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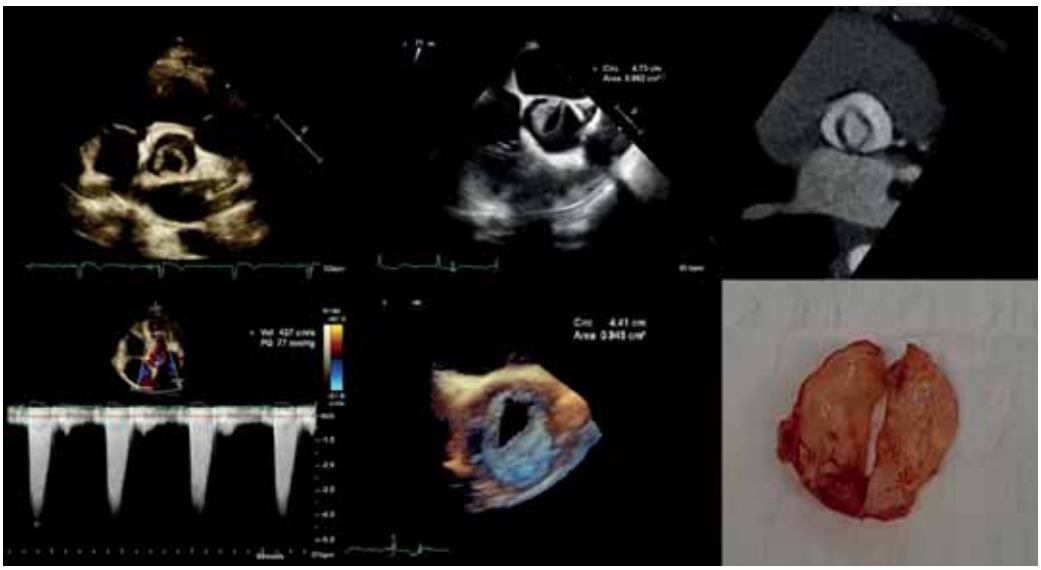

A 42-year-old female with a unicuspid aortic valve, see p. 1148

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Table of contents

Sex differences in occurrence and reporting of adverse drug reactions in hypertension: What are the clinical implications?

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Related article
By Polaczyk et al.

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Hypertension is a major cardiovascular and renal risk factor and a leading cause of premature death which affects both men and women [1]. However, blood pressure is a sexually dimorphic trait, and as reported recently [2], there are clear sex differences in the prevalence, pathophysiology, and consequences of hypertension between males and females. For example, one important difference is an interaction between blood pressure and age. Indeed, the rate of hypertension is significantly higher in males compared to age-matched females until the sixth decade, but thereafter, the prevalence of hypertension increases steeply to become higher in females than in males [3]. International recommendations for the management of hypertension in adults do not differ substantially for males and females in terms of diagnosis, investigational procedures, drug therapy, or follow-up [4, 5]. The main exceptions are, of course, pregnancy and the use of some antihypertensive drugs, such as blockers of the renin-angiotensin system, in women with childbearing potential. Yet, one should perhaps be more sensitive to the fact that sexual dimorphism concerns not only the prevalence and pathophysiology of hypertension but also the pharmacology of antihypertensive drugs and risk of developing major blood pressure-related complications [6].

When considering the use of medications for the treatment of hypertension, there is evidence that sex-specificities modulate the pharmacological response to antihypertensive drugs. Indeed, there are well-described pharmacokinetic differences between males and females regarding bioavailability, distribution, and elimination of drugs. Thus, females tend to have a lower ratio of lean-to-fat tissue, lower circulating plasma volume, and lower glomerular filtration rate [7]. Sex variations in the activity of several enzymes of the cytochrome P450 (CYP) system metabolizing antihypertensive drugs are also well documented [8]. Most of the time, these pharmacokinetic aspects are not taken into consideration for therapeutic recommendations because they are thought to have little impact on efficacy and tolerability of antihypertensive medications. Nonetheless, they may result in higher drug exposure in females and hence may increase their susceptibility to dose-dependent adverse drug reactions. Hence, women may respond differently to the prescription of some antihypertensive medications both in terms of efficacy and development of adverse reactions.

In the present issue of *Kardiologia Polska* (*Kardiol Pol*, *Polish Heart Journal*), Polaczyk et al. [9] present the results of a recent survey performed among hypertensive patients hospitalized for arterial hypertension and patients treated in an outpatient clinic for their hypertension. The main objective of the survey was to assess the prevalence of adverse drug reactions in women and men with arterial hypertension and comorbidities and to assess the specific predisposing factors for adverse drug reactions by sex. The study enrolled 1000 consecutive patients (560 women and 440 men; mean age, 62.8 years) starting in 2019. In this population, cardiovascular comorbidities were more frequent among males, whereas endocrine (but not diabetes)

and rheumatoid diseases were more frequent among females. The survey consisted of 22 questions, covering various demographic and clinical factors, which the patients filled in independently or with the help of a research team member. The main observation of the study is that the frequency of reported adverse drug-induced symptoms was significantly higher in female (54%) than in male patients (41%) even though females were taking significantly fewer drugs. Interestingly, this was true also for drug intolerance associated with using antibiotics or analgesics. In both sexes, the reporting of adverse drug reactions increased with age mainly due to an increased number of prescribed drugs. In males, the prescription of other cardiovascular drugs (statins, antiplatelet agents, etc.) contributed significantly to the increased reporting of adverse drug reactions. On the other hand, in females, the risk of developing adverse drug reactions was rather associated with using respiratory drugs and, to a lower degree, with using anti-rheumatoid drugs and antiplatelet agents.

The results of this interesting survey confirm previous observations from various countries suggesting that women are more likely to report adverse drug reactions for most common antihypertensive drugs and are more likely to be admitted to the hospital because of drug-induced adverse reactions [10]. The reasons why women tend to report more adverse drug reactions or drug intolerance are not completely understood. Whether reported events are genuine pharmacological reactions or only perceived events is not always well defined, and the reality is they are probably a mix of both. Thus, it is interesting to note that in placebo-controlled studies, up to 14% of men receiving classical antihypertensive drugs report side effects leading to discontinuation of the drugs, and with statins, this figure may reach 25% [11, 12]. One of the possible reasons for the sex difference may be that women have less confidence in potential benefits of drugs and a different perception of health risks related to their hypertension. One important issue is that the reporting of adverse reactions or multiple drug intolerance, as observed in Polaczyk's study [9], is an important determinant of poor adherence and drug withdrawal. Indeed, the report of several side effects is often an indirect signal for patients to indicate that they are not willing to continue some of their medications. In this respect, it is interesting to mention that observational studies have often reported a lower level of adherence to antihypertensive medications among females than males [13]. However, this observation remains controversial. Actually, a systematic review and meta-analyses of 82 studies (15 517 457 men and 18 537 599 women) did not provide definitive evidence of sex differences in adherence to antihypertensive therapy [14].

Another potential clinical consequence of frequent reporting of drug-related adverse reactions might be poor control of blood pressure mediated by lower adherence to antihypertensive medications. Partial or complete non-adherence is a well-recognized factor associated with a worst control of blood pressure and increased risk of developing cardiovascular outcomes [15]. Unfortunately, Polaczyk et al. [9] did not provide any information on blood pressure values in men and women reporting, or not, adverse drug reactions. This information would have been interesting in evaluating clinical impact of multiple drug intolerance or occurrence of adverse drug reactions.

The data presented by Polaczyk et al. [9] have several clinical implications. As mentioned by the authors, the first is the need to discuss regularly with patients and, in particular, with women how they tolerate their antihypertensive medications and how they feel about them to modify the drug prescription if necessary. In the case of multiple drug intolerance, the possibility of low adherence should be envisaged, and drug adherence should be monitored if blood pressure is poorly controlled. Whenever possible, the pill burden should be reduced using single-pill combinations, and patients should be well informed about the side-effect profile of antihypertensive drugs before they start to take them. At last, the most effective approach is probably to dedicate more time to discuss with patients possible barriers and beliefs that might interfere with their perception of benefits and risks of antihypertensive medications.

Article information

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REFERENCES

1. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nat Rev Nephrol. 2020; 16(4): 223–237, doi: 10.1038/s41581-019-0244-2, indexed in Pubmed: 32024986.
2. Connelly PJ, Currie G, Delles C. Sex differences in the prevalence, outcomes and management of hypertension. Curr Hypertens Rep. 2022; 24(6): 185–192, doi: 10.1007/s11906-022-01183-8, indexed in Pubmed: 35254589.
3. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics-2022 update: A report from the American Heart Association. Circulation. 2022; 145(8): e153–e639, doi: 10.1161/CIR.0000000000001052, indexed in Pubmed: 35078371.
4. 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.
5. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 2020; 75(6): 1334–1357, doi: 10.1161/HYPERTENSIONAHA.120.15026, indexed in Pubmed: 32370572.
6. Ji H, Niiranen TJ, Rader F, et al. Sex differences in blood pressure associations with cardiovascular outcomes. Circulation. 2021; 143(7): 761–763, doi: 10.1161/CIRCULATIONAHA.120.049360, indexed in Pubmed: 33587655.

7. Oertelt-Prigione S, Regitz-Zagrosek V. Gender aspects in cardiovascular pharmacology. J Cardiovasc Transl Res. 2009; 2(3): 258–266, doi: 10.1007/s12265-009-9114-9, indexed in Pubmed: 20560015.
8. Spoletini I, Vitale C, Malorni W, et al. Sex differences in drug effects: interaction with sex hormones in adult life. Handb Exp Pharmacol. 2012(214): 91–105, doi: 10.1007/978-3-642-30726-3_5, indexed in Pubmed: 23027447.
9. Polaczyk M, Olszanecka A, Wojciechowska W, et al. The occurrence of drug-induced side effects in women and men with arterial hypertension and comorbidities. Kardiol Pol. 2022; 80(11): 1094–1103, doi: 10.33963/KP.a2022.0232, indexed in Pubmed: 36226759.
10. Rydberg DM, Mejyr S, Loikas D, et al. Sex differences in spontaneous reports on adverse drug events for common antihypertensive drugs. Eur J Clin Pharmacol. 2018; 74(9): 1165–1173, doi: 10.1007/s00228-018-2480-y, indexed in Pubmed: 29804162.
11. Preston RA, Materson BJ, Reda DJ, et al. Placebo-associated blood pressure response and adverse effects in the treatment of hypertension: observations from a Department of Veterans Affairs Cooperative Study. Arch Intern Med. 2000; 160(10): 1449–1454, doi: 10.1001/archinte.160.10.1449, indexed in Pubmed: 10826457.
12. Rief W, Avorn J, Barsky AJ. Medication-attributed adverse effects in placebo groups: implications for assessment of adverse effects. Arch Intern Med. 2006; 166(2): 155–160, doi: 10.1001/archinte.166.2.155, indexed in Pubmed: 16432082.
13. Consolazio D, Gattoni ME, Russo AG. Exploring gender differences in medication consumption and mortality in a cohort of hypertensive patients in Northern Italy. BMC Public Health. 2022; 22(1): 768, doi: 10.1186/s12889-022-13052-9, indexed in Pubmed: 35428215.
14. Biffi A, Rea F, Iannaccone T, et al. Sex differences in the adherence of antihypertensive drugs: a systematic review with meta-analyses. BMJ Open. 2020; 10(7): e036418, doi: 10.1136/bmjopen-2019-036418, indexed in Pubmed: 32641331.
15. Burnier M, Egan BM. Adherence in hypertension. Circ Res. 2019; 124(7): 1124–1140, doi: 10.1161/CIRCRESAHA.118.313220, indexed in Pubmed: 30920917.

The occurrence of drug-induced side effects in women and men with arterial hypertension and comorbidities

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Related article
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Cardiovascular disease (CVD) has been traditionally considered a male disease, and for many years it has been underestimated and underrecognized in women. Nevertheless, CVD remains the leading cause of mortality and morbidity in women in western countries.

It is both comforting and worrying that much of CVD could be avoided through adequate prevention strategies. Preventing the incidence of these diseases essentially means tackling modifiable cardiovascular risk factors. Among these, arterial hypertension (AH) plays a leading role [1]. AH represents a major steadily increasing therapeutic challenge to healthcare systems, affecting almost one billion people worldwide. Although various pharmacological treatment options exist, blood pressure (BP) control is still suboptimal and major efforts are required to improve patients' awareness and compliance, as well as physicians' adherence to treatment guidelines [2].

There is evidence of sex dimorphism in epidemiology, pathophysiology, management, and treatment of AH. Many studies highlight sex differences in the pharmacokinetics and pharmacodynamics of cardiovascular drugs [3]. Disparities may be related to biological factors (body composition) and physiology (hormonal influences during the menstrual cycle, menopause, and pregnancy); furthermore, women are less often treated with evidence-based drugs, experience more relevant adverse drug reactions (ADRs), and remain underrepresented in most clinical trials [4]. Thus, current guidelines are based on trials conducted predominantly in middle-aged men and translated to women without evidence [5].

Despite the increasing awareness of sex-related differences, the latest European Society of Hypertension/European Society of Cardiology [6] and American Heart Association [7] guidelines (2017) recommend the same BP targets and treatments for both sexes. The only certainties we have nowadays regarding AH therapy in women are limited and concern mainly the therapeutic strategy to use (or to avoid) to treat BP pregnancy-related disorders, and the treatment of AH associated with some women's comorbidities such as thiazide use and risk for osteoporotic fractures. Finally, isolated systolic AH is more frequent in elderly women, and its treatment is often associated with orthostatic hypotension, caused or exacerbated by a list of well-known drugs [8].

In this issue of *Kardiologia Polska* (*Kardiol Pol*, *Polish Heart Journal*), Polaczyk et al. [9] present an elegant and detailed analysis of the frequency of ADRs in women and men with AH and comorbidities to assess the sex-specific predisposing factors leading to their occurrence. Based on 1000 consecutive patients (560 women and 440 men) diagnosed with AH, a 22-question structured questionnaire was used to gather demographic and clinical data. Women in the study were significantly older, had longer hypertensive disease duration, and fewer comorbid CVDs than men. Women were more likely to report ADRs, and the risk increased significantly with age and coexistence of any respiratory disease. Regarding specific side effects, women more frequently reported hypotension, coughing,

edema, bradycardia, and skin lesions than men. In male patients, the risk of ADRs increased with the occurrence of hypercholesterolemia and or other metabolic diseases (such as diabetes, gout, obesity, and osteoporosis).

The review of the literature shows that the incidence of ADRs by sex has not always been sufficiently investigated in the controlled clinical trials on which our current treatment guidelines are based and, therefore, useful information on sex differences may have been left out: this omission could prevent an effective personalization of the antihypertensive therapy.

There are at least three good reasons for reading the article by Polaczyk et al. [9] in this issue.

(1) It is focused on an area of care that is increasingly important in cardiology and public health; the awareness of the existence of sex differences in CVD and AH is increasing, but there is still a lack of defined knowledge.

(2) It underlines an important aspect of AH, namely the conditions of discontinuation of the therapeutic strategy. ADRs may significantly affect the quality of life of patients with AH, as well as their disease acceptance and therapy compliance, leading to worse BP control and, thus, poorer prognosis.

(3) It is an attempt to provide a comparative view of possible ARDs in different medical and clinical settings. As AH is a condition linked to aging, it is often associated with multiple other comorbidities that can affect both clinical outcomes and therapeutic strategies.

There are at least three reasons to suggest that the results should be taken as a stimulus for looking ahead, rather than reliable information on which to concentrate technical discussion: (1) despite validation processes, questionnaires remain rather poor instruments for investigating practices; (2) the comparability and representativeness of the selected sample may not be considered satisfactory as it was limited to a single center and a relatively short period, which creates limitations and need for caution while interpreting findings and their generalizability; (3) men are more often prescribed angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists and beta-blockers than women, while more women than men receive diuretics and calcium antagonists. In the present study, women took angiotensin receptor blockers more frequently than men. This could be due to the fact that the female participants were significantly older than their male counterparts and post-menopausal. Moreover, the sample included both hospitalized and outpatient clinic patients; however, it can be assumed that the incidence of ADRs may be higher in patients not requiring hospitalization.

Based on the current analysis by Polaczyk et al. [9], a better understanding of sex-related differences is essential to improve safety (and subsequently efficacy) of AH drugs and to develop proper individualized cardiovascular therapeutic strategies. According to the present study, special attention should be paid to female and elderly patients, as well as people with numerous comorbidities.

Several advances have been made to increase knowledge and awareness of sex differences in CVD. The main issue hindering a comprehensive approach seems to be the lack of consistent sex-specific data. With the advent of personalized medicine, there is consensus that sex differences in pharmacotherapy should be studied systematically, and sex should be included in covariate analyses and not only in *post hoc* analysis [10].

Article information

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REFERENCES

1. Lodi E, Stefani O, Reggianini L, et al. Gender differences in cardiovascular risk factors. J Intern Med. 2013; 274(2): 176–191, doi: 10.1111/joim.12073, indexed in Pubmed: 23565931.
2. Thoenes M, Neuberger HR, Volpe M, et al. Antihypertensive drug therapy and blood pressure control in men and women: an international perspective. J Hum Hypertens. 2010; 24(5): 336–344, doi: 10.1038/jhh.2009.76, indexed in Pubmed: 19798089.
3. Cadeddu C, Franconi F, Cassisa L, et al. Arterial hypertension in the female world: pathophysiology and therapy. J Cardiovasc Med (Hagerstown). 2016; 17(4): 229–236, doi: 10.2459/JCM.0000000000000315, indexed in Pubmed: 26910607.
4. Tamargo J, Rosano G, Walther T, et al. Gender differences in the effects of cardiovascular drugs. Eur Heart J Cardiovasc Pharmacother. 2017; 3(3): 163–182, doi: 10.1093/ehjcvp/pvw042, indexed in Pubmed: 28329228.
5. Strocchi E, Baffoni E, Bragagni A, et al. The attention on gender in studies on the treatment of hypertension: Was it enough? Ital J Gender-Specific Med. 2021; 7(2): 94–101, doi: 10.1723/3600.35813.
6. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018; 39(33): 3021–3104, doi: 10.1093/eurheartj/ehy339, indexed in Pubmed: 30165516.
7. 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: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018; 71(19): e127–e248, doi: 10.1016/j.jacc.2017.11.006, indexed in Pubmed: 29146535.
8. Lodi E, Carollo A, Martinotti V, et al. Hypertension and pharmacological therapy in women. High Blood Press Cardiovasc Prev. 2018; 25(2): 147–150, doi: 10.1007/s40292-018-0257-0, indexed in Pubmed: 29623553.
9. Polaczyk M, Olszanecka M, Wojciechowska W. The occurrence of drug-induced side effects in women and men with arterial hypertension and comorbidities. Kardiol Pol. 2022; 80(11): 1094–1103, doi: 10.33963/KP.a2022.0232.
10. Kalibala J, Pechère-Bertschi A, Desmeules J. Gender differences in cardiovascular pharmacotherapy-the example of hypertension: a mini review. Front Pharmacol. 2020; 11: 564, doi: 10.3389/fphar.2020.00564, indexed in Pubmed: 32435193.

Association of left atrial enlargement and increased left ventricular wall thickness with arrhythmia recurrence after cryoballoon ablation for atrial fibrillation

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Related article
by Warminski et al.

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Cryoballoon-based (CB) catheter ablation is a safe and effective method to maintain sinus rhythm in symptomatic patients with atrial fibrillation (AF) and to improve quality of life. Postablation AF recurrence is associated with AF duration, patient age, left atrial size, renal dysfunction, substrate visualization by magnetic resonance imaging (MRI), or the abundance of epicardial fat tissue [1]. The use of risk prediction models for AF recurrence would be a necessary means to assess patients at risk, but these have only moderate performance [1].

Multiple studies addressed the effect of left atrial size and left ventricular ejection fraction (LVEF) on the recurrence of AF after catheter ablation [1, 2]. Long-term efficacy is highly influenced by left atrial enlargement (LAE), but less so in the case of coincidently reduced LVEF [2], or normal or mildly decreased LVEF [3]. Additionally, left ventricular wall thickness (LVWT) correlates with LAE and atrial arrhythmias [1, 4, 5]. Moreover, wall thickness is also known to be associated with unfavorable outcomes (higher rate of ventricular arrhythmias and death [6]), and it has also been linked to the prevalence and recurrence of atrial fibrillation [7–9]. However, we only possess restricted data on LVWT's role in AF recurrence after catheter ablation.

Warmiński et al. studied LVWT to predict AF recurrence after cryoballoon catheter ablation for the first time. The authors presented a retrospective analysis of the effect of concurrent increased LVWT and the presence of LAE on AF recurrence. LVWT and LAE were measured with the use of two-dimensional echocardiography and computed tomography (CT). Even though CT identified more frequently common or accessory pulmonary veins, echocardiographic and CT measurements of LAE had similar predictive values. In the case of concurrent increased LVWT and LAE, a high prevalence of cardiomyopathy and transient ischemic attack or stroke was observed. Patients with concomitant increased LVWT and LAE experienced the highest rate of AF recurrence (61.9%) up to 2 years. The recurrence rate decreased in patients with LAE without LVWT, in the presence of increased LVWT without LAE, and was the lowest in patients without an increased LVWT and LAE. Concomitant increased LVWT and LAE were independent predictors of AF recurrence with a 1.8-fold increased risk [10].

Beyond having these new results on easily measured parameters such as LVWT with LAE and AF recurrence after CB ablation, the article by Warmiński et al. is important for everyday clinical practice. It is of utmost importance to aid physicians in identifying patients at risk of AF recurrence. These patients need strict follow-up, especially those with heart failure. Studies such as the one conducted by Warmiński et. al give us easily assessable factors and prediction models with variables like LVWT or left atrial size to identify patients needing close medical attention.

Article information

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REFERENCES

1. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021; 42(5): 373–498, doi: 10.1093/eurheartj/ehaa612, indexed in Pubmed: 32860505.
2. Demarchi A, Neumann L, Rordorf R, et al. Long-term outcome of catheter ablation for atrial fibrillation in patients with severe left atrial enlargement and reduced left ventricular ejection fraction. Europace. 2021; 23(11): 1751–1756, doi: 10.1093/europace/euab213, indexed in Pubmed: 34534277.
3. Jin X, Pan J, Wu H, et al. Are left ventricular ejection fraction and left atrial diameter related to atrial fibrillation recurrence after catheter ablation?: A meta-analysis. Medicine (Baltimore). 2018; 97(20): e10822, doi: 10.1097/MD.0000000000010822, indexed in Pubmed: 29768386.
4. Simek CL, Feldman MD, Haber HL, et al. Relationship between left ventricular wall thickness and left atrial size: comparison with other measures of diastolic function. J Am Soc Echocardiogr. 1995; 8(1): 37–47, doi: 10.1016/s0894-7317(05)80356-6, indexed in Pubmed: 7710749.
5. Xu HF, He YM, Qian YX, et al. Left ventricular posterior wall thickness is an independent risk factor for paroxysmal atrial fibrillation. West Indian Med J. 2011; 60(6): 647–652, indexed in Pubmed: 22512222.
6. Biton Y, Goldenberg I, Kutyifa V, et al. Relative wall thickness and the risk for ventricular tachyarrhythmias in patients with left ventricular dysfunction. J Am Coll Cardiol. 2016; 67(3): 303–312, doi: 10.1016/j.jacc.2015.10.076, indexed in Pubmed: 26796396.
7. Seko Y, Kato T, Haruna T, et al. Association between atrial fibrillation, atrial enlargement, and left ventricular geometric remodeling. Sci Rep. 2018; 8(1): 6366, doi: 10.1038/s41598-018-24875-1, indexed in Pubmed: 29686287.
8. Shah N, Badheka AO, Grover PM, et al. Influence of left ventricular remodeling on atrial fibrillation recurrence and cardiovascular hospitalizations in patients undergoing rhythm-control therapy. Int J Cardiol. 2014; 174(2): 288–292, doi: 10.1016/j.ijcard.2014.04.011, indexed in Pubmed: 24794553.
9. Li SN, Wang Lu, Dong JZ, et al. Electrocardiographic left ventricular hypertrophy predicts recurrence of atrial arrhythmias after catheter ablation of paroxysmal atrial fibrillation. Clin Cardiol. 2018; 41(6): 797–802, doi: 10.1002/clc.22957, indexed in Pubmed: 29604089.
10. Warmiński G, Urbanek P, Orczykowski M, et al. Association of left atrial enlargement and increased left ventricular wall thickness with arrhythmia recurrence after cryoballoon ablation for atrial fibrillation. Kardiol Pol. 2022; 80(11): 1104–1111, doi: 10.33963/KP.a2022.0191, indexed in Pubmed: 35950547.

Treatment of arrhythmia disorders in adults with congenital heart disease: A lesion-specific review

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ABSTRACT

There are now more adults living with a history of congenital heart disease than there are children. Modern electrophysiologists must familiarize themselves with the most common congenital lesions requiring electrophysiologic care as adults. Advancements in this field have been made most notably with high-resolution 3D imaging and electroanatomic mapping, left ventricular cannulation techniques, alternative pacing strategies, intracardiac echo, and transeptal access tools.

Key words: congenital heart disease, arrhythmia, ICD, ablation, pacemaker

INTRODUCTION

Adults living with a history of congenital heart disease (ACHD) comprise a growing proportion of patients seen in modern cardiac electrophysiology laboratories. This is largely due to improvements in surgical palliations during infancy, which have improved survival rates into adulthood to over 90% [1]. In Europe alone, there are estimated 1.8 million ACHD patients [2]. There are currently more adults living with congenital heart disease than there are children [3].

Rhythm disorders are common in ACHD and are accompanied by significant morbidity, mortality, and decreased quality of life. A detailed understanding of the diagnosis and management of arrhythmias in ACHD is paramount. The objective of this review is to provide an update on the electrophysiologic care of an adult with congenital heart disease according to the most encountered lesions. The review is divided into 3 sections: (1) implantable cardioverter-defibrillator (ICD) implantation and sudden death risk assessment; (2) pacing therapy, and (3) ablation of arrhythmias. Each section will include the specific and commonly encountered congenital lesion (Table 1).

ICD IMPLANTATION/SUDDEN DEATH RISK ASSESSMENT

Lesion: Tetralogy of Fallot

Sudden cardiac death (SCD) and ventricular arrhythmias are important long-term complications in tetralogy of Fallot (TOF) patients. The cumulative risk of sudden cardiac death is roughly 8% after 35 years after surgical repair,

Table 1. Relative importance of each EP therapeutic approach according to lesion type. The number of marks denote the relative prevalence/importance for each (blank = rare, X = infrequent, XXXX = very common)

	ICD /sudden death	Pacing	Ablation
Tetralogy of Fallot	XX		XXX
Atrial switch D-TGA	X	XXXX	XXX
Fontan	X	XX	XXXX
L-TGA	X	XXX	XX
Left-sided obstructive lesions	XXX		
Ebstein's		X	XXX
VSD or AVSD		X	XX

Abbreviations: AVSD, atrioventricular septal defect; D-TGA, D-transposition of the great arteries; L-TGA, levo-transposition of the great arteries; VSD, ventricular septal defect

with a latency period of around 10 to 20 years, suggestive of the role of scar and remodeling in the pathophysiology of ventricular tachycardia (VT) [4].

Pulmonary valve regurgitation is the most commonly associated hemodynamic lesion, and in a multicenter series was associated with all cases of sudden cardiac arrest (SCA) and 94% of cases of VT [4]. Prolonged QRS duration >150–180 ms is also a predictor of SCA [5]. Other risk factors include ventricular dysfunction (subaortic and subpulmonary), history of multiple cardiac surgeries, older age at repair, right ventricular hypertrophy and scarring, atrial tachyarrhythmias, and symptomatic nonsustained VT [6, 7].

In addition to risk factors based on history, programmed ventricular stimulation predicts VT and VF, with an adjusted relative risk of 4.7 [8]. In the most recent guidelines, electrophysiology studies (EPS) with ventricular stimulation are considered appropriate for symptomatic patients or those who have additional risk factors for VT mentioned earlier, such as LV dysfunction, QRS length >180 ms, extensive RV scarring, before or after pulmonary valve replacement, and in patients undergoing ablation for atrial tachyarrhythmias [2, 9]. Additionally, the conducting properties of anatomic isthmuses in monomorphic VT help estimate the risk of subsequent VT, discussed further in the ablation section. In our center, a diagnostic EPS is used for risk stratification on sudden death based on the point score outlined by Khairy et al. [9, 10].

Implantable cardioverter defibrillator (ICD) should be considered in patients in whom stable monomorphic VT can be induced and mapped on EPS, in those with documented sustained VT, and for secondary prevention due to aborted SCA. While efficacious against sudden cardiac death (SCD), ICD implantation is associated with a significant rate of complications, with 20.7% of patients having lead-related complications in a multicenter study [11]. Transvenous ICDs continue to be favored for this population due to the ability to pace terminate scar-based reentrant arrhythmias. However, the transvenous ICD has drawbacks, including the relatively young age of this patient group and concomitant tricuspid valve regurgitation which may be worsened by longstanding RV leads. One promising therapy for adults with TOF that requires ICD is the placement of a subcutaneous ICD that communicates with a transcatheter leadless pacemaker so that ATP can be delivered without the drawbacks of a traditional transvenous system. This technology is currently being evaluated as part of a clinical trial (Empower/Modular ATP, Boston Scientific Natick, MA). In many adults with TOF who have preexisting bioprosthetic or mechanical tricuspid valves, a "tricuspid-sparing" transvenous ICD system with pacing capability has been described [12] (Figure 1).

PULMONARY VALVE REPLACEMENT (PVR) AND TIMING OF EPS

Pulmonary regurgitation is strongly associated with SCA. However, PVR does not totally mitigate the risk of VT. In a retrospective study, VT incidence after PVR was estimated at 9.5% over 6.7 years [13]. Thus, strategies to further reduce VT risk after PVR were needed. A strategy of open and empirical intraoperative right ventricular outflow tract surgical cryoablation concomitant with PVR is effective [13].

However, a residual risk remains. In a report on 70 patients who underwent surgical cryoablation and postoperative EPS, 45% had residual inducible VT [14]. At our center, since management is guided by the results of

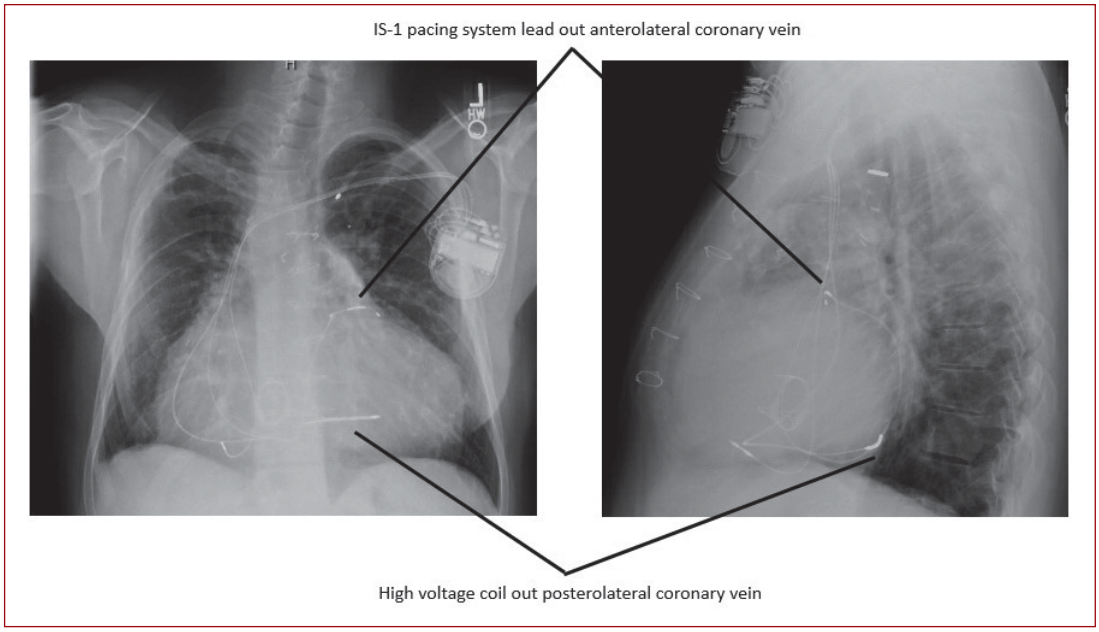

Figure 1. "Tricuspid sparing" transvenous implantable cardioverter-defibrillator (ICD) system implant for those in need of pacing, ICD, and mechanical or bioprosthetic tricuspid valves

postoperative EPS, we perform postoperative EPS only in this TOF patient subgroup.

Lesion: Atrial switch procedures for D-transposition of the great arteries (D-TGA)

SCD is responsible for around 13 to 45% of all-cause deaths in D-TGA and atrial switch [15]. In two comprehensive meta-analyses, the greatest predictor of SCD was a history of atrial tachyarrhythmias, increasing SCD 4 to 21-fold. Other risk factors included the Mustard procedure compared with Senning (OR, 2.9; 95% CI, 1.9–4.5), complex D-TGA compared with simple D-TGA (OR, 4.4; 95% CI, 2.2–8.8), and right ventricular (RV) dysfunction [15]. Interestingly, inducible VT does not appear to be predictive of SCD in D-TGA [16].

The risks associated with ICDs are significant in D-TGA. In our center, the rate of appropriate shocks was 11.5% over a median of 3 years. When compared to TOF patients, D-TGA patients had lower systemic ejection fraction (EF) but also had lower rates of appropriate ICD therapies. Therefore, ICD implantation based on left ventricular ejection fraction (LVEF) may not apply to this population compared to standard ischemic or nonischemic left ventricular heart failure patients [17]. Similar findings were seen in a multicenter cohort of atrial switch D-TGA patients after ICD implantation, with a rate of appropriate shocks in the primary prevention cohort of only 0.5% per year, and 6.6% for inappropriate shocks [16]. Thus, the risk-benefit ratio is slim in the primary prevention cohort, and somewhat stringent criteria are generally used for ICD implantation.

The 2020 European Society of Cardiology (ESC) guidelines for the management of ACHD give a class IIb recommendation for ICD implantation for patients with systemic RV dysfunction (systemic RVEF <35%) in the presence of additional risk factors including QRS >140 ms, severe AV valve regurgitation, nonsustained VT, and New York Heart Association (NYHA) symptom class II/III. Our approach is similar to the 2020 guidelines, but we also consider the history of atrial tachyarrhythmias.

Lesion: Fontan circulation

SCD is the second most common cause of death in Fontan patients, after advanced heart failure, but these sudden deaths may not solely be attributable to arrhythmia [18]. Tachyarrhythmia, thromboembolism, and protein-losing enteropathy are the strongest predictors of Fontan circulation failure and death [19].

In the 2018 European Heart Rhythm Association (EHRA) position paper, syncope in the setting of ventricular dysfunction, or LVEF <35% were factors to consider for ICD implantation [1]. Transvenous ICD placement is precluded in Fontan patients because the RV is inaccessible from the venous system. Subcutaneous ICD placement is effective for patients that do not require pacing. In a multicenter retrospective study, there was only one device-related complication, 21% of patients had inappropriate shocks, and 5% had appropriate shocks [20]. Given the high risk of positive pressure ventilation in this congenital lesion, subcutaneous ICD implants with moderate sedation only are favored over epicardial ICD lead placement in our center (Figure 2).

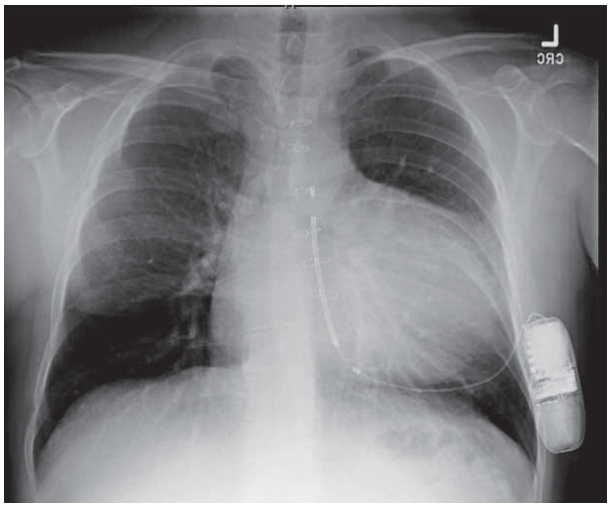

Figure 2. Subcutaneous ICD in a patient with single-ventricle physiology. Most patients with the Fontan circulation pass vector screening for this device.

Abbreviations: see Figure 1

Lesion: Levo-transposition of the great arteries (L-TGA)

The accumulated incidence of SCD in L-TGA is around 3% at age 40 [21]. Subaortic RV function is a potential predictor of SCD [22]. However, recent literature has been challenging this notion. In a retrospective cohort of over 3 500 patients, the rate of SCD was <1% per year, and none of the SCD patients had severely reduced RV function [23]. Nevertheless, MRI assessment of RV size and function (as opposed to echocardiographic) did strongly predict SCD [24].

The EHRA paper on arrhythmias in congenital heart disease uses low RVEF, complex ventricular arrhythmias, unexplained syncope, QRS duration >140 ms, or severe systemic AV valve regurgitation, as risk factors that warrant consideration for an ICD [1]. Generally, cardiac MRI should be performed for improved RV function quantitation. ICD implantation should be considered in patients with a history of syncope, nonsustained VT, or RV dysfunction in MRI.

Lesion: Left-sided obstructive lesions

LV obstructive lesions — especially aortic coarctation and Shone's complex — are associated with the highest risk of SCD due to VT and VF, and second in SCD after Eisenmenger's [25]. These patients are at risk of hemodynamic collapse due to low cardiac output during tachycardia caused by the fixed obstructive lesion and decreased preload during tachycardia, often in the setting of elevated left-sided and pulmonary pressures [26]. In the largest congenital heart disease database on arrhythmic SCD, LV

outflow obstructive lesions had the strongest association with arrhythmic SCD with an odds ratio of 10.7 [27]. While no specific guidance is given in the guidelines for this population, ICD should be strongly considered in patients with nonsustained VT, unexplained syncope, or LV dysfunction.

Lesion: Ebstein's anomaly

Ventricular arrhythmias, especially VT, can be common in Ebstein's. In a retrospective study with 79 patients with Ebstein's undergoing cardiac MRI, RV and LV dysfunction were predictors of SCD; after a median follow-up of 3 years, there were 5% of SCD and 3% of sustained VT [28]. VT usually arises from the congenitally abnormal muscle in the atrialized portion of the RV, can be focal or macroreentrant, and electrograms exhibit fractionated mid-diastolic waveforms [29]. VT ablation success rates appear to be around 90% [30].

Current guidelines give a class 1 indication for ICD implantation for patients with sustained VT/VF or SCA. No specific guidance is given for primary prevention [2]. An important consideration is the risk of worsening tricuspid regurgitation, even in patients with previous cone reconstruction. A tricuspid valve-sparing ICD implant technique has been described by our group as mentioned earlier [12].

PACING THERAPY

Lesion: Atrial switch procedures for D-TGA

D-TGA patients with a history of atrial switch surgery frequently have sinus node dysfunction, with a lifetime risk of at least 50% [31]. In the atrial switch anatomy, the systemic venous system ultimately drains to the left atrium. Thus, pacemaker leads are implanted in the subpulmonic left atrium and left ventricle via the baffles, however, certain precautions are necessary.

Active fixation leads to excitable left atrial tissue with aggressive challenging of the lead to ensure fixation is typical. The left atrial appendage is often unavoidable and is a stable site for atrial lead placement, but phrenic nerve capture, an issue uncommon in typical atrial lead implants, is a common obstacle and must be excluded. Steerable catheter delivery systems are sometimes useful. The sub-pulmonic LV lead goes through the mitral valve and tends to traject onto the left lateral wall. For small-French defibrillator leads, this has led to late perforation through the lateral wall [32]. It is therefore our practice to place these leads on the LV septum as guided by the standard left-anterior-oblique views which warrant artful stylet shaping (Figure 3).

ATRIAL PACING VS. DUAL-CHAMBER PACING

Subpulmonic LV pacing can impair systemic RV function, which is the most important cause of morbidity and mortality in atrial switch patients [33]. It is our practice to place single atrial lead systems in Mustard/Senning patients with isolated sinus node dysfunction. In patients with dual-chamber devices, DDD® with a long AV delay and low backup rate should be used. Nevertheless, due to long AV delays and increased total refractory period, the maximum tracking rate may be limited, which is an issue in a young population. Additionally, a single lead facilitates the extraction and baffle stenting strategy for baffle stenosis, avoiding a ventricular lead extraction and its potential complications.

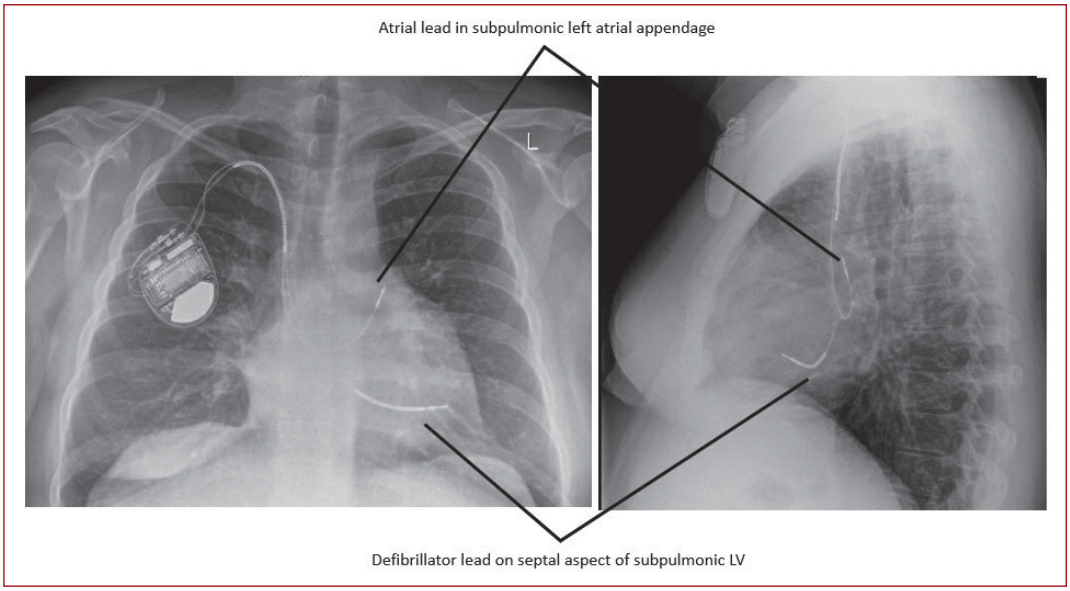

Figure 3. Dual chamber system in a patient with a Senning procedure for D-TGA. Non-standard stylet shaping is required to deliver the subpulmonic LV lead tip onto the septum and avoid the lateral free wall

Abbreviations: see Table 1

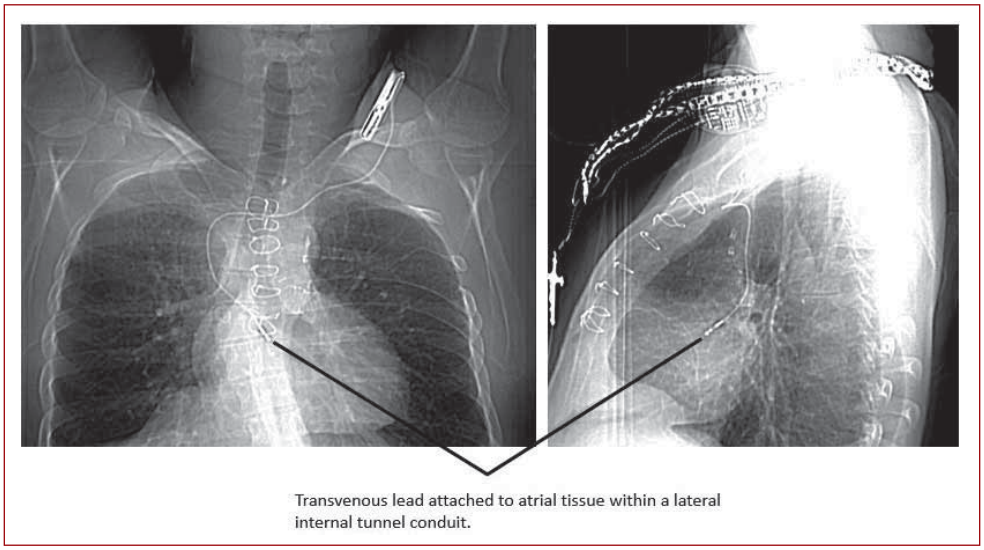

Figure 4. Atrial pacing system within a lateral tunnel Fontan. The lead is attached to a dual chamber impulse generator with a pin plug in the ventricular port. In this way, the device can be programmed DDD (dual chamber pacing) with minimal ventricular output, which allows automated antitachycardia pacing to be delivered regardless of intrinsic atrioventricular conduction

SPECIAL CONSIDERATIONS FOR PACING

Cardiac resynchronization therapy (CRT) is challenging in atrial switch D-TGA because of the inaccessibility of the coronary sinus ostium necessitating epicardial approaches. When needed, an anterior epicardial electrode placed on the subaortic RV requires relatively less dissection. This is then tunneled to the transvenous dual chamber system. Conduction system pacing is an interesting alternative, with only very limited evidence [34]. CRT in atrial switch D-TGA is an area of ongoing research and is still considered experimental in the 2020 EHRA guidelines [1].

THE NEED FOR SVC BAFFLE STENTING WITH PREEXISTING PACER (OUR EXTRACTION PROCESS)

Baffle obstruction and baffle leak affect up to 60% of atrial switch patients [35]. Percutaneous baffle stenting is a safe technique to treat these lesions. Concomitant device extraction, baffle stenting, and lead reimplantation (to avoid lead jailing) are commonly performed in our center and have also been described elsewhere as safe and effective [36]. This intervention typically occurs in a hybrid operating room with an on-call surgeon in case a sternotomy is required. Preprocedural imaging with a CT scan or MRI is performed to obtain the distance between the RV and chest wall, check the feasibility of venous access, assess atrial-baffle anatomy and lead position. Recently, transcatheter leadless pacing has been described in this patient population as well and could offer a leadless alternative [37].

Lesion: Fontan circulation

Half of adults with Fontan circulation will develop sinus node dysfunction, and even with modern surgical techniques (extracardiac conduit and lateral tunnel), the 10-year postoperative incidence was around 15% [38]. The purported causes are surgery near the cavoatrial junction in proximity to the sinus node, autonomic denervation, myocardial fibrosis, and injury to the sinus node artery. During junctional rhythm, there is systolic flow reversal from the left atrium to the Fontan chamber, and normal hemodynamics can be restored with atrial pacing and resumption of atrioventricular synchrony [39].

There are two options for implantation of pacemaker leads: surgical or transvenous. The right atrium is commonly fibrotic and thick, increasing the risk of transvenous lead failure. Nonetheless, due to the more invasive nature of epicardial systems, this is typically reserved for patients in need of ventricular pacing. In those cases, a surgical approach is preferred through a right thoracotomy. The transvenous approach is favored in adult patients with accessible atrial tissue (classic or lateral internal tunnel anatomy) (Figure 4).

Transvenous lead placement in extracardiac Fontan is more challenging because there is no direct communication between the venous system and the right atrium. A transpulmonary artery approach has been described with a puncture from the pulmonary artery to the pulmonary venous atrium, tunneling the lead to an infraclavicular pocket [40]. To avoid the potential thromboembolic complications of having a lead in the left atrium, a transvenous atrial epicardial approach can be performed. It involves accessing the venous system and advancing to the left pulmonary artery through the extracardiac Fontan. Then, the pulmonary artery is punctured inferiorly, and the lead tip is left in the intrapericardial space on the epicardial surface of the left atrium [41]. This technique is not routine and currently, most patients with an extracardiac Fontan circuit receive epicardial leads.

The role of antitachycardia pacing

Intra-atrial reentrant tachycardia (IART) is a major cause of morbidity and mortality in Fontan patients. In addition to catheter ablation, antitachycardia pacing (ATP) is a useful therapeutic tool. While ATP does not prevent the occurrence of SVT, it can terminate it, sparring the patient from the deleterious hemodynamic effect of prolonged SVT. In a large cohort, ATP was associated with lower risks of AT/AF events lasting ≥1 day (HR, 0.81), ≥7 days (HR, 0.64), and ≥30 days (HR, 0.56) [42]. In another study, ATP decreased the need for urgent direct current cardioversion and successfully converted 72% of IART episodes to normal sinus rhythm [43]. We recommend implanting ATP-capable devices even in patients receiving a single-lead pacemaker. This can be achieved by attaching a single atrial lead to a dual-chamber impulse generator. A pin plug is placed in the ventricular port. The device is then programmed DDD with minimal RV output (which is going to the pin plug).

Anticoagulation

Thromboembolism is common in Fontan patients, and many, if not most patients, end up requiring anticoagulation. The 2014 PACE/HRS consensus document gave non-vitamin K antagonist oral anticoagulants (NOAC) a class III recommendation to prevent thromboembolism, and vitamin K antagonists (VKAs) were preferred [44]. However, there is no evidence that VKAs are superior to NOACs, and newer evidence has emerged showing excellent safety and efficacy with NOACs in this population [45]. In a retrospective cohort study, the annual risk of bleeding was 3.1% per patient per year, with 0.7% per patient per year thromboembolic events [46]. In our center, because of better adherence, NOACs are sometimes used in this patient population.

LESION: L-TGA

Risk of complete heart block and device type

Patients with L-TGA are at risk of high-grade AV block, with an incidence of 2% per year and a lifetime risk of at least 50% [47]. This contrasts with patients with atrial switch D-TGA, in whom sinus node dysfunction predominates. The etiology of AV node dysfunction is related to abnormal atrioventricular communication and malalignment. The AV node is displaced posteriorly and is frequently hypoplastic. There is an additional anterior AV node that usually sits below the right atrial appendage. This AV node then connects to a long penetrating bundle of His which meets the ventricular myocardium in the subpulmonic area. This long area of tenuous His bundle tissue with surrounding fibrosis is at risk of degeneration and consequent AV block. Due to this abnormality, surgical correction with atrial and arterial switch ("double switch") does not appear to reduce the risk of AV block [48].

Univentricular pacing is a strong predictor of RV worsening function (HR, 4.7; 95% CI, 1.1–20.6), and that effect is mitigated by CRT [33]. Consequently, the EHRA working group suggests CRT can be useful for patients with a systemic RV with an EF ≤35%, NYHA functional class II, ambulatory IV, and wide QRS complex ≥150 ms with complete right bundle branch block QRS morphology (spontaneous or paced). No specific pacing burden recommendations are noted, but given that most patients receiving a pacemaker in this population have persistent high-grade AV block and thus a high pacing burden is expected (>20%), we routinely implant CRT devices as a first choice in this population, as recommended in the 2021 ESC guidelines on cardiac pacing [49].

CORONARY SINUS (CS) LEAD PLACEMENT

Lead positioning for CRT can be challenging in L-TGA, and the best location (for transvenous or epicardial leads) is not well established. The systemic venous system drains to the right atrium, which drains to the morphologic left ventricle. The CS drains to the right atrium and follows the RV but can have aberrant anatomy. Due to this difficulty in the CS lead placement, early experience relied heavily on epicardial lead placement [50].

In a more recent retrospective study, 95% of L-TGA patients undergoing CRT had a successful CS lead implantation, but all patients had advanced cardiac imaging with CT or MRI before the procedure and intraprocedural ventricular activation mapping before lead implantation. Of 21 patients, 14 had standard posteroseptal ostium cannulation, 2 via the vein of Marshall, and 2 via the superior ectopic ostium [51]. Thus, most patients with L-TGA can receive effective CRT, but significant preprocedural planning is required. Conduction system pacing should be considered for those who do not have an accessible CS (Figure 5).

LESION: EBSTEIN'S ANOMALY

RV resynchronization

Patients with Ebstein's anomaly are at increased risk of RV dysfunction and worsening of tricuspid regurgitation due to ventricular dyssynchrony with right bundle branch block (RBBB) (especially if QRS duration >150 ms). Accordingly, based on indirect data [52], current guidelines state "CRT may be considered for patients with a severe subpulmonary RV dysfunction and dilatation despite interventions to decrease RV volume overload, NYHA functional class II—ambulatory IV and wide QRS complex ≥150 ms due to a complete right bundle branch block" [1].

RV-CRT is performed by atrial-synchronized RV free wall pacing. The pacing location must be chosen by mapping late RV activation similar to standard CRT. RV function, contraction efficiency, and volumes show substantial acute short-term improvement with strategy [53].

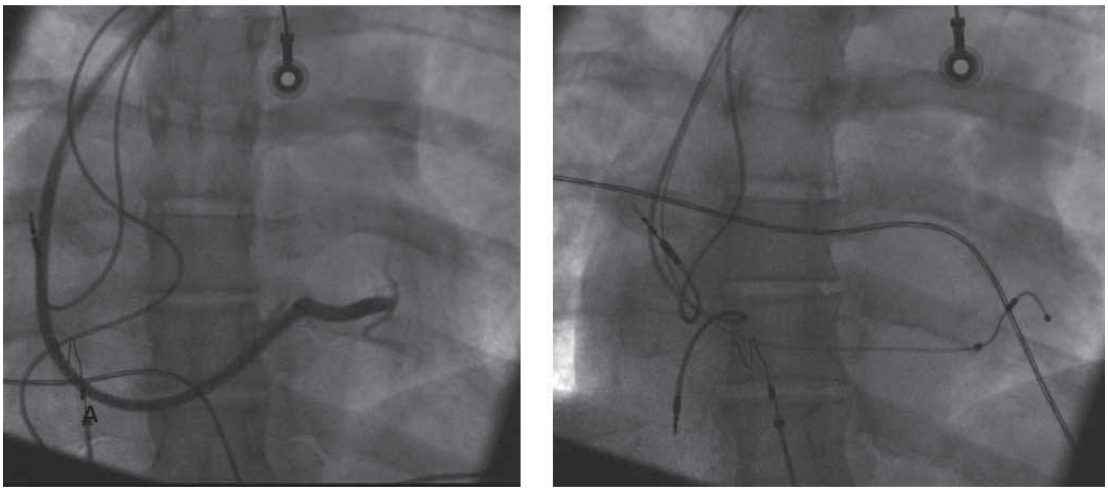

Figure 5. Anteroposterior venogram (left) of the coronary venous system in a patient with L- TGA and mesocardia. While the coronary sinus system usually follows the atrial situs, which in this lesion would be normally oriented, atretic venous systems or unusual origins of the CS ostium are not uncommon in L-TGA. Final CRT-P lead position (right)

Abbreviations: see Table 1

LOCATION OF CS OSTIUM AFTER TVR

The CS may be aberrant after tricuspid reconstruction. During cone surgery, surgeons sometimes perform an inferior annuloplasty band, anchored with a suture in the CS [54]. In other situations, such as tricuspid valve replacement, the CS ostium may end up inferior to the prosthetic valve [55]. Thus, some patients require an epicardial LV lead [56].

LESION: ASD, AVSD REPAIRS

Patients with repaired atrial septal defect (ASD) and atrioventricular septal defect (AVSD) are at increased risk of sinus node dysfunction and heart block, and pacemaker implantation is thus common [57, 58]. CS anatomy is abnormal, and it is frequently absent or with atretic ostia [59].

Thus, CRT, when necessary, is sometimes performed with an epicardial LV lead. Inadvertent placement of leads in the left heart can occur due to gaps in patch material, and care must be taken during device implantation [60].

ABLATION OF ARRHYTHMIAS

Lesion: Tetralogy of Fallot and RV outflow obstructive lesions

VT in TOF is usually macroreentrant and located in the subendocardium of the right ventricular outflow tract obstruction (RVOT). VT induction with entrainment can be poorly tolerated, and substrate mapping techniques in sinus rhythm are preferred in TOF. In 2007, Zeppenfeld described 4 anatomic RV isthmuses in TOF around the area of surgical repair [61]. They were located between the tricuspid annulus and anterior RVOT repair, the pulmonary annulus and RVOT free wall, the pulmonary annulus and septal patch, and the septum repair and tricuspid annulus. In a 2017 follow-up report, 74 patients underwent substrate mapping regardless of their history of VT. Anatomical isthmuses in patients with VT were longer and had slower conduction [61].

Technical aspects of VT ablation

VT ablation can be performed in sinus rhythm using standard 3D mapping, similar to ischemic VT. The anatomic isthmuses above are sought. Steerable sheaths, intracardiac echocardiography, and sheath-in-sheath techniques are often required to navigate the right ventricle.

Lesion: Atrial switch procedures for D-TGA

Atrial arrhythmias are common in atrial switch D-TGA patients. They are also a prominent cause of hospitalization, corresponding to roughly a third of cardiovascular hospitalizations in atrial switch D-TGA [62]. Atrial tachyarrhythmias with rates of 150 to 250 bpm can lead to rapid ventricular node conduction (due to 1:1 AV node conduction) and SCD.

IART is the most common (61.6%), followed by atrial fibrillation (AF) (28.8%), and focal atrial tachycardia (9.5%) [63]. AF is associated with older age and is the most common atrial arrhythmia in ACHD patients over 50 [63]. Many patients present initially with IART and develop AF over time. IART occurs due to macroscopic circuits which have been delineated by electroanatomic mapping and are usually cavotricuspid isthmus (CTI) dependent circuit [64]. In our center, the most frequent arrhythmia is subaortic tricuspid isthmus flutter. The reentrant circuits stem from atrial fibrosis histologically, which was correlated to prolonged right atrial volume overload [65] (9.5%) [63].

Catheter ablation

In atrial switch patients, the CTI sits on both sides of the baffle. Thus, CTI ablation requires biatrial access, crossing the surgical suture line. In our center, the most common approach to access the pulmonary venous atrium for a CTI

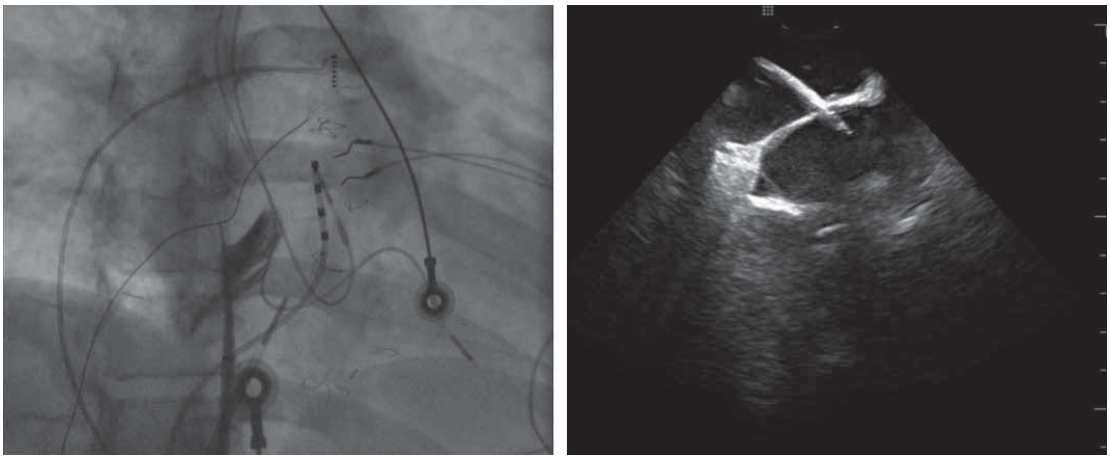

Figure 6. Trans-baffle puncture using fluoroscopy, a mechanical needle, and contrast in D-TGA atrial switch (left), and intracardiac echocardiography with an energized needle in lateral tunnel Fontan (right). Despite theoretical shortcomings of an energized needle in non-biologic conduit material, we have found success with this tool in most trans-baffle punctures

Abbreviations: see Table 1

ablation is the transbaffle puncture. Standard approaches, such as retrograde aortic, offer limited efficacy of around 70% and cause poor stability of the ablation catheter and valvular injury [66, 67].

After transbaffle puncture, when electroanatomic activation and entrainment mapping confirm IART, this can be followed by radiofrequency by the CTI and the pulmonary venous atrium (PVA) posterolateral scar [68]. The use of radiofrequency needles and/or wires has greatly assisted this technique (Figure 6). Predictors of recurrences are non-CTI locations, long PR intervals, and previous or induced AF [69]. The most best long-term predictor of freedom from recurrence is acute procedural success [70].

Lesion: Fontan circulation

IART is the most common arrhythmia in Fontan patients, and atriopulmonary connection is a risk factor compared to modern techniques such as the lateral tunnel or extracardiac Fontan's. Fontan conversion by converting those with an atriopulmonary to an extracardiac Fontan circuit, with an intraoperative maze procedure, had a freedom from recurrence of 51% [71]. Thus, in patients with atriopulmonary connections, this may be the initial management strategy.

Approach to access for IART ablation according to Fontan type (extracardiac, internal tunnel, atriopulmonary)

Access to the pulmonary venous atrium for catheter ablation in atriopulmonary Fontan is more straightforward due to access from the venous system. IART is the most common mechanism, and most patients have multiple circuits. In a retrospective study, the most common locations of critical isthmuses were lateral, inferolateral, posterolateral, or septal systemic venous atrium, and only 10% in the pulmonary venous atrium [72].

The modern total extracardiac conduit decreases the incidence of IART because it avoids pressure and volume overload to the pulmonary venous atrium. However, catheter ablation in extracardiac Fontan patients is challenging due to no readily available connection between the venous system and the right atrium. Access is achieved by identifying a large (>14 mm) cavoatrial overlap region through advanced cardiac imaging. In most patients, a cavoatrial overlap can be identified. In a retrospective study of 17 patients, 14 had an identifiable overlap [73].

The lateral tunnel Fontan is an intermediate between total extracardiac Fontan and atriopulmonary connection in terms of ease of access. A transbaffle approach is common or through a pre-existing fenestration [74]. In our cohort, the internal tunnel anatomy is the most common Fontan circulation with recurrent atrial flutters. A large amount of suture line along each side of the baffle may account for the numerous and difficult circuits these patients may encounter in adulthood.

LESION: L-TGA

Monckeberg sling and very difficult AVNRTs

The AV conduction system in L-TGA is aberrant. The "regular" AV node is frequently hypoplastic, and the anterior AV node is in the area of fibrous continuity between pulmonary and mitral valves [75]. Communication of the anterior and posterior AV nodes causes dual-node AVNRT. This was initially described by Monckeberg in 1913 in a patient with double-outlet RV, and by Uher in L-TGA, with a "sling" between the AV nodes. Both AV nodes can have one or more atrionodal connections in addition to the Monckeberg sling. Thus, reentry can occur by one of many permutations of retrograde and antegrade connections between the AV nodes and the atria, or antegrade and retrograde down each AV node's His bundle causing a reciprocating tachycardia.

For ablation, the slow pathway is targeted. If one confirms a reciprocating tachycardia involving both AV nodes

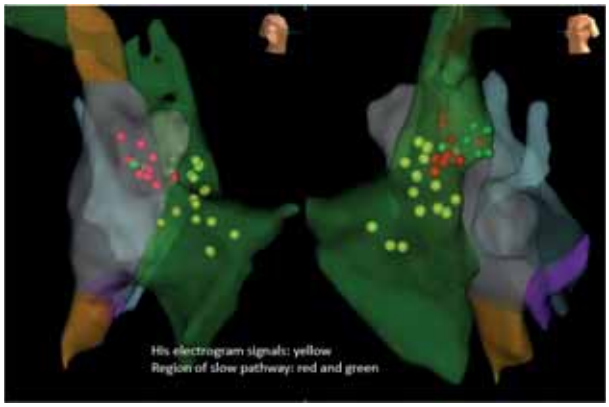

Figure 7. Ablation of atrioventricular nodal reciprocating tachycardia (AVNRT) in L-TGA. The reentrant course in this congenital lesion can be very challenging, requiring left-sided and pulmonary arterial mapping. Regions of the slow pathway can be anterior and require creative approaches to ablation

Abbreviations: see Table 1

and His bundles, one of the 2 AV nodes would require ablation if the remaining node offered appropriate AV conduction. If other SVT mechanisms are excluded, and the point of earliest activation is on the septum behind the Tendon of Todaro, then, anatomically guided slow pathway ablation can be performed empirically [75]. In cases in which the anterior AV node is the culprit, ablation of the slow pathway of the anterior AV node can be performed through the pulmonic valve sinus [76].

In summary, AVNRT ablation in L-TGA can be extremely complex and carries a higher risk of iatrogenic AV block due to the anatomic changes intrinsic to L-TGA but can be performed safely in experienced centers (Figure 7).

Transseptal puncture and its unusual orientation

Contrast-enhanced computed tomography and 3-dimensional reconstruction of the atria are helpful for an atrial septal puncture in L-TGA [77]. Intracardiac echocardiography is extremely important for this procedure. The best area for a transseptal puncture, also described in percutaneous valve edge-to-edge repair of the tricuspid valve in L-TGA, is level with the midline of the tricuspid valve on fluoroscopy in the 20° right anterior oblique projection and at the inferior edge of the fossa ovalis on transesophageal echocardiography [78].

Lesion: Ebstein's anomaly and other TV lesions

Up to 30% of Ebstein's patients have accessory pathways (APs). They are usually located in the posterior and septal borders of the tricuspid valve where the valve leaflets are most abnormal [79, 80]. The absence of a RBBB in Ebstein's is usually proof of the presence of a right-sided accessory pathway [81]. In a retrospective cohort of Ebstein's anomaly patients undergoing EPS, there were 30 APs in 21 patients. Of the 30 APs, 26 were atrioventricular and 4 were "Mahaim" fibers. APs due to Mahaim fibers are characterized by decremental conduction, the absence of delta waves on the surface electrocardiography (ECG,) and no retrograde conduction.

The residual atrioventricular ridge between the true right atrium and the "atrialized" right ventricle is where most APs are located [82, 83]. The atrioventricular ridge complicates catheter ablation because it limits catheter tip steering. Recurrence rates continue to be high (20% to 40%) at experienced centers [84]. Ablation failures are likely related to fractionated low-amplitude ventricular electrograms recorded from atrialized RV, multiple accessory pathways, difficulty identifying the true AV groove, and inability to retroflex the catheter tip under TV leaflets to improve stability [29].

Intracardiac echocardiography or a right atrial angiography can be used to locate the "true" AV ridge. Long sheaths should be used in patients with enlarged RA and RV cavities [29]. The next step is pacing along the lateral RA wall until fiber conduction is located and a characteristic high-frequency waveform is noted [29]. Published success rates are between 80 and 100% [84]. Finally, an EPS for the localization and ablation of APs is recommended empirically for patients who will undergo cone reconstruction surgery due to the high prevalence of APs and the technical difficulty in ablation afterward [85].

LESION: ASD, AVSD REPAIRS

The long-term risk of atrial arrhythmias is estimated to be around 25% in AVSD patients [58]. Most patients younger than 40 have IART, which is surpassed by AF at the age of 45 years. ASD is more common than AVSD. The left-to-right-shunt causes RA enlargement, and the duration of RA overload correlates better with atrial arrhythmias than age. Atrial arrhythmias usually occur due to macroreentry on surgical repair sites, and possibly due to heterogeneity of atrial conduction abnormalities in the RA and Bachman's bundle [86].

After repair, most patients with ASD will be considered to have mild ACHD. Younger adults, especially adults with mild ACHD have a higher burden of classical atherosclerotic risk factors such as obesity, hypertension, and dyslipidemia. Thus, strategies to prevent sudden death in this population include statins, smoking cessation, weight loss, and anti-hypertensive therapies, similar to the general population.

