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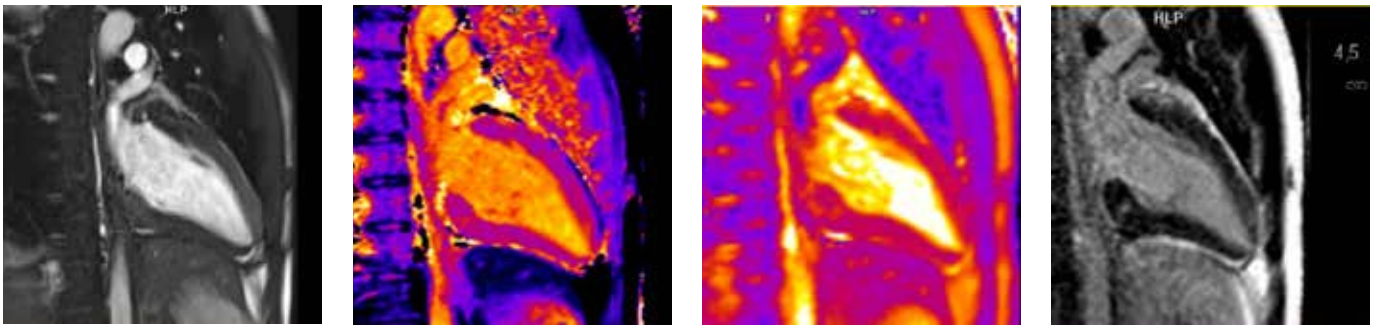

Post COVID-19 myocarditis on cardiac magnetic resonance in a 20-year-old man, p. 584

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Address
Kardiologia Polska
ul. Prądnicka 80, bud M–IX, p. 41
31–202 Kraków
phone: +48 126143004
e-mail: kardiologiapolska@ptkardio.pl
www.kardiologiapolska.pl

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

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KARDIOLOGIA POLSKA
Polish Heart Journal

Table of contents

SHORT COMMUNICATION

CLINICAL VIGNETTE

EXPERT OPINION AND POSITION PAPER

New publisher of *Kardiologia Polska*: what do we hope for in May 2021?

Anetta Undas[1, 2]

[1]Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland
[2]John Paul II Hospital, Kraków, Poland

Correspondence to:
Prof. Anetta Undas, MD, PhD, Institute of Cardiology, Jagiellonian University Medical College, Prądnicka 80, 31–202 Kraków, Poland, phone: +48 12 614 30 04, e-mail: mmundas@cyf-kr.edu.pl

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May 2021 marks the start with a new publishing house which leads to many changes for *Kardiologia Polska* (*Kardiol Pol*, *Polish Heart Journal)*. As announced in April 2021, *Kardiol Pol* is being published by Via Medica on behalf of the Polish Cardiac Society. Given a well-established position of Via Medica in the field of academic publishing, as reflected by nearly 50 regular medical journals in its portfolio, a new publisher opens new opportunities, although the beginning has been full of grave problems and technical challenges noticed by our readers and supporters who sent emails and made phone calls asking about the current status and expressing their concerns about the future of the journal. Again, I would like to apologize to all of you for problems with access to full texts of all articles for 10 days. All articles can be now read in PDF format.

Some visible changes have already been implemented by Via Medica. As you may have noticed from the look of the front cover and will see as you browse through this month's issue, the journal has a new appearance with an updated article type style, and a new layout.

From May 2021, all the articles from *Kardiol Pol* will be hosted on the publisher's website (*journals.viamedica.pl/kardiologia_polska*). All interested readers will be allowed to access the journal's full content free of charge, as previously, including Polish versions of the ESC guidelines published in Educational Issues of *Kardiol Pol*. We will do our best to publish peer-reviewed articles Online First within a few days ahead of the issue publication. At the time of Online First publication, the text of an article will be fully searchable and citable by its Digital Object Identifier (DOI), along with Publons, via the Editorial Manager to which most authors and reviewers got used to. The journal's website developed in the current version within a few days by Via Medica will be improved to provide a user-friendly and fully searchable homepage for the journal.

For the last two years, we have been working on reorganizing our Editorial Team to guarantee a fair and high-quality review process and a rapid editorial turnaround we have been known for in 2019 and 2020. We have decided to maintain the proofreading of the accepted papers and their uniform appearance. To increase visibility and boost the number of citations, we intend to carry on the initiatives implemented in previous years, including rapid publication upon acceptance (within 2–3 months) and swift production process, copyrights with the authors, responsive editorial service, preparation in various formats (HTML, PDF) for online publication, and social media activity.

Our team has the ambition to build on this success and make *Kardiol Pol* one of the top forums for publication of new scientific observations in the field of cardiology at an international level. The editorial team, in cooperation with authors and the new publisher, will strive to continue to produce the highest quality content in the best possible forms and in the shortest possible editorial time. We also hope that the new publisher will provide interactive content to physicians, researchers and the medical community.

We look forward to this new era for *Kardiol Pol* and to productive interactions with Via Medica, our new partner in publishing, supporting our vision of the journal.

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Cost-effectiveness of different models of cardiac telerehabilitation

Martijn Scherrenberg[1, 2], Maarten Falter[1–3], Paul Dendale[1, 2]

[1]Heart Center Hasselt, Jessa Hospital, Hasselt, Belgium
[2]Mobile Health Unit, Faculty of Medicine and Life Sciences, Hasselt University, Hasselt, Belgium
[3]KU Leuven, Faculty of Medicine, Leuven, Belgium

Related article
by Niewada et al.,
see p. 510

Correspondence to:
Martijn Scherrenberg, MD, Heart Center Hasselt, Jessa Hospital, Stadsomvaart 11, 3500 Hasselt, Belgium, phone: 0032 11 33 70 89, e-mail: martijn.scherrenberg@jessazh.be

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Both European and American guidelines recommend cardiac rehabilitation (CR) as a priority in the secondary prevention and follow-up of both ischemic heart disease as heart failure [1, 2]. Despite the clear benefits of CR, the participation rates are disappointingly low across the globe [3]. Cardiac telerehabilitation and home-based CR are often considered as novel methods to increase adherence and participation. However, it is currently not proven that providing cardiac telerehabilitation can increase participation rates. On the other hand, it is well-established in multiple (small sample size) trials that telerehabilitation could be as effective as center-based CR with similar healthcare costs [4]. It is important to recognize that almost all previous studies used different models of cardiac telerehabilitation, and cost-effectiveness studies are rare.

Telerehabilitation models can have a hybrid approach where patients first start with center-based CR for several sessions and then start with a telerehabilitation program [5]. Other studies have examined the effectiveness of a combination of center-based CR and telerehabilitation [6]. The third approach is replacing center-based CR with telerehabilitation [7]. For all these telerehabilitation models, studies have shown that the results are non-inferior in comparison with standard care, but no study compared the different models [5–7]. The way of delivering cardiac telerehabilitation can have a significant impact on the effectiveness and especially on the costs [4]. Two methods of delivery can be distinguished synchronous and asynchronous. Synchronous cardiac telerehabilitation refers to real-time interaction between the patient and healthcare provider. This has the advantage of very close follow-up and better personalization. However, it is also associated with a higher workload for the healthcare professionals and therefore also higher costs, especially when providing individual synchronous cardiac telerehabilitation. This type of telerehabilitation is therefore probably best indicated in high-risk populations such as heart failure. In asynchronous telerehabilitation, there is no real-time interaction or follow-up between the patient and healthcare providers. Patients send their data to the hospital and are only monitored intermittently at fixed moments or if alerts occur. The advantage of asynchronous monitoring is that it is less labor-extensive and less costly providing the opportunity to follow-up large groups of patients simultaneously. However, most studies using this approach focused on stable low-risk patients.

The TELEREH-HF trial used a hybrid and synchronous telerehabilitation program for heart failure patients. The trial revealed a significant impact on quality of life but no impact on cardiovascular or overall mortality [5]. Niewada et al. [8] demonstrated that the TELEREH-HF approach was cost-effective in comparison with standard care in the Polish healthcare setting. It is important to note that most patients (88%) in the standard care group did not participate in any form of CR, it remains to be studied if the TELEREH-HF approach is cost-effective compared to center-based CR. However, it is encouraging to see that a very elaborated telerehabilitation approach in

high-risk patients is cost-effective in the Polish setting. This again highlights the enormous potential value of cardiac telerehabilitation as an alternative to center-based CR.

The different models of cardiac telerehabilitation have all demonstrated effectiveness and value as alternatives for center-based CR. In the future, it will be important to choose the right model for the right patients to further improve the cost-effectiveness of telerehabilitation interventions. A simple approach such as asynchronous telerehabilitation with only a few devices could be safe and cost-effective in low-risk patients, whereas a more complex approach with real-time exercise and electrocardiogram monitoring is needed to ensure safe remote exercise in high-risk patients. Further research is needed to create recommendations for risk assessment and level of supervision before cardiac telerehabilitation. Other factors will also play a role in the determination of the right model for an individual patient such as the preferences of the patient, the motivation level of the patients, the moments that patients want to exercise, or even the presence of kinesiophobia.

