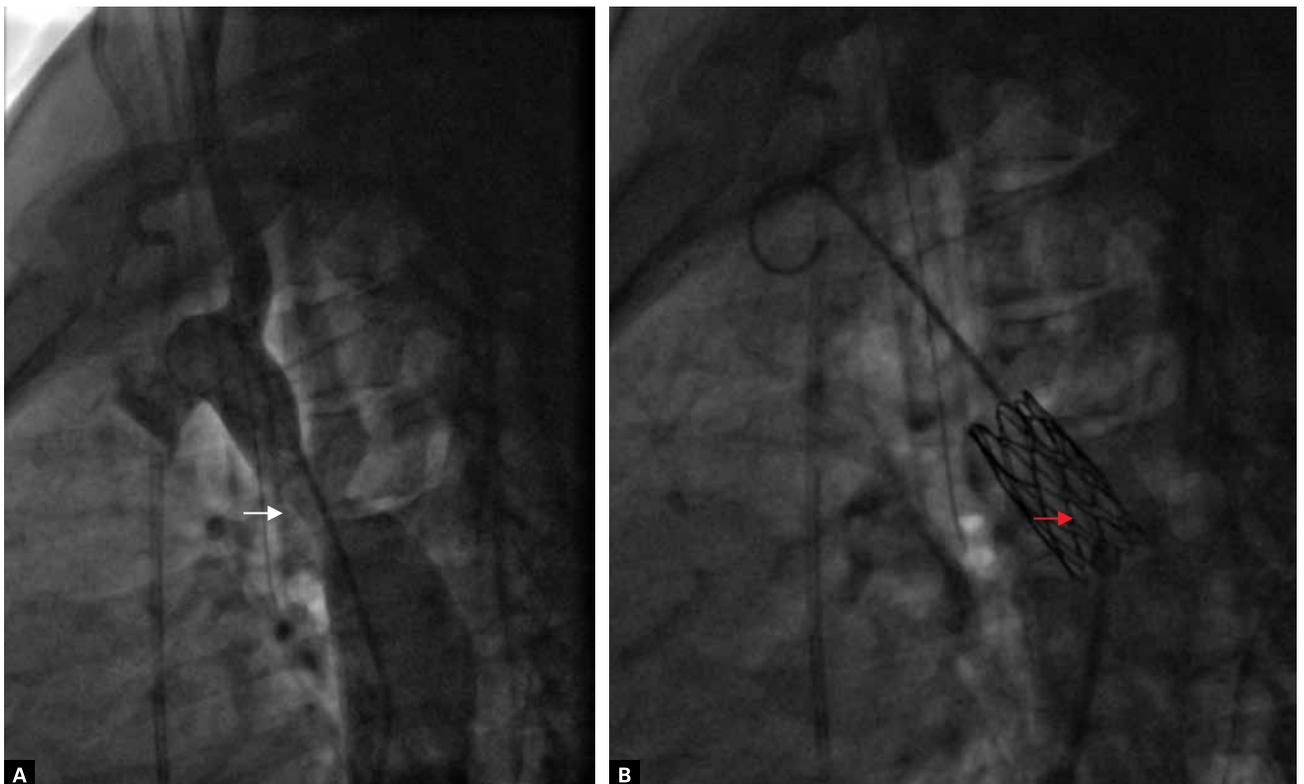


**Fig. 1.** Transthoracic echocardiography Parasternal short-axis view. Bicuspid aortic valve. (white arrow) Continuous-wave Doppler ultrasound showed moderate aortic valve regurgitation **C.** Parasternal long-axis view. The diameter of the ascending aorta, 54 mm; the aortic index, 39 mm<sup>2</sup>. LV – left ventricle, LA – left atrium, Ao – aorta. **D.** Suprasternal view. Systolic gradient of aortic coarctation, 41 mm Hg

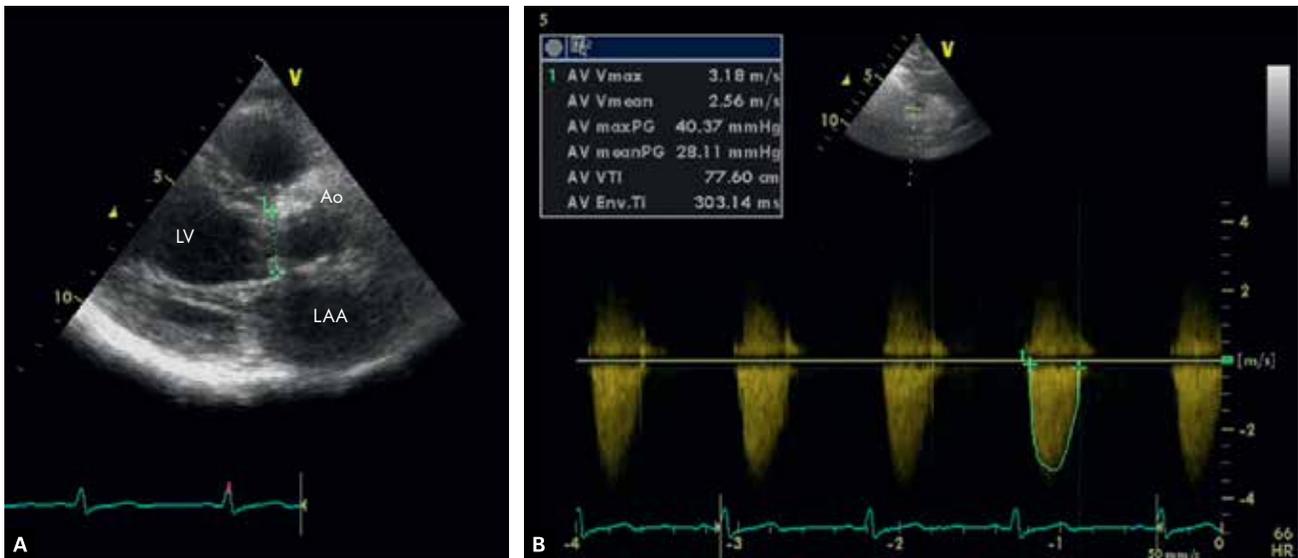


**Fig. 2.** Cardiovascular magnetic resonance. Ascending aorta dilatation (red arrow) and narrowing of the aortic isthmus above 50% (white arrow)

The patient had not received systematic cardiac care. The first echocardiographic examination was performed at 4 weeks of pregnancy, and aortic aneurysm was diagnosed. Laboratory test results were within the normal ranges. The patient was informed about high risk associated with her pregnancy. She did not present any symptoms and her general condition was good. Over the base of the heart, diastolic murmur was heard. A resting electrocardiogram (ECG) showed sinus rhythm with a heart rate of 80 beats/min. Holter monitoring did not reveal significant cardiac arrhythmias and conduction disturbances. Oxygen saturation of arterial blood at rest was 94%. The blood pressure in 24-hour monitoring was normal. The blood pressure measured on the left arm was about 24 mm Hg lower than that measured on the right arm. The blood pressure measured on the lower extremity was the same as that measured on the left upper extremity. Transthoracic echocardiography showed normal size and function of the right and left ventricles, normal left and right atrial diameter, and bicuspid aortic valve with moderate regurgitation (fig. 1A,B). The diameter of the ascending aorta was enlarged and measure 54 mm; the aortic index was 39 mm/m<sup>2</sup> (fig. 1C). The peak systolic gradient in aortic coarctation was about 41 mm Hg (fig. 1D). Doppler ultrasonography showed retrograde vertebral flow on the left side and normal diameter of the left subclavian artery. The flow in the right vertebral artery, in the carotid arteries and femoral arteries on both sides was normal. Cardiac magnetic resonance of the ascending aorta showed the narrowing of the aortic isthmus above 50% (fig. 2).



**Fig. 3.** Aortography. **A.** Aortic coarctation (white arrow). **B.** Percutaneous balloon angioplasty of aortic coarctation with stent implantation (red arrow). Ao – aorta



**Fig. 4.** Transthoracic echocardiography after the Bentall de Bono procedure. **A.** Parasternal long-axis view – normal aortic diameter. **B.** Suprasternal view. Systolic gradient of aortic coarctation, 40 mm Hg. LA – left atrium, LV – left ventricle, Ao – aorta

Medical treatment consisted of metoprolol at a dose of 75 mg/d. Clinical and echocardiographic examination was performed every 2 weeks until delivery. The patient was clinically stable with normal blood pressure; there were no changes in the left ventricular size and aortic diameter on repeated echocardiograms. At 24 weeks of pregnancy, after gynecologic consultation, prednisone was administered to prepare the patient for preterm delivery. At 34 weeks of pregnancy, she delivered a healthy baby (weight, 2100 g; Apgar score of 9 with normal karyotype). A cesarean section was performed in a cardiothoracic surgery unit, and, after delivery, percutaneous angioplasty of aortic coarctation was performed with stent implantation (fig. 3). After the procedure, the gradient at the aortic isthmus decreased from 20 mm Hg to 0 mm Hg. The patient was clinically stable and the diameter of aortic aneurysm did not change. Six weeks after delivery, the Bentall de Bono procedure with artificial aortic valve implantation was performed. Six months after the procedure, the patient was in good general condition. Echocardiography showed a normal diameter of the ascending aorta (fig. 4). The case was discussed during the 2nd Symposium on Rare Cardiovascular Diseases of the European Society of Cardiology (ESC) in Munich, 2012 [4].

## Discussion

The majority of patients with Turner syndrome have primary hypertension. In the remainder, the syndrome is associated with cardiovascular or kidney abnormalities, including aortic coarctation. The prevalence of aortic root dilatation ranges from 8.8% to 42% in this patient group [1,2]. The analysis of 85 cases of aortic dissection in patients with Turner syndrome showed that 89% of them had at least one established risk factor of aortic rupture such as aortic coarctation, bicuspid aortic valve, and hypertension [3].

Patients with Turner syndrome typically have gonadal dysfunction, which results in sterility. For the majority of such women, oocyte donation represents the only way to become pregnant [5,6]. In some cases, the so called mosaicism occurs, that is, the chromosome is missing only in some cells and these women may successfully become pregnant and carry their pregnancies to term [7].

In Turner syndrome, pregnancy may be a risk factor for cardiovascular complications in the mother. Several studies suggested an increased risk of aortic dissection in pregnancy, especially in patients with Turner syndrome and the presence of any of the following risk factors for aortic rupture: aortic coarctation, bicuspid aortic valve, and hypertension. Aortic complications during pregnancy are associated with maternal mortality of up to 11%, attributed mainly to type A dissection. The risk of eclampsia or preeclampsia is increased, and treatment of hypertension is important, especially during pregnancy [8–10].

According to the 2011 ESC guidelines on the management of cardiovascular diseases in pregnancy, women with Turner syndrome with aortic aneurysm are classified as class IV of the modified World Health Organization risk classification [11].

In patients with aortic dilatation exceeding 50 mm in aortic disease associated with bicuspid aortic valve and with severe coarctation, pregnancy is contraindicated but, if they become pregnant and will not consider termination, monthly or bimonthly check-up is needed.

Because of low height, thoracic aortic diameters must be evaluated in relation to the body surface area. An aortic diameter index of 27 mm/m<sup>2</sup> is associated with high risk of dissection of the aorta, and surgery should be considered before pregnancy [11].

Repeated echocardiography every 4 or 8 weeks should be performed during pregnancy in patients with ascending aorta dilatation. During pregnancy, patients should be treated with  $\beta$ -blockers [11].

When progressive dilatation or aortic rupture occurs during pregnancy, before the fetus is viable, aortic repair with the fetus in utero should be considered. When the fetus is viable, a cesarean delivery followed directly by aortic surgery is recommended. A cesarean section should be performed in a hospital in which cardiothoracic surgery and neonatal intensive care units are available [11].

## Expert opinion – CRCD

**J.W. Roos-Hesselink:** Concerning the Turner patient: that is indeed a very high-risk patient. I would give her low dose of a  $\beta$ -blocker, because her blood pressure is low, but still try to protect her from rupturing. I would follow her closely with echo (every 2–4 weeks) and, if the diameter is increasing during her pregnancy, you must consider a surgery. Otherwise try to reach 32 to 34 weeks of pregnancy and then do a cesarean section. Especially the last trimester is associated with a very high risk of rupture. Also, during the first weeks after delivery, she is still at high risk.

**Piotr Hoffman:** In patients with aortic dilatation associated with bicuspid aortic valve and with severe coarctation, pregnancy is contraindicated but, if they become pregnant and will not consider termination, a bimonthly review is needed. A cesarean section should be performed in a hospital in which cardiothoracic surgery and neonatal intensive care units are available.

**Zbigniew Gąsior:** Patients with Turner syndrome with aortic aneurysm and aortic coarctation are classified as class IV according to the WHO risk classification. The patient should be closely monitored every 2 weeks. After delivery, percutaneous angioplasty of aortic coarctation should be considered.

**Krzysztof Rytlewski:** In cases of acute dissection of the aortic root during pregnancy, medical management depends on the stage of pregnancy:

- before 25 weeks of gestation, emergency aortic root surgery with extracorporeal circulation, fetus in utero, with cardiotocography. The risk of maternal and/or fetal death is high
- after 25 weeks of gestation, emergency Cesarean section, immediately followed by aortic root surgery.

A cesarean section should be performed in a hospital in which cardiothoracic surgery and neonatal intensive care units are available.

## Management strategy

### Before pregnancy

Symptoms: systemic hypertension – high risk of aortic dissection.

Echocardiogram – bicuspid aortic valve, aortic coarctation, aortic aneurysm – high risk of aortic dissection. An aortic diameter index of  $27 \text{ mm/m}^2$  – a prophylactic surgery should be considered.

### During pregnancy

Patient with systemic hypertension, severe coarctation, bicuspid aortic valve, and aortic aneurysm – WHO risk class IV – clinical and echocardiographic monitoring of the patient with blood pressure measurements every 2 weeks.

Medical treatment:  $\beta$ -blocker and antihypertensive therapy.

### Delivery

A cesarean section should be performed in a hospital in which cardiothoracic surgery and neonatal intensive care units are available.

When progressive dilatation or aortic rupture occurs during pregnancy, before the fetus is viable, aortic repair with the fetus in utero should be considered. When the fetus is viable, a cesarean delivery followed directly by aortic surgery is recommended [11].

### After delivery

The Bentall de Bono procedure with artificial aortic valve implantation should be performed.

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## Pregnant woman with Ebstein's anomaly and atrial septal defect (RCD code: VII-IV-1D.1b)

Agata Leśniak-Sobelga, Lidia Tomkiewicz-Pająk, Jacek Pająk, Piotr Podolec

### Background

Ebstein's anomaly is a rare congenital heart defect with the prevalence of 0.3% to 0.5% in the general population. It is characterized primarily by abnormalities of the tricuspid valve and right ventricle (RV) [1]. The survival of patients with Ebstein's anomaly during childhood and adolescence has improved dramatically: after 35 months of diagnosis, the Kaplan–Meier survival probability remains stable at 80% (95% confidence interval, 0.72–0.89) [2]. Survival into adulthood is common; survivals of up to 85 years have also been reported [3]. Ebstein's anomaly may manifest clinically at any age and has a highly variable clinical course. Adults often present with cyanosis, dyspnea, palpitations, decreasing exercise tolerance, and fatigue [4–9]. In the presence of an interatrial communication, the risk of paradoxical embolization, brain abscess, and sudden cardiac death increases. Exercise tolerance is dependent on heart size and oxygen saturation [8–11].

### Case presentation

A 34-year-old woman with Ebstein's anomaly diagnosed at early childhood presented at our center at 19 weeks of her first pregnancy. Her main symptoms included syncope, with the last episode at 6 weeks of pregnancy, dyspnea, and, occasionally, palpitations. During the first examination, she was classified as the New York Heart Association (NYHA) functional class II.

A physical examination revealed systemic blood pressure of 110/80 mm Hg, heart rate (HR) of 78 beats/min, and body mass index of 24.9 kg/m<sup>2</sup>. Her oxygen saturation (SatO<sub>2</sub>) in room air was decreased to 90%; however, no signs of cyanosis were observed. On auscultation, a holosystolic murmur along the low left sternal border was heard.

Blood test results were normal. An electrocardiogram revealed the following findings:

- sinus rhythm of 71 beats/min with first-degree atrioventricular block (PQ, 0.22s)
- right-axis deviation
- prolonged QTc to 458 ms
- mitral P
- signs of RV hypertrophy (S in V<sub>6</sub> >3 mm), and
- nonspecific interventricular conduction disturbances.

In 24-hour Holter monitoring, maximal HR was 142 beats/min, minimal HR was 57 beats/min, and mean HR was 74 beats/min. There were 124 isolated supraventricular premature beats, 4 episodes of

supraventricular tachycardia (longest run at the rate of 124 beats/min, and 8 ventricular premature beats).

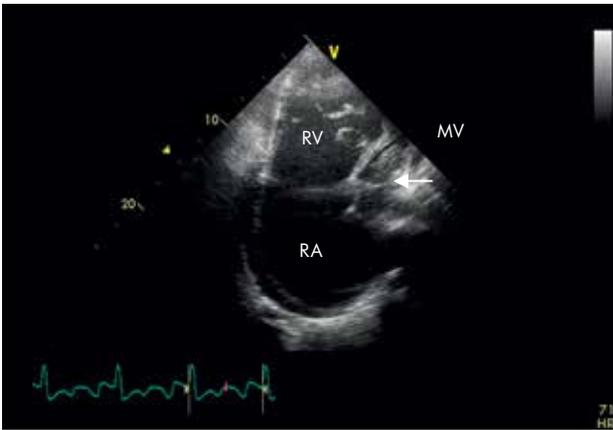
Transthoracic echocardiography showed typical signs of Ebstein's anomaly, such as caudal (inferior) displacement of the septal and posterior leaflets of the tricuspid valve (>8 mm/m<sup>2</sup>) with severe tricuspid regurgitation and right atrial and RV enlargement (areas, 89.1 and 74.6 cm<sup>2</sup>, respectively) and small left ventricle (LV) (area, 17 cm<sup>2</sup>). Additionally, a large ostium secundum atrial septal defect (ASD II) with the left-to-right shunt and estimated RV systolic pressure of 46 mm Hg were detected (fig. 1, 2, 3). The pulmonary-to-systemic flow (Qp/Qs) ratio was difficult to estimate due to inadequate imaging of the pulmonary valve.

In the 6-minute walk test, the patient walked 420 m with an increase of HR from 77 beats/min before to 109 beats/min after the test and an increase of SatO<sub>2</sub> from 93% to 96% after the test. There were no indications for right heart catheterization during pregnancy.

A gynecological examination with fetal ultrasonography showed normal condition of the fetus.

The patient was prescribed long-acting metoprolol (50 mg/d) and anticoagulant therapy with low-molecular-weight heparin (LMWH), enoxaparin (2 × 60 mg subcutaneously). She underwent clinical examination and echocardiography every month until delivery. There were no changes in the RV size and function on repeated echocardiograms. The results of serial measurements of N-terminal pro-B-type natriuretic peptide (NT-proBNP) were as follows: 203.9 pg/mL, 123.1 pg/mL, and 148.7 pg/mL (normal range, <125 pg/mL). The course of pregnancy was uneventful.

The patient delivered a healthy male baby vaginally at 36 weeks of pregnancy (weighing, 2140 g; Apgar score, 10). On the 6th day after delivery, she experienced tachycardia, dyspnea, and dizziness. She was referred to the cardiac department. On admission, her heart rate was 80 beats/min and blood pressure was 90/60 mm Hg. On a physical examination, there was slight edema on the legs, which resolved after intravenous administration of furosemide (20 mg). Electro- and echocardiography did not reveal any abnormalities – there were no signs of right heart failure or changes in hemodynamic factors. SatO<sub>2</sub> was stable – 94%. Laboratory test results revealed anemia: hemoglobin, 9.9 g/dL (normal range, 12–16 g/dL); hematocrit, 30.2% (normal range, 37%–47%); E, 3.25 × 10<sup>6</sup>/mm<sup>3</sup> (normal range, 3.7–5.1 × 10<sup>6</sup>/mm<sup>3</sup>). NT-proBNP levels were elevated: 825.8 pg/mL and 451 pg/mL. The remaining parameters were within the normal ranges: D-dimers, 0.75 mg/; sodium, 138 mmol/L; potassium, 4.8 mmol/L; C-reactive protein, 3.0 mg/L; total protein, 54 g/L; albumins, 30 g/L; and fibrinogen degradation product, <5.0 µg/mL. The patient was treated with long-acting metoprolol, furosemide, LMWH, folic acid, and iron supplementation. She was referred to a cardiac surgeon and scheduled for a surgical correction of Ebstein's anomaly and ASD II, but she decided to postpone the operation for about a year. After 4 days, she was discharged home.



**Fig. 1.** Transthoracic echocardiography. Four-chamber view. Apical displacement of septal and posterior leaflets of the tricuspid valve (25.5 mm, 8.8 mm/m<sup>2</sup>). Small pericardial effusion. RA – right atrium, RV – right ventricle, MV – mitral valve (arrow)

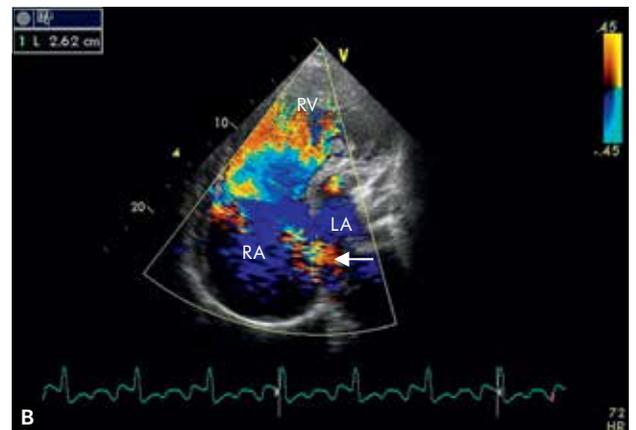


**Fig. 2.** Transthoracic echocardiography. Four-chamber view. Right atrial and right ventricular enlargement, depressed left ventricle. RA – right atrium, RV – right ventricle, LA – left atrium, LV – left ventricle

## Discussion

Ebstein's anomaly is a malformation characterized by adherence of the septal and posterior leaflets of the tricuspid valve to the underlying myocardium, apical displacement of the functional annulus exceeding 8 mm/m<sup>2</sup> of the body surface area, dilation of the atrialized portion of the RV, redundancy fenestrations and tethering of the anterior leaflet, and dilation of the right atrioventricular junction [9,12]. The spectrum of malformations may range from minimal displacement of the septal and posterior leaflets to imperforate membrane between the inlet and trabecular zones of the RV [9].

According to the Carpentier anatomic classification of Ebstein's anomaly [13], the patient was classified as B/C; according to the Celermajer echocardiographic grading score [8], she was considered as grade 3 (ratio of 1.2). The ratio provides information about prognosis: when the ratio is 1.5, 100% mortality is likely, while the ratio of 0.1 indicates 92% survival. However, there are no publications regarding its use in pregnancy [5,14].



**Fig. 3.** Transthoracic echocardiography Four-chamber view. Large atrial septal defect II (white arrows) with the left-to-right shunt. **A.** Two-dimensional imaging. **B.** Color Doppler imaging. RA – right atrium, RV – right ventricle, LA – left atrium, LV – left ventricle

An interatrial communication (ASD, persistent foramen ovale) is present in 80% to 94% of the patients with Ebstein's anomaly [15,16]. Our patient had ASD II with the left-to-right-shunt. Accessory pathways (Wolff–Parkinson–White syndrome) are commonly associated with Ebstein's anomaly (6%–36% of the cases) and may lead to supraventricular tachycardia [5,9]. First-degree heart block is observed in up to 50% of the patients (it may be associated with right atrial dilatation and stretch). Right bundle branch block is another typical finding [3,17,18]. Our patient did not present any signs of preexcitation, and an electrocardiogram revealed first-degree atrioventricular block.

Other cardiac defects associated with Ebstein's anomaly include ventricular septal defect, pulmonary outflow obstruction, patent ductus arteriosus, coarctation of aorta, parachute mitral valve, cleft anterior leaflet of the mitral valve, mitral valve prolapse, bicuspid aortic valve, corrected transposition of the great arteries, subaortic stenosis, tetralogy of Fallot, and left ventricular noncompaction [9,19,20].

Ebstein's anomaly does not have any effect on fertility, even in women with cyanosis [4]. According to the current guidelines, women with Ebstein's anomaly without cyanosis and heart failure are classified as class II according to the World Health Organization (WHO) risk classification and usually tolerate pregnancy well [21].

In contrast, symptomatic patients with cyanosis and/or heart failure should be treated before pregnancy or counseled against pregnancy. Hemodynamic abnormalities observed during pregnancy depend on the severity of tricuspid regurgitation and the functional capacity of the RV.

Heart failure, stroke, arrhythmias, and paradoxical embolism can occur even in asymptomatic patients. The presence of arrhythmia or cyanosis in the mother is associated with increased maternal and fetal risk, and requires closer maternal and fetal monitoring during pregnancy and delivery [22].

While pregnant patients with Ebstein's anomaly are usually acyanotic, those with interatrial shunting can develop shunt reversal and cyanosis in pregnancy. The parameters of bad prognosis include SatO<sub>2</sub> of less than 85% and hemoglobin exceeding 18 g/dL, which is associated with an increased rate of fetal loss. Mild cyanosis is associated with increased premature deliveries, low-birth weight, and thromboembolic complications [23].

The largest series reporting the outcome of 111 pregnancies in 44 women with Ebstein's anomaly was described by Connolly and Warnes [4]. In this report, 16 patients were cyanotic and 20 had an interatrial communication (ASD / persistent foramen ovale). The majority of pregnancies (76%) resulted in live births, 89% were delivered vaginally, and 11% by cesarean section. The mean birth weight of infants born to cyanotic women was significantly lower than that of newborns of acyanotic women (2530 vs. 3140 g,  $P < 0.001$ ) [4].

Donnelly et al. [22] described 42 pregnancies in 12 patients with Ebstein's anomaly. Most of the pregnancies were well-tolerated, resulting in 36 live births. Mild dyspnea in the third trimester of pregnancy was common; moreover, 1 patient had paroxysmal atrial tachycardia (in the first pregnancy) and atrial fibrillation (in the second pregnancy), and 1 patient had right heart failure.

Chopra et al. [5] analyzed the outcome of 8 pregnancies in 4 patients with Ebstein's anomaly, of whom 1 had right heart failure and 2 had arrhythmia.

In patients with Ebstein's anomaly, the physiological changes of pregnancy may affect hemodynamic parameters. In pregnant women with impaired RV size and function, the increased stroke volume may be poorly tolerated and result in worsening of tricuspid regurgitation, raised atrial pressures, and increased right-to-left shunting [24]. No correlation has been demonstrated between the symptoms and the degree of displacement of tricuspid valve leaflets [22,25]. Even severe tricuspid regurgitation with heart failure can usually be managed medically during pregnancy. Treatment includes therapy for heart failure and arrhythmia. In our patient,  $\beta$ -blocker therapy with metoprolol at a dose of 50 mg/d (due to prolonged QTc interval and symptoms of syncope) and anticoagulant therapy with LMWH were used. Palpitations and supraventricular arrhythmias on Holter monitoring in a patient with two clinically relevant nonmajor risk factors (heart failure, female sex, CHA<sub>2</sub>DS<sub>2</sub>-VASc = 2)

constitute an indication for anticoagulation. Moreover, the patient presented with pulmonary hypertension secondary to the large ASD II with the left-to-right shunt. Additional risk factors include a procoagulant state related to pregnancy, sedentary lifestyle, and weight gain. All of these factors may increase the risk for thromboembolic events, i.e., paradoxical embolism. An increased risk of fetal loss, prematurity, and low birth weight in babies born to mothers with cyanosis have been reported [4,22].

The preferred mode of delivery is vaginal in almost all cases [21]. The management during labor should aim at eliminating factors leading to congestive heart failure, cyanosis, and arrhythmias [5,26]. To maintain normal sinus rhythm during labor, adequate pain relief in the form of epidural analgesia is helpful and can be upgraded to anesthesia if cesarean section is indicated [27–29]. During the second stage of labor, Valsalva maneuver causes an increase in intrathoracic pressure and right-to-left shunt, and assisted vaginal delivery is indicated [5,30].

The risk of congenital heart disease in the offspring is reported in 4% to 6% of the cases, and familial Ebstein's anomaly in 0.6% [4,31]. We did not identify any congenital abnormalities in the baby of our patient.

Endocarditis prophylaxis in the peripartum period is not indicated in pregnant women with Ebstein's anomaly [32].

## Opinion of experts at the Center of Rare Cardiovascular Diseases

**Jacek Pająk:** According to the presentation, the patient is at least in the B/C Carpentier class and 3 Celermeyer class, with significant depression of the left ventricle by enlarged right heart. In this situation, she should have undergone a surgery prior to becoming pregnant. Her decision is to continue pregnancy despite associated risks. In my opinion, her pregnancy should be very closely monitored, and the possibility of circulation decompression, which will involve preterm delivery, should be considered, especially in the third trimester of pregnancy. After a successful delivery and puerperium period, correction of Ebstein's anomaly should be recommended to the patient.

**Katarzyna Mizia-Stec:** Anticoagulant therapy should be considered. There are indications for oral anticoagulant treatment in the second and third trimester (until the 35th week of pregnancy) and for LMWH from the 36th week of pregnancy and peripartum period. Palpitations and supraventricular arrhythmias observed on 24-hour monitoring in the patient with two clinically relevant nonmajor risk factors (heart failure, female sex, CHA<sub>2</sub>DS<sub>2</sub>-VASc = 2) constitute an indication for oral anticoagulant treatment. Moreover, the patient presented with pulmonary hypertension secondary to the large ASD with the left-to-right shunt. According to the 2009 guidelines of the European

Society of Cardiology, oral anticoagulant treatment may be considered in patients with associated pulmonary arterial hypertension (class IIb, level C). Additionally, we should be mindful of a procoagulant state typically observed in pregnancy as well as sedentary lifestyle and weight gain. All of these factors may increase a risk for thromboembolic events, i.e., paradoxical embolism.

**Krzysztof Rytlewski:** Ebstein's anomaly does not have any effect on fertility, even in women with cyanosis. The presence of Ebstein's anomaly in a pregnant woman is not an indication for termination of pregnancy or advice against becoming pregnant. These women require regular follow-up during the antenatal period and must be closely monitored during the peripartum period for any complications. Arrhythmia may be treated pharmacologically or, if an accessory pathway is present, with radiofrequency ablation. The displaced septal leaflet is associated with discontinuity of the central fibrous body, which causes a potential substrate for accessory pathways and preexcitation. Preexcitation and Wolff–Parkinson–White syndrome are more frequently associated with this anomaly (10%–29%), and it is recommended that women with mild symptoms and structurally normal hearts receive therapy only if supraventricular tachycardia symptoms are intolerable or the arrhythmia causes hemodynamic compromise [4].

In all such cases, a standard fetal ultrasound in the direction of fetal malformations should be performed.

## Management strategy

### Before pregnancy

Symptoms: cyanosis, right heart failure, poor exercise tolerance, NYHA classes III through IV – pregnancy contraindicated.

Echocardiogram (Celermajer classification): impaired RV size and function, right-to-left shunting, pulmonary hypertension, Celermajer grade 4 – pregnancy contraindicated.

Holter monitoring: any severe arrhythmias should be treated before pregnancy;  $\text{SatO}_2 < 85\%$  – pregnancy contraindicated.

### During pregnancy

Patients with Ebstein's anomaly without cyanosis, heart failure, pulmonary hypertension, and arrhythmia (WHO class II): clinical and echocardiographic monitoring every trimester of pregnancy and after delivery.

Patients with Ebstein's anomaly with pulmonary hypertension and supraventricular arrhythmia: close clinical and echocardiographic monitoring every 2 to 4 weeks during the first and second trimesters of pregnancy and once a week after the 28 week of pregnancy in tertiary center with experience in the management of patients with congenital heart diseases. Holter monitoring and serial measurements of oxygen saturation and NT-proBNP levels are recommended. Obstetric

and fetal ultrasound should be regularly performed. Medical treatment: heart failure and arrhythmia therapy based on clinical status.

### Delivery

Assisted vaginal delivery with epidural analgesia. Cesarean section in case of maternal or fetal complications.

### After pregnancy

Right heart catheterization and correction of Ebstein's anomaly are recommended.

The present patient had been a subject of a preliminary report published in the *Journal of Rare Cardiovascular Diseases*.

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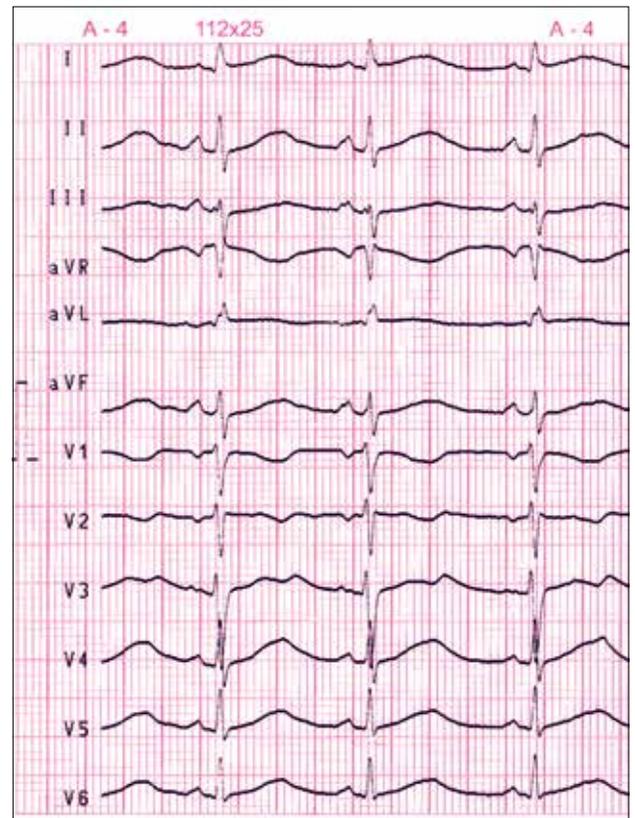
## Long QT syndrome diagnosed in the postpartum period (RCD code: VII-V-1A.2)

Piotr Kukla, Marek Jastrzębski,  
Agnieszka Zienciuk-Krajka

### Case Report

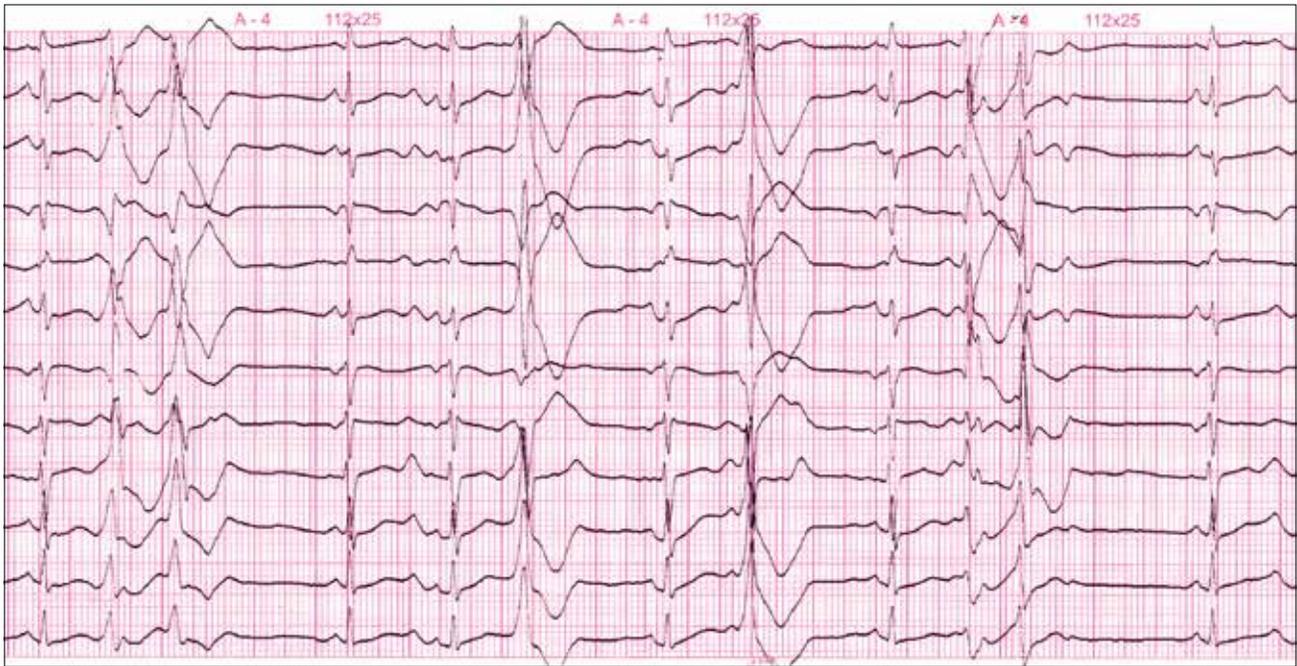
The present patient had been a subject of a preliminary report published elsewhere [1]. A 22-year-old woman, after delivery of her first child 6 months earlier, was transferred to our department by an emergency ambulance following syncope with involuntary micturition at home (blood pressure measured at home, 60/40 mm Hg). On admission, the patient's mentation was good and she reported feeling weak; on examination, tachycardia of 100 beats/min was noted; blood pressure on admission was 90/60 mm Hg. The results of laboratory tests were normal, with the exception of low serum magnesium level (0.56 mmol/L). A resting electrocardiogram (ECG) demonstrated sinus tachycardia of 110 beats/min with an isolated ventricular arrhythmia of dual morphology. Treatment included intravenous fluid and magnesium supplementation.

An ECG on the following day demonstrated a normal heart rate of up to 76 beats/min, an elongated QT interval of up to 460 ms, and a QTc interval of 517 ms. Other findings included atypical T-wave morphology in leads V<sub>2</sub> through V<sub>4</sub> (a camel-hump, bipartite T wave) (fig. 1). A suspicion of long QT syndrome (LQTS) was raised. On a resting ECG, a pronounced morphology of terminal T-wave phase in leads V<sub>2</sub> through V<sub>4</sub> (fig. 2). On the following days, the QT interval measured by standard ECG in the morning ranged from 520 to 540 ms and after QTc correction it ranged from 536 to 547 ms. Findings in Holter ECG monitoring included a mean sinus rhythm rate of 67 beats/min (with a maximum of 145 beats/min, minimum of 45 beats/min), an isolated premature ventricular contraction (PVC) with dual morphology (340 PVC s/d), a circadian T-wave polymorphism (5 morphological types of the T wave) (fig. 3). The QT interval ranged from 412 to 583 ms and the QTc from 425 to 618 ms. Mean QT and QTc were 516 ms and 538 ms, respectively. The so called postextrasystolic T-wave changes were observed with increased T-wave amplitude and significant QT-interval elongation in sinus beats directly following the premature ventricular beats when compared with the sinus beats preceding the PVCs (fig. 2, 4). A treadmill exercise stress test demonstrated initially exacerbated ventricular arrhythmia (including bigeminy), while at >135 beats/min, it subsided and reappeared in the resting phase. An ECG performed directly after completion of the exercise stress test demonstrated a shortened QT interval of 440 ms and a QTc of 419 ms. The QT interval/QTc response at peak exercise load and throughout the stress test could not be assessed because of numerous ventricular arrhythmias. Due to the variable T-wave morphology (camel-hump T



**Fig. 1.** Electrocardiogram on admission after the first syncope episode. Heart rate, 76 beats/min; QT interval, 460 ms; QTc interval, 517 ms. Bipartite, camel-hump T wave in leads V<sub>2</sub> through V<sub>4</sub>

wave), we suggested an initial diagnosis of LQTS type 2 [2]. The patient scored 5 points in the Schwartz scale, i.e., high likelihood of LQTS. She supplied an ECG trace performed 1 year earlier during a routine health check, demonstrating a QTc interval of 480 ms. An echocardiogram was carried out and no structural pathology of the heart was detected. A family history revealed no sudden cardiac death (SCD); however, the patient's mother sustained an ischemic stroke at the age of 45 years, which was attributed to aortic insufficiency. A  $\beta$ -blocker (metoprolol) was started at a dose of 75 mg/d. The treatment resulted in QT-interval reduction from 520 ms to 460 ms. Metoprolol dose was gradually increased in one-week intervals from 25 mg/d to 200 mg/d under ECG and Holter monitoring. The patient's family members were also screened with ECG: the father, mother, sister, and the 6-month-old son of the patient had no features of LQTS. A follow-up Holter ECG trace revealed episodes of ventricular bigeminy and ventricular pairs. No episodes of complex ventricular arrhythmia were observed. The patient took metoprolol regularly at 200 mg/d. After 2 years, 3 months after delivery of the second child, the patient had an episode of complete syncope. At that time, she was using metoprolol at 50 mg/d. The patient reduced the  $\beta$ -blocker dose on her own because of frequent hypotensive episodes and poor tolerance of high metoprolol doses (exceeding 100 mg/d). On admission, the ECG demonstrated ventricular bigeminy. Two consecutive 24-hour Holter ECG tests, despite increased  $\beta$ -blocker doses, revealed episodes of



**Fig. 2.** Electrocardiogram on the second day of follow-up. There is an evident increase in the T-wave amplitude in sinus beats following the premature ventricular beats (so called postextrasystolic T-wave changes)

polymorphic *torsade-de-pointes* (TdP) ventricular tachycardia – 4 episodes lasting up to 7 seconds (fig. 5). A cardioverter-defibrillator device (ICD) was implanted. Over the 15-month follow-up, no appropriate device interventions were observed.

## Discussion

LQTS is associated with elongated QT, variable T-wave morphology, and typical clinical symptoms (loss of consciousness, presyncope, palpitations, cardiac arrest, or incidents of malignant ventricular arrhythmia) [2]. The characteristic arrhythmia pattern is polymorphous TdP ventricular tachycardia initiated with a typical short–long–short sequence. Dangerous ventricular arrhythmias increase the risk of SCD.

Very commonly, congenital LQTS is characterized by paucity of symptoms and the abnormal repolarization period is exacerbated only in pregnancy and the postpartum period, triggering arrhythmia.

Pregnancy and the postpartum period result in elevated activity of the sympathetic system, which, in the presence of LQTS, is associated with elevated risk of arrhythmia. In addition, estrogen and progesterone levels are elevated in pregnancy, stimulating the adrenergic receptors. The above hormones affect the protein and potassium channel kinetics. A recent outstandingly well-designed and documented experimental model study conducted by Odening et al. [3], evidenced an arrhythmogenic effect of estradiol and a protective antiarrhythmic effect of progesterone. In the editorial comment to this study in the *Heart Rhythm*, Arthur Moss stated that the initial analysis of an international LQTS registry (not yet published) indicates that women

using contraceptives experience far fewer cardiac events than women who do not use such drugs [4]. It is possible that contraceptives containing an increased ratio of progesterone to estradiol will become a “new” group of antiarrhythmic drugs targeted for women with LQTS, notably LQTS type 2 [5].

In the postpartum period, the heart rate becomes slower, which is associated with increased QT interval. Stress associated with baby care and the altered sleep/rest patterns are associated with elevated sympathetic system activity possibly leading to dangerous ventricular arrhythmias. Rashba et al. [6] have evidenced in the LQTS registry that in a group of 442 patients and relatives the cardiac incidents were especially frequent in the postpartum period (the first 40 weeks following delivery). Almost 10% of the patients experienced their first cardiac incident in the postpartum period. Cardiac incidents were observed before pregnancy in 3.8% of the patients, and in 9% and in 23% in pregnancy and postpartum period, respectively.  $\beta$ -blocker treatment throughout pregnancy and in the postpartum period was associated with a significant reduction of cardiac incidents.

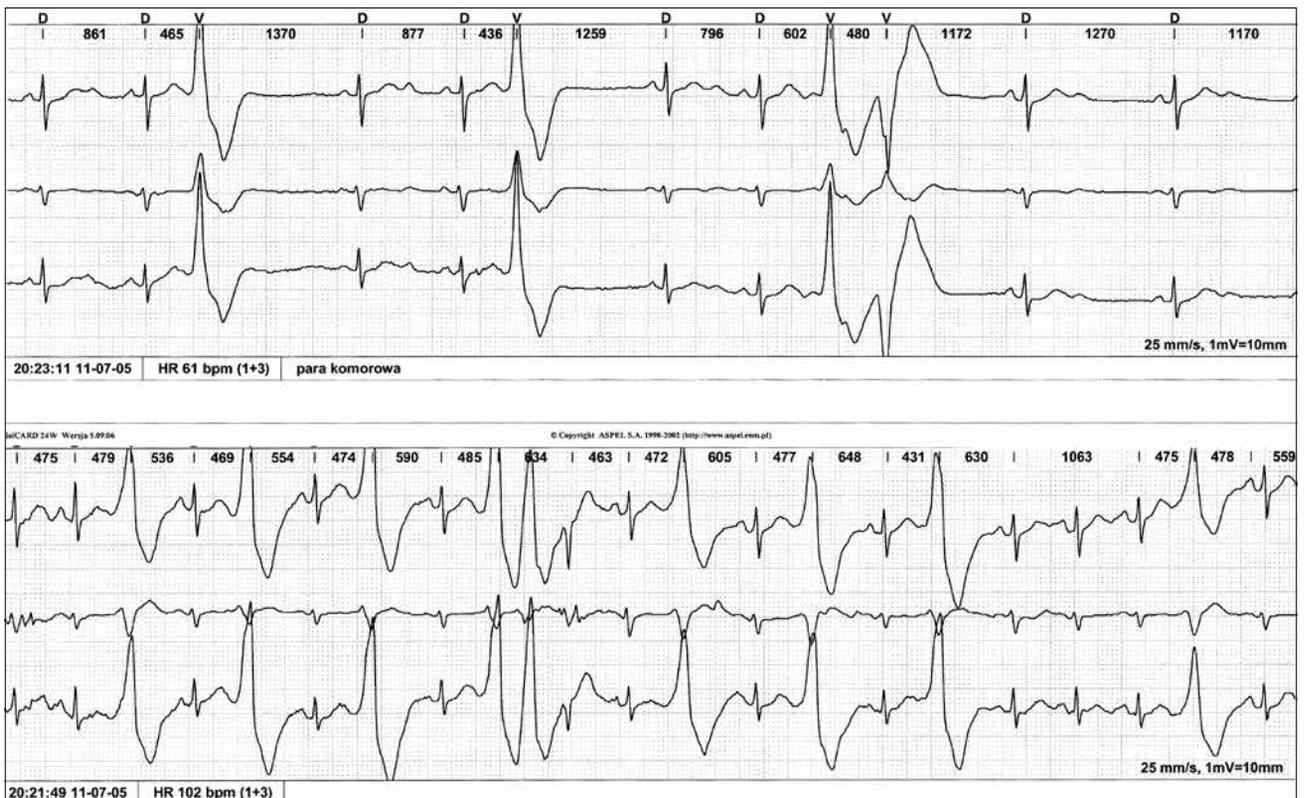
Our patient is a typical example of the initial cardiac incident in the postpartum period. The recommended management includes a  $\beta$ -blocker and its continuation throughout pregnancy, breastfeeding, and the postpartum period [6].

According to Priori et al. [7],  $\beta$ -blocker treatment is associated with a significant benefit in LQTS type 1, whereas in types 2 and 3,  $\beta$ -blockers do not significantly reduce the incidence of cardiac incidents. The incidents were observed in 10% of the patients with LQTS type 1, in 23% with LQTS type 2, and in 32% of the patients with LQTS type 3.

Furthermore, patients with QTc interval above 500 ms and those who had their first cardiac episode



**Fig. 3.** Holter electrocardiogram trace. Different periods of the day. The trace demonstrates T-wave polymorphism. Reprint with permission of *Kardiologia Polska* Editorial Board and the Via Medica Publishing Company, Gdańsk, Poland



**Fig. 4.** Holter electrocardiogram trace. Ventricular arrhythmia; episode of ventricular bigeminy. Reprint with permission of *Kardiologia Polska* Editorial Board and Via Medica Publishing Company, Gdańsk, Poland



Fig. 5. A, B. 24-hour Holter electrocardiogram monitoring. Two consecutive tests where *torsade-de-pointes* episodes were noted

before the age of 7 years are especially susceptible to cardiac incidents despite  $\beta$ -blocker treatment.

The recent analysis by Priori et al. [7] indicates that the risk of a cardiac incident in LQTS patients not receiving treatment is 13% per year. The risk in LQTS type 1 depends primarily on the QTc-interval duration. Men with LQTS type 1 and QTc interval above 500 ms are more susceptible to cardiac incidents in childhood, while women with QTc interval above 500 ms have unchanging prognosis independent of the age. In LQTS type 2, female sex is a predictor of cardiac incidents independently of the QTc interval. In LQTS type 3, the prognosis is sex-dependent – males are a high-risk group, especially before the age of 40 years. Khositseth et al. [8] have recently demonstrated that women with LQTS type 2 are especially susceptible to cardiac incidents such as SCD, circulatory arrest, or syncope in the postpartum period. Of all patients followed up with one of the above endpoints, 93% had LQTS type 2. Postpartum cardiac incidents were significantly more common in patients with LQTS type 2 when compared with patients with LQTS type 1 (16% vs. 1%, respectively). The study by Seth et al. [9] also confirmed the prior observations by Khositseth et al. [8] indicating that pregnancy in women with

LQTS is associated with lower risk of cardiac incidents. The postpartum period, notably its first 9 months, is associated with elevated risk, especially in patients with LQTS type 2 [9]. The use of  $\beta$ -blockers is associated with a significant reduction of cardiac incidents, notably in the high-risk postpartum period. The genetic studies to establish accurate diagnosis and determine the LQTS type (mutation type) are especially important and required for risk assessment and clinical decision making.

## Recommended treatment

The following  $\beta$ -blockers and doses are recommended in the treatment of LQTS [10]:

- Metoprolol (1.8 mg/kg/d)
- Propranolol (2.9 mg/kg/d)
- Nadolol (1.4 mg/kg/d)
- Atenolol (1.3 mg/kg/d)

The current European Society of Cardiology / American Heart Association / American College of Cardiology 2006 guidelines recommend the following treatment of LQTS [11]:

**Class I recommendations**

1. Lifestyle modification in patients with clinical and/or molecular LQTS diagnosis (*evidence level B*).
2.  $\beta$ -blockers in patients with clinical diagnosis of LQTS (with long QT interval on ECG) (*evidence level B*).
3. Implantation of an ICD +  $\beta$ -adrenolytics in patients with LQTS who previously survived cardiac arrest (*evidence level A*).

**Class IIa recommendations**

1.  $\beta$ -blockers in patients with normal QT interval and molecularly confirmed LQTS (*evidence level B*).
2. ICD implantation +  $\beta$ -adrenolytics in prevention of SCD in patients with syncope or recorded ventricular tachycardia episodes during treatment with  $\beta$ -blockers (*evidence level B*).

**Class IIb recommendations**

1. Ablation of the left stellate ganglion (left sympathetic cardiac denervation, LCS D) can be considered in patients with syncope, TdP tachycardia, or circulatory arrest during treatment with  $\beta$ -blockers (*evidence level B*).
2. ICD implantation + treatment with  $\beta$ -adrenolytics in primary prevention of SCD in probable high-risk patients such as LQT2 and LQT3 (*evidence level B*).

Various treatment and risk stratification schemes have been proposed. Recently, Schwartz et al. [12] suggested the following LQTS patient groups as candidates for ICD implantation:

1. All patients who survived cardiac arrest during  $\beta$ -blocker treatment
2. Most patients who survived cardiac arrest without prior  $\beta$ -blocker treatment
3. Symptomatic patients (syncope) despite full  $\beta$ -blocker dose, where the LCS D option is unavailable or not accepted by the patient
4. All patients with 2 mutations who remain symptomatic despite treatment with full  $\beta$ -blocker dose
5. Exceptionally, asymptomatic patients with significant QTc elongation  $>550$  ms, who present with electrical instability, for example, T wave or very long pauses favoring early after depolarizations and consequently TdP.

Despite the numerous risk stratification schemes, the clinical question of which LQTS patients should only receive a  $\beta$ -blocker and which should additionally be implanted with an ICD is difficult. The current recommendations (2006) for ICD implantation in prevention of SCD in LQTS appear to be defective.

In our case, syncope episodes were always observed in the postpartum period. However, the first episode occurred without  $\beta$ -blocker treatment when the patient was not yet diagnosed with LQTS. The second episode of complete syncope was observed during  $\beta$ -blocker

treatment. However, the patient was on a suboptimal  $\beta$ -blocker dose at that time. Furthermore, when hospitalized and with increased  $\beta$ -blocker dose, the ECG monitoring revealed TdP episodes. The decision of ICD implantation in the young patient is always controversial and difficult. We made the decision of ICD implantation considering the following factors:

1. syncope with documented TdP during  $\beta$ -blocker treatment
2. significantly elongated QTc interval in Holter ECG monitoring; max QTc – 618 ms
3. maternity and care of two children by our patient and periodic suboptimal  $\beta$ -blocker dosing because of the tendency for recurrent hypotensive episodes and intolerance of high  $\beta$ -blocker doses.

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## Ablation of incessant supraventricular tachycardia in pregnancy (RCD code: VII-V-3A)

Marek Jastrzębski, Renata Rajtar-Salwa, Danuta Czarnecka

### Introduction

Previous supraventricular arrhythmias may become exacerbated and new arrhythmias may occur in pregnancy. However, supraventricular tachycardia is observed only in approximately 0.024% of pregnancies [1]. It is usually triggered by episodes of nodal reentrant tachycardia or atrioventricular tachycardia in the presence of a latent accessory pathway; focal atrial tachycardia is less commonly observed. Treatment of arrhythmia in pregnancy constitutes a significant therapeutic challenge because the main treatment modalities, namely, pharmacotherapy and ablation, are burdened with significant risks for the fetal health.

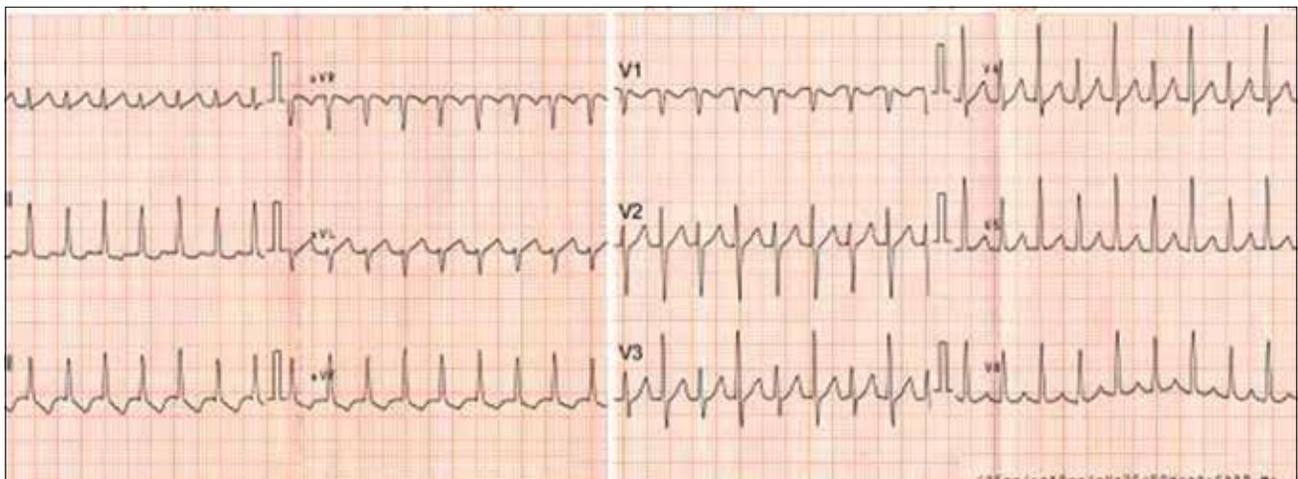
### Case report

A 40-year-old woman, 4-months pregnant (in vitro fertilization), was admitted to a district hospital due to incessant supraventricular tachycardia with a rate of 187 beats/min (fig. 1). Attempts to stop the arrhythmia (3×cardioversion, verapamil IV) were unsuccessful; after cardioversion, tachycardia recurred after a few sinus beats. The patient was transferred to the university hospital for interventional management of arrhythmia. An electrocardiogram showed long RP-interval tachycardia [2]. The remaining tests (echocardiography, biochemical studies) showed no significant abnormalities. It was decided to attempt pharmacotherapy again (adenosine IV, metoprolol IV, metoprolol PO) without

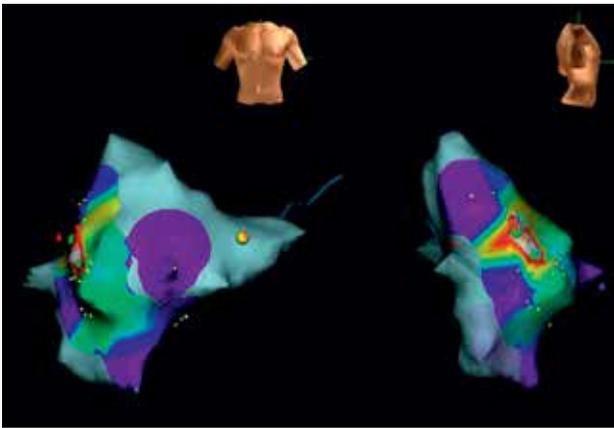
success. In the view of poor arrhythmia tolerance (hypotonia, dyspnea) and the risks associated with incessant tachycardia (placental hypoperfusion, development of tachyarrhythmic cardiomyopathy), it was decided to perform an electrophysiology study and ablation [3-5]. The procedure was carried out with the use of a computer mapping system (Ensite NavX, St Jude Medical, USA), aiming to minimize standard fluoroscopy use [6]. The electrophysiology study indicated the presence of focal right-atrial tachycardia (fig. 2). In this situation, geometric and activation mapping of the right atrium was carried out, visualizing the arrhythmogenic focus in the inferolateral portion of the tricuspid ring (fig. 3). After several radiofrequency (RF) applications, arrhythmia subsided and sustained sinus rhythm was restored (fig. 4). After 30 minutes of observation and attempts to induce arrhythmia by stimulation and isoprenaline infusion, the procedure was terminated. Total fluoroscopy time in the procedure was only 90 seconds; the total radiation exposure was 12 mGy. In addition, the abdomen of the pregnant woman was shielded with lead gowns from both sides, thus nearly completely eliminating the fetal radiation exposure. After 4 weeks, the arrhythmia returned (fig. 5), again in the form of incessant tachycardia with a rate of 150–180 beats/min, which was found to be resistant to drugs (verapamil IV, metoprolol 3×50 mg PO). Recurrence of arrhythmia was thought to result from incomplete ablation of the ectopic focus due to instability of the ablation catheter during the initial procedure. A repeat ablation was carried out in an identical fashion as the index procedure, again with the use of spatial mapping and only minimal fluoroscopy time (62 s, 10mGy), this time successfully stopping the arrhythmia. Throughout the observation period, no recurrence of tachycardia was observed.

### Discussion

The causes for exacerbation of supraventricular arrhythmia in pregnancy have not been well studied; factors such as the effect of autonomous and endocrine



**Fig. 1.** Electrocardiogram. QRS tachycardia; rate, 185 beats/min. P waves poorly visible overshadowed by the ST-T complex of the preceding evolutions; negative in leads II, III, aVF, and aVR; positive in leads I and aVL. QRS alternans in precordial leads and ST depressions in leads II, III, and aVF



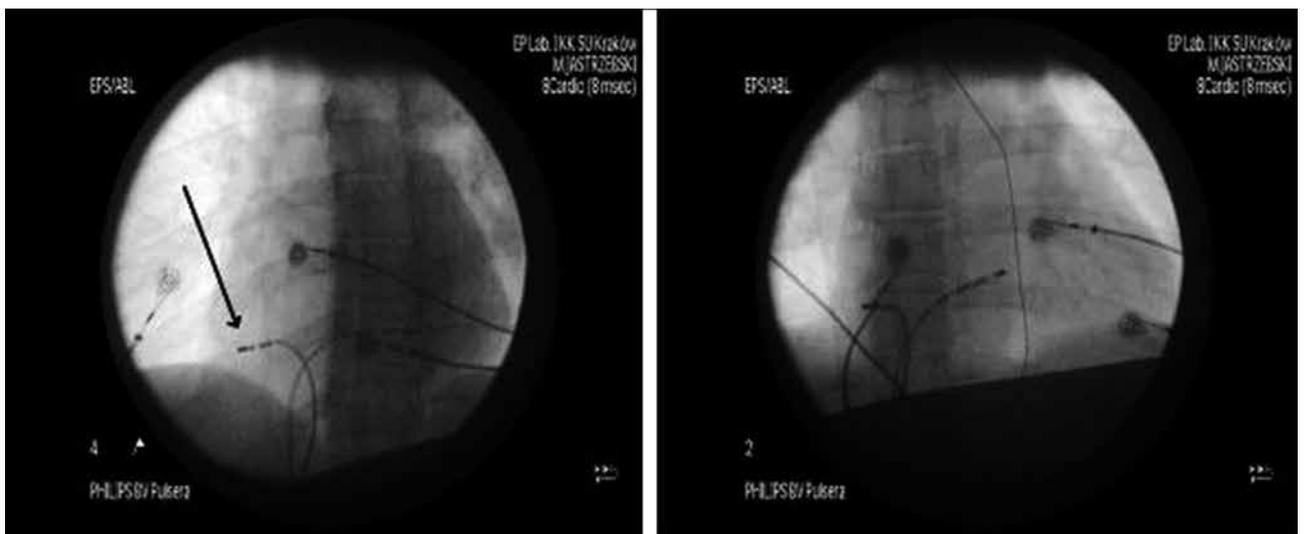
**Fig. 2.** Geometric and activation mapping of the right atrium in anteroposterior and lateral views. Red and white colors denote the sites of most early activation during tachycardia

systems, emotional status, and hemodynamic changes in pregnancy (increased cardiac output, hypervolemia, atrial distension/enlargement) have been proposed. Among pregnant women with supraventricular tachycardia present before pregnancy, approximately 22% to 44% will experience arrhythmia exacerbation in pregnancy; for 3.9% of the pregnant women, arrhythmia in pregnancy is the first manifestation of the disease [7–9].

The use of antiarrhythmic drugs in pregnancy raises justified concerns about adverse effects on the fetus. It should be noted that despite general acceptance and a long tradition of the use of some drugs such as  $\beta$ -blockers (with the exception of atenolol), digoxin, verapamil, and, less commonly, flecainide and propafenone, these drugs have not been well studied in this clinical setting and, therefore, are classified as Food and Drug Administration, USA, (FDA) class C, i.e., “Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential

benefits may warrant use of the drug in pregnant women despite potential risks” [6,10]. Therefore these drugs, although relatively safe for short-time use, are suboptimal for chronic prophylactic use, especially at higher doses and in the first trimester of pregnancy. Even the safe  $\beta$ -blockers are associated with reduced placental perfusion and preterm birth; therefore, they are hazardous for normal fetal development. Other drugs such as amiodarone have documented adverse effects and are classified as FDA class D [11]. Nevertheless, there are reports of the use of amiodarone in the management of supraventricular tachycardia in pregnancy [9]; this practice should be considered inadequate in the age of ablation. In our case, the use of antiarrhythmic drugs was unsuccessful and we decided against amiodarone administration.

Even less evidence is available regarding the RF ablation treatment of arrhythmia in pregnancy than regarding pharmacotherapy. The available literature only includes a few case reports and small patient series ( $n = 9$ ) [3,4,12–18]. Most of the reported cases are reentrant tachycardias with well-defined background, often in standard location (the slow pathway of the atrioventricular node, accessory pathway); only a few case reports of pregnant women treated with ablation due to focal atrial tachycardia are available in the literature [4,12,13,18]. Computer-based three-dimensional mapping systems have facilitated the positioning of ablation catheters without the use of fluoroscopy and have become the standard of care. Thanks to this technology, it is possible to completely eliminate or minimize fluoroscopy exposure during ablation. The current guidelines for cardiology care of pregnant women support the RF ablation in cases where drug therapy has been ineffective and in cases of poor hemodynamic tolerance of arrhythmia; the proposed recommendation class is IIb (i.e., treatment to be considered in selected cases) [5]. Without doubt, a thorough analysis of indications is



**Fig. 3.** Fluoroscopy image demonstrating the diagnostic catheter position in the coronary sinus and the ablation catheter (black arrow) in the inferolateral area at the tricuspid ring; this was the site of effective radiofrequency ablation. Left oblique (left panel) and right oblique (right panel) views



**Fig. 4.** Electrocardiogram. After ablation: 12-lead ECG demonstrating sinus rhythm; normal trace

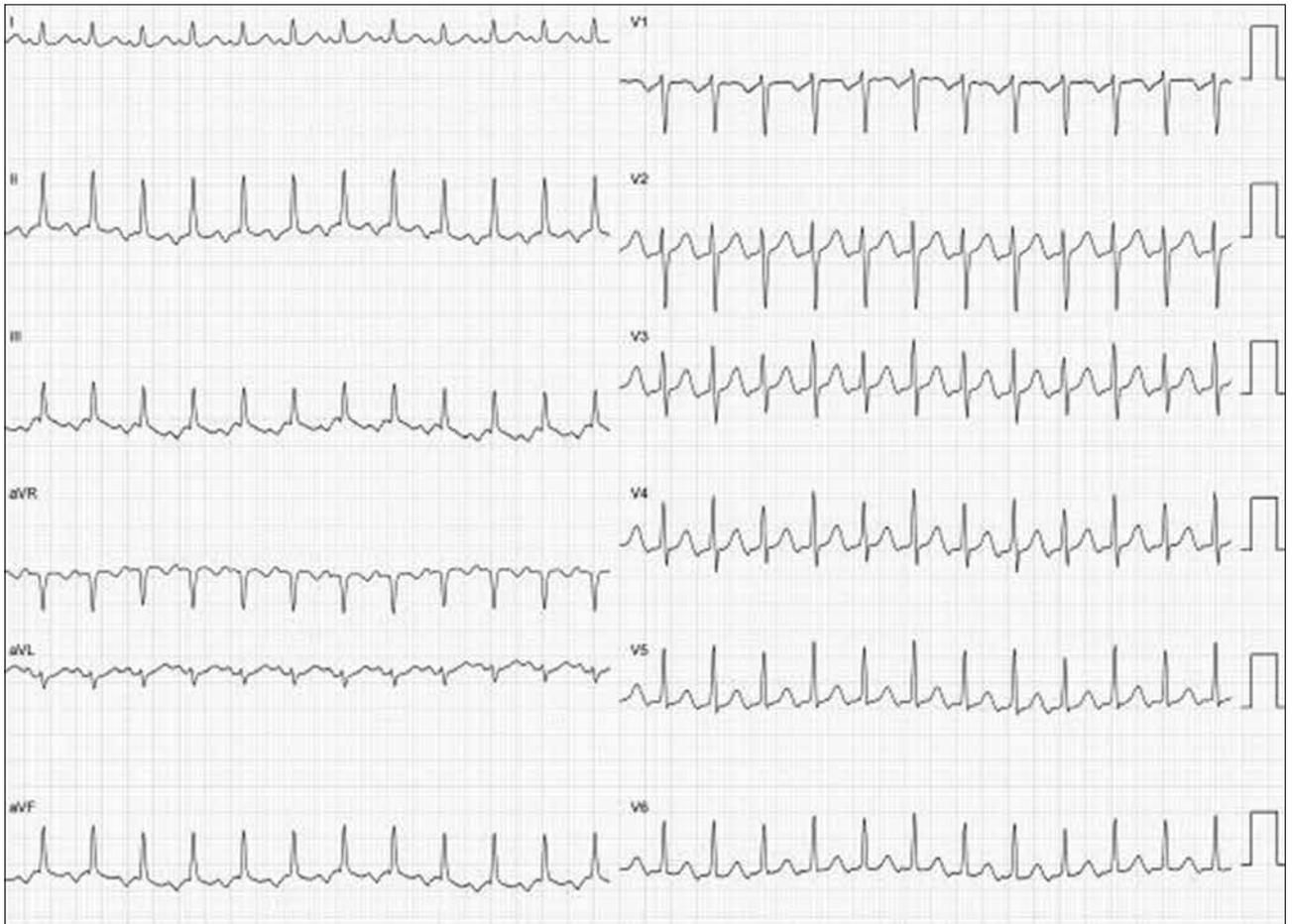
mandatory in each case and the procedure should be reserved for experienced operators.

Incessant long RP-interval tachycardia (fig. 5) constitutes a diagnostic challenge [2]. This ECG picture (negative P waves in leads II, III, and aVF directly preceding the QRS complexes) can be a manifestation of persistent junctional reciprocating tachycardia, re-entrant nodal tachycardia (atypical forms), or focal atrial tachycardia. In the presence of nondecisive electrocardiogram, the differential diagnosis should be based on electrophysiology maneuvers (response to entrainment and ventricular single-impulse stimulation in the His bundle refraction period). In our case, the atrioventricular dissociation during the entrainment attempts excluded accessory pathway tachycardia as a diagnosis and the activation mapping documenting the nonconcentric atrial activation in the septal region (as in nodal reentrant tachycardia), but eccentrically located in the lateral portion of the tricuspid ring, enabled us to make certain diagnosis of focal atrial tachycardia. The atrial ectopic focus can be located anywhere in the left or right atrium. The P-wave morphology is a certain hint. In the presented case, negative P waves in leads II, III, and aVF indicated a focus location in the inferior portion of the atria, whereas positive P waves in leads I and aVL and negative in lead aVR – a right-atrial focus, respectively; this was fully confirmed by endocavitary activation mapping. There are several areas in

the right atrium where ectopic foci are preferentially located, including the crista terminalis, mitral ring, coronary sinus ostium, His bundle area, and auricula. In our case, the ectopic focus was located in the ring area and therefore falls within this rule.