Transseptal puncture through surgical material

Ablation of left atrial arrhythmias including AF can be challenging in ASD and ventricular septal defect (VSD) patients because often the ASD patch repair must be punctured at the level of the original fossa ovalis. Transseptal access in these cases almost always involves radiofrequency [87]. Intracardiac or transesophageal ultrasound is essential.

SUMMARY

Modern electrophysiologists must familiarize themselves with the most common congenital lesions requiring electrophysiologic care in adults. The main challenges among this group remain to be the prevention of SCD, effective pacing, given access and anatomical difficulties, and ablation of arrhythmias in the context of abnormal anatomy and a large amount of arrhythmogenic substrate.

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REFERENCES

1. Hernández-Madrid A, Paul T, Abrams D, et al. Arrhythmias in congenital heart disease: a position paper of the European Heart Rhythm Association (EHRA), Association for European Paediatric and Congenital Cardiology (AEPC), and the European Society of Cardiology (ESC) Working Group on Grown-up Congenital heart disease, endorsed by HRS, PACES, APHRS, and SOLAECE. Europace. 2018; 20(11): 1719–1753, doi: 10.1093/europace/eux380, indexed in Pubmed: 29579186.
2. Khairy P, Hare GV, Balaji S, et al. PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart Disease. Heart Rhythm. 2014; 11(10): e102–e165, doi: 10.1016/j.hrthm.2014.05.009.
3. Gilboa SM, Devine OJ, Kucik JE, et al. Congenital Heart Defects in the United States: Estimating the Magnitude of the Affected Population in 2010. Circulation. 2016; 134(2): 101–109, doi: 10.1161/CIRCULATIONAHA.115.019307, indexed in Pubmed: 27382105.
4. Gatzoulis MA, Balaji S, Webber SA, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. Lancet. 2000; 356(9234): 975–981, doi: 10.1016/S0140-6736(00)02714-8, indexed in Pubmed: 11041398.
5. Berul CI, Hill SL, Geggel RL, et al. Electrocardiographic markers of late sudden death risk in postoperative tetralogy of Fallot children. J Cardiovasc Electrophysiol. 1997; 8(12): 1349–1356, doi: 10.1111/j.1540-8167.1997.tb01031.x, indexed in Pubmed: 9436772.
6. Aboulhosn JA, Lluri G, Gurvitz MZ, et al. Arrhythmia burden in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. Circulation. 2010; 122(9): 868–875, doi: 10.1161/CIRCULATIONAHA.109.928481, indexed in Pubmed: 20713900.
7. Koyak Z, de Groot JR, Bouma BJ, et al. Symptomatic but not asymptomatic non-sustained ventricular tachycardia is associated with appropriate implantable cardioverter therapy in tetralogy of Fallot. Int J Cardiol. 2013; 167(4): 1532–1535, doi: 10.1016/j.ijcard.2012.04.103, indexed in Pubmed: 22608897.
8. Khairy P, Landzberg MJ, Gatzoulis MA, et al. Value of programmed ventricular stimulation after tetralogy of fallot repair: a multicenter study. Circulation. 2004; 109(16): 1994–2000, doi: 10.1161/01.CIR.0000126495.11040.BD, indexed in Pubmed: 15051640.
9. Cohen MI, Khairy P, Zeppenfeld K, et al. Preventing Arrhythmic Death in Patients With Tetralogy of Fallot: JACC Review Topic of the Week. J Am Coll Cardiol. 2021; 77(6): 761–771, doi: 10.1016/j.jacc.2020.12.021, indexed in Pubmed: 33573746.
10. Probst J, Diller GP, Reinecke H, et al. Prevention of sudden cardiac death in patients with Tetralogy of Fallot: Risk assessment and long term outcome. Int J Cardiol. 2018; 269: 91–96, doi: 10.1016/j.ijcard.2018.06.107, indexed in Pubmed: 29980366.
11. Khairy P, Harris L, Landzberg MJ, et al. Implantable cardioverter-defibrillators in tetralogy of Fallot. Circulation. 2008; 117(3): 363–370, doi: 10.1161/CIRCULATIONAHA.107.726372, indexed in Pubmed: 18172030.
12. Blank E, Shah AD, Rosenblum JM, et al. "Valve-sparing" transvenous defibrillator systems after tricuspid valve intervention. Heart Rhythm. 2021; 18(12): 2212–2214, doi: 10.1016/j.hrthm.2021.09.024, indexed in Pubmed: 34583059.
13. Sabate Rotes A, Connolly HM, Warnes CA, et al. Ventricular arrhythmia risk stratification in patients with tetralogy of Fallot at the time of pulmonary valve replacement. Circ Arrhythm Electrophysiol. 2015; 8(1): 110–116, doi: 10.1161/CIRCEP.114.001975, indexed in Pubmed: 25416756.
14. Sandhu A, Ruckdeschel E, Sauer WH, et al. Perioperative electrophysiology study in patients with tetralogy of Fallot undergoing pulmonary valve replacement will identify those at high risk of subsequent ventricular tachycardia. Heart Rhythm. 2018; 15(5): 679–685, doi: 10.1016/j.hrthm.2018.01.020, indexed in Pubmed: 29330130.
15. Venkatesh P, Evans AT, Maw AM, et al. Predictors of Late Mortality in D-Transposition of the Great Arteries After Atrial Switch Repair: Systematic Review and Meta-Analysis. J Am Heart Assoc. 2019; 8(21): e012932, doi: 10.1161/JAHA.119.012932, indexed in Pubmed: 31642369.
16. Khairy P, Harris L, Landzberg MJ, et al. Sudden death and defibrillators in transposition of the great arteries with intra-atrial baffles: a multicenter study. Circ Arrhythm Electrophysiol. 2008; 1(4): 250–257, doi: 10.1161/CIRCEP.108.776120, indexed in Pubmed: 19808416.
17. Kella DK, Merchant FM, Veledar E, et al. Lesion-specific differences for implantable cardioverter defibrillator therapies in adults with congenital heart disease. Pacing Clin Electrophysiol. 2014; 37(11): 1492–1498, doi: 10.1111/pace.12434, indexed in Pubmed: 24889130.
18. Alsaied T, Bokma JP, Engel ME, et al. Predicting long-term mortality after Fontan procedures: A risk score based on 6707 patients from 28 studies. Congenit Heart Dis. 2017; 12(4): 393–398, doi: 10.1111/chd.12468, indexed in Pubmed: 28480627.
19. Allen KY, Downing TE, Glatz AC, et al. Effect of Fontan-Associated Morbidities on Survival With Intact Fontan Circulation. Am J Cardiol. 2017; 119(11): 1866–1871, doi: 10.1016/j.amjcard.2017.03.004, indexed in Pubmed: 28385177.
20. Moore JP, Mondésert B, Lloyd MS, et al. Clinical Experience With the Subcutaneous Implantable Cardioverter-Defibrillator in Adults With Congenital Heart Disease. Circ Arrhythm Electrophysiol. 2016; 9(9): e004338, doi: 10.1161/CIRCEP.116.004338, indexed in Pubmed: 27635073.
21. Dobson R, Danton M, Nicola W, et al. The natural and unnatural history of the systemic right ventricle in adult survivors. J Thorac Cardiovasc Surg. 2013; 145(6): 1493–501; discussion 1501, doi: 10.1016/j.jtcvs.2013.02.030, indexed in Pubmed: 23490252.
22. Verheugt CL, Uiterwaal CS, van der Velde ET, et al. Mortality in adult congenital heart disease. Eur Heart J. 2010; 31(10): 1220–1229, doi: 10.1093/eurheartj/ehq032, indexed in Pubmed: 20207625.
23. McCombe A, Touma F, Jackson D, et al. Sudden cardiac death in adults with congenitally corrected transposition of the great arteries. Open Heart. 2016; 3(2): e000407, doi: 10.1136/openhrt-2016-000407, indexed in Pubmed: 27493760.
24. Lewis MJ, Van Dissel A, Kochav J, et al. Cardiac MRI predictors of adverse outcomes in adults with a systemic right ventricle. ESC Heart Fail. 2022; 9(2): 834–841, doi: 10.1002/ehf2.13745, indexed in Pubmed: 35048545.
25. Vehmeijer JT, Koyak Z, Leerink JM, et al. Identification of patients at risk of sudden cardiac death in congenital heart disease: The PRospEctiVE study on implaNTable cardIOverter defibrillator therapy and suddeN cardiac death in Adults with Congenital Heart Disease (PREVENTION-ACHD). Heart Rhythm. 2021; 18(5): 785–792, doi: 10.1016/j.hrthm.2021.01.009, indexed in Pubmed: 33465514.
26. Jain CC, Warnes CA, Egbe AC, et al. Hemodynamics in Adults With the Shone Complex. Am J Cardiol. 2020; 130: 137–142, doi: 10.1016/j.amjcard.2020.06.024, indexed in Pubmed: 32703525.
27. Koyak Z, Harris L, de Groot JR, et al. Sudden cardiac death in adult congenital heart disease. Circulation. 2012; 126(16): 1944–1954, doi: 10.1161/CIRCULATIONAHA.112.104786, indexed in Pubmed: 22991410.
28. Rydman R, Shiina Y, Diller GP, et al. Major adverse events and atrial tachycardia in Ebstein's anomaly predicted by cardiovascular magnetic

resonance. Heart. 2018; 104(1): 37–44, doi: 10.1136/heartjnl-2017-311274, indexed in Pubmed: 28684436.
29. Walsh EP. Ebstein's Anomaly of the Tricuspid Valve: A Natural Laboratory for Re-Entrant Tachycardias. JACC Clin Electrophysiol. 2018; 4(10): 1271–1288, doi: 10.1016/j.jacep.2018.05.024, indexed in Pubmed: 30336873.
30. Moore JP, Shannon KM, Gallotti RG, et al. Catheter Ablation of Ventricular Arrhythmia for Ebstein's Anomaly in Unoperated and Post-Surgical Patients. JACC Clin Electrophysiol. 2018; 4(10): 1300–1307, doi: 10.1016/j.jacep.2018.05.009, indexed in Pubmed: 30336876.
31. Hayes CJ, Gersony WM. Arrhythmias after the Mustard operation for transposition of the great arteries: a long-term study. J Am Coll Cardiol. 1986; 7(1): 133–137, doi: 10.1016/s0735-1097(86)80270-4, indexed in Pubmed: 3941200.
32. Danik SB, Mansour M, Heist EK, et al. Timing of delayed perforation with the St. Jude Riata lead: a single-center experience and a review of the literature. Heart Rhythm. 2008; 5(12): 1667–1672, doi: 10.1016/j.hrthm.2008.09.017, indexed in Pubmed: 19084802.
33. Yeo WT, Jarman JWE, Li W, et al. Adverse impact of chronic subpulmonary left ventricular pacing on systemic right ventricular function in patients with congenitally corrected transposition of the great arteries. Int J Cardiol. 2014; 171(2): 184–191, doi: 10.1016/j.ijcard.2013.11.128, indexed in Pubmed: 24374205.
34. O'Connor M, Ho SY, McCarthy KP, et al. Left bundle pacing in transposition of the great arteries with previous atrial redirection operation. HeartRhythm Case Rep. 2022; 8(3): 176–179, doi: 10.1016/j.hrcr.2021.12.001, indexed in Pubmed: 35492840.
35. De Pasquale G, Bonassin Tempesta F, Lopes BS, et al. High prevalence of baffle leaks in adults after atrial switch operations for transposition of the great arteries. Eur Heart J Cardiovasc Imaging. 2017; 18(5): 531–535, doi: 10.1093/ehjci/jew276, indexed in Pubmed: 28064156.
36. Laredo M, Waldmann V, Chaix MA, et al. Lead Extraction With Baffle Stenting in Adults With Transposition of the Great Arteries. JACC Clin Electrophysiol. 2019; 5(6): 671–680, doi: 10.1016/j.jacep.2019.01.023, indexed in Pubmed: 31221353.
37. Kotschet E, Alasti M, Alison J. Micra implantation in a patient with transposition of great arteries. Pacing Clin Electrophysiol. 2019; 42(2): 117–119, doi: 10.1111/pace.13520, indexed in Pubmed: 30288752.
38. Ben Ali W, Bouhout I, Khairy P, et al. Extracardiac Versus Lateral Tunnel Fontan: A Meta-Analysis of Long-Term Results. Ann Thorac Surg. 2019; 107(3): 837–843, doi: 10.1016/j.athoracsur.2018.08.041, indexed in Pubmed: 30315799.
39. Hasselman T, Schneider D, Madan N, et al. Reversal of fenestration flow during ventricular systole in Fontan patients in junctional or ventricular paced rhythm. Pediatr Cardiol. 2005; 26(5): 638–641, doi: 10.1007/s00246-005-0879-6, indexed in Pubmed: 16132285.
40. Moore JP, Shannon KM. Transpulmonary atrial pacing: an approach to transvenous pacemaker implantation after extracardiac conduit Fontan surgery. J Cardiovasc Electrophysiol. 2014; 25(9): 1028–1031, doi: 10.1111/jce.12447, indexed in Pubmed: 24786766.
41. Hoyt WJ, Moore JP, Shannon KM, et al. Epicardial atrial pacing after the extracardiac Fontan operation: Feasibility of an entirely transvenous approach. J Cardiovasc Electrophysiol. 2022; 33(1): 128–133, doi: 10.1111/jce.15285, indexed in Pubmed: 34716972.
42. Crossley GH, Padeletti L, Zweibel S, et al. Reactive atrial-based antitachycardia pacing therapy reduces atrial tachyarrhythmias. Pacing Clin Electrophysiol. 2019; 42(7): 970–979, doi: 10.1111/pace.13696, indexed in Pubmed: 30977146.
43. Kramer CC, Maldonado JR, Olson MD, et al. Safety and efficacy of atrial antitachycardia pacing in congenital heart disease. Heart Rhythm. 2018; 15(4): 543–547, doi: 10.1016/j.hrthm.2017.12.016, indexed in Pubmed: 29246827.
44. Khairy P, Van Ha, Balaji S, et al. PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart Disease: Developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology (ACC), the American Heart Association (AHA), the European Association (EHRA), the Canadian Society (CHRS), and the International Society for Adult Congenital Heart Disease (ISACHD). Heart Rhythm. 2014; 11(10): e102–e65.
45. Kazerouninia A, Georgekutty J, Kendsersky P, et al. A Multisite Retrospective Review of Direct Oral Anticoagulants Compared to Warfarin in Adult Fontan Patients. Cardiovasc Drugs Ther. 2022 [Epub ahead of print], doi: 10.1007/s10557-021-07298-5, indexed in Pubmed: 35022950.
46. Pujol C, Müssigmann M, Schiele S, et al. Direct oral anticoagulants in adults with congenital heart disease - a single centre study. Int J Cardiol. 2020; 300: 127–131, doi: 10.1016/j.ijcard.2019.09.077, indexed in Pubmed: 31668654.
47. Oliver JM, Gallego P, Gonzalez AE, et al. Comparison of outcomes in adults with congenitally corrected transposition with situs inversus versus situs solitus. Am J Cardiol. 2012; 110(11): 1687–1691, doi: 10.1016/j.amjcard.2012.07.039, indexed in Pubmed: 22935525.
48. Brizard CP, Lee A, Zannino D, et al. Long-term results of anatomic correction for congenitally corrected transposition of the great arteries: A 19-year experience. J Thorac Cardiovasc Surg. 2017; 154(1): 256–265.e4, doi: 10.1016/j.jtcvs.2017.03.072, indexed in Pubmed: 28476422.
49. Glikson M, Nielsen JC, Kronborg MB, et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: Developed by the Task Force on cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology (ESC) With the special contribution of the European Heart Rhythm Association (EHRA). Eur Heart J. 2021; 42(35): 3427–520, doi: 10.1093/eurheartj/ehab364, indexed in Pubmed: 34455430.
50. Janousek J, Tomek V, Chaloupecký VA, et al. Cardiac resynchronization therapy: a novel adjunct to the treatment and prevention of systemic right ventricular failure. J Am Coll Cardiol. 2004; 44(9): 1927–1931, doi: 10.1016/j.jacc.2004.08.044, indexed in Pubmed: 15519030.
51. Moore JP, Cho D, Lin JP, et al. Implantation techniques and outcomes after cardiac resynchronization therapy for congenitally corrected transposition of the great arteries. Heart Rhythm. 2018; 15(12): 1808–1815, doi: 10.1016/j.hrthm.2018.08.017, indexed in Pubmed: 30125719.
52. Sakaguchi H, Miyazaki A, Yamada O, et al. Cardiac resynchronization therapy for various systemic ventricular morphologies in patients with congenital heart disease. Circ J. 2015; 79(3): 649–655, doi: 10.1253/circj.CJ-14-0395, indexed in Pubmed: 25746550.
53. Janoušek J, Kovanda J, Ložek M, et al. Cardiac Resynchronization Therapy for Treatment of Chronic Subpulmonary Right Ventricular Dysfunction in Congenital Heart Disease. Circ Arrhythm Electrophysiol. 2019; 12(5): e007157, doi: 10.1161/CIRCEP.119.007157, indexed in Pubmed: 30991822.
54. Dearani JA. Ebstein repair: How I do it. JTCVS Tech. 2020; 3: 269–276, doi: 10.1016/j.xjtc.2020.05.033, indexed in Pubmed: 34317896.
55. Hwang J, Han S, Park HS, et al. Implantation of a leadless pacemaker in a patient with mechanical tricuspid valve. HeartRhythm Case Rep. 2022; 8(4): 284–287, doi: 10.1016/j.hrcr.2022.01.010, indexed in Pubmed: 35497483.
56. Mah DY, O'Leary ET, Harrild DM, et al. Resynchronizing Right and Left Ventricles With Right Bundle Branch Block in the Congenital Heart Disease Population. JACC Clin Electrophysiol. 2020; 6(14): 1762–1772, doi: 10.1016/j.jacep.2020.06.006, indexed in Pubmed: 33357572.
57. Albæk DHR, Udholm S, Ovesen ASL, et al. Pacemaker and conduction disturbances in patients with atrial septal defect. Cardiol Young. 2020; 30(7): 980–985, doi: 10.1017/S1047951120001365, indexed in Pubmed: 32498739.
58. Jacquemart E, Bessière F, Combes N, et al. Incidence, risk factors, and outcomes of atrial arrhythmias in adult patients with atrioventricular septal defect. JACC Clin Electrophysiol. 2022; 8(3): 331–340, doi: 10.1016/j.jacep.2021.09.004, indexed in Pubmed: 35331427.
59. Shum JSF, Kim SM, Choe YH. Multidetector CT and MRI of ostial atresia of the coronary sinus, associated collateral venous pathways and cardiac anomalies. Clin Radiol. 2012; 67(12): e47–e52, doi: 10.1016/j.crad.2012.07.013, indexed in Pubmed: 22974567.
60. Teshome M, Ifedili I, Nayyar M, et al. Diagnosis and management of inadvertently placed pacemaker lead in the left ventricle following sinus venosus atrial septal defect repair surgery. HeartRhythm Case Rep. 2020; 6(5): 279–282, doi: 10.1016/j.hrcr.2020.01.010, indexed in Pubmed: 32461895.
61. Zeppenfeld K, Schalij MJ, Bartelings MM, et al. Catheter ablation of ventricular tachycardia after repair of congenital heart disease: electroanatomic identification of the critical right ventricular isthmus. Circulation. 2007; 116(20): 2241–2252, doi: 10.1161/CIRCULATIONAHA.107.723551, indexed in Pubmed: 17967973.

62. Verheugt CL, Uiterwaal CS, van der Velde ET, et al. The emerging burden of hospital admissions of adults with congenital heart disease. Heart. 2010; 96(11): 872–878, doi: 10.1136/hrt.2009.185595, indexed in Pubmed: 20406765.
63. Labombarda F, Hamilton R, Shohoudi A, et al. AARCC. Increasing Prevalence of Atrial Fibrillation and Permanent Atrial Arrhythmias in Congenital Heart Disease. J Am Coll Cardiol. 2017; 70(7): 857–865, doi: 10.1016/j.jacc.2017.06.034, indexed in Pubmed: 28797355.
64. Lukac P, Pedersen AK, Mortensen PT, et al. Ablation of atrial tachycardia after surgery for congenital and acquired heart disease using an electroanatomic mapping system: Which circuits to expect in which substrate? Heart Rhythm. 2005; 2(1): 64–72, doi: 10.1016/j.hrthm.2004.10.034, indexed in Pubmed: 15851267.
65. Ueda A, Adachi I, McCarthy KP, et al. Substrates of atrial arrhythmias: histological insights from patients with congenital heart disease. Int J Cardiol. 2013; 168(3): 2481–2486, doi: 10.1016/j.ijcard.2013.03.004, indexed in Pubmed: 23541611.
66. Khairy P, Fournier A, Ruest P, et al. Transcatheter ablation via a sternotomy approach as a hybrid procedure in a univentricular heart. Pacing Clin Electrophysiol. 2008; 31(5): 639–640, doi: 10.1111/j.1540-8159.2008.01058.x, indexed in Pubmed: 18439186.
67. Yap SC, Harris L, Silversides CK, et al. Outcome of intra-atrial re-entrant tachycardia catheter ablation in adults with congenital heart disease: negative impact of age and complex atrial surgery. J Am Coll Cardiol. 2010; 56(19): 1589–1596, doi: 10.1016/j.jacc.2010.04.061, indexed in Pubmed: 21029876.
68. Laredo M, Karsenty C, Ladouceur M, et al. Posterolateral Line. JACC: Clinical Electrophysiology. 2019; 5(1): 134–135, doi: 10.1016/j.jacep.2018.09.004.
69. Roca-Luque I, Rivas-Gándara N, Dos Subirà L, et al. Long-Term Follow-Up After Ablation of Intra-Atrial Re-Entrant Tachycardia in Patients With Congenital Heart Disease: Types and Predictors of Recurrence. JACC Clin Electrophysiol. 2018; 4(6): 771–780, doi: 10.1016/j.jacep.2018.04.011, indexed in Pubmed: 29929671.
70. Grubb C, Lewis M, Whang W, et al. Catheter ablation for atrial tachycardia in adults with congenital heart disease. JACC: Clinical Electrophysiology. 2019; 5(4): 438–447, doi: 10.1016/j.jacep.2018.10.011.
71. Egbe AC, Connolly HM, Khan AR, et al. Outcomes in adult Fontan patients with atrial tachyarrhythmias. Am Heart J. 2017; 186: 12–20, doi: 10.1016/j.ahj.2016.12.015, indexed in Pubmed: 28454826.
72. Moore BM, Anderson R, Nisbet AM, et al. Ablation of atrial arrhythmias after the atriopulmonary fontan procedure: mechanisms of arrhythmia and outcomes. JACC Clin Electrophysiol. 2018; 4(10): 1338–1346, doi: 10.1016/j.jacep.2018.08.012, indexed in Pubmed: 30336880.
73. Moore JP, Gallotti RG, Tran E, et al. Ten-year outcomes of transcaval cardiac puncture for catheter ablation after extracardiac Fontan surgery. Heart Rhythm. 2020; 17(10): 1752–1758, doi: 10.1016/j.hrthm.2020.05.007, indexed in Pubmed: 32438019.
74. Correa R, Sherwin ED, Kovach J, et al. Mechanism and ablation of arrhythmia following total cavopulmonary connection. Circ Arrhythm Electrophysiol. 2015; 8(2): 318–325, doi: 10.1161/CIRCEP.114.001758, indexed in Pubmed: 25583982.
75. Baruteau AE, Abrams DJ, Ho SY, et al. Cardiac conduction system in congenitally corrected transposition of the great arteries and its clinical relevance. J Am Heart Assoc. 2017; 6(12), doi: 10.1161/JAHA.117.007759, indexed in Pubmed: 29269355.
76. Noheria A, Asirvatham SJ, McLeod CJ. Unusual atrioventricular reentry tachycardia in congenitally corrected transposition of great arteries: a novel site for catheter ablation. Circ Arrhythm Electrophysiol. 2016; 9(6), doi: 10.1161/CIRCEP.116.004120, indexed in Pubmed: 27217343.
77. Hu F, Liang E, Zheng L, et al. Successful case of complex atrial flutter occurring in a patient with congenitally corrected transposition of the great arteries, aberrant left atrial appendage, and situs inversus. Int J Arrhyth. 2019; 20(1), doi: 10.1186/s42444-019-0004-1.
78. Abudayyeh I, Jolly GP, Kuhn MA, et al. Transcatheter systemic AV valve-in-valve implantation in a patient with LTGA and Ebstein anomaly. JACC Case Rep. 2022; 4(9): 551–555, doi: 10.1016/j.jaccas.2022.02.018, indexed in Pubmed: 35573851.
79. Hebe J. Ebstein's anomaly in adults. Arrhythmias: diagnosis and therapeutic approach. Thorac Cardiovasc Surg. 2000; 48(4): 214–219, doi: 10.1055/s-2000-6897, indexed in Pubmed: 11005595.
80. Wackel P, Cannon B, Dearani J, et al. Arrhythmia after cone repair for Ebstein anomaly: The Mayo Clinic experience in 143 young patients. Congenit Heart Dis. 2018; 13(1): 26–30, doi: 10.1111/chd.12566, indexed in Pubmed: 29316261.
81. Kastor JA, Goldreyer BN, Josephson ME, et al. Electrophysiologic characteristics of Ebstein's anomaly of the tricuspid valve. Circulation. 1975; 52(6): 987–995, doi: 10.1161/01.cir.52.6.987, indexed in Pubmed: 1182962.
82. Lev M, Gibson S, Miller RA. Ebstein's disease with Wolff-Parkinson-White syndrome; report of a case with a histopathologic study of possible conduction pathways. Am Heart J. 1955; 49(5): 724–741, doi: 10.1016/0002-8703(55)90218-0, indexed in Pubmed: 14376326.
83. Ho SY, Goltz D, McCarthy K, et al. The atrioventricular junctions in Ebstein malformation. Heart. 2000; 83(4): 444–449, doi: 10.1136/heart.83.4.444, indexed in Pubmed: 10722549.
84. Roten L, Lukac P, DE Groot N, et al. Catheter ablation of arrhythmias in ebstein's anomaly: a multicenter study. J Cardiovasc Electrophysiol. 2011; 22(12): 1391–1396, doi: 10.1111/j.1540-8167.2011.02161.x, indexed in Pubmed: 21914017.
85. Shivapour JKL, Sherwin ED, Alexander ME, et al. Utility of preoperative electrophysiologic studies in patients with Ebstein's anomaly undergoing the Cone procedure. Heart Rhythm. 2014; 11(2): 182–186, doi: 10.1016/j.hrthm.2013.10.045, indexed in Pubmed: 24513916.
86. Houck CA, Lanters EAH, Heida A, et al. Distribution of conduction disorders in patients with congenital heart disease and right atrial volume overload. JACC Clin Electrophysiol. 2020; 6(5): 537–548, doi: 10.1016/j.jacep.2019.12.009, indexed in Pubmed: 32439038.
87. Fitzgerald JL, May AN, Mahmoodi E, et al. Cryoballoon ablation from above, through a prosthetic patch atrial septal defect repair. HeartRhythm Case Rep. 2020; 6(6): 357–361, doi: 10.1016/j.hrcr.2020.03.004, indexed in Pubmed: 32577395.

Current challenges in the diagnosis and management of acute coronary syndromes in women

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ABSTRACT

Cardiovascular disease remains the leading cause of death among women nowadays. However, there is a persistent lack of awareness of the impact of different risk factors on women's cardiovascular health, in specific pregnancy-related complications, hormonal changes, and psychological aspects. Moreover, there is still not enough awareness of the importance of coronary artery disease (CAD) in women, which leads to a delay in the diagnosis and prompt treatment, particularly during emergent coronary scenarios. Although guidelines suggest the same treatment for women and men who present with acute coronary syndrome (ACS), women are still undertreated. Contemporary data show an improvement over time in the management of ACS in women, however, women are still less likely than men to receive revascularization and pharmacological treatments. Women have higher rates of complications and mortality, in particular the young population, in which all outcomes are still worse in women compared to men. In this review, we aim to emphasize the importance of women's risk factors, women-specific pathophysiology, and clinical presentation in the setting of ACS. This is a review of current challenges in the diagnosis and treatment of women with ACS.

Key words: acute coronary syndrome, women

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death among women [1]. In fact, a third of all women in their fourth decade will develop coronary artery heart disease [1]. Although there has been a decline in mortality from acute myocardial infarction (AMI) in both sexes, younger women, under the age of fifty-five still have the highest mortality rate with no significant improvement in the last two decades [1, 2]. Sex-related differences in women presenting with ACS are well known. Women with ACS have different clinical presentations, they are older and have multiple comorbidities compared with men.

Despite the updated current recommendations on CVD prevention of women [3], a nationwide survey demonstrated that although 74% of women had one or more CVD risk factors, only 16% of the women were informed that they were at risk of heart disease. Additionally, only 22% of primary care physicians and 42% of cardiologists felt well-prepared to assess CVD in women [4]. The persistent lack of awareness about the importance of CAD in women leads to a delay in the diagnosis and prompt treatment, particularly during emergent scenarios [5, 6].

RISK FACTORS

Women have both traditional and women-specific CAD risk factors. While traditional risk factors are widely known, the fact that their impact on CVD outcomes differs between sexes is less known. Moreover, specific CAD risk factors are often overlooked (Table 1).

Hypertension prevalence is the same in women and men. However, the incidence of hypertension increases 2-3-fold in women taking oral contraception. Furthermore, hypertension has a more profound impact on CVD in women over the age of 60 compared with men [7].

Diabetes mellitus is a strong risk factor for CVD, and its impact on the risk of coronary death is significantly greater for women than

Table 1. Coronary artery disease risk factors

Traditional risk factors	Sex-specific risk factors
Hypertension	Age of menarche
Diabetes mellitus	Preterm delivery
Dyslipidemia	Pregnancy related conditions: gestational hypertension, sever preeclampsia, eclampsia, amniotic fluid embolism, postpartum hemorrhage, low birth weight, placental abruption, and stillbirth.
Smoking	Polycystic ovary syndrome
	Endometriosis
	Breast cancer

men. In a meta-analysis addressing sex differences in the outcomes of diabetic patients, the relative risk of coronary death from diabetes was 2.58 (95% confidence interval [CI], 2.05–3.26) for women compared to 1.85 (1.47–2.33) for men ($P = 0.045$) [8].

Dyslipidemia is common in women. The risk of CVD increases greatly after menopause and in some studies, the increase in risk was found to be related to a change in the lipid blood profile and especially to the increase in total cholesterol and low-density lipoprotein cholesterol (LDL-C) amongst premenopausal women [9]. A study, which explored the changes during menopausal transition, found an increase in total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), and apolipoprotein A-I (ApoA1) around the onset of menopause. The greatest increase in HDL-C and ApoA1 levels occurred within a year after the onset of menopause and then leveled off or declined, suggesting that HDL-C may be paradoxically associated with an increase in atherosclerosis progression in the postmenopausal phase [10].

Smoking is the leading preventable cause of cardiovascular death in the general population. Although women smoke less than men [11], smoking in women is probably more harmful than in men because female smokers have a significantly increased risk of ST-segment elevation myocardial infarction (STEMI) than men, with the greatest risk in women aged 18 to 49 years old [12].

A history of menarche before the age of ten and delayed menarche after the age of twenty-five are associated with an increased risk of CVD [13].

Pregnancy is a unique period in the woman's life in which several medical conditions may predict an increase in the risk of future cardiovascular events. Preterm delivery, which is defined as births before 37 weeks of gestation, is associated with an increased maternal risk of future cardiovascular events, cardiovascular death, CHD, CHD death, and stroke [14]. The adjusted risk ranged between 1.4- and 2-fold compared with those without a history of preterm birth. This increased risk is greatest in preterm births that occur before 32 weeks of gestation [14]. Gestational hypertension of any sort was found to increase the risk of CVD, including heart failure, myocardial injury, stroke, and mortality [15]. Pregnancy may be complicated with severe maternal morbidity which includes severe preeclampsia, eclampsia, amniotic fluid embolism, postpartum hemorrhage, and obstetric shock, which are considered life-threatening during pregnancy [16]. A comprehensive review of the literature on the relationship between severe maternal morbidity and CVD demonstrated a higher future risk of any cardiovascular disease in women who suffer severe maternal morbidity during pregnancy [16]. Gestational diabetes increases both the risk of future diabetes and CVD [17].

Other pregnancy complications with an increased risk of subsequent CVD include low birth weight, placental abruption, and stillbirth [18].

Fertility treatment is not considered an independent risk factor for CVD, but studies demonstrate that women who have failed this treatment are at more risk of CVD [19]. Moreover, no association is reported between CVD and contraceptive usage in healthy women [20].

Polycystic ovary syndrome is a condition in which the ovaries produce an abnormal amount of androgens. It is strongly associated with metabolic syndrome and diabetes mellitus, eventually increasing the risk of CVD in an indirect way [21]. However, it is unclear whether it poses an independent risk factor for CVD [22].

Endometriosis is a common gynecologic condition in which endometrial tissue is present outside the uterine cavity [23]. A retrospective cohort study investigating the cardiovascular risk among women with endometriosis demonstrated a higher composite of CVD (ischemic heart disease IHD, cerebrovascular accident (CVA), and heart failure) in this group compared with women without endometriosis, 1.03% and 0.75% respectively [24]. Similar results were reported by other studies investigating the role of endometriosis in CVD [25].

Breast cancer history is associated with increased CVD risk through several mechanisms, including mainly breast cancer treatment [26, 27]. Medications commonly used such as anthracycline and trastuzumab have potential for direct cardiac injury. Studies investigating these medications demonstrate an increased risk of developing heart failure: 32.1% when treated with trastuzumab and 41.9% when treated simultaneously with both medications. Radiation therapy, a mainstay treatment of breast cancer, also increases the risk of CVD by 7.4%. The increase in risk begins within a few years of exposure and lasts for approximately twenty years [26, 27].

PATHOGENESIS OF ISCHEMIC HEART DISEASE (IHD) AND ACS

Sex hormones play a key role in the pathophysiology of CAD in women [28]. Specific hormone-related receptors in the cytosol and nuclear compartments of various cell types (including the endothelium and vascular smooth muscle) have been identified through their effect on vascular function reactivity, tone, and structure [28]. Moreover, women undergo intense hormonal changes during their lifetime exposing the vascular bed to radical changes.

Although plaque rupture is the leading cause of AMI in both sexes, it is responsible for only 55% of cases in women [29]. Several studies demonstrated a higher prevalence of plaque erosion in women presenting with ACS, especially in young premenopausal women [29–31], suggesting a possible protective effect of estrogen [32]. Moreover, atherosclerosis is usually found to be less extensive in women [33, 34]. A study investigating coronary angiograms demonstrated that nearly one-third of women presenting with ACS had no obstructive CAD [33]. In coronary plaque assessment using coronary computed tomography angiography (CTA), women had significantly fewer atherosclerotic plaques; however, as with men, a low-attenuation plaque burden predicted future myocardial infarction [34].

The Women's Ischemia Syndrome Evaluation (WISE) study demonstrated that 50% of women presenting with chest pain with the absence of an obstructive CAD had coronary artery dysfunction [35]. The study also demonstrated that an abnormal response to acetylcholine (ACH) was found to be an independent predictor of adverse cardiovascular events, including hospitalization for worsening angina, AMI, congestive heart failure, stroke, revascularization, other vascular events, and death [36]. It is important to mention that vascular dysfunction can be detected early in several pregnancy-associated conditions such as hypertensive disorder in pregnancy – HDP [37]. Recent studies suggest that endothelial dysfunction is a marker for early atherosclerosis even before structural changes to the vessel have occurred [36, 38–41].

Epicardial coronary arteries in women are smaller than in men, regardless of their body size [28, 41]. These differences are also attributed to sex hormones as demonstrated in several studies of transsexuals where brachial artery size in genetic men taking estrogens is smaller compared with the control group of men [43, 44]. Furthermore, women taking androgens show larger arteries than the control group of women [45]. In addition, in women treated with coronary artery bypass surgery, a higher mortality rate was attributed to the average diameter of the grafted vessel as demonstrated in the CASS registry [46].

CLINICAL PRESENTATION OF ACS IN WOMEN

Women presenting with ACS are usually older than men, and often have a greater burden of cardiovascular risk factors [47]. The "typical" symptoms of myocardial ischemia are well-known. These include precordial chest discomfort, pain, heaviness or fullness, dyspnea, and radiation to the left arm. For years, a misconception prevailed that women with ACS present often with "atypical" symptoms. Past data demonstrated that women were more likely to present with ACS without chest pain [48]. Furthermore, large cohorts showed that 37% of women eventually diagnosed with ACS, presented with atypical chest pain [48–51]. Nonetheless, more contemporary data suggest no differences regarding ACS symptoms between women and men. The VIRGO study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients) assessed sex differences in the presentation and perception of symptoms among young patients (<55 years old) with ACS. The results demonstrated that the majority of women, like men, present with a predominant complaint of chest pain (87.0% vs. 89.5%; $P = 0.19$) [50]. This was also confirmed in another study in 1941 patients (39% women). Chest pain was the most common presenting symptom, reported by 92% of women and 91% of men with suspected ACS.[51] Pain with typical characteristics, the presence of radiation, and additional symptoms were all more common in women with suspected ACS. Also, women are more likely to report >3 associated symptoms of ACS such as shortness of breath, discomfort in another body part, pain radiating to the jaw, vomiting, fatigue, and general weakness [50].

EVALUATION OF WOMEN WITH CHEST PAIN AND SUSPECTED ACS

According to the current chest pain evaluation guidelines, men and women with chest pain symptoms should not be assessed differently [52]. Initial assessment of patients presenting with acute chest pain is based on focused history that includes characteristics and duration of symptoms, as well as associated features and cardiovascular risk factors. The purpose of the assessment is first to identify patients with immediately life-threatening conditions such as STEMI and secondly to risk-stratify patients suspected of ACS into low versus intermediate- or high-risk groups. This is achieved by using clinical decision pathways (CDPs) to decide what is the best diagnostic test (functional tests, such as an exercise test, stress echocardiography, and myocardial perfusion imaging versus anatomical evaluation, such as cardiac computed tomography, angiography, and invasive coronary angiography) [52].

An initial ECG should be performed accompanied by serial ECGs to detect potential ischemic changes in addition to cardiac biomarker measurement. The preferred biomarker to detect or exclude myocardial injury is cardiac troponin I or T (cTn) because of its high sensitivity and specificity for myocardial tissue. Myocardial injury is defined as an increase in blood levels of cTn above the 99th percentile upper reference limit (URL) with no sex differences [52]. The High-STEACS (High-Sensitivity Troponin in the Evaluation of Patients with Suspected ACS) was the first randomized controlled trial to evaluate the introduction of the high-sensitivity cardiac troponin I (hs-cTnI) assay with sex-specific thresholds into clinical practice [53]. Pre-specified secondary analysis of this study evaluated the impact of implementing sex-specific diagnostic thresholds on investigation and treatments for CHD and clinical outcomes in women and men separately. Myocardial injury was defined as high-sensitivity cardiac troponin I concentration >99th centile of 16 ng/l in women and 34 ng/l in men [54]. The primary outcome was recurrent myocardial infarction or cardiovascular death at 1 year. The study demonstrated that the use of a hs-cTnI assay with sex-specific thresholds

identified five times more women with myocardial injury compared with men [54]. This approach is still controversial, however, the fourth universal definition of myocardial infarction article recommends using sex-specific thresholds for the diagnosis of myocardial infarction [55].

DELAY IN PRESENTATION AND TIME TO TREATMENT

Women compared with men tend to ignore or not recognize their CVD risk factors and are more likely to misattribute their pain to a non-cardiac cause [50]. A study investigating women who were admitted to the hospital after an AMI found that most women did not recognize their risk factors as possible contributors to cardiac disease, with hypertension being the least recognized risk factor for cardiac diseases [56]. Moreover, the VIRGO study demonstrated that even when women recognize the signs, they attribute their pain to stress/anxiety, a fact that probably explains the delay of women in seeking medical attention [50]. Also, among patients with AMI, 35% of women as opposed to 23% of men, present to the hospital with a delay of 6 hours or more [50]. Delay in seeking medical help in women has also been observed in other studies, suggesting a median delay in presentation between 2 to 5 hours [57, 58]. An additional delay occurs upon presentation, with numerous studies demonstrating a delay in the care of women presenting with signs of AMI. The VIRGO study demonstrated that 29.5% of women and 22.1% of men sought medical care for similar symptoms; however, 53% of women's symptoms as opposed to 37% in men were attributed to non-cardiac causes (P <0.001) [59]. A study investigating patients diagnosed with STEMI demonstrated a delay between first medical contact and hospital presentation in cases of female patients, which was primarily attributed to the lack of early diagnosis and/or lower priority for ambulance transport to a percutaneous coronary intervention (PCI)-capable hospital. Nevertheless, no significant difference was found in the usage rate of the emergency medical system (EMS) among women and men [60]. Moreover, women suffer from significantly delayed proper reperfusion therapies [61]. The median door-to-balloon time and door-to-needle time was longer for young women presenting with STEMI compared with men, exceeding the recommended time guidelines for PCI [61]. Additionally, women with >50% coronary occlusion documented on cardiac catheterization were less likely to receive reperfusion treatment than men [61].

TREATMENT GAPS IN WOMEN WITH ACS

According to the ACS international guidelines, treatment should not differ between men and women [58, 59]. However, women often receive less intensive therapy and much less secondary prevention treatment than men, thus leading to poorer prognosis and outcomes.

Reperfusion strategies

Several studies examining treatment with thrombolysis in women demonstrated a higher mortality rate than in men [64, 65]. In the GUSTO-1 trial (The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) women treated with thrombolysis had more complications such as shock, heart failure, reinfarction, recurrent ischemia, bleeding, and stroke compared with men [66]. The study also demonstrated that the risk of moderate to severe bleeding was increased 1.43-fold in women [66]. Moreover, female sex was found to be an independent predictor of bleeding after thrombolytic treatment [64].

Primary angioplasty is the main treatment in developed countries for AMI, yet studies show underutilization of PCI and a higher mortality rate in women [67, 68]. A recent meta-analysis of sex differences in presentation, treatment, and outcomes in ACS including 24 hospitals, demonstrated that women were less likely to undergo coronary angiography, regardless of the indication for PCI (STEMI, non-ST-segment elevation myocardial infarction [NSTEMI] and unstable angina) [69]. The study also investigated temporal trends between 2006–2010 and 2012–2016 and found a marked increase in the percentages of patients who underwent coronary angiography and PCI in both sexes across all ACS groups between the latter and the earlier period, but the change was less pronounced in women [69]. Studies investigating sex influences on safety and efficacy of drug-eluting stents (DES) compared with bare metal stents (BMS) demonstrated that DES use was associated with lower rates of clinically driven revascularization and low rates of in-hospital events, including MI, coronary artery bypass surgery (CABG), and death independent of sex [70]. A large meta-analysis of 26 randomized clinical trials (RCTs) investigated the long-term safety and efficacy of new-generation DES in women [71]. The trial confirmed the results of RCTs performed in predominantly male populations and consolidated new-generation DES as the standard of care for women with ACS [71]. However, studies still show underuse of stents in women who undergo PCI regardless of the indication [72, 73].

A systemic review of 23 studies found that women were referred less frequently to CABG, referred later in the course of the disease, and were more likely to undergo urgent surgery [74]. Women in these studies were older than men and more often had diabetes, hypertension, congestive heart failure, and severe noncardiac disease. Surgical technique was also different in women. Arterial grafts, especially internal mammary artery grafts, were less used although it is known that arterial grafting has higher potency and reduces CABG mortality [74]. The Society of Thoracic Surgeons Adult Cardiac Surgery Database studied patients who underwent first-time CABG in the United States (>1 000 000 patients, 25% female) [75]. The study demonstrated that female sex was associated with lower

unadjusted rates of revascularization with an internal mammary artery graft (93.9% vs. 95.9%; *P* <0.001), bilateral internal mammary artery graft (2.9% vs. 5.6%; *P* <0.001), or radial artery graft (3.2% vs. 5.6%; *P* <0.001) [75].

Pharmacological strategies

Post-ACS treatment includes antiplatelet agents, beta-blockers, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), and statins. The guidelines recommend that women with ACS be treated with the same pharmacological agents as those used in men for both acute care and secondary prevention of AMI [62, 63].

The NCVD-ACS registry and ACC-NCDR demonstrated that women diagnosed with ACS were less likely to be treated with aspirin (ASA) [69, 76]. In the CCC-ACS project (Improving Care for CVD in China–ACS) which included 82196 patients with ACS (25.6% women), women were less likely to be treated with dual antiplatelet therapy during hospitalization and at discharge compared to men (89% vs. 93.5%; *P* <0.001, 82.2% vs. 90.1%; *P* <0.001 respectively) [77]. The START-ANTIPLATELET investigated whether sex influences the choice of antiplatelet treatment upon admission for ACS and its impact on 1-year clinical outcomes [73]. The study showed that a significantly higher proportion of female patients diagnosed with NSTEMI were treated without dual antiplatelet therapy (DAPT) compared to men. When DAPT was prescribed regardless of the indication, the combination of ASA plus ticagrelor was the preferred one, regardless of patients' sex. Prasugrel prescription was significantly lower in women compared to men, while clopidogrel was more often used for DAPT in women. Nevertheless, the study showed that the $P2Y_{12}$ inhibitor choice did not affect the 1-year clinical outcome [73]. Several studies investigated the optimal duration of DAPT in women. A meta-analysis of 11 473 patients comparing clinical outcomes of short (6-month) with prolonged (12-months) DAPT after DES implantation in women versus men demonstrated that short-term DAPT was associated with similar rates of major adverse cardiac events (MACE), including the composite of cardiac death, AMI, or definite/probable stent thrombosis, but lower rates of bleeding as compared with prolonged DAPT in both men and women [78]. In the GLOBAL LEADERS trial, after one year of follow-up, women were at greater risk of bleeding than men, however, after two years of follow-up, the risk of bleeding was similar in both sexes [79]. A sex-based analysis of the TWILIGHT study demonstrated similar ischemic events between sexes and higher bleeding events, however, after adjustment for baseline characteristics, the incremental bleeding risk associated with female sex was no longer significant [80]. Nonetheless, the female subgroup in these trials was modest in size, yet those studies emphasize the need for careful examination of the patient's profile and not just his/her sex to tailor the right treatment [80].

Regarding beta-blockers and ACE-I, only 64.8% of women were treated with beta-blockers as a secondary prevention [76]. In the NCVD-ACS registry, the Malaysian National CVD Database, women presented with STEMI and NSTEMI were less likely to be treated with ACE-I during hospitalization than men (43.8% vs. 40.5%; *P* = 0.003) [69].

Statin therapy is another mainstay of post-MI pharmacotherapy. The long-term intervention with pravastatin in ischemic disease (LIPID study) demonstrated a reduction in the mortality rate in both sexes [81]. In the Pravastatin or PROVE IT-TIMI 22 trial, which included 21.9% women, intensive therapy in women was associated with a significant 25% relative reduction in the primary composite endpoint compared with a 14% reduction in men [82]. Nevertheless, target cholesterol levels are less often achieved in women, partially due to a lower likelihood of receiving lipid-lowering therapy prescriptions. A study investigating the usage of high-intensity statin therapy following an MI among women and men demonstrated that women were less likely than men to have filled a prescription for high-intensity statin dosages (50% vs. 60%) [83]. Sex differences in the use of high-intensity statins following AMI were present in all subgroups but more pronounced among those without prior statin use or with prior low/moderate intensity statins, the youngest and oldest individuals, and those without prevalent comorbid conditions [83]. The study also examined the sex-specific temporal trends in the intensity of dosages of statin therapy from 2007 to 2015 and found no change by sex in the use of high-intensity statins post-MI between 2007 and 2015 [83]. As for PCSK9 inhibitors, data from the FOURIER trial demonstrated that inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL-C levels in all subgroups with no sex differences [84]. However, only one multicenter registry investigated sex-related differences in PCSK9 inhibitors' efficacy [85]. The study demonstrated that women had substantially higher LDL-C levels and a lower LDL-C reduction compared with men (47.4% vs. 56.9%; *P* = 0.0002) [85].

A study that assessed the level of adherence to the guidelines for secondary prevention of cardiovascular disease in everyday clinical practice showed that even though women were better responders than men, women achieved worse glycemic control than men and worse control of total cholesterol and HDL fraction cholesterol levels [86].

BLEEDING COMPLICATIONS

Bleeding during the course of elective or urgent PCI is one of the factors contributing to higher mortality rates in women. Increased bleeding risk in women is attributed to vascular access and at least in part to inappropriate dosing of thrombotic treatment [87]. Women treated with antithrombotic therapy have a higher risk of bleeding independently of age, weight, baseline blood pressure, renal function, baseline hematocrit, and other potential confounders [88, 89]. The SAFE-PCI study investigated PCI

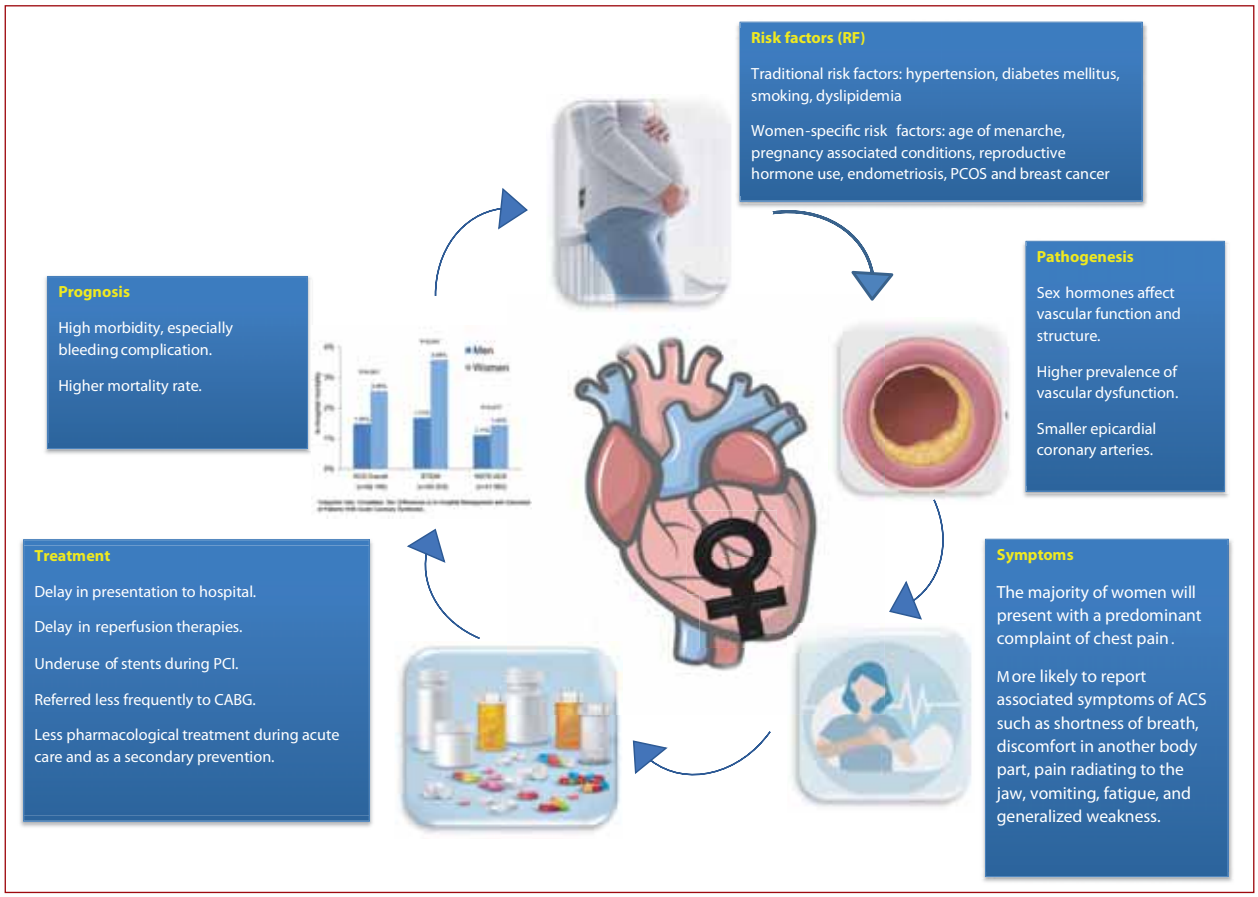

Figure 1. Central illustration

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass surgery; PCI, percutaneous coronary intervention; PCOS, polycystic ovary syndrome

access strategies in women undergoing elective or urgent cardiac catheterization and demonstrated reductions in bleeding and vascular complications with the radial access approach [90]. The CathPCI registry also studied the effectiveness of various bleeding avoidance strategies (vascular closure devices, bivalirudin treatment, radial access, and a combined approach) and found that women had significantly higher rates of bleeding than men (12.5% vs. 6.2%; P <0.01) when avoidance strategies were not used [91].

PROGNOSIS

Several factors, including older age, multiple comorbidities, and delay in diagnosis and treatment, contribute to higher mortality rates observed in women diagnosed with ACS. Delays in presentation to the hospital and providing proper care for women are one of the reasons for the higher mortality rate among women [60]. A study investigating sex-related differences in timely access to care among STEMI patients demonstrated higher 30-day mortality in women (10.8% vs. 5.3%) [60].

Studies have also examined variability in mortality stratified by sex after PCI. Results from a large registry identified 13 752 patients (4761 female, 34.6%). Unadjusted post-PCI mortality rates were higher in females versus males; however, multivariable regression analyses failed to identify female sex as an independent predictor of mortality [92]. Similar results were shown in a meta-analysis of observational studies that examined differences in mortality by sex in patients with STEMI treated with primary PCI; in the adjusted analysis, the association between women and a higher risk of all-cause mortality was attenuated [93].

Nevertheless, data from large registries from the United Kingdom and Sweden found that female sex was an independent predictor of all-cause mortality at 30 days and 1 year [94]. A large cohort of 6.5 million PCI discharges across the United States from 2004 to 2014, demonstrated higher in-hospital mortality rate that also persisted over time with women consistently at 20% greater risk compared to men, even after adjustment [95]. Moreover, several studies showed that sex-based differences in survival varied according to age, with younger women, below the age of 55 years old, having a higher mortality rate than men [96, 97]. Long-term follow-up data from a large Polish acute myocardial infarction demonstrated lower mortality risk at 5-year follow-up in women compared with men. The study also shows a decline in relative survival with increasing age in both sexes with a stronger impact in women compared with men. However, in-hospital survival was lower in women, especially in women below the age of 55 [98].

The operative mortality rate is also higher in women. A study that analyzed data from 121 hospitals with a total of 10 708 women and 29 669 men who underwent CABG between 2003 and 2004 found a higher mortality rate among women (4.6% vs. 2.5%; *P* <000.1), with the highest likelihood of death in younger women, under the age of 65 years (odds ratio [OR], 2.13; *P* <0.001) [99]. The specific reasons for the higher mortality rate in women undergoing CABG are not well elucidated, yet it is probably related to female risk factors, delay in referral to CABG treatment, and the underuse of internal mammary grafting [99].

In summary, cardiovascular disease and CAD are among the leading causes of morbidity and mortality in women. Thus, it is of utmost importance to understand the major gaps in diagnosis treatments and outcomes in women with ACS. Even in the contemporary era, issues such as women-specific risk factors, hormonal influences, and different pathophysiological mechanisms are under-researched and under-recognized. There is an unmet need for improving our understanding, diagnosis, and treatment of women with ischemic heart disease, specifically with ACS. Raising public awareness, educating medical teams, involving more women in research trials, and women-specific guidelines can narrow existing disparities.

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REFERENCES

1. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics - 2022 update: A report from the American Heart Association. Circulation. 2022; 145(8): e153–e639, doi: 10.1161/CIR.0000000000001052, indexed in Pubmed: 35078371.
2. Arora S, Stouffer GA, Kucharska-Newton AM, et al. Twenty year trends and sex differences in young adults hospitalized with acute myocardial infarction. Circulation. 2019; 139(8): 1047–1056, doi: 10.1161/CIRCULATIONAHA.118.037137, indexed in Pubmed: 30586725.
3. Cho L, Davis M, Elgendy I, et al. Summary of Updated Recommendations for Primary Prevention of Cardiovascular Disease in Women: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020; 75(20): 2602–2618, doi: 10.1016/j.jacc.2020.03.060, indexed in Pubmed: 32439010.
4. Bairey Merz CN, Andersen H, Sprague E, et al. Knowledge, attitudes, and beliefs regarding cardiovascular disease in women: The Women's Heart Alliance. J Am Coll Cardiol. 2017; 70(2): 123–132, doi: 10.1016/j.jacc.2017.05.024, indexed in Pubmed: 28648386.
5. Norris CM, Yip CYY, Nerenberg KA, et al. State of the science in women's cardiovascular disease: A Canadian perspective on the influence of sex and gender. J Am Heart Assoc. 2020; 9(4): e015634, doi: 10.1161/JAHA.119.015634, indexed in Pubmed: 32063119.
6. Pinn VW. Sex and gender factors in medical studies: implications for health and clinical practice. JAMA. 2003; 289(4): 397–400, doi: 10.1001/jama.289.4.397, indexed in Pubmed: 12533102.
7. Fryar CD, Ostchega Y, Hales CM. Hypertension prevalence and control among adults: United States, 2015-2016. NCHS Data Brief No. 289, October 2017.
8. Lee WL, Cheung AM, Cape D, et al. Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. Diabetes Care. 2000; 23(7): 962–968, doi: 10.2337/diacare.23.7.962, indexed in Pubmed: 10895847.
9. Cífková R, Krajčoviechová A. Dyslipidemia and cardiovascular disease in women. Curr Cardiol Rep. 2015; 17(7): 609, doi: 10.1007/s11886-015-0609-5, indexed in Pubmed: 26026998.
10. Matthews KA, Crawford SL, Chae CU, et al. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? J Am Coll Cardiol. 2009; 54(25): 2366–2373, doi: 10.1016/j.jacc.2009.10.009, indexed in Pubmed: 20082925.
11. Creamer MR, Wang TW, Babb S, et al. Tobacco product use and cessation indicators among adults - United States, 2018. MMWR Morb Mortal Wkly Rep. 2019; 68(45): 1013–1019, doi: 10.15585/mmwr.mm6845a2, indexed in Pubmed: 31725711.
12. Palmer J, Lloyd A, Steele L, et al. Differential risk of ST-segment elevation myocardial infarction in male and female smokers. J Am Coll Cardiol. 2019; 73(25): 3259–3266, doi: 10.1016/j.jacc.2019.03.525, indexed in Pubmed: 31248546.
13. Lee JJ, Cook-Wiens G, Johnson BD, et al. Age at menarche and risk of cardiovascular disease outcomes: findings from the national heart lung and blood institute-sponsored women's ischemia syndrome evaluation. J Am Heart Assoc. 2019; 8(12): e012406, doi: 10.1161/JAHA.119.012406, indexed in Pubmed: 31165670.
14. Wu P, Gulati M, Kwok CS, et al. Preterm delivery and future risk of maternal cardiovascular disease: a systematic review and meta-analysis. J Am Heart Assoc. 2018; 7(2), doi: 10.1161/JAHA.117.007809, indexed in Pubmed: 29335319.
15. Khosla K, Heimberger S, Nieman KM, et al. Long-Term cardiovascular disease risk in women after hypertensive disorders of pregnancy: recent advances in hypertension. Hypertension. 2021; 78(4): 927–935, doi: 10.1161/HYPERTENSIONAHA.121.16506, indexed in Pubmed: 34397272.
16. Ukah UV, Auger N. Severe maternal morbidity and risk of cardiovascular disease: Recent advances. Kardiol Pol. 2022; 80(6): 638–643, doi: 10.33963/KP.a2022.0119, indexed in Pubmed: 35521721.
17. Kramer CK, Campbell S, Retnakaran R. Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. Diabetologia. 2019; 62(6): 905–914, doi: 10.1007/s00125-019-4840-2, indexed in Pubmed: 30843102.
18. Parikh NI, Gonzalez JM, Anderson CAM, et al. Adverse pregnancy outcomes and cardiovascular disease risk: Unique opportunities for cardiovascular disease prevention in women: a scientific statement from the American Heart association. Circulation. 2021; 143(18): e902–e916, doi: 10.1161/CIR.0000000000000961, indexed in Pubmed: 33779213.
19. Udell JA, Lu H, Redelmeier DA. Failure of fertility therapy and subsequent adverse cardiovascular events. CMAJ. 2017; 189(10): E391–E397, doi: 10.1503/cmaj.160744, indexed in Pubmed: 28385819.
20. Chasan-Taber L, Stampfer MJ. Epidemiology of oral contraceptives and cardiovascular disease. Ann Intern Med. 1998; 128(6): 467–477, doi: 10.7326/0003-4819-128-6-199803150-00008, indexed in Pubmed: 9499331.
21. Azziz R. Polycystic Ovary Syndrome. Obstet Gynecol. 2018; 132(2): 321–336, doi: 10.1097/AOG.0000000000002698, indexed in Pubmed: 29995717.
22. Osibogun O, Ogunmoroti O, Michos ED. Polycystic ovary syndrome and cardiometabolic risk: Opportunities for cardiovascular disease prevention. Trends Cardiovasc Med. 2020; 30(7): 399–404, doi: 10.1016/j.tcm.2019.08.010, indexed in Pubmed: 31519403.
23. Hoffman BLO, Schorge JOM, Halvorson LMA, et al. Williams Gynecology. 4 ed. McGraw Hill / Medical 2020.
24. Okoth K, Wang J, Zemedikun D, et al. Risk of cardiovascular outcomes among women with endometriosis in the United Kingdom: a retrospective matched cohort study. BJOG. 2021; 128(10): 1598–1609, doi: 10.1111/1471-0528.16692, indexed in Pubmed: 33683770.

25. Chiang HJ, Lan KC, Yang YH, et al. Risk of major adverse cardiovascular and cerebrovascular events in Taiwanese women with endometriosis. J Formos Med Assoc. 2021; 120(1 Pt 2): 327–336, doi: 10.1016/j.jfma.2020.10.005, indexed in Pubmed: 33268157.
26. Bradshaw PT, Stevens J, Khankari N, et al. Cardiovascular disease mortality among breast cancer survivors. Epidemiology. 2016; 27(1): 6–13, doi: 10.1097/EDE.0000000000000394, indexed in Pubmed: 26414938.
27. Gulati M, Mulvagh SL. The connection between the breast and heart in a woman: Breast cancer and cardiovascular disease. Clin Cardiol. 2018; 41(2): 253–257, doi: 10.1002/clc.22886, indexed in Pubmed: 29446841.
28. Orshal JM, Khalil RA. Gender, sex hormones, and vascular tone. Am J Physiol Regul Integr Comp Physiol. 2004; 286(2): R233–R249, doi: 10.1152/ajpregu.00338.2003, indexed in Pubmed: 14707008.
29. Falk E, Nakano M, Bentzon JF, et al. Update on acute coronary syndromes: the pathologists' view. Eur Heart J. 2013; 34(10): 719–728, doi: 10.1093/eurheartj/ehs411, indexed in Pubmed: 23242196.
30. Farb A, Burke AP, Tang AL, et al. Coronary plaque erosion without rupture into a lipid core. A frequent cause of coronary thrombosis in sudden coronary death. Circulation. 1996; 93(7): 1354–1363, doi: 10.1161/01.cir.93.7.1354, indexed in Pubmed: 8641024.
31. Arbustini E, Dal Bello B, Morbini P, et al. Plaque erosion is a major substrate for coronary thrombosis in acute myocardial infarction. Heart. 1999; 82(3): 269–272, doi: 10.1136/hrt.82.3.269, indexed in Pubmed: 10455073.
32. Mehta LS, Beckie TM, DeVon HA, et al. Acute myocardial infarction in women: A scientific statement from the American Heart Association. Circulation. 2016; 133(9): 916–947, doi: 10.1161/CIR.0000000000000351, indexed in Pubmed: 26811316.
33. Chokshi NP, Iqbal SN, Berger RL, et al. Sex and race are associated with the absence of epicardial coronary artery obstructive disease at angiography in patients with acute coronary syndromes. Clin Cardiol. 2010; 33(8): 495–501, doi: 10.1002/clc.20794, indexed in Pubmed: 20734447.
34. Williams MC, Kwiecinski J, Doris M, et al. Sex-Specific computed tomography coronary plaque characterization and risk of myocardial infarction. JACC Cardiovasc Imaging. 2021; 14(9): 1804–1814, doi: 10.1016/j.jcmg.2021.03.004, indexed in Pubmed: 33865779.
35. Reis SE, Holubkov R, Conrad Smith AJ, et al. Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: results from the NHLBI WISE study. Am Heart J. 2001; 141(5): 735–741, doi: 10.1067/mhj.2001.114198, indexed in Pubmed: 11320360.
36. von Mering GO, Arant CB, Wessel TR, et al. Abnormal coronary vasomotion as a prognostic indicator of cardiovascular events in women: results from the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). Circulation. 2004; 109(6): 722–725, doi: 10.1161/01.CIR.0000115525.92645.16, indexed in Pubmed: 14970106.
37. Pepine CJ, Kerensky RA, Lambert CR, et al. Some thoughts on the vasculopathy of women with ischemic heart disease. J Am Coll Cardiol. 2006; 47(3 Suppl): S30–S35, doi: 10.1016/j.jacc.2005.09.023, indexed in Pubmed: 16458168.
38. Sitia S, Tomasoni L, Atzeni F, et al. From endothelial dysfunction to atherosclerosis. Autoimmun Rev. 2010; 9(12): 830–834, doi: 10.1016/j.autrev.2010.07.016, indexed in Pubmed: 20678595.
39. Schamroth Pravda N, Karny-Rahkovich O, Shiyovich A, et al. Coronary artery disease in women: A comprehensive appraisal. J Clin Med. 2021; 10(20), doi: 10.3390/jcm10204664, indexed in Pubmed: 34682787.
40. Marchio P, Guerra-Ojeda S, Vila JM, et al. Targeting early atherosclerosis: A focus on oxidative stress and inflammation. Oxid Med Cell Longev. 2019: 8563845, doi: 10.1155/2019/8563845, indexed in Pubmed: 31354915.
41. Bugiardini R, Bairey Merz CN. Angina with "normal" coronary arteries: a changing philosophy. JAMA. 2005; 293(4): 477–484, doi: 10.1001/jama.293.4.477, indexed in Pubmed: 15671433.
42. Sheifer S, Canos M, Weinfurt K, et al. Sex differences in coronary artery size assessed by intravascular ultrasound. American Heart Journal. 2000; 139(4): 649–652, doi: 10.1016/s0002-8703(00)90043-7.
43. New G, Timmins KL, Duffy SJ, et al. Long-term estrogen therapy improves vascular function in male to female transsexuals. J Am Coll Cardiol. 1997; 29(7): 1437–1444, doi: 10.1016/s0735-1097(97)00080-6, indexed in Pubmed: 9180101.
44. McCrohon J, Walters W, Robinson J, et al. Arterial reactivity is enhanced in genetic males taking high dose estrogens. J Am Coll Cardiol. 1997; 29(7): 1432–1436, doi: 10.1016/s0735-1097(97)00063-6, indexed in Pubmed: 9180100.
45. McCredie RJ, McCrohon JA, Turner L, et al. Vascular reactivity is impaired in genetic females taking high-dose androgens. J Am Coll Cardiol. 1998; 32(5): 1331–1335, doi: 10.1016/s0735-1097(98)00416-1, indexed in Pubmed: 9809944.
46. Myers W, Blackstone E, Davis K, et al. CASS registry. Long term surgical survival. J Am Coll Cardiol. 1999; 33(2): 488–498, doi: 10.1016/s0735-1097(98)00563-4, indexed in Pubmed: 9973030.
47. Canto JG, Rogers WJ, Goldberg RJ, et al. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. JAMA. 2012; 307(8): 813–822, doi: 10.1001/jama.2012.199, indexed in Pubmed: 22357832.
48. Goldberg RJ, O'Donnell C, Yarzebski J, et al. Sex differences in symptom presentation associated with acute myocardial infarction: a population-based perspective. Am Heart J. 1998; 136(2): 189–195, doi: 10.1053/hj.1998.v136.88874, indexed in Pubmed: 9704678.
49. Milner KA, Vaccarino V, Arnold AL, et al. Gender and age differences in chief complaints of acute myocardial infarction (Worcester Heart Attack Study). Am J Cardiol. 2004; 93(5): 606–608, doi: 10.1016/j.amjcard.2003.11.028, indexed in Pubmed: 14996588.
50. Lichtman JH, Lorenze NP, D'Onofrio G, et al. Variation in recovery: Role of gender on outcomes of young AMI patients (VIRGO) study design. Circ Cardiovasc Qual Outcomes. 2010; 3(6): 684–693, doi: 10.1161/CIRCOUTCOMES.109.928713, indexed in Pubmed: 21081748.
51. Ferry AV, Anand A, Strachan FE, et al. Presenting symptoms in men and women diagnosed with myocardial infarction using sex-specific criteria. J Am Heart Assoc. 2019; 8(17): e012307, doi: 10.1161/JAHA.119.012307, indexed in Pubmed: 31431112.
52. Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021; 144(22): e368–e454, doi: 10.1161/CIR.0000000000001029, indexed in Pubmed: 34709879.
53. Shah ASV, Anand A, Strachan FE, et al. High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: a stepped-wedge, cluster-randomised controlled trial. Lancet. 2018; 392(10151): 919–928, doi: 10.1016/S0140-6736(18)31923-8, indexed in Pubmed: 30170853.
54. Lee KK, Ferry AV, Anand A, et al. Sex-Specific thresholds of high-sensitivity troponin in patients with suspected acute coronary syndrome. J Am Coll Cardiol. 2019; 74(16): 2032–2043, doi: 10.1016/j.jacc.2019.07.082, indexed in Pubmed: 31623760.
55. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). J Am Coll Cardiol. 2018; 72(18): 2231–2264, doi: 10.1016/j.jacc.2018.08.1038, indexed in Pubmed: 30153967.
56. Murphy B, Worcester M, Higgins R, et al. Causal attributions for coronary heart disease among female cardiac patients. J Cardiopulm Rehabil. 2005; 25(3): 135–43; quiz 144, doi: 10.1097/00008483-200505000-00002, indexed in Pubmed: 15931015.
57. Rosenfeld AG, Lindauer A, Darney BG. Understanding treatment-seeking delay in women with acute myocardial infarction: descriptions of decision-making patterns. Am J Crit Care. 2005; 14(4): 285–293, indexed in Pubmed: 15980419.
58. Moser DK, Kimble LP, Alberts MJ, et al. Reducing delay in seeking treatment by patients with acute coronary syndrome and stroke: a scientific statement from the American Heart Association Council on Cardiovascular Nursing and Stroke Council. J Cardiovasc Nurs. 2007; 22(4): 326–343, doi: 10.1097/01.JCN.0000278963.28619.4a, indexed in Pubmed: 17589286.
59. Lichtman JH, Leifheit EC, Safdar B, et al. Sex Differences in the Presentation and Perception of Symptoms Among Young Patients With Myocardial Infarction: Evidence from the VIRGO Study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients). Circulation. 2018; 137(8): 781–790, doi: 10.1161/CIRCULATIONAHA.117.031650, indexed in Pubmed: 29459463.
60. Bugiardini R, Ricci B, Cenko E, et al. Delayed care and mortality among women and men with myocardial infarction. J Am Heart Assoc. 2017; 6(8), doi: 10.1161/JAHA.117.005968, indexed in Pubmed: 28862963.

61. D'Onofrio G, Safdar B, Lichtman JH, et al. Sex differences in reperfusion in young patients with ST-segment-elevation myocardial infarction: results from the VIRGO study. Circulation. 2015; 131(15): 1324–1332, doi: 10.1161/CIRCULATIONAHA.114.012293, indexed in Pubmed: 25792558.
62. Corrigendum to: 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2021; 42(23): 2298, doi: 10.1093/eurheartj/ehab285, indexed in Pubmed: 33983428.
63. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018; 39(2): 119–177, doi: 10.1093/eurheartj/ehx393, indexed in Pubmed: 28886621.
64. Reynolds HR, Farkouh ME, Lincoff AM, et al. Impact of female sex on death and bleeding after fibrinolytic treatment of myocardial infarction in GUSTO V. Arch Intern Med. 2007; 167(19): 2054–2060, doi: 10.1001/archinte.167.19.2054, indexed in Pubmed: 17954798.
65. Woodfield S, Lundergan C, Reiner J, et al. Gender and acute myocardial infarction: Is there a different response to thrombolysis? J Am Coll Cardiol. 1997; 29(1): 35–42, doi: 10.1016/s0735-1097(96)00449-4, indexed in Pubmed: 8996292.
66. Weaver WD, White HD, Wilcox RG, et al. Comparisons of characteristics and outcomes among women and men with acute myocardial infarction treated with thrombolytic therapy. GUSTO-I investigators. JAMA. 1996; 275(10): 777–782, indexed in Pubmed: 8598594.
67. Smilowitz NR, Mahajan AM, Roe MT, et al. Mortality of Myocardial Infarction by Sex, Age, and Obstructive Coronary Artery Disease Status in the ACTION Registry-GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines). Circ Cardiovasc Qual Outcomes. 2017; 10(12): e003443, doi: 10.1161/CIRCOUTCOMES.116.003443, indexed in Pubmed: 29246884.
68. Liu J, Elbadawi A, Elgendy IY, et al. Age-Stratified sex disparities in care and outcomes in patients with ST-elevation myocardial infarction. Am J Med. 2020; 133(11): 1293–1301.e1, doi: 10.1016/j.amjmed.2020.03.059, indexed in Pubmed: 32417118.
69. Lu HT, Nordin R, Wan Ahmad WA, et al. Sex differences in acute coronary syndrome in a multiethnic asian population: results of the malaysian national cardiovascular disease database-acute coronary syndrome (NCVD-ACS) registry. Glob Heart. 2014; 9(4): 381–390, doi: 10.1016/j.gheart.2014.06.001, indexed in Pubmed: 25592791.
70. Abbott JD, Vlachos HA, Selzer F, et al. Gender-based outcomes in percutaneous coronary intervention with drug-eluting stents (from the National Heart, Lung, and Blood Institute Dynamic Registry). Am J Cardiol. 2007; 99(5): 626–631, doi: 10.1016/j.amjcard.2006.09.109, indexed in Pubmed: 17317361.
71. Giustino G, Harari R, Baber U, et al. Long-term safety and efficacy of new-generation drug-eluting stents in women with acute myocardial infarction: From the Women in Innovation and Drug-Eluting Stents (WINDES) collaboration. JAMA Cardiol. 2017; 2(8): 855–862, doi: 10.1001/jamacardio.2017.1978, indexed in Pubmed: 28658478.
72. Russ MA, Wackerl C, Zeymer U, et al. Gender based differences in drug eluting stent implantation - data from the German ALKK registry suggest underuse of DES in elderly women. BMC Cardiovasc Disord. 2017; 17(1): 68, doi: 10.1186/s12872-017-0500-y, indexed in Pubmed: 28241861.
73. Cirillo P, Di Serafino L, Patti G, et al. Gender-Related differences in antiplatelet therapy and impact on 1-year clinical outcome in patients presenting with ACS: the START ANTIPLATELET registry. Angiology. 2019; 70(3): 257–263, doi: 10.1177/0003319718783866, indexed in Pubmed: 29969919.
74. Kim C, Redberg RF, Pavlic T, et al. A systematic review of gender differences in mortality after coronary artery bypass graft surgery and percutaneous coronary interventions. Clin Cardiol. 2007; 30(10): 491–495, doi: 10.1002/clc.20000, indexed in Pubmed: 17880013.
75. Jawitz OK, Lawton JS, Thibault D, et al. Sex differences in coronary artery bypass grafting techniques: a society of thoracic surgeons database analysis. Ann Thorac Surg. 2022; 113(6): 1979–1988, doi: 10.1016/j.athoracsur.2021.06.039, indexed in Pubmed: 34280377.
76. Akhter N, Milford-Beland S, Roe MT, et al. Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). Am Heart J. 2009; 157(1): 141–148, doi: 10.1016/j.ahj.2008.08.012, indexed in Pubmed: 19081410.
77. Hao Y, Liu J, Liu J, et al. Sex differences in in-hospital management and outcomes of patients with acute coronary syndrome. Circulation. 2019; 139(15): 1776–1785, doi: 10.1161/CIRCULATIONAHA.118.037655, indexed in Pubmed: 30667281.
78. Sawaya FJ, Morice MC, Spaziano M, et al. Short-versus long-term Dual Antiplatelet therapy after drug-eluting stent implantation in women versus men: A sex-specific patient-level pooled-analysis of six randomized trials. Catheter Cardiovasc Interv. 2017; 89(2): 178–189, doi: 10.1002/ccd.26653, indexed in Pubmed: 27426936.
79. Chichareon P, Modolo R, Kerkmeijer L, et al. Association of sex with outcomes in patients undergoing percutaneous coronary intervention: a subgroup analysis of the GLOBAL LEADERS randomized clinical trial. JAMA Cardiol. 2020; 5(1): 21–29, doi: 10.1001/jamacardio.2019.4296, indexed in Pubmed: 31693078.
80. Vogel B, Baber U, Cohen DJ, et al. Sex differences among patients with high risk receiving ticagrelor with or without aspirin after percutaneous coronary intervention: A subgroup analysis of the TWILIGHT randomized clinical trial. JAMA Cardiol. 2021; 6(9): 1032–1041, doi: 10.1001/jamacardio.2021.1720, indexed in Pubmed: 33991416.
81. Hague W, Forder P, Simes J, et al. Effect of pravastatin on cardiovascular events and mortality in 1516 women with coronary heart disease: results from the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study. Am Heart J. 2003; 145(4): 643–651, doi: 10.1067/mhj.2003.1, indexed in Pubmed: 12679760.
82. Rouleau J. Improved outcome after acute coronary syndromes with an intensive versus standard lipid-lowering regimen: results from the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial. Am J Med. 2005; 118 Suppl 12A: 28–35, doi: 10.1016/j.amjmed.2005.09.014, indexed in Pubmed: 16356805.
83. Peters SAE, Colantonio LD, Zhao H, et al. Sex differences in high-intensity statin use following myocardial infarction in the United States. J Am Coll Cardiol. 2018; 71(16): 1729–1737, doi: 10.1016/j.jacc.2018.02.032, indexed in Pubmed: 29673463.
84. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017; 376(18): 1713–1722, doi: 10.1056/NEJMoa1615664, indexed in Pubmed: 28304224.
85. Cordero A, Fernández Del Olmo MR, Cortez Quiroga GA, et al. Sex differences in low-density lipoprotein cholesterol reduction with PCSK9 inhibitors in real-world patients: the LIPID-REAL registry. J Cardiovasc Pharmacol. 2022; 79(4): 523–529, doi: 10.1097/FJC.0000000000001205, indexed in Pubmed: 34983910.
86. Krawczyk-Ożóg A, Płotek A, Hołda M, et al. Assessment of the implementation level of the guidelines for secondary prevention of cardiovascular disease in everyday clinical practice. Kardiol Pol. 2021; 79(4): 434–441, doi: 10.33963/KP.15856, indexed in Pubmed: 33687867.
87. Ndrepepa G, Berger PB, Mehilli J, et al. Periprocedural bleeding and 1-year outcome after percutaneous coronary interventions: appropriateness of including bleeding as a component of a quadruple end point. J Am Coll Cardiol. 2008; 51(7): 690–697, doi: 10.1016/j.jacc.2007.10.040, indexed in Pubmed: 18279731.
88. Lindsey J, Marso S, Pencina M, et al. Prognostic impact of periprocedural bleeding and myocardial infarction after percutaneous coronary intervention in unselected patients. JACC: Cardiovascular Interventions. 2009; 2(11): 1074–1082, doi: 10.1016/j.jcin.2009.09.002.
89. Burgess SN, Juergens CP, Nguyen TL, et al. Comparison of late cardiac death and myocardial infarction rates in women vs men with ST-elevation myocardial infarction. Am J Cardiol. 2020; 128: 120–126, doi: 10.1016/j.amjcard.2020.04.044, indexed in Pubmed: 32650905.
90. Rymer JA, Kaltenbach LA, Kochar A, et al. Comparison of rates of bleeding and vascular complications before, during, and after trial enrollment in the SAFE-PCI trial for women. Circ Cardiovasc Interv. 2019; 12(5): e007086, doi: 10.1161/CIRCINTERVENTIONS.118.007086, indexed in Pubmed: 31014090.

91. Baklanov DV, Kim S, Marso SP, et al. Comparison of bivalirudin and radial access across a spectrum of preprocedural risk of bleeding in percutaneous coronary intervention: analysis from the national cardiovascular data registry. Circ Cardiovasc Interv. 2013; 6(4): 347–353, doi: 10.1161/CIRCINTERVENTIONS.113.000279, indexed in Pubmed: 23922144.
92. Kovacic JC, Mehran R, Karajgikar R, et al. Female gender and mortality after percutaneous coronary intervention: results from a large registry. Catheter Cardiovasc Interv. 2012; 80(4): 514–521, doi: 10.1002/ccd.23338, indexed in Pubmed: 22045678.
93. Pancholy SB, Shantha GP, Patel T, et al. Sex differences in short-term and long-term all-cause mortality among patients with ST-segment elevation myocardial infarction treated by primary percutaneous intervention: a meta-analysis. JAMA Intern Med. 2014; 174(11): 1822–1830, doi: 10.1001/jamainternmed.2014.4762, indexed in Pubmed: 25265319.
94. Kunadian V, Qiu W, Lagerqvist Bo, et al. Gender differences in outcomes and predictors of all-cause mortality after percutaneous coronary intervention (data from United Kingdom and Sweden). Am J Cardiol. 2017; 119(2): 210–216, doi: 10.1016/j.amjcard.2016.09.052, indexed in Pubmed: 27816119.
95. Potts J, Sirker A, Martinez SC, et al. Persistent sex disparities in clinical outcomes with percutaneous coronary intervention: Insights from 6.6 million PCI procedures in the United States. PLoS One. 2018; 13(9): e0203325, doi: 10.1371/journal.pone.0203325, indexed in Pubmed: 30180201.
96. MacIntyre K, Stewart S, Capewell S, et al. Gender and survival: a population-based study of 201,114 men and women following a first acute myocardial infarction. J Am Coll Cardiol. 2001; 38(3): 729–735, doi: 10.1016/s0735-1097(01)01465-6, indexed in Pubmed: 11527625.
97. Vaccarino V, Parsons L, Every NR, et al. Sex-based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 Participants. N Engl J Med. 1999; 341(4): 217–225, doi: 10.1056/NEJM199907223410401, indexed in Pubmed: 10413733.
98. Wojtyniak B, Gierlotka M, Opolski G, et al. Observed and relative survival and 5-year outcomes of patients discharged after acute myocardial infarction: the nationwide AMI-PL database. Kardiol Pol. 2020; 78(10): 990–998, doi: 10.33963/KP.15465, indexed in Pubmed: 32631026.
99. Bukkapatnam RN, Yeo KK, Li Z, et al. Operative mortality in women and men undergoing coronary artery bypass grafting (from the California Coronary Artery Bypass Grafting Outcomes Reporting Program). Am J Cardiol. 2010; 105(3): 339–342, doi: 10.1016/j.amjcard.2009.09.035, indexed in Pubmed: 20102945.

The occurrence of drug-induced side effects in women and men with arterial hypertension and comorbidities

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ABSTRACT

Background: Women have been underrepresented in large clinical trials in hypertension, and the incidence of adverse drug reactions by sex has been not sufficiently described.

Aims: The aim of the study was to determine the prevalence of adverse drug reactions in women and men with arterial hypertension and comorbidities and to assess the specific predisposing factors for adverse drug reactions by sex.

Methods: The study population comprised consecutive hospitalized patients diagnosed with arterial hypertension and patients treated in an outpatient clinic, whose recruitment started in January 2019 aiming to reach 1000 participants. A structured questionnaire was used to gather the patients' demographic and clinical data and current or past cases of adverse drug reactions.

Results: The study included 560 women and 440 men, with mean (standard deviation) age of 62.84 (14.96) years. Women were older than men, had a longer hypertension history, and suffered less frequently from other cardiovascular diseases. Women reported more frequently adverse drug reactions. The risk of drug-induced side effects in women increased with age ($P = 0.03$) and with coexistence of any respiratory disease ($P = 0.04$). In the case of male sex, the risk of adverse drug reactions increased with the occurrence of hypercholesterolemia ($P = 0.03$), and coexistence of any analyzed metabolic diseases ($P = 0.04$).

Conclusions: Adverse drug reactions were reported more frequently by women. Older age and the presence of any respiratory disease increased the risk of adverse drug reactions in women, while in men, the risk was increased mainly by the presence of hypercholesterolemia or other metabolic diseases.

Key words: comorbidities, drug-related adverse events, hypertension

INTRODUCTION

Elevated blood pressure is one of the leading causes of premature morbidity and mortality worldwide. The number of patients with arterial hypertension has been steadily increasing, according to the Non-Communicable Diseases Risk Factor Collaboration analysis, doubling between 1990 and 2019 to amount to over 1.2 billion people by the end of that period. According to a data forecast for 2025, 1.5 billion people will have hypertension by 2025 [1]. Such a high prevalence of arterial hypertension is being reported throughout the world, regardless of the wealth of a given country [2].

Hypertension rarely occurs as an isolated disease entity. It is often accompanied by other risk factors for cardiovascular diseases, such as type 2 diabetes, hypercholesterolemia, gout, or obesity, as well as clinically overt complications of the cardiovascular system,

WHAT'S NEW?

Among men and women with arterial hypertension, older age and the presence of any respiratory disease are associated with a more frequent history of adverse drug reactions in women, while in men such association of adverse drug reactions was detected mainly for the presence of hypercholesterolemia or other metabolic diseases.

such as ischemic heart disease, heart failure (HF), and atrial fibrillation (AF), which thus constitute an additional therapeutic challenge [3].

Treatment for high blood pressure involves two main approaches applied alone or most often in combination, i.e., lifestyle changes and drug therapy. For patients with hypertension and comorbidities, pharmacological treatment is necessary in the vast majority of cases since the cardiovascular risk for these patients is high or very high.

The main goal of treatment is to maintain blood pressure within the correct range, which thereby reduces the risk of complications and premature cardiovascular mortality and is also of key importance in ensuring patient adherence to a pharmacotherapy regimen [4].

Patients with arterial hypertension and comorbidities are for the most part elderly subjects on multiple medications. Such a patient profile is closely associated with the problem of disease acceptance, which is defined as acknowledging and coming to terms with the existence of a medical condition that cannot be changed permanently and to which the patient must become accustomed [5]. Poor disease acceptance is often associated with arbitrary discontinuation of drug therapy [6].

The current European Society of Cardiology/European Society of Hypertension 2018 guidelines for the management of arterial hypertension recommend the same target blood pressure values and therapeutic management program for both sexes, although in actual clinical practice a correlation exists between a patient's sex and the management and effects of their treatment [3]. Population-wise, control of arterial hypertension is least effective in young men and older women. Sex is another factor that impacts the choice of antihypertensive drug class [7, 8]. Men are more often prescribed angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists and beta-blockers than women, while more women than men receive diuretics and calcium antagonists [8]. Despite a large number of clinical drug trials for hypertension, women are underrepresented in these trials, or no sex sub-analysis is performed with regard to the effects of treatment. Likewise, the incidence of adverse drug reactions by sex is insufficiently reported in the literature. Meanwhile, the occurrence of adverse drug reactions may significantly affect the quality of life of patients with arterial hypertension and comorbidities, as well as their disease acceptance, and result in arbitrary drug discontinuation, thereby leading to a poorer cardiovascular prognosis.

This study aimed to determine the frequency of adverse drug reactions in women and men with arterial hypertension and comorbidities and to assess the sex-specific predisposing factors leading to their occurrence.

METHODS

The study included patients of both sexes hospitalized in the Department of Cardiology, Interventional Electrocardiology and Hypertension at the University Hospital in Kraków, in whom arterial hypertension was the underlying diagnosis or had been identified as comorbidity, as well as patients undergoing chronic treatment in the outpatient hypertension clinic. The recruitment started in January 2019 aiming to reach 1000 participants.

The study population comprised 1000 people, of whom 560 were women.

The inclusion criteria for the study were as follows: age over 18 years, a diagnosis of essential arterial hypertension, duration of the disease of more than one year, and signed informed consent to participate in the study. Exclusion criteria were as follows: symptoms of dementia severe enough to prevent the participant from completing the questionnaires, secondary arterial hypertension.

The study was conducted in line with the Declaration of Helsinki and approved by the local Bioethics Committee (no. 1072.6120.261.2017). Before the study began, each participant had signed informed consent.

For the study, the authors used a structured proprietary questionnaire, which the patients filled in independently or with the help of a research team member either during their hospitalization or while waiting for an appointment at the clinic. The survey consisted of 22 questions covering various demographic and clinical factors. The patients' declared comorbidities and risk factors for cardiovascular diseases, as well as all medications currently being taken. All those data were verified by analyzing available medical documentation. The patients also indicated when their arterial hypertension was diagnosed and they started to be treated.

The next part of the questionnaire focused on the occurrence of any drug-related adverse events experienced by the patients either at present or in the past. If the answer was affirmative, the patient was asked to provide the name of the drug, the type of symptoms they experienced, and their severity. The patients also provided information about their reactions to the occurrence of side effects (arbitrary drug discontinuation, additional consultation with a doctor, reading medication leaflets). Multiple-drug intolerance was

defined as the occurrence of side effects after taking 3 or more classes of drugs.

Statistical analysis

The analysis was performed using the R statistical package, version 3.5.1 (http://cran.r-project.org). The normality of the distribution of quantitative variables was verified with the Shapiro-Wilk test, as well as on the basis of a visual assessment of the histograms. Nominal data were described using frequency measures: n count and % of the group. The ordinal data were presented on the basis of the median (interquartile range [IQR]) and quantitative variables using the mean and standard deviation. A comparison of the groups with regard to individual parameters was made using the following tests: χ^2 or Fisher's exact tests for nominal variables and Student's t-tests, Mann-Whitney U tests for ordinal and quantitative variables, depending on the situation. Additionally, logistic regression analysis was performed to identify the parameters that predict the occurrence of drug-induced side effects. A multivariable analysis was performed with selected variables based on the stepwise "backward" method and applying the Akaike information criterion. As a starting point for the multivariable models, the variables applied were those that in one-dimensional models had a value of P <0.25 in the Wald test.

A multivariable regression model was provided using the stepwise method based on the Akaike information criterion. The model evaluation criteria included: the χ^2 test (P <0.001), Nagelkerke's pseudo r-squared measures = 0.08, the Hosmer-Lemeshow goodness-of-fit test (P = 0.14), and variance inflation factor index (range: 1.01–1.12).

The significance level adopted in the tests was $\alpha = 0.05$.

RESULTS

A total of 1 000 patients participated in the study, 560 of whom were women and 440 men. The mean (standard deviation [SD]) age of the group as a whole was 62.84 (14.96) years, and their ages ranged from 19 to 103 years. The average (SD) body mass index of the study cohort was 27.86 (4.84) kg/m^2.

A comparison between men and women in the study group revealed significant differences in terms of age (P = 0.004), the duration of hypertension (P = 0.04), and the number of cardiovascular diseases reported (P <0.001). Women were significantly older, had longer hypertensive disease duration, and had fewer comorbid cardiovascular diseases than men.

Women suffered from certain comorbidities significantly less frequently than men: coronary artery disease (CAD) (P <0.001), past myocardial infarction (MI) (P <0.001), HF (P <0.001), AF (P = 0.004), and hypercholesterolemia (P = 0.001), but they reported a higher prevalence of rheumatoid diseases (P = 0.001) and endocrine disorders (P <0.001).

Women took significantly fewer drugs of any class (P = 0.02), as well as fewer cardiac drugs (per tablet), other than antihypertensive drugs (P <0.001). As regards particular classes of drugs, women received the following significantly more frequently than men: angiotensin receptor antagonists (P = 0.008) and rheumatological drugs (P = 0.03). On the other hand, they were prescribed the following far less frequently: antiplatelet drugs (P <0.001), statins (P = 0.003), and cardiac drugs, other than antihypertensive drugs (P = 0.02) (Table 1).

More women than men reported a history of drug intolerance (P <0.001). The same was true in the case of multiple-drug intolerance (P = 0.006). Far more women than men experienced intolerance to such drugs as antibiotics (P = 0.004) and analgesics (P = 0.004). Women were also far more likely to report side effects (P <0.001). As regards specific side effects, women reported the following conditions far more frequently than men: hypotension (P = 0.02), coughing (P <0.001), edema (P = 0.001), bradycardia (P = 0.04), and skin lesions (P = 0.01) (Table 2).

Significant differences in terms of age were observed between women reporting adverse drug reactions and women not reporting such effects (P <0.001), with women from the former group being older. Women who experienced side effects also reported a significantly higher number of cardiac diseases (P = 0.02), other diseases (P <0.001), and any diseases in general (P <0.001). The following specific comorbidities were more common among women reporting adverse drug reactions compared to women without such reactions: CAD (P = 0.02), past MI (P = 0.02), HF (P = 0.002), respiratory diseases (P = 0.02), and rheumatoid diseases (P = 0.03) (Table 3).

No significant difference was observed between the two groups of women in terms of the number of drugs taken of any class (P = 0.51), in the number of tablets of antihypertensive drugs taken (P = 0.34), or in the number of cardiovascular drugs taken per tablet without antihypertensive drugs (P = 0.44). In the case of specific drug classes, antiplatelet drugs were prescribed significantly more frequently to women reporting adverse drug reactions than to women without adverse drug-induced symptoms (24% vs. 12%; P <0.001), but calcium antagonists were received significantly less frequently by women with adverse drug reaction than by women who had no adverse drug reactions (30% vs. 48%; P <0.001) (Table 3).

Then, a multivariable analysis was performed to determine the occurrence of drug-induced side effects in women. First, single-factor models were constructed, on the basis of which the variables were selected in the multi-factor model.

The multivariable logistic regression model indicated that the risk of drug-induced side effects in women increased significantly with age, odds ratio (OR), 1.01; 95% confidence interval (CI), 1.002, 1.03; P = 0.03, as well as with the presence of respiratory diseases; OR, 1.76; 95% CI, 1.02, 3.10; P = 0.04. The other variables in the multivariable model remained insignificant for the risk of drug side effects (Figure 1A).

Table 1. Characteristics of the study population by sex

	Men (n = 440)	Women (n = 560)	*P*-value
Age, years, mean (SD)	61.29 (15.43)	64.05 (14.49)	0.004
BMI, kg/m^2, mean (SD)	27.96 (4.52)	27.78 (5.07)	0.55
Duration of hypertension, median (IQR)	10.00 (5.00–17.25)	23.00 (10.00–30.00)	0.04
Cardiovascular diseases, number, median (IQR)	3.00 (1.00–4.00)	2.00 (1.00–2.00)	<0.001
Other diseases, number, median (IQR)	1.00 (0.00–3.00)	2.00 (1.00–3.00)	0.44
Diseases in general, number, median (IQR)	4.00 (2.00–7.00)	3.00 (2.00–5.25)	0.05
Comorbidities, n (%)			
CAD	136 (30.9)	105 (18.8)	<0.001
Past MI	90 (20.5)	56 (10.0)	<0.001
HF	104 (23.6)	75 (13.4)	<0.001
Heart arrhythmia	55 (12.5)	66 (11.8)	0.81
AF	84 (19.1)	69 (12.3)	0.004
Hypercholesterolemia	244 (55.5)	248 (44.3)	0.001
Other cardiovascular diseases	123 (28.0)	144 (25.7)	0.47
Respiratory diseases	52 (11.8)	68 (12.1)	0.95
Gastrointestinal diseases	55 (12.5)	80 (14.3)	0.47
Neurological diseases	40 (9.1)	47 (8.4)	0.78
Dermatological diseases	12 (2.7)	11 (2.0)	0.56
Rheumatoid disorders	28 (6.4)	74 (13.2)	0.001
Metabolic disorders	99 (22.5)	120 (21.4)	0.74
Diabetes	130 (29.5)	144 (25.7)	0.20
Mental disorders	12 (2.7)	24 (4.3)	0.25
Endocrine disorders	36 (8.2)	136 (24.3)	<0.001
Cancer	26 (5.9)	37 (6.6)	0.75
Non-cardiovascular diseases	172 (39.1)	189 (33.8)	0.09
Concomitant diseases, n (%)	327 (74.3)	430 (76.8)	0.41
Total number of drugs taken, median (IQR)	6.00 (3.00–7.00)	5.00 (3.00–7.00)	0.02
Classes of drug, n (%)			
ACEI	246 (55.9)	293 (52.3)	0.29
Beta-blockers	282 (64.1)	331 (59.1)	0.12
ARB	64 (14.5)	119 (21.3)	0.008
Calcium antagonists	167 (38.0)	215 (38.4)	0.94
Diuretics	231 (52.5)	281 (50.2)	0.51
Antihypertensive drugs	91 (20.7)	93 (16.6)	0.12
Antiplatelet medications	140 (31.8)	103 (18.4)	<0.001
Anticoagulants	81 (18.4)	77 (13.8)	0.06
Statins	243 (55.2)	255 (45.5)	0.003
Other cardiovascular drugs	211 (48.0)	267 (47.7)	0.98
Cardiovascular medications	418 (95.0)	525 (93.8)	0.48
Antihypertensive drugs	410 (93.2)	508 (90.7)	0.20
Cardiovascular medications without antihypertensive drugs	327 (74.3)	378 (67.5)	0.02
Number of cardiovascular medications in tablet form without antihypertensive drugs, median (IQR)	2.00 (0.00–3.00)	1.00 (0.00–2.00)	<0.001
Number of antihypertensive drugs in tablet form, median (IQR)	2.00 (1.00–3.00)	2.00 (1.00–3.00)	0.43
Drugs for respiratory disorders	23 (5.2)	28 (5.0)	0.99
Drugs for neurological disorders	20 (4.5)	14 (2.5)	0.11
Drugs for mental disorders	15 (3.4)	19 (3.4)	0.99
Drugs for dermatological disorders	1 (0.2)	3 (0.5)	0.79
Drugs for metabolic disorders	120 (27.3)	140 (25.0)	0.46
Drugs for rheumatoid disorders	2 (0.5)	13 (2.3)	0.03
Other non-cardiovascular drugs	130 (29.5)	182 (32.5)	0.35
Any other medications	223 (50.7)	294 (52.5)	0.61
Any drugs in total	421 (95.7)	535 (95.5)	0.99

The data are presented as n (of the group) unless otherwise stated. The groups were compared using the χ^2 test or Fisher's exact test for percentages and Student's t-test or the Mann-Whitney U test for quantitative variables

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; HF, heart failure; IQR, interquartile range; MI, myocardial infarction; SD, standard deviation

Table 2. Prevalence of drug intolerance and side effects by sex

	Men (n = 440)	Women (n = 560)	*P*-value
Drug intolerance, n (%)	179 (40.7)	300 (53.6)	<0.001
1 drug	133 (30.2)	184 (32.9)	0.40
2 drugs	23 (5.2)	59 (10.5)	0.003
3 drugs or more	23 (5.2)	57 (10.2)	0.006
Incidences of drug intolerance, median (IQR)	0.00 (0.00–1.00)	1.00 (0.00–1.00)	<0.001
ACEI	18 (4.1)	27 (4.8)	0.69
Beta-blockers	7 (1.6)	14 (2.5)	0.44
ARB	5 (1.1)	5 (0.9)	0.95
Calcium antagonists	9 (2.0)	18 (3.2)	0.35
Diuretics	7 (1.6)	10 (1.8)	>1.00
Antihypertensive drugs	4 (0.9)	11 (2.0)	0.27
Antiplatelet medications	7 (1.6)	21 (3.8)	0.063
Anticoagulants	7 (1.6)	6 (1.1)	0.66
Statins	6 (1.4)	13 (2.3)	0.39
Antibiotics	52 (11.8)	105 (18.8)	0.004
Analgesics	26 (5.9)	64 (11.4)	0.004
Other cardiovascular drugs	6 (1.4)	12 (2.1)	0.50
Other non-cardiovascular medications	80 (18.2)	137 (24.5)	0.02
Adverse effects, n (%)	178 (40.5)	292 (52.1)	<0.001
1 adverse effect	84 (19.1)	116 (20.7)	0.58
2 adverse effects	30 (6.8)	57 (10.2)	0.08
3 adverse effects	43 (9.8)	62 (11.1)	0.58
4 adverse effects	10 (2.3)	26 (4.6)	0.07
5 or more	11 (2.5)	31 (5.5)	0.03
Adverse effects, median (IQR)	0.00 (0.00–1.00)	1.00 (0.00–2.00)	<0.001
Type of adverse effect, n (%)			
Electrolyte imbalances	1 (0.2)	4 (0.7)	0.53
Hypotonia	15 (3.4)	39 (7.0)	0.02
Cough	15 (3.4)	53 (9.5)	<0.001
Edema	14 (3.2)	48 (8.6)	0.001
Bradycardia	8 (1.8)	24 (4.3)	0.04
Skin lesions	64 (14.5)	117 (20.9)	0.01
Gastrointestinal disorders	21 (4.8)	43 (7.7)	0.08
Other	139 (31.6)	226 (40.4)	0.005
Allergic reaction	76 (17.3)	125 (22.3)	0.06
Bleeding	9 (2.0)	11 (2.0)	>0.999
Abnormal laboratory test results	3 (0.7)	7 (1.3)	0.57
Muscle pain	5 (1.1)	10 (1.8)	0.56

Data are presented as n (% of the group) unless otherwise stated. The groups were compared using the χ^2 test or Fisher's exact test for percentages and the Mann-Whitney U-test for quantitative variables

Abbreviations: see Table 1

A comparison of men reporting adverse drug reactions with those not confirming such reactions revealed a significant age difference ($P = 0.001$), with men from the former group being older. The men who experienced no side effects also reported a significantly greater number of cardiovascular diseases ($P < 0.001$), other diseases ($P < 0.001$), and any diseases in general ($P < 0.001$) compared with other men. For specific comorbidities, men reported adverse drug reactions from the following conditions significantly more frequently than men without adverse drug reactions: CAD ($P < 0.001$), past MI ($P = 0.004$), HF ($P = 0.001$), AF ($P = 0.01$), hypercholesterolemia ($P = 0.02$), and metabolic diseases ($P = 0.02$) (Table 4).

Men reporting side effects took significantly more drugs of any class ($P = 0.04$) and received far more cardiovascular drugs per tablet except antihypertensive drugs ($P < 0.001$). When it came to specific classes of drugs, men reported adverse drug reactions for the following medications more frequently than men without adverse drug reactions: antiplatelet drugs ($P = 0.02$), anticoagulants ($P = 0.03$), and cardiovascular medications, except for antihypertensive drugs ($P = 0.006$). For calcium antagonists (CA), men receiving CA significantly less often reported adverse drug reactions than those not treated by CA ($P = 0.02$) (Table 4).

First, single-factor models were constructed, on the basis of which variables were selected for the multi-factor model. Then, a multivariable analysis was performed to determine predictors of drug-induced side effects in men.

The multivariable logistic regression model for men indicated that the risk of drug-induced side effects increased with hypercholesterolemia (OR, 1.53; 95% CI, 1.03–2.27;

Table 3. Comparison of women reporting adverse drug reactions with women not reporting adverse drug reactions in association with comorbidities and classes of drug taken

Women	Reporting no adverse drug reactions (n = 260)	Reporting adverse drug events (n = 300)	*P*-value
Age, years, mean (SD)	61.74 (13.81)	66.06 (14.78)	<0.001
BMI, kg/m^2, mean (SD)	27.74 (5.01)	27.81 (5.14)	0.86
Cardiovascular diseases, number, median (IQR)	2.00 (1.00–2.00)	2.00 (1.00–3.00)	0.02
Other diseases, number, median (IQR)	1.00 (0.00–3.00)	2.00 (1.00–3.00)	<0.001
Diseases in general, number, median (IQR)	3.00 (2.00–5.00)	4.00 (2.00–6.00)	<0.001
Comorbidities, n (%)			
CAD	37 (14.2)	68 (22.7)	0.02
Past MI	17 (6.5)	39 (13.0)	0.02
HF	22 (8.5)	53 (17.7)	0.002
Heart arrhythmia	33 (12.7)	33 (11.0)	0.63
AF	28 (10.8)	41 (13.7)	0.36
Hypercholesterolemia	113 (43.5)	135 (45.0)	0.78
Other cardiovascular drugs	57 (21.9)	87 (29.0)	0.07
Cardiovascular system	259 (99.6)	299 (99.7)	>0.99
Respiratory system	22 (8.5)	46 (15.3)	0.02
Gastrointestinal system	30 (11.5)	50 (16.7)	0.11
Nervous system	22 (8.5)	25 (8.3)	>0.99
Dermatological diseases	4 (1.5)	7 (2.3)	0.71
Rheumatoid disorders	25 (9.6)	49 (16.3)	0.03
Metabolic disorders	50 (19.2)	70 (23.3)	0.28
Diabetes	67 (25.8)	77 (25.7)	>0.99
Mental disorders	9 (3.5)	15 (5.0)	0.49
Endocrine disorders	55 (21.2)	81 (27.0)	0.13
Cancer	13 (5.0)	24 (8.0)	0.21
Non-cardiovascular diseases	182 (70.0)	248 (82.7)	0.001
Concomitant diseases	260 (100.0)	300 (100.0)	>0.99
Total number of drugs taken, median (IQR)	5.00 (3.00–7.00)	5.00 (3.00–7.00)	0.51
Classes of drug, n (%)			
ACEI	144 (55.4)	149 (49.7)	0.21
Beta-blockers	157 (60.4)	174 (58.0)	0.63
ARB	52 (20.0)	67 (22.3)	0.57
Calcium antagonists	124 (47.7)	91 (30.3)	<0.001
Diuretics	132 (50.8)	149 (49.7)	0.86
Antihypertensive drugs	51 (19.6)	42 (14.0)	0.10
Antiplatelet medications	30 (11.5)	73 (24.3)	<0.001
Anticoagulants	32 (12.3)	45 (15.0)	0.42
Statins	124 (47.7)	131 (43.7)	0.39
Other cardiovascular drugs	120 (46.2)	147 (49.0)	0.56
Cardiovascular medications	247 (95.0)	278 (92.7)	0.34
Antihypertensive drugs	239 (91.9)	269 (89.7)	0.44
Cardiovascular medications without antihypertensive drugs	175 (67.3)	203 (67.7)	0.99
Number of cardiovascular medications in tablet form without antihypertensive drugs, median (IQR)	1.00 (0.00–2.00)	1.00 (0.00–3.00)	0.44
Number of antihypertensive drugs in tablet form, median (IQR)	2.00 (1.00–3.00)	2.00 (1.00–3.00)	0.34
Drugs for respiratory disorders	8 (3.1)	20 (6.7)	0.08
Drugs for neurological disorders	4 (1.5)	10 (3.3)	0.28
Drugs for mental disorders	8 (3.1)	11 (3.7)	0.88
Drugs for dermatological disorders	1 (0.4)	2 (0.7)	0.99
Drugs for metabolic disorders	66 (25.4)	74 (24.7)	0.92
Drugs for rheumatoid disorders	5 (1.9)	8 (2.7)	0.76
Other non-cardiovascular drugs	76 (29.2)	106 (35.3)	0.15
Any other medications	127 (48.8)	167 (55.7)	0.13
Any drugs in total	252 (96.9)	283 (94.3)	0.20

Data are presented as n (% of the group) unless otherwise stated. The groups were compared using the χ^2 test or Fisher's exact test for percentages and Student's t-test or the Mann-Whitney U test for quantitative variables

Abbreviations: see Table 1

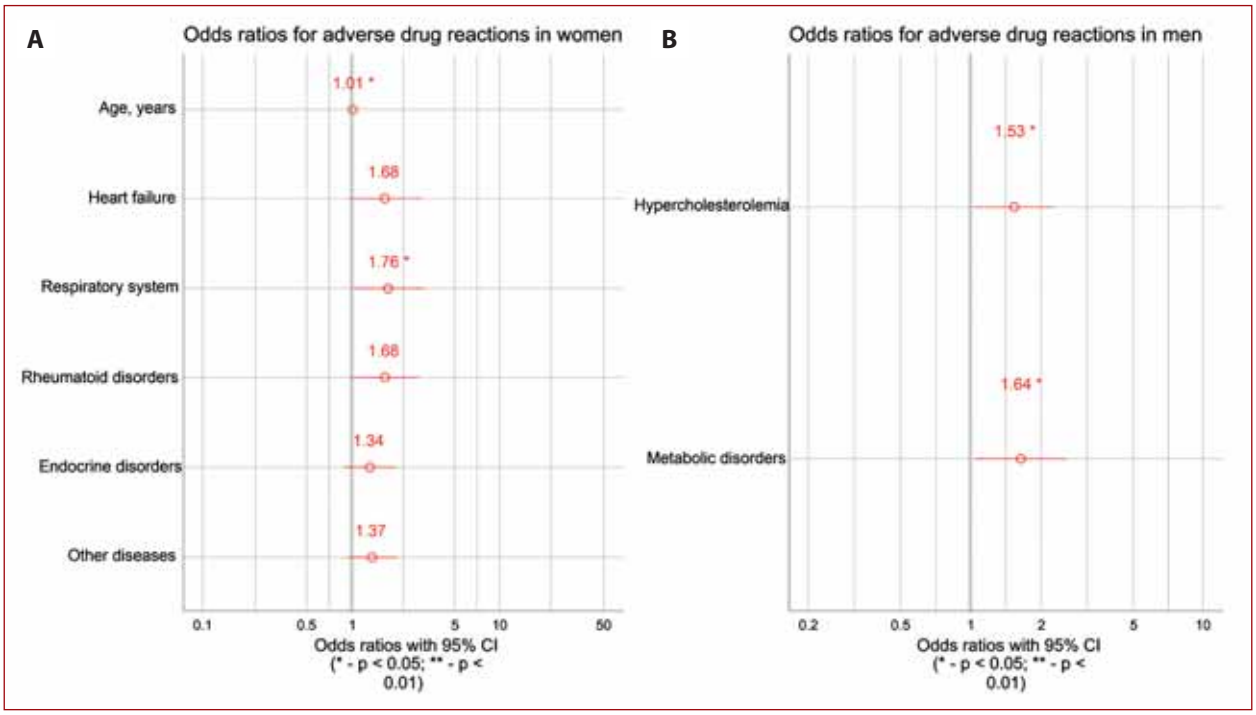

Figure 1. Multivariable logistic regression analysis for adverse drug reactions in women (**A**) and men (**B**)

P = 0.03) and metabolic diseases (OR, 1.64; 95% CI, 1.03, 2.59; P = 0.04) (Figure 1B).

DISCUSSION

In the present study, we observed the frequent incidence of adverse drug reactions in women and men with hypertension. The occurrence of drug-induced adverse events is a common phenomenon in healthcare and is inevitable given the polypharmacotherapy regimens followed today.

In a meta-analysis of 33 studies covering a total of over 1.5 million patients in general practice, the average incidence of drug-induced adverse events was estimated at 8.32%. However, this figure depended largely on the characteristics of the study population and ranged from 0.87% in a Spanish study of young healthy participants up to 65.35% in a study of American general practice treating elderly patients with comorbidities [9].

The frequency of adverse drug-induced symptoms in our participants, i.e., 54% in the case of the female patients and 41% for the male patients, was related with the age of the study population, the average being 62.84 years, as well as the presence of various comorbidities such as CAD, HF, AF, hypercholesterolemia, diabetes, respiratory disorders, and diseases of the digestive system, i.e., factors which promote polypharmacy and, as a result, increase a patient's risk of any drug-related events [10].

A review of the literature, encompassing 47 articles describing the incidence of drug-induced adverse reactions in European hospitals or clinics, showed that, based on 22 studies, the average rate of hospitalization for drug-induced adverse reactions was 3.5%, while drug-induced symptoms observed during hospitalization affected on average 10.1% of patients, based on 13 studies.

Only 5 studies were included that assessed outpatient drug-related adverse events. This indicates a lack of information on the epidemiology of drug-induced adverse events among general practitioners or specialist clinics.

However, it can be assumed that the incidence of such events may be higher than in patients requiring hospitalization [11].

The factors that increased the risk of drug-induced adverse events in our female study participants included age and respiratory diseases, while the predisposing factors leading to an increased risk of adverse drug reactions in men were hypercholesterolemia and other metabolic diseases such as diabetes, gout, obesity, and osteoporosis. The occurrence of adverse effects after taking drugs used to treat respiratory diseases, especially inhaled drugs, has been described in the data collected by the pharmaceutical regulatory authority in Portugal over a period of 10 years [12]. A review of the literature covering 75 studies, including 3 meta-analyses, found that the incidence of adverse reactions increased significantly with age, e.g., in the case of cardiovascular drugs, the rate was 20% of the general population, and this percentage increased to 50% in older populations [13].

The frequent occurrence of drug-induced adverse events in patients with metabolic diseases, especially diabetes, was also noted in the Portuguese data, although in the latter case the problem was more frequently ob-

Table 4. A comparison of men reporting adverse drug reactions associated with comorbidities and classes of drug taken with men not reporting adverse drug reactions

Men	Not reporting adverse drug reactions (n = 261)	Reporting adverse drug reactions (n = 179)	*P*-value
Age, years, mean (SD)	59.28 (14.86)	64.21 (15.83)	0.001
BMI, kg/m^2, mean (SD)	27.97 (4.78)	27.95 (4.14)	0.97
Cardiovascular diseases, number, median (IQR)	2.00 (1.00–3.00)	3.00 (2.00–4.50)	<0.001
Other diseases, number, median (IQR)	1.00 (0.00–2.00)	2.00 (1.00–4.00)	<0.001
Diseases in general, number, median (IQR)	3.00 (2.00–5.00)	5.00 (3.00–8.00)	<0.001
Comorbidities, n (%)			
CAD	60 (23.0)	76 (42.5)	<0.001
Past MI	41 (15.7)	49 (27.4)	0.004
HF	46 (17.6)	58 (32.4)	0.001
Heart arrhythmia	30 (11.5)	25 (14.0)	0.53
AF	39 (14.9)	45 (25.1)	0.01
Hypercholesterolemia	132 (50.6)	112 (62.6)	0.02
Other cardiovascular drugs	53 (20.3)	70 (39.1)	<0.001
Cardiovascular system	261 (100.0)	179 (100.0)	1
Respiratory system	25 (9.6)	27 (15.1)	0.11
Gastrointestinal system	29 (11.1)	26 (14.5)	0.36
Nervous system	22 (8.4)	18 (10.1)	0.68
Dermatological diseases	5 (1.9)	7 (3.9)	0.34
Rheumatoid disorders	19 (7.3)	9 (5.0)	0.45
Metabolic disorders	48 (18.4)	51 (28.5)	0.02
Diabetes	77 (29.5)	53 (29.6)	1
Mental disorders	5 (1.9)	7 (3.9)	0.34
Endocrine disorders	21 (8.0)	15 (8.4)	1
Cancer	12 (4.6)	14 (7.8)	0.23
Other non-cardiovascular diseases	80 (30.7)	92 (51.4)	<0.001
Other diseases	188 (72.0)	139 (77.7)	0.22
Diseases of any kind	261 (100.0)	179 (100.0)	1
Total number of drugs taken, median (IQR)	5.00 (3.00–7.00)	6.00 (3.50–8.00)	0.04
Classes of drug, n (%)			
ACEI	154 (59.0)	92 (51.4)	0.14
Beta-blockers	166 (63.6)	116 (64.8)	0.88
ARB	35 (13.4)	29 (16.2)	0.50
Calcium antagonists	111 (42.5)	56 (31.3)	0.02
Diuretics	145 (55.6)	86 (48.0)	0.15
Antihypertensive drugs	55 (21.1)	36 (20.1)	0.90
Antiplatelet medications	71 (27.2)	69 (38.5)	0.02
Anticoagulants	39 (14.9)	42 (23.5)	0.03
Statins	136 (52.1)	107 (59.8)	0.14
Other cardiovascular drugs	110 (42.1)	101 (56.4)	0.004
Cardiovascular medications	249 (95.4)	169 (94.4)	0.81
Antihypertensive drugs	246 (94.3)	164 (91.6)	0.38
Cardiovascular medications without antihypertensive drugs	181 (69.3)	146 (81.6)	0.006
Number of cardiovascular medications in tablet form without antihypertensive drugs (IQR)	1.00 (0.00–2.00)	2.00 (1.00–3.00)	<0.001
Number of antihypertensive drugs in tablet form, median (IQR)	2.00 (1.00–3.00)	2.00 (1.00–3.00)	0.53
Respiratory system	10 (3.8)	13 (7.3)	0.17
Nervous system	12 (4.6)	8 (4.5)	1
Psychotropic	7 (2.7)	8 (4.5)	0.46
Dermatological	1 (0.4)	0 (0.0)	1
Metabolic group	77 (29.5)	43 (24.0)	0.25
Rheumatoid	2 (0.8)	0 (0.0)	0.65
Other	66 (25.3)	64 (35.8)	0.02
Other medications	130 (49.8)	93 (52.0)	0.73
All drugs in total	249 (95.4)	172 (96.1)	0.91

Data are presented as n (% of the group) unless otherwise stated. The groups were compared using the χ^2 test or Fisher's exact test for percentages and Student's t-test or the Mann-Whitney U test for quantitative variables

Abbreviations: see Table 1

served in women [12]. Our observations of a correlation between age and the frequency of adverse reactions in women, but not in men, could be due to the fact that the female participants were significantly older than their male counterparts. On the other hand, in the present study population, we observed in men a higher prevalence of certain risk factors for cardiovascular diseases such as hypercholesterolemia and other metabolic diseases, and as a consequence, they were also more inclined to suffer from other cardiovascular diseases. Such a combination of numerous cardiovascular risk factors, on the one hand, and cardiovascular diseases on the other, could promote polypharmacy and, as a result, make men with metabolic disorders more susceptible to the occurrence of adverse drug reactions.

In our patients' history, we noted both non-specific symptoms, such as skin lesions or gastrointestinal disorders, as well as symptoms specific to a particular drug class. Drug-induced side effects were significantly more common in women than in men. As regards specific side effects, women were significantly more likely to experience hypotension, cough, edema, bradycardia, and skin lesions.

An analysis of different classes of drugs revealed that both single-drug intolerance and multiple-drug intolerance were significantly more common in women than in men. A multivariable analysis showed that intolerance of such drugs as antibiotics and analgesics occurred far more often among women. In the case of women, adverse reactions following antibiotic administration were most frequently reported, for example, after using ceftriaxone and for anti-tuberculosis drugs [14]. In a retrospective cohort study evaluating the incidence of adverse reactions after analgesics, women reported such symptoms almost twice as often as men [15].

It should also be noted that the frequency of adverse reactions after taking analgesics, especially nonsteroidal anti-inflammatory drugs, may be underreported because in many countries, including Poland, they are available as over-the-counter drugs.

The women in our study received fewer drugs of any class than the men, and fewer cardiovascular drugs (tablets) other than antihypertensive drugs. When it came to specific types of drugs, women took angiotensin receptor blockers and rheumatological drugs more frequently than men. The female study participants who received angiotensin receptor blockers were older and post-menopausal. In addition, rheumatic disorders were significantly more common in women than in men. On the other hand, women used antiplatelet drugs, statins, or cardiological drugs other than antihypertensive drugs more rarely than men, which was due to the more frequent presence of cardiovascular risk factors and concomitant cardiological diseases in men.

A comparison between women reporting side effects and women not reporting them showed that the former group was significantly older and had more comorbidities, including cardiovascular diseases. Specific diseases that were significantly more prevalent in women with side effects included CAD, history of MI, HF, respiratory diseases, and rheumatic disorders. Our analysis indicates once more that morbidity-related polypharmacy is a major risk factor for a history of drug-induced adverse reactions.

There was, however, no difference between the two groups of women in terms of the number of drugs taken of any class, the number of antihypertensive medications (in tablet form), and the number of non-antihypertensive cardiovascular medications (in tablet form). Women who reported adverse drug-induced symptoms took antiplatelet medications far more often than those who did not report such symptoms, but, at the same time, received fewer calcium antagonists. Antiplatelet medications, e.g., acetylsalicylic acid, are indicated for hypertensive patients with atherosclerotic cardiac complications, while calcium antagonists are used mainly for female patients of reproductive age, which explains their less frequent application in the study population.

A comparison of men reporting adverse drug reactions with men not reporting such reactions showed that patients in the former group were older and had a significantly higher number of cardiovascular diseases and comorbidities. When it came to specific diseases, men reporting side effects were more likely to suffer from coronary heart disease, past MI, HF, AF, hypercholesterolemia, and metabolic diseases. In addition, men reporting adverse drug reactions were significantly more likely to take more classes of drugs, including antihypertensive medications, and cardiovascular medications other than antihypertensive drugs, than men who did not report such events. When it came to specific classes of drugs, men reporting adverse drug reactions much more frequently used antiplatelet medications, anticoagulants, and cardiovascular medications other than antihypertensive drugs than men not reporting drug-induced side effects, but at the same time they took fewer calcium antagonists. Our male subgroup analysis showed a correlation between polypharmacy and an increased risk of adverse reactions. We also observed a correlation between adverse reactions and the number of medications and tablets taken. The use of combination drugs, recommended in the European guidelines, not only makes it possible to reduce the number of tablets taken by a patient per day, but also to reduce the dosage of single drugs. As a consequence, the use of single-pill combination medications may prevent the occurrence of drug-induced side effects [16].

The guidelines for the treatment of chronic diseases, including hypertension, emphasize the need to ensure safe treatment by monitoring a patient's tolerance to such treatment over a short period of approximately 1 month after the introduction of one drug because only such an approach would allow the patient to avoid arbitrary drug withdrawal as a result of adverse reactions in connection with taking a particular medication [3, 17, 18].

At every medical visit, the patient should be asked about the tolerance of the medications they are taking. Poorer drug tolerance affects the overall quality of a patient's life, which in hypertensive patients translates into worse blood pressure control and thus a higher risk of premature morbidity and mortality.

Based on the current analysis, special attention should be paid to female patients and elderly patients, as well as people with numerous comorbidities.

Article information

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REFERENCES

1. Burnier M. Controversies in the management of patients with arterial hypertension. Kardiol Pol. 2019; 77(10): 902–907, doi: 10.33963/KP.15002, indexed in Pubmed: 31571674.
2. Zhou B, Carrillo-Larco R, Danaei G, et al. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet. 2021; 398(10304): 957–980, doi: 10.1016/S0140-6736(21)01330-1, indexed in Pubmed: 34450083.
3. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. J Hypertens. 2018; 36(10): 1953–2041, doi: 10.1097/hjh.0000000000001940, indexed in Pubmed: 30234752.
4. Peacock E, Joyce C, Craig L, et al. Medication adherence is associated with decline in health-related quality of life: results of a longitudinal analysis among older women and men with hipertension. J Hypertens. 2021; 39(1): 153–161, doi: 10.1097/HJH.0000000000002590, indexed in Pubmed: 32675745.
5. Journiac J, Vioulac C, Jacob A, et al. What do we know about young adult cardiac patients' experience? A systematic review. Front Psychol. 2020; 11: 1119, doi: 10.3389/fpsyg.2020.01119, indexed in Pubmed: 32733301.
6. Albasri A, Hattle M, Koshiaris C, et al. Association between antihypertensive treatment and adverse events: systematic review and meta-analysis. BMJ. 2021; 372: n189, doi: 10.1136/bmj.n189, indexed in Pubmed: 33568342.
7. Kalibala J, Pechère-Bertschi A, Desmeules J. Sex differences in cardiovascular pharmacotherapy-the example of hypertension: a mini review. Front Pharmacol. 2020; 11: 564, doi: 10.3389/fphar.2020.00564, indexed in Pubmed: 32435193.
8. Tamargo J, Rosano G, Walther T, et al. Sex differences in the effects of cardiovascular drugs. Eur Heart J Cardiovasc Pharmacother. 2017; 3(3): 163–182, doi: 10.1093/ehjcvp/pvw042, indexed in Pubmed: 28329228.
9. Insani WN, Whittlesea C, Alwafi H, et al. Prevalence of adverse drug reactions in the primary care setting: A systematic review and meta-analysis. PLoS One. 2021; 16(5): e0252161, doi: 10.1371/journal.pone.0252161, indexed in Pubmed: 34038474.
10. Bijak M, Olszanecka A, Pałczyńska E, et al. Factors determining acceptance of illness in patients with arterial hypertension and comorbidities. Kardiol Pol. 2021; 79(4): 426–433, doi: 10.33963/KP.15860, indexed in Pubmed: 33687869.
11. Bouvy JC, De Bruin ML, Koopmanschap MA. Epidemiology of adverse drug reactions in Europe: a review of recent observational studies. Drug Saf. 2015; 38(5): 437–453, doi: 10.1007/s40264-015-0281-0, indexed in Pubmed: 25822400.
12. Fonseca W, Monteiro C, Taborda-Barata L. Inhaled drug therapy-associated adverse reactions in obstructive respiratory diseases: a review of a decade of reporting to the Portuguese Pharmacovigilance System. Int J Environ Res Public Health. 2021; 18(23), doi: 10.3390/ijerph182312411, indexed in Pubmed: 34886135.
13. Paradissis C, Cottrell N, Coombes I, et al. Patient harm from cardiovascular medications. Ther Adv Drug Saf. 2021; 12: 20420986211027451, doi: 10.1177/20420986211027451, indexed in Pubmed: 34367546.
14. Zhou J, Ma X, Tian J, et al. Spatial distribution and risk factors of adverse treatment outcomes of tuberculosis in Guizhou, China, 2013-2018. Sci Rep. 2021; 11(1): 7706, doi: 10.1038/s41598-021-86994-6, indexed in Pubmed: 33833283.
15. Lopes GS, Bielinski S, Moyer AM, et al. Sex differences in type and occurrence of adverse reactions to opioid analgesics: a retrospective cohort study. BMJ Open. 2021; 11(6): e044157, doi: 10.1136/bmjopen-2020-044157, indexed in Pubmed: 34193479.
16. Law MR, Wald NJ, Morris JK, et al. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. BMJ. 2003; 326(7404): 1427, doi: 10.1136/bmj.326.7404.1427, indexed in Pubmed: 12829555.
17. Buse JB, Wexler DJ, Tsapas A, et al. 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2020; 43(2): 487–493, doi: 10.2337/dci19-0066, indexed in Pubmed: 31857443.
18. Kotalczyk A, Lip GYh, Calkins H. The 2020 ESC Guidelines on the Diagnosis and Management of Atrial Fibrillation. Arrhythm Electrophysiol Rev. 2021; 10(2): 65–67, doi: 10.15420/aer.2021.07, indexed in Pubmed: 34401177.

Association of left atrial enlargement and increased left ventricular wall thickness with arrhythmia recurrence after cryoballoon ablation for atrial fibrillation

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ABSTRACT

Background: Left atrial enlargement (LAE) predicts atrial fibrillation (AF) recurrence after cryoballoon-based pulmonary vein isolation (CB). Increased left ventricular wall thickness (LVWT) is pathophysiologically associated with LAE and atrial arrhythmias.

Aims: To assess effect of increased LVWT on long-term outcomes of CB depending on coexistence of LAE.

Methods: LAE was defined using either echocardiography (>48 cm^3/m^2) or multislice computer tomography (MSCT, ≥63 cm^3/m^2). Increased LVWT was echocardiographic septal/posterior wall thickness >10 mm in males and >9 mm in females. All patients achieved 2-year follow-up.

Results: Of 250 patients (median [interquartile range, IQR] age of 61 [49.0–67.3] years; 30% female) with AF (40% non-paroxysmal), 66.5% had hypertension, and 27.2% underwent redo procedure. MSCT was done in 76%. During follow-up of 24.5 (IQR, 6.0–31.00) months the clinical success rate was 72%, despite 46% of patients having arrhythmia recurrence. Arrhythmia recurrence risk was increased by LAE and increased LVWT (hazard ratio [HR], 1.801; $P = 0.002$ and HR, 1.495; $P = 0.036$; respectively). The highest arrhythmia recurrence (61.9% at 2 years) was among patients with LAE and increased LVWT (33.6% of patients); intermediate (41.8%) among patients with isolated LAE; and lowest among patients with isolated increased LVWT or patients without LAE or increased LVWT (36.8% and 35.2% respectively, $P = 0.004$). After adjustment for body mass index (BMI), paroxysmal AF, CHA_2DS_2-VASc score, clinically-significant valvular heart disease, and cardiomyopathy, patients with LAE and concomitant increased LVWT diagnosis had a 1.8-times increased risk of arrhythmia recurrence (HR, 1.784; 95% confidence interval [CI], 1.017–3.130; $P = 0.043$).

Conclusion: Joint occurrence of LAE and increased LVWT is associated with the highest rate of arrhythmia recurrence after CB for AF.

Key words: arrhythmia recurrence, atrial fibrillation, catheter ablation, cryoballoon, pulmonary vein isolation

WHAT'S NEW?

Cryoballoon-based pulmonary vein isolation (CB) for atrial fibrillation (AF) can be effective for maintaining sinus rhythm in many patients. This analysis assesses the effect of increased left ventricular wall thickness (LVWT) on long-term outcomes of CB depending on the coexistence of left atrial enlargement (LAE). The analysis was done in a real-life scenario in consecutive patients in a tertiary center. LAE in the setting of increased LVWT substantially increased the arrhythmia recurrence rate after CB for AF.

INTRODUCTION

Cryoballoon-based (CB) pulmonary vein isolation is an effective option for rhythm control in atrial fibrillation (AF) [1]. Having the ability to predict post-procedural AF recurrence would have a great impact on procedural planning, costs to the health care system, and patient outcomes. There have been multiple attempts to predict the recurrence of AF utilizing different risk factors and risk scores with moderate results [2, 3]. Left atrial (LA) enlargement (LAE), which is associated with the progression of structural remodeling and fibrosis of LA tissues, affects catheter ablation outcomes [2, 4]. The American and European Cardiology Society guidelines recommend measuring left atrial volume index as a reliable indicator of LA size [5]. Multislice computed tomography (MSCT) may be more accurate and operator-independent, offering higher visual resolution than two-dimensional (2D) echocardiography [6].

Increased left ventricular wall thickness (LVWT), leading to diastolic dysfunction and elevation of cardiac filling pressures, can lead to LAE [7]. Increased LVWT is associated with an increased rate of AF recurrence [8]. Left ventricular (LV) hypertrophy, with its increased LVWT prerequisite, was shown to be associated with the development of atrial arrhythmias, particularly AF [9], and the prevalence of AF is higher in patients with hypertrophic remodeling [10]. The purpose of this article is to assess the combined predictive value of LAE and increased LVWT for AF recurrence after CB ablation.

METHODS

Study population

This is a single-center retrospective study of 250 consecutive patients with AF who underwent CB for *de novo* or redo procedures of AF between May 2017 and April 2019. All patients were qualified for CB according to the current European guidelines [1].

Based on the presence of LAE and increased LVWT, the patients were divided into four study groups: (1) neither increased LVWT nor LAE (increased LVWT [–]LAE[–] group); (2) patients with increased LVWT only (increased LVWT [+] LAE[–] group); (3) patients with isolated LAE (increased LVWT [–]LAE[+] group), and (4) patients with LAE concomitant with increased LVWT (increased LVWT [+]LAE[+] Group). LAE was defined using either baseline echocardiography (>48 cm^3/m^2) [5] or MSCT (≥63 cm^3/m^2) [11]. Increased LVWT was echocardiographic septal/posterior wall thickness >10 mm in males and >9 mm in females [5].

As the present study was a retrospective analysis of previously obtained data, and the patients were treated routinely with the best current practice, the institutional ethics committee approval did not require patient-signed informed consent. Relevant data were extracted from the electronic medical records stored at our institution.

Cryoballoon ablation procedure

Ablation was performed under conscious sedation. Via femoral venous access, a quadripolar catheter was placed in the coronary sinus. LA access was obtained by a transseptal puncture. Intravenous heparin was administered before and during ablation with a targeted activated clotting time of ≥300 seconds. A dedicated 15F delivery sheath (FlexCath; Medtronic Inc, Minneapolis, MN, US) was introduced into the LA over-the-wire. A 23- or 28-mm diameter cryoballoon was advanced through the FlexCath sheath into the LA and placed into the antrum of the pulmonary vein (PV) with a dedicated inner lumen mapping catheter (Achieve; Medtronic). The inflated cryoballoon was advanced towards the antral surface of the PV, and adequate PV occlusion with the balloon was determined by injection of a radiopaque contrast agent through the distal end of the catheter. The inner lumen circular mapping catheter was used, the electrodes were positioned as closely as possible to the PV antrum to monitor for PV isolation, and cryoapplication was initiated. The cryoballoon application time was the recommended 120 seconds from isolation of the PV, up to 240 seconds per ablation; however, the number and duration of cryoapplications were according to physician preference. Phrenic nerve pacing was conducted using a diagnostic catheter at the level of the right subclavian vein during right-sided PV ablation, and diaphragmatic movement was monitored. Cryoapplication was immediately terminated upon weakened diaphragmatic response. Systemic anticoagulation was recommended for at least 3 months after the procedure.

Left ventricular thickness and LA volume measurements

Before the CB procedure, all patients underwent two-dimensional transthoracic echocardiography (2D-echo; GE Vivid E95, General Electric, Boston, MA, US) with evaluation of LV ejection fraction (LVEF) and LV wall thickness. To assess

PV variants (common/accessory veins) and to exclude LA thrombus, all patients underwent either transesophageal 2D echocardiography (GE Vivid E95) or contrast-enhanced ECG-gated MSCT (384-slice SOMATOM Definition Flash, Dual Source, Siemens Healthcare GmbH, Erlangen, Germany), depending on their availability. Both 2D echocardiography (2D-echo) and MSCT acquired images were recorded for offline analysis, using EchoPAC™ version 204 (General Electric) or syngo.via (Siemens Healthcare GmbH), respectively. The 2D-echo LV wall thickness and maximum LA volume were measured as recommended [5]. The 2D-echo LA volumes were measured at the end of LV systole considering the mitral annulus as an LA atrioventricular border, using the modified biplane Simpson's disc summation method [12]. Using the MSCT, LA volume was calculated automatically (syngo.via) by a modified Simpson's method after manual tracing of the endocardial borders in the 10–20 sequential/successive LA cross-sections at LV end-systole in oblique sagittal and long-axis MSCT angiograms [13]. Maximal LA volume was defined at LV end-systole just before mitral valve opening, with the mitral annulus being the LA atrioventricular border. Measured LA volumes were indexed for corresponding body surface area calculated using the DuBois and DuBois formula [14].

Definitions

Concomitant clinically relevant valvular heart disease (VHD) was diagnosed on echocardiography as severe mitral or tricuspid insufficiency (MI/TI) or a history of any artificial valve replacement. Cardiomyopathy (CM) risk factors included dilated (DCM), hypertrophic (HCM), ischemic (ICM) or arrhythmogenic right ventricular dysplasia, CHA_2DS_2-VASc — Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category (female). Significant clinical improvement is associated with European Heart Rhythm Association (EHRA) scale reduction of at least 1 point assuming that the EHRA score is not greater than II.

Follow-up assessment

Observation was based on planned visits to the outpatient clinic or telephone interviews. The primary endpoint of the study was recurrence of any atrial arrhythmia lasting more than 30 seconds on ECG-Holter monitoring, implantable cardiac device memory, telemetry in emergency departments, or arrhythmia recorded on standard 12-lead ECG. The first 3 months post-ablation were considered a blanking period during which the primary endpoint could not be reached. All patients were followed for at least 2 years after ablation.

Statistical analysis

Using the Shapiro-Wilk test, the hypothesis of normal distribution was rejected in all of the studied continuous variables, and they have been presented as median with interquartile range (IQR). Categorical variables have been presented as frequencies and percentages. Differences between continuous variables were determined as appropriate either by the Mann-Whitney or Kruskal-Wallis tests, and Wilcoxon for paired variables. Differences between categorical variables were determined by Fisher's exact test. Prognostic values of increased LVWT and LAE were analyzed in a multivariable Cox regression model adjusted for the relevant clinical data with a well-established prognostic value and associated with cardiac remodeling (BMI, paroxysmal AF, CHA_2DS_2-VASc score, VHD, and CM) [15–17]. We calculated respective hazard ratios (HR) and corresponding 95% confidence intervals (CI). Kaplan-Meier curves were compared with the log-rank test. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL, US).

RESULTS

Study population

There were 250 patients treated with CB at median age of 61 years (IQR 49.0–67.3 years; minimum 23 years — maximum 81 years). The majority were male (70.0%). Most had paroxysmal AF (60.4%, n = 151); 22.0% (n = 55) had persistent and 17.6% (n = 44) long-persistent AF. The median EHRA score was II (II–III), and the CHA_2DS_2-VASc score was 2.0 (1.0–3.0). CB was a redo procedure in 27.2% (n = 68) of patients. VHD was present in 4.8% (n = 12) and CM in 17.2% (n = 43), and 38 patients (15.2%) had coronary artery disease. LVEF <60% was found in 29.6% (n = 74), and 11 patients (4.4%) had implanted cardiac resynchronization therapy (CRT)/an implantable cardioverter defibrillator (ICD).

Anatomy and study groups

Median LA indexed volume was bigger among patients examined with MSCT (76%) than using 2D-echo (64.8 [54.3–78.6] vs. 55.9 [39.6–72.5] cm^3/m^2; $P = 0.001$); however, LAE was diagnosed with similar frequency using the two modalities (53.2% vs. 63.3%; $P = 0.18$). Increased LVWT was seen in 56.4% (n = 141), with median thickness of septal and posterior wall being 11.5 mm (11.0–12.8) and 11.0 mm (9.3–11.0) among females and 12.0 mm (11.0–13.0) and 11.0 mm (10.4–12.0) in males. LAE was of similar frequency among patients with and without increased LVWT (59.6% vs. 50.5%, $P = 0.16$). Overall, 21.6% of patients had neither increased LVWT nor LAE (n = 54), 22.8% (n = 57) had only increased LVWT, and 22.0% (n = 55) had isolated LAE. In 84 patients (33.6%), there was concomitant LAE and increased LVWT.

Table 1 displays a comparison of baseline characteristics among the studied groups. Patients with LAE were older and had more persistent/long-persistent (vs. paroxysmal) AF. Patients with increased LVWT were more often men and had a higher CHA_2DS_2–VASc score and more hypertension. The increased LVWT (+)LAE(+) group had a high prevalence of cardiomyopathy (almost a third of patients)

Table 1. Comparison of demographic and baseline clinical characteristics among the studied groups stratified according to LAE and increased LVWT

	↑LVWT(–) LAE(–) (n = 54, 21.6%)	↑LVWT(+) LAE(–) (n = 57, 22.8%)	↑LVWT(–) LAE(+) (n = 55, 22.0%)	↑LVWT(+) LAE(+) (n = 84, 33.6%)	*P*-value
Age, years, median (IQR)	58.5 (41.0–66.0)	59.0 (47.5–65.0)	62.0 (56.0–67.0)[a]	63.0 (54.0–71.0)[a]	0.006
BMI, kg/m^2, median (IQR)	27.4 (25.0–29.1)	27.8 (25.5–30.5)	27.2 (25.0–28.9)	27.8 (25.7–30.6)	0.30
Female, n (%)	26 (48.1)	10 (17.5)[a]	20 (36.4)	19 (22.6)[a]	0.001
EHRA score, median (IQR)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	0.84
CHA_2DS_2–VASc, median (IQR)	1.0 (0.0–2.0)	2.0 (1.0–3.0)	1.0 (1.0–3.0)	2.0 (1.0–3.0)[a]	0.03
Paroxysmal AF, n (%)	44 (81.5)	42 (73.7)	29 (52.7)[a]	36 (42.9)[a]	<0.001
Persistent AF, n (%)	6 (11.1)	13 (22.8)	8 (14.5)	28 (33.3)[a]	0.008
Long-persistent AF, n (%)	4 (7.4)	2 (3.5)	18 (32.7)[a]	20 (23.8)[a]	<0.001
Redo CB, n (%)	14 (25.9)	15 (26.3)	15 (27.3)	24 (28.6)	0.99
DM, n (%)	5 (9.3)	5 (8.8)	4 (7.3)	7 (8.3)	0.99
Hypertension, n (%)	29 (53.7)	44 (77.2)[a]	33 (60.0)	63 (75.0)[a]	0.01
CAD, n (%)	5 (9.3)	12 (21.1)	5 (9.1)	16 (19.0)	0.14
Stroke/TIA, n (%)	0 (0)	6 (10.5)[a]	5 (9.1)	11 (13.1)[a]	0.06
Baseline eGFR, ml/min/1.73m^2, median (IQR)	66.8 (60.0–85.7)	72.5 (60.0–90.0)	67.3 (60.0–82.0)	68.9 (60.0–81.1)	0.78
Prior pacemaker, n (%)	2 (3.2)	4 (6.2)	3 (6.4)	4 (5.3)	0.86
ICD/CRT, n (%)	2 (3.7)	2 (3.5)	1 (1.8)	6 (7.1)	0.47
Overall CM, n (%)	4 (7.4)	8 (14.0)	7 (12.7)	24 (28.6)[a]	0.006
ICM, n (%)	1 (1.9)	2 (3.5)	0 (0)	6 (7.1)	0.14
DCM, n (%)	1 (1.9)	4 (7.0)	7 (12.7)	9 (10.7)	0.14
HCM, n (%)	0 (0)	2 (3.5)	0 (0)	9 (10.7)	0.004
ARVD, n (%)	2 (3.7)	0 (0)	0 (0)	0 (0)	0.06
Overall VHD, n (%)	1 (1.9)	1 (1.8)	4 (7.3)	6 (7.1)	0.27
Follow-up period, months, median (IQR)	28.5 (6.8–33.0)	27.1 (10.0–32.5)	26.0 (6.0–31.0)	12.0 (3.0–26.8)	<0.001

[a]*P* <0.05 for difference in comparison to the reference group (↑LVWT [–]LAE[–])

Abbreviations: AF, atrial fibrillation; ARVD, arrhythmogenic right ventricular dysplasia; BMI, body mass index; CAD, coronary artery disease; CB, cryoballoon-based pulmonary vein isolation; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category (female); CM, cardiomyopathy; CRT, cardiac resynchronization therapy; DCM, dilative cardiomyopathy; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; EHRA, European Heart Rhythm Association; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; ICM, ischemic cardiomyopathy; IQR, interquartile range; LAE, left atrial enlargement; ↑LVWT, increased left ventricular wall thickness; TIA, transient ischemic attack; VHD, valvular heart disease

and prior stroke/transient ischemic attack history. CB done as a redo procedure was equally common in the studied groups (Table 1).

Table S1 presents a comparison of the drug therapy used in the studied groups. Overall, 185 (74%) patients were receiving Vaughan Williams class I/III antiarrhythmic agents in the hospital or at discharge, with an overall similar frequency across the studied groups but more frequent amiodarone use among subjects in the increased LVWT (+)LAE(+) group. Statins were used more often among subjects with increased LVWT, whereas patients with LAE were more often treated with vitamin K antagonists.

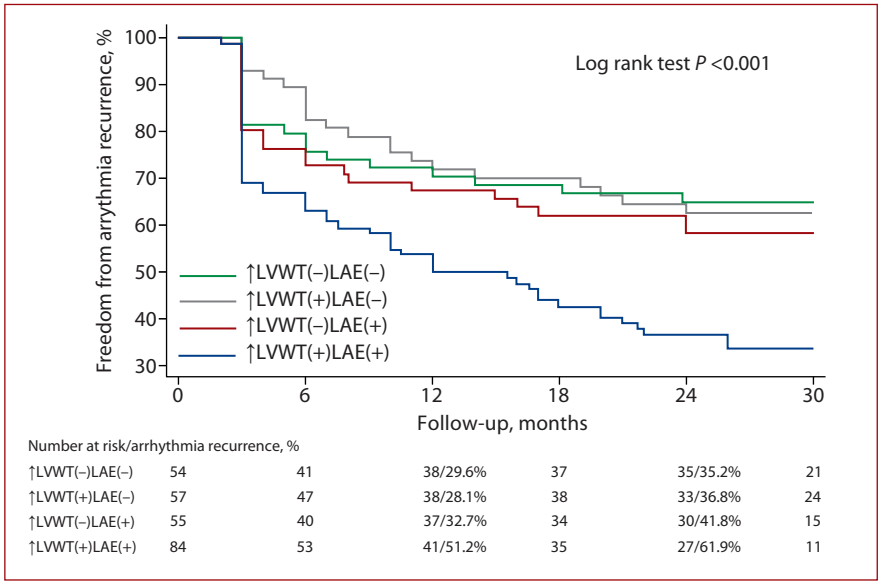
Table S2 presents a comparison of baseline anatomy assessed using 2D-echo or MSCT among the studied groups. Common/accessory PVs were identified with similar frequency across the groups, but more frequently using MSCT than transesophageal echocardiography (TEE) (41.6% vs. 11.7%; *P* <0.001, respectively).

Table S3 presents a comparison of the procedural parameters among the studied groups. Patients with either LAE or increased LVWT were treated with bigger balloons (28 mm). Overall, LA dwell time and the number of freezing applications and their duration were all similar in the studied groups and did not differ between groups with vs. without common/accessory PVs. Patients with LAE had longer fluoroscopy time (20.0 [14.4–24.5] vs. 17.2 [12.0–23.0] minutes in subjects without LAE, *P* = 0.027).

Short and long-term outcomes

Median follow-up was 24.5 (IQR, 6.0–31.00) months, with 100% of patients who achieved 2-year follow-up with no deaths. There was only one serious potentially procedure-related adverse event (stroke) — it manifested early (within hours) post-procedure, was documented by magnetic resonance as a single acute ischemic lesion, and occurred despite the fact that the patient had been on warfarin up to the ablation procedure and the TEE index excluded LA thrombus. There were no other major complications such as major bleeding (with blood transfusion), cardiac tamponade, phrenic nerve palsy, esophageal perforation/fistula, or death. Overall, 34.1% (63/185) of patients with antiarrhythmic drugs (class I/III) at discharge had the drugs subsequently discontinued (Supplementary material, *Table S1*), but this was less frequent among patients from the increased LVWT (+)LAE(+) group.

Despite overall arrhythmia recurrence rates of 37.2% (n = 93) at 1-year and 46.0% (n = 115) at 2-year follow-up, significant improvement in arrhythmia-related symptoms was noticed in 38.3% of these (*P* <0.001). The highest rate of 2-year arrhythmia recurrence was encountered in the increased LVWT (+)LAE(+) group (61.9%); the intermediate rate – among subjects with isolated LAE (41.8%); and the lowest – among patients with isolated increased LVWT or increased LVWT (–)LAE(–) (36.8% and 35.2%, respectively; Figure 1; *P* = 0.004). Long-term outcomes were similar



Number at risk/arrhythmia recurrence, %

↑LVWT(–)LAE(–)	54	41	38/29.6%	37	35/35.2%	21
↑LVWT(+)LAE(–)	57	47	38/28.1%	38	33/36.8%	24
↑LVWT(–)LAE(+)	55	40	37/32.7%	34	30/41.8%	15
↑LVWT(+)LAE(+)	84	53	41/51.2%	35	27/61.9%	11

Figure 1. Kaplan-Meier curves of freedom from arrhythmia recurrence for the studied groups (100% of patients accomplished 2-year follow-up)

Abbreviations: ↑LVWT, increased left ventricular wall thickness; LAE, left atrial enlargement

Table 2. Predictors of arrhythmia recurrence

	Univariate			Multivariable		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
BMI	1.039	0.985–1.096	0.164	1.014	0.959–1.071	0.63
Paroxysmal AF	0.517	0.360–0.741	<0.001	0.593	0.401–0.877	0.009
CHA_2DS_2-VASc score	1.134	0.999–1.288	0.052	1.083	0.951–1.233	0.23
VHD	1.930	0.977–3.811	0.058	1.480	0.735–2.980	0.27
CM	0.918	0.578–1.458	0.717	0.747	0.461–1.210	0.24
↑LVWT(+)LAE(-)[a]	1.037	0.557–1.929	0.909	0.947	0.507–1.770	0.87
↑LVWT(–)LAE(+)[a]	1.282	0.702–2.340	0.419	1.062	0.570–1.977	0.85
↑LVWT(+)LAE(+)[a]	2.268	1.344–3.828	0.002	1.784	1.017–3.130	0.04

[a]Versus the risk of the reference group: ↑LVWT(–)LAE(–)

Abbreviations: CI, confidence interval; HR, hazard ratio; other — see Table 1

between the groups with vs. without common/accessory PV (correspondingly arrhythmia recurrence at 2 years of 48.8% vs. 44.5%; $P = 0.59$).

Both LAE and increased LVWT raise the risk of arrhythmia recurrence (HR, 1.801; 95% CI, 1.230–2.636; $P = 0.002$ and HR 1.495; 95% CI, 1.028–2.175; $P = 0.04$, respectively). There was no evidence of difference in the predictive value of LAE defined by MSCT (HR, 1.842; 95% CI, 1.195–2.838; $P = 0.006$) and 2D-echo (HR, 1.659; 95% CI, 0.734–3.748; $P = 0.22$) (*P*-value for interaction = 0.74). Paroxysmal AF was associated with a lower rate of arrhythmia recurrence (29.1% at 1 year and 37.1% at 2 years vs. 49.5% and 59.6% in other patients, both $P = 0.001$). There was a trend for a higher CHA_2DS_2-VASc score and more frequent VHD among patients with arrhythmia recurrence ($P = 0.09$ and $P = 0.07$). CB ablation was similarly effective in patients with the first or redo procedure (44.5% vs. 50% of arrhythmia recurrence at 2 years; $P = 0.48$, respectively).

After adjustment for BMI, paroxysmal AF, CHA_2DS_2-VASc score, VHD, and CM, patients with LAE and concomitant increased LVWT had a 1.8-times increased risk of arrhythmia recurrence, whereas, with paroxysmal AF, the risk was 1.7-times lower (Table 2).

DISCUSSION

This is the first study to report the prognostic importance of concomitant increased LVWT and LAE on arrhythmia recurrence in patients treated with CB for AF, regardless of whether it is the first or a redo procedure. The main findings were as follows: (1) CB procedural safety was excellent, with only one serious potentially procedure-related adverse event; (2) whereas the overall 1-year and 2-year arrhythmia recurrence were 37.2% and 46.0%, respectively, substantial (38.3%) improvement in arrhythmia-related symptoms and EHRA was noted among subjects with subsequent arrhythmia; (3) even though increased LVWT without LAE was not

associated with a higher risk of arrhythmia recurrence, joint diagnosis of LAE and increased LVWT was associated with the highest arrhythmia recurrence: 51.2% at 1 year and 61.9% at 2 years, with paroxysmal AF being an independent predictor of a lower risk of arrhythmia recurrence; (4) neither common/accessory PV nor a redo procedure was associated with arrhythmia recurrence; (5) there was no evidence of a difference in the predictive value of LAE defined by MSCT vs. 2D-echo; it might warrant future studies to compare the predictive performance of these in terms of baseline LV remodeling assessment.

The procedural safety of CB in our experience is in line with large-scale real-life observational studies [18]. In our study, there was only one serious potentially procedure-related adverse event — stroke — manifesting early (within hours) post-procedure, which occurred despite anticoagulation and exclusion of LA thrombus by TEE index. It was the only stroke in the 2016–2021 period, during which 912 AF ablations were performed. Recent studies suggested a role of gas emboli, but not clot formation, in the pathophysiology of ischemic brain lesions associated with a CB procedure. Thus, procedural factors should be taken into consideration to lower ischemic lesions risks [19].

In a large German study of 605 patients treated with CB for AF, arrhythmia recurrence at >12 months was 38%, lower than the current 46% rate at 2 years (our 1-year rate was 37.2%); however, the percentage of paroxysmal AF patients was 96% in the German study and only 60% in our study. Importantly, in the current analysis, paroxysmal AF appears to be the strongest predictor of favorable long-term outcomes. Substantial differences in CHA_2DS_2-VASc and frequency of arterial hypertension were also noted between the German patients' group and our cohort (0.7 vs. 2.0 and 42% vs. 68%, respectively) [20]. Furthermore, in almost a third of current cases, CB was a redo ablation, and 17.6% of our subjects had long-persistent AF, typically excluded in most of the published studies [20–22]. In large prospective studies, significant improvement in the quality of life after AF ablation is reported on average in 42%–56% and even up to 76% of patients with arrhythmia recurrence at 12 months, which is similar to the current results [22, 23]. In our study among patients with arrhythmia recurrence, significant EHRA reduction was noticed in follow-up, P <0.001; in consequence, only 36% of patients with arrhythmia recurrence (42/115) were qualified for re-ablation.

Our findings were in line with the broad literature indicating that major predictors of arrhythmia recurrence after CB were non-paroxysmal AF and LAE [2, 4, 24]. Both factors were associated with more advanced atrial cardiomyopathy, suggesting its main role in arrhythmia recurrence [25]. Only the joint diagnosis of LAE and increased LVWT was associated with a significantly elevated arrhythmia recurrence rate, and not isolated increased LVWT. The effect of increased LVWT might be mediated by its association with more advanced atrial remodeling in the setting of LAE. Notably, indexed LA volumes measured with MSCT in the current study were bigger than those assessed with 2D-echo, with an average difference of 9.0 (3.5) cm^3/m^2 being similar to the extent of LA volume underestimation reported for 2D-echo vs. cardiac magnetic resonance [26].

Our results might indicate that echocardiography identifies common/accessory PVs less frequently than MSCT despite an overall 34.4% frequency of patients with common/accessory PVs in our study, similar to a reported 39.7% rate in the other studies [27, 28]. Contrary to a previous study suggesting an association of accessory PVs with a higher recurrence rate after CB for AF, we did not find such a relationship [29]. The previous study [27] documenting such a relationship created a composite score defining an "unfavorable" LA-PV anatomy, with detailed evaluation of the LA cavity and PV antral anatomies (including dimensions, eccentricity indexes, and angles) in addition to the presence of an accessory PV. Patients with an "unfavorable" LA-PV anatomy, identified using the above score, required longer cryoablation, similar to our results documenting longer fluoroscopy times among patients with LAE. Since we did not find a predictive value of an accessory PV, our results supported the notion that it was actually LA dimensions and not "unfavorable" LA-PV anatomy that predicted arrhythmia recurrence, similar to a previously published study [30].

Only advanced imaging modalities (cardiovascular magnetic resonance/angio-computed tomography) can precisely evaluate the LA cavity, structure, and its function (strain and ejection fraction); all provide novel metrics that might possess additional prognostic value (e.g. posterior left atrial adipose tissue attenuation as a promising predictor of arrhythmia recurrence after catheter ablation) [31, 32]. Our findings are in line with current knowledge of the potential impact of various LAE etiologies, with a frequent LAE finding in patients with preserved systolic LV function, but hypertrophic LV and its diastolic dysfunction [33].

Limitations

This was a single-center retrospective study. The follow-up was partly conducted during the COVID-19 pandemic. The use of regular 7-day Holter monitoring or implantable continuous loop recorders would make it possible to determine the type of arrhythmia recurrence and its burden and thus an accurate recurrence rate (the current one might be overestimated). This is particularly relevant for subjects treated for persistent and long-persistent AF in whom the therapeutic target relies more on significant arrhythmic burden reduction rather than on its total elimination. More profound insights into LV remodeling stratified according to its relative wall thickness and mass would have allowed for a better understanding of different LAE etiologies [34, 35].

CONCLUSIONS

Joint diagnosis of increased LVWT and LAE increases substantially the risk of arrhythmia recurrence after cry-

oballoon ablation for AF. The simplest echocardiographic measure of LVWT adds substantial prognostic information allowing for a reliable, easy, fast, and early risk stratification. Prevention and accurate treatment of arterial hypertension, the major cause of increased LVWT and thus left atrial myopathy [36], is of particular importance among patients with AF scheduled for CB procedures.

Article information

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REFERENCES

1. Kirchhof P, Benussi S, Kotecha N, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016; 37(38): 2893–2962, doi: 10.1093/eurheartj/ehw210, indexed in Pubmed: 27567408.
2. Quan D, Huang He, Kong B, et al. Predictors of late atrial fibrillation recurrence after cryoballoon-based pulmonary vein isolation: a meta-analysis. Kardiol Pol. 2017; 75(4): 376–385, doi: 10.5603/KP.a2016.0186, indexed in Pubmed: 28150281.
3. Deng H, Bai Y, Shantsila A, et al. Clinical scores for outcomes of rhythm control or arrhythmia progression in patients with atrial fibrillation: a systematic review. Clin Res Cardiol. 2017; 106(10): 813–823, doi: 10.1007/s00392-017-1123-0, indexed in Pubmed: 28560516.
4. Njoku A, Kannabhiran M, Arora R, et al. Left atrial volume predicts atrial fibrillation recurrence after radiofrequency ablation: a meta-analysis. Europace. 2018; 20(1): 33–42, doi: 10.1093/europace/eux013, indexed in Pubmed: 28444307.
5. Lang RM, Badano L, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015; 16(3): 233–271, doi: 10.1093/ehjci/jev014, indexed in Pubmed: 25712077.
6. Abecasis J, Dourado R, Ferreira A, et al. Left atrial volume calculated by multi-detector computed tomography may predict successful pulmonary vein isolation in catheter ablation of atrial fibrillation. Europace. 2009; 11(10): 1289–1294, doi: 10.1093/europace/eup198, indexed in Pubmed: 19632980.
7. Appleton CP, Galloway JM, Gonzalez MS, et al. Estimation of left ventricular filling pressures using two-dimensional and Doppler echocardiography in adult patients with cardiac disease. Additional value of analyzing left atrial size, left atrial ejection fraction and the difference in duration of pulmonary venous and mitral flow velocity at atrial contraction. J Am Coll Cardiol. 1993; 22(7): 1972–1982, doi: 10.1016/0735-1097(93)90787-2, indexed in Pubmed: 8245357.
8. Shah N, Badheka AO, Grover PM, et al. Influence of left ventricular remodeling on atrial fibrillation recurrence and cardiovascular hospitalizations in patients undergoing rhythm-control therapy. Int J Cardiol. 2014; 174(2): 288–292, doi: 10.1016/j.ijcard.2014.04.011, indexed in Pubmed: 24794553.
9. Chatterjee S, Bavishi C, Sardar P, et al. Meta-analysis of left ventricular hypertrophy and sustained arrhythmias. Am J Cardiol. 2014; 114(7): 1049–1052, doi: 10.1016/j.amjcard.2014.07.015, indexed in Pubmed: 25118122.
10. Seko Y, Kato T, Haruna T, et al. Association between atrial fibrillation, atrial enlargement, and left ventricular geometric remodeling. Sci Rep. 2018; 8(1): 6366, doi: 10.1038/s41598-018-24875-1, indexed in Pubmed: 29686287.
11. Khan MA, Yang EY, Zhan Y, et al. Association of left atrial volume index and all-cause mortality in patients referred for routine cardiovascular magnetic resonance: a multicenter study. J Cardiovasc Magn Reson. 2019; 21(1): 4, doi: 10.1186/s12968-018-0517-0, indexed in Pubmed: 30612579.
12. Ujino K, Barnes ME, Cha SS, et al. Two-dimensional echocardiographic methods for assessment of left atrial volume. Am J Cardiol. 2006; 98(9): 1185–1188, doi: 10.1016/j.amjcard.2006.05.040, indexed in Pubmed: 17056324.
13. Stojanovska J, Cronin P, Patel S, et al. Reference normal absolute and indexed values from ECG-gated MDCT: left atrial volume, function, and diameter. AJR Am J Roentgenol. 2011; 197(3): 631–637, doi: 10.2214/AJR.10.5955, indexed in Pubmed: 21862805.
14. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. Nutrition. 1989; 5(5): 303–313, indexed in Pubmed: 2520314.
15. Sivasambu B, Balouch MA, Zghaib T, et al. Increased rates of atrial fibrillation recurrence following pulmonary vein isolation in overweight and obese patients. J Cardiovasc Electrophysiol. 2018; 29(2): 239–245, doi: 10.1111/jce.13388, indexed in Pubmed: 29131442.
16. Letsas KP, Efremidis M, Giannopoulos G, et al. CHADS2 and CHA2DS2-VASc scores as predictors of left atrial ablation outcomes for paroxysmal atrial fibrillation. Europace. 2014; 16(2): 202–207, doi: 10.1093/europace/eut210, indexed in Pubmed: 23813452.
17. Sultan A, Lüker J, Andresen D, et al. Predictors of atrial fibrillation recurrence after catheter ablation: data from the German ablation registry. Sci Rep. 2017; 7(1): 16678, doi: 10.1038/s41598-017-16938-6, indexed in Pubmed: 29192223.
18. Földesi C, Misiková S, Ptaszyński P, et al. Safety of cryoballoon ablation for the treatment of atrial fibrillation: First European results from the cryo AF Global Registry. Pacing Clin Electrophysiol. 2021; 44(5): 883–894, doi: 10.1111/pace.14237, indexed in Pubmed: 33813746.
19. Miyazaki S, Kajiyama T, Yamao K, et al. Silent cerebral events/lesions after second-generation cryoballoon ablation: How can we reduce the risk of silent strokes? Heart Rhythm. 2019; 16(1): 41–48, doi: 10.1016/j.hrthm.2018.07.011, indexed in Pubmed: 30017816.
20. Vogt J, Heintze J, Gutleben KJ, et al. Long-term outcomes after cryoballoon pulmonary vein isolation: results from a prospective study in 605 patients. J Am Coll Cardiol. 2013; 61(16): 1707–1712, doi: 10.1016/j.jacc.2012.09.033, indexed in Pubmed: 23199518.
21. Wilber WS, Reddy VY, Bhasin K, et al. Cryoballoon ablation of pulmonary veins for persistent atrial fibrillation: Results from the multicenter STOP Persistent AF trial. Heart Rhythm. 2020; 17(11): 1841–1847, doi: 10.1016/j.hrthm.2020.06.020, indexed in Pubmed: 32590151.
22. Andrade JG, Champagne J, Dubuc M, et al. Cryoballoon or radiofrequency ablation for atrial fibrillation assessed by continuous monitoring: a randomized clinical trial. Circulation. 2019; 140(22): 1779–1788, doi: 10.1161/CIRCULATIONAHA.119.042622, indexed in Pubmed: 31630538.
23. Boveda S, Metzner A, Nguyen DQ, et al. Single-procedure outcomes and quality-of-life improvement 12 months post-cryoballoon ablation in persistent atrial fibrillation: Results from the multicenter CRYO4PERSISTENT AF trial. JACC Clin Electrophysiol. 2018; 4(11): 1440–1447, doi: 10.1016/j.jacep.2018.07.007, indexed in Pubmed: 30466850.
24. Ferrero-De-Loma-Osorio Á, Cózar R, García-Alberola A, et al. Primary results of the Spanish Cryoballoon Ablation Registry: acute and long-term outcomes of the RECABA study. Sci Rep. 2021; 11(1): 17268, doi: 10.1038/s41598-021-96655-3, indexed in Pubmed: 34446764.
25. Rivner H, Mitrani RD, Goldberger JJ. Atrial myopathy underlying atrial fibrillation. Arrhythm Electrophysiol Rev. 2020; 9(2): 61–70, doi: 10.15420/aer.2020.13, indexed in Pubmed: 32983526.
26. Perez de Isla L, Feltes G, Moreno J, et al. Quantification of left atrial volumes using three-dimensional wall motion tracking echocardiographic technology: comparison with cardiac magnetic resonance. Eur Heart J Cardiovasc Imaging. 2014; 15(7): 793–799, doi: 10.1093/ehjci/jeu001, indexed in Pubmed: 24480243.
27. Vaishnav AS, Alderwish E, Coleman KM, et al. Anatomic predictors of recurrence after cryoablation for atrial fibrillation: a computed tomography based composite score. J Interv Card Electrophysiol. 2021; 61(2): 293–302, doi: 10.1007/s10840-020-00799-7, indexed in Pubmed: 32602004.
28. Tsyganov A, Petru J, Skoda J, et al. Anatomical predictors for successful pulmonary vein isolation using balloon-based technologies in atrial

fibrillation. J Interv Card Electrophysiol. 2015; 44(3): 265–271, doi: 10.1007/s10840-015-0068-3, indexed in Pubmed: 26475792.
29. Chun KR, Okumura K, Scazzuso F, et al. Safety and efficacy of cryoballoon ablation for the treatment of paroxysmal and persistent AF in a real-world global setting: Results from the Cryo AF Global Registry. J Arrhythm. 2021; 37(2): 356–367, doi: 10.1002/joa3.12504, indexed in Pubmed: 33850577.
30. Takarada K, Ströker E, Abugattas JP, et al. Impact of an additional right pulmonary vein on second-generation cryoballoon ablation for atrial fibrillation: a propensity matched score study. J Interv Card Electrophysiol. 2019; 54(1): 1–8, doi: 10.1007/s10840-018-0373-8, indexed in Pubmed: 29679186.
31. El Mahdiui M, Simon J, Smit JM, et al. Posterior left atrial adipose tissue attenuation assessed by computed tomography and recurrence of atrial fibrillation after catheter ablation. Circ Arrhythm Electrophysiol. 2021; 14(4): e009135, doi: 10.1161/CIRCEP.120.009135, indexed in Pubmed: 33720759.
32. Beyer C, Tokarska L, Stühlinger M, et al. Structural cardiac remodeling in atrial fibrillation. JACC Cardiovasc Imaging. 2021; 14(11): 2199–2208, doi: 10.1016/j.jcmg.2021.04.027, indexed in Pubmed: 34147453.
33. Cuspidi C, Negri F, Sala C, et al. Association of left atrial enlargement with left ventricular hypertrophy and diastolic dysfunction: a tissue Doppler study in echocardiographic practice. Blood Press. 2012; 21(1): 24–30, doi: 10.3109/08037051.2011.618262, indexed in Pubmed: 21992028.
34. Lim DYZ, Sng G, Ho WHH, et al. Machine learning versus classical electrocardiographic criteria for echocardiographic left ventricular hypertrophy in a pre-participation cohort. Kardiol Pol. 2021; 79(6): 654–661, doi: 10.33963/KP.15955, indexed in Pubmed: 33885269.
35. Matusik PS, Bryll A, Matusik PT, et al. Electrocardiography and cardiac magnetic resonance imaging in the detection of left ventricular hypertrophy: the impact of indexing methods. Kardiol Pol. 2020; 78(9): 889–898, doi: 10.33963/KP.15464, indexed in Pubmed: 32598106.
36. Verbrugge FH, Reddy YNV, Attia ZI, et al. Detection of left atrial myopathy using artificial intelligence-enabled electrocardiography. Circ Heart Fail. 2022; 15(1): e008176, doi: 10.1161/CIRCHEARTFAILURE.120.008176, indexed in Pubmed: 34911362.

Improved outcomes in survivors of cardiac arrest qualified for early coronary angiography: A single tertiary center study

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ABSTRACT

Introduction: Most cardiac arrests in adults are related to coronary artery disease (CAD), and the role of early invasive cardiology procedures remains unclear.

Aims: We investigated the prognosis for patients hospitalized for out-of-hospital cardiac arrest (OHCA) or in-hospital cardiac arrest (IHCA) who were referred within 24 hours to a tertiary cardiology department, with a focus on the role of early coronary angiography (CA) and percutaneous coronary intervention (PCI).

Methods: This was an observational, single-center study using retrospective and prospective cohorts. Consecutive patients hospitalized for OHCA or IHCA and referred within 24 hours to a cardiology department were included in the study. Survival until hospital discharge was the primary outcome.

Results: One hundred and forty-eight patients aged 71 (14) years were included, 68 hospitalized for OHCA, and 80 patients after IHCA. Overall, in-hospital survival in the study group was 45% (66/148). In a multivariable logistic regression model, independent predictors of death were ejection fraction (EF) ≤30% (odds ratio [OR], 4.1; 95% confidence interval [CI], 1.69–10.03), blood oxygen saturation (SpO_2) ≤90% (OR, 2.77; 95% CI, 1.19–6.46), non-ST-segement elevation myocardial infarction (NSTEMI) (OR, 2.71; 95% CI, 1.02–7.21). The risk of death was lower in patients who underwent early CA (OR, 0.28; 95% CI, 0.1–0.74) or received at least one defibrillation (OR, 0.11; 95% CI, 0.05–0.27), even after adjustment for other factors.

Conclusions: In this series from a tertiary cardiac center, patients who underwent early CA had improved outcomes after cardiac arrest. In the multivariable logistic regression model, lower SpO_2, lower EF, and NSTEMI were independent risk factors of death, whereas early CA and initial shockable rhythm improved survival.

Key words: out-of-hospital cardiac arrest, percutaneous coronary intervention, sudden cardiac death

INTRODUCTION

Sudden cardiac death is a major public health issue, even though over the last years, cardiac arrest management has changed in all stages of the "chain of survival", starting from the implementation of public education programs, such as early call-out of emergency services and basic cardiopulmonary resuscitation (CPR), to the evolution of automatic external defibrillators (AED) and use of in-hospital therapeutic hypothermia [1].

However, outcomes after out-of-hospital cardiac arrest (OHCA) are unfavorable due to frequent irreversible cerebral and cardiac injury. Approximately 70% of these patients suffer from significant stenosis or acute occlusion of the coronary artery, and a significant target of treatment is, therefore, to achieve adequate reperfusion quickly and consequently to stabilize rhythm and hemodynamics [2, 5].

According to the recent European Resuscitation Council Guidelines for Resuscitation, emergency cardiac catheterization (and percutaneous coronary intervention [PCI] if required) is recommended in adult patients with the return of spontaneous circulation (ROSC) after OHCA of a suspected cardiac origin with ST-segment elevation (STE) on

WHAT'S NEW?

In this analysis from a tertiary cardiology department, subjects suffering from a cardiac arrest, who qualified for early coronary angiography had improved outcomes in terms of survival and neurological status. In the multivariable logistic regression model, we identified lower blood oxygen saturation, lower left ventricular ejection fraction, and non-ST-segment elevation myocardial infarction as independent risk factors of death, while qualification to early coronary angiography, as well as initial shockable rhythms, improved survival.

the electrocardiogram (ECG) [1]. Considering a consensus statement from the European Association for Percutaneous Cardiovascular Interventions/Stent for Life groups, cardiac catheterization should be performed immediately in the presence of STE and considered as soon as possible (within 2 hours) in other patients in the absence of an obvious non-coronary cause, particularly if they are hemodynamically unstable [3]. Among patients resuscitated from ventricular fibrillation/pulseless ventricular tachycardia (VF/pVT) OHCA with STE on their post-resuscitation ECG, the prevalence of coronary artery disease (CAD) varied between 70% to 85% (more than 90% of these patients underwent successful PCI). Conversely, among patients resuscitated from VF/pVT OHCA without STE on their post-resuscitation ECG, the prevalence of CAD was lower and varied between 25% to 50% [4].

As opposed to the scenario with obvious ST-segment elevation myocardial infarction (STEMI) signs, the impact of early routine qualification for invasive cardiology procedures on prognosis remains unclear. Therefore, in this single-center study, we investigated outcomes of patients hospitalized in a tertiary cardiology department within the first 24 hours after OHCA or after in-hospital cardiac arrest (IHCA), with a focus on the role of early coronary angiography (CA) and PCI.

METHODS

This was an observational single-center study using retrospective and prospective cohorts in the 2010–2017 period. The data regarding analyzed subjects were extracted through a medical record review and included consecutive patients who were hospitalized in the tertiary cardiology center within the first 24 hours after OHCA or IHCA (108 subjects were analyzed retrospectively and 40 — prospectively). The study was approved by the Local Institutional Review Board (no. RNN/189/15/KE). Patients provided written informed consent to participate in the study.

The decision to qualify a patient for CA was made by a physician on duty, and it was based on synthetic, individualized clinical assessment of the likelihood that cardiac arrest was due to an acute manifestation of CAD — according to the recent European Resuscitation Council Guidelines for Resuscitation.

PCI success was determined as Thrombolysis in Myocardial Infarction (TIMI) level 3 flow in the target vessel following coronary angioplasty [6], less than 50% residual stenosis, and resolution of STE (in STEMI patients) by at least 70% on an ECG recorded after 60–90 min after the procedure. Data concerning the cardiac arrest incident were investigated using Utstein-Style guidelines [7]. Survival till hospital discharge was the primary measured endpoint, and we aimed to identify prognostic factors related to survival.

Post-arrest neurologic status was evaluated at discharge with a cerebral performance category (CPC) measure [8].

Statistical analysis

Statistical analysis was performed using MedCalc version 12.0 (MedCalc Software, Ostend, Belgium) and STATISTICA version 13.1 (StatSoft, Kraków, Poland). We made a wide analysis of demographics and relevant clinical characteristics. Data were presented as percentages for categorical variables and as mean with standard deviation (SD) or median with interquartile range (IQR) for continuous variables depending on their distribution. The normality of data distribution was tested using the Shapiro-Wilk test. Student's t-test for independent variables or the Mann-Whitney U-test were applied to test intergroup differences. The categorical variable analysis was performed with the χ^2 test and Fisher's exact probability test. For continuous variables, the receiver operating curves analysis was performed to establish optimal cut-off values for endpoint prediction. Based on single-variable tests, the multivariable logistic regression model (including variables with *P*-value <0.2 in single variable analysis) was applied to identify independent predictors of death, and odds ratios (OR) with 95% confidence interval (CI) were presented. All *P*-values were 2-sided, and *P*-values of less than 0.05 were considered statistically significant.

RESULTS

Baseline clinical characteristics of the study group are presented in Table 1, and angiographic characteristics of studied patients are shown in Table 2.

Overall, 148 patients (61 females), mean (SD) age 71 (14) years (range 26–95) were included; 68 patients were hospitalized for OHCA and 80 patients were after IHCA, 46 were further transferred to the intensive care unit.

The proportion of patients discharged home in the study group was 45% (66/148) (54% after OHCA, 36% after IHCA). Early CA (<24 hours from admission) was performed in 99 (66.9%) patients (including immediate procedure

Table 1. Baseline characteristics of the study subjects

	Early CA group (n = 99)	No CA (n =49)	*P*-value
Age, years, mean (SD)	71 (12)	72 (17)	0.15
Male, n (%)	64 (65)	23 (47)	0.06
Survivors (%)	55 (56)	11 (22)	<0.001
Arrest witnessed, n (%)	87 (88)	42 (86)	0.91
VF/pVT, n (%)	56 (57)	16 (33)	0.01
PEA/asystole, n (%)	43 (43)	33 (67)	0.01
ROSC, n (%)	86 (87)	35 (71)	0.03
Transfer to ICU, n (%)	41 (41)	20 (41)	0.91
Defibrillation attempts, median (IQR)	1 (0–2)	0 (0–1)	0.005
Admission SBP, mm Hg, median (IQR)	109 (99–120)	95 (80–116)	0.02
Admission DBP, mm Hg, median (IQR)	68 (60–70)	60 (50–70)	0.15
Admission SpO_2%, median (IQR)	90 (90–93)	90 (85–92)	0.005
STEMI, n (%)	39 (39)	2 (4)	<0.001
NSTEMI, n (%)	37 (37)	6 (12)	0.003
UA, n (%)	11 (11)	1 (2)	0.11
PCI, n (%)	74 (75)	0 (0)	<0.001
Cerebral Performance Category at discharge, median (IQR)	3 (1–5)	5 (3–5)	0.003
OHCA/HCA, n (%)	45 (45)/54 (55)	23 (47)/26 (53)	0.99
Admission EF (%), median (IQR)	35 (25–44)	30 (20–49)	0.31
Admission hs-cTnT, ng/ml, median (IQR)	0.25 (0.10–1.48)	0.25 (0.05–0.25)	0.006
Admission CK-MB mass, ng/ml, median (IQR)	14.4 (4.7–60.5)	5.7 (2.8–15.1)	0.008
Admission NT-proBNP, pg/ml, median (IQR)	1862 (874–5651)	6446 (1792–8150)	0.03
Hypercholesterolemia, n (%)	82 (83)	28 (57)	0.25
Diabetes, n (%)	36 (36)	23 (47)	0.29
Hypertension, n (%)	85 (86)	39 (80)	0.99
Nicotine addiction, n (%)	27 (27)	2 (4)	0.002

Abbreviations: CA, coronary angiography; CK-MB mass, creatine kinase-MB isoenzyme; DBP, diastolic blood pressure; EF, ejection fraction; HCA, hospital cardiac arrest; hs-cTnT, high sensitivity cardiac troponin T; ICU, intensive care unit; IQR, interquartile range; NSTEMI, non-ST-segment elevation myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide: OHCA, out-of-hospital cardiac arrest; PCI, percutaneous coronary intervention; PEA, pulseless electrical activity; pVT, pulseless ventricular tachycardia; ROSC, return of spontaneous circulation; SBP, systolic blood pressure; SD, standard deviation; SpO_2, peripheral oxygen saturation; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina; VF, ventricular fibrillation

Table 2. Characteristics of patients who underwent coronary angiography

	Survivors (n = 55)	Non-survivors (n = 44)	*P*-value
No lesion, n (%)	10 (18)	8 (18)	0.087
Single vessel disease, n (%)	18 (33)	7 (16)	
Two vessel disease, n (%)	12 (22)	7 (16)	
Three vessel disease, n (%)	15 (27)	22 (50)	
Target vessel revascularization (n = 74; 100%)			
LMCA, n (%)	2 (5)	8 (25)	0.05
LAD, n (%)	21 (50)	14 (44)	
LCx, n (%)	9 (21)	7 (22)	
RCA, n (%)	10 (24)	3 (9)	
PCI, n (%)	42 (76)	32 (73)	0.85
PCI successful, n (%)	36 (65)	26 (59)	0.84
STEMI, n (%)	24 (44)	15 (34)	0.33
NSTEMI, n (%)	17 (31)	20 (45)	
UA, n (%)	8 (15)	3 (7)	
No ACS, n (%)	6 (10)	6 (13)	
Defibrillation attempts, median (IQR)	1 (1–2)	0 (0–1)	<0.001
Admission SpO_2, %, median (IQR)	92 (90–94)	90% (88–92)	<0.001
Shockable rhythm, n (%)	43 (78)	13 (30)	<0.001
Admission SBP, mm Hg, median (IQR)	110 (100–120)	100 (85–120)	0.03
Admission DBP, mm Hg, median (IQR)	69 (60–70)	65 (50–70)	0.25
Admission EF (%), median (IQR)	40 (28–47)	30 (20–38)	0.002
Admission hs-cTnT, ng/ml, median (IQR)	0.41 (0.10–1.87)	0.25 (0.10–1.12)	0.94
Admission CK-MB mass, ng/ml, median (IQR)	13.4 (4.4–44.1)	19.4 (6.3–72.0)	0.23
Admission NT-proBNP, pg/ml, median (IQR)	1604 (551–5127)	2372 (1444–5929)	0.28

Abbreviations: ASC, acute coronary syndrom; LAD, left anterior descending artery; LCx, left circumflex artery; LMCA, left main coronary artery; RCA, right coronary artery; other — see Table 1

Table 3. OHCA vs. IHCA comparison

	OHCA (n = 68)	IHCA (n = 80)	*P*-value
Age, years, mean (SD)	69 (14)	73 (13)	0.03
Male, n (%)	46 (67)	41 (51)	0.04
Survivors (%)	37 (54)	29 (36)	0.03
VF/pVT, n (%)	49 (72)	23 (28)	<0.001
PEA/asystole, n (%)	19 (28)	57 (71)	<0.001
ROSC, n (%)	66 (97)	55 (69)	<0.001
Transfer to ICU, n (%)	38 (56)	23 (29)	0.02
Coronary angiography, n (%)	45 (66)	54 (67)	0.86
PCI, n (%)	24 (53)	38 (70)	0.05
Defibrillation attempts, median (IQR)	1 (1–3)	0 (0–1)	<0.001
SBP, mm Hg, median (IQR)	110 (95–120)	100 (90–118)	0.19
DBP, mm Hg, median (IQR)	63 (60–70)	60 (56–73)	0.95
SpO_2, %, median (IQR)	90 (89–93)	90 (88–93)	0.26
STEMI, n (%)	15 (22)	26 (32)	0.47
NSTEMI, n (%)	20 (29)	23 (29)	
UA, n (%)	7 (10)	5 (6)	
No ACS, n (%)	26 (38)	26 (32)	
EF, %, median (IQR)	32 (25–47)	30 (25–44)	0.92
hs-cTnT, ng/ml, median (IQR)	0.25 (0.08–0.81)	0.25 (0.10–0.60)	0.88
CK-MB mass, ng/ml, median (IQR)	12.6 (4.4–49.7)	9.5 (4.0–42.6)	0.71
NT-proBNP, pg/ml, median (IQR)	1716.5 (512.5–4783.0)	5372.0 (1867.5–8137.8)	0.002

Abbreviations: IHCA, in-hospital cardiac arrest; TIMI, Thrombolysis in Myocardial Infarction; other — see Table 1 and 2

when infarction was suspected), more frequently in survivors (83.3% vs. 53.7%; *P* <0.001), similarly to PCI (59% vs. 37%; *P* = 0.006). The survival rate was 55% in those who qualified for CA, 22% in those who were disqualified, and 55% in those with successful PCI. The PCI success rate was similar in survivors 85% (36/42) vs. 81% (26/32) in non-survivors (*P* = 0.84). Mean (SD) duration of hospitalization was 12.8 (4.7) days for survivors and 10.7 (5.8) days for decedents (*P* = 0.02). Patients qualified for CA had better CPC than patients disqualified (median [IQR]: 3 [1–5] for subjects qualified vs. 5 [3–5] for patients disqualified [*P* = 0.003]).

Comparative analysis (Table 3) revealed that patients with OHCA vs. IHCA were younger (mean [SD], 69 (14) years vs. 76 years [13]; *P* = 0.03), mostly male (67% vs. 51%; *P* = 0.04), more frequently had VF/pVT (72% vs. 28%; *P* <0.001), more frequently achieved ROSC (97% vs. 69%; *P* <0.001), had more defibrillation attempts (median [IQR], 1 [1–3] vs. 0 [0–1]), and had lower N-terminal pro-B-type natriuretic peptide (NT-proBNP) (median [IQR]: 1716.5 [512.5–4783.0] pg/ml vs. 5372.0 [1867.5–8137.8]; *P* = 0.002). Survival till hospital discharge was lower in patients with IHCA than with OHCA (36% vs. 54%; *P* = 0.03).

In the OHCA group, survivors had higher systolic blood pressure (SBP) (median [IQR]): 110 (100–125) mm Hg vs. 100 (80–110) mm Hg; *P* <0.001, as well as diastolic blood pressure (DBP; median [IQR]): 70 (60–75) mm Hg vs. 60 (50–67) mm Hg; *P* = 0.002 and SpO_2 (median [IQR]): 92 (90–94)% vs. 90 (85–92)%; *P* = 0.01 (Supplementary material, *Table S1*).

In the IHCA group, non-survivors were less likely to have shockable CA mechanism (VF/pVT[%]), 18 (62%) vs. 5 (10%); *P* <0.001, rarely achieved ROSC (%) 29 (100%) vs. 26 (51%); *P* <0.001. Defibrillation attempts were more frequent in the survivor group (median [IQR]): 1 [0–1] vs. 0 [0–0]; *P* <0.001), who also had higher SpO_2 (median [IQR]: 92 [90–95]% vs. 90 [85–90]%), more frequent PCI (19 [66%] vs. 19 [37%]; *P* = 0.028), and higher EF (median [IQR]): 43 (30–50)% vs. 29 (20–35)%; *P* <0.001 (Supplementary material, *Table S2*).

Patients referred to CA had significantly higher systolic blood pressure (median [IQR]; SBP: 109 [99–120] mm Hg vs. 95 [80–116] mm Hg; *P* = 0.02), higher sensitivity cardiac troponin T (hs-cTnT) (median [IQR]: 0.25 [0.05–0.25] ng/ml vs. 0.25 [0.10–1.48] ng/ml; *P* = 0.006) and MB isoenzyme of creatine kinase (CK-MB mass) (median [IQR]: 14.4 [4.7–60.5] ng/ml vs. 5.7 [2.8–15.1] ng/ml; *P* = 0.008) and lower NT-proBNP levels (median [IQR], 1862 [874–5651] pg/ml vs. 6446 [1792–8150] pg/ml; *P* = 0.03). They also had more frequently shockable rhythms (pVT/VF, 56% vs. 33%; *P* = 0.006), non-ST-segment elevation myocardial infarction (NSTEMI), 37% vs. 12%; *P* = 0.002 or with STE (STEMI), 39% vs. 4%; *P* <0.001 and lower CPC (median [IQR]: 3 [1–5] vs. 5 [3–5]; *P* = 0.003). Acute coronary syndromes (ACS) were diagnosed in 96 patients — more frequently in survivors (74% vs. 56%; *P* = 0.02), especially STEMI (36.4% vs. 20.7%; *P* = 0.04) and unstable angina (13.6% vs. 3.7%; *P* = 0.03).

For continuous variables, receiver operating curves analysis was performed to establish optimal cut-off values for endpoint prediction used further in the multivariable analysis — we identified left ventricular ejection fraction (LVEF) ≤30% with area under the curve (AUC) 0.734, *P* <0.001 and SpO_2 ≤90% with AUC 0.615; *P* = 0.01 (Supplementary material, *Table S3*).

Table 4. Independent predictors of death in the entire cohort identified in the multivariable logistic regression analysis

Variable	Odds ratio (95% CI)	*P*-value
Admission EF ≤30%	4.11 (1.69–10.03)	0.002
SpO_2 ≤90%	2.77 (1.19– 6.46)	0.02
NSTEMI	2.71 (1.03–7.21)	0.04
Early CA	0.28 (0.10–0.74)	0.01
Defibrillation	0.11 (0.05–0.27)	<0.001

Adjustment was made for the following variables: admission ejection fraction (EF); age; coronary artery disease history; systolic blood pressure; diastolic blood pressure; diabetes mellitus; sex; non-ST-segment elevation myocardial infarction (NSTEMI); percutaneous coronary intervention; any defibrillation attempt; pulseless ventricular tachycardia/ventricular fibrillation; peripheral oxygenation (SpO_2); coronary angiography (CA)

Abbreviations: see Table 1

In the multivariable logistic regression analysis, the following 5 independent predictors related to mortality were identified (Table 4). LVEF ≤30% on admission (OR, 4.11; 95% CI, 1.69–10.03), SpO_2 ≤90% on admission (OR, 2.77; 95% CI, 1.19–6.46), and initial NSTEMI diagnosis (OR, 2.71; 95% CI, 1.02–7.21) were related to higher mortality. The risk of death was lower in patients who underwent early CA (OR, 0.28; 95% CI, 0.10–0.74) or received at least one defibrillation (OR, 0.11; 95% CI, 0.05–0.27). No prognostic significance was identified for other analyzed factors including STEMI, unstable angina, PCI, CAD history, pVT/VF, pulseless electrical activity, systolic blood pressure, diastolic blood pressure, diabetes mellitus, hs-cTnT, age, sex, or serum creatinine level.

DISCUSSION

The main finding of our study is that cardiac arrest patients qualified for early CA differed considerably from those disqualified; however, in the multivariate analysis early invasive management strategy appears to be protective regarding short-term survival.

Our analysis was performed in a single tertiary cardiology center with access to the intensive care unit and overall survival was 45% — significantly higher than reported in most publications [9, 10]. Notably, our data seem consistent with reports from the Swedish Health Care Registry on Heart Disease (SWEDEHEART) [11]. Their reports gave information on angiographic findings and survival from all consecutive patients who had undergone CA due to sudden cardiac arrest (SCA) in western Sweden between 2005 and 2013. Mortality within the first 24 hours among all patients who underwent CA was 56 (9%) in the SCA group and 153 (1%) in the ACS group. After one week, 161 (26%) SCA patients and 412 (2%) ACS patients died. Total mortality at any time during the study period was 42% in the SCA and 14% in the ACS groups.

HACORE (HAnnover Cooling REgistry [12] presented the influence of obligatory therapeutic hypothermia and cardiac catheterization in the absence of a clear non-cardiac cause of arrest as part of the Hannover Cardiac Resuscitation Algorithm before intensive care admittance. Overall, 30-day mortality of all the subjects treated according to the prespecified algorithm and receiving hypothermia after OHCA was 41%; for those with ROSC before arrival at the hospital, it was 39%. Patients with ongoing CPR on hospital admission, necessitating either ongoing mechanical or extracorporeal CPR, had the highest in-hospital mortality rate of 58%.

Our study confirms that CAD may be the most common cause of OHCA. Acute coronary culprit lesions were observed in 87% of patients who qualified for early CA. Qualification to coronary angiography was followed by nearly 85% successful PCI procedures. These findings are similar to those reported by Garcia et al. [13] who assessed subjects resuscitated from shockable rhythms who got early admission to the cardiac catheterization laboratory. In this study, 197 (63%) patients survived until hospital discharge with positive neurological outcomes (CPC of 1 or 2), and 121 (52%) patients who underwent early CA also underwent percutaneous coronary intervention, whereas 15 (7%) were qualified for coronary artery bypass grafting.

In our multivariable logistic regression analysis, the risk of death was lower in patients who underwent early CA (OR, 0.28; 95% CI, 0.10–0.74). Coherent findings were described in a meta-analysis by Camuglia et al. [14] where overall survival in the acute angiography group was 58.8% vs. 30.9% in the control group (OR, 2.77; 95% CI, 2.06–3.72). Survival with good neurological results (as per the Utstein template) in the early angiography group was 58% vs. 35.8% in the control group (OR, 2.20; 95% CI, 1.46–3.32).

Receiving at least one defibrillation (OR, 0.11; 95% CI, 0.05–0.27) was an independent predictor of survival. Analysis by Moutacalli et al. [15] concerning benefits of immediate CA in survivors of out-of-hospital cardiac arrest without an obvious extracardiac cause confirmed that patients who received defibrillation (n = 127) had a mortality rate of 48%, compared to 88% in 33 patients with an initial non-shockable rhythm (primary asystole or pulseless electrical activity) (P <0.001). In the study by Zijlstra et al. [16], which investigated diverse defibrillation strategies in survivors after out-of-hospital cardiac arrest, 2289 (81%) survivors with a known defibrillation status were defibrillated, 1349 (59%) were defibrillated by emergency medical service (EMS), 454 (20%) were defibrillated by a first-responder AED, and 429 (19%) were defibrillated by an onsite AED. The percentage of survivors defibrillated by first-responder AEDs (from 13% in 2008 to 26% in 2013; P <0.001) and onsite AEDs (from 14% in 2008 to 30% in 2013; P <0.001) increased. The improved use of these non-EMS AEDs was correlated with the rise in the survival rate of subjects with a shockable initial rhythm.

In the POL-OHCA registry, which was a case-control study established on medical records, 3 400 000 emergency visits were recorded. Patients who were treated by EMS ambulance team using defibrillation and/or ordering at least 1 dose of 1 mg of epinephrine were regarded to have OHCA managed by CPR attempts. Defibrillation at OHCA site was identified as a positive marker of survival

to hospital admission with OR 1.29 (95% CI, 1.18–1.41; *P* <0.001) [17].

We identified admission LVEF ≤30% as a strong independent predictor of death (OR, 4.11; 95% CI, 1.69–10.03), and that finding is consistent with observations made by Burstein et al. [18]. In their study, mean LVEF at 24 hours was 36.4% for survivors and 34.7% for non-survivors. LVEF <40% was not a significant predictor of survival in univariate analysis. In addition, it was not predictive either if the analysis was restricted to patients admitted to CCU or those qualified for cardiac catheterization.

In the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study, which enrolled 1284 patients with recent MI, patients with LVEF of 35%–50% had a relative risk of 2.5 for cardiac mortality compared with patients with LVEF >50%, whereas in patients with LVEF <35%, the relative risk was 7.3 [19]. In an interesting analysis made by Narayanan et al. [20], LV diameter added to the risk stratification for sudden cardiac death (SCD) independently of LVEF. In multivariable analysis, severe LV dilatation was an independent predictor of SCD (OR, 2.5; 95% CI, 1.03–5.9; *P* = 0.04). In addition, subjects with both EF ≤35% and severe LV dilatation had higher odds for SCD compared with those with low EF only (OR, 3.8 [95% CI, 1.5–10.2] for both vs. 1.7 [95% CI, 1.2–2.5] for low EF only), implying that severe LV dilatation additively enhanced SCD risk.

We identified non-ST-segment elevation myocardial infarction as an independent predictor of death (OR, 2.71; 95% CI, 1.02–7.21). In the study by Lemkes et al. [21], which randomly assigned 552 patients who had cardiac arrest without signs of STEMI to undergo direct CA or CA that was postponed until after neurologic recovery, among patients who had been successfully resuscitated after out-of-hospital cardiac arrest and had no signs of STEMI, an approach of immediate angiography was not found to be better than a strategy of delayed angiography with respect to overall survival at 90 days. At 90 days, 176 of 273 patients (64.5%) in the immediate angiography group and 178 of 265 patients (67.2%) in the delayed angiography group were alive (OR, 0.89; 95% CI, 0.62–1.27; *P* = 0.51).

In the study by Behnes et al. [22], which sought to evaluate the predictive effect of acute myocardial infarction with STEMI and NSTEMI in patients with ventricular tachyarrhythmias and SCA on admission, multivariable Cox regression models exposed non-acute myocardial infarction (hazard ratio [HR] 1.46; *P* = 0.001) and NSTEMI (HR 1.46; *P* = 0.04) as connected with increasing long-term all-cause mortality at 2.5 years, which was also demonstrated after propensity-score matching.

In our multivariable logistic regression analysis, we identified the qualification for CA itself, as a negative predictor of death with OR 0.28 (95% CI, 0.10–0.74). Contrary to our study, in the previously described analysis made by Lemkes et al. [20], which was further analyzed after one-year follow-up [23], patients successfully resuscitated from out-of-hospital cardiac arrest and without signs of STEMI, an urgent angiography approach was not found to be superior to a strategy of postponed angiography regarding clinical consequences at 1 year. The Immediate Unselected Coronary Angiography Versus Delayed Triage in Survivors of Out-of-hospital Cardiac Arrest Without ST-segment Elevation (TOMAHAWK) trial by Desch et al. [24] evaluated 554 patients with positively resuscitated out-of-hospital cardiac arrest of possible coronary origin. The patients underwent either immediate CA (immediate-angiography group) or initial intensive care assessment with delayed or selective angiography (delayed-angiography group). At 30 days, 143 of 265 patients (54%) in the immediate-angiography group and 122 of 265 patients (46%) in the delayed-angiography group died (HR 1.28; 95% CI, 1.00–1.63; *P* = 0.06). The composite of death or severe neurologic deficit occurred more frequently in the immediate-angiography group (in 164 of 255 patients [64.3%]) than in the delayed-angiography group (in 138 of 248 patients [55.6%]), for relative risk (RR) of 1.16 (95% CI, 1.00–1.34). In the recently published EMERGE trial [25] which evaluated the 180-day survival rate with CPC 1 or 2 of patients who experienced an OHCA without STE on ECG and underwent emergency CA vs. delayed CA, there was no difference in the overall survival rate (emergency CA, 36.2% [51 of 141] vs. delayed CA, 33.3% [46 of 138]; HR 0.86; 95% CI, 0.64–1.15; *P* = 0.31) or in secondary outcomes between the 2 groups. Patients' populations in the above-cited studies were significantly different from ours and included only subjects without signs of STEMI.

Limitations

Our study has several limitations that should be taken into consideration while interpreting the results. The cohorts and interventions of the cited studies are different from the subjects and interventions of this study. This is a single-center study where all the patients were hospitalized in a tertiary cardiology department, which could shift the profile of subjects, especially the OHCA subset towards those with suspected myocardial infarction. Thus, the observed outcomes may not be fully recognizable although they reflect clinical practice in many multidisciplinary hospitals.

The absence of a clear impact of PCI upon survival is puzzling but may reflect, on the one hand, clarification of optimal management strategy even in the absence of acute coronary syndrome, and, on the other hand, difficulties in obtaining effective tissue reperfusion in cardiac arrest victims.

Our follow-up was limited to the in-hospital phase. Importantly, the study was not randomized so no comparisons regarding management strategies can be directly drawn although the result might be hypothesis-generating. A substantial number of patients were analyzed retrospectively based on medical records, which may have led to selection bias, even though no intervention factor existed in the prospectively cohort.

We must acknowledge the potential bias from mixed analysis of patients with OHCA and early IHCA.

CONCLUSIONS

In this single-center study of a tertiary cardiology department, those patients after cardiac arrest who were qualified for early CA had improved outcomes. In the multivariable logistic regression model, lower SpO_2, lower EF, and NSTEMI were independent risk factors of death, whereas early CA angiography and shockable rhythm improved survival.

Article information

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REFERENCES

1. Nikolaou NI, Arntz HR, Bellou A, et al. European Resuscitation Council Guidelines for Resuscitation 2015 Section 8. Initial management of acute coronary syndromes. Resuscitation. 2015; 95: 264–277, doi: 10.1016/j.resuscitation.2015.07.030, indexed in Pubmed: 26477416.
2. Aurore A, Jabre P, Liot P, et al. Predictive factors for positive coronary angiography in out-of-hospital cardiac arrest patients. Eur J Emerg Med. 2011; 18(2): 73–76, doi: 10.1097/MEJ.0b013e32833d469a, indexed in Pubmed: 20664351.
3. Noc M, Fajadet J, Lassen JF, et al. Invasive coronary treatment strategies for out-of-hospital cardiac arrest: a consensus statement from the European Association for Percutaneous Cardiovascular Interventions (EAPCI)/Stent For Life (SFL) groups. EuroIntervention. 2014; 10(1): 31–37, doi: 10.4244/EIJV10I1A7, indexed in Pubmed: 24832635.
4. Yannopoulos D, Bartos JA, Aufderheide TP, et al. The evolving role of the cardiac catheterization laboratory in the management of patients with out-of-hospital cardiac arrest: a scientific statement from the American Heart Association. Circulation. 2019; 139(12): e530–e552, doi: 10.1161/CIR.0000000000000630, indexed in Pubmed: 30760026.
5. Bendz B, Eritsland J, Nakstad AR, et al. Long-term prognosis after out-of-hospital cardiac arrest and primary percutaneous coronary intervention. Resuscitation. 2004; 63(1): 49–53, doi: 10.1016/j.resuscitation.2004.04.006, indexed in Pubmed: 15451586.
6. Sheehan FH, Braunwald E, Canner P, et al. The effect of intravenous thrombolytic therapy on left ventricular function: a report on tissue-type plasminogen activator and streptokinase from the Thrombolysis in Myocardial Infarction (TIMI Phase I) trial. Circulation. 1987; 75(4): 817–829, doi: 10.1161/01.cir.75.4.817, indexed in Pubmed: 3103950.
7. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the 'Utstein style'. Prepared by a Task Force of Representatives from the European Resuscitation Council, American Heart Association, Heart and Stroke Foundation of Canada, Australian Resuscitation Council. Resuscitation. 1991; 22(1): 1–26, indexed in Pubmed: 1658890.
8. Safar P. Resuscitation after brain ischemia. In: Grenvik A, Safar P. ed. Brain failure and resuscitation. Churchill Livingstone, New York 1981: 155–184.
9. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation. 2017; 135(10): e146–e603, doi: 10.1161/CIR.0000000000000485, indexed in Pubmed: 28122885.
10. Dumas F, Cariou A, Manzo-Silberman S, et al. Immediate percutaneous coronary intervention is associated with better survival after out-of-hospital cardiac arrest: insights from the PROCAT (Parisian Region Out of hospital Cardiac ArresT) registry. Circ Cardiovasc Interv. 2010; 3(3): 200–207, doi: 10.1161/CIRCINTERVENTIONS.109.913665, indexed in Pubmed: 20484098.
11. Redfors B, Råmunddal T, Angerås O, et al. Angiographic findings and survival in patients undergoing coronary angiography due to sudden cardiac arrest in western Sweden. Resuscitation. 2015; 90: 13–20, doi: 10.1016/j.resuscitation.2014.11.034, indexed in Pubmed: 25698668.
12. Akin M, Sieweke JT, Zauner F, et al. Mortality in patients with out-of-hospital cardiac arrest undergoing a standardized protocol including therapeutic hypothermia and routine coronary angiography: experience from the HACORE registry. JACC Cardiovasc Interv. 2018; 11(18): 1811–1820, doi: 10.1016/j.jcin.2018.06.022, indexed in Pubmed: 30236353.
13. Garcia S, Drexel T, Bekwelem W, et al. Early access to the cardiac catheterization laboratory for patients resuscitated from cardiac arrest due to a shockable rhythm: the Minnesota resuscitation consortium twin cities unified protocol. J Am Heart Assoc. 2016; 5(1): e002670, doi: 10.1161/JAHA.115.002670, indexed in Pubmed: 26744380.
14. Camuglia AC, Randhawa VK, Lavi S, et al. Cardiac catheterization is associated with superior outcomes for survivors of out of hospital cardiac arrest: review and meta-analysis. Resuscitation. 2014; 85(11): 1533–1540, doi: 10.1016/j.resuscitation.2014.08.025, indexed in Pubmed: 25195073.
15. Moutacalli Z, Georges JL, Ajlani B, et al. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest without obvious extracardiac cause: Who benefits? Ann Cardiol Angeiol (Paris). 2017; 66(5): 260–268, doi: 10.1016/j.ancard.2017.09.008, indexed in Pubmed: 29029774.
16. Zijlstra JA, Koster RW, Blom MT, et al. Different defibrillation strategies in survivors after out-of-hospital cardiac arrest. Heart. 2018; 104(23): 1929–1936, doi: 10.1136/heartjnl-2017-312622, indexed in Pubmed: 29903805.
17. Nadolny K, Zyśko D, Obremska M, et al. Analysis of out-of-hospital cardiac arrest in Poland in a 1-year period: data from the POL-OHCA registry. Kardiol Pol. 2020; 78(5): 404–411, doi: 10.33963/KP.15241, indexed in Pubmed: 32191020.
18. Burstein B, Jayaraman D, Husa R. Early left ventricular ejection fraction as a predictor of survival after cardiac arrest. Acute Card Care. 2016; 18(2): 35–39, doi: 10.1080/17482941.2017.1293831, indexed in Pubmed: 28328299.
19. La Rovere MT, Bigger JT, Marcus FI, et al. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Lancet. 1998; 351(9101): 478–484, doi: 10.1016/s0140-6736(97)11144-8, indexed in Pubmed: 9482439.
20. Narayanan K, Reinier K, Teodorescu C, et al. Left ventricular diameter and risk stratification for sudden cardiac death. J Am Heart Assoc. 2014; 3(5): e001193, doi: 10.1161/JAHA.114.001193, indexed in Pubmed: 25227407.
21. Spoormans EM, Lemkes JS, Janssens GN, et al. Coronary angiography after cardiac arrest without ST-segment elevation. N Engl J Med. 2019; 380(15): 1397–1407, doi: 10.1056/NEJMoa1816897, indexed in Pubmed: 30883057.
22. Behnes M, Mashayekhi K, Weiß C, et al. Prognostic impact of acute myocardial infarction in patients presenting with ventricular tachyarrhythmias and aborted cardiac arrest. J Am Heart Assoc. 2018; 7(19): e010004, doi: 10.1161/JAHA.118.010004, indexed in Pubmed: 30371335.
23. Lemkes JS, Janssens GN, van der Hoeven NW, et al. Coronary angiography after cardiac arrest without ST segment elevation: one-year outcomes of the COACT randomized clinical trial. JAMA Cardiol. 2020; 5(12): 1358–1365, doi: 10.1001/jamacardio.2020.3670, indexed in Pubmed: 32876654.
24. Desch S, Freund A, Akin I, et al. Angiography after out-of-hospital cardiac arrest without ST-segment elevation. N Engl j Med. 2021; 385(27): 2544–2553, doi: 10.1056/nejmoa2101909, indexed in Pubmed: 34459570.
25. Hauw-Berlemont C, Lamhaut L, Diehl JL, et al. Emergency vs delayed coronary angiogram in survivors of out-of-hospital cardiac arrest: results of the randomized, multicentric EMERGE trial. JAMA Cardiol. 2022; 7(7): 700–707, doi: 10.1001/jamacardio.2022.1416, indexed in Pubmed: 35675081.