To conclude, evidence suggest that different models of cardiac telerehabilitation are effective and also cost-effective. In the future, it will be important to choose the right model of cardiac telerehabilitation for an individual patient from an economic and a safety perspective.

Article information

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Dobutamine stress echocardiography for low gradient aortic stenosis: current practice in Poland

Sahrai Saeed[1], Øyvind Bleie[1], John B Chambers[2]

[1]Department of Heart Disease, Haukeland University Hospital, Bergen, Norway
[2]Cardiothoracic Centre, Guy's and Saint Thomas' Hospital, London, United Kingdom

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Correspondence to:
Sahrai Saeed, MD, PhD, FESC, Department of Heart Disease, Haukeland University Hospital, Jonas Lies veg, 5021 Bergen, Norway, phone: +47 55 97 50 00, e-mail: sahrai_saeed@hotmail.com

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The differentiation of severe and less severe aortic stenosis (AS) can be challenging as there are often discrepancies between mean gradient and effective orifice area. Current guidelines [1] divide severe AS with calculated aortic valve area (AVA) <1.0 cm^2 into 4 flow-gradient subtypes (Figure 1).

Dobutamine stress echocardiography (DSE) is indicated for the subtype in which there is a mean pressure gradient (MPG) <40 mm Hg associated with left ventricular ejection fraction (LVEF) <50% [2]. The aim is to differentiate true severe from pseudosevere AS. The former is expected to benefit from aortic valve intervention but the latter should be treated medically.

In the current issue of *Polish Heart Journal* (*Kardiol Pol*), Płońska-Gościniak et al. presented results from a Polish multicenter registry (Pol-LAS-SE registry) evaluating how stress echocardiography was used to make management decisions in low gradient AS [3]. A total of 163 patients (52% males) with low gradient AS underwent stress echocardiography at 16 cardiology centers using dobutamine in 157 and exercise in 6 patients.

The registry study provides interesting information on the current practice of using low dose DSE as part of diagnostic workup in low gradient AS. There are, however, some methodological constraints that limit the gen-

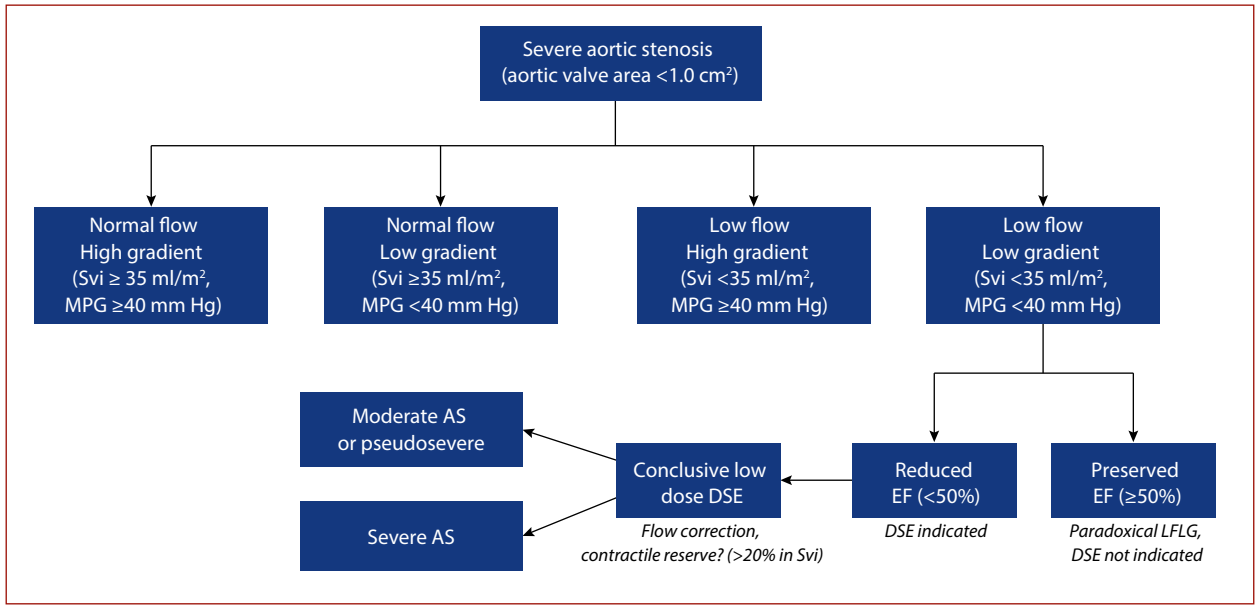

Figure 1. Flow-gradient subtypes of AS and indications for DSE.

Abbreviations: AS, aortic stenosis; DSE, dobutamine stress echocardiography; EF, ejection fraction; LFLG, low flow low gradient; MPG, mean pressure gradient; Svi, stroke volume index

eralizability of the study. First, the indications for stress echocardiography somehow diverged from international guidelines. DSE is indicated for low gradient AS with reduced LVEF while it is better to obtain a calcium score on computed tomography when the LVEF is normal. This is because when the left ventricular (LV) cavity is normal or small, dobutamine often causes severe subaortic flow acceleration which is potentially dangerous and also makes it impossible to interpret the study. Calcium scoring could also have been performed for the 14 patients with non-diagnostic stress results as a result of the absent contractile reserve.

A second problem is that an AVA <1.0 cm^2 was an inclusion criterion, however, there were patients included with a baseline AVA >1.0 cm^2. The discussion refers also to patients with 'trivial stenosis'. In some of them, there was a thickened valve but uncertainty about the grade of AS because of low flow. In others, there was mild aortic valve thickening and the indication for the study was to check whether the valve should be replaced at the same time as coronary artery bypass grafting. There is no randomized controlled trial or other published evidence for using DSE to decide this question. If the decision is made on gradients obtained on mean dobutamine doses of 20 µg/kg/min, it is possible that the gradients through a replacement aortic valve were higher than before surgery.

The purpose of DSE is to assess LV contractile reserve and to differentiate true severe from 'pseudosevere' or moderate AS. Usually, it is easy to differentiate moderate from severe AS provided there is an adequate contractile reserve or overall flow normalization is achieved (stroke volume index ≥35 ml/m^2). The authors considered AS severe if there was >20% increase in LV stroke volume, and any increase in LVEF during stress echocardiography and if the MPG was ≥40 mm Hg and AVA remained ≤1.0 cm^2, which is straightforward. Moderate AS was defined as an AVA between 1.0 cm^2 and 1.5 cm^2 and MPG <40 mm Hg during DSE, however, with no reflection on the LVEF, the presence of contractile reserve or overall flow normalization. Pseudosevere AS was defined as an increase in LV stroke volume of >20% with an increase in ejection fraction associated with an MPG <40 mm Hg and AVA >1.0 cm^2. This definition of pseudosevere AS is consistent with moderate AS so the reason for the separate categories is not clear. Of note, current American and European guidance for the echocardiographic assessment of AS also stresses the fundamental division of AS severity by DSE (true severe vs pseudosevere/moderate) and does not describe pseudosevere as a third separate group in addition to moderate and severe [4].

A further problem is that there is no independent standard or follow-up outcome measures to determine whether stress echocardiography resulted in the best management decision. There is also no information comparing outcomes of patients having stress echocardiography with those who did not.

Overall, the study shows that DSE in AS is safe and feasible. The authors are to be congratulated on their careful recording of data. It is important to examine clinical practice. Their retrospective and descriptive results suggest the need to collect prospective data including outcome measures to prove the benefit of stress testing in AS.

Article information

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REVIEW ARTICLE

Non-cardiovascular comorbidities in heart failure patients and their impact on prognosis

Michele Correale[1], Stefania Paolillo[2, 3], Valentina Mercurio[4], Gaetano Ruocco[5], Carlo G Tocchetti[6, 7], Alberto Palazzuoli[8]

[1]Department of Cardiology, University Hospital Foggia, Foggia, Italy
[2]Department of Advanced Biomedical Sciences, Federico II University of Naples, Naples, Italy
[3]Mediterranea Cardiocentro, Naples, Italy
[4]Department of Translational Medical Sciences, Federico II University, Naples, Italy
[5]UOC Cardiologia, Ospedali Riuniti della Valdichiana, Azienda USL Sud Est Toscana, Montepulciano, Siena, Italy
[6]Department of Translational Medical Sciences, Interdepartmental Center for Clinical and Translational Research (CIRCET), Napoli, Italy
[7]Interdepartmental Hypertension Research Center (CIRIAPA), Federico II University, Naples, Italy
[8]Cardiovascular Diseases Unit Department of Internal Medicine, University of Siena, Siena, Italy

Correspondence to:
Michele Correale, MD, PhD,
Viale Pinto 1,
71122 Foggia, Italy,
phone: +39 328 2918518
e-mail: opsfco@tin.it

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ABSTRACT

With the aging of the population and improvement of life expectancy of patients with heart disease, there is an increase in non-cardiovascular (CV) comorbidities affecting chronic heart failure (HF) patients. The increased prevalence of different CV and non-CV comorbidities is a rising problem in the management of patients with HF, mostly because these comorbidities may lead to poor prognosis, increase of hospitalizations and mortality rate. Recently, important data from multicenter randomized studies point to diabetes mellitus or iron deficiency as new pharmacological targets, and this highlights the need of broad expertise for the 21st-century cardiologist. The management of HF should take into account non-CV comorbidities. In this review, we discuss novel aspects of non-CV comorbidities in HF patients and emphasize the impact on prognosis.

Key words: heart failure, chronic obstructive pulmonary disease, cardio-oncology, chronic kidney disease, diabetes

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INTRODUCTION

In industrialized countries, the prevalence of chronic heart failure (CHF) is estimated to be 1%–3% of the population, exceeding 30% in people over 85 years [1]. The increased prevalence of the different comorbidities leads to problems in the management of HF patients, mostly because these comorbidities may lead to poor prognosis, increased hospitalization and mortality rate. The correct management of comorbidities may be one of the strategies that reduce hospitalizations and death in this condition [2].

In heart failure (HF) patients, regardless of ejection fraction (EF), comorbidities can be divided into cardiovascular (CV) and non-CV.

Previous studies on outpatients with CHF showed that the highest prevalence among the non-CV comorbidities refers to iron deficiency (prevalence of 53%–65%), renal failure (prevalence of up to 55%), anemia (prevalence of up to 37%), diabetes mellitus (prevalence of between 23% and 47%), depression (prevalence of up to 61%), and chronic lung disease (prevalence of up to 63%) [1, 3, 4].

With the aging of the population, there is an increase in non-CV comorbidities affecting CHF patients [5]. In elderly patients with HF, the coexistence of non-CV comorbidities can exacerbate symptoms and signs of HF. This can hinder the diagnosis of HF and delay the prescription of appropriate therapies.

Among non-CV comorbidities, chronic obstructive pulmonary disease (COPD), diabetes mellitus, anemia, and obesity are more prevalent in HF with preserved ejection fraction (HFpEF) patients [6]. This underlines the possible role of non-CV comorbidities in the progression of HF in HFpEF and the importance of managing these comorbidities in HFpEF in order to slow HF progression and reduce rehospitalization rate and mortality.

Non-CV comorbidities are independent prognostic factors in HF populations regardless of EF and HF etiology

(ischemic vs. non-ischemic). Furthermore, the evaluation of the severity of these non-CV comorbidities could significantly worsen the prognosis in non-selected HF populations [7].

Among non-CV comorbidities, chronic renal failure, anemia and diabetes are the comorbidities most frequently associated with hospitalizations [8, 9].

In this review, we report an update on the non-CV comorbidities in patients with HF emphasizing the impact on the prognosis of HF patients.

METHODS

A focused literature search was performed on PubMed until November 2020, in order to identify relevant original research and review articles by using the following key words, alone or in combination: heart failure, chronic obstructive pulmonary disease, cancer, chronic kidney disease, obstructive and central sleep apnea, diabetes, hypothyroidism and hyperthyroidism, hyperuricemia, vitamin D deficiency, anabolic hormones, iron deficiency, depression, cognitive impairment. Only articles in English were selected for this review, focusing on the most consistent, recent, and relevant trials and original papers, preferentially involving humans. Titles and abstracts from these searches were reviewed, full-text articles were obtained for relevant manuscripts, and reference lists were reviewed to identify additional manuscripts appropriate for the review.

CANCER AND HEART FAILURE

In the last few years, along with population aging, an important increase in the prevalence of cancer and HF has been reported [10]. Patients affected by HF show an increased risk of cancer (patients affected by HF carry a 68% higher risk of cancer diagnosis) and their prognosis is worse compared with cancer patients without HF [11]. Both these conditions may affect quality of life and, above all, prognosis. To date, most of the attention has been focused on the investigation of potential CV side effects of different antineoplastic regimens, including chemo-, radio- or immuno--therapy that may lead to the development of HF [12]. Indeed, antineoplastic drugs might induce left ventricular (LV) systolic dysfunction (as a reduction of left ventricular ejection fraction [LVEF] by more than 10 percentage points or a reduction under 50%) in up to 50% of patients [13]. However, besides chemotherapy-induced cardiotoxicity, we have to take into account other possible bidirectional interactions between HF and neoplastic diseases.

Recently, some authors speculated that HF per se may be a risk factor for developing tumors [14]. For example, recently diagnosed cancer patients may already have a history of LV dysfunction or HF, and this overlap of pathologies could make treatment of cancer patients and HF patients difficult. Patients affected by HF have a higher incidence of cancer compared to the general population [15]. Also, patients affected by HF and cancer have a poorer prognosis [16]. Even though the same risk factors (such as hypertension, obesity, diabetes and tobacco smoking) may be found in HF and in cancer patients; this similarity only in part can justify the close association between these conditions, such as hypertension, obesity, diabetes, and tobacco smoking [17]. In the last few years, some common molecular and pathophysiological mechanisms have been demonstrated among cancer patients and HF.

SLEEP-DISORDERED BREATHING

Sleep-related breathing (SBD) disorders are often present in patients affected by the high prevalence of SDB (47%–81%) [18] in HF with reduced ejection fraction (HFrEF) patients (obstructive sleep apnea [OSA] 29% and central sleep apnea [CSA] 31%) and in HFpEF (40% had OSA and 29% CSA) and are associated with poor prognosis. In particular, the *apnea*–hypopnea index (AHI; i.e., the number of apneas and hypopneas per hour of recording) is a powerful independent predictor of adverse outcome in clinically stable CHF [19]. OSA and CSA are related to the increased readmission in CHF [20, 21]. An increased risk of death was observed in patients affected by HFrEF with untreated OSA, independently of confounding factors [22].

Cheyne stokes respiration (CSR) is an abnormal pattern of breathing characterized by numerous central apneas alternating with hyperventilation. It is associated with a poor prognosis in patients with HF. Recently, in HFrEF patients, optimization of HF therapy with sacubitril/valsartan has affected phenotypic traits of CSR indicating improvements of hemodynamic parameters and chemosensitivity [23].

In HFrEF patients with predominantly CSA, enrolled in the SERVE-HF (Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo-Ventilation in Patients with Heart Failure) trial [24], CV and all-cause mortality were more present in the auto-servo--ventilation subgroup [25]. Following these results in the last European Society of Cardiology (ESC) HF guidelines [1], adaptive servo-ventilation (ASV) is not recommended in HFrEF (Class of recommendation: III and Level of evidence: B). Results by a SERVE-HF substudy analysis showed that patients with HFrEF and CSA who experienced serious adverse events had longer CSR cycle length.

In hospitalized HF patients with moderate-to-severe sleep apnea, adding ASV to optimal medical therapy did not improve cardiovascular prognosis [26]. These results need further confirmatory data from ongoing studies. Among these ongoing studies, the retrospective FACE study was designed to evaluate the possible effect of adding ASV to standard care on morbidity and mortality in patients with different forms of HF distinguished according to the value of EF (HFpEF, mid-range, or HFrEF) who have SDB with an indication for ASV [27].

Phrenic nerve stimulation may be a promising treatment [28]. In our opinion, all HF patients should be screened for SDB.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease, a chronic inflammatory lung disease characterized by airflow limitation, is among the most common comorbidities in HF. The prevalence is similar within HFrEF and HFpEF (16% vs 14%) and ranges from 9% to 41% in European cohorts [29].

On the other hand, the prevalence of HF in COPD patients is high (from 20% to 70%) and often it is under-diagnosed and under-treated, with obvious prognostic implications [30]. COPD patients have a higher rate of hospitalization and death, coronary heart disease, stroke and CHF have been reported [31] as the most frequent causes.

Heart failure patients with COPD were older and presented with more comorbidities and lower exercise capacity [32]. The coexistence of COPD with HF is related to increased morbidity and mortality risk in both CHF [33] and acute HF (AHF) [34].

Issues regarding potential bronchoconstriction are the main reasons for the underutilization of β-blockers in these patients particularly after hospitalization for AHF or decompensation of HF [35]. HF guidelines stated that COPD "is not a contra-indication" to β-blocker therapy [1]. The benefits of the cardio-selective β-blockers in HF overcome any potential risk derived from the β-blocker use also in the case of patients with severe COPD [36].

Lung hyperinflation may play a pivotal role regarding cardiac chamber dimensions and cardiac dysfunction in patients affected by COPD. Hyperinflation (inspiratory capacity-to-total lung capacity ratio [IC/TLC], functional residual capacity, and residual volume) demonstrated stronger relation to cardiac dimensions than airway obstruction or diffusion capacity. IC/TLC correlated better with cardiac dimensions and was an independent predictor of cardiac dimensions [37]. The cardiac chambers dimensions decreased with increasing GOLD (Global Initiative for Obstructive Lung Disease) stage. There is an ongoing debate with conflicting results for the CV safety of drugs for COPD. Inhaled therapy with bronchodilators is the cornerstone of the COPD therapy. Bronchodilators include the long-acting β_2-agonists (LABA), long-acting muscarinic antagonist (LAMA), or a combination of LABA-LAMA. Bronchodilators reduce hyperinflation and improve breathlessness and cardiac output. Bronchodilators may prevent acute exacerbations of COPD, thus reducing the risk of CV events. Tiotropium, a LAMA, improves hyperinflation, CV responses to exercise in COPD patients [38], LV diastolic function in COPD patients [39] and it has been associated with decreased mortality (CV and no-CV) [40]. LV and right ventricular end-diastolic volume increase and LV and right ventricular stroke volume increase have been reported as effects of LABA-LAMA in COPD [41].

Lung-deflating medications (fluticasone furoate/vilanterol [ICS-LABA]) were proven to increase LV, right ventricle, and left atrium volumes [42]. Stone et al. [43] showed that right ventricular function remained unchanged.

Fluticasone/vilanterol/umeclidinium (ICS-LABA-LAMA) reduce all-cause mortality with lower rates of CV deaths [44]. Roflumilast, administered orally, indicated for frequent exacerbations of COPD, was related to the lower rate of CV events [45].

In our opinion, all HF patients should be screened for COPD, performing spirometry, a simple, cost-effective, non-invasive exam. Advances in COPD treatment could lead to a reduction of the readmissions in HF.

GLUCOSE METABOLISM DISORDERS

Diabetes mellitus (DM) is commonly reported in patients affected by HF and a strict bidirectional interaction exists between these two conditions. DM has a prevalence in HF that varies from 10% to 30% in outpatients and rises up to 40% in hospitalized patients with HF [46]. A state of insulin resistance, even in absence of overt DM, is frequently reported in HF, with a prevalence of about 70% [47]. On the other hand, LV dysfunction is a common finding in diabetic patients. Patients with DM are 2–5 times more likely to develop HF compared to the general population. In the Framingham Heart Study [48], HF was twice more common in men and 5 times more common in women with DM aged 45–74 years compared with similar non-diabetic controls. Older age, longer duration of DM, insulin therapy, and lower body mass index were identified as independent risk factors for the development of HF in DM patients.

In particular, diabetic patients may present with two different types of heart dysfunction. The first is a typical myocardial dysfunction secondary to coronary artery disease. The second is diabetic cardiomyopathy, a typical complication of DM, characterized by cardiac dysfunction that can be easily and simply assessed by echocardiography, and was reported for the first time in 1972 by Rubler et al. [49], describing post-mortem data of diabetic patients. In the last ESC Position Statement on the management of DM and HF [49], diabetic cardiomyopathy was defined as cardiac dysfunction occurring in diabetic patients in absence of coronary artery disease, relevant valvular heart disease, uncontrolled hypertension, or congenital heart disease. Two stages can be distinguished in diabetic cardiomyopathy: an early stage characterized by LV concentric hypertrophy increased filling pressures, and diastolic dysfunction, and a late stage characterized by progression of diastolic dysfunction, and systolic impairment. However, Seferovic et al. [49] recently proposed two different phenotypes of diabetic cardiomyopathy (a restrictive/HFpEF phenotype and a dilated/HFrEF phenotype) rather than two stages that belong to the same disease.

The pathophysiology of diabetic cardiomyopathy is still not clear and many hypotheses have been proposed. The main mechanisms are endothelial and microvascular dysfunction, excessive neurohormonal response, change in cardiac metabolism, accompanied by mitochondrial dysfunction, dysfunctional endoplasmic reticulum, and impaired calcium handling, all probably contributing to the

manifestation of diabetic cardiomyopathy and representing in the next future potential new therapeutic targets.

With regards to the long-term prognostic impact of the coexistence of DM and HF, the ESC-HFA Registry [50] reported a higher cumulative incidence (all-cause death, CV death, and hospitalization for worsening HF) in HF outpatients with DM compared to non-diabetics even after adjustment for multiple risk factors. These data were confirmed by a recent meta-analysis including 381 725 patients with AHF and CHF [51]. The authors reported that the coexistence of DM and HF is related to a 30% increased risk of all-cause death, and a 35% increased risk of CV death and hospitalization during a 3-year follow-up. Looking at the parameters used in the multiparametric prognostic scores more frequently used in HF (Seattle Heart failure Model, MECKI score, HF-ACTION risk score) diabetes does not appear a determinant prognosticator. Moreover, in an analysis of the MECKI score database, that evaluated nearly 4000 HFrEF patients, a worse prognosis was demonstrated in diabetic patients with poor glycemic control (HbA_{1c} >8%), instead the presence of diabetic status and hypoglycemic drugs were not associated with prognosis after correction for various confounders [52]. Thus, probably, the population of diabetic patients cannot be considered as a unique entity, but it will be necessary to assess specific parameters, as glycemic control or drugs response, in order to appropriately evaluate every patient.

As for the treatment of HF in diabetic patients, the majority of the beneficial effects of HF treatments, reported in randomized controlled trials, are consistent with and without DM at baseline, thus the recommendations for the treatment of HF in the setting of DM are the same as in the general HF population.

Conversely, regarding the therapeutic approach to DM in HF patients, European guidelines [53] suggest the use of gliflozins as first choice, or as second choice in patients already taking metformin, starting from the excellent prognostic results of SGLT2-inhibitors in terms of prevention of HF-related events. Moreover, after the positive results in terms of CV protection derived by gliflozins, a busy trials schedule started to assess the benefit of gliflozins in patients affected by HF regardless of the presence of DM. The first study was the DAPA-HF trial [54], assessing the efficacy of dapagliflozin vs placebo in 4744 HFrEF patients on a primary composite outcome of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy) or CV death. In a follow-up of 18.2 months, and on top of HF therapy, the primary endpoint occurred in 386 (16.3%) dapagliflozin subjects and in 502 (21.2%) placebo patients with a relevant relative risk reduction of 26% and a number needed to treat of 21, and a 30% reduction of HF hospitalization with an 18% reduction in CV mortality. The recently published EMPEROR-Reduced [55] trial similarly assessed the effect of empagliflozin vs placebo in 3730 HFrEF subjects on a primary composite outcome of HF hospitalizations or CV death. During a follow-up of 16 months, in a sicker population, the trial reported an important reduction in the primary outcome (–25%) regardless of the presence or absence of diabetes, and confirmed a 30% reduction in HF hospitalizations, without a significant effect on CV death. International medical regulatory agencies approved the use of dapagliflozin for HFrEF patients regardless of the presence of DM. Thus gliflozins will be used as HF-specific drugs.

OTHER ENDOCRINE DISORDERS

Both HFpEF and HFrEF may coexist with other systemic conditions or even develop as possible consequences of such diseases. In particular, some endocrine disorders may have CV manifestations or may worsen a pre-existing HF.

Thyroid disease and HF

Besides their role in energetic homeostasis, thyroid hormones have a relevant impact on cardiac activity by acting on the cardiovascular system.

Hyperthyroidism, with excessive production of thyroid hormones leading to a hypermetabolic state and hemodynamic changes, is characterized by high cardiac output. HF with high cardiac output without heart disease could be secondary to the following factors: tachycardia, increased cardiac preload, decreased systemic vascular resistance, high ventricular filling pressure, raised pulmonary arterial pressure [56]. Furthermore, HF with low cardiac output in elderly patients with heart disease could be secondary to the following factors: increased cardiac preload, impaired LV filling, presence of atrial fibrillation, rapid ventricular rate, raised systemic vascular resistance, reduced contractile reserve.

Hypothyroidism is characterized by insufficient production of thyroid hormones. In this case, HF in patients with overt hypothyroidism or elderly patients with subclinical hypothyroidism could be secondary to the following factors: bradycardia, impairment of cardiac function (and systolic function and diastolic function), raised systemic vascular resistances, and arterial stiffness.

Both hyperthyroidism and hypothyroidism may affect patients with HFrEF. In particular, hyperthyroidism, especially in the acute setting, is a common trigger of exacerbation or acute decompensation of HF [57]. Although little is known on thyroid dysfunction in HFpEF, hypothyroidism is believed to be a negative prognostic factor in HFpEF [58].

Indeed, fT3, fT4, and TSH should be monitored every 6–12 months in patients affected by HF (every 3 months in patients treated with amiodarone). Hyperthyroidism and hypothyroidism are frequent complications of amiodarone use [59]. Two fundamental mechanisms are known as the cause of amiodarone-induced hyperthyroidism: increased synthesis of thyroid hormone due to iodide load (type 1), or destructive thyroiditis (type 2) [60]. Amiodarone-induced hypothyroidism is linked to the reduction in thyroid hormone secondary to intake of a large amount of iodine, and it is treated with T4.

Finally, euthyroid sick syndrome, known as "low-T3 syndrome" is another thyroid disorder often associated with HF. This condition is described by the presence of low T3 circulating levels. It was reported in patients with acute or chronic illness and can be induced by weight loss due to chronic caloric restriction. Patients with HF frequently present with low serum T3 levels, and this condition may negatively affect functional status and prognosis [61]. In particular, it is a strong predictor of death. The effect of T3 supplementation in HF patients with low T3 syndrome is not known.

Hyperuricemia

Hyperuricemia is a common metabolic alteration in both HFrEF and HFpEF and is both a comorbidity and a "biomarker". It could be secondary to the upregulation of the xanthine oxidase [62]. It is associated with a significant clinical impact on prognosis. Hyperuricemia independently predicted the risk of incident CHF events [63]. Hyperuricemia has a relevant association with poor outcomes in HF patients without chronic kidney disease (CKD) but not in those with CKD [64].

Despite concerns over febuxostat safety, the CARES [65] and FAST [66] trials showed its non-inferiority vs allopurinol regarding CV events and its use in patients with gout and at least one additional CV risk factor is not related to an increased risk of death compared with allopurinol.

The possible beneficial effects of xanthine oxidase inhibitors (allopurinol or febuxostat) on clinical outcome in HF are still unclear. Allopurinol did not improve the clinical status, exercise capacity, quality of life, or LVEF at 24 weeks in patients affected by HFrEF with elevated uric acid levels [67]. Instead, whether febuxostat compared to conventional treatment improves the clinical outcomes in CHF with hyperuricemia is being investigated by the LEAF-CHF trial [68].

Vitamin D deficiency

As demonstrated by cross-sectional and case-control studies, both vitamin D deficiency and increase in parathyroid hormone are related to increased prevalence of HF [69]. Furthermore, vitamin D deficiency can influence the onset and/or progression of HF and LV dysfunction. Indeed, vitamin D deficiency is related to more adverse prognosis in HF patients [70]. Until today there is no evidence for the impact of vitamin D supplementation on outcome improvement in HF patients [71, 72].

Anabolic hormones

Acromegalia is a disease characterized by increased and disproportionate production of growth hormone (GH) and, consequently, insulin-like growth factor-1 (IGF-1) and caused mostly by a GH-secreting pituitary adenoma [73]. It is frequently associated with CV manifestations including arterial hypertension, and congestive HF may represent a late manifestation of a typical cardiomyopathy characterized by biventricular hypertrophy, mainly involving the LV [74].

Some case reports bring evidence on the association between dilated cardiomyopathy and acromegalia [75]. On the other hand, a reduction of anabolic hormones, including GH and IGF-1, is common in chronic HFrEF and HFpEF and it is related to impaired functional capacity and clinical outcome [76]. Whether treatment of GH deficit could improve clinical outcome is still a matter of debate [77].

CHRONIC KIDNEY DISEASE

The heart and kidneys are strictly related. The dysfunction of one of these organs leads to poor prognosis through diverse mechanisms such as inflammation, oxidative stress, impaired hydro-saline homeostasis and diuretic resistance [78]. Renal dysfunction (RD) prevalence in HF ranges from 30% to 50% of patients [79]. However, the clinical scenario of RD in AHF and CHF should be highlighted. In the acute setting, both CKD and acute RD should be observed. CKD (defined as estimated glomerular filtration rate [GFR] <60 ml/min/m^2) in AHF represents a detrimental condition, related to poor prognosis [80]. Congestion is the essential hemodynamic determinant of renal function in HF [80–82]. Acute renal dysfunction in AHF recognizes different definitions according to cardiologists' and nephrologists' points of view. Indeed, Acute Kidney Injury Network criteria defined acute renal impairment as acute kidney injury according to the proportional increase in serum creatinine together with urine output reduction. Conversely, cardiologists defined renal deterioration as worsening renal function (WRF) considering serum creatinine increase ≥0.3 mg/dl or eGFR increase ≥20% or 25% with respect to baseline levels [83]. The differences regarding these definitions do not help physicians in renal impairment detection and management. The latest findings from HF studies suggest evaluating WRF in a specific clinical setting. For example, WRF due to aggressive diuretic therapy with effective decongestion seems to be related to a better prognosis than renal function in-hospital improvement with clinical congestion persistence. Due to these different conditions, WRF was classified as "true" and "pseudo" according to clinical deterioration and improvement, respectively [83]. The pathophysiological view of acute RD in AHF consists of two main mechanisms: hemodynamic derangement and neuro-hormonal overdrive. Reduced renal blood flow due to systolic and/or diastolic dysfunction and concomitant renal venous congestion represent the main actors of hemodynamic impairment. Reduced renal perfusion due to hemodynamic derangement contributes to increased sympathetic activity, renin–angiotensin–aldosterone system activation, and arginine–vasopressin release. These mechanisms contribute to aggravate the clinical status and prognosis of HF patients through vasoconstriction and water retention [79]. It appears mandatory to insert renal function evaluation in the clinical setting of HF patients, because of the benefits induced by decongestive thera-

pies. Conversely, patients with pre-existing CKD or chronic congestion develop "true" WRF with a worse outcome despite decongestive therapies [79].

Both CKD and sudden RD should be monitored in CHF patients. The decrease in cardiac output and thus renal blood flow is the main pathophysiological mechanisms involved. This condition is not sustained by the kidneys due to HF medication. Moreover, subclinical congestion, due to water and sodium retention leads to worse clinical condition and renal function [79]. All these alterations of the cardio-renal axis in a chronic setting contribute to worse the prognosis causing frequent hospitalization and mortality.

In conclusion, both CKD and WRF in acute and CHF are related to poor prognosis [84]. A specific approach should be considered due to the different clinical meanings of RD in different clinical settings of HF patients.

IRON DEFICIENCY IN HEART FAILURE

Anemia is a very common comorbidity in subjects affected by HFrEF and HFpEF [4]. It is justified in HF patients by nutritional deficiencies, loss of blood through the gastrointestinal system, reduced iron absorption, and reduced release of stored iron. It is an independent predictor of recurrent hospitalizations and it may negatively affect reduced exercise capacity and the quality of life. After the RED-HF trial [85] results (increasing hemoglobin to 12–13 g/dl with erythropoietin does not improve outcomes in HF patients with anemia) the focus has been shifted to the role of iron deficiency.

Iron deficiency (ID), frequent in patients with HF, is characterized by insufficient iron stores to meet the body requirements. There are different forms of ID: absolute and functional ID, both with or without anemia. In absolute ID, ferritin levels are <100 µg/ml. In functional ID, typical in chronic inflammatory diseases and CKD, ferritin is normal with a transferrin saturation <20%. This condition may increase hemodynamic instability, re-hospitalization, and mortality rates in patients with HF [86].

The results of the IRON-HF [87] and IRONOUT-HF [88] trials have demonstrated that oral iron supplementation is unsuccessful.

Ferric carboxymaltose (FCM) intravenous (IV) treatment seems to improve both ID and symptoms in HF patients. The FAIR-HF trial results demonstrated an improvement of functional class and a decreased impairment of renal function after 24 weeks of treatment with FCM [89]. The CONFIRM-HF trial [90] showed an exercise capacity improvement and a relevant decrease in the hospitalization rate after 12 months of FCM therapy in HF patients with ID and normal hemoglobin levels. Recently, Ponikowski et al. [91] demonstrated that FCM therapy was safe and able to decrease the risk of HF hospitalizations, without apparent effect on the risk of cardiovascular death, in stabilized patients after AHF with ID and LVEF <50%. Data from a substudy of the Myocardial-IRON trial [92] in patients with HFrEF with ID, showed FCM was related to short-term improvement in LVEF and right ventricular ejection fraction.

According to the latest ESC HF guidelines recommendations [1], all newly diagnosed HF patients should be routinely tested for ID and FCM IV the administration should be considered in HF patients (if serum ferritin <100 µg/l, or if ferritin between 100 and 299 µg/l and transferrin saturation <20%) in order to improve HF symptoms, and increase exercise capacity and the quality of life (Class recommendations: IIa, Level of evidence: A).

The ongoing FAIR-HF 2 trial (ClinicalTrials.gov Identifier: NCT03036462) was designed in order to further evaluate the possible benefit of IV iron in HF patients with ID. The IRON-CRT trial [93] will determine the effect of FCM on cardiac reverse remodeling and cardiac contractility in HFrEF patients. Furthermore, an ongoing FAIR-HFpEF trial (ClinicalTrials.gov Identifier: NCT03074591) will verify any benefits of IV iron in relation to survival in HFpEF patients. These results may suggest that ID could be a new therapeutic target for HF therapy.

DEPRESSION

Depression (also called major depressive disorder) is a mental disorder characterized by a persistent feeling of sadness and loss of interest. It may lead to different emotional problems. It is a common comorbidity in HF, above all in CHF and advanced HF. The prevalence rates are similar in studies of HFrEF and HFpEF (24% vs 25%) [94]. Depression is associated with poor prognosis (and all-cause mortality and rehospitalization) in both HFrEF and HFpEF [95]. Pharmacological therapy for depression in HF has not affected the prognosis [96]. Tricyclic antidepressants should be avoided because they might lead to significant hypotension, arrhythmias, and decompensation of HF [1]. The association between antidepressants and HF prognoses remains controversial. Recently, a meta-analysis demonstrated that patients with HF and depression taking antidepressants had increased risks of all-cause death and CV death. Compared with nonusers, the use of selective serotonin reuptake inhibitors, tricyclics, and selective serotonin reuptake inhibitors significantly increased the rate of all-cause death [97]. Instead, the combination of cognitive behavioral therapy with a selective serotonin reuptake inhibitors was reported as the best management of depression in HF patients in a position paper from the Study Group on Heart and Brain Interaction of the Heart Failure Association [98].

Recently, a reduction in depressive symptomatology in heart transplant waiting list patients treated with sacubitril/valsartan was demonstrated [99].

In HFpEF patients enrolled in the TOPCAT (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function) trial, randomization to spironolactone was related to a mild decrease in depressive symptoms [100].

Table 1. Key results of the studies about non-cardiovascular comorbidities in heart failure patients differentiating between acute heart failure and chronic heart failure and between heart failure with preserved ejection fraction and heart failure with reduced ejection fraction

Non-CV comorbidities		AHF	CHF	HFpEF	HFrEF
Cancer	**Prevalence:** The prevalence of 2 chronic diseases like cancer and HF usually increases with age. **Prognosis:** The presence of cancer obviously worsens the prognosis of HF patients, while CV diseases are the first non-cancer cause of death in cancer patients				
Obstructive sleep apnea	Prevalence prognosis	61% HR: 1.53 (time to death)	54% OR: 2.38 (increased risk readmission)	39.8% AHI ≥20/h 5 <AHI <20/h poor prognosis	29%
Central sleep apnea	Prevalence prognosis	21% HR: 1.61 (time to death)	27% AHI ≥30/h Poor prognosis	29.5% AHI ≥20/h 5< AHI <20/h poor prognosis	31% Rate ratio: 1.53 (cardiac readmission)
Chronic obstructive pulmonary disease	Prevalence prognosis	19.3% OR: 1.65 (in-hospital non-CV mortality)	15% HR: 1.37 (all-cause death)	14% HR: 1.6 (all-cause death)	16% HR: 1.25 (all-cause death)
Diabetes mellitus	Prevalence prognosis	39.1% HR: 1.77 (in-hospital mortality) HR: 1.16 (all-cause mortality) HR: 1.32 (re-hospitalization)	31.4% HR: 1.74 (all-cause death)	29.3% HR: 0,85 (all-cause death)	32.3% HR: 1.25 (all-cause death)
Hypothyroidism	Prevalence prognosis	7% (reported as thyroid disease)	9% HR: 1.31 (all-cause death) HR: 1.46 (HF hospitalization)	8% negative prognostic factor	10% HR: 1.58 (mortality)
Hyperthyroidism	Prevalence prognosis	7% (reported as thyroid disease)	3% HR: 1.16 (all-cause death) HR: 1.07 (HF hospitalization)	3%	4% HR: 1.85 (mortality)
Vitamin D deficiency	Prevalence prognosis		20< vitamin D <29 ng/ /ml 2.4% vitamin D <20 ng/ml 3.2% HR:1,52 (mortality)	HR: 1.55 (mortality) HR: 1.74 (CV hospitalization)	HR: 1.09 (death or HF hospitalization) HR: 1.10 (all-cause mortality)
Hyperuricemia	Prevalence prognosis	43% in HFrEF 57% in HFpEF HR: 1.48 in HFrEF HR: 2.38 in HFpEF (death or HF hospital)	39% in HFrEF 19.5% in HFpEF HR: 1.37 (all-cause death)	19.5% HR:1.98 (all-cause death)	39% HR: 1.35 (mortality)
Anabolic hormones depletion (focus on total testosterone and growth hormone deficiency)	Prevalence prognosis	—	GHD 30% Higher all-cause mortality Total testosterone HR: 0.929 (all-cause mortality)	45% of patients with 2 or more signs of hormone deficiency	Deficiencies in DHEAS, total testosterone, free testosterone, and IGF-1 (defined as serum levels at or below the 10th percentile)
Chronic kidney disease	Prevalence prognosis	26.3% OR: 2.34 (all-cause death)	41% HR: 1.5 (all-cause death) HR: 1.59 (HF hospitalization)	39% HR: 1.39 (mortality)	41% HR: 1.49 (mortality)
Iron deficiency	Prevalence prognosis	69%–75% (absolute ID) HR: 1.72 (higher risk of readmission)	42.5% HR: 1.42 (mortality)	58.4% (non-impact on death or hospitalization)	52.2%–65.1% HR: 0.043 (all-cause death) HR: 1.58 (death)
Depression	Prevalence prognosis	6.4%–12.3% HR: 1.43 (CV readmission and death)	21.5% OR: 2.23 (mortality at 1-year)	25% HR: 1.05 (CV hospitalization)	24% HR: 1.56 (death/CV hospitalization)

Abbreviations: AHF, acute heart failure; *AHI, apnea*–hypopnea index; CHF, chronic heart failure; CV, cardiovascular; DHEAS, dehydroepiandrosterone sulfate; GHD, growth hormone deficiency; HF, heart failure; HFpEF, heart failure with preserved ejection fraction, HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; ID, iron deficiency; IGF-1, insulin-like growth factor-1; OR, odds ratio

According to the ESC HF guidelines recommendations [1], psychosocial intervention, behavior cognitive therapy and exercise training (low- to moderate-intensity aerobic training) might be helpful in patients with HFrEF and depression.

Table 1 summarizes the principal results of studies about non-CV comorbidities in HF patients about prevalence and prognosis of the comorbidities, differentiating between AHF and CHF and between HFpEF and HFrEF.

CONCLUSIONS

Comorbidities are very common in HF patients (HFrEF and HFpEF), with differences secondary to type of HF and sex. Non-CV comorbidities confer a relevant contribution to outcomes and in HFrEF and HFpEF. Recent data, derived by new trials, seem to suggest some comorbidities as new pharmacological targets in HF. The comprehensive management of patients affected by HF should include the management of comorbidities, with focus on to anemia and

iron deficiency, mental and behavioral disorders, diabetes mellitus, and respiratory diseases. The right treatment of these comorbidities may positively affect prognosis, hospitalization, and the health-related quality of life.

Article information

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REVIEW ARTICLE

Can sodium-glucose cotransporter 2 inhibitors be beneficial in patients with acute myocardial infarction?

Dirk von Lewinski[1], Martin Benedikt[1], Norbert Tripolt[2], Markus Wallner[1, 3, 4], Harald Sourij[2], Ewald Kolesnik[1]

[1]Department of Cardiology, Medical University of Graz, Graz, Austria
[2]Department of Endocrinology and Diabetology, Medical University of Graz, Graz, Austria
[3]Cardiovascular Research Center, Lewis Katz School of Medicine, Temple University, Philadelphia, PA, United States
[4]Center for Biomarker Research in Medicine, CBmed GmbH, Graz, Austria

Correspondence to:
Dirk von Lewinski, MD, Department of Cardiology, Medical University of Graz, Auenbruggerplatz 15, 8036 Graz, Austria
phone: 4331638580684, e-mail: dirk.von-lewinski@medunigraz.at

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ABSTRACT

The sodium-glucose cotransporter 2 inhibitors (SGLT2i), empagliflozin, dapagliflozin, and canagliflozin, have shown impressive beneficial effects in patients with type 2 diabetes mellitus in mandatory cardiovascular outcome trials. Retrospective data analysis revealed signals that pointed towards positive effects independent of the antidiabetic effects. This could be confirmed for empagliflozin and dapagliflozin in chronic heart failure with reduced ejection fraction alone, where rates of hospitalization for heart failure and cumulative major adverse cardiovascular events were reduced to a similar extent in patients with and without diabetes mellitus as in corresponding outcome trials. Cardiac remodeling following myocardial infarction leads to heart failure with reduced ejection fraction in many patients and aggravates morbidity and mortality. Clinical data of SGLT2i treatment after acute myocardial infarction is sparse. This review focuses on available experimental data on the effects of SGLT2i used before, during, and after myocardial infarction as well as already published and currently ongoing clinical trials.

Key words: sodium-glucose cotransporter 2 inhibitors, myocardial infarction, metabolism, clinical trials

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INTRODUCTION

Diabetes mellitus is a risk factor and aggravates other potential risk factors of the cardiovascular system, such as arterial hypertension [1] or smoking [2], and is associated with increased levels of blood lipids, and obesity [3]. These conditions pave the way towards coronary artery disease (CAD), which indeed represents a common disease in diabetic patients [4]. CAD often triggers heart failure (HF) via myocardial infarction (MI) and ischemia/reperfusion damages that induce acute and/or chronic maladaptive remodeling processes. CAD and HF represent the two most important causes of cardiovascular morbidity and mortality. Therefore, the central therapeutic aim in CAD is the prevention of MI in patients at atherosclerotic risk, and reducing the burden of HF in patients after MI. Attention has been caught recently by 3 clinical trials that proved impressive beneficial effects of sodium-glucose cotransporter 2 inhibitors (SGLT2i) on HF hospitalization in diabetic patients with either established atherosclerotic cardiovascular diseases or multiple risk factors — namely the EMPA-REG OUTCOMES trial for empagliflozin [5], the CANVAS program for canagliflozin [6], and the DECLARE TIMI-58 trial for dapagliflozin [7]. More than 50% of the patients included in these 3 trials had CAD, and relevant subgroups had experienced previous MI, as shown in Table 1. A meta-analysis of these 3 outcome trials revealed an 11% reduction of major adverse cardiovascular events defined as MI, stroke, and cardiovascular death mainly driven by a strong effect in patients with established atherosclerotic cardiovascular disease. In detail, this analysis showed an overall reduction of MI by 11% in all patients and by 15% in those with previous atherosclerotic cardi-

Table 1. The number of patients with myocardial infarction (MI) and/or coronary artery disease (CAD) within each trial

	Previous MI	CAD
EMPA-REG-OUTCOME [5]	3273 (46.6)	5308 (75.6)
DECLARE-TIMI [7]	3584 (20.9)	5658 (32.9)
CANVAS [6}	Not reported	5721 (56.4)

Data are presented as number (percentage)

ovascular disease [8]. This data is confirmed by a broader and earlier meta-analysis of 71 trials including more than 47 000 diabetic patients treated with all available SGLT2i that demonstrated a reduction of MI by 23% after SGLT2i treatment [9]. A recent comparative cohort study on newly initiated therapy with SGLT2i or dipeptidyl-peptidase 4 inhibitors in diabetic patients also revealed significantly reduced rates of MI in those initiating SGLT2i, in this analysis with the strongest effects observed in patients without previously known cardiovascular disease [10]. Similar results were derived from a huge retrospective analysis comparing newly initiated SGLT2i matched with any other newly initiated oral antidiabetic drug in over 470 000 diabetic patients [11]. Comparable effect sizes can also be observed with some glucagon-like peptide 1 receptor agonists [12–14] and — to a smaller degree and retrospectively analyzed — with metformin [15]. Therefore, SGLT2i, metformin, and glucagon-like peptide 1 receptor agonists should be considered in all patients with increased risk of MI.

Based on the available convincing data and given the fact that some other antidiabetic concepts did not consistently show a reduction in major adverse cardiovascular events in diabetic patients [16–18], SGLT2i were soon after examined in HF patients irrespective of their diabetes status. So far, two landmark trials with SGLT2i in HF have been published [19, 20] and SGLT2i are likely to be integrated into the treatment algorithm for HF with reduced ejection fraction (HFrEF) in diabetic and non-diabetic patients soon. Although more than half of the patients in those 2 trials had ischemic heart disease as their principal cause of HF, no data on MI incidence during the study periods is reported, yet. More data in this context might soon also be derived from the DAPA-CKD trial [21] leaving the question of whether SGLT2i may exert beneficial effects in patients after MI, too.

PATHOPHYSIOLOGY OF MYOCARDIAL INFARCTION AND EARLY TREATMENT INITIATION

Myocardial damage in MI derives mainly from two different causes. Firstly, acute ischemia causes energy depletion within the area at risk and irreversible necrotic cell damage within the infarcted area. Secondly, acute MI triggers a neurohumoral response mainly driven by an uncontrolled upregulation of the renin–angiotensin–aldosterone system and activation of the sympathetic nervous system. Both processes induce myocardial remodeling that will finally affect non-ischemic areas of the heart, too. Therefore, therapies improving the acute damage need to be present during the index event, whereas therapies interacting with the remodeling process might also be efficient if applied afterward. As remodeling starts immediately after the ischemic event, early initiation of a potentially beneficial drug seems to be desirable. Robust evidence exists for all drug classes used in HF with reduced ejection fraction (HFrEF) that show beneficial effects in post MI treatment, and early initiation of these drugs obviously improves these beneficial effects. A huge meta-analysis including ~100 000 patients indicated that 85% of the survival benefit with angiotensin-converting-enzyme inhibitors after MI was accomplished within the first 7 days after MI [22]. Early initiation of β-blocker therapy is recommended in the guidelines [23] — even before the intervention of the affected coronary vessel — as an anti-anginal and energy-saving drug [24, 25], but very early therapy needs to be limited to patients without increased risk of cardiogenic shock that can be triggered or aggravated by the negative inotropic and negative chronotropic effects of β-blockers as shown in the COMMIT trial [26]. Mineral receptor antagonist treatment with eplerenone within 24 hours after MI in the setting of ST-segment myocardial infarction (STEMI) improved the primary endpoint of the REMINDER trial [27]. The same is true for the STEMI-subgroup of the ALBATROSS trial that investigated the early use of spironolactone after MI [28], while in the non-STEMI subgroup no beneficial treatment effect could be observed indicating that larger MI will benefit most from (early) initiation of mineral receptor antagonist treatment. Outcome data on early angiotensin receptor-neprilysin inhibitor treatment is not yet available. However, the PARADISE-MI trial comparing sacubitril-valsartan vs ramipril starting within 7 days after the index event just completed final visits and data will be available soon. So far, hardly any clinical data is available on SGLT2i in STEMI patients. Figure 1 summarizes respective clinical trials for empagliflozin [29] and dapagliflozin where first outcome data will be published soon. For other SGLT2i, such as canagliflozin, sotagliflozin, ipragliflozin, and tofogliflozin, currently, no trials after acute MI are ongoing. Yet, more and more experimental data sheds light on the potential beneficial effects of SGLT2i after MI.

SGLT2 INHIBITOR TREATMENT BEFORE MYOCARDIAL INFARCTION

Various animal models describe attenuated MIs after SGLT2i pretreatment. In a study focusing on SGLT2i mediated protective effects in the setting of ischemia/reperfusion, Andreadou et al. [30] used a mice model being fed for 6 weeks with empagliflozin before a temporal surgical ligation of the left anterior descending coronary artery (LAD) was performed for 30 minutes followed by reperfusion period of 2 hours. Empagliflozin pretreatment reduced infarct size by approximately 50% and left ventricular fractional shortening was improved from 41% to 44% compared to vehicle-treated control animals post ischemia. Detailed biochemical analysis revealed significant activation of signal transducer and activator of transcription 3 (STAT3) transcription factor expression and phosphorylation in the empagliflozin-treated animals while reduced levels of myocardial interleukin-6 and inducible nitric oxide (NO) synthase expression were measured. Potential other candidates of mediating protective effects such as Akt, eNos, p44/42 MAPK, or AMPKa phosphorylation were not affected by empagliflozin pretreatment. Similar data

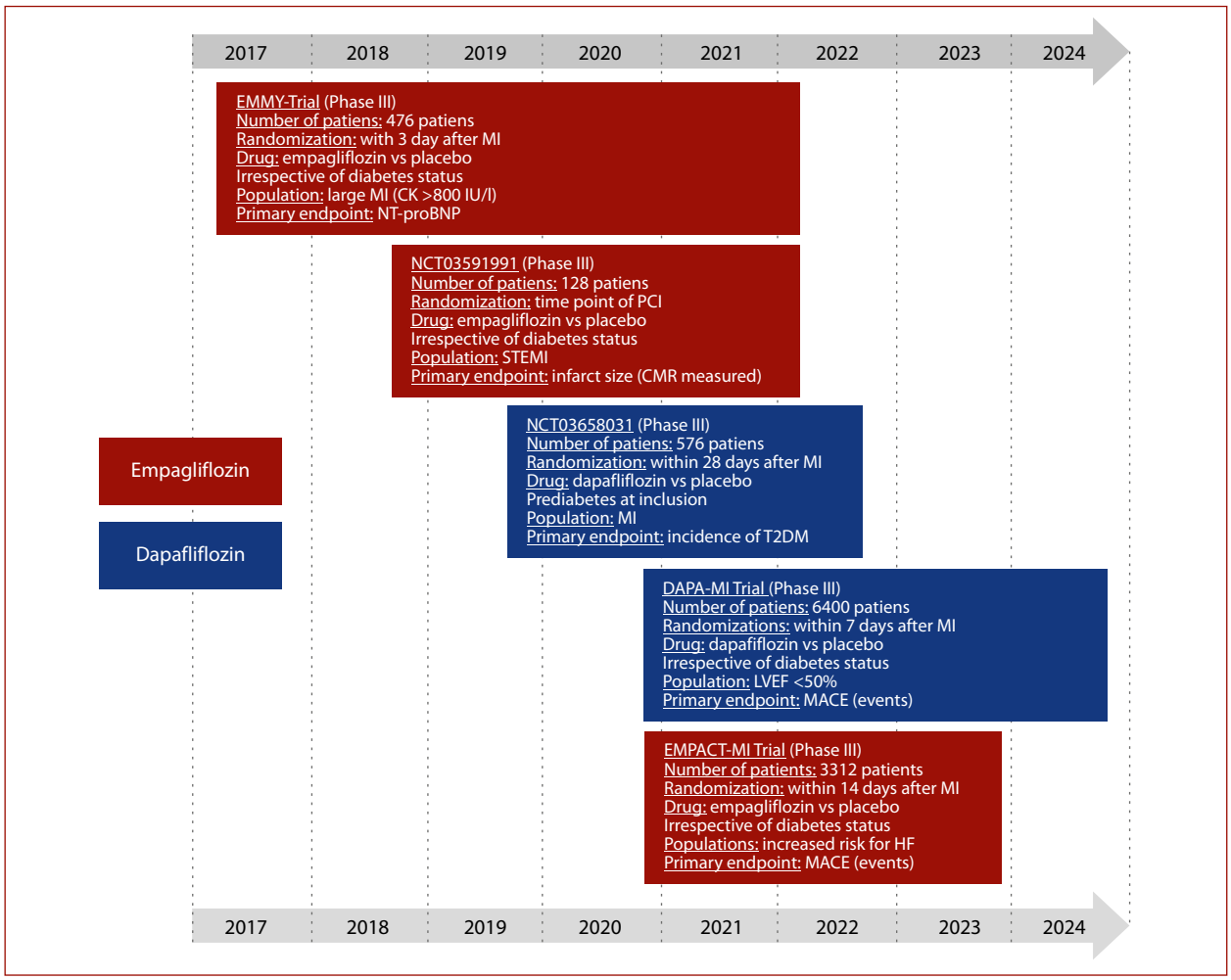

Figure 1. Timeline of already completed and still running trials with sodium-glucose cotransporter 2 inhibitors after myocardial infarction. Blue: dapagliflozin. Red: empagliflozin. Trial name, inclusion criterion, end points, and the number of planned included patients are given. End date is assumed based on the information given at www.clinicaltrials.org. All trials tested drugs versus placebo.

Abbreviations: CK, creatinine kinase; CMR, cardiac magnetic resonance; HF, heart failure; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MI, myocardial infarction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; T2DM, type 2 diabetes mellitus

was observed by Lopez et al. [31] in rats after permanent surgical ligation of the LAD. Pretreatment of 25 days with empagliflozin reduced the infarct size by 30%–40% in non-diabetic and streptozotocin-induced diabetic rats. This effect was accompanied by significantly better contractility analyzed by left ventricular fractional shortening and left ventricular ejection fraction (LVEF). Within this model, significantly reduced concentrations of inducible NO synthase and superoxide levels were measured, too. The authors expanded their analysis towards the cardiac GTP enzyme cyclohydrolase 1 (cGCH1) which is rate-limiting and the first enzyme in the biosynthesis of the essential cofactor of all 3 NO isoforms of tetrahydrobiopterin (BH4). They observed significantly increased concentrations of myocardial cGCH1 and BH4 in the empagliflozin pretreated groups. Intriguingly, blocking this pathway using cGCH1 knockout models also abolished effects of empagliflozin treatment on BH4 concentrations, cell area, and the NO system including superoxide concentrations. In summary, this points towards a reduction of oxidative stress in the empagliflozin-treated hearts via this cGCH1-BH4 pathway.

Metabolic changes have been suggested as the underlying mechanism for the effects of SGLT2i by Oshima et al. [32]. Empagliflozin pretreatment 14 days before permanent occlusion of a marginal branch of the LAD resulted in increased myocardial and blood β-ydroxybutyrate (β-OHB) levels of diabetic rats as well as metabolomic patterns of increased glucose and ketone utilization. Metabolomic effects of external β-OHB in SGLT2i naive rats mimicked the empagliflozin effects indicating this as a potential mechanism of action. Empagliflozin pretreatment significantly improved 48-hour survival (40% vs 84%) despite unaltered infarct size. Interestingly, MI-induced acute kidney injury was also attenuated within the same model by empagliflozin pretreatment [33]. The functional protective data was also confirmed in a set of experiments by Lim et al. [34]

using canagliflozin in rats. After 4-week oral pre-treatment with canagliflozin the hearts were harvested and examined in a Langendorff setup. After 40 minutes of stabilization, a 35-minute regional ischemia was applied and followed by 2-hours of reperfusion. Canagliflozin pre-treatment significantly reduced ischemia/reperfusion injury by approximately 50% in both diabetic as well as in non-diabetic rats compared to vehicle-treated animals. The area at risk was not different in all groups.

SGLT2 INHIBITOR TREATMENT DURING MYOCARDIAL INFARCTION

In contrast to these matching beneficial results within various studies for chronic pretreatment, the acute treatment showed heterogeneous effects. The setting of initiating an SGLT2i shortly before or during ischemia excludes chronic changes in metabolism or myocardial energetics as underlying mechanisms of potential protective effects.

Lu et al. [35] treated murine cardiomyocytes with either empagliflozin, the adenosine monophosphate-activated protein kinase (AMPK) inhibitor compound C, both substances, and vehicle buffer solution briefly before these cardiomyocytes were exposed to hypoxic conditions for 20 minutes followed by a re-oxygenation period of another 20 minutes [35]. Empagliflozin triggered phosphorylation of AMPK, its upstream activator liver kinase B1, as well as its downstream target the peroxisome proliferator-activated receptor γ coactivator-1α (PGC1α) within minutes. Interestingly, persistent activation of the AMPK-dependent pathway with empagliflozin was accompanied by improved cardiac contractility. Moreover, these beneficial molecular and functional effects were almost completely abolished in cells pretreated with the AMPK inhibitor compound C. These experiments were extended to an in-vivo model in which mice were treated with empagliflozin alone or in combination with compound C for 3 days before surgical temporal LAD ligation for 45 minutes followed by 24 hours of reperfusion. Rapidly performed post-procedural echocardiography indicated a preserved LVEF in the empagliflozin-treated mice while mice also pretreated with compound C had a reduced LVEF comparable to the LVEF in the vehicle-treated group. Interestingly, histological analysis revealed reduced infarction areas in the empagliflozin-treated mice. Lahnwong et al. [36] reported beneficial effects after pretreatment with dapagliflozin only 15 minutes before ischemia/reperfusion in a rat model expressed by improved LVEF, reduction of arrhythmias, reduced infarct size, and reduced rate of apoptosis. These effects were mainly attributed to mitochondrial protection, attenuation of reactive oxygen species production, and upregulation of antiapoptotic proteins. Translating a short pretreatment period into a large animal, Baker el al. [37] treated swine with a weight of approximately 50 kg with canagliflozin 24 hours before 60-minutes of total LAD occlusion. Canagliflozin pretreatment resulted in a 60% reduction in infarct size, higher stroke volume, and better myocardial efficiency (cardiac work divided by oxygen consumption) compared to non-treated animals.

On the other hand, Lim et al. [34] treated isolated non-diabetic rat hearts in a Langendorff setup with canagliflozin only throughout the perfusion protocol. This approach failed to reduce infarct size despite areas at risk comparable to those in the protocol using 4-week pre-treatment. This observation is confirmed by unaltered MI size with only 2 days of empagliflozin pretreatment before MI in a rat model published by Yurista et al. [38]. However, this data might be biased as all animals with infarct areas smaller than 15% were excluded from the analysis. Nevertheless, mitochondrial protection could be demonstrated to a similar extent compared to the group that received an empagliflozin pretreatment for 2 weeks. Jespersen et al. [39] also described no effect on infarct size after a 10 minute pretreatment with empagliflozin in non-diabetic rats but acute improvements in mitochondrial function.

SGLT2 INHIBITION POST MYOCARDIAL INFARCTION

Treatment initiated after ischemia and reperfusion obviously cannot provide beneficial effects within the very early stages of MI. But the contribution of metabolic properties, cardiac remodeling, and potential arrhythmias following MI can be investigated in such experiments.

The first evidence was provided in 2017. Lee et al. [40] treated male Wistar rats with dapagliflozin 24 hours after MI induced by ligation of the LAD. Infarct size could not be changed with this delayed treatment, but dapagliflozin improved contractile kinetics and reduced structural changes (cardiac fibrosis) compared to the vehicle-treated group at the end of the study period of 4 weeks. Moreover, a reduced lung weight to body weight ratio was found indicating better remodeling in the treated group. The underlying mechanism seemed to be an early STAT3 dependent attenuation of activation of oxidative stress measured as increases of superoxide and nitrotyrosine already after 3 days of treatment. Co-administered of the STAT3 inhibitor S3I-201 dramatically reduced or nullified these effects.

This post-MI data was extended to a large animal model by Santos-Gallego et al. [42] using female Yorkshire pigs treated with 2-hour balloon occlusion of the LAD. Pigs were randomized to either empagliflozