ISSN 0022–9032

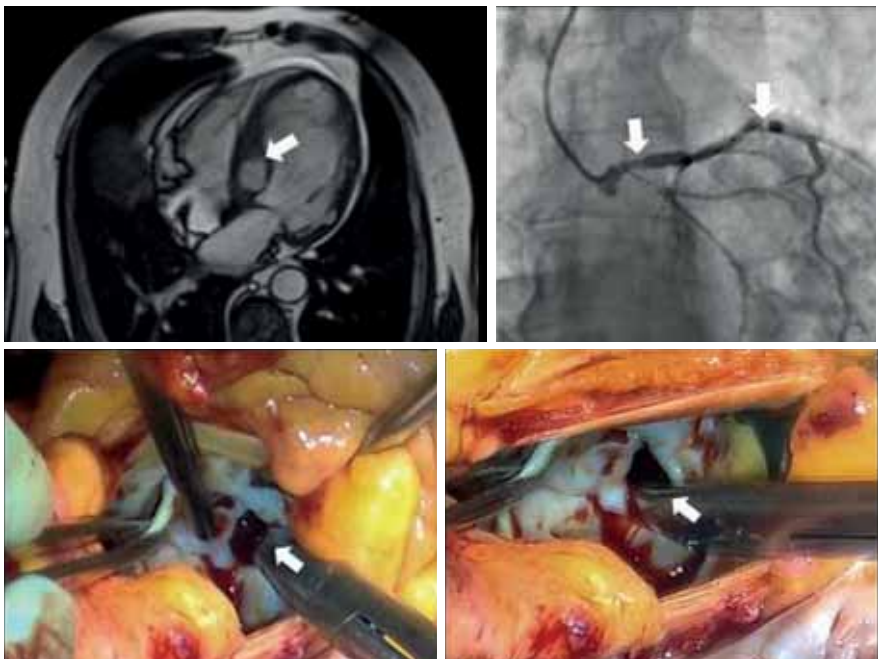
e-ISSN 1897–4279

May 2023, vol. 81, number 5

KARDIOLOGIA POLSKA

Polish Heart Journal

The Official Peer-reviewed Journal
of the Polish Cardiac Society
since 1957



Cardiac pseudoaneurysm following acute myocardial infarction, see p. 527

https://journals.viamedica.pl/kardiologia_polska

VIA MEDICA

Kieszonkowe wytyczne ESC

APLIKACJA MOBILNA
KIESZONKOWE WYTYCZNE ESC

- **Wszystkie wytyczne od 2014 roku** dostępne w jednym miejscu
- Bieżąca aktualizacja o nowo ukazujące się wytyczne ESC
- Możliwość korzystania przy łóżku pacjenta
- Łatwa nawigacja
- Możliwość tworzenia zakładek z wybranymi przez użytkownika zagadnieniami
- Możliwość skalowania **tekstu**

APLIKACJA DOSTĘPNA BEZPŁATNIE DLA WSZYSTKICH UŻYTKOWNIKÓW:

Pobierz w App Store

POBIERZ Z Google Play

21-0050.019.005

VIA MEDICA

KARDIOLOGIA POLSKA

Polish Heart Journal

The official peer-reviewed journal of the Polish Cardiac Society since 1957

Indexed in Chemical Abstract Service (CAS), CrossRef, EBSCO, EMBASE, Free Medical Journals, Google Scholar, Index Copernicus (IC), Index Scholar, MEDLINE, Polish Medical Library (GBL), Scopus, Polish Ministry of Education and Science, Ulrich's Periodicals Directory, Web of Science

Address
Kardiologia Polska
ul. Prądnicka 80, bud. M–IX
31–202 Kraków
phone: +48 126 143 004
e-mail: kardiologiapolska@ptkardio.pl
www.kardiologiapolska.pl

Polskie Towarzystwo Kardiologiczne
ul. Stawki 3 A lok. 1–2
00–193 Warszawa

Publisher

VIA MEDICA

VM Media Group sp. z o.o.,
Grupa Via Medica
ul. Świętokrzyska 73
80–180 Gdańsk
phone: +48 58 320 94 94
e-mail: journals@viamedica.pl
https://journals.viamedica.pl

ISSN 0022-9032
e-ISSN 1897-4279

Subscription rates: Paper subscription, 12 issues incl. package and postage individual 150€
Paper subscription, 12 issues incl. package and postage institutional 250€
Payment should be made to: BNP Paribas Bank Polska SA, Gdańsk, Poland,
Acc.: PL 41 1600 1462 0008 1377 1035 9168.
Single issues, subscriptions orders and requests for sample copies should be send to e-mail: prenumerata@viamedica.pl Electronic orders option available at: https://journals.viamedica.pl/kardiologia_polska/user/subscriptions

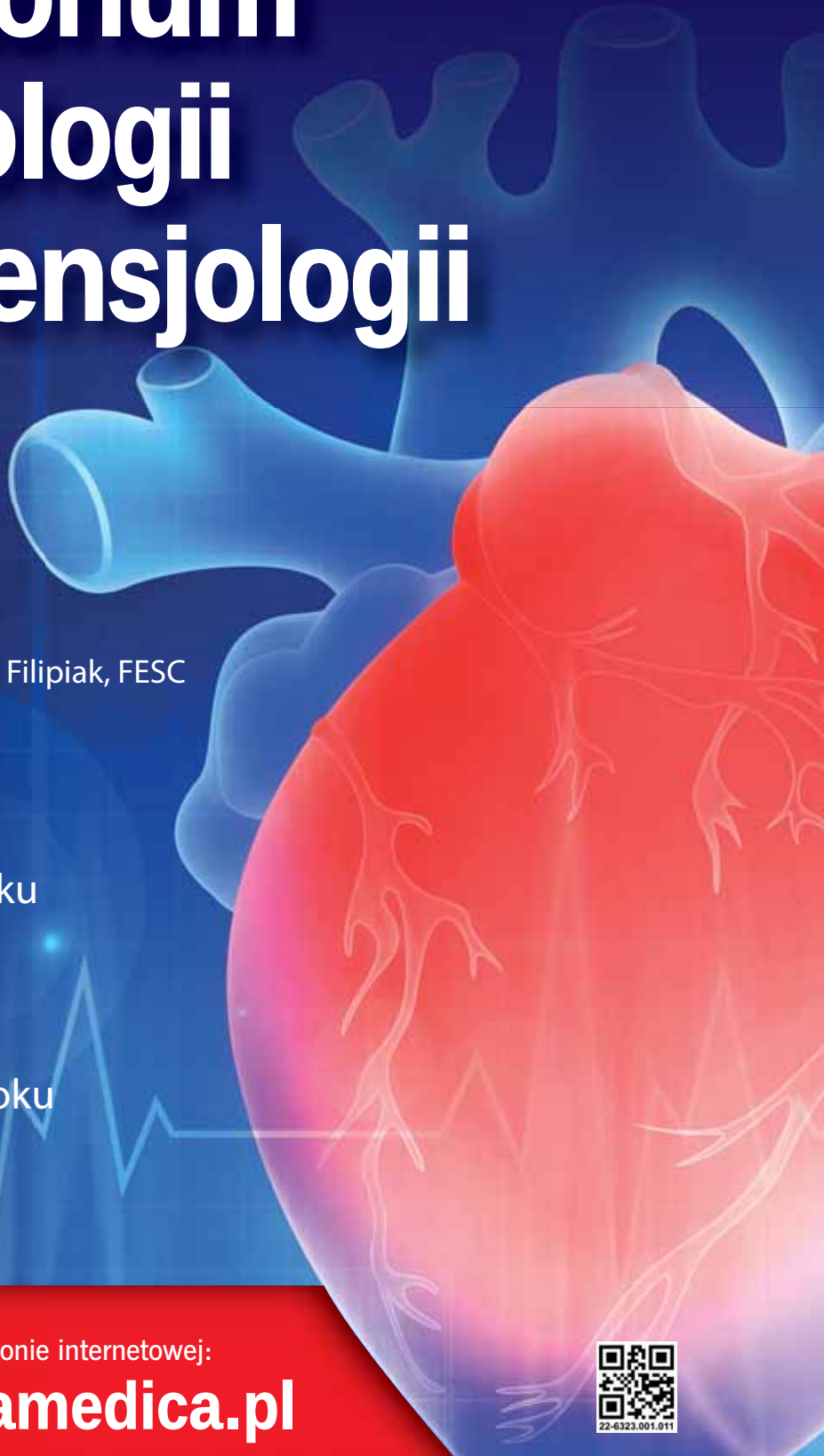
Advertising: For details on media opportunities within this journal please contact the Advertising Sales Department, ul. Świętokrzyska 73, 80–180 Gdańsk, Poland, phone: +48 58 320 94 94; e-mail: dsk@viamedica.pl.

Editorial policy and information for authors available on https://journals.viamedica.pl/kardiologia_polska/about/submissions#authorGuidelines.

Polish Ministry of Education and Science score: 100 pts.

The project on the development of the journal „Kardiologia Polska" is co-financed from the state budget under the „Development of Scientific Journals" program as per the Regulation of the Minister of Education and Science of August 3, 2021 on the „Development of Scientific Journals" program (Journal of Laws of 2021, item Scientific Journals").

Repetytorium z Kardiologii i Hipertensjologii 2023



Przewodniczący Komitetu Naukowego
prof. dr hab. n. med. Krzysztof J. Filipiak, FESC

- **LETNIE**
  Trójmiasto
  9–10 czerwca 2023 roku
- **JESIENNE**
  VIRTUAL MEETING
  7 października 2023 roku

Więcej informacji i rejestracja na stronie internetowej:
www.kardio.viamedica.pl

22-6323.001.011

Cykl konferencji jest skierowany do wszystkich osób zainteresowanych tematyką. Sesje satelitarne firm farmaceutycznych, sesje firm farmaceutycznych oraz wystawy firm farmaceutycznych są skierowane tylko do osób uprawnionych do wystawiania recept lub osób prowadzących obrót produktami leczniczymi — podstawa prawna: Ustawa z dnia 6 września 2001 r. Prawo farmaceutyczne (Dz. U. z 2017 r. poz. 2211. z późn. zm.).

ORGANIZATOR
VIA MEDICA 30 LAT

KARDIOLOGIA POLSKA
Polish Heart Journal

Table of contents

SHORT COMMUNICATION

CLINICAL VIGNETTE

EXPERT OPINION

PATRONAT MERYTORYCZNY

Sekcja Farmakoterapii Sercowo-Naczyniowej • PTK •

VIII Konferencja

CARDIOLIPID

pod patronatem

Sekcji Farmakoterapii Sercowo-Naczyniowej
Polskiego Towarzystwa Kardiologicznego

GDYNIA,
1–3 WRZEŚNIA 2023 ROKU

Przewodniczący Komitetu Naukowego:

prof. dr hab. n. med. Krzysztof J. Filipiak, FESC
dr hab. n. med. Iwona Gorczyca-Głowacka

www.cardiolipid.viamedica.pl

ORGANIZATOR VIA MEDICA

PATRONAT MEDIALNY tvmed

PARTNER ikamed.pl

Konferencja jest skierowana tylko do osób uprawnionych do wystawiania recept lub osób prowadzących obrót produktami leczniczymi — podstawa prawna: ustawa z dnia 6 września 2001 r. Prawo farmaceutyczne (t.j. Dz.U. z 2020 r. poz. 944).

22-6339.001.011

Think S-ICD first: The time has come

Giovanni Luca Botto, Fabio Lorenzo Canevese, Maria Carla Casale

Division of Cardiology — Electrophysiology, Department of Medicine, ASST Rhodense, Rho and Garbagnate M.se Hospitals, Milan, Italy

Related article
by Kempa et al.

Correspondence to:
Giovanni Luca Botto, MD, FEHRA, FESC,
Division of Cardiology — Electrophysiology, ASST Rhodense, Viale Forlanini 95, 20024, Garbagnate Milanese, Milan, Italy,
phone: +39 02 99430 3340,
e-mail: gbotto@asst-rhodense.it

DOI: 10.33963/KP.a2023.0100

Received:
April 25, 2023

Accepted:
April 26, 2023

Early publication date:
May 2, 2023

Implantable cardioverter defibrillator (ICD) is an effective therapy in patients with a primary and secondary indication for sudden cardiac arrest (SCA) prevention according to landmark clinical trials [1, 2]. Unfortunately, ICD therapy comes with the risk of device-related complications [3]. At 10 years, the risk of lead failure in patients with transvenous ICD (TV-ICD) can be as high as 25% [4].

The subcutaneous ICD (S-ICD) is a completely extravascular device, designed to avoid intravascular and intracardiac hardware and address the limitations of conventional TV-ICD systems. Actually, the S-ICD has become a safe and viable alternative for TV-ICD therapy [5, 6], and its use has increased significantly [7].

The European and US guidelines recommend the S-ICD (class IIa) as an alternative to TV-ICD in patients who meet the indication for an ICD, and in the absence of bradycardia with a need for pacing, monomorphic ventricular tachycardia presumed to be responsive to anti-tachycardia pacing (ATP), and an indication for cardiac resynchronization therapy (CRT) [8, 9]. The US guidelines also recommend the S-ICD (class I) in patients with inadequate venous access or at high risk of infection [8].

However, despite those recommendations, the early adoption of S-ICD was low, in part due to considering the S-ICD as only a niche device and also due to its cost and delay in economic reimbursement in some countries. However, over the past few years, the use of S-ICDs has increased, for instance, in the US [7] although there has still been hesitancy in its use due to the lack of pacing capabilities.

Therefore, the S-ICD is currently considered mainly in younger patients to avoid long-term transvenous leads and in those who are at higher risk of infection, such as patients with previous ICD infection or undergoing hemodialysis.

An observational study prospectively included consecutive patients who underwent *de novo* ICD implantation in 33 Italian centers for three months in 2015 [10]. A CRT device was implanted in 39% (369/947) of patients. An S-ICD was implanted in 12% of patients with no CRT indication (7% of the total population). S-ICD patients were younger than patients who received TV-ICD, more often had channelopathies, and more frequently received their device for secondary prevention of SCA. More frequently, the clinical reason for preferring a TV-ICD over an S-ICD was the need for pacing (45%), ATP (36%), or the expected future need for CRT (26%).

Some physicians have been concerned that patients will later need bradycardia pacing or CRT although the need for pacing appears to be low if the patient does not require pacing at the time of implantation. In the SCD-HeFT study, the 5-year rate of crossover to ICD or CRT due to pacing need in patients enrolled in the amiodarone arm (845 patients) or in the placebo arm (847 patients) was 11.7% and 10.5%, respectively, nearly 2% per year [11].

In this issue of the journal, Kempa et al. [12] have published an analysis of the data from the Polish S-ICD Registry run by the Polish Cardiac Society between May 2020 and September 2022 to monitor the implementation of S-ICD therapy in Poland. The data include reports on about 440 procedures including 411 *de novo* procedures, representing 75% of the total number of ICD implantations in Poland during that period. The median age of the population was 42 years. Most of the

patients (93.9%) were in sinus rhythm, 89.5% were in New York Heart Association class I–II, and their median left ventricular ejection fraction (LVEF) was 0.33%. Secondary prevention indication was present in one-third of the patients, and ischemic cardiomyopathy was reported in only one-fourth of the patients. Not surprisingly, young age was the main reason for choosing an S-ICD in three-fourths of the patients, while a higher risk of infective complication was present in fewer than one-fifth of the patients.

Those clinical characteristics are representative of a patient population very similar to that designated to utilize S-ICD in the early years after approval of the device by the Food and Drug Administration in the US. In 2012, only 2% of patients having the indications for ICD therapy in the US received an S-ICD [13], which was, therefore, often used as a "niche" device.

However, it should be noted that patients included in the earlier registries conducted in the US and Europe, which have demonstrated the safety and feasibility of the S-ICD system for the prevention of SCA, also included patients with heart failure, low LVEF, and multiple comorbidities [14, 15].

In a pooled analysis of 882 patients with a mean follow-up of 22 months, 42% had congestive heart failure, 35% had previous myocardial infarction, and the S-ICD continued to demonstrate its favorable safety and efficacy [15]. As expected, the study also noted a very low rate of lead issues (<1%) and infection (<2%) in 3-year follow-up.

The UNTOUCHED study included 1111 patients implanted with a S-ICD only for primary prevention, and, for the first time with LVEF ≤35% [6]. Mean LVEF in UNTOUCHED was very similar to that of MADIT-RIT [2], which included only TV-ICDs (27 ± 7% vs. 26 ± 6%, respectively). The S-ICD was proven to be safe and effective, even in older patients (mean age, 55.8 ± 12.4 years) with multiple comorbidities and poorer cardiovascular function [8]. The most important strength of the UNTOUCHED trial was that it enrolled a majority of US participants and those with a high morbidity burden, therefore, its results should be generalizable to many patients seen in real-world practice.

The PRAETORIAN was the first head-to-head trial comparing the S-ICD with the conventional TV-ICD in the general population undergoing ICD implantation, who did not have pacing indications [5]. At a median follow-up of 49.1 months, the S-ICD was deemed non-inferior to the TV-ICD in the primary composite end-point with respect to device-related complications and inappropriate shocks (hazard ratio [HR], 0.99; $P = 0.01$) [5].

Nowadays available evidence strongly supports the use of S-ICD also in the population with heart failure, lower LVEF, and multiple comorbidities; therefore, the S-ICD should not be considered anymore a "niche" device. The previous guidelines had been written before data from more recent trials were available.

We think that the S-ICD can be considered in all primary (and even secondary) prevention patients without any pacing indication (including cardiac pacing, need for ATP, or CRT) regardless of age and underlying heart disease. It is anticipated that the actual level of recommendation will be raised with the next guideline update.

Article information

Conflict of interest: GLB received specker's fees (small amount) from Abbott, Biotronik, Boston Scientific, Medtronic, Microport.

Funding: None.

REFERENCES

1. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002; 346(12): 877–883, doi: 10.1056/NEJMoa013474, indexed in Pubmed: 11907286.
2. Moss AJ, Schuger C, Beck CA, et al. MADIT-RIT Trial Investigators. Reduction in inappropriate therapy and mortality through ICD programming. N Engl J Med. 2012; 367(24): 2275–2283, doi: 10.1056/NEJMoa1211107, indexed in Pubmed: 23131066..
3. Tarakji KG, Wazni OM, Harb S, et al. Risk factors for 1-year mortality among patients with cardiac implantable electronic device infection undergoing transvenous lead extraction: the impact of the infection type and the presence of vegetation on survival. Europace. 2014; 16(10): 1490–1495, doi: 10.1093/europace/euu147, indexed in Pubmed: 25087154.
4. Koneru JN, Jones PW, Hammill EF, et al. Risk Factors and Temporal Trends of Complications Associated With Transvenous Implantable Cardiac Defibrillator Leads. J Am Heart Assoc. 2018; 7(10), doi: 10.1161/JAHA.117.007691, indexed in Pubmed: 29748177.
5. Knops RE, Pepplinkhuizen S, Delnoy PP, et al. Rationale and design of the PRAETORIAN trial: a Prospective, RAndomizEd comparison of subcuTaneOus and tRansvenous ImplANtable cardioverter-defibrillator therapy. Am Heart J. 2012; 163(5): 753–760.e2, doi: 10.1016/j.ahj.2012.02.012, indexed in Pubmed: 22607851.
6. Gold M, Lambiase P, El-Chami M, et al. Primary Results From the Understanding Outcomes With the S-ICD in Primary Prevention Patients With Low Ejection Fraction (UNTOUCHED) Trial. Circulation. 2021; 143(1): 7–17, doi: 10.1161/circulationaha.120.048728.
7. Friedman DJ, Parzynski CS, Varosy PD, et al. Trends and In-Hospital Outcomes Associated With Adoption of the Subcutaneous Implantable Cardioverter Defibrillator in the United States. JAMA Cardiol. 2016; 1(8): 900–911, doi: 10.1001/jamacardio.2016.2782, indexed in Pubmed: 27603935.
8. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2018; 138(13): e272–e391, doi: 10.1161/CIR.0000000000000549, indexed in Pubmed: 29084731.
9. Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al. 2022 ESCguidelines for the management of patients with ventricular arrhythmias and the preven-tion of sudden cardiac death. Eur Heart J. 2022; 43: 3997–4126, doi: 10.1093/eurheartj/ehac262, indexed in Pubmed: 36017572.
10. Botto GL, Forleo GB, Capucci A, et al. The Italian subcutaneous implantable cardioverter-defibrillator survey: S-ICD, why not? Europace. 2017; 19(11): 1826–1832, doi: 10.1093/europace/euw337, indexed in Pubmed: 28011803.
11. Poole JE, Olshansky B, Mark DB, et al. Long-Term Outcomes of Implantable Cardioverter-Defibrillator Therapy in the SCD-HeFT. J Am Coll Cardiol. 2020; 76(4): 405–415, doi: 10.1016/j.jacc.2020.05.061, indexed in Pubmed: 32703511.

12. Kempa M, Budrejko S, Tajstra M, et al. Sucutaneous implantable cardioverter defibrillator therapy in Poland: Results of the Polish S-ICD Registry. Kardiol Pol. 2023; 81(5): 455–462, doi: 10.33963/KP.a2023.0046, indexed in Pubmed: 36871295.
13. Kremers MS, Hammill SC, Berul CI, et al. The National ICD Registry Report: version 2.1 including leads and pediatrics for years 2010 and 2011. Heart Rhythm. 2013; 10(4): e59–e65, doi: 10.1016/j.hrthm.2013.01.035, indexed in Pubmed: 23403056.
14. Lambiase PD, Barr C, Theuns DA, et al. Worldwide experience with a totally subcutaneous implantable defibrillator: early results from the EFFORTLESS S-ICD Registry. Eur Heart J. 2014; 35(25): 1657–1665, doi: 10.1093/eurheartj/ehu112, indexed in Pubmed: 24670710.
15. Burke MC, Gold MR, Knight BP, et al. Safety and Efficacy of the Totally Subcutaneous Implantable Defibrillator: 2-Year Results From a Pooled Analysis of the IDE Study and EFFORTLESS Registry. J Am Coll Cardiol. 2015; 65(16): 1605–1615, doi: 10.1016/j.jacc.2015.02.047, indexed in Pubmed: 25908064.

COVID-19-induced myocarditis: A multicenter cardiovascular magnetic resonance study

Matthias G Friedrich[1, 2], Ria Garg[3]

[1]Departments of Cardiology and Diagnostic Radiology, McGill University Health Center, Montréal, QC, Canada
[2]Courtois CMR Research Group at the Research Institute of the McGill University Health Center, Montreal, QC, Canada
[3]Department of Internal Medicine, Geisinger Wyoming Valley Hospital, Wilkes-Barre, PA, United States

Related article
by Haberka et al.

Correspondence to:
Matthias G Friedrich, MD, PhD, Departments of Cardiology and Diagnostic Radiology, McGill University Health Center, 1001 Decarie Blvd, Montréal, QC H4A 3J1, Canada, phone: +1 514 934 1934, e-mail: matthias.friedrich@mcgill.ca

DOI: 10.33963/KP.a2023.0101

Received:
April 28, 2023

Accepted:
April 28, 2023

Early publication date:
May 2, 2023

Since the onset of the COVID-19 pandemic in early 2020, several studies on its cardiovascular complications and the importance of cardiovascular magnetic resonance (CMR) in diagnosis of myocarditis have been published. "A distinct septal pattern of late gadolinium enhancement specific for COVID-19-induced myocarditis: A multicenter cardiovascular magnetic resonance study" [1] compares patients with COVID-19-related myocarditis and non-COVID-19 myocarditis, for CMR findings.

The study was a multicenter, observational study conducted in 5 centers. The authors recruited 552 COVID-19 patients prospectively and 221 patients retrospectively, as the non-COVID-19 group, between 2018 and 2019. The median time interval between acute COVID-19 disease symptoms and CMR was 12 weeks. The COVID-19 group showed a lesser extent of late gadolinium enhancement (LGE), better left ventricular systolic function, lower left ventricular end-diastolic volume (LVEDV) but a higher rate of pericarditis and septal predilection of LGE as compared to the control group. About half of the patients showed a myocarditis-like injury with only 7.5% also having myocardial edema (only 3 had myocardial edema). In those patients, the LGE areas were larger, and pericarditis was more frequent (13.6% vs. 6%; $P = 0.03$). The control group had a higher rate of myocarditis-like injury and pericardial effusion. The authors did not find any relation between the LGE extent and obesity or age.

The use of Lake Louise Criteria (LLC) as markers for myocardial inflammation is useful in patients with a clinical presentation consistent with acute myocardial inflammation [2]. But in patients without clinical evidence of myocarditis, areas with abnormal LGE may just reflect scars but not acute inflammation. Therefore, observed injuries in patients without associated edema as visualized by T2-dependent CMR may be scars or fibrosis due to other reasons, without active inflammation.

Septal fibrosis, as reported, is not specific for inflammation but, instead, is a frequent pattern in non-ischemic myocardial disease, such as dilated [3] and hypertrophic cardiomyopathy [4] and sarcoidosis [5] and can even be seen in healthy individuals [6]. Myocardium that is exposed to stress may show LV remodeling with myocyte hypertrophy and diffuse interstitial fibrosis, which may also include replacement fibrosis [7]. Therefore, such septal LGE patterns are unlikely due to inflammation and thus, in this context, should be interpreted with caution. Inflammatory injury due to viral disease is usually located in basal to mid-inferolateral regions [8], and studies in post-COVID related myocarditis have reported non-ischemic scar patterns, with some studies showing elevated T1 and T2 values [9] and others with T2 elevation only [10]. Wherever reported though, the pattern of injury was non-ischemic with the most common inferior, inferolateral, basal to mid-region scar [9, 11, 12].

One major limitation, as also pointed out by the authors, is the lack of access to T1 and T2 mapping, which was not available in all centers. In the context of COVID-related myocardial injury, mapping may be the most

accurate test for detecting myocardial inflammation and injury [9].

Pericarditis has not been a frequent finding in COVID--19 patients although in some studies [9, 13], the reported prevalence of pericardial inflammation was up to 40% [13], and most frequently it was adjacent to the lateral wall. It might be important to investigate the extent and prevalence of pericardial injury in those patients to explain the prolonged symptom duration.

COVID-19-related myocardial inflammation appears to follow similar injury patterns as in other viral diseases and, in affected patients, may reflect involvement of their vulnerable myocardial tissue. While the study by Haberka et al. [1] provides interesting results, it contradicts a large body of evidence and confirmatory studies would be needed to demonstrate that septal injury is indeed a specific marker for COVID-19 myocarditis, instead of non-specific fibrosis.

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Haberka M, Rajewska-Tabor J, Wojtowicz D. A distinct septal pattern of late gadolinium enhancement specific for COVID-19-induced myocarditis: A multicenter cardiovascular magnetic resonance study. Kardiol Pol. 2023; 81(5): 463–471, doi: 10.33963/KP.a2023.0054, indexed in Pubmed: 36871296.
2. Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation: Expert Recommendations. J Am Coll Cardiol. 2018; 72(24): 3158–3176, doi: 10.1016/j.jacc.2018.09.072, indexed in Pubmed: 30545455.
3. Becker MAJ, Allaart CP, Zweerink A, et al. Correlation between septal midwall late gadolinium enhancement on CMR and conduction delay on ECG in patients with nonischemic dilated cardiomyopathy. Int J Cardiol Heart Vasc. 2020; 26: 100474, doi: 10.1016/j.ijcha.2020.100474, indexed in Pubmed: 32021905.
4. Ellims AH, Iles LM, Ling Lh, et al. A comprehensive evaluation of myocardial fibrosis in hypertrophic cardiomyopathy with cardiac magnetic resonance imaging: linking genotype with fibrotic phenotype. Eur Heart J Cardiovasc Imaging. 2014; 15(10): 1108–1116, doi: 10.1093/ehjci/jeu077, indexed in Pubmed: 24819852.
5. Okasha O, Kazmirczak F, Chen KHA, et al. Myocardial Involvement in Patients With Histologically Diagnosed Cardiac Sarcoidosis: A Systematic Review and Meta-Analysis of Gross Pathological Images From Autopsy or Cardiac Transplantation Cases. J Am Heart Assoc. 2019; 8(10): e011253, doi: 10.1161/JAHA.118.011253, indexed in Pubmed: 31070111.
6. Joncas S, Kolman L, Lydell C, et al. Differentiation of physiologic versus pathologic basal septal fibrosis: Proposed diagnostic criteria and associations with clinical and CMR-based markers of cardiovascular disease. J Cardiovasc Magn Reson. 2014; 16(S1), doi: 10.1186/1532-429x-16-s1-p104.
7. Hara H, Takeda N, Komuro I. Pathophysiology and therapeutic potential of cardiac fibrosis. Inflamm Regen. 2017; 37: 13, doi: 10.1186/s41232-017-0046-5, indexed in Pubmed: 29259712.
8. Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. J Am Coll Cardiol. 2009; 53(17): 1475–1487, doi: 10.1016/j.jacc.2009.02.007, indexed in Pubmed: 19389557.
9. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020; 5(11): 1265–1273, doi: 10.1001/jamacardio.2020.3557, indexed in Pubmed: 32730619.
10. Huang Lu, Zhao P, Tang D, et al. Cardiac Involvement in Patients Recovered From COVID-2019 Identified Using Magnetic Resonance Imaging. JACC Cardiovasc Imaging. 2020; 13(11): 2330–2339, doi: 10.1016/j.jcmg.2020.05.004, indexed in Pubmed: 32763118.
11. Huang Lu, Zhao P, Tang D, et al. Cardiac Involvement in Patients Recovered From COVID-2019 Identified Using Magnetic Resonance Imaging. JACC Cardiovasc Imaging. 2020; 13(11): 2330–2339, doi: 10.1016/j.jcmg.2020.05.004, indexed in Pubmed: 32763118.
12. Małek ŁA, Marczak M, Miłosz-Wieczorek B, et al. Cardiac involvement in consecutive elite athletes recovered from COVID-19: A magnetic resonance study. J Magn Reson Imaging. 2021; 53(6): 1723–1729, doi: 10.1002/jmri.27513, indexed in Pubmed: 33474768.
13. Brito D, Meester S, Yanamala N, et al. High Prevalence of Pericardial Involvement in College Student Athletes Recovering From COVID-19. JACC Cardiovasc Imaging. 2021; 14(3): 541–555, doi: 10.1016/j.jcmg.2020.10.023, indexed in Pubmed: 33223496.

REVIEW

Risks associated with intensive blood pressure control in older patients

Giulia Rivasi, Ludovica Ceolin, Marco Capacci, Giulia Matteucci, Giuseppe Dario Testa, Andrea Ungar

Division of Geriatric and Intensive Care Medicine, Careggi Hospital and University of Florence, Florence, Italy

Correspondence to:
Giulia Rivasi, MD,
Division of Geriatric and Intensive Care Medicine,
Careggi Hospital and University of Florence, Largo Brambilla 3, 50139, Florence, Italy,
phone: +39 055 794 95 58,
e-mail: giulia.rivasi@unifi.it

DOI: 10.33963/KP.a2022.0297

Received:
March 9, 2023

Accepted:
March 24, 2023

Early publication date:
March 26, 2023

ABSTRACT

Hypertension management forms a cornerstone of cardiovascular prevention. Strong evidence is available supporting the benefits of blood pressure (BP) lowering in older adults, and recent studies indicate that intensive BP control may provide additional advantages concerning cardiovascular and mortality risk, also at older ages. Yet, in older adults, the cardiovascular benefit of intensive treatment may come at the expense of an increase in adverse events. Indeed, advanced age and frailty may modify the risk/benefit ratio of BP lowering due to a greater predisposition to hypotension and more severe consequences deriving from treatment-related adverse effects. This mostly applies to individuals with poor health status and limited life expectancy, in whom aggressive BP lowering may not lead to cardiovascular benefits but rather increase the risk of short-term treatment-related complications. Furthermore, potential harms of intensive BP control might be underestimated in clinical trials due to exclusion criteria that preclude patients with frailty and multimorbidity from being eligible. Syncope and falls are the most frequently mentioned safety concerns related to antihypertensive treatment, but aggressive BP lowering may affect negatively also renal function, cognitive performance, quality of life, and survival. With the growing emphasis on intensive treatment strategies, raising the awareness of potential harms associated with aggressive BP lowering might help improve hypertension management in older adults and encourage implementation of clinical research on safety. Given these premises, we present a narrative review illustrating the most relevant risks associated with intensive BP control in older patients.

Key words: dementia, falls, hypertension, hypotension, mortality, renal function

INTRODUCTION

Hypertension is one of the most important modifiable risk factors for cardiovascular disease, and mortality and blood pressure (BP) management represents an essential pillar of cardiovascular prevention [1]. The prevalence of hypertension steadily rises with age, exceeding 60%–70% in individuals aged 60 years or older [2].

In Italian epidemiological studies involving individuals over the age of 65, the prevalence of hypertension varied from 65% up to over 80%, with higher rates reported in women [3]. Recent studies analyzing trends in hypertension prevalence in Polish older adults reported consistent data, with prevalence rates reaching 72%–75% in men and 79%–87% in women, and the highest prevalence observed in people over the age of 85 [4, 5]. Given the progressive increase in life expectancy and population aging, the prevalence of hypertension is expected to increase dramatically in the near future, especially in older individuals, which calls for greater attention to this condition in the geriatric population.

Over the last decades, several studies have provided compelling evidence that antihypertensive treatment substantially reduces cardiovascular morbidity and mortality in old and very old adults [6–8]. Consistently, the European Society of Cardiology guidelines advise not to consider age alone as a barrier to antihypertensive treatment [9]. More recent studies seem to support an intensive approach to BP lowering, targeting tight BP control [10]. In the STEP trial involving older adults aged 60–80 years, targeting systolic

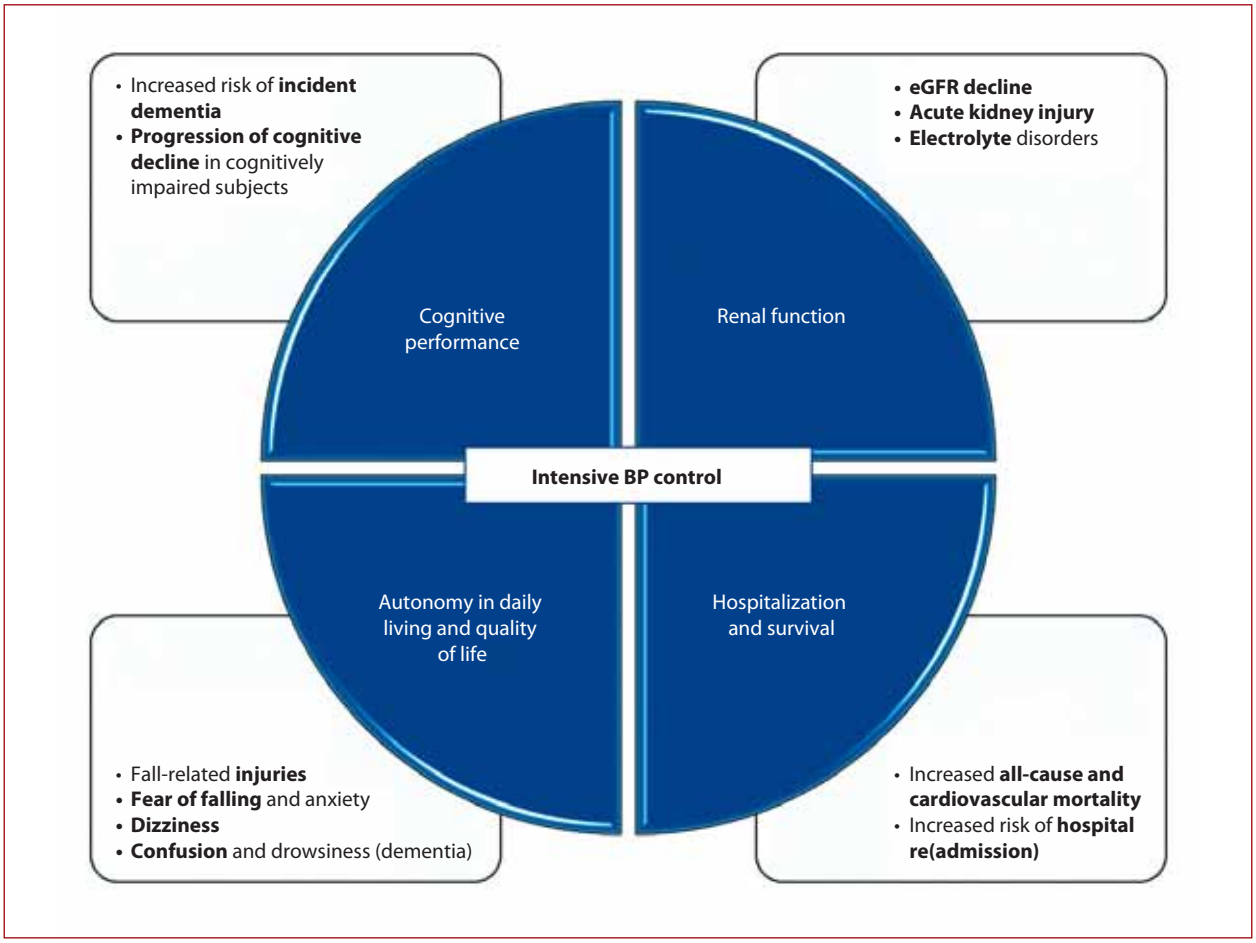


Figure 1. Potential risks of intensive blood pressure (BP) control in older adults
Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate

BP of 110–130 mm Hg reduced the risk of cardiovascular events compared with standard treatment targeting systolic BP of 130–150 mm Hg [11]. Similarly, data from the Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that treating hypertensive adults to reach systolic BP <120 mm Hg reduced the number of cardiovascular events and deaths compared with a systolic BP target <140 mm Hg [12]. The benefits of intensive treatment were also confirmed in individuals aged 75 years or older [13], thus prompting a paradigm shift in hypertension guidelines from less intensive to more intensive BP targets for older adults [14, 15].

The cardiovascular benefits of intensive therapy may come at the expense of relevant drawbacks [16], particularly in older patients who typically present a higher risk of hypotension-related complications [17]. Indeed, multiple observational studies involving older individuals suggest increased potential for serious adverse effects in patients receiving intensive antihypertensive treatment, even more so if they are frail [18–23]. Many experts and analyses have thus argued against aggressive antihypertensive treatment in older patients, highlighting a discrepancy between clinical trials and the real world [24, 25]. Trial evidence that underpins guidelines usually includes patients with relatively good health status and no or mild frailty, who are more likely to benefit from long-term advantages of intensive BP control. By contrast, patients with higher levels of frailty and multimorbidity, who are particularly vulnerable to adverse events, are typically excluded [26, 27]. As a result, data from clinical trials may encourage the pursuit of aggressive BP control while potentially underestimating the risk of adverse events. As life expectancy and time available to experience long-term benefits of antihypertensive treatment decrease, attention should be given to avoiding early complications, including treatment-related adverse events.

Syncope and falls are the most frequently mentioned antihypertensive treatment-related safety concerns. However, aggressive BP lowering may negatively impact also renal function, cognitive performance, quality of life, and survival (Figure 1). The knowledge of potential harms associated with intensive BP lowering may be helpful to improve hypertension management in older adults while drawing attention to clinical research on safety. Therefore, this article presents a narrative review that outlines and discusses the risks of intensive BP control in older adults.

FALLS, FUNCTIONAL AUTONOMY, AND QUALITY OF LIFE

Hypotension represents the most common cause of syncope and falls in older adults [28–31]. Iatrogenic events related to drug-induced hypotension are especially common, particularly in frailer individuals receiving polypharmacy with hypotensive effects [32, 33]. Nevertheless, limited data are available on the association between intensive BP control and the risk of falls and injuries in older patients.

In the SPRINT cohort, including a subgroup of participants aged 75 years and older, intensive treatment was associated with increased risk of hypotension and syncope but not injurious falls, i.e., falls resulting in emergency department or hospital admissions [16]. Observational studies carried out in community-dwelling older adults describe a different scenario. Indeed, in a community-based cohort of subjects aged 75 years or older meeting the inclusion criteria for the SPRINT and undergoing a follow-up of comparable duration, rates of injurious falls and syncope were approximately 5-fold higher than in the standard care group in the SPRINT [25], suggesting limited generalizability of the trial results. Moreover, in a real-world sample including 477 516 treated hypertensive individuals at a mean age of 65 years, mean systolic BP <110 mm Hg carried a 50% higher risk of serious falls and syncope compared with mean systolic BP ≥110 mm Hg [34].

Fall risk seems to be especially relevant during the early phases of antihypertensive treatment. Indeed, introduction of antihypertensive medications was found to be associated with 69% and 94% increased risk of falls during the first 45 and 14 days of treatment initiation, respectively, independently of the drug class used [35]. Consistently, the risk of a serious fall injury was consistently and significantly increased in the 15 days after antihypertensive medication initiation and intensification in a large sample of older Medicare beneficiaries [36].

Although falls are recognized as possible adverse events related to antihypertensive treatment, their deleterious consequences on older patients' health and well-being are often overlooked. Fall-related injuries are usually more severe in older than in younger people and represent a significant cause of disability and mortality. A cohort study of 754 community-dwelling older adults investigating recovery from disability after serious fall-related injuries showed little or no recovery in 64% of participants. Moreover, 44%–59% of participants with no or mild-to-moderate pre-fall disability did not return to the pre-fall level of functioning [37]. Indeed, major injuries such as fractures and head traumas frequently lead to hospitalization, prolonged bed rest and deconditioning, impaired autonomy in daily living, and nursing home admission in more severe cases [38–40]. Falls that do not result in major injuries are also clinically important, potentially causing a "post-fall syndrome" characterized by fear of falling, anxiety, depression, restrictions in daily activities, and loss of functional autonomy [41–43]. Finally, falls represent the leading cause of injury-related deaths in persons aged ≥65 years [44].

Falls aside, aggressive BP lowering in older patients may be responsible for a number of symptoms such as dizziness, light-headedness, and unsteadiness, which impair quality of life and may lead to activity restriction.

Moreover, hypotension has been associated with mental fluctuations, confusion, and drowsiness in patients with dementia [45].

RENAL FUNCTION AND ELECTROLYTE BALANCE

High BP is a modifiable risk factor for chronic kidney disease and antihypertensive treatment is known to reduce the risk of renal function decline. However, uncertainties remain on the renal benefits of intensive BP control [46, 47].

In the SPRINT cohort, a >30% reduction in estimated glomerular filtration rate (eGFR) occurred in the 4% and 1.1% of participants in the intensive and standard treatment arms, respectively, and intensive treatment was associated with a significantly higher risk of a >30% reduction in eGFR (hazard ratio [HR], 3.69; 95% confidence interval [CI], 2.54–5.36) [48]. In a systematic review and meta-analysis assessing the efficacy and safety of intensive BP lowering in older adults, intensive treatment was consistently associated with a 2-fold increase in the risk of renal failure [10]. Moreover, a systematic review of clinical trials involving patients with non-diabetic chronic kidney disease demonstrated that intensive BP treatment does not slow renal function decline nor reduce the risk of renal outcomes, such as doubling of serum creatinine or a 50% reduction in GFR, although stricter BP control might be beneficial in selected subgroups of patients with higher levels of proteinuria [49].

In addition to unclear benefits for renal function and preventing renal disease progression, intensive BP lowering may also predispose to acute kidney injury (AKI) events. Data from primary care indicate that AKI is more likely to occur in older adults with low systolic BP values (i.e., <100 mm Hg) [50]. In the SPRINT study, the incidence of AKI events was 3.8% vs. 2.3% in the intensive and standard arms, respectively [51], and intensive treatment was identified as an independent predictor of AKI (adjusted HR, 1.83; 95% CI, 1.43–2.33) [48]. Although AKI events in the SPRINT participants were generally mild and largely reversible [51], they meaningfully raised the risk of cardiovascular events and all-cause death [48]. One may thus suppose that intensive BP lowering results in more pronounced alterations of intrarenal hemodynamics, leading to an increased probability of BP falling below the autoregulatory threshold for kidney perfusion. However, long-term follow-up data are needed to better evaluate the effects of intensive BP control strategies on worsening of renal function.

Electrolyte disorders also deserve mention although they are rarely assessed in detail in hypertension trials [10, 47]. In older adults participating in the SPRINT, severe

electrolyte disorders were significantly more common in the intensive treatment arm, with particular reference to hyponatremia [13]. Indeed, the risk of electrolyte disorders is especially high in older patients due to comorbidities, additional predisposing medications (e.g., benzodiazepines, antidepressants) [52], and a tendency for poor hydration. Diuretic therapy is recognized as the most important independent risk factor for electrolyte disorders, particularly hypokalemia, and hyponatremia [53]. Hyponatremia is most frequently associated with thiazide or thiazide-like agents, but it may occur also in patients receiving loop and potassium-sparing diuretics, particularly when different diuretic classes are combined [54]. Potassium-sparing diuretics also predispose to hyperkalemia, especially in patients with renal impairment, and/or receiving angiotensin system antagonists. By contrast, thiazide and loop diuretics predispose to hypokalemia, with higher risk at increased doses [53]. As electrolyte disorders are associated with several adverse outcomes including increased mortality [52], electrolyte monitoring is advisable during antihypertensive treatment intensification, particularly in older patients receiving diuretic therapy.

COGNITIVE PERFORMANCE

Numerous studies have shown that midlife hypertension is associated with increased risk of dementia in later life [55–58]. However, this association modifies with advancing age and high BP seems to no longer be a risk factor in older individuals [57, 59–61].

In a longitudinal observational study of over 8000 individuals, systolic BP ≥130 mm Hg at the age of 50 was associated with increased risk of dementia independently of cardiovascular disease, whereas no association was observed between high BP and incident dementia at the ages of 60 or 70 years [57]. The Rotterdam Study and the Leiden 85-plus Study [62] reported consistent results: in individuals aged 65–74 years, higher BP was associated with worse cognitive function in later life, while this association reversed in older participants — particularly in the oldest subgroup (age 85+ years) — in whom higher baseline BP was associated with better cognitive function. Van Dalen and colleagues [63] recently investigated the association between BP and dementia risk in 7 cohort studies involving a total of 17 286 participants: a non-linear association was reported in older participants that appeared to be U-shaped in groups aged 75 to 95 years, with the lowest risk points at systolic BP of approximately 160–170 mm Hg. In recent years, a relevant number of cohort studies have reported comparable findings, suggesting that the association between high BP and risk of incident dementia attenuates or even reverts at an advanced age [59, 60, 64, 65], particularly in treated hypertensive patients [66, 67]. Increasing evidence consistently suggests that aggressive BP lowering might not be beneficial or may even be harmful. In 8563 subjects included in the SPRINT MIND substudy (mean age 67 years), intensive BP control did not significantly reduce the incidence of probable dementia over a 5.1-year follow-up although potential benefits were reported on reducing the risk of mild cognitive impairment and of the composite outcome of mild cognitive impairment plus dementia, with a 15% risk reduction estimate [68]. In 1 626 individuals involved in the HOPE-3 cognitive substudy (mean age 74 years), the addition of antihypertensive treatment (candesartan plus hydrochlorothiazide) to standard treatment showed no beneficial effect on cognitive performance after a 5.7-year follow-up [69]. Moreover, in a subgroup analysis, a lower cognitive decline was observed in the placebo arm in subjects with lower baseline systolic BP (<133 mm Hg), with a significant blood pressure/treatment group interaction [69]. Similarly, the Sydney Memory and Aging Study [70] showed worse global cognition trajectories in a cohort of treated hypertensive patients aged 70–90 years with systolic BP values ≤120 mm Hg compared to those not receiving antihypertensive medications. Recent data from a large national population database [67] described an U-shaped association of BP with the risk of dementia and Alzheimer's disease, independently of antihypertensive use. By contrast, the risk of vascular dementia seems to differ by antihypertensive treatment. Indeed, in individuals not taking antihypertensive medications, the risk of vascular dementia was greater as SBP increased. In those taking antihypertensive treatment, the risk of vascular dementia was greatest at systolic SBP ≥160 mm Hg, lowest at systolic BP of 120–140 mm Hg, and increased at systolic BP of 100–120 mm Hg.

Based on the above, there seems to be a gradual shift with age from high BP being a risk factor for cognitive impairment to high BP potentially helping to preserve cognitive function in the oldest individuals. Whether low BP is causally related to dementia or the result of the dementia process remains unclear. It can be assumed that high BP values may help maintain adequate cerebral perfusion and normal cognition in the face of age-associated vascular changes [71]. However, some data indicate that BP declines in the years preceding dementia onset and further decreases over the disease course, with a more rapid decline compared to subjects with no diagnosis of dementia [59, 61, 72]. This may suggest an inverse association between BP and dementia risk, with lower BP values resulting from neurodegenerative processes in preclinical stages of dementia [73].

While a large body of literature has explored the association between BP and dementia risk, few studies provide information on BP control in patients with dementia, who are usually excluded from randomized clinical trials [8]. In the SPRINT study, a significant interaction between benefits from intensive treatment and cognitive performance was reported. Indeed, participants with higher baseline scores on the Montreal Cognitive Assessment derived strong benefits from intensive treatment, while no appreciable benefits were observed in participants with lower

cognitive function [74]. Consistently, in an Italian clinical sample of 172 patients with dementia or mild cognitive impairment (mean age 79 years), lower daytime systolic BP in ambulatory BP monitoring (mean daytime systolic BP <129 mm Hg) was associated with greater progression of cognitive decline at 9 months in patients receiving antihypertensive treatment [75].

In addition to uncertain benefits for cognitive function, individuals with cognitive impairment may be particularly liable to harms associated with antihypertensive treatment and may experience higher rates of adverse effects related to intensive BP control, particularly as regards falls [76]. On the whole, available data suggest that benefits of BP lowering may be attenuated in patients with coexisting cognitive impairment and recommend caution against excessive BP lowering in this subgroup.

HOSPITALIZATION AND MORTALITY

Over the last decades, several observational studies have provided evidence of an attenuated or even inverted relationship between BP and mortality in older individuals. Moreover, available evidence clearly demonstrates that physical performance, cognitive status, and functional level modulate the BP-mortality association in old age [77–79].

In a post-hoc analysis of the Systolic Hypertension in the Elderly Program (SHEP), antihypertensive treatment was associated with a lower rate of mortality and myocardial infarction in patients with preserved functional autonomy but not in those with disability [80]. In National Health and Nutrition Examination Survey (NHANES) participants aged 65 or older, BP was positively correlated with mortality in faster but not in slower walkers (gait speed <0.8 m/s), while BP was negatively associated with risk of death in those unable to complete the walk test [79]. In the Swedish population-based Swedish National Study on Aging and Care (SNAC-K) study involving 3 014 older subjects (mean age 73 years), systolic BP values <130 mm Hg were associated with the lowest mortality in "biologically young" participants, but with the highest mortality in "biologically older" participants, i.e., those with mobility limitations (gait velocity <0.8 m/sec) and/or cognitive impairment.

Based on this evidence, one might suppose that intensive BP control may not provide mortality benefits in older patients, particularly in frailer ones. Indeed, while the unfavorable prognostic impact of high BP tends to reduce with advancing age, low BP increasingly becomes a negative prognostic marker, especially in subjects with frailty or worse health status [81–83]. In agreement with this hypothesis, systolic BP <120 mm Hg was found to be associated with increased risk for mortality in nursing home residents [19, 84]. Moreover, observational studies indicate that also systolic BP <140 mm Hg may not be beneficial to older people. Six-year follow-up data from the Italian cohort study "Fiesole Misurata" showed lower mortality in community-dwelling older adults with systolic BP 140–159 mm Hg as compared with systolic BP 120–139 mm Hg (HR, 0.54; 95% CI, 0.33–0.89) [85]. Similarly, Oates and colleagues [86] reported reduced 5-year survival in hypertensive adults aged 80 or older with BP values <140/90 mm Hg (HR, 0.84; 95% CI, 0.78– 0.89, and HR, 0.91; 95% CI, 0.87–0.96, for each 10-point increase in SBP and DBP, respectively), while BP was not associated with survival in individuals with uncontrolled hypertension (HR, 1.01; 95% CI, 0.98–1.05; and HR, 0.89; 95% CI, 0.67–1.19, for each 10-point increase in systolic and diastolic BP ≥140/90 mm Hg, respectively). Finally, in a recent systematic review and meta-analysis, no mortality difference was observed between frail older people with systolic BP <140 mm Hg and those with higher BP values. Conversely, mortality was lower in non-frail individuals with systolic BP <140 mm Hg compared to those with higher systolic BP [87]. As regards diastolic BP, low values were found to predict all-cause mortality in older hypertensive outpatients [88].

A possible explanation of these findings is that older people have higher susceptibility to organ hypoperfusion due to vascular stiffness and impaired autoregulation, multimorbidity, and polypharmacy with hypotensive effects [32, 89, 90]. Therefore, in parallel with high cardiovascular risk, older people also show a significant predisposition to hypotension, which may diminish or even revert the potential benefits of intensive BP control due to increased vulnerability to treatment-related complications. Moreover, in frailer patients, the time-until-benefit of antihypertensive treatment might exceed the life expectancy due to coexisting conditions that substantially impact patients' prognosis and reduce the prognostic relevance of high BP [91]. However, reverse causality cannot be excluded, as low BP may represent an epiphenomenon of an overall decline in health status which would be responsible for the increased risk of mortality.

Uncertainties remain on the benefits of intensive BP control even in older patients with very high cardiovascular risk, e.g., those with previous cardiovascular events. In a secondary analysis of the INternational VErapamil SR-Trandolapril STudy (INVEST) including 22 576 hypertensive coronary artery disease patients, the systolic BP value corresponding to the nadir risk for the composite outcome of all-cause mortality, myocardial infarction and stroke increased with increasing age, being lowest (110 mm Hg) in participants <60 years and highest for those aged 80 years or older (140 mm Hg) [92]. In older patients with hypertension and coronary artery disease enrolled in the CLARIFY (ProspeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease) registry, BP values <120/70 mm Hg were consistently associated with higher all-cause mortality, myocardial infarction, and stroke [93]. In contrast to these studies, data from the Secondary Prevention of Small Subcortical Strokes (SPS3) Trial suggest possible benefits of intensive BP control (systolic BP target <120 mm Hg) for the risk of disabling and fatal strokes in subjects older than 75 years with previous lacunar events [94].

In addition to mortality, hospitalization should also be considered as a possible complication related to intensive BP control. In a recent study involving older adults hospitalized for non-cardiac conditions, intensification of antihypertensive therapy on hospital discharge was not associated with reduced cardiac events or improved BP control within one year but was associated with increased risk of readmission and cardiovascular events in the short term [20]. These associations were not observed in patients with previously elevated BP but mostly applied to patients with well-controlled baseline BP, suggesting that the increased rate of adverse events may be at least partially explained by overtreatment [20]. Similarly, in hypertensive nursing home residents, increased intensity of antihypertensive treatment was significantly associated with a small increase in hospitalization risk although no significant association with mortality was reported [22].

CONCLUSIONS

With the growing emphasis on intensive BP control, attention should be given to the potential for treatment-related adverse events in the geriatric population. When considering intensive BP control in older hypertensive adults, clinicians need to individually weigh benefits against potential risks deriving from increased vulnerability to adverse events. Indeed, advanced age and frailty may modify the risk/benefit ratio of BP lowering due to an increased predisposition to hypotension and more severe consequences deriving from its complications. This mostly applies to individuals with poor physical performance, cognitive impairment, and disability, in whom aggressive BP lowering may not lead to cardiovascular benefits, but rather increase the risk of hypotension and treatment-related adverse events. In these patients, a more prudent BP lowering strategy seems to be advisable and a target range of 130–150 mm Hg systolic BP has been suggested to minimize the risk of hypotension-related adverse outcomes while providing adequate cardiovascular protection [19]. Additional trials are needed to thoroughly investigate the effects of intensive BP control and optimal BP targets in older adults.

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021; 42(34): 3227–3337, doi: 10.1093/eurheartj/ehab484, indexed in Pubmed: 34458905.
2. Yoon SS, Carroll MD, Fryar CD. Hypertension Prevalence and Control Among Adults: United States, 2011–2014. NCHS Data Brief. 2015(220): 1–8, indexed in Pubmed: 26633197.
3. Antonelli In, Cesari M, Leosco D, et al. Manuale di Geriatria. Manual of Geriatrics [in Italian], Edra 2019.
4. Pająk A, Jankowski P, Zdrojewski T. The burden of cardiovascular disease risk factors: A current problem. Kardiol Pol. 2022; 80(1): 5–15, doi: 10.33963/KP.a2022.0018, indexed in Pubmed: 35137945.
5. Niklas AA, Flotyńska A, Zdrojewski T, et al. Trends in hypertension prevalence, awareness, treatment, and control among Polish adults 75 years and older during 2007-2014. Cardiol J. 2018; 25(3): 333–344, doi: 10.5603/CJ.a2018.0043, indexed in Pubmed: 29671863.
6. Moraes AAI, Baena CP, Muka T, et al. Achieved systolic blood pressure in older people: a systematic review and meta-analysis. BMC Geriatr. 2017; 17(1): 279, doi: 10.1186/s12877- 017-0672-4, indexed in Pubmed: 29207946.
7. Weiss J, Freeman M, Low A, et al. Benefits and Harms of Intensive Blood Pressure Treatment in Adults Aged 60 Years or Older: A Systematic Review and Meta-analysis. Ann Intern Med. 2017; 166(6): 419–429, doi: 10.7326/M16-1754, indexed in Pubmed: 28114673.
8. Benetos A, Petrovic M, Strandberg T. Hypertension Management in Older and Frail Older Patients. Circ Res. 2019; 124(7): 1045–1060, doi: 10.1161/CIRCRESAHA.118.313236, indexed in Pubmed: 30920928.
9. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens . 2018; 36(10): 1953–2041, doi: 10.1097/HJH.0000000000001940, indexed in Pubmed: 30234752.
10. Bavishi C, Bangalore S, Messerli FH. Outcomes of Intensive Blood Pressure Lowering in Older Hypertensive Patients. J Am Coll Cardiol. 2017; 69(5): 486–493, doi: 10.1016/j.jacc.2016.10.077, indexed in Pubmed: 28153104.
11. Zhang W, Zhang S, Deng Y, et al. Trial of Intensive Blood-Pressure Control in Older Patients with Hypertension. N Engl J Med. 2021; 385(14): 1268–1279, doi: 10.1056/NEJMoa2111437, indexed in Pubmed: 34491661.
12. Wright JT, Williamson JD, Whelton PK, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015; 373(22): 2103–2116, doi: 10.1056/NEJMoa1511939, indexed in Pubmed: 26551272.
13. Williamson J, Supiano M, Applegate W, et al. Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged ≥75 Years. JAMA. 2016; 315(24): 2673, doi: 10.1001/jama.2016.7050, indexed in Pubmed: 27195814.
14. Lamb SA, Al Hamarneh YN, Houle SKD, et al. Hypertension Canada's 2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults. Can J Cardiol. 2017; 33(5): 557–576, doi: 10.1016/j.cjca.2017.03.005, indexed in Pubmed: 28449828.
15. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ /ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task F. Hypertension. 2018; 71(6): 1269–1324, doi: 10.1161/HYP.0000000000000066, indexed in Pubmed: 29133354.
16. Sink KM, Evans GW, Shorr RI, et al. Syncope, Hypotension, and Falls in the Treatment of Hypertension: Results from the Randomized Clinical Systolic Blood Pressure Intervention Trial. J Am Geriatr Soc. 2018; 66(4): 679–686, doi: 10.1111/jgs.15236, indexed in Pubmed: 29601076.
17. Rivasi G, Tortù V, D'Andria MF, et al. Hypertension management in frail older adults: a gap in evidence. J Hypertens. 2021; 39(3): 400–407, doi: 10.1097/HJH.0000000000002685, indexed in Pubmed: 33239551.
18. van der Wardt V, Harrison JK, Welsh T, et al. Withdrawal of antihypertensive medication: a systematic review. J Hypertens. 2017; 35(9): 1742–1749, doi: 10.1097/HJH.0000000000001405, indexed in Pubmed: 28486271.
19. Benetos A, Labat C, Rossignol P, et al. Treatment With Multiple Blood Pressure Medications, Achieved Blood Pressure, and Mortality in Older Nursing Home Residents: The PARTAGE Study. JAMA Intern Med. 2015; 175(6): 989–995, doi: 10.1001/jamainternmed.2014.8012, indexed in Pubmed: 25685919.

20. Anderson TS, Jing B, Auerbach A, et al. Clinical Outcomes After Intensifying Antihypertensive Medication Regimens Among Older Adults at Hospital Discharge. JAMA Intern Med. 2019; 179(11): 1528–1536, doi: 10.1001/jamainternmed.2019.3007, indexed in Pubmed: 31424475.
21. Bahat G, İlhan B, Tufan A, et al. Hypotension Under Antihypertensive Treatment and Incident Hospitalizations of Nursing Home Residents. Drugs Aging. 2022; 39(6): 477–484, doi: 10.1007/s40266-022-00951-0, indexed in Pubmed: 35701577.
22. Boockvar KS, Song W, Lee S, et al. Hypertension Treatment in US Long-Term Nursing Home Residents With and Without Dementia. J Am Geriatr Soc. 2019; 67(10): 2058–2064, doi: 10.1111/jgs.16081, indexed in Pubmed: 31328791.
23. Song W, Intrator O, Lee S, et al. Antihypertensive Drug Deintensification and Recurrent Falls in Long-Term Care. Health Serv Res. 2018; 53(6): 4066–4086, doi: 10.1111/1475- 6773.13074, indexed in Pubmed: 30353536.
24. Bress AP, Kramer H, Cooper RS, et al. Potential Deaths Averted and Serious Adverse Events Incurred From Adoption of the SPRINT (Systolic Blood Pressure Intervention Trial) Intensive Blood Pressure Regimen in the United States: Projections From NHANES (National Health and Nutrition Examination Survey). Circulation. 2017; 135(17): 1617– 1628, doi: 10.1161/CIRCULATIONAHA.116.025322, indexed in Pubmed: 28193605.
25. Sexton DJ, Canney M, O'Connell MDL, et al. Injurious Falls and Syncope in Older Community-Dwelling Adults Meeting Inclusion Criteria for SPRINT. JAMA Intern Med. 2017; 177(9): 1385–1387, doi: 10.1001/jamainternmed.2017.2924, indexed in Pubmed: 28715566.
26. Russo G, Liguori I, Aran L, et al. Impact of SPRINT results on hypertension guidelines: implications for "frail" elderly patients. J Hum Hypertens. 2018; 32(8-9): 633–638, doi: 10.1038/s41371-018-0086-6, indexed in Pubmed: 29991704.
27. Anderson TS, Odden MC, Penko J, et al. Characteristics of Populations Excluded From Clinical Trials Supporting Intensive Blood Pressure Control Guidelines. J Am Heart Assoc. 2021; 10(7): e019707, doi: 10.1161/JAHA.120.019707, indexed in Pubmed: 33754796.
28. Ceccofiglio A, Mussi C, Rafanelli M, et al. Increasing Prevalence of Orthostatic Hypotension as a Cause of Syncope With Advancing Age and Multimorbidity. J Am Med Dir Assoc. 2019; 20(5): 586–588, doi: 10.1016/j.jamda.2019.01.149, indexed in Pubmed: 30926410.
29. Finucane C, O'Connell MDL, Donoghue O, et al. Impaired Orthostatic Blood Pressure Recovery Is Associated with Unexplained and Injurious Falls. J Am Geriatr Soc. 2017; 65(3): 474–482, doi: 10.1111/jgs.14563, indexed in Pubmed: 28295143.
30. Madden KM, Feldman B, Meneilly GS. Blood pressure measurement and the prevalence of postprandial hypotension. Clin Invest Med. 2019; 42(1): E39–E46, doi: 10.25011/cim.v42i1.32391, indexed in Pubmed: 30904035.
31. Ungar A, Mussi C, Ceccofiglio A, et al. Etiology of Syncope and Unexplained Falls in Elderly Adults with Dementia: Syncope and Dementia (SYD) Study. J Am Geriatr Soc. 2016; 64(8): 1567–1573, doi: 10.1111/jgs.14225, indexed in Pubmed: 27351866.
32. Rivasi G, Rafanelli M, Mossello E, et al. Drug-Related Orthostatic Hypotension: Beyond Anti-Hypertensive Medications. Drugs Aging. 2020; 37(10): 725–738, doi: 10.1007/s40266- 020-00796-5, indexed in Pubmed: 32894454.
33. van der Velde N, Stricker BH, Pols HAP, et al. Risk of falls after withdrawal of fall-risk- increasing drugs: a prospective cohort study. Br J Clin Pharmacol. 2007; 63(2): 232–237, doi: 10.1111/j.1365-2125.2006.02736.x, indexed in Pubmed: 16939531.
34. Sim JJ, Zhou H, Bhandari S, et al. Low Systolic Blood Pressure From Treatment and Association With Serious Falls/Syncope. Am J Prev Med. 2018; 55(4): 488–496, doi: 10.1016/j.amepre.2018.05.026, indexed in Pubmed: 30166081.
35. Butt DA, Mamdani M, Austin PC, et al. The risk of hip fracture after initiating antihypertensive drugs in the elderly. Arch Intern Med. 2012; 172(22): 1739–1744, doi: 10.1001/2013.jamainternmed.469, indexed in Pubmed: 23165923.
36. Shimbo D, Barrett Bowling C, Levitan EB, et al. Short-Term Risk of Serious Fall Injuries in Older Adults Initiating and Intensifying Treatment With Antihypertensive Medication. Circ Cardiovasc Qual Outcomes. 2016; 9(3): 222–229, doi: 10.1161/CIRCOUTCOMES.115.002524, indexed in Pubmed: 27166208.
37. Gill TM, Murphy TE, Gahbauer EA, et al. The course of disability before and after a serious fall injury. JAMA Intern Med. 2013; 173(19): 1780–1786, doi: 10.1001/jamainternmed.2013.9063, indexed in Pubmed: 23958741.
38. James SL, Lucchesi LR, Bisignano C, et al. Burden of injuries in Nepal, 1990-2017: findings from the Global Burden of Disease Study 2017. Inj Prev. 2020; 26(Supp 1): i57– i66, doi: 10.1136/injuryprev-2019-043309, indexed in Pubmed: 31915272.
39. Tinetti ME, Williams CS. Falls, injuries due to falls, and the risk of admission to a nursing home. N Engl J Med. 1997; 337(18): 1279–1284, doi: 10.1056/NEJM199710303371806, indexed in Pubmed: 9345078.
40. Stewart Williams J, Kowal P, Hestekin H, et al. Prevalence, risk factors and disability associated with fall-related injury in older adults in low- and middle-incomecountries: results from the WHO Study on global AGEing and adult health (SAGE). BMC Med. 2015; 13: 147, doi: 10.1186/s12916-015-0390-8, indexed in Pubmed: 26099794.
41. Arfken CL, Lach HW, Birge SJ, et al. The prevalence and correlates of fear of falling in elderly persons living in the community. Am J Public Health. 1994; 84(4): 565–570, doi: 10.2105/ajph.84.4.565, indexed in Pubmed: 8154557.
42. Scheffer AC, Schuurmans MJ, van Dijk N, et al. Fear of falling: measurement strategy, prevalence, risk factors and consequences among older persons. Age Ageing. 2008; 37(1): 19–24, doi: 10.1093/ageing/afm169, indexed in Pubmed: 18194967.
43. Vellas BJ, Wayne SJ, Romero LJ, et al. Fear of falling and restriction of mobility in elderly fallers. Age Ageing. 1997; 26(3): 189–193, doi: 10.1093/ageing/26.3.189, indexed in Pubmed: 9223714.
44. Burns E, Kakara R. Deaths from Falls Among Persons Aged ≥65 Years – United States, 2007–2016. MMWR Morb Mortal Wkly Rep. 2018; 67(18): 509–514, doi: 10.15585/mmwr.mm6718a1, indexed in Pubmed: 29746456.
45. Freidenberg DL, Shaffer LET, Macalester S, et al. Orthostatic hypotension in patients with dementia: clinical features and response to treatment. Cogn Behav Neurol. 2013; 26(3): 105–120, doi: 10.1097/WNN.0000000000000003, indexed in Pubmed: 24077570.
46. Lewis JB. Blood pressure control in chronic kidney disease: is less really more? J Am Soc Nephrol. 2010; 21(7): 1086–1092, doi: 10.1681/ASN.2010030236, indexed in Pubmed: 20576804.
47. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet. 2016; 387(10017): 435–443, doi: 10.1016/S0140-6736(15)00805-3, indexed in Pubmed: 26559744.
48. Dieter BP, Daratha KB, McPherson SM, et al. Association of Acute Kidney Injury with Cardiovascular Events and Death in Systolic Blood Pressure Intervention Trial. Am J Nephrol. 2019; 49(5): 359–367, doi: 10.1159/000499574, indexed in Pubmed: 30939480.
49. Tsai WC, Wu HY, Peng YS, et al. Association of Intensive Blood Pressure Control and Kidney Disease Progression in Nondiabetic Patients With Chronic Kidney Disease: A Systematic Review and Meta-analysis. JAMA Intern Med. 2017; 177(6): 792–799, doi: 10.1001/jamainternmed.2017.0197, indexed in Pubmed: 28288249.
50. Morrissey Y, Bedford M, Irving J, et al. Older people remain on blood pressure agents despite being hypotensive resulting in increased mortality and hospital admission. Age Ageing. 2016; 45(6): 783–788, doi: 10.1093/ageing/afw120, indexed in Pubmed: 27496937.
51. Rocco MV, Sink KM, Lovato LC, et al. Effects of Intensive Blood Pressure Treatment on Acute Kidney Injury Events in the Systolic Blood Pressure Intervention Trial (SPRINT). Am J Kidney Dis. 2018; 71(3): 352–361, doi: 10.1053/j.ajkd.2017.08.021, indexed in Pubmed: 29162340.
52. Liamis G, Liberopoulos E, Barkas F, et al. Spurious electrolyte disorders: a diagnostic challenge for clinicians. Am J Nephrol. 2013; 38(1): 50–57, doi: 10.1159/000351804, indexed in Pubmed: 23817179.
53. Liamis G, Milionis H, Elisaf M. Blood pressure drug therapy and electrolyte disturbances. Int J Clin Pract. 2008; 62(10): 1572–1580, doi: 10.1111/j.1742-1241.2008.01860.x, indexed in Pubmed: 18822027.
54. Liamis G, Liberopoulos E, Barkas F, et al. Spurious electrolyte disorders: a diagnostic challenge for clinicians. Am J Nephrol. 2013; 38(1): 50–57, doi: 10.1159/000351804, indexed in Pubmed: 23817179.
55. Launer LJ, Ross GW, Petrovitch H, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. Neurobiol Aging. 2000; 21(1): 49–55, doi: 10.1016/s0197- 4580(00)00096-8, indexed in Pubmed: 10794848.