## Summary

The treatment of arrhythmia in pregnancy with RF ablation is the last resort; however, the available evidence indicates good efficacy and safety of the method. It enables to discontinue the potentially harmful drugs and facilitates further management of pregnancy and delivery. Further development/standardization of the radiation-free methods in the future will possibly make ablation a method of choice in pregnancy, thus rendering chronic antiarrhythmic pharmacological treatment superfluous. To minimize the need for ablation procedures in pregnancy, women with a history of arrhythmia should be referred for an electrophysiology consult before planned pregnancy.



**Fig. 5.** 12-lead electrocardiogram obtained after arrhythmia recurrence. Typical long RP-interval tachycardia. Negative P waves in leads II, III, and aVF; positive P waves in leads I and aVL – indicating the triggering of atrial activation within the inferior portion of the right atrium. Such image can be observed in nodal reentrant (atypical) tachycardia, atrioventricular reentrant tachycardia (including persistent junctional reciprocating tachycardia), or atrial focal tachycardia

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## Cardiac tumor in a pregnant woman (RCD code: VII-VI-1A2a)

Magdalena Kostkiewicz, Agata Leśniak-Sobelga, Małgorzata Urbańczyk-Zawadzka, Robert Banyś, Piotr Podolec

### Background

Primary cardiac tumors are uncommon. In an autopsy series, the prevalence rates of cardiac tumors among all age groups were found to range between 0.0017% and 0.28% [1]. The most common primary tumor is myxoma, which is followed in frequency by fibroma [2]. Fibromas are intramural and usually arise from the free wall of the left ventricle or interventricular septum. Involvement of the right ventricle is extremely rare [3]. Although cardiac fibroma is a benign and solitary tumor [6] composed of fibroblasts and collagen [7,8], it is clinically important as it may present with symptoms such as inflow and outflow obstruction, conduction system disease, and sudden death. Fibromas may not require resection unless they are causing obstruction or severe symptoms. We present a case of a pregnant woman with primary cardiac fibroma that originated in the interventricular septum.

### Case presentation

A 24-year-old woman was admitted to the hospital at 13 weeks of pregnancy, complaining of slight chest pain and the feeling of rhythm disturbance. Blood pressure was recorded at 110/70 mm Hg and respiratory rate at 16 breaths/min. Cardiac rhythm was normal (90 beats/min). There were no murmurs, clicks, third or fourth heart sounds, or pericardial friction rub. There was no evidence of jugular venous distention, and peripheral arterial pulses were normal and equal. A pulmonary examination revealed no abnormality. There was no peripheral edema, and the remainder of the physical examination revealed no major abnormalities. Laboratory tests showed hematocrit levels of 42.1%, white blood cell count of 10,100/mm with 92% of neutrophils and 4% of bands; the other hematological parameters were normal and there were no electrolyte abnormalities or evidence of metabolic, renal, or hepatic dysfunction. The levels of creatine kinase and lactic dehydrogenase isoenzymes were normal. During the observation, the patient remained asymptomatic but was noted to have ventricular ectopia on Holter monitoring. The cardiac rhythm normalized after administration of a  $\beta$ -blocker. The findings of an echocardiographic examination showed a cardiac mass originating from the intraventricular septum, measuring 32/34 mm (fig. 1, 2). The mass extended into the left and right ventricles and slightly obstructed the left



**Fig. 1.** Transthoracic echocardiography. Apical images. A large oval mass in the interventricular septum (arrows). RV – right ventricle, LV – left ventricle, LA – left atrium, RA – right atrium



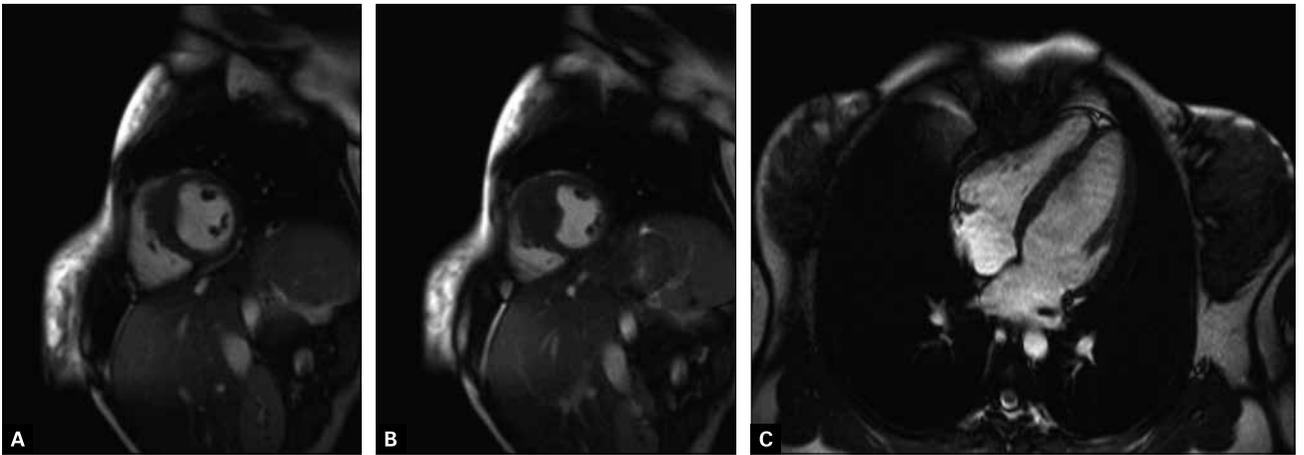
**Fig. 2.** Transthoracic echocardiography. Longitudinal long axis. A large nonhomogeneous mass in the interventricular septum (arrows). RV – right ventricle, LV – left ventricle, LA – left atrium

and the right ventricular inflow. The interventricular septal movement was preserved except in the area of the tumor, which appeared to be fixed.

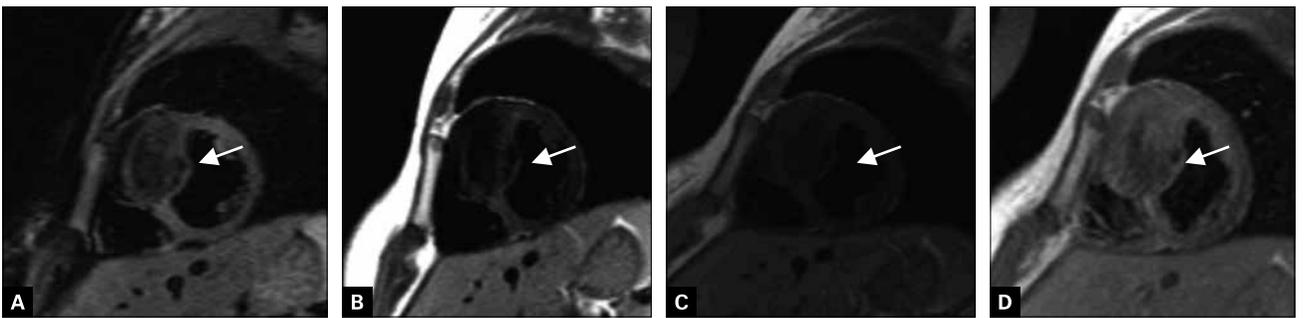
The differential diagnosis included a fibroma, hematoma, and rhabdomyoma. The T1-weighted magnetic resonance image revealed a large mass arising from the interventricular septum confirming the echocardiographic diagnosis of a fibroma (fig. 3). During pregnancy, the patient was asymptomatic with  $\beta$ -blocker treatment and she delivered her baby vaginally without complications. The patient is now waiting for an operation.

### Discussion

Congenital cardiac fibromas are rare lesions that are more common in infants and children than in adults. These tumors are benign proliferations of the connective tissue, and their tissues blend with or infiltrate normal myocardium [3,4]. In neonates and young infants, the tumors are cellular and have fibromyxoid stroma with a varying number of collagen and elastic fibers. As



**Fig. 3.** Cardiac magnetic resonance imaging. Cine GE (gradient echo) images shows a large mass in the intraventricular septum (arrows). **A, B.** Short-axis view. **C.** Four-chamber view



**Fig. 4.** Cardiac magnetic resonance imaging. Morphology short-axis view images shows a large mass in the intraventricular septum (arrows). **A.** T2 weighted Short Time Inversion Recovery (STIR) image. **B.** T2 weighted image. **C.** T1 weighted image before contrast agent (gadolinium) injection. **D.** T1 weighted image after contrast agent (gadolinium) injection

an infant with a fibroma matures, collagen and elastin depositions increase and cellularity decreases [5]. Echocardiographic findings show a homogeneous echogenic mass usually arising from the interventricular septum and the free wall of the left ventricle. There may be hyalinization or cystic degeneration in the central part of a fibroma. In the case of cystic degeneration, the tumors can show nonhomogeneous echogenicity. In patients with ventricular septal involvement, the symptoms may include heart failure, arrhythmias, sudden death, cyanosis, and chest pain. Cardiac fibroma involving the interventricular septum more frequently induces conduction system disease. Tachyarrhythmias, primarily ventricular tachycardia, are the presenting manifestation in a substantial number of patients with cardiac fibroma, and, in many others, these arrhythmias develop during the clinical course.

Usually, an arrhythmogenic tumor involves the ventricular wall. Syncope or near syncopal episodes, palpitations, and shock-like states due to decreased cardiac output can result from tachyarrhythmias. In these cases, electrical defibrillation or cardioversion may be required. Deterioration of arrhythmia into ventricular fibrillation might have been responsible for some cases of sudden death.

The two-dimensional echocardiographic study remains the primary initial technique to identify the presence of a fibroma. Newer noninvasive imaging

techniques are aimed at enhancing the capability for definitive diagnosis by clearer tissue definition.

### Management strategy

In our patient, the fibroma was growing from the interventricular septum and echocardiography showed a large nonhomogeneous echogenic mass along the septum. The optimal management of pregnant patients with a fibroma has not been established. In the absence of severe structural anomaly or congestive heart failure, there is no need to modify standard obstetrical management, but delivery in a tertiary care center where a pediatric cardiologist is immediately available is mandatory. After delivery, the surgical removing of the tumor should be considered because of the risk of sudden death. The lethal potential of cardiac fibroma is suggested by the fact that in 10% of the reported cases, death was the initial manifestation (prior to discovery of a tumor), while in another 10%, death was the terminal event (soon after discovery of a tumor). Sudden death was more frequent if the tumor involved the interventricular septum, and, according to McAllister and Fenoglio [9], it was caused either by compression or invasion of the conduction system.

With the preoperative diagnostic possibilities now available, the procedure may be planned before the patient arrives in the surgical suite. The operative management of cardiac fibroma depends on tumor size and site. If partial or complete excision is not possible (which is rare and rather unlikely), cardiac transplantation may be considered.

## Conclusion

In summary, fibroma should be considered in the differential diagnosis in patients in whom echocardiography reveals solid masses originating in the interventricular septum and showing nonhomogeneous echogenicity. Magnetic resonance imaging provides additional information on tissue components. After delivery, the surgical removal of the tumor should be considered because of the risk of sudden death.

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# Part 10

Unclassified rare cardiovascular diseases  
– RCD class VIII

**Editor: Jakub Podolec**



# Introduction

Jakub Podolec

In everyday practice, even that based on great experience of high-volume cardiac centers, investigations reach the point where current knowledge provides no direct answers. These are the cases of patients in whom standard diagnostic and treatment methods are not helpful or difficult to interpret. It is also often the case that typical diseases coexist in one patient and a multidisciplinary approach including experts of various fields is needed to provide an adequate diagnosis and advice regarding the way of treatment. For example, a 62-year-old patient has severe aortic stenosis, significant right coronary artery stenosis, and vascular malformation in the intestine causing severe bleedings resulting in severe anemia. The patient is often hospitalized and blood transfusions are needed. At this point, an important question is – what would you do? What to start with? Is this patient a candidate for aortic valve replacement and bypass grafting to the right coronary artery while severe bleeding from the intestine artery is highly probable during the extracorporeal circulation? Should the vascular malformation be treated first with a substantial risk of circulatory hemodynamic instability? Numerous such case presentations with expert opinions and conclusions are contained in this part on unclassified rare cardiovascular diseases.



# Unclassified rare cardiovascular diseases: Perspective of the Centre for Rare Cardiovascular Diseases

## ■ **Unclassified cardiovascular diseases**

Jakub Podolec

With knowledge based on the Orphanet database, our Centre experts' experience and the increasing number of patients recognized with rare or rare combination of cardiovascular diseases this class is rapidly growing. Our efforts to classify these diseases to the above published of Krakow Rare Cardiovascular Diseases (RCD) Classification classes were not fulfilling the main criteria used in order to classify them. At last but not the least, these patients in whom just few case presentations are published in the medical databases will be collected and presented to the CRCDC audience.

Examples of unclassified rare cardiovascular diseases derived from [www.orpha.net](http://www.orpha.net):

1. Anophthalmia- megalocornea- cardiopathy- skeletal anomalies
2. Dopamine beta-hydroxylase deficiency.
3. HEC syndrome
4. Brachydactyly – mesomelia – intellectual deficit – heart defects
5. Amoebiasis due to free-living amoebae
6. Congenital adrenal hyperplasia
7. Aceruloplasminemia
8. Alström syndrome
9. Autoimmune hemolytic anemia, warm type
10. Autosomal recessive cutis laxa type 1
11. Carney complex
12. Cutis laxa
13. Sclerosis
14. Erdheim-Chester disease
15. Primary lipodystrophy

16. Hereditary hemochromatosis
17. Hallermann-Streiff syndrome
18. Systemic capillary leak syndrome
19. PAGOD syndrome
20. Kearns-Sayre syndrome

In this RCD Classification unclassified class VIII the following diseases will be published:

- case presentations concerning rare cardiovascular diseases of which just few examples were published and the experience is strongly limited,
- multiorgan diseases with significant cardiovascular diseases,
- cardiovascular diseases which significantly influence the uptodate diagnostic and therapeutic guidelines of cardiovascular diseases and induce the need to create new insights and therapeutic algorithms,
- diseases or combinations of them which involve all parts of the cardiovascular system and are not fulfilling the above mentioned criteria of other classes.

Since cardiology knowledge is developing rapidly throughout the last decade, it is very probable that many of diseases described in this class will be classified and moved to more specific class in the future. The more we know and are able to classify, the more advantages we build for those patients based on the expanded groups of case presentations.



# Unclassified rare cardiovascular diseases: Clinical examples

## A 62-year-old woman with Heyde's syndrome (RCD code: VIII-1)

Hanna Dziejcz-Oleksy, Jakub Podolec,  
Agnieszka Sarnecka, Jakub Stępniewski,  
Monika Komar, Grzegorz Kopeć, Piotr Podolec

### Background

Heyde's syndrome is defined as a combination of gastrointestinal (GI) bleeding from GI angiodysplasia in patients with aortic stenosis. Edward Heyde was the first to publish, in 1958, a report of 10 patients with both aortic stenosis and GI bleeding. [1]. In 1992, Olearczyk identified this association of symptoms as Heyde's syndrome [2]. Furthermore, it has been proved that GI bleeding terminates after the aortic valve replacement surgery [3].

### Case presentation

A 62-year-old Caucasian woman with a history of familial thrombocytopenia was referred for cardiac evaluation because of heart murmur before a scheduled surgical procedure of the vascular malformation in the ascending part of the colon. Until that time, she had no problems with the cardiovascular system. Other medical conditions included thrombocytopenia, left adrenal adenoma (in the course of diagnosis), glaucoma of the right eye, and blindness of the left eye due to glaucoma.

In November and December 2012, recurrent bleedings from the lower part of the GI tract occurred. The patient was each time hospitalized because of hemorrhagic anemia and required multiple blood transfusion (a total of 10 units). Repeated colonoscopy and gastroscopy revealed no abnormalities.

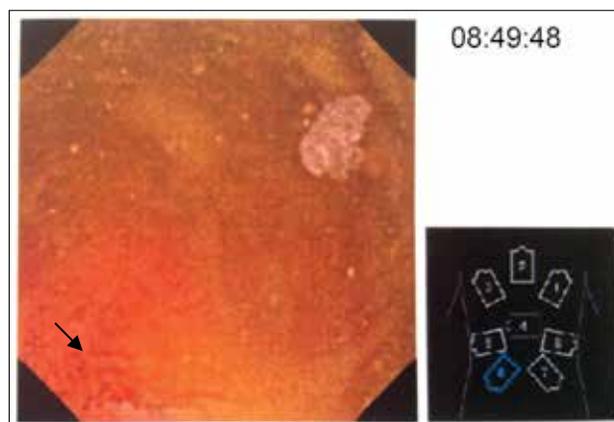
In December 2012, the patient was consulted by a hematologist because of familial thrombocytopenia, also diagnosed in the patient's daughter, siblings, and mother. At that time, the platelet count was 100 000/ $\mu$ L; there were no symptoms of skin or mucosa

bleeding (also in the patient's history) and no splenomegaly on an abdominal ultrasound. The conclusion stated that mild thrombocytopenia cannot be recognized as the cause of the recurrent bleedings, and further diagnostic procedures should be undertaken to find the cause (to exclude thrombocytopathies and von Willebrand disease). It was also advised to administer tranexamic acid and etamsylate for at least 2 weeks after the bleeding, to transfuse platelet concentrate in case of recurrent bleeding, and to avoid antiplatelet medications. After discharge, the patient did not show up at the hematology department and no diagnostic tests were performed.

In April 2013, GI bleeding occurred again. The patient was again hospitalized because of hemorrhagic anemia. This time, she was diagnosed with vascular malformation of the ascending part of the colon (fig. 1) and scheduled for a surgical removal of the malformation.

At that time, she was referred for the general evaluation before the surgical procedure. A general practitioner heard the murmur on heart auscultation and requested cardiac evaluation.

On admission to the department of cardiology, the patient presented with the symptoms of dizziness, which so far had been connected with anemia and eye problems. She denied fatigue, shortness of breath on exertion, chest pain, or arrhythmia. On a physical



**Fig. 1.** Capsule endoscopy. Vascular malformation (arrow) in the ascending colon

**Table 1.** Abnormal laboratory tests revealing posthemorrhagic anemia and hypercholesterolemia

Parameter	Value	Units	Reference
WBC	5.35	10 <sup>3</sup> /mCL	[3.80–10.00]
RBC	3.54	10 <sup>6</sup> /mCL	[3.70–5.10]
HGB	9.8	g/dL	[12.0–16.0]
HCT	31.8	%	[37.0–47.0]
MCV	89.8	fL	[80.0–99.0]
MCH	27.7	pg	[27.0–35.0]
MCHC	30.8	g/dL	[32.0–37.0]
RDW	19.0	%	[11.5–14.5]
PLT	140.0	10 <sup>3</sup> /mCL	[140–440]
T-CHOL	7.58	mmol/L	[3.10–5.00]
LDL-C	6.04	mmol/L	[<3.00]
HDL-C	1.35	mmol/L	[>1.20]
TG	1.34	mmol/L	[<1.70]

HCT – hematocrit, HDL-C – high density lipoprotein cholesterol, HGB – hemoglobin, LDL-C – low density lipoprotein cholesterol, MCV – mean corpuscular volume, MCH – mean corpuscular hemoglobin, MCHC – mean corpuscular hemoglobin concentration, PLT – platelets, T-C – total cholesterol, TG – triglycerides, RBC – red blood cells, RDW – red cell width, WBC – white blood cells

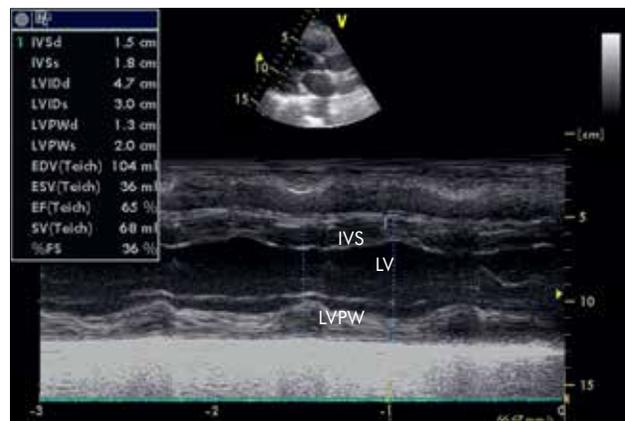
examination, her skin and conjunctiva were pale; on auscultation of the heart, a holosystolic murmur was heard, which was the loudest at the upper right sternal border, at the 2nd right intercostal space, radiating to the carotid arteries bilaterally.

The basic blood laboratory test revealed posthemorrhagic anemia and hypercholesterolemia (Table 1).

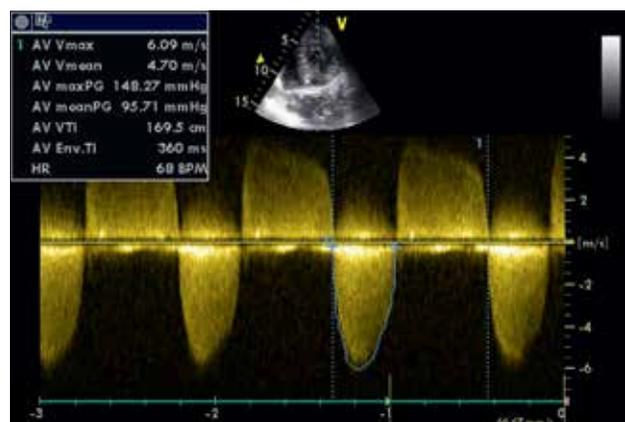
On echocardiography, the normal size of the left ventricle (47/30 mm) was seen with the hypertrophy of the heart muscle (left ventricular posterior wall, 13/20 mm; intraventricular septum, 15/18mm). There were no wall motion abnormalities and the ejection fraction was 65% (fig. 2). On echocardiography, severe aortic stenosis with moderate regurgitation was diagnosed. The aortic leaflets were thickened and calcified; the transvalvular gradient was 148/95 mm Hg; and the measurement of the aortic valve area was 0.4 cm<sup>2</sup> (fig. 3).

During diagnostic work-up, coronarography was performed revealing the left coronary artery without stenosis, left descending artery that gives one diagonal branch and strong septal branch with mild wall atherosclerosis, circumflex artery that gives two marginal branches, with mild wall atherosclerosis and narrowed (75%) lumen of the right coronary artery between the first and second segments (fig. 4). Aortography showed calcification of the aortic ring and valve leaflets and aortic stenosis with mild aortic regurgitation.

Because of the suspicion of Heyde's syndrome, the von Willebrand factor (vWF) and antigen as well as factor VIII were tested (Table 2).



**Fig. 2.** Transthoracic echocardiography. Parasternal long-axis view. M-mode presentation. LV – left ventricle, IVS – interventricular septum, LVPW – left ventricle posterior wall



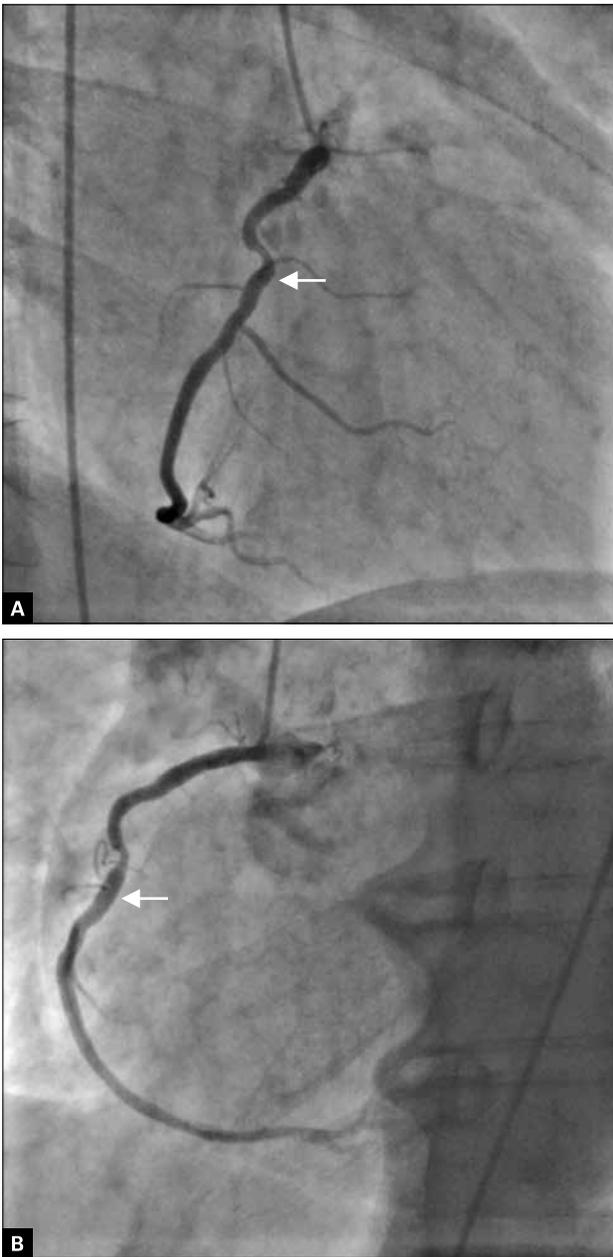
**Fig. 3.** Transthoracic echocardiography. Apical four-chamber view. Increased gradient across aortic valve (148/96 mm Hg)

The patient was again consulted by a hematologist, who reported that vWF activity and level were in the normal range with the 0.76 activity/antigen ratio; therefore, a multimer analysis of von Willebrand factor should be performed to confirm or exclude the diagnosis. Platelet aggregation studies should also be performed to exclude congenital or acquired thrombocytopeny as the cause of bleeding manifestations.

## Pathogenesis

An acquired vWF deficiency secondary to aortic stenosis is considered to be the major abnormality in Heyde's syndrome [4]. vWF plays an important role in the process of the adhesion of platelets to the subendothelium of injured vessels, inducing their aggregation.

In Heyde's syndrome, stenotic aortic valve causes proteolysis of the vWF protease (ADAMTS13), which induces conformational change of the vWF multimers. A reduced number of the multimers impairs platelet-mediated hemostasis especially in the areas of high shear stress, such as angiodysplastic vessels, and causes the bleeding. Angiodysplasia is a small microvascular malformation of the GI tract. It results from



**Fig. 4.** Coronary angiography. **A.** Right anterior oblique view. **B.** Left anterior oblique view. Significant stenosis of the right coronary artery, segment 2 (arrow)

multiple episodes of increasing wall tension during colonic contractions. This eventually causes dilation of the submucosal veins resulting in angiodysplasia.

In healthy vessels, the presence of high-molecular-weight vWF multimers is substantial for hemostasis [5,6].

## Management strategy

The management of Heyde's syndrome requires cooperation of different specialists: cardiologists, gastroenterologists, hematologists, surgeons, and others. In most cases, aortic valve replacement (AVR) provides definitive therapy and decreases GI bleeding in most patients with angiodysplasia (about 93%), while the

**Table 2.** Platelet aggregation panel

AGAA	93%	[74–99]
AGADP10	74%	[71–88]
AGEPINE	82%	[78–88]
AGKOLAG	73%	[70–94]
AGRIS15	85% L	[87–102]

[Due to the low platelet count 156 000/mcL the result may be unreliable.]  
 AGAA – Aggregation with arachidonic acid in concentration 0.5 mM,  
 AGADP – Aggregation with ADP in concentration 10  $\mu$ M, AGEPINE – Aggregation with epinephrine in concentration 1  $\mu$ g/mL, AGKOLAG – Aggregation with Collagen in concentration 1  $\mu$ g/mL, AGRIS15 – Aggregation with Ristocetin in concentration 1.5 mg/mL

**Table 3.** Hemostasis factors

Factor VIII	184.2% H	[50–150]
von Willebrand factor (activity of ristocetin cofactor)	129%	[50–150]
von Willebrand factor (antigen)	170% H	[50–150]

GI surgery has a very low durable remission rate of approximately 5% [5,7].

However, AVR is associated with the risk of bleeding. A surgical procedure requires administration of heparin intraoperatively for the cardiopulmonary bypass. Another important factor to consider is that anticoagulant therapy is necessary after AVR. Bioprosthetic valve may be used although not in all patients [5,8].

General surgery procedures for the treatment of GI bleeding due to vascular malformations involves endoscopic, selective artery embolization and colectomy. However, it is important to remember that endoscopic treatment may be ineffective because of the multifocal pattern of angiodysplasia, selective artery embolization may increase the risk of bowel infarction, and colectomy is a serious invasive procedure [5].

For unstable patients before AVR surgery, therapeutic alternatives include supplementation of vWF or perioperative Contact F (a combination of vWF and factor VIII). Fresh-frozen plasma, 1-desamino-8-darginine vasopressin, cryoprecipitate, or recombinant vWF do not have sufficient success rate in acquired von Willebrand syndrome. For elderly patients who refuse AVR, the treatment includes iron supplementation and regular blood transfusion, if necessary [5].

## Expert opinions

**Anetta Undas** (expert in coagulation disorders): This 62-year-old patient with severe aortic stenosis (mean transvalvular gradient, >90 mm Hg) and recurrent bleeding from intestinal angiodysplasia has Heyde's

syndrome. Disorders of platelet adhesion induced by destruction of high-molecular-weight vWF multimers on stenotic aortic valve at a normal enzyme ADAMTS13 activity, clearly suggest that this patient requires aortic valve replacement, after which the recurrence of bleeding is rare. Further evaluation of vWF multimer distribution seems not to be necessary in this case, considering moderate sensitivity of the available methods and literature reports that show postoperative cessation of bleeding even in patients with aortic stenosis and normal distribution of vWF multimers. Preoperative administration of tranexamic acid and etamsylate should be considered. Platelet concentrate transfusion is not recommended by platelet count of 140 000/mcL unless postoperative bleeding occurs and platelet count drops. The administration of cyclooxygenase-1 inhibitors is contraindicated in the perioperative period.

**Joanna Zdziarska (hematologist):** Acquired von Willebrand syndrome may complicate congenital and acquired heart defects. It usually manifests with mild bleeding symptoms or remains clinically silent, but may also cause severe or unexpected hemorrhages. In contrast to congenital von Willebrand disease, vWF synthesis is normal but its plasma level or function is affected by various mechanisms. In heart defects, loss of large vWF multimers is attributed to pathological shear stress activating platelets and promoting vWF multimers adsorption. Other mechanisms were also suggested in aortic valve stenosis, such as mechanical impairment of multimers or increased proteolysis of vWF by the ADAMTS13 enzyme. The hemostatic defect is corrected after the cause is removed (e.g., the valve replaced). Treatment options in the case of severe bleeds include desmopressin, vWF containing concentrates, intravenous immunoglobulin, plasmapheresis, or recombinant factor VIIa.

Acquired von Willebrand syndrome should be suspected in patients with cardiovascular diseases who present with unexplained bleeds (especially if they have a negative bleeding history). In view of difficult access to specialized tests (vWF multimer analysis, vWF propeptide, inhibitor detection), this condition is usually diagnosed/suspected on the basis of lowered vWF activity and/or diminished vWF activity/antigen ratio, in the context of clinical picture, bleeding pattern, and family history.

In the patient, the issue of familiar thrombocytopenia requires further investigation: type 2B von Willebrand disease, pseudo-von Willebrand disease, and other platelet function defects need to be excluded. Family testing would be helpful because the patient's condition and comorbidities can affect plasma vWF levels. It is also possible that mild asymptomatic thrombocytopenia is only coincidentally present within the family, regardless of the true cause of bleeds in the index patient.

**Neal Uren:** This patient has critical aortic stenosis with relatively few symptoms attributable to severe valve obstruction despite recurrent bleeding and chronic anemia in the context of acquired von Willebrand

disease and the association with GI bleeding. She requires aortic valve replacement as a definitive therapy, which will improve her longevity and lead to complete resolution of her GI mucosal bleeding risk and her potential for anemia. As such, it would seem reasonable to offer the patient a mechanical aortic valve replacement, which would commit her to life-long anticoagulation with warfarin. If she was less willing to consider this (given her previous experience), consideration could be given to a tissue bioprosthesis without the need for anticoagulation. Although she is relatively young and likely to outlive the durability of such a valve, given the development of transcatheter valve technology, it is likely that a failing bioprosthetic valve could be considered for a valve-in-valve transcatheter aortic valve replacement in 10 to 15 years' time as an alternative strategy.

As regards the perioperative risk of bleeding during or after cardiac bypass, this could be easily controlled with tranexamic acid (or specific clotting factor infusion) as required. To keep bypass time to a minimum, I would contend that there is no indication for coronary artery bypass grafting to the right coronary artery as the patient has no angina despite critical aortic stenosis, and the distal artery appears to subtend a relatively small area of myocardium (small posterior descending artery). Should angina develop in the future, the lesion is easily amenable to percutaneous coronary intervention. Given the patient's severe hypercholesterolemia, she should be on intensive lipid-lowering therapy to reduce the potential for lesion progression.

## Conclusions

Although the association between aortic valve stenosis and intestinal angiodysplasia does not seem to be obvious, it is essential to notice it for proper proceeding. Aortic valve replacement rather than GI surgery is a treatment of choice and offers long-term resolution of GI bleeding.

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## A 49-year-old patient with factor VII deficiency, chronic heart failure, and thrombus in the left ventricle (RCD code: VIII-2)

Monika Smaś-Suska, Agata Leśniak-Sobelga, Lidia Tomkiewicz-Pajak, Lech Kucharski, Marzena Paryła, Piotr Podolec

### Background

Heart failure (HF) is characterized by a decrease in cardiac function and subsequent hypoperfusion, inadequate according to the body needs. HF can be caused by numerous malfunctions, but approximately two-thirds of the cases of systolic HF is a consequence of coronary artery disease. Other causes of HF include hypertension, arrhythmias, viral infections, alcohol abuse, chemotherapy, and idiopathic dilated cardiomyopathy (believed to be related to genetic disorders) [1]. According to the American Heart Association, HF accounts for 32.8% of cardiovascular-related deaths [2], being the leading cause of hospitalization in people older than 65 years [3]. Treatment predominantly focuses on improving the symptoms and attenuating the progression of the disease by restoring appropriate perfusion and oxygen delivery to the organs. Beside drug therapy (including angiotensin-converting-enzyme inhibitors, angiotensin receptor antagonists,  $\beta$ -receptor blockers, and aldosterone antagonists), different cardiac interventions such as intracardiac defibrillator and/or cardiac resynchronization device implantation can be used for supporting the declining left ventricular function [4]. In the terminal stage, special devices can be applied (such as ventricular assist device, intra-aortic balloon pump, and artificial heart). Ultimately, heart transplantation may be considered [5] although in recent years effective treatment based on up-to-date guidelines has led to a substantial reduction in hospitalization rates by 30% to 50% and a significant decrease in mortality [6].

### Case presentation

A 49-year-old patient with chronic HF was admitted to the Department of Cardiac and Vascular Diseases at the John Paul II Hospital in Krakow because of progressive loss of exercise capacity and easy fatigue. According to the patient, he was in New York Heart Association (NYHA) class III a few weeks before admission; however, on admission his symptoms progressed to NYHA class IV. He reported no episodes of presyncope or syncope and cases of sudden death in his family. Concomitant diseases and risk factors in the patient included obesity, hypertension, type 2 diabetes (complicated by nephropathy), varicose veins of the lower extremities, statin-induced myopathy, smoking, alcohol

abuse, and advanced dental caries. The patient also reported one episode of severe bleeding during dental procedure in the past, but he refused to visit a hematologist for further diagnostic work-up. In 2008, HF was diagnosed but the patient did not take drug therapy prescribed by a cardiologist. Moreover, he did not comply with recommendations regarding hypertension and diabetes treatment. Two weeks before admission to the Department of Cardiac and Vascular Diseases, he was hospitalized at the internal medicine ward of the Żeromski Hospital in Krakow where echocardiography revealed the presence of thrombus in the left ventricle (LV) (fig. 1). During hospitalization, he was consulted by a cardiac surgeon in case of evacuating the thrombus from the LV but owing to abnormal laboratory test results (international normalized ratio [INR], 8.8) of unknown cause, he was not considered for surgery.

On admission to our department, the patient was hemodynamically stable. He reported dyspnea NYHA class III/IV with chest pain. His weight was 111 kg and height 190 cm (body mass index [BMI], 31 kg/m<sup>2</sup>). On examination, the heart rate was regular (70 beats/min) and blood pressure was 110/70 mm Hg. The signs of pulmonary congestion (class II by the Killip score) and peripheral edema were also present.

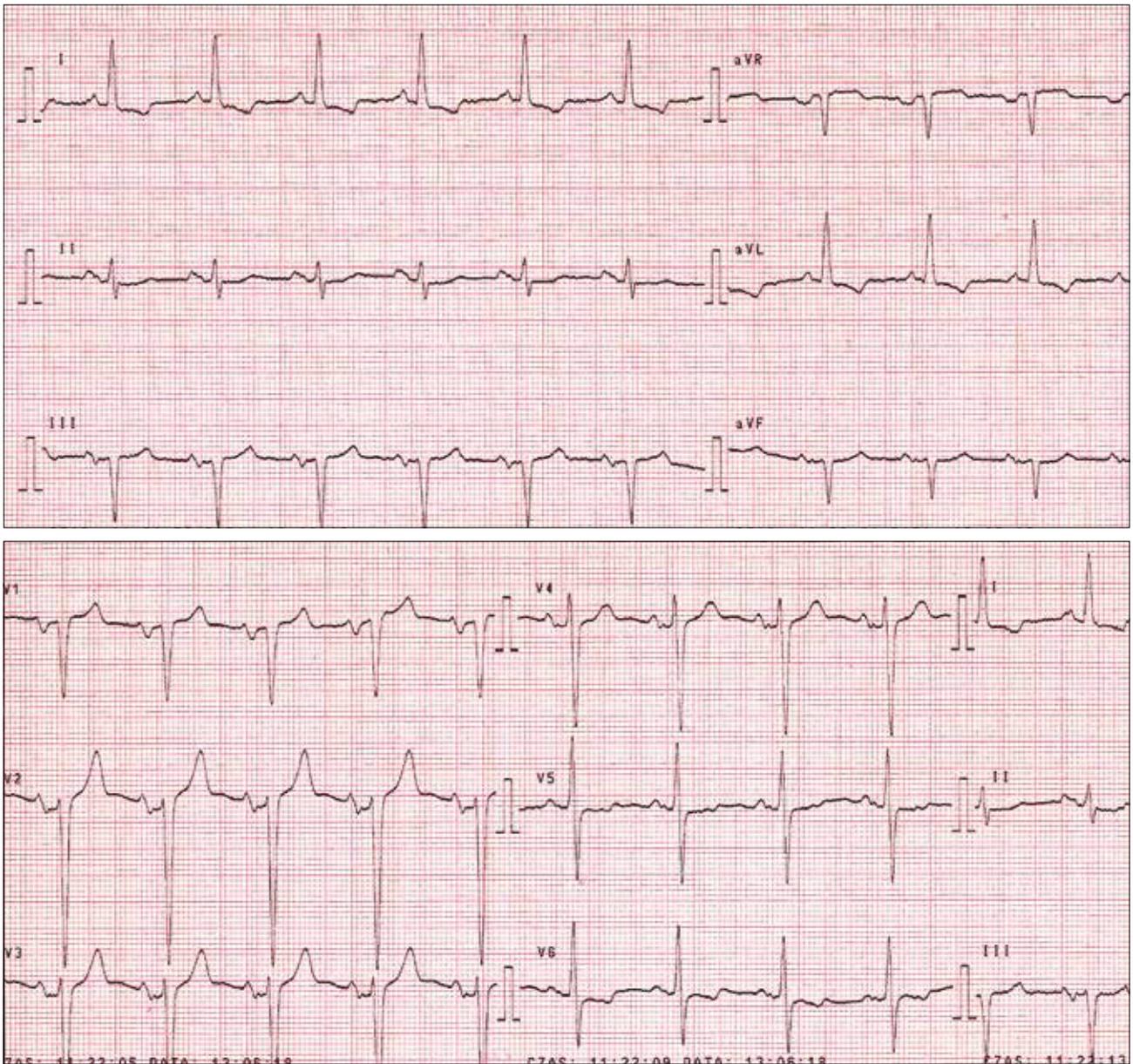


**Fig. 1.** Transthoracic echocardiography. **A.** Four-chamber view. **B.** Parasternal short-axis view. Thrombus in the left ventricle (arrow). LV – left ventricle

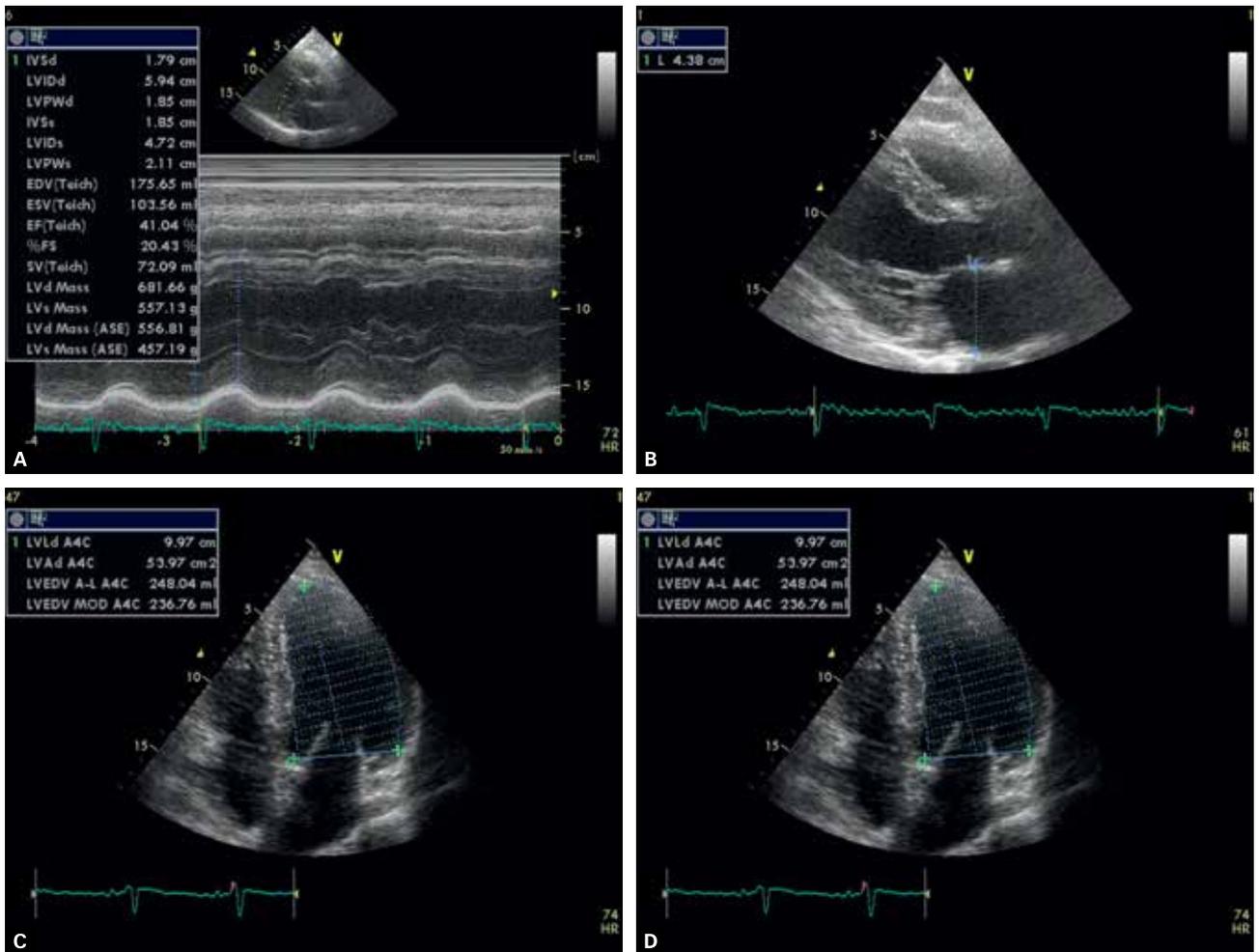
**Table 1. Results of the laboratory tests**

Parameter	Value	Parameter	Value	Parameter	Value
WBC ↑	14.33 103/μL	INR ↑	8.8/5.7/6.58	GGTP ↑ (N: <60)	74 U/L
NEUT ↑	10.3 103/μL	PT ↓ (N: 82–121)	8 %	AIAT	33 U/L
LYM	1.62 103/μL	PT sec ↑ (N: 10.4–13)	73,8	AspAT	25 U/L
MONO ↑	1.7 103/μL	Fibrinogen	9 g/L	ALP ↑ (N: 40–130)	158 U/L
RBC	6.29 106/μL	APTT	30.4 s	Bilirubin	18.7 μmol/L
Hb	14.8 g/dL	Glucose ↑	9.4 mmol/L	NT-proBNP ↑ (N:<125)	2037 pg/mL
HCT	46.9 %	Creatinine	106 μmol/L	CRP ↑	50 mg/L
PLT ↑	522 103/μL	eGFR	64	Albumin	37 g/L

ALAT – alanine transaminase, AspAT – aspartate transaminase, APTT – activated partial thromboplastin time, CRP – C-reactive protein, eGFR – estimated glomerular filtration rate, GGTP – gamma-glutamyl transpeptidase, HCT – hematocrit, Hb – hemoglobin, INR – international normalized ratio, LYM – lymphocytes, MONO – monocytes, NEUT – neutrophils, NT-proBNP – N terminal pro brain natriuretic peptide, PLT – platelets, PPT – prothrombin time, RBC – red blood cells, WBC – white blood cells



**Fig. 2.** Electrocardiogram. Sinus rhythm 70 bpm, left axis deviation, QRS 100 ms, ST segment depression in I, aVL, V4 – V6 with inverted T waves in I, aVL, V4 – V6, signs of left atrial enlargement



**Fig. 3.** Transthoracic echocardiography. **A.** Parasternal long-axis view. M-mode. Hypertrophy and dilation of left ventricle. **B.** Parasternal long-axis view. Left atrial enlargement – 44 mm. **C.** Apical four-chamber view. Increased left ventricular end diastolic volume to 248 mL (N: 67–155 mL). **D.** Apical four-chamber view. Left ventricular systolic dysfunction. EF 37%

Blood tests revealed elevated levels of white blood cells ( $14.33 \times 10^3/\mu\text{L}$ ), neutrophils ( $10.3 \times 10^3/\mu\text{L}$ ), C-reactive protein (50 mg/L), INR (8.8; during follow-up, 5.7 and 6.58). After a careful analysis and additional examination (urine test, chest X-ray, abdominal ultrasonography), severe dental caries was considered to be the most probable cause of the elevated levels of inflammatory markers. Additionally, we observed elevated levels of N-terminal pro-B-type natriuretic peptide, a marker of HF (2037 pg/mL). The levels of hepatic parameters were also increased: alkaline phosphatase (ALP), 158 U/L;  $\gamma$ -glutamyl transpeptidase (GGTP), 74 U/L. The levels of alanine and aspartate transaminase as well as bilirubin were normal (complete results of blood tests are shown in Table 1).

An electrocardiogram revealed a sinus rhythm of 70 beats/min, left axis deviation, QRS of 100 ms, ST segment depression in leads I, aVL, and  $V_4$  through  $V_6$  with inverted T waves in leads I, aVL,  $V_4$  through  $V_6$ , and signs of left atrial enlargement (fig. 2).

Echocardiography showed:

- dilatation of the LV: LV end-diastolic diameter of 60 mm; LV end-systolic diameter of 47 mm with hypertrophy of the LV muscle (fig. 3)
- left atrial enlargement (fig. 3)

- impaired systolic function of the LV with the ejection fraction (EF) of 37% (fig. 3)
- diastolic dysfunction of LV – impaired relaxation (fig. 4)
- spontaneous echo contrast in the LV with no thrombus in the LV (fig. 3, 5)
- enlargement of the right atrium,  $57 \times 38$  mm (reference range, 10–18  $\text{cm}^2$ ); enlargement of the right ventricle
- impaired systolic function of the right ventricle
- mild mitral regurgitation

Owing to the symptoms and presence of risk factors for coronary artery disease, the diagnostic work-up was extended by computed tomography, which excluded coronary artery disease.

Cardiac magnetic resonance imaging was also performed, which confirmed the absence of the thrombus in the LV, enlargement of the LV (LV end-diastolic volume, 214 mL; LV mass, 235 g) with systolic dysfunction (EF, 25%), enlargement of the right atrium ( $27.5 \text{ cm}^2$ ) and right ventricle ( $27.2 \text{ cm}^2$ ) (fig. 7). The examination revealed also mid-myocardial late gadolinium enhancement in the middle segment of the anterior wall and in the middle segment of the connection between

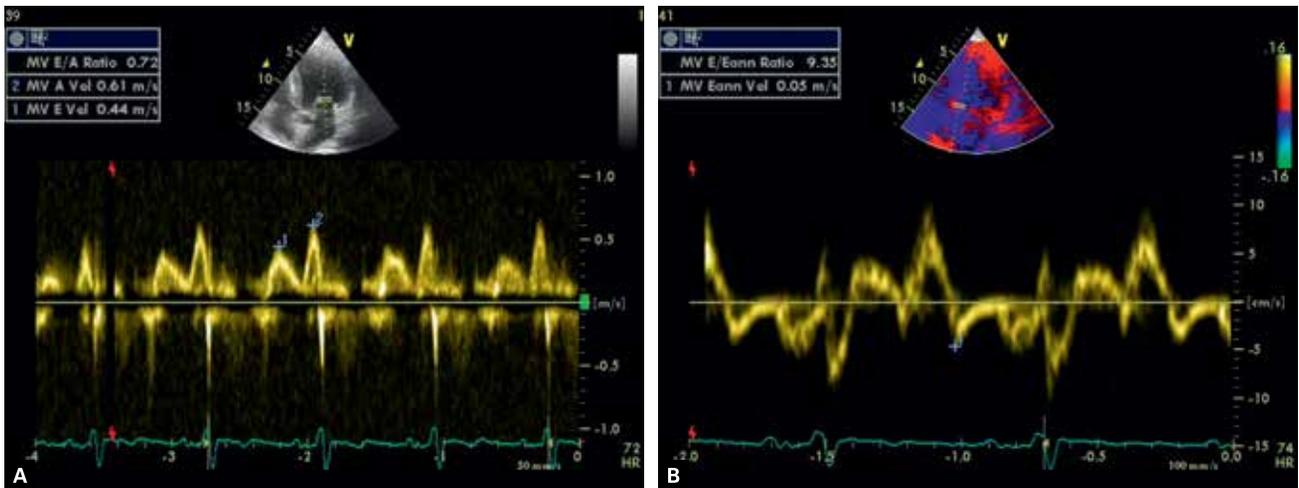


Fig. 4. Transthoracic echocardiography. A. Pulse waved Doppler. B. Tissue Doppler. E/A = 0.72. E/E' = 9. Impaired relaxation of the left ventricle

the lateral and posterior walls, corresponding to non-ischemic myocardium damage.

During hospitalization, the patient was treated by furosemide IV, bisoprolol, and ramipril insulin. Anticoagulant therapy was not necessary at the time of hospitalization. After a few days, the patient's condition gradually improved – he reported dyspnea NYHA class I/II with no other symptoms. Because of abnormalities in laboratory test results (INR, 8.8; during follow-up, 5.7 and 6.58) without anticoagulant therapy and the presence of thrombus in the LV in previous echocardiography, the patient was consulted by a specialist from the Department of Cardiac, Vessel Surgery and Transplantology of the Jagiellonian University Medical College, Professor Anetta Undas, who recommended to extend the diagnostic work-up by factor VII (FVII) deficiency. Targeted laboratory test confirmed the reduced activity of FVII below 5% (reference range, 50%–129%). Furthermore, Professor Undas pointed out that there is no good correlation between blood FVII levels and the risk of severe bleeding, especially in patients with FVII activity below 5%, who may suffer thrombotic complications (such as in the case of the consulted patient). The expert suggested that in the case of considering coronarography, radial artery access should be selected. To assure good hemostasis after catheter removal, 2 mg of NovoSeven® should be administered (with contingent repeat of the same dose after 4 hours; NovoSeven®  $t_{1/2}$  ~3 hours), which will account for 22  $\mu\text{g}/\text{kg}$  of the body weight. Typically, in patients with FVII activity of less than 10%, a dose of 15 to 30  $\mu\text{g}/\text{kg}$  of the body weight should be used. Importantly, it is the duration of hemostasis that has to be adjusted: short within the procedure, longer during the recovery. In the case of hematoma after catheter removal, NovoSeven® may be administered at the intervals of 4 to 6 hours. INR may be assessed but the goal is to decrease rather than to normalize the INR level (to avoid thrombotic complications). Finally, Professor Undas emphasized that because of the lack of precise guidelines for invasive diagnostics in FVII-deficient patients, a consultation

with a hematologist is advisable. Thus, we consulted a hematologist who recommended perioperative substitution of FVII (NovoSeven®) in the case of surgery or invasive procedures. Moreover, anticoagulant therapy (with the exception of acetylsalicylic acid) has to be used with NovoSeven® supplementation, at least until FVII activity exceeds 10%–15%. The patient's data were submitted to the National Blood Center. Finally, the patient was consulted by a hepatologist. The general condition of the liver on a physical examination was good. Laboratory tests revealed normal levels of transaminases and protein, including albumin. A slight increase in GGTP and ALP levels was observed, probably caused by alcohol abuse; however, it did not explain an increased INR value. The hepatologist confirmed that the probable cause of increased INR levels was factor VII deficiency rather than liver malfunction.