Total arterial revascularization coronary artery bypass surgery in patients with atrial fibrillation

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ABSTRACT

Background: Atrial fibrillation (AF) is a relatively common comorbidity among patients referred for coronary artery bypass grafting (CABG) and is associated with poorer prognosis. However, little is known about how surgical technique influences survival in this population.

Aim: The current analysis aimed to determine whether total arterial revascularization (TAR) is associated with improved long-term outcomes in patients with preoperative AF.

Methods: We analyzed patients' data from the HEIST (HEart surgery In atrial fibrillation and Supraventricular Tachycardia) registry. The registry, to date, involves five tertiary high-volume centers in Poland. Between 2006 and 2019, 4746 patients presented with preoperative AF and multivessel coronary artery disease and underwent CABG. We identified cases of TAR and used propensity score matching to determine non-TAR controls. Median follow-up was 4.1 years (interquartile range [IQR], 1.9–6.8 years).

Results: Propensity matching resulted in 295 pairs of TAR vs. non-TAR. The mean (standard deviation [SD]) number of distal anastomoses was 2.5 (0.6) vs. 2.5 (0.6) ($P = 0.94$), respectively. Operative and 30-day mortality was not different between TAR and non-TAR patients (hazard ratio [HR] and 95% confidence intervals [CIs], 0.17 (0.02–1.38); $P = 0.12$ and 0.74 [0.40–1.35]; $P = 0.33$, respectively). By contrast, TAR was associated with nearly 30% improved late survival: HR, 0.72 (0.55–0.93); $P = 0.01$. This benefit was sustained in subgroup analyses, yet most pronounced in low-risk patients (<70 years old; EuroSCORE II <2; no diabetes) and when off-pump CABG was performed.

Conclusions: TAR in patients with preoperative AF is safe and associated with improved survival, with particular survival benefits in younger low-risk patients undergoing off-pump CABG.

Key words: arterial grafts, atrial fibrillation, CABG, survival, total arterial revascularization

WHAT'S NEW?

Recent studies showed that preoperative atrial fibrillation (AF) is associated with worse short and long-term prognosis after coronary artery bypass grafting (CABG). Consequently, surgeons are less inclined to perform more advanced techniques that prolong operative time, such as total arterial revascularization (TAR). In our propensity-matched study of 590 patients with AF and multivessel coronary artery disease, TAR was associated with a nearly 30% survival benefit. Despite their high-risk profile, patients with preoperative AF may benefit from TAR. A more courageous approach should be considered.

INTRODUCTION

International guidelines on coronary artery bypass grafting (CABG) and myocardial revascularization provide a strong recommendation in single-vessel coronary artery disease (CAD) to supply the left anterior descending (LAD) coronary artery with the left internal mammary artery (LIMA) [1, 2]. In the case of multivessel CAD, complete surgical revascularization should be attempted [2]. However, the guideline recommendations are scarce about the choice of a second or third conduit during CABG surgery. Over the last years, arterial conduits including the right internal mammary artery (RIMA) and radial artery (RA) became more often chosen, constantly extending the concept of total arterial revascularization (TAR). The 2016 Society of Thoracic Surgeons position paper states that arterial graft should be considered as a second conduit in appropriate patients (class of recommendation IIA) [3]. Given the superior long-term patency of arterial conduits, lower rates of myocardial infarction (MI) and repeat revascularizations, TAR may also translate to improved long-term survival, as compared to traditional saphenous vein grafts (SVG) [4, 5]. Previous observational studies suggested the association of a greater number of arterial grafts with superior long-term survival benefits [6–8]. However, the Arterial Revascularization Trial (ART), the first randomized study to compare patients receiving one vs. two arterial grafts, found no significant difference in terms of 10-year survival [9]. A large crossover ratio could substantially affect the results of the analysis performed "per-protocol" as opposed to "intention to treat"; indeed, recent *post-hoc* analysis of the ART trial suggests a slight advantage of TAR over venous revascularization [10]. Total arterial revascularization was further shown to be beneficial in several comorbidities, including diabetes and dyslipidemia [11]. While preoperative atrial fibrillation (AF) remains an independent risk factor for increased post-CABG mortality [12], no single study has yet assessed the impact of TAR in this population. Because of the lack of consensus on the choice of arterial conduits in this higher-risk setting, the current study aimed to assess long-term prognosis of TAR vs. non-TAR in patients with preoperative atrial fibrillation.

METHODS

Study population, definitions, and endpoints

Due to the retrospective nature of the study, the ethics committee approval was waived (PCN/CBN/0052/KB/118/22). Long-term survival data are derived from the Ministry of Health through individual files of the KROK registry (Krajowy Rejestr Operacji Kardiochirurgicznych). Our investigation was part of the HEIST (Heart Surgery In atrial fibrillation and Supraventricular tachycardia) study (NCT04860882). We included all consecutive AF patients, over 18 years old, admitted to 5 tertiary centers in Poland between January 2006 and December 2019 who had isolated CABG with or without concomitant ablation performed. The current analysis was restricted to patients with AF undergoing CABG for multivessel coronary artery disease (MV-CAD). (Supplementary material, *Figure S1*). We excluded from the analyses: (1) patients who had no diagnosis of AF; (2) patients with single-vessel CAD; (3) patients in whom the number of distal anastomoses and/or type of graft material used could not be determined; or (4) patients for whom complete revascularization (revascularization of all angiographically significant lesions) was not obtained,.

The primary efficacy endpoint was long-term mortality following CABG with TAR versus CABG without TAR. Follow-up regarding mortality was obtained from National Health Fund — a nationwide obligatory public insurance institution in Poland. Total arterial revascularization was defined as using exclusively arterial grafts to achieve complete revascularization. Conversely, non-TAR was defined as complete revascularization using at least one venous graft. Analyses of early postoperative (<24 hours) mortality rates together with in-hospital complications and lengths of stays in the intensive care unit (ICU) and hospital (HLoS) are reported. Baseline clinical characteristics are reported following the pertinent definitions in the EuroSCORE II calculator.

Statistical analysis

Continuous variables were summarized as mean (SD) if normally distributed; non-normal distributions were summarized as median and interquartile range (IQR) and compared with the Mann-Whitney U test or Student's t-test as appropriate. Categorical variables (number [%]) were compared with Fisher's exact test. Propensity score (PS) matching was performed to limit selection bias by identifying a set of TAR/non-TAR pairs matched for numerous risk factors. A PS was generated for each patient from a non-parsimonious multivariable logistic regression model that was based on baseline characteristics (age, sex, number of vessels diseased [occlusion greater than >50% on coronary angiography], previous MI, smoking,

diabetes, hypertension, hyperlipidemia, chronic kidney disease, EuroSCORE II, left ventricle ejection fraction [LVEF], Canadian Cardiovascular Society and New York Heart Association [NYHA] scores) and procedural covariates (number of distal anastomoses and type of surgery [Off-Pump, On-Pump], surgical ablation, procedure urgency) as independent variables with treatment type (TAR vs. non-TAR) as a binary dependent variable. A greedy match using a nearest-neighbor method was used and a one-to-one ratio, without re-placement, within a specific caliper width of 0.2 SD of the LOGIT of the estimated propensity score. A one-to-one ratio was chosen to reduce potential bias occurring in numerically unbalanced comparisons [13]. Standardized mean differences (SMDs) were computed to verify the balance between the TAR versus non-TAR groups after matching. Risk ratios (RRs) were used for in-hospital outcomes, whereas Cox proportional-hazards models were used to determine factors related to event-free survival at long-term follow-up. Hazard ratios (HRs) point estimates and 95% confidence intervals (95% CIs) were calculated with ensuing statistical models. Mortality was assessed with Kaplan-Meier survival curves fitted after PS matching. As a further sensitivity analysis, defined subgroup analyses stratified on age, use of cardiopulmonary bypass, CAD extent, diabetes, LVEF, previous MI, and EuroSCORE II were performed to assess mortality in different scenarios. STATA MP v13.0 software (StataCorp, College Station, TX, US) was used for computations.

RESULTS

During the 13-year study period, 4746 AF patients were admitted for isolated CABG because of MV-CAD. The subjects were then divided into the TAR (295 patients, 6.2%) and non-TAR (4451 patients, 93.8%) groups. Baseline characteristics of the TAR and non-TAR groups are presented in Supplementary material, *Table S1*. Each patient in the TAR group was matched with a non-TAR patient and thus 295 pairs were obtained with similar baseline and operative characteristics (Tables 1 and 2). Analyses of standardized mean differences of a wide spectrum of baseline and procedural variables (not all included in the PS model) before and after PS matching suggested a covariate balance across the groups (Supplementary material, *Figure S2*).

Table 1. Preoperative characteristics after propensity score-matching

	Total matched (590)	Non-TAR matched (295)	TAR matched (295)	*P*-value[a]	Non-TAR unmatched (4451)	*P*-value[b]
Baseline characteristics						
Age, years, median (IQR)	68 (63–74)	68 (63–74)	68 (62–74)	0.63	70 (63–75)	<0.001
Male sex, n (%)	459 (77.8)	231 (78.3)	228 (77.3)	0.84	3,441 (77.3)	>0.99
EuroSCORE II, median (IQR)	1.30 (0.83–2.35)	1.28 (0.83–2.37)	1.31 (0.83–2.33)	0.33	1.32 (0.87–2.32)	0.02
Diabetes, n (%)	247 (41.9)	131 (44.4)	116 (39.3)	0.24	1,853 (41.3)	0.46
Insulin ± oral hypoglycemic drugs, n (%)	103 (17.5)	51 (17.3)	52 (17.6)	>0.99	730 (16.4)	0.57
Active smoking, n (%)	400 (67.8)	205 (69.5)	195 (66.1)	>0.99	2,732 (61.4)	0.11
Hypertension, n (%)	527 (89.3)	265 (89.8)	262 (88.8)	0.79	4,037 (90.7)	0.30
Hyperlipidemia, n (%)	373 (63.2)	194 (65.8)	179 (60.7)	0.23	2,955 (66.4)	0.05
Poor mobility[c], n (%)	28 (4.7)	15 (5.1)	13 (4.4)	0.85	233 (5.2)	0.68
BMI, kg/m^2, median (IQR)	28.63 (25.80–31.46)	28.40 (25.45–31.97)	28.72 (26.26–30.58)	0.68	28.39 (25.71–31.44)	0.70
Pulmonary hypertension[d], n (%)	25 (4.2)	15 (5.1)	10 (3.4)	0.41	215 (4.8)	0.32
Severe (PA systolic >55 mm Hg), n (%)	0 (0)	0 (0)	0 (0)	>0.99	18 (0.4)	0.62
Renal impairment, n (%)	166 (28.1)	83 (28.1)	83 (28.1)	>0.99	1,318 (29.6)	0.65
Dialysis (regardless of CC), n (%)	2 (0.3)	2 (0.7)	0 (0)	0.50	26 (0.58)	0.40
Peripheral artery disease, n (%)	88 (14.9)	51 (17.3)	37 (12.5)	0.13	698 (15.7)	0.16
Cerebrovascular disease, n (%)	49 (8.3)	29 (9.8)	20 (6.8)	0.23	471 (10.6)	0.04
History of stroke, n (%)	19 (3.2)	12 (4.1)	7 (2.4)	0.35	181 (4.1)	0.17
History of TIA, n (%)	20 (3.4)	11 (3.7)	9 (3.05)	0.82	188 (4.2)	0.45
Chronic lung disease, n (%)	60 (10.2)	28 (9.5)	32 (10.9)	0.68	376 (8.5)	0.16
LVEF, %, median (IQR)[d]	50 (40–55)	48 (40–55)	50 (40–55.25)	0.08	50 (40–55)	0.10
3 vessel CAD, n (%)	249 (42.2)	125 (42.4)	124 (42.0)	>0.99	2,667 (59.9)	<0.001
LM disease, n (%)	165 (28.0)	88 (29.8)	77 (26.1)	0.36	1,400 (31.5)	0.06
Previous MI, n (%)	329 (55.8)	176 (59.7)	153 (51.9)	0.07	2,484 (55.8)	0.20
Previous PCI, n (%)	152 (25.8)	76 (25.8)	76 (25.8)	>0.99	992 (22.3)	0.17
NYHA, class IV, n (%)	15 (2.5)	8 (2.7)	7 (2.4)	>0.99	132 (3.0)	0.72
CCS 4, n (%)	60 (10.2)	35 (11.9)	25 (8.5)	0.22	549 (12.3)	0.05
ACS, n (%)	26 (4.4)	12 (4.1)	12 (4.1)	>0.99	123 (2.8)	0.10

[a]*P*-value for comparison of matched TAR vs. non TAR cohorts. [b]*P*-value for comparison of matched TAR vs. unmatched non TAR cohorts. [c]Defined according to EuroSCORE II as severe impairment of mobility secondary to musculoskeletal or neurological dysfunction. [d]Missing data

Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; CAD, coronary artery disease; CC, creatinine clearance; CCS, Canadian Cardiovascular Society; IQR, interquartile range; LM, left main; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PA, pulmonary artery; PCI, percutaneous coronary intervention; TAR, total arterial revascularization; TIA, transient ischemic attack

Table 2. Operative characteristics after propensity score-matching

	Total (590)	Non-TAR (295)	TAR (295)	*P*-value
Procedural characteristics				
Redo surgery, n (%)	8 (1.4)	2 (0.7)	6 (2)	0.29
Critical preoperative state, n (%)	8 (1.4)	5 (1.7)	3 (1)	0.73
CPR, n (%)	1 (0.2)	1 (0.3)	0 (0)	>0.99
IABP, n (%)	20 (3.4)	12 (4.1)	8 (2.7)	0.50
IV inotropes, n (%)	19 (3.2)	11 (3.7)	8 (2.7)	0.64
OPCAB, n (%)	440 (74.6)	219 (74.2)	221 (74.9)	0.93
CPB, min, median (IQR)[a]	80 (58.5–100.5)	80 (60–105)	75 (58–95)	0.28
X-clamp, min[a], median (IQR)	44 (31–55)	42 (32–55)	38 (28–55.75)	0.33
Conversion to ONCAB, n (%)	8 (1.4)	4 (1.4)	4 (1.4)	>0.99
Concomitant ablation, n (%)	54 (9.2)	25 (8.5)	29 (9.8)	0.67
Concomitant LAAO, n (%)	6 (1)	3 (1)	3 (1)	>0.99
N of distal anastomoses, mean (SD)	2.5 (0.9)	2.5 (0.6)	2.5 (0.6)	0.94
2	319 (54.1)	159 (53.9)	160 (54.2)	>0.99
3	243 (41.2)	122 (41.4)	121 (41)	
4	26 (4.4)	13 (4.4)	13 (4.4)	
5 and more	2 (0.3)	1 (0.3)	1 (0.3)	

[a]Missing data

Abbreviations: CPB, cardiopulmonary bypass; CPR, cardiopulmonary resuscitation; IABP, intra-aortic balloon pump; IV, intravenous; LAAO, left atrial appendage occlusion; ONCAB, on-pump coronary artery bypass; OPCAB, off-pump coronary artery bypass; SD, standard deviation; other — see Table 1

Table 3. Grafts and anastomoses after propensity score-matching

	Total (590)	Non-TAR (295)	TAR (295)	*P*-value
LIMA, n (%)	556 (94.2)	261 (88.5)	295 (100)	<0.001
RIMA, n (%)	96 (16.3)	1 (0.3)	95 (32.2)	<0.001
BIMA, n (%)	96 (16.3)	1 (0.3)	95 (32.2)	<0.001
Pedicled IMA[a], n (%)	251 (42.5)	153 (51.9)	98 (33.2)	<0.001
Skeletonized IMA[a], n (%)	250 (42.4)	75 (25.4)	175 (59.3)	<0.001
Radial artery, n (%)	95 (16.1)	1 (0.3)	94 (31.9)	<0.001
Sequential anastomoses[a], n (%)	243 (16.5)	76 (10.3)	167 (22.7)	<0.001
Composite anastomoses[a], n (%)	107 (7.3)	32 (4.3)	75 (10.2)	<0.001
Number of arterial grafts (LIMA + RIMA + RA), mean (SD)	1.6 (0.9)	0.9 (0.4)	2.2 (0.7)	<0.001

[a]Missing data

Abbreviations: BIMA, bilateral internal mammary artery; LIMA, left internal mammary artery; RA, radial artery; RIMA, right internal mammary artery; SD, standard deviation; other — see Table 1

Concomitant ablation was reported in 54 (9.2%) cases (29 vs. 25; $P = 0.67$ in TAR and non-TAR CABG, respectively). Left internal mammary artery grafts were used in 94.2% of patients (100% vs. 88.5%; $P < 0.001$); skeletonized internal mammary artery (IMA) was preferred over pedicled IMA in the TAR group. The RIMA was used in 32.2% and the radial artery in 31.9% of TAR cases. Further details on grafts and anastomoses are described in Table 3. The median (IQR) HLoS was 8 (6–11) days in the TAR group and 7 (6–12) days in the non-TAR group (P for difference = 0.25). The median ICU stay was 15.4 (12.0–19.7) hours in the TAR group vs. 15.1 (12.0–18.7) hours in the non-TAR group ($P = 0.47$). There was no difference between TAR and non-TAR patients in hospital outcomes (Table 4), as well as in 30-day mortality rates: HR, 0.74 (0.40–1.35); $P = 0.33$ (Figure 1). The median follow-up of the study was 4.1 (IQR, 1.9–6.8, max. 15.1) years. Total arterial revascularization was associated with an almost 30% reduction in mortality hazard at late follow-up: HR, 0.72 (0.55–0.93); $P = 0.01$ (Figure 2).

Figure 3 lists the subgroup estimates after PS matching. The direction of benefit with TAR was maintained across subgroups of patients, yet most pronounced in younger patients (age <70 years; $P_{interaction} = 0.03$) who underwent off-pump surgery ($P_{interaction} = 0.03$). The effect was also more pronounced in patients with lower EuroSCORE II and no diabetes but without statistically significant between-subgroup differences. In a separate analysis restricted to patients receiving TAR or non-TAR according to LAD grafts only, it was found that the use of LIMA for LAD revascularization in the TAR group was associated with superior survival as compared to the use of a vein for LAD revascularization: HR, 0.33 (0.20–0.53); $P < 0.001$ for long-term mortality (Supplementary material, *Figure S3*).

DISCUSSION

The main findings of the current study are that in propensity-matched patients with underlying AF: (1) perioperative and 30-day mortality was no different between TAR and

Table 4. In-hospital outcomes after propensity score-matching

	Non-TAR (295)	TAR (295)	Risk ratio (95%CI)	*P*-value
Early postoperative mortality (<24 hours), n (%)	6 (2)	1 (0.3)	0.17 (0.02–1.38)	0.12
Cardiac tamponade and/or rethoracotomy, n (%)	17 (5.8)	9 (3.1)	0.53 (0.24–1.17)	0.16
Periprocedural MI, n (%)	6 (2)	8 (2.7)	1.33 (0.47–3.80)	0.78
Respiratory failure, n (%)	23 (7.8)	24 (8.1)	1.04 (0.60–1.81)	>0.99
Prolonged ICU stay (> 48 hours), n (%)	8 (2.7)	8 (2.7)	1.00 (0.38–2.63)	>0.99
Neurologic complications, n (%)	9 (3.1)	7 (2.4)	0.78 (0.30–2.06)	0.80
Multiorgan failure, n (%)	6 (1.0)	4 (0.7)	0.67 (0.19–2.34)	0.75
Gastrointestinal complications, n (%)	5 (1.7)	5 (1.7)	1.00 (0.29–3.42)	>0.99
Acute kidney failure and/or dialysis, n (%)	12 (4.1)	11 (3.7)	0.92 (0.41–2.04)	>0.99
Superficial sternal wound infection, n (%)	5 (1.7)	8 (2.7)	1.60 (0.53–4.83)	0.58
Deep sternal wound infection, n (%)	4 (1.4)	4 (1.4)	1.00 (0.25–3.96)	>0.99
Mediastinitis, n (%)	2 (0.7)	3 (1)	1.50 (0.25–8.91)	>0.99
PPI, n (%)	0 (0)	1 (0.3)	3.00 (0.12–73.35)	>0.99
ECMO, n (%)	0 (0)	0 (0)	NA	NA
IABP, n (%)	12 (4.1)	8 (2.7)	0.67 (0.28–1.61)	0.50

Abbreviations: CI, confidence interval; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; ICU, intensive care unit; MI, myocardial infarction; NA, not applicable; PPI, permanent pacemaker implantation; other — see Table 1

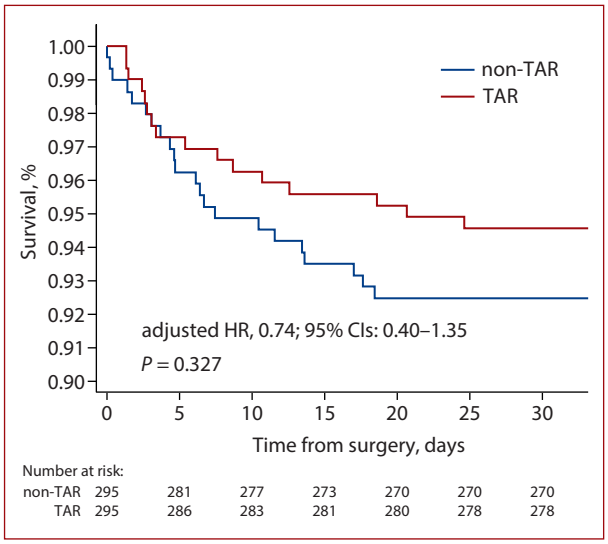

Figure 1. Thirty-day mortality. Kaplan–Meier survival curves. Comparison of TAR vs. non-TAR CABG for the analysis of 30-day mortality. Hazard ratios and respective 95% confidence intervals in TAR as compared to non-TAR CABG adjusted for propensity scores

Abbreviations: CABG, coronary-artery bypass grafting; other — see Table 1

non-TAR; (2) TAR was associated with 30% improved late survival, sustained in subgroup analyses, as appraised in low-risk patients (<70 years old; EuroSCORE II <2; no diabetes); (3) LAD grafting with LIMA, as compared to venous graft, resulted in 70% disproportionately higher late survival benefit in this higher risk population.

Few randomized controlled trials (RCTs) assessed the benefit of TAR; the two biggest failed to show a survival benefit with this approach although they were limited by only one-year follow-up [11, 14]. In the study by Damgaard et al. [14], no differences were observed between the TAR and non-TAR groups in graft patency and cardiac events, although the reported 85% RA graft patency is somewhat lower than what was observed in other studies [15–17]. Indeed, a patient-level meta-analysis of 6 RCTs reported patency of RA at 92% at 5-year mean follow-up [5]. Large observational studies almost unequivocally point to survival benefits with TAR [18, 19]. The analysis of 2132 matched patients showed significant benefits of TAR in terms of survival and MI [19]. Furthermore, the meta-analysis of

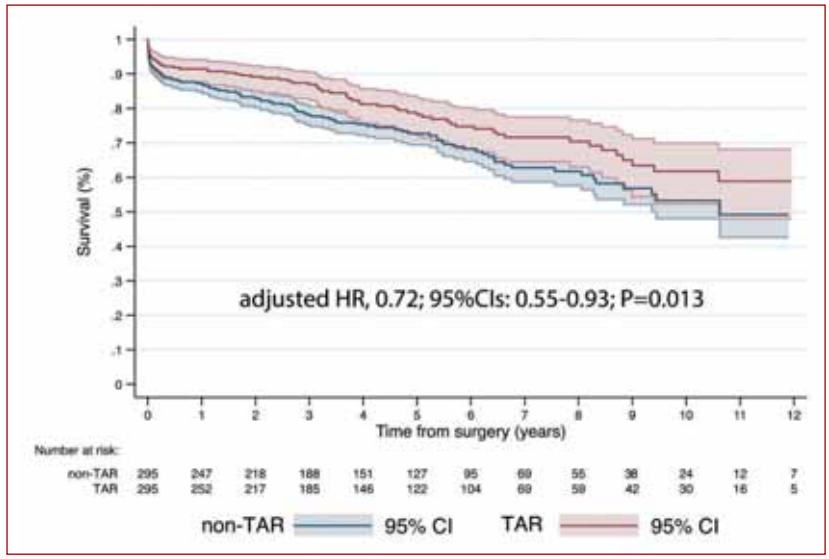

Figure 2. Long-term mortality. Kaplan–Meier survival curves. Comparison of TAR vs. non-TAR CABG for the analysis of long-term survival. Hazard Ratios and respective 95% confidence intervals in TAR as compared to non-TAR CABG adjusted for propensity scores

Abbreviations: see Table 1 and Figure 1

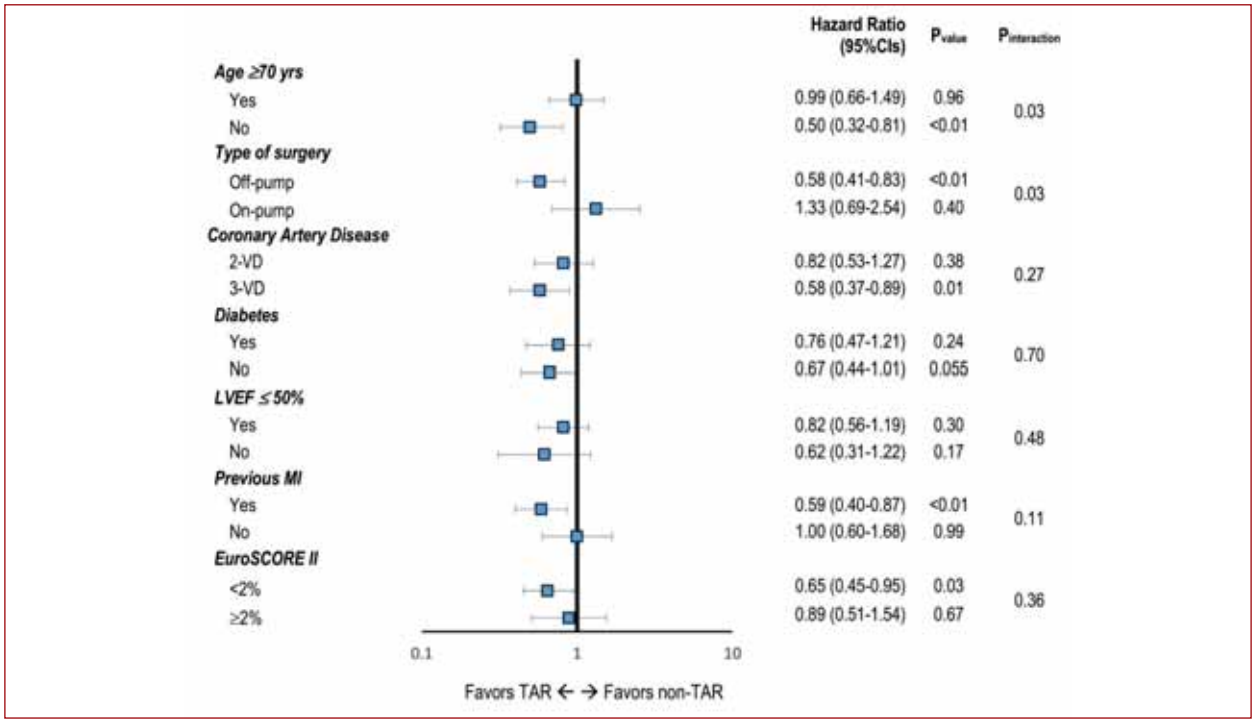

Figure 3. Subgroup analysis. Hazard ratios and 95% confidence intervals for death from any cause in TAR as compared to non-TAR according to selected characteristics

Abbreviations: LVEF, left ventricular ejection fraction; MI, myocardial infarction; SAG, single arterial grafting; VD, vessel disease; other — see Table 1

130 305 patients suggested that TAR is associated with lower long-term all-cause mortality compared to conventional CABG including the use of venous conduits [20].

Despite the available evidence, the use of TAR is low, the analysis by Rocha et al. [19] reported TAR in only 4.9% of patients. In the analysis of the Society of Thoracic Surgeons database by Schwann et al. [21], use of multiple arterial grafting (MAG) was 11.3% with a decreasing trend. Several reasons prevent the adoption of TAR; firstly, the absence of compelling evidence from RCTs. Observational studies are prone to bias due to patient selection. Surgeons tend to choose younger and healthier patients for arterial grafts because these patients can truly benefit from higher patency rates later in the follow-up, indeed, often forgetting that repeat revascularization of stenotic venous graft happens much sooner [22, 23]. Safety concerns, especially in the context of sternal wound infections (SWIs) with bilateral IMA grafting, are often raised as an argument against MAG and TAR. However, an analysis of wound infections in the ART trial demonstrated that the risk is only significantly higher when two pedicled grafts are used; the prevalence of sternal wound infections in the bilateral IMA group with skeletonized IMAs did not differ from the one in the single IMA group [24]. A meta-analysis by Deo et al. [25] reached the same conclusion for diabetic patients. In our current study, we also observed no increased risk of wound infections associated with TAR although a relatively high proportion of Ras, as compared to bilateral IMAs, must be noted.

The number of individuals referred for CABG with preoperative AF is reported to be between 8%–10% [26, 27] although in an analysis of the Medicare Database, which could be more accurate, the number of patients with preoperative AF and undergoing isolated CABG was 20% [28]. Preoperative AF is a known marker of high-risk patients as it was repeatedly shown to negatively influence survival after CABG [26, 29, 30]. Our previous study showed a marked survival benefit associated with MAG in this population; however, again, no randomized study has ever addressed this issue [31]. In the current analysis, the frequency of TAR was 6.2% (295 out of 4746) of CABG patients with preoperative AF. Interestingly, an analysis of Medicare patients with preoperative AF showed a significantly lower prevalence of arterial grafting in this population compared to sinus rhythm patients with few differences between the AF and no-AF groups in venous grafting [31]. In a recent retrospective sub-analysis of the ART study, TAR patients, despite propensity matching, suffered from preoperative AF half as often compared to single arterial grafting patients [32]. In the same analysis, preoperative AF was the strongest predictor of mortality and major adverse cardiac events although the overall prevalence of AF was low (1.3%).

The current study is the first to present long-term outcomes in AF patients undergoing CABG for MV-CAD, stratified by the choice of grafting material. Most contemporary operators opt for prompt revascularization that shortens CABG surgery time to reduce the high periprocedural risk

for AF patients [27, 33]. Our data, however, show that while the choice of TAR vs. no-TAR was not associated with an increased risk of perioperative or short-term mortality, it resulted in long-term mortality reduction in the propensity-matched population. Notably, the survival benefit became apparent as soon as 2 years post operation, therefore sooner than in previous studies concerning TAR [14, 19]. Whether it is a result of preoperative AF or other patient factors not included in our PS model is yet to be determined.

Another interesting finding, that reinforces the importance of TAR is the fact that LIMA to LAD is associated with overwhelmingly superior long-term survival as compared to SVG to LAD. More importantly, the mortality rates for vein to LAD were as high as 59% at 4.1 years (Supplementary material, Figure S3) which is much higher than vein to LAD in the non-AF population [34]. This underscores the importance of LIMA to LAD, especially in AF patients. However, it must be noted that the sub-analysis of vein vs. LIMA to LAD was not adjusted for con-founders as no additional PS matching was performed, therefore the results have to be treated cautiously.

Limitations

Certain limitations to our study must be acknowledged. In AF patients undergoing CABG, concomitant ablation improves survival [33]; while in our cohort the ablation rates were low and could influence the mortality prevalence, they were balanced between two matched groups. Some data were not available (AF duration and type, angiographic follow-up, heart rhythm at discharge, repeat revascularizations, dual antiplatelet therapy and anticoagulation regimen, and drug compliance after surgery). Future studies focused on detailed revascularization analysis and concurrent AF management should be performed to address those issues specifically. Furthermore, we acknowledge that a 30% survival benefit in median follow-up of 4.1 years is higher, as compared to data from a meta-analysis of RCTs in the general population [18]. Lastly, differences between centers with regard to TAR adoption and techniques, as well as post-procedural patient management may remain. Although we addressed potential selection bias with propensity score matching according to baseline clinical variables; there exists risk, however, for hidden confounders to have influenced the results with respect to patient allocation and choice of grafting strategy. While we acknowledge the non-randomized nature of the current study, and at the same time paucity of randomized data and subanalyses of RCTs, an analysis of different revascularization strategies across AF and non-AF populations may add further insights into the role of arterial revascularization in this particular groups of patients.

CONCLUSIONS

We conclude that TAR in patients with preoperative AF is safe and possibly associated with improved survival. We observed particular survival benefits in younger low-risk patients undergoing off-pump CABG.

Supplementary material

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

Article information

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REFERENCES

1. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery. Circulation. 2011; 124(23): e652–735, doi: 10.1161/cir.0b013e31823c074e, indexed in Pubmed: 22064599.
2. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. et al.. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J. 2019; 40(2): 87–165, doi: 10.1093/eurheartj/ehy394, indexed in Pubmed: 30165437.
3. Aldea GS, Bakaeen FG, Pal J, et al. The Society of Thoracic Surgeons clinical practice guidelines on arterial conduits for coronary artery bypass grafting. Ann Thorac Surg. 2016; 101(2): 801–809, doi: 10.1016/j.athoracsur.2015.09.100, indexed in Pubmed: 26680310.
4. Yamasaki M, Deb S, Tsubota H, et al. Radial artery and saphenous vein patency more than 5 years after coronary artery bypass surgery: results from RAPS (Radial Artery Patency Study). J Am Coll Cardiol. 2012; 60(1): 28–35, doi: 10.1016/j.jacc.2012.03.037, indexed in Pubmed: 22742399.
5. Gaudino M, Benedetto U, Fremes S, et al. Radial-artery or saphenous-vein grafts in coronary-artery bypass surgery. N Engl J Med. 2018; 378(22): 2069–2077, doi: 10.1056/nejmoa1716026, indexed in Pubmed: 29708851.
6. Iribarne A, Schmoker JD, Malenka DJ, et al. Does use of bilateral internal mammary artery grafting reduce long-term risk of repeat coronary revascularization? A multicenter analysis. Circulation. 2017; 136(18): 1676–1685, doi: 10.1161/CIRCULATIONAHA.117.027405, indexed in Pubmed: 29084776.
7. Kelly R, Buth KJ, Légaré JF. Bilateral internal thoracic artery grafting is superior to other forms of multiple arterial grafting in providing survival benefit after coronary bypass surgery. J Thorac Cardiovasc Surg. 2012; 144(6): 1408–1415, doi: 10.1016/j.jtcvs.2012.01.030, indexed in Pubmed: 22306219.
8. Lytle BW, Blackstone EH, Sabik JF, et al. The effect of bilateral internal thoracic artery grafting on survival during 20 postoperative years. Ann Thorac Surg. 2004; 78(6): 2005–2012, doi: 10.1016/j.athoracsur.2004.05.070, indexed in Pubmed: 15561021.
9. Taggart DP, Benedetto U, Gerry S, et al. Bilateral versus single internal-thoracic-artery grafts at 10 years. N Engl J Med. 2019; 380(5): 437–446, doi: 10.1056/NEJMoa1808783, indexed in Pubmed: 30699314.
10. Taggart DP, Gaudino MF, Gerry S, et al. Effect of total arterial grafting in the Arterial Revascularization Trial. J Thorac Cardiovasc Surg. 2022; 163(3): 1002–1009, doi: 10.1016/j.jtcvs.2020.03.013, indexed in Pubmed: 32305186.
11. Muneretto C, Bisleri G, Negri A, et al. Total arterial myocardial revascularization with composite grafts improves results of coronary surgery in elderly: a prospective randomized comparison with conventional coronary artery bypass surgery. Circulation. 2003; 108(Suppl 1): II29–II33, doi: 10.1161/01.cir.0000087941.75337.f5, indexed in Pubmed: 12970204.
12. Ngaage DL, Schaff HV, Mullany CJ, et al. Does preoperative atrial fibrillation influence early and late outcomes of coronary artery bypass grafting? J Thorac Cardiovasc Surg. 2007; 133(1): 182–189, doi: 10.1016/j.jtcvs.2006.09.021, indexed in Pubmed: 17198809.

13. Austin PC. Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score. Am J Epidemiol. 2010; 172(9): 1092–1097, doi: 10.1093/aje/kwq224, indexed in Pubmed: 20802241.
14. Damgaard S, Wetterslev J, Lund JT, et al. One-year results of total arterial revascularization vs. conventional coronary surgery: CARRPO trial. Eur Heart J. 2009; 30(8): 1005–1011, doi: 10.1093/eurheartj/ehp048, indexed in Pubmed: 19270315.
15. Goldman S, Sethi GK, Holman W, et al. Radial artery grafts vs saphenous vein grafts in coronary artery bypass surgery: a randomized trial. JAMA. 2011; 305(2): 167–174, doi: 10.1001/jama.2010.1976, indexed in Pubmed: 21224458.
16. Buxton BF, Raman JS, Ruengsakulrach P, et al. Radial artery patency and clinical outcomes: five-year interim results of a randomized trial. J Thorac Cardiovasc Surg. 2003; 125(6): 1363–1371, doi: 10.1016/s0022-5223(02)73241-8, indexed in Pubmed: 12830056.
17. Collins P, Webb CM, Chong CF, et al. Radial artery versus saphenous vein patency randomized trial: five-year angiographic follow-up. Circulation. 2008; 117(22): 2859–2864, doi: 10.1161/CIRCULATIONAHA.107.736215, indexed in Pubmed: 18506009.
18. Royse A, Pawanis Z, Canty D, et al. The effect on survival from the use of a saphenous vein graft during coronary bypass surgery: a large cohort study. Eur J Cardiothorac Surg. 2018; 54(6): 1093–1100, doi: 10.1093/ejcts/ezy213, indexed in Pubmed: 29893823.
19. Rocha RV, Tam DY, Karkhanis R, et al. Long-term outcomes associated with total arterial revascularization vs non-total arterial revascularization. JAMA Cardiol. 2020; 5(5): 507–514, doi: 10.1001/jamacardio.2019.6104, indexed in Pubmed: 32074240.
20. Yanagawa B, Verma S, Mazine A, et al. Impact of total arterial revascularization on long term survival: A systematic review and meta-analysis of 130,305 patients. Int J Cardiol. 2017; 233: 29–36, doi: 10.1016/j.ijcard.2017.02.010, indexed in Pubmed: 28185702.
21. Schwann TA, Habib RH, Wallace A, et al. Operative outcomes of multiple-arterial versus single-arterial coronary bypass grafting. Ann Thorac Surg. 2018; 105(4): 1109–1119, doi: 10.1016/j.athoracsur.2017.10.058, indexed in Pubmed: 29453002.
22. Li R, Lan B, Zhu T, et al. Preventing graft restenosis after coronary artery bypass grafting with tissue-type plasminogen activator. Eur J Med Res. 2017; 22(1): 18, doi: 10.1186/s40001-017-0259-8, indexed in Pubmed: 28606123.
23. Gürbak İ, Panç C, Şahin AA, et al. CHA2DS2-VASc score as a predictor of no-reflow phenomenon after saphenous vein graft percutaneous coronary intervention in patients with non-ST-segment elevation acute coronary syndromes. Kardiol Pol. 2020; 78(11): 1129–1136, doi: 10.33963/KP.15603, indexed in Pubmed: 32955817.
24. Benedetto U, Altman DG, Gerry S, et al. Pedicled and skeletonized single and bilateral internal thoracic artery grafts and the incidence of sternal wound complications: Insights from the Arterial Revascularization Trial. J Thorac Cardiovasc Surg. 2016; 152(1): 270–276, doi: 10.1016/j.jtcvs.2016.03.056, indexed in Pubmed: 27112712.
25. Deo SV, Shah IK, Dunlay SM, et al. Bilateral internal thoracic artery harvest and deep sternal wound infection in diabetic patients. Ann Thorac Surg. 2013; 95(3): 862–869, doi: 10.1016/j.athoracsur.2012.11.068, indexed in Pubmed: 23352296.
26. Malaisrie SC, McCarthy PM, Kruse J, et al. Burden of preoperative atrial fibrillation in patients undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2018; 155(6): 2358–2367.e1, doi: 10.1016/j.jtcvs.2018.01.069, indexed in Pubmed: 29523404.
27. Batra G, Ahlsson A, Lindahl B, et al. Atrial fibrillation in patients undergoing coronary artery surgery is associated with adverse outcome. Ups J Med Sci. 2019; 124(1): 70–77, doi: 10.1080/03009734.2018.1504148, indexed in Pubmed: 30265179.
28. McCarthy PM, Davidson CJ, Kruse J, et al. Prevalence of atrial fibrillation before cardiac surgery and factors associated with concomitant ablation. J Thorac Cardiovasc Surg. 2020; 159(6): 2245–2253.e15, doi: 10.1016/j.jtcvs.2019.06.062, indexed in Pubmed: 31444073.
29. Batra G, Ahlsson A, Lindahl B, et al. Atrial fibrillation in patients undergoing coronary artery surgery is associated with adverse outcome. Ups J Med Sci. 2019; 124(1): 70–77, doi: 10.1080/03009734.2018.1504148, indexed in Pubmed: 30265179.
30. Zyśko D, Persson A, Obremska M, et al. The importance of the longest R-R interval on 24-hour electrocardiography for mortality prediction in patients with atrial fibrillation. Kardiol Pol. 2021; 79(3): 311–318, doi: 10.33963/KP.15820, indexed in Pubmed: 33599460.
31. Kowalewski M, Pasierski M, Litwinowicz R, et al. Multiple versus single arterial coronary arterial bypass grafting surgery for multivessel disease in atrial fibrillation. Semin Thorac Cardiovasc Surg. 2021; 33(4): 974–983, doi: 10.1053/j.semtcvs.2020.11.015, indexed in Pubmed: 33188882.
32. Lin MH, Kamel H, Singer DE, et al. Perioperative/postoperative atrial fibrillation and risk of subsequent stroke and/or mortality. Stroke. 2019; 50(6): 1364–1371, doi: 10.1161/STROKEAHA.118.023921, indexed in Pubmed: 31043148.
33. Tyras DH, Barner HB, Kaiser GC, et al. Bypass grafts to the left anterior descending coronary artery. J Thorac Cardiovasc Surg. 1980; 80(3): 327–333, doi: 10.1016/s0022-5223(19)37757-8, indexed in Pubmed: 6968006.
34. Suwalski P, Kowalewski M, Jasiński M, et al. Surgical ablation for atrial fibrillation during isolated coronary artery bypass surgery. Eur J Cardiothorac Surg. 2020; 57(4): 691–700, doi: 10.1093/ejcts/ezz298, indexed in Pubmed: 31665277.

Subcostal echocardiographic assessment of tricuspid annular kick (SEATAK): A novel independent predictor of 30-day mortality in patients with acute pulmonary embolism

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ABSTRACT

Background: The most commonly used parameter of right ventricular (RV) systolic function — tricuspid annular plane systolic excursion (TAPSE) — is unavailable for some patients. Subcostal echocardiographic assessment of tricuspid annular kick (SEATAK) has been proposed as its alternative.

Aim: The study aimed to assess the feasibility of SEATAK use in patients with acute pulmonary embolism (PE) and its value in prognosis after PE.

Methods: The observational study included 164 consecutive patients (45.7% men; average age, 70 years) with a high clinical probability of PE referred for computed tomography pulmonary angiography.

Results: SEATAK was unavailable due to inadequate quality of echocardiogram in 2.8% of patients, whereas TAPSE could not be calculated in 4.9%, both parameters were not estimated only in 0.6%. SEATAK and TAPSE values did not differ between groups of patients with PE (n = 82) and without (n = 82). In the whole study, SEATAK correlated positively with TAPSE (r = 0.71; 95% confidence interval [CI], 0.62–0.78; P <0.001), fractional area change of the RV, left ventricular ejection fraction, and peak systolic tricuspid annular velocity assessed with tissue Doppler imaging. There were only 3 echocardiographic predictors of 30-day all-cause mortality in patients with with PE (n = 10): SEATAK, pulmonary acceleration time, and the 60/60 sign. SEATAK predicted 30-day all-cause mortality with AUC (area under the curve) 0.726 (95% CI, 0.594–0.858; P = 0.01) and 30-day PE-related mortality (n = 4) with AUC, 0.772 (95% CI, 0.506–0.998; P = 0.03).

Conclusions: SEATAK is a promising practicable echocardiographic parameter reflecting RV systolic function and might be an accurate alternative to TAPSE. Moreover, SEATAK could be an independent predictor of all-cause and PE-related 30-day mortality in patients with acute PE.

Key words: echocardiography, pulmonary embolism, tricuspid annular plane systolic excursion, subcostal view

INTRODUCTION

Recent years have brought much interest in the physiology and pathology of the right ventricle (RV) [1]. Echocardiographic assessment of RV systolic function becomes relevant for multiple cardiopulmonary conditions including acute pulmonary embolism (PE) [2, 3]. Since the muscle fiber arrangement in the RV makes its contraction occur primarily in the longitudinal plane, it can be simply assessed with classic echocardiography [4]. The most commonly used parameter of RV systolic function in M-mode is tricuspid annular plane systolic excursion (TAPSE), which was introduced almost 40 years ago, in 1984, by Kaul and colleagues [5]. TAPSE has been demonstrated to be accurate, reproducible, and simple to evaluate. It has its place in

WHAT'S NEW?

Transthoracic echocardiography is an underestimated tool in acute pulmonary embolism. Tricuspid annular plane systolic excursion has been demonstrated to be an accurate, reproducible, and simple-to-evaluate echocardiographic parameter, but due to technical reasons, it is not appropriate for a significant number of patients. We found that a novel tool — subcostal echocardiographic assessment of tricuspid annular kick is an accurate alternative to the conventional tricuspid annular plane systolic excursion, highly reflective of right ventricular systolic function and also is an independent predictor of all-cause and pulmonary embolism-related 30-day mortality in patients with acute pulmonary embolism.

current guidelines as a part of a transthoracic echocardiographic examination (TTE) [6, 7]. Furthermore, TAPSE shows prognostic significance in patients with acute PE and pulmonary hypertension [2, 8].

Nevertheless, TAPSE is dependent on the transducer position and alignment with the tricuspid annulus, often requiring a change of the patient's position to left lateral decubitus. It might be problematic, inter alia, in patients in the intensive care unit, individuals in serious conditions, or during cardiopulmonary resuscitation. Furthermore, inadequate visualization of the tricuspid annulus in the apical view poses another disadvantage. This is commonly encountered in persons with chronic lung diseases, mechanical ventilation, or obesity [4].

The subcostal echocardiographic view is free of some of these limitations. It can be obtained more easily in some patients with chronic lung disease and RV enlargement and in immobilized ones. The assessment of movement of the tricuspid annulus within the subcostal view in PE has never been investigated. The semiquantitative evaluation of RV systolic function using M-mode in the modified subcostal view with the systolic excursion assessment of tricuspid annular kick (SEATAK) was proposed by Díaz-Gómez et al. in 2016 as an alternative to TAPSE in critically ill patients [9]. Thus, SEATAK evaluates the same phenomenon as TAPSE but from a different perspective.

The study aimed to assess the feasibility of SEATAK use in assessment of RV systolic function in patients with PE and the role of this echocardiographic parameter in the short-term prognosis of patients with acute PE.

METHODS

Study group

This was a cross-sectional observational single-center study. The study population included consecutive patients of the Internal Medicine Department and the Special Care Cardiac Unit with a high clinical probability of PE referred for computed tomography pulmonary angiography (CTPA) between August 1, 2018 and August 31, 2020. The treatment followed the guidelines on PE management of the European Society of Cardiology [10, 11]. In summary, unfractionated heparin was used exclusively in high-risk PE patients along with alteplase. All non-high-risk patients and high-risk patients at a later stage of treatment received enoxaparin subsequently replaced with dabigatran, on rare occasions with warfarin or acenocoumarol, alternatively apixaban or rivaroxaban from the beginning of the PE treatment.

The exclusion criteria included recurrent PE, chronic thromboembolic pulmonary hypertension, echocardiograms of inadequate quality, severe valvular defects, and tricuspid valve replacement.

A standard diagnostic protocol comprised determination in all patients on the day of admission to the ward the laboratory parameters including, inter alia, creatinine, estimated creatinine clearance calculated with the Cockcroft-Gault equation, troponin T concentrations determined with high-sensitivity automated sandwich electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany), N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels measured using the enzyme-linked immunosorbent assay (ELISA, Roche Diagnostics GmbH, Mannheim, Germany) and D-dimer concentrations using an automated enzyme-linked fluorescent assay (VIDAS D-dimer Exclusion, bioMerieux, Marcy-l'Étoile France).

Echocardiographic assessment

Transthoracic echocardiograms were performed within 24 hours after admission to the ward by an experienced sonographer cardiologist (JW) using commercially available echocardiographic systems of Vivid S60N or Vivid S6 (General Electric Company, Boston, MA, US) according to the same protocol. The measurements were made based on the current guidelines with real-time electrocardiographic recording to precisely define the phases of the heart cycle. The estimation of SEATAK was utilized according to the method by Díaz-Gómez and colleagues from the Mayo Clinic. Briefly, the subcostal four-chamber view was obtained with an average depth of 20 to 24 cm. Then a counterclockwise rotation was applied to acquire the subcostal short-axis view upon which the right atrium, RV, tricuspid annulus, and inferior vena cava could be identified. Subsequently, the cursor was aligned in real-time with M-mode echocardiographic imaging with the tricuspid annulus to obtain a linear measurement from end-diastole to end-systole i.e. SEATAK [9, 12]. The average values of every single echocardiographic parameter were

calculated from 3 cardiac cycles using the incorporated sonography software.

Study endpoint

The study endpoints were 30-day overall mortality and 30-day PE-related mortality. Data about mortality was based on hospital records (the only hospital operating in the district), the government electronic system collecting data about individuals covered by public insurance, and phone calls to primary care physicians, patients, and their families. The cause of death was determined mainly based on hospital records, possibly on documentation from the facility where the patient died (other hospitals, nursing homes, etc.) or corresponding general practitioners.

Ethical issues

The study protocol complied with the Declaration of Helsinki and was approved by the Bioethics Committee of the Regional Medical Chamber in Tarnow, Poland (no. 3/0177/2019).

Statistical analysis

Quantitative variables with normal distribution are expressed as mean with standard deviation, whereas quantitative variables with non-normal distribution as median with interquartile range. Student's t-test or the Mann-Whitney U test were accordingly used for their comparisons. Qualitative variables are expressed as numbers (percentage), Fisher's test or the χ^2 test were used for comparisons, when adequate. Pearson or Spearman correlations were calculated to assess the relationship between SEATAK and other RV systolic parameters.

Early mortality and PE-related mortality were treated as right-censored data. Standard Kaplan-Mayer curves were used for 30-day survival analysis, the log-rank test was used for comparisons. Hazard risk was calculated using Cox proportional-hazards regression for early mortality. The proportional hazard assumption was checked with the Grambsch-Therneau test. Due to an insufficient number of events, we withdrew from regression analysis of PE-related mortality. Receiver operating characteristic analysis was performed, and areas under curves (AUC) were calculated. Optimal cut-off values were delineated according to the maximum sensitivity method. Sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively), and the corresponding 95% confidence interval (CI) were calculated for SEATAK and TAPSE. Two-sided *P*-values <0.05 were considered statistically significant and were not adjusted for multiple testing. Statistical analysis was performed with the R Project for Statistical Computing version 3.6.3 (The R-Foundation for Statistical Computing, Free Software Foundation Inc., Vienna, Austria).

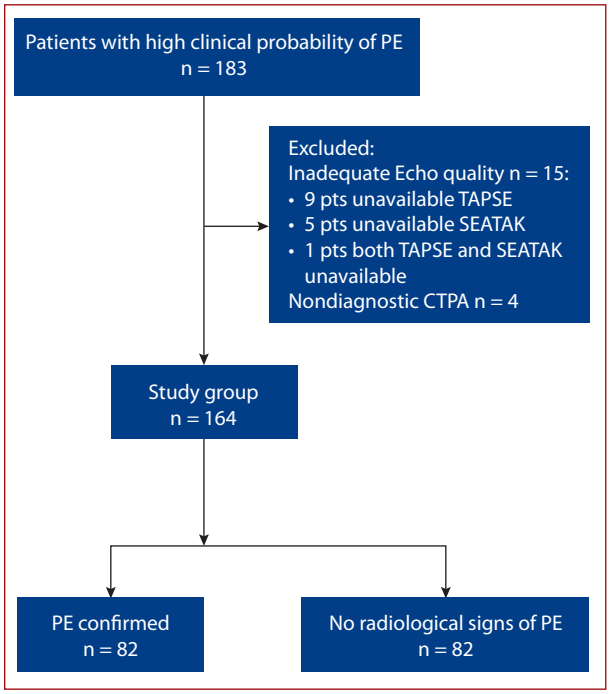

Figure 1. Flow chart of the study

Abbreviations: CTPA, computed tomography pulmonary angiography; PE, pulmonary embolism; SEATAK, subcostal echocardiographic assessment of tricuspid annular kick; TAPSE, tricuspid annular plane systolic excursion

RESULTS

The study comprised 183 consecutive patients. Twelve patients had echocardiograms of poor quality; in 9 (4.9%) individuals TAPSE could not be calculated, in further 5 (2.8%), SEATAK was not available, and in one (0.6%) both parameters were not estimated. Four subjects had nondiagnostic CTPA (Figure 1). Excluded patients had similar clinical characteristics, and there were no significant differences in age, sex, presence of PE, or studied echocardiographic parameters. Finally, 164 individuals were eligible to be enrolled in the study. The baseline characteristics and biochemical parameters of these patients are presented in Table 1. Exactly half of the participants had PE confirmed: 37 subjects had central PE (45.12%), whereas 45 individuals (54.88 %) had peripheral PE. Within this group, 4 patients were classified with high-risk PE, 23 with intermediate-high risk, 32 with intermediate-low risk, and 23 with low-risk PE.

The patients with PE, compared to subjects without PE, had higher body mass index, D-dimer serum concentration, and less often presented with coronary artery disease and chronic heart failure (Table 1).

Ten study participants (12.2%) of the PE group died during the 30-day follow-up. Four patients (4.88%) required thrombolysis within 24 hours from admission to the ward. Two of them (2.44%) died, and two (2.44%) survived. Another 2 patients (2.44%) died due to PE which in effect caused refractory RV heart failure. In the next 6 subjects (7.32%), PE contributed to death by aggravating

Table 1. Clinical characteristics and selected biochemical parameters of the study participants: all patients, subgroups of individuals with and without acute pulmonary embolism, deceased subjects, and survivors within 30-days of observation

	All subjects (n = 164)	Patients with PE (n = 82)	Patients with no PE (n = 82)	*P*-value	Non-survivors (n = 10)	Survivors (n = 72)	*P*-value
Male sex, n (%)	75 (45.73)	40 (48.78)	35 (42.68)	0.43	2 (20)	38 (52.78)	0.09
Age, years, median (IQR)	70 (59.75–80)	70 (58.25–80)	70.5 (60.25–79)	0.90	79.5 (72.25–89.75)	67.5 (57–79.25)	0.006
BMI, kg/m^2, mean (SD)	27.36 (5.95)	28.32 (5.49)	26.43 (6.25)	0.043	28.26 (6.6)	28.33 (5.38)	0.98
Arterial hypertension, n (%)	59 (35.98)	27 (32.93)	32 (39.02)	0.42	6 (60)	21 (29.17)	0.07
Hyperlipidemia, n (%)	43 (26.22)	18 (21.95)	25 (30.49)	0.21	3 (30)	15 (20.83)	0.68
Diabetes mellitus, n (%)	19 (11.59)	12 (14.63)	7 (8.54)	0.22	4 (40)	8 (11.11)	0.04
Coronary artery disease, n (%)	31 (18.9)	8 (9.76)	23 (28.05)	0.003	1 (10)	7 (9.72)	1
Chronic heart failure, n (%)	29 (17.68)	9 (10.98)	20 (24.39)	0.02	3 (30)	6 (8.33)	0.07
Atrial fibrillation (present or prior), n (%)	16 (9.76)	4 (4.88)	12 (14.63)	0.06	0 (0)	4 (5.56)	1
History of stroke, n (%)	3 (1.83)	0 (0)	3 (3.66)	0.23	0 (0)	0 (0)	1
Active smoking, n (%)	19 (11.59)	9 (10.98)	10 (12.2)	1	1 (10)	8 (11.11)	1
Chronic lung disease, n (%)	11 (6.71)	3 (3.66)	8 (9.76)	0.21	1 (10)	2 (2.78)	0.33
Active malignancy, n (%)	35 (21.34)	17 (20.73)	18 (21.95)	0.81	3 (30)	14 (19.44)	0.69
Acute infection, n (%)	25 (15.24)	13 (15.85)	12 (14.63)	0.83	3 (30)	10 (13.89)	0.19
Wells rule — original version, points, median (IQR)	3 (1.5–4.5)	3 (1.5–5.5)	1.5 (1.125–4.5)	0.13	3.75 (1.875–4.75)	3 (0.75–5.5)	0.84
Revised Geneva rule — original version, points, median (IQR)	5 (4–6)	5 (4–7)	5 (4.125–6)	0.57	6 (6–7.25)	5 (4–6.25)	0.07
PESI, median (IQR)	94 (80–118)	97 (81–123)	93 (79.25–116.5)	0.44	126.5 (106–141.5)	94 (79–111)	0.003
sPESI, median (IQR)	1 (0–2)	1 (0–2)	1 (0–2)	0.88	2.5 (2–3)	1 (0–2)	0.004
Troponin T, pg/ml, , median (IQR)	22.18 (12.06–57.87)	27.8 (11.21–65.61)	19 (13–49.93)	0.40	70.65 (52.965–168.885)	22.6 (10.82–51.63)	0.01
NT-proBNP, pg/ml, median (IQR)	1077 (201– 4454)	1232 (155–3623)	947 (249–4813)	0.61	3837 (1839 – 11688)	597 (143–2944)	0.02
D-dimer, µg/ml, median (IQR)	4050 (1991–7301)	5531 (2915–8477)	3197 (1630–5141)	<0.001	8477 (4737–10000)	5369 (2712 –7823)	0.09
Creatinine clearance, ml/min, median (IQR)	82.45 (61.85–103.63)	82.4 (65.5–102)	82.5 (60.1–103.9)	0.68	65.5 (37.7–112.5)	83.55 (69.60–101.48)	0.27

Abbreviations: PE, pulmonary embolism; BMI, body mass index; PESI, Pulmonary Embolism Severity Index; sPESI, simplified Pulmonary Embolism Severity Index; NT-proBNP, N-terminal pro-B-type natriuretic peptide

other decompensated diseases: heart failure in 2 (2.44%), pneumonia in 2 (2.44%), kidney failure in 1 (1.22%), and disseminated neoplastic disease in 1 (1.22%). None of the study participants required rescue thrombolysis in the observational period. The median time of hospitalization was 9 days ranging from 1 to 30 days.

The patients who died in the follow-up, compared to survivors, were older, less frequently had diabetes mellitus; however, they had higher scores in the Pulmonary Embolism Severity Index (PESI) and simplified PESI (sPESI), increased troponin T and NT-proBNP serum concentrations (Table 1).

Echocardiographic parameters

In the whole study group, SEATAK showed smaller values than TAPSE (18.22 ± 5.63 mm vs. 20.17 ± 5.9 mm, P <0.001).

SEATAK and TAPSE did not differ between the groups of patients with and without PE (Table 2).

Patients with PE compared to individuals with no signs of PE upon CTPA had higher values of the ratio of basal right ventricular end-diastolic diameter measured in the transverse view (RVTD) to basal left ventricular end-diastolic diameter measured in the transverse view (LVTD), decreased values of pulmonary artery acceleration time (Act). On the other hand, they presented more frequently with the 60/60 and McConnell signs (Table 2).

Non-survivors had reduced values of SEATAK, TAPSE, RVTD, and Act but more often showed a positive 60/60 sign when compared to the survivors (Table 2).

Relation of SEATAK to other echocardiographic parameters

In the whole study, SEATAK correlated positively with TAPSE (r = 0.71; 95% CI, 0.62–0.78; P <0.001), fractional area change of the RV (FAC) (r = 0.29; 95% CI, 0.02–0.53; P = 0.04), left ventricular ejection fraction (LVEF; r = 0.36; 95% CI, 0.22–0.48; P <0.001), and peak systolic tricuspid annular velocity assessed with tissue Doppler imaging (TSV TDI) (r = 0.47; 95% CI, 0.34–0.58; P <0.001). Neither was SEATAK associated with a Right Ventricular Index of Myocardial Performance (Tei index) measured with tissue Doppler imaging (r = 0.01; 95% CI, –0.15–0.18; P = 0.87) nor with Pulsed-Wave Doppler mode (r = 0.07; 95% CI, –0.1–0.22; P = 0.43).

Echocardiographic predictors of 30-day mortality

The univariable Cox proportional-hazard regression analysis revealed 3 echocardiographic predictors of 30-day all-cause mortality in patients with acute PE: SEATAK, Act,

Table 2. Selected echocardiographic parameters

	Patients with PE (n = 82)	Patients with no PE (n = 82)	*P*-value	Non-survivors (n = 10)	Survivors (n = 72)	*P*-value
SEATAK, mm	17.68 ± 5.71	18.76 ± 5.52	0.22	13.90 ± 3.96	18.21 ± 5.74	0.009
TAPSE, mm	19.93 ± 6.06	20.41 ± 5.77	0.60	16.60 ± 4.12	20.39 ± 6.16	0.02
TASV TDI, cm/s	15.12 ± 4.74	15.72 ± 5.68	0.47	15.44 ± 4.72	15.08 ± 4.78	0.83
RVTD, mm	40 (37–43)	38 (35–42)	0.09	36 (35–38)	40.5 (37–44.25)	0.03
LVTD, mm	42.82 ± 7.1	43.84 ± 7.72	0.39	38.56 ± 6.41	43.38 ± 7.04	0.06
RVTD/LVTD	0.94 (0.83–1.06)	0.87 (0.78–1.03)	0.04	1.03 (0.88–1.1)	0.94 (0.83–1.06)	0.61
Act, ms	70 (55–88)	93 (71.75–115)	<0.001	59 (48–59)	74 (57–90.25)	0.02
TRV, m/s	2.9 ± 0.79	2.8 ± 0.71	0.44	2.95 ± 0.78	2.89 ± 0.8	0.82
TRPG, mm Hg	36 (27–52.5)	36 (27–48)	0.75	40 (34–48)	35.5 (26.25–52.75)	0.64
60/60 sign, n (%)	20 (24.39)	5 (6.1)	0.001	6 (60.00)	14 (19.44)	0.003
McConnell sign, n (%)	9 (10.98)	1 (1.22)	0.02	1 (10)	8 (11.11)	1
IVS flattening, n (%)	4 (4.88)	6 (7.32)	0.75	0	4 (5.56)	1
Distended IVC with diminished inspiratory collapsibility, n (%)	7 (8.54)	4 (4.88)	0.54	1 (10)	6 (8.33)	1
LVEF, %	54.5 (49.25–61.5)	55.5 (45–64.75)	0.96	54 (43.5–59)	54.5 (49.75–62)	0.70

Abbreviations: Act, pulmonary acceleration time; IVC, inferior vena cava; IVS, interventricular septum; LVEF, left ventricular ejection fraction; LVTD, basal left ventricular end-diastolic diameter measured in the transverse view; RVTD, basal right ventricular end-diastolic diameter measured in the transverse view; SEATAK, subcostal echocardiographic assessment of tricuspid annular kick; TAPSE, tricuspid annular plane systolic excursion; TASV TDI, tricuspid annulus' peak systolic velocity measured with tissue Doppler imaging; TRV, tricuspid regurgitation jet velocity; TRPG, tricuspid valve peak systolic gradient; other — see Table 1

Table 3. Univariable analysis of echocardiographic predictors of all-cause 30-day mortality in patients with acute pulmonary embolism (n = 82)

	All-cause 30-day mortality	
	HR (95% CI)	*P*-value
SEATAK, mm	0.86 (0.76–0.98)	0.02
TAPSE, mm	0.90 (0.80–1.00)	0.06
RVTD, mm	0.90 (0.79–1.01)	0.08
LVTD, mm	0.91 (0.82–1.00)	0.06
Act, ms	0.95 (0.91–1.00)	0.04
TRV, m/s	1.11 (0.49–2.54)	0.80
TRPG, mm Hg	1 (0.97–1.04)	0.94
60/60 sign, %	5.39 (1.519–19.11)	0.009
Distended IVC with diminished inspiratory collapsibility, %	1.14 (0.14–8.97)	0.90

Abbreviations: CI, confidence interval; HR, hazard ratio; RVTD, basal right ventricular end-diastolic diameter measured in the transverse view; LVTD, basal left ventricular end-diastolic diameter measured in the transverse view; other — see Table 2

and 60/60 sign. TAPSE did not reach statistical significance. Additionally, the 60/60 sign was present in all the subjects who died of PE (Table 3).

SEATAK and TAPSE as predictors of 30-day mortality

The receiver operating characteristic investigation disclosed that SEATAK is a good predictor of 30-day all-cause mortality (AUC, 0.726) and 30-day PE-related mortality (AUC, 0.772). TAPSE was a predictor of PE-related mortality (AUC, 0.793) and death from any cause (AUC, 0.690) (Figure 2).

Optimal cut-offs for predicting all-cause mortality were <20 mm for SEATAK and <21 for TAPSE. With those cut-offs, both SEATAK and TAPSE showed high sensitivity (100% and 90%, respectively) and PPV (100% and 97%, respectively) but low specificity (43% and 50%, respectively) and NPV (20% both) for adverse prognosis.

Optimal cut-offs for predicting PE-related mortality were <17 mm for both SEATAK and TAPSE. With those cut-offs, both SEATAK and TAPSE showed again high sensitivity (75% and 74%, respectively) and PPV (98% both) but low specificity (54% and 72%, respectively) and NPV (8% and 12%, respectively) for fatal outcomes.

Kaplan-Meier analysis showed favorable outcomes for patients with SEATAK ≥20 mm and TAPSE ≥21 mm in terms of all-cause mortality and for individuals with SEATAK and TAPSE ≥17 mm regarding PE-related death (Figure 3).

SEATAK and TAPSE were neither correlated with age (Spearman correlation coefficient, 0.04 and –0.11, $P = 0.63$ and 0.17, respectively) nor with D-dimer levels (Spearman correlation coefficients, –0.10 and –0.03; $P = 0.26$ and 0.68, respectively). In multivariable analysis, SEATAK was a predictor of overall mortality when controlled with age ($P = 0.03$).

DISCUSSION

TTE is not a mandatory part of routine diagnostics in hemodynamically stable patients with PE [11]. Although short-term outcomes in acute PE are mainly conditioned by the hemodynamic status, RV dysfunction detected, inter alia, in TTE is associated with an increased risk of short-term mortality even in normotensive individuals [13, 14]. Moreover, TTE enables close monitoring to detect hemodynamic decompensation and may help to identify possible candidates for rescue reperfusion therapy. Complex RV geometry precludes determination of a single parameter that could reliably reflect the RV size and function. Dysfunction of RV evoked by acute PE has been evaluated with different echocardiographic techniques, and its criteria differed among studies [11].

The assessment of TAPSE was unsuccessful even in 25% of cases in previous studies, whereas SEATAK was achievable

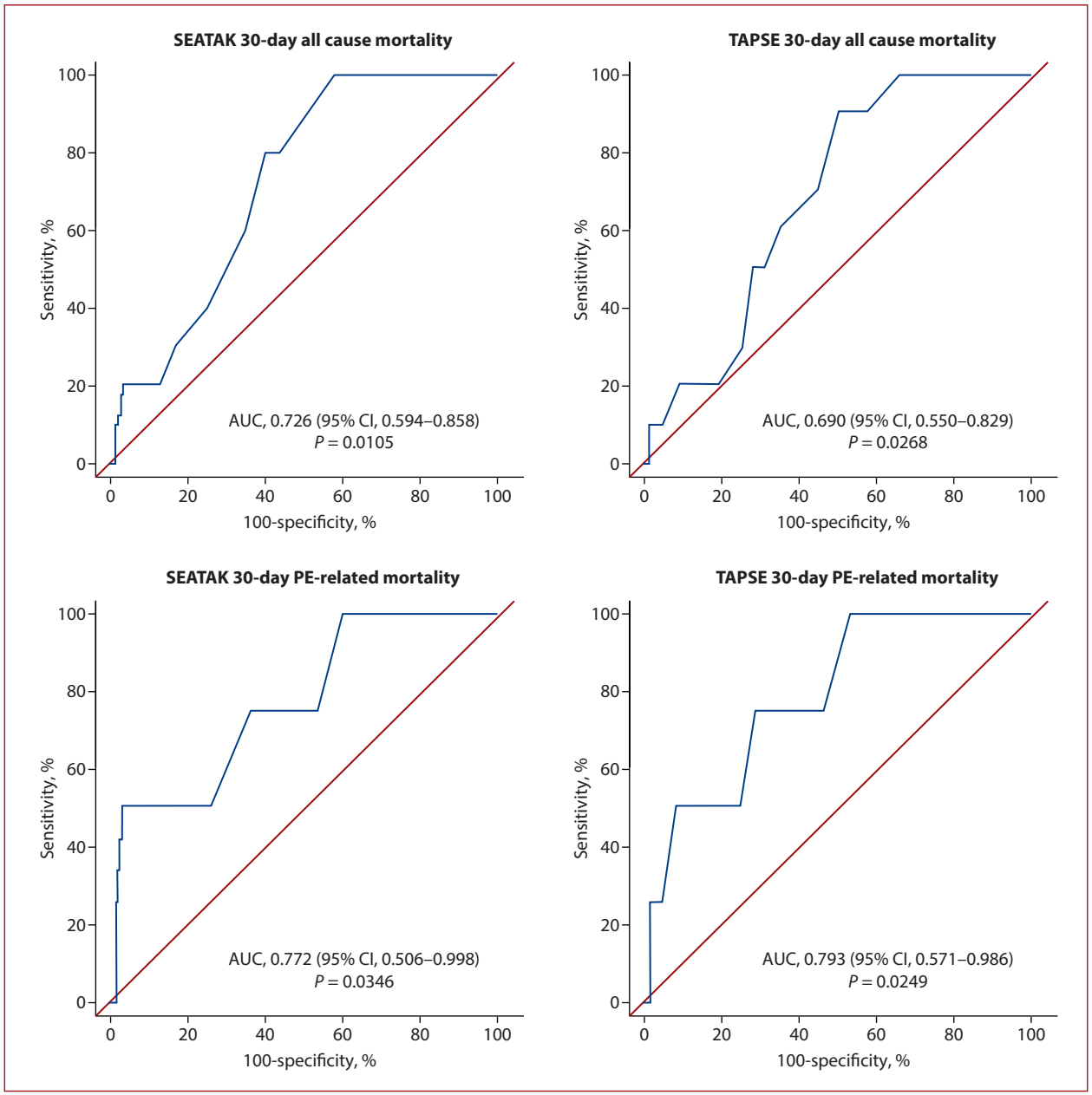

Figure 2. Receiver-operating characteristic (ROC) analysis of tricuspid annular kick (SEATAK) and tricuspid annular plane systolic excursion (TAPSE) in 30-day all-cause mortality and PE related mortality prediction in 82 patients with acute pulmonary embolism (all deaths n = 10; PE-related deaths n = 4)

Abbreviations: AUC, area under the curve; CI, confidence interval; PE, pulmonary embolism

in all subjects [9, 15–17]. In our group rates of failure to determine TAPSE and SEATAK were 4.9% and 2.8%, respectively. Importantly, only in 0.6% of study participants, these two parameters could not be calculated. Thus, SEATAK may be very valuable in RV function appraisal in patients in whom TAPSE is not possible. The estimation of tricuspid annular movement in the subcostal view is getting more attention. "Subcostal TAPSE" has been assessed with anatomical M-mode and B-mode in adult and pediatric populations and proved to be a feasible and accurate alternative to conventional TAPSE with adequate efficacy in the identification of RV dysfunction [18–20]. Nevertheless, it has never been investigated in PE diagnostics and prognosis.

SEATAK showed positive correlations with RV systolic TTE parameters: TAPSE, FAC, TSV TDI, and LVEF, which is in concordance with the results of the studies by Díaz-Gómez et al. on critically ill patients and the SEATAK validation article by Sadek et al. [9, 21] on consecutive subjects with different disorders referred to the echocardiography laboratory. Although TTE examinations were performed in groups of various clinical characteristics, in our analysis, as well as in previous publications, the correlations between SEATAK and TAPSE were all strong (r = 0.71; P <0.001; r = 0.86; P = 0.03 and r = 0.82; P <0.001, respectively). The values of SEATAK were smaller than TAPSE in all these studies with the overall mean difference of 1.9 mm, 1.5 mm, and 2.6 mm,

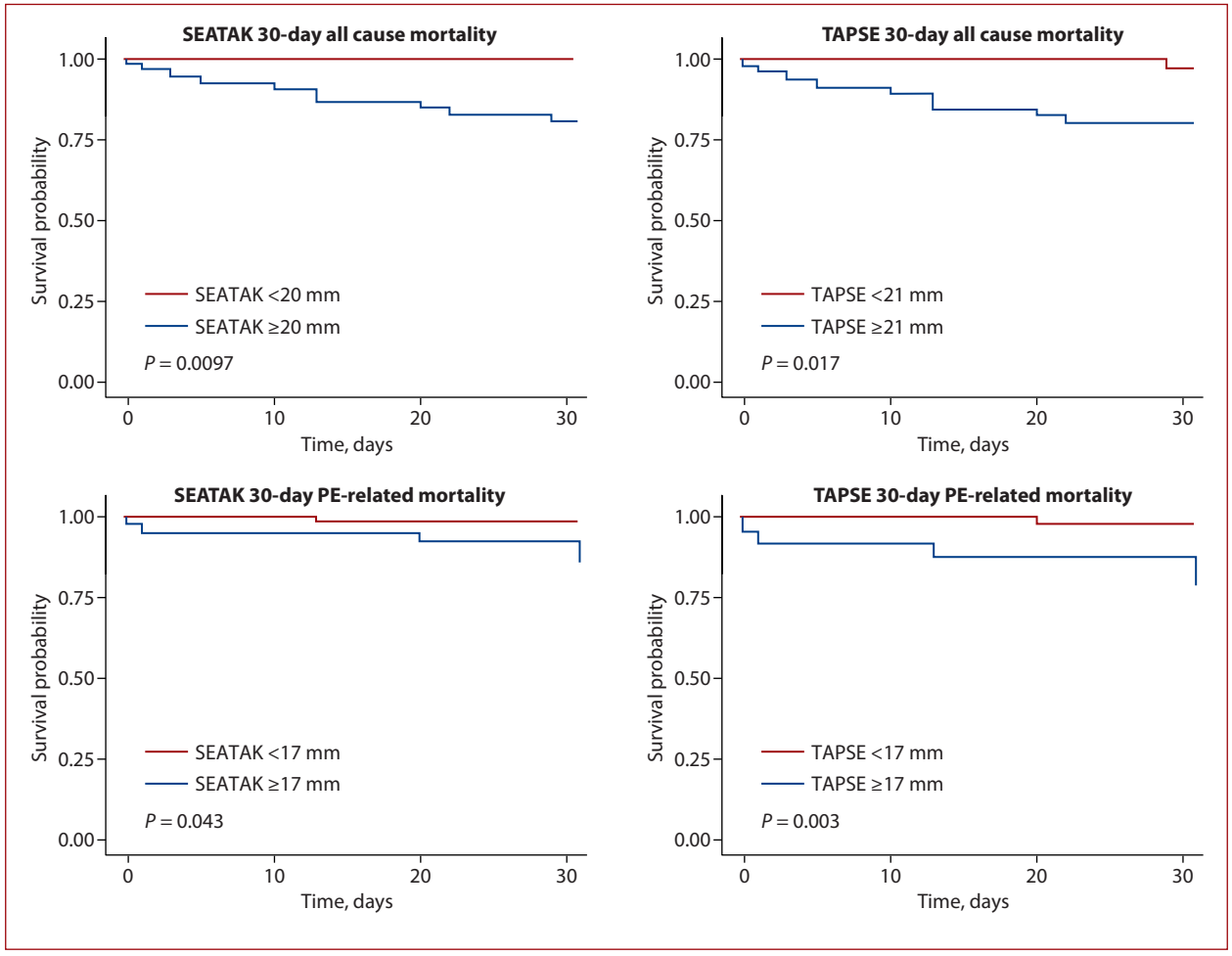

Figure 3. Kaplan-Meier analysis of tricuspid annular kick (SEATAK) and tricuspid annular plane systolic excursion (TAPSE) of 30-day survival in 82 patients with acute pulmonary embolism (PE). N of groups: SEATAK <20 mm 51 pts (62.2%), SEATAK ≥20 mm 31 pts (37.8%), SEATAK <17 mm 37 pts (45.12%), SEATAK ≥17 mm 45 pts (54.88%), TAPSE <21 mm 45 pts (54.88%), TAPSE ≥21 mm 37 pts (45.12%), TAPSE <17 mm 25 pts (30.49%), TAPSE ≥17 mm 57 (69.51%)

Abbreviations: see Tables 1–3

respectively [9, 21]. Notably, during TAPSE calculation in the 4-chamber apical view, in most cases, the M-mode is aligned almost perpendicularly to the tricuspid valve plane while in the subcostal long-axis view it is at an angle, which could explain decreased values of SEATAK. Moreover, in SEATAK calculation, a specific movement of the analyzed lateral part of the tricuspid annulus is observed; a slight rotation towards the left ventricle, which is accurately reflected in the parameter's name with the denotation "kick". This kick might be more dependent on performance of the basic part of the free wall of the RV, while TAPSE is more related to performance of other parts of the RV wall. Thus, in PE where there are, in some patients, regional motion abnormalities of the RV free wall, including subjects with the McConnell sign, the differences between SEATAK and TAPSE could be more pronounced.

Significant positive correlations between TAPSE and other RV systolic TTE parameters and LVEF were reported earlier, inter alia, in a group of 900 patients with different diseases [22]. In the analysis of available hemodynamic profiles, SEATAK correlated with cardiac output, cardiac index, and central venous pressure and showed an inverse relationship with the heart rate and pulmonary arterial occlusion pressure. Díaz-Gómez et al. [9], based on their results, assume that SEATAK might be affected more by preload, whereas TAPSE reflects the isolated intrinsic systolic function of the RV.

Neither in the aforementioned study by Sadek et al. [21] nor in ours, SEATAK correlated with the right ventricular index of myocardial performance, calculated in that article with tissue Doppler imaging and in our study with TDI and Pulsed Doppler of tricuspid inflow and right ventricular outflow tract flow. Importantly, the Tei index is a global estimate of both systolic and diastolic function of the RV, and this diastolic component is most likely the confounding factor [1, 21].

In our study, SEATAK, like TAPSE, showed no utility in PE diagnosis. Both parameters serve as indicators of RV systolic function but not of the presence of thrombi in pulmonary arteries. PE might not affect RV systolic performance or influence it to a different extent, just like other heart disorders, including left heart diseases [11].

Other echocardiographic parameters more specific for PE detection, related to the presence of obstacles in pulmonary arteries and RV pressure overload e.g. shortened Act, the 60/60 sign, increased RVTD to LVTD ratio, and the McConnell sign were different in our subgroups of participants with and without PE . Apart from SEATAK, shortened Act and the 60/60 sign were echocardiographic predictors of unfavorable prognosis in our analysis. Act <81 ms was associated with 30-day mortality in a prospective blinded study [23]. The 60/60 sign was shown to be a good predictor of in-hospital mortality in PE patients (odds ratio [OR], 6.13; 95% CI, 1.11–59.21; $P = 0.03$) [24]. In the analysis of the echocardiographic pattern of 511 consecutive patients with acute PE, the coexistence of the 60/60 sign with the McConnell sign and an enlarged hypokinetic RV was recognized as the most useful echocardiographic criterion for RV dysfunction [25]. Notably, RV dysfunction was superior to the PESI and Bova clinical scores in risk stratification in 571 individuals with acute PE [26].

In our analysis, TAPSE showed good prognostic value in the prediction of 30-day mortality. As reported previously by Pruszczyk and colleagues in a group of normotensive patients with acute PE, TAPSE was the only independent TTE outcome predictor from a broad array of echocardiographic parameters [27]. Similar findings come from the study by Lobo et al. [28]. Moreover, in the article by Kurnicka et al. [29], TAPSE was superior to TSV TDI in the prediction of 30-day adverse outcomes. Notably, assessment of RV function with tissue Doppler imaging correlated with pulmonary artery thromboembolic burden and was successfully utilized to monitor RV performance and filling pressure in PE [30, 31]. In another study, TAPSE was preferable to echocardiographic evaluation of the RV to the left ventricle ratio and the counterpart of this RV pressure overload marker in multidetector computed tomography in 30-day mortality prognosis [32]. The cut-off values for TAPSE considering PE-related outcome measures varied from ≤15 mm to <18 mm as abnormal and ≥18 mm to >20 mm as normal in different studies [2, 27, 28, 32–34]. Our results of TAPSE and SEATAK cut-offs are at a similar level.

A single-center setting with a relatively small number of patients, especially in the non-survivor group, should make our promising results be appraised with caution. Further studies on larger patient groups are advised.

Even though PE is an old topic, new significance is being attached to echocardiography as a useful tool in evaluating this condition and its complications. In the review by Pruszczyk and Konstantinides, elevated echocardiography imaging indexes are included in risk factors that may affect initially normotensive patients with PE and move them to the group of patients with intermediate-risk [35]. Another study aimed to assess usefulness of classic echocardiographic parameters indexed to height and body surface area for prediction of acute PE in patients with a high clinical probability of PE referred for computed tomography pulmonary angiography [36]. The authors of an expert opinion screening for patients with chronic thromboembolic pulmonary hypertension after acute PE claim that TTE is a preferred screening test for chronic thromboembolic pulmonary hypertension and should be performed in any patient with dyspnea of unclear cause after a history of acute PE and at least 3 months of optimal antithrombotic therapy [37].

Study limitations

The main limitation of the presented study is a small number of patients, especially within the non-survivor subgroup. Furthermore, echocardiograms were not repeated, and thus variability of echocardiographic parameters could not be assessed. The prognostic value of biomarkers with different recognized cut-off values was not investigated.

CONCLUSIONS

SEATAK is a promising practicable and useful echocardiographic parameter reflecting RV systolic function and might be an accurate alternative to TAPSE. Moreover, SEATAK could be an independent predictor of all-cause and PE-related 30-day mortality in patients with acute PE.

Supplementary material

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

Article information

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REFERENCES

1. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2010; 23(7): 685–713; quiz 786, doi: 10.1016/j.echo.2010.05.010, indexed in Pubmed: 20620859.
2. Alerhand S, Hickey SM. Tricuspid Annular Plane Systolic Excursion (TAPSE) for Risk Stratification and Prognostication of Patients with Pulmonary Embolism. J Emerg Med. 2020; 58(3): 449–456, doi: 10.1016/j.jemermed.2019.09.017, indexed in Pubmed: 31735658.
3. Hirasawa K, Izumo M, Mizukoshi K, et al. Prognostic significance of right ventricular function during exercise in asymptomatic/minimally symptomatic patients with nonobstructive hypertrophic cardiomyopathy. Echocardiography. 2021; 38(6): 916–923, doi: 10.1111/echo.15075, indexed in Pubmed: 33971038.

4. Aloia E, Cameli M, D'Ascenzi F, et al. TAPSE: An old but useful tool in different diseases. Int J Cardiol. 2016; 225: 177–183, doi: 10.1016/j.ijcard.2016.10.009, indexed in Pubmed: 27728861.
5. Kaul S, Tei C, Hopkins JM, et al. Assessment of right ventricular function using two-dimensional echocardiography. Am Heart J. 1984; 107(3): 526–531, doi: 10.1016/0002-8703(84)90095-4, indexed in Pubmed: 6695697.
6. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015; 16(3): 233–270, doi: 10.1093/ehjci/jev014, indexed in Pubmed: 25712077.
7. Lipiec P, Bąk J, Braksator W, et al. Transthoracic echocardiography in adults — guidelines of the Working Group on Echocardiography of the Polish Cardiac Society [article in Polish]. Kardiol Pol. 2018; 76(2): 488–493, doi: 10.5603/KP.2018.0051, indexed in Pubmed: 29457625.
8. Ghio S, Pica S, Klersy C, et al. Prognostic value of TAPSE after therapy optimisation in patients with pulmonary arterial hypertension is independent of the haemodynamic effects of therapy. Open Heart. 2016; 3(1): e000408, doi: 10.1136/openhrt-2016-000408, indexed in Pubmed: 27175288.
9. Díaz-Gómez JL, Alvarez AB, Danaraj JJ, et al. A novel semiquantitative assessment of right ventricular systolic function with a modified subcostal echocardiographic view. Echocardiography. 2017; 34(1): 44–52, doi: 10.1111/echo.13400, indexed in Pubmed: 27739100.
10. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014; 35(43): 3033–69, 3069a, doi: 10.1093/eurheartj/ehu283, indexed in Pubmed: 25173341.
11. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Heart J. 2020; 41(4): 543–603, doi: 10.1093/eurheartj/ehz405, indexed in Pubmed: 31504429.
12. Recommended Reading on Echocardiography (n.d.). Available from: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines [Access: February 2,2022].
13. Barco S, Mahmoudpour SH, Planquette B, et al. Prognostic value of right ventricular dysfunction or elevated cardiac biomarkers in patients with low-risk pulmonary embolism: a systematic review and meta-analysis. Eur Heart J. 2019; 40(11): 902–910, doi: 10.1093/eurheartj/ehy873, indexed in Pubmed: 30590531.
14. Wiliński J, Chukwu O, Ciuk K, et al. Clinical and linguistic validation of a Polish version of the Pulmonary Embolism Quality of Life Questionnaire: a disease-specific quality of life questionnaire for patients after acute pulmonary embolism. Kardiol Pol. 2021; 79(9): 1019–1021, doi: 10.33963/KP.a2021.0074, indexed in Pubmed: 34331310.
15. Kjaergaard J, Petersen CL, Kjaer A, et al. Evaluation of right ventricular volume and function by 2D and 3D echocardiography compared to MRI. Eur J Echocardiogr. 2006; 7(6): 430–438, doi: 10.1016/j.euje.2005.10.009, indexed in Pubmed: 16338173.
16. Damy T, Kallvikbacka-Bennett A, Goode K, et al. Prevalence of, associations with, and prognostic value of tricuspid annular plane systolic excursion (TAPSE) among out-patients referred for the evaluation of heart failure. J Card Fail. 2012; 18(3): 216–225, doi: 10.1016/j.cardfail.2011.12.003, indexed in Pubmed: 22385942.
17. Ueti OM, Camargo EE, Ueti Ad, et al. Assessment of right ventricular function with Doppler echocardiographic indices derived from tricuspid annular motion: comparison with radionuclide angiography. Heart. 2002; 88(3): 244–248, doi: 10.1136/heart.88.3.244, indexed in Pubmed: 12181215.
18. Kurath-Koller S, Avian A, Cantinotti M, et al. Normal Pediatric Values of the Subcostal Tricuspid Annular Plane Systolic Excursion (S-TAPSE) and Its Value in Pediatric Pulmonary Hypertension. Can J Cardiol. 2019; 35(7): 899–906, doi: 10.1016/j.cjca.2019.01.019, indexed in Pubmed: 31292089.
19. Main AB, Braham R, Campbell D, et al. Subcostal TAPSE: a retrospective analysis of a novel right ventricle function assessment method from the subcostal position in patients with sepsis. Ultrasound J. 2019; 11(1): 19, doi: 10.1186/s13089-019-0134-7, indexed in Pubmed: 31456096.
20. Škulec R, Parizek T, Stadlerova B, et al. Subcostal TAPSE measured by anatomical M-mode: prospective reliability clinical study in critically ill patients. Minerva Anestesiol. 2021; 87(11): 1200–1208, doi: 10.23736/S0375-9393.21.15464-1, indexed in Pubmed: 33982987.
21. Sadek DEDM, Al-Deftar MI, Attia WM, et el. Value of Semiquantitative Assessment of Right Ventricular Systolic Function with A Modified Subcostal Echocardiographic View. Egypt J Hosp Med. 2019; 75(4): 2601–2605, doi: 10.21608/ejhm.2019.31449.
22. Tamborini G, Pepi M, Galli CA, et al. Feasibility and accuracy of a routine echocardiographic assessment of right ventricular function. Int J Cardiol. 2007; 115(1): 86–89, doi: 10.1016/j.ijcard.2006.01.017, indexed in Pubmed: 16750277.
23. Shmueli H, Steinvil A, Aviram G, et al. Re-Appraisal of Echocardiographic Assessment in Patients with Pulmonary Embolism: Prospective Blinded Long-Term Follow-Up. Isr Med Assoc J. 2020; 11(22): 688–695, indexed in Pubmed: 33249789.
24. Shah BR, Velamakanni SM, Patel A, et al. Analysis of the 60/60 Sign and Other Right Ventricular Parameters by 2D Transthoracic Echocardiography as Adjuncts to Diagnosis of Acute Pulmonary Embolism. Cureus. 2021; 13(3): e13800, doi: 10.7759/cureus.13800, indexed in Pubmed: 33842172.
25. Kurnicka K, Lichodziejewska B, Goliszek S, et al. Echocardiographic Pattern of Acute Pulmonary Embolism: Analysis of 511 Consecutive Patients. J Am Soc Echocardiogr. 2016; 29(9): 907–913, doi: 10.1016/j.echo.2016.05.016, indexed in Pubmed: 27427291.
26. Chen YuL, Wright C, Pietropaoli AP, et al. Right ventricular dysfunction is superior and sufficient for risk stratification by a pulmonary embolism response team. J Thromb Thrombolysis. 2020; 49(1): 34–41, doi: 10.1007/s11239-019-01922-w, indexed in Pubmed: 31375993.
27. Kurnicka K, Lichodziejewska B, Ciurzyński M, et al. Prognostic value of echocardiography in normotensive patients with acute pulmonary embolism. JACC Cardiovasc Imaging. 2014; 7(6): 553–560, doi: 10.1016/j.jcmg.2013.11.004, indexed in Pubmed: 24412192.
28. Lobo JL, Holley A, Tapson V, et al. PROTECT and RIETE investigators. Prognostic significance of tricuspid annular displacement in normotensive patients with acute symptomatic pulmonary embolism. J Thromb Haemost. 2014; 12(7): 1020–1027, doi: 10.1111/jth.12589, indexed in Pubmed: 24766779.
29. Kurnicka K, Lichodziejewska B, Ciurzyński M, et al. Peak systolic velocity of tricuspid annulus is inferior to tricuspid annular plane systolic excursion for 30 days prediction of adverse outcome in acute pulmonary embolism. Cardiol J. 2020; 27(5): 558–565, doi: 10.5603/CJ.a2018.0145, indexed in Pubmed: 30484266.
30. Kjaergaard J, Schaadt BK, Lund JO, et al. Quantification of right ventricular function in acute pulmonary embolism: relation to extent of pulmonary perfusion defects. Eur J Echocardiogr. 2008; 9(5): 641–645, doi: 10.1093/ejechocard/jen033, indexed in Pubmed: 18296399.
31. Rydman R, Larsen F, Caidahl K, et al. Right ventricular function in patients with pulmonary embolism: early and late findings using Doppler tissue imaging. J Am Soc Echocardiogr. 2010; 23(5): 531–537, doi: 10.1016/j.echo.2010.03.002, indexed in Pubmed: 20381312.
32. Paczyńska M, Sobieraj P, Burzyński Ł, et al. Tricuspid annulus plane systolic excursion (TAPSE) has superior predictive value compared to right ventricular to left ventricular ratio in normotensive patients with acute pulmonary embolism. Arch Med Sci. 2016; 12(5): 1008–1014, doi: 10.5114/aoms.2016.57678, indexed in Pubmed: 27695491.
33. Ciurzyński M, Kurnicka K, Lichodziejewska B, et al. Tricuspid Regurgitation Peak Gradient (TRPG)/Tricuspid Annulus Plane Systolic Excursion (TAPSE) - A Novel Parameter for Stepwise Echocardiographic Risk Stratification in Normotensive Patients With Acute Pulmonary Embolism. Circ J. 2018; 82(4): 1179–1185, doi: 10.1253/circj.CJ-17-0940, indexed in Pubmed: 29375106.
34. Schmid E, Hilberath JN, Blumenstock G, et al. Tricuspid annular plane systolic excursion (TAPSE) predicts poor outcome in patients undergoing acute pulmonary embolectomy. Heart Lung Vessel. 2015; 7(2): 151–158, indexed in Pubmed: 26157741.
35. Pruszczyk P, Konstantinides S. Where to treat patients with acute pulmonary embolism? Kardiol Pol. 2020; 78(1): 15–19, doi: 10.33963/KP.15143, indexed in Pubmed: 31939451.
36. Wiliński J, Skwarek A, Borek R, et al. Right ventricular wall thickness indexed to body surface area as an echocardiographic predictor of acute pulmonary embolism in high-risk patients. Kardiol Pol. 2022; 80(2): 205–207, doi: 10.33963/KP.a2021.0180, indexed in Pubmed: 34904219.
37. Ciurzyński M, Kurzyna M, Kopeć G, et al. An expert opinion of the Polish Cardiac Society Working Group on Pulmonary Circulation on screening for chronic thromboembolic pulmonary hypertension patients after acute pulmonary embolism: Update. Kardiol Pol. 2022; 80(6): 723–732, doi: 10.33963/KP.a2022.0141, indexed in Pubmed: 35665906.

Impact of anxiety-trait level and coping styles on a six-minute walk test in patients undergoing cardiac rehabilitation

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INTRODUCTION

The six-minute walk test (6MWT) is a simple test, useful in assessing physical capacity, eligibility for rehabilitation, and its effectiveness [1]. There is a demonstrated impact of depression on the distance covered during 6MWT, but the impact of anxiety remains inconclusive [2, 3]. Additionally, a question arises whether coping styles related to anxiety and depression affect the course of 6MWT. For fibromyalgia patients, a positive correlation was found between the 6MWT and active strategies [4]. There are no data on cardiac rehabilitation patients.

The protocol for the 6MWT recommends the test be performed twice. Repetition affects results, and the second test is considered reliable. The change in distance is attributed to learning effect [5].

Study objectives included (1) analysis of the influence of anxiety trait and coping styles on learning process of the 6MWT; (2) analysis of the influence of anxiety trait and coping styles on rehabilitation outcomes.

METHODS

The study involved patients participating in second-stage cardiac rehabilitation for 21–35 days under stationary conditions at the Military Institute of Medicine in Warsaw. Patients were recruited consecutively. Criteria for exclusion from the study included respiratory failure, infections, neurological deficits, mobility deficits, and cognitive or somatic deficits preventing completion of paper-pencil tests. All patients gave their written consent to participate in the study. The study was approved by the Bioethics Commission at the Military Institute of Medicine in Warsaw.

The measure of the learning process (Objective 1) was defined as the difference between results obtained in the second and first 6MWT (Δ6MWT2-1), and the effect of the rehabilitation process (Objective 2) was measured by the difference between results of the last and second study (Δ6MWT3-2).

The first 6MWT was performed between the first and third day after admission and was repeated on the following day. The final test was performed during the last two days of the rehabilitation process. The test was conducted by a skilled physiotherapist.

Anxiety trait was defined as a relatively permanent personality characteristic and was measured with the State-Trait Anxiety Inventory (STAI) [6]. Coping styles were measured with the Coping Inventory for Stressful Situations (CISS) [7] and were defined as a relatively permanent disposition toward reactions to stress across different situations and over time. Psychological tests were filled out by patients between the first and third days of the rehabilitation process.

Statistical analysis

Results were subject to statistical analysis using SPSS 26.0. Quantitative variables distribution was examined with the Shapiro-Wilk test. In descriptive statistics, data were presented in the form of mean, standard deviation median, and interquartile range (IQR). Frequency distributions were prepared for categorical variables. For Objective 1, Spearman correlation and linear regression analyses were applied; for Objective 2, only Spearman correlation

Table 1. Mean, median values and Spearman correlation coefficients between distance covered in the 6MWT, difference between the results of the 6MWT and anxiety trait and different styles of coping with stressful situations

					6MWT1	6MWT2	6MWT3	Δ6MWT 2-1	Δ6MWT 3-2	Δ6MWT 3-1
			Mean (SD)		—	497.80 (120.95)	541.88 (107.20)	38.75 (53.95)	—	—
			Median (IQR)		471.00 (401.00–538.00)	—	—	—	47.00 (12.00–90.00)	90.00 (50.00–135.70)
Anxiety trait		Mean (SD)	42.39 (8.90)	rho	–0.28	–0.37	–0.30	–0.23	0.14	–0.03
		Median (IQR)	–	*P*	<0.001	<0.001	<0.001	0.004	0.10	0.74
Coping styles	Task oriented style	Mean (SD)	56.09 (9.57)	rho	0.22	0.15	0.27	–0.04	0.04	0.09
		Median (IQR)	–	*P*	0.01	0.10	0.004	0.65	0.64	0.33
	Emotion oriented style	Mean (SD)	–	rho	–0.16	–0.25	–0.10	–0.18	0.16	0.03
		Median (IQR)	40.00 (34–50)	*P*	0.08	0.006	0.30	0.048	0.09	0.73
	Avoidant style	Mean (SD)	41.83 (9.07)	rho	–0.07	–0.15	–0.09	–0.24	0.09	–0.03
		Median (IQR)	–	*P*	0.47	0.10	0.36	0.007	0.36	0.76

Abbreviations: 6MWT, six-minute walk test; Δ6MWT2-1, difference between results of the second and the first six-minute walk tests; Δ6MWT3-2, difference between results of the third and the second six-minute walk test; Δ6MWT3-1, difference between results of the third and the first six-minute walk test; IQR, interquartile range; SD, standard deviation; rho, Spearman correlation coefficient

analysis. For Objective 1, two hierarchical regression models were calculated. The difference between results obtained in the second and first 6MWT (Δ6MWT2-1) was the explained variable in both models. In the first model, the first measurement of the 6MWT was entered in the first block, and then anxiety trait was added in the second block. In the second model, the first 6MWT was entered in the first block, and then task-oriented coping, emotion-oriented coping, and avoidant coping were entered in the second block. Therefore, the analyzed models included the first 6MWT as a controlled variable. In the first model, anxiety trait was analyzed as the predictor of Δ6MWT2-1. In the second model, coping styles were analyzed as predictors of Δ6MWT2-1. The variables with distributions different from normal were log transformed before regression analysis. The value of $P < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

The study involved 170 patients (115 men and 55 women; aged from 28 to 88 years) recovering from cardiovascular events (detailed data in Supplementary material, *Table S1*).

The tests' course was uncomplicated, with no significant deviations from the norm in terms of basic clinical parameters. Patients' heart rate, blood pressure, oxygen saturation value, and Borg subjective effort scores were within limits. As stipulated in the psychological assessment (STAI and CISS), patients were diverse.

Spearman correlation analysis was performed for all variables. An association was observed between Δ6MWT2-1 and the level of anxiety trait (rho = –0.23; $P = 0.004$), avoidant style (rho = –0.24; $P = 0.007$), and emotion-oriented style (rho = –0.18; $P = 0.048$). No correlation was noted between psychological variables and Δ6MWT3-2 (Table 1).

The analysis was enhanced by linear regression analysis. According to the value of the determination coefficient, anxiety trait along with the results of the first 6MWT accounted for 6% of variability of results of Δ6MWT2-1 ($R^2 = 0.06$; SE = 50.16; $P = 0.01$); only anxiety trait was statistically significant (β = –0.23; $P = 0.007$). According to the value of the determination coefficient, coping styles with the results of the first 6MWT explain 10% of result variability of Δ6MWT2-1 ($R^2 = 0.10$, SE = 47.73, $P = 0.01$). Avoidant style (β = –0.20; $P = 0.03$), and results of the first 6MWT (β = –0.21; $P = 0.02$) were statistically significant (detailed results in supplementary material, *TableS2*). Statistical analysis confirmed that anxiety trait and avoidant style were good predictors of an increase in the distance between the first and second 6MWT. Patients with a higher level of anxiety trait achieved a smaller increase in distance in the repeated 6MWT than persons with a lower level of anxiety trait. In other words, for these patients, the learning effect was less visible. The 6MWT is based on spatial capabilities, including spatial memory. Studies conducted by Thoresen [8] indicated that persons with a higher level of anxiety trait and lesser spatial capabilities are less effective in cognitive processing of spatial representations. Their ability to learn in stressful situations is inferior, explaining worse results achieved in the 6MWT by patients with a higher level of anxiety trait. Most probably a person with higher levels of anxiety trait, when performing a consecutive 6MWT, must devote more attention to processing spatial information, which impacts test results negatively.

The difference in the distance between the second and first 6MWT is lower for patients with an avoidant style. Lack of focus on the task, i.e. a walk at the highest pace possible, impairs patient performance. In other words, for patients with an avoidant style, the learning effect will also be less visible.

Surprising is the lack of influence of psychological factors on the increase in the distance between the final

and second 6MWT. Studies indicated that an increased risk of cardiac diseases and related mortality occur in people with type-D personality (more susceptible to stressful situations) and high anxiety [9]. Thus, the fact that anxiety had no significant impact on rehabilitation results in this study leads to questions about the psychological mechanism determining effectiveness of cardiac rehabilitation. Cardiac rehabilitation aims, inter alia, to reduce emotional tension [10] and so it might reduce the significance of the 6MWT as a stress-inducing agent and of anxiety trait and coping styles. Another possible hypothesis is that the results obtained were caused by the impact of social support provided during stationary rehabilitation. These hypotheses require further analysis.

CONCLUSION

The study indicated that it is beneficial to take patients' anxiety proneness and coping styles into consideration when interpreting the 6MWT, as these psychological traits may influence the results in addition to the physical capacity of patients.

Supplementary material

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

Article information

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REFERENCES

1. Bellet RN, Adams L, Morris NR. The 6-minute walk test in outpatient cardiac rehabilitation: validity, reliability and responsiveness--a systematic review. Physiotherapy. 2012; 98(4): 277–286, doi: 10.1016/j.physio.2011.11.003, indexed in Pubmed: 23122432.
2. Uszko-Lencer NH, Mesquita R, Janssen E, et al. Reliability, construct validity and determinants of 6-minute walk test performance in patients with chronic heart failure. Int J Cardiol. 2017; 240: 285–290, doi: 10.1016/j.ijcard.2017.02.109, indexed in Pubmed: 28377186.
3. Chialà O, Vellone E, et al. Klompstra, L, Relationships between exercise capacity and anxiety, depression, and cognition in patients with heart failure. Heart Lung. 2018; 47: 465–470, doi: 30087002, indexed in Pubmed: 10.1016/j.hrtlng.2018.07.010.
4. Carbonell-Baeza A, Ruiz JR, Aparicio VA, et al. The 6-minute walk test in female fibromyalgia patients: relationship with tenderness, symptomatology, quality of life, and coping strategies. Pain Manag Nurs. 2013; 14(4): 193–199, doi: 10.1016/j.pmn.2011.01.002, indexed in Pubmed: 24315242.
5. Wu G, Sanderson B, Bittner V. The 6-minute walk test: how important is the learning effect? Am Heart J. 2003; 146(1): 129–133, doi: 10.1016/S0002-8703(03)00119-4, indexed in Pubmed: 12851620.
6. Wrześniewski K, Sosnowski T, Matusik D. State Trait Anxiety Inventory STAI Polish adaptation STAI Manual [in Polish]. Pracownia Testów Psychologicznych Polskiego Towarzystwa Psychologicznego. Warszawa 2002.
7. Strelau J, Jaworowska A, Wrześniewski K, et al. Coping Inventory for Stressful Situations CISS: Manual for Polish normalization [in Polish]. Kwestionariusz Radzenia Sobie w Sytuacjach Stresowych CISS: Podręcznik do polskiej normalizacji [Coping Inventory for Stressful Situations CISS: Manual for Polish normalization] Warsaw: Pracownia Testów Psychologicznych Polskiego Towarzystwa Psychologicznego. Pracownia Testów Psychologicznych Polskiego Towarzystwa Psychologicznego. Warszawa 2005.
8. Thoresen JC, Francelet R, Coltekin A, et al. Not all anxious individuals get lost: Trait anxiety and mental rotation ability interact to explain performance in map-based route learning in men. Neurobiol Learn Mem. 2016; 132: 1–8, doi: 10.1016/j.nlm.2016.04.008, indexed in Pubmed: 27108599.
9. Roest AM, Martens EJ, de Jonge P, et al. Anxiety and risk of incident coronary heart disease: a meta-analysis. J Am Coll Cardiol. 2010; 56(1): 38–46, doi: 10.1016/j.jacc.2010.03.034, indexed in Pubmed: 20620715.
10. Jegier A, Szalewska D, Mawlichanów A, et al. Comprehensive cardiac rehabilitation as the keystone in the secondary prevention of cardiovascular disease. Kardiol Pol. 2021; 79(7- 8): 901–916, doi: 10.33963/KP.a2021.0066, indexed in Pubmed: 34268725.

Application and optimization of the rate response function in dual-chamber pacemakers: Prospective, randomized, cross-over clinical trial study protocol

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INTRODUCTION

Pacemakers are equipped with a function that adjusts the pacing frequency to the patient's current needs ("rate response" function) [1]. However, the impact of this function in dual-chamber pacemakers on the physical performance remains to be fully elucidated [2–3]. Results from previously conducted studies are inconsistent as to the method of optimal programming of the rate response function [4–9]. The European Society of Cardiology guidelines do not contain exhaustive recommendations on how to program, and for which parameters to optimize, the rate response function in patients with cardiological disorders coexisting with chronotropic insufficiency [2–3].

METHODS

Aim

This study aims to assess the impact of rate-responsive pacing on physical performance and to compare benefits and side effects of the rate response function with numerous clinical parameters, with different settings of rate response function used at each stage of the study. The results of the study will reveal which patients benefit the most from pacing with rate response functions.

Study group eligibility criteria

The study group will consist of 100 patients who have had a transvenous dual chamber pacemaker implanted, with more than 50% atrial pacing at study entry. All participants of the study will be at least 18 years of age. Exclusion criteria include the presence of cardiac contraindications, conditions limiting participants' ability to perform an electrocardiographic exercise test or the 6- minute walk test (6MWT), persistent atrial fibrillation, and using a pacing mode other than dual chamber sequential pacing (DDD) for any reason. Patients with conduction system pacing will not be included in the study.

Study endpoints

The primary endpoints of the study are a change in the distance in the 6MWT, a change in the maximum metabolic equivalent of task (MET) achieved during the exercise test, and a change in quality of life assessed by the 36-Item Short Form Survey (SF-36). Secondary endpoints include changes in the percentage of atrial and ventricular pacing, changes in atrial arrhythmia burden, and a change in the New York Heart Association (NYHA) classification when comparing the results of tests performed in DDD and rate-responsive dual chamber sequential pacing (DDDR) modes.

Trial design

At each stage of the trial (visits at 0, 3, and 6 months), patients will have the following tests: 6MWT, International Physical Activity Questionnaire, SF-36 questionnaire, electrocardiographic exercise test (Bruce Protocol), and pacemaker follow-up. The parameters of the rate response function will be set as appropriate to the randomly selected group.

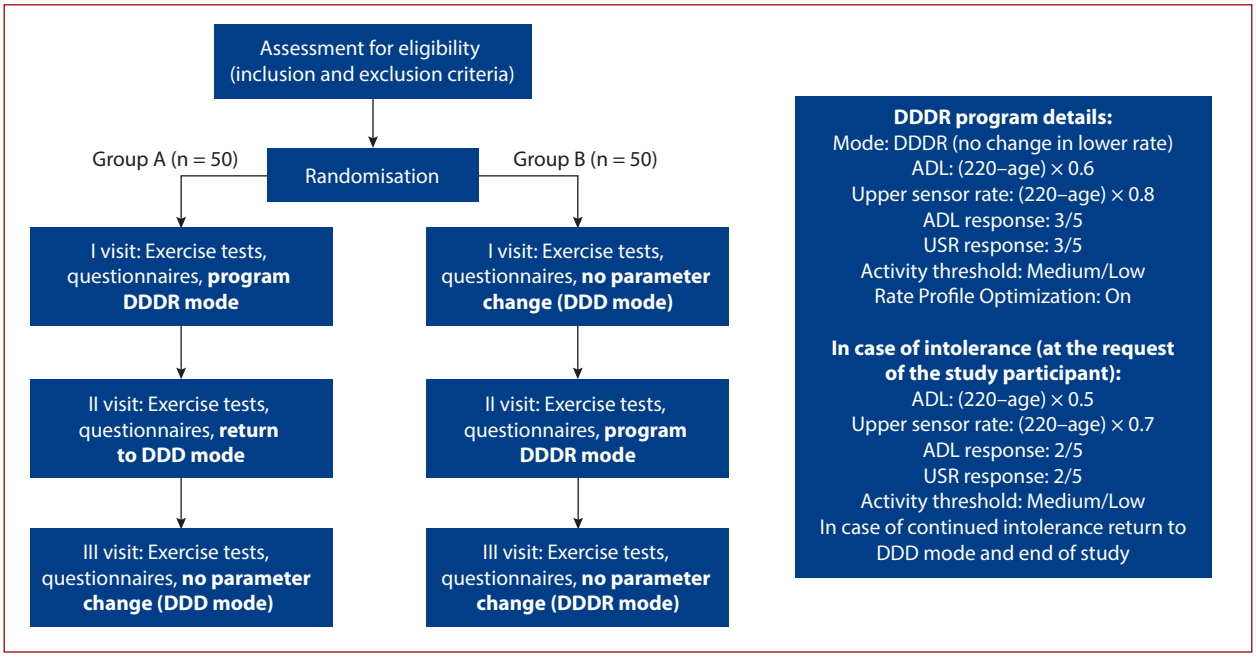

Figure 1. Follow-up and pacemaker programming flowchart

Abbreviations: ADL, Activities of Daily Living Rate; DDD, dual chamber sequential pacing; DDDR, rate-responsive dual chamber sequential pacing; USR, Upper Sensor Rate

The results of those tests will be analyzed in groups with comparable age, sex, body mass index, NYHA class, Canadian Cardiovascular Society class left ventricular ejection fraction, diseases (myocardial infarction, coronary artery disease, hypertension, heart failure, valvular diseases, cardiomyopathies, congenital heart diseases), pharmacotherapy, indications for pacemaker implantation, percentage of pacing, and atrial arrhythmias burden. The study is a single-blinded cross-over trial. Each participant of the study will have repeated diagnostic tests included in the scheme, both in the DDD and DDDR stimulation modes, to objectify the results of exercise tests and questionnaires. The A and B arms of the study groups differ in the order of introducing the same modification of the pacing mode from DDD to DDDR and vice versa. Details of rate response pacing parameters and the order of parameter changes in both groups are provided in Figure 1.

At the end of participation in the study, the decision to leave the pacemaker in DDD or DDDR mode will be made by the patient with support and consultation of a cardiologist, taking into account the results of all diagnostic tests performed during their participation.

Follow-up and pacemaker parameters

At each visit, the following data will be retrieved from the pacemaker device: pacing mode, lower rate, atrioventricular delay after pacing and sensing, percentage of atrial and ventricular pacing, heart rate histograms, and the number of recorded arrhythmias in the device's memory (duration/percentage of episodes). Apart from the rate response function settings, no other parameters are expected to be standardized. Any changes to other parameters, if necessary, will be recorded and considered for any possible impact on the test results. The effect of native or paced rhythm during exercise tests will be considered for impact on the test results. This study includes pacemaker models with accelerometric sensors. Due to technological differences in the algorithms and functioning of pacemakers from different companies, the study will be conducted only on Medtronic and Vitatron pacemakers. Parameters selected for use in this study are partly in line with those described in previous original studies in this area and with the programming recommendations described in review papers [1, 10, 11].

Statistical analysis

Assuming a 350 (127) m standardized mean difference in the 6MWT and 6.0 (1.5) MET standardized mean difference in the exercise test, with a significance level of 5%, a power of 80%, and a drop-out rate of 10%, 100 patients are needed in both groups. Initial statistical analysis of results will consist of validation of the appropriateness of the randomization method and analysis of the distribution of continuous data. Randomization will be carried out using the functionality of the statistical program (R version 4.0.3), with the matching of variables for the purpose of this study. Patients will be randomly assigned to groups A or B, maintaining similarity of the compared arms in terms of the number, age, and sex. Continuous data will be represented as arithmetic means and standard deviation or as medians and interquartile ranges. The distribution of data will be assessed for normality using the Shapiro-Wilk test. Comparison of continuous data between the groups will be based on Student's t-test or the Mann-Whitney U test,

as determined by normality of distribution. Ordinal data will be evaluated by the Kruskal-Wallis H test. An analysis of variance for repeated measures will be performed to compare the groups (either the non-parametric equivalent of the Friedman test or the aligned rank analysis of variance). For multiple comparisons, Bonferroni or Holm-Bonferroni correction will be applied.

Registration and ethics

This study will be performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee Medical University of Warsaw No. KB/173/2021.

Expected results

Our hypothesis assumes an improvement in physical capacity (expressed as an improvement of maximum MET achieved in an electrocardiographic exercise test) with rate-responsive pacing, in comparison with DDD mode pacing with constant base rate.

RESULT AND DISCUSSION

The current state of knowledge on the use and optimization of the function of frequency adaptation in pacemakers is insufficient due to the small number of studies available and the contradictory results that have been recorded [4–9]. Furthermore, specific recommendations in the guidelines of the European Society of Cardiology on cardiac pacing and cardiac resynchronization therapy are limited [2, 3]. Many studies rely on the electrocardiographic treadmill exercise test as an objective method of assessment of physical performance and progress in cardiac rehabilitation or for optimization of settings of implantable devices and cardiac [7, 12, 13]. Therefore, this study will deepen the research on the impact of the rate response function on physical performance in a homogeneous group of patients and will reveal which patients would benefit the most from rate-adapted pacing.

Article information

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REFERENCES

1. Trohman RG, Huang HD, Larsen T, et al. Sensors for rate-adaptive pacing: How they work, strengths, and limitations. J Cardiovasc Electrophysiol. 2020; 31(11): 3009–3027, doi: 10.1111/jce.14733, indexed in Pubmed: 32877004.
2. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Europace. 2013; 15(8): 1070–1118, doi: 10.1093/europace/eut206, indexed in Pubmed: 23801827.
3. 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.
4. Gierula J, Paton MF, Lowry JE, et al. Rate-Response programming tailored to the force- frequency relationship improves exercise tolerance in chronic heart failure. JACC Heart Fail. 2018; 6(2): 105–113, doi: 10.1016/j.jchf.2017.09.018, indexed in Pubmed: 29226818.
5. Sharma AD, Richards M, Olshansky B, et al. Heart rate score, a measure related to chronotropic incompetence in pacemaker patients. Heart Rhythm O2. 2021; 2(2): 124–131, doi: 10.1016/j.hroo.2021.02.002, indexed in Pubmed: 34113914.
6. Gierula J, Lowry JE, Paton MF, et al. Personalized rate-response programming improves exercise tolerance after 6 months in people with cardiac implantable electronic devices and heart failure: A phase II study. Circulation. 2020; 141(21): 1693–1703, doi: 10.1161/CIRCULATIONAHA.119.045066, indexed in Pubmed: 32299222.
7. Proff J, Merkely B, Papp R, et al. Impact of closed loop stimulation on prognostic cardiopulmonary variables in patients with chronic heart failure and severe chronotropic incompetence: a pilot, randomized, crossover study. Europace. 2021; 23(11): 1777–1786, doi: 10.1093/europace/euab110, indexed in Pubmed: 33982093.
8. Nägele H, Rödiger W, Castel MA. Rate-responsive pacing in patients with heart failure: long-term results of a randomized study. Europace. 2008; 10(10): 1182–1188, doi: 10.1093/europace/eun213, indexed in Pubmed: 18723519.
9. Lamas GA, Knight JD, Sweeney MO, et al. Impact of rate-modulated pacing on quality of life and exercise capacity--evidence from the Advanced Elements of Pacing Randomized Controlled Trial (ADEPT). Heart Rhythm. 2007; 4(9): 1125–1132, doi: 10.1016/j.hrthm.2007.05.021, indexed in Pubmed: 17765608.
10. van Hemel NM, Holwerda KJ, Slegers PC, et al. The contribution of rate adaptive pacing with single or dual sensors to health-related quality of life. Europace. 2007; 9(4): 233–238, doi: 10.1093/europace/eum021, indexed in Pubmed: 17350981.
11. Freedman RA, Hopper DL, Mah J, et al. Assessment of pacemaker chronotropic response: implementation of the Wilkoff mathematical model. Pacing Clin Electrophysiol. 2001; 24(12): 1748–1754, doi: 10.1046/j.1460-9592.2001.01748.x, indexed in Pubmed: 11817808.
12. Smarż K, Jaxa-Chamiec T, Bednarczyk T, et al. Electrocardiographic exercise testing in adults: performance and interpretation. An expert opinion of the Polish Cardiac Society Working Group on Cardiac Rehabilitation and Exercise Physiology. Kardiol Pol. 2019; 77(3): 399–408, doi: 10.5603/KP.a2018.0241, indexed in Pubmed: 30566222.
13. Jegier A, Szalewska D, Mawlichanów A, et al. Comprehensive cardiac rehabilitation as the keystone in the secondary prevention of cardiovascular disease. Kardiol Pol. 2021; 79(7-8): 901–916, doi: 10.33963/KP.a2021.0066, indexed in Pubmed: 34268725.

An urgent in-hospital upgrade to resynchronization therapy is associated with lower likelihood of survival as compared to planned procedures

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INTRODUCTION

Cardiac resynchronization therapy (CRT) is known to reduce mortality and symptoms of heart failure (HF) and improve the quality of life in carefully selected patients [1–4].

According to the European CRT Survey, upgrades from previously implanted pacemakers or implantable cardioverter-defibrillators constitute close to a quarter of all CRT implantations [5]. As stated in the European Society of Cardiology (ESC) Guidelines, CRT is a treatment option for patients with reduced left ventricular ejection fraction (LVEF) ≤35% and QRS duration ≥130 ms, with the highest class of recommendation for patients with QRS ≥150 ms of left bundle branch block morphology [6]. An upgrade to CRT should be considered in patients with a high percentage of right ventricular pacing and worsening of HF symptoms despite optimal medical therapy [6].

Despite these guidelines, there are reports of successful off-label *de novo* CRT implantations in inotropy-dependent patients or on mechanical support [7, 8]. However, there are only limited data on off-label CRT upgrades [9, 10]. Our study aimed to analyze the frequency and follow-up of patients who underwent an upgrade to CRT that was not fully in accordance with the current guidelines.

METHODS

Between January 2010 and December 2014 in the National Institute of Cardiology, 94 consecutive CRT upgrade procedures were performed. We retrospectively analyzed indications for those CRT upgrades, medical characteristics, and follow-up of these patients.

The study group consisted of 24 patients who underwent procedures that were assigned as "urgent" and were performed due to acute cardiac decompensation (non-ambulatory New York Heart Association [NYHA] class IV) or an electrical storm, which implies that these upgrades were not performed following the current guidelines. The group of 70 patients who underwent scheduled upgrade CRT implantation served as a control group. Patient survival was defined as the time from CRT implantation to all-cause mortality. The data on mortality and heart transplantation were sourced from the national databases provided by the Ministry of Digital Affairs and POLTRANSPLANT. Follow-up was limited to 60 months.

The study was approved by the Bioethics Committee of the National Institute of Cardiology (IK-NPIA-0021-98/1677/17).

Statistical analysis

Statistical analysis was performed with R software. The Shapiro-Wilk test indicated that the sample data was not normally distributed. Continuous data were presented as median (interquartile range [IQR]). Categorical data were presented as the absolute number and percentage of patients in each group. *P*-values <0.05 were considered statistically significant. The Mann-Whitney U test for continuous variables and the χ^2 test for nominal variables were used. Survival was estimated with the Kaplan-Meier curve. The plots were compared

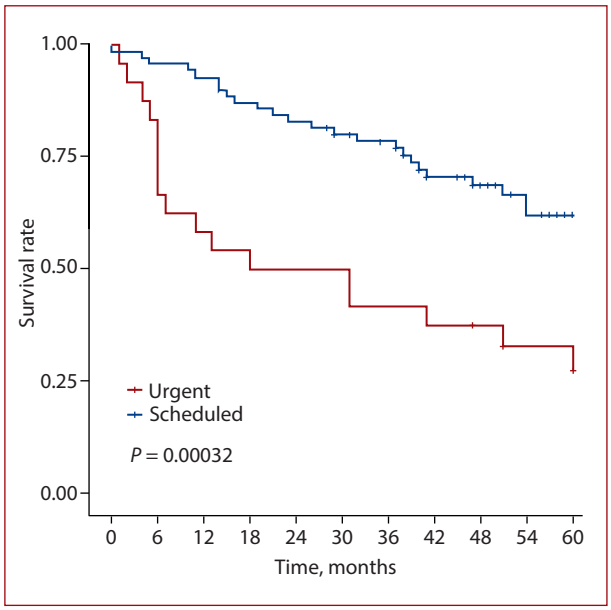

Figure 1. Survival in urgent versus scheduled cardiac resynchronization therapy upgrade

using the log-rank test. A univariate Cox regression analysis was used to evaluate factors affecting survival.

RESULTS AND DISCUSSION

In the study group, acute cardiac decompensation was an indication for 19 procedures and an electrical storm in 5 cases.

There were no significant differences between the two groups in age, sex, LVEF, presence of AF, diabetes or pacing dependency, and history of myocardial infarction. (Supplementary material, *Table S1*). The only statistically significant difference was found in HF etiology (non-ischemic cardiomyopathy was present in 67% of patients in the study group and 40% of patients in the control group) and NYHA class at baseline. The median follow-up in the study group was 29 (6–53) months while in the control group 44 (33–60) months, and the difference in the length of follow-up was statistically significant. Survival was found to be worse in patients that underwent a CRT upgrade in an urgent mode compared with planned procedures (hazard ratio 3.3 with 95% confidence interval [CI], 1.9–5.9, P <0.001) (Figure 1).

Ten patients (42%) died within the first year after the upgrade, and only 6 patients (25%) survived five years after the procedure. Three patients survived until cardiac transplantation.

Multivariable Cox-regression analyses showed that among all patients the urgent mode of the procedure along with the absence of a high RV pacing burden were associated with worse survival (Supplementary material, *Table S2*). However, no statistically significant predictor of poor prognosis was found in the study group (Supplementary material, *Table S3*).

Six patients were dependent on continuous intravenous inotropic therapy, which was defined as the inability to withdraw or decrease the dose of drugs without the occurrence of hypotension — systolic blood pressure <90 mm Hg, oliguria <20 ml/h and/or hypoxemia. The median time to complete withdrawal of inotrope support was 6 (1.25–13.75) days. Four patients did not survive the first year of follow-up, and one underwent cardiac transplantation.

Nine patients (38%) in the study group had indications for CRT during the previous implantation or device replacement. That group consisted of patients referred from centers that did not consider CRT at the time of previous intervention or their attempt to perform a CRT implantation was unsuccessful.

Patients with end-stage HF are poorly represented in clinical trials on CRT. According to an article by Nisha et al. [11], the current guidelines were based on studies that consisted of only 5% of NYHA class IV individuals. Nonetheless, the ESC guidelines do not exclude NYHA class IV patients from being candidates for CRT [6]. The treatment alternatives for HF patients who do not respond to medical therapy are mechanical circulatory support devices and heart transplantation [6].

Our research showed that patients who underwent an urgent CRT upgrade have a higher risk of death than those who had a scheduled procedure. Forty-one percent of patients from the study group died in the first year of follow-up. In comparison, only 7% of patients from the control group died in the same period. Only 25% of patients from the study group survived 5 years, two of them after heart transplantation.

The worst outcomes were observed among inotropy-dependent patients. Only two out of six patients survived the first year of follow-up after an upgrade procedure. However, few studies showed a beneficial effect of CRT *de novo* implantation in inotropy-dependent end-stage heart failure patients. Sokal et al. [7] reported 100% success in weaning from inotropes in eleven individuals after a CRT implantation. In a meta-analysis by Hernandez et al. [8], weaning from inotropes was successful in 93% of patients, and the 1-year survival rate was 69% after CRT *de novo* implantation.

Given the unfavorable outcomes presented in our study, it must be underlined that patients with end-stage heart disease had initially poor prognosis, and a CRT upgrade served as a rescue therapy or "bridge-to--transplant" for these individuals, especially considering the time of the investigation when not many alternative treatment options were available [12]. Considering that in some studies upgrades constitute almost half of all CRT procedures [13], it would be valuable to identify the factors for poor response in this group. It is also important to make careful clinical assessment of patients during implantation or exchange of devices to avoid delaying initiation of CRT therapy as had happened in 38% of patients in the study group.

Supplementary material

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

Article information

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REFERENCES

1. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med. 2001; 344(12): 873–880, doi: 10.1056/NEJM200103223441202, indexed in Pubmed: 11259720.
2. Cleland J, Daubert JC, Erdmann E, et al. The CARE-HF study (CArdiac REsynchronisation in Heart Failure study): rationale, design and end-points. Eur J Heart Fail. 2001; 3(4): 481–489, doi: 10.1016/s1388-9842(01)00176-3.
3. Lenarczyk R, Jędrzejczyk-Patej E, Mazurek M, et al. Quality of life in cardiac resynchronization recipients: association with response and impact on outcome. Pacing Clin Electrophysiol. 2015; 38(1): 8–17, doi: 10.1111/pace.12523, indexed in Pubmed: 25319879.
4. Cleland JGF, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005; 352(15): 1539–1549, doi: 10.1056/NEJMoa050496, indexed in Pubmed: 15753115.
5. Dickstein K, Normand C, Auricchio A, et al. CRT Survey II: a European Society of Cardiology survey of cardiac resynchronisation therapy in 11 088 patients-who is doing what to whom and how? Eur J Heart Fail. 2018; 20(6): 1039–1051, doi: 10.1002/ejhf.1142, indexed in Pubmed: 29457358.
6. 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.
7. Sokal A, Jędrzejczyk E, Lenarczyk R, et al. Efficacy of cardiac resynchronisation therapy in the treatment of end-stage inotrope-dependent heart failure patients. Kardiol Pol. 2014; 72(9): 777–782, doi: 10.5603/KP.a2014.0090, indexed in Pubmed: 24846358.
8. Hernandez GA, Blumer V, Arcay L, et al. Cardiac resynchronization therapy in Inotrope-Dependent heart failure patients: a systematic review and meta-analysis. JACC Heart Fail. 2018; 6(9): 734–742, doi: 10.1016/j.jchf.2018.02.016, indexed in Pubmed: 30098968.
9. Michael KA, Paisey JR, Mayosi BM, et al. A hybrid form of cardiac resynchronisation therapy in patients with failing systemic right ventricles. J Interv Card Electrophysiol. 2008; 23(3): 229–233, doi: 10.1007/s10840-008-9296-0, indexed in Pubmed: 18836823.
10. Mörtsell D, Thilén U, Tydén P, et al. Transvenous interventional implantation of CRT-D in a critically ill Mustard patient waiting for heart transplant. Clin Case Rep. 2019; 7(7): 1415–1418, doi: 10.1002/ccr3.2183, indexed in Pubmed: 31360501.
11. Almeida ND, Suarthana E, Dendukuri N, et al. Cardiac resynchronization therapy in heart failure: do evidence-based guidelines follow the evidence? Circ Cardiovasc Qual Outcomes. 2017; 10(12), doi: 10.1161/CIRCOUTCOMES.117.003554, indexed in Pubmed: 29222164.
12. Actuarial risk of sudden death while awaiting cardiac transplantation in patients with atherosclerotic heart disease. Am J Cardiol. 1991; 68(5): 545–546, doi: 10.1016/0002-9149(91)90796-n.
13. Grymuza M, Katarzyńska-Szymańska A, Chmielewska-Michalak L, et al. Follow-up and characteristics of recipients of cardiac resynchronization therapy with and without a defibrillator. Kardiol Pol. 2022; 80(7-8): 806–812, doi: 10.33963/KP.a2022.0125, indexed in Pubmed: 35545837.

The HF-POL study — the first real-life multicenter study of Polish patients with heart failure and left ventricular ejection fraction >40%: Study rationale and design

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INTRODUCTION

According to the new classification of heart failure (HF) presented in the 2021 guidelines of the European Society of Cardiology (ESC), HF with left ventricular ejection fraction (LVEF) higher than 40% covers 3 distinct phenotypes: HF with mildly reduced LVEF (41%–49%), HF with preserved LVEF (>50%), and HF with improved LVEF [1].

Data from the National Health Fund revealed that in in 2020 there were more than 740 000 patients with HF in Poland, about half of whom had LVEF >40% [2]. Considering the statistics and increasing healthcare costs, HF constitutes a significant clinical and economic burden in Poland. Hospitalizations are the key cost category in the HF setting. Despite advances in HF diagnosis and treatment, the rates of costly and at least partially preventable hospitalizations remain high in Poland. According to the 2019 report of the Organization for Economic Co-operation and Development (OECD), Poland had the highest HF-related hospitalization rates in 2018 among OECD members, and these rates are more than twice as high as the OECD average [3]. Moreover, in 2020, the number of HF-related deaths accounted for 26% of all deaths in Poland (123 316/477 355, respectively) [2].

In Poland, HF is the most common direct cause of death. Numerous international studies showed that HF with LVEF >40% is associated with a serious prognosis [4–6]. In contrast to HF with reduced LVEF, treatment aimed at improving prognosis in patients with LVEF >40% has a lower class of recommendation (up to IIa), based largely on weaker evidence and/or expert opinions — in the 2021 ESC (class IIb) and 2022 ACC/ACC/HFSA (class IIa) guidelines [1, 7, 8]. However, the results of the recently published trials (EMPEROR-Preserved and DELIVER) call for review of this HF population [9, 10].

The population of Polish patients with HF and LVEF >40% has not been well described so far. This is partly due to limitations in the International Classification of Disease coding, which does not reflect the classification of HF based on LVEF values. This is an important barrier to determining the actual percentage of HF patients with LVEF >40% in Poland. We still need reliable data on HF. Therefore, to assess this population in Poland, the Heart Failure Association of the Polish Cardiac Society designed a multicenter observational study as part of the Society's Scientific Platform initiative. The study aims to collect data on Polish patients with HF and LVEF >40% and to provide a better understanding of medical practice, based on observational data, including diagnosis, treatment, and prognosis over 1-year follow-up. The study will be a valuable source of clinical practice data and will provide useful information that will guide decisions and policies to improve the management and prognosis of patients with HF, as well as prevent hospitalizations in Poland.

METHODS

The Heart Failure Poland (HF-POL) study is a multicenter observational study including patients with HF and LVEF >40%, conducted by the Heart Failure Association of the Polish Cardiac Society in cooperation with the Com-

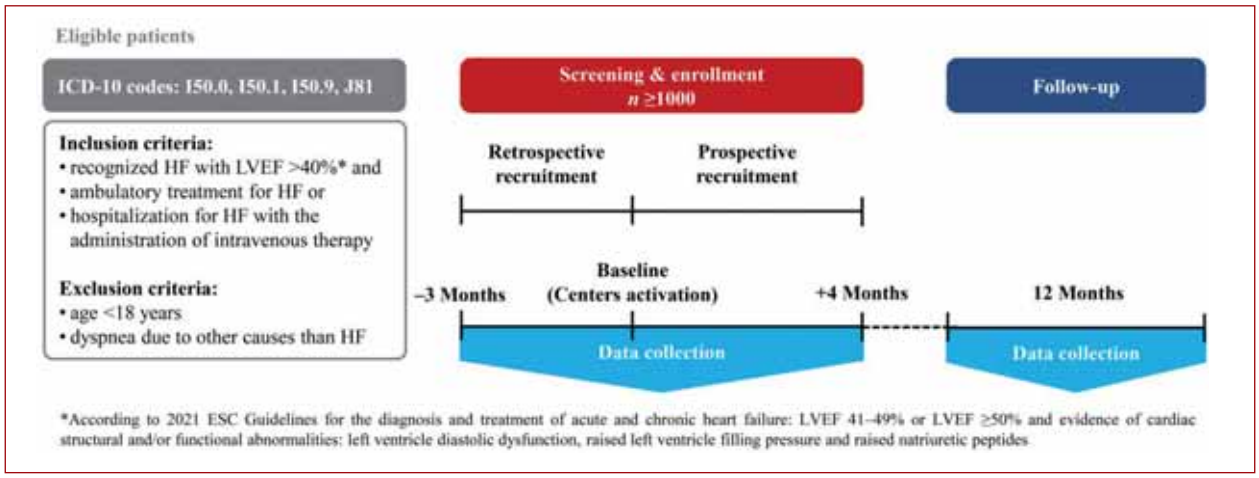

Figure 1. Study flowchart

Abbreviations: ESC, European Society of Cardiology; HF, heart failure; LVEF, left ventricular ejection fraction

mittee for Clinical Initiatives of the Executive Board as part of the Scientific Platform initiative. The leading center of the study is the Military Medical Academy Memorial Teaching Hospital of the Medical University of Lodz, Poland. The Primary Investigator is Malgorzata Lelonek; the Steering Committee includes Malgorzata Lelonek, Mariusz Gasior, and Marcin Grabowski.