56. Kivipelto M, Helkala EL, Laakso MP, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ. 2001; 322(7300): 1447– 1451, doi: 10.1136/bmj.322.7300.1447, indexed in Pubmed: 11408299.
57. Abell JG, Kivimäki M, Dugravot A, et al. Association between systolic blood pressure and dementia in the Whitehall II cohort study: role of age, duration, and threshold used to define hypertension. Eur Heart J. 2018; 39(33): 3119–3125, doi: 10.1093/eurheartj/ehy288, indexed in Pubmed: 29901708.
58. Whitmer RA, Sidney S, Selby J, et al. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology. 2005; 64(2): 277–281, doi: 10.1212/01.WNL.0000149519.47454.F2, indexed in Pubmed: 15668425.
59. Ruitenberg A, Skoog I, Ott A, et al. Blood pressure and risk of dementia: results from the Rotterdam study and the Gothenburg H-70 Study. Dement Geriatr Cogn Disord. 2001; 12(1): 33–39, doi: 10.1159/000051233, indexed in Pubmed: 11125239.
60. Li Ge, Rhew IC, Shofer JB, et al. Age-varying association between blood pressure and risk of dementia in those aged 65 and older: a community-based prospective cohort study. J Am Geriatr Soc. 2007; 55(8): 1161–1167, doi: 10.1111/j.1532-5415.2007.01233.x, indexed in Pubmed: 17661953.
61. Qiu C, Winblad B, Fratiglioni L. Low diastolic pressure and risk of dementia in very old people: a longitudinal study. Dement Geriatr Cogn Disord. 2009; 28(3): 213–219, doi: 10.1159/000236913, indexed in Pubmed: 19752556.
62. Euser SM, van Bemmel T, Schram MT, et al. The effect of age on the association between blood pressure and cognitive function later in life. J Am Geriatr Soc. 2009; 57(7): 1232– 1237, doi: 10.1111/j.1532-5415.2009.02264.x, indexed in Pubmed: 19453303.
63. van Dalen JW, Brayne C, Crane PK, et al. Association of Systolic Blood Pressure With Dementia Risk and the Role of Age, U-Shaped Associations, and Mortality. JAMA Intern Med. 2022; 182(2): 142–152, doi: 10.1001/jamainternmed.2021.7009, indexed in Pubmed: 34901993.
64. Corrada MM, Hayden KM, Paganini-Hill A, et al. Age of onset of hypertension and risk of dementia in the oldest-old: The 90+ Study. Alzheimers Dement. 2017; 13(2): 103–110, doi: 10.1016/j.jalz.2016.09.007, indexed in Pubmed: 28108119.
65. Sabayan B, Oleksik AM, Maier AB, et al. High blood pressure and resilience to physical and cognitive decline in the oldest old: the Leiden 85-plus Study. J Am Geriatr Soc. 2012; 60(11): 2014–2019, doi: 10.1111/j.1532-5415.2012.04203.x, indexed in Pubmed: 23126669.
66. Streit S, Poortvliet RKE, Gussekloo J. Lower blood pressure during antihypertensive treatment is associated with higher all-cause mortality and accelerated cognitive decline in the oldest-old. Data from the Leiden 85-plus Study. Age Ageing. 2018; 47(4): 545–550, doi: 10.1093/ageing/afy072, indexed in Pubmed: 29741555.
67. Lee CJ, Lee JY, Han K, et al. Blood Pressure Levels and Risks of Dementia: a Nationwide Study of 4.5 Million People. Hypertension. 2022; 79(1): 218–229, doi: 10.1161/HYPERTENSIONAHA.121.17283, indexed in Pubmed: 34775786.
68. Williamson JD, Pajewski NM, Auchus AP, et al. Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia: A Randomized Clinical Trial. JAMA. 2019; 321(6): 553–561, doi: 10.1001/jama.2018.21442, indexed in Pubmed: 30688979.
69. Bosch J, O'Donnell M, Swaminathan B, et al. Effects of blood pressure and lipid lowering on cognition: Results from the HOPE-3 study. Neurology. 2019; 92(13): e1435–e1446, doi: 10.1212/WNL.0000000000007174, indexed in Pubmed: 30814321.
70. Lennon MJ, Lam BC, Crawford J, et al. Does Antihypertensive Use Moderate the Effect of Blood Pressure on Cognitive Decline in Older People? J Gerontol A Biol Sci Med Sci. 2021; 76(5): 859–866, doi: 10.1093/gerona/glaa232, indexed in Pubmed: 33225353.
71. Kitagawa K, Oku N, Kimura Y, et al. Relationship between cerebral blood flow and later cognitive decline in hypertensive patients with cerebral small vessel disease. Hypertens Res. 2009; 32(9): 816–820, doi: 10.1038/hr.2009.100, indexed in Pubmed: 19575014.
72. Skoog I, Lernfelt B, Landahl S, et al. 15-year longitudinal study of blood pressure and dementia. Lancet. 1996; 347(9009): 1141–1145, doi: 10.1016/s0140-6736(96)90608-x, indexed in Pubmed: 8609748.
73. Skoog I, Andreasson LA, Landahl S, et al. A population-based study on blood pressure and brain atrophy in 85-year-olds. Hypertension. 1998; 32(3): 404–409, doi: 10.1161/01.hyp.32.3.404, indexed in Pubmed: 9740603.
74. Pajewski NM, Berlowitz DR, Bress AP, et al. Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged ≥75 Years: A Randomized Clinical Trial. JAMA. 2016; 315(24): 2673–2682, doi: 10.1001/jama.2016.7050, indexed in Pubmed: 27195814.
75. Mossello E, Pieraccioli M, Nesti N, et al. Effects of low blood pressure in cognitively impaired elderly patients treated with antihypertensive drugs. JAMA Intern Med. 2015; 175(4): 578–585, doi: 10.1001/jamainternmed.2014.8164, indexed in Pubmed: 25730775.
76. Welsh TJ, Gordon AL, Gladman JRF. Treatment of Hypertension in People With Dementia: A Multicenter Prospective Observational Cohort Study. J Am Med Dir Assoc. 2019; 20(9): 1111–1115, doi: 10.1016/j.jamda.2019.03.036, indexed in Pubmed: 31109906.
77. Liang Y, Fratiglioni L, Wang R, et al. Effects of biological age on the associations of blood pressure with cardiovascular and non-cardiovascular mortality in old age: A population- based study. Int J Cardiol. 2016; 220: 508–513, doi: 10.1016/j.ijcard.2016.06.118, indexed in Pubmed: 27390978.
78. Ogliari G, Westendorp RGJ, Muller M, et al. Blood pressure and 10-year mortality risk in the Milan Geriatrics 75+ Cohort Study: role of functional and cognitive status. Age Ageing. 2015; 44(6): 932–937, doi: 10.1093/ageing/afv141, indexed in Pubmed: 26504116.
79. Odden MC, Peralta CA, Haan MN, et al. Rethinking the association of high blood pressure with mortality in elderly adults: the impact of frailty. Arch Intern Med. 2012; 172(15): 1162–1168, doi: 10.1001/archinternmed.2012.2555, indexed in Pubmed: 22801930.
80. Charlesworth CJ, Peralta CA, Odden MC. Functional Status and Antihypertensive Therapy in Older Adults: A New Perspective on Old Data. Am J Hypertens. 2016; 29(6): 690–695, doi: 10.1093/ajh/hpv177, indexed in Pubmed: 26541570.
81. van Bemmel T, Gussekloo J, Westendorp RGJ, et al. In a population-based prospective study, no association between high blood pressure and mortality after age 85 years. J Hypertens. 2006; 24(2): 287–292, doi: 10.1097/01.hjh.0000200513.48441.8e, indexed in Pubmed: 16508574.
82. Molander L, Lövheim H, Norman T, et al. Lower systolic blood pressure is associated with greater mortality in people aged 85 and older. J Am Geriatr Soc. 2008; 56(10): 1853–1859, doi: 10.1111/j.1532-5415.2008.01948.x, indexed in Pubmed: 18811610.
83. Rea F, Cantarutti A, Merlino L, et al. Antihypertensive Treatment in Elderly Frail Patients: Evidence From a Large Italian Database. Hypertension. 2020; 76(2): 442–449, doi: 10.1161/HYPERTENSIONAHA.120.14683, indexed in Pubmed: 32507038.
84. Rådholm K, Festin K, Falk M, et al. Blood pressure and all-cause mortality: a prospective study of nursing home residents. Age Ageing. 2016; 45(6): 826–832, doi: 10.1093/ageing/afw122, indexed in Pubmed: 27496923.
85. Rivasi G, Lucenteforte E, Turrin G, et al. Blood pressure and long-term mortality in older patients: results of the Fiesole Misurata Follow-up Study. Aging Clin Exp Res. 2020; 32(10): 2057–2064, doi: 10.1007/s40520-020-01534-y, indexed in Pubmed: 32227283.
86. Oates DJ, Berlowitz DR, Glickman ME, et al. Blood pressure and survival in the oldest old. J Am Geriatr Soc. 2007; 55(3): 383–388, doi: 10.1111/j.1532-5415.2007.01069.x, indexed in Pubmed: 17341240.
87. Todd OM, Wilkinson C, Hale M, et al. Is the association between blood pressure and mortality in older adults different with frailty? A systematic review and meta-analysis. Age Ageing. 2019; 48(5): 627–635, doi: 10.1093/ageing/afz072, indexed in Pubmed: 31165151.
88. Ungar A, Pepe G, Lambertucci L, et al. Low diastolic ambulatory blood pressure is associated with greater all-cause mortality in older patients with hypertension. J Am Geriatr Soc. 2009; 57(2): 291–296, doi: 10.1111/j.1532-5415.2008.02123.x, indexed in Pubmed: 19207144.
89. Monahan KD, Ray CA, Monahan KD. Aging, opioid-receptor agonists and antagonists, and the vestibulosympathetic reflex in humans. J Appl Physiol (1985). 2004; 96(5): 1761–1766, doi: 10.1152/japplphysiol.00528.2003, indexed in Pubmed: 14729722.
90. Finucane C, O'Connell MDL, Fan CW, et al. Age-related normative changes in phasic orthostatic blood pressure in a large population study: findings from The Irish Longitudinal Study on Ageing (TILDA). Circulation. 2014;

130(20): 1780–1789, doi: 10.1161/CIRCULATIONAHA.114.009831, indexed in Pubmed: 25278101.
91. Romero-Ortuno R, Fouweather T, Jagger C. Cross-national disparities in sex differences in life expectancy with and without frailty. Age Ageing. 2014; 43(2): 222–228, doi: 10.1093/ageing/aft115, indexed in Pubmed: 23917483.
92. Denardo SJ, Gong Y, Nichols WW, et al. Blood pressure and outcomes in very old hypertensive coronary artery disease patients: an INVEST substudy. Am J Med. 2010; 123(8): 719–726, doi: 10.1016/j.amjmed.2010.02.014, indexed in Pubmed: 20670726.
93. Vidal-Petiot E, Ford I, Greenlaw N, et al. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. Lancet. 2016; 388(10056): 2142–2152, doi: 10.1016/S0140-6736(16)31326-5, indexed in Pubmed: 27590221.
94. White CL, Szychowski JM, Pergola PE, et al. Can blood pressure be lowered safely in older adults with lacunar stroke? The Secondary Prevention of Small Subcortical Strokes study experience. J Am Geriatr Soc. 2015; 63(4): 722–729, doi: 10.1111/jgs.13349, indexed in Pubmed: 25850462.

Subcutaneous implantable cardioverter-defibrillator therapy in Poland: Results of the Polish S-ICD Registry

Maciej Kempa[1], Szymon Budrejko[1], Mateusz Tajstra[2], Paweł Syska[3], Michał Lewandowski[3], Tomasz Fabiszak[4], Marcin Michalak[5], Adrian Stanek[6], Krzysztof Nowak[7], Przemysław Mitkowski[8], Krzysztof Kaczmarek[9], Zbigniew Orski[10], Marcin Janowski[11], Piotr Szafarz[12], Artur Filipecki[13], Adam Sokal[14, 15], Marek Szołkiewicz[16], Dariusz Jagielski[17], Andrzej Przybylski[12, 18]

[1]Department of Cardiology and Electrotherapy, Medical University of Gdansk, Gdańsk, Poland
[2]3rd Department of Cardiology, School of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland
[3]2nd Department of Heart Arrhythmia, National Institute of Cardiology, Warszawa, Poland
[4]Department of Cardiology and Internal Medicine, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland
[5]1st Department of Cardiology, Medical University of Warsaw, Warszawa, Poland
[6]Department of Electrocardiology, John Paul II Hospital, Kraków, Poland
[7]Institute of Heart Diseases, Wroclaw Medical University, Wrocław, Poland
[8]1st Department of Cardiology, University of Medical Sciences, Poznań, Poland
[9]Department of Electrocardiology, Medical University of Lodz, Łódź, Poland
[10]Department of Cardiology and Internal Diseases, Military Institute of Medicine — National Research Institute, Warszawa, Poland
[11]Chair and Department of Cardiology Medical University of Lublin, Lublin, Poland
[12]1st Department of Cardiology with the Acute Coronary Syndromes Subdivision, Clinical Provincial Hospital No. 2, Rzeszów, Poland
[13]1st Chair and Department of Cardiology, Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
[14]1st Department of Cardiology and Angiology, Silesian Center for Heart Diseases, Zabrze, Poland
[15]Medical University of Silesia, Faculty of Health Sciences, Department of Dietetics, Bytom, Poland
[16]Department of Cardiology and Interventional Angiology, Kashubian Center for Heart and Vascular Diseases, Pomeranian Hospitals, Wejherowo, Poland
[17]Department of Cardiology, Center for Heart Diseases, 4th Military Hospital, Wrocław, Poland
[18]Medical College of Rzeszow University, Rzeszów, Poland

Editorial
by Botto et al.

Correspondence to:
Szymon Budrejko, MD, PhD,
Department of Cardiology
and Electrotherapy,
Medical University of Gdansk,
Smoluchowskiego 17,
80–214 Gdańsk, Poland,
phone: +48 58 584 47 60,
e-mail: budrejko@gumed.edu.pl

DOI: 10.33963/KP.a2023.0046

Received:
January 12, 2023

Accepted:
February 12, 2023

Early publication date:
February 19, 2023

ABSTRACT

Background: The use of subcutaneous implantable cardioverter-defibrillators (S-ICD) has been growing in Poland since 2014. The Polish Registry of S-ICD Implantations was run by the Heart Rhythm Section of the Polish Cardiac Society between May 2020 and September 2022 to monitor the implementation of that therapy in Poland.

Aims: To investigate and present the state-of-the-art of S-ICD implantation in Poland.

Methods: Implanting centers reported clinical data of patients undergoing S-ICD implantations and replacements, including age, sex, height, weight, underlying disease, history of pacemaker and defibrillator implantations, indications for S-ICD, electrocardiographical parameters, procedural techniques, and complications.

Results: Four hundred and forty patients undergoing S-ICD implantation (411) or replacement (29) were reported by 16 centers. Most patients were in New York Heart Association class II (218 patients, 53%) or I (150 patients, 36.5%). Left ventricular ejection fraction was 10%–80%, median (IQR) was 33% (25%–55%). Primary prevention indications were present in 273 patients (66.4%). Non-ischemic cardiomyopathy was reported in 194 patients (47.2%). The main reason for the choice of S-ICD were: young age (309, 75.2%), risk of infectious complications (46, 11.2%), prior infective endocarditis (36, 8.8%), hemodialysis (23, 5.6%), and immunosuppressive therapy (7, 1.7%). Electrocardiographic screening was performed in 90% of patients. The rate of adverse events was low (1.7%). No surgical complications were observed.

Conclusions: Qualification for S-ICD in Poland was slightly different when compared to the rest of Europe. The implantation technique was mostly consistent with the current guidelines. S-ICD implantation was safe, and the complication rate was low.

Key words: implantable cardioverter-defibrillator, subcutaneous implantable cardioverter-defibrillator, sudden cardiac death, ventricular arrhythmia

INTRODUCTION

Implantation of a subcutaneous cardioverter-defibrillator (S-ICD) is commonly used for prevention of sudden cardiac death due to ventricular arrhythmias, which is in line with the European and American guidelines [1, 2]. That method of treatment has been employed in Poland since 2014 [3]. During the early period, the number of implantations was limited by the lack of reimbursement, decisions were made on a post-hoc, patient-by-patient basis by the National Healthcare Fund, which discouraged wide application of the new method due to the high cost of the system resulting in the procedure being a high-risk investment for any hospital involved. Complete reimbursement by the National Healthcare Fund was introduced as late as 2019 (under specific conditions: only for experienced, high-volume tertiary cardiology centers, performing at least 30 lead extraction procedures annually, and having cardiac or thoracic surgery backup on-site) [4]. That led to a substantial increase in the number of procedures in the following months. Despite that fact, no national system was established to monitor the growing experience of Polish centers with the new modality of treatment. Therefore, the executive board of the Heart Rhythm Section of the Polish Cardiac Society decided to create the Polish S-ICD Registry to monitor the safety, technical issues, complications, and clinical outcomes of the implementation of that method in Poland. The registry was launched on May 1, 2020 [5]. Centers implanting S-ICD systems reported data of patients undergoing implantation or exchange of the device. Participation of the centers in the registry was not intended to influence their clinical decisions, and data were sent after implantation-related hospitalization. The initial report comprised the data of 123 patients. Low complication rates were observed, as there were no in-hospital surgical complications, and only 2 adverse events were described (pocket hematoma treated conservatively, and unilateral paresis of the lower limb with no apparent pathology of the central nervous system). The most frequent indication for S-ICD and not a transvenous implantable cardioverter--defibrillator (TV-ICD) was patients' young age, similar to other reports.

During the first year of data collection, the initial results were also published, comparing Poland to other European countries in terms of characteristics of the population of patients undergoing S-ICD implantation, as well as the reasons for choosing subcutaneous systems over transvenous ones [6]. In that report, we concluded that S-ICD systems in Poland were implanted in patients at a more advanced stage of chronic heart failure when compared to other European countries. The most frequent reason for choosing S-ICD and not TV-ICD was the young age of patients, similar to other countries.

The registry data were also compared with the historical small cohort of S-ICD recipients treated during the initial year after the introduction of this new method of treatment in Poland [7]. In that report, we observed a tendency to incorporate new operational techniques (such as intermuscular pocket and 2-incision technique) used in more experienced European centers, with no increase in the perioperative complication rate.

After significant volume of data was gathered by the participating centers, a decision was made to close the registry at the end of September 2022. Our current analysis aimed to investigate and present the state-of-the-art of S-ICD implantation in Poland based on the data reported to the registry during the whole period of two and a half years of its duration.

METHODS

The analysis was based on patients' records reported between May 2020 and September 2022 to the multicenter registry of S-ICD implantations in Poland. The registry was designed, launched, and run by the Heart Rhythm Section of the Polish Cardiac Society, and it was approved by the Bioethical Committee at the Regional Medical Board in Rzeszów (approval no. 35/B/2020). Centers' participation

WHAT'S NEW?

The use of subcutaneous implantable cardioverter-defibrillator (S-ICD) systems in Poland has been growing since 2014, with a significant rise after introduction of full reimbursement. The Polish Registry of S-ICD Implantations was run by the Heart Rhythm Section of the Polish Cardiac Society between May 2020 and September 2022 to monitor the implementation of that modern therapy in Poland. We present data regarding 440 procedures reported to the registry, including 411 *de novo* S-ICD implantations that represent 75% of the total number of implantations in Poland during that period. There were no perioperative surgical complications, and the rate of adverse events was low.

in the registry was by no means associated with any influence on qualification of patients, procedural technique, or further course of follow-up care. Required data were reported once the index hospitalization of a given patient had finished. The records included information such as age, sex, height, weight and body mass index, underlying disease, history of implantation of other implantable cardiac electronic devices (pacemakers and defibrillators) and their extraction, indications for S-ICD implantation, basic electrocardiographical parameters (including any conduction disturbances and QRS widening), procedural techniques (type of anesthesia, use of 2-incision or 3- incision techniques), results of the implantation procedure, and any complications occurring until the end of patient' hospitalization. Data were reported digitally on a dedicated web-based platform created for that purpose.

Statistical analysis

Continuous variables were presented as mean and standard deviation or median and interquartile range in the case of non-normal distribution. Categorical parameters were presented as numbers and percentages. The normality of distribution was tested with the Shapiro-Wilk test. Groups were compared with the Pearson's χ^2 test and post-hoc proportion test with Bonferroni's correction for multiple comparisons. Fisher's exact test was used in the case of low sample sizes. A *P*-value of below 0.05 was considered statistically significant. Data management and statistical analysis were performed with Microsoft Excel, Statistica 13.1 software (TIBCO Software, Palo Alto, CA, US), and R version 4.1.2 (November 1, 2021, "Bird Hippie", The R Foundation for Statistical Computing, Vienna, Austria) and R-studio software (September 2, 2021 build 382).

RESULTS

Data of 440 patients undergoing S-ICD implantation (411 patients) or device replacement (29 patients) were reported to the registry by 16 centers in Poland. That number represented 75% of all procedures performed in Poland during the period of interest, as we estimated on the basis of unpublished data acquired from the manufacturer of the system. The growth rate of the cumulative number of records was constant during the whole duration of the registry. A quarterly number of new records was between 43 and 49, except for the first (19) and last (25 records) quarters. Among 411 patients undergoing first-time implantation, 297 (72.3%) were male and 114 (27.7%) were female. Patients' age was between 12 and 82 years, with a median (interquartile range [IQR]) value equal to 42 (31–55) years.

Most patients were classified as New York Heart Association (NYHA) class II (218, 53%) or I (150, 36.5%), with all the others being in class III. Left ventricular ejection fraction (LVEF) was between 10 and 80% and median (IQR) was 33% (25%–55%). In 273 patients (66.4%), S-ICD was implanted for primary prevention of sudden cardiac death (SCD). Non-ischemic cardiomyopathy was the predominant underlying disease in that cohort, as it was reported in 194 patients (47.2%). Detailed clinical data are presented in Table 1.

Table 1. Clinical characteristics of patients undergoing first-time implantation of a subcutaneous implantable cardioverter-defibrillator

Clinical feature	Value
Age, years, median (IQR)	42 (31–55)
Male sex, n (%)	297 (72.3)
Height, cm, median (IQR)	175 (168–181)
Weight, kg, median (IQR)	80 (70–94)
BMI, kg/m^2, median (IQR)	26 (23–30)
Sinus rhythm, n (%)	386 (93.9)
Prior sternotomy, n (%)	40 (9.7)
LVEF, %, median (IQR)	33 (25–55)
Underlying disease	
NICM, n (%)	194 (47.2)
ICM, n (%)	112 (27.3)
Primary VF, n (%)	46 (11.2)
LQTS, n (%)	11 (2.7)
HCM, n (%)	7 (1.7)
LVNC, n (%)	7 (1.7)
Brugada syndrome, n (%)	6 (1.5)
Myocarditis, n (%)	5 (1.2)
Congenital heart disease, n (%)	5 (1.2)
ARVC, n (%)	2 (0.5)
CPVT, n (%)	2 (0.5)
MAD, n (%)	1 (0.2)

Abbreviations: ARVC, arrhythmogenic right ventricular cardiomyopathy; BMI, body mass index; CPVT, catecholaminergic polymorphic ventricular tachycardia; HCM, hypertrophic cardiomyopathy; ICM, ischemic cardiomyopathy; IQR, interquartile range; LQTS, long QT syndrome; LVEF, left ventricular ejection fraction; LVNC, left ventricular non-compaction; MAD, mitral annular disjunction; NICM, nonischemic cardiomyopathy; VT, ventricular tachycardia

Electrocardiography and other cardiac implantable electronic devices (CIED)

Data representing cardiac rhythm, conduction disturbances, and the presence of other CIEDs at the time of S-ICD implantation are presented in Table 2.

Reasons for preference of S-ICD over TV-ICD

The main reason for the choice of S-ICD (instead of a traditional TV-ICD) was patients' young age and long life expectancy, and it was reported as such in 309 patients (75.2%). The other significant group of reasons declared by the implanting physicians fell into the category of increased risk of infectious complications or recurrent infection due to (sorted by decreasing frequency): chronic infectious states — in 46 patients (11.2%), prior infective endocarditis — in 36 patients (8.8%), hemodialysis — in 23 patients (5.6%), and immunosuppressive therapy — in 7 patients (1.7%). Lead failure of a previously implanted transvenous lead was reported as the main reason in 27 cases (6.6%) and difficult vascular access in 18 cases (4.4%). In the majority of patients (370 — 90%), the decision to qualify for S-ICD

Table 2. Electrocardiography and other cardiac implantable electronic devices

Sinus rhythm, n (%)	386 (93.9)
Atrial fibrillation, n (%)	25 (6.1)
Paced rhythm, n (%)	4 (1)
Bundle branch block, n (%)	20 (4.9)
Right bundle branch block, n (%)	14 (3.4)
Left bundle branch block, n (%)	6 (1.5)
No history of CIED before S-ICD, n (%)	338 (82.2)
Previous ICD-VR, n (%)	53 (12.9)
Previous ICD-DR, n (%)	18 (4.4)
Previous CRT-D, n (%)	5 (1.2)
Previous CRT-P, n (%)	1 (0.2)
Previous TV-ICD not removed, only deactivated, n (%)	10 (2.4)

Abbreviations: CIED, cardiac electronic implantable device; CRT-D, cardiac resynchronization therapy cardioverter-defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; ICD-DR, dual-chamber implantable cardioverter-defibrillator; ICD-VR, single chamber implantable cardioverter-defibrillator; TV-ICD, transvenous implantable cardioverter-defibrillator; S-ICD, subcutaneous implantable cardioverter-defibrillator

Table 3. Results of preoperative electrocardiography screening, which was performed in 370 of 411 patients undergoing first-time implantation

Number of vectors positive for a given patient	Number of patients (%)
3	190 (51.4)
2	171 (46.2)
1	9 (2.4)
Number and percentage of positive results for a given vector in the whole cohort	**Number of patients (%)**
Primary	346 (93.5)
Secondary	334 (90.3)
Alternate	241 (65.1)

implantation was preceded by electrocardiographic (ECG) screening, as presented in Table 3.

S-ICD implantation procedure

S-ICD systems were implanted mostly by cardiologists. A cardiac surgeon was involved only in 8 cases (1.9%). The procedure was performed most frequently under general anesthesia (302 patients, 73.5%), using a 2-incision technique (323 patients, 78.6%), and creating an intermuscular (over the serratus anterior muscular fascia and beneath the latissimus dorsi muscle) device pocket (367 patients, 89.3%). A defibrillation test was performed in 322 patients out of 411 undergoing first-time implantation (78.3%). The test shock was set to 65J in 309 cases, 70J in 10, 72J in 2, and 80J in one case. In 89 patients the defibrillation test was waived, and the predominant reasons for avoiding the test were: extremely low LVEF (17 patients, 19.1%), thromboembolic material within heart chambers (14 patients, 15.8%), and transvenous lead extraction (possibly increasing the risk of complications) performed just before S-ICD implantation (10 patients, 11.2%).

During data collection, we observed an evolution of operational techniques, that is the number of incisions, location of the device pocket, and the type of anesthesia used for the implantation procedure. To trace that evolution, we divided the whole duration of the registry into 4 equal 7-month periods (1st period: May 2020–December 2020, 2nd period: January 2021–July 2021, 3rd period: August 2021–February 2022, 4th period: March 2022–September 2022). During the first period, the 3-incision technique was used in 53.2% of cases, with predominant intermuscular pocket (96.4%) and the procedure was performed under general anesthesia (72.1%). In the last period, more procedures were reported to have been performed with the 2-incision technique (93.3%; P <0.001) with a lower rate of intermuscular pocket (80.9%; P = 0.01). The rates of proce-

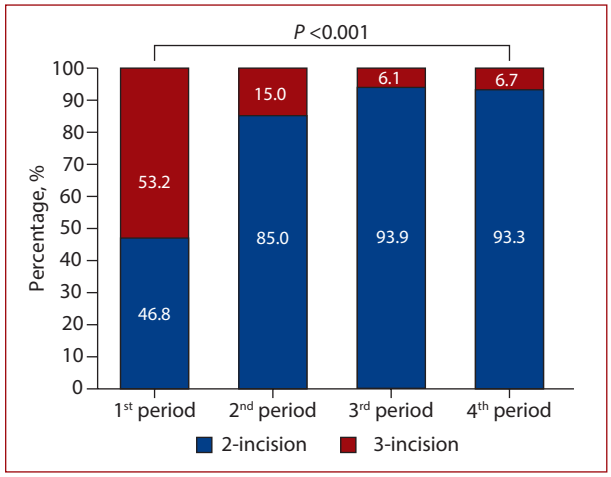


Figure 1. Evolution of the implantation technique — percentages of 2- and 3-incision procedures in 4 consecutive 7-month periods of the registry (1st period: May 2020–December 2020, 2nd period: January 2021–July 2021, 3rd period: August 2021–February 2022, 4th period: March 2022–September 2022). P <0.001 for inter-group difference; P <0.001 for 1st vs. 4th period comparison

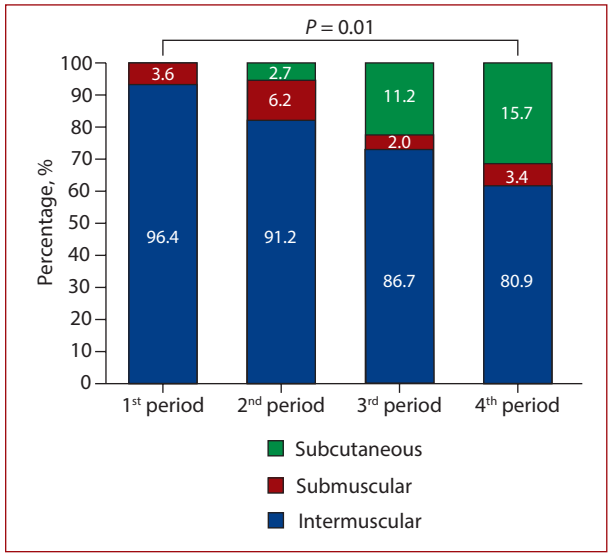


Figure 2. Evolution of the implantation technique — location of the device pocket in 4 consecutive 7-month periods of the registry (1st period: May 2020–December 2020, 2nd period: January 2021–July 2021, 3rd period: August 2021–February 2022, 4th period: March 2022–September 2022). The submuscular pocket is located under the serratus anterior muscle; the intermuscular pocket is located between the latissimus dorsi and serratus anterior muscles. P <0.01 for inter-group difference; P = 0.01 for 1st vs. 4th period comparison

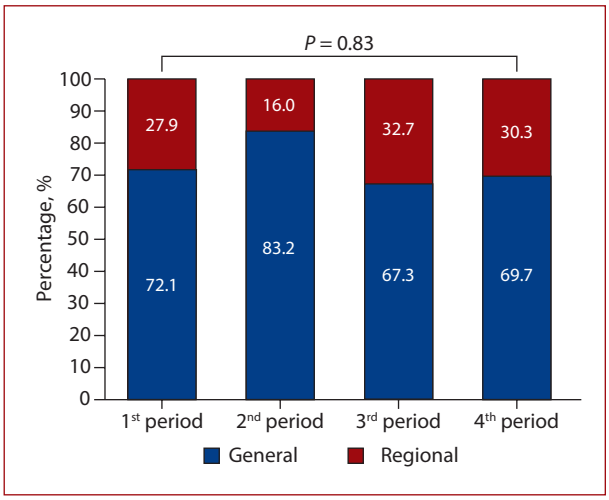


Figure 3. Evolution of the implantation technique — type of anesthesia in 4 consecutive 7-month periods of the registry (1st period: May 2020–December 2020, 2nd period: January 2021–July 2021, 3rd period: August 2021–February 2022, 4th period: March 2022–September 2022). $P = 0.04$ for inter-group difference; $P = 0.83$ for 1st vs. 4th period comparison

dures performed under general anesthesia or fascial plane block were not significantly different ($P = 0.83$). Detailed data are presented in Figures 1–3.

Periprocedural adverse events and complications related to S-ICD implantation or replacement

S-ICD replacement procedures (29 patients) were not associated with any adverse events. In 411 patients undergoing first-time implantation, 7 adverse events were observed (1.7%) during the periprocedural period (in-hospital, before discharge from the implantation-related hospitalization). Inappropriate interventions were reported in 4 cases (1%), and they were due to inappropriate sensing resulting most probably from air entrapment in the device pocket or the tunnel around the lead course (4 patients, 1%), as well as low amplitude of the R wave (in addition) in 1 of those patients (0.2%). Subcutaneous emphysema was reported in one patient (0.2%). Moreover, one patient (0.2%) suffered from transient atrioventricular conduction disturbances immediately after the defibrillation test shock. In one patient (0.2%), paresis of the right lower extremity was observed, and an in-depth diagnostic investigation did not reveal any neurological reason that could explain that complication. No surgical complications, infections, or early system revisions were reported.

DISCUSSION

Data collected in that multicenter registry were used for previously published analyses comparing indications and clinical characteristics of populations of patients undergoing S-ICD implantation in Poland and other European countries [8]. When considering the complete registry duration of 2.5 years, the percentages and trends did not change significantly. Among patients receiving S-ICD systems, the percentage of subjects in NYHA class I is approximately 40%, and in class III — around 11%. Those percentages are different than in the rest of Europe, where more patients are in class I (67.7%) and fewer in class III (2.9%), as we reported before [8]. In our extended registry cohort, mean LVEF was still below 40%; hence, the tendency of Polish patients to have more advanced heart failure at the time of S-ICD implantation remained unchanged. That result is concordant with the findings of the Heart Failure Pilot Survey [9]. S-ICD was invariably less frequently implanted in patients with no structural heart disease in Poland than in the rest of Europe. That finding is surprising because, in a recently published survey, the majority of Polish experts in S-ICD implantation declared that patients with inherited arrhythmic syndromes should be qualified for S-ICD rather than TV-ICD unless a history of ventricular tachycardia eligible for antitachycardia pacing was present [10].

Interesting results were found in the analysis of reasons for selection of an S-ICD instead of a TV-ICD. Polish centers reported patients' young age as the predominant reason. The second most important factor was the fear of infectious complications. Those results are in conformity with both the European and American guidelines, where the long-life expectancy and the risk of infection or infection recurrence are recommended for consideration during qualification and should favor S-ICD systems [1, 2]. The above observations are also in line with the results of a survey study, where 92% of Polish experts declared a history of transvenous CIED-related infection resulting in the extraction of that system as the reason for the subsequent choice of S-ICD, and the age below 50 years should favor the choice of S-ICD and not TV-ICD irrespective of the etiology of heart failure [10]. Importantly, according to legal regulations in Poland, complete reimbursement of the S-ICD system is granted only on declaration of the indication predefined by the healthcare fund [4]. Therefore, the reasons such as an active lifestyle, cosmetic effect, or patients' preference cannot justify the choice of S-ICD, and then an additional reason should be reported for reimbursement, even if it is not predominant.

In the majority of patients, a decision to implant S-ICD was preceded by ECG screening. Three acceptable vectors were recorded in 51.4% of patients, and only one — in 2.4% of cases. According to the S-ICD manual, at least one vector passing in all the tested body positions is considered sufficient to proceed with S-ICD implantation. Most of the authors of this study consider that insufficient and prefer to have at least two vectors positive in both supine and standing body positions. Unfortunately, we do not have information on how many of the patients initially considered for S-ICD implantation failed ECG screening, as only S-ICD implantations were reported to the registry, and not preoperative qualification.

Surgical techniques used during S-ICD implantation were in line with the current European Heart Rhythm Association (EHRA) recommendations [11]. Implantation pro-

cedures were performed mostly under general anesthesia, using the 2-incision technique and an intermuscular device pocket. The recommended 2-incision technique was used with an increasing rate from the first period of the registry to the last one. There was no significant difference in the rates of regional anesthesia and fascial plane block between the consecutive periods. We also made a surprising observation that the rate of using subcutaneous (and not intermuscular) pocket location increased during the time of data collection. Such a technique is not recommended, as it increases the risk of infectious complications. The most probable explanation for this phenomenon is that new centers with less experienced operators joined the registry during ongoing data collection. A conclusion may be drawn that some form of training requirements for operators, and not only legal requirements for centers, should be considered to promote appropriate operational techniques.

A defibrillation test was performed in 322 of 411 patients undergoing first-time S-ICD implantation. It means that the test is abandoned increasingly more often despite being a recommended step in the implantation procedure [11]. The main reason for skipping the test was very low LVEF (and thus the fear of worsening heart failure with induced ventricular fibrillation). Another reason was transvenous lead extraction directly preceding S-ICD implantation. Mechanical strain applied to the vessel walls and heart chambers during lead extraction may impair their integrity and increase the risk of subsequent rupture and perforation due to increased pressure trauma, which may be related to abrupt chest muscle contraction during the induction and defibrillation of ventricular fibrillation. Although that fear is based on the experience of physicians performing lead extractions and has no sound data to support it, it is not limited to us. In a recent report of S-ICD implantation up to several days after transvenous lead extraction, defibrillation testing was performed only in 47% of S-ICD recipients, and "physician's choice" was also among the reasons behind skipping the test [12].

In 309 patients, a test shock of 65J was effective. The remaining 13 patients were tested with higher energy. Induced arrhythmias were successfully terminated in all cases. That result seems to be slightly better than the percentages reported in clinical studies [13, 14]. It may be related to a high rate of using intermuscular pocket location (which is nowadays the preferred device location). In the majority of patients reported to the registry, the device pocket was dissected under the border of the latissimus dorsi muscle, as recommended. It forces a more dorsal position of the device compared to the subcutaneous pocket and results in high efficacy of the test shock due to a relatively low impedance of the defibrillation pathway [15, 16]. Unfortunately, not all operators declared such a location (i.e. intermuscular and not subcutaneous) as their default choice for the device pocket.

In 10 cases, previously implanted ICDs were not removed before S-ICD implantation. The reasons for that decision were not specifically reported in the registry. In general, in such cases, TV-ICDs may be either planned for removal after S-ICD implantation or they may be switched off and abandoned. The latter approach is possible only in the case of non-infectious complications (such as lead failure), but in our opinion, it should be avoided if only possible. That approach is still under investigation [17] and conclusive evidence is lacking.

In the group of 411 *de novo* S-ICD implantations, 7 adverse events were reported. Most of them were inappropriate interventions of the system. The occurrence of those interventions resulted predominantly from a recognized phenomenon of air entrapment in the device pocket and along the lead course after the implantation procedure [18]. The problem typically resolves by itself, with air being resorbed within several days. To avoid such events, every operator should carefully evacuate air during implantation, and some authors recommend filling the lead tunnel and the device pocket with sterile saline [19]. Delayed activation of the system, up to 48 hours after implantation, may also be considered. Nonetheless, such an event does not require surgical intervention. According to the results of the UNTOUCHED study, the common use of the 2-incision technique may contribute to a higher rate of air entrapment within the subcutaneous lead tunnel [20]. In 3 of those 4 patients in our group, the 2-incision technique was used for implantation. Such a complication may also occur after device replacement when the new can is smaller than the old one, but no such case was reported in our patient population.

Subcutaneous emphysema and transient atrioventricular conduction disturbances were also incidentally observed in our study, but they did not require any additional intervention. The most serious reported complication was a neurological event in one patient, whose mechanism remained unclear despite thorough evaluation. Therefore, a complication requiring additional diagnostic and therapeutic measures could be attributed only to that single case. That rate is very low, and lower than reported in the available studies. Surgical complications such as dislocation of system components and inappropriate healing of a postoperative wound have been described in up to 3% of patients during the first month after implantation [21]. In our group, none of the patients had surgical complications after *de novo* implantation, but the initial observation period was relatively short, as it continued only until patients' discharge from the hospital.

Limitations

The main limitation of our analysis is a relatively low number of patients despite multicenter involvement. The registry covered only 75% of patients undergoing S-ICD implantation or replacement during that specific time in

Poland. Participation was voluntary, not all implanting centers joined the registry, new centers were launched after the registry was started, and they did not decide to join. Underreporting from the participating centers cannot be excluded. The registry was launched by the Heart Rhythm Section, it included specific clinical centers, and local coordinators were responsible for data collection and transfer, but we did not verify or confirm the reported data in any way, and therefore possibly limited data reliability may also be an issue. The COVID-19 pandemic might have also influenced the clinical routine, as the availability of S-ICD implantation, device choice, and other clinical decisions might have been altered during the pandemic [22]. ECG screening was not performed in 10% of patients.

CONCLUSION

The analysis of data collected in the registry showes that a certain dissimilarity exists in qualification for S-ICD implantation between Poland and other European countries. The course of the procedure and implantation technique are in most cases consistent with the current guidelines. Good outcomes and an almost complete lack of serious complications during the early postoperative period demonstrate that implanting centers were appointed appropriately, and the implanting teams were well-trained.

Article information

Conflict of interest: MK received speaker/proctoring fees from Boston Scientific. PS received speaker/proctoring fees from Boston Scientific. ML received lecture honoraria and a proctorship agreement from Boston Scientific. PM received a speaker fee from Boston Scientific Poland. KK received proctor and consulting fees from Boston Scientific Poland. AS — consultancy agreement Boston Scientific; AP received advisory board fee from Boston Scientific. Other authors declare no conflict of interest.

Funding: The registry was partially supported by a research grant from Boston Scientific for the Polish Cardiac Society.

REFERENCES

1. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2018; 72(14): 1677–1749, doi: 10.1161/CIR.0000000000000548, indexed in Pubmed: 29084733.
2. Aktaa S, Tzeis S, Gale CP, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J. 2022; 43(40): 3997–4126, doi: 10.1093/eurheartj/ehac262, indexed in Pubmed: 36017572.
3. Kaczmarek K, Kempa M, Grabowski M, et al. A subcutaneous implantable cardioverter-defibrillator – the first implantation in Poland. Kardiol Pol. 2015; 73(1): 62, doi: 10.5603/KP.2015.0010, indexed in Pubmed: 25625342.
4. Regulation of the Polish Minister of Health of January 9, 2019. Regulation on the procedure guaranteed in the field of hospital treatment [in Polish]. Available online: http://isap.sejm.gov.pl/isap.nsf/download.xsp/WDU20190000077/O/D20190077.pdf. [Access: February 4, 2023].
5. Kempa M, Przybylski A, Budrejko S, et al. Multicenter Registry of Subcutaneous Cardioverter-Defibrillator Implantations: a preliminary report. Kardiol Pol. 2021; 79(6): 697–699, doi: 10.33963/KP.a2021.0002, indexed in Pubmed: 34013514.
6. Kempa M, Przybylski A, Budrejko S, et al. Utilization of Subcutaneous Cardioverter-Defibrillator in Poland and Europe-Comparison of the Results of Multi-Center Registries. Int J Environ Res Public Health. 2021; 18(13), doi: 10.3390/ijerph18137178, indexed in Pubmed: 34281115.
7. Kempa M, Przybylski A, Budrejko S, et al. Evolution of implantation technique and indications for a subcutaneous cardioverter-defibrillator: over 7 years of experience in Poland. Kardiol Pol. 2021; 79(9): 1016–1018, doi: 10.33963/KP.a2021.0048, indexed in Pubmed: 34176114.
8. Jędrzejczyk-Patej E, Boveda S, Kalarus Z, et al. Factors determining the choice between subcutaneous or transvenous implantable cardioverter-defibrillators in Poland in comparison with other European countries: a sub-study of the European Heart Rhythm Association prospective survey. Kardiol Pol. 2018; 76(11): 1507–1515, doi: 10.5603/KP.a2018.0155, indexed in Pubmed: 30091137.
9. Sosnowska-Pasiarska B, Bartkowiak R, Wożakowska-Kapłon B, et al. Population of Polish patients participating in the Heart Failure Pilot Survey (ESC-HF Pilot). Kardiol Pol. 2013; 71(3): 234–240, doi: 10.5603/KP.2013.0034, indexed in Pubmed: 23575777.
10. Kempa M, Opielowska-Nowak B, Budrejko S, et al. A survey study of the use of a subcutaneous implantable cardioverter-defibrillator in various clinical scenarios by expert electrophysiologists in Poland. Cardiol J. 2022 [Epub ahead of print], doi: 10.5603/CJ.a2022.0073, indexed in Pubmed: 35975797.
11. Boersma LV, El-Chami M, Steinwender C, et al. Practical considerations, indications, and future perspectives for leadless and extravascular cardiac implantable electronic devices: a position paper by EHRA/HRS/LAHRS/APHRS. Europace. 2022; 24(10): 1691–1708, doi: 10.1093/europace/euac066, indexed in Pubmed: 35912932.
12. Giacomin E, Falzone PV, Dall'Aglio PB, et al. Subcutaneous implantable cardioverter defibrillator after transvenous lead extraction: safety, efficacy and outcome. J Interv Card Electrophysiol. 2022 [Epub ahead of print], doi: 10.1007/s10840-022-01293-y, indexed in Pubmed: 35831772.
13. Lambiase PD, Barr C, Theuns DA, et al. Worldwide experience with a totally subcutaneous implantable defibrillator: early results from the EFFORTLESS S-ICD Registry. Eur Heart J. 2014; 35(25): 1657–1665, doi: 10.1093/eurheartj/ehu112, indexed in Pubmed: 24670710.
14. Boersma L, Barr C, Knops R, et al. Implant and Midterm Outcomes of the Subcutaneous Implantable Cardioverter-Defibrillator Registry: The EFFORTLESS Study. J Am Coll Cardiol. 2017; 70(7): 830–841, doi: 10.1016/j.jacc.2017.06.040, indexed in Pubmed: 28797351.
15. Quast AFBE, Baalman SWE, Brouwer TF, et al. A novel tool to evaluate the implant position and predict defibrillation success of the subcutaneous implantable cardioverter-defibrillator: The PRAETORIAN score. Heart Rhythm. 2019; 16(3): 403–410, doi: 10.1016/j.hrthm.2018.09.029, indexed in Pubmed: 30292861.
16. Heist EK, Belalcazar A, Stahl W, et al. Determinants of subcutaneous implantable cardioverter-defibrillator efficacy: a computer modeling study. JACC Clin Electrophysiol. 2017; 3(4): 405–414, doi: 10.1016/j.jacep.2016.10.016, indexed in Pubmed: 29759454.
17. Russo V, Viani S, Migliore F, et al. Lead Abandonment and Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD) Implantation in a Cohort of Patients With ICD Lead Malfunction. Front Cardiovasc Med. 2021; 8: 692943, doi: 10.3389/fcvm.2021.692943, indexed in Pubmed: 34395560.
18. Iavarone M, Rago A, Nigro G, et al. Inappropriate shocks due to air entrapment in patients with subcutaneous implantable cardioverter-defibrillator: A meta-summary of case reports. Pacing Clin Electrophysiol. 2022; 45(10): 1210–1215, doi: 10.1111/pace.14584, indexed in Pubmed: 35983947.
19. Nishinarita R, Kishihara J, Matsuura G, et al. Early inappropriate shock in a subcutaneous cardiac defibrillator due to subcutaneous air.

J Arrhythm. 2019; 35(4): 682–684, doi: 10.1002/joa3.12210, indexed in Pubmed: 31410242.
20. Gold MR, Lambiase PD, El-Chami MF, et al. Primary Results From the Understanding Outcomes With the S-ICD in Primary Prevention Patients With Low Ejection Fraction (UNTOUCHED) Trial. Circulation. 2021; 143(1): 7–17, doi: 10.1161/CIRCULATIONAHA.120.048728, indexed in Pubmed: 33073614.
21. Boersma LV, El-Chami MF, Bongiorni MG, et al. Understanding Outcomes with the EMBLEM S-ICD in Primary Prevention Patients with Low EF Study (UNTOUCHED): Clinical characteristics and perioperative results. Heart Rhythm. 2019; 16(11): 1636–1644, doi: 10.1016/j.hrthm.2019.04.048, indexed in Pubmed: 31082539.
22. Budrejko S, Kempa M, Królak T, et al. Procedural volume of cardiac electrotherapy procedures does not have to be reduced during COVID-19 pandemic – one year analysis from a tertiary Polish center. Kardiol Pol. 2021; 79(7-8): 848–850, doi: 10.33963/KP.a2021.0001, indexed in Pubmed: 34013513.

A distinct septal pattern of late gadolinium enhancement specific for COVID-19-induced myocarditis: A multicenter cardiovascular magnetic resonance study

Maciej Haberka[1, 2], Justyna Rajewska-Tabor[3], Dagmara Wojtowicz[4], Anna Jankowska[5], Karol Miszalski-Jamka[6], Magdalena Janus[3], Karolina Dorniak[7], Dorota Kulawiak-Gałąska[8], Bartłomiej Stasiow[2], Szymon Rozmiarek[3], Jadwiga Fijałkowska[9], Waldemar Elikowski[10], Marzena Ławrynowicz[4], Mateusz Śpiewak[11], Marek Koziński[4], Małgorzata Pyda[3]

[1]Department of Cardiology, School of Health Sciences, Medical University of Silesia, Katowice, Poland
[2]Department of Cardiovascular Imaging, Upper Silesian Medical Center of the Medical University of Silesia, Katowice, Poland
[3]1st Department of Cardiology, Poznan University of Medical Sciences, Poznań, Poland
[4]Department of Cardiology and Internal Diseases, Institute of Maritime and Tropical Medicine, Medical University of Gdańsk, Gdynia, Poland
[5]Department of Cardiology, Stefan Cardinal Wyszynski Regional Specialist Hospital, Lublin, Poland
[6]Diagnostic Imaging Department, Silesian Center for Heart Diseases, Zabrze, Poland
[7]Department of Noninvasive Cardiac Diagnostics, Medical University of Gdańsk, Gdańsk, Poland
[8]Department of Radiology, Medical University of Gdańsk, Gdańsk, Poland
[9]2nd Department of Radiology, Medical University of Gdańsk, Gdańsk, Poland
[10]Infectious Diseases Hospital for COVID-19, Józef Strus Municipal Hospital, Poznań, Poland
[11]Magnetic Resonance Unit, Department of Radiology, National Institute of Cardiology, Warszawa, Poland

Editorial
by Friedrich et al.

Correspondence to:
Maciej Haberka, MD, PhD, Department of Cardiology, School of Health Sciences, Medical University of Silesia, Ziołowa 45/47, 40–635 Katowice, Poland, phone: +48 32 252 74 07, e-mail: mhaberka@sum.edu.pl

DOI: 10.33963/KP.a2023.0054

Received:
October 17, 2022

Accepted:
January 15, 2023

Early publication date:
March 5, 2023

ABSTRACT

Background: COVID-19 is a great medical challenge as it provokes acute respiratory distress and has pulmonary manifestations and cardiovascular (CV) consequences.

Aims: This study compared cardiac injury in COVID-19 myocarditis patients with non-COVID-19 myocarditis patients.

Methods: Patients who recovered from COVID-19 were scheduled for cardiovascular magnetic resonance (CMR) owing to clinical myocarditis suspicion. The retrospective non-COVID-19 myocarditis (2018–2019) group was enrolled (n = 221 patients). All patients underwent contrast-enhanced CMR, the conventional myocarditis protocol, and late gadolinium enhancement (LGE). The COVID study group included 552 patients at a mean (standard deviation [SD]) age of 45.9 (12.6) years.

Results: CMR assessment confirmed myocarditis-like LGE in 46% of the cases (68.5% of the segments with LGE <25% transmural extent), left ventricular (LV) dilatation in 10%, and systolic dysfunction in 16% of cases. The COVID-19 myocarditis group showed a smaller median (interquartile range [IQR]) LV LGE (4.4% [2.9%–8.1%] vs. 5.9% [4.4%–11.8%]; P <0.001), lower LV end-diastolic volume (144.6 [125.5–178] ml vs. 162.8 [136.6–194] ml; P <0.001), limited functional consequence (left ventricular ejection fraction, 59% [54.1%–65%] vs. 58% [52%–63%]; P = 0.01), and a higher rate of pericarditis (13.6% vs. 6%; P = 0.03) compared to non-COVID-19 myocarditis. The COVID-19-induced injury was more frequent in septal segments (2, 3, 14), and non-COVID-19 myocarditis showed higher affinity to lateral wall segments (P <0.01). Neither obesity nor age was associated with LV injury or remodeling in subjects with COVID-19 myocarditis.

Conclusions: COVID-19-induced myocarditis is associated with minor LV injury with a significantly more frequent septal pattern and a higher pericarditis rate than non-COVID-19 myocarditis.

Key words: CMR, COVID-19, myocarditis, myocardial injury, LGE

WHAT'S NEW?

To our knowledge, this large prospective multicenter study, which assessed consecutive patients with suspected COVID-19 myocarditis, is the only study comparing those findings with a retrospective non-COVID-19 myocarditis group. Myocardial injury related to COVID-19 was confirmed in half of the cases and was associated with preserved cardiac function in most cases. COVID-induced myocarditis showed a significantly smaller myocardial area with a lesser transmural extent, higher left ventricular ejection fraction, but more frequent pericarditis than non-COVID-19 myocarditis. Finally, COVID-induced myocarditis showed significantly higher affinity to left ventricular septal segments, and non-COVID-19 myocarditis was more prevalent in left ventricular lateral wall segments.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was responsible for the coronavirus disease-19 (COVID-19) global pandemic. According to the World Health Organization, over 280 million people globally were COVID-19-positive at the end of December 2021 [1]. Most cases were mild or moderate, and the respiratory system was the primary disease target for the virus [2]. However, primary studies suggest that myocardial injury is associated with COVID-19 and provided various data on the prevalence and severity of the symptoms [3, 4]. There is considerable heterogeneity among studies, which originated mainly from small study groups, various clinical characteristics, and different times between the infection and study evaluation, hindering the process of arriving at clear conclusions [5].

Moreover, obesity, immune system abnormalities, and older age were some of the important risk factors for COVID-19 [6]. However, whether there is a correlation between obesity and severity of COVID-19-related myocarditis is unknown.

Given the high prevalence of obesity and large numbers of infected patients, a considerable group of patients with mild cardiac injury would require cardiovascular screening. Cardiovascular magnetic resonance (CMR) is a comprehensive imaging tool that delivers accurate results and reproducibility in evaluating cardiac chambers, function, and myocardial injury [7]. CMR examination is a gold standard for patients recovering from COVID-19 and with clinical suspicion of myocardial injury.

This study aimed to evaluate cardiac injury in patients with suspected COVID-19 myocarditis compared to non-COVID-19 myocarditis. In addition, we verified the correlation between obesity and SARS-CoV-2 myocarditis.

METHODS

Study patients

All the study patients recovered from COVID-19, and they were scheduled for CMR (April 2020–October 2021) due to cardiac symptoms and suspected myocardial injury. The inclusion criteria were: (1) SARS-CoV-2 infection previously confirmed by a reverse transcription polymerase chain reaction (RT-PCR) swab test; (2) suspected myocarditis related to SARS-CoV-2 infection as the main indication for CMR. The exclusion criteria were as follows: (1) SARS-CoV-2 infection diagnosed only on the basis of clinical symptoms or other means that RT-PCR swap test; (2) a history of myocardial infarction or previous myocarditis; (3) a history of significant valve diseases, congenital heart diseases, cardiomyopathy or previous cardiac surgery; (4) contraindication to gadolinium contrast; (5) suboptimal CMR image quality due to arrhythmia or patients' incompliance. The severity of COVID-19 was classified according to the guidelines [8].

Data on the control group of non-COVID-19 myocarditis were collected retrospectively using a CMR database in each of the CMR center. The search included all the consecutive patients scheduled for CMR due to myocarditis, which was performed between January 2018 and December 2019. Patients with the following chronic cardiovascular (CV) diseases were excluded: a history of myocardial infarction, significant valve diseases, congenital heart diseases, cardiomyopathy, or previous cardiac surgery.

This was a multicenter, observational study with a prospective enrollment of the study group (COVID-19) and a retrospective enrollment of the control group performed in 5 CMR centers covering different regions in Poland. All the CMR centers have cardiac teams experienced in CMR and research leaders in the Board of the Polish Cardiac Society Section for Cardiac CMR and Computed Tomography. The study was conducted in accordance with the principles of the Declaration of Helsinki and the local ethics committee.

Clinical characteristics

Diabetes (DM) was reported in patients with prior diagnosis or abnormal fasting plasma glucose concentration (≥126 mg/dl) or HbA1c (≥6.5%) or 2-hour post-load plasma glucose (≥200 mg/dl) in the case of discrepancies [9, 10]. Dyslipidemia was determined based on plasma lipid levels or prior diagnosis and current treatment [11]. The diagnosis of hypertension was confirmed by taking office blood pressure or prior diagnosis and current treatment [11]. Obesity was classified according to body mass index (BMI, body mass [kg]/height [m^2]) as normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obesity (≥30.0 kg/m^2): class 1 (30.0–34.9 kg/m^2), class 2 (35.0–39.9 kg/m^2), and class 3 (≥40.0 kg/m^2). Chronic kidney disease was determined based on the estimated glomerular filtration rate (<60 ml/min/1.73 m^2) or prior diagnosis and treatment.

Coronary artery disease (CAD) was included in the clinical characteristics in patients with prior diagnosis, which was based on either coronary angiography or computed tomography angiography. Chronic pulmonary disease was reported in individuals with prior diagnosis and/or specific pharmacotherapy.

Cardiovascular magnetic resonance imaging

All the CMR images were obtained on the 1.5T systems: GE Optima MR450w (GE Healthcare, Waukesha, WI, US), Magnetom Aera (Siemens, Erlangen, Germany), Magnetom Avanto (Siemens, Erlangen, Germany) with dedicated phased array cardiac coils or body matrix coil. The CMR studies were ECG-gated and based on routine clinical protocols according to the guidelines [12, 13]. The CMR protocol included: (1) conventional non-contrast multi-planar cine acquisitions (steady state free precession, SSFP) for functional sequences; (2) T2-weighted triple inversion recovery (short tau inversion recovery, STIR) for edema imaging; (3) late gadolinium enhancement (LGE) for viability imaging obtained 10–15 minutes after contrast injection (0.1 mmol/kg of body weight of Gadovist). Functional sequences consisted of a stack of short-axis views from base to apex and 3 long-axis views (2-chamber view, 4-chamber view, and left outflow track view). LGE acquisitions were based on the same planes as the short- and long-axis cines. The STIR images were based on the same imaging planes as the long-axis cines and the short-axis planes covering LV.

All the CMR images were assessed by experienced teams in each of the centers (5–20 years of experience in CMR). Cardiac volumes, mass, and function (left [LV] and right ventricular [RV] end-diastolic and end-systolic volumes [V]; ejection fraction [EF]; mass [M]) were analyzed using dedicated commercial software. All the volumes and mass were indexed to body surface area (BSA) [14]. Afterward, individual LV parameters indexed to BSA were interpreted according to the normal LV reference values adjusted for sex and age, which were presented in the European Association of Cardiovascular Imaging guidelines [15].

The LV myocardium was divided into 17 segments as recommended by the American Heart Association [16]. The contractility of each of the LV segments was assessed as normal (1 point), hypokinetic (2 points), akinetic (3 points), or dyskinetic (4 points). Afterward, the wall motion score index (WMSI) [17] was calculated as the sum of the points for all segments divided by 17.

Myocardial edema was defined as an abnormal ratio (>2.0) between myocardial to skeletal muscle signal intensity on STIR [12, 13]. The presence, location, distribution, and severity of LGE were assessed in all patients. Finally, the total percentage of LV LGE was manually calculated in a semi-quantitative manner using short-axis slices covering all 17 segments of the LV.

Myocarditis-like injury was reported according to the CMR expert recommendations [12, 13] (Lake Louise Criteria), and it also included typical non-ischemic mid-wall and/or subepicardial LGE. Pericarditis was reported based on gadolinium uptake within the pericardium (LGE) and any of the following: pericardial thickening, edema on STIR imaging, or the presence of pericardial effusion.

Statistical analysis

The distribution of variables was tested for normality with the Kolmogorov-Smironov test. Numerical variables were expressed as mean with standard deviation (SD) or median with interquartile range (IQR), and categorical variables were presented as numbers and percentages. Baseline clinical parameters and the measures were compared between subgroups using t-tests for normally distributed continuous variables (unpaired Student's t-test) or the Mann-Whitney test if the distribution of the samples was not normal. The χ^2 test was used to test the differences between the proportions. Associations between numerical variables were assessed using Pearson or Spearman correlation. The cut-off values of the baseline clinical parameters for prediction of myocardial injury or dysfunction were determined in receiver operating characteristic (ROC) curve analysis. A *P*-value <0.05 was considered statistically significant. Statistical analysis was undertaken using Medcalc software (version 19.1, Osten, Belgium).

RESULTS

Study groups

COVID study group

A total of 552 patients who recovered from COVID-19 were enrolled in the COVID-19 study group. Median time between scheduled CMR and the disease onset was 12 (8–20) weeks. The clinical indication for CMR was a suspicion of COVID-19-related myocardial injury. The COVID-19 study group included mostly middle-aged patients (age 45.9 [12.6] years old; 52% females) with obesity (25%), hypertension (25%), and diabetes (6%). All the studies were performed within 10 months from the COVID-19 onset (88% within 7 months), and the infection was mostly moderate (Table 1). There were 3 cases of cardiogenic shock, 3 cases of acute pulmonary embolism, 2 cases of cerebral infarction, and 1 case of miscarriage related to the acute phase of COVID-19.

We found dilatation (10%) and moderate (11%) or severe (5%) systolic dysfunction of the LV with wall motion abnormalities (13.5%) in COVID-19 patients. We also found dilatation (4.7%) and dysfunction of the RV (EF <45%) in 37 cases (6.7%). Moreover, half of the CMR studies (n = 256 patients; 46%) revealed a myocarditis-like injury (LGE) in the LV myocardium, including 41 patients (7.5%) with myocardial edema (Table 2). Finally, 3 patients had only myocardial edema (no LGE), and one patient was found to have a subendocardial scar within the inferior wall (Figure 1).

Table 1. Clinical characteristics of the study groups

	COVID-19 group (n = 552)	Non-COVID-19 group (n = 221)	*P*-value
Age, years, mean (SD)	45.9 (12.6)	39.3 (14.6)	<0.001
Female/male sex, n (%)	285 (52) / 267 (48)	81 (36) / 140 (64)	0.01
Diabetes, n (%)	35 (6)	15 (7)	0.6
Dyslipidemia, n (%)	41 (7)	24 (11)	0.07
Hypertension, n (%)	140 (25)	45 (25)	1.0
Coronary artery disease, n (%)	21 (3.8)	15 (7)	0.08
Chronic pulmonary diseases, n (%)	41 (7.5)	12 (5.5)	0.32
Body mass index, kg/m^2, mean (SD)	27.2 (4.9)	26.3 (4.5)	0.3
Normal weight, n (%)	199 (36)	61 (27)	0.01
Overweight, n (%)	216 (39)	124 (56)	<0.001
Obesity, n (%)	137 (25)	36 (16)	<0.01
Chronic kidney disease, n (%)	2 (0.4)	2 (1)	0.3
Atrial fibrillation, n (%)	12 (2.2)	7 (3)	0.51
COVID-19			
Confirmed by PCR test, n (%)	552 (100)		
Disease onset and CMR, weeks, mean (SD)	15 (9)		
Moderate, n (%)	416 (75)		
Severe, n (%)	133 (24)		
Critical, n (%)	3 (0.5)		
Cardiovascular magnetic resonance			
Myocardial injury			
Myocarditis			
LV LGE, n (%)	256 (46)	200 (90)	<0.001
Pericardium			
Pericardial effusion, n (%)	73 (13.2)	48 (21)	0.01
Pericarditis, n (%)	40 (7)	12 (5.5)	0.44
Pleural effusion, n (%)	16 (2.8)	42 (19)	0.001

Abbreviations: BSA, body surface area; CMR, cardiac magnetic resonance; EDV, end-diastolic volume; EF, ejection fraction; LGE, late gadolinium enhancement; LV, left ventricle; PCR, polymerase chain reaction; RV, right ventricle; SD, standard deviation

In the patients who recovered from COVID-19, myocardial LGE was found more often in males (69% vs. 56%; *P* <0.001), but it was not related to age (45.6 [11.8] years vs. 46.3 [13.5] years; *P* = 0.5) or BMI (26.9 [5] kg/m^2 vs. 27.1 [4.9] kg/m^2; *P* = 0.6).

The median number of injured LV segments was 3 (2–4), which was 4.4% (2.9%–8.1%) of the LV mass. The majority of injured segments (68%) showed only a mild degree of LGE (<25% transmural extent), and the most frequently diseased LV segments were: 2, 3, and 4 (Figure 2). Finally, every fifth patient showed a pericardial effusion, and co-existing pericarditis was found in 35 patients (13.6%) with predominantly mild manifestations.

The patients' age, obesity, body mass index (BMI), or time from the COVID-19 onset were not associated with total LGE mass (data not shown). Time of CMR from the onset of the disease was similar between males and females (12 [8–20] vs. 12 [8–20]; *P* = 0.1), and it showed only a weak association with LV end-diastolic volume (EDV)/BSA (r = –0.2; *P* = 0.01), LV mass/BSA (r = –0.3; *P* <0.001), RV EDV/BSA (r = –0.2; *P* <0.01), but not with any other CMR parameters, including LVEF or RVEF. As expected, patients with pericarditis confirmed on CMR showed larger LGE area compared to patients without pericarditis (7.35% [4.4%–23.5%] vs. 4.4% [2.9%–7.3%]; *P* <0.0001).

Among baseline parameters, LVEF ≤56% showed a statistical trend (area under the curve [AUC], 0.560; sensitivity, 37%; specificity, 80%; *P* = 0.07), and WMSI>1.0 (AUC, 0.589; sensitivity, 25%; specificity, 93%; *P* <0.01) was the predictor of myocardial injury (LGE).

Non-COVID control group

A total of 221 consecutive patients were included in the control group with non-COVID-19 myocarditis (age, 39.3 [14.6] years; 64% males). The clinical characteristics and main CMR parameters in comparison with the COVID study group are presented in Table 1. In brief, the non-COVID group included slightly younger patients, mostly males, more overweight individuals, but fewer with obesity; there were no other clinical differences. However, CMR confirmed myocarditis-like LGE at a significantly higher rate in the control group (90% vs. 46%; *P* <0.001), with a higher rate of pericardial (21% vs. 13%; *P* = 0.01) and pleural (19% vs. 2.8%; *P* = 0.001) effusions.

The subgroups of COVID-19 and non-COVID-19 patients with myocarditis confirmed on CMR are presented in Table 2. The total LV LGE and the number of involved segments were significantly smaller, and the severity of segmental injury (transmural extent) was lesser in COVID-19-myocarditis compared to non-COVID-19 myocarditis, except for the

Table 2. Clinical characteristics of the studied patients with late gadolinium enhancement

	COVID-19 LGE(+) (n = 256)	Non-COVID-19 LGE (+) (n = 200)	*P*-value
Age, years, mean (SD)	46.3 (13.5)	38.8 (14.7)	<0.001
Female/male sex, n (%)	113 (44) / 143 (56)	64 (32) / 136 (68)	<0.01
Diabetes, n (%)	24 (9)	14 (6)	0.3
Dyslipidemia, n (%)	25 (10)	19 (9)	0.7
Hypertension, n (%)	59 (23)	58 (29)	0.15
Coronary artery disease, n (%)	10 (6.5)	13 (6)	0.8
Chronic pulmonary diseases, n (%)	13 (5)	10 (4.5)	0.8
Body mass index, kg/m^2, mean (SD)	27.2 (4.8)	26.1 (4.7)	0.01
Obesity, n (%)	60 (23.4)	36 (18)	0.12
Chronic kidney disease, n (%)	2 (0.8)	3 (1.3)	0.6
Atrial fibrillation, n (%)	6 (2.3)	7 (3.1)	0.6
Cardiovascular magnetic resonance			
Left and right ventricular remodeling			
LV EDV, median (IQR)	144.6 (125.5–178)	162.8 (136.6–194)	<0.001
LV EDV/BSA, ml/m^2, median (IQR)	75.8 (62–86.3)	84.2 (71.6–96)	<0.0001
Dilated LV, n (%)	25 (10)	39 (19.5)	0.08
LV mass, g, median (IQR)	117 (94–142)	133.1 (111–143.3)	<0.0001
LV mass/BSA, g/m^2, median (IQR)	54.4 (42–64)	66.8 (54.2–75.5)	<0.0001
LV hypertrophy, n (%)	9 (3.5)	13 (6.5)	0.25
LVEF, %, median (IQR)	59 (54.1–65)	58 (52–63)	0.01
LVEF ≥50%, n (%)	215 (84)	157 (78)	0.2
LVEF 40%–49%, n (%)	28 (11)	21 (10.5)	0.7
LVEF <40%, n (%)	13 (5)	22 (11)	<0.01
LV WMSI, median (IQR)	1 (1–1)	1 (1–1.2)	<0.001
Wall motion abnormalities, n (%)	59 (23)	74 (37)	<0.01
RV EDV, ml, median (IQR)	135.5 (116–165)	139 (122–168)	0.1
RV EDV/BSA, median (IQR)	68.4 (56.4–80)	70.1 (62.1–82)	0.1
Dilated RV, n (%)	12 (4.7)	18 (9)	0.3
RVEF, %, median (IQR)	55 (50–61)	54 (49–59.7)	0.25
Myocardial injury			
Myocarditis			
LV LGE, n (%)	256 (100)	200 (100)	
Nb of LV segments with LGE, median (IQR)	3 (2–4)	4 (2–5.5)	<0.01
Total LGE in LV mass, %, median (IQR)	4.4 (2.9–8.1)	5.9 (4.4–11.8)	<0.001
Patients with LGE in LV segment, n (%)			
51%–75%	20 (7.8)	20 (10)	0.02
26%–50%	61 (24)	67 (33.5)	<0.001
≤25%	174 (68)	109 (54.5)	<0.0001
LV edema, n (%)	42 (16.4)	75 (37.5)	0.05
Pericardium			
Pericardial effusion			
<10 mm, n (%)	40 (15.5)	38 (19)	0.32
≥10 mm, n (%)	4 (1.5)	6 (3)	0.56
Pericarditis, n (%)	35 (13.6)	12 (6)	0.03
Severity of LGE in the pericardium			
Mild, n (%)	29 (11.3)	7 (3.5)	<0.01
Moderate, n (%)	6 (2.3)	4 (2)	0.83
Severe, n (%)	0	0	

Abbreviations: BSA, body surface area; CMR, cardiac magnetic resonance; EDV, end-diastolic volume; EF, ejection fraction; LGE, late gadolinium enhancement; LV, left ventricle; PCR, polymerase chain reaction; RV, right ventricle; SD, standard deviation

transmural injury (0.4 vs. 2 %; $P = 0.09$) (Table 2). There was a trend toward a less frequent LV edema reported in the COVID-19 subgroup (16.4% vs. 37.5%; $P = 0.05$). Moreover, patients with non-COVID-19 myocarditis demonstrated a significantly lower LVEF with a doubled rate of significant LV dysfunction (LVEF <40%), more frequent LV wall motion abnormalities, and LV remodeling compared to the post-COVID-19 patients (Table 2). Nevertheless, COVID myocarditis resulted in a higher rate of pericarditis (13.6% vs. 6%; $P = 0.03$), which was mostly mild (11.3% vs. 3.5%; $P < 0.01$), with a small pericardial effusion <10 mm in both groups. Finally, the distribution of LGE within LV showed significant differences between both groups (Figure 2). COVID-19-induced myocarditis was significantly more fre-

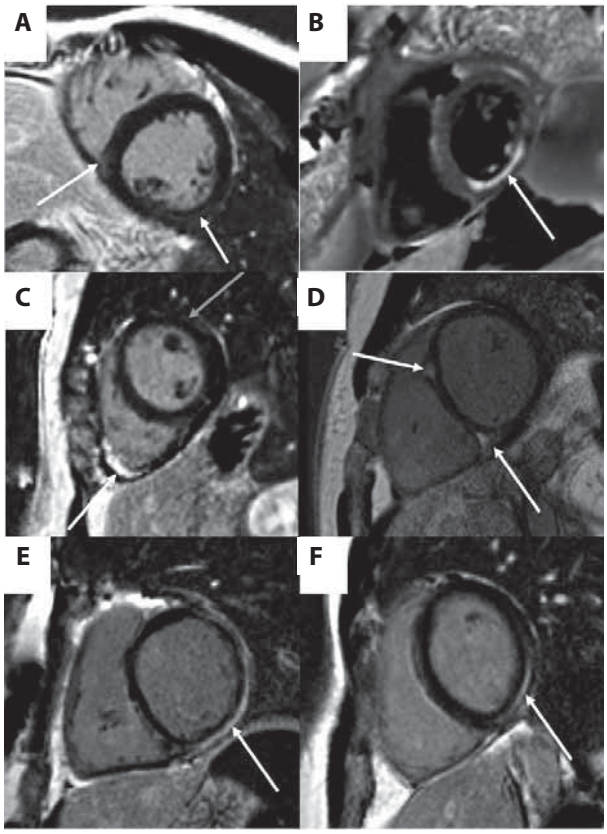


Figure 1. Myocardial injury (late gadolinium enhancement [LGE]) after COVID-19 (**A**–**D**) and after non-COVID-19 inflammation (**E**–**F**). **A.** Intramyocardial injury (arrows) on late gadolinium enhancement sequence in a 23-year-old male with documented myocarditis during COVID-19 (arrows). **B.** Subendocardial scar on dark blood late gadolinium enhancement sequence in a 64-year-old male (arrow). **C.** Pericarditis (white arrow) with pericardial effusion and myocardial injury (grey arrow) on late gadolinium enhancement sequence (arrows) in a 54-year-old female. **D.** Intramyocardial injury on late gadolinium enhancement sequence in a 40-year-old male (arrows). **E** and **F.** Subepicardial and intramyocardial injuries in late gadolinium enhancement sequence

quent in the 2nd (37% vs. 28%; $P = 0.04$), 3rd (44.1% vs. 30.5%; $P < 0.01$), and 14th (11.7% vs. 6%; $P = 0.03$) segments, and non-COVID-19 cases were more frequent in the lateral wall: 5th (36% vs. 57%; $P < 0.01$), 6th (18% vs. 32%; $P < 0.01$), 11th (19% vs. 41.5%; $P < 0.001$), and 12th (16.8% vs. 27%; $P < 0.01$). Moreover, post-COVID-19 patients with obesity showed a significantly more frequent injury within the 3rd LV segment compared to non-obese post-COVID-19 cases (53.5% vs. 39%; $P = 0.04$).