## Discussion

FVII is one of the plasma proteins involved in the coagulation cascade. It is a serine protease produced by the liver – its synthesis depends on vitamin K availability. FVII interacts with tissue factor (TF/factor III) to initiate the process of coagulation. Normally, tissue factor is not exposed to the bloodstream; however, during the vessel injury TF/factor III becomes accessible to the circulating FVII. Activated FVII (FVIIa) leads to thrombin (factor IIa) elevation, which transforms fibrinogen into fibrin.

Congenital FVII deficiency is a very rare bleeding disorder caused by mutations in the gene coding for FVII with an autosomal recessive pattern of inheritance. It affects 1 per 500 000 people [7]. Heterozygotes are usually asymptomatic, whereas homozygotes and compound heterozygotes can be affected by hemorrhagic diathesis. However, symptomatology varies from severe to mild or even asymptomatic forms, due to the fact that the activity of FVII does not correlate with bleeding tendency [8]. What is more, bleeding may

not be observed in patients with very poor FVII activity. Nevertheless, individuals with the activity below 1% are predisposed to severe intra-articular bleeding, which can lead to arthropathy and intracranial or extraperitoneous bleeding. Bleeding episodes are predominantly mucosal and, if clinically significant, require treatment with FVII concentrate. Perioperative substitution of FVII is also necessary [8]. According to the guidelines, the prevention and treatment of bleeding requires the replacement of the missing factor. One of the recommended option is recombinant activated FVII concentrates, administered in the initial doses of 10–30 IU/kg and 15–30 µg/kg respectively [7]. In the case of mild bleeding, the 5%–10% activity of FVII is usually sufficient, whereas in the case of surgical procedures the FVII activity at 15%–25% of the control level is necessary.

Although FVII deficiency is a rare bleeding disorder, it affects 1 per 200 000 individuals in the Polish population [8]. At the same time, this group of patients may have common risk factors for coronary artery disease, such as hypertension, type 2 diabetes, high blood cholesterol, or obesity and may require diagnosis with percutaneous coronary intervention (PCI).

There are limited data describing the feasibility of coronarography and angioplasty in FVII deficiency. Because of the increased perioperative bleeding risk, FVII substitution as well as the antithrombotic and antiplatelet treatment before PCI are required and have to be strictly time-controlled. Recently, the first report of successful PCI in FVII-deficient patient has been published [9]. The procedure was performed in obese (BMI, 42 kg/m<sup>2</sup>), hypertensive, and diabetic patient without a history of significant bleeding events. PCI was performed by radial approach to minimize hemorrhagic complications, with heparin administration to avoid radial artery thrombosis. Following the hematologist recommendation (to diminish the risk of severe bleeding), 1 mg of recombinant activated FVII (NovoSeven<sup>®</sup>, 50 000 UI) was administered before arterial sheath removal, achieving successful hemostasis after 4 hours of radial compressive bandage. The second step of the treatment was angioplasty, which was not preceded by FVII administration because the stent implantation is considered as a formal contraindication for recombinant activated FVII administration because of its thrombin generation enhancement and coronary thrombosis predisposition.

Chronic HF with reduced LVEF is menacing disorder associated with high mortality and morbidity rates. It is a prothrombotic state, that is, many complications related to HF can be also related to thrombosis. It can lead to the clinical consequences of sudden death, stroke, systemic thromboembolism, and venous thromboembolism [10]. The risk of thromboembolic events in HF patients is estimated to be in the range of 1% to 4.5% per year [11]. What is important, intracardiac thrombi and mural endocardial plaques are present at necropsy in more than 50% of the patients with dilated cardiomyopathy [12]. The pathophysiology of thrombogenesis in HF can be explained in the context of the Virchow's triad. Low cardiac output due to poor

contractility leads to “abnormal flow”, abnormalities of hemostasis and platelets (that is, “abnormal blood constituents”) and endothelial dysfunction (“vessel wall abnormalities”) – all contributing to a prothrombotic or hypercoagulable state. Consequently, it can increase the risk of thrombosis in HF and impair the LV systolic function [13]. Limited data suggest that anticoagulant therapy could outweigh the risks in some cases, such as EF of less than 20%, systolic dysfunction of the LV and a history of previous stroke, and known thrombus in the left or right ventricle [11]. However, the current guidelines do not recommend the routine use of aspirin, antiplatelet agents, or anticoagulation in patients with HF and sinus rhythm [4].

Importantly, the occasional occurrence of thrombosis in patients with congenital bleeding disorders, such as FVII-deficient patients, has received considerable attention during the past decade due to the relatively high frequency of thrombotic phenomena [14]. It was speculated that a special form or variant of FVII deficiency could exist [15,16]. The presence of associated prothrombotic risk factors (such as HF, inflammation, obesity, or coronary artery disease) has been reported to be present in these patients but it has not been thoroughly investigated so far. The available literature strongly suggests that the occurrence of thrombosis in FVII deficiency may be due to common prothrombotic risk factors and that FVII deficiency does not protect from thrombosis [14]. The present patient confirms these findings. Severe HF and coexisting inflammation (dental caries) – classical prothrombotic factors – may be responsible for thrombus formation in LV (fig. 1). A surprising disappearance of the thrombus without anticoagulant therapy could be the result of fibrinolysis activation.

## Management strategy

According to the 2012 European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic HF, our patient has a regular cardiac follow-up at the Outpatient Clinic for Heart Failure [17]. Medical treatment was included: angiotensin-converting-enzyme inhibitor (ramipril, 5 mg/d, gradually elevated to 10 mg/d) and a β-blocker (bisoprolol, 10 mg/d). Mineralocorticoid receptor antagonist could not be used because of high potassium level (5.4 mmol/L). To relieve the signs and symptoms of congestion, a diuretic (furosemide, 40 mg/d) was continued. The patient is scheduled for a follow-up visit in the clinic after 3 months for the assessment of his general condition. Echocardiography is planned to estimate the EF and potential complications of the diseases. A cardiopulmonary exercise test will be also performed to monitor such parameters as time of exercise, peak oxygen uptake, VE/VCO<sub>2</sub> slope, chronotropic and blood pressure response, and exercise-induced arrhythmias. After the examination, implantable cardioverter-defibrillator as primary prevention will be considered.

Because of severe dental caries, dental treatment is necessary. In the case of dental surgery, the patient

will require NovoSeven® supplementation to increase FVII activity above 15%. The patient remains under the care of a cardiologist, hematologist, and hepatologist.

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## A 24-year-old patient with vein thrombosis and thrombus in the apex of the heart during ascariasis (RCD code: VIII-3)

Dawid Kudliński, Magdalena Kostkiewicz, Paweł Rubiś, Grzegorz Kopeć, Piotr Podolec

### Background

In the age of progressive sterilization of human environment, parasitic diseases are still a serious challenge for the modern medicine. However, they rather rarely have serious cardiac consequences. The most frequent parasitic disease in the world is ascariasis. It is caused by *Ascaris lumbricoides*, a human roundworm that can reach a length of up to 45 cm and a diameter of 5 mm.

The worldwide prevalence of ascariasis is estimated at 25% of the general population [1]. According to the World Health Organization, this usually asymptomatic disease causes as many as 60 000 deaths per year in the world [2]. Infections tend to be chronic and may last for many years. In Europe, including Poland, the prevalence of ascariasis is much lower than in the developing countries. In the South-East Asia or South America, as many as 80% of the population suffer from this infection. In Poland, its prevalence is estimated at about 3.3% of the population [3].

### Case presentation

We present a case of a 24-year-old Caucasian woman suffering from hypereosinophilia during the course of ascariasis. From early childhood, she had allergy to dog and cat hair, grass pollen, and dust; moreover, she had psoriasis.

In February and March 2012, she complained of severe pain and swelling in both knees and ankle joints that were more intensive at night.

In March and April 2012, she observed swelling and bruising of the right upper extremity. Ultrasonography of the extremity showed a hyperechogenic thrombus with minimal blood flow in the vein. The patient was diagnosed with axillary and right subclavian vein thrombosis. The blood test revealed lymphocytosis of  $12.3 \times 10^9/L$  with eosinophil granulocyte count of  $11 \times 10^9/L$  and a low level of red blood cells. Enoxaparin was introduced and clinical improvement was observed.

In May 2012, the patient was admitted to the Department of Rheumatology because of chronic pain in the musculoskeletal system. The initial working diagnosis was psoriatic arthritis. A blood test revealed leukocytosis ( $11\,500/uL$ ), elevated erythrocyte sedimentation rate [49], increased levels of C-reactive protein ( $10.7\text{ mg/L}$ ; normal range,  $<3.0\text{ mg/L}$ ) and

troponin I ( $0.414\text{ ng/mL}$ , normal range,  $<0.0013\text{ ng/mL}$ ), as well as the presence of antinuclear antibodies. A radiograph of the hand and foot did not reveal any abnormalities. An electrocardiogram (ECG) revealed sinus tachycardia of 100 beats/min and negative T wave in leads II, III, aVF, and  $V_2$  through  $V_6$ . Considering an elevated hsT level, a decision was made to transfer the patient to the Department of Cardiology.

The blood test was repeated and confirmed leukocytosis with a high absolute eosinophil granulocyte level ( $4190/uL$ ). Echocardiography showed a hyperechogenic thrombus in the apex of the heart, clamping of apical heart segments, and dynamic gradient of up to 16 mm Hg on the aortic valve. The pericardial thickening and minimal pericardial liquid of up to 2 mm were present. Chest radiography, abdominal ultrasonography, and 24-hour ECG did not show any abnormalities.

In June 2012, the patient started to complain about chronic cough and skin lesions. She was admitted to the Department of Allergology and Immunology owing to suspicion of hypereosinophilic syndrome. A physical examination revealed two small nodules over the right eyebrow and no other abnormalities. A blood test revealed leukocytosis of up to  $14\,000/uL$  with normal eosinophil granulocyte count. The level of inflammatory markers was normal. A parasitological study revealed numerous *Ascaris lumbricoides* eggs in the feces. Mebendazole was introduced. Echocardiography showed a hyperechogenic thrombus in the apex of the heart of up to 7 mm (which was smaller than the previous one) and the left ventricle with preserved systolic function and a diameter of 40/24 mm. Magnetic resonance imaging revealed a hyperintensive thrombus in the apex of the heart, clamping of apical heart segments, pericardial thickening, and minimal pericardial liquid of up to 2 mm. A 4-week treatment with mebendazole resulted in the improvement of the clinical state; no parasite eggs were observed during follow-up.

### Discussion

#### Involvement of the cardiovascular system

Ascariasis may cause numerous complications in the human body. Although *Ascaris lumbricoides* may lead to iron deficiency and chronic ascariasis may be the cause of microcytic anemia, such cases have been rarely described in the literature. Anemia is more typical for other helminths such as a tapeworm [4]. Complications in the course of ascariasis do not correlate with the severity of infection. Usually, a blood test reveals normal full blood count. Helminth infection is the most common cause of eosinophilia, next to atopic disease [5].

Cardiac disease is the major cause of death in the course of sustained eosinophilia, whether reactive or clonal. In the heart, the eosinophilic infiltration can produce myocarditis, intramural thrombus formation,

constrictive pericarditis, and fibroblastic endocarditis. Mitral and tricuspid regurgitation may occur in the course of eosinophilia and ascariasis. An aneurysm of the sinus of Valsalva and multiple coronary artery aneurysms have been reported [6,7]. German researchers described a case of a young woman with high levels of eosinophils and myocardial infarction due to coronary artery thrombi [8]. French authors reported a case of a patient with acute necrotizing pancreatitis and transient complete atrioventricular block complicating the course of ascariasis [9]. The atrioventricular block disappeared after 9 weeks of treatment with albendazole. There have been a few cases of heart block caused by cardiac echinococcosis or other helminths, but only one case refers to ascariasis [10].

## Management strategy

### Diagnosis

Cardiac follow-up of patients with eosinophilia (also reactive) is necessary. Echocardiography should be performed in each case although it may suggest Loeffler endocarditis [10]. Loeffler endocarditis is cardiac damage caused by eosinophil granule proteins. Therefore, it is essential to perform myocardial biopsy to verify the diagnosis. It is also recommended to measure the level of troponin T as a noninvasive method to confirm heart disease. Eosinophilic myocarditis is diagnosed based on increased eosinophil counts in peripheral blood and significantly increased eosinophil infiltrates, as well as degranulation and degeneration of cardiomyocytes on biopsy. The time of onset of increased eosinophil counts in peripheral blood differs between individuals [11].

Histological findings in eosinophilic myocarditis include eosinophil infiltrates, degranulation of eosinophils, disappearance and fusion of cardiomyocytes, and interstitial edema and fibrosis. Occasionally, endocarditis is observed [12,13].

The diagnosis of infestation is based on a stool test that is used to confirm the presence of *Ascaris lumbricoides* eggs. Both fertilized and unfertilized eggs may be present in the excrement. Unfertilized eggs are bigger and more oval. The presence of unfertilized eggs indicates that only female forms are present in the intestine. Blood examination usually does not reveal any abnormalities beside eosinophilia or hypereosinophilic syndrome, which can be observed in the majority of infected patients [14].

The most frequent consequence of helminthiasis is eosinophilia. This complication is the most significant problem in the process of *Ascaris lumbricoides* infection. The eosinophil count in the blood is normally between  $0.02\text{--}0.5 \times 10^9/\text{L}$ . Hypereosinophilia is classified as mild when the blood eosinophil count is between 0.6 and  $1.5 \times 10^9/\text{L}$ , moderate when it is 1.5 to  $5 \times 10^9/\text{L}$ , and severe when it is  $>5 \times 10^9/\text{L}$  [15]. Sustained hypereosinophilia may lead to eosinophilic end-organ damage. Of note, cardiac involvement does not correlate with the level of blood eosinophilia. There

**Table 1. Diagnosis of eosinophilic myocarditis**

1. Minimally required conditions
Increased eosinophil count in peripheral blood ( $>500/\text{mm}^3$ )
Chest pain, dyspnea, and cardiac symptoms such as palpitations
Elevated enzymes indicating myocardial injury, including creatine kinase-MB and the myocardial constitutive protein, including cardiac troponin T
ECG changes
Transient left ventricular wall thickening and abnormal wall motion on echocardiography
2. Useful information
Approximately one-third of patients with eosinophilic myocarditis have allergic conditions (such as bronchial asthma, rhinitis and urticaria)
Approximately two-thirds of patients with eosinophilic myocarditis have previous flu-like symptoms (such as fever, sore throat and cough)
3. Endomyocardial biopsy

may be considerable eosinophilic tissue infiltration by a low level of eosinophil granulocytes in the blood.

### Treatment

Importantly, a patient with ascariasis who has other helminth infections should first undergo treatment for ascariasis [16]. The treatment of hypereosinophilia related to ascariasis should include eradication of parasite and is aimed at reduction of eosinophil blood count. Eradication of helminths reduces eosinophilia but additional treatment with steroids is usually required. Patients with mild eosinophilic myocarditis recover naturally [17]. If the patient has heart failure or serious arrhythmia, corticosteroid treatment is necessary. Cardiac improvement after treatment with steroids has been noted in myocardial biopsies. To prevent cardiac wall thrombi, anticoagulants are used. In the case of recurrent massive infestation of *Ascaris lumbricoides*, it is crucial to consider a psychiatric consultation toward mental illness. Owing to teratogenicity of medications used for ascariasis treatment, a pregnancy test in women of childbearing age should be considered.

The drug of choice is mebendazole at a dose of 100 mg in the morning and evening for 3 days or at a single dose of 500 mg. An alternative option is albendazole at a single dose of 400 mg orally (or 200 mg in children younger than 2 years). In some countries, ivermectin is popular although in Poland, it is used in veterinary medicine. Piperazine can be used in pregnant women at a dose of 75 mg/kg of the body weight up to a maximal dose of 4 g for 2 consecutive days; pyrantel pamoate can also be used at a single dose of 10 mg/kg of the body weight. Piperazine can be also

used in bowel or biliary obstruction. Therapy is effective if no parasites are observed in a stool sample after 3 weeks of treatment [14]. If a patient presents with heart failure with mild-to-severe symptoms and the ejection fraction exceeding 40%,  $\beta$ -blockers (asthma is not a contraindication), angiotensin-converting-enzyme inhibitors, and diuretics should be included. Vitamin K antagonists are recommended in patients with a thrombus in heart chambers or thrombosis.

## Prognosis

The prognosis is good if complications do not damage the organs. If the treatment is started early enough, the infestation does not leave any signs of illness in the body. In the acute phase, the management of myocarditis heart failure and potentially fatal arrhythmias is the major clinical challenge. The prognosis of myocarditis varies depending on the pathogenesis and type of the disease. Eosinophilic myocarditis is a rare and potentially fatal disease if left untreated but the prognosis is generally good [13,18,19].

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