Patients have been recruited at each participating center since that center's activation on the eCRF.biz platform (a clinical data management system, https://rejestr.gbbsoft.pl/hf-pol). All consecutive patients meeting the inclusion and exclusion criteria are being enrolled. Patients are diagnosed and treated according to the current clinical practice guidelines and the standard of care at participating centers. Indications for diagnostic procedures and therapeutic interventions are assessed by the physicians at participating centers.

A phone interview with the patient or his or her family is scheduled 1 year after enrollment to the study, and the following data will be collected: general medical condition, HF-related or all-cause hospitalization, and death.

The study was approved by the Bioethics Committee at the Medical University of Lodz (No. RNN/240/21/KE; October 21, 2021). The study execution is regulated by the Rules and Regulations of the Scientific Platform of the Polish Cardiac Society and an agreement between the Polish Cardiac Society, participating centers, and Primary Investigator.

The study population includes patients with HF and LVEF >40%. In total, a minimum of 1000 patients from 14 Polish centers (Supplementary material, *Table S1*) will be enrolled. The study will include consecutive patients with the ICD codes I50 (I50.0, I50.1, I50.9) and J81, who fulfill the following inclusion criteria: have recognized HF with documented LVEF >40% and are either treated for HF on ambulatory basis or hospitalized for HF (HF exacerbation or HF de novo) with administration of intravenous therapy (diuretics and/or catecholamines). HF should be recognized according to the 2021 ESC guidelines [1]. The study allows recruitment based on results from medical records, especially for outpatients with a history of HF. However, not all patients had their results documented within 12 months before screening. In the case of HF de novo, the 2021 ESC guidelines criteria for this diagnosis should be applied as symptoms and/or signs, LVEF >40%, and for heart failure with preserved ejection fraction (HFpEF), objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of left ventricular diastolic dysfunction/raised left ventricle filling pressure, including raised natriuretic peptides [1]. The exclusion criteria are age <18 years and dyspnea due to causes other than HF. The flowchart presents the study design (Figure 1).

Because of the COVID-19 pandemic, patients have been recruited retrospectively over 3 months before the activation of the centers on the eCRF.biz platform and prospectively over 4 months. The total duration of recruitment will be 7 months. The study started in January 2022.

Statistical analysis

Normally distributed continuous variables were reported as mean (SD) values. Not normally distributed continuous variables and ordinal variables were presented as median values and interquartile ranges (IQR). Categorical data were reported as the number and percentage of patients. The statistics were calculated with STATISTICA 13 software (TIBCO Software, Palo Alto, CA, US).

PRELIMINARY RESULTS AND DISCUSSION

Until May 26, 2022, a total of 790 patients were recruited to the study (mean age, 72.9 [11.2] years; range 31–106 years; 51% male). More than half of patients have an ischemic etiology of HF (57%). The following cardiovascular risk factors and comorbidities were reported: hypertension (87%), diabetes (73%), hyperlipidemia (67%), atrial fibrilla-

tion (58%), chronic obstructive pulmonary disease (12%), and cancer (11%). COVID-19 was reported in 18% of the studied population.

In most patients, a history of hospitalization in the previous 12 months was reported (80%) while 53% of patients were enrolled in the study during HF hospitalization. Most patients were in New York Heart Association functional class II and III (332 and 311 patients, respectively). The mean blood pressure was reported at 132/77 (19.85/12.56) mmHg; body mass index, 29.6 (6.2) kg/m^2; LVEF of 52.7 (7.5) %, median N-terminal pro-B-type natriuretic peptide level of 1 177 (430-12 798) pg/ml; estimated glomerular filtration rate, 62 (24.79) ml/min/1.73 m^2; and six-minute walk distance, 287.5 (105-310) m. At baseline, 72% of the studied patients were on angiotensin-II converting enzyme inhibitor/angiotensin-II receptor blocker (ACEI/ARB), 67% had loop diuretics, 79% beta-blockers, 61% mineralocorticoid receptor antagonists (MRA), 71% statins, and 12% flozins.

Our preliminary results are consistent with the literature and other registries apart from the higher concentration of NT-proBNP, higher frequency of HF hospitalization, diabetes, MRA therapy, and male sex.

Limitations

The presented study has limitations typical of such projects. These are limited information on clinical characteristics, treatment, and adverse events. The participating centers have been selected, and the majority of them represent university centers with involved teams of experienced cardiologists, which may not reflect clinical practice of regional and local reference centers. For technical and budgetary reasons, opportunities for verifying the entered data, monitoring and detailed follow-up are also restricted. On the other hand, cardiovascular registries play an integral role in providing real-world data. An additional limitation is the retrospective-prospective design of the study, which was caused by the pandemic. Moreover, not all outpatients had their laboratory and echocardiographic results, which was also caused by the pandemic.

CONCLUSIONS

The HF-POL study is the first real-life national multicenter observational study including patients with HF and LVEF >40%, conducted by the Heart Failure Association of the Polish Cardiac Society. The population of patients with HF and LVEF >40% has been growing and constitutes an increasing health burden. Considering the statistical, economic, and epidemiological real-life data for Poland, it is necessary to identify prognostic factors that could help improve the management of these patients by reducing the risk of hospitalizations and death.

Supplementary material

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

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REFERENCES

1. 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.
2. Maps of Heath Needs. System and Impementation Analysis Database Platform. Epidemiology. Available online: https://basiw.mz.gov.pl/mapy-informacje/mapa-2022-2026/analizy/epidemiologia/. Accessed: November 27, 2022.
3. Organization for Economic Co-operation and Development. 2019. Health at a glance 2019. OECD Publishing: Paris, France.
4. Savarese G, Stolfo D, Sinagra G, et al. Heart failure with mid-range or mildly reduced ejection fraction. Nat Rev Cardiol. 2022; 19(2): 100–116, doi: 10.1038/s41569-021-00605-5, indexed in Pubmed: 34489589.
5. Lelonek M. Heart failure with preserved ejection fraction after the PARAGON-HF trial results: current knowledge and future directions. Kardiol Pol. 2020; 78(12): 1199–1205, doi: 10.33963/KP.15639, indexed in Pubmed: 33021355.
6. Correale M, Paolillo S, Mercurio V, et al. Non-cardiovascular comorbidities in heart failure patients and their impact on prognosis. Kardiol Pol. 2021; 79(5): 493–502, doi: 10.33963/KP.15934, indexed in Pubmed: 34125921.
7. 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. J Am Coll Cardiol. 2022; 79(17): e263–e421, doi: 10.1016/j.jacc.2021.12.012, indexed in Pubmed: 35379503.
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. Butler J, Filippatos G, Siddiqi TJ, et al. Evaluation of the effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: rationale for and design of the EMPEROR-Preserved Trial. Eur J Heart Fail. 2019; 21(10): 1279–1287, doi: 10.1002/ejhf.1596, indexed in Pubmed: 31523904.
10. Solomon S, McMurray J, 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.

Severe stenosis of a unicuspid aortic valve

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We present a case of a 42-year-old female with a unicuspid aortic valve identified by echocardiography and confirmed by cardiac computed tomography. This woman was referred to our department for a diagnostic workup of progressive significant breathlessness at exercise and suspected arrhythmia. On admission, she was in stable clinical condition without significant abnormalities on physical examination except for a loud systolic murmur at the aortic valve.

Transthoracic echocardiography (2D TTE) showed a unicuspid unicommissural aortic valve with severe, high-gradient aortic stenosis. The aortic valve area (AVA) was 0.9 cm^2 with peak velocity of 4.4 m/s with a mean gradient of 42 mmHg. Additional findings of mild aortic regurgitation and dilatation of the ascending aorta (51 mm) were made with no signs of aortic coarctation. Transesophageal echocardiography (2D, 3D TEE) confirmed the defect in the aortic valve. Findings were consistent with severe aortic stenosis. For surgical planning, the patient underwent a computed tomography (CT) scan which showed no evidence of coronary artery stenosis and confirmed unicuspid aortic valve.

During cardiac surgery, replacement of the unicuspid aortic valve was performed and a biological prosthesis was implanted. Moreover, the ascending aorta was replaced with a graft.

Unicuspid, unicommissural aortic valve is an extremely rare congenital anomaly of the

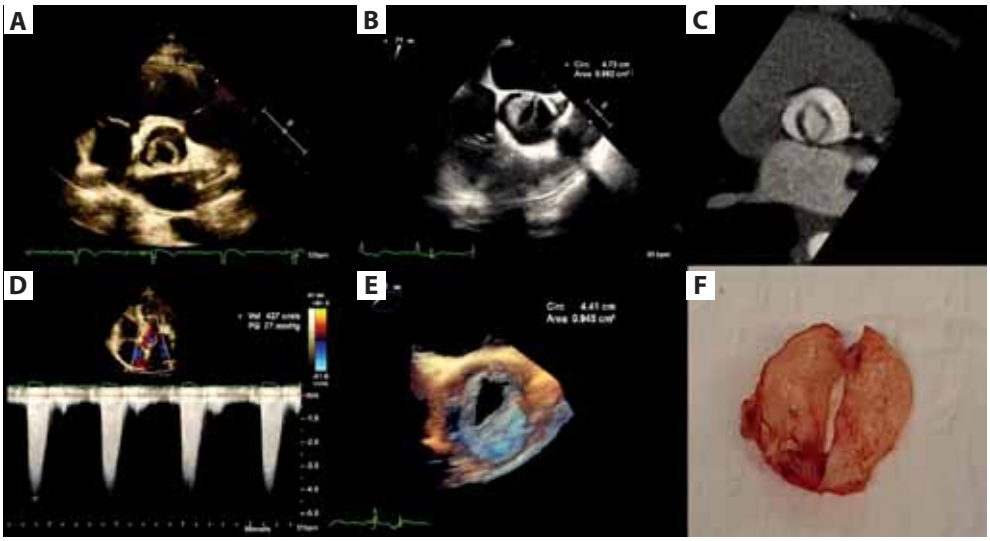

Figure 1. A. Unicuspid aortic valve (the arrow); short axis view, 2D TTE. **B.** Peak velocity >4 m/sec measured using continuous-wave Doppler, TTE. **C.** Measurement of an aortic-valve area using planimetric two-dimensional (2D) TOE. **D.** Measurement of an aortic valve area using planimetric three-dimensional (3D) TOE. **E.** CT image of the unicuspid aortic valve. **F.** The unicuspid aortic valve after cardiac surgery

Abbreviations: 2D TTE, two-dimensional transthoracic echocardiography; 3D-TOE, three-dimensional transesophageal echocardiography; CT, computed tomography

aortic valve [1]. The estimated frequency of its occurrence is 0.02% and is 100 times less common than a bicuspid aortic valve (BAV). Importantly, unicuspid aortic valves are associated with rapid progression of valvular dysfunction and aortic dilatation.

In the case of our patient, the performed examinations (TTE, TEE CT) showed three major criteria for a unicuspid valve: single commissural zone of attachment, rounded leaflet-free edge on the opposite side of the commissural attachment zone, and eccentric valvular orifice during systole [2].

In conclusion, this case report confirms the steps that should be taken to accurately assess a rare defect like unicuspid aortic valves using accessible non-invasive methods.

Supplementary material

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

Article information

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REFERENCES

1. Mladenovic Z, Vranes D, Obradovic S, et al. Diagnostic significance of three-dimensional echocardiography in asymptomatic unicuspid aortic valve. Echocardiography. 2018; 35(8): 1247–1249, doi: 10.1111/echo.14039, indexed in Pubmed: 29864199.
2. Ewen S, Karliova I, Weber P, et al. Echocardiographic criteria to detect unicuspid aortic valve morphology. Eur Heart J Cardiovasc Imaging. 2019; 20(1): 40–44, doi: 10.1093/ehjci/jex344, indexed in Pubmed: 29346529.
3. Vahanian A, Beyersdorf F, Praz F, et al. ESC/EACTS Guidelines for the management of valvular heart disease. The Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2022; 43(7): 561–632, doi: 10.1093/eurheartj/ehab395, indexed in Pubmed: 34453165.
4. Golińska Grzybała K, Kabłak-Ziembicka A, Gackowski A. Unicuspid aortic valve prolapse with severe regurgitation. Kardiol Pol. 2021; 79(4): 465–466, doi: 10.33963/KP.15862, indexed in Pubmed: 33687871.
5. Novak M, Cerny V, Hlubocka Z, et al. A unique case of unicuspid aortic valve with severe regurgitation combined with coronary-pulmonary fistula. Kardiol Pol. 2022; 80(2): 220–222, doi: 10.33963/KP.a2021.0178, indexed in Pubmed: 34897629.

Intramural left atrial hematoma after transcatheter radiofrequency ablation of atrial fibrillation

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The incidence of major life-threatening complications from radiofrequency catheter ablation (RFCA) for atrial fibrillation (AF) is less than 1%. They include pericardial effusion, stroke, hemorrhagic shock, respiratory failure, and myocardial infarction [1, 2]. In this clinical vignette, we report a rare but potentially life-threatening complication after AF ablation.

A 53-year-old female, with no past medical history, was admitted to our hospital for persistent AF with a rapid ventricular response which was refractory to drugs. Relevant examinations including transthoracic echocardiographic (TTE) (Figure 1A) were performed before RFCA. High-power and short-duration ablation (45–50 W for durations of 2–10 seconds on the posterior wall and 5–15 seconds at other locations) was performed during pulmonary vein isolation, as well as left atrial roof and posterior lines ablation. Two days after the procedure, the patient complained of an uncomfortable feeling while swallowing. TTE (Figure 1B, C) and computed tomography angiography (CTA; Figure 1F) were immediately reviewed and showed a large intramural hematoma in the posterior wall of the left atrium. Cardiac magnetic resonance (CMR) imaging demonstrated very clearly the anatomic boundaries, showing the size was 23 × 56 mm (Figure 1D, E). To avoid further aggravation of the hematoma, the anticoagulation drug was suspended for one week. After a month of follow-up, the hematoma was gradually absorbed (Supplementary material, *Figure S1*).

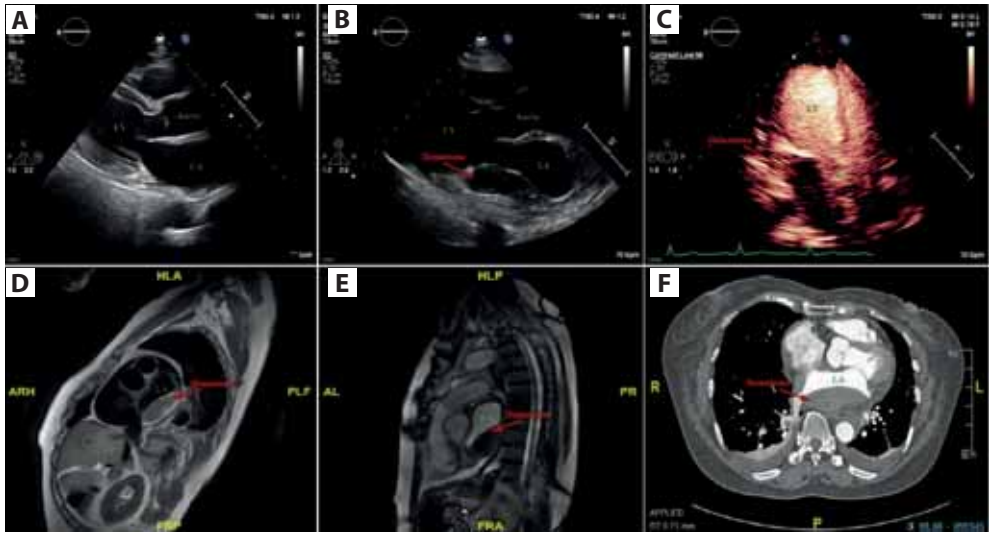

Figure 1. A. The preoperative transthoracic echocardiographic image. **B.** The postoperative transthoracic echocardiographic parasternal long-axis view showed a hematoma (indicated by the arrowhead) in the posterior wall of the left atrium. **C.** Myocardial contrast echocardiography image of the hematoma (the arrowhead). Dual inversion recovery black-blood MR sequences **D.** Dual inversion recovery black-blood MR sequence. **E.** Cine CMR: SSFP cine sequence (FIESTA). **F.** Postoperative CTA of the intramural hematoma (indicated by the arrowhead)

Abbreviations: CMR, cardiac magnetic resonance; CTA, computed tomography angiography; MR, magnetic resonance

In the present case, the patient had no other complaints except for the uncomfortable feeling while swallowing. Conservative treatment was applied because her hemodynamic status was stable. However, the hematoma was close to the mitral valve, which may induce acute mitral valve stenosis. Unlike other life-threatening complications, intramural hematoma can gradually be absorbed, and the symptoms are often not apparent and may easily be overlooked in clinical practice. However, potential obstruction of the mitral valve or rupture of hematoma may be severe and even fatal. There have been few cases of left atrial intramural hematoma after catheter ablation, and the mechanism is still unclear. Traumatic catheter manipulation-related injuries at the weakened sites or pulmonary laceration could be possible reasons [3]. A case study by Anand et al. [4] reported an acute left atrial intramural hematoma after an attempt to recanalize the circumflex artery. Due to subtotal occlusion of left atrial outflow, the patient underwent an emergency thoracotomy, which showed that the whole left atrium appeared bruised with no obvious hematoma. Anand et al. speculated that contained atrial intramural coronary vascular rupture or subepicardial perivascular damage might be the main causes [4].

Postoperative TEE is useful in evaluating intracardiac complications of AF patients undergoing RFCA. Transthoracic echocardiography and CTA can be used to evaluate the severity of hematoma, while CMR can offer a better atrial tissue characterization. The main differential diagnoses include pericardial effusion and left atrial dissection. The optimal treatment strategies for left atrial intramural hematoma remain unclear. Suspension of anticoagulation may help prevent hematoma expansion. For patients with stable hemodynamic status, conservative treatment might be advisable as intramural hematoma can be gradually absorbed in most cases. However, surgical intervention is necessary once the patient's hemodynamic status becomes unstable. This case highlights that it is necessary to be gentle during the ablation procedure, especially during the posterior wall ablation, to avoid similar complications. Even in the absence of symptoms, a silent intramural hematoma is still potentially life-threatening and requires special attention in clinical practice.

Supplementary material

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

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REFERENCES

1. Abdur Rehman K, Wazni OM, Barakat AF, et al. Life-Threatening Complications of Atrial Fibrillation Ablation: 16-Year Experience in a Large Prospective Tertiary Care Cohort. JACC Clin Electrophysiol. 2019; 5(3): 284–291, doi: 10.1016/j.jacep.2018.11.013, indexed in Pubmed: 30898229.
2. Buchta P, Sierpiński R, Myrda K, et al. New hope for patients and challenges for the multidisciplinary arrhythmia team: a hybrid convergent approach for atrial fibrillation treatment. Kardiol Pol. 2020; 78(12): 1243–1253, doi: 10.33963/KP.15640, indexed in Pubmed: 33021356.
3. Haseeb S, Kutyifa V. Left Atrial Intramural Hematoma After Radiofrequency Catheter Ablation: Beware of the Unexpected. JACC Case Rep. 2020; 2(2): 227–229, doi: 10.1016/j.jaccas.2019.11.043, indexed in Pubmed: 34317209.
4. Jothidasan A, Attaran S, Hunter D, et al. Management of a left atrial intramural hematoma after percutaneous intervention. Ann Thorac Surg. 2014; 97(6): 2196–2197, doi: 10.1016/j.athoracsur.2013.08.025, indexed in Pubmed: 24882308.

Unexpected severe coronary artery disease in a young patient with only one modifiable risk factor

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A 34-year-old man was referred to a catheterization laboratory for urgent diagnosis and treatment of ST-segment elevation myocardial infarction (STEMI) of the anterior wall. The symptoms began two days before the admission and were typical of myocardial ischemia. The vital signs were in the normal range. A family history of premature heart disease was negative, and the patient had no chronic diseases. The only reported cardiovascular (CV) risk factor was heavy smoking. Coronary angiography showed an occlusion in the left ascending artery (LAD). Immediate percutaneous coronary intervention was performed with deployment of a drug-eluting stent (Figure 1). Transthoracic echocardiography revealed a decreased left ventricular ejection fraction of 45%–48%, driven by regional contractility abnormalities of the anterior wall and interventricular septum. Further hospitalization in the intensive cardiac care unit was uneventful. Surprisingly, the lipid profile did not appear abnormal (Supplementary material, *Table S1*). During the hospital stay, the patient was rehabilitated and mobilized without any signs or symptoms of cardiac ischemia. He was discharged home after 5 days on 1 × 75 mg aspirin, 2 × 90 mg ticagrelor, 1 × 1.25 mg bisoprolol, 1 × 5 mg perindopril, 1 × 20 mg rosuvastatin, and 1 × 20 mg pantoprazole. He was referred to a further cardiac rehabilitation program.

Based on the guidelines of the European Society of Cardiology (ESC) for the management of

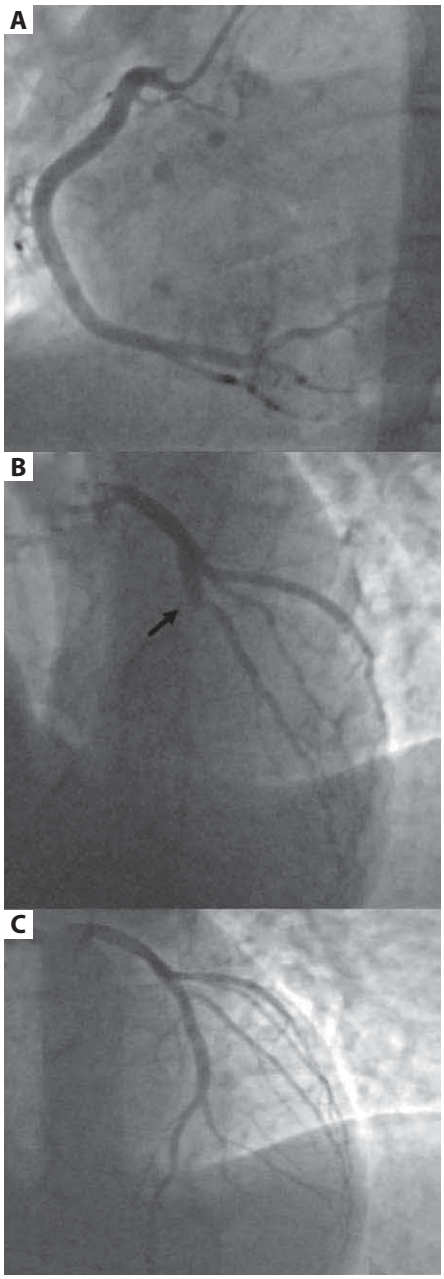

Figure 1. A. Baseline angiography of the right coronary artery. **B.** Baseline angiography of the left coronary artery with an occlusion in the mid-left descending coronary artery (LAD, the arrow). Diffuse non-significant disease of remaining vessels. **C.** The final result of percutaneous coronary intervention within LAD

STEMI, an immediate coronary invasive diagnosis and treatment were performed in the presented case [1]. Although the patient was young, physically active, without elevated blood pressure, with a normal lipidogram and without a family history of premature ischemic heart disease, severe atherosclerosis of LAD was confirmed.

In 2021, new ESC guidelines on CV prevention were released. Those recommend using the updated SCORE algorithm — SCORE2/SCORE2-OP to estimate an individual's 10-year risk of fatal and non-fatal CV events (myocardial infarction, stroke) in apparently healthy people aged 40–89 years with risk factors that are untreated or have been stable for several years [2]. Although our patient's estimated CV risk might have been low, this case report suggests that more attention should be paid to younger patients. The introduction of dedicated scales to assess CV risk in such patients might be justified.

There are few differences in epidemiology of CV risk factors between younger and older patients with coronary artery disease. Dyslipidemia is more common among patients <45 years with coronary artery disease than among older counterparts. It was also found that the younger population had a less extensive coronary disease and a better prognosis [3]. Nonetheless, despite a recent decline in tobacco use, smoking remains the strongest modifiable risk factor of ischemic heart disease in young individuals. Quitting smoking reduces CV risk and is essential in cardiological assessment and treatment. According to the Centers for Disease Control and Prevention, most smokers want to cease smoking. However, without professional medical support, only 4% of cigarette users succeed in quitting [4]. Non-pharmacological methods (e.g. "very brief advice", mood-management therapies in patients with current or past depression) and pharmacological methods (nicotine-replacement therapy, bupropion, varenicline, and cytisine) can be used to increase the chance of quitting [2, 4]. It is important to educate all patients after percutaneous coronary intervention [5].

Certainly, in addition, a family history of premature CV disease and suspected familial hypercholesterolemia should also receive close attention [2].

Supplementary material

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REFERENCES

1. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018; 39(2): 119–177, doi: 10.1093/eurheartj/ehx393, indexed in Pubmed: 28886621.
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. Arantes C, Martins J, Braga CG, et al. Acute coronary syndrome in young adults. European Heart Journal. 2013; 34(suppl 1): P3134, doi: 10.1093/eurheartj/eht309.p3134.
4. Centers for Disease Control and Prevention. Smoking & Tobacco Use. https://www.cdc.gov/tobacco/data_statistics/index.htm (April 6, 2022).
5. Wójcicki K, Krycińska R, Tokarek T, et al. Knowledge and prevalence of risk factors for coronary artery disease in patients after the first and repeated percutaneous coronary intervention. Kardiol Pol. 2020; 78(2): 147–153, doi: 10.33963/KP.15070, indexed in Pubmed: 31761895.

In-stent balloon rupture and entrapment during post-dilatation in an infarct-related artery followed by successful retrieval

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A 49-year-old patient was admitted to the cardiology department with a diagnosis of non-ST-segment elevation myocardial infarction (NSTEMI). He was treated for 3 days using aspirational thrombectomy for ischemic stroke. An echocardiogram showed preserved left ventricular ejection fraction with regional hypokinesia of the lateral and posterior wall of the left ventricle. The coronary angiography exhibited a well-organized thrombus in the mid-circumflex artery (mid-Cx) (Figure 1A). Aspirational thrombectomy was performed via the Export Aspiration System (Medtronic, Minneapolis, MN, US) following pre-dilatation with a 3.5 × 20 mm semi-compliant balloon. Despite inflation of the balloon, the optical coherence tomography intravascular probe did not cross the lesion. Based on angiography, a 4.0 × 38 mm drug-eluting stent was implanted. During post-dilatation, a 4.5 × 15 mm non-compliant balloon inflated at 24 atm ruptured and was removed "en-bloc" with a guidewire and guide catheter (Figure 1B). The shaft and the distal end of the ruptured balloon were entrapped in the vessel (Figure 1C). The patient remained hemodynamically stable; therefore, bailout surgery was deferred. The guiding catheter was switched to a 7F system. Attempts of crossing the lesion with Runthrough NS, BMW II and Whisper MS guidewires were unsuccessful. Eventually, the Gaia Second (Asahi Intecc Co., Nagoya, Japan) was delivered into the distal end of the vessel. A 3.0 × 20 mm semi-compliant balloon was inflated to 18 atm, allowing us to cross the defragmented balloon with 4 mm/175 cm AndraSnare Micro ASM-4 (Andramed GmbH, Reutlingen, Germany) and successfully retrieve the defragmented balloon (Figure 1E). After removal, the stent was post-dilatated with a 4.0 × 15 non-compliant balloon catheter. Intravascular ultrasound was applied to rule out significant calcifications and confirm the optimal outcome of the procedure (Figure 1F). Post-procedural hospitalization was uneventful, and the patient was discharged 3 days later.

Entrapment of an intra-coronary device is rare, but it is, nonetheless, a serious complication. Calcifications, tortuous anatomy, and non-dilatable lesions increase the risk of device entrapment [1]. In the majority of cases, balloon rupture with subsequent entrapment occurs during pre-dilatation or stent implantation. Unexpectedly, in this case, the balloon rupture and entrapment took place during post-dilatation. Moreover, the vessel was not heavily calcified or tortuous. This proves that device entrapment is unpredictable and can occur during any stage of the procedure. Devices allowing successful management of such complications should be available at every catheterization laboratory. Such devices were used in many clinical scenarios [2]. The AndraSnare Micro system is based on an angled nitinol loop allowing retrieval of foreign bodies in coronary and peripheral vessels. In the case of retrieval failure, "burying" the object under a new stent or bail-out surgical management may be considered.

Article information

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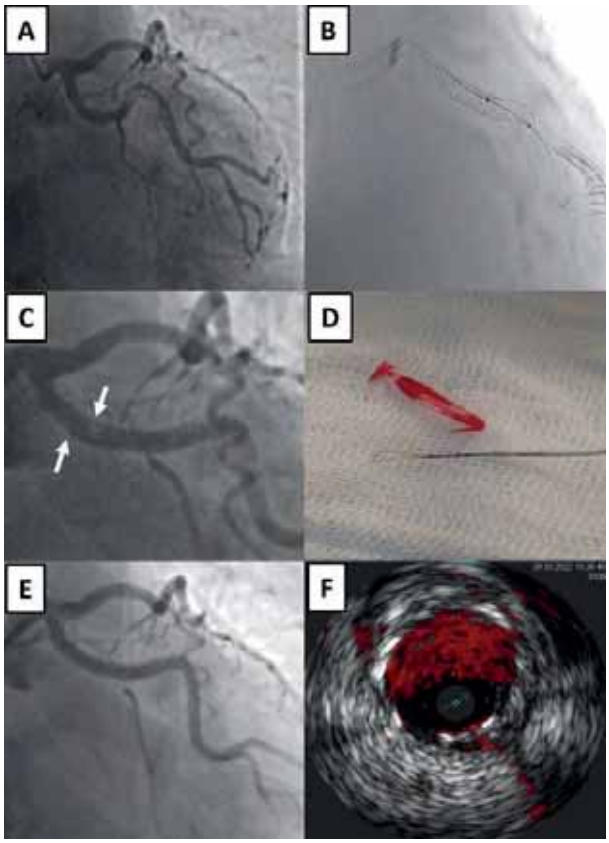

Figure 1. A. Initial left coronary artery angiography with the thrombus in mid-Cx (the arrow). **B.** Post-dilatation of the stent with a 4.5 × 20 mm non-compliant balloon inflated to 24 atm. **C.** Control angiography showing distal marker and fragment of the defragmented balloon (the arrows); **D**. Retrieved distal part of the ruptured balloon and The AndraSnare Micro ASM-4 system. **E.** Final angiography after retrieval of the ruptured balloon. **F.** Intravascular ultrasound of Cx confirming good stent apposition and precluding significant calcifications

Abbreviations: Cx, circumflex artery

REFERENCES

1. Giannini F, Candilio L, Mitomo S, et al. A practical approach to the management of complications during percutaneous coronary intervention. JACC Cardiovasc Interv. 2018; 11(18): 1797–1810, doi: 10.1016/j.jcin.2018.05.052, indexed in Pubmed: 30236352.
2. Kern A, Gil R, Bojko K, et al. A mysterious fluff in the ascending aorta retrieved with a snare system. Kardiol Pol. 2021; 79(4): 467–468, doi: 10.33963/KP.15861, indexed in Pubmed: 33687870.

Myocardial infarction with nonobstructive coronary arteries in a woman: Takotsubo cardiomyopathy or true myocardial infarction?

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Myocardial infarction with nonobstructive coronary arteries (MINOCA) is a working diagnosis for patients with a manifestation of myocardial infarction, no significant coronary stenosis on angiography, and no other specific pathology responsible for acute presentation [1]. Patients with MINOCA constitute a diagnostic and therapeutic challenge in everyday practice. Diagnostic algorithms recommend several tests, including cardiac magnetic resonance (CMR) [1]. Recent studies underscore the important role of early CMR (median: 3 days from index event), which allows for establishing the diagnosis in 77% of patients, with Takotsubo cardiomyopathy (TC; 33%), myocardial infarction (22%), and myocarditis (17%) as most frequent pathologies [2]. We present this case to underscore the role of (1) early CMR in the diagnostic algorithm of MINOCA; (2) ischemic cause of MINOCA in women.

A 52-year-old hypertensive woman presented to the emergency department with 24-hour recurrent chest pain. The electrocardiogram showed abnormalities typical of inferior ST-segment elevation myocardial infarction. Coronary angiography revealed minimal luminal irregularities (Supplementary material, *Videos S1–S6*). In the laboratory tests, the troponin T and CK-MB (creatine kinase-muscle/brain) levels were elevated (695 pg/ml, 44.6 U/l), while other parameters were within the normal range. Echocardiography showed akinetic apex and apical segments of the left ventricle with mildly reduced left ventricular ejection fraction (LVEF) — 45%. The patient reported emotional stress in the previous weeks. Given female sex, history of emotional stress, no obstructive coronary stenosis on angiography, and the echocardiographic presentation, the initial diagnosis of TC was established. The control echocardiography performed on day 4 showed improvement in LVEF (52%) with partial resolution of wall motion abnormalities, which was another argument for the diagnosis of TC. To confirm the initial diagnosis, CMR was performed on day 4.

CMR revealed preserved LVEF (50%) and akinesis of apical inferior segment and adjacent fragment of apical septal segment of the left ventricle. Within the akinetic segments, edema on T2-weighted imaging with fat suppression and subendocardial lesion in late gadolinium enhancement sequences were detected (Figure 1A–D). Stress CMR with regadenoson showed subendocardial ischemia (Figure 1E and Supplementary material, *Video S7*). Ultimately, the diagnosis was changed into myocardial infarction. Twelve-month dual antiplatelet therapy (aspirin and clopidogrel) along with a statin, beta-adrenergic receptor blocker, and angiotensin-converting enzyme inhibitor were recommended, and the patient was referred for cardiac rehabilitation. The control MR performed 12 weeks after the index event confirmed the presence of post-myocardial scar within the apical inferior and apical septal segments (Figure 1F).

In our case, early CMR allowed for establishment of proper diagnosis and implemen-

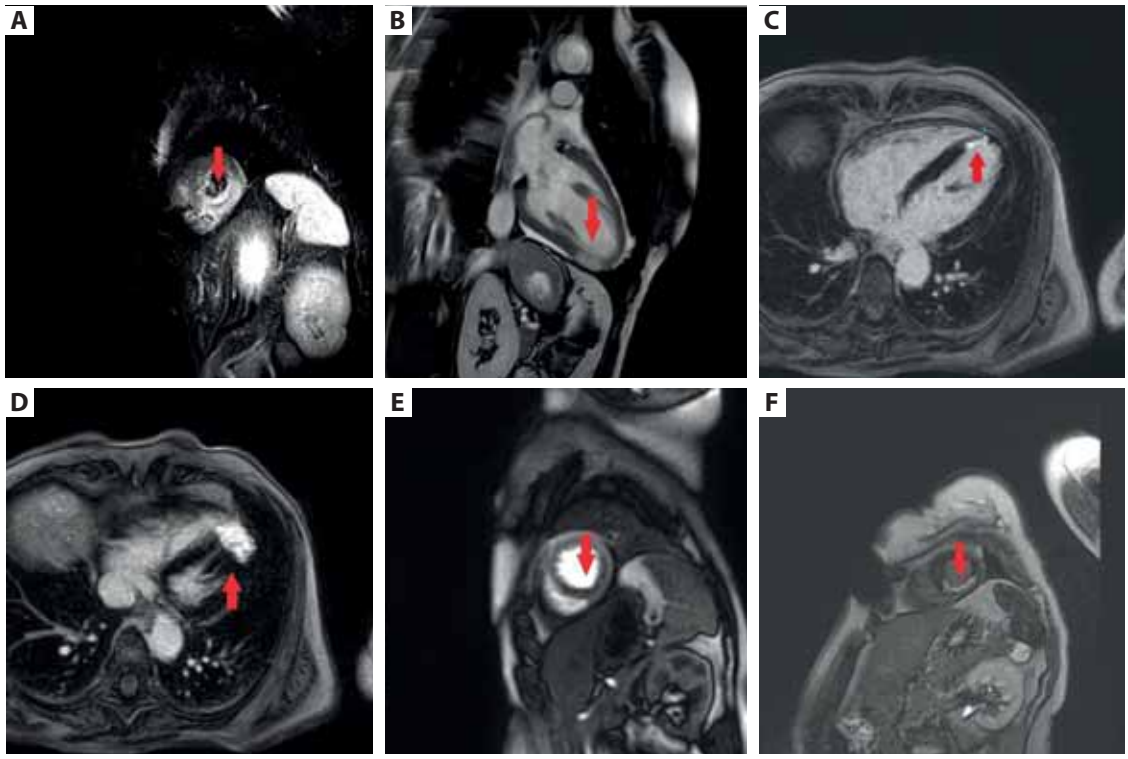

Figure 1. A–E. Initial examination. **A.** T2-STIR image, short axis view: transmural signal hyperintensity (myocardial edema) in apical inferior and adjacent fragment of the apical septal segment of the left ventricle (the arrow). **B.** sBTF cine imaging, 2-chamber view: transmural signal hyperintensity (myocardial edema) in the apical inferior segment of the left ventricle (the arrow). **C.** 4-chamber view: subendocardial distribution of late gadolinium enhancement (LGE) within the apical septal segment (the arrow). **D.** 4-chamber view: LGE within the apical inferior and apical septal segment (the arrow). **E.** Stress CMR with regadenoson, short-axis view: impaired subendocardial perfusion within the apical inferior and apical septal segment. Follow-up examination (the arrow). **F.** Follow-up examination, short axis view: subendocardial LGE within the apical inferior and apical septal segments of the left ventricle (post-myocardial scar; the arrow)

tation of targeted therapy and rehabilitation. It is estimated that more than one-third of MINOCA patients do not receive proper pharmacotherapy [3]. Our patient at first presented as typical TC, and her sex and history of emotional stress were major arguments for that. Female sex is a strong predictor of TC, accounting for the majority of points in the InterTAK score. However, some studies show that it is myocardial infarction, not TC, which constitutes the most frequent pathology in middle-aged women with MINOCA [4]. Another challenging problem is possible co-occurrence of myocardial infarction and TC, which has previously been described in the literature [5]. Therefore, each patient with MINOCA requires multimodality assessment, including early CMR and advanced coronary techniques (not performed in our case because of the presumption of TC).

Supplementary material

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

Article information

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REFERENCES

1. Agewall S, Beltrame JF, Reynolds HR, et al. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. Eur Heart J. 2017; 38(3): 143–153, doi: 10.1093/eurheartj/ehw149, indexed in Pubmed: 28158518.
2. Sörensson P, Ekenbäck C, Lundin M, et al. Early comprehensive cardiovascular magnetic resonance imaging in patients with myocardial infarction with nonobstructive coronary arteries. JACC Cardiovasc Imaging. 2021; 14(9): 1774–1783, doi: 10.1016/j.jcmg.2021.02.021, indexed in Pubmed: 33865778.
3. Pitts R, Daugherty SL, Tang F, et al. Optimal secondary prevention medication use in acute myocardial infarction patients with nonobstructive coronary artery disease is modified by management strategy: insights from the TRIUMPH Registry. Clin Cardiol. 2017; 40(6): 347–355, doi: 10.1002/clc.22686, indexed in Pubmed: 28387960.
4. Reynolds HR, Kwong RY, Maehara A, et al. Coronary optical coherence tomography and cardiac magnetic resonance imaging to determine underlying causes of myocardial infarction with nonobstructive coronary arteries in women. Circulation. 2021; 143(7): 624–640, doi: 10.1161/CIRCULATIONAHA.120.052008, indexed in Pubmed: 33191769.
5. Konishi T, Funayama N, Yamamoto T, et al. Acute anterior myocardial infarction complicated by takotsubo syndrome: the value of multimodality imaging. Kardiol Pol. 2020; 78(10): 1055–1056, doi: 10.33963/KP.15492, indexed in Pubmed: 32633477.

Cardioneuroablation for the effective treatment of recurrent vasovagal syncope to restore driving abilities

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Approximately half of the general population will have one syncopal event during their lifetime, and its most frequent cause is reflex syncope. Recurrent syncope may significantly worsen the quality of life and may have serious consequences for traffic safety. According to the European Society of Cardiology (ESC) guidelines published in 2018, patients with reflex syncope, which is recurrent, severe, or takes place while driving, are advised not to drive until successful treatment is established [1].

Cardioneuroablation (CNA), which decreases vagal tone and modifies circulatory system reflexes, was an effective treatment in our patient in restoring driving abilities [1–4].

Our patient was a 56-year-old man with 8 syncopal episodes in the previous 6 months. His first loss of consciousness occurred while driving a car and ended with a car collision. Other episodes took place at home, mainly in a standing position. He was hospitalized 3 times without detecting any disorders except mild hypertension. After this life-threatening syncope, according to the ESC guidelines and Polish law, the patient was informed about contraindications to driving until proper diagnosis and treatment were established [1]. He accepted the restriction, so there was no need to issue an official statement. Syncope while driving a car and a high frequency of episodes resulted in symptoms of depression requiring pharmacotherapy.

We did a tilt table test for our patient, with syncope in the seventh minute after sublingual nitroglycerin sensitization, which was caused by a sinus pause lasting 19 seconds (Figure 1A). He was diagnosed with cardioinhibitory vasovagal syndrome type II B according to the Vasovagal Syncope International Study. He also underwent a breathing test, Valsalva maneuver, carotid sinus massage with no abnormalities detected, and an atropine test, which resulted in an increase in heart rate from 71 to 121 bpm and showed him as an appropriate responder to CNA. Before he was referred for CNA, cardiac pacing was considered (class IIb recommendation of the ESC guidelines) [1]. Since there are conflicting results of randomized trials including patients with dual-chamber pacing for the treatment of cardioinhibitory vasovagal syncope and following the patient's preferences, CNA was recommended [5].

Anatomically-guided biatrial and binodal CNA with bilateral extracardiac vagal nerve stimulation (ECANS) was performed under general anesthesia according to Pachon's method [6]. After a basic electrophysiological study with normal parameters and three-dimensional electroanatomical mapping of the atria and pulmonary veins (Figure 1B), ultrasound-guided ECANS was done, which revealed sinus arrest lasting 11.5 seconds. Afterward, radiofrequency applications were performed in the regions of parasympathetic innervation of the heart. Control ECANS did not reveal sinus arrest.

Eight weeks later, we did a control procedure. During right ECANS, a sinus pause lasting 11 seconds occurred, and radiofrequency (RF) applications of the parasympathetic ganglia were repeated. Denervation was confirmed pharmacologically by administration of 2 mg intravenous atropine (sinus rhythm increased from 80 to 85 bpm at 10 minutes — <7%).

Three months later, the patient underwent a tilt table test and control ECANS without any abnormalities.

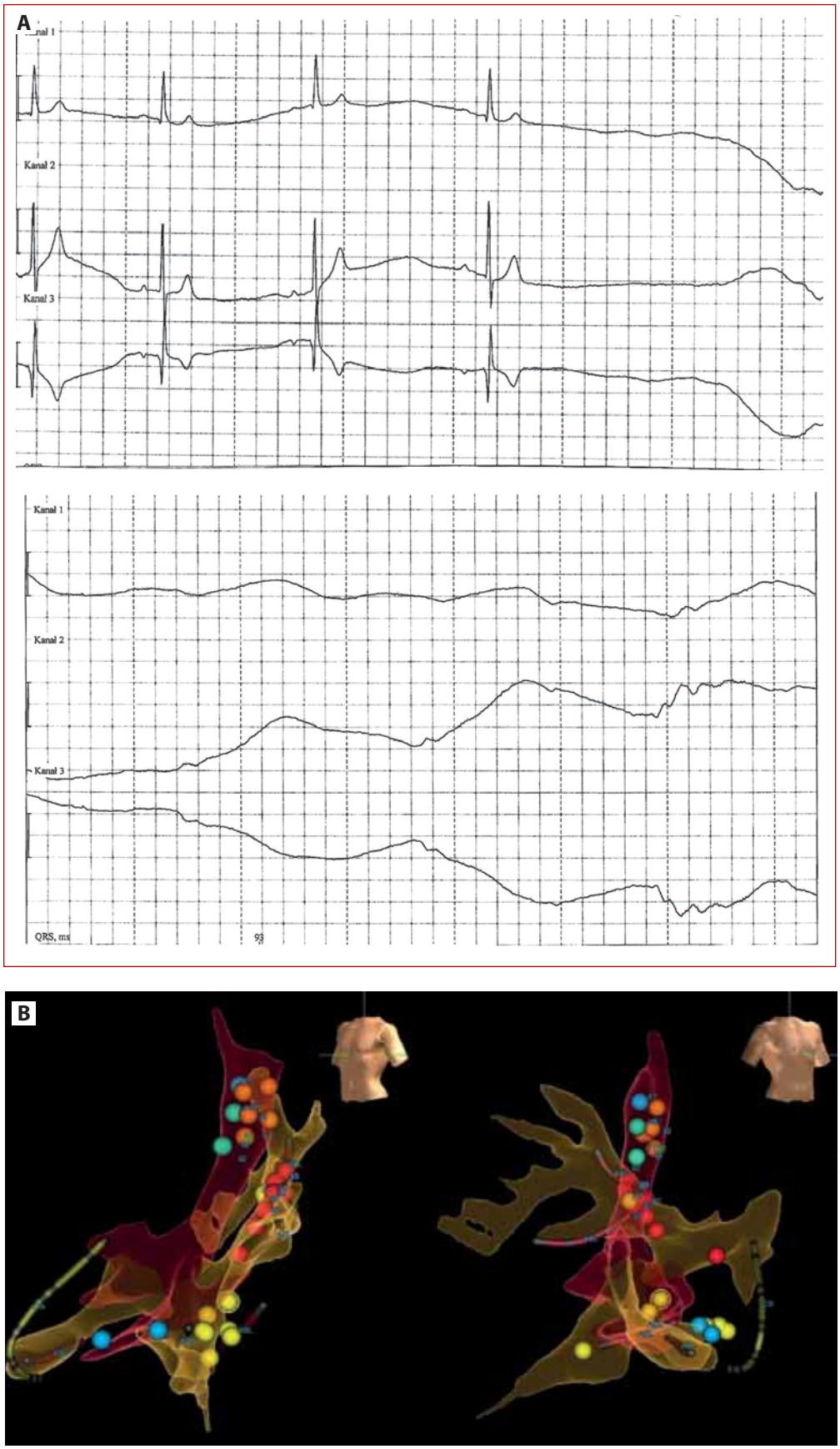

Figure 1. A. Electrocardiogram monitoring during head-up tilt test after sublingual nitroglicerin sensitization — the pause causing syncope. **B.** Electroanatomical map depicting ablation sites. CS — shadow of decapolar catheter on the tricuspid annulus. Blue dots indicate points with His EGM registration or phrenic nerve stimulation. Red, yellow, and orange dots indicate ablation points in the right superior pulmonary vein, ostium of the coronary sinus, and superior vena cava, respectively. Numbers indicate the highest registered sinus rate during applications

Abbreviations: EGM, electrogram

According to the ESC guidelines, the patient was allowed to drive a car again after receiving effective treatment [1]. At 30-month follow-up, the patient remains asymptomatic also while driving, his mental health improved so he no longer requires antidepressants, and he supports other patients after the CNA procedure.

Our case shows the usefulness of CNA as an effective treatment, improving the quality of life by restoring driving ability. Nevertheless, further research on this method is required.

Article information

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REFERENCES

1. Brignole M, Moya A, de Lange FJ, et al. 2018 ESC Guidelines for the diagnosis and management of syncope. Eur Heart J. 2018; 39(21): 1883–1948, doi: 10.1093/eurheartj/ehy03, indexed in Pubmed: 29562304.
2. Piotrowski R, Baran J, Kułakowski P, et al. Cardioneuroablation using an anatomical approach: a new and promising method for the treatment of cardioinhibitory neurocardiogenic syncope. Kardiol Pol. 2018; 76(12): 1736–1738, doi: 10.5603/KP.a2018.0200, indexed in Pubmed: 30338504.
3. Pachon JC, Pachon EI, Pachon JC, et al. "Cardioneuroablation" — new treatment for neurocardiogenic syncope, functional AV block and sinus dysfunction using catheter RF-ablation. Europace. 2005; 7(1): 1–13, doi: 10.1016/j.eupc.2004.10.003, indexed in Pubmed: 15670960.
4. Wróblewska A, Wileczek A, Reichert A, et al. Cardioneuroablation for the treatment of vagally mediated atrial fibrillation and vasovagal syncope. Kardiol Pol. 2021; 79(10): 1151–1152, doi: 10.33963/KP.a2021.0073, indexed in Pubmed: 34292561.
5. Sud S, Massel D, Klein GJ, et al. The expectation effect and cardiac pacing for refractory vasovagal syncope. Am J Med. 2007; 120(1): 54–62, doi: 10.1016/j.amjmed.2006.05.046, indexed in Pubmed: 17208080.
6. Pachon-M EI, Pachon-Mateos JC, Higuti C, et al. Relation of fractionated atrial potentials with the vagal innervation evaluated by extracardiac vagal stimulation during cardioneuroablation. Circ Arrhythm Electrophysiol. 2020; 13(4): e007900, doi: 10.1161/CIRCEP.119.007900, indexed in Pubmed: 32188285.

Fever-induced type-1 Brugada pattern: A sign of revealed Brugada syndrome or just a Brugada phenocopy?

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Brugada syndrome (BrS) is a hereditary channelopathy of the right ventricular outflow tract that might potentially lead to malignant arrhythmogenesis and sudden cardiac death [1, 2]. Currently, the diagnosis of this phenomenon is largely based on detection of spontaneous or induced type- 1 Brugada pattern (manifesting as a coved ST-segment elevation [≥2 mm] in the right precordial leads) on electrocardiogram (ECG) [2]. In their recently published article, Franke et al. [1] have reported a coincidental detection of type-1 Brugada pattern in two little girls in the setting of SARS-CoV-2-related-multisystem inflammatory syndrome (MIS) presenting with a high fever. In this context, we would like to highlight potential implications of the fever-induced type-1 Brugada pattern.

In clinical practice, hyperthermia might have the potential to convert concealed BrS (with type-2 [saddleback type] or 3 ECG pattern, or rarely normal ECG at baseline) to overt BrS (with type-1 ECG pattern) [1, 2]. Importantly, hyperthermia has also been regarded as an adverse factor that should be strictly avoided in patients with an established diagnosis of BrS (regardless of whether it is overt or concealed) [1, 2]. In this setting, the adverse impact of fever might be associated with emergence of further disturbances in depolarization and repolarization currents (further inactivation of sodium and/or activation of potassium currents), all of which appear to be central to the pathogenesis of BrS [2]. Importantly, asymptomatic subjects with a fever-induced type-1 Brugada pattern (as reported in [1]) were previously suggested to have a worse prognosis due to the higher risk of future arrhythmic events [2]. Accordingly, did the authors plan further risk-stratification of the patients through advanced tests including an electrophysiological study?

As a distinct phenomenon, Brugada phenocopy is well known to constitute a variety of diverse and reversible conditions (including myocardial ischemia, myopericarditis, ionic abnormalities, hypothermia, etc.) that present with Brugada-like ECG patterns [2]. Importantly, patients with a Brugada phenocopy usually do not suffer BrS-related symptoms or have a negative drug challenge (mostly performed with sodium channel blockers including ajmaline) [2–4]. However, a portion of patients with a Brugada phenocopy might also have ambiguous genetic testing, as well as a family history of sudden cardiac death. This may suggest an overdiagnosis of BrS, particularly in those with a phenocopy [2].

In contrast to hypothermia [2], hyperthermia has been an underrecognized etiology of Brugada phenocopy in previously healthy subjects. Accordingly, the exact mechanisms of fever-induced Brugada phenocopy are still nebulous. However, this phenomenon might emerge in the presence of substantially higher body temperatures (as compared with revealed BrS) potentially suggesting alternative mechanisms other than ionic current disturbances. Specifically, febrile conditions including MIS and Kawasaki disease might serve as potential etiologies of Brugada phenocopy largely through mechanisms including right ventricular outflow tract inflammation, cytokine storm, etc. In the literature, fever-induced reversible type-1 and type-2 ECG patterns have been rarely reported and termed as "Brugada-like ECG changes" [3, 4]. Importantly, the absence of BrS-related symptoms and family history, and more importantly a negative drug

challenge emerged as important characteristics of these patients [3, 4].

Based on the above-mentioned notions, it seems necessary to differentiate between revealed BrS and Brugada phenocopy in the setting of hyperthermia. In this context, we hold the opinion that fever-induced conversion from a baseline type-2 or type-3 ECG pattern to a type-1 ECG pattern most likely suggests revealed BrS. On the other hand, fever-induced conversion from a normal baseline ECG pattern to a type-2 or type-3 ECG pattern most likely suggests a Brugada phenocopy. These conditions might not warrant a drug challenge following defervescence and restoration of

the baseline ECG pattern. However, fever-induced conversion from a normal baseline ECG pattern to a type-1 ECG pattern (as in the patients reported [1]) might suggest either a phenocopy or revealed BrS. This potentially warrants a drug challenge for the final diagnosis. Therefore, did the authors perform or plan a drug challenge for their patients? Finally, evolution of malignant arrhythmias following the fever-induced type-1 ECG pattern strongly suggests revealed BrS. In conclusion, Franke et al. [1] should be congratulated for their thought-provoking clinical vignette. Hyperthermia has important implications both in the settings of BrS and Brugada phenocopy [1–4]. However, further aspects of Brugada phenocopy associated with hyperthermia still need to be established.

Article information

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REFERENCES

1. Franke M, Książczyk TM, Pietrzak R, et al. Incidental diagnosis of Brugada syndrome in two girls hospitalized for pediatric inflammatory multisystem syndrome related to COVID- 19 (PIMS-TS). Kardiol Pol 2022; 80(10): 1045–1046, doi: 10.33963/KP.a2022.0183, indexed in Pubmed: 35924994.
2. Tomé G, Freitas J. Induced Brugada syndrome: Possible sources of arrhythmogenesis. Rev Port Cardiol. 2017; 36(12): 945–956, doi: 10.1016/j.repc.2017.06.015, indexed in Pubmed: 29233646.
3. Unlu M, Bengi F, Amasyali B, et al. Brugada-like electrocardiographic changes induced by fever. Emerg Med J. 2007; 24(1): e4, doi: 10.1136/emj.2006.041202, indexed in Pubmed: 17183028.
4. Mody P, Pandey A, Joglar J. Fever-induced electrocardiographic changes. J Gen Intern Med. 2015; 30(1): 136–137, doi: 10.1007/s11606-014-2992-9, indexed in Pubmed: 25205622.

Fever-induced type-1 Brugada pattern: A sign of revealed Brugada syndrome or just a Brugada phenocopy? Author's reply

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We would like to sincerely thank Yalta et al. [1] for their letter to the editor regarding our recent publication on the incidental diagnosis of Brugada syndrome in two young girls in the setting of pediatric inflammatory multisystem syndrome (PIMS-TS). The interest in our article underscores the importance of the presented subject.

Brugada syndrome (BrS), a rare but potentially fatal channelopathy, has recently become one of the most widely discussed cardiac disorders due to its still incompletely understood pathophysiology and clinical course. BrS is usually diagnosed upon finding type-1 Brugada changes on the echocardiogram (ECG), presenting spontaneously, during fever or induced by drugs. However, uncertainties concerning the final diagnosis and its prognosis remain (partly because of the phenomenon of Brugada phenocopies [BrP]), which has led to the development of more complex diagnostic criteria such as the Shanghai Score System [2].

In their recently published letter to the editor, Yalta et al. [1] emphasized the importance of scrupulous exclusion of all possible reasons for Brugada pattern phenocopy, such as metabolic conditions, mechanical compression, myocardial ischemia, pulmonary embolism, or even poor ECG filter [3], which could lead to a false and premature diagnosis of BrS. They also raise a very interesting, yet still not fully answered, question: what is the mechanism and prognostic value of hyperthermia revealing the concealed Brugada pattern? Some experts see it as equal to spontaneous appearance of the type-1 pattern, while others (including the authors of the Shanghai Score System) take a more cautious approach. Whether hyperthermia alone, especially in the context of a multisystem inflammatory condition (PIMS-TS), could be a cause of Brugada pattern phenocopy is a valid question; however, there are currently insufficient data to provide an answer. Also, there are still not enough data to distinguish between the BrS and BrP, based on the ECG obtained after resolution of the type-1 pattern although we agree that the appearance of Brugada pattern 2 or 3 makes a diagnosis of BrS more likely.

In both cases presented in our clinical vignette, we have searched for the possible reasons for Brugada phenocopies and evaluated the patients using the criteria proposed by Anselm et al. [3] to exclude BrP. It is worth mentioning that laboratory abnormalities typical for PIMS-TS, such as hyponatremia or elevated concentrations of cardiac biomarkers, were present. However, in both patients, the ECG normalized only after defervescence, while the other results, including laboratory tests and echocardiogram, remained abnormal.

As we stated in our article, a cascade family screening for BrS led to a diagnosis of ajmaline challenge in Patient 1's father. The patient's genetic testing revealed a variant of unknown significance in the SCN5A gene, and there was a history of sudden cardiac death in the paternal grandfather; therefore, in this family, we believe the diagnosis of BrS is well established. The family screening of Patient 2 was negative, and genetic testing remains in progress. In this case, a differential diagnosis of BrP caused by fever and PIMS could be considered; however, a diagnosis of BrS is equally probable. Since the patient is young and so far asymptomatic, we have advised only lifestyle modifications and planned for regular follow-up in our

department. The provocative test with ajmaline would be useful here, but its value in prepubertal children is limited. Our strategy is to postpone the test until after 16 years of age. Similarly, we would not perform an electrophysiological study at this stage in a young, asymptomatic, and incidentally diagnosed patient. In both cases, we have recommended lifestyle modifications (as routinely given to BrS patients) and regular follow-up while more invasive tests will be considered later in life if symptoms occur [4].

Managing asymptomatic patients with features of BrS is challenging, mainly due to gaps in current medical knowledge. It seems even more difficult to guide asymptomatic pediatric patients although there are attempts to risk stratify children with a diagnosis of BrS [5]. Sinus node dysfunction, atrial arrhythmias, and conduction disorders have been shown to be markers of a high risk of life-threatening events, which is also why we decided to keep both patients in follow-up and monitor for the occurrence of any of the above. Nevertheless, at our center when we communicate with the families, we try to emphasize the low risk of life-threatening arrhythmias in incidentally diagnosed individuals.

Once again, we would like to thank Yalta et al. [1] for their important contribution to the discussion about controversies in diagnosing patients with BrS, especially in the pediatric population.

Article information

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REFERENCES

1. Yalta K, Taylan G, Ozturk C, et al. Fever-induced type-1 Brugada pattern: A sign of an unmasked Brugada syndrome or just a Brugada phenocopy? Kardiol Pol 2022; 80(11): 1161–1162, doi: 10.33963/KP.a2022.0193, indexed in Pubmed: 35971996.
2. Antzelevitch C, Yan GX, Ackerman MJ, et al. J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge. Europace. 2017; 19(4): 665–694, doi: 10.1093/europace/euw235, indexed in Pubmed: 28431071.
3. Anselm DD, Evans JM, Baranchuk A. Brugada phenocopy: A new electrocardiogram phenomenon. World J Cardiol. 2014; 6(3): 81–86, doi: 10.4330/wjc.v6.i3.81, indexed in Pubmed: 24669289.
4. Conte G, de Asmundis C, Ciconte G, et al. Follow-up from childhood to adulthood of individuals with family history of Brugada syndrome and normal electrocardiograms. JAMA. 2014; 312(19): 2039–2041, doi: 10.1001/jama.2014.13752, indexed in Pubmed: 25399282.
5. Gonzalez Corcia MC, Sieira J, Sarkozy A, et al. Brugada syndrome in the young: an assessment of risk factors predicting future events. Europace. 2017; 19(11): 1864–1873, doi: 10.1093/europace/euw206, indexed in Pubmed: 27738063.

Carcinoid heart disease: An immense challenge despite medical and surgical advances

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In their recently published clinical vignette, Waligóra et al. [1] reported an interesting case of symptomatic carcinoid heart disease (CHD) in a 49-year-old male, after successful treatment of severe tricuspid regurgitation with implantation of a bioprosthesis followed by resection of the primary tumor localized in the ileum. The authors also reported tricuspid valve deterioration throughout the follow-up period, which they linked to the interval between the abdomen and cardiac surgery and the exposure of the prosthetic valve to high levels of serotonin metabolites before initial tumor resection [1]. As CHD is the most serious consequence of carcinoid syndrome [2] and serotonin activity appears to be crucial in the development of valvular CHD [3], we would like to write a short comment.

CHD development is linked to increased morbidity and mortality. It generally results in increasing malfunction of the valves involved (mainly tricuspid and pulmonary) and patient disability. CHD has a poor prognosis if not treated, with 3-year survival as low as 31%. However, the prognosis for individuals with diagnosed CHD has improved in recent decades, possibly as a result of advances in cardiac imaging techniques, anticancer treatments, perioperative care, and cardiac surgery.

Transthoracic echocardiography assessed by a clinician familiar with typical CHD valve morphology is still the method of choice for diagnosis of CHD. Several biomarkers for the prevalence and severity of CHD have been found in studies. The most relevant biomarker to date is N-terminal pro-B-type natriuretic peptide (NT-proBNP), which has been demonstrated to be both diagnostic of and prognostic for cardiac involvement. Other essential biomarkers used in disease diagnosis and monitoring include urinary 5-hydroxyindoleacetic acid (u5-HIAA), chromogranin A, and activin A [2]. Accordingly, we wonder whether the patient [1] had other biomarkers tested before the final diagnosis of carcinoid syndrome and CHD.

There are several serotonergic 5-HT1 and 5-HT2 receptor subtypes found in cardiac valve tissues, with subtype 5-HT2B receptors being the most prevalent and having a significant role in valve disease [4]. Treatment with somatostatin analogs, which are meant to lower circulating tumor metabolites (including 5-HT), has been demonstrated to generate a biochemical and clinical response in 60% to 70% of patients and an antiangiogenetic/antitumoral response in 5% to 10% [2].

As was done in the reported case [2], cardiac catheterization provides a direct method of assessing the degree of valve insufficiency by invasive hemodynamic pressure measurement [3]. In individuals with significant cardiac involvement and well-controlled carcinoid syndrome, valve replacement surgery is an effective therapy method that can reduce persistent symptoms and contribute to better outcomes. However, the appropriate time for valve replacement surgery in relation to severity of valve dysfunction and symptoms has not been determined. According to guidelines, patients referred for cardiac surgery should present with symptoms of right heart failure and at least 12 months of expected post-operative survival from their neuroendocrine tumor condition [2]. Early investigations of valve surgery found 30-day perioperative mortality to be as high as 63%, but with increased expertise and surgical procedures, 30-day perioperative mortality has recently been reported to be as low as

3.7% [3]. It is also worth noting that even in the context of advanced valve disease, patients with normal natriuretic peptide levels had a favorable prognosis [3]. Unfortunately, CHD can progress rapidly [2].

In all patients with neuroendocrine neoplasms of the small intestine (with and without CHD), primary tumor resection with metastatic disease (resectable and unresectable) has been found to increase survival. This might be due to decreased production of vasoactive substances and a reduction in potentially fatal consequences such as intestinal obstruction generated by tumor progression and occlusion [5]. Accordingly, we wonder if the authors of the presented case [1] could provide more information on tumor characteristics, echocardiographic findings, as well as on levels of 5-HIAA and chromogranin A after primary tumor resection.

CHD treatment is complicated since both the systemic malignant disease and cardiac involvement should be managed at the same time [2]. However, it is not always as simple as in the guidelines. The reported case by Waligóra et al. [1] emphasized that patient management requires involvement of a multidisciplinary team to adequately select patients for valve or primary tumor surgeries, and plan preoperative and perioperative treatment procedures. It should be highlighted that the authors took up this extremely difficult challenge and that the cardiac surgery and primary tumor resection were successful without any complications [2].

In conclusion, all of these facts prove that nowadays, it is crucial to concentrate on precise patient diagnosis, treatment, and management, all under the guidance of a multidisciplinary team, to increase the overall survival of patients with CHD.

REFERENCES

1. Waligóra M, Suder B, Magoń W, et al. Staged treatment of carcinoid syndrome complicated with severe tricuspid regurgitation. Kardiol Pol 2022; 80(7–8): 867–868, doi: 10.33963/KP.a2022.0157, indexed in Pubmed: 35735072.
2. Davar J, Connolly HM, Caplin ME, et al. Diagnosing and managing carcinoid heart disease in patients with neuroendocrine tumors: an expert statement. J Am Coll Cardiol. 2017; 69(10): 1288–1304, doi: 10.1016/j.jacc.2016.12.030, indexed in Pubmed: 28279296.
3. Hassan SA, Palaskas NL, Agha AM, et al. Carcinoid heart disease: a comprehensive review. Curr Cardiol Rep. 2019; 21(11): 140, doi: 10.1007/s11886-019-1207-8, indexed in Pubmed: 31745664.
4. Ayme-Dietrich E, Lawson R, Da-Silva S, et al. Serotonin contribution to cardiac valve degeneration: new insights for novel therapies? Pharmacol Res. 2019; 140: 33–42, doi: 10.1016/j.phrs.2018.09.009, indexed in Pubmed: 30208338.
5. Fox DJ, Khattar RS. Carcinoid heart disease: presentation, diagnosis, and management. Heart. 2004; 90(10): 1224–1228, doi: 10.1136/hrt.2004.040329, indexed in Pubmed: 15367531.

Staged treatment of carcinoid syndrome complicated with severe tricuspid regurgitation. Author's reply

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We thank Dr. Konsek-Komorowska and Prof. Pęczkowska for their interest [1] in our case report about a patient with carcinoid heart disease (CHD) [2]. We agree that management of CHD is complex, not always predictable, and requires multidisciplinary cooperation. While the largest cohort of patients with CHD including 240 operated patients presents a 33-year history of treatment approach [3], most current data come only from small case series or case reports [4]. Accordingly, it is a challenge to determine the preferred and optimal treatment approach in complex patients. In our patient, we decided to perform initially valve repair and then primary tumor extraction as the risk of abdominal surgery was considered too high.

At the time of diagnosis, the carcinoid tumor was in an advanced stage and the serum level of chromogranin A was 196 nmol/l (N: 0–6 nmol/l) and the urinary excretion of 5- hydroxyindoleacetic acid (5-HIAA) was 329.3 mg/24 h (N: 2–9 mg/24 h). Pathohistological grading was assessed as 2. Further examination of resected ileum showed proliferative activity of Ki67 (4%). Immunohistochemistry staining revealed a positive reaction to synaptophysin, chromogranin, and expression of somatostatin receptor 2 in all tumor cells. Staining for cytokeratin 7 and thyroid transcription factor 1 was negative. The overall staging was pT2 N1 PN1 LV1 M1c according to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) 2017 classification (in order of appearance: primary tumor diameter of 2–5 cm, presence of regional lymph node metastasis, perineural invasion, invasion into lymphatic vessels, metastases to distant organs). The resected primary tumor appeared relatively small with a diameter of 3 cm without macroscopic infiltration to the ileal mucosa. There were no metastases to the appendix.

After abdominal surgery, N-terminal pro-B-type natriuretic peptide (NT-proBNP) level was slightly elevated to 182 pg/ml (<125). However, in the 12 months following surgery, the patient required reintroduction of low doses of loop diuretics due to progression of tricuspid regurgitation (which was observed first in September 2021: 6 months after cardiac and 2 months after abdominal surgeries).

A recent study has shown that 6.7% of patients operated for CHD needed cardiac re-intervention on follow-up due to tissue or mechanical valve dysfunction; however, only in 3 patients, a late valve dysfunction was due to carcinoid involvement of the artificial valve [3]. In our patient, we cannot definitively state the mechanism of biological valve dysfunction at least partly due to the lack of the results of 5-HIAA and chromogranin A, after primary tumor resection. However, we did not identify any other factors (i.e. infective endocarditis, pulmonary hypertension, right ventricle dilatation, etc.) that could contribute to bioprosthesis degeneration besides residual excretion of polypeptides by the tumor and its metastases [5]. Since the primary tumor resection, the tricuspid regurgitation, which was moderate at that point, did not progress in the following months. That supports a thesis that reduction of tissue mass prevented further valve damage. Currently, 18 months after cardiac surgery, the patient is treated with somatostatin analogs and telotristat ethyl. He is in New York Heart Association class II with

a NT-proBNP serum level of 983 pg/ml. Echocardiography shows stable moderate-grade tricuspid regurgitation and stable moderate dysfunction of the pulmonary valve (current mean gradient of 18 mm Hg vs. 15 mm Hg before cardiac surgery and PHT of 164 vs. 174 ms, respectively).

Article information

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REFERENCES

1. Konsek-Komorowska SJ, Pęczkowska M. Carcinoid heart disease — an immense challenge despite medical and surgical advances. Kardiol Pol. 2022; 80(11): 1165–1166, doi: 10.33963/KP.a2022.0162, indexed in Pubmed: 35775450.
2. Waligóra M, Suder B, Magoń W, et al. Staged treatment of carcinoid syndrome complicated with severe tricuspid regurgitation. Kardiol Pol. 2022; 80(7-8): 867–868, doi: 10.33963/KP.a2022.0157, indexed in Pubmed: 35735072.
3. Nguyen A, Schaff HV, Abel MD, et al. Improving outcome of valve replacement for carcinoid heart disease. J Thorac Cardiovasc Surg. 2019; 158(1): 99–107.e2, doi: 10.1016/j.jtcvs.2018.09.025, indexed in Pubmed: 30527716.
4. Konsek-Komorowska SJ, Kolasińska-Ćwikła AD, Różański J, et al. Outcomes of cardiac surgical treatment for carcinoid heart disease. Kardiol Pol. 2022; 80(2): 202– 204, doi: 10.33963/KP.a2021.0189, indexed in Pubmed: 34939659.
5. Gut P, Czarnywojtek A, Sawicka-Gutaj N, et al. Assessment of serotonin concentration in patients with a small-intestine neuroendocrine neoplasm and carcinoid syndrome treated with somatostatin analogues. Pol Arch Intern Med. 2020; 130(10): 903–905, doi: 10.20452/pamw.15504, indexed in Pubmed: 32643913.

Lung transplantation in patients with pulmonary arterial hypertension: The opinion of the Polish Cardiac Society Working Group on Pulmonary Circulation

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ABSTRACT

Pulmonary arterial hypertension is a rare but progressive disease that leads to death. Modern drug treatment slows the progression of the disease and prolongs patients' lives, but often, even maximal treatment with parenteral prostacyclin does not prevent deterioration. In the case of inadequate clinical response to drug treatment, lung transplantation (LTx) should be considered. This article aims to analyze thoroughly indications to refer a patient for consultation with a transplant center, the optimal timing of listing for LTx, contraindications for the procedure, bridging techniques, as well as tests needed before and after transplantation. We outline the technique of the procedure and evaluate psychological aspects of LTx.

Key words: lung transplantation, pulmonary arterial hypertension, pulmonary arterial hypertension treatment

EPIDEMIOLOGY OF PULMONARY ARTERIAL HYPERTENSION

The prevalence of pulmonary arterial hypertension (PAH) in Poland in the adult population is 30.8 cases per million while the incidence is 5.2 cases per million per year [1, 2]. Women are affected more frequently than men (69.8% of the patient population). The majority of patients at the time of diagnosis are in functional class III (72.1%) and, less frequently, in functional class IV (10.9%), or II (16.4%). Idiopathic PAH is most commonly diagnosed (45.8%), followed by PAH associated with congenital heart defects (36.7%) and connective tissue diseases (13.6%). PAH associated with portal hypertension, human immunodeficiency virus (HIV) infection, or caused by drugs or toxins is less common. The mean age at diagnosis of PAH is 46.8 ± 22.3 years, with 33.2% of patients aged ≥65 years. Data obtained from the Polish Registry of Pulmonary Hypertension (BNP-PL) collected for this publication show that the mortality rate from PAH in the Polish population is 89 cases per year (6.8%). Therapy with three specific drugs is used in 13.8% of patients and with two drugs in 43% of patients. Among patients with PAH who died between October 1, 2018 and August 31, 2020, therapy with three specific drugs was used by 25.6% of patients, and treatment with parenteral prostacyclin was used by 45.1% of patients. Data collected from two centers in Poland that perform lung transplantation (LTx) (Gdansk Medical University, Silesian Center for Heart Diseases in Zabrze) show that in 2019–2020 a total of 8 transplants were performed in PAH patients aged 21 to 45, three of whom died as a result of graft failure, multiple organ failure, and brain edema (data collected for this publication).

The first successful LTx in a PAH patient performed by a team from the Department of Chest Diseases at the Institute of Tuberculosis and Lung Diseases in Warsaw took place in 2006 and was led by Prof. Walter Klepetko's team at AKH Vienna. The patient then remained under the care of the Zabrze team [3].

The above data indicate that maximal therapy is not used frequently enough in the PAH patient population and that an LTx program needs to be developed in this group of patients.

MAXIMAL MEDICAL THERAPY

PAH is an aggressive, rapidly progressive disease, whose essence is endothelial damage and remodeling of pulmonary arterioles. Abnormal functioning of three pathways involving endothelin, nitric oxide, and prostacyclin contributes to vascular changes [4]. Drugs used to treat PAH, affecting the above-mentioned three pathways, correct these abnormalities. All of these drugs exert a vasodilatory effect and also have antiproliferative effects.

According to the recommendations of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), assessment of the risk of death determines the choice of initial therapy and timing of treatment escalation. Risk can be estimated using the REVEAL scale, ESC risk tables, or based on the French, Swedish, and COMPERA registries. In Poland, ESC risk tables are most commonly used. The goal of treatment is always to achieve low-risk-of--death status, which is associated with a good prognosis [5].

If the patient is in the low- or intermediate-risk group at the time of diagnosis, combination therapy with two oral drugs from the groups of endothelin receptor antagonists (ERAs) and nitric oxide antagonists (phosphodiesterase-5 inhibitors [PDE-5i]) is started. If low-risk status is not achieved after 3–6 months, therapy must be escalated to oral three-drug therapy or, if the patient is in the intermediate-high or high-risk group, to maximal therapy. In contrast, if the patient is a high-risk patient at baseline, the maximal therapy is started immediately.

Maximal medical therapy is maximal conservative treatment of PAH, which consists of triple combination therapy with prostacyclin (PCA) intravenously (IV) or subcutaneously (SC) [6]. Using three drugs from different groups simultaneously corrects all the pathophysiological pathways responsible for vascular changes. Initial therapy with drugs from two groups (ERA plus PDE-5i) results in a greater reduction in pulmonary vascular resistance (PVR) than monotherapy with any drug, and initial triple-drug therapy (ERA plus PDE-5i plus PCA) results in the greatest reduction in PVR by about 70%. Parenteral prostacyclins are characterized by the strongest effects. In a randomized trial involving 81 patients in New York Heart Association (NYHA) class III and IV, three-month IV administration of epoprostenol resulted in a significant reduction in mortality compared to patients in the placebo group. The treatment also improved physical performance, quality of life, and hemodynamics [7]. The addition of sildenafil to long-term epoprostenol in the PACES trial resulted in a longer time to clinical deterioration and improved physical performance and hemodynamic parameters [8]. In two small observational studies of NYHA class III and IV patients who received maximal therapy as initial treatment, very good results were obtained. Eighteen patients patients who received combination therapy with epoprostenol plus bosentan plus sildenafil and 21 patients who received combination therapy with treprostinil SC plus ambrisentan plus tadalafil, showed improvement in functional, physical capacity, hemodynamics, and achievement of low-risk status after 4–6 months and after one year [9, 10]. Also, an observational study of 1611 patients based on the French registry showed that patients treated with maximal therapy from the start had the best chance of achieving low-risk status [11].

According to the ESC/ERS recommendations, implementation of maximal therapy in a patient or insufficient clinical response to initial oral combination therapy should be an indication to consider referring the patient for a consultation with an LTx center, and failure of maximal therapy should be an indication to place the patient on a waiting list for LTx [5].

CRITERIA FOR REFERRING A PATIENT TO A LUNG TRANSPLANT CENTER AND CRITERIA FOR PLACING A PATIENT WITH PAH ON THE LIST OF RECIPIENTS (INCLUDING CONTRAINDICATIONS)

Advances in drug therapy have changed the prognosis of patients with PAH, but some patients still do not achieve an adequate clinical response despite receiving maximum treatment. For these patients, LTx remains an important therapeutic option. The risk of perioperative death in patients with PAH is the highest of all indications for LTx. On the other hand, PAH patients have the best prognosis among those who survive the first 6 months if adequate preparation and optimal timing of transplantation are ensured [12]. Selecting potential candidates for transplantation is a difficult task not only because of the risks of surgery but also because the risk of infection and rejection is much greater than in other organ transplants.

Defining the optimal time to refer a patient with PAH and qualify for LTx is a key issue for successful transplantation.

The 2021 International Society for Heart and Lung Transplantation (ISHLT) recommendations [13] describe a candidate for LTx as a person who has:

- a high (>50%) risk of death from lung disease in the next 2 years;
- a high probability (>80%) of survival for more than 5 years after transplantation provided normal graft function.

The intensive development of pharmacological treatments affects the long-term prognosis of people with PAH, which requires using modern means of assessing prognosis, such as the REVEAL 2.0 scale, proposed in the recommendations of the 6th World Symposium on Pulmonary Hypertension (WSPH) in Nice in 2018 [14]. Ideally, survival assessment methods should be validated on a local population, and analysis of perioperative prognosis should take into account medical capabilities, experience, and post-transplant prognosis in the PAH population.

The arguments for earlier transplantation include:

- aggressive disease progression and cardiovascular decompensation;
- a high probability of complications that will prevent transplantation at a later stage, such as progressive cachexia, sarcopenia, and osteoporosis in the course of the disease;
- risk of sudden death in case of delayed surgery;
- progressive damage to other organs (kidneys, liver) by circulatory failure, which will increase the risk of transplantation.

Given the difficulties involved in determining the timing of LTx, it is essential for physicians treating PAH with pharmacological therapy to work closely with transplant centers and jointly determine the optimal individualized management strategy. For this reason, both ISHLT, as well as ESC/ERS and WSPH, present two stages of qualification:

- referral for transplantation at a transplant center;
- listing for transplantation by a transplant center.

The recent ESC/ERS guidelines published in August 2022 and endorsed by ISHLT indicate that consultation at a transplant center is recommended in the following situations [5]:

- potentially eligible patients for whom LTx might be an option in case of treatment failure;
- ESC/ERS intermediate-high or high risk or REVEAL risk score >7 on appropriate PAH medication;
- progressive disease or recent hospitalization for worsening PAH;
- need for IV or SC. prostacyclin therapy;
- known or suspected high-risk variants, such as pulmonary veno-occlusive disease (PVOD) or pulmonary capillary hemangiomatosis, systemic sclerosis, or large and progressive pulmonary artery aneurysms;
- signs of secondary liver or kidney dysfunction due to PAH or other potentially life-threatening complications of PAH, such as recurrent hemoptysis, which are expected to improve after successful transplantation.

The first stage of qualification includes a full medical evaluation for PAH severity, risk of death, and the presence of contraindications to transplantation. It allows the qualified person to get acquainted with the center, interact with transplant patients and prepare mentally for major surgery. Early referral gives time to fully evaluate the patient, perform necessary consultations, as well as take steps to eliminate potentially reversible contraindications, such as obesity or infection. It also makes it possible to take measures to reduce the risk of complications, such as diagnosis and potential embolization of bronchial vessels in cases of recurrent hemoptysis. Such evaluation should also include an assessment of exercise capacity to tailor pre- and postoperative rehabilitation programs to individual patient needs. Earlier initiation of collaborative patient care does not necessarily result in placing the patient on the waiting list if the patient responds well to the management used, but it will allow for immediate inclusion on the list if there is unfavorable disease progression.

Criteria for including patients on the waiting list for LTx according to ISHLT and ESC/ERS [5, 13] are:

- high risk score >10, according to ESC or REVEAL, on targeted PAH treatment including prostacyclins SC or IV;
- progressive hypoxemia, especially in patients with PVOD or pulmonary capillary hemangiomatosis;
- observation of progressive (but not end-stage) renal or hepatic failure resulting from PAH;
- life-threatening hemoptysis occurs.

Rather than placing importance on specific numerical cutoff points (e.g. six-minute walk test [6MWT distance]), especially in terms of hemodynamic criteria (pulmonary artery pressure, cardiac output, or right atrial pressure), attention should be paid to comprehensive assessment of risks and potential benefits by a multidisciplinary team. The same 6MWT, right atrial pressure, or cardiac output

values in a young person with rapid disease progression may indicate a significantly different prognosis than in an older person with other comorbidities and a slow disease course. Therefore, all measurements should be analyzed taking into account both the person's current situation, his/her history, and capabilities of the treating centers.

A key component of LTx eligibility is the exclusion of contraindications that unacceptably increase the risk of the procedure or subsequent treatment. The period between consultation and listing allows time to rule out or treat such comorbid conditions. According to ISHLT, absolute contraindications to LTx include [13]:

- lack of patient consent;
- malignant neoplasm with a high risk of cancer-related recurrence or death;
- renal failure with estimated-glomerular filtration rate (eGFR) <40 ml/min/1.73 m^2, unless multiorgan transplantation is considered;
- acute coronary syndrome or myocardial infarction in the last 30 days;
- stroke in the last 30 days;
- liver cirrhosis with portal hypertension or significantly impaired liver function (multi-organ transplantation to be considered);
- acute liver failure;
- acute renal failure with an increase in creatinine or the need for renal replacement therapy (with a low probability for the return of normal kidney function);
- septic shock;
- active extrapulmonary or disseminated infection;
- active tuberculosis;
- HIV infection with a detectable viral load;
- limited functional status (e.g., inability to move) with low potential for post-transplant rehabilitation;
- progressive cognitive impairment;
- repeated episodes of non-compliance with medical recommendations, lack of cooperation (in the case of pediatric patients, this is not an absolute contraindication and constant evaluation of non-compliance should be carried out, as children go through different stages of development);
- active substance use or addiction, including current smoking of cigarettes,
- e-cigarettes, marijuana, and intravenous drug use;
- another severe uncontrolled condition that can limit survival after transplantation.

In certain situations, despite the presence of relative contraindications, transplantation may be considered. It mainly depends on the experience of the transplant center. In its 2021 recommendations, ISHLT distinguishes two groups among relative contraindications [13]:

- Factors that cause an increased or significantly increased risk of transplant failure:
  - age >70 years;
  - coronary artery disease requiring coronary artery bypass grafting during transplantation;
  - reduced left ventricular (LV) ejection fraction (EF), EF <40%;
  - significant cerebrovascular disease;
  - severe esophageal motility disorders;
  - untreatable hematological disorders, including hemorrhagic diathesis, thrombophilia, or significant bone marrow dysfunction;
  - body mass index (BMI) >35 kg/m^2;
  - BMI <16 kg/m^2;
  - limited functional status, but with the possibility of rehabilitation after transplantation;
  - psychiatric, psychological, or cognitive conditions that may interfere with compliance with post-transplant recommendations;
  - lack of social support;
  - lack of understanding of the disease and/or pre- and post-transplant management despite education;
  - infection with *Mycobacterium abscessus*, *Lomentospora prolificans*, *Burkholderia cenocepacia*, or *Burkholderia gladioli*;
  - hepatitis B or C virus infection with detectable viral load and liver fibrosis;
  - a deformity of the thorax or spine that may cause restriction after transplantation;
  - the need for extracorporeal life-support techniques for transplant bypass.
- Factors causing a moderately increased risk of transplant failure:
  - age 65–70 years;
  - eGFR 40–60 ml/min/1.73 m^2;
  - coronary artery disease (including one that can be revascularized by percutaneous coronary intervention before transplantation);
  - history of coronary artery bypass grafting;
  - reduced LVEF, EF 40%–50%;
  - peripheral vascular disease;
  - systemic connective tissue diseases (scleroderma, lupus, inflammatory myopathies);
  - reflux disease or esophageal motility disorders;
  - thrombocytopenia, leukopenia, or anemia with a high probability of occurrence after transplantation;
  - osteoporosis;
  - BMI 30–34.9 kg/m^2;
  - BMI 16–17 kg/m^2;
  - frailty syndrome;
  - hypoalbuminemia;
  - uncontrolled diabetes;
  - oral marijuana use;
  - *Scedosporium apiospermum* infection;
  - HIV infection with an undetectable viral load;
  - history of thoracic surgery;
  - pleurodesis in anamnesis;
  - need for mechanical ventilation.

In justified cases of PAH with significant impairment of cardiac function, qualification for heart-lung transplantation (HLT) should be considered. This may be especially the case

in Eisenmenger syndrome with an inoperable heart defect [5]. It should be noted that the last successful lung and heart transplant in Poland took place in 2001 [15], and ISHLT reports only a few dozen such procedures per year [12].

Qualifying patients with PAH for LTx is a difficult and potentially lengthy process, and deciding whether to list them for LTx requires close cooperation among the patient's attending physicians, the transplant center, and the patient himself, along with his immediate family. The qualification procedure, which includes evaluation of disease progression and its natural course, exclusion of significant comorbid contraindications, and selection of optimal timing, are undoubtedly important elements affecting the outcome of transplantation.

SPECIFIC INDICATIONS FOR LUNG TRANSPLANTATION

Pulmonary artery aneurysm (PAA) is a rare anomaly of the pulmonary vessels. The incidence estimated from autopsy studies is 1 in 14 000 [16]. The etiology is varied and in more than 50% of cases is associated with congenital heart defects such as persistent Botallo duct, ventricular septal defect (VSD), atrial septal defect (ASD), pulmonary valve defects, or connective tissue defects (Marfan and Ehlers-Danlos syndromes).

In other cases, PAA can occur in the course of vasculitis, PAH; the aneurysm can be also idiopathic. While PAA may be asymptomatic for a long time, it is known to lead to life-threatening conditions such as massive hemoptysis, rupture/dilatation, or compression of the left coronary artery trunk leading to acute coronary syndrome [17–23].

PAA (as opposed to pseudoaneurysm) refers to a focal dilatation involving the entire vessel wall. Currently, there is no defined dimension of the pulmonary artery at which we diagnose an aneurysm. Based on imaging studies, the normal dimension of the pulmonary artery in healthy adults is believed to be 25 mm ± 3 mm, with 29 mm being the upper limit of normal in men and 27 mm in women. Some authors consider any dilatation of the pulmonary trunk above this standard as an aneurysm, while others adopt a higher cutoff point, i.e., above 1.5 times the upper limit of normal without differentiating by sex. Currently, a dimension of 40 mm is most commonly accepted as the criterion for the diagnosis of PAA [24, 25] (according to Restrepo and Carswell, for the pulmonary artery trunk it is 45 mm, and for the pulmonary artery it is 30 mm).

Due to the rarity of the disease, there are no specific guidelines, but it is considered advisable to consider surgical treatment [26] when:

- maximum aneurysm diameter is >55 mm;
- PAA diameter increases by 5 mm in 6 months;
- there is a coexisting pulmonary valve pathology;
- there are symptoms of pressure on surrounding structures, such as symptoms from bronchial compression (cough, pneumonia, and bronchitis);
- a thrombus in the aneurysm is detected;
- there are clinical symptoms (shortness of breath, chest pain, fainting, palpitations);
- PAA occurs in the course of leaky heart defects;
- there are symptoms of rupture or dissection.

In patients with PAH, the presence of PAA should precipitate the decision to qualify for LTx. Qualification for LTx is not the sum of the indications for treatment of PAA and PAH, as each patient requires an individual assessment that takes into account the course and severity of both diseases.

Hemoptysis

The term hemoptysis refers to the expectoration of blood or sputum mixed with blood coming from the lung parenchyma or airways.

Depending on the amount of expectorated pure blood or its content in expectorated sputum, we distinguish:

- hemoptysis: a small/trace amount not exceeding 20 ml per day;
- massive hemoptysis (hemoptoe), 20–200 ml of blood per day;
- pulmonary hemorrhage >200 ml/day or 600 ml over 48 hours [27].

In practice, quantitative assessment of hemoptysis is often difficult and in many cases may be under- or overestimated by patients. Therefore, the concept of "life-threatening hemoptysis" is more commonly used and defined not only by the amount of expectorated blood but also by the rate of bleeding and its clinical consequences (e.g., hemoptysis requiring transfusion, intubation, airway obstruction, hypoxemia requiring mechanical ventilation) [28–33]. Massive hemoptysis refractory to interventional treatment is one of the elements that should always be considered in the qualification process for LTx in patients with PAH, chronic thromboembolic pulmonary hypertension (CTEPH), PVOD, and cystic fibrosis [34].

DIAGNOSIS OF THE PATIENT BEFORE REFERRAL TO THE TRANSPLANT CENTER

Before being referred to a transplant center, both at the stage of initial notification (referral), as well as for qualification for transplantation (listing), the patient should have a thorough evaluation confirming the key indications for the procedure and the absence of absolute contraindications. Studies should reflect the clinical status in recent months and confirm the failure to achieve prognostically relevant treatment goals. They should include

- clinical evaluation focused on right heart failure, NYHA functional class, and presence of syncope with consideration of the rate of disease progression and response to treatment escalation;
- assessment of cardiovascular capacity based on the 6MWT, spiroergometry, and measurement of natriuretic peptides;

- assessment of hemodynamics in right heart catheterization (SvO2-mixed venous oxygen saturation, cardiac index, and right atrial pressure);
- cardiac imaging (echocardiogram, MRI–CMR) always with attention to the presence/absence of fluid around the heart;
- if treatment goals have been achieved with parenteral drugs, then this is independent prognostic information.

The above data, once an LTx candidate is enrolled, should be systematically updated in communication between the attending cardiologist at the PAH center and the transplant center.

The expanded panel for evaluating a patient qualified for LTx includes elements of physical examination, laboratory tests, and imaging.

In terms of **physical examination**, blood pressure and heart rate, as well as the clinical diagnosis of renal failure, are complementary components of the assessment, using the REVEAL 2.0 calculator. Assessment of body mass index is necessary, allowing qualification of patients with BMI <35 kg/m^2. Any hospitalization in the preceding 6 months should be carefully reviewed. Before qualification, a psychological consultation is advisable, and in the case of PAH associated with connective tissue diseases, a rheumatologic evaluation of the involvement of individual organ systems [35]. It should specifically include an evaluation of esophageal involvement, with possible consideration of imaging and functional studies of the esophagus and bronchoalveolar lavage (BAL) for exclusion of hydrochloric acid/biliary accumulation and of the musculoskeletal system in relation to postoperative rehabilitation.

Extended **laboratory tests** should address the evaluation of renal function (GFR, proteinuria, and possibly cystatin). Elevated and dynamically rising bilirubin and creatinine levels may be important in determining the urgency of transplantation or disqualification from transplantation since belated qualification in the phase of multiple organ failure significantly worsens treatment outcomes [36].

Among the most commonly used **imaging tests** in patients transferred to transplantation units are echocardiography, CT scans, and, in recent years, cardiac MRI, which is considered the gold standard for evaluating the right ventricle (RV) in the course of PAH [37].

In terms of imaging tests, important are:

- Extended evaluation of the function of both chambers of the heart – for the success of LTx and further favorable course of treatment, proper functioning of the LV is also of great importance. Increasingly, before initiating specific therapy and before qualifying for surgical treatment, an in-depth assessment of its function is made by echocardiography (using the full capabilities of myocardial velocity and strain assessment and three-dimensional analysis), but also by MRI. Contrast-enhanced MRI allows for assessment of fibrosis within the ventricular walls (late enhancement) and estimating chances of retrograde remodeling and return of normal RV function after LTx.
- An up-to-date contrast-enhanced chest CT scan allows assessment of the bony structures of the chest, lung tissue, vasculature, and heart, facilitating surgical planning. It should be emphasized that the finding on CT of features suggestive of pulmonary capillary hemangiomatosis or pulmonary vein obliteration disease is a separate indication for transplant qualification due to the inability to treat in the manner typical of PAH.

Invasive testing includes right heart catheterization (RHC) and, in patients with suspected coronary artery disease, an up-to-date coronary angiography (similarly, exclusion of other locations of increased arteriosclerosis, such as the carotid arteries, by vascular testing). Current data from RHC (no older than 12 months) are indispensable for qualification at the optimal stage of the disease. Right atrial pressure >15 mm Hg and low cardiac index (<1.8–2 l/min/m^2) are among the criteria that increase the urgency of listing.

The described procedures before transplant qualification do not exhaust the examinations and consultations necessary to establish indications and contraindications for LTx used in most centers in Poland and around the world. These include also cardiological, pulmonological, and gastroenterological qualification, in the case of women, gynecological, psychiatric/psychological consultation, assessment of socioeconomic situation determining adequate cooperation in the postoperative period, panel of serological tests (cytomegalovirus [CMV], Epstein-Barr virus [EBV], toxoplasmosis, hepatitis C virus [HCV], hepatitis B virus [HBV], HIV), basic tumor markers and densitometries.

MONITORING A PATIENT LISTED FOR LUNG TRANSPLANTATION

Once a patient is qualified for LTx and placed on the active list of recipients, treatment management should be carried out in close cooperation with the transplant team. It is important to be aware that the waiting time for the procedure can be up to several years, so information about significant changes in the patient's condition should be promptly communicated to the transplant center. The goal of treatment should be to keep the patient as physically and mentally fit as possible, as well as to avoid performing procedures that could hinder the LTx procedure. Assessment of immunization levels with panel reactive antibody (PRA) should be updated every 3–6 months. For highly immunized patients, securing serum for cross-testing is recommended at 6-week intervals. It is important to remember to monitor and manage adverse effects of PAH drug treatment such as thrombocytopenia [38], anemia, hyperthyroidism [39], or hepatotoxicity. The function of central catheters [40], subcutaneous punctures, and implantable pumps [41] used for prostanoid therapy should also be closely monitored. Hospitalizations related to heart

failure exacerbations are associated with an unfavorable prognosis [42], with infections being the most common identifiable cause [43]. Infectious exacerbations during the waiting period for transplantation are also associated with poorer outcomes of the LTx procedure [44]. Every effort should be made to avoid cachexia and malnutrition in a patient awaiting LTx. In the case of symptomatic or asymptomatic iron deficiency, iron replacement therapy should be used [45]. Improvements in physical fitness and overall condition of the potential recipient can be achieved by conducting a program of supervised rehabilitation [46]. Patients should be vaccinated against influenza (once a year), pneumococcus (once every five years), and tetanus (once every 10 years), as well as COVID, hepatitis, and chickenpox if they have not had these vaccinations before [47]. As far as possible, standard oncological surveillance and periodic examinations recommended for the age category should not be neglected. Patients qualified for LTx should have ongoing access to psychological support and should be referred to palliative care if they are removed from the list of recipients [48]. Patients with uncontrolled fluid retention despite diuretic therapy or recurrent collapses should be considered for atrial septostomy [49], optimally with implantation of a device to ensure patency of the created cavity [50]. In patients with supra-systemic PAH, especially at a younger age, a Potts anastomosis between the pulmonary artery and descending aorta may be considered [51]. If the pulmonary artery is significantly dilated (>41mm), the risk of sudden death increases, most likely due to pulmonary artery dissection [23] or compression of the left coronary artery [22]. Implantation of a stent into the trunk of the left coronary artery is an effective method of managing its significant stenosis, but the choice of the stent and the timing of dual antiplatelet treatment should be discussed with the transplant team. The antiplatelet effect of prostacyclin derivatives should also be considered [52]. Hemoptysis and airway bleeding occur in advanced PAH and are associated with a poor prognosis in PAH unrelated to Eisenmenger syndrome [34]. Typically, the source of bleeding is dilated bronchial arteries, which can be successfully embolized [53]. Atrial arrhythmias associated with significant right atrial enlargement are also a complication typical of advanced PAH and should be expected in patients qualified for LTx. In the case of complex forms of atrial arrhythmias, ablation should be attempted, while taking into account the incomplete therapeutic effect of the procedure [54].

SURGICAL ASPECTS OF LUNG TRANSPLANTATION IN IPAH

General information

Donor-recipient selection takes into account the blood group (same or compatible), height (±5%), followed by clinical condition, age, and other variables. The individual immunization status of a given recipient may influence the decision to reject a given organ donor despite the aforementioned indications of desirable selection.

For the surgeon who is to perform the transplantation, the results of imaging studies of CT, X-ray, ultrasound (US; evaluation of anomalies of the thoracic structure, width of the pulmonary vessels, presence of intracardiac leaks, cardiac function, and structure, etc.), the results of coagulation tests (some of the drugs used in the treatment of IPAH deteriorate platelet function), as well as the evaluation of flows (US, Doppler US) in peripheral vessels (carotid and femoral) necessary for optimal selection of the site of implantation of cannulas of the extracorporeal membrane oxygenation (ECMO) system are important. Other tests are performed according to the standard qualification protocol for LTx.

Preparation of the patient in the operating room

- Intubation with a double-lumen endotracheal tube — the lung that is not currently being transplanted should be ventilated, as this avoids the need to maintain a high output on ECMO, and NO can be insufflated.
- Central puncture in the jugular vein.
- Swan-Ganz catheter and pulmonary artery pressure measurement.
- Cannulation with vascular catheters of the radial artery, femoral artery, and femoral vein — obtaining blood pressure measurements.
- DefiPads — high risk of arrhythmias including ventricular fibrillation (VF) and ventricular tachycardia (VT) and lack of rapid access directly to the heart.
- Cellsaver — long surgery and frequent clotting disorders necessitate blood-saving methods.
- Blood preparations — secured in the hospital blood bank.
- Drugs: antibiotics according to recent cultures of both recipient and donor or routinely used in the center.
- Immunosuppressive drugs depending on the protocol used at the center.
- Venous-arterial ECMO (ECMO VA) and a set of cannulas (in addition, a fully prepared, complete system for classic extracorporeal circulation [ECC] in the operating room).

Surgery

A feature that clearly distinguishes LTx in IPAH/PAH from transplantation in other disease entities is that these procedures are always performed using circulatory support techniques. With the widespread availability of ECMO technology, it has become the number one assistive technique for LTx surgery displacing classic ECC. A key feature of modern ECMO, because of which surgeons choose it more readily than ECC, is the lack of need for heparin during surgery and thus operating in a bloodless field.

Depending on the center's preferred protocols, different vascular access routes are used for cannulation, including femoral, subclavian, and carotid vessels, as well as directly by the aorta and cardiac structures. Direct can-

nulation or cannulation through synthetic vascular grafts sewn to the vessels is used. This shows the importance of the aforementioned multiple imaging techniques in the LTx qualification process. In most cases, the cannulation strategy is planned in advance. However, there are times when it is necessary to change plans on an ad hoc basis under the influence of unforeseen events. The wider is the range of surgical access routes available for the team, the easier it is to respond to difficult situations.

Finally connected and vented, the ECMO system starts working at the moment most convenient for the operating surgeon. It is not necessary to use heparin in the first 24 hours. The preferred access is an anterolateral mini-thoracotomy usually through the fourth or fifth intercostal space. The order in which lungs are transplanted is determined on an individual basis. Surgical steps are usually performed according to the scheme:

- release of the lung from adhesions if present and dissection of the hilar structures;
- separation of the pulmonary ligament from the diaphragm;
- pulmonary artery clamping;
- ligation of pulmonary veins as peripherally as possible;
- cutting off the inferior pulmonary vein then the superior pulmonary vein and later the pulmonary artery;
- bronchial resection;
- removal of the lung from the pleural cavity;
- opening the pericardial sac around the pulmonary veins;
- hemostasis in the pleural cavity.

At the same time, an assisting surgeon performs the separation and preparation of the donor's lungs for implantation.

If anterior access is used (preferred at the centers in Gdansk and Zabrze), the steps are as follows:

- Lung implantation begins with bronchial anastomosis, which can be immediately verified by bronchoscopy or video images from an endotracheal tube equipped with a camera (if available). The suture site is covered with tissue adhesive.
- The next step is to perform an arterial anastomosis frequently requiring surgical correction of the recipient's artery.
- Venous anastomosis is the connection of the recipient's left atrium to a portion of the donor's atrium, performed as the final step.

After completion of the anastomosis and before tying the sutures on the vessels, there is a need to remove air lingering in the donor's vascular bed. This is a critical moment. Once the blood flow is started, any air left in the pulmonary vessels and especially in the venous system is pushed out to the "left heart" and further to the aorta from where it has an open path to the coronary and cephalic vessels, potentially leading to air embolisms. The steps are as follows:

- unclamping and venting of the pulmonary artery — the vascular clamps are slowly loosened giving controlled blood flow to the lung — antegrade venting;
- venting from the pulmonary veins — retrograde venting;
- tying of the sutures on both vessels;
- removal of clamps;
- transesophageal echocardiography (TEE) control for the presence of air in the left heart and aorta;
- hemostasis;
- initiation of ventilation of the transplanted lung is preceded by recruitment maneuvers (opening of collapsed alveoli);
- insertion of a drain into the dorsal region of the costophrenic angle.

When the local and general condition is satisfactory, transplantation of the lung on the other side can begin. It seems important that the time between the unclamping of the vessels on the side transplanted first and the placement of the clamps on the pulmonary artery on the other side be no less than 1 hour. This allows the transplanted lung to adapt to the prevailing hemodynamic conditions minimizing the risk of lung swelling. After the second lung is transplanted, additional drains are placed into both pleural peaks, and the chest is closed once acceptable hemostasis is achieved. The patient is intubated with a typical cuffed endotracheal tube and has a bronchial tree lavage performed before leaving the operating room. The patient is then transferred to the postoperative ward.

With the use of ECMO systems for LTx surgery, especially in patients with IPAH/PAH, and a better understanding of the mechanisms leading to the hemodynamic crises and LV failure in the postoperative course after LTx, some centers have developed a program of routinely prolonging ECMO support, and some have developed less invasive methods to prevent such situations. In choosing this strategy, it is recognized that benefits of maintaining hemodynamic stability in the first few days after LTx and allowing time for the cardiovascular system to adapt to the new situation outweigh the patient's exposure to complications from prolonging the use of ECMO VA beyond the time of the operation itself, even though this involves the need for heparinization.

In contrast, other transplant teams have developed postoperative protocols seeking to avoid cardiorespiratory instability without invasive methods. In centers preferring this procedure, the ECMO system is usually (80%) disconnected from the patient in the operating room before transferring him/her to the postoperative ward. The use of new hemodynamic monitoring techniques, such as the ability to continuously measure cardiac output, has definitely improved immediate diagnosis and allows rapid implementation of non-invasive or less invasive treatment although also not without side effects. At the moment,

there are too few studies available to consider any of the already proposed strategies as more effective, but it is worth looking for new solutions since the early mortality rate after LTx in IPAH/PAH worldwide is the highest among all LTx performed for other conditions.

URGENT LUNG TRANSPLANTATION — CRITERIA, ROLE OF MAINTENANCE THERAPIES INCLUDING ECMO

Urgent qualification for LTx in patients with PAH includes situations in which the disease poses an immediate threat to life or is expected to lead to death within days or weeks.

Indications for emergency LTx in patients with PAH:

- Clinical deterioration is defined as:
  - functional class IV;
  - persistent RV decompensation (ascites, peripheral edema, jugular venous congestion, recurrent hemoptysis) despite optimal drug therapy; including treatment with intravenous, escalated to maximally tolerated, doses of parenteral prostacyclins — rapidly progressive disease, unresponsive to escalation of specific therapy, including maximal therapy.
- Signs of RV failure in patients with PVOD and/or pulmonary hemangiomatosis in whom pulmonary arterial targeted therapy is contraindicated or poorly tolerated.

Maintenance therapies, bridges to urgent transplantation:

- Atrial septostomy in its new form, Atrial Flow Regulator (AFR), a 4–10 mm diameter nitrile implant inserted into the atrial septum to create an artificial opening (shunt) in patients in whom maximal drug therapy, using parenteral prostacyclins, is ineffective [49]. The procedure decompresses the right atrium, reduces symptoms of heart failure, improves exercise capacity, and is an established option for bridging to LTx for patients with severe RV failure [50, 55, 56]. At the same time, by directing part of the output to the left side, it improves the output of the LV and, in this mechanism, enables it to "train", preparing it to receive a higher volume after LTx.
- Potts procedure is possible only in the case of supra-systemic pulmonary artery pressure. It provides a connection between the left pulmonary artery and the descending aorta reducing pulmonary artery pressure and is a transitional alternative to transplantation and/or a bridge to LTx for patients with severe RV failure and utilizing optimal drug therapy [57, 58].
- ECMO is used in 3 cases including:
  - bypass for transplantation — in the best transplant centers in the world this is the most commonly used bypass method. To ensure improved cardiac output and decompress the failing RV, only a veno-arterial configuration is used, i.e., blood is withdrawn from the right atrium (cannula[s] inserted through the right internal jugular vein and/or the right/left femoral vein) and returned after oxygenation through a cannula inserted through the right/left common femoral artery into the descending aorta (or, alternatively, through the right/left common femoral artery into the descending aorta), through the right subclavian artery/right common carotid artery as in the upper body ECMO configuration [59, 60];
  - for multiorgan conditioning — the failing heart and other failing organs in patients in the most advanced stage of PAH while constituting a bridge to decision c) as an absolute requirement and component of typical LTx surgery.
- Therapies whose theoretical basis and preliminary results of clinical trials are encouraging:
  - pulmonary artery sympathetic denervation (PADN) [61, 62];
  - the ARIA system, a fully implantable system that reduces RV work and simultaneously increases RV output by synchronously inflating and deflating a balloon inserted into the pulmonary artery trunk [63];
  - RV resynchronization/stimulation [64].

FOLLOW-UP AFTER LUNG TRANSPLANTATION

LTx aims not only to prolong life but also to improve its quality in patients with chronic respiratory diseases. Therefore, it is particularly important to manage patients after this procedure due to several complications that can occur both in the early postoperative period and later. Most patients experience acute graft rejection despite immunosuppressive therapy, and nearly 50% experience chronic rejection (after a year or more) [65]. Other common problems include infections, respiratory complications, graft failure, and serious extrapulmonary conditions [66–69].

Managing these patients requires experience and often engagement of specialists from different fields. The main issues involved are outlined below.

- An LTx patient should remain under constant monitoring by the transplant center where the procedure was performed and the periodic control of the center that referred the patient for transplantation and provided care for the patient before transplantation.
- Nearly half of the centers use induction of immunosuppression, administering interleukin-2 (IL-2) receptor antibodies or antithymocyte immunoglobulin or (most rarely) alemtuzumab in the first days after transplantation [67].
- Chronic treatment usually involves three-drug therapy, including (1) a calcineurin inhibitor: cyclosporine or tacrolimus; (2) a drug that inhibits lymphocyte proliferation: mycophenolate mofetil or azathioprine; and (3) a glucocorticosteroid [65, 67–69].
- Acute cellular rejection occurs in most patients within a year after transplantation, most often in the first six months. Symptoms of graft rejection are not very characteristic (fever, cough, shortness of breath) and

need to be differentiated from infection or failure of the transplanted lungs from other causes. It is necessary to perform a few tests including laboratory (CRP, procalcitonin), microbiological (material obtained from the airways during bronchoscopy), imaging (chest X-ray and CT), and histopathological [66–68].

- Antibody-dependent rejection requires a detailed immunological diagnosis [66], including determination of donor antigen-specific antibodies and the dynamics of their titer increase, if any, along with simultaneous evaluation of changes in the transplanted organ (complement system activation). Treatment includes inhibiting the production of antibodies and removing them. First-line treatment is administration of intravenous immunoglobulin (IVIg) and plasmapheresis [65, 69].
- In the treatment of acute rejection, intravenous methylprednisolone 500–1000 mg/day is used for 3 consecutive days, followed by oral prednisone at a dose of 0.5–1 mg/kg of body weight for another 1–2 weeks and a gradual reduction in its dose thereafter [67].
- Chronic rejection occurs in the majority of patients (in 70% at 10 years post-transplantation). In selected cases, it can manifest itself as early as 3 months after LTx and is the factor that most determines long-term survival. Chronic rejection of the transplant usually takes the form of bronchiolitis obliterans (BO), and spirometry testing is crucial in its diagnosis and monitoring of patients. However, the final diagnosis of the so-called bronchiolitis obliterans syndrome (BOS) is based on histopathological examination of a lung fragment. Due to the process of chronic rejection, which can be slowed but not inhibited by immunosuppressive treatment, chronic lung allograft dysfunction (CLAD) develops, leading to pulmonary fibrosis [65, 66, 68, 70]. There is no effective treatment for CLAD. Halting the progression of BOS after total irradiation of lymphoid tissue has been observed, but the method is not widely used. Another method is administration of alemtuzumab, which is a monoclonal antibody against the CD52 lymphocyte glycoprotein, or antithymocyte globulin [65, 71]. Lung retransplantation procedures are also being performed, but this is successful in a small number of patients [65, 69, 72]. The problem is selection of the optimal surgical technique and identification of patients for whom this procedure can provide the expected benefit.
- Infections associated with immunosuppression are usually caused by opportunistic bacteria characterized by drug resistance [68-70]. The most common etiological agents are *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, but infections with atypical microorganisms (*Legionella, Chlamydophila, Mycoplasma*) also occur. Infections of fungal etiology are dominated by mold (e.g., *Aspergillus*), and less frequently by *Pneumocystis jiroveci* (formerly pneumocystis carinii). Among viral infections, pneumonia caused by cytomegalovirus (CMV) is particularly dangerous. Infections that occur after LTx have a particularly severe clinical course.
- Caring for patients after LTx requires:
  - monitoring of immunosuppression in terms of pharmacology (determination of concentrations of immunosuppressive drugs to ensure desired levels), as well as toxicity (parameters of renal function, lipogram, glycemia, evaluation for the development of diabetes, hypertension, chronic kidney disease, osteoporosis, and the onset of cancer);
  - availability of a bronchoscopy laboratory with the ability to perform interventional bronchial procedures and transbronchial biopsies (preferably cryobiopsy);
  - availability of a specialized bacteriological and virological laboratory, with the ability to diagnose rare pathogens by the most sensitive methods (PCR, molecular diagnostics);
  - the possibility of performing total lymphoid irradiation (TLI) or photophoresis;
  - availability of a transplant immunology laboratory; an HLA laboratory, monitoring occurrence of *de novo* antibodies to donor-specific antibodies (DSA);
- Scheduled follow-ups for LTx patients are carried out every 14 days for the first 3 months, then every month for up to 6 months, then every 2–3 months until the end of the first year, and then every 3–6 months.

HOW TO TALK TO A PATIENT BEFORE A LUNG TRANSPLANT PROCEDURE?

The prospect of LTx as a treatment for PAH can be emotionally difficult. In the minds of some patients (but also doctors), this method of treatment is seen as definitive, associated with significant disease progression and "failure" of drug treatment. Others, on the other hand, may see it as "the beginning of the end" or simply replacement of one disease with another.

Although LTx can be a difficult process, discussing the possibility of transplantation early on (even before it is actually needed) will allow both the patient and family to consider it as a treatment option in the future.

PAH is a rare disease with an unfavorable prognosis. New drugs, opportunities for up-front combination therapies, and the strategy of pursuing a rapid low-risk profile to a greater extent than some years ago have increased (in the minds of both patients and doctors) the time to qualification for LTx. However, it is important that the option of transplantation should already be on the table when treatment first begins. The first hospitalization and initiation of therapy (and especially prostacyclin therapy) is an extremely important moment in the patient-doctor relationship. A conversation about the disease, its etiology, progression, and the chosen therapy regimen should clearly explain to the patient the process of treatment and monitoring of disease progression and the stage at which qualification for LTx should be considered.

It is important that all people with PAH who need or may need an LTx in the future understand what the transplant process is all about and receive information to make an informed decision. Early referral to a transplant center gives patients a chance to meet with a multidisciplinary transplant team before the qualification procedure and inclusion on the waiting list. Anyone living with PAH knows that the course of the disease can be unpredictable (especially in patients on parenteral prostacyclin therapy) and clinical deterioration can occur very quickly, necessitating urgent referral for LTx.

An important part of the conversation about LTx is to explain to patients the concept of the so-called "transplantation window", i.e., the optimal time to perform the procedure, in which the patient is sick enough to need a transplant, but also healthy enough to recover after the operation.

An important part of preparing for transplantation is giving the patient the opportunity to get to know the transplant team, who will explain the procedure to the patient and his or her relatives, as well as outline a plan for cooperation in the post-transplant period.

Once on the waiting list, the waiting period for a transplant begins, which can be unpredictable. The patient should be prepared emotionally for the possibility of a "false alarm" in the case of inadequate donor lungs and assured that this is not linked to removal from the transplant list. There are many emotions associated with the prospect of transplantation, including anxiety, depression, and even coming to terms with a progressive disease such as PAH. Support from the referring team, the transplant team, and the family is vital in overcoming these and other emotions surrounding transplantation. Difficulties with getting help to cope with emotional challenges should not affect transplant candidacy, but lack of help can hinder access to medical care, including transplantation.

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REFERENCES

1. Kopeć G, Kurzyna M, Mroczek E, et al. Database of Pulmonary Hypertension in the Polish Population (BNPPL): design of the registry. Kardiol Pol. 2019; 77(10): 972–974, doi: 10.33963/KP.14988, indexed in Pubmed: 31553328.
2. Kopeć G, Kurzyna M, Mroczek E, et al. Characterization of patients with pulmonary arterial hypertension: data from the Polish Registry of Pulmonary Hypertension (BNP-PL). J Clin Med. 2020; 9(1): 173, doi: 10.3390/jcm9010173, indexed in Pubmed: 31936377.
3. Wawrzyńska L, Remiszewski P, Kurzyna M, et al. A case of a patient with idiopathic pulmonary arterial hypertension treated with lung transplantation: a "bumpy road" to success [article in Polish]. Pol Arch Med Wewn. 2006; 115(6): 565–571, indexed in Pubmed: 17263229.
4. 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): 1801887, doi: 10.1183/13993003.01887-2018, indexed in Pubmed: 30545970.
5. Humbert M, Kovacs G, Hoeper M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022; 43(38): 3618–3731, doi: 10.1093/eurheartj/ehac237, indexed in Pubmed: 36017548.
6. Galiè N, Channick RN, Frantz RP, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. Eur Respir J. 2019; 53(1): 1801889, doi: 10.1183/13993003.01889-2018, indexed in Pubmed: 30545971.
7. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med. 1996; 334(5): 296–301, doi: 10.1056/NEJM199602013340504, indexed in Pubmed: 8532025.
8. Simonneau G, Rubin LJ, Galiè N, et al. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. Ann Intern Med. 2008; 149(8): 521–530, doi: 10.7326/0003-4819-149-8-200810210-00004, indexed in Pubmed: 18936500.
9. Sitbon O, Jaïs X, Savale L, et al. Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study. Eur Respir J. 2014; 43(6): 1691–1697, doi: 10.1183/09031936.00116313, indexed in Pubmed: 24627535.
10. D'Alto M, Badagliacca R, Argiento P, et al. Risk reduction and right heart reverse remodeling by upfront triple combination therapy in pulmonary arterial hypertension. Chest. 2020; 157(2): 376–383, doi: 10.1016/j.chest.2019.09.009, indexed in Pubmed: 31563498.
11. Boucly A, Savale L, Jaïs X, et al. Association between initial treatment strategy and long-term survival in pulmonary arterial hypertension. Am J Respir Crit Care Med. 2021; 204(7): 842–854, doi: 10.1164/rccm.202009-3698OC, indexed in Pubmed: 34185620.
12. Chambers DC, Cherikh WS, Goldfarb SB, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-fifth adult lung and heart-lung transplant report-2018; Focus theme: Multiorgan Transplantation. J Heart Lung Transplant. 2018; 37(10): 1169–1183, doi: 10.1016/j.healun.2018.07.020, indexed in Pubmed: 30293613.
13. Leard LE, Holm AM, Valapour M, et al. Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2021; 40(11): 1349–1379, doi: 10.1016/j.healun.2021.07.005, indexed in Pubmed: 34419372.
14. Hoeper MM, Benza RL, Corris P, et al. Intensive care, right ventricular support and lung transplantation in patients with pulmonary hypertension. Eur Respir J. 2019; 53(1): 1801906, doi: 10.1183/13993003.01906-2018, indexed in Pubmed: 30545979.
15. Zembala M, Religa Z, Large S, et al. An 18-year follow-up after the first successful heart-lung transplant in Poland. Authors' tribute to the pioneers of heart and lung transplantation. Kardiol Pol. 2020; 78(7-8): 773–775, doi: 10.33963/KP.15420, indexed in Pubmed: 32500995.
16. Deterling RA, Clagett OT. Aneurysm of the pulmonary artery: Review of the literature and report of a case. Am Heart J. 1947; 34(4): 471–499, doi: 10.1016/0002-8703(47)90527-9, indexed in Pubmed: 20266464.

17. Demkow M, Kalińczuk Ł, Kepka C, et al. Left main artery compression by pulmonary artery aneurysm and ostial athero-stenosis of left anterior descending artery in a young female with pulmonary arterial hypertension. Eur Heart J. 2012; 33(20): 2621, doi: 10.1093/eurheartj/ehs195, indexed in Pubmed: 22782942.
18. Pan HC, Wang KY, Liang KW. Left main coronary artery stenting to relieve extrinsic compression by a giant pulmonary artery aneurysm in a patient with idiopathic pulmonary artery hypertension. Heart Lung Circ. 2016; 25(10): e122–e125, doi: 10.1016/j.hlc.2016.02.020, indexed in Pubmed: 27085308.
19. Nesta M, Cammertoni F, Mangini S, et al. Angina in left main coronary artery occlusion by pulmonary artery aneurysm. Asian Cardiovasc Thorac Ann. 2017; 25(3): 216–218, doi: 10.1177/0218492315603212, indexed in Pubmed: 26307054.
20. Jurado-Román A, Hernández-Hernández F, Ruíz-Cano MJ, et al. Compression of the left main coronary artery by a giant pulmonary artery aneurysm. Circulation. 2013; 127(12): 1340–1341, doi: 10.1161/CIRCULATIONAHA.112.152199, indexed in Pubmed: 23529535.
21. Alkhouli M, Huda N, Bashir R, et al. Left main coronary artery compression syndrome and spontaneous coronary artery dissection: coincidence or pathologic association? Heart Lung. 2014; 43(4): 284–285, doi: 10.1016/j.hrtlng.2014.03.008, indexed in Pubmed: 24751338.
22. Żyłkowska J, Kurzyna M, Florczyk M, et al. Pulmonary artery dilatation correlates with the risk of unexpected death in chronic arterial or thromboembolic pulmonary hypertension. Chest. 2012; 142(6): 1406–1416, doi: 10.1378/chest.11-2794, indexed in Pubmed: 22797193.
23. Florczyk M, Wieteska M, Kurzyna M, et al. Acute and chronic dissection of pulmonary artery: new challenges in pulmonary arterial hypertension? Pulm Circ. 2018; 8(2): 2045893217749114, doi: 10.1177/2045893217749114, indexed in Pubmed: 29251549.
24. Duijnhouwer AL, Navarese EP, Van Dijk APJ, et al. Aneurysm of the pulmonary artery, a systematic review and critical analysis of current literature. Congenit Heart Dis. 2016; 11(2): 102–109, doi: 10.1111/chd.12316, indexed in Pubmed: 26555132.
25. Restrepo CS, Carswell AP. Aneurysms and pseudoaneurysms of the pulmonary vasculature. Semin Ultrasound CT MR. 2012; 33(6): 552–566, doi: 10.1053/j.sult.2012.04.001, indexed in Pubmed: 23168064.
26. Kreibich M, Siepe M, Kroll J, et al. Aneurysms of the pulmonary artery. Circulation. 2015; 131(3): 310–316, doi: 10.1161/CIRCULATIONAHA.114.012907, indexed in Pubmed: 25601950.
27. Johnston H, Reisz G. Changing spectrum of hemoptysis. Underlying causes in 148 patients undergoing diagnostic flexible fiberoptic bronchoscopy. Arch Intern Med. 1989; 149(7): 1666–1668, doi: 10.1001/archinte.149.7.1666, indexed in Pubmed: 2742442.
28. Ibrahim WH. Massive haemoptysis: the definition should be revised. Eur Respir J. 2008; 32(4): 1131–1132, doi: 10.1183/09031936.00080108, indexed in Pubmed: 18827169.
29. Cordovilla R, Bollo de Miguel E, Nuñez Ares A, et al. Diagnosis and treatment of hemoptysis. Arch Bronconeumol. 2016; 52(7): 368–377, doi: 10.1016/j.arbres.2015.12.002, indexed in Pubmed: 26873518.
30. Flume PA, Yankaskas JR, Ebeling M, et al. Massive hemoptysis in cystic fibrosis. Chest. 2005; 128(2): 729–738, doi: 10.1378/chest.128.2.729, indexed in Pubmed: 16100161.
31. Ong TH, Eng P. Massive hemoptysis requiring intensive care. Intensive Care Med. 2003; 29(2): 317–320, doi: 10.1007/s00134-002-1553-6, indexed in Pubmed: 12594593.
32. Holsclaw DS, Grand RJ, Shwachman H. Massive hemoptysis in cystic fibrosis. J Pediatr. 1970; 76(6): 829–838, doi: 10.1016/s0022-3476(70)80362-6, indexed in Pubmed: 5444576.
33. Garzon AA, Cerruti MM, Golding ME. Exsanguinating hemoptysis. J Thorac Cardiovasc Surg. 1982; 84(6): 829–833, indexed in Pubmed: 7144217.
34. Żyłkowska J, Kurzyna M, Pietura R, et al. Recurrent hemoptysis: an emerging life-threatening complication in idiopathic pulmonary arterial hypertension. Chest. 2011; 139(3): 690–693, doi: 10.1378/chest.10-1134, indexed in Pubmed: 21362657.
35. George MP, Champion HC, Pilewski JM. Lung transplantation for pulmonary hypertension. Pulm Circ. 2011; 1(2): 182–191, doi: 10.4103/2045-8932.83455, indexed in Pubmed: 22034605.
36. Bartolome S, Hoeper MM, Klepetko W. Advanced pulmonary arterial hypertension: mechanical support and lung transplantation. Eur Respir Rev. 2017; 26(146): 170089, doi: 10.1183/16000617.0089-2017, indexed in Pubmed: 29263172.
37. Benza R, Biederman R, Murali S, et al. Role of cardiac magnetic resonance imaging in the management of patients with pulmonary arterial hypertension. J Am Coll Cardiol. 2008; 52(21): 1683–1692, doi: 10.1016/j.jacc.2008.08.033, indexed in Pubmed: 19007687.
38. Rogula SP, Mutwil HM, Gąsecka A, et al. Antiplatelet effects of prostacyclin analogues: Which one to choose in case of thrombosis or bleeding? Cardiol J. 2021; 28(6): 954–961, doi: 10.5603/CJ.a2020.0164, indexed in Pubmed: 33200814.
39. Menon AA, Sahay S, Braverman LE, et al. Thyroid dysfunction in patients with pulmonary artery hypertension (PAH): the effect of therapies affecting the prostanoid pathway. Lung. 2019; 197(6): 761–768, doi: 10.1007/s00408-019-00283-8, indexed in Pubmed: 31696306.
40. Kopeć G, Waligóra M, Stępniewski J, et al. Indwelling central venous catheter occlusion during chronic epoprostenol infusion. J Heart Lung Transplant. 2018; 37(7): 938–940, doi: 10.1016/j.healun.2018.03.018, indexed in Pubmed: 29731239.
41. Kurzyna M, Małaczyńska-Rajpold K, Koteja A, et al. An implantable pump Lenus pro® in the treatment of pulmonary arterial hypertension with intravenous treprostinil. BMC Pulm Med. 2017; 17(1): 162, doi: 10.1186/s12890-017-0474-7, indexed in Pubmed: 29195500.
42. McLaughlin VV, Hoeper MM, Channick RN, et al. Pulmonary arterial hypertension-related morbidity is prognostic for mortality. J Am Coll Cardiol. 2018; 71(7): 752–763, doi: 10.1016/j.jacc.2017.12.010, indexed in Pubmed: 29447737.
43. Kurzyna M, Zyłkowska J, Fijałkowska A, et al. Characteristics and prognosis of patients with decompensated right ventricular failure during the course of pulmonary hypertension. Kardiol Pol. 2008; 66(10): 1033–1041, indexed in Pubmed: 19006024.
44. Luong ML, Morrissey O, Husain S. Assessment of infection risks prior to lung transplantation. Curr Opin Infect Dis. 2010; 23(6): 578–583, doi: 10.1097/QCO.0b013e32833f9f93, indexed in Pubmed: 20847696.
45. Quatredeniers M, Montani D, Cohen-Solal A, et al. Iron deficiency in pulmonary arterial hypertension: perspectives. Pulm Circ. 2021; 11(3): 20458940211021301, doi: 10.1177/20458940211021301, indexed in Pubmed: 34178305.
46. Grünig E, Eichstaedt C, Barberà JA, et al. ERS statement on exercise training and rehabilitation in patients with severe chronic pulmonary hypertension. Eur Respir J. 2019; 53(2), doi: 10.1183/13993003.00332-2018, indexed in Pubmed: 30578391.
47. National Center for Immunization and Respiratory Diseases. General recommendations on immunization — recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2011; 60(2): 1–64, indexed in Pubmed: 21293327.
48. Sobański PZ, Brzezińska Rajszys G, Grodzicki T, et al. Palliative care for people living with cardiac disease. Kardiol Pol. 2020; 78(4): 364–373, doi: 10.33963/KP.15276, indexed in Pubmed: 32336071.
49. Kurzyna M, Dabrowski M, Bielecki D, et al. Atrial septostomy in treatment of end-stage right heart failure in patients with pulmonary hypertension. Chest. 2007; 131(4): 977–983, doi: 10.1378/chest.06-1227, indexed in Pubmed: 17426198.
50. Janus M, Sławek-Szmyt S, Araszkiewicz A, et al. Atrial flow regulator as a bridge to lung transplant in a young patient with drug-resistant idiopathic pulmonary arterial hypertension. Kardiol Pol. 2020; 78(5): 461–462, doi: 10.33963/KP.15178, indexed in Pubmed: 32024808.
51. Salna M, van Boxtel B, Rosenzweig EB, et al. Modified potts shunt in an adult with idiopathic pulmonary arterial hypertension. Ann Am Thorac Soc. 2017; 14(4): 607–609, doi: 10.1513/AnnalsATS.201701-057LE, indexed in Pubmed: 28362533.
52. Gąsecka A, Banaszkiewicz M, Nieuwland R, et al. Prostacyclin analogues inhibit platelet reactivity, extracellular vesicle release and thrombus formation in patients with pulmonary arterial hypertension. J Clin Med. 2021; 10(5): 1024, doi: 10.3390/jcm10051024, indexed in Pubmed: 33801460.
53. Olasińska-Wiśniewska A, Mularek-Kubzdela T, Araszkiewicz A, et al. The man from the kingdom of the near-dead - modern treatment of pulmonary hypertension [article in Polish]. Kardiol Pol. 2011; 69(11): 1171–1173, indexed in Pubmed: 22090231.
54. Małaczyńska-Rajpold K, Komosa A, Błaszyk K, et al. The management of supraventricular tachyarrhythmias in patients with pulmonary arte-

rial hypertension. Heart Lung Circ. 2016; 25(5): 442–450, doi: 10.1016/j.hlc.2015.10.008, indexed in Pubmed: 26643289.
55. Gorbachevsky SV, Shmalts AA, Dadabaev GM, et al. Outcomes of atrioseptostomy with stenting in patients with pulmonary arterial hypertension from a large single-institution cohort. Diagnostics (Basel). 2020; 10(9): 725, doi: 10.3390/diagnostics10090725, indexed in Pubmed: 32967148.
56. Sandoval J. The long and winding road of atrial septostomy. Diagnostics (Basel). 2020; 10(11): 971, doi: 10.3390/diagnostics10110971, indexed in Pubmed: 33227906.
57. Baruteau AE, Serraf A, Lévy M, et al. Potts shunt in children with idiopathic pulmonary arterial hypertension: long-term results. Ann Thorac Surg. 2012; 94(3): 817–824, doi: 10.1016/j.athoracsur.2012.03.099, indexed in Pubmed: 22704329.
58. Aggarwal M, Grady RM, Choudhry S, et al. Potts shunt improves right ventricular function and coupling with pulmonary circulation in children with suprasystemic pulmonary arterial hypertension. Circ Cardiovasc Imaging. 2018; 11(12): e007964, doi: 10.1161/CIRCIMAGING.118.007964, indexed in Pubmed: 30558504.
59. Stącel T, Urlik M, Antończyk R, et al. Extracorporeal membrane oxygenation as a bridge to lung transplantation: first Polish experience. Transplantation Proc. 2020; 52(7): 2110–2112, doi: 10.1016/j.transproceed.2020.02.114, indexed in Pubmed: 32241635.
60. Stącel T, Latos M, Urlik M, et al. Interventional and surgical treatments for pulmonary arterial hypertension. J Clin Med. 2021; 10(15): 3326, doi: 10.3390/jcm10153326, indexed in Pubmed: 34362109.
61. Hoeper MM, Galiè N. Letter by Hoeper and Galiè regarding article, "Hemodynamic, functional, and clinical responses to pulmonary artery denervation in patients with pulmonary arterial hypertension of different causes: phase II results from the pulmonary artery denervation-1 study". Circ Cardiovasc Interv. 2016; 9(1): e003422, doi: 10.1161/CIRCINTERVENTIONS.115.003422, indexed in Pubmed: 26755573.
62. Hwalek A, Rosenheck JP, Whitson BA. Lung transplantation for pulmonary hypertension. J Thorac Dis. 2021; 13(11): 6708–6716, doi: 10.21037/jtd-2021-20, indexed in Pubmed: 34992846.
63. Treatment of Pulmonary Arterial Hypertension Using the Aria CV Pulmonary Hypertension System (ASPIRE PH). https://clinicaltrials.gov/ct2/show/NCT04555161 (July 20, 2021).
64. Right Ventricular Pacing in Pulmonary Arterial Hypertension. https://clinicaltrials.gov/ct2/show/NCT04194632.
65. Bedair B, Hachem RR. Management of chronic rejection after lung transplantation. J Thorac Dis. 2021; 13(11): 6645–6653, doi: 10.21037/jtd-2021-19, indexed in Pubmed: 34992842.
66. Yoshiyasu N, Sato M. Chronic lung allograft dysfunction post-lung transplantation: The era of bronchiolitis obliterans syndrome and restrictive allograft syndrome. World J Transplant. 2020; 10(5): 104–116, doi: 10.5500/wjt.v10.i5.104, indexed in Pubmed: 32864356.
67. Kim SY, Jeong SuJ, Lee JG, et al. Critical care after lung transplantation. Acute Crit Care. 2018; 33(4): 206–215, doi: 10.4266/acc.2018.00360, indexed in Pubmed: 31723887.
68. Potestio C, Jordan D, Kachulis B. Acute postoperative management after lung transplantation. Best Pract Res Clin Anaesthesiol. 2017; 31(2): 273–284, doi: 10.1016/j.bpa.2017.07.004, indexed in Pubmed: 29110799.
69. Verleden SE, Gottlieb J, Dubbeldam A, et al. "White-Out" after lung transplantation: a multicenter cohort description of late acute graft failure. Am J Transplant. 2017; 17(7): 1905–1911, doi: 10.1111/ajt.14268, indexed in Pubmed: 28296181.
70. Costa J, Benvenuto LJ, Sonett JR. Long-term outcomes and management of lung transplant recipients. Best Pract Res Clin Anaesthesiol. 2017; 31(2): 285–297, doi: 10.1016/j.bpa.2017.05.006, indexed in Pubmed: 29110800.
71. January SE, Fester KA, Bain KB, et al. Rabbit antithymocyte globulin for the treatment of chronic lung allograft dysfunction. Clin Transplant. 2019; 33(10): e13708, doi: 10.1111/ctr.13708, indexed in Pubmed: 31494969.
72. Verleden SE, Todd JL, Sato M, et al. Impact of CLAD phenotype on survival after lung retransplantation: a multicenter study. Am J Transplant. 2015; 15(8): 2223–2230, doi: 10.1111/ajt.13281, indexed in Pubmed: 25940517.

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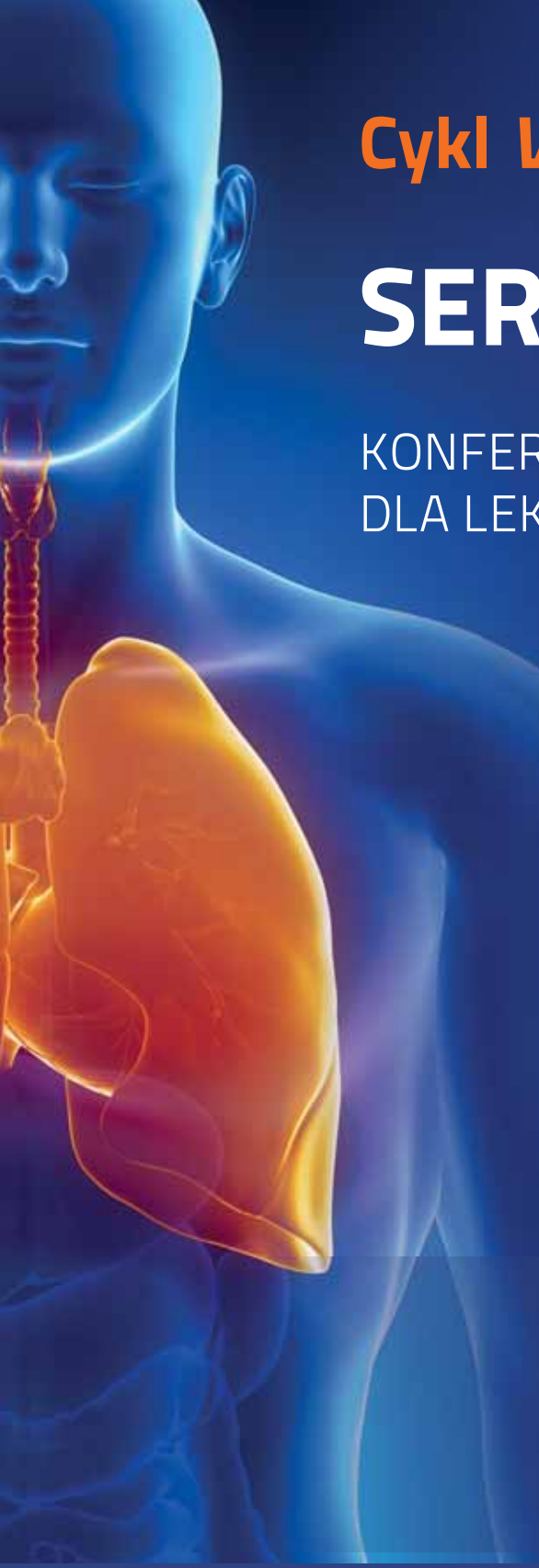

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- **19 listopada 2022,** sobota godz. 17:00–19:00
- **9 grudnia 2022,** piątek godz. 17:00–19:00
- **3 lutego 2023,** piątek godz. 17:00–19:00
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