There was no difference in the LV LGE area between obese and non-obese patients in the COVID-19 group (4.4% [2.9%–10.3%] vs. 4.4% [3%–7.35%]; $P = 0.1$). There was also no difference in LV LGE between obese and non-obese individuals (8.1% [4.4%–14.7%] vs. 5.8% [2.9%–11.8%]; $P = 0.18$) in the non-COVID-19 group. Finally, there was a weak association between BMI and LV LGE in this subgroup ($r = 0.15$; $P = 0.04$)

In the non-COVID-19 subgroup, the patients' age showed a weak association with total LV LGE ($r = 0.25$; $P < 0.01$) and WMSI ($r = 0.35$; $P < 0.001$).

DISCUSSION

To the best of our knowledge, this is currently the largest prospective multicenter study assessing consecutive patients with suspected COVID-19-induced myocarditis and the only study comparing those findings with a retrospective non-COVID-19 myocarditis group. First, myocardial injury was confirmed in half of the patients despite their middle age and mostly a moderate infection. Second, COVID-19-induced myocarditis was in most cases associated with preserved LV and RV systolic function. Third, COVID-19-induced myocarditis revealed a significantly smaller myocardial injury (LGE) with a lesser transmural extent and higher LV EF but more frequent pericarditis

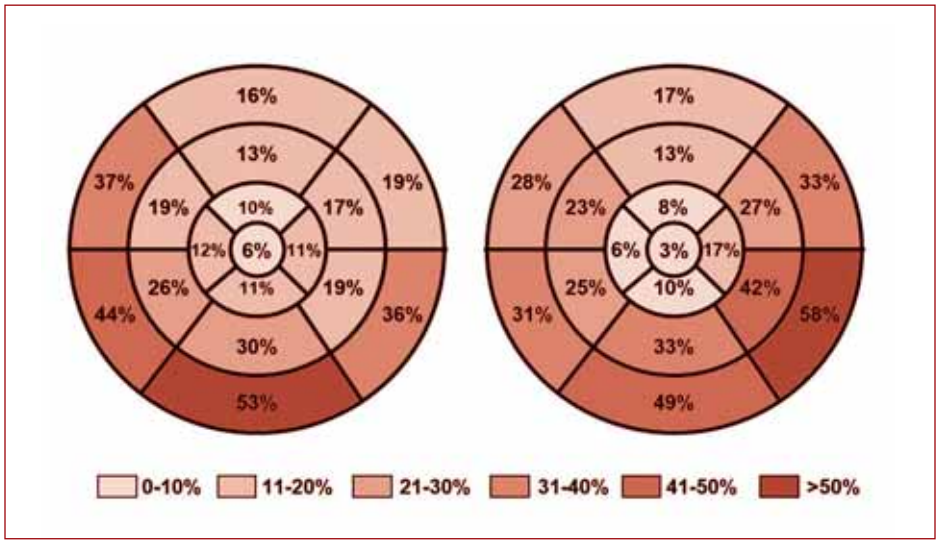


Figure 2. Bull's eye plots showing location and distribution of late gadolinium enhancement according to the 17-segment AHA (American Heart Association 17-segment model) rates of injured segments in patients with COVID-19-related myocarditis (**A**) and non-COVID-19 myocarditis (**B**)

than non-COVID-19 myocarditis. Finally, COVID-19-induced myocarditis showed higher affinity to LV septal segments, and non-COVID-19 myocarditis was more prevalent in LV lateral wall segments.

COVID-19 and CMR

The ongoing pandemic and millions of confirmed cases provided a growing body of evidence on COVID-19-related cardiovascular injury. However, this is mainly based on small and heterogenous studies [5]. The rate of abnormal CMR results in post-COVID-19 patients found in our study was consistent with meta-analyses of smaller studies [5, 18]. Up to 60% of the study patients were found to have at least one or more abnormalities on CMR depending on the time from the onset and severity of the disease [5, 18–21]. Huang et al. [19] found that half of the patients assessed with CMR had abnormal myocardial edema and/or LGE. The myocardial injury did not affect LV volumes or systolic function compared to healthy controls. This study showed a decrease in RV functional parameters during an early post-COVID-19 period (first 2 months). Although Kotecha et al. [20] found that half of the study patients showed a myocardial injury, every fifth patient showed ischemic LGE. However, the exact time of coronary scar and its correlation with COVID-19 is unknown.

Moreover, one-third of the patients had a severe clinical manifestation of the ventilatory disorder. A limited functional consequence was observed despite myocardial injury. Another study by Puntmann et al. [21] reported a higher rate of myocarditis on CMR (60%), irrespective of the clinical manifestation or time from acute COVID-19. However, lower rates of post-COVID-19 myocardial injury were also reported in other studies [5, 18, 22]. For obvious reasons, no studies assessed acute myocardial injury in CMR patients with severe COVID-19.

Nevertheless, an autopsy study confirmed myocarditis as the cause of death only in 4% of patients with COVID-19, which is in line with our study showing a relatively high prevalence of any myocardial injury (LGE) and lower rates of LV systolic dysfunction. Moreover, LV wall motion abnormalities (WMA) were reported in only one in four [23%] patients with COVID-19-induced myocarditis. Therefore, despite using high-quality CMR images, the baseline WMA showed low sensitivity and predictive value for myocardial injury (LGE).

Our study also showed preserved RV systolic function and normal RV volume in most cases, consistent with previous studies [19–22]. The right heart is a passive conduit, dilated in an earlier phase of COVID-19.

Our non-COVID-19 group showed a higher rate of LV dilatation, systolic dysfunction, and wall motion abnormalities, resulting from more severe LV injury. We failed to show that obesity was associated with the presence, severity, and structural or functional abnormalities in COVID-19-induced myocarditis. This seems to be a feature of COVID-19 myocarditis important for clinical practice.

Finally, novel CMR techniques, including mapping and strain, showed a COVID-19-related myocardial injury, but the additional data were mostly consistent with LGE-based injury [20, 22, 23].

Septal LGE pattern specific for COVID-19

Based on the outcomes of our study, COVID-19-induced myocarditis was located mainly in LV septal segments, especially in patients with obesity. Most previous studies confirmed only a non-ischemic pattern of LGE as the main finding [5], and small studies provided divergent findings suggesting the most frequent locations of COVID-19-related injury [18, 19, 22]. This was the first study providing novel data regarding the most frequent COVID-related injury compared to non-COVID-19 myocarditis. We found that COVID-19-induced myocarditis is more specific to inferospetal and anterospetal segments than non-COVID myocarditis, and it is usually found in basal or mid-cavity lateral segments [24]. Higher affinity of SARS-CoV-2 to septal segments increases the risk of injury within the conduction system. QT prolongation and atrioventricular or ventricular block were reported in 12% and 13% of COVID-19 patients [25]. Moreover, an LGE septal location was more frequent in myocarditis (unrelated to COVID-19), which may result in heart failure and arrhythmias in the following months or years [24]. It was significantly associated with malignant ventricular arrhythmias [26] and left bundle branch block (LBBB) [25]. Finally, a new onset LBBB results in LV dyssynchrony and may lead to LV systolic dysfunction [27]. Myocardial LGE is clinically equal to myocardial injury in several cardiac conditions, which include myocarditis [28]. LGE is a well-evidenced independent predictor of cardiac and all-cause mortality [29, 30]. In addition, LGE plays a role in the pathophysiology of dilated cardiomyopathy [31, 32]. Future studies should assess the long-term consequence of LGE on LV dilatation and/or dysfunction in COVID-19-induced myocarditis. Given the mean age of study patients, even a mild residual myocardial injury plays a role in progression to cardiomyopathy, heart failure, ventricular arrhythmias, or even sudden cardiac death.

COVID-19 and myocardial injury

The main mechanisms of COVID-19 myocardial injury include a direct viral myocardial inflammation through angiotensin-converting enzyme 2 receptors or an indirect injury induced by a high inflammatory burden and an overexpressed immune response [33, 34]. Endomyocardial biopsy in patients with severe active myocarditis showed active lymphocytic inflammation with no evidence of viral genome [21]. An autopsy study confirmed myocardial infiltration and mononuclear inflammatory cells in patients who died from COVID-19 [35]. SARS-CoV-2 is the cause of endothelial dysfunction and thrombotic complications, which is another potential pathomechanism of myocardial

injury [36, 37]. However, we barely found any subendocardial scars in the COVID-19 study group.

COVID-19 and pericarditis

Seven patients in our study group who recovered from COVID-19 with myocarditis demonstrated mild pericarditis. We found that it was related to a larger area of myocardial injury, which seems understandable. Similar data were found in other studies, with differences most likely depending on clinical disease severity [19–22]. However, an unexpectedly high pericardial (27%) and low myocardial involvement (16%) were reported in young athletes with asymptomatic or mild COVID-19 [38], suggesting that young convalescents may be more prone to pericarditis. Our study patients were older, and we found a higher rate of pericarditis in patients with COVID-19-induced myocarditis than in non-COVID-19 myocarditis. The pathomechanism, which includes either a direct viral infection or generalized COVID-19 multisystemic inflammatory syndrome, remains unclear. However, we observed no pleural effusions in those individuals. Future research is required to explain the clinical effects of angiogenesis and an increased activity of the angiotensin converting enzyme receptor in pericardial mesothelial cells related to SARS-CoV-2 infection [39, 40].

Limitations

We collected data from middle-aged patients with mostly moderate clinical presentations of COVID-19. Our study participants do not reflect a complete spectrum of the disease. However, the study group was recruited from consecutive patients referred for CMR, and a postmortem study showed a small number of descendants who died from COVID-19-related myocarditis [26]. Second, we did not have lab markers of cardiac injury or natriuretic peptides for our study patients as they were mostly not hospitalized during the SARS-CoV-2 infection. We also did not have baseline CMR to verify the exact time of myocardial injury, which is similar to the outcomes of other studies. In addition, we did not have data to evaluate the clinical severity of non-COVID-19 myocarditis in the control group.

Moreover, we do not present CMR mapping as it was unavailable at all CMR centers. Still, T1/T2/ECV CMR mapping and LV strain were mostly consistent with conventional CMR sequences [20, 22, 23, 41]. Finally, all the study patients had clinical indications for CMR, which constitutes a potential selection bias.

CONCLUSIONS

Our large prospective multicenter study confirmed COVID-19-induced myocarditis in nearly half of the patients who recovered from COVID-19. COVID-19-related myocardial injury and functional sequelae were smaller than in the non-COVID-19 myocarditis cases.

This is the first study to show that septal LGE is more specific for COVID-19-induced injury, which may result in LV dyssynchrony and systolic dysfunction or arrhythmia. A regular follow-up of post-COVID-19 patients should verify the impact of a residual injury on clinical outcomes.

Article information

Conflict of interest: None declared.

Funding: The study was partially supported by the University Center of Maritime and Tropical Medicine in Gdynia, Medical University of Gdańs,k and with a non-commercial grant from the Medical University of Silesia (PCN-1-114/N/1/K).

REFERENCES

1. WHO coronavirus disease (COVID-19) dashboard. Geneva: World Health Organization, 2020. Available online: https://covid19.who.int/. [Access: January 2, 2023].
2. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis. 2020; 20(4): 425–434, doi: 10.1016/S1473-3099(20)30086-4, indexed in Pubmed: 32105637.
3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395(10223): 497–506, doi: 10.1016/S0140-6736(20)30183-5, indexed in Pubmed: 31986264.
4. Wang D, Hu Bo, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020; 323(11): 1061–1069, doi: 10.1001/jama.2020.1585, indexed in Pubmed: 32031570.
5. Kim JY, Han K, Suh YJ. Prevalence of abnormal cardiovascular magnetic resonance findings in recovered patients from COVID-19: a systematic review and meta-analysis. J Cardiovasc Magn Reson. 2021; 23(1): 100, doi: 10.1186/s12968-021-00792-7, indexed in Pubmed: 34479603.
6. Petrakis D, Margină D, Tsarouhas K, et al. Obesity a risk factor for increased COVID19 prevalence, severity and lethality (Review). Mol Med Rep. 2020; 22(1): 9–19, doi: 10.3892/mmr.2020.11127, indexed in Pubmed: 32377709.
7. Schulz-Menger J, Bluemke DA, Bremerich J, et al. Standardized image interpretation and post-processing in cardiovascular magnetic resonance - 2020 update : Society for Cardiovascular Magnetic Resonance (SCMR): Board of Trustees Task Force on Standardized Post-Processing. J Cardiovasc Magn Reson. 2020; 22(1): 19, doi: 10.1186/s12968-020-00610-6, indexed in Pubmed: 32160925.
8. National Institutes of Health. COVID-19 treatment guidelines. Available online: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum. [Access: January 1, 2023].
9. World Health Organization (WHO) Consultation. Definition and diagnosis of diabetes and intermediate hyperglycaemia. 2006. Available online: http://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_new.pdf. [Access: January 2023].
10. World Health Organization (WHO), Abbreviated report of aWHO consultation. Use of glycated hemoglobin (HbA1c) in the diagnosis if diabetes mellitus. 2011. Available online: http://www.who.int/diabetes/publications/diagnosis_diabetes2011/en/. Access: January 2023].
11. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016; 37(29): 2315–2381, doi: 10.1093/eurheartj/ehw106, indexed in Pubmed: 27222591.
12. Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation: Expert Recom-

mendations. J Am Coll Cardiol. 2018; 72(24): 3158–3176, doi: 10.1016/j.jacc.2018.09.072, indexed in Pubmed: 30545455.
13. Kramer CM, Barkhausen J, Bucciarelli-Ducci C, et al. Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2020 update. J Cardiovasc Magn Reson. 2020; 22(1): 17, doi: 10.1186/s12968-020-00607-1, indexed in Pubmed: 32089132.
14. Du Bois D, Du Bois EF. A to estimate the approximate surface area if height and weight be known. Arch Intern Med. 1916; 17: 863–871.
15. Maceira AM, Prasad SK, Khan M, et al. Normalized left ventricular systolic and diastolic function by steady state free precession cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2006; 8(3): 417–426, doi: 10.1080/10976640600572889, indexed in Pubmed: 16755827.
16. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation. 2002; 105(4): 539–542, doi: 10.1161/hc0402.102975, indexed in Pubmed: 11815441.
17. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr. 1989; 2(5): 358–367, doi: 10.1016/s0894-7317(89)80014-8, indexed in Pubmed: 2698218.
18. Petersen SE, Friedrich MG, Leiner T, et al. Cardiovascular Magnetic Resonance for Patients With COVID-19. JACC Cardiovasc Imaging. 2022; 15(4): 685–699, doi: 10.1016/j.jcmg.2021.08.021, indexed in Pubmed: 34656482.
19. Huang L, Zhao P, Tang D, et al. Cardiac Involvement in Patients Recovered From COVID-2019 Identified Using Magnetic Resonance Imaging. JACC Cardiovasc Imaging. 2020; 13(11): 2330–2339, doi: 10.1016/j.jcmg.2020.05.004, indexed in Pubmed: 32763118.
20. Kotecha T, Knight DS, Razvi Y, et al. Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance. Eur Heart J. 2021; 42(19): 1866–1878, doi: 10.1093/eurheartj/ehab075, indexed in Pubmed: 33596594.
21. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020; 5(11): 1265–1273, doi: 10.1001/jamacardio.2020.3557, indexed in Pubmed: 32730619.
22. Wang H, Li R, Zhou Z, et al. Cardiac involvement in COVID-19 patients: mid-term follow up by cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2021; 23(1): 14, doi: 10.1186/s12968-021-00710-x, indexed in Pubmed: 33627143.
23. Urmeneta Ulloa J, Martínez de Vega V, Salvador Montañés O, et al. Cardiac magnetic resonance in recovering COVID-19 patients. Feature tracking and mapping analysis to detect persistent myocardial involvement. Int J Cardiol Heart Vasc. 2021; 36: 100854, doi: 10.1016/j.ijcha.2021.100854, indexed in Pubmed: 34368419.
24. Di Bella G, Camastra G, Monti L, et al. Left and right ventricular morphology, function and late gadolinium enhancement extent and localization change with different clinical presentation of acute myocarditis Data from the ITAlian multicenter study on MYocarditis (ITAMY). J Cardiovasc Med (Hagerstown). 2017; 18(11): 881–887, doi: 10.2459/JCM.0000000000000574, indexed in Pubmed: 28915139.
25. Deluigi CC, Ong P, Hill S, et al. ECG findings in comparison to cardiovascular MR imaging in viral myocarditis. Int J Cardiol. 2013; 165(1): 100–106, doi: 10.1016/j.ijcard.2011.07.090, indexed in Pubmed: 21885134.
26. Hooper JE, Padera RF, Dolhnikoff M, et al. A Postmortem Portrait of the Coronavirus Disease 2019 (COVID-19) Pandemic: A Large Multi-institutional Autopsy Survey Study. Arch Pathol Lab Med. 2021; 145(5): 529–535, doi: 10.5858/arpa.2020-0786-SA, indexed in Pubmed: 33449998.
27. Sharma S, Barot HV, Schwartzman AD, et al. Risk and predictors of dyssynchrony cardiomyopathy in left bundle branch block with preserved left ventricular ejection fraction. Clin Cardiol. 2020; 43(12): 1494–1500, doi: 10.1002/clc.23467, indexed in Pubmed: 32940385.
28. Schumm J, Greulich S, Wagner A, et al. Cardiovascular magnetic resonance risk stratification in patients with clinically suspected myocarditis. J Cardiovasc Magn Reson. 2014; 16(1): 14, doi: 10.1186/1532-429X-16-14, indexed in Pubmed: 24461053.
29. Grün S, Schumm J, Greulich S, et al. Long-term follow-up of biopsy-proven viral myocarditis: predictors of mortality and incomplete recovery. J Am Coll Cardiol. 2012; 59(18): 1604–1615, doi: 10.1016/j.jacc.2012.01.007, indexed in Pubmed: 22365425.
30. Barone-Rochette G, Augier C, Rodière M, et al. Potentially simple score of late gadolinium enhancement cardiac MR in acute myocarditis outcome. J Magn Reson Imaging. 2014; 40(6): 1347–1354, doi: 10.1002/jmri.24504, indexed in Pubmed: 24293405.
31. Verdonschot JAJ, Merlo M, Dominguez F, et al. Phenotypic clustering of dilated cardiomyopathy patients highlights important pathophysiological differences. Eur Heart J. 2021; 42(2): 162–174, doi: 10.1093/eurheartj/ehaa841, indexed in Pubmed: 33156912.
32. Becker MAJ, Cornel JH, van de Ven PM, et al. The Prognostic Value of Late Gadolinium-Enhanced Cardiac Magnetic Resonance Imaging in Nonischemic Dilated Cardiomyopathy: A Review and Meta-Analysis. JACC Cardiovasc Imaging. 2018; 11(9): 1274–1284, doi: 10.1016/j.jcmg.2018.03.006, indexed in Pubmed: 29680351.
33. Zheng YY, Ma YT, Zhang JY, et al. COVID-19 and the cardiovascular system. Nat Rev Cardiol. 2020; 17(5): 259–260, doi: 10.1038/s41569-020-0360-5, indexed in Pubmed: 32139904.
34. Oudit GY, Kassiri Z, Jiang C, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Invest. 2009; 39(7): 618–625, doi: 10.1111/j.1365-2362.2009.02153.x, indexed in Pubmed: 19453650.
35. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020; 8(4): 420–422, doi: 10.1016/S2213-2600(20)30076-X, indexed in Pubmed: 32085846.
36. Maiese A, Manetti AC, La Russa R, et al. Autopsy findings in COVID-19-related deaths: a literature review. Forensic Sci Med Pathol. 2021; 17(2): 279–296, doi: 10.1007/s12024-020-00310-8, indexed in Pubmed: 33026628.
37. Violi F, Pignatelli P, Cammisotto V, et al. COVID-19 and thrombosis: Clinical features, mechanism of disease, and therapeutic implications. Kardiol Pol. 2021; 79(11): 1197–1205, doi: 10.33963/KP.a2021.0154, indexed in Pubmed: 34847237.
38. Brito D, Meester S, Yanamala N, et al. High Prevalence of Pericardial Involvement in College Student Athletes Recovering From COVID-19. JACC Cardiovasc Imaging. 2021; 14(3): 541–555, doi: 10.1016/j.jcmg.2020.10.023, indexed in Pubmed: 33223496.
39. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med. 2020; 383(2): 120–128, doi: 10.1056/NEJMoa2015432, indexed in Pubmed: 32437596.
40. Sousa IR, Pereira IC, Morais LJ, et al. Pericardial Parietal Mesothelial Cells: Source of the Angiotensin-Converting-Enzyme of the Bovine Pericardial Fluid. Arq Bras Cardiol. 2017; 109(5): 425–431, doi: 10.5935/abc.20170155, indexed in Pubmed: 29267626.
41. Fijałkowska J, Sobolewski J, Glińska A, et al. Cardiac abnormalities detected by echocardiography and cardiac magnetic resonance in healthcare professionals recovered from non-severe COVID-19. Kardiol Pol. 2021; 79(11): 1256–1258, doi: 10.33963/KP.a2021.0114, indexed in Pubmed: 34599499.

A randomized comparison of His bundle pacing versus right ventricular pacing: Effect on left ventricular function and biomarkers of collagen metabolism

Jan Mizner[1], Petr Waldauf[2], Domenico Grieco[3], Hana Linkova[1], Oana Ionita[1], Pugazhendhi Vijayaraman[4], Robert Petr[1], Radka Raková[1], Jana Vesela[1], Petr Stros[1], Dalibor Herman[1], Pavel Osmancik[1], Karol Curila[1]

[1]Cardiocenter, 3rd Faculty of Medicine, Charles University and University Hospital Kralovske Vinohrady, Prague, Czech Republic
[2]Department of Anesthesia and Intensive Care, Charles University and University Hospital Kralovske Vinohrady, Prague, Czech Republic
[3]Department of Cardiology, Policlinico Casilino of Rome, Rome, Italy
[4]Geisinger Heart Institute, Wilkes Barre, Pennsylvania, United States

Correspondence to:
Karol Curila, MD, PhD, MSc, Cardiocenter, 3rd Faculty of Medicine, Charles University and University Hospital Kralovske Vinohrady, Srobarova 50, 100 34 Prague, Czech Republic, phone: +420 2 6716 2621, e-mail: karol.curila@fnkv.cz

DOI: 10.33963/KP.a2023.0065

Received: November 1, 2022

Accepted: January 2, 2023

Early publication date: March 9, 2023

ABSTRACT

Background: Right ventricular pacing (RVP) can result in pacing-induced cardiomyopathy (PICM). It is unknown whether specific biomarkers reflect differences between His bundle pacing (HBP) and RVP and predict a decrease in left ventricular function during RVP.

Aims: We aimed to compare the effect of HBP and RVP on the left ventricular ejection fraction (LVEF) and to study how they affect serum markers of collagen metabolism.

Methods: Ninety-two high-risk PICM patients were randomized to HBP or RVP groups. Their clinical characteristics, echocardiography, and serum levels of transforming growth factor β1 (TGF-β1), matrix metalloproteinase 9 (MMP-9), suppression of tumorigenicity 2 interleukin (ST2-IL), tissue inhibitor of metalloproteinase 1 (TIMP-1), and galectin 3 (Gal-3) were studied before pacemaker implantation and six months later.

Results: Fifty-three patients were randomized to the HBP group and 39 patients to the RVP group. HBP failed in 10 patients, who crossed over to the RVP group. Patients with RVP had significantly lower LVEF compared to HBP patients after six months of pacing (−5% and −4% in as-treated and intention-to-treat analysis, respectively). Levels of TGF-β1 after 6 months were lower in HBP than RVP patients (mean difference −6 ng/ml; $P = 0.009$) and preimplant Gal-3 and ST2-IL levels were higher in RVP patients, with a decline in LVEF ≥5% compared to those with a decline of <5% (mean difference 3 ng/ml and 8 ng/ml; $P = 0.02$ for both groups).

Conclusion: In high-risk PICM patients, HBP was superior to RVP in providing more physiological ventricular function, as reflected by higher LVEF and lower levels of TGF-β1. In RVP patients, LVEF declined more in those with higher baseline Gal-3 and ST2-IL levels than in those with lower levels.

Key words: His bundle pacing, markers of collagen metabolism, right ventricular pacing

INTRODUCTION

Myocardial pacing of the right ventricle (RVP) is responsible for declining left ventricular (LV) function and heart failure in some patients. The highest risk of these adverse consequences is seen in older patients with a high burden of RV pacing, decreased left ventricular function, coronary artery disease (CAD), and wider spontaneous or paced QRS complexes [1]. His bundle pacing (HBP) preserves synchronous ventricular activation and represents the most physiological method of ventricular pacing [2, 3]. This pacing method is more complex, with longer procedure times and higher radiation doses, and requires more sophisticated equipment [4]. For these reasons, HBP is best suited for patients who would gain the most from physiological ventricular activation. However, the benefit of HBP in high-risk populations has never been described.

Although RV pacing is non-physiological, most patients tolerate it even for extended

WHAT'S NEW?

In patients at high risk of pacing-induced cardiomyopathy, His bundle pacing does not worsen left ventricular function in contrast to right ventricular pacing, which leads to its decline. Higher galectin 3 and suppression of tumorigenicity 2 interleukin (ST2-IL) levels in patients treated with right ventricular pacing are associated with decline in left ventricular ejection fraction after six months of pacing. Galectin 3 and ST2-IL may improve identification of patients in whom right ventricular pacing will not be associated with decline in left ventricular function.

periods [5]. Currently, we cannot precisely tell (before pacemaker implantation) which patients will experience deterioration in ventricular function after RV pacing. The period after which pacing-induced cardiomyopathy (PICM) starts to develop is estimated to be 2–3 years. However, subtle changes in LV function (i.e., ≥5% decline) can present sooner, and these patients are at the highest risk of further heart failure [6]. Remodeling and altered LV function are present together with changes in the ventricular microstructure. These changes are reflected by perfusion changes in particular ventricular segments, abnormal myocardial metabolism, increased fibrosis, and myocardial disarray [7]. It was already shown that subtle myocardial microstructure changes in patients after myocardial infarction or heart failure could be evaluated using collagen metabolism biomarkers [7]. However, their significance in patients with a permanent pacemaker has not been established yet. Demonstrating their relevance to LV performance in these patients could be an important marker of increased risk of further heart failure.

Our study aimed to assess the effect of RVP and HBP on LV function in patients at high risk of heart failure after cardiac pacing. Another goal was to identify laboratory markers that can predict or detect the adverse effects of RV pacing on LV performance.

METHODS

Patients

This was a prospective open-label randomized study with the anticipated recruitment of 120 patients. The project was approved by the Ethics Committee of the Faculty Hospital Kralovske Vinohrady, Prague, Czech Republic; all subjects signed informed consent before enrollment. Only patients with conduction disease and an indication for permanent cardiac pacing per the 2013 European Society of Cardiology (ESC) guidelines were enrolled. Patients had to have a permanent conduction disease with an anticipated high burden of the RV pacing and life expectancy greater than two years. Also, at least one of the following criteria had to be fulfilled: (1) left ventricular ejection fraction (LVEF) ≤60%; (2) QRS duration >115 ms; (3) presence of ischemic heart disease (defined as previous myocardial infarction or coronary intervention due to significant occlusion of coronary arteries or angina pectoris requiring pharmacological treatment).

Exclusion criteria were as follows: a severe valvular disease with a planned intervention, cardiac surgery due to valvular disease or CAD in the previous three months, permanent or persistent atrial fibrillation, dilated or hypertrophic cardiomyopathy, active myocarditis and an indication for cardioverter-defibrillator implantation or cardiac resynchronization therepy. Patients were randomized to the HBP or RVP arms with a 4:3 ratio; the anticipated His bundle pacing success rate was 80%–90%. After randomization, patients were informed which arm of the study they were enrolled in. After pacemaker implantation, outpatient clinic follow-ups were at six weeks and six months. During these visits, the pacemaker was checked (with data collection), patient clinical status was assessed, and a physical examination was performed. Blood sampling and echocardiography were performed before pacemaker implantation and at the six-month follow-up visit.

Pacemaker implantation

His bundle pacing was performed using Select Secure leads (model 3830, 69 cm, Medtronic Inc., Minneapolis, MN, US) delivered through a fixed-curve sheath (C315 HIS, Medtronic, Minneapolis, MN, US) preferentially from the left subclavian approach. The end of the sheath was delivered to the tricuspid annulus over the guidewire, and then the pacing lead was advanced through the sheath 1–2 mm beyond the tip of the catheter. The His bundle area was mapped in unipolar settings using an electrophysiology system (Lab system Pro, Boston Scientific, Marlborough, MA, US) at a sweep speed of 200 mm/s. After the His bundle signal was identified, the lead was fixed by 3–5 clockwise rotations, and pacing from the lead tip was initiated. For the implant procedure to be considered successful, selective, or nonselective, His bundle capture had to be present during the pacing with a pacing output below 2.5 V at 1 ms.

RV septal pacing was performed using Tendril® (Abbott, Little Canada, MN, US) or Ingevity® (Boston Scientific, Marlborough, MA, US) pacing leads, preferably from the left subclavian approach. Once the lead was placed in the RV outflow tract/pulmonary artery, the stylet was pre-shaped, and the lead was fixed in the RV septum using the RAO projection and counter-clockwise torque on the leads' stylet. The lead tip septal position was verified in the RAO 30° and LAO 30° projections.

Echocardiography

Echocardiography assessments were performed one day before and six months after pacemaker implantation by three cardiac sonographers using a GE Vivid E95 Cardiovascular Ultrasound (Boston, MA, US). Two evaluators blinded to the studied groups measured and calculated end-diastolic and end-systolic volumes from the apical 4- and 2-chamber views, and LVEF was calculated using the formula: EF = ([LVEDV − LVESV] ÷ LVEDV) (modified Simpson's method) (definitions: EF, ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume). The mean value of LVEF calculated by each evaluator was used for statistical analyses.

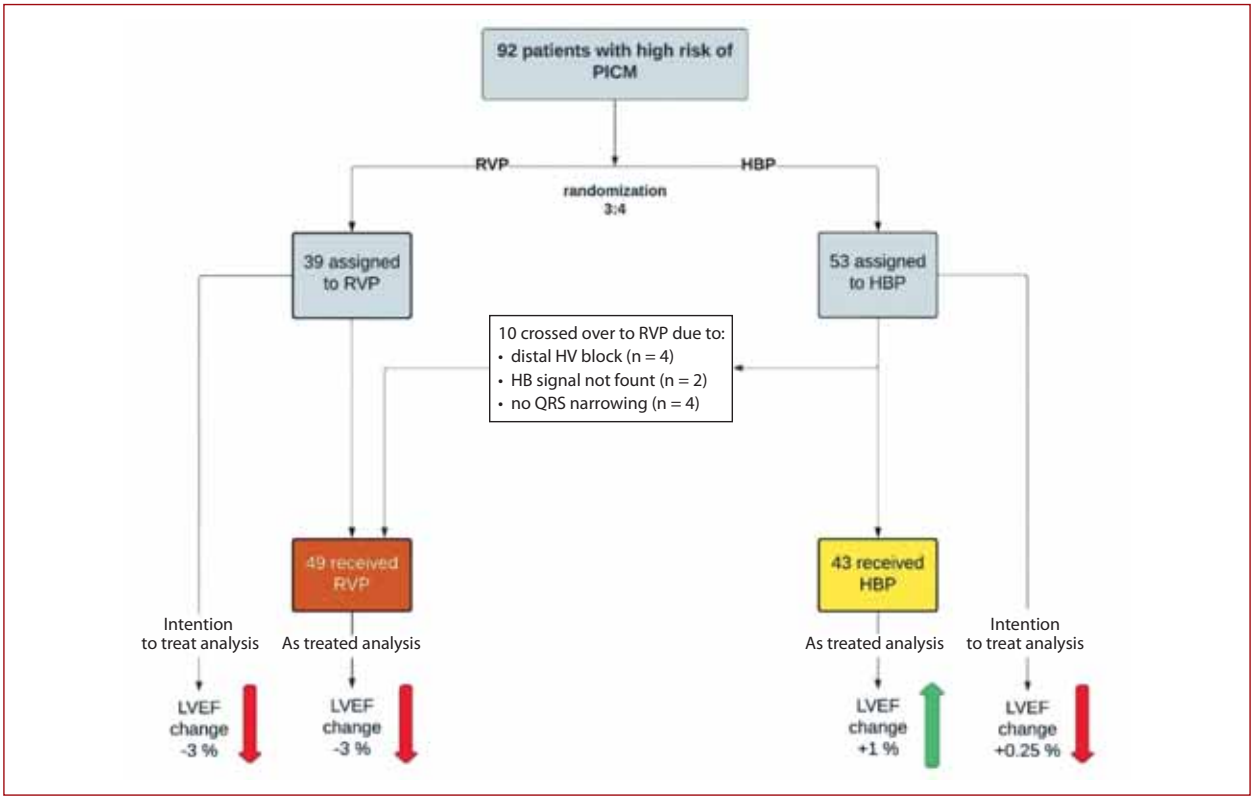
Blood sample collections and quantification of cytokines

Approximately four mL of peripheral venous blood were collected from each patient. Blood samples were centrifugated at 950 g for 20 minutes. Serum samples were aliquoted and stored at −80 °C. Samples were thawed before quantifying transforming growth factor β1 (TGF-β1), matrix metalloproteinase 9 (MMP-9), suppression of tumorigenicity 2 interleukin (ST2-IL), tissue inhibitor of metalloproteinase 1 (TIMP-1), and galectin 3 (Gal-3) levels. Per the manufacturer's instructions, the measurements of the selected biomarkers were performed using specific Quantikine ELISA kits (R&D Systems, Minneapolis, MN, US).

Statistical analysis

Statistical analysis was performed using Software: R version 4.0.5 (March 31, 2021). Exploratory data analysis was performed for all variables. Categorical data were presented as count with frequency and continuous data as mean with standard deviation (SD) or median with interquartile ranges (IQR) for nonparametric data. Kolmogorov and Smirnov tests were used for normality testing, and further statistical analysis included a linear mixed effect model with random intercept, Student's t-test, Fisher's exact test, and χ^2 test.

For the linear mixed effect model, the fixed part of the model is represented by the interaction between two binary parameters: stimulation site (His vs. septum) and visitation (Day 0 vs. Day 180). The random part of the model is represented by the random intercept, which is the patient identification number. A maximum likelihood estimator was used to fit models (function lmer of package lme4) [8]. Post-hoc analysis was performed using the emmeans package. Intention-to-treat and as-treated analyses were performed. For nonparametric data, the Wilcoxon test and Mann-Whitney U test were used. A $P<0.05$ was considered statistically significant. The area under the curve (AUC) of the receiver operating characteristic (ROC) curve was calculated for ST2-IL and Gal-3 to assess their predictive value for LVEF deterioration. The optimal cut points of both markers were calculated using maximization of the Youden index (sensitivity + [specificity − 1]). This was a pilot feasibility



Central illustration. Study flow-chart and the effect of right ventricular pacing and His bundle pacing on LVEF after six months of pacing in intention-to-treat and as-treated analyses

Abbreviations: HBP, His bundle pacing; LVEF, left ventricular ejection fraction; PICM, pacing-induced cardiomyopathy; RVP, right ventricular myocardial pacing

Table 1. Baseline clinical characteristics of the study population

	Intention-to-treat			As-treated		
	RVP (n = 39)	HBP (n = 53)	*P*-value	RVP (n = 49)	HBP (n = 43)	*P*-value
Age, years, mean (SD)	78 (7)	78 (8)	0.99	79 (7)	77 (8)	0.33
Male sex, n (%)	39 (80)	38 (88)	0.26	33 (85)	44 (83)	0.84
LVEF, %, mean (SD)	58 (7)	60 (5)	0.27	59 (6)	59 (4)	0.54
Arterial hypertension, n (%)	38 (97)	51 (96)	0.75	48 (98)	41 (95)	0.49
Diabetes mellitus, n (%)	16 (41)	20 (38)	0.75	18 (37)	18 (42)	0.62
CAD, n (%)	15 (38)	23 (43)	0.64	18 (37)	20 (47)	0.34
Myocardial infarction in history, n (%)	5 (14)	14 (27)	0.15	8 (17)	11 (26)	0.32
Spontaneous QRSd, ms,mean (SD)	126 (27)	125 (25)	0.80	126 (26)	126 (27)	0.98
Spontaneous QRS morphology, n (%)						
BBB	16 (41)	20 (38)	0.78	19 (39)	17 (40)	0.66
Narrow (<115 ms)	12 (31)	20 (38)		16 (33)	17 (40)	
NIVCD	11 (28)	13 (24)		14 (28)	9 (20)	
Pacing indication, n (%)						
AV block I. degree	5 (13)	7 (13)	0.95	6 (12)	6 (14)	0.94
AV block II. degree	16 (41)	25 (47)		21 (43)	20 (47)	
AV block III. degree	16 (41)	19 (36)		20 (41)	15 (35)	
BBB + syncope	2 (5)	2 (4)		2 (4)	2 (4)	

Abbreviations: AV block, atrioventricular block; BBB, bundle branch block; CAD, coronary artery disease; NIVCD, non-specific intraventricular conduction delay; other — see Central illustration

trial, and no power calculation was performed before the initiation of the study.

RESULTS

Ninety-two patients were enrolled in the study. The mean age was 78 years, and all had atrioventricular conduction disease as the pacing indication. Planned patient recruitment was not reached, and randomization was stopped due to challenges during the COVID-19 pandemic. Fifty-three patients were randomized to the His bundle pacing (HBP) group, and 39 were randomized to the right ventricular pacing (RVP) group. Lead placement in the HB region failed in 10 of 53 patients (19%) randomized to the HBP group. The lead was then successfully placed in the RV with myocardial capture in all patients. However, two of these patients (20%) required ventricular lead revision due to pacing threshold rise. The reasons for lead implant failure in the HB region were as follows: (1) in two patients, the HB signal was not found; (2) in four patients, the distal HV block could not be corrected by HB pacing; and (3) in four patients, pacing the HB region did not lead to conductive tissue capture with QRS narrowing. As a result, 49 patients had RVP (47 septal and two apical lead positions), and 43 had HBP. No difference in clinical characteristics was observed between groups relative to intention-to-treat and as-treated analyses (Table 1).

HBP required a longer fluoroscopy time (in intention-to-treat analysis), higher acute and chronic pacing thresholds, and presented with lower acute and chronic ventricular sensing than RVP. However, there was no difference in rates of lead repositions due to higher pacing thresholds between HBP and RVP groups (Table 2).

There was no difference between HBP and RVP groups in the preimplant LVEF in both intention-to-treat and as-treated comparisons. However, LVEF significantly decreased after six months of RVP but remained the same in the HBP group. Also, LVEF was significantly lower in the RVP group than in the HBP group after six months of follow-up in both as-treated (P <0.001) and intention-to-treat analysis (P = 0.008) (Figure 1).

A decline in LVEF ≥5% after six months of pacing was observed in 13 of 46 patients (28%) in the RVP group but in none in the HBP group. Among patients with RVP, a decline in LVEF ≥10% was observed in nine patients (20%); and in eight patients (17%), the resultant LVEF was ≤ 45% after six months of pacing.

There was no difference in baseline serum levels of TGF-β1, MMP-9, ST2-IL, TIMP-1, and Gal-3 between patients with HBP vs. patients with RVP (both as-treated and intention-to-treat comparison). In the RVP group, in an as-treated comparison, a significant decline in the levels of ST2-IL and TIMP-1 was observed after six months of pacing, but no difference in the serum levels of TGF-β1, MMP-9, and Gal-3 was detected. In the HBP group, a significant decline in the serum level of ST2-IL, MMP-9, and TGF-β1 was seen after six months of pacing; the levels of Gal-3 and TIMP-1 remained statistically the same. When comparing differences in serum levels of studied biomarkers between HBP and RVP patients six months after pacemaker implantation, the only difference was observed in the levels of TGF-β1, which were significantly lower in the HBP group than in the RVP group (Figure 2).

To determine whether cytokine levels before pacemaker implantation could predict an LVEF decline of ≥5%, we compared cytokine levels in patients with RVP and an LVEF decline of ≥5% (13 patients) vs. cytokine levels in patients with RVP and an LVEF decline < 5% (36 patients). Patients in both groups did not differ with respect to age, sex, pre-

Table 2. Procedural and follow-up pacing characteristics

		Intention-to-treat			As-treated		
		RVP	HBP	*P*-value	RVP	HBP	*P*-value
Pacing thresholds, V, at 0.4 ms, mean (SD)	D1	0.7 (0.3)	1.4 (0.6)	<0.001	0.8 (0.4)	1.5 (0.6)	<0.001
	D180	0.9 (0.6)	1.7 (1.1)	0.004	1.1 (0.7)	1.7 (1.1)	0.005
	D1 vs. D180 *P*-value	0.35	0.11		0.40	0.21	
Ventricular sensing, mV, mean (SD)	D1	9.4 (3.5)	4.5 (3.3)	<0.001	9.3 (3.7)	3.5 (2.0)	<0.001
	D180	9.5 (2.9)	4.3 (3.2)	<0.001	9.3 (3.1)	3.2 (2.0)	<0.001
	D1 vs. D180 *P*-value	0.91	0.75		0.98	0.54	
Fluoroscopy time, sec, median (IQR)		242 (171–413)	505 (270–835)	<0.001	329 (190–553)	399 (249–679)	0.34
Burden of ventricular pacing after 180 days, mean (SD)		92 (18)	98 (4)	0.02	95 (17)	98 (4)	0.09
Threshold rise requiring lead revision, n (%)		2 (5)	4 (8)	0.64	4 (8)	2 (5)	0.50

Abbreviations: see Central Illustration

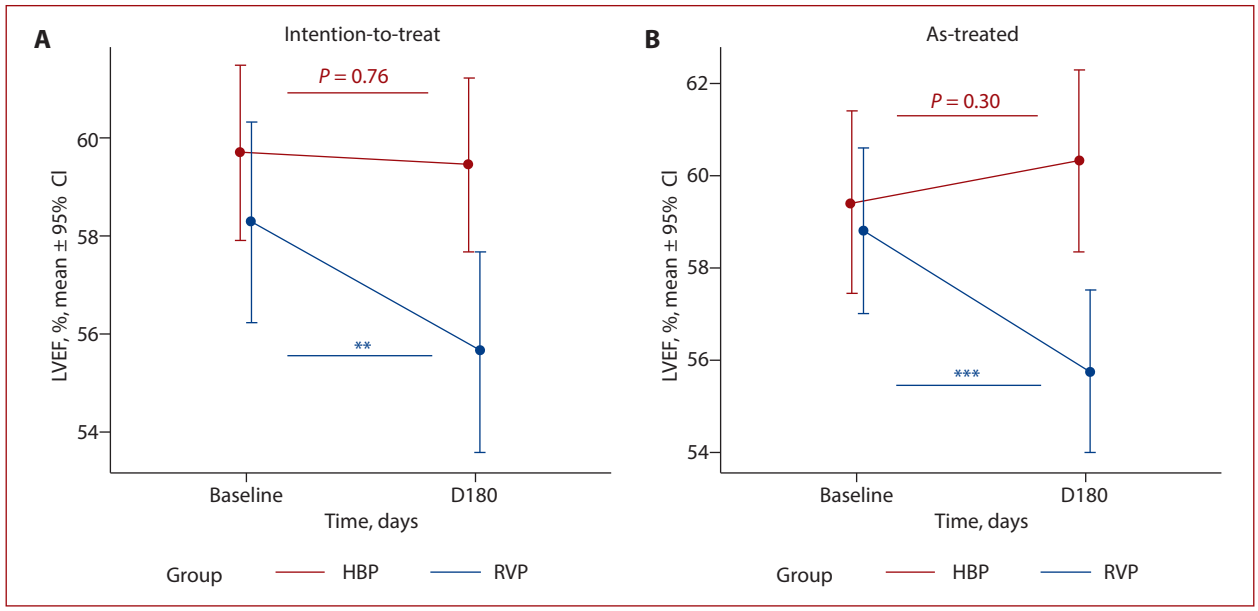


Figure 1. Comparison of LVEF in the HBP and RVP groups using per intention-to-treat (**A**) and as-treated (**B**) analyses
***P* <0.01. ****P* <0.001

Abbreviations: see Central illustration

implant LVEF, QRS duration during spontaneous rhythm, the prevalence of CAD, myocardial infarction, hypertension, or diabetes mellitus.

Patients with an LVEF decline of ≥ 5% after six months of RVP had higher baseline levels of Gal-3 and ST2-IL. After six months, the elevations of both markers persisted and were higher than in patients with an LVEF decline of < 5% in the primary analysis and also after adjustment to the baseline levels of both molecules (Figure 3 and Supplementary material, *Figure S1*). During RVP, a decline in TIMP-1 was observed in patients without deterioration of LVEF (P = 0.04). No difference in serum levels of the other studied biomarkers was found before and after six months of RVP (Figure 3). The ROC analysis showed an AUC of 0.79 for Gal-3 and 0.71 for ST2-IL relative to the prediction of a decline in LVEF ≥5% (Figure 4). Gal-3 serum concentrations ≥8.88 ng/ml were 100% sensitive and 61% specific, with a positive predictive value of 45%, a negative predictive value of 100%, and an accuracy of 72%; ST2-IL concentrations ≥19 ng/ml showed 90% specificity and 52% specificity, with a positive predictive value of 38%, a negative predictive value of 94%, and an accuracy of 71% for detection of patients with a decline in LVEF ≥5% after six months of RV pacing.

In the HBP group, patients with higher baseline Gal-3 (>8.88 ng/ml) and ST2-IL (>19 ng/ml) levels did not differ in LVEF change after 6 months of follow-up in comparison to patients with lower baseline Gal-3 and ST2-IL levels (LVEF change 1 vs. 1% and 1 vs. 1%; P = 0.66 and P = 0.72, respectively).

DISCUSSION

This study compared the effect of His bundle pacing and RV myocardial pacing on LVEF in patients at high risk of pacing-induced cardiomyopathy. Also, this is the first trial studying fibrosis biomarkers in patients with pacemak-

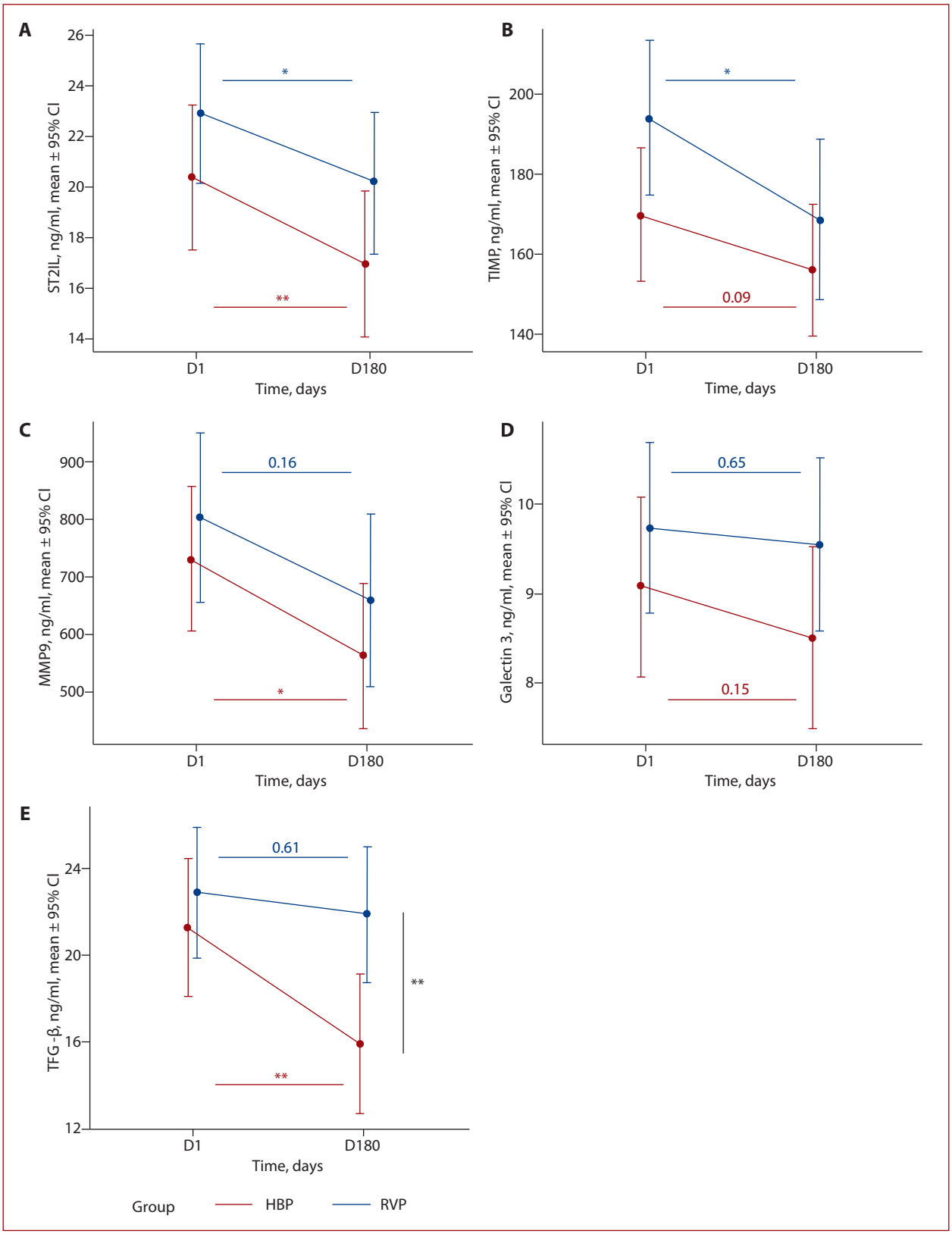


Figure 2. Comparison of serum levels of ST2-IL, TIMP-1, MMP-9, galectin 3, and TGF-β1 at baseline and after six months of pacing in the HBP vs. RVP groups per as-treated analysis
*P <0.05. **P <0.01

Abbreviations: MMP-9, matrix metalloproteinase-9; ST2-IL, suppression of tumorigenicity 2 interleukin; TGF-β1, transforming growth factor β1; TIMP-1, tissue inhibitor of metalloproteinase-1; other — see Central illustration

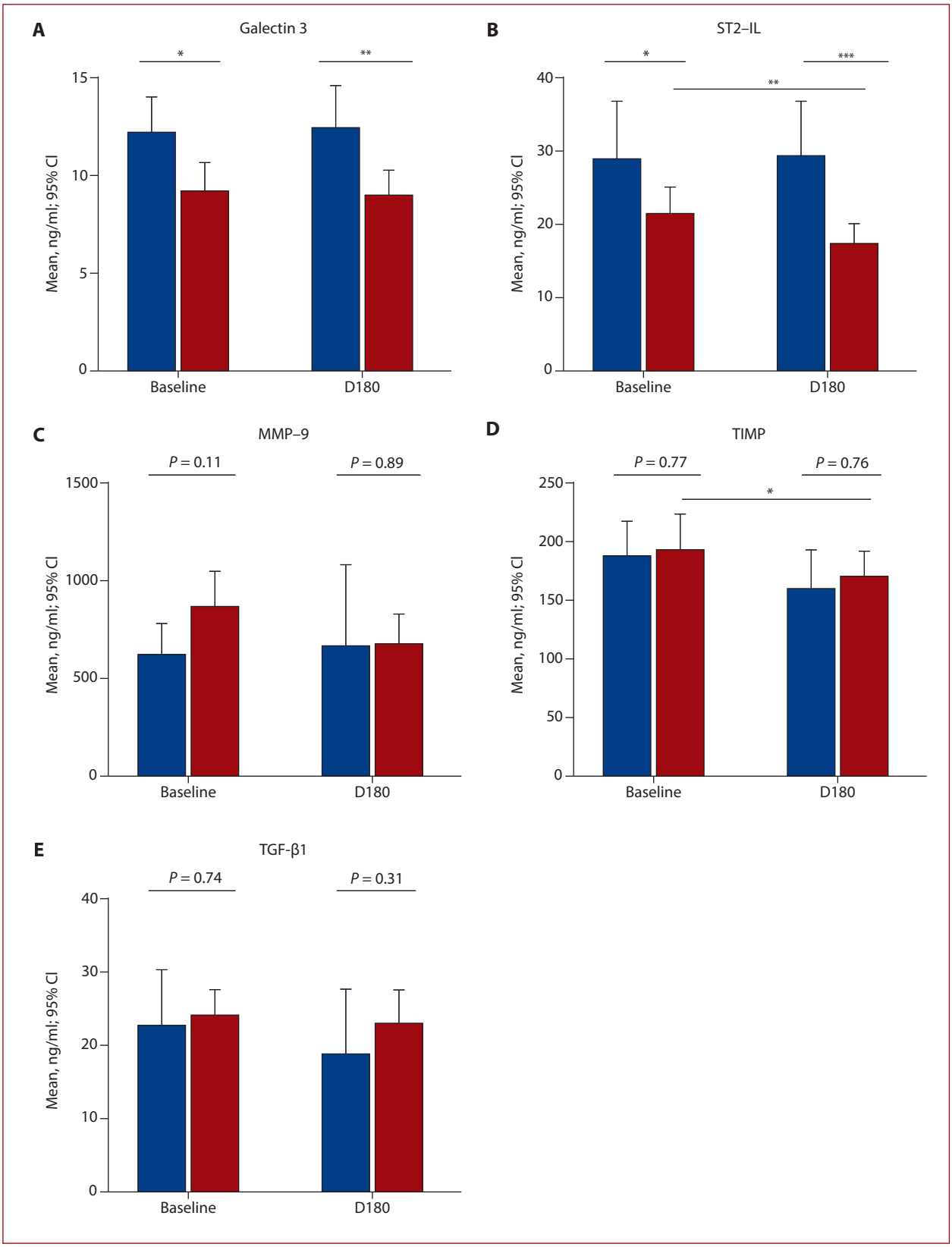


Figure 3. Comparison of serum levels of galectin 3, ST2-IL, MMP-9, TIMP-1, and TFG-β1 before implant and after six months of pacing in patients with RVP and preserved LVEF vs. patients with reduced LVEF by ≥5%

Abbreviations: see Central illustration and Figure 2

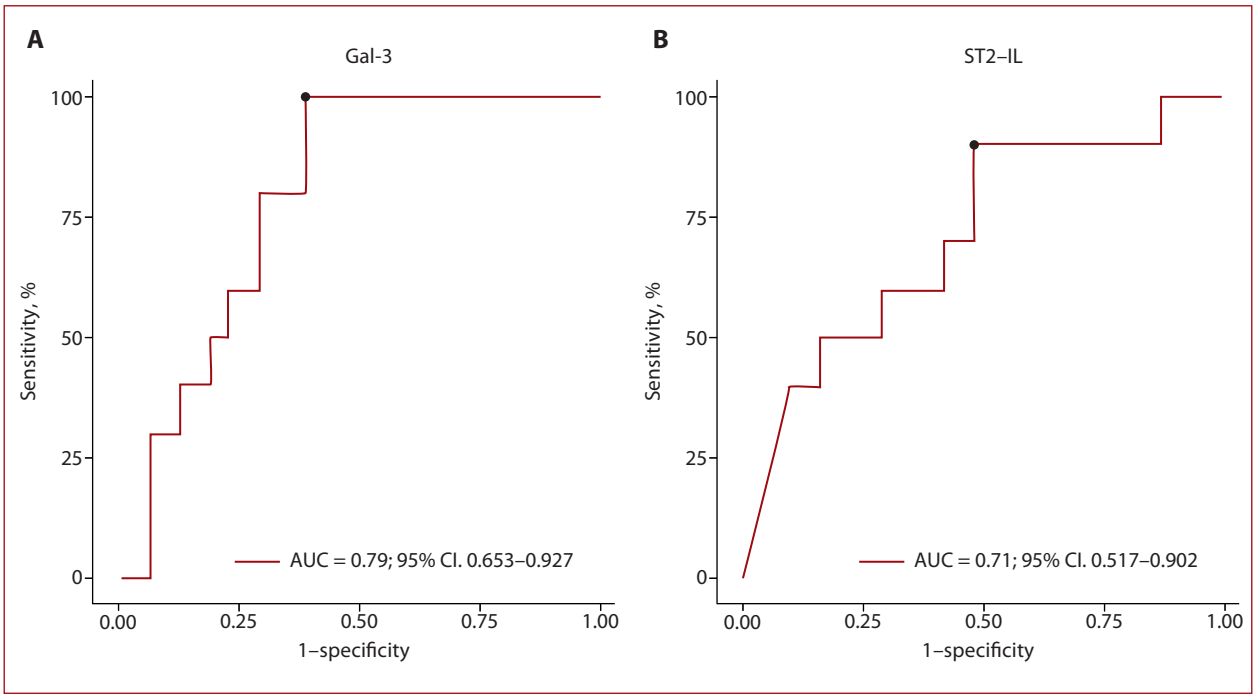


Figure 4. Receiver operating characteristic (ROC) curves of galectin 3 (**A**) and ST2-IL (**B**) in patients with and without decrease in LVEF of ≥5% after six months of RVP

Abbreviations: see Central illustration and Figure 2

ers. We showed that the adverse effect on LV function with a LVEF decline of ≥5% after pacing was not uncommon and affected almost one-third of patients with RV pacing, with LVEF falling below 45% in 17% of patients in that group. On the other hand, HBP preserved LV function in all patients. We also showed that initiation of permanent cardiac pacing resulted in changes in the serum levels of some of the studied biomarkers, with serum TGF-β1 levels reflecting different ventricular activation during HBP and RVP. Lastly, patients with a decline in LVEF of ≥5% due to non-physiological RV pacing had significantly higher serum levels of Gal-3 and ST2-IL than patients with a <5% decline in LVEF, both at the baseline and after six months of RV pacing.

HBP vs. RVP

His bundle pacing is well established, and guidelines support the treatment option in selected patients with bradycardia [9]. However, data from randomized trials supporting its use in a wider spectrum of patients are missing. So far, only one randomized trial comparing His bundle pacing to right ventricular septal pacing in patients with conduction disease has been published [10]. It used a crossover design, with HBP and RV pacing being utilized in the same patients for 12 months, and the number of randomized patients was small. Moreover, the studied population differed from our group, e.g., it only had patients with narrow QRS complexes (the average was 93 ms), and most were without coronary artery disease. The study showed that HBP preserved LVEF and ventricular synchrony better than right ventricular septal pacing, which resulted in a significant decline in LVEF (mean decline of 4 ± 1%). A similar level of LVEF deterioration during RVP occurred in a shorter period in our study; possibly reflecting the higher risk profile of our patients. Coronary artery disease was present in one-third of our patients, and the average QRS duration was 126 ms; both have been associated with higher risk of adverse LV remodeling during pacing [1]. Considering the relationship between the severity of the LVEF decline and the duration of non-physiological RV pacing, it is possible that the difference in LVEF between HBP and RVP patients would be even greater with a longer follow-up. In our study, a ≥5% decrease in LVEF was seen only in patients with RV pacing. Although a 5% decline in LVEF could be considered clinically negligible, it was previously shown that patients who demonstrate a slight decrease in LVEF soon after the pacemaker implantation were at the highest risk of further PICM [11]. PICM is often defined as a decline in LVEF of more than 10% and/or LVEF <50% [1]. Using this definition, 20 % of patients in our high-risk population developed PICM after six months of pacing. This agrees with the numbers reported by other investigators; however, PICM occurred later after pacemaker implantation than in our study [1].

The difference in serum levels of studied cytokines between HBP and RVP

In patients with bradycardia and pacemaker implantation, we studied serum levels of collagen metabolism and fibrosis biomarkers, which were already shown to play a role in adverse ventricular remodeling in different clinical sce-

narios [12–15]. Right ventricular myocardial pacing leads to non-physiological ventricular activation with adverse remodeling and LVEF deterioration in some patients [7]. These changes should be reflected in serum levels of biomarkers of fibrosis although they have yet to be studied in patients with pacemakers. We showed that cardiac pacing (HBP or RVP) led to a decline in the serum levels of some of the studied cytokines; however, after six months of pacing, the groups differed only in the levels of TGF-β1. TGF-β1 is a pleiotropic cytokine critically involved in cardiac injury, repair, remodeling, and fibrogenesis. It also exerts potent matrix-preserving actions by suppressing the activity of MMPs and by inducing the synthesis of protease inhibitors, such as TIMP-1. Elevated TGF-β1 levels in experimental vivo models of heart failure were associated with increased myocardial stiffness, fibrosis, and LV diastolic dysfunction [16]. We found that TGF-β1 declined after the institution of HBP but remained the same in RVP patients. This may reflect normalization of atrioventricular synchrony with truly physiological ventricular activation in HBP patients [17]. In RVP patients, AV synchrony was also normalized, but at the cost of non-physiological ventricular activation due to RV pacing, which is associated with worsening LV diastolic function [18].

New pacing strategies, such as His bundle pacing and left bundle branch area pacing, reduce the risk of adverse LV remodeling and heart failure in bradycardia patients [3, 19]. However, because they are more complex, the techniques may be best suited for those with the highest risk of LVEF deterioration after RVP. This remains a challenge because we still cannot accurately predict which patients will have a decline in LVEF due to RVP. Our theory was that the detrimental effect of RVP would be seen mostly in patients susceptible to the harmful effect of RV pacing, i.e., with pre-existing conditions, such as increased myocardial fibrosis, which could be reflected in serum levels of studied biomarkers. Therefore, we compared these biomarkers in patients with an LVEF decline of ≥5% vs. those with preserved LVEF during RVP (i.e., <5%). The only cytokines that showed different preimplant levels were Gal-3 and ST2-IL, both known as prognostic biomarkers in heart failure patients and involved in collagen metabolism and ventricular remodeling [14, 15]. Data on their significance in patients with pacemakers are scarce. However, it was already shown that higher preimplant Gal-3 levels were negatively associated with response to cardiac resynchronization therapy and higher levels of myocardial fibrosis in ventricular myocardium, as seen on preimplant cardiac magnetic resonance [20]. It is possible that increased levels of Gal-3 and ST2-IL in our patients with a more significant decline in LVEF during RVP reflected a higher degree of pre-implant myocardial fibrosis, which led to a more deleterious effect of RV pacing on LV performance. On the other hand, patients without significant myocardial fibrosis have a greater ability to compensate for dyssynchronous ventricular activation during RVP while maintaining LVEF.

Limitations

This was a single-center study with echocardiographic follow-up restricted to six months, which prohibited tracking LVEF changes and clinical outcomes over a more extended period. Potential bias could have been present during the evaluation of echocardiographic measurements. Although the evaluator was blinded to the randomization of patients to the studied groups, the position of the pacing lead in the His bundle or RV septal region could be seen during the evaluation. An LVEF decline of 5%, which was used to compare groups, is relatively small and difficult to measure precisely, especially in patients with LV dyssynchrony due to pacing. The burden of ventricular pacing was taken from the programmer's printouts, and we did not study the incidence of fused pacing beats during Holter-ECG monitoring, which could lead to a higher burden of ventricular pacing as was, in fact, present. Finally, the number of patients in the RVP group and, more specifically, those with a decline in LVEF after pacing was small, preventing more robust conclusions about the PICM prediction based on specific levels of studied molecules.

CONCLUSIONS

In patients at high risk of PICM, right ventricular pacing led to a decline in LVEF compared to His bundle pacing, which preserved LV function after six months of pacing. Gal-3 and ST2-IL have the potential to better identify patients in whom right ventricular pacing does not pose a significant risk. Further studies with more patients, longer follow-up, and clinical endpoints are needed to verify their predictive value relative to pacing-induced cardiomyopathy.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: None declared.

Funding: This paper was supported by the Charles University Research Center program Cooperatio–Cardiovascular Science, National Institute for Research of Metabolic and Cardiovascular Diseases (Programme EXCELES, ID Project No. LX22NPO5104) – funded by the European Union – Next Generation EU and Ministry of Health of the Czech Republic, grant number NU21-02-00584 [to KC].

REFERENCES

1. Khurshid S, Epstein AE, Verdino RJ, et al. Incidence and predictors of right ventricular pacing-induced cardiomyopathy. Heart Rhythm. 2014; 11(9): 1619–1625, doi: 10.1016/j.hrthm.2014.05.040, indexed in Pubmed: 24893122.
2. Curila K, Jurak P, Halamek J, et al. Ventricular activation pattern assessment during right ventricular pacing: Ultra-high-frequency ECG study. J Cardiovasc Electrophysiol. 2021; 32(5): 1385–1394, doi: 10.1111/jce.14985, indexed in Pubmed: 33682277.
3. Abdelrahman M, Subzposh FA, Beer D, et al. Clinical outcomes of his bundle pacing compared to right ventricular pacing. J Am Coll Cardiol. 2018; 71(20): 2319–2330, doi: 10.1016/j.jacc.2018.02.048, indexed in Pubmed: 29535066.
4. Vijayaraman P, Herweg B, Dandamudi G, et al. Outcomes of His-bundle pacing upgrade after long-term right ventricular pacing and/or pacing-induced cardiomyopathy: Insights into disease progression. Heart Rhythm. 2019; 16(10): 1554–1561, doi: 10.1016/j.hrthm.2019.03.026, indexed in Pubmed: 30930330.
5. Dreger H, Maethner K, Bondke H, et al. Pacing-induced cardiomyopathy in patients with right ventricular stimulation for >15 years. Europace. 2012; 14(2): 238–242, doi: 10.1093/europace/eur258, indexed in Pubmed: 21846642.
6. Fang F, Zhang Q, Chan JYS, et al. Early pacing-induced systolic dyssynchrony is a strong predictor of left ventricular adverse remodeling: analysis from the Pacing to Avoid Cardiac Enlargement (PACE) trial. Int J Cardiol. 2013; 168(2): 723–728, doi: 10.1016/j.ijcard.2012.08.005, indexed in Pubmed: 22944596.
7. Ahmed FZ, Khattar RS, Zaidi AM, et al. Pacing-induced cardiomyopathy: pathophysiological insights through matrix metalloproteinases. Heart Fail Rev. 2014; 19(5): 669–680, doi: 10.1007/s10741-013-9390-y, indexed in Pubmed: 23856884.
8. Bates D, Mächler M, Bolker B, et al. Fitting linear mixed-effects models using lme4. Journal of Statistical Software. 2015; 67(1), doi: 10.18637/jss.v067.i01.
9. Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2019; 140(8): e382–e482, doi: 10.1161/CIR.0000000000000628, indexed in Pubmed: 30586772.
10. Kronborg MB, Mortensen PT, Poulsen SH, et al. His and para-His pacing in AV block: feasibility and electrocardiographic findings. J Interv Card Electrophysiol. 2011; 31(3): 255–262, doi: 10.1007/s10840-011-9565-1, indexed in Pubmed: 21465234.
11. Chan JYS, Fang F, Zhang Q, et al. Biventricular pacing is superior to right ventricular pacing in bradycardia patients with preserved systolic function: 2-year results of the PACE trial. Eur Heart J. 2011; 32(20): 2533–2540, doi: 10.1093/eurheartj/ehr336, indexed in Pubmed: 21875860.
12. Morishita T, Uzui H, Mitsuke Y, et al. Association between matrix metalloproteinase-9 and worsening heart failure events in patients with chronic heart failure. ESC Heart Fail. 2017; 4(3): 321–330, doi: 10.1002/ehf2.12137, indexed in Pubmed: 28772055.
13. Dobaczewski M, Chen W, Frangogiannis NG. Transforming growth factor (TGF)-β signaling in cardiac remodeling. J Mol Cell Cardiol. 2011; 51(4): 600–606, doi: 10.1016/j.yjmcc.2010.10.033, indexed in Pubmed: 21059352.
14. Imran TF, Shin HJ, Mathenge N, et al. Meta-Analysis of the Usefulness of Plasma Galectin-3 to Predict the Risk of Mortality in Patients With Heart Failure and in the General Population. Am J Cardiol. 2017; 119(1): 57–64, doi: 10.1016/j.amjcard.2016.09.019, indexed in Pubmed: 28247849.
15. Aimo A, Vergaro G, Passino C, et al. Prognostic Value of Soluble Suppression of Tumorigenicity-2 in Chronic Heart Failure: A Meta-Analysis. JACC Heart Fail. 2017; 5(4): 280–286, doi: 10.1016/j.jchf.2016.09.010, indexed in Pubmed: 27816512.
16. Brooks WW, Conrad CH. Myocardial fibrosis in transforming growth factor beta(1)heterozygous mice. J Mol Cell Cardiol. 2000; 32(2): 187–195, doi: 10.1006/jmcc.1999.1065, indexed in Pubmed: 10722796.
17. Pastore G, Aggio S, Baracca E, et al. Hisian area and right ventricular apical pacing differently affect left atrial function: an intra-patients evaluation. Europace. 2014; 16(7): 1033–1039, doi: 10.1093/europace/eut436, indexed in Pubmed: 24473501.
18. Fang F, Zhang Q, Chan JYS, et al. Deleterious effect of right ventricular apical pacing on left ventricular diastolic function and the impact of pre-existing diastolic disease. Eur Heart J. 2011; 32(15): 1891–1899, doi: 10.1093/eurheartj/ehr118, indexed in Pubmed: 21531741.
19. Sharma PS, Patel NR, Ravi V, et al. Clinical outcomes of left bundle branch area pacing compared to right ventricular pacing: Results from the Geisinger-Rush Conduction System Pacing Registry. Heart Rhythm. 2022; 19(1): 3–11, doi: 10.1016/j.hrthm.2021.08.033, indexed in Pubmed: 34481985.
20. Andre C, Piver E, Perault R, et al. Galectin-3 predicts response and outcomes after cardiac resynchronization therapy. J Transl Med. 2018; 16(1): 299, doi: 10.1186/s12967-018-1675-4, indexed in Pubmed: 30390680.

Safety and feasibility of minimally invasive coronary artery bypass surgery early after drug-eluting stent implantation due to acute coronary syndrome

Krzysztof Sanetra[1, 2], Piotr P Buszman[3–5], Justyna Jankowska-Sanetra[4], Marta Konopko[3], Monika Slabon-Turska[6], Krzysztof Białek[2, 7], Krzysztof Milewski[4, 5, 8], Witold Gerber[2, 7], Andrzej Bochenek[2, 5, 7], Mateusz Kachel[1, 2, 5], Paweł Kaźmierczak[9], Paweł E Buszman[10], Marek Cisowski[11]

[1]Division of Cardiovascular Surgery, Andrzej Frycz Modrzewski Krakow University, Kraków, Poland
[2]Department of Cardiac Surgery, American Heart of Poland, Bielsko-Biała, Poland
[3]Department of Cardiology, Andrzej Frycz Modrzewski Krakow University, Kraków, Poland
[4]Department of Cardiology, American Heart of Poland, Bielsko-Biała, Poland
[5]Center for Cardiovascular Research and Development, American Heart of Poland, Katowice, Poland
[6]Department of Gynecology and Obstetrics, Holy Family Hospital, Warszawa, Poland
[7]Department of Cardiac Surgery, Academy of Silesia, Katowice, Poland
[8]Department of Cardiology, Academy of Silesia, Katowice, Poland
[9]American Heart of Poland, Katowice, Poland
[10]Department of Epidemiology, Medical University of Silesia, Katowice, Poland
[11]Department of Cardiac Surgery, University Hospital, Institute of Medical Sciences, University of Opole, Opole, Poland

Correspondence to:
Krzysztof Sanetra, MD, PhD, Department of Cardiac Surgery, American Heart of Poland, Armii Krajowej 101, 43–316 Bielsko-Biała, Poland, phone: +48 692 030 003, e-mail: krzyssan@poczta.onet.pl

DOI: 10.33963/KP.a2023.0066

Received:
November 5, 2022

Accepted:
March 3, 2023

Early publication date:
March 9, 2023

ABSTRACT

Background: The evidence on performing minimally invasive coronary artery surgery early after drug-eluting stent (DES) implantation due to acute coronary syndrome (ACS) is limited.

Aim: The study aimed to determine the safety and feasibility of this approach.

Methods: This registry included 115 (78% male) patients treated from 2013 to 2018, who underwent non-left anterior descending (LAD) percutaneous coronary intervention (PCI) due to ACS with contemporary DES implantation (39% diagnosed with myocardial infarction at baseline), followed by endoscopic atraumatic coronary artery bypass (EACAB) surgery within 180 days, after temporary $P2Y_{12}$ inhibitor discontinuation. Primary composite endpoint of MACCE (major adverse cardiac and cerebrovascular events), defined as death, myocardial infarction (MI), cerebrovascular incident, and repeat revascularization was evaluated in long-term follow-up. The follow-up was collected via a telephone survey and in line with National Registry for Cardiac Surgery Procedures.

Results: The median (interquartile range [IQR]) time interval separating both procedures was 100.0 (62.0–136.0) days. Median (IQR) follow-up duration was 1338.5 (753.0–2093.0) days and was completed for all patients with regard to mortality. Eight patients (7%) died; 2 (1.7%) had a stroke; 6 (5.2%) suffered from MI, and 12 (10.4%) required repeat revascularization. Overall, the incidence of MACCE was 20 (17.4%).

Conclusions: EACAB is a safe and feasible method of LAD revascularization in patients who received DES for ACS within 180 days before surgery despite early dual antiplatelet therapy discontinuation. The adverse event rate is low and acceptable.

Key words: antiplatelet, acute coronary syndrome, EACAB, hybrid, MIDCAB

WHAT'S NEW?

The evidence on use of the surgical approach after temporary withdrawal of dual antiplatelet therapy in patients who received drug-eluting stent (DES) for acute coronary syndrome treatment is limited. In the current study, we evaluate a cohort of patients who underwent percutaneous revascularization for acute coronary syndrome and were referred for endoscopic, atraumatic coronary artery bypass grafting (EACAB) as a second stage of revascularization in a maximal time interval of 180 days. The occurence of the composite endpoint of MACCE (major adverse cardiac and cerebrovascular events), defined as death, myocardial infarction, cerebrovascular incident, and repeat revascularization was evaluated. Despite temporary withdrawal of $P2Y_{12}$ inhibitor before surgery, the long-term outcomes were satisfactory in this group, presenting a 17.4% occurrence rate of MACCE in a median follow-up of 1338.5 days (3.7 years). As such, EACAB is a safe and feasible method of revascularization in patients who received DES within 180 days before the surgery.

INTRODUCTION

The definition of hybrid coronary revascularization is not well established, but it surely addresses the initially planned strategy of performing concomitant or staged surgical and percutaneous revascularization. When considering the hybrid strategy, most studies refer to sternal-sparing surgical procedures, such as minimally invasive direct coronary artery bypass grafting (MIDCAB), endoscopic atraumatic coronary artery bypass grafting (EACAB), or totally endoscopic coronary artery bypass grafting (TECAB). Some reports consider traditional full-sternotomy OPCAB (off-pump coronary artery bypass grafting) surgery with full sternotomy as a stage of planned hybrid procedure as well. Although the definition of hybrid treatment is unclear, there is a group of patients that seems to be beyond its scope.

In many acute coronary syndrome cases (ACS), particularly myocardial infarction (MI), direct revascularization of the infarct-related artery is of the highest priority. Those patients often undergo successful percutaneous treatment. The procedure is urgent, and it is acceptable not to gather a Heart Team to treat the target lesions. Other arteries with significant stenosis need a decision on a further strategy.

If complementary left anterior descending (LAD) revascularization is required, those subjects may be referred to a cardiac surgeon for minimally invasive bypass grafting with the use of the left internal thoracic artery (LITA). In such cases, a decision to merge percutaneous and surgical procedures is made after the first stage of treatment. However, such a strategy requires temporary $P2Y_{12}$ inhibitor withdrawal, which still generates doubts regarding increased perioperative and long-term risk of adverse cardiovascular events.

Clinical guidelines underline the efficacy of coronary artery bypass grafting (CABG) as a treatment for multivessel coronary artery disease and the essential role of LITA-LAD (left internal thoracic artery-left anterior descending) bypass graft [1]. This role was the basis for the development of minimally invasive approaches, such as EACAB.

It must be noted that the classic CABG procedure has its drawbacks. Firstly, saphenous vein grafts have limited patency and may be inferior to new-generation drug-eluting stents. Furthermore, the risk of various wound complications associated with sternotomy is estimated at 0.4%–8.0% [2–4]. A minimally invasive approach may reduce morbidity, pain, scarring, and recovery time when compared to classic bypass grafting with sternotomy. The EACAB procedure with the use of endoscopic internal thoracic artery harvesting provides optimal quality and long-term patency of LITA-LAD grafts [5].

When a significant lesion is diagnosed in the LAD during percutaneous revascularization of other arteries, which are infarct-related, the proper timing of surgical LAD treatment remains a matter of debate. Some studies referring to hybrid revascularization report an interval of a few hours separating the procedures as optimal while others consider a 180-day interval acceptable [6]. However, no reports refer to hybrid revascularization of acute coronary syndrome cases. Regardless, early temporary withdrawal of the $P2Y_{12}$ inhibitor is required for the surgical stage of revascularization.

This study aimed to determine the safety and feasibility of minimally invasive coronary artery bypass surgery early after drug-eluting stent implantation due to acute coronary syndrome.

METHODS

Patients

Consecutive patients initially hospitalized in our center (Center of Cardiology and Cardiac Surgery, American Heart of Poland, Bielsko-Biała) for ACS in the years 2013––2018 were eligible for treatment and retrospective analysis if they had met several criteria based on the Heart Team assessment. First, the arterial anatomy and distribution of lesions were verified by both a cardiologist and a cardiac surgeon (LAD needed to be suitable for bypass grafting and other diseased arteries for PCI). Furthermore, patients were eligible for endoscopy-assisted CABG based on anatomy (severe obesity excludes patients) and medical course (patients with pleural adhesions, after chest radiation, and with severe respiratory disease and no option to ventilate

only one lung were excluded). Notably, in acute MI, Heart Team's assessment was not mandatory for the treatment of infarct-related artery; in those cases, Heart Team consultation following the percutaneous procedure was acceptable. Consent for surgical treatment was required at the time of the assessment by the Heart Team. Finally, the urgency of LAD revascularization was taken into consideration; we aimed to continue dual antiplatelet therapy without interruption for at least 2 months (preferably 3 months, if possible). In all other cases, different revascularization options were considered. Every case was treated individually to choose the optimal protocol for each patient.

The acceptable maximal time interval separating both procedures was 180 days. Consequently, patients who exceeded this timeframe were excluded from the analysis. Patients who underwent revascularization of LAD as an ACS-related artery or an unsuccessful attempt at LAD revascularization as a single procedure or did not receive drug-eluting stents (DES) for non-LAD revascularization were excluded. There were no further exclusion criteria, as both the number of treated vessels and device selection are highly dependent on the patient and the procedure itself.

Procedures

Percutaneous revascularization: percutaneous revascularization of the acute coronary syndrome-related artery was conducted in a hemodynamic room, urgently after admission to the cardiac department. All the patients had significant LAD stenosis based on angiography, which was evaluated by the entire Heart Team. The decision on whether to proceed with functional assessment of the LAD stenosis was based on Heart Team consultation. In the entire cohort, 22 (19.1%) patients had fractional flow reserve (FFR)/instantaneous wave-free ratio (iFR) confirming LAD stenosis.

EACAB surgery: each patient underwent EACAB surgery with the use of a thoracoscope for internal mammary harvesting and left anterolateral mini-thoracotomy for LITA-LAD anastomosis. After entering the operating room and induction of anesthesia, each patient was intubated with a double-lumen endotracheal tube. After positioning (the patient was slightly elevated on the left side with a suspension of the left arm), single right lung ventilation was initiated. The 3rd (anterior axillary line), 5th (medial axillary line), and 7th (anterior axillary line) intercostal spaces were used for port introduction. The LITA was harvested using a harmonic blade (Ethicon, Bridgewater, NJ, US) under endoscopic vision (Karl Storz, Tuttlingen, Germany). Before LITA clipping, heparin was given in a dose of 1.5 mg/kg. Target-activated clotting time (ACT) was 200–300 seconds. Left anterolateral mini-thoracotomy was made to expose the LAD. The LITA-LAD anastomosis was made using a continuous 8.0 Prolene suture during epicardial LAD stabilization (Octopus Nuvo stabilizer; Medtronic, Minneapolis, MN, US).

Procedure hospitalization

Percutaneous procedure: Blood pressure, saturation, electrocardiogram, and diuresis monitoring were conducted for 24 hours after the procedure. Dual antiplatelet therapy was initiated before the stenting procedure, and $P2Y_{12}$ antagonists were used obligatorily. Echocardiography was performed before (if possible) and after the procedure. The patient was usually discharged two or three days following an uncomplicated procedure.

Surgical procedure: No control coronary angiography was performed routinely after the percutaneous procedure. Clopidogrel or ticagrelor were withdrawn 5 or 3 days before the surgical treatment, respectively. None of the patients received prasugrel. No heparin bridging therapy was administered routinely. However, in case of need for oral anticoagulation, the patients were switched to a low-molecular-weight heparin instead of their oral medication 7 days before surgery. Aspirin treatment was not discontinued before surgery. The EACAB procedure was performed on the second day following admission to the hospital. After surgery, constant invasive blood pressure, saturation, electrocardiogram (ECG) diuresis, and drainage monitoring was conducted for 48 hours. Dual antiplatelet therapy was initiated on the first day following surgery and maintained for at least one year from the percutaneous procedure. A chest X-ray was done after surgery and after 24 hours following surgery after removal of the chest tube. Control echocardiography was performed 48 hours after the procedure and whenever it was indicated in accordance with the patient's clinical status. The patients were discharged to the rehabilitation department for rehabilitation and 30-day follow-up.

Follow-up

On their admission to the hospital, the patients gave their consent for data processing and long-term follow-up evaluation as a part of quality assessment for hospital recognition purposes. Therefore, a telephone survey database was created and analyzed to assess the outcome and primary endpoint in this group of patients. Whenever the patient was unavailable, a person authorized by the patient was contacted. In addition, the National Registry for Cardiac Surgery Procedures. was checked to obtain 100% follow-up regarding mortality.

Research ethics board consent

No formal ethical approval was necessary for the quantitative part of the study. The report was a dataset analysis, the data were readily available and did not include any interventions for the patients or participants. The patients gave their permission for data processing for clinical and scientific purposes upon their admission to the hospital.

Primary endpoints

Progression towards the composite endpoint of MACCE (major adverse cardiac and cerebrovascular events), de-

fined as death, MI, stroke, and repeat revascularization, was evaluated through both hospitalization and long-term follow-up.

Secondary endpoints

Secondary endpoints included hospitalization complications (atrial fibrillation; kidney injury which was defined in accordance with RIFLE [Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease] classification criteria as 2-fold postoperative creatine raise; fall in ejection fraction; cardiac biomarker release after surgical treatment).

Statistical analysis

The data were presented as numbers (percentages) or medians (interquartile range [IQR]). The chi-square test was used for categorical data comparison. Kaplan-Maier curves for MACCE and its components were used to determine mortality and morbidity in the long-term follow-up. The log-rank test was used to compare Kaplan-Meier estimates in subgroups. The *P*-value <0.05 was considered to be statistically significant. The data were analyzed using MedCalc v.18.5 (MedCalc Software, Ostend, Belgium).

Data availability statement

The data discussed in this article will be shared on reasonable request to the corresponding author.

RESULTS

In the years 2013–2018, there were 2364 unstable angina hospital admissions, 1841 non-ST-segment elevation MI (NSTEMI) admissions, and 998 ST-segment elevation MI (STEMI) admissions. Among those cases, 1257 unstable angina patients (53.2%), 1196 NSTEMI cases (64.9%), and 513 (51.4%) STEMI cases had significant LAD stenosis treated invasively (2966 cases). The current study reports on 3.9% of those patients.

The patient baseline characteristics were typical of a population with multivessel coronary artery disease (Table 1). All of them underwent percutaneous ACS target vessel revascularization and received drug-eluting stents. Before EACAB surgery, a median left ventricular ejection fraction was 55% (Table 2).

We did not notice any cases of MI, stroke, or death between the procedures in the analyzed group. However, two patients were hospitalized for NSTEMI while being on the list for EACAB, which caused a change in the initial strategy and their referral to other treatments whereby they were excluded from further analysis (this study addressed the safety and feasibility of EACAB surgery). Although no control coronary angiography was performed routinely between the procedures, in three cases it was done due to clinical symptoms. It confirmed significant LAD stenosis in all patients. However, the strategy remained unchanged, and those patients received surgery as planned.

During the surgical procedure, each patient received a LITA-LAD graft. Perioperatively, three patients required chest revision for bleeding. Other complications were few. They mostly included pleurocentesis and atrial fibrillation (AF) (Table 3).

Two deaths (1.7%) and two (1.7%) repeat LAD revascularization procedures were reported in the perioperative period. Seventeen patients (14.8%) were lost to long-term follow-up. In total, 8 patients (7%) died (follow-up regarding mortality is complete), 6 (5.2%) suffered from MI, repeat target vessel revascularization was performed in 12 (10.4%) cases, and 2 patients (1.7%) had a stroke (Tables 4 and 5, Figure 1). Notably, two late LAD revascularization procedures were required due to LITA-LAD graft malfunction and one due to a new stenosis distally from the graft.

Table 1. Patient characteristics

Baseline patient characteristics	n = 115
Male sex, n (%)	90 (78)
Female sex, n (%)	25 (22)
Age, years, median (IQR)	63.0 (57.0–70.0)
Acute coronary syndrome: STEMI, n (%)	23 (20)
Acute coronary syndrome: NSTEMI, n (%)	22 (19.1)
Acute coronary syndrome: unstable angina, n (%)	70 (60.9)
Percutaneous target vessel (non-LAD) revascularization for ACS, n (%)	115 (100)
More than one vessel treated, n (%)	8 (6.9)
Number of implanted drug-eluting stents, median (IQR)	1.0 (1.0–2.0)
Treated artery	
Circumflex/obtuse margin, n (%)	49 (42.6)
Right coronary artery, n (%)	68 (59.1)
Intermediate branch, n (%)	4 (3.5)
Diagonal branch, n (%)	2 (1.7)
Diabetes, n (%)	32 (27.8)
Insulin therapy, n (%)	15 (13)
Arterial hypertension, n (%)	105 (91.3)
Hypercholesterolemia, n (%)	98 (85.2)
Active smoking, n (%)	41 (35)
Asthma, n (%)	2 (1.7)
Chronic obstructive pulmonary disease, n (%)	2 (1.7)
Renal insufficiency, n (%)	5 (4.3)
History of stroke/TIA, n (%)	9 (7.8)
Atrial fibrillation, n (%)	3 (2.6)
Obesity, n (%)	25 (21.7)
BMI, kg/m^2, median (IQR)	27.78 (25.65–30.70)

Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; LAD, left anterior descending; NSTEMI, non-ST-segment elevation myocardial infaction; STEMI, ST-segment elevation myocardial infarction;TIA, transient ischemic attack

Table 2. Echocardiographic parameters before EACAB

Patient characteristics	n = 115
EF, %, median (IQR)	55.0 (45.0–60.0)
LA, mm, median (IQR)	39.0 (36.0–42.0)
LV ESD, mm, median (IQR)	35.0 (30.0–38.0)
LV EDD, mm, median (IQR)	52.0 (48.0– 6.0)
PW, mm, median (IQR)	10.0 (10.0–12.0)
IVS, mm, median (IQR)	11.25 (10.0–12.0)
RV, mm, median (IQR)	26.0 (24.0–29.0)

Abbreviations: EACAB, endoscopic atraumatic coronary artery bypass grafting; EF, ejection fraction; IVS, intraventricular septum; LA, left atrium; LV EDD, left ventricular end-diastolic diameter; LV ESD, left ventricular end-systolic diameter; RV, right ventricle

Table 3. Procedural aspects of EACAB surgery

EACAB procedure, number of patients, n (%)	115 (100)
Time interval separating both stages, days, median (IQR)	100.0 (62.0–136.0)
LITA-LAD, n (%)	115 (100)
Chest revision, n (%)	3 (2.6)
Perioperative AF, n (%)	12 (10.4)
Renal injury (RIFLE classification — creatinine × 2), n (%)	4 (3.5)
PRBC transfusion, n (%)	11 (9.6)
>2 units of PRBC, n (%)	4 (3.4)
Pleurocentesis, n (%)	16 (13.9)
Perioperative EF, %, median (IQR)	50.0 (50.0–55.0)

Abbreviations: LAD, left anterior descending artery; LITA, left internal thoracic artery; PRBC, packed red blood cells; RIFLE, classification for renal failure (risk, injury, failure, loss of function, end-stage disease); other — see Table 2

Table 4. Long-term follow-up analysis

Number of patients, n (%)	115 (100)
Follow-up time, days from EACAB, median (IQR)	1338.5 (753.0–2093.0)
Follow-up completion for mortality, n (%)	115 (100)
Follow-up completion for other endpoints, n (%)	98 (85.2)
Overall MACCE (including mortality), n (%)	20 (17.4)
MACCE perioperative observation, n (%)	4 (3.5)
MACCE long-term observation, n (%)	16 (13.9)
Mortality (100% follow-up), n (%)	8 (6.9)
Mortality perioperative observation, n (%)	2 (1.7)
Mortality long-term observation, n (%)	6 (5.2)
Myocardial infarction, n (%)	6 (5.2)
Perioperative observation	0
Long-term observation, n (%)	6 (5.2)
Overall repeat revascularization in treated arteries, n (%)	12 (10.4)
Repeat revascularization, LAD, n (%)	5 (4.3)
Perioperative observation, n (%)	2 (1.7)
Long-term observation, n (%)	3 (2.6)
Repeat revascularization, non-LAD, n (%)	7 (6.1)
Perioperative observation	0
Long-term observation, n (%)	7 (6.1)
PCI in other coronary arteries, n (%)	2 (1.7)
Coronary angiography with no intervention, n (%)	6 (5.2)
Stroke, n (%)	2 (1.7)
Perioperative observation	0
Long-term observation, n (%)	2 (1.7)

Abbreviations: CCS, Canadian Cardiovascular Society grading for angina; MACCE, major adverse cardiac and cerebrovascular events (death, myocardial infarction, cerebrovascular incident and repeat target vessel revascularization); PCI, percutaneous coronary intervention; other — see Table 2

Overall primary composite endpoint of MACCE was estimated at 17.4% (Table 4, Figure 1). Six patients (5.2%) underwent coronary angiography due to suspicion of critical stenosis, but no intervention was required.

When comparing diabetic to non-diabetic cases, patients with diabetes had a significantly higher MI prevalence during the follow-up (15.6% vs. 1.2%; $P = 0.002$) (Table 5). Patients with no diagnosis of arterial hypertension (and thus limited HA-dedicated treatment) had a significantly higher incidence of MACCE during follow-up (15.2% vs. 40%; $P = 0.049$) (Table 5).

Although we did not show the impact of baseline MI on mortality following EACAB surgery or composite MACCE endpoint, a trend towards an increase of adverse events in this group was visible (Figure 2).

DISCUSSION

As evidence on using the surgical approach after temporary withdrawal of dual antiplatelet therapy in patients who received DES for ACS treatment is very limited, the current study provides reliable data on this matter and has the longest follow-up.

Despite all disadvantages of surgical treatment, in multivessel coronary disease, CABG confers a long-term survival benefit over PCI-DES because of achieving higher rates of complete revascularization [7]. This should be considered when adjusting the treatment to patients' needs. Hybrid revascularization must provide the advantages of both techniques while achieving complete revascularization.

Although reported treatment cannot be presented as a planned hybrid strategy per se, its final long-term efficacy needs to be studied in comparison to hybrid procedures. The impact of initial acute coronary syndrome and consequences of early temporary discontinuation of dual antiplatelet therapy can only be discussed when studies of planned hybrid revascularization procedures with none of those factors are taken into comparative analysis.

Adams et al. [8] reported the five-year clinical outcome for one-stage hybrid coronary revascularization — they demonstrated 91% survival, 94% freedom from angina, and 87% freedom from any form of coronary intervention, which is quite similar to our results. Other studies report 88.5% survival at 5 years and 76% at 10 years, with only 10% of patients requiring repeat revascularization [9, 10]. Our analysis confirms satisfactory outcomes and low MACCE rates. From the clinical perspective, it is important to note that the LITA-LAD procedure reduces the need for future revascularization in the non-LAD vessels while providing long-term relief from angina episodes [11].

The LITA-LAD anastomosis has been shown to be more durable than other arterial and vein grafts as well as coronary stents for treatment of LAD disease, with patency rates >90% at 5-year follow-up [2, 11, 12]. During the follow-up evaluation, we noticed only two incidents of repeat LAD revascularization due to graft failure. When internal thoracic artery (ITA) graft failure occurs, a technical error is the most common cause in the early postoperative period. In the subsequent weeks and months, localized neointimal hyperplasia may occur at the cleft between the native artery and the ITA graft at the anastomotic suture site, on the hood, and on the floor of the native LAD, which can result in localized stenosis [13, 14]. The rate of diagnosed graft failures in our report is low and acceptable.

Six incidences of MI were reported in the long-term follow-up (5.2%). Furthermore, we reported no MI perioperatively. Recent metanalysis concludes that 3.2% of patients

Table 5. Distribution of attributes in the groups defined by mortality, myocardial infarction, repeat revascularization, stroke, and composite endpoint during follow-up

	Mortality (n = 8)	Myocardial infarction (n = 6)	Repeat revascularization in treated arteries (n = 12)	Stroke (n = 2)	Composite endpoint (MACCE: death, stroke, repeat revascularization) (n = 20)
Age, years	70.0 (59.5–76.2)	65.5 (63.0–70.0)	63.0 (58.0–69.0)	65.5	64.0 (58.5–70.2)
Diabetes mellitus (32 patients at baseline)	4 (50%)	5 (83.3%)	2 (16.7%)	0	8 (40%)
Subgroup analysis:	Diabetic vs. non-diabetic[a]: 4/32 (12.5%) vs. 4/83 (4.8%) $P = 0.15$	Diabetic vs. non-diabetic[a]: 5/32 (15.6%) vs. 1/83 (1.2%) $P = 0.002$	Diabetic vs. non-diabetic[a]: 2/32 (6.25%) vs. 10/83 (12%) $P = 0.36$	Diabetic vs. non-diabetic[a]: 0/32 vs. 2/83 (2.4%) $P = 0.39$	Diabetic vs. non-diabetic[a]: 8/32 (25%) vs. 12/83 (14.5%) $P = 0.18$
AH (105 patients at baseline)	6 (75%)	5 (83.3%)	10 (83.3%)	2 (100%)	16 (80%)
Subgroup analysis:	AH vs. non-AH[a]: 6/105 (5.7%) vs. 2/10 (20%) $P = 0.09$	AH vs. non-AH[a]: 5/105 (4.8%) vs. 1/10 (10%) $P = 0.48$	AH vs. non-AH[a]: 10/105 (9.5%) vs. 2/10 (20%) $P = 0.30$	AH vs. non-AH[a]: 2/105 (1.9%) vs. 0/10 $P = 0.66$	AH vs. non-AH[a]: 16/105 (15.2%) vs. 4/10 (40%) $P = 0.049$
Active smoking (41 patients at baseline)	3 (37.5%)	2 (33.3%)	5 (41.7%)	0	8 (40%)
Subgroup analysis:	Smokers vs. no-smokers[a]: 3/41 (7.3%) vs. 5/74 (6.7%) $P = 0.91$	Smokers vs. no-smokers[a]: 2/41 (4.9%) vs. 4/74 (5.4%) $P = 0.90$	Smokers vs. no-smokers[a]: 5/41 (12.2%) vs. 7/74 (9.5%) $P = 0.65$	Smokers vs. no-smokers[a]: 0/41 vs. 2/74 (2.7%) $P = 0.29$	Smokers vs. no-smokers[a]: 8/41 (19.5%) vs. 12/74 (16.2%) $P = 0.56$
Male sex (90 patients at baseline)	5 (62.5%)	4 (66.7%)	10 (83.3%)	1 (50%)	16 (80%)
Subgroup analysis:	Male vs. female[a]: 5/90 (5.6%) vs. 3/25 (12%) $P = 0.26$	Male vs. female[a]: 4/90 (4.4%) vs. 2/25 (8%) $P = 0.48$	Male vs. female[a]: 10/90 (11.1%) vs. 2/25 (8%) $P = 0.65$	Male vs. female[a]: 1/90 (1.1%) vs. 1/25 (4%) $P = 0.33$	Male vs. female[a]: 16/90 (17.8%) vs. 4/25 (16%) $P = 0.84$
Obesity (25 patients at baseline)	3 (37.5%)	3 (50%)	2 (16.7%)	0	5 (25%)
Subgroup analysis:	Obese vs. non-obese[a]: 3 /25 (12%) vs. 5/90 (5.6%) $P = 0.26$	Obese vs. non-obese[a]: 3/25 (12%) vs. 3/90 (3.3%) $P = 0.09$	Obese vs. non-obese[a]: 2/25 (8%) vs. 10/90 (11.1%) $P = 0.65$	Obese vs. non-obese[a]: 0/25 vs. 2/90 (2.2%) $P = 0.45$	Obese vs. non-obese[a]: 5/25 (20%) vs. 15/90 (16.7%) $P = 0.70$

Data are presented as numbers (percentage) and medians (interquartile range). [a]χ^2 test

Abbreviations: AH, arterial hypertension; other — see Table 4

treated with hybrid coronary revascularization (HCR) suffered from MI compared with 2.6% of patients undergoing CABG, with no statistical significance [15]. The low rate of MI may be a result of not only the revascularization strategy but also adequate timing of both procedures.

From the obtained follow-up, 12 patients required urgent repeat target vessel revascularization; 7 (6.1%) of them were in DES-treated arteries. This result is satisfactory, but further observation may be crucial, as some studies report 21% DES-treated vessel failure at 5-year follow-up [12]. As mentioned previously, some cases of restenosis may remain undiagnosed, as angina may not be present due to patent LITA-LAD anastomosis [11].

We diagnosed no stroke in the perioperative period and two cases of stroke during the follow-up. A low incidence of cerebrovascular episodes is considered a significant advantage of the minimally invasive approach, as cardiopulmonary bypass and aortic manipulation during CABG create a direct danger and may cause stroke. In a recently published analysis, the incidence of cerebrovascular events in the HCR group was 0.9% compared with 1.4% in CABG patients [15]. In general, the risk of stroke after CABG varies across studies ranging from 0.0 % to 5.2 %, depending on study design, patient risk profile, operative techniques, and the length of study follow-up [16, 17]. A cerebrovascular incident following CABG remains one of the most devastating complications after CABG surgery, entailing permanent disability and a 3–6 fold increase in the risk of death with a case-fatality rate of up to 20% [18–19].

Kidney injury and failure following coronary artery bypass grafting are concerning. The injury following the surgery is the second most common cause of acute kidney injury (AKI) in the intensive care setting (after sepsis) and is associated with increased morbidity and mortality [20]. It must be noted that the mortality rate (hospital discharge or 30-day mortality) is between 3.8% and 54.4% in patients who develop the injury and increases progressively with the degree of renal impairment. The 3.5% rate of kidney

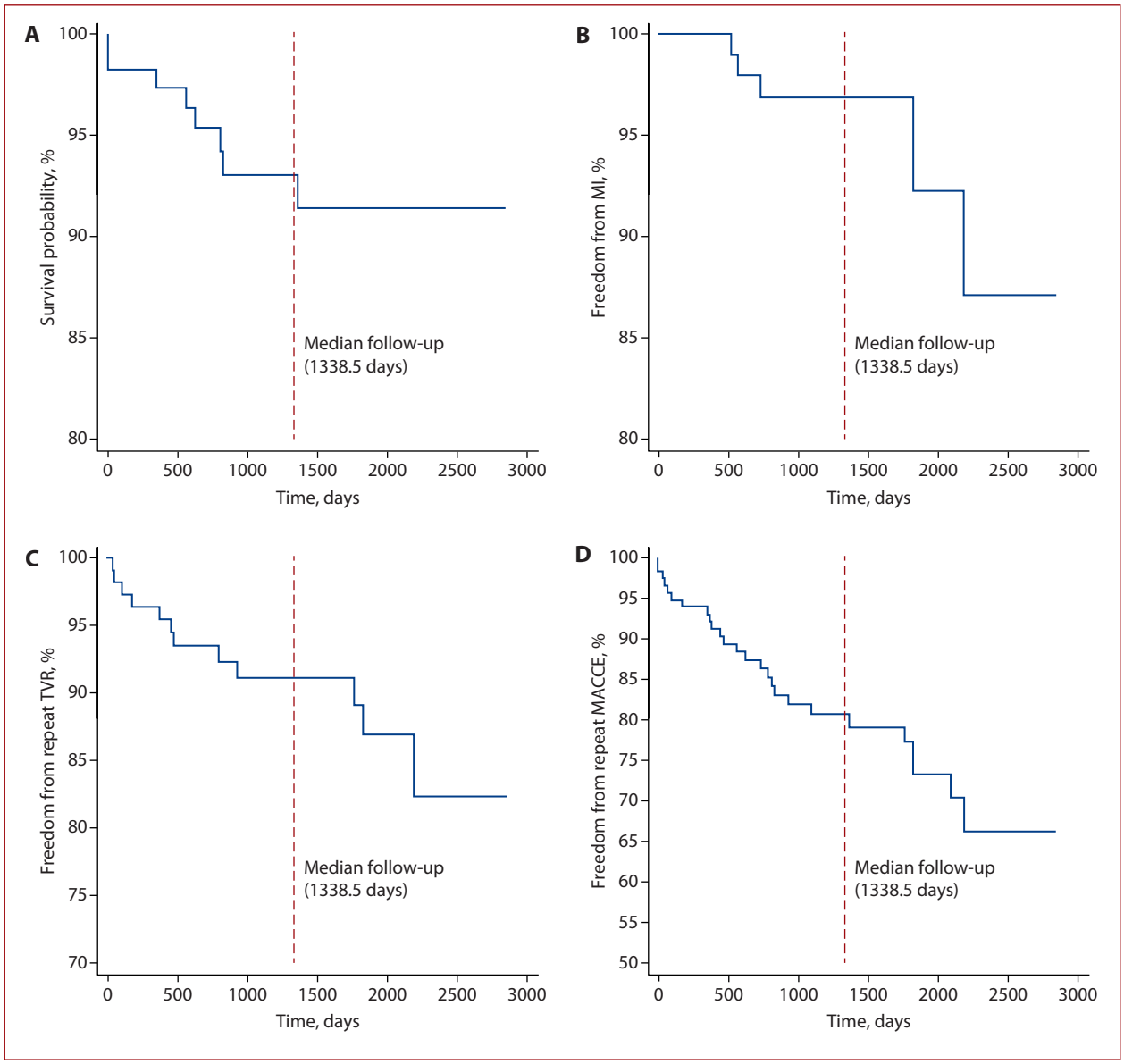


Figure 1. Kaplan-Meier curves for mortality (**A**), freedom from myocardial infarction (**B**), freedom from repeat revascularization (**C**), and freedom from MACCE **(D)** following EACAB surgery

Abbreviations: EACAB, endoscopic atraumatic coronary artery bypass grafting; MACCE, major adverse cardiac and cerebrovascular incidents (death, myocardial infarction, stroke, repeat revascularization); PCI, percutaneous coronary intervention

injury in the perioperative period is low and acceptable. However, some reports indicate that renal failure following a hybrid procedure is estimated at 1.7%, compared with 2.6% in the CABG groups [15].

Atrial fibrillation is a very common complication after surgical procedures. There are multiple concepts for pathogenesis, but no clear evidence regarding triggers for arrhythmia onset. Nonetheless, it worsens the postoperative state and prognosis and increases considerably the length of intensive care unit (ICU) stay and hospitalization as well as hospital costs [21, 22]. Seven studies examined the incidence of postoperative AF in the HCR group, and the incidence of fibrillation was 17%, compared with 19.2% in the CABG group [15]. We report an even lower number of AF occurrences in the perioperative period, which according to most reports, makes this method superior to CABG in this context.

It has been reported that 22.8% of HCR patients receive blood transfusion [15]. Our results are encouraging, as only 9.2% received blood products. However, this may be the result of the time interval separating both surgical and percutaneous procedures, which could reach 180 days. Narrowing the time interval would probably increase the rate of transfusion, as coronary angiography with angioplasty may lower the blood parameters.

In a recent randomized trial comparing CABG, hybrid coronary revascularization, and multivessel percutaneous intervention, residual myocardial ischemia and MACCE were similar at 12 months [23]. Notably, more than one-half of the patients had prior MI (55.5%). The HCR patients had

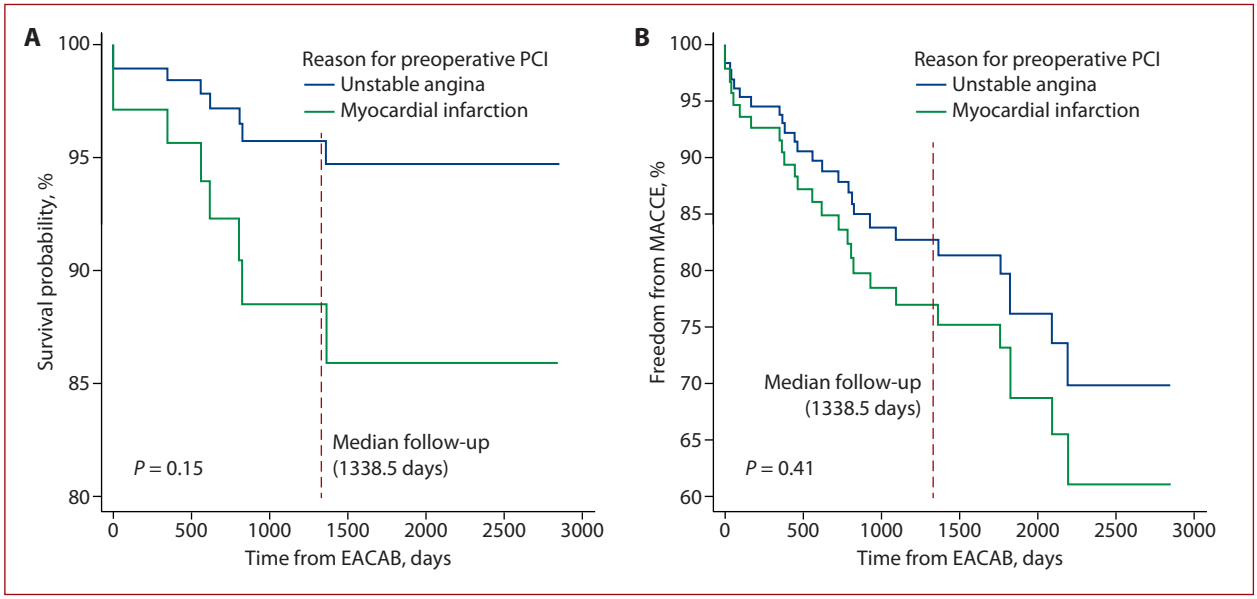


Figure 2. Kaplan-Meier curves for mortality (**A**) and freedom from MACCE (**B**) with relation to preoperative acute coronary syndrome. The *P*-values are for the log-rank test

Abbreviations: see Figure 1, Table 4

PCI within 3 days (in most cases at 24–48 hours) after undergoing minimally invasive direct coronary artery bypass (MIDCAB) LITA-LAD. The advantage of that protocol was assessing the early LITA-LAD patency. The coronary angiogram showed LITA thrombotic occlusion in 1 case (2.1%). Angiographic control at 12 months demonstrated 9 saphenous vein grafts (SVGs) and 1 LITA stenosis/occlusion in the CABG group (10/49, 20.4%), 3 LITA stenoses/occlusions and 1 in-segment restenosis in the HCR group (4/49, 8.2%). A long-term follow-up is expected. The protocol for mandatory angiography provides some reasonable results regarding graft patency. However, invasiveness of the procedure must be taken into consideration. Our follow-up protocol did not assume routine angiography in asymptomatic patients.

The MERGING clinical trial provided late clinical outcomes of myocardial hybrid revascularization versus coronary artery bypass grafting for a three-vessel coronary artery disease [24]. The percutaneous phase was performed 48–72 hours after withdrawal of the chest tubes and administering a loading dose of clopidogrel (600 mg). The 2-year rate of major cardiovascular events defined as death, MI, stroke, or repeat revascularization was evaluated. However, the authors noted that hybrid coronary revascularization was associated with increased rates of MACCE during 2 years of clinical follow-up while the control group treated with conventional surgery presented with low complication rates during the same period. The adverse events included mainly unplanned revascularization, whose rates increased over time in both groups, reaching 14.5% vs. 5.9% in the hybrid and the CABG groups, respectively. The authors point out that the patients underwent two invasive procedures either simultaneously or within days. Also, iodine contrast and antithrombotic medications (for the PCI step) were used in proximity to major surgery (the CABG step) so the minimally invasive nature of PCI is virtually canceled by the surgical procedure. In this matter, our study reports quite a different perspective, assuming that a longer interval between both procedures may not necessarily worsen the outcomes. As restenosis can result from several mechanisms including inflammation and oxidative stress [25], the beneficial effect of separating both procedures may be hypothesized. Those factors are present in on-pump as well as off-pump surgical procedures [26].

Study limitations

This study has its drawbacks: it was a single-center, retrospective analysis with no control group. Furthermore, although follow-up regarding mortality was complete, only 85.2% of follow-up data regarding MI, stroke, and repeat revascularization were available. Coronary angiography was not performed routinely in patients with no symptoms.

CONCLUSIONS

EACAB is safe and a feasible method of LAD revascularization in patients who received DES for ACS within 180 days before surgery, despite early dual antiplatelet therapy discontinuation. The adverse events rate in the long-term follow-up was low and acceptable.

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J. 2019; 40(1): 87–165, doi: 10.1093/eurheartj/ehy394, indexed in Pubmed: 30165437.
2. Harskamp R, Zheng Z, Alexander J, et al. Status quo of hybrid coronary revascularization for multi-vessel coronary artery disease. Ann Thorac Surg. 2013; 96(6): 2268–2277, doi: 10.1016/j.athoracsur.2013.07.093, indexed in Pubmed: 24446561.
3. Green K, Lynch D, Chen T, et al. Combining PCI and CABG: the role of hybrid revascularization. Curr Cardiol Rep. 2013; 15(4), doi: 10.1007/s11886-013-0351-9, indexed in Pubmed: 23420447.
4. Balachandran S, Lee A, Denehy L, et al. Risk factors for sternal complications after cardiac operations: a systematic review. Ann Thorac Surg. 2016; 102(6): 2109–2117, doi: 10.1016/j.athoracsur.2016.05.047.
5. Abusamra R, Król M, Milewski K, et al. Short and long-term results of endoscopic atraumatic coronary artery off-pump bypass grafting in patients with left anterior descending artery stenosis. Cardiol J. 2021; 28(1): 86–94, doi: 10.5603/cj.a2019.0006, indexed in Pubmed: 30701513.
6. Verhaegh A, Accord R, Garsse Lv, et al. Hybrid coronary revascularization as a safe, feasible, and viable alternative to conventional coronary artery bypass grafting: what is the current evidence? Minim Invasive Surg. 2013; 2013: 1–10, doi: 10.1155/2013/142616, indexed in Pubmed: 23691303.
7. Kowalewski M, Gozdek M, Zieliński K, et al. Long-term mortality after percutaneous coronary intervention with drug-eluting stents compared with coronary artery bypass grafting for multivessel and left main disease: a meta-analysis. Kardiol Pol. 2020; 78(7-8): 759–761, doi: 10.33963/kp.15397, indexed in Pubmed: 32483953.
8. Adams C, Burns D, Chu M, et al. Single-stage hybrid coronary revascularization with long-term follow-up. Eur J Cardiothorac Surg. 2013; 45(3): 438–443, doi: 10.1093/ejcts/ezt390, indexed in Pubmed: 23956269.
9. Rosenblum J, Harskamp R, Hoedemaker N, et al. Hybrid coronary revascularization versus coronary artery bypass surgery with bilateral or single internal mammary artery grafts. J Thorac Cardiovasc Surg. 2016; 151(4): 1081–1089, doi: 10.1016/j.jtcvs.2015.10.061, indexed in Pubmed: 26687889.
10. Farid S, Ali JM, Stohlner V, et al. Long-Term Outcome of Patients Undergoing Minimally Invasive Direct Coronary Artery Bypass Surgery: A Single-Center Experience. Innovations. Phila. 2018; 13: 23–28, doi: 10.1097/IMI.0000000000000466, indexed in Pubmed: 29462051.
11. Hawkes A, Nowak M, Bidstrup B, et al. Outcomes of coronary artery bypass graft surgery. Vasc Health Risk Manag. 2006; 2(4): 477–484, doi: 10.2147/vhrm.2006.2.4.477, indexed in Pubmed: 17323602.
12. Etienne PY, D'hoore W, Papadatos S, et al. Five-year follow-up of drug-eluting stents implantation vs minimally invasive direct coronary artery bypass for left anterior descending artery disease: a propensity score analysis. Eur J Cardiothoracic Surg. 2013; 44(5): 884–890, doi: 10.1093/ejcts/ezt137, indexed in Pubmed: 23492989.
13. Otsuka F, Yahagi K, Sakakura K, et al. Why is the mammary artery so special and what protects it from atherosclerosis? Ann Cardiothorac Surg. 2013; 2: 519–526, doi: 10.3978/j.issn.2225-319X.2013.07.06, indexed in Pubmed: 23977631.
14. Harskamp R, Alexander J, Ferguson T, et al. Frequency and predictors of internal mammary artery graft failure and subsequent clinical outcomes. Circulation. 2016; 133(2): 131–138, doi: 10.1161/circulationaha.115.015549, indexed in Pubmed: 26647082.
15. Reynolds AC, King N. Hybrid coronary revascularization versus conventional coronary artery bypass grafting: Systematic review and meta-analysis. Medicine (Baltimore). 2018; 97(33): e11941, doi: 10.1097/MD.0000000000011941, indexed in Pubmed: 30113498.
16. Goy JJ, Kaufmann U, Goy-Eggenberger D, et al. A prospective randomized trial comparing stenting to internal mammary artery grafting for proximal, isolated de novo left anterior coronary artery stenosis: the SIMA trial. Stenting vs Internal Mammary Artery. Mayo Clin Proc. 2000; 75(11): 1116–1123, doi: 10.4065/75.11.1116, indexed in Pubmed: 11075740.
17. Roach G, Kanchuger M, Mangano C, et al. Adverse cerebral outcomes after coronary bypass surgery. N Engl J Med. 1996; 335(25): 1857–1864, doi: 10.1056/nejm199612193352501, indexed in Pubmed: 8948560.
18. Dacey LJ, Likosky DS, Leavitt BJ, et al. Perioperative stroke and long-term survival after coronary bypass graft surgery. Ann Thorac Surg. 2005; 79(2): 532–536; discussion: 537, doi: 10.1016/j.athoracsur.2004.07.027, indexed in Pubmed: 15680829.
19. Tarakji KG, Sabik JF, Bhudia SK, et al. Temporal onset, risk factors, and outcomes associated with stroke after coronary artery bypass grafting. JAMA. 2011; 305(4): 381–390, doi: 10.1001/jama.2011.37, indexed in Pubmed: 21266685.
20. Mao H, Katz N, Ariyanon W, et al. Cardiac surgery-associated acute kidney injury. Cardiorenal Med. 2013; 3(3): 178–199, doi: 10.1159/000353134, indexed in Pubmed: 24454314.
21. Auer J, Weber T, Berent R, et al. Postoperative atrial fibrillation independently predicts prolongation of hospital stay after cardiac surgery. Europace. 2005; 7: S1–S1, doi: 10.1016/j.eupc.2005.08.003.
22. Banach M, Ostrowski S, Zasłonka J, et al. Is there a relation between preoperative atrial fibrillation and increased mortality after cardiac surgery? Folia Cardiol. 2005; 12(Suppl D): 102–104.
23. Ganyukov V, Kochergin N, Shilov A, et al. Randomized Clinical Trial of Surgical vs. Percutaneous vs. Hybrid Revascularization in Multivessel Coronary Artery Disease: Residual Myocardial Ischemia and Clinical Outcomes at One Year—Hybrid coronary REvascularization Versus Stenting or Surgery (HREVS). J Interv Cardiol. 2020: 5458064, doi: 10.1155/2020/5458064, indexed in Pubmed: 31969796.
24. Esteves V, Oliveira M, Feitosa F, et al. Late clinical outcomes of myocardial hybrid revascularization versus coronary artery bypass grafting for complex triple-vessel disease: Long-term follow-up of the randomized MERGING clinical trial. Catheter Cardiovasc Interv. 2020; 97(2): 259–264, doi: 10.1002/ccd.28710, indexed in Pubmed: 31922359.
25. Kornowski R, Hong M, Tio F, et al. In-Stent Restenosis: Contributions of Inflammatory Responses and Arterial Injury to Neointimal Hyperplasia. J Am Coll Cardiol. 1998; 31(1): 224–230, doi: 10.1016/s0735-1097(97)00450-6, indexed in Pubmed: 9426044.
26. Abrantes R, Hueb A, Hueb W, et al. Behavior of Ultrasensitive C-Reactive Protein in Myocardial Revascularization with and without Cardiopulmonary Bypass. Braz J Cardiovasc Surg. 2018; 33(6): 535–541, doi: 10.21470/1678-9741-2018-0235, indexed in Pubmed: 30652741.

Validity of the Pneumonitor for RR intervals acquisition for short-term heart rate variability analysis extended with respiratory data in pediatric cardiac patients

Jakub S Gąsior[1*], Marcel Młyńczak[2*], Maciej Rosoł[2], Piotr Wieniawski[1], Iwona Walecka[3], Gerard Cybulski[2], Bożena Werner[1]

[1]Department of Pediatric Cardiology and General Pediatrics, Medical University of Warsaw, Warszawa, Poland
[2]Faculty of Mechatronics, Institute of Metrology and Biomedical Engineering, Warsaw University of Technology, Warszawa, Poland
[3]Department of Pediatric Cardiology and General Pediatrics, Doctoral School Medical University of Warsaw, Warszawa, Poland
*Both authors equally contributed to the study

Correspondence to:
Jakub S Gąsior, PhD,
Department of Pediatric Cardiology and General Pediatrics, Medical University of Warsaw,
Żwirki i Wigury 63A,
02–091 Warszawa, Poland,
phone: +48 793 199 222,
e-mail: jakub.gasior@wum.edu.pl

DOI: 10.33963/KP.a2023.0070

Received:
December 1, 2022

Accepted:
February 22, 2023

Early publication date:
March 16, 2023

ABSTRACT

Background: Breathing pattern alterations change the variability and spectral content of the RR intervals (RRi) on electrocardiogram (ECG). However, there is no method to record and control participants' breathing without influencing its natural rate and depth in heart rate variability (HRV) studies.

Aim: This study aimed to assess the validity of the Pneumonitor for acquisition of short-term (5 minutes) RRi in comparison to the reference ECG method for analysis of heart rate (HR) and HRV parameters in the group of pediatric patients with cardiac disease.

Methods: Nineteen patients of both sexes participated in the study. An ECG and Pneumonitor were used to record RRi in 5-minute static rest conditions, the latter also to measure the relative tidal volume and respiratory rate. The validation comprised Student's t-test, Bland-Altman analysis, intraclass correlation coefficient, and Lin's concordance correlation. The possible impact of respiratory activity on the agreement between ECG and the Pneumonitor was also assessed.

Results: An acceptable agreement for the number of RRi, mean RR, hazard ratio (HR), and HRV measures calculated based on RRi acquired using the ECG and Pneumonitor was presented. There was no association between the breathing pattern and RRi agreement between devices.

Conclusions: The Pneumonitor might be considered appropriate for cardiorespiratory studies in the group of pediatric cardiac patients in rest condition.

Key words: heart rate variability, impedance pneumography, Pneumonitor, RR intervals, validation

INTRODUCTION

Heart rate variability (HRV), calculated based on consecutive RR intervals (RRi) between adjacent QRS complexes resulting from sinus node depolarizations [1], has been used to investigate cardiac autonomic responsiveness in various populations [2]. Importantly, HRV is affected by respiratory parameters [3–5]. The classical interpretation of the high frequency (HF) component of HRV as the vagal influence on the heart rate (HR) is flawed in subjects with 3–9 breaths per minute (breaths/min) [6]. The respiratory rate (RespRate) below 6-7 breaths/min results in the respiration-related part of the spectrum being within (partly or totally) the low frequency (LF) band. Additionally, variability in respiratory period and mean tidal volume (TV) generates LF respiratory oscillations, even if the RespRate is within the HF band [7]. The highest value of the root mean square of successive RRi differences (RMSSD) was obtained at 7 breaths/min [8]. On the other hand, in populations known to breathe faster — more than 24 breaths/min — a wider than generally recommended [1] frequency bands for HF should be set [9, 10]. Despite the evidence that the respiratory alterations change the variability and the

WHAT'S NEW?

This article describes the validity assessment of a research device — Pneumonitor — for the simultaneous acquisition of single-lead electrocardiogram (ECG) and impedance-based respiratory activity from the same set of electrodes. It enables to derive RR intervals (RRi) along with instantaneous frequency and depth of breathing. Importantly, the two latter signals can be directly measured as changes in trans-thoracic impedance and are not solely derived from ECG or photoplethysmography. Both pieces of information can be utilized to perform heart rate variability (HRV) analysis supported not only by assessment of RRi stationarity (requirement for the frequency domain calculations) but also by assessment of respiratory stationarity and the activity itself (e.g. HRV analysis can be distorted by a too slow breathing pattern). The assessment was performed in the specific clinical context, in pediatric cardiac patients, and demonstrated an acceptable agreement of RRi and HRV with the reference device.

spectral content of the RRi, there is no optimal method to record and control breathing without influencing its natural pattern in HRV studies [4, 11].

The electrocardiogram (ECG) is a gold standard for RRi acquisition [1] but can be also used to derive the RespRate [12]. ECG-derived respiration might avoid the potential influence of masks or belts on breathing parameters. However, costs of multi-lead ECG recorders and Holter monitors, their limited portability, and limited stationarity of signal acquisition during activities reduce their practical utility in real-world settings [13].

Recently, new convenient wearable devices have been developed to record parameters in cardiovascular populations more easily, quickly, and with increased frequency [14–16]. Pneumonitor is a portable, academically developed device designed for environmental physiology and sports medicine analyses, which offers synchronized recording of RRi (single-lead ECG) and respiratory mechanics using the impedance pneumography (IP) technique with the same set of electrodes [17]. IP records changes in trans-thoracic impedance as a result of changes in the amount of air in lungs and thorax movements. It was shown that a specific electrode configuration enables obtaining a linear relationship between impedance and TV [18]. However, these relationships depend on subjects' demographic parameters, e.g., sex and weight [19]. Therefore, to measure TV in liters, each participant should perform calibration before the main session, which is considered logistically challenging. However, this can be omitted, as the very high linear agreement between impedance and TV allows relying on relative volume changes (even divided into inspiratory- and expiratory-TV) [20]. On the other hand, detected respiratory onsets can be used to determine the RespRate series.

Before using a new tool or method of measurement in clinical practice, it is crucial to verify its agreement with the gold standard [21, 22]. The absence of measurement validation is a barrier to the widespread use of wearable medical technologies in current practice [23]. Importantly, most wearable biosensors have not been designed for children despite a great number of pediatric cardiac diseases that could benefit from this technology [16]. IP has been already applied in the pediatric population [24]. Adding an ECG registration, especially using the same electrode configuration, does not affect the application of impedance measurement. This study aimed to assess the validity of the Pneumonitor for acquisition of short-term RRi for analysis of vagally-mediated HRV in comparison to the reference ECG method in a group of pediatric cardiac patients. Furthermore, this study aimed to extend the typically used setup with a separate cardiac recording with simultaneous acquisition of data on respiration.

METHODS

Population

The study group consisted of 19 (7 female) pediatric cardiac patients of both sexes. The inclusion criteria were age between 7 and 18 years, absence of infection, and in cases of constant pharmacological treatment — no change in medications in the last 3 months. The study was approved by the University Bioethical Committee (KB/70/2021) and followed the rules and principles of the Helsinki Declaration, all parents or legal guardians and patients 16 years old and older gave their informed written consent.

Procedures and measurement conditions

Patients and their parents/legal guardians were informed about the study objectives, measurement protocol, potential risks involved, and its benefits in conversation. Recordings were performed between 8:30 am and 2:00 pm in a hospital room, which was quiet and bright, with stable, controlled temperature and humidity. Patients were instructed to refrain from physical activity the day before and on the day of study, avoid junk food, sugar drinks, snacking, and to use the toilet (if needed) before examinations. The examination was carried out at least 1 hour after breakfast.

RRi data acquisition using an ECG and the Pneumonitor

For ECG, 10 electrodes were placed in standard positions. For the Pneumonitor, 5 electrodes were placed according to the scheme presented elsewhere [17]. Patients were placed in the supine position for 5 minutes to stabilize HR. RRi were recorded simultaneously using ECG (Custo cardio 100 12-channel PC ECG system; sampling frequency fs = 1000 Hz, Custo med GmbH, Ottobrunn, Germany) and the Pneumonitor in the supine position for 6 minutes.

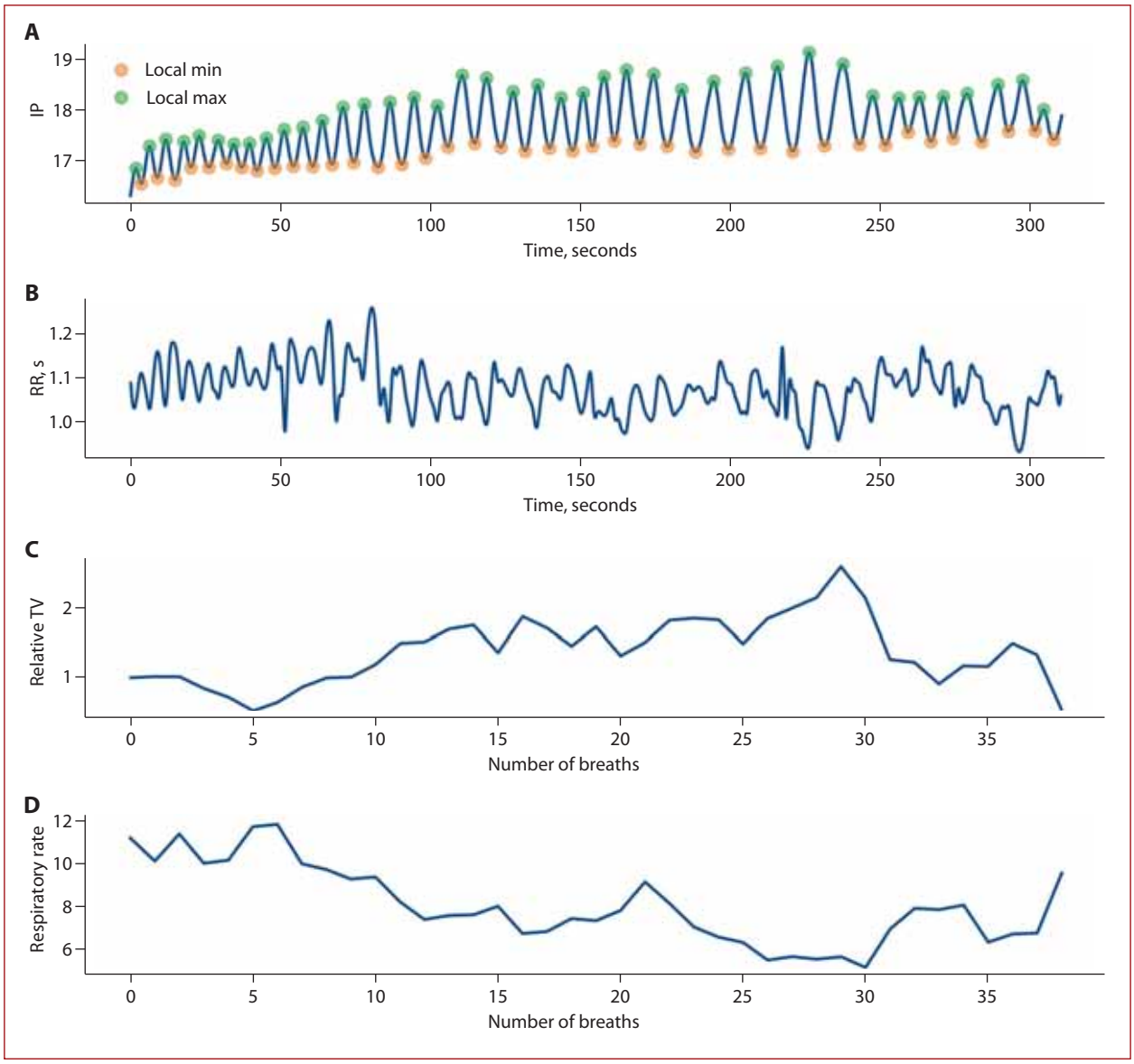


Figure 1. Sample series of IP signal (top) with marked local minima and maxima enabling calculation of the respiratory rate (bottom) and the course of relative TV (second from the bottom), along with the interpolated RR intervals (second from the top); the only example with the nonstationary (decreasing) respiratory rate

Abbreviations: IP, impedance pneumography; s, seconds; RR, time elapsed between two successive R waves of the QRS signal on the electrocardiogram; TV, tidal volume

The Pneumonitor measured single-lead ECG signals along with IP with the same set of electrodes (standard Holter-type, disposable), with fs = 250 Hz, considered sufficient for HRV analysis [1]. For the Pneumonitor, ECG signal pre-processing comprised: (1) baseline alignment; (2) R peaks detection using Stationary Wavelet Transform [25]; (3) manual correction of mistakenly detected R peaks (if applicable, based on the visual inspection); and (4) estimation of RRi between successive R peaks. The IP signal was measured with the tetrapolar method using a specified electrode configuration [18]. RespRates were estimated as follows: (1) raw IP was smoothed (1-second window) to remove the cardiac component [26]; (2) respiratory onsets were found based on the differentiated, flow-related signal; (3) RespRates were estimated between successive respiratory onsets.

We did not transform impedance into volume in liters, assuming impedance changes reproduce the TV signal in terms of shape [20]. The first breath was hence assigned with the value of 1, and all next ones were related to this first. Inspiratory and expiratory phases were detected from the differentiated signal, and then, inspiratory- and expiratory-TV were estimated as the difference between the maximum after the inspiration and the minimum before the inspiration, and between the maximum before the expiration and the minimum after the expiration, respectively (Figure 1).

Data synchronization, artifacts identification, and correction

Registered ECGs were inspected by a pediatric cardiologist to confirm sinus rhythm and identify ectopic beats. The RRi were exported from the ECGs software and the analytical scripts prepared for Pneumonitor data, then imported into a single Excel spreadsheet file to carry out raw RRi time series synchronization, identify artifacts based on graphical presentation of raw RRi from both devices, and implement manual editing according to recommendations [27]. Physiological artifacts (ectopic beats, premature atrial, and/or ventricular beats) were replaced by RRi interpolated from adjacent RRi [28].

Stationarity assessment

Stationarity, the requirement for spectral HRV indices [29], was verified before HRV analysis (Statistical analysis).

HR and HRV

The corrected RRi from both devices were imported into Kubios HRV Standard 3.4 software (University of Eastern Finland, Kuopio, Finland) [30] to calculate mean RR, mean HR (HR), time-domain (standard deviation of NN intervals — SDNN, RMSSD), and frequency-domain (low frequency — LF, HF, LF/HF) parameters based on 5-minute recordings. Smoothness priors based on the detrending approach was applied (smoothing parameter, Lambda value = 500) [31], and then, RRi series were transformed to an evenly sampled time series using a cubic spline interpolation followed by 4-Hz resampling. The detrended and interpolated RRi series were used to compute spectra by employing a fast-Fourier transform with Welch's periodogram method (300-second window, without overlap). The following bands for spectral components were set: LF (0.04–0.10 Hz) and HF (0.10–0.40 Hz). The power at both bands was estimated in absolute (ms^2). Natural log-transformed (ln) absolute powers in the LF (lnLF) and HF (lnHF) bands were also presented.

Statistical analysis

All analyses were carried out in Python 3.9. The stationarity analyses were performed using the Phillips-Perron test [32] for patients' RRi and RespRate series separately for ECG and the Pneumonitor. Agreement of parameters between ECG and the Pneumonitor was verified using a Bland-Altman plot with limits of agreement (LoA) [21, 33] and intraclass correlation coefficient (ICC, model 3.1) with the a priori interpretation: 0–0.30 – small, 0.31–0.49 — moderate, 0.50–0.69 — large, 0.70–0.89 — very large, and 0.90–1.00 — nearly perfect [34]. An agreement sufficient for the interchangeable use of two methods is suggested when a lower 95% confidence interval (CI) value exceeded 0.75 [35]. To compare the values of parameters obtained using both devices, Student's t-test was used. The smallest worthwhile change (SWC) was calculated by multiplying the between-subject ECG standard deviation values by 0.2 ($SWC_{0.2}$ small effect) and 0.6 ($SWC_{0.6}$ medium effect) and used to define the maximum allowed difference between methods presented in Bland-Altman plots. Two methods are considered in agreement if the LoA do not exceed the SWC between methods. Lin's concordance correlation coefficient (CCC) was also calculated [36]. To assess whether the agreement between ECG and the Pneumonitor is affected by the respiratory depth and rate, Pearson correlation tests were performed between standard deviations of relative TV and RespRate, and the difference between HRV parameters calculated using ECG and the Pneumonitor. Descriptive data for quantitative features with normal distribution were presented as mean and standard deviation (SD). In all cases, the significance level was set at $\alpha = 0.05$.

RESULTS

Participants characteristics

Results of 3 patients of 19 were excluded due to poor signal quality (n = 2) and non-confirmed diagnosis (n = 1). Consequently, results of 16 (6 female) pediatric Polish Caucasian cardiac patients (congenital heart disease n = 5, cardiac arrhythmia n = 4, cardiomyopathy n = 7) from the following voivodeships in Poland: Mazowieckie (n = 11), Lubuskie (n = 1), Podlaskie (n = 1), Kujawsko-Pomorskie (n = 1), Podkarpackie (n = 1), and Świętokrzyskie (n = 1) were included in the analysis. The mean (SD) age, body mass, stature, and body mass index (BMI) were 12.6 years (3.4), 57.8 kg (25.3), 158.4 cm (18.1), and 21.8 kg/m^2 (5.5), respectively.

Number of RRi, synchronization, artifacts identification and correction, stationarity

There were 5917 and 5813 RRi from ECG and Pneumonitor recordings, respectively. Data from both devices required synchronization for 6 patients — from 5 to 11 RRi from the beginning of the ECG signal were excluded. There were 27 technical artifacts notified on both ECG and Pneumonitor recordings — 0.005% error rate. The most often detected type of error included a short interval, followed by a long interval (n = 21) and missed interval(s) on the Pneumonitor, equivalent to 2 or 3 ECG RRi (n = 6). RRi series obtained using both devices appeared stationary for all patients.

Agreement of HR and HRV parameters

Results of agreement statistics for parameters calculated based on RRi obtained using ECG and the Pneumonitor are presented in Table 1. There were no significant differences between parameters ($P > 0.66$ for all). Mean absolute percentage difference between parameters ranged from 1.5% to 15.8%. ICC and CCC ranged between 0.96 and 1.00. The Bland-Altman plots are presented in Figure 2. $SWC_{0.2}$, $SWC_{0.6}$, and the number of patients for whom LoA exceeded the defined SWC (LoA > SWC) for selected parameters are presented in Table 2.

Table 1. Results of agreement statistics for HRV parameters

Parameter	Mean (SD) ECG	Mean (SD) Pneumonitor	Mean difference (95% CI)	LoA	95% CI for lower; upper LoA	ICC (95% CI)	CCC
RRi, n	348.7 (55.3)	342.6 (54.0)	6.1 (5.3–7.0)	3.1; 9.1	(1.7–4.5); (7.7–10.6)	1.00 (1.00–1.00)	0.99
Mean RR, ms	881.4 (124.8)	896.9 (126.6)	–15.5 (–17.0 to –14.0)	–20.7; –10.3	(–23.2 to –18.2); (–12.8 to –7.9)	1.00 (1.00–1.00)	0.99
HR, bpm	69.7 (10.9)	68.5 (10.8)	1.2 (1.0–1.4)	0.4; 2.0	(0.1–0.8); (1.6–2.3)	1.00 (1.00–1.00)	0.99
SDNN, ms	45.8 (17.4)	48.2 (16.9)	–2.4 (–3.6 to –1.2)	–6.7; 1.9	(–8.7 to –4.7); (–0.2–3.9)	0.99 (0.98–1.00)	0.98
RMSSD, ms	52.2 (22.7)	55.7 (21.6)	–3.5 (–5.7 to –1.4)	–11.1; 3.9	(–14.6 to –7.5); (0.4–7.5)	0.99 (0.96–0.99)	0.97
LF, ms^2	433.6 (298.5)	479.6 (324.4)	–46.0 (–76.7 to –15.3)	–155.3; 63.3	(–207.2 to –103.4); (11.4–115.2)	0.98 (0.95–0.99)	0.97
lnLF	5.8 (0.8)	5.9 (0.8)	–0.1 (–0.2–0.0)	–0.5; 0.3	(–0.7 to –0.3); (0.1–0.4)	0.97 (0.91–0.99)	0.96
HF, ms^2	1529.3 (1141.8)	1601.9 (1105.4)	–72.6 (–137.5 to –7.8)	–303.6; 158.3	(–413.2 to –193.9); (48.7–267.9)	0.99 (0.98–1.00)	0.99
lnHF	6.9 (1.1)	7.0 (1.0)	–0.1 (–0.1–0.0)	–0.3; 0.1	(–0.4 to –0.2); (0.0–0.2)	1.00 (0.99–1.00)	0.99
LF/HF	0.42 (0.28)	0.42 (0.25)	0.00 (–0.03 – 0.04)	–0.12; 0.13	(–0.18 – –0.06); (0.07–0.18)	0.97 (0.92–0.99)	0.97

Data for quantitative features with normal distribution were presented as mean and standard deviation (SD)

Abbreviations: CI, confidence interval; LoA, limits of agreement; ICC, intraclass correlation coefficient; CCC, concordance correlation coefficient; RR, time elapsed between two successive R waves of the QRS signal on the electrocardiogram; RRi, RR intervals; ms, milliseconds; ms^2, milliseconds squared; HR, heart rate; bpm, beats per minute; SDNN, standard deviation of NN intervals; RMSSD, root mean square of successive RRi differences; LF, low frequency; HF, high frequency; ln, natural log-transformed

Table 2. Smallest worthwhile change (SWC) and the number of patients for whom LoA exceeded the defined SWC

	Mean RR, ms	HR, bpm	SDNN, ms	RMSSD, ms	LF, ms^2	lnLF	HF, ms^2	lnHF	LF/HF
$SWC_{0.2}$	11.4	2.3	3.6	4.7	61.7	0.16	236	0.2	0.06
LoA >$SWC_{0.2}$	None	None	4	4	4	1	2	2	2
$SWC_{0.6}$	34.3	6.8	10.8	14.1	185.0	0.48	708	0.7	0.18
LoA >$WC_{0.6}$	None	None	None	None	None	1	None	None	1

Abbreviations: RR, time elapsed between two successive R waves of the QRS signal on the electrocardiogram; ms, milliseconds; ms^2, milliseconds squared; HR, heart rate; bpm, beats per minute; SDNN, standard deviation of NN intervals; RMSSD, root mean square of successive RRi differences; LF, low frequency; HF, high frequency; ln, natural log-transformed; LoA, limits of agreement

Respiratory rate and its stationarity, TV-relative changes

The RespRate was between 8 and 25 breaths/min and was stationary for all patients with one exception (Figure 1). There was no statistically significant correlation between either the standard deviation of relative TV or the standard deviation of the RespRate, and the difference between parameters calculated using ECG and the Pneumonitor (R between –0.36 and 0.38; $P > 0.14$ for all), which suggests no association between breathing pattern and RRi agreement between devices.

DISCUSSION

The number of RRi, mean RR, HR, and HRV parameters calculated based on edited RRi acquired during rest condition using ECG and the Pneumonitor presented sufficient agreement in pediatric cardiac patients.

The widespread use of wearable devices in medical practice is hampered due to the lack of validation studies [23]. A polar chest strap seems to be the most popular wearable device used to register RRi, validated mostly in adults and rarely in children [37, 38]. Nevertheless, breathing monitoring is not incorporated into such wearable sensors [39]. As mentioned in numerous previous studies, information on breathing is necessary to interpret HRV data accurately (see [4]), especially in populations with respiratory disturbances. An increased RespRate is a common symptom in children with congestive heart failure [40], integral to the diagnosis of acute lower respiratory infection [41].

A Pneumonitor can be considered a wearable device that allows recording both cardiac and respiratory activity and raises the possibility of evaluating cardiorespiratory coupling and cardiorespiratory fitness [42] in various measurement conditions (also dynamic), while still preserving the quantitative nature of the results. This enables assessing the flow between the cardiac and respiratory systems within the causal domain (to identify the directionality and strength of cardiorespiratory coupling and interactions) [43]. The relationships were studied both from methodological and physiological perspectives [44–46]. Procedures and tests developed to explore the coupling between time series in general (e.g., Granger causality) applied for cardiorespiratory data recorded during spontaneous and controlled activity showed ambiguous insights into the causal relationship. Cardiorespiratory interaction has been regarded as primarily respiration-to-heart rate [47] heart rate-to-respiration [48], quasi-cyclical (TV through HR changes, rate to RespRate [45]), or bidirectional [49]. However, these differences probably depend on different analytical techniques employed [4], which could be studied further with the Pneumonitor and applied specifically in the pediatric cohort [50].

The following limitations can be pointed out: the exploratory character of the study, relatively small size and heterogenous nature of the study, lack of inclusion of healthy pediatric subjects as a control group, differences in sampling frequencies between devices, and the procedure assuming only static conditions. An extension of the study

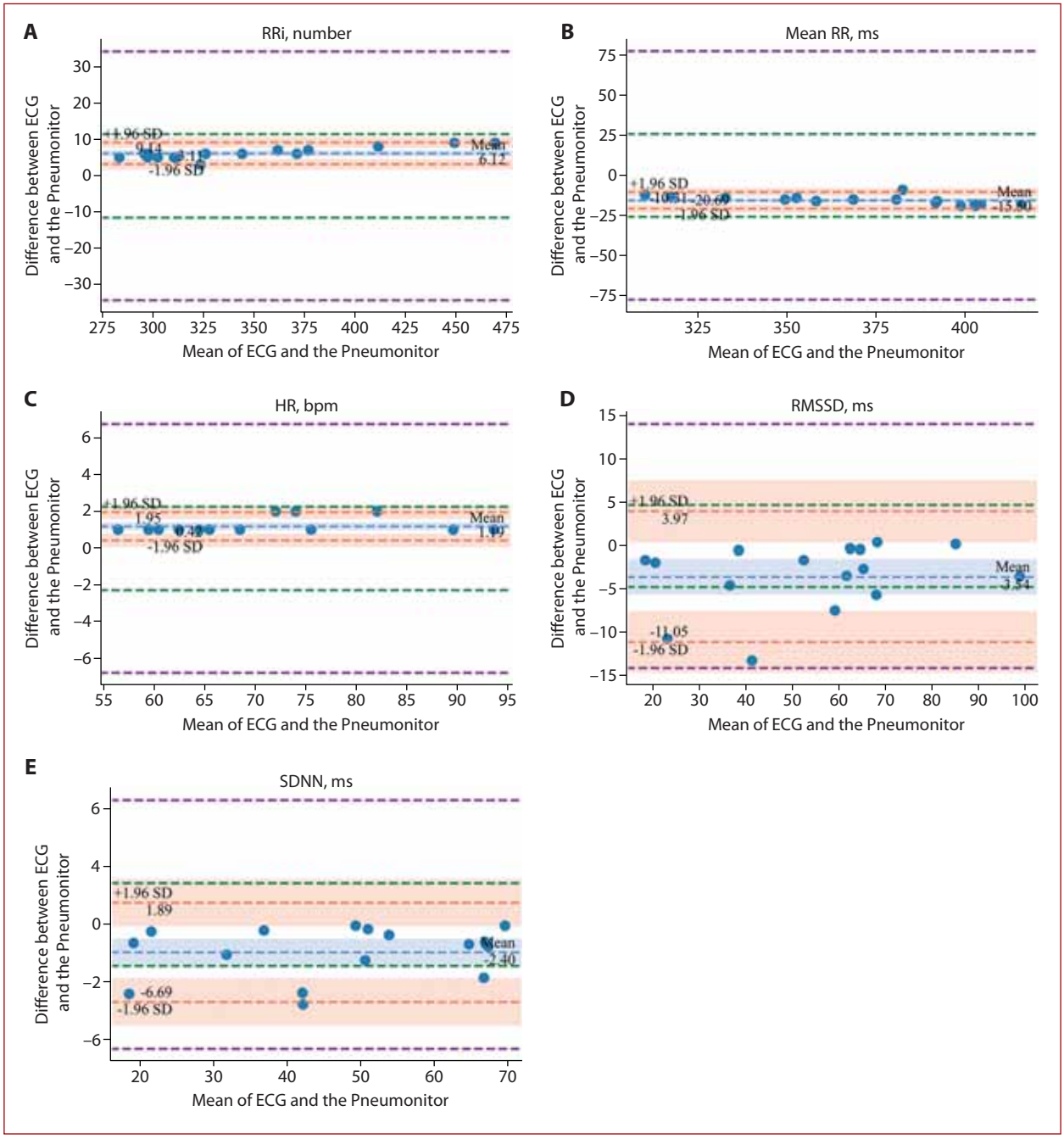


Figure 2. Bland-Altman plots for the number of RRi, mean RR, HR, and time-domain HRV calculated based on RRi obtained using ECG and the Pneumonitor. The dashed blue line presents mean difference, dashed orange lines represent LoA. The blue and orange areas highlight the confidence intervals for the mean and LoA, respectively. The dashed green and purple lines show the $SWC_{0.2}$ and $SWC_{0.6}$

Abbreviations: RRi, RR intervals; ms, milliseconds; HR, heart rate; bpm, beats per minute; RMSSD, root mean square of successive RRi differences; SDNN, standard deviation of NN intervals; other — see Figure 1

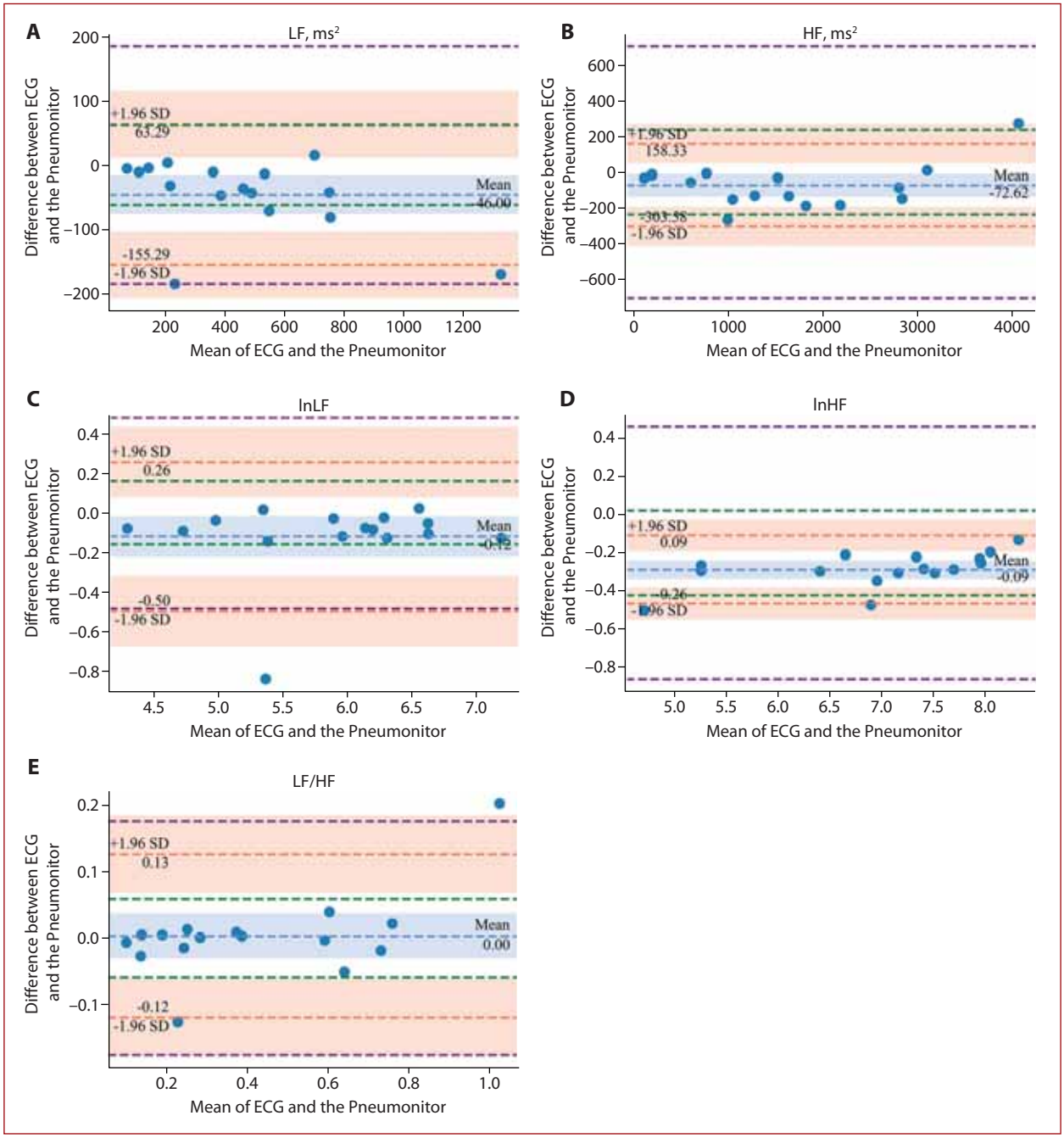


Figure 3. Bland-Altman plots for the number of RRi, mean RR, HR, and time-domain HRV calculated based on RRi obtained using ECG and the Pneumonitor. The dashed blue line presents mean difference, dashed orange lines represent LoA. The blue and orange areas highlight the confidence intervals for the mean and LoA, respectively. The dashed green and purple lines show the $SWC_{0.2}$ and $SWC_{0.6}$

Abbreviations: HF, high frequency; LF, low frequency; ms2, milliseconds squared; ln, natural log-transformed

could be the Lomb-Scargle periodogram — a method that allows more efficient computation of a Fourier-like power spectrum estimator from unevenly sampled data.

The Pneumonitor might be considered appropriate for cardiorespiratory studies in the group of pediatric cardiac patients in rest condition.

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation. 1996; 93(5): 1043–1065, doi: 10.1161/01.CIR.93.5.1043, indexed in Pubmed: 8598068.
2. Malik M, Hnatkova K, Huikuri HV, et al. CrossTalk proposal: Heart rate variability is a valid measure of cardiac autonomic responsiveness. J Physiol. 2019; 597(10): 2595–2598, doi: 10.1113/JP277500, indexed in Pubmed: 31006862.
3. Gąsior JS, Sacha J, Jeleń PJ, et al. Heart Rate and Respiratory Rate Influence on Heart Rate Variability Repeatability: Effects of the Correction for the Prevailing Heart Rate. Front Physiol. 2016; 7: 356, doi: 10.3389/fphys.2016.00356, indexed in Pubmed: 27588006.
4. Quintana DS, Heathers JAJ. Considerations in the assessment of heart rate variability in biobehavioral research. Front Psychol. 2014; 5: 805, doi: 10.3389/fpsyg.2014.00805, indexed in Pubmed: 25101047.
5. Grossman P, Taylor EW. Toward understanding respiratory sinus arrhythmia: relations to cardiac vagal tone, evolution and biobehavioral functions. Biol Psychol. 2007; 74(2): 263–285, doi: 10.1016/j.biopsycho.2005.11.014, indexed in Pubmed: 17081672.
6. Hayano J, Yuda E. Pitfalls of assessment of autonomic function by heart rate variability. J Physiol Anthropol. 2019; 38(1): 3, doi: 10.1186/s40101-019-0193-2, indexed in Pubmed: 30867063.
7. Beda A, Simpson DM, Carvalho NC, et al. Low-frequency heart rate variability is related to the breath-to-breath variability in the respiratory pattern. Psychophysiology. 2014; 51(2): 197–205, doi: 10.1111/psyp.12163, indexed in Pubmed: 24423137.
8. Soer R, Six Dijkstra MW, Bieleman HJ, et al. Influence of respiration frequency on heart rate variability parameters: A randomized cross-sectional study. J Back Musculoskelet Rehabil. 2021; 34(6): 1063–1068, doi: 10.3233/BMR-200190, indexed in Pubmed: 34024811.
9. Martín-Montero A, Gutiérrez-Tobal GC, Kheirandish-Gozal L, et al. Heart rate variability spectrum characteristics in children with sleep apnea. Pediatr Res. 2021; 89(7): 1771–1779, doi: 10.1038/s41390-020-01138-2, indexed in Pubmed: 32927472.
10. Gąsior JS, Sacha J, Pawłowski M, et al. Normative Values for Heart Rate Variability Parameters in School-Aged Children: Simple Approach Considering Differences in Average Heart Rate. Front Physiol. 2018; 9: 1495, doi: 10.3389/fphys.2018.01495, indexed in Pubmed: 30405445.
11. Plaza-Florido A, Sacha J, Alcantara J. Short-term heart rate variability in resting conditions: methodological considerations. Kardiol Pol. 2021; 79(7-8): 745–755, doi: 10.33963/KP.a2021.0054, indexed in Pubmed: 34227676.
12. Cysarz D, Zerm R, Bettermann H, et al. Comparison of respiratory rates derived from heart rate variability, ECG amplitude, and nasal/oral airflow. Ann Biomed Eng. 2008; 36(12): 2085–2094, doi: 10.1007/s10439-008-9580-2, indexed in Pubmed: 18855140.
13. Smulyan H. The Computerized ECG: Friend and Foe. Am J Med. 2019; 132(2): 153–160, doi: 10.1016/j.amjmed.2018.08.025, indexed in Pubmed: 30205084.
14. Bayoumy K, Gaber M, Elshafeey A, et al. Smart wearable devices in cardiovascular care: where we are and how to move forward. Nat Rev Cardiol. 2021; 18(8): 581–599, doi: 10.1038/s41569-021-00522-7, indexed in Pubmed: 33664502.
15. Sana F, Isselbacher EM, Singh JP, et al. Wearable Devices for Ambulatory Cardiac Monitoring: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020; 75(13): 1582–1592, doi: 10.1016/j.jacc.2020.01.046, indexed in Pubmed: 32241375.
16. Tandon A, de Ferranti SD. Wearable Biosensors in Pediatric Cardiovascular Disease. Circulation. 2019; 140(5): 350–352, doi: 10.1161/CIRCULATIONAHA.119.038483, indexed in Pubmed: 31356135.
17. Młyńczak M, Niewiadomski W, Zylinski M, et al. Ambulatory devices measuring cardiorespiratory activity with motion. In Proceedings of the 10th International Joint Conference on Biomedical Engineering Systems and Technologies (BIOSTEC 2017), Porto, Portugal, 21–23 February 2017: 91–97.
18. Seppä VP, Hyttinen J, Uitto M, et al. Novel electrode configuration for highly linear impedance pneumography. Biomed Tech (Berl). 2013; 58(1): 35–38, doi: 10.1515/bmt-2012-0068, indexed in Pubmed: 23348215.
19. Młyńczak M, Niewiadomski W, Żyliński M, et al. Assessment of calibration methods on impedance pneumography accuracy. Biomed Tech (Berl). 2016; 61(6): 587–593, doi: 10.1515/bmt-2015-0125, indexed in Pubmed: 26684348.
20. Młyńczak M, Krysztofiak H. Cardiorespiratory Temporal Causal Links and the Differences by Sport or Lack Thereof. Front Physiol. 2019; 10: 45, doi: 10.3389/fphys.2019.00045, indexed in Pubmed: 30804797.
21. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986; 1(8476): 307–310, indexed in Pubmed: 2868172.
22. Zaki R, Bulgiba A, Ismail R, et al. Statistical methods used to test for agreement of medical instruments measuring continuous variables in method comparison studies: a systematic review. PLoS One. 2012; 7(5): e37908, doi: 10.1371/journal.pone.0037908, indexed in Pubmed: 22662248.
23. Pevnick JM, Birkeland K, Zimmer R, et al. Wearable technology for cardiology: An update and framework for the future. Trends Cardiovasc Med. 2018; 28(2): 144–150, doi: 10.1016/j.tcm.2017.08.003, indexed in Pubmed: 28818431.
24. Milagro J, Gracia-Tabuenca J, Seppa VP, et al. Noninvasive Cardiorespiratory Signals Analysis for Asthma Evolution Monitoring in Preschool Children. IEEE Trans Biomed Eng. 2020; 67(7): 1863–1871, doi: 10.1109/TBME.2019.2949873, indexed in Pubmed: 31670660.
25. Kalidas V, Tamil L. Real-time QRS detector using stationary wavelet transform for automated ECG analysis. 2017 IEEE 17th International Conference on Bioinformatics and Bioengineering. 2017: 457–461, doi: 10.1109/BIBE.2017.00-12..
26. Młyńczak M, Cybulski G. Decomposition of the Cardiac and Respiratory Components from Impedance Pneumography Signals. Proceedings of the 10th International Joint Conference on Biomedical Engineering Systems and Technologies. 2017(4): 26–33, doi: 10.5220/0006107200260033.
27. Giles DA, Draper N. Heart Rate Variability During Exercise: A Comparison of Artefact Correction Methods. J Strength Cond Res. 2018; 32(3): 726–735, doi: 10.1519/JSC.0000000000001800, indexed in Pubmed: 29466273.
28. Cilhoroz B, Giles D, Zaleski A, et al. Validation of the Polar V800 heart rate monitor and comparison of artifact correction methods among adults with hypertension. PLoS One. 2020; 15(10): e0240220, doi: 10.1371/journal.pone.0240220, indexed in Pubmed: 33031480.
29. Seely AJE, Macklem PT. Complex systems and the technology of variability analysis. Crit Care. 2004; 8(6): R367–R384, doi: 10.1186/cc2948, indexed in Pubmed: 15566580.
30. Tarvainen MP, Niskanen JP, Lipponen JA, et al. Kubios HRV: heart rate variability analysis software. Comput Methods Programs Biomed. 2014; 113(1): 210–220, doi: 10.1016/j.cmpb.2013.07.024, indexed in Pubmed: 24054542.
31. Tarvainen MP, Ranta-Aho PO, Karjalainen PA. An advanced detrending method with application to HRV analysis. IEEE Trans Biomed Eng. 2002; 49(2): 172–175, doi: 10.1109/10.979357, indexed in Pubmed: 12066885.

32. Phillips P, Perron P. Testing for a unit root in time series regression. Biometrika. 1988; 75(2): 335–346, doi: 10.1093/biomet/75.2.335.
33. Abu-Arafeh A, Jordan H, Drummond G. Reporting of method comparison studies: a review of advice, an assessment of current practice, and specific suggestions for future reports. Br J Anaesth. 2016; 117(5): 569–575, doi: 10.1093/bja/aew320, indexed in Pubmed: 27799171.
34. Hopkins WG, Marshall SW, Batterham AM, et al. Progressive statistics for studies in sports medicine and exercise science. Med Sci Sports Exerc. 2009; 41(1): 3–13, doi: 10.1249/MSS.0b013e31818cb278, indexed in Pubmed: 19092709.
35. Lee J, Koh D, Ong CN. Statistical evaluation of agreement between two methods for measuring a quantitative variable. Comput Biol Med. 1989; 19(1): 61–70, doi: 10.1016/0010-4825(89)90036-x, indexed in Pubmed: 2917462.
36. Lin LK. A concordance correlation coefficient to evaluate reproducibility. Biometrics. 1989; 45(1): 255, doi: 10.2307/2532051.
37. Gamelin FX, Baquet G, Berthoin S, et al. Validity of the polar S810 to measure R-R intervals in children. Int J Sports Med. 2008; 29(2): 134–138, doi: 10.1055/s-2007-964995, indexed in Pubmed: 17614016.
38. Speer KE, Semple S, Naumovski N, et al. Measuring Heart Rate Variability Using Commercially Available Devices in Healthy Children: A Validity and Reliability Study. Eur J Investig Health Psychol Educ. 2020; 10(1): 390–404, doi: 10.3390/ejihpe10010029, indexed in Pubmed: 34542492.
39. Charlton PH, Bonnici T, Tarassenko L, et al. An assessment of algorithms to estimate respiratory rate from the electrocardiogram and photoplethysmogram. Physiol Meas. 2016; 37(4): 610–626, doi: 10.1088/0967-3334/37/4/610, indexed in Pubmed: 27027672.
40. Kay JD, Colan SD, Graham TP. Congestive heart failure in pediatric patients. Am Heart J. 2001; 142(5): 923–928, doi: 10.1067/mhj.2001.119423, indexed in Pubmed: 11685182.
41. Smyth RL. Lessons from normal heart and respiratory rates in children. Lancet. 2011; 377(9770): 974–975, doi: 10.1016/S0140-6736(11)60102-5, indexed in Pubmed: 21411135.
42. Muntaner-Mas A, Martinez-Nicolas A, Lavie CJ, et al. A Systematic Review of Fitness Apps and Their Potential Clinical and Sports Utility for Objective and Remote Assessment of Cardiorespiratory Fitness. Sports Med. 2019; 49(4): 587–600, doi: 10.1007/s40279-019-01084-y, indexed in Pubmed: 30825094.
43. Acampa M, Voss A, Bojić T. Editorial: Cardiorespiratory Coupling-Novel Insights for Integrative Biomedicine. Front Neurosci. 2021; 15: 671900, doi: 10.3389/fnins.2021.671900, indexed in Pubmed: 33897367.
44. Rosoł M, Młyńczak M, Cybulski G. Granger causality test with nonlinear neural-network-based methods: Python package and simulation study. Comput Methods Programs Biomed. 2022; 216: 106669, doi: 10.1016/j.cmpb.2022.106669, indexed in Pubmed: 35151111.
45. Młyńczak M, Krysztofiak H. Discovery of Causal Paths in Cardiorespiratory Parameters: A Time-Independent Approach in Elite Athletes. Front Physiol. 2018; 9: 1455, doi: 10.3389/fphys.2018.01455, indexed in Pubmed: 30425645.
46. Nuzzi D, Stramaglia S, Javorka M, et al. Extending the spectral decomposition of Granger causality to include instantaneous influences: application to the control mechanisms of heart rate variability. Philos Trans A Math Phys Eng Sci. 2021; 379(2212): 20200263, doi: 10.1098/rsta.2020.0263, indexed in Pubmed: 34689615.
47. Zhu Y, Hsieh YH, Dhingra RR, et al. Quantifying interactions between real oscillators with information theory and phase models: application to cardiorespiratory coupling. Phys Rev E Stat Nonlin Soft Matter Phys. 2013; 87(2): 022709, doi: 10.1103/PhysRevE.87.022709, indexed in Pubmed: 23496550.
48. Tzeng YC, Larsen PD, Galletly DC. Cardioventilatory coupling in resting human subjects. Exp Physiol. 2003; 88(6): 775–782, doi: 10.1113/eph8802606, indexed in Pubmed: 14603377.
49. Porta A, Castiglioni P, Di Rienzo M, et al. Cardiovascular control and time domain Granger causality: insights from selective autonomic blockade. Philos Trans A Math Phys Eng Sci. 2013; 371(1997): 20120161, doi: 10.1098/rsta.2012.0161, indexed in Pubmed: 23858489.
50. Joshi R, Kommers D, Long Xi, et al. Cardiorespiratory coupling in preterm infants. J Appl Physiol (1985). 2019; 126(1): 202–213, doi: 10.1152/japplphysiol.00722.2018, indexed in Pubmed: 30382810.

ECMO in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension as a bridge to therapy

Alejandro Cruz-Utrilla[1, 2], Elena Puerto García Martín[2, 3], Laura Domínguez Pérez[2, 3], Anibal Ruiz Curiel[2, 4], Andrés Quezada[2, 5], Alejandro Durante López[2, 3], Lourdes Vicent[2, 3], Roberto Martín Asenjo[2, 3], Williams Hinojosa[1, 2], Andrea Eixerés[2, 6], Laura Forcén Acebal[2, 7], María Galindo[2, 8], Fernando Arribas Ynsaurriaga[2, 4, 9, 10], Pilar Escribano-Subias[1, 2, 9, 10], Héctor Bueno[2, 4, 9, 10]

[1]Pulmonary Hypertension Unit, Department of Cardiology, Hospital Universitario 12 de Octubre, Madrid, Spain
[2]European Reference Network of Rare Respiratory Disease (ERN-Lung), Brussels, Belgium
[3]Intensive Cardiac Care Unit, Department of Cardiology, Hospital Universitario 12 de Octubre, Madrid, Spain
[4]Department of Cardiology, Hospital Universitario 12 de Octubre, Madrid, Spain
[5]Department of Pneumology, Hospital Universitario 12 de Octubre, Madrid, Spain
[6]Department of Cardiac Surgery, Hospital Universitario 12 de Octubre, Madrid, Spain
[7]Department of Obstetrics and Gynecology, Hospital Universitario 12 de Octubre, Madrid
[8]Department of Reumatology, Hospital Universitario 12 de Octubre, Madrid, Spain
[9]Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Instituto de Salud Carlos III (ISCIII), Madrid, Spain
[10]Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain

Correspondence to:
Pilar Escribano-Subias, MD, Pulmonary Hypertension Unit, Department of Cardiology, Hospital Universitario 12 de Octubre, Avenida de Córdoba S/N. 28041, Madrid, C. Madrid, Spain, phone: +34 629 019 500. e-mail: pilar.escribano.subias@gmail.com

DOI: 10.33963/KP.a2023.0055

Received:
September 3, 2022

Accepted:
January 4, 2023

Early publication date:
February 28, 2023

INTRODUCTION

Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are severe diseases in which pulmonary vasculopathy may cause the failure of the right ventricle and ventilatory lung function [1]. The use of pulmonary endarterectomy (PEA) or balloon pulmonary angioplasty in CTEPH [2, 3] and pulmonary vasodilators in both entities has led to an important increase in life expectancy [4]. Cardiogenic shock (CS) is a catastrophic complication in these patients, either as the initial presentation or developed after a triggering event in previously stable cases [5]. In recent years, the use of extracorporeal membrane oxygenation (ECMO) in patients with refractory CS or massive pulmonary embolism (PE) has expanded. This may be an option in critically ill patients with PAH or CTEPH. However, evidence in this setting is scarce [6]. A multidisciplinary approach to determine a specific strategy in each case is crucial [7]. We present the first results of a newly created ECMO program in CS as a bridge to therapy (BTTh) for PAH/CTEPH in our critical cardiovascular care unit (CCCU).

METHODS

We included consecutive patients with PAH or CTEPH needing ECMO from January 2021 until June 2022 in the Hospital Universitario 12 de Octubre (Madrid, Spain). Clinical management was decided individually upon daily consensus, including PAH and CCCU specialists in coordination with other specialists of the multidisciplinary pulmonary hypertension (PH) unit. This unit is one of the two Spanish reference centers for PH, with the capacity for lung transplantation and complete interventional management of PAH and CTEPH. All patients signed informed consent before their inclusion in the Spanish Registry of Pulmonary Hypertension (REHAP).

RESULTS AND DISCUSSION

An ECMO was implanted in four patients in that period as a BTTh, with a veno-arterial (VA) configuration in two cases and venovenous (VV) in the remaining two. Weaning of the mechanical support was possible in three patients, and hospital discharge was possible in two cases (Table 1). Only one patient is still alive after two years of follow-up.

Table 1. PAH and CTEPH cases undergoing ECMO in the 2020–2021 period

	Case 1	Case 2	Case 3	Case 4
Previous condition				
Age, years	46	32	56	59
Sex	Female	Female	Male	Female
Weight, kg	55	95	89	85
BMI, kg/m^2	22.6	34.9	29.7	31.2
PH group	PAH associated with CTD	PAH associated with overlap mixed CTD and primary biliary cirrhosis	CTEPH	CTEPH
Time to diagnosis of PH	7 years	3 weeks	12 months	2 months
Predominant clinical status on admission	Respiratory insufficiency	Cardiogenic shock	Respiratory insufficiency	Cardiogenic shock
Previous treatment	Bosentan, tadalafil, and selexipag	Ursobilane, levothyroxine, and omeprazole	Tadalafil and ambrisentan	Insulin and enoxaparin
HR, bpm	100	110	115	100
Situation prior ECMO cannulation				
BP, mm Hg	110/66	110/65	95/55	127/89
pH	—	7.52	7.49	7.31
Pre-ECMO lactic acid, mmol/l	1.8	1.5	0.7	10
$PaCO_2$, mm Hg	—	20	41	29
PaO_2, mm Hg)	—	108	46	68
Creatinine, mg/dl	1.21	0.55	1.36	1.99
Hemoglobin, g/dl	11	12.8	11.3	10.3
Platelet count, cc	91000	32000	81000	161000
NT-proBNP, pg/ml	2992	4495	8295	—
Baseline oxygen saturation, %	60	98	86	91
TTE parameters				
RV diameter, mm	37	61	63	54
Diastolic EI	1.2	1.9	1.2	1.6
Estimated RVSP, mm Hg	109	117	70	86
TAPSE, mm	14	14	19	13
S', cm/s	15	8	14	8
FAC, %	27	10	20	22.5
TR, 0–4	1	4	2–3	4
RA area, cm^2	19	23	39	22
LVIV, cc/m^2	43	—	67	—
LV diameter, mm	35	27	37	41
LVEF, %	72	60	72	60
LV diastolic function, 1–4	2	2	2	2
IVC, dilated	Yes	Yes	Yes	Yes
IVC, collapse >50%	No	No	No	No
Pericardial effusion, 0–4	2–3	1	1	0
RV hemodynamics				
mPAP, mm Hg	71	70	45	52
RAP, mm Hg	6	14	19	28
RVSP, mm Hg	94	120	85	96
PCWP, mm Hg	9	14	16	—[a]
Cardiac output, l/min	4	—	2.6	—
Cardiac index, l/min/m^2	2.5	—	1.5	—
PVR (WU)	15.5	—	11	—
Associated conditions	Neumonitis of unknown origin	12-week pregnancy, severe thrombocytopenia, and alveolar hemorrhage	Interstitial edema after initiation of intravenous epoprostenol	Subacute PE on a previously unknown chronic CTEPH
ECMO				
Time from ICCU admission to ECMO implantation, days	6	5	1	1
Initial configuration	VV	VA	VV	VA
Configuration change	No	VAV and VV	VAV (peripheral and central)	No
Distal perfusion cannula during VA or VAV ECMO	No	No	Yes	Yes
Initial blood flow, lpm	3.3	3.2	3.3	3.4

Table 1. (cont.) PAH and CTEPH cases undergoing ECMO in the 2020–2021 period

	Case 1	Case 2	Case 3	Case 4
Initial sweep gas flow rate (lpm) and FiO_2 ECMO (%). HFNC (lpm/FiO_2) or LFNC (lpm)	7 and 1. HFNC 40/0.9.	0.3 and 0.6. HFNC 30/100.	3 and 1. HFNC 50/40.	2 and 0.8. LFNC a 0.5.
Duration of ECMO support, days	12	21	34	13
Peak lactic acid, mmol/l, during ECMO	2.9	6.4	0.7	10
Hemoglobin, g/dl, nadir	8.9	9.3	8.7	7.8
Platelet count, cc, nadir	34 000	16 000	41 000	52 000
Serious bleeding event	Yes	Yes	Yes	No
Transfusion required	Yes	Yes	Yes	Yes
Membrane thrombosis	No	No	Yes	No
Cerebral, lower limb, or another embolic event	No	No	No	No
Clinically significant lower limb ischemia	–	No	No	No
Peak creatinine, mg/dl, during ECMO	1.92	0.76	2.06	2.2
Requires CRRT	No	No	Yes	No
Definite infection requiring antibiotic	Yes	No	Yes	Yes
Type of infection	Pneumonia	—	Pneumonia	Urinary tract infection and bacteremia
Antibiotic without confirmed infection	—	Yes	—	—
Treatment while being on ECMO				
Pulmonary vasodilators				
PDE5 inhibitor	Tadalafil	Sildenafil	Tadalafil	—
Endothelin receptor antagonist	—	Macitentan	Macitentan	—
Inhaled vasodilator	—	—	—	—
Intravenous or subcutaneous prostacyclins	Epoprostenol 8 ng/kg/min	Epoprostenol 20 ng/kg/ /min	Epoprostenol 8 ng/kg/min	—
Inotropic support	Dobutamine	Dobutamine	Dobutamine	Dobutamine
Vasopressors	No	Norepinephrine	Norepinephrine and vasopressin	No
Systemic vasodilator	No	No	No	Nitroprusside
Maximum ventilatory support	HFNC	HFNC	IMV (maximum PEEP of 18 cm H_2O)	LFNC
Duration of mechanical ventilation, days	—	—	—	—
Duration of HFNC, days	24	25	12	—
Tracheostomy during hospitalization	No	No	Yes	No
Additional treatments	Corticosteroids	Pregnancy termination, corticosteroids, cyclophosphamide, rituximab, and immunoglobulin G	Balloon pulmonary angioplasty	Pulmonary endarterectomy
Outcome	Discharged alive	Discharged alive	Died while on ECMO	Weaned from ECMO. Death in the post-operative period of PEA
ICCU length of stay, days	25	30	32	14
Hospital length of stay, days	67	46	38	27

[a]PCWP not achieved due to PE

Abbreviations: BMI, body mass index; BP, blood pressure; cc, cubic centimeters per minute; CCU, coronary care unit; CTD, connective tissue disease; CRRT, continuous renal replacement therapy; CTEPH, chronic thromboembolic pulmonary hypertension; ECMO, extracorporeal membrane oxygenation; EI, eccentricity index; FAC, fractional area change of right ventricle; FiO_2, fraction of inspired oxygen; HFNC, high-flow nasal cannula; HR, heart rate; IMV, invasive mechanical ventilation; IVC, inferior vena cava; LFNC, low flow nasal cannula; LV diastolic function (1–4), 1 normal, 2 impaired relaxation, 3 pseudo-normal pattern, 4 restrictive pattern; LVEF, left ventricular ejection fraction; LVIV, left ventricular index volume; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PaO_2, partial pressure of oxygen in arterial blood; PCWP, pulmonary capillary wedge pressure; PDE5 inhibitor, phosphodiesterase type 5 inhibitor; PE, pulmonary embolism; PEEP, positive end-expiratory pressure; PEA, pulmonary endarterectomy; Pericardial effusion (0–4), 0 absent, 1 light, 2 moderate, 3 serious, 4 pericardial tamponade; PH, pulmonary hypertension; PVR (WU), pulmonary vascular resistance (Wood units); RA, right atrium; RAP, right atrial pressure; RV, right ventricle; RVSP, right ventricle systolic pressure; TTE, transthoracic echocardiogram parameters; TR (0–4), tricuspid regurgitation (0 absent, 1 light, 2–3 moderate, 4 serious); VA, veno-arterial; VAV, veno-arterio-venous; VV, veno-venous

Case 1. A 46-year-old woman with previously known PAH associated with systemic sclerosis on triple vasodilator therapy and severe immunosuppressive therapy presented a rapid respiratory deterioration attributed to immune-related pneumonitis. Considering the severity of respiratory insufficiency, the patient needed mechanical support with VV-ECMO. Treatment with corticosteroids caused rapid clinical amelioration, allowing ECMO weaning and patient discharge. Eleven months later, the patient died due to severe COVID-19 bilateral pneumonia.

Case 2. A 32-year-old woman without known PAH was admitted to the hospital in CS. She was found to be 12 weeks pregnant at that moment. A VA-ECMO was implanted as a bridge to pregnancy termination, which was then successfully carried out. Nevertheless, she developed severe thrombocytopenia and an alveolar hemorrhage,

which caused a progressive decline in lung function, whereby we changed the configuration of the ECMO to VAV. After initiation of immunosuppressive drugs and up-titration of pulmonary vasodilators and a dramatic hemodynamic improvement, the patient could be weaned from ECMO. She was finally discharged on triple vasodilator therapy.

Case 3. A 56-year-old male with severe distal CTEPH presented severe bilateral interstitial edema after the initiation of intravenous epoprostenol, which finally needed VV-ECMO implantation. Due to further hemodynamic impairment, a switch to VA-ECMO was done. After stabilization, balloon pulmonary angioplasty (BPA) was used as a rescue therapy. Despite an initial improvement after three BPA procedures, he presented severe repetitive episodes of hemoptysis, which required tracheal intubation and mechanical ventilation. The patient died due to ventilator-associated pneumonia after 34 days of mechanical support while being still supported by ECMO at that moment.

Case 4. A 59-year-old woman presented with CS and severe respiratory insufficiency. The initial evaluation revealed a probable subacute episode of PE on top of a previously unknown central CTEPH. Treatment with percutaneous mechanical thrombectomy was administered. During the procedure, the patient further deteriorated hemodynamically, and a VA-ECMO was emergently implanted in the cath laboratory. The patient remained stable for one week when elective PEA was done, with excellent results. The ECMO was withdrawn two days after surgery. Thirteen days later, while being clinically stable at that moment, the patient died suddenly due to a new episode of massive PE.

ECMO as a BTTh may be a useful option in critically ill patients with PAH or CTEPH. Our results are in line with those published by Rosenzweig et al. [8]. In that last study, survival of 31.6% was facilitated by ECMO as a bridge to recovery (BTR), and more than 75% of patients survived until ECMO decannulation. The selection of candidates for mechanical support is of critical importance [9]. Likely, the reduction of right ventricular pressure overload and increase in systemic blood pressure are key features involved in the hemodynamic improvement after ECMO cannulation. Additionally, the reduction in the hypoxic pulmonary vasoconstrictive response and of the right-to-left shunting might also be beneficial effects of ECMO implantation. Our experience suggests that cases with acute decompensation triggered by factors like immune disorders or pregnancy could be good candidates for ECMO as a BTTh. We presented a case of VA-ECMO as a bridge to pregnancy termination, representing one of the first reports in the literature [10]. CTEPH is a more challenging scenario for ECMO support, as ventilatory impairment and coagulation disturbances are usually more advanced. Nevertheless, ECMO during the postoperative period of PEA as a BTR has usually good results [2]. The use of ECMO as a bridge to lung transplantation in Spain demonstrates good results [11]. A complementary and interesting option for end-stage patients, or those waiting for lung transplantation, could be the creation of an interatrial septostomy [12].

ECMO management in pulmonary hypertension requires specific considerations. The initial configuration should be based on the severity of hemodynamic impairment and respiratory insufficiency, trying to minimize the need for tracheal intubation and mechanical ventilation, considering the high risk of clinical deterioration during sedation in cases of right ventricular dysfunction. In candidates for lung transplantation, tracheal intubation should also be avoided, as this is a relative contraindication for transplantation. We opted for VA-ECMO when a more profound shock was established (Society for Cardiovascular Angiography and Intervention [SCAI] index stage D in both cases) and for initial VV-ECMO when respiratory impairment was the predominant problem (SCAI index C). The dose of inotropic or vasopressor therapy was similar in both groups, with comparable vasoactive-inotropic scores. CCCU specialists should also be aware of the possibility of upper-body hypoxemia since the perfusion of coronary arteries and the brain in VA-ECMO is frequently provided by deoxygenated blood, especially when lung gas exchange is impaired. In cases of baseline impaired lung function or expectation of worsening after cannulation, an initial axillar configuration or switching to VAV-ECMO could provide adequate oxygenation for the upper body. After the initiation and up-titration of pulmonary vasodilators, with hemodynamic improvement, the arterial cannula can often be removed. In these cases, if respiratory amelioration continues, ECMO weaning is feasible. Thrombocytopenia is another relevant aspect. In our series, three patients started with a moderate or severe reduction of the platelet count, all of them with bleeding episodes. None of our patients had ischemic or embolic events. Therefore, our protocol recommends the maintenance of high ECMO flows and low coagulation times, especially in patients at risk of bleeding events.

In conclusion, we report the initial experience of a multidisciplinary PH unit with ECMO support as a BTTh in patients with PAH or CTEPH. The positive results, with ECMO weaning possible in three of four critically ill cases, emphasize the need to maintain a coordinated approach involving different specialists in this complex scenario.

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Humbert M, Guignabert C, Bonnet S, et al. Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. Eur Respir J. 2019; 53(1), doi: 10.1183/13993003.01887-2018, indexed in Pubmed: 30545970.
2. Papamatheakis DG, Poch DS, Fernandes TM, et al. Chronic thromboembolic pulmonary hypertension: JACC focus seminar. J Am Coll Cardiol. 2020; 76(18): 2155–2169, doi: 10.1016/j.jacc.2020.08.074, indexed in Pubmed: 33121723.
3. López-Gude MJ, Blanco I, Benito-Arnáiz V, et al. Pulmonary thromboendarterectomy in chronic thromboembolic pulmonary hypertension: the Spanish experience. Ann Cardiothorac Surg. 2022; 11(2): 151–160, doi: 10.21037/acs-2021-pte-18, indexed in Pubmed: 35433371.
4. Hassoun PM. Pulmonary arterial hypertension. N Engl J Med. 2021; 385(25): 2361–2376, doi: 10.1056/NEJMra2000348, indexed in Pubmed: 34910865.
5. Tejwani V, Patel DC, Zein J, et al. Survival after an ICU hospitalization for pulmonary hypertension. Chest. 2018; 154(1): 229–231, doi: 10.1016/j.chest.2018.03.028, indexed in Pubmed: 30044743.
6. Torbic H, Hohlfelder B, Krishnan S, et al. A review of pulmonary arterial hypertension treatment in extracorporeal membrane oxygenation: A case series of adult patients. J Cardiovasc Pharmacol Ther. 2022; 27: 10742484211069005, doi: 10.1177/10742484211069005, indexed in Pubmed: 35006031.
7. Tycińska A, Grygier M, Biegus J, et al. Mechanical circulatory support. An expert opinion of the Association of Intensive Cardiac Care and the Association of Cardiovascular Interventions of the Polish Cardiac Society. Kardiol Pol. 2021; 79(12): 1399–1410, doi: 10.33963/KP.a2021.0169, indexed in Pubmed: 34861044.
8. Rosenzweig EB, Gannon WD, Madahar P, et al. Extracorporeal life support bridge for pulmonary hypertension: A high-volume single-center experience. J Heart Lung Transplant. 2019; 38(12): 1275–1285, doi: 10.1016/j.healun.2019.09.004, indexed in Pubmed: 31582284.
9. Benza RL, Ghofrani HA, Grünig E, et al. Intensive care, right ventricular support and lung transplantation in patients with pulmonary hypertension. Eur Respir J. 2019; 53(1): 1172–1180, doi: 10.1183/13993003.01906-2018, indexed in Pubmed: 30545979.
10. Ortiz-Bautista C, López-Gude MJ, Grande García J, et al. Extracorporeal membrane oxygenation support during pregnancy in pulmonary veno-occlusive disease. Rev Esp Cardiol (Engl Ed). 2019; 72(2): 174–175, doi: 10.1016/j.rec.2018.01.001, indexed in Pubmed: 29428338.
11. Quezada-Loaiza CA, de Pablo Gafas A, Pérez V, et al. Lung transplantation in pulmonary hypertension: a multidisciplinary unit's management experience. Transplant Proc. 2018; 50(5): 1496–1503, doi: 10.1016/j.transproceed.2018.02.073, indexed in Pubmed: 29880377.
12. Velázquez Martín M, Albarrán González-Trevilla A, Jiménez López-Guarch C, et al. Use of atrial septostomy to treat severe pulmonary arterial hypertension in adults. Rev Esp Cardiol (Engl Ed). 2016; 69(1): 78–81, doi: 10.1016/j.rec.2015.09.006, indexed in Pubmed: 26643769.

Cognitive impairment in patients after myocardial infarction

Dominika Kasprzak[1*], Teresa Ganowicz-Kaatz[1*], Janusz Rzeźniczak[1*], Marek Słomczyński[1], Katarzyna Kaczmarek-Majer[2, 3], Jan Budzianowski[4], Konrad Pieszko[4], Jarosław Hiczkiewicz[4], Andrzej Tykarski[5], Paweł Burchardt[1, 5]

[1]Department of Cardiology, J. Struś Hospital, Poznań, Poland
[2]Department of Stochastic Methods, System Research Institute, Polish Academy of Sciences, Warszawa, Poland
[3]Information Technologies for Psychiatry Foundation, Poznań, Poland
[4]University of Zielona Góra, Zielona Góra, Poland
[5]Department of Hypertension, Angiology, and Internal Medicine, Poznan University of Medical Sciences, Poznań, Poland
*These authors equally contributed to the study

Correspondence to:
Dominika Kasprzak,
Department of Cardiology,
J. Struś Hospital,
Szwajcarska 3, 61–285 Poznań,
Poland,
phone: +48 618 739 395,
e-mail:
domi.kasprzak@gmail.com

DOI: 10.33963/KP.a2023.0056

Received:
May 18, 2022

Accepted:
February 18, 2023

Early publication date:
March 5, 2023

INTRODUCTION

Both cognitive impairment (CI) and dementia as well as cardiovascular disease (CVD), including myocardial infarction (MI), are a significant burden on the health and social care systems. Currently, 50 million people worldwide suffer from dementia, while CVDs are still the leading cause of death [1]. Unfortunately, assessment of cognitive function is not part of routine clinical practice, especially in cardiac patients. Nevertheless, a growing body of evidence points to an association between CVD, including ischemic heart disease, and the occurrence of CI. The mechanisms responsible for this remain largely unknown. The problem of the prevalence of psychiatric disorders in cardiac patients is also highlighted by the latest guidelines on cardiovascular prevention. They indicate that all mental disorders are associated with the development of CVD while the onset of CVD is associated with a 2–3 times higher risk of mental disorders. It is estimated that the annual prevalence of psychiatric disorders in patients with CVD is around 40%, leading to a significantly worse prognosis [2]. Given these clinical implications, we have undertaken an assessment of cognitive functioning in people after MI and 6 months later and attempted to identify factors that may influence it.

METHODS

Study design and patient population

This is a pilot study and precedes a larger prospective study. This prospective study was conducted at the Cardiology Department of J. Struś Hospital in Poznań, and its protocol was approved by the Local Bioethics Committee (approval no. 1201/16). Two hundred and twenty patients hospitalized for MI treated by percutaneous coronary intervention (PCI) participated in this pilot study. All participants were clinically assessed on two occasions: during the first MI-related hospitalization on days 2–3 following PCI, and 6 months later. Available medical records including a health history questionnaire, laboratory tests, and echocardiography were collected, and mental state was assessed with the Mini-Mental State Examination (MMSE), Schulman's clock-drawing test (CDT), Beck Depression Inventory (BDI), Athens Insomnia Scale (AIS), and Insomnia Severity Index (ISI) (Table 1 presents the main statistical characteristics of all variables). At baseline, the MMSE scores were corrected according to age and education. Due to the comparable results, the absolute values were used for further analysis. CI was defined as MMSE <27 points or CDT level ≥1. Depression was defined as BDI ≥12, and insomnia was defined as ISI ≥ 15. All tests used in the study have been adapted and validated for the Polish setting.

We distinguished 4 groups of patients depending on the changes in their mental status: (1) permanent CI — presented both at baseline and after 6 months; (2) transient — with deficits at baseline but with a normal test result after 6 months; (3) new onset CI — only after 6 months; and (4) without CI during follow-up.

Table 1. Statistical characteristics of all variables considered in this pilot study were collected during the first MI-related hospitalization on days 2–3 following PCI, and 6 months later (follow-up)

Variable	First hospitalization	Follow-up (after 6 months)
	Mean (SD)/median (IQR)[a]	Mean (SD)/median (IQR)[a]
Age, years	60.1 (9.3)	Not collected
Hgb, g/dl	13.7 (1.6)	14.4 (13.6–15.2)
Hct, %	40.2 (4.2)	42.9 (41–44.9)
RBC, million/µl	4.5 (4.2–4.9)	4.8 (0.4)
WBC, thousand/µl	9.6 (7.8–11.7)	7.6 (6.3–8.8)
PLT, thousand/µl	221 (189–258)	235 (202.2–265.5)
Na, mmol/l	140.5 (139–142)	141 (140–143)
K, mmol/l	4.3 (4–4.5)	4.6 (4.4–4.9)
Creatinine, µmol/l	79 (69–91)	81 (69–91)
Urea, mmol/l	5.3 (4.4–6.3)	5.7 (4.9–6.7)
TN, ng/l	740 (86.5–4153)	9 (9–12)
ALAT, U/l	36 (24–51.5)	24 (18–32)
HDL-C, mmol/l	1.2 (0.9–1.4)	1.3 (1.1–1.5)
LDL-C, mmol/l	3.2 (2.4–3.8)	1.9 (1.6–2.4)
TG, mmol/l	1.4 (1.1–1.9)	1.3 (1–1.7)
TSH, µlU/ml	1 (0.6–1.7)	1.1 (0.8–1.6)
CK, IU/l	51.5 (24.8–128.2)	108 (83–158)
BNP, pg/ml	110.3 (54–199.8)	Not collected
SYNTAX, points	9 (6–14)	Not collected
EF, %	50 (40–50)	50 (50–60)
BDI, points	9 (5–14)	8 (4–13)
Absolute MMSE score, points	27 (25–29)	28 (26–29)
MMSE adjusted score, points	27 (25–28)	28 (26–29)
ISI, points	8 (4–13)	6 (3–11)
CDT, level	0 (0–1)	0 (0–1)
AIS, points	6 (4–9)	5 (3–8)

[a]Mean (SD) is reported if normal distribution was confirmed by the Shapiro-Wilk test. Otherwise, median (IQR) is reported. As a result, mean (SD) are reported for age, Hgb, and Hct variables for the first hospitalization and for RBC for a follow-up visit

Abbreviations: AIS, Athens Insomnia Scale; ALAT, alanine transaminase; BDI, Beck depression inventory; BNP, brain natriuretic peptide; CDT, clock-drawing test; CK, creatine kinase; EF, ejection fraction; Hct, hematocrit; HDL-C, high-density lipoprotein cholesterol; Hgb, hemoglobin; ISI, Insomnia Severity Index; K, potassium; LDL-C, low-density lipoprotein cholesterol; MMSE, Mini-Mental State Examination; Na. sodium; PLT, platelet count; RBC, red blood cells; TG, triglycerides; Tn, troponin; TSH, thyroid stimulating hormone; WBC, white blood cells

Statistical analysis

Continuous variables were reported as means (standard deviation [SD]) or medians (interquartile ranges [IQR]), as appropriate. Normal distribution was tested using the Shapiro-Wilk test. The differences in the numerical variables were tested using the Kruskal-Wallis test. Next, the Mann-Whitney test was performed as a post-hoc test sequentially for 2 groups, and the Bonferroni correction was applied. All analyses were done using programming language R and STATISTICA 10 (StatSoft). Two-sided *P*-values <0.05 were considered to be statistically significant.

RESULTS AND DISCUSSION

The main characteristics of the pilot study sample are presented in the Supplementary material, *Table S1*. At baseline, we identified CI in 40.5% (n = 89) of patients according to the MMSE, and in 34.5% (n = 76) using the CDT. In the follow-up, CI was observed in 33.6% (n = 74) of patients using MMSE and 26.8% (n = 59) using the CDT. Statistical characteristics of age (years), ISI (points), ejection fraction (%), brain natriuretic peptide (BNP, pg/ml), SYNTAX (points), troponin (ng/l), and BDI (points) in the identified four groups are presented in the Supplementary material, *Table S2*.

Patients with permanent deficits (Group 1) in the CDT compared to those without CI (Group 4) had lower peri-infarction ejection fraction (50% [40%–50%] vs. 50% [50%–60%]; $P = 0.006$) and a higher level of peri-infarction BNP (149.6% [91.3%–242.8%] vs. 87.7% [46%–140.8%]; $P = 0.003$)

The prevalence of previously undiagnosed CI in patients hospitalized for MI was high (nearly 40%). These disorders can be either temporary or permanent. Currently, we do not know the specific factors that would allow us to predict these cognitive disorders. However, we can hypothesize that there are different underlying causes of CI following MI. Permanent deficits may be involved in neurodegeneration but so can a higher burden of vascular risk factors. Therefore, the etiology is most likely mixed.

In patients with transient deficits, the cause may be psychological stress after MI and acute phase of the disease but also appropriate treatment and vascular risk factors reduction.

On the other hand, new-onset CI may be connected with accumulating mental health disorders, such as sleep disturbances, and worse control of vascular risk factors. The latter is less likely because our participants had optimal treatment.

While analyzing variables that may affect cognitive function, it is also important to bear in mind depressive disorders, which often occur following MI. Thirty-three percent of the participants in our study presented them during their first hospitalization. This is consistent with previous data reporting depression in 20%–40% of MI patients [3]. CI is among the main symptoms of depression, and its presence is a predictor of dementia development [4].

It is also important to highlight the influence of age, which is a major risk factor for both CI and MI. In our project, patients with persistent CI were significantly older than those without CI during the study. Those included in our project represent a younger population than the average MI patient (60.1 vs. 65.1 for men and 72 for women) [5]. It can be, therefore, assumed that the prevalence of cognitive deficits is underestimated and is higher in clinical practice.

Little is also known about the impact of arrhythmias on cognitive function. Most researchers have focused on atrial fibrillation (AF), associating its presence with higher risk of CI and dementia [6]. Preliminary results of our project did not show that AF significantly affected CI in patients after MI, whereas in those with peri-infarct non-sustained ventricular tachycardia (NSVT), CI was significantly more frequent after 6 months of follow-up ($P = 0.02$). Chen et al. [7] also showed that NSVT was independently associated with CI occurrence and with impairment of executive function in particular. This may suggest that the occurrence of asymptomatic episodes of arrhythmia during follow-up in patients with peri-infarct NSVTs results in ischemic brain lesions. Therefore, they may represent a risk group and should be subject to more careful follow-up.

The results presented here are part of a pilot study. A larger population study is currently being conducted to analyze in detail the factors affecting cognitive function in patients with acute coronary syndrome. We are living longer, but longevity must be accompanied by the quality. CI significantly affects daily functioning not only of those affected but also carers. It is, therefore, important to proactively detect CI at an early stage and try to modify potentially reversible risk factors. If we detect changes in cognitive functioning early, we can implement appropriate management and have time to refer patients to other specialists such as psychologists or neurologists.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Acknowledgments: This work was partially supported by Analyx sp. z o.o. within the pro bono research project. The authors thank Katarzyna Dylewska, Ada Grabarczyk, Justyna Hińcza, Katarzyna Janiszewska, Katarzyna Klamecka-Pol, Lidia Kweizer, Maciej Łobiński, Agnieszka Sęk, and Katarzyna Sulowska for their support in data preparation and statistical analysis.

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. World Health Organization. Global action plan on the public health response to dementia 2017–2025. Geneva 2017.
2. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021; 42(34): 3227–3337, doi: 10.1093/eurheartj/ehab484, indexed in Pubmed: 34458905.
3. Saquib J, AlRomaih NA, Al-Mutairi HM, et al. Correlates of memory loss and depression among myocardial infarction patients in Al-Qassim, Saudi Arabia. J Saudi Heart Assoc. 2018; 30(3): 240–246, doi: 10.1016/j.jsha.2018.04.001, indexed in Pubmed: 29983498.
4. Sáez-Fonseca JA, Lee L, Walker Z. Long-term outcome of depressive pseudodementia in the elderly. J Affect Disord. 2007; 101(1-3): 123–129, doi: 10.1016/j.jad.2006.11.004, indexed in Pubmed: 17184844.
5. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation. 2019; 139(10): e56–e5e528, doi: 10.1161/CIR.0000000000000659, indexed in Pubmed: 30700139.
6. Sawicki S, Mierzyńska A, Krauze A, et al. Silent atrial fibrillation episodes and cognitive impairment in patients with cardiac implantable devices. Protocol of the SAFE-COG ongoing observational single-center non-experimental case-control clinical study. Kardiol Pol. 2021; 79(12): 1362–1364, doi: 10.33963/KP.a2021.0162, indexed in Pubmed: 34845712.
7. Chen L, Agarwal S, Lopez F, et al. Abstract 12946: Higher Burden of Atrial Fibrillation is Independently Associated With Lower Cognitive Function: The Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2014; 130(suppl_2), doi: 10.1161/circ.130.suppl_2.12946.

Coronary Sinus Reducer implantation in refractory angina: Short-term outcomes based on the Lower Silesia Sinus Reducer Registry (LSSRR)

Szymon Włodarczak[1], Piotr Rola[2, 3], Artur Jastrzębski[1], Felix Woitek[4], Mateusz Barycki[3], Łukasz Furtan[3], Adrian Doroszko[5], Adrian Włodarczak[1, 2], Marek Grygier[6], Maciej Lesiak[6]

[1]Department of Cardiology, The Copper Health Center (MCZ), Lubin, Poland
[2]Faculty of Health Science and Physical Culture, Witelon Collegium State University, Legnica, Poland
[3]Department of Cardiology, Provincial Specialized Hospital in Legnica, Legnica, Poland
[4]Department of Internal Medicine and Cardiology, Herzzentrum Dresden, Technische Unversitaet Dresden, Dresden, Germany
[5]Clinical Department of Internal Medicine and Occupational Diseases, Hypertension and Clinical Oncology, Faculty of Medicine, Wroclaw Medical University, Wrocław, Poland
[6]1st Department of Cardiology, University of Medical Sciences, Poznań, Poland

Correspondence to:
Szymon Włodarczak, MD, Department of Cardiology, The Copper Health Center (MCZ), M Skłodowskiej-Curie 66, 59–300 Lubin, Poland, phone: +48 781 201 753, e-mail: wlodarczak.szy@gmail.com

DOI: 10.33963/KP.a2023.0057

Received:
December 29, 2022

Accepted:
February 24, 2023

Early publication date:
March 5, 2023

INTRODUCTION

Despite the undeniable improvement in the field of pharmacological and interventional treatment of coronary artery disease (CAD), still even up to 10% of patients [1] can experience refractory angina pectoris (RAP)-reversible myocardial ischemia which cannot be adequately controlled despite implementation of all available revascularization and pharmacological therapeutic options [2]. RAP has got heterogeneous pathophysiology and involves patients with CAD unsuitable for revascularization (diffuse disease, high risk-benefit profile; diseases affecting distal segments of arteries) along with other than obstructive CAD coronary disorders. RAP significantly affects values that are important from patients' perspective — the quality of life and mortality rate [3]. Recently, a novel device dedicated to patients with RAP has been introduced into clinical practice [4] which was reflected in the latest European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guidelines [2]. Coronary Sinus (CS) Reducer (Neovasc Inc., Richmond, Canada) is a balloon-expandable hourglass-shaped scaffold implanted percutaneously into the coronary sinus creating a narrowing to delay blood outflow and establishing a backward pressure gradient in the coronary artery system. This promotes blood redistribution from less ischemic to more ischemic myocardial regions. In this brief report, we present short-term outcomes based on the Lower Silesia Sinus Reducer Registry (LSSRR).

METHODS

This observational, single-center, single-arm registry included 22 consecutive patients who were referred to the Cardiac Department of Copper Health Center due to chronic disabling refractory angina pectoris (Canadian Cardiovascular Society [CCS] classes II–IV) despite maximally tolerated anti-angina medical therapy. All patients were evaluated by the local Heart Team and considered not eligible for percutaneous or surgical revascularization procedures. After the Heart Team evaluation, patients were qualified for the procedure of Coronary Sinus Reducer implantation unless they met one of the exclusion criteria. The study exclusion criteria were: (1) recent acute coronary syndrome (<3 months); (2) recent coronary revascularization (<3 months); (3) a mean right atrial pressure higher than 15 mm Hg; (4) CS proximal diameter <10 mm and >14 mm; (5) life expectancy under 12 months; (6) heart failure (New York Heart Association [NYHA] classification, classes III–IV); (7) being a potential cardiac resynchronization therapy defibrilator (CRT-D) implantation candidate.

Initial patient evaluation (before device implantation) consisted of past medical history, actual clinical assessment with an evaluation of CCS class, Seattle Angina

Questionnaire — (SAQ-7) questionnaire, 6-minute walk test (6MWT), and echocardiography. First, a follow-up visit was scheduled 1 month after the implantation procedure. All patients provided informed consent for the Reducer implantation procedure and written consented to participate in this study. The study had the approval of the local ethics community (Lower Silesian Medical Chamber, ref number 02/BOBD/2022, date of approval: 13.07.2022). The study had a license agreement with Outcomes Instruments, LLC, Missouri for the use of SAQ-7 (Project ID: 11117).

Statistical analysis

Depending on the normality of distribution (assessed by the Shapiro-Wilk test), the data were presented as mean with the standard deviation (SD) or median with the interquartile range (IQR). Categorical data were analyzed using the McNemar-Bowker test, continuous data were analyzed using Student's paired t-test or the Wilcoxon paired signed rank test depending on the results of the Shapiro-Wilk test for normality. Changes in CCS levels were compared using the McNemar-Bowker test. For the t-test, a sample mean and 95% confidence interval for mean were used and for the Wilcoxon test, a sample pseudomedian and 95% confidence interval (CI) for pseudomedian were shown. A significance level of alpha = 0.05 was assumed for all tests. All analyses were made using the statistical package R.

RESULTS AND DISCUSSION

We retrospectively analyzed short-term outcomes of 22 consecutive subjects after Reducer device implantation performed between April and September 2022. There were no specific exclusion criteria from the study. In this article, we presented data of all patients qualified for CS Reducer implantation for whom a full 1-month follow-up was available. The vast majority of patients were male (86.3%) at an average age of 71.1 years and with history of previous coronary revascularization. In the study cohort, we noticed a high prevalence of cardiovascular risk factors (hypertension [100%], hyperlipidemia [81.8%], and diabetes [63.6%]). Despite previous revascularization procedures and intensive pharmacological treatment (average of four antianginal drugs per patient), in most subjects, clinical symptoms of angina were poorly controlled (90.9% initially referred with CCS III or IV). In our cohort study, we observed successful implantation of CS Reducer in all subjects. Apart from one case (hospitalization prolonged due to symptomatic gastric ulcer disease), all patients were discharged the next day after the procedure. In terms of clinical outcomes after a one-month follow-up in 9 subjects, we observed an improvement by one CSS class (CCS IV to III — 1 subject; CCS III to II — 6 subjects; CCS II to I — 2 subjects). In 10 patients, we reported the reduction of symptoms by two CSS classes (CCS IV to II — 2 subjects; CCS III to I — 8 subjects). One subject achieved the highest possible improvement in symptom control (de-escalation from CCS IV to CCS I). All clinical data are presented in Table 1.

Refractory angina pectoris is resistant to classical therapeutic options for CAD patients. The prevalence of this disorder is relatively high and can reach up to 5%–10% of the stable CAD population [5]. It is well documented [1, 3, 5] that RAP is associated with poor quality of life, resulting in recurrent hospitalization, leading to a high level of healthcare resource utilization (in our cohort nearly four angina-related hospital admissions in cardiology departments per year for each study subject). In the current article, we present the first Polish experience with CS Reducer. What needs to be emphasized is that so far data available from our country are mainly related to case studies [6, 7].

The main findings of the study are: (1) CS Reducer implantation is a relatively safe procedure. In the presented study cohort despite high comorbidity, no serious adverse events related to the procedure were observed; (2) short-term clinical effectiveness was noticeable and showed a significant improvement in angina control along with an increase in the 6MWT, and in terms of quality of life assessed by the SAQ-7 score.

Despite including the CS Reducer in the guidelines for the management of chronic coronary syndromes [2], still "real-world" data related to the safety and efficacy of this device are limited to small-sized studies [4, 8, 9]. In our study cohort, all procedures finished with successful implantation of the CS Reducer device without any periprocedural complications. All patients were discharged on the following day after the implantation procedure. Similar to our findings, recently published data confirmed the safety and efficacy of the procedure [7–11]. Nevertheless, we observed a slightly higher success rate in comparison to other studies. Our encouraging results are undeniably related to an advanced proctoring program applied in our Cardiac Center along with the relatively high number of procedures performed in a short training period. It allowed achieving a quick gain of the necessary experience and flattened the learning curve. The clinical outcomes obtained in our registry are encouraging, and we noticed a statistically significant improvement in all evaluated angina gauges (6MWT and CCS score). Additionally, significant improvement was observed in terms of the quality-of-life rate (SAQ-7 score). All data regarding clinical outcomes were pooled in Table 1.

The present study has limitations that should be acknowledged. It is a single-center observational registry with a relatively small number of enrolled patients and the absence of a control group. Additionally, the study refers to short-term outcomes mainly related to the quality-of-life parameters. Despite these limitations, the study included the largest number of patients treated with CS Reducer in Poland and confirmed the short-term safety and clinical efficiency of the CS Reducer device in a real-world setting.

Table 1. LSSRR clinical data

Variables	Study cohort (n = 22)
Age, mean (SD)	71.1 (7.2)
Male sex, n (%)	19 (86.3)
Female sex, n (%)	3 (13.6)
BMI, kg/m^2, mean (SD)	29.4 (4.4)
Hypertension, n (%)	22 (100)
Type 2 diabetes mellitus, n (%)	14 (63.6)
Hyperlipidemia, n (%)	18 (81.8)
Cigarette smoker, n (%)	7 (31.8)
Atrial fibrillation, n (%)	7 (31.8)
Peripheral arterial disease, n (%)	11 (50)
LVEF, %, median (IQR)	55 (40–60)
Heart failure, n (%)	9 (40.9)
Coronary artery disease — illness duration, years, mean (SD)	18.4 (8.3)
Antianginal drugs, median (IQR)	4 (3–4.75)
Admissions to Department of Cardiology — during previous year, median (IQR)	3 (3–4.75)
History of revascularization	
PCI, n (%)	19 (86.4)
CABG, n (%)	18 (81.8)
PCI + CABG, n (%)	15 (68.2)
History of ACS	
STEMI, n (%)	8 (36.4)
NSTEMI, n (%)	8 (36.4)
STEMI + NSTEMI, n (%)	2 (9.1)

Change in CCS class[1]						*P* = 0.003
CCS class		1-month FU				
		I	II	III	IV	Total
Baseline	I	0	0	0	0	0 (0%)
	II	2	0	0	0	2 (9.1%)
	III	8	6	2	0	16 (72.7%)
	IV	1	2	1	0	4 (18.2%)
	Total	11 (50%)	8 (36.4%)	3 (13.6%)	0 (0%)	22 (100%)

6MWT	Baseline	1-month FU	*P*-value	Group difference and CI
Distance, m, mean (SD)	224.4 (99.9)	300.7 (124.1)	<0.001	76.33 (41.5–111.14)
Duration, sec, median (IQR)	360 (247.5–360)	360 (338.5–360)	0.02	79.48 (20–162.5)
Borg's scale score, mean (SD)	3.05 (1.36)	1.68 (1.36)	0.001	–1.36 (–2.11 to –0.62)
SAQ-7	**Baseline**	**1-month FU**	***P*-value**	**Group difference and CI**
SAQ-7 total score, mean (SD)	33.3 (13.88)	54.53 (19.44)	<0.001	21.24 (12.16–30.32)
SAQ-7-PL, mean (SD)	35.23 (18.71)	54.17 (22.23)	<0.001	18.94 (9.39–28.49)
SAQ-7-AF median (IQR)	40 (22.5–57.5)	65 (52.5–80)	0.001	30 (15–45)
SAQ-7-QL median (IQR)	18.75 (12.5–37.5)	43.75 (25–59.4)	<0.001	25 (12.5–43.75)

[1]Table cells colored red correspond to an increase in CCS grade, yellow cells correspond to no change in CCS grade, green cells correspond to a decrease in CCS grade

Abbreviations: 6MWT, six-minute walk test; ACS, acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; CI, mean or pseudomedian difference 95% confidence interval; FU, follow-up; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SAQ-7, Seattle Angina Questionnaire — 7 items; SAQ-7-AF, Angina Frequency Score; SAQ-7-PL, Physical Limitation Score; SAQ-7-QL, Quality of Life Score; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Povsic TJ, Henry TD, Ohman EM. Therapeutic approaches for the no-option refractory angina patient. Circ Cardiovasc Interv. 2021; 14(2): e009002, doi: 10.1161/CIRCINTERVENTIONS.120.009002, indexed in Pubmed: 33541098.
2. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020; 41(3): 407–477, doi: 10.1093/eurheartj/ehz425, indexed in Pubmed: 31504439.
3. Gallone G, Baldetti L, Tzanis G, et al. Refractory angina: from pathophysiology to new therapeutic nonpharmacological technologies. JACC Cardiovasc Interv. 2020; 13(1): 1–19, doi: 10.1016/j.jcin.2019.08.055, indexed in Pubmed: 31918927.

4. Jolicoeur EM, Verheye S, Henry TD, et al. Efficacy of a device to narrow the coronary sinus in refractory angina. N Engl J Med. 2015; 372(6): 519–527, doi: 10.1056/NEJMoa1402556, indexed in Pubmed: 25651246.
5. Mannheimer C, Camici P, Chester MR, et al. The problem of chronic refractory angina; report from the ESC Joint Study Group on the Treatment of Refractory Angina. Eur Heart J. 2002; 23(5): 355–370, doi: 10.1053/euhj.2001.2706, indexed in Pubmed: 11846493.
6. Wojciech Z, Kuliczkowski W, Reczuch K. Coronary sinus reducer implantation in patients with refractory angina: first experience in Poland. Kardiol Pol. 2021; 79(4): 471–472, doi: 10.33963/KP.15866, indexed in Pubmed: 33687874.
7. Wańczura PM, Stecko W, Curzytek A, et al. Coronary sinus reductor - a novel approach in "no-option" patients. Postepy Kardiol Interwencyjnej. 2021; 17(2): 242–243, doi: 10.5114/aic.2021.107514, indexed in Pubmed: 34400935.
8. Giannini F, Baldetti L, Ponticelli F, et al. Coronary Sinus Reducer Implantation for the Treatment of Chronic Refractory Angina: A Single-Center Experience. JACC Cardiovasc Interv. 2018; 11(8): 784–792, doi: 10.1016/j.jcin.2018.01.251, indexed in Pubmed: 29673511.
9. D'Amico G, Giannini F, Massussi M, et al. Usefulness of coronary sinus reducer implantation for the treatment of chronic refractory angina pectoris. Am J Cardiol. 2021; 139: 22–27, doi: 10.1016/j.amjcard.2020.09.045, indexed in Pubmed: 32998007.
10. Mrak M, Pavšič N, Ponticelli F, et al. Efficacy of coronary sinus reducer implantation in patients with chronic total occlusion of the right coronary artery. Kardiol Pol. 2022; 80(1): 25–32, doi: 10.33963/KP.a2021.0132, indexed in Pubmed: 34643262.
11. Konigstein M. Coronary sinus Reducer: An adjunctive tool for the treatment of patients with chronic total occlusion of the right coronary artery. Kardiol Pol. 2022; 80(1): 1–2, doi: 10.33963/KP.a2022.0001, indexed in Pubmed: 34981825.

Factors associated with terminal activation duration in young athletes

Zoran Šarčević[1, 2], Andreja Tepavčević[3, 4]

[1]Novi Sad Health Care Center, Sports Medicine Center, Novi Sad, Serbia
[2]Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia
[3]Faculty of Sciences, University of Novi Sad, Novi Sad, Serbia
[4]Mathematical Institute of Serbian Academy of Sciences and Arts, Serbia

Correspondence to:
Zoran Šarčević, MD, PhD,
Novi Sad Health Care Center,
Sports Medicine Center,
Bulevar Cara Lazara 75,
21000 Novi Sad, Serbia,
phone: +38 16 386 401 66,
email: sarceviczoranat@gmail.com

DOI: 10.33963/ KP.a2023.0052

Received:
August 3, 2022

Accepted:
January 3, 2023

Early publication date:
February 27, 2023

INTRODUCTION

Electrocardiogram (ECG) changes in athletes are common and occur because of electrical and structural adaptations due to sports activities. The correct interpretation of ECG is essential because sometimes results indicating underlying cardiovascular disease may be misinterpreted as regular changes due to exercise [1]. Pediatric athletes have a greater prevalence of training-related or unrelated ECG changes than non-athletes [2]. In athletes, arrhythmogenic right ventricular cardiomyopathy (ARVC) is a symptom of myocardial damage and severe ventricular arrhythmias characterized by fibro-fatty replacement of the right ventricular myocardium. It is associated with sudden cardiac death [3]. ARVC is caused mainly by inherited mutations in proteins of the desmosomal complex [4]. It is unclear whether ARVC can be exercise-induced, but it has been recognized that extreme exercise can worsen the disease resulting in earlier and more severe phenotypic expression [5]. Physiological cardiac adaptation to regular exercise may create diagnostic overlap with this syndrome [6].

An indicator of activation delay — prolonged terminal activation of QRS (QRS delayed S-wave upstroke with a terminal activation duration [TAD] ≥55 ms in the right precordial leads) is a factor of superior sensitivity and high specificity, as it was included in the modification of Task Force Criteria for the clinical diagnosis of ARVC [7, 8]. Our observational study aimed to find factors associated with terminal activation delay in young athletes.

METHODS

This retrospective observational study was conducted at Novi Sad Healthcare Center, Sports Medicine Center. There were 254 participants, young, healthy athletes involved in regular training, aged 6–15 years, 168 males and 86 females. Characteristics of participants are given in Table 1. The study group consisted of healthy children who had regular pre-participation examinations performed by sports physicians consecutively from July 1 to November 1, 2020.

Exclusion criteria were COVID-19 or another infection in the previous three months, abnormalities in the P wave, QRS complex, ST-segment, T waves, and QT interval, or rhythm and conduction abnormalities. This research study was conducted retrospectively based on the data obtained for clinical purposes. The study was approved by the Ethical Committee of the Novi Sad Healthcare Center (approval no. 21/1-1 of 21.1.2021).

The ECG examination of all children was done using HeartScreen 60-IKO (Innomed, Inc., Savannah, GA, US). The speed of the ECG paper was 25 mm/s, and the gain was 10 mm/mV. The assessment of TAD was done by two independent investigators.

The training duration concerns only children involved in selected sports disciplines since every child has 5 hours of regular physical activity at school. This is the same for all children; only duration data on children in training were considered here.

Terminal activation duration of QRS was measured as the time from the nadir of the S wave to the end of all depolarization deflec-

tions in leads V1–V3. It is prolonged if it is greater than or equal to 55 ms in any of the V1–V3 leads in the absence of complete right bundle branch block [8].

The children were divided into three groups according to age, body mass index (BMI) status: normal, overweight, and obese, according to the BMI-for-age percentile chart [9], and duration of training per week and into four groups according to the years in training (Supplementary material, *Table S2*).

Statistical analysis

In the final analysis, 254 children were included. Nineteen participants were excluded due to missing data (3) and the exclusion criteria (16). Categorical variables were presented as numbers and percentages. Continuous variables were expressed as mean (SD) or median (interquartile range [IQR]). The Mann-Whitney U-test and Kruskal-Wallis tests with Dunn post-hoc test were used to compare the differences in TAD between groups. Spearman rank correlation was used to assess the relationships between numerical variables. The *P*-value of <0.05 was considered to be statistically significant. We analyzed the data using MedCalc® Statistical Software version 20.104 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022), TIBCO Software Inc. (2020), Data Science Workbench, version 14 (http://tibco.com).

RESULTS AND DISCUSSION

The characteristics of the study participants are given in Table 1 (sports, age, sex, height, weight, BMI, physical activity level, and years in training). The distribution of TAD in the whole sample had a median (IQR) of 40 (30–40) ms. In the Supplementary material, *Table S1*, TAD is compared according to sex, age, body mass index (BMI) hours of training per week, and years in training.

There was a significant difference in TAD between males and females ($P = 0.02$). There was no significant difference in TAD in the three BMI status groups or in the three age groups.

Regarding activity level per week, there was a statistically significant difference among the three groups ($P < 0.001$). According to the Dunn post-hoc test, it was determined that there was no statistical difference between the first and the second groups, but there was a difference between the first (and the second) and the third groups ($P < 0.001$). Regarding the number of years in training, there was a statistically significant difference among the four groups ($P = 0.04$). Correlations between TAD and age, BMI, the number of hours of training per week, and the number of training years are presented in Supplementary material, *Table S2*.

A terminal activation duration of 55 ms or more is a minor criterion for diagnosing possible arrhythmogenic cardiomyopathy [10]. We determined factors associated with an increase in activation duration. We used a mathematical principle of continuity which assumes that the terminal activation duration increases gradually. Hence, the values close to 55 ms meant that they could be over 55 ms at some point if the tendency influenced by this factor persists. We found that TAD is associated with years in training and level of activity but not with the age of children or other characteristics. The question is whether the high intensity of exercise can influence the prolonged activation duration and the related physiological phenomena. In the group of 254 children, only 18 had prolonged TAD (≥55 ms), and they underwent further investigations at the cardiac department. On echocardiographic examination, all the results were normal. They did not have a genetic study, but the family history of cardiovascular disease was considered. Concerning further investigation, diagnosing myocarditis might be challenging. According to the cardiac protocol in Serbia, further analyses were not recommended, but the children were under close surveillance.

Table 1. Characteristics of study participants

	All
Number	254
Age, years, mean (SD)	10.63 (2.01)
Sports, n	
Soccer	33
Volleyball	15
Dancing	13
Basketball	11
Swimming	11
Martial arts	10
Athletics	4
Gymnastics	2
Handball	1
Height, cm, mean (SD)	149.80 (14.61)
Weight, kg, mean (SD)	44.07 (14.34)
BMI, kg/m^2, mean (SD)	19.19 (3.74)
Physical activity level, hours per week, median (IQR)	3 (3–4)
Years in training, years, median (IQR)	3 (2–4)

Abbreviations: BMI, body mass index

In order to establish ARVC or myocarditis diagnosis, it is necessary to perform magnetic resonance, so in our study, reaching any conclusions about the reason for abnormal TAD was impossible. We are planning to perform magnetic resonance of the heart in a further study, which would give us data about the size and state of the myocardium of the right ventricle.

The terminal activation delay of ≥55 ms was associated with larger right ventricle (RV) volume and lower RV ejection fraction [11] in patients with ARVC. Hence, TAD might be a factor connected to exercise-induced cardiac remodeling. It was indicated that endurance training influences the cardiac remodeling of male preadolescent athletes with increased RV dimensions and preserved RV function [12].

It was found that the terminal activation delay was the only ECG abnormality in the asymptomatic mutation carriers not fulfilling the 2010 Task Force Criteria and without a history of ventricular arrhythmias (in 26% of cases) [13]. The limitation of the study is that further testing (except

echocardiography) was not conducted on children with prolonged TAD.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Basu J, Malhotra A. Interpreting the Athlete's ECG: Current State and Future Perspectives. Curr Treat Options Cardiovasc Med. 2018; 20(12): 104, doi: 10.1007/s11936-018-0693-0, indexed in Pubmed: 30456469.
2. McClean G, Riding NR, Ardern CL, et al. Electrical and structural adaptations of the pediatric athlete's heart: a systematic review with meta-analysis. Br J Sports Med. 2018; 52(4): 230, doi: 10.1136/bjsports-2016-097052, indexed in Pubmed: 28363973.
3. Li KaH, Bazoukis G, Liu T, et al. Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) in clinical practice. J Arrhythm. 2018; 34(1): 11–22, doi: 10.1002/joa3.12021, indexed in Pubmed: 29721109.
4. Ohno S. The genetic background of arrhythmogenic right ventricular cardiomyopathy. J Arrhythm. 2016; 32(5): 398–403, doi: 10.1016/j.joa.2016.01.006, indexed in Pubmed: 27761164.
5. Sawant AC, Bhonsale A, te Riele AS, et al. Exercise has a disproportionate role in the pathogenesis of arrhythmogenic right ventricular dysplasia/cardiomyopathy in patients without desmosomal mutations. J Am Heart Assoc. 2014; 3(6): e001471, doi: 10.1161/JAHA.114.001471, indexed in Pubmed: 25516436.
6. Zaidi A, Sheikh N, Jongman JK, et al. Clinical Differentiation Between Physiological Remodeling and Arrhythmogenic Right Ventricular Cardiomyopathy in Athletes With Marked Electrocardiographic Repolarization Anomalies. J Am Coll Cardiol. 2015; 65(25): 2702–2711, doi: 10.1016/j.jacc.2015.04.035, indexed in Pubmed: 26112193.
7. Hauer RNW, Cox MG, Groeneweg JA. Impact of new electrocardiographic criteria in arrhythmogenic cardiomyopathy. Front Physiol. 2012; 3: 352, doi: 10.3389/fphys.2012.00352, indexed in Pubmed: 23015790.
8. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation. 2010; 121(13): 1533–1541, doi: 10.1161/CIRCULATIONAHA.108.840827, indexed in Pubmed: 20172911.
9. Body mass index-for-age percentiles. Available online: /www cdc gov/growthcharts/data/set1clinical/cj41l023.pdf. [Accessed: April 7, 2022].
10. Platonov PG, Calkins H, Hauer RN, et al. High interobserver variability in the assessment of epsilon waves: Implications for diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia. Heart Rhythm. 2016; 13(1): 208–216, doi: 10.1016/j.hrthm.2015.08.031, indexed in Pubmed: 26304715.
11. De Lazzari M, Zorzi A, Cipriani A, et al. Relationship Between Electrocardiographic Findings and Cardiac Magnetic Resonance Phenotypes in Arrhythmogenic Cardiomyopathy. J Am Heart Assoc. 2018; 7(22): e009855, doi: 10.1161/JAHA.118.009855, indexed in Pubmed: 30571483.
12. D'Ascenzi F, Pelliccia A, Valentini F, et al. Training-induced right ventricular remodelling in pre-adolescent endurance athletes: The athlete's heart in children. Int J Cardiol. 2017; 236: 270–275, doi: 10.1016/j.ijcard.2017.01.121, indexed in Pubmed: 28185706.
13. Mast TP, Teske AJ, Te Riele AS, et al. Prolonged Electromechanical Interval Unmasks Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy in the Subclinical Stage. J Cardiovasc Electrophysiol. 2016; 27(3): 303–314, doi: 10.1111/jce.12882, indexed in Pubmed: 26585103.

Successful treatment of severe ACURATE neo2 valve underexpansion in a setting of severe aortic stenosis with massive calcifications

Jarosław Trębacz[1], Janusz Konstanty-Kalandyk[2, 3], Robert Sobczyński[3], Maciej Stąpór[1], Michał Okarski[4], Krystian Mróz[1], Bogusław Kapelak[2, 3], Jacek Legutko[1, 5], Paweł Kleczyński[1, 5]

[1]Clinical Department of Interventional Cardiology, John Paul II Hospital, Kraków, Poland
[2]Clinical Department of Cardiac Surgery and Transplantation, John Paul II Hospital, Kraków, Poland
[3]Department of Cardiac Surgery and Transplantation, Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland
[4]Student Scientific Group of Modern Cardiac Therapy at the Department of Interventional Cardiology, Jagiellonian University Medical College, Kraków, Poland
[5]Department of Interventional Cardiology, Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland

Correspondence to:
Paweł Kleczyński, MD, PhD, FESC, Department of Interventional Cardiology, Institute of Cardiology, Jagiellonian University Medical College, John Paul II Hospital, Prądnicka 80, 31–202 Kraków, Poland, phone: +48 12 614 35 01, e-mail: kleczu@interia.pl

DOI: 10.33963/KP.a2023.0063

Received:
January 21, 2023

Accepted:
February 18, 2023

Early publication date:
March 5, 2023

Severe prosthesis underexpansion during transcatheter aortic valve implantation (TAVI) may have serious consequences and requires immediate corrective measures. Migration of the device into the aorta can be solved interventionally or conservatively or even surgically in the case of aortic injury [1]. Deep ventricular embolization, on the other hand, requires urgent open-heart surgery in the vast majority of cases [1].

A 77-year-old female patient was referred for elective TAVI. She had earlier received a permanent pacemaker for a complete atrioventricular block. Her comorbidities included osteoporosis, dyslipidemia, and previous hip replacement. Baseline transthoracic echocardiography (TTE) documented severe aortic stenosis with mean gradient of 67 mm Hg while left ventricular ejection fraction was preserved. Coronary angiography revealed no significant coronary lesions. A computed tomography scan showed diffuse iliac and aortic atherosclerosis but no contraindications to the left transfemoral approach. The right femoral artery was rather unsuitable for any sheath bigger than 8 F. The aortic valve was confirmed as tricuspid with extensive diffuse leaflet calcification (Figure 1A). An aortic annulus perimeter of 72.2 mm combined with an expandable hydrophilic 14 F delivery sheath (iSleeve, Boston Scientific, Marlborough, MA, US) facilitated ACURATE neo2 M (Boston Scientific) device choice [2].

Right radial access was used for 6 F pigtail insertion. Proglide-assisted 14 F sheath insertion over the Amplatz Ultra Stiff guidewire was completed with some difficulties, followed by a standard introduction of Safari S (Boston Scientific) pre-shaped guidewire. Based on an area-derived annular diameter of 22.6 mm, a non-compliant 22/40 mm VACS III (Osypka, Germany) balloon was chosen for aggressive predilatation, which was successfully executed with the support of left-ventricular guidewire rapid pacing (Supplementary material, *Video S1*). Then, routine ACURATE neo2 M valve implantation was performed. To our surprise, unexpected high-grade valve underexpansion was visualized in both 3-cusp and overlap views (Figure 1B, C), which made removal of the delivery system impossible without increased risk for valve pop-out. As both the hemodynamic status of the patient and valve position remained stable, initially a conservative strategy was chosen, but there was no spontaneous improvement of valve expansion after 10 minutes of watchful waiting. An 8 F sheath was inserted into the right femoral artery and used for standard ACURATE neo2 valve crossing and parallel Safari S introduction, followed by 8 F-compatible semi-compliant 20/40 mm Osypka VACS II balloon (Osypka, Germany) postdilatation (Figure 1D, Supplementary material, *Video S2*). It resulted in partial but significant valve expansion, which allowed for successful delivery

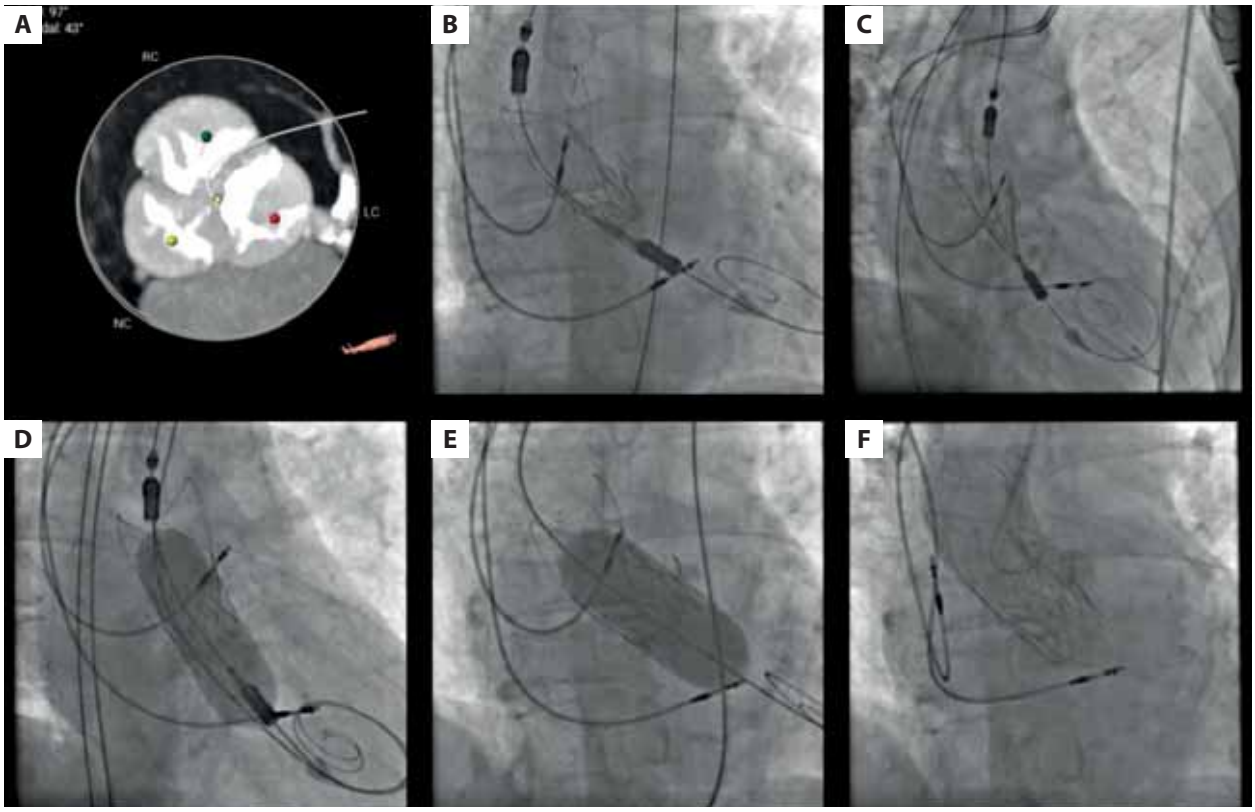


Figure 1. A. Massive aortic valve calcifications showed on computed tomography. **B.** Severe valve mal opening, three-cusp coplanar view. **C.** Extreme valve mal opening, cusp overlap coplanar view. **D.** Initial postdilatation with a semi-compliant 20 mm/40 mm 8 F sheath compatible balloon via an additional guidewire inserted into the left ventricle across the valve prosthesis. **E.** Postdilatation with a non-compliant 22 mm/40 mm balloon. **F.** Final angiographic result of ACURATE neo2 implantation

system removal. As moderate paravalvular leak (PVL) was still present, final valve postdilatation with a non-compliant 22/40 mm Osypka VACS III (Osypka, Germany) balloon was performed (Supplementary material, *Video S3*). Both the final aortogram (Figure 1E) and TTE confirmed optimal valve position and function with only trace PVL and 13/6 mm Hg gradient (Figure 1F). The patient was discharged two days later as per local practice and remains asymptomatic in short-term follow-up.

Significant ACURATE neo2 valve underexpansion precluding safe delivery system removal can occur in the presence of massive aortic valve calcifications [3]. If not resolved spontaneously, it can be treated with parallel guidewire insertion and postdilatation [3, 4].

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Kim WK, Schäfer U, Tchetche D, et al. Incidence and outcome of peri-procedural transcatheter heart valve embolization and migration: the TRAVEL registry (TranscatheteR HeArt Valve EmboLization and Migration). Eur Heart J. 2019; 40(38): 3156–3165, doi: 10.1093/eurheartj/ehz429, indexed in Pubmed: 31230081.
2. Scotti A, Pagnesi M, Kim WK, et al. Haemodynamic performance and clinical outcomes of transcatheter aortic valve replacement with the self-expanding ACURATE neo2. EuroIntervention. 2022; 18(10): 804–811, doi: 10.4244/EIJ-D-22-00289, indexed in Pubmed: 35678222.
3. Wiktorowicz A, Wit A, Malinowski KP, et al. Paravalvular leak prediction after transcatheter aortic valve replacement with self-expandable prosthesis based on quantitative aortic calcification analysis. Quant Imaging Med Surg. 2021; 11(2): 652–664, doi: 10.21037/qims-20-669, indexed in Pubmed: 33532265.
4. Kleczyński P, Dziewierz A, Daniec M, et al. Impact of post-dilatation on the reduction of paravalvular leak and mortality after transcatheter aortic valve implantation. Kardiol Pol. 2017; 75(8): 742–748, doi: 10.5603/KP.2017.0152, indexed in Pubmed: 28819953.

Percutaneous coronary intervention for iatrogenic occlusion of the circumflex artery following mitral valve replacement surgery

Jacek Zawiślak[1*], Klaudia Artykiewicz[1], Janusz Stążka[2], Kamil Baczewski[2], Andrzej Wysokiński[1], Tomasz Zapolski[1*]

[1]Department of Cardiology, Medical University of Lublin, Lublin, Poland
[2]Department of Cardiac Surgery, Medical University of Lublin, Lublin, Poland
*Both authors equally contributed to the study

Correspondence to:
Jacek Zawiślak, MD, PhD, Department of Cardiology, Medical University of Lublin, al. Racławickie 1, 20–059 Lublin, Polska, phone: 48 81 448 50 00, e-mail: jacekzawislakmd@gmail.com

DOI: 10.33963/KP.a2023.0072

Received:
January 15, 2022

Accepted:
February 18, 2023

Early publication date:
March 16, 2023

Iatrogenic coronary artery occlusion is a rare and frequently overlooked but life-threatening complication of mitral valve surgery [1]. The incidence is reported to be 0.15% to 1.8% of all cardiac procedures [4].

Although the possibility of such a complication has been known for a long time, an increasing number of cardiac surgeries makes the awareness of this complication lose its importance, which is confirmed by the current prevention and management algorithms published in 2021 [4]. There are still no uniform standards or guidelines for the treatment in such clinical situations. Even expert opinions are missing [5]. The risk of damage to the circumflex coronary artery (Cx) is caused by its proximity to the posterior segment of the mitral annulus [2]. The most common pathomechanism is direct damage to the circumflex artery through suture ligation, laceration, or annuloplasty device distortion during mitral valve repair [3].

We present a case of a 73-year-old male patient with severe mitral regurgitation, clinically known single-vessel ischemic heart disease, chronic New York Heart Association (NYHA) class III heart failure, and persistent atrial fibrillation (AF). He was admitted to the Department of Cardiac Surgery for surgical treatment. Transthoracic echocardiography (TTE) examination revealed mildly reduced left ventricular ejection fraction (LVEF, 48%), enlarged left atrium (LA, 5.6 cm), enlarged left ventricle (LV, 5.7 cm), and interventricular septum hypertrophy (IVSD, 1.3 cm). The patient underwent surgical implantation of a biological mitral valve prosthesis (Perimount-27, Edwards-Lifesciences) combined with coronary artery bypass grafting (Left-Internal-Mammary-Artery to Left Anterior Descending-Artery, LIMA-LAD), and surgical ablation of the AF substrate in the left atrium.

Cardiac surgery was conducted under extremely challenging anatomical conditions, which may explain the occurrence of the complication. The procedure was performed via medial sternotomy and extracorporeal circulation. The heart was enlarged. There were poor anatomical conditions: a deeply located atrium with a corrugated wall. Due to chordal rupture and a restricted anterior-mitral-valve-leaflet in the mitral valve, plastic surgery was not performed. The subvalvular apparatus was left. The bioprosthetic valve was implanted with single mattress sutures.

After surgery, a 12-lead-electrocardiogram showed acute inferior myocardial infarction with ST-segment elevation (Figure 1A). In laboratory tests, a significant increase in cardiac troponin I was detected (18043.3 ng/l; n <46.47 ng/l). TTE revealed decreased left ventricular systolic function (EF, 43%), hypokinesis of the inferior wall, proper valve function with no paravalvular leak, mean gradient of 6 mmHg, and maximum gradient of 17 mm Hg). Urgent coronary angiography was performed, confirming iatrogenic closure of Cx (Figure 1B–D). Since the Cx closure was diagnosed after the end of cardiac surgery, according to the currently proposed algorithm, we decided to attempt percutaneous intervention [4]. At the same time, a successful percutaneous coronary intervention of Cx was performed after numerous attempts at

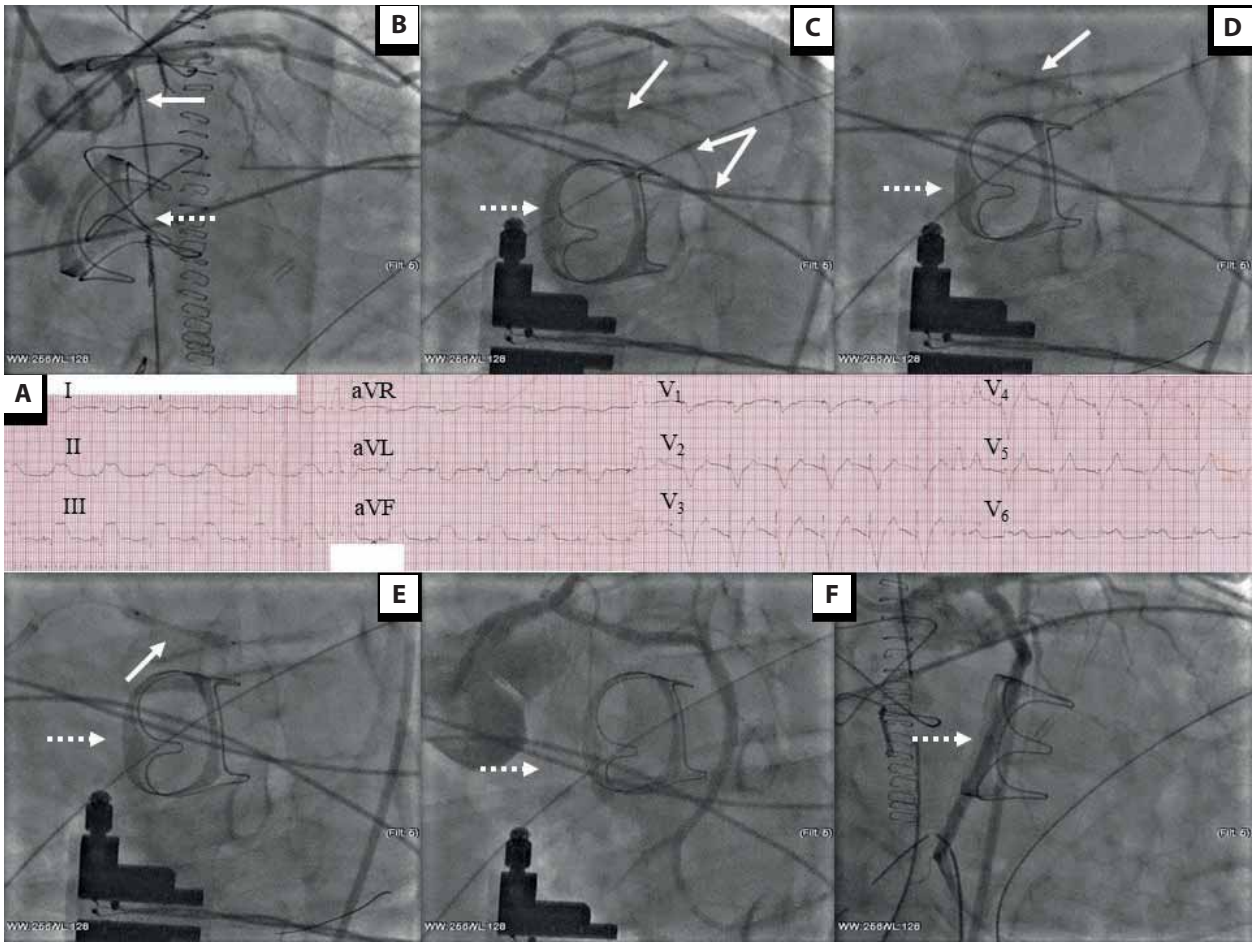


Figure 1. A. ECG: effective ventricular pacing with visible ST-T segment elevation on the inferior wall (leads II, III, and aVF) and lateral wall (lead V_6) with ST-T and reciprocal mirror reflections on the anterior wall (leads I and aVL). ECG recorded at a paper speed of 25 mm/s and a voltage of 10 mm/mV. **B.** CA (RAO 26, CAU 24): occlusion in the proximal part (eleventh segment) of the CX (the arrow is pointing at the occlusion site) close to the mitral valve bioprosthesis (dashed arrow). **C.** PCI (LAO 26, CAU 18): occlusion in the proximal part (eleventh segment) of the CX (the arrow is pointing at the occlusion site) close to the mitral valve bioprosthesis (dashed arrow); the double solid arrows are pointing at the guidewire. **D.** PCI (LAO 32, CAU 18): angioplastic balloon inflation in the proximal part (eleventh segment) of the CX (solid arrow); the dashed arrow is pointing at the mitral valve bioprosthesis. **E.** PCI (LAO 32, CAU 18): the initial stage of stent expansion at the lesion site with visible modeling in the center of the balloon in the proximal part (eleventh segment) of the CX (solid arrow); the dashed arrow is pointing at the mitral valve bioprosthesis. **F.** (on the left) CA (LAO 36, CAU 13) and (on the right) — CA (RAO 8, CAU 31): good final angiographic result with TIMI 3 flow; the dashed arrow is pointing at the artificial valve

Abbreviations: CA, coronary angiography; CAU, caudal view; CX, circumflex branch of the left coronary artery; ECG, electrocardiogram; LAO, left anterior oblique view; PCI, percutaneous coronary intervention; RAO, right anterior oblique view; TIMI, Thrombolysis in Myocardial Infarction

predilatation with balloons of progressively larger sizes by slowly escalating the inflation pressures and carefully observing the modeling of the vessel on the balloon.

The gradation of the balloon sizes (Mini Trek, 2.0/15; Trek, 2.5/20, Abbott, Chicago, IL, US) was applied as an equivalent of intravascular ultrasound (IVUS) assessment, as it was not possible to perform it in the on-call situation. Another justification for this approach was an intention to carefully test for a potentially possible tear or cut on the Cx balloon caused by its stitching. Finally, after using the last balloon (NC, Solarice 3,0/20; Medtronic, Minneapolis, MI, US), due to the "recoil" of the vessel, a drug-eluting stent (DES, Xience 3.5/25, Abbott) was implanted with a very good angiographic effect (Figure 1E–F). The patient was discharged home 9 days after surgery in good condition.

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Fortunato GA, Misfeld M, Battellini R, et al. Situation awareness for circumflex artery injury during mitral valve surgery. Ann Thorac Surg. 2019; 108(5): e329–e332, doi: 10.1016/j.athoracsur.2019.02.054, indexed in Pubmed: 30928545.

2. Grande AM, Fiore A, Massetti M, et al. Iatrogenic circumflex coronary lesion in mitral valve surgery: case report and review of the literature. Tex Heart Inst J. 2008; 35(2): 179–183, indexed in Pubmed: 18612492.
3. Caruso V, Shah U, Sabry H, et al. Mitral valve annulus and circumflex artery: In vivo study of anatomical zones. JTCVS Tech. 2020; 4: 122–129, doi: 10.1016/j.xjtc.2020.09.013, indexed in Pubmed: 34317983.
4. Bargagna M, Trumello C, Sala A, et al. Left Circumflex Artery Injury After Mitral Valve Surgery: An Algorithm Management Proposal. Ann Thorac Surg. 2021; 111(3): 899–904, doi: 10.1016/j.athoracsur.2020.05.160, indexed in Pubmed: 32745514.
5. Płońska-Gościniak E, Wojakowski W, Kukulski T, et al. Management of patients after heart valve interventions. Expert opinion of the Working Group on Valvular Heart Diseases, Working Group on Cardiac Surgery, and Association of Cardiovascular Interventions of the Polish Cardiac Society. Kardiol Pol. 2022; 80(3): 386–402, doi: 10.33963/KP.a2022.0055, indexed in Pubmed: 35290659.

Crossed aorta or retroaortic anomalous coronary sign in the presence of a mechanical aortic valve in a patient after Bentall operation

Karina Wierzbowska-Drabik[1], Maria Możdżan[1], Konrad Szymczyk[2], Marlena Broncel[1], Tomasz Rechciński[2]

[1]Department of Internal Diseases and Clinical Pharmacology, Medical University of Lodz, Łódź, Poland
[2]1st Department and Chair of Cardiology, Medical University of Lodz, Łódź, Poland

Correspondence to:
Karina Wierzbowska-Drabik, MD, PhD,
Department of Internal Diseases and Clinical Pharmacology,
Medical University of Lodz,
Bieganski Hospital,
Kniaziewicza 1/5,
91–347 Łódź, Poland,
phone: +48 42 251 60 03,
e-mail: wierzbowska@ptkardio.pl

DOI: 10.33963/KP.a2023.0073

Received:
January 23, 2023

Accepted:
March 13, 2023

Early publication date:
March 19, 2023

We present transthoracic echocardiographic (TTE) findings suggesting a retroaortic course of the coronary artery (CA) related to an anomalous origin of the circumflex or whole left CA from the proximal part of the right CA or right Valsalva sinus, named formerly as a "crossed aorta" or "retroaortic anomalous coronary" (RAC) sign [1, 2].

A 57-year-old man treated surgically for aortic aneurysm and regurgitation with an implanted mechanical bileaflet aortic valve SJM 27/28 (St. Jude Medica, Inc., Little Canada, MN, US) with conduit, suffered heart palpitation three months after surgery. On admission, atrial fibrillation was diagnosed, and TTE showed good function of aortic prosthesis, preserved left ventricular ejection fraction (LVEF) of 50%, and mild impairment of right ventricular function. In apical view, two parallel bright echo lines separated with 2–3 mm hypoechogenic space were visible near the level of the aortic annulus through the whole heart cycle (Figure 1A and Supplementary material, *Video S1*). This image corresponded to the "crossed aorta" sign, described later also as the RAC sign, with estimated 63% sensitivity and 94% specificity for the retroaortic course of CA diagnosis [1, 3]. The crossed aorta sign reflects a long cross-section of the CA and, if true positive, should be accompanied by a "bleb sign" rendering the short-axis of the CA in the parasternal long-axis view on TTE seen more clearly on transesophageal echocardiography, see Figure B1–B4. [3] Our patient, however, did not present a "bleb sign," and computed tomography (CT) done before surgery displayed a normal origin of the left CA from the left Valsalva sinus, revealing, however, an additional vessel behind the proximal part of the descending aorta (Figure A2–A5 and Supplementary material, *Video S2*).

This vignette illustrates the situation when the suspected crossed aorta sign or very similar manifestation did not correspond with the diagnosis of anomalous origin of the left or circumflex CA in a patient after Bentall surgery and with an additional extracoronary, retroaortic vessel on CT, and such circumstances should be taken into account since, so far, false positive RAC signs were ascribed only to the presence of valve and annulus calcification [4]. On the other hand, data are accumulating that the retroaortic course of the CA may, in many specific circumstances, pose a significant health risk to patients (related e.g. to ischemia or increased risk during surgical procedures), underscoring the importance of echocardiographic screening based on a broad knowledge of described signs and enabling an effective preliminary diagnosis [5]. The detection of the crossed aorta sign during TTE should prompt the diagnosis of potential ischemia of the inferolateral or posterior wall (e.g. with dobutamine) since both – possible pressure by close structures and more advanced atherosclerosis of the anomalous artery – were reported in the literature. This, as well as the awareness of the possible false positives, such as calcification (devoid, however, of hypoechogenic center and moving synchronously with valve leaflets) and the coronary sinus or atypical vessel in the retroaortic region, may enhance the utility of TTE examination.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

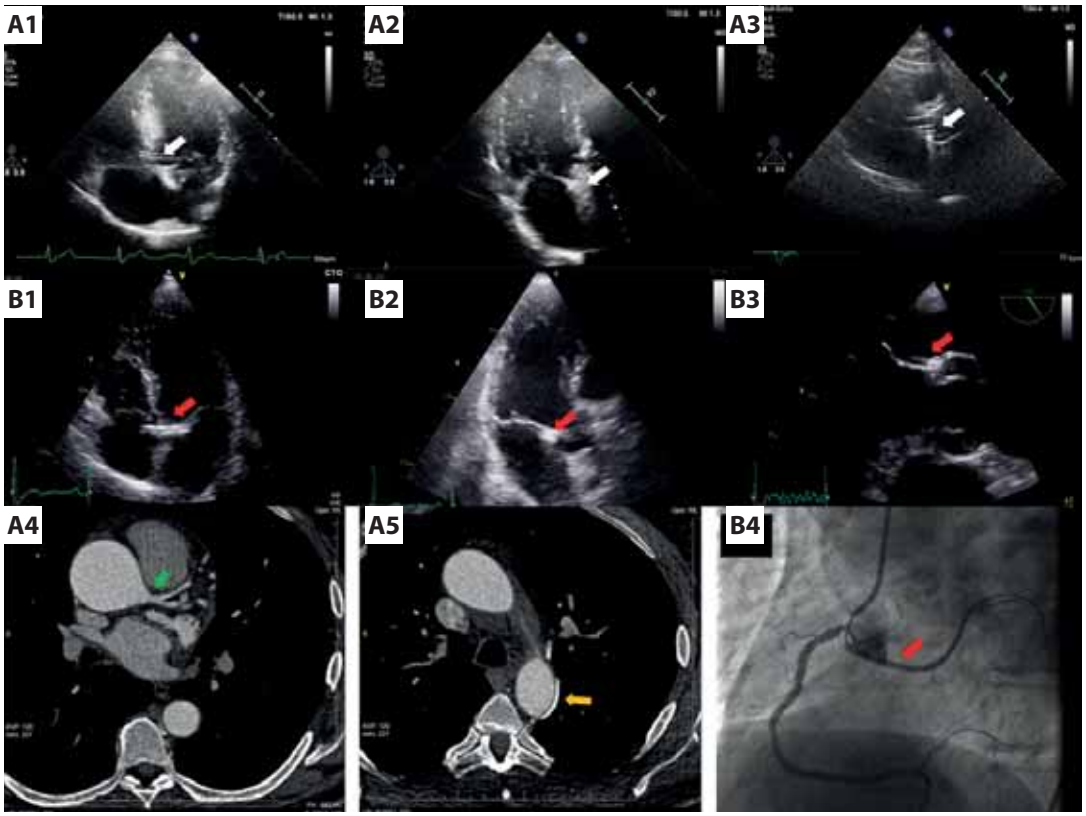


Figure 1. Apposition of the images of a mechanical bileaflet aortic valve presenting a "crossed aorta" sign despite normal anatomy of the origin and proximal course of the left CA (images labeled with letter **A**) with the images (from another patient) of anomalous origin of the circumflex CA from the right coronary artery forming a true positive for the retroaortic course of the CA "crossed aorta" or RAC sign as well as a "bleb sign" on a transesophageal study (images labeled with letter **B**). **A1–A3.** False-positive or pseudo-crossed aorta sign. **A1.** Crossed aorta sign (white arrow) in the apical view. **A2.** Echo shadow originating from the posterior aortic valve disc obliterates the retroaortic region at the base of the mitral leaflet when the presence of a "bleb sign" should be assessed (white arrow). **A3.** The opened mechanical aortic discs form parallel lines inside the aortic lumen in the long-axis parasternal view during systole (white arrow). **B1–B3.** Special version of a true positive crossed aorta sign (with coronary stent inside). **B1.** Crossed aorta sign (red arrow) in the apical view, image is formed by the retroaortic course of the circumflex CA which additionally has a stent implanted in its proximal part enhancing the image of the vessel wall (**B2**) Cross-section of the stented retroaortic circumflex artery is visible as hyperechogenic speckle in the aorto-mitral angle (red arrow) (**B3**) the same region examined with better resolution on transesophageal echocardiography shows very clearly cross-section of the anomalous circumflex artery with an implanted stent, forming a special version of stented "bleb sign" with the hypoechogenic vessel lumen inside the hyperechogenic ring (red arrow). **A4**. Normal origin and division of the left main CA on CT examination performed before Bentall surgery (green arrow). **A5.** Additional vessel coursing in the posterior region of the descending aorta visible in the contrast phase of the CT study assessed as a collateral vessel without clinical significance for coronary circulation — for this vessel, however, the probability of it being responsible for forming the crossed aorta sign was assessed by a radiologist as low (yellow arrow). **B4.** Coronary angiography of the patient with a true crossed aorta and bleb sign documenting the retroaortic course of the circumflex CA originating from the right CA. Some images shown in panels **B** were published previously in [1]

Abbreviations: CA, coronary artery; CT, computed tomography; RAC, retroaortic coronary artery

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Wierzbowska-Drabik K, Kasprzak JD, Mrozowska-Peruga E, et al. Circumflex Origin from Right Coronary Artery – The Anomaly That Should Not Be Omitted during Echocardiography – "Crossed Aorta" and "Bleb Sign" Presentation after Stents Implantation. Echocardiography. 2016; 33(4): 659–660, doi: 10.1111/echo.13141, indexed in Pubmed: 26667990.
2. Witt CM, Elvert LA, Konik EA, et al. The RAC Sign: Retroaortic Anomalous Coronary Artery Visualization by Transthoracic Echocardiography. JACC Cardiovasc Imaging. 2018; 11(4): 648–649, doi: 10.1016/j.jcmg.2017.06.011, indexed in Pubmed: 28917682.
3. Wierzbowska-Drabik K, Szymczyk K, Kasprzak JD. Anomalous circumflex origin from the right coronary artery forming 'bleb sign' in transoesophageal echocardiography. Eur Heart J Cardiovasc Imaging. 2014; 15(8): 932, doi: 10.1093/ehjci/jeu025, indexed in Pubmed: 24578412.
4. Mancinelli A, Golino M, Miglierina E, et al. Three Echocardiographic Signs to Identify Anomalous Origin of the Circumflex Coronary Artery from the Right Sinus of Valsalva: A Case Report. CASE (Phila). 2020; 4(5): 324–327, doi: 10.1016/j.case.2020.07.008, indexed in Pubmed: 33117920.
5. Możeńska O, Buller P, Różańska M, et al. Anomalous origin and retroaortic course of the left circumflex artery: a mystery of a grownup patient with congenital heart disease solved after 15 years. Kardiol Pol. 2021; 79(4): 475–476, doi: 10.33963/KP.15872, indexed in Pubmed: 33723976.

Dented bladder sign: An early marker of retroperitoneal hemorrhage

Andreas S Triantafyllis[1], Ignatios Ikonomidis[2], Andreas S Kalogeropoulos[3]

[1]Department of Cardiology, Asklepeion General Hospital, Athens, Greece
[2]Department of Cardiology, ATTIKON University Hospital, Athens, Greece
[3]Department of Cardiology, Mitera General Hospital, Athens, Greece

Correspondence to:
Andreas S Triantafyllis, MD, PhD, EAPCI certified, Department of Cardiology, Asklepeion General Hospital, Leoforos Vasileos Pavlou 1, Voula, PC 16673, Athens, Greece, phone: +30 6948 80 60 16, e-mail: andtridoc@yahoo.gr, andreas.triantafyllis@gmail.com,

DOI: 10.33963/KP.a2023.0077

Received:
January 16, 2023

Accepted:
March 19, 2023

Early publication date:
March 26, 2023

A 69-year-old diabetic and overweight woman underwent elective coronary angiography (CAG) for the treatment of severe right coronary artery stenosis. CAG was performed through the right femoral artery (RFA), after multiple puncture attempts, since the radial/ulnar arteries were not palpable. During the procedure, she reported back pain and developed severe hypotension. Fluoroscopy revealed indentation of the margin of the bladder (Figure 1, white arrowheads, Supplementary material, *Video S1*), known as the "dented bladder sign", and contrast extravasation lateral to the RFA (Figure 1, black arrow, Supplementary material, *Video S1*) suggesting the diagnosis of retroperitoneal hemorrhage (RPH). An urgent bedside ultrasound confirmed RPH. The "dented bladder sign" is a finding noted during fluoroscopy, X-ray, or CT-scan in the contrast-filled bladder suggestive of external compression and is an important early marker of RPH [1]. Our patient was stabilized after administration of intravenous fluids, blood transfusion, and vasopressors and underwent urgent vascular surgery. The postoperative course was uneventful.

Patients who undergo angiography receive sufficient contrast volume that a potentially useful cystogram can be visualized by the end of the procedure. External compression of the margin of the bladder after cardiac or peripheral catheterization can occur due to blood accumulation through a perforated

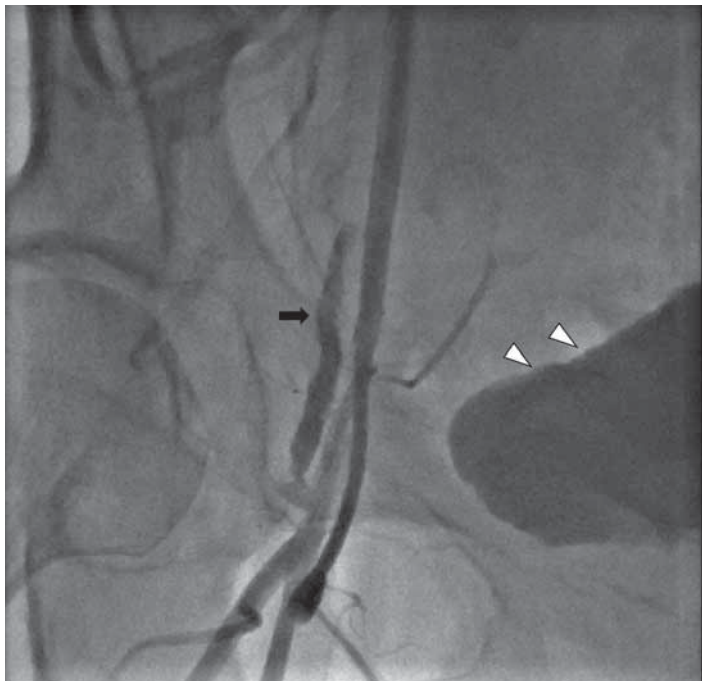


Figure 1. Fluoroscopy showing indentation of the margin of the contrast-filled bladder (white arrowheads) suggestive of external compression known as the "dented bladder sign" and contrast extravasation lateral to the right femoral artery (black arrow), prompting the diagnosis of retroperitoneal hemorrhage

femoral or iliac artery after a high puncture [1]. Female sex, body surface area extremes, high puncture over the inferior epigastric artery, glycoprotein IIb/IIIa inhibitor use, sheath size >8 F, and the use of vascular closure devices have been described as serious risk factors for RPH while ultrasound-guided cannulation of the femoral artery is associated with lower rates of vascular access complications [1–3]. Treatment includes fluid resuscitation, reversal of anticoagulation, transfusion of blood products, percutaneous intervention with balloon inflation or covered stent implantation, and surgical intervention [1].

The adoption of the radial artery as default vascular access for interventional cardiologists can decrease competency in the femoral approach. Nonetheless, the femoral strategy is still used during CAG, complex coronary, or valve interventions underpinning the importance of skill maintenance and early identification of possible complications. The retroperitoneum can harbor a substantial volume of blood before specific symptoms and signs occur, delaying RPH diagnosis with detrimental consequences. Bleeding — especially RPH — following percutaneous coronary interventions carries a dismal prognosis [1]. A recent study highlighted that vascular access complications were among the 3 most common etiologies of bleeding events in Polish cardiac wards [4]. Therefore, sheath angiography and fluoroscopy of the bladder are tools of utmost importance for prompt diagnosis of RPH.

While RPH is an uncommon complication of catheterization, it is associated with high morbidity and mortality, requiring vigilance and timely recognition. In the era of radial access for the new generation of interventional cardiologists, the "dented bladder sign" is an easily identifiable and highly specific marker of RPH and can be depicted on an incidental cystogram during catheterization.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Freilich MI, Gossman DE, Applegate RJ, et al. The "bladder sign" - an important early marker of retroperitoneal hemorrhage. Catheter Cardiovasc Interv. 2012; 79(1): 158–165, doi: 10.1002/ccd.23141, indexed in Pubmed: 21542107.
2. Kwok CS, Kontopantelis E, Kinnaird T, et al. Retroperitoneal Hemorrhage After Percutaneous Coronary Intervention: Incidence, Determinants, and Outcomes as Recorded by the British Cardiovascular Intervention Society. Circ Cardiovasc Interv. 2018; 11(2): e005866, doi: 10.1161/CIRCINTERVENTIONS.117.005866, indexed in Pubmed: 29445000.
3. Sorrentino S, Nguyen P, Salerno N, et al. Standard Versus Ultrasound-Guided Cannulation of the Femoral Artery in Patients Undergoing Invasive Procedures: A Meta-Analysis of Randomized Controlled Trials. J Clin Med. 2020; 9(3), doi: 10.3390/jcm9030677, indexed in Pubmed: 32138283.
4. Kuliczkowski W, Gierlotka M, Zawiślak B, et al. Bleeding events in Polish cardiology wards: the results of a 2-week survey. Kardiol Pol. 2021; 79(3): 327–330, doi: 10.33963/KP.15815, indexed in Pubmed: 33599455.

How multislice computed tomography of the coronary arteries can change the chronic total occlusion recanalization procedure

Anna Kańtoch[1], Bernadeta Chyrchel[1, 2], Sławomir Surowiec[1], Michał Chyrchel[1, 2], Łukasz Rzeszutko[1, 2], Andrzej Surdacki[1, 2], Stanisław Bartuś[1, 2], Leszek Bryniarski[1, 2]

[1]Department of Cardiology and Cardiovascular Interventions, University Hospital, Kraków, Poland
[2]2nd Department of Cardiology, Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland

Correspondence to:
Prof. Leszek Bryniarski, MD, PhD, FESC,
Department of Cardiology and Cardiovascular Interventions, Institute of Cardiology, Jagiellonian University Medical College, Jakubowskiego 2, 30–688 Kraków, Poland,
phone: +48 12 400 22 50,
e-mail: l_bryniarski@poczta.fm

DOI: 10.33963/KP.a2023.0078

Received:
February 10, 2023

Accepted:
March 19, 2023

Early publication date:
March 26, 2023

The Euro CTO Club guidelines advise against performing ad hoc coronary intervention (PCI) of chronic total occlusion (CTO) — it should be done after a careful analysis of coronary angiography [1]. However, performing multislice computed tomography (MSCT) of the coronary arteries before coronary angiography may change this strategy.

MSCT of the coronary arteries was performed in a 58-year-old man with arterial hypertension, hypercholesterolemia, type 2 diabetes mellitus, and Canadian Cardiovascular Society (CCS) class II angina over a period of 12 months. MSCT showed a 10 mm occlusion (Figure 1A, 1C) in the proximal segment of the dominant right coronary artery (RCA). In addition, there was critical stenosis distal to the occlusion.

Angiography (Figure 1B, 1D), in contrast to the MSCT results, revealed a 40 mm long RCA CTO with bifurcation at the distal cap. The CTO had an ambiguous proximal cap, and the distal part of the vessel could be visualized with ipsilateral and contralateral collaterals (J-CTO score 2 — intermediate category of difficulty).

Based on the information from MSCT (visible entry and length — CT-RECTOR score — 0 — easy difficulty category), in contrast to the angiography result, the dedicated CTO operator decided to perform ad hoc PCI CTO from right femoral arterial access.

Using Gaia Second and Confianza wires and a microcatheter, the lesion was crossed in 25 seconds. After pre-dilation, a Xience Pro drug-eluting stent (3.5 × 48 mm) was implanted, followed post-dilation by an NC balloon inflated to 18 atmospheres (Figure 1E). The CTO procedure lasted 20 minutes (45 minutes with angiography), with a radiation dose of 0.229 Gy, fluoroscopy time — 16.1 minutes, and contrast — 200 ml. The periprocedural period was uncomplicated.

In conclusion, distal RCA stenosis blocked the retrograde flow of contrast, mimicking a much longer CTO lesion in angiography. Based on the MSCT reconstruction, *ad hoc* PCI CTO could be performed.

Coronary CT angiography has become a significant step forward in evaluating the benefit-risk balance of the CTO PCI procedure [2]. The main purpose of using MSCT before CTO PCI is to quantify the structure of atherosclerotic plaque and to provide detailed anatomical information about coronary vascularity [2].

According to the literature, pre-procedural coronary CT guidance for CTO was associated with fewer direct periprocedural complications, including periprocedural myocardial infarction and coronary perforation [3]. The intra-procedural use of CT may be limited by the need for additional doses of radiation and contrast in patients undergoing PCI [4]. However, CT-guided CTO procedures have been found to have significantly higher success rates than procedures performed without CT [4, 5]. What is more, CT-guided PCI is associated with a shorter procedure duration, so it can be hypothesized that the dose of radiation and contrast during these procedures may be lower than in patients not undergoing CT scans [4].

Coronary CT angiography is becoming the basic tool in the treatment of CTO from

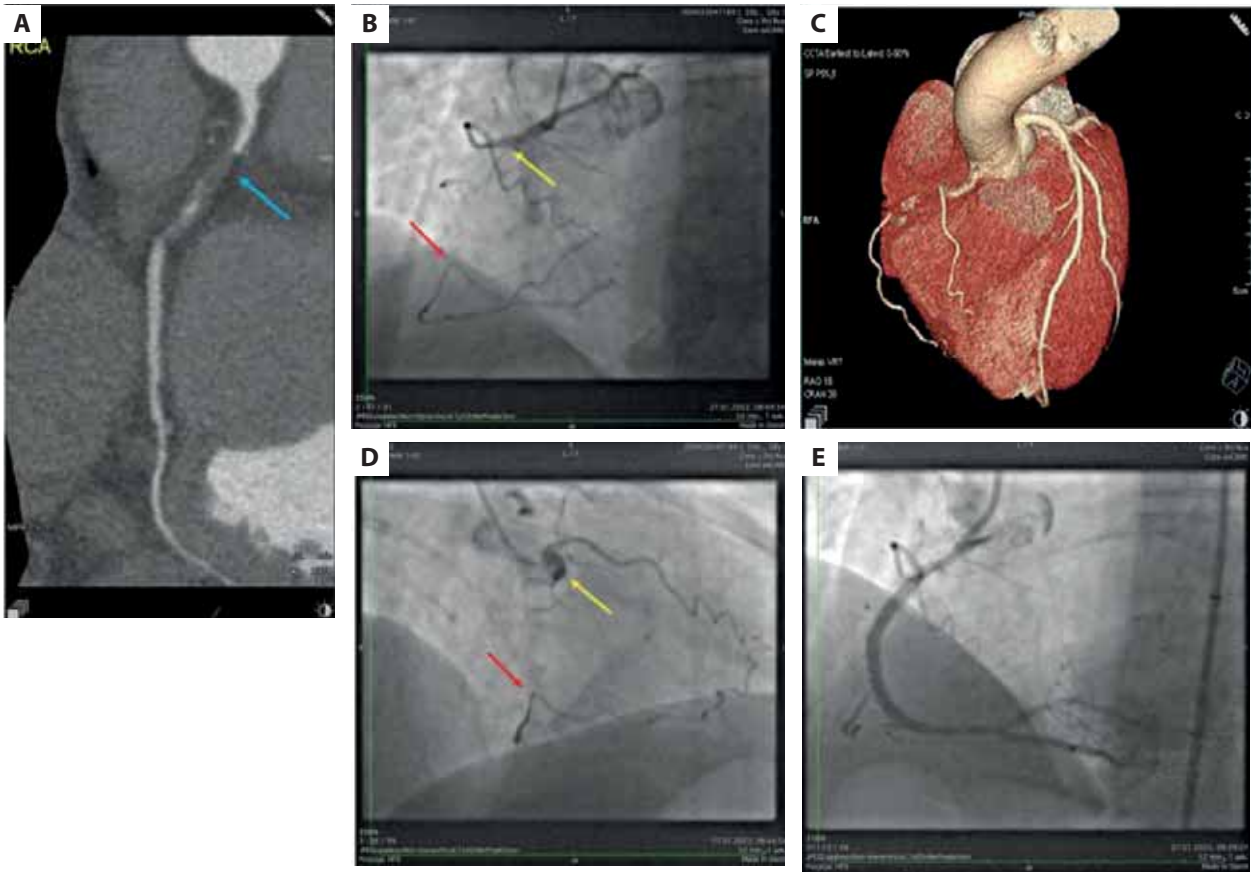


Figure 1. A. Multislice computed tomography (MSCT) — a 10 mm occlusion (blue arrow) in the proximal segment of the dominant right coronary artery (RCA). **B.** Right coronary artery (RAO 30° projection) — proximal occlusion (yellow arrow), blunt stump visible. From the ipsilateral collateral circulation, the middle and distal sections fill. End of occlusion (red arrow). The length of the occlusion assessed angiographically — approx. 40–45 mm. **C.** MSCT (RAO 18) — a 10 mm occlusion in the proximal segment of the dominant right coronary artery (RCA). **D.** Right coronary artery (LAO 30° projection) — proximal occlusion (yellow arrow), blunt stump visible. From the ipsilateral collateral circulation, the middle and distal sections fill. End of occlusion (red arrow). Angiographically assessed occlusion length — approx. 40–45 mm. **E.** Right coronary artery (RAO 30° projection), image after stent implantation

pre-procedural evaluation and intra-procedural control to follow-up [4]. A new horizon in interventional cardiology could be the use of CT scans directly in the catheterization lab for real-time PCI [4].

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Galassi AR, Werner GS, Boukhris M, et al. Percutaneous recanalisation of chronic total occlusions: 2019 consensus document from the EuroCTO Club. EuroIntervention. 2019; 15(2): 198–208, doi: 10.4244/EIJ-D-18-00826, indexed in Pubmed: 30636678.
2. Tzimas G, Gulsin GS, Takagi H, et al. Coronary CT Angiography to Guide Percutaneous Coronary Intervention. Radiol Cardiothorac Imaging. 2022; 4(1): e210171, doi: 10.1148/ryct.210171, indexed in Pubmed: 35782760.
3. Hong SJ, Kim BK, Cho I, et al. CT-CTO Investigators. Effect of Coronary CTA on Chronic Total Occlusion Percutaneous Coronary Intervention: A Randomized Trial. JACC Cardiovasc Imaging. 2021; 14(10): 1993–2004, doi: 10.1016/j.jcmg.2021.04.013, indexed in Pubmed: 34147439.
4. Melotti E, Belmonte M, Gigante C, et al. The Role of Multimodality Imaging for Percutaneous Coronary Intervention in Patients With Chronic Total Occlusions. Front Cardiovasc Med. 2022; 9: 823091, doi: 10.3389/fcvm.2022.823091, indexed in Pubmed: 35586657.
5. Rolf A, Werner GS, Schuhbäck A, et al. Preprocedural coronary CT angiography significantly improves success rates of PCI for chronic total occlusion. Int J Cardiovasc Imaging. 2013; 29(8): 1819–1827, doi: 10.1007/s10554-013-0258-y, indexed in Pubmed:

Post-infarction revelation of the inflammatory bicuspid aortic cusp perforation to the intraventricular septum pseudoaneurysm cavity

Wojciech Skorupski[1], Aneta Klotzka[1], Piotr Buczkowski[2], Sławomir Kępski[3], Marek Jemielity[2], Maciej Lesiak[1]

[1]1st Department of Cardiology, Poznan University of Medical Sciences, Poznań, Poland
[2]Department of Cardiac Surgery and Transplantology, Poznań University of Medical Sciences, Poznań, Poland
[3]Department of Cardiology, Provincial Integrated Hospital, Konin, Poland

Correspondence to:
Wojciech Skorupski, MD,
1st Department of Cardiology,
Poznan University
of Medical Sciences,
Długa 1/2 , 61–848 Poznań,
Poland,
phone: +48 61 854 92 22,
e-mail: wojtek.skorupski@wp.pl

DOI: 10.33963/KP.a2022.0249

Received:
June 11, 2022

Accepted:
August 29, 2022

Early publication date:
November 3, 2022

A patient with a diagnosed bicuspid aortic valve, mild aortic regurgitation was hospitalized in 2014 with symptoms of chronic heart failure (CHF; New York Heart Association [NYHA] class II), multiple unexplained ventricular and supraventricular arrhythmias, episodes of supraventricular tachycardia, paroxysmal atrial fibrillation, and preserved ejection fraction (EF; 55%). Coronary angiography showed nonsignificant atherosclerosis. In 2015, he was admitted with CHF symptoms (NYHA III) and multiple supraventricular arrhythmias. Echocardiography (ECHO) showed global left ventricular (LV) hypokinesis, reduced EF (40%), and no signs of aortic valve and interventricular septum (IVS) distortion. Until then, the cardiac inflammatory process had not been established.

Six years later (2021), he was admitted to the hospital with a non-ST-segment elevation myocardial infarction (NSTEMI). Admission ECHO revealed LV enlargement (63 mm), segmental contractility abnormalities (EF, 45%), bicuspid aortic valve with mild systolic gradient, and moderate regurgitation. Additionally, ECHO showed a cavity (28 ×18 mm) with diastole filling and systole emptying in the basal part of the IVS (Figure 1A). Coronary angiography was postponed until urgent cardiac magnetic resonance (CMR) was performed. CMR confirmed segmental akinesia in the basal segment of the lateral wall and inferoseptal segment in the location of the described cavity in the LV outflow tract (Figure 1B, C). The IVS cavity communicated with the lumen of the LV, filled during diastole, and emptied partially in systole. Additionally, a perforation in the non-coronary cusp communicating with this cavity was revealed. Performed coronary angiography showed critical left main coronary artery (LM) stenosis on bifurcation with the left anterior descending artery (LAD) and left circumflex coronary artery ostium along with subtotal stenosis of the LAD on bifurcation with a large diagonal branch (Figure 1D). Due to advanced coronary artery disease and the bicuspid aortic cusp perforation to the cavity in the IVS, the patient was qualified for cardiac surgery (Figure 1E, F). Successful aortic valve replacement with mechanical AVR 21 ONX prosthesis, IVS cavity closure, and coronary artery bypass grafts with left internal mammary artery to left anterior descending artery (LIMA-LAD), Saphenous vein bypass graft to the diagonal artery (SVBG-Diag) were performed. Histopathology of the aortic leaflet revealed a chronic atypical inflammatory process, without bacterial vegetations.

In this myocardial infarction (MI) patient without an active inflammatory process, ECHO raised suspicion of an IVS rupture within the ischemic zone with the formation of a pseudoaneurysm. Cardiac pseudoaneurysms are a rare complication of MI or bacterial endocarditis [1] [2]. Further ECHO examinations and CMR raised suspicion of the inflammatory damage to the aortic leaflet with a reverse jet towards the injured IVS. The atypical inflammatory process without bacterial vegetation was confirmed in cardiac surgery and histopathology.

Nevertheless, the patient had not been previously diagnosed with cardiac inflammatory disease, and numerous recurrent

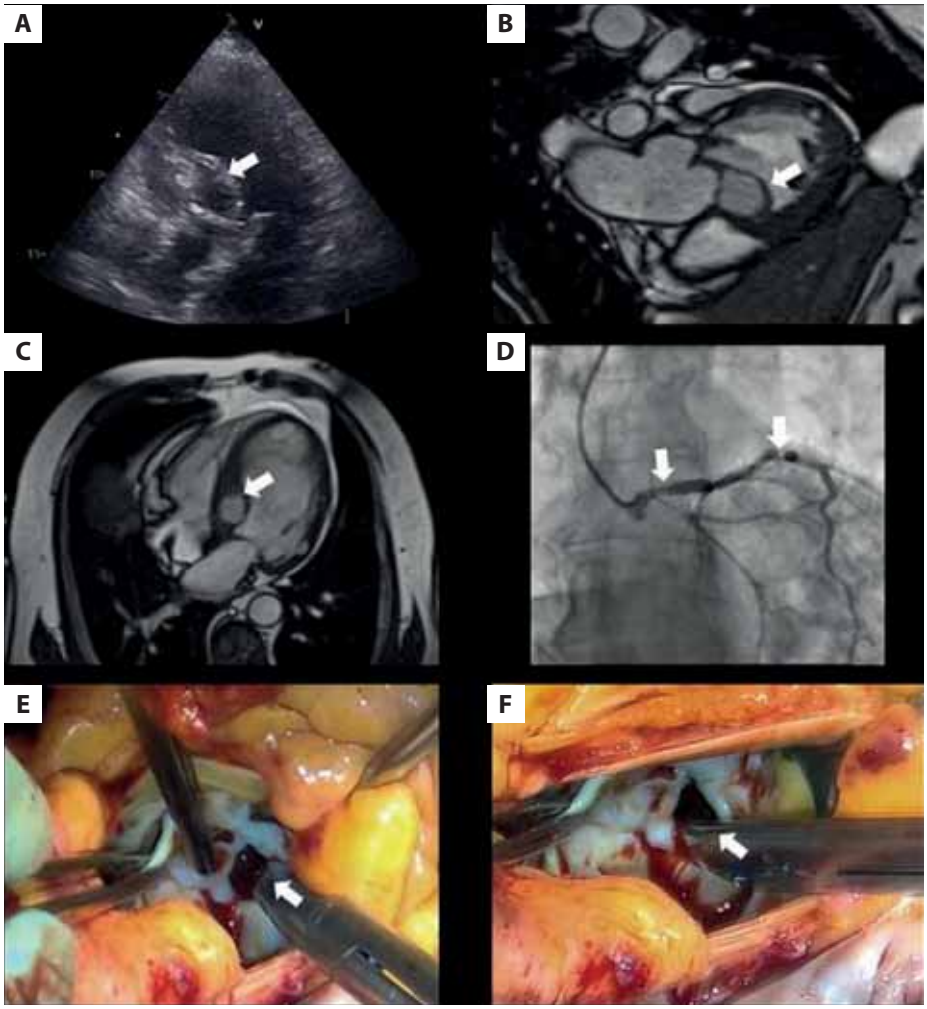


Figure 1. A. Transthoracic echocardiography — a cavity in the basal part of the interventricular septum (arrow). **B.** Cardiac magnetic resonance (CMR) — a cavity in the basal part of the interventricular septum (arrow). **C.** CMR — a cavity in the basal part of the interventricular septum (arrow). **D.** Coronary angiography — a caudal view of left main coronary artery stenosis on bifurcation with the left anterior descending artery and left circumflex coronary artery ostium (Medina 1-1-1) (arrow); subtotal stenosis of the left anterior descending artery on bifurcation with a large diagonal branch (Medina 1-1-1) (arrow). **E.** Intraoperative view of the intraventricular septum pseudoaneurysm cavity (arrow). **F.** Intraoperative view of the intraventricular septum pseudoaneurysm cavity (arrow)

arrhythmias could reflect the subclinical inflammatory process. Because coronary angiography demonstrated critical LM bifurcation stenosis with deep ischemia causing NSTEMI, even after surgery, it could not be ruled out whether the IVS post-inflammatory cavity contacted the LV outflow tract before MI or whether this cavity perforated to the LV lumen in the course of post-infarction tissue necrosis.

Imaging is crucial for establishing a diagnosis and guiding appropriate treatment, CMR and tomography are the basis of anatomical characterization and differentiation from other diseases, such as a true LV aneurysm [3–5]. This case presents a situation where pre-coronary angiography ECHO in acute MI influenced the decision process.

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Akins EW, Slone RM, Wiechmann BN, et al. Perivalvular pseudoaneurysm complicating bacterial endocarditis: MR detection in five cases. AJR Am J Roentgenol. 1991; 156(6): 1155–1158, doi: 10.2214/ajr.156.6.2028858, indexed in Pubmed: 2028858.
2. Hulten EA, Blankstein R. Pseudoaneurysms of the heart. Circulation. 2012; 125(15): 1920–1925, doi: 10.1161/CIRCULATIONAHA.111.043984, indexed in Pubmed: 22508841.
3. Frances C, Romero A, Grady D. Left ventricular pseudoaneurysm. J Am Coll Cardiol. 1998; 32(3): 557–561, doi: 10.1016/s0735-1097(98)00290-3, indexed in Pubmed: 9741493.
4. Sitta J, Howard CM. Left ventricular pseudoaneurysm: An unexpected finding. Radiol Case Rep. 2021; 16(3): 538–542, doi: 10.1016/j.radcr.2020.12.028, indexed in Pubmed: 33384752.
5. Ballard DH, Jokerst C, Raptis CA, et al. Myocardial cut-off sign is a sensitive and specific cardiac computed tomography and magnetic resonance imaging sign to distinguish left ventricular pseudoaneurysms from true aneurysms. J Thorac Imaging. 2022; 37(1): 58–65, doi: 10.1097/RTI.0000000000000525, indexed in Pubmed: 32427649.

Leadless pacemaker implantation in a univentricular heart in a patient with a double-inlet left ventricle and L-transposition of the great arteries

Mateusz Tajstra[1], Elżbieta Adamowicz-Czoch[1], Anna Kurek[1], Jolanta Nowak[1], Jan Głowacki[2], Karol Miszalski-Jamka[2], Zbigniew Kalarus[3], Mariusz Gąsior[1], Oskar Kowalski[3]

[1]3rd Department of Cardiology, Silesian Center for Heart Diseases, Medical University of Silesia, Zabrze, Poland
[2]Department of Diagnostic Imaging, Silesian Center for Heart Disease, Zabrze, Poland
[3]Department of Cardiology, Congenital Heart Disease and Electrotherapy, Silesian Medical University, Silesian Center for Heart Diseases, Zabrze, Poland

Correspondence to:
Mateusz Tajstra, MD, PhD,
Silesian Center for Heart Diseases,
Szpitalna 2,
41–800 Zabrze, Poland,
phone: +48 32 3733674,
e-mail: mateusztajstra@wp.pl

DOI: 10.33963/KP.a2023.0082

Received:
January 19, 2023

Accepted:
February 9, 2023

Early publication date:
March 29, 2023

Leadless pacemakers (LP) should be viewed as an alternative to conventional transvenous systems to address typical limitations including venous route issues, lead-related complications, and infections [1, 2]. Additionally, they may be considered in complex patients [3]. Published data regarding LP implantation in adults with congenital heart disease (ACHD) are scarce [4, 5]. ACHD patients with complex cardiovascular anatomy are at high risk of conduction disturbances including complete heart block. This report describes a successful LP (Micra™ VR, Medtronic Inc., Dublin, Ireland) implantation in an ACHD patient with a univentricular heart.

A 42-year-old male with a single, double-inlet, significantly enlarged left ventricle (LV), with good global contractility, hypoplastic right ventricle (RV), ventricular septal defect, subvalvular pulmonary stenosis, aneurysmal dilated main pulmonary artery, and L-transposition of the great arteries (Figure 1A–C,

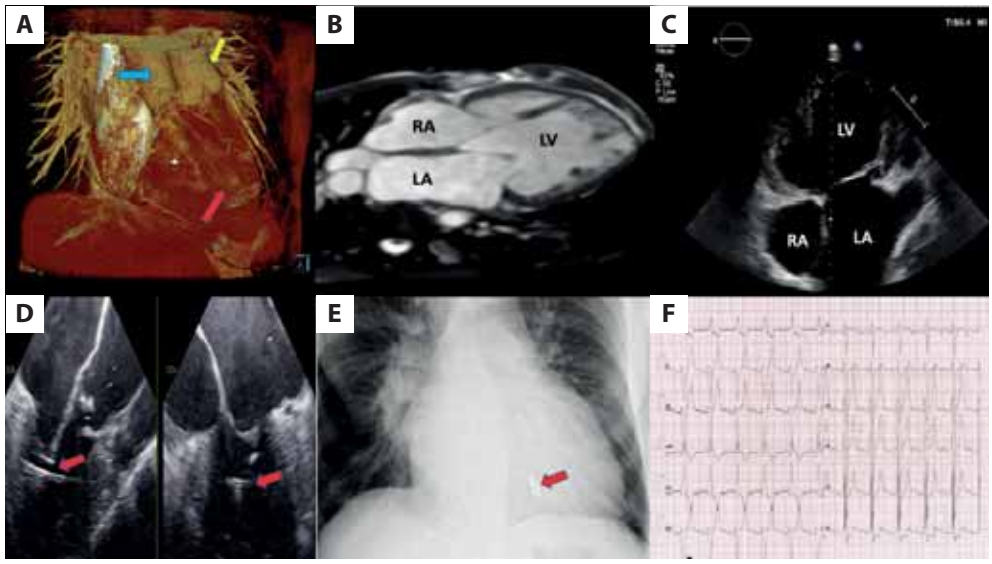


Figure 1. A. Computed tomography scan — Volume Rendering Technique. L-transposition of the great arteries — the main pulmonary artery (blue arrow) and the aorta (yellow arrow) are in transposition. A significantly functionally enlarged single ventricle (red arrow). **B.** Cardiac magnetic resonance. Double-inlet left ventricle (LV) with two separate atrioventricular valves, enlarged left (LA) and right atrium (RA), rudimentary right ventricle, ventricular septal defect, and transposition of the great arteries. **C.** Transthoracic echocardiogram. Double-inlet LV with two separate atrioventricular valves, enlarged LA and RA. **D.** Transesophageal echocardiogram. Positioning of the leadless pacemaker. Delivery system (red arrows). **E.** Chest X-ray after the implantation; in anteroposterior view, the position of leadless pacemaker (red arrow). **F.** Electrocardiogram after leadless pacemaker implantation showing a successful ventricular-paced rhythm with underlying atrial fibrillation

Supplementary material, *Video S1*), and permanent atrial fibrillation was admitted for symptomatic complete heart block. Several concerns were recorded regarding the higher risk of transvenous or epicardial system implantation, mainly including infective issues, potential lead-related thrombus formation and its embolization into the systemic circulation, and last but not least, lead-related mechanical complications (fracture, dislodgement), and the need for many re-do interventions. Using a multiple imaging modalities evaluation and following a careful discussion between the Heart Team and the patient, a decision was made to implant an LP into the LV.

The LP procedure was carried out under general anesthesia, based on fluoroscopy and transesophageal echocardiogram navigation. A 12 F vascular sheath was introduced after the left femoral vein puncture and upsized through the 18 F to a 27 F Micra delivery system. The system with a Micra LP was directed from the right atrium to the LV with an attempt to place it in the LV apex (Figure 1D, Supplementary material, *Video S2*). Most probably, due to unfavorable angulation between the enormous right atrium and very large LV, effective LP implantation was technically demanding and the device, after initial release, was dislocated several times (with no possibility to push the LP against the LV wall), or unacceptable electrical parameters were noted (pacing threshold above 3 V/0.4 ms). As a result, the entire LP system was removed, and the patient was checked and prepared once again. Additionally, the delivery sheath was manually reshaped to obtain larger curvature (Supplementary material, *Video S3*). Consequently, the LP system was successfully placed near the LV apex (Supplementary material, *Video S4*). Multiple stability "tug" tests and electrical parameters (R wave of 11.4 mV, threshold of 0.5 V@0.4 ms, and impedance of 640 ohms) were evaluated before ultimate LP system deployment (Supplementary material, *Video S5, S6*). The device was released and its position rechecked for the stability, and electrical parameters on the day following the implantation were measured (Figure 1E–F). The patient was discharged two days later in good clinical condition.

We have shown that LP implantation, though challenging, is safe and feasible in a patient with a univentricular heart. It may be presumed that the number of ACHD patients with a high incidence of severe atrioventricular conduction disturbances secondary to disease progression and multiple interventions will grow. LP implantation seems to be a very attractive clinical option in this population.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Glikson M, Nielsen JC, Kronborg MB, et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart J. 2021; 42(35): 3427–3520, doi: 10.1093/eurheartj/ehab364, indexed in Pubmed: 34455430.
2. Kempa M, Mitkowski P, Kowalski O, et al. Expert opinion of a Working Group on Leadless Pacing appointed by the National Consultant in Cardiology and the Board of the Heart Rhythm Section of the Polish Cardiac Society. Kardiol Pol. 2021; 79(5): 604–608, doi: 10.33963/KP.15982, indexed in Pubmed: 34125944.
3. Okabe T, Afzal MR, Houmsse M, et al. Tine-Based leadless pacemaker: strategies for safe implantation in unconventional clinical scenarios. JACC Clin Electrophysiol. 2020; 6(10): 1318–1331, doi: 10.1016/j.jacep.2020.08.021, indexed in Pubmed: 33092762.
4. Sterliński M, Demkow M, Plaskota K, et al. Percutaneous extraction of a leadless Micra pacemaker from the pulmonary artery in a patient with complex congenital heart disease and complete heart block. EuroIntervention. 2018; 14(2): 236–237, doi: 10.4244/EIJ-D-17-00660, indexed in Pubmed: 28943497.
5. Dunne L, Breatnach C, Walsh KP. Systemic ventricular implantation of a leadless pacemaker in a patient with a univentricular heart and atrioventricular node calcification. HeartRhythm Case Rep. 2020; 6(5): 265–267, doi: 10.1016/j.hrcr.2020.01.008, indexed in Pubmed: 32461891.

Concomitant high-risk pulmonary embolism and paradoxical ischemic stroke: Aspiration thrombectomy as a treatment option

André Alexandre[1, 2*], David Sá-Couto[1, 2*], Andreia Campinas[1], Mariana Santos[1], Raquel Baggen-Santos[1, 2], Bruno Brochado[1, 2], João Silveira[1, 2], Severo Torres[1, 2], André Luz[1–3]

[1]Department of Cardiology, Porto University Hospital Center, Porto, Portugal

[2]ICBAS — School of Medicine and Biomedical Sciences, University of Porto, Porto, Portugal

[3]Cardiovascular Research Group, UMIB — Unit for Multidisciplinary Research in Biomedicine, ICBAS — School of Medicine and Biomedical Sciences, University of Porto, Porto, Portugal

*Both authors equally contributed to the study

Correspondence to:
André Alexandre, MD, Department of Cardiology, Porto University Hospital Center, Largo do Prof. Abel Salazar, 4099–001, Porto, Portugal, phone: +351 22 207 7500, e-mail: andrealexandre_1@msn.com

DOI: 10.33963/KP.a2023.0081

Received: January 29, 2023

Accepted: February 25, 2023

Early publication date: March 29, 2023

A 31-year-old man, with a history of steroid-dependent Crohn's disease and paraparesis, experienced simultaneous pulmonary embolism (PE) and paradoxical ischemic stroke. This patient was admitted to the emergency department with sudden dyspnea and chest discomfort. Initial examination revealed that the patient was hemodynamically stable but with severe (type 1) respiratory failure and hypocapnia. His electrocardiogram showed sinus tachycardia (166/minute) and slight ST-segment depression in the left precordial leads. Bedside transthoracic echocardiography revealed pulmonary artery acceleration time of 83 msec, moderate tricuspid regurgitation with estimated pulmonary artery systolic pressure of 35 mm Hg, mild right ventricular dilation with preserved systolic function, no signs of short axis pressure overload, non-dilated inferior vena cava with normal inspiratory collapse, and preserved left ventricular function. Cardiac biomarkers were elevated (high-sensitivity troponin T was 0.147 ng/ml [reference values 0.000–0.014] and NT-proBNP was 2275 pg/ml [reference value <300]). Considering the clinical presentation of acute respiratory failure in the patient with prolonged immobilization, we assumed there was a high clinical probability of PE, and anticoagulation with enoxaparin was initiated without delay. Pulmonary computed tomography (CT) angiography further confirmed bilateral PE with a subocclusive thrombus in the right pulmonary artery and segmental thrombi in the left branches with filling defects (Supplementary material, *Figure S1*).

One hour after admission, the patient suddenly developed focal neurological deficits. An urgent CT angiography of the cerebral arteries revealed an endoluminal thrombus occluding the proximal M1 and M2 segments of the right middle cerebral artery. Due to anticoagulation used initially for PE treatment, tissue plasminogen activator was not used for management of stroke, and thrombectomy of the right middle cerebral artery was performed with neurological improvement (Supplementary material, *Figure S2*, *Videos S1*, *S2*). At first, a conservative PE treatment with anticoagulation was favored since the patient was hemodynamically stable (intermediate-high risk PE). Nevertheless, the patient evolved with shock and transthoracic echocardiography showed progressive signs of right heart chambers overload: dilated right ventricle (44 mm) with signs of short axis pressure overload, pulmonary artery systolic pressure of 52 mm Hg, hypokinesia of the right ventricular mid-free wall, and dilated inferior vena cava (22 mm) with normal respiratory variability. Considering the catastrophic progression to high-risk PE and the formal contraindication to systemic thrombolysis (concomitant ischemic stroke), we decided to proceed with pulmonary aspiration thrombectomy. Pulmonary thrombectomy was successfully performed with the Indigo aspiration system (Indigo CAT 8Fr XTORQ) (Figure 1, Supplementary material, *Videos S3–S11*). During the

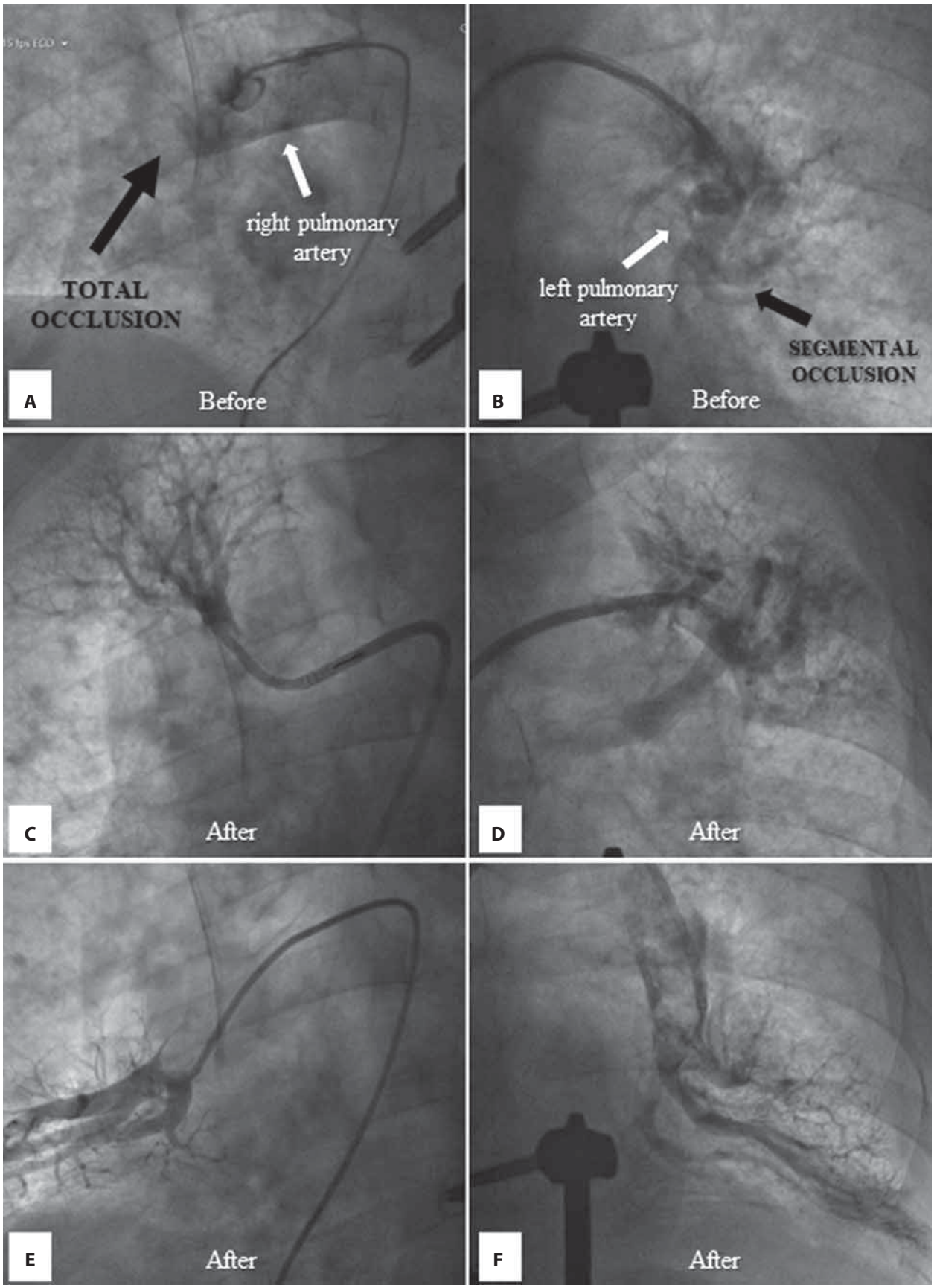


Figure 1. Pulmonary aspiration thrombectomy for management of concomitant high-risk pulmonary embolism (PE) and paradoxical stroke. **A.** Pulmonary angiography showing total occlusion (black arrow) of the right pulmonary artery (white arrow). **B.** Pulmonary angiography revealing segmental occlusion (black arrow) of the left pulmonary artery (white arrow) and filling defects of its branches. **C–F.** Pulmonary angiography showing the final result with improved lung perfusion after aspiration thrombectomy

procedure, mean pulmonary artery pressure dropped from 37 mm Hg to 25 mm Hg, improving lung perfusion and resolving the obstructive shock (catecholamine support was stopped within the following hour).

This clinical case illustrates the catastrophic possibility of synchronous high-risk PE and ischemic stroke due to an intracardiac shunt (a bubble study further revealed the presence of a patent foramen ovale in this patient) [1]. Concomitant presentation of massive PE and paradoxical ischemic stroke is considered a "double jeopardy" since the risk of brain hemorrhage contraindicates systemic thrombolysis for combined high-risk PE [2]. Currently, there is no agreed-upon standard treatment in this situation [2]. Since systemic thrombolysis leads to a higher risk of hemorrhagic complications, percutaneous catheter-directed strategies (such as pulmonary aspiration thrombectomy and catheter-directed thrombolysis) are emerging as potential alternatives [3–5]. In this case, pulmonary aspiration thrombectomy turned out to be a reliable and safe treatment option for patients who experience concomitant high-risk PE and ischemic stroke.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Le Moigne E, Timsit S, Ben Salem D, et al. Patent foramen ovale and ischemic stroke in patients with pulmonary embolism: A prospective cohort study. Ann Intern Med. 2019; 170(11): 756–763, doi: 10.7326/M18-3485, indexed in Pubmed: 31060047.
2. Lio KaU, Jiménez D, Moores L, et al. Clinical conundrum: concomitant high-risk pulmonary embolism and acute ischemic stroke. Emerg Radiol. 2020; 27(4): 433–439, doi: 10.1007/s10140-020-01772-7, indexed in Pubmed: 32211984.
3. Ciampi-Dopazo JJ, Romeu-Prieto JM, Sánchez-Casado M, et al. Aspiration thrombectomy for treatment of acute massive and submassive pulmonary embolism: Initial single-center prospective experience. J Vasc Interv Radiol. 2018; 29(1): 101–106, doi: 10.1016/j.jvir.2017.08.010, indexed in Pubmed: 29102272.
4. Sista AK, Horowitz JM, Tapson VF, et al. Indigo Aspiration System for Treatment of Pulmonary Embolism: Results of the EXTRACT-PE Trial. JACC Cardiovasc Interv. 2021; 14(3): 319–329, doi: 10.1016/j.jcin.2020.09.053, indexed in Pubmed: 33454291.
5. Toma C, Bunte M, Cho K, et al. Percutaneous mechanical thrombectomy in a real-world pulmonary embolism population: Interim results of the FLASH registry. Catheter Cardiovasc Interv. 2022; 99(4): 1345–1355, doi: 10.1002/ccd.30091, indexed in Pubmed: 35114059.

Rescue balloon aortic valvuloplasty in a patient with cardiogenic shock followed by transcatheter aortic valve implantation

Łukasz Niewiara[1, 2], Rafał Badacz[2, 3], Jarosław Trębacz[2], Anna Kabłak-Ziembicka[2, 3], Maciej Stąpór[2], Janusz Konstanty-Kalandyk[4, 5], Michał Okarski[6], Krystian Mróz[6], Jacek Legutko[2, 3], Paweł Kleczyński[2, 3]

[1]Department of Emergency Medicine, Faculty of Health Sciences, Jagiellonian University Medical College, Kraków, Poland
[2]Clinical Department of Interventional Cardiology, John Paul II Hospital, Kraków, Poland
[3]Department of Interventional Cardiology, Institute of Cardiology, Jagiellonian University Medical College, John Paul II Hospital, Kraków, Poland
[4]Clinical Department of Cardiac Surgery and Transplantation, John Paul II Hospital, Kraków, Poland
[5]Jagiellonian University Medical College, Institute of Cardiology, Department of Cardiac Surgery and Transplantation, John Paul II Hospital, Kraków, Poland
[6]Student Scientific Group of Modern Cardiac Therapy at the Department of Interventional Cardiology, Jagiellonian University Medical College, Kraków, Poland

Correspondence to:
Paweł Kleczyński, MD, PhD, FESC, Department of Interventional Cardiology, Institute of Cardiology, Jagiellonian University Medical College, John Paul II Hospital, Prądnicka 80, 31–202 Kraków, Poland, phone: +48 12 614 35 01, e-mail: kleczu@interia.pl

DOI: 10.33963/KP.a2023.0083

Received:
January 5, 2023

Accepted:
March 19, 2023

Early publication date:
March 29, 2023

Balloon aortic valvuloplasty (BAV) is a technique for the treatment of severe aortic valve stenosis (AS) which is used less frequently in contemporary practice; however, according to the current ESC guidelines, it still may be considered a bridge to further therapy in decompensated patients [1, 2]. Recently published data suggest that over half of the procedures may be performed as a bailout strategy [3].

A 71-year-old male with a history of arterial hypertension, chronic obstructive pulmonary disease, and paroxysmal atrial fibrillation was admitted for evaluation of his AS. Moreover, he was diagnosed with advanced coxarthrosis and required walking assistance. The patient was symptomatic, in class II/III according to the New York Heart Association (NYHA) classification; however, no signs of decompensation were present on admission. Transthoracic echocardiography (Figure 1A) confirmed severe AS with mean gradient of 58 mm Hg and aortic valve area (AVA) of 0.3 cm^2 with mildly reduced left ventricular ejection fraction (40%). Immediately after non-invasive testing on the same day, the patient developed severe dyspnea, hypotonia, and finally, cardiogenic shock within several minutes. Due to pulmonary edema with low blood pressure, the patient was intubated and mechanically ventilated. An urgent remote Heart Team assessment was performed, and the patient was qualified for coronary angiography with concomitant rescue BAV. The coronary angiogram revealed no significant coronary lesions (Figures 1B and 1C). Due to severe calcifications of leaflets, a 22 mm Osypka VACS II (Osypka, Rheinfelden, Germany) balloon was unable to cross the aortic valve so additional predilatation with 8.0 × 50 mm and 9.0 × 50 mm (Figure 1D1) peripheral balloon catheters was performed. Eventually, a 22 × 50 mm balloon catheter was successfully introduced and BAV was performed (Figure 1D2). Periprocedural echocardiography confirmed a decrease in mean gradient to 38 mm Hg with AVA of 1.0 cm^2. Pre-transcatheter aortic valve implantation (TAVI) was abandoned at the time due to unknown neurological status of the patient. The patient was hospitalized in the intensive care unit for 2 days. After his recovery, additional imaging with computed tomography, according to the TAVI workup, was performed to assess the valve and vascular access (Figure 1E). Within a week, a TAVI procedure was performed (Figure 1F) using a self-expanding Navitor 25 valve (Abbott, Chicago, IL, US). Post-procedural echocardiography showed 9/5 mmHg gradient and mild perivalvular leak. The patient was successfully discharged home after 16 days of in-hospital treatment. He attended the 30-day follow-up appointment alone, with almost no signs of physical and mental decline.

Symptomatic severe AS is still a life-threatening condition. Balloon aortic valvuloplasty

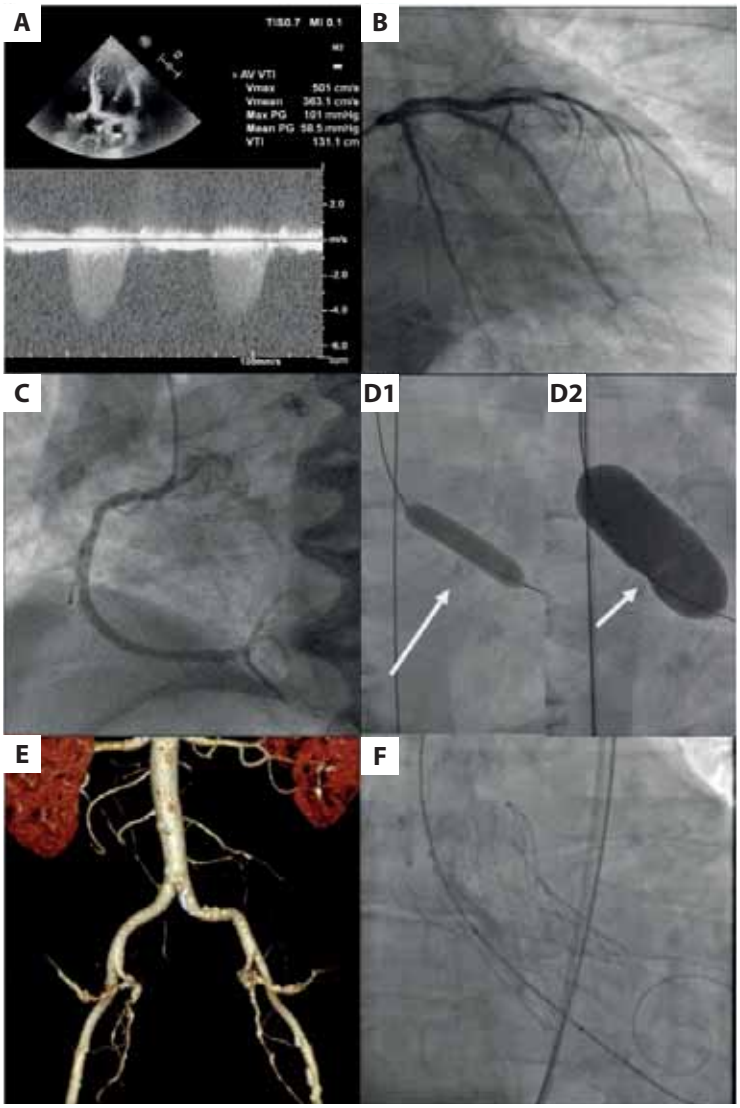


Figure 1. A. Baseline transthoracic echocardiography showing severe aortic valve stenosis. **B.** Coronary angiography of the left coronary system with no significant lesions. **C.** Coronary angiography of the right coronary artery with a moderate lesion in its proximal segment. **D1.** A 9.0 × 50 mm peripheral angioplasty balloon that passed across the stenosed valve. **D2.** The final 22 × 50 mm valvuloplasty balloon (white arrows — calcifications). **E.** Computed tomography angiography assessment showing optimal femoral access. **F.** Self-expanding aortic valve implantation

remains a feasible method that can be used as a bridge-to-therapy as well as a bailout strategy in critical cases and followed by definite treatment [4].

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2022; 43(7): 561–632, doi: 10.1093/eurheartj/ehab395, indexed in Pubmed: 34453165.
2. Kleczynski P, Kulbat A, Brzychczy P, et al. Balloon aortic valvuloplasty for severe aortic stenosis as rescue or bridge therapy. J Clin Med. 2021; 10(20), doi: 10.3390/jcm10204657, indexed in Pubmed: 34682783.
3. Tyczyński P, Chmielak Z, Dąbrowski M, et al. Elective versus rescue balloon aortic valvuloplasty for critical aortic stenosis. Kardiol Pol. 2020; 78(10): 982–989, doi: 10.33963/KP.15299, indexed in Pubmed: 32329317.
4. Kleczynski P, Brzychczy P, Kulbat A, et al. Balloon aortic valvuloplasty for severe aortic stenosis may reduce mitral regurgitation in mid-term follow-up. Postepy Kardiol Interwencyjnej. 2022; 18(3): 255–260, doi: 10.5114/aic.2022.121004, indexed in Pubmed: 36751280.

Intracoronary and left ventricular thrombi in a 29-year-old COVID-19 convalescent with ST-segment elevation myocardial infarction

Jacek Legutko[1, 2], Paweł Kleczyński[1, 2], Bartłomiej Guzik[1, 2], Anetta Undas[3], Krzysztof Bryniarski[1, 2]

[1]Department of Interventional Cardiology, Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland
[2]Clinical Department of Interventional Cardiology, John Paul II Hospital, Kraków, Poland
[3]Department of Thromboembolic Disorders, Institute of Cardiology, Jagiellonian University Medical College, John Paul II Hospital, Kraków, Poland

Correspondence to:
Krzysztof Bryniarski, MD, PhD, FESC,
Department of Interventional Cardiology, Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland,
phone: +48 603 516 797,
e-mail: kbrynia@gmail.com

DOI: 10.33963/KP.a2022.0280

Received:
October 3, 2022

Accepted:
November 27, 2022

Early publication date:
December 5, 2022

A 29-year-old overweight male with no previous medical history and without family history of premature myocardial infarction, who recently recovered from a mild COVID-19 disease treated at home, was admitted for anterior and lateral ST-segment elevation myocardial infarction (STEMI).

Transthoracic echocardiography (Supplementary material, *Video A1*) revealed left ventricular ejection fraction (LVEF) of 55% with apex akinesis and a left ventricular (LV) thrombus in the apical region. Coronary angiography showed a large thrombus in the proximal left anterior descending artery (LAD) with Thrombolysis in Myocardial Infarction (TIMI) 2 flow (Figure 1A, Supplementary material, *Video SA2*). Successful aspiration thrombectomy was performed, and TIMI 3 flow was restored (Figure 1B, Supplementary material, *Video SB1*). The aspirated thrombus was analyzed using spectroscopy presented in hematoxylin and eosin (H&E) staining and color map distribution of organic matter indicating lipid-rich areas, hem and lipid class, and fibrin class (Figure 1C). Intravascular ultrasound imaging demonstrated an eccentric plaque in

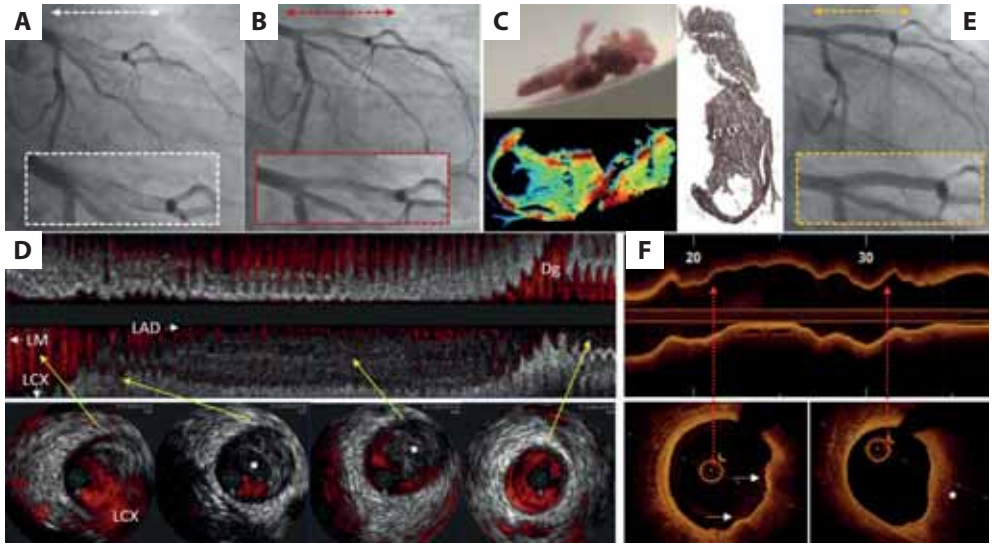


Figure 1. Multimodality assessment of the patient with ST-segment myocardial infarction successfully treated with a non-stenting strategy. Baseline coronary angiography with haziness in the proximal left anterior descending artery (**A**) and angiography after thrombectomy (**B**). **C.** Aspirated thrombus with results of Fourier and Raman Spectroscopy. **D.** Intravascular ultrasound imaging with a plaque in the proximal part of the LAD covered by thrombus protruding to the medial LAD (asterisk). **E.** Control angiography and optical coherence tomography (**F**) with a thrombus (arrow) and lipid plaque (asterisks)

Abbreviations: LAD, left anterior descending artery; LCx, left circumflex artery; LM, left main

the ostial and proximal LAD covered by a residual thrombus (Figure 1D, Supplementary material, *Video SD1*), which led to the administration of eptifibatide and stenting deferral. The patient received enoxaparin along with aspirin and ticagrelor. Cardiac magnetic resonance confirmed thrombus in the LV apex (Supplementary material, *Figure SA1*). Control coronary angiography performed 8 days after the index procedure showed no significant stenosis (Figure 1E). Optical coherence tomography demonstrated almost complete thrombus resolution in the proximal part of the LAD without any signs of plaque rupture (Figure 1F, Supplementary material, *Video SF1*). Since there was no significant lesion in the LAD, we decided not to perform stenting, and the patient was discharged on warfarin (target INR 2–2.5) and clopidogrel. The patient was assessed for hypercoagulability state in the outpatient department; however, no abnormalities were found. Echocardiography performed 6 months after hospital discharge showed LVEF of 60% with hypokinesis of the apex. Furthermore, the patient did not develop any new symptoms or needed another hospitalization.

SARS-CoV-2 infection increases thromboembolic risk including a higher risk of STEMI [1]. Intracoronary thrombus formation in young patients free of significant stenosis is infrequent during severe infection, including COVID-19. It is yet to be determined for how long patients in the convalescent phase of COVID-19 may have an increased risk of cardiovascular events.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Violi F, Pignatelli P, Cammisotto V, et al. COVID-19 and thrombosis: Clinical features, mechanism of disease, and therapeutic implications. Kardiol Pol. 2021; 79(11): 1197–1205, doi: 10.33963/KP.a2021.0154, indexed in Pubmed: 34847237.

Pharmacotherapy of heart failure A.D. 2023. Expert opinion of Working Group on Cardiovascular Pharmacotherapy, Polish Cardiac Society

Jarosław D Kasprzak[1], Iwona Gorczyca-Głowacka[2], Maria Sobczak-Kaleta[1], Marcin Barylski[3], Jarosław Drożdż[4], Krzysztof J Filipiak[5], Agnieszka Kapłon-Cieślicka[6], Małgorzata Lelonek[7], Artur Mamcarz[8], Dorota Ochijewicz[6], Anna Ryś-Czaporowska[6], Katarzyna Starzyk[2, 9], Filip M Szymański[10], Marcin Wełnicki[8], Beata Wożakowska-Kapłon[2, 9]

[1]1st Department of Cardiology, Medical University of Lodz, Łódź, Poland
[2]Collegium Medicum, Jan Kochanowski University in Kielce, Kielce, Poland
[3]Department of Internal Diseases and Cardiac Rehabilitation, Medical University of Lodz, Łódź, Poland
[4]2nd Department of Cardiology, Medical University Lodz, Łódź, Poland
[5]Institute of Clinical Sciences, Maria Sklodowska-Curie Medical Academy, Warszawa, Poland
[6]1st Chair and Department of Cardiology, Medical University of Warsaw, Warszawa, Polska
[7]Nonivasive Cardiology Unit, Chair of Internal Medicine and Cardiology, Medical University of Lodz, Łódź, Poland
[8]3rd Department of Internal Medicine and Cardiology, Medical University of Warsaw, Warszawa, Poland
[9]1st Department of Cardiology and Electrotherapy, Świętokrzyskie Cardiology Center, Kielce, Poland
[10]Department of Civilization Diseases, Faculty of Medicine, Collegium Medicum, Stefan Cardinal Wyszynski University in Warsaw, Warszawa, Poland

Correspondence to:
Jarosław D Kasprzak, MD, PhD, 1st Department of Cardiology, Medical University of Lodz, Kniaziewicza 1/5, 91–347 Łódź, Poland, phone: +48 602 632 632, e-mail: kasprzak@ptkardio.pl

DOI: 10.33963/KP.a2023.0110

Received:
April 21, 2023

Accepted:
April 21, 2023

Early publication date:
May 2, 2023

ABSTRACT

Heart failure (HF) remains one of the most common causes of hospitalization and mortality among Polish patients. The position of the Section of Cardiovascular Pharmacotherapy presents the currently applicable options for pharmacological treatment of HF based on the latest European and American guidelines from 2021–2022 in relation to Polish healthcare conditions. Treatment of HF varies depending on its clinical presentation (acute/chronic) or left ventricular ejection fraction. Initial treatment of symptomatic patients with features of volume overload is based on diuretics, especially loop drugs. Treatment aimed at reducing mortality and hospitalization should include drugs blocking the renin-angiotensin-aldosterone system, preferably angiotensin receptor antagonist/neprilysin inhibitor, i.e. sacubitril/valsartan, selected beta-blockers (no class effect — options include bisoprolol, metoprolol succinate, or vasodilatory beta-blockers — carvedilol and nebivolol), mineralocorticoid receptor antagonist, and sodium-glucose cotransporter type 2 inhibitor (flozin), constituting the 4 pillars of pharmacotherapy. Their effectiveness has been confirmed in numerous prospective randomized trials. The current HF treatment strategy is based on the fastest possible implementation of all four mentioned classes of drugs due to their independent additive action. It is also important to individualize therapy according to comorbidities, blood pressure, resting heart rate, or the presence of arrhythmias. This article emphasizes the cardio- and nephroprotective role of flozins in HF therapy, regardless of ejection fraction value. We propose practical guidelines for the use of medicines, profile of adverse reactions, drug interactions, as well as pharmacoeconomic aspects. The principles of treatment with ivabradine, digoxin, vericiguat, iron supplementation, or antiplatelet and anticoagulant therapy are also discussed, along with recent novel drugs including omecamtiv mecarbil, tolvaptan, or coenzyme Q10 as well as progress in the prevention and treatment of hyperkalemia. Based on the latest recommendations, treatment regimens for different types of HF are discussed.

Key words: ACC/AHA/HFSA guidelines, ESC guidelines, heart failure, pharmacoeconomics, pharmacotherapy

Table 1. Definitions of heart failure with lowered, mildly reduced, and preserved left ventricular ejection fraction [2]

Type HF	HFrEF	HFmrEF	HFpEF
	Symptoms ± signs	Symptoms ± signs	Symptoms ± signs
	LVEF ≤40%	LVEF 41%–49%	LVEF ≥50%
	—	Recognition more likely in the presence of structural abnormalities of the heart or impaired filling of LV	Features of structural and/or functional abnormalities, corresponding to diastolic dysfunction of LV, increased filling pressure of LV, increased concentration of natriuretic peptides

Abbreviations: HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricle; LVEF, left ventricular ejection fraction

INTRODUCTION

There are approximately 1.2 million patients with symptomatic heart failure (HF) in Poland, i.e. 3.2% of the population of our country, and around 140 000 patients die annually. Up to 40% of patients with HF die within 5 years of diagnosis [1]. These historic data may no longer be true with optimal HF therapy, yet HF remains a very frequent cause of death. The goal of HF treatment is primarily to reduce mortality and morbidity (relieve symptoms, improve quality of life, decrease the need for hospital treatment) and prevent the progression of the disease. Most of hospital admissions, frequent in this group, are associated with deterioration in the clinical condition of the patient, which often results from inadequate disease control, including suboptimal pharmacotherapy — the primary method of HF treatment. The degree of implementation of existing treatment recommendations for HF patients is influenced by many different factors, such as the education of doctors, patient characteristics (e.g. age, concomitant diseases), and socioeconomic factors, including specific costs and availability of medicines and other treatments.

This expert opinion represents a consensus of experts designated by the Working Group on Cardiovascular Pharmacotherapy of the Polish Society of Cardiology (SFSN PTK) commenting upon the latest guidelines of the European Society of Cardiology (ESC, 2021) [2] and American scientific societies (American Heart Association [AHA], American College of Cardiology [ACC], Heart Failure Society of America — 2022 [HFSA]), and taking into account specific features of the Polish healthcare system [3]. We present characteristics of groups of drugs currently used in HF therapy, recommended in the guidelines, paying particular attention to practical aspects — possible problems during the inclusion of individual groups of drugs, monitoring after initiation of treatment, contraindications to treatment, and recommendations for the patient receiving specific therapies.

DEFINITIONS OF HEART FAILURE AND DIFFERENCES IN THERAPEUTIC RECOMMENDATIONS

Heart failure is a complex clinical syndrome resulting from any structural or functional impairment of ventricular filling or ejection, including symptoms (e.g. dyspnea, decreased exercise tolerance) that may be accompanied by signs (e.g. peripheral edema, pulmonary rales, or crackles). HF most often results from myocardial dysfunction, which can be systolic and/or diastolic. Other causes or factors contributing to HF may include abnormalities of the valves, pericardium, and endocardium, as well as arrhythmias or cardiac conduction disorders. There are usually two clinical forms of HF: chronic heart failure (CHF) and acute heart failure (AHF). The diagnosis of CHF refers to patients who have previously been diagnosed with heart failure or who have developed symptoms gradually. The term AHF refers to the rapid or gradual development of signs or symptoms of HF that are so severe that the patient requires urgent medical attention, initiation or intensification of treatment, including intravenous therapy or surgical procedures. AHF may be the first manifestation of HF (*de novo* HF) or result from acute decompensation of CHF.

The latest ESC [2] and American AHA/ACC/HFSA guidelines [3] introduced a new HF classification depending on left ventricular ejection fraction (LVEF) values (Table 1):

- HF with reduced LVEF (≤40%) — HFrEF (heart failure with reduced ejection fraction);
- HF with mildly reduced LVEF (41%–49%) — HFmrEF (heart failure with mildly reduced ejection fraction);
- HF with preserved LVEF (≥50%) — HFpEF (heart failure with preserved ejection fraction).

Pharmacotherapy is the basis for the treatment of HFrEF and aims to reduce mortality, prevent re-hospitalization due to HF severity and improve clinical condition and physical performance. Importantly, therapeutic recommendations vary from type to type of HF. The broadest set of studies concerns HFrEF, and the scientific evidence for the effectiveness of therapies of other types comes from recently completed studies. Importantly, HFrEF patients who improve ejection fraction even to values ≥50% should continue effective HFrEF pharmacotherapy and are categorized as HFimpEF (heart failure with improved EF). The dynamic development of research led to the situation where the ESC 2021 guidelines did not represent the current state of knowledge (with regard to use of flozins) as early as on the day of their presentation.

In order to achieve symptomatic improvement in patients with any type of HF and fluid overload features, diuretics (most often loop diuretics) are necessary (at least at certain stages of treatment) — although they are not categorized as prognosis-improving drugs when used long-term.

In order to reduce the risk of death or hospitalization for HF (improvement of prognosis) in HFrEF, each patient should possibly receive the following four groups of drugs:

- Renin-angiotensin-aldosterone (RAA) axis inhibitors (RAASi) — optimally sacubitril-valsartan, i.e. an angiotensin receptor antagonist in combination with a neprilysin inhibitor, which prevents the breakdown of endogenous natriuretic peptides (ARNI, angiotensin receptor-neprilysin inhibitor). These were previously preferred in HFrEF as a class of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs). They are acceptable in the case of ACEI intolerance but offer a lower degree of protection.
- Beta-blockers (BB) tested in the treatment of HFrEF (4 drugs — bisoprolol, carvedilol, extended-release metoprolol, nebivolol — a class effect is not accepted)
- Mineralocorticoid receptor antagonists (MRA) — spironolactone or eplerenone.
- Flozin (sodium-glucose cotransporter type 2 inhibitor [SGLT2i]), with evidence of benefit in the treatment of HF independently of coexisting diabetes mellitus and/or chronic kidney disease — i.e. empagliflozin or dapagliflozin.

Doses of HF medications (except flozins, having only one dose level) should be gradually increased to the doses used in clinical trials (or, if this is not possible, to the maximum tolerated doses). ARNI, originally recommended as a replacement for ACEI in stable symptomatic patients, should now be considered a first-line treatment, instead of ACEI, also after hospitalization for exacerbated HFrEF, preferably with initiation in the pre-discharge period.

In patients with HFmrEF and HFpEF, SGLT2i (dapagliflozin or empagliflozin) have become the most recommended drug class, which reduces the risk of death or hospitalization for heart failure, regardless of the coexistence of diabetes. In HFmrEF, drugs typical of HFrEF, i.e. RAASi, BB, and MRA can be used with a lower class of recommendations. Since many patients with HFmrEF/HFpEF also have chronic coronary syndrome, hypertension, or atrial fibrillation, they are still candidates for drugs from the above groups, as optimal treatment of the above-mentioned diseases is essential. According to the American recommendations, ARNI can also be used across the spectrum of heart failure.

It should be emphasized, that HF patients with EF improvement — HFimpEF (HF with improved EF) who meet the HFrEF criteria, regardless of the current LVEF value that increased thanks to typical HFrEF therapy, should absolutely continue the HFrEF treatment regimen. This group was analyzed in a targeted way by the DELIVER study, confirming the beneficial effects of dapagliflozin [4].

New strategy for the treatment of heart failure — rapid implementation of comprehensive pharmacotherapy

The conventional approach to HFrEF treatment based on initiating a single drug therapy and increasing the dose to the maximum tolerated/target before adding another drug, was based solely on the historic in which these 4 groups of drugs were tested in prospective randomized clinical trials. Unfortunately, this strategy took 6 to 12 months, during which HF progressed. Currently, a different approach is recommended, leading to the fastest possible initiation and rapid escalation of ARNI, BB, and MRA dosage, simultaneously with the initial optimal dose of SGLT2i. Each of these four drug classes provides independent and additive benefits, obtained early after starting treatment. It is the responsibility of the members of the multidisciplinary HF Team to ensure the rapid and safe implementation of these four basic treatments for HFrEF [2]. The ESC guidelines outline a treatment strategy to reduce mortality, indicating drugs and non-pharmacological therapies of first choice in HFrEF patients, taking into account the HF etiology. The new strategy for the implementation of treatment for HFrEF patients and the shift towards an individual approach to treatment depending on the clinical profile of the patient is recommended by this writing group [5] (Figure 1).

The experts' proposal for the use of the main HFrEF therapies assumes the four groups of recommended drugs ("pillars of HF therapy", "drugs of the first step", "the big four") should be optimally initiated at the same time or, alternatively, stepwise — depending on the clinical profile of the patient, but within a period not exceeding 4 weeks. The American ACC/AHA/HFSA guidelines specify that one can start treatment simultaneously or sequentially. The crucial practical recommendations are as follows:

- Simultaneous initiation takes place at the initial (low) doses recommended for HFrEF (except for SGLT2i, which are dosed from the beginning at the optimal dose), assuming monitoring of potency and side effects (including kidney function).
- Alternatively, drugs can be switched on sequentially, depending on clinical or other factors, without having to reach the target dose before starting the next drug — the priority is to complete the "four pillars of therapy" **as soon as possible**.
- Drug doses should be increased to target values according to tolerability.
- Doses of drugs can be increased faster in the hospital setting than in outpatients.
- The initiation of all four therapies is prioritized before the full dose escalation of any single "pillar".

Proper treatment of HF patients should, therefore, mainly take into account the pursuit of maximum or maximally tolerated doses of included drugs, appropriate control of drug-specific biochemical parameters, and the possibility of individualization of therapy depending on coexisting loads (this does not apply to SGLT2 inhibitors, as they are used in a single dose). The sequence can be adapted to the patient's profile and the doctor's experience.

It is suggested that beta-blockers should be included after compensation (i.e. the patient's "dry and warm" pro-

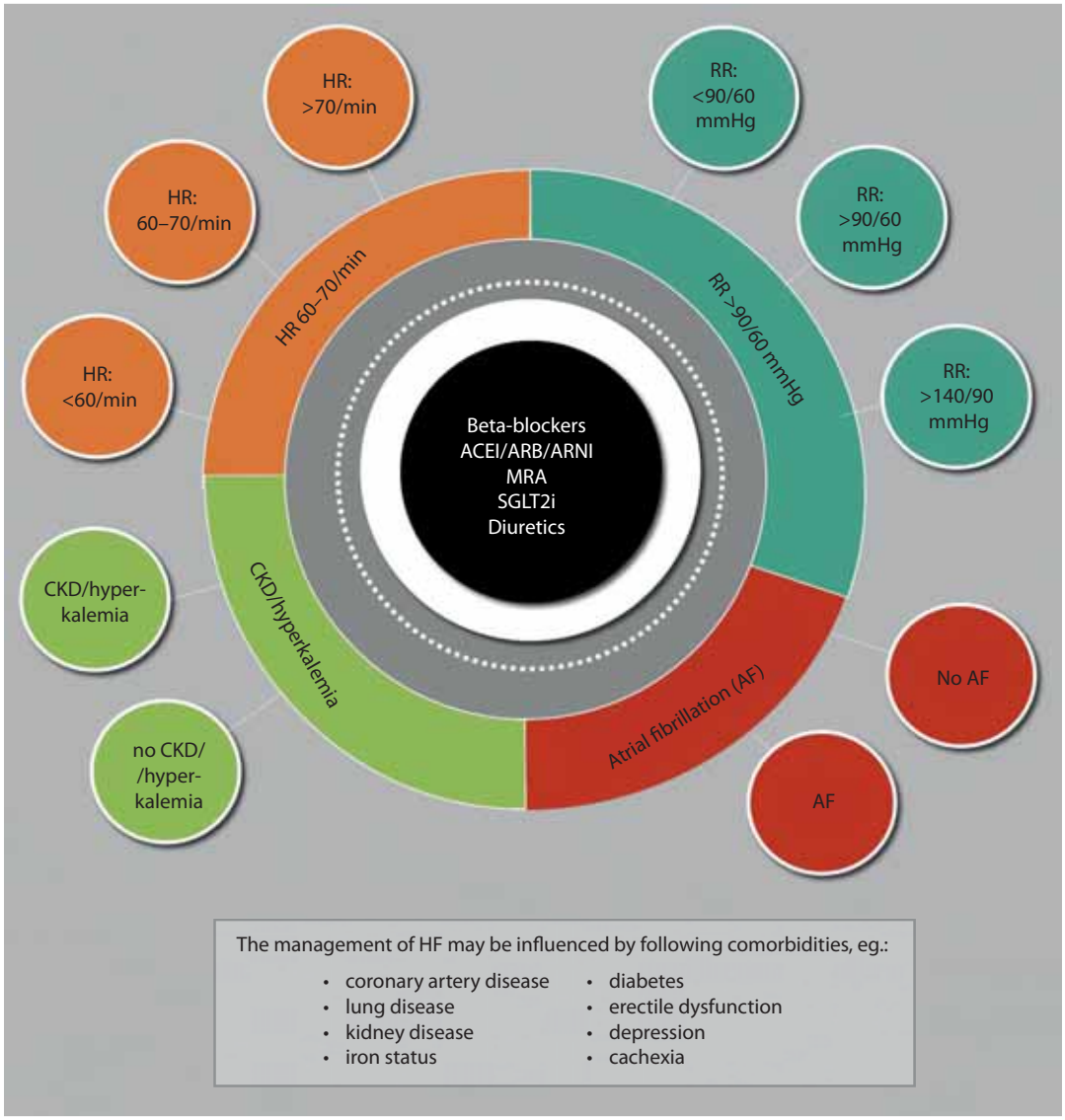


Figure 1. Profiling HFrEF treatment depending on clinical characteristics of the patient. Modified according to [4]
Abbreviations: AF, atrial fibrillation; CKD, chronic kidney disease; other — see Table 1

file), and other of the above-mentioned drugs even during a period of incomplete cardiac compensation [2]; however, the prerequisite is still the stabilization of volume status and arterial pressure.

The guidelines emphasize the superior efficacy of sacubitril/valsartan over ACEI, and the selection of appropriate therapy requires patients in New York Heart Association (NYHA) class II–III to convert from a classic RAA blockade to ARNI use to reduce mortality. The indications for use of ARNI have been significantly expanded, also with regard to hospital initiation without prior ACEI/ARB treatment, including patients hospitalized as a result of acute, decompensated HFrEF after hemodynamic stabilization [6, 7]. In addition, compared to ACEI alone, sacubitril/valsartan reduces the rate of deterioration in renal function over time, and this, together with the observation that ARNI and SGLT2i reduce the risk of hyperkalemia and improve MRA tolerance, means that the use of these two drugs in patients may increase the likelihood of safe introduction and long-term use of MRA.

Due to the unique mechanism of action of SGLT2i, these drugs can be safely initiated in most patients without end-stage renal failure. SGLT2i studies assumed prior use of RAASi/MRA/BB [2] although the benefits appear to be independent of other first-line drugs. In some patients with newly-diagnosed HFrEF, e.g. in the case of low blood pressure and impaired renal function, flozins may be initiated early to facilitate the subsequent introduction of other class I recommended drugs [8].

It is extremely important to provide the patient (and often also his/her family) with reliable information about the available possible HF pharmacotherapy with costs per month of therapy and to discuss with the patient what amount of money from the household budget can be allocated to medicines. In good communication practice, the doctor informs the patient about the indication for a given

treatment. If the recommended drug is not reimbursed, the patient should be informed about the price, without emotional interpretation, and then the patient's decision as to the possibility of buying drugs should be noted in the medical documentation. It is also important to explain to the patient that the pharmacological therapy of HF will not last one month only but will be long-term. Special issues related to treatment modifications requiring a dedicated explanation include, for example, the principles of safe conversion from ACEI to ARNI (36-hour interval before the first dose) or dose equivalence (e.g. torasemide vs. furosemide).

BLOCKADE OF THE RENIN-ANGIOTENSIN-ALDOSTERONE AXIS

Excessive activation of the renin-angiotensin-aldosterone (RAA) system is one of the main pathophysiological mechanisms of HF. Drugs that correct this pathological mechanism work by inhibiting the activity of the angiotensin-converting enzyme (ACEI), blocking the AT1 receptor for angiotensin II (ARB) or mineralocorticoid receptor (MRA, see paragraph 6) [9]. They improve survival provided that they are used continuously and at the recommended maximum tolerated doses. The latest 2021 ESC guidelines for the management of heart failure clearly strengthen the indication for sacubitril/valsartan (the only representative of ARNI to date) [2]. It is recommended for all symptomatic HFrEF patients as a first-line treatment in place of the ACEI recommended earlier. It is extremely important to explain to the patient the potential benefits of switching from the current ACEI/ARB treatment to ARNI, e.g. greater improvement in quality of life, and reduction in risk of rehospitalization for HF exacerbation, or cardiovascular death. At the same time, the patient should be informed about an increase in the cost of therapy.

Practical advice for using ARNI

1. Switching on the drug can be started in stable outpatients, as well as in patients during the stabilization period (after cardiovascular decompensation) during hospitalization — with systolic RR ≥100 mm Hg and potassium concentration ≤5.4 mmol/l;
2. Before starting treatment, kidney and liver function, serum potassium concentration, blood pressure, and volume status should be assessed; contraindications to ARNI are very similar to those to ACEI.
3. A 36-hour interval should be maintained between the last dose of ACEI (but not ARB if previously used) and the first dose of sacubitril/valsartan when switching from one drug to another; the drug can be administered with or without food;
4. As standard, the starting dose should be 49 mg/51 mg twice daily; it is possible to start with a dose of 24 mg/26 mg twice daily when the patient has not been previously treated with ACEI/ARB, has taken low doses of ACEI/ARB, or presents with systolic pressure of 100–110 mm Hg, moderate or severe renal impairment (glomerular filtration rate [GFR] below 60 ml/min/1.73 m^2) or moderate hepatic impairment;
5. If well tolerated, the initial dose of the drug should be doubled after 2-4 weeks until the target dose is reached;
6. Control of serum potassium and creatinine 1–2 weeks after the onset of treatment and after reaching the target dose, subsequent control every 4 months;
7. A slight increase in urea, creatinine, and potassium levels after therapy inititation is not uncommon; the indication for dose reduction or discontinuation may be intolerable hypotension, less frequently, clinically significant hyperkalemia or renal impairment;
8. Monitoring of treatment should be based on the determination of plasma concentration of NT-proBNP, but not BNP.

Practical guidance on the use of ACEI/ARB

Angiotensin-converting enzyme inhibitors should be used in all patients with HFrEF who have not received ARNI — the class effect is accepted in relation to improved prognosis although only some molecules have controlled prospective studies in this area. They should also be used in asymptomatic HFmrEF/HFrEF. The use of angiotensin receptor antagonists (ARBs) is recommended as an alternative treatment in patients with HFrEF who are intolerant to ACEI and ARNI to reduce the risk of hospitalization and cardiovascular death. It is worth noting that both the guidelines and the Summary of Product Characteristics allow only the use of candesartan or valsartan in this indication. Conversion from previous ARB/ACEI therapy to ARNI should be proposed to all symptomatic HFrEF patients (the benefits with EF ≥40% are poorly documented) — in Poland, a significantly higher cost of therapy represents a practical problem:

- the use of the drug should be started in stable outpatients and also in patients during the period of stabilization after decompensation of the circulatory system during hospitalization;
- kidney function and electrolyte concentration should be assessed before starting treatment and excessive diuretic treatment should be avoided;
- to minimize the risk of hypotension, treatment can be started in the evening, before bedtime;
- urea, creatinine, and serum potassium should be measured 1–2 weeks after starting treatment and 1–2 weeks after escalation of the dose; subsequent control tests should be performed every 4 months (more often in patients with renal impairment and/or a tendency to electrolyte disturbances);
- do not discontinue ACEI too hastily due to reported cough — it rarely excludes the use of the drug. It is important to consider alternative causes (pulmonary congestion, smoking, lung disease); determination of intolerance should be preceded by a few weeks of discontinuation followed by rechallenge and testing ACEI with a lower coughing potential (e.g. imidapril, perindopril, zofenopril)

Contraindications to the use of ACEI/ARB are:

- history of angioedema (absolute — for ACEI, as well as ARNI)
- bilateral renal artery stenosis
- stenosis of the renal artery of the only active or dominant kidney
- pregnancy or planned pregnancy.

BETA-BLOCKERS

Beta-blockers (BBs) are an important component of HF pharmacotherapy. Excessive activation of the sympathetic system in the course of HF and related stimulation of β1 receptors triggers a number of molecular processes leading to the activation of apoptotic processes in the heart muscle. Although the use of this group of drugs in HF pharmacotherapy was initially avoided, the effectiveness of 4 drugs in the class in HF treatment was documented in controlled prospective clinical studies (the class effect is not accepted) [10]. The efficacy of bisoprolol, carvedilol (the only non-cardioselective BB used in HF), and prolonged-release metoprolol succinate has been demonstrated, as included in both the European and American guidelines. Results of randomized BB trials in HF patients showed a reduction in the risk of death by more than a third compared to placebo, also in patients in NYHA class IV. The use of BB in HF is beneficial from the pharmacological and economic point of view. The fourth BB with proven efficacy in HF therapy, exerting (like carvedilol) a vasodilatory effect, is nebivolol. In the SENIORS trial, the benefit of nebivolol (reduced risk of composite endpoint defined as all-cause mortality or cardiovascular hospital admission, albeit without statistically significant reduction in mortality alone) has been demonstrated in patients ≥70 years of age with HF regardless of the ejection fraction value [11].

Treatment of HF with BB requires gradual escalation of doses with control of, among others, the chronotropic effect and arterial pressure — typical dose ranges are:

- Bisoprolol 1 × 1.25 mg → 1 × 10 mg
- Carvedilol 2 × 3.125 mg → 2 × 25 mg (in patients >85 kg — 2 × 50 kg)
- Metoprolol succinate 1 × 12.5 mg → 1 × 200 mg
- Nebivolol 1 × 1.25 mg → 1 × 10 mg

When deciding to start treatment with BB in HF patients, several important contraindications to their use should be taken into account. In clinical practice, these will most often be all conditions of exacerbation of HF symptoms, occurring with decompensation of the circulatory system and atrioventricular fluid overload disorders. When using BB, the patient requires monitoring of heart rate values, especially in combination with anti-arrhythmic drugs or digitalis glycosides and arterial blood pressure values. The most common side effects are due to a blockage of the sympathetic system and include mainly bradycardia and arterial hypotension, as well as an increase in exercise intolerance in the initial period of use. Depending on other risk factors, co-morbidity, hemodynamic status, and tolerance of such treatment, HF patients should ultimately achieve an average heart rate (HR) over the course of a day in the range of 60–69/min.

MINERALOCORTICOID RECEPTOR ANTAGONISTS

MRAs (eplerenone and spironolactone) are recommended in all patients with HFrEF as one of the four pillars of pharmacotherapy alongside beta-blockers, SGLT2 and ARNI (or ACEI/ARB). Their use is associated with a reduction in HF symptoms, risk of hospitalization for HF, and mortality. In contrast to the previous 2016 guidelines, which recommended the inclusion of MRAs in those patients with HFrEF which persisted despite ACEI and BB treatment, the current 2021 ESC guidelines assume that therapy with the above four drug groups (with class I recommendations) should be initiated concurrently or directed towards the rapid achievement of the "four pillars" in stages, depending on the clinical profile of the patient if possible. After 4–8 weeks, it is recommended to optimize the dose (for both drugs, the initial dose is 25 mg, and the target — 50 mg) before considering other forms of pharmacotherapy or implantable devices. In the HFmrEF group, both ESC and AHA/ACC/HFSA guidelines recommend MRA in class IIb in combination therapy. In HFpEF patients, the AHA/ACC/HFSA guidelines recommend MRA in class IIb in combination therapy, while the ESC guidelines do not provide any recommendations for this group of patients. In HFpEF, MRAs appear to be more effective in patients with lower EF (closer to 50%). In TOPCAT, spironolactone was associated with a reduction in the risk of hospitalization for HF in patients with HF and EF >45%. Eplerenone is more specific for blocking aldosterone-binding mineralocorticoid receptors than spironolactone (100–1000 times lower affinity for androgen-binding receptors and progesterone) and, therefore, less likely to cause gynecomastia/mastodynia (0.5% vs. 10%) in males and genital bleeding in females. In Poland, spironolactone is reimbursed and cheaper for the patient than eplerenone.

The new non-steroidal selective MRA — finerenone — reduced the risk of cardiovascular events in the group of patients with renal failure and type 2 diabetes [12, 13]. The analysis of the results of the available studies provided promising evidence of a reduction in the risk of HF diagnosed for the first time, reduction in hospitalization for HF, and cardiovascular mortality [14]. Further studies are needed to assess its effectiveness and safety in the treatment of patients with HF — the drug has no recommendations in this regard.

Practical recommendations for the use of MRA are mainly related to kidney function control. Particular caution should be exercised in patients with renal impairment and hyperkalemia:

- It is advisable to perform control tests for creatinine and electrolytes at 1 and 4 weeks after starting treatment or increasing the dose at 8 and 12 weeks, 6, 9, and 12 months, and then every 4 months.

- When estimated GFR ≤30 ml/min/1.73 m^2 or potassium ≥5.0 mEq/l, initiation of MRA therapy is contraindicated.
- In the case of potassium >5.5 mmol/l or creatinine >221 µmol/l (2.5 mg/dl)/estimated GFR <30 ml/min/1.73 m^2, the MRA dose should be reduced by half, and the patient should be carefully monitored. In the case of potassium >6.0 mmol/l or creatinine >310 µmol/l (3.5 mg/dl)/estimated GFR <20 ml/min/1.73 m^2, MRA should be withheld immediately.
- Other agents likely to increase serum potassium (e.g. potassium-sparing diuretics such as triamterene and amiloride, trimethoprim/trimethoprim-sulfamethoxazole, salt substitutes with high potassium content) are nephrotoxic agents (e.g. NSAIDs) and potent CYP3A4 inhibitors such as ketoconazole, itraconazole, nefazodone, telithromycin, clarithromycin, ritonavir, and nelfinavir (when eplerenone is used), which should be avoided during treatment.

FLOZINS — INHIBITORS OF SODIUM-GLUCOSE COTRANSPORTER TYPE 2

Inhibitors of sodium-glucose cotransporter type 2 (SGLT2i, flozins) are a new group of drugs of critical importance in the pharmacotherapy of HF patients. The multidirectional mechanism of action of SGLT2i consists in reducing glucose reabsorption and lowering the renal threshold for glucose and thus increasing glucose excretion, nephroprotective effect, and reduction of the pre- and post-load of the left ventricle due to increased osmotic diuresis, reduced plasma volume, and blood pressure. Recently, numerous non-renal SGLT2i signaling pathways with potential cardioprotective significance have been identified — related, among others, to the processes of inflammation, fibrosis, apoptosis, and cardiomyocyte energetics [15].

According to the current guidelines [2, 3], 2 SGLT2i drugs – dapagliflozin or empagliflozin – are strongly recommended (class I) in patients with heart failure (NYHA class II-IV) with reduced left ventricular ejection fraction (LVEF ≤40%) to reduce the risk of hospitalization for heart failure and death. At the moment, only the newer AHA/ACC/HFSA guidelines extend this recommendation to all categories of HF according to the current state of knowledge, taking into account the reduction in the risk of deaths or hospitalization caused by HF (as well as nephroprotective effects) also in patients with HFmrEF and HFpEF.

The DAPA-HF trial evaluated the long-term prognosis in patients with heart failure in NYHA class II-IV with reduced LVEF (≤40%). In the DAPA-HF trial, patients treated with dapagliflozin showed a 30% reduction in the risk of worsening of heart failure/hospitalization for heart failure, a 17% reduction in the relative risk of all-cause death, and an improvement in patients' quality of life and reduced severity of HF symptoms compared to placebo [16]. The clinical benefit of dapagliflozin was observed independently of the diagnosis of type 2 diabetes mellitus. The EMPEROR-Reduced study also demonstrated a beneficial effect of the SGLT2-empagliflozin inhibitor on the prognosis of patients with symptoms in NYHA class II–IV with reduced LVEF (≤40%). Empagliflozin, regardless of the diagnosis of type 2 diabetes mellitus, reduced the incidence of cardiovascular death or hospitalization for heart failure by 25% (primary endpoint) and the first and subsequent hospital admissions for heart failure by 30% (secondary endpoint) [17]. The results of both studies are consistent, suggesting the effect of SGLT2i to improve survival in HFrEF patients.

Since May 2022, dapagliflozin and empagliflozin have become reimbursed in Poland (at the level of 30% of costs), which will probably improve the availability of these drugs for HF patients. The reimbursement indications refer to patients with CHF with reduced LVEF (≤40%) regardless of the co-occurrence of diabetes mellitus who remain in NYHA class II–IV despite the use of beta-adrenolytic-based therapy, ACEI/ARB/ARNI and, if such treatment is indicated, mineralocorticoid receptor antagonists. From a practical point of view, it is important that reimbursed treatment with SGLT2 inhibitors may be initiated by a physician of any specialty who takes care of an HF patient.

Practical advice for the use of SGLT2 inhibitors in patients with HF:

- the use of dapagliflozin or empagliflozin (at doses of 1 × 10 mg/day, without the need for adjustment) is beneficial when taking other medicines recommended for the treatment of HFrEF;
- no dose adjustment is necessary due to renal impairment; however, the use in the treatment of HF in patients with eGFR <20 ml/min/1.73 m^2 (empagliflozin) and <25 ml/min/1.73 m^2 (dapagliflozin) is contraindicated;
- in the initial phase of treatment, a temporary increase in renal parameters can be observed, which is transient — the SGLT2i class is characterized by long-term nephroprotective effect; however, this effect may add up with a similar effect of initiating or escalating other drugs, e.g. ACEI/ARB — the decision on simultaneous or rapid sequential implementation of the "4 pillars of therapy" should be individualized;
- SGLT2i increases the risk of fungal infections (most commonly Candida albicans) of the external genitourinary organs of mild or moderate severity, and if they occur, SGLT2i treatment needs not be discontinued; recurrences of this complication are rare; SGLT2i initiation, however, make it imperative to instruct patients about the importance of perineal hygiene;
- due to increased osmotic diuresis and natriuresis, it may be necessary to increase fluid supply and modify the dose of loop diuretics [1], and in patients treated with insulin or sulphonylureas – to adjust the strength of hypoglycemic drugs.

IVABRADINE

Ivabradine is a drug that slows down spontaneous depolarization in the sinoatrial node of the cardiac conduction system by blocking the flow of ions through channels I_f, acting as a negative chronotropic agent only in patients with sinus rhythm. The unique mechanism of action, its metabolic neutrality, absence of negative inotropic effect or the effect on preload or afterload result in the lack of adverse decrease in myocardial contractility and blood pressure. Slowing the heart rate causes a beneficial hemodynamic effect in patients with HFrEF through improved coronary perfusion, better filling of the left ventricle, increased systolic deformation, and expansion of the aortic wall. The negative chronotropic effect is proportional to the baseline sinus rhythm rate, and the recommended doses typically reduce the heart rate by 10 beats/min. In the current guidelines [2, 3], we find a recommendation for its use in patients with HFrEF and a sinus rhythm rate of ≥70 beats/min based on the results of the SHIFT study [18]. In this study, ivabradine was added to optimal background therapy for HF in patients with symptomatic HFrEF (EF ≤ 35%), NYHA class II–IV, and sinus rhythm ≥70/min, resulting in a reduction in cardiovascular mortality and subsequent hospitalization for HF over 12 months of follow-up.

Ivabradine is recommended in two clinical situations:

- consideration should be given to its use in symptomatic patients with LVEF ≤35%, sinus rhythm, and resting heart rate ≥70 beats/min despite the use of optimal background therapy including BB at maximum tolerated dose, ACEI (or ARNI), and MRA (recommendation class IIa/B);
- and for these patients who are intolerant to or have contraindications to BB, they should receive ACEI (or ARNI) and MRA (Class IIa/C recommendation) concomitantly.

Activation of ivabradine may occur in a patient with stable HFrEF in class II–IV, (with extreme caution in patients in NYHA class IV and with worsening symptoms of the disease, e.g. within fewer than 4 weeks of hospitalization for HF decompensation). It is very important that the patient receives standard, guideline-compliant background therapy, including BB at the maximum tolerated dose. The dose of BB should be optimized first, not stopping at the initial dose of therapy — the optimal dose for the patient should be determined within a month, after which the resting heart rate should be checked — and ivabradine should be added if the value exceeds 70/min.

When starting treatment with ivabradine, it is important to remember the differences in Polish reimbursement indications (lump sum). They concern HF with systolic dysfunction, NYHA class II–IV, with a documented ECG-confirmed sinus rhythm ≥75/min (rather than ≥70/min, in the guidelines) with or without the concomitant use of standard therapy, with or without beta-blocker, when its use is contraindicated or intolerable. This heart rate was approved by the European Medicines Agency (EMA) for improved survival (decrease in overall mortality) in the SHIFT HF subgroup in patients with HR ≥75/min.

Starting treatment with ivabradine at a dose of 5 mg twice a day (in patients over 75 years of age up to 2.5 mg twice a day), one should be aiming at a target dose of 7.5 mg twice a day. The dose should be optimized in intervals no shorter than 2 weeks, and the dose is left unchanged if HR is within the range of 50–60/min. The dose of ivabradine must be reduced with HR less than 50/min or with symptomatic bradycardia, and the possibility of adverse interactions should be rechecked if new drugs are used. If atrial fibrillation occurs, ivabradine should be discontinued (although the medicine may still be of benefit in patients with paroxysmal atrial fibrillation [AF], who spend most of their time in sinus rhythm).

Contraindications to the use of ivabradine [2] are any conditions of circulatory instability, atrial fibrillation, pregnancy, and breastfeeding (due to the potential risk of fetal harm), severe liver or kidney dysfunction (no pharmacokinetic and safety data at creatinine clearance <15 ml/min), and adverse or allergic reactions.

Situations requiring special attention during ivabradine therapy, apart from NYHA class IV discussed above, are a resting heart rate < 50/min, moderate liver damage, and chronic retinal diseases (a typical fully reversible effect after discontinuation of the drug are visual disturbances — "phosphenes" usually presenting as flashes provoked by sudden changes in ambient light intensity). Possible drug interactions should be considered when related to the risk of bradycardia and QT prolongation (concomitant use of verapamil, diltiazem, amiodarone, digoxin, and ranolazine) and strong inhibitors of the hepatic isoenzyme CYP 3A4, which are involved in the metabolism of ivabradine in the liver and intestines (antifungal agents such as ketoconazole, macrolide antibiotics including clarithromycin, HIV protease inhibitors, and nefazodone).

DIURETICS

Diuretics are considered the foundation of treatment for HF patients with exacerbation of symptoms, edema, or pulmonary congestion. In everyday clinical practice, they are the drugs of choice for the treatment of acute HF. The effectiveness of loop diuretics in reducing mortality and hospitalization rates has been confirmed in many non-randomized studies, most recently in the analysis of the OPTIMIZE-HF registry [19]. Depending on the mechanism of action and the gripping point, diuretic drugs can be divided into several classes, shown in Figure 2 (modified according to [20]).

Loop diuretics are essential for HF patients. The results of the recently published TRANSFORM-HF study [21] did not confirm differences in overall mortality of HF patients treated with furosemide and torasemide. It should be remembered that, unlike furosemide, torasemide is used once a day (despite doses covering a wide range of 5–200 mg/day) thanks to better bioavailability and longer

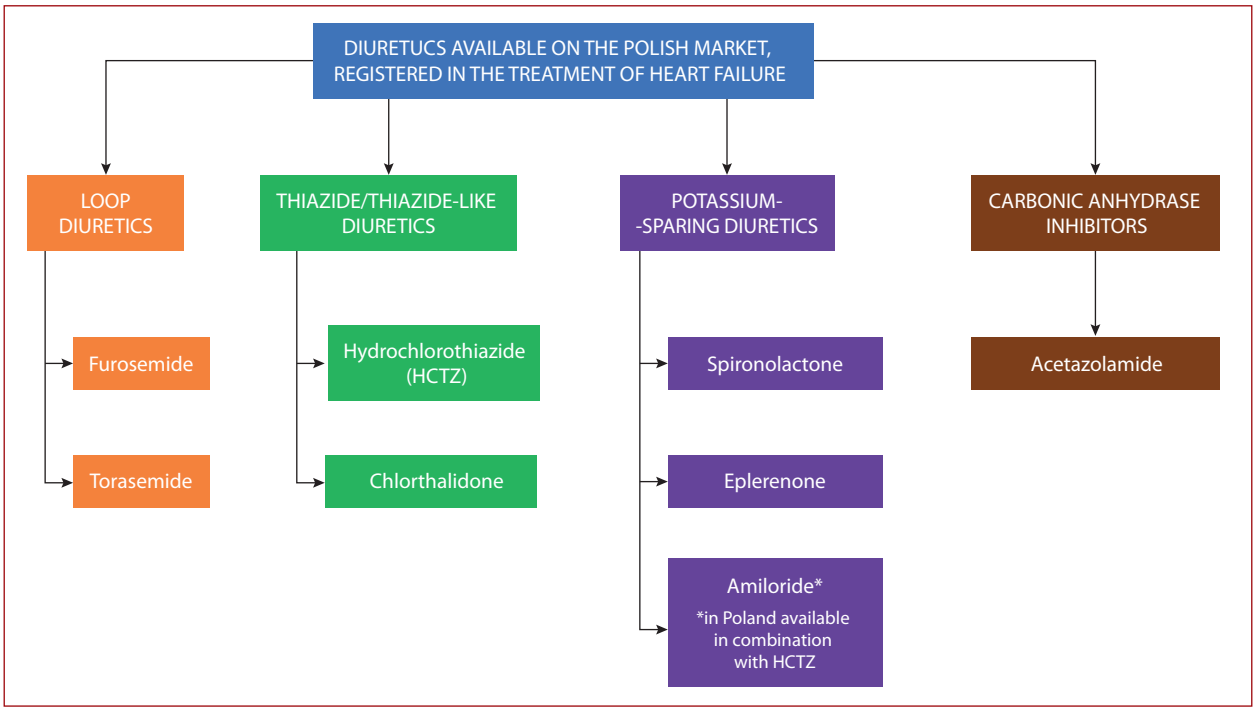


Figure 2. Practical classification of diuretic drugs registered in Poland in the treatment of heart failure (developed on the basis of Ali S et al. [20]). Sodium-glucose cotransporter 2 inhibitors are not shown as they are not used as a typical diuretic although they induce osmotic diuresis. Similarly, the purpose of mineralocorticoid receptor use is different from diuretic effect). Thiazide-like diuretics indapamide and clopamide available in Poland are not registered for HF

Abbreviations: HCTZ, hydrochlorothiazide

duration of action (which reduces the burden of therapy and improves the quality of life compared to furosemide). In patients with HF, one tablet of furosemide (40 mg) usually corresponds to 15–20 mg of torasemide.

The recently completed ADVOR study demonstrated the efficacy of three-day intravenous administration of 500 mg/day of acetazolamide during the initial phase of treatment with intravenous loop diuretics in HF patients with exacerbation in achieving a faster resolution of fluid overload [22]. In Poland, only the orally administered form of the drug is available, which also ensures good bioavailability.

Thiazide/thiazide-like diuretics can also be used in HF as monotherapy (especially when GFR is preserved) or in combination with loop diuretics. Such combination therapy is particularly useful in cases of resistance to loop diuretics, observed in 20% to even 50% of hospitalized patients [23].

In diuretic therapy, patients with HF should be primarily monitored for blood pressure (risk of hypotension, especially in combination with other drugs used in HF — ACEI, ARNI), electrolyte levels (especially potassium), and renal parameters (the possibility of exacerbation of renal failure, e.g. in the pre-renal mechanism). Particular caution should be exercised in patients with concomitant liver disease or chronic kidney disease while in people taking chronic non-steroidal anti-inflammatory drugs, the effect of diuretics may be weakened [2].

TREATMENT OF IRON DEFICIENCY

Anemia is a common comorbidity in HF patients. Its presence indicates a more advanced stage of the disease and the occurrence of additional concomitant diseases. It is clearly and closely linked to a worse prognosis. Its occurrence in HF does not depend on the age or the value of left ventricular ejection fraction. Sideropenia, or iron deficiency, has been treated for many years almost as a synonym of anemia and is seen as the underlying cause in HF patients. Today, we know that this concept is much complex and also includes situations where iron deficiency is accompanied by normal hemoglobin concentration. The function of iron in the body is not limited to the formation of hemoglobin — it is an essential element of a number of cellular processes, and its deficiency strongly worsens the prognosis in HF. The importance of the problem is now better understood in the current ESC guidelines — the treatment of iron deficiency is already determined by three recommendations, resulting from the FAIR-HF [24], CONFIRM-HF [25], and AFFIRM-AHF studies [26]. The first (class I) concerns the appropriateness of active screening for anemia and iron deficiency in all HF patients. The second (class IIa) recommends considering intravenous iron administration as an iron-carboxymaltose complex to reduce symptoms and improve exercise capacity and quality of life in symptomatic patients with HF and ejection fraction <45% and iron deficiency (defined as plasma ferritin <100 µg/l or ferritin 100–299 µg/l with

Table 2. Definitions of iron management disorders in the context of HF

	Description	Desirable values in patients with heart failure	Values indicative of sideropenia in heart failure
Anemia	Hemoglobin levels in whole blood below normal	>12.0 g/dl in women >13.0 g/dl in men	—
Ferritin	Liver protein storing iron ions	In plasma: 100–400 µg/l in women 100–200 µg/l in men	In plasma: <100 µg/l In plasma: 100–299 µg/l concomitant TSAT<20%
Transferrin	Primary plasma iron carrier	15–50 µmol/l	
TIBC — total iron binding capacity	The maximum amount of iron required for complete saturation of transferrin,	250–400 µmol/l	
TSAT — iron saturation of transferrin	(Iron/TIBC total iron binding capacity) × 100%	>20%	

transferrin saturation <20%). The third recommendation (class IIa), going one step further, increases the target group by patients with EF<50%, recently hospitalized for heart failure, thus covering not only the entire HFrEF group but also HFmrEF. It is worth noting that the cut-off points for ferritin and iron saturation of transferrin as an indication for iron administration have remained unchanged since 2016 — the basic definitions are presented in Table 2. The US 2022 guidelines approach this issue similarly, formulating one simple recommendation — in patients with HFrEF and iron deficiency, regardless of anemia, intravenous iron administration is justified for improving the functional state and quality of life.

It should be added that administration of erythropoietin alone is not recommended to reduce morbidity and mortality in HF. Oral iron substitution is ineffective, as demonstrated in the IRON-OUT study [27] — the only recommended form of iron supplementation remains the the intravenous form. The iron-carboxymaltose complex in this form is available in Poland, it is administered both in hospitals and in outpatient conditions, and the occurrence of adverse symptoms is extremely rare. The beneficial effect of reducing the risk of cardiovascular hospitalization and improving the quality of life is obtained after a single or double administration of the drug, and this effect lasts for many months or even years. These benefits only apply to the intravenous form and are not observed with oral iron administration preparations. It should be added that the results of the IRONMAN study announced at the end of 2022 [28] document a similar range of benefits in over two and a half years of follow-up (however, without a significant decrease in hospitalization for HF confirmed in AFFIRM-HF) with intravenous administration of iron complex with derisomaltose, a drug also available in Poland.

DIGOXIN

Digoxin is a cardiac glycoside, isolated from the woolly foxglove, affecting the heart muscle, striated and smooth muscles, renal tubules, and the vagus nerve center, already known in ancient Greece and Egypt.

In HFrEF therapy, digoxin can be considered, in accordance with the European guidelines, as an adjunct in symptomatic patients with HFrEF (NYHA class II–IV despite treatment with ACEI or ARNI, BB, and MRA) at sinus rhythm to reduce the risk of hospitalization (both for all causes and because of HF) — this is a low class IIb/B recommendation. It is mainly based on the DIG study (the Digitalis Investigation Group, using digoxin vs. placebo, in patients treated concomitantly with ACEI and a diuretic) published in 1997 [29], with a different standard of primary HF treatment. The American guidelines allow the use of digoxin (recommendation class IIb) in symptomatic HFrEF class II–III according to NYHA, and it is not possible to use the original therapy due to its poor tolerance. In clinical practice, the use of digoxin in this indication is rare. The justification for the low class of recommendations for digoxin is the fact that only one randomized trial produced no mortality reduction, demonstrating a moderate reduction in the risk of a composite endpoint (mortality or hospitalization rates, along with symptom reduction), which is also consistent with the results of the meta-analyses of clinical trials [30].

A common and widely accepted indication for digoxin is symptomatic heart failure or decompensation of heart failure, caused/exacerbated by the rapid rate of ventricular rhythm in the course of AF. Digoxin should be considered in AF patients with rapid ventricular function (>110 bpm) despite beta-blocker use, in the absence of hemodynamic instability, and administered in 0.25–0.5 mg boluses intravenously, if not previously used. The dose of the drug should be adjusted taking into account the narrow therapeutic window, especially in patients with factors affecting its metabolism, such as chronic kidney disease, elderly age, female sex, frailty syndrome, hypokalemia, malnutrition, and possible drug interactions. To determine the correct maintenance dose, the concentration of digoxin in the serum should be determined — the optimal concentration in the serum is 0.5–0.9 ng/ml. The concentration of 1.2 ng/ml should not be exceeded, as the risk of death increases linearly at higher values.

Digoxin is also a useful drug for achieving the recommended control of ventricular frequency in AF [2, 31] — initial lenient rare control (<110/min) with the use of beta-blockers before digoxin, used as an alternative or auxiliary drug, is allowed. Strict control of ventricular

function (<80/min at rest and <110/min at moderate exercise) should be sought in the following days of therapy if symptoms persist or if cardiac dysfunction is likely to be associated with tachycardia (tachycardia induced cardiomyopathy). Optimal heart rate control is also a strategy for patients with atrial fibrillation and hemodynamically stable heart failure — it should be obtained using beta-blockers, digoxin, or amiodarone. In the absence of clinical improvement, performing procedures such as electrical or pharmacological cardioversion, atrial fibrillation ablation, or modification of the atrioventricular junction in patients not responding to pharmacotherapy should be considered. The strategy of maintaining sinus rhythm with the use of ablation is gaining importance [3] in the light of newer studies and their meta-analyses, showing the advantage of the procedure based on ablation of atrial fibrillation consisting in improving the prognosis: reduction of mortality from all causes (reduction of risk by 49%), hospitalization frequency (reduction of risk by 56%), improvement of left ventricular function and quality of life [32]. This may further reduce the role of digoxin in the treatment of HF in the near future.

VERICIGUAT

The new molecule recommended for the treatment of HF is vericiguat — a drug registered in the European Union in 2021 (tablets: 2.5, 5, and 10 mg), which can be considered in selected HFrEF patients who have experienced a deterioration in HF while using first-line therapies (RAA system inhibitor/ARNI, BB, and MRA). In the case of the ESC guidelines, this recommendation has an IIbB class and in the case of the AHA/ACC/HFSA guidelines — 2bR-B.

Vericiguat is a soluble guanylate cyclase (sGC) stimulator. A drug with a similar mechanism of action, riociguat, is already used in thromboembolic therapy and primary pulmonary hypertension (as part of drug programs), but in the case of HF, the NO-sGC-cGMP pathway is a completely new point of reference for pharmacotherapy [33]. In the course of heart failure, the function of the NO-sGC-cGMP pathway is impaired. An increase in sGC activity inhibits the processes of fibrosis and cell hypertrophy, reduces inflammation, and relaxes smooth muscle cells. In turn, an increase in cGMP activity through activation of phosphodiesterase 2 also reduces excessive cAMP activity, which can stimulate the sympathetic system, RAA system, and, in consequence, pathological cardiac remodeling [34].

The clinical benefit of vericiguat (a significant 10% reduction in the risk of death or rehospitalization for HF) was demonstrated in the VICTORIA study in patients with recent HF exacerbation (EF <45%, NYHA class II–IV). However, it is noteworthy that vericiguat was added to the HFrEF pharmacotherapy conducted in accordance with the guidelines available during the design phase, i.e. not including the flozins. Only 60% of patients received "standard pharmacotherapy" at that time, and only 15% used ARNI. The effect on the primary endpoint became noticeable after approximately 4 months of therapy. At the time of writing of this article, vericiguat already has Polish-language characteristics of the medicinal product (MPCh), but it is not available in pharmacies and its price is not known. Although the idea of including a new neurohormonal pathway in the therapy is very interesting and it is worth following the results of subsequent clinical trials taking into account the use of this molecule, in practice it is difficult to predict whether adding vericiguat to the current quadruple regimen (ACEI/ARA/ARNI+BB+MRA+SGLT2i) will provide similar benefits. Based on the data from the MPCh (www.ema.europa.eu/en/documents/product-information/verquvo-epar-product-information_en.pdf), it is worth remembering that the drug has a half-life of approximately 30 hours in HF patients, it is administered orally with a meal at a dose of 1 × 2.5 mg once a day, doubling every 3 weeks to the target dose of 1 × 10 mg per day. Specific contraindications are pregnancy and breast-feeding, hypotension <100 mm Hg SBP, and a significant reduction in renal function (eGFR <15 ml/min/1.73 m^2). It must not be co-administered with riociguat or nitrates. Typical side effects are hypotension, anemia, dyspepsia or gastroesophageal reflux disease, and dizziness or headache.

ANTIPLATELET AND ANTICOAGULANT DRUGS

The current HF guidelines, both the 2021 ESC document and the 2022 AHA/ACC/HFSA document, do not comment in any new way on antiplatelet therapy — so one should assume that the recommendations described in the documents dedicated to such entities, such as chronic coronary syndromes, peripheral atherosclerosis, or stroke are to be followed.

In the HF documents, there is some new content on the principles of anticoagulation (affecting the plasma coagulation system) used for the prevention of stroke and venous thromboembolic disease or in situations where we find the presence of blood clots in the vessels. An important subgroup of HF patients includes those with coexisting AF. In such a situation, the very fact of diagnosing heart failure implies at least 1 point on the CHA_2DS_2-VaSC scale — anticoagulant treatment should, therefore, at least be considered, and in the vast majority of cases it will be indicated. The American guidelines emphasize that the risk of thromboembolic complications of AF in HF patients, as the only additional risk factor, is several times higher than without it. The American guidelines also point out that the use of anticoagulants is a reasonable course of action for patients with AF and amyloidosis of the heart, regardless of the CHA_2DS_2-VaSC score. The principles of prophylaxis in HF-associated AF do not deviate from the general principles with a preference for non-vitamin K antagonist oral anticoagulant (NOAC) due to higher effectiveness and better safety profile in the context of intracranial bleeding. The decisions in this matter are individual and must take into account, among others, the financial capabilities of the

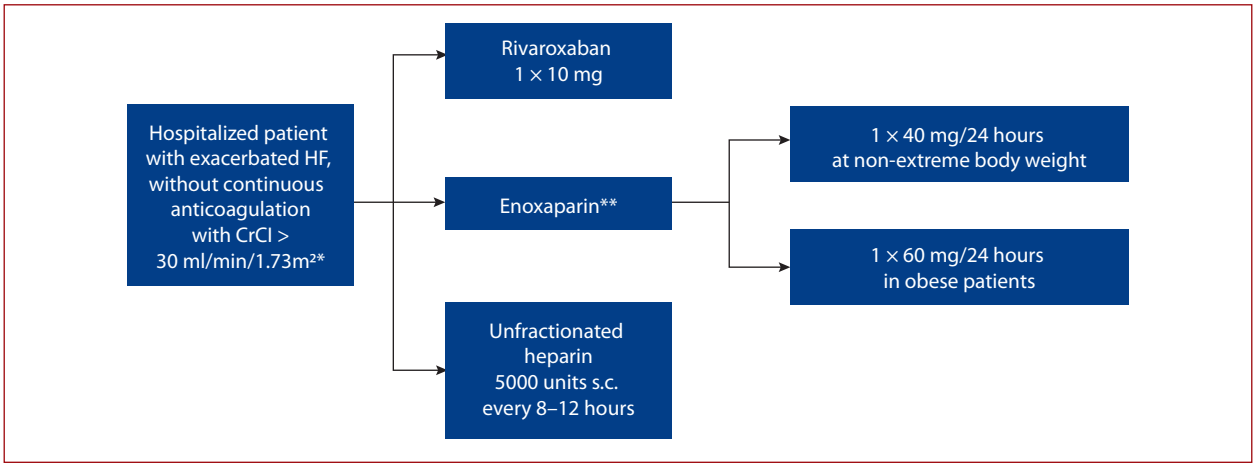


Figure 3. The strategy for the prevention of thromboembolic complications in patients hospitalized for heart failure exacerbation according to the American guidelines

*The American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) guidelines indicate that data on efficacy of various thromboembolic complication prevention strategies are derived from randomized trials in patients with creatinine clearance (CrCl) >30 ml/min. The US guidelines do not provide management recommendations for patients with CrCl ≤30 ml/min. **The European Society of Cardiology guidelines suggest using low molecular weight heparin, without further specific recommendations

patient — in the case of NOAC in Poland, the refund applies only to prevention or deep vein thrombosis (30%/S), so it can be used by HF patients with a history of pulmonary embolism or venous thromboembolic disease, but not with AF as an indication.

According to the 2022 ESC guidelines for heart failure, anticoagulation with low molecular weight heparin (LMWH) is recommended as part of the management of acute heart failure (IA) if the patient does not have contraindications or does not use chronic anticoagulants for other indications. The American guidelines also confirm this indication, however, allowing not only the use of LMWH but also fondaparinux or NOAC. Suggestions for the principles of anticoagulation prophylaxis in the case of hospitalization of patients with HF exacerbation, not using anticoagulants for other indications, are presented in Figure 3.

It should be emphasized that both European and American guidelines do not recommend the use of anticoagulants in HF patients without accompanying typical indications for this treatment. The issue of the appropriateness of using vitamin K antagonists (VKA) or NOAC in patients with HFrEF without confirmed AF, which was discussed for many years, has been resolved. In the randomized, prospective COMMANDER study evaluating the effects of complementing the standard pharmacotherapy regimen in patients with HFrEF, a concomitant coronary heart disease but without rivaroxaban AF at a dose of 2 × 2.5 mg, it was not shown that such a course of action was associated with a reduction in the risk of stroke, heart attack, or death [35]. A systematic review in the Cochrane database finds no evidence that the use of anticoagulants in HF patients without AF is associated with any clinical benefits [36].

PHARMACOTHERAPY IN HFMREF

Treatment of patients diagnosed with HF with mildly reduced left ventricular ejection fraction (41%–49%) is largely similar to treatment of HFrEF. Symptomatic treatment in patients with fluid overload/congestion features is based on diuretics, currently in the first class of European and American recommendations. Prognosis-enhancing therapies have lower classes of recommendation in HFmrEF, with the notable exception of SGLT2i — empagliflozin and dapagliflozin — which tested positive in large prospective trials involving patients with HFmrEF and HFpEF. These were the first drugs, the studies on which achieved the expected endpoints in the HFmrEF/HFpEF prognosis, and the obtained benefits were consistent in those subgroups of patients.

The results of the EMPEROR-Preserved and DELIVER studies confirmed similar efficacy of empagliflozin and dapagliflozin in both patients with preserved and mildly [36] reduced ejection fraction [37] (in the case of DELIVER — also patients with HFimpEF [37]). A statistically significant reduction in the incidence of the primary endpoint in the form of worsening [38, 39] of HF symptoms or cardiovascular mortality compared to the placebo group was achieved. These studies allowed SGLT2i to be placed in recommendation class 2a as the most strongly recommended class of drugs improving prognosis in HFmrEF [3]. The scheme HFmrEF recommendations by the ACC/AHA/HRSA [3] are presented in Figure 4.

Therefore, considering the available evidence, the standard pharmacotherapy of HFmrEF should include one of the above-mentioned flozins, and an increase in their class of recommendations is expected soon (due to two successful prospective studies). Their high position in the

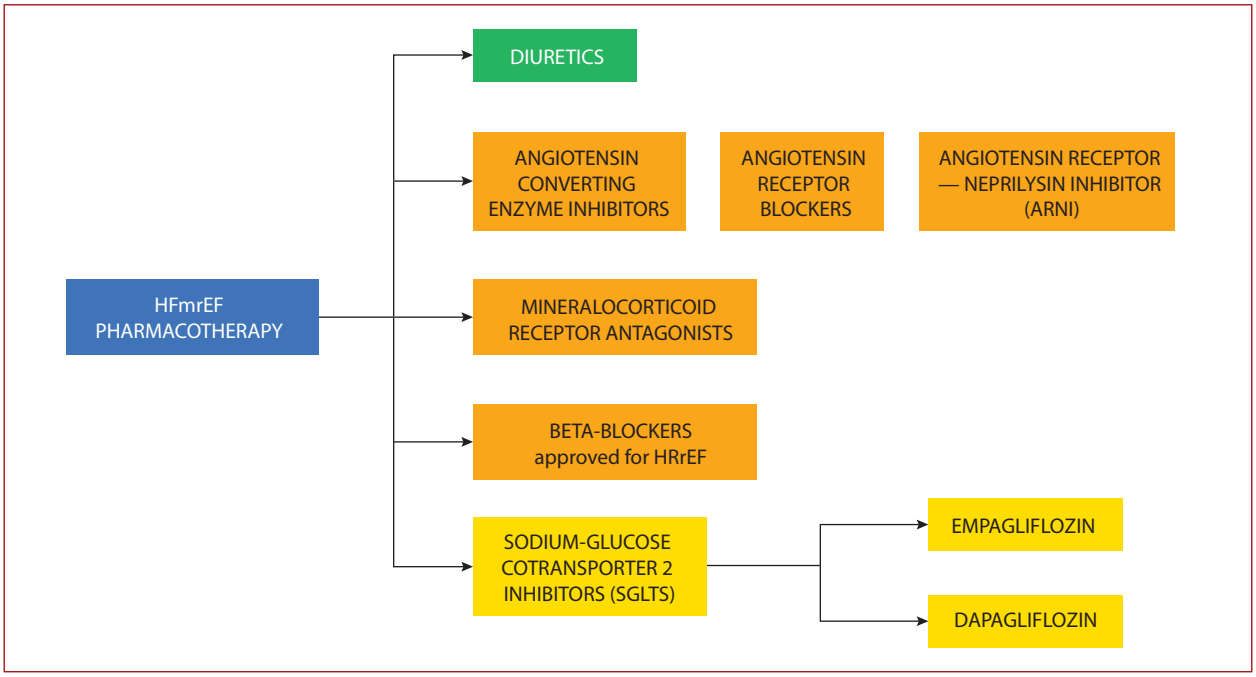


Figure 4. Pharmacotherapeutic regimen for HFmrEF proposed in the American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) [3] guidelines (colors correspond to the classes of recommendations: green — recommended drugs; yellow — drugs to be considered for use; orange — drugs that can be considered in therapy). The level of recommendations for sodium glucose cotransporter 2 inhibitors is likely to increase due to the consistent, favorable results of two prospective trials

Abbreviations: see Table 1

recommendations proves the considerable effectiveness and, importantly, safety of this group of drugs.

PHARMACOTHERAPY IN HFPEF

The 2021 ESC guidelines do not include recommendations for modifying the course of HFpEF because they were created before the announcement of the groundbreaking positive results of the EMPEROR-Preserved [37] and DELIVER trials [36]. Screening for risk factors and conditions associated with HFpEF and their treatment are recommended, as well as treatment aimed at reducing the symptoms of fluid retention with diuretics — loop diuretics are preferred. The authors of the 2021 ESC guidelines emphasize that the US Food and Drug Administration (FDA) has approved the use of sacubitril/valsartan and spironolactone in HFpEF patients. In a subgroup analysis of the PARAGON-HF study, a reduction in the incidence of hospitalization for heart failure was shown among patients with LVEF <57%. In a meta-analysis of the PARADIGM-HF and PARAGON-HF studies, a reduction in the incidence of cardiovascular death and hospitalization for heart failure was demonstrated [40].

According to the newer guidelines published in 2022 [3] (after the presentation of EMPEROR-Preserved), the use of SGLT2i should be considered in HFpEF patients to reduce cardiovascular mortality and the risk of hospitalization (class IIa). The use of ARBs, ARNI, and MRAs to reduce the risk of hospitalization (class IIb) may also be considered. It is emphasized that the clinical benefits of ARB, ARNI, and MRA are greatest for patients in whom LVEF is close to 50% [3].

The success of studies with empagliflozin and dapagliflozin [36, 37] allowed for the first time to include in the recommendations drugs that reduce the risk of death and hospitalization caused by exacerbation of HF in HFpEF. In the EMPEROR-Preserved study published in 2021, it was shown that in patients with HF and LVEF >40%, NT-proBNP concentration above 300 pg/ml (>900 pg/ml in the case of AF) and GFR not lower than 20 ml/min/1.73 m^2, joining the standard empagliflozin treatment (vs. placebo) reduced the risk of cardiovascular death or hospitalization for heart failure over 26 months and was associated with a lower rate of deterioration in renal function. A reduction in the risk of the main endpoint was observed both in the subgroup of patients with diabetes and patients without diabetes [41]. Similarly, the DELIVERY study presented at the 2022 ESC Heart Failure Congress in Madrid (therefore, not available when the guidelines were developed) showed that dapagliflozin significantly reduced the risk of cardiovascular death or HF exacerbation in patients with HFpEF/HFmrEF. Patient inclusion criteria were very similar (LVEF>40%, NT-proBNP concentration above 300 pg/ml and >600 pg/ml for AF and GFR not lower than 25ml/min/1.73 m^2, HFimpEF patients were also accepted [41]). Both studies also showed benefits in terms of quality of life for patients treated with flozin. These consistent results of key [42] conceptually similar studies allow us to expect recommendations for flozins in HFpEF and HFmrEF in the upcoming guidelines of higher classes. Therefore, dapagliflozin or empagliflozin treatment is a key treatment method available to Polish patients in

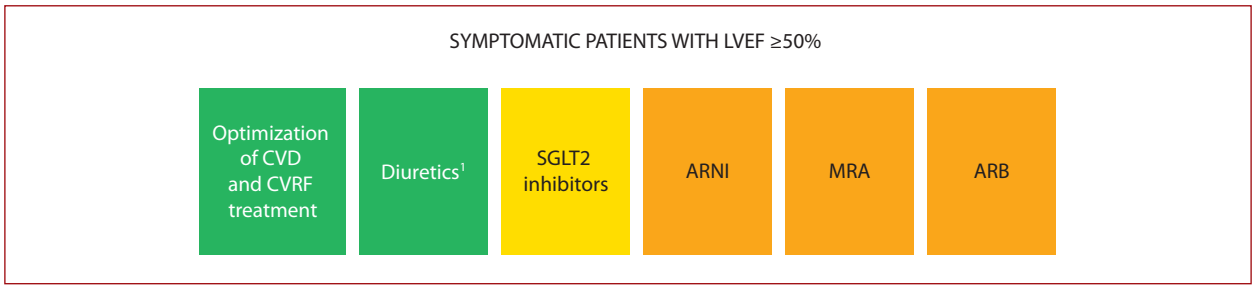


Figure 5. Basic principles of pharmacotherapy in patients with HFpEF (modified according to [3]) — the order according to the decreasing classes of recommendations; the class of recommendations SGLT2i is likely to increase

[1]In patients with congestion/fluid overload features

Abbreviations: ARNI, angiotensin receptor-neprilysin inhibitor; ARB, angiotensin II receptor blockers; CVD, cardiovascular diseases underlying HFpEF; CVRF, cardiovascular risk factors; MRA, mineralocorticoid receptor antagonists; SGLT2i, sodium glucose cotransporter 2 inhibitors

these numerous patient populations in which we have not yet had clearly effective treatment methods.

Recently a beneficial effect of SGLT2i independent of the EF value was also observed in patients with exacerbated HF recruited to the EMPULSE study [43]. Patients receiving empagliflozin for 9 days of follow-up had a 36% reduction in the risk of cardiovascular death, hospitalization for heart failure, and improved quality of life (Figure 5).

KEY ELEMENTS OF AHF PHARMACOTHERAPY

According to the ESC guidelines, the pharmacotherapy strategy for acute heart failure should depend on its clinical form:

- In patients with acute decompensated heart failure (ADHF) who gradually accumulate sodium and water, therapy should be based on diuretics (with the addition of inotropes/vasoconstrictors in cases of coexistence of peripheral hypoperfusion/hypotension);
- In patients with pulmonary edema, who are predominantly affected by rapid redistribution of pulmonary circulation fluid, often due to increased subsequent load, vasodilators are used in addition to diuretics,
- In patients with cardiogenic shock, inotropes/vasoconstrictors are indicated;
- In patients with isolated right ventricular failure, as in ADHF, mainly diuretics are used along with inotropes/vasoconstrictors in the case of arterial hypotension.

In the American guidelines, AHF therapy is also based on assessment of congestion and perfusion. Similarly, in both documents, therapy priorities include the search for reversible causes of AHF and their treatment.

Although there is still no breakthrough in the available pharmacotherapy of AHF, the presented regimens are helpful in the care of AHF patients. The main novelty is the practical algorithm for the use of diuretics in AHF (referring to the algorithm proposed by the Heart Failure Association ESC [44] in 2019 — see below).

The guidelines clarify selected recommendations for AHF pharmacotherapy:

- Diuretics (ESC, AHA/ACC/HFSA: recommendation class I). Treatment with loop diuretics should be initiated intravenously with furosemide 20–40 mg or torasemide 10–20 mg (dosage for patients not previously treated with diuretics). For patients previously treated with diuretics, a dose equal to or doubling the long-term daily oral dose of the loop diuretic should be administered.
- The assessment of the efficacy of the therapy should be based on the evaluation of natriuresis (efficacy criterion: sodium concentration in a single urine sample at 2 hours ≥50–70 mmol/l) and/or diuresis (efficacy criterion: hourly diuresis at 6 hours ≥100–150 ml/hour). In the case of insufficient response to treatment, the dose of loop diuretic should be doubled with subsequent re-evaluation.
- A combination of a loop diuretic with thiazide (recommendation class IIa) or acetazolamide should be considered. In the recently published ADVOR study, the addition of acetazolamide (3 days, 500 mg/day intravenously) to loop diuretics in patients with AHF increased the effectiveness of diuretic treatment and shortened hospitalization time [22]. An alternative may be the use of flozins (SGLT2i). Such a strategy, the so-called "sequential nephron blockade" by drugs inhibiting sodium resorption at different levels of the nephron (SGLT2 inhibitors and acetazolamide — in the proximal tubule, thiazides, and aldosterone antagonists — in the distal tubule), may help overcome the so-called "resistance to loop diuretics" [44].
- Vasodilators: nitrates or sodium nitroprusside (ESC, AHA/ACC/HFSA: recommendation class IIb) may be considered as initial therapy in patients with systolic blood pressure (SBP) >110 mm Hg to reduce congestion symptoms.
- Inotropic drugs (ESC: recommendation class IIb, AHA/ACC/HFSA: recommendation class I) may be considered in patients with SBP <90 mm Hg and features of hypoperfusion who do not respond to standard therapy including fluid administration.

- Vasoconstrictors (ESC: recommendation class IIb) may be considered in patients with cardiogenic shock; noradrenaline is preferred.
- Opioids (ESC: recommendation class III). ESC 2021 guidelines do not recommend routine opioid use except for severe/persistent pain or anxiety.

Both ESC and US guidelines emphasize the importance of discharging a patient from the hospital without residual congestion, initiation and optimization of pharmacotherapy to improve prognosis, and scheduling a follow-up visit 1–2 weeks after discharge. Most patients with AHF in Poland are treated in internal disease wards. Hospitals of lower referentiality may not have access to the full range of diagnostic tests or therapeutic procedures, which may lead to differences in AHF procedures among Polish hospitals [45], e.g. in many centers, no determination of urine sodium concentration is performed (despite the low cost of the test).

PRACTICAL ADVICE FOR HANDLING AHF

Below is the most important practical advice for the treatment of acute heart failure (medicines available in Poland).

Recommendations for the use of diuretics:

- Dosage — usually initiated i.v. with a subsequent switch to the oral route;
- Loop diuretics — initially an intravenous bolus in diuretic naive patients:
  - Furosemide — starting dose: 20–40 mg, typical chronic daily dose: 40–240 mg; can be administered as 2–3 boluses per day or in a continuous infusion — efficacy is similar; maximum daily dose 400–600 mg (up to 1000 mg in patients with severe renal insufficiency),
  - Torasemide — usually parenteral initiation switched to the oral form – starting dose: 10–20 mg, typical chronic daily dose: 10–20 mg in one dose; maximum daily dose 200–300 mg;
- Thiazide diuretics:
  - Hydrochlorothiazide — starting dose: 25 mg, usual dose: 12.5–100 mg;
- Carbonic anhydrase inhibitor:
  - Acetazolamide — starting dose: 250–375 mg, usual dose: 500 mg (recommended in ADVOR study for 3 days i.v. – in Poland only oral formulation is available);
- Once an evident negative fluid balance has been achieved, the dose of diuretics should be gradually reduced;
- The switch from intravenous to oral therapy should be initiated after the patient has achieved stable clinical status and continued at the lowest possible dose to avoid signs of congestion;
- The most common side effects of diuretics:
  - hypokalemia, hyponatremia, and metabolic alkalosis,
  - hypomagnesemia, hypocalcemia, and hyperuricemia,
  - hypovolemia, hypotension, and renal dysfunction;
- Monitoring of the therapy: clinical signs of congestion, fluid balance, urine sodium, blood pressure, serum blood urea/nitrogen, creatinine, sodium, potassium, and calcium,
- Recommendations for the use of vasodilators:
  - May be considered at systolic blood pressure >110 mm Hg,
  - Administration of these drugs can be started with small doses, which are then gradually increased to achieve clinical improvement and control of blood pressure;
- Dosage:
  - Nitroglycerin — initially 10–20 μg/min, can be increased to 200 μg/min,
  - Sodium nitroprusside — initially 0.3 μg/kg/min, can be increased to 5 μg/kg/min;
- Hypotension resulting from excessive reduction of preload and afterload should be avoided;
- Caution should be exercised in patients with left ventricular hypertrophy and/or severe aortic valve stenosis.
- Nitroglycerin tolerance and cross-tolerance to other nitrate and nitrite preparations may occur. In order to avoid the phenomenon of tolerance, the lowest effective doses of the drug, asymmetrical dosage, and periodic administration of nitroglycerin alternately with other vasodilators should be used;
- Adverse reactions: hypotension, headache, tachycardia, nausea, and vomiting;
- Monitoring of therapy: blood pressure measurements, ECG;
- Rules for the use of inotropic and vasospasmodic drugs. Dosage:
  - Dobutamine — 2–20 μg/kg/min (beta-adrenergic effect),
  - Dopamine — 3–5 μg/kg/min: inotropic effect (beta-adrenergic effect),
  - >5 μg/kg/min: inotropic (beta-adrenergic effect) and vasospasmodic (alpha-adrenergic effect),
  - Milrinon — 0.375–0.75 μg/kg/min,
  - Levosimendan — 0.1 μg/kg/min, dose range: 0.05–0.2 μg/kg/min,
  - Noradrenaline — 0.2–1.0 μg/kg/min — a drug preferred in severe arterial hypotension,
  - Adrenaline — 0.05–0.5 μg/kg/min;
- Adverse reactions: tachycardia, arrhythmias, myocardial ischemia, sympathetic system stimulation symptoms, hypotonia, hypertension, and peripheral tissue ischemia;
- Monitoring: ECG, blood pressure measurements, gasometry.

FUTURE PERSPECTIVES OF THE HEART FAILURE TREATMENT

Omecamtiv mecarbil (oral tablets used twice a day in doses of 25–50 mg) is a new, selective activator of cardiac myosin for patients with HF and with impaired fraction of

the left ventricle. It is not registered in Europe, the procedure of its registration in the US is ongoing. The drug can be classified as an inotropic substance, but unlike most of them, strengthening muscle contraction is not associated with greater energy, oxygen demand, or an increase in the heart rate. The drug supports stronger binding of myosin to the actin filament, which translates into an increase in the number of these bonds and an increase in the strength of myofibrillar contraction. In the GALACTIC-HF trial, in more than 8 000 patients with symptomatic HF and LVEF ≤35% adding omecamtiv to standard therapy reduced the relative risk of HF patients' decompensation by 10% over 2 years (absolute risk reduction of 2.1%) [46]. A slightly stronger effect in patients with the lowest EF values is worth pointing out. However, the GALACTIC-HF study did not meet the modern requirements of basic optimal HF therapy due to the lack of standard use of flozins. The drug is mentioned once in the latest ESC guidelines for heart failure and is currently unavailable.

Tolvaptan (once-daily tablets in doses of 7.5, 15, and 30 mg — higher registered doses for people with polycystic kidney disease) is a selective vasopressin type 2 receptor antagonist. It is registered for the treatment of hyponatremia in the course of chronic HF, cirrhosis of the liver, polycystic kidney disease, and Schwartz-Bartter syndrome (inappropriate release of vasopressin syndrome); it has been available commercially for many years in the US and Europe. The latest 2021 ESC guidelines list tolvaptan as therapy to be considered for persistent hyponatremia with stagnation but recall the lack of results of randomized clinical trials indicating clear cardiovascular benefits in this patient group [47].

The HF guidelines omit a substance that improves prognosis for heart failure as indicated in a randomized prospective double-blind placebo-controlled trial. This substance is coenzyme Q10. In the Q-SYMBIO study involving 420 patients with heart failure in NYHA class III-IV, high doses of coenzyme Q10 3 × 100 mg daily were used. In a two-year follow-up, coenzyme Q10 reduced the risk of cardiovascular events in this group by 50% (11% absolute risk reduction), the relative risk reductions were: 43%, 42%, and 41% for cardiovascular mortality, total mortality, the need for hospitalization for heart failure, respectively. [48]. The above results were confirmed in the analysis of a subgroup of Europeans participating in the Q-SYMBIO study [49]. The problem with using coenzyme Q10 lies in the fact that only in some countries it is registered in such large doses as a drug, while in many countries it is simply an ingredient in dietary supplements, in several times smaller doses. In the QSYMBIO study, ubiquinone was used, but some preparations sold on the Polish pharmaceutical market contain ubiquinol. In the Q-SYMBIO study, a dose of 3 × 100 mg per day was deliberately used because the bioavailability of ubiquinone is so low that similar effective serum concentrations (concentrations above 2.5 mcg/ml) are not achieved using a single daily dose of 300 mg. However, the Q-SYMBIO study identifies an easily available, relatively inexpensive drug for adjuvant chronic HF therapy [50]. Further studies are awaited to precisely define its clinical benefits in HF patients.

Except for the medications shown in Figure 6, no other novel oral drugs of interest in HF are mentioned in the current guidelines. Recently, however, significant progress has been made in the pharmacotherapy of hyperkalemia, through the introduction of modern potassium-binding drugs. So far, none of these drugs has specified registered indications for use in hyperkalemia in chronic HF, but knowledge of these therapeutic options for doctors dealing with NS patients may be important — hyperkalemia is a typical problem precluding the administration of full doses of RAA blocking drugs, including MRA. These drugs bind potassium in the digestive tract, reducing its absorption. These include medicines as old as sodium or calcium polystyrene sulphonate introduced to the pharmaceutical markets 70 years ago and newer ones — zirconium cyclo-silicate introduced in 2018 and patiromer introduced in 2015 in the US and in 2017 in Europe. Patiromer — a medicine in the form of sachets containing 8.4,16.8, or 25.2 g of this agent is currently the only one with a clinical trial in the population of people with NS and hyperkalemia. The results of the DIAMOND study involving nearly 900 patients with chronic HFrEF, announced in 2022, showed that patiromer reduced the risk of significant hyperkalemia (>5.5 mmol/l) by 37% compared to placebo and the need to reduce the dose of the aldosterone antagonist by 38% [51].

Since there are currently no registered indications for the treatment of chronic hyperkalemia in this patient population, this can only be done "off label" — apart from the registered indications – based on the results of the DIAMOND study. Thus one can consider such treatment in adult patients with NS in NYHA class II-IV, with LVEF fraction ≤40%, who have laboratory-detected hyperkalemia (>5.0 mmol/l) or are currently characterized by normokalemia during such treatment. However, last year there were episodes where hyperkalemia caused the need for dose reduction or prevented the inclusion/optimization of a dose of a drug that inhibits the renin-angiotensin system, regardless of the drug class (ACE inhibitor, sartan, sacubitril/valsartan, MRA). The criteria for exclusion from the DIAMOND study were chronic kidney disease with GFR <30 ml/min/1.73 m^2, hypotension <90 mmHg, and general poor prognosis due to comorbidities.

WHAT'S NEW? WHAT ARE THE CHALLENGES IN THE POLISH HEALTHCARE SYSTEM

The latest guidelines for HF pharmacotherapy — both European from 2021 and American from 2022 — are groundbreaking for clinical practice. They introduce not only new key drug groups but also new pharmacotherapy regimens based on the principle of phenotyping in HFrEF and take into account new populations of HF patients for whom therapeutic effectiveness has been documented.

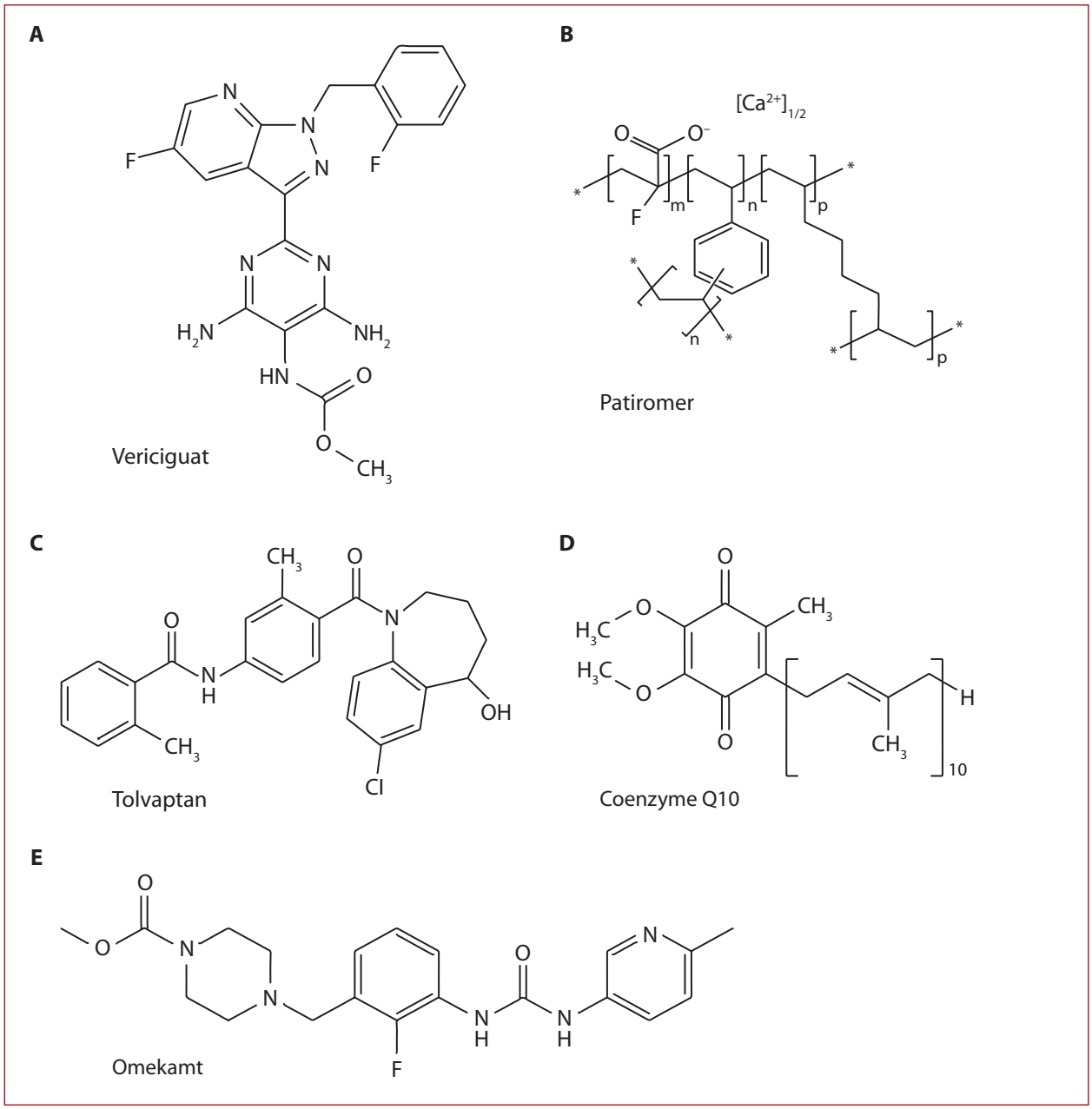


Figure 6. Structural formulas of new drugs with potential usefulness in heart failure: vericiguat (**A**), patiromer (**B**), tolvaptan (**C**), coenzyme Q10 (**D**), omecamtiv (**E**)

After many years of research in the field of HF with EF >40%, we have seen recommendations for HFmrEF and HFpEF. Similar progress concerns patients hospitalized for acute HF, for whom discharge from the hospital is a key moment for the implementation of evidence-based treatment, enabling the improvement of the prognosis of this group of patients. Recommendations for the discharge period, formulated through the prism of national circumstances, were prepared by the Polish Heart Failure Association (ANS) experts of the Polish Cardiac Society (PTK) in cooperation with the College of Family Physicians and the Polish Society of Family Medicine [7]. This document discusses a number of important aspects of the management in the discharge period, including the importance of iron deficiency.

The 2022 ACC recommendations were the first to consider SGLT2i for patients with HFmrEF and HFpEF. ARNI and MRA were also recommended in HFpEF and HFmrEF, with a slightly lower positioning. It is worth emphasizing here that at the time of publication of the ACC 2022 recommendations, the results of the DELIVER study were not available. Currently, we have data that allow using SGLT2i (empagliflozin and dapagliflozin [52]) in HF regardless of EF, i.e. across the entire HF spectrum [41].

We support the proposed current scheme and recommend, in Polish conditions, therapy based on pillars improving prognosis with clinically effective drugs highly positioned in the guidelines. Importantly, we recommend acting quickly to bring benefits already in the first month

of use. Modern pharmacotherapies also have a very well-documented beneficial effect on the quality of life. The current document does not cover new drugs that change the prognosis and quality of life in specific forms of HF, e.g. in cardiac amyloidosis (e.g. tafamidis) or hypertrophic cardiomyopathy (mavacamten), but they have become available outside clinical research programs and progress in the development of such therapies also falls within the broadly-understood contemporary HF pharmacotherapy.

But as usual, novelties are expensive, and not all currently recommended modern drugs are reimbursed for Polish patients. However, it is noteworthy that the introduction of dapagliflozin and empagliflozin reimbursement for HFrEF in May 2022 improved access to these drugs. Extension of reimbursement (July 2022) for patients with chronic kidney disease (CKD) (at the moment only for dapagliflozin) allows implementing the reimbursed drug in those HFmrEF and HFpEF patients in whom CKD coexists and the conditions for reimbursement for CKD are met. Similarly, HFpEF/HFmrEF patients may benefit from empagliflozin and dapagliflozin reimbursement options after modifications to SGLT2i reimbursement terms in the treatment of diabetes. In order to meet the needs of clinical practice, ANS experts have prepared a document on patient identification in accordance with the requirements of reimbursement for SGLT2 inhibitor therapy [53]. Unfortunately, there is still no refund for sacubitril/valsartan for Polish patients. However, thanks to the reduction in the price of this drug by the manufacturer, it has become more accessible to patients with HFrEF, and a shared decision on its inclusion should be made in each patient with symptomatic HF, taking into account his/her economic possibilities.

The problem in Poland is not only the limited availability of treatment with modern drugs but also the organization of HF patient care, which creates barriers to implementation of optimal pharmacotherapy with the possibility of achieving target doses, patient monitoring, and initiation of therapy based on the evidence-based medicine (EBM). This is of particular prognostic importance for patients after hospitalization for the acute manifestation of HF, i.e. for a patient in the "post-discharge sensitive phase". Long waiting times for a visit to a cardiologist, inertia of doctors, or economic aspects are classic barriers that the patient encounters during his/her illness. For effective treatment of HF, the following elements are also necessary: education of the patient and his/her family, the ability to self-control, including weight monitoring, and patient knowledge of the basic elements of pharmacotherapy (diuretic treatment) as well as the long-term adherence and compliance with the treatment. The 2021 ESC guidelines emphasize the role of the heart failure nurse in the care of HF patients. In Poland, since 2021, an education platform for nurses has been launched (www.edu.slabeserce.pl), addressed to those who would like to become educators for HF patients. The Education and Certification Program was created under the auspices of PTK, ANS PTK, and the Supreme Chamber of Nurses and Midwives.

The 2021ESC guidelines also refer, in the first class of recommendations, to multi-specialty care programs for HF patients. Including HF patients in this model of care has been shown to reduce HF mortality by as much as 25%, hospitalization for HF by 26%, and the total number of hospital admissions by 19% [54]. In Poland, such solutions do not work, and the developed KONS comprehensive care program has not been implemented. Expectations for new solutions included in the National Cardiac Care Network, currently in the pilot phase, must therefore be high, especially as it assumes unlimited financing for the treatment of heart failure.

Article information

Conflict of interest: JDK: lecture honoraria, grants, advisory boards: Adamed, AstraZeneca, Bausch Health, Bayer, Berlin-Chemie Menarini, Boehringer Ingelheim, Ewopharma, Novartis, Novo Nordisk, Pfizer, Polpharma, Sandoz, TEVA, Servier. IGG: lecture honoraria: Bayer, Boehringer Ingelheim, Krka, NovoNordisk, Promed. MB: lecture honoraria: Adamed, Aurovitas Pharma, Bausch Health, Bayer, Biofarm, Bioton, Boehringer Ingelheim, Egis, Gedeon Richter, Krka, Merck, MSD, Pfizer, Polfarmex, Ranbaxy, Recordati, Sandoz, Sanofi, Servier, USP Zdrowie, Viatris, Zentiva. JD: lecture honoraria, grants, institutional sponsoring- AstraZeneca, Bayer, Berlin-Chemie Menarini, Boehringer Ingelheim, Novartis, Vifor. KJF: lecture honoraria, grants, advisory boards: Adamed, AstraZeneca, Bausch Health, Bayer, Boehringer Ingelheim, Krka, Mundipharma, Mylan, Novartis, Sandoz, Servier. AKC: lecture honoraria: Angelini Pharma, Astra Zeneca, Bayer, Bausch Health, Boehringer Ingelheim, Krka, Pfizer, Polpharma, Servier. ML: lecture honoraria, grants, advisory boards: Amgen, AstraZeneca, Bausch Health, Bayer, Boehringer Ingelheim, Ewopharma, Novartis, Novo Nordisk, Servier. AM: lecture honoraria: Adamed, AstraZeneca, Aurovitas Pharma, Bayer, BerlinChemie Menarini, Boehringer Ingelheim, Celon, Egis, Gedeon Richter, Krka, Lilly, MSD, Novo Nordisk, Pfizer, Polpharma, Promed, Recordati, Sandoz, Sanofi, Servier, USP Zdrowie, Viatris, Zentiva. FMS: lecture honoraria: Astra Zeneca, Adamed, Boehringer Ingelheim, Krka, Recordati, Zentiva. MW: lecture honoraria: Adamed, Apotex, AstraZeneca, Aurovitas, Bayer, Berlin-Chemie Menarini, Boehringer Ingelheim, Egis, Krka, Novartis, NovoNordisk, Pfizer, Polpharma PromedSandoz, SanofiAvensis, Servier, Teva. BWK: lecture honoraria, advisory boards: Adamed, Astra Zeneca, Bausch Health, Bayer, Berlin-Chemie Menarini, Boehringer Ingelheim, Egis, Krka, Novartis, Pfizer, Sandoz, Sanofi. Other authors declare no conflict of interest.

Funding: None.

REFERENCES

1. Kałużna-Oleksy M. Heart failure in Poland. Reality, costs, suggestions for improving the situation [article in Polish]. Available online: https://marfan.org.pl/wpcontent/uploads/2021/01/Niewydolnos%CC%81c%CC%81-RAPORT-A4-2021-NET.pdf. [Accessed: January 25, 2022].
2. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021; 42(36): 3599–3726, doi: 10.1093/eurheartj/ehab368, indexed in Pubmed: 34447992.

3. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022; 145(18): e895–e1032, doi: 10.1161/CIR.0000000000001063, indexed in Pubmed: 35363499.
4. Vardeny O, Fang JC, Desai AS, et al. Dapagliflozin in heart failure with improved ejection fraction: a prespecified analysis of the DELIVER trial. Nat Med. 2022; 28(12): 2504–2511, doi: 10.1038/s41591-022-02102-9, indexed in Pubmed: 36522606.
5. Rosano GMC, Moura B, Metra M, et al. Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2021; 23(6): 872–881, doi: 10.1002/ejhf.2206, indexed in Pubmed: 33932268.
6. Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin-Neprilysin inhibition in acute decompensated heart failure. N Engl J Med. 2019; 380(6): 539–548, doi: 10.1056/NEJMoa1812851, indexed in Pubmed: 30415601.
7. Wachter R, Senni M, Belohlavek J, et al. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. Eur J Heart Fail. 2019; 21(8): 998–1007, doi: 10.1002/ejhf.1498, indexed in Pubmed: 31134724.
8. Lelonek M, Grabowski M, Kasprzak JD, et al. An expert opinion of the Heart Failure Association of the Polish Cardiac Society on the 2021 European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure: Heart failure guidelines from a national perspective. Kardiol Pol. 2022; 80(2): 239–246, doi: 10.33963/KP.a2022.0021, indexed in Pubmed: 35076082.
9. Werner CM, Böhm M. The therapeutic role of RAS blockade in chronic heart failure. Ther Adv Cardiovasc Dis. 2008; 2(3): 167–177, doi: 10.1177/1753944708091777, indexed in Pubmed: 19124420.
10. Ghionzoli N, Gentile F, Del Franco AM, et al. Current and emerging drug targets in heart failure treatment. Heart Fail Rev. 2022; 27(4): 1119–1136, doi: 10.1007/s10741-021-10137-2, indexed in Pubmed: 34273070.
11. Flather MD, Shibata MC, Coats AJS, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J. 2005; 26(3): 215–225, doi: 10.1093/eurheartj/ehi115, indexed in Pubmed: 15642700.
12. Pitt B, Filippatos G, Agarwal R, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. N Engl J Med. 2021; 385(24): 2252–2263, doi: 10.1056/NEJMoa2110956, indexed in Pubmed: 34449181.
13. Filippatos G, Anker SD, Agarwal R, et al. Finerenone and cardiovascular outcomes in patients with chronic kidney disease and type 2 diabetes. Circulation. 2021; 143(6): 540–552, doi: 10.1161/CIRCULATIONAHA.120.051898, indexed in Pubmed: 33198491.
14. Filippatos G, Anker SD, Agarwal R, et al. Finerenone reduces risk of incident heart failure in patients with chronic kidney disease and type 2 diabetes: analyses from the FIGARO-DKD trial. Circulation. 2022; 145(6): 437–447, doi: 10.1161/CIRCULATIONAHA.121.057983, indexed in Pubmed: 34775784.
15. Zannad F, Ferreira JP, Butler J, et al. Effect of empagliflozin on circulating proteomics in heart failure: mechanistic insights into the EMPEROR programme. Eur Heart J. 2022; 43(48): 4991–5002, doi: 10.1093/eurheartj/ehac495, indexed in Pubmed: 36017745.
16. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019; 381(21): 1995–2008, doi: 10.1056/NEJMoa1911303, indexed in Pubmed: 31535829.
17. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020; 383(15): 1413–1424, doi: 10.1056/NEJMoa2022190, indexed in Pubmed: 32865377.
18. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010; 376(9744): 875–885, doi: 10.1016/S0140-6736(10)61198-1, indexed in Pubmed: 20801500.
19. Faselis C, Arundel C, Patel S, et al. Loop diuretic prescription and 30-day outcomes in older patients with heart failure. J Am Coll Cardiol. 2020; 76(6): 669–679, doi: 10.1016/j.jacc.2020.06.022, indexed in Pubmed: 32762901.
20. Ali S, Jung S, Nandkeolyar S, et al. Inpatient diuretic management of acute heart failure: a practical review. Am J Cardiovasc Drugs. 2021; 21(6): 595–608, doi: 10.1007/s40256-020-00463-5, indexed in Pubmed: 33709346.
21. Mentz RJ, Anstrom KJ, Eisenstein EL, et al. Effect of torsemide vs furosemide after discharge on all-cause mortality in patients hospitalized with heart failure: the TRANSFORM-HF randomized clinical trial. JAMA. 2023; 329(3): 214–223, doi: 10.1001/jama.2022.23924, indexed in Pubmed: 36648467.
22. Mullens W, Dauw J, Martens P, et al. Acetazolamide in acute decompensated heart failure with volume overload. N Engl J Med. 2022; 387(13): 1185–1195, doi: 10.1056/NEJMoa2203094, indexed in Pubmed: 36027559.
23. Côté JM, Bouchard J, Murray PT, et al. Diuretic strategies in patients with resistance to loop-diuretics in the intensive care unit: A retrospective study from the MIMIC-III database. J Crit Care. 2021; 65: 282–291, doi: 10.1016/j.jcrc.2021.06.009, indexed in Pubmed: 34298494.
24. Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med. 2009; 361(25): 2436–2448, doi: 10.1056/NEJMoa0908355, indexed in Pubmed: 19920054.
25. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency†. Eur Heart J. 2015; 36(11): 657–668, doi: 10.1093/eurheartj/ehu385, indexed in Pubmed: 25176939.
26. Ponikowski P, Kirwan BA, Anker SD, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. Lancet. 2020; 396(10266): 1895–1904, doi: 10.1016/S0140-6736(20)32339-4, indexed in Pubmed: 33197395.
27. Lewis GD, Malhotra R, Hernandez AF, et al. Effect of oral iron repletion on exercise capacity in patients with heart failure with reduced ejection fraction and iron deficiency: the IRONOUT HF randomized clinical trial. JAMA. 2017; 317(19): 1958–1966, doi: 10.1001/jama.2017.5427, indexed in Pubmed: 28510680.
28. Kalra PR, Cleland JGF, Petrie MC, et al. Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial. Lancet. 2022; 400(10369): 2199–2209, doi: 10.1016/S0140-6736(22)02083-9, indexed in Pubmed: 36347265.
29. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med. 1997; 336(8): 525–533, doi: 10.1056/NEJM199702203360801, indexed in Pubmed: 9036306.
30. Ambrosy AP, Butler J, Ahmed A, et al. The use of digoxin in patients with worsening chronic heart failure: reconsidering an old drug to reduce hospital admissions. J Am Coll Cardiol. 2014; 63(18): 1823–1832, doi: 10.1016/j.jacc.2014.01.051, indexed in Pubmed: 24613328.
31. Kasprzak JD, Stępińska J, Wożakowska-Kapłon B, et al. Cardiac Society Working Group on Cardiovascular Drug Therapy. Optimum heart rate - the current goal of cardiovascular therapy. Position statement of the Cardiac Society Working Group on Cardiovascular Drug Therapy [article in Polish]. Kardiol Pol. 2012; 70(10): 1081–1094, indexed in Pubmed: 23080109.
32. Chen S, Pürerfellner H, Meyer C, et al. Rhythm control for patients with atrial fibrillation complicated with heart failure in the contemporary era of catheter ablation: a stratified pooled analysis of randomized data. Eur Heart J. 2020; 41(30): 2863–2873, doi: 10.1093/eurheartj/ehz443, indexed in Pubmed: 31298266.
33. Lombardi CM, Cimino G, Pagnesi M, et al. Vericiguat for heart failure with reduced ejection fraction. Curr Cardiol Rep. 2021; 23(10): 144, doi: 10.1007/s11886-021-01580-6, indexed in Pubmed: 34410527.
34. Kassis-George H, Verlinden NJ, Fu S, et al. Vericiguat in heart failure with a reduced ejection fraction: patient selection and special considerations. Ther Clin Risk Manag. 2022; 18: 315–322, doi: 10.2147/TCRM.S357422, indexed in Pubmed: 35386181.
35. Zannad F, Anker SD, Byra WM, et al. Rivaroxaban in patients with heart failure, sinus rhythm, and coronary disease. N Engl J Med. 2018; 379(14): 1332–1342, doi: 10.1056/NEJMoa1808848, indexed in Pubmed: 30146935.
36. Shantsila E, Kozieł M, Lip GYh. Anticoagulation versus placebo for heart failure in sinus rhythm. Cochrane Database Syst Rev. 2021; 5(5): CD003336, doi: 10.1002/14651858.CD003336.pub4, indexed in Pubmed: 34002371.
37. Vardeny O, Fang JC, Desai AS, et al. Dapagliflozin in heart failure with improved ejection fraction: a prespecified analysis of the DELIVER trial.

Nat Med. 2022; 28(12): 2504–2511, doi: 10.1038/s41591-022-02102-9, indexed in Pubmed: 36522606.
38. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med. 2022; 387(12): 1089–1098, doi: 10.1056/NEJMoa2206286, indexed in Pubmed: 36027570.
39. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021; 385(16): 1451–1461, doi: 10.1056/NEJMoa2107038, indexed in Pubmed: 34449189.
40. Mc Causland FR, Lefkowitz MP, Claggett B, et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. Circulation. 2020; 141(5): 352–361, doi: 10.1161/CIRCULATIONAHA.119.044586, indexed in Pubmed: 31736342.
41. Packer M, Butler J, Zannad F, et al. Effect of empagliflozin on worsening heart failure events in patients with heart failure and preserved ejection fraction: emperor-preserved trial. Circulation. 2021; 144(16): 1284–1294, doi: 10.1161/CIRCULATIONAHA.121.056824, indexed in Pubmed: 34459213.
42. Vaduganathan M, Docherty KF, Claggett BL, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. Lancet. 2022; 400(10354): 757–767, doi: 10.1016/S0140-6736(22)01429-5, indexed in Pubmed: 36041474.
43. Kosiborod MN, Angermann CE, Collins SP, et al. Effects of empagliflozin on symptoms, physical limitations, and quality of life in patients hospitalized for acute heart failure: results from the EMPULSE trial. Circulation. 2022; 146(4): 279–288, doi: 10.1161/CIRCULATIONAHA.122.059725, indexed in Pubmed: 35377706.
44. Mullens W, Damman K, Mullens W, et al. The use of diuretics in heart failure with congestion – a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019; 21(2): 137–155, doi: 10.1002/ejhf.1369, indexed in Pubmed: 30600580.
45. Fedyk-Łukasik M, Wizner B, Opolski G, et al. Quality of care of hospitalised patients with heart failure in Poland in 2013: results of the second nationwide survey. Kardiol Pol. 2017; 75(6): 527–534, doi: 10.5603/KP.a2017.0040, indexed in Pubmed: 28353316.
46. Teerlink JR, Diaz R, Felker GM, et al. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. N Engl J Med. 2021; 384(2): 105–116, doi: 10.1056/NEJMoa2025797, indexed in Pubmed: 33185990.
47. Kostam MA, Gheorghiade M, Brunett JC, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA. 2007; 297(12): 1319–1331, doi: 10.1001/jama.297.12.1319, indexed in Pubmed: 17384437.
48. Mortensen SA, Rosenfeldt F, Kumar A, et al. The effect of coenzyme Q10 on morbiditiy and mortality in chronic heart failure: results from Q-SYMBIO – a randomised double-blind trial. JACC Heart Fail. 2014; 2(6): 641–649, doi: 10.1016/j.jchf.2014.06.008, indexed in Pubmed: 25282031.
49. Mortensen AL, Rosenfeldt F, Filipiak KJ. Effect of coenzyme Q10 in Europeans with chronic heart failure: A sub-group analysis of the Q-SYMBIO randomized double-blind trial. Cardiol J. 2019; 26(2): 147–156, doi: 10.5603/CJ.a2019.0022, indexed in Pubmed: 30835327.
50. Filipiak KJ, Surma S, Romańczyk M, et al. Heart failure-do we need new drugs or have them already? A case of coenzyme Q10. J Cardiovasc Dev Dis. 2022; 9(5): 161, doi: 10.3390/jcdd9050161, indexed in Pubmed: 35621872.
51. Butler J, Anker SD, Lund LH, et al. Patiromer for the management of hyperkalemia in heart failure with reduced ejection fraction: the DIAMOND trial. Eur Heart J. 2022; 43(41): 4362–4373, doi: 10.1093/eurheartj/ehac401, indexed in Pubmed: 35900838.
52. Nessler J, Siniarski A, Leszek P, et al. Reviewers. Expert opinion of the Heart Failure Working Group of the Polish Cardiac Society on the use of dapagliflozin in the treatment of heart failure with reduced ejection fraction. Kardiol Pol. 2021; 79(3): 363–370, doi: 10.33963/KP.15859, indexed in Pubmed: 33687868.
53. Lelonek M, Grabowski M, Kasprzak JD et al. An expert opinion of the Heart Failure Association of the Polish Cardiac Society on the 2021 European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure: Heart failure guidelines from a national perspective. Kardiol Pol. 2022; 80(2): 239–246, doi: 10.33963/KP.a2022.0021. 2022(3): 128–132.
54. McAlister FA, Stewart S, Ferrua S, et al. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: a systematic review of randomized trials. J Am Coll Cardiol. 2004; 44(4): 810–819, doi: 10.1016/j.jacc.2004.05.055, indexed in Pubmed: 15312864.

XII Zaawansowany kurs hipertensjologii dla specjalistów

PATRONAT

Farmakoterapii Sercowo-Naczyniowej · Sekcja PTK

Szczecin, 16–17 czerwca 2023 roku

Szczegółowe informacje oraz rejestracja:

www.zaawansowanykurs.viamedica.pl

ORGANIZATOR

VIA MEDICA 30 LAT

PATRONAT MEDIALNY

tvmed

PARTNER

ikamed.pl internetowa księgarnia medyczna

23-0071.001.011

Konferencja jest skierowana tylko do osób uprawnionych do wystawiania recept lub osób prowadzących obrót produktami leczniczymi — podstawa prawna: ustawa z dnia 6 września 2001 r. Prawo farmaceutyczne (t.j. Dz.U. z 2020 r. poz. 944).

XV Konferencja

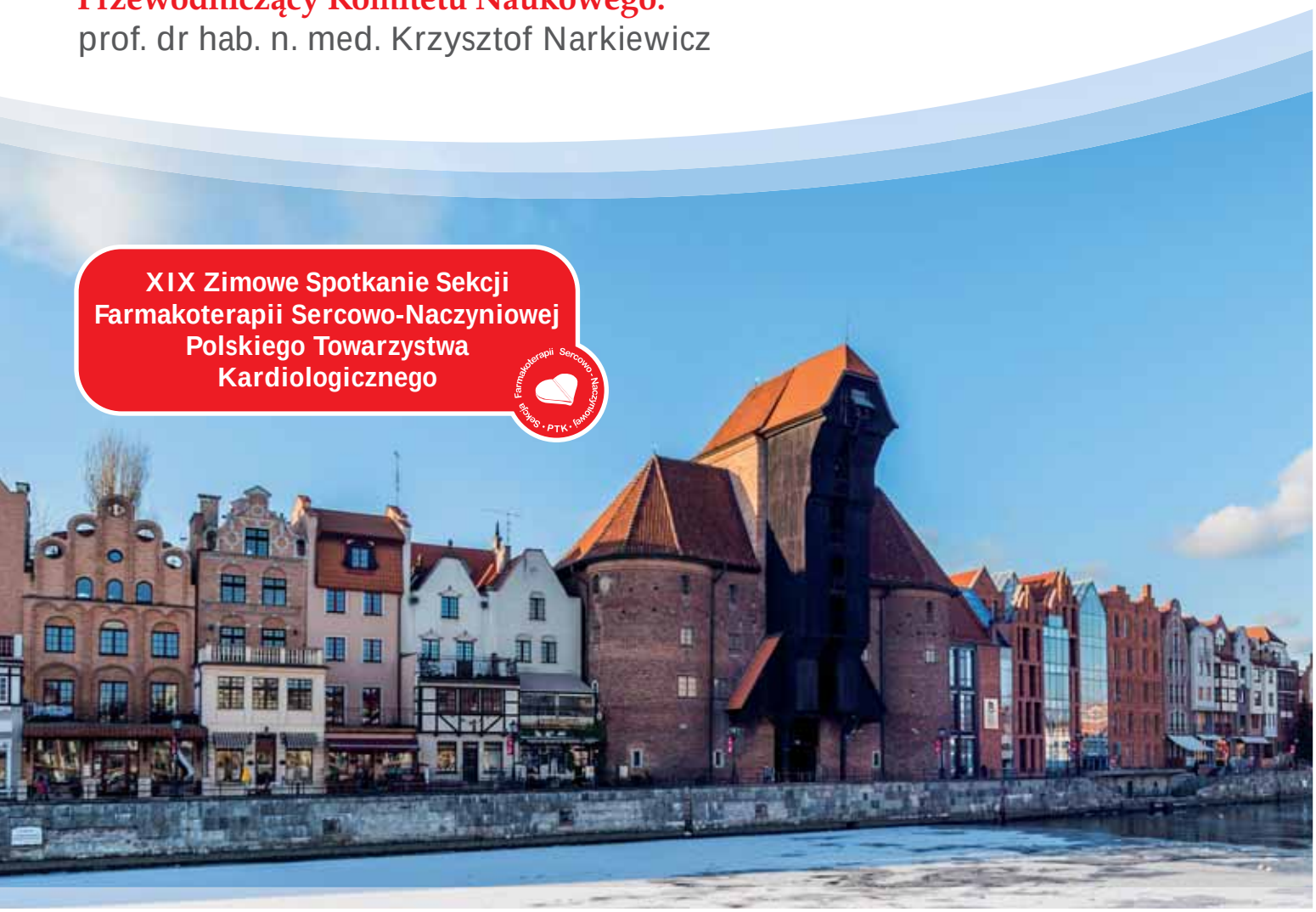
Choroby Serca i Naczyń

Gdańsk, 7–9 grudnia 2023 roku

Radisson Hotel & Suites

Przewodniczący Komitetu Naukowego:
prof. dr hab. n. med. Krzysztof Narkiewicz

XIX Zimowe Spotkanie Sekcji Farmakoterapii Sercowo-Naczyniowej Polskiego Towarzystwa Kardiologicznego



Szczegółowe informacje i rejestracja na stronie internetowej:
www.chorobyserca.viamedica.pl

ORGANIZATOR

PATRONAT MEDIALNY

Konferencja jest skierowana tylko do osób uprawnionych do wystawiania recept lub osób prowadzących obrót produktami leczniczymi — podstawa prawna: ustawa z dnia 6 września 2001 r. Prawo farmaceutyczne (t.j. Dz.U. z 2020 r. poz. 944).

22-5413.001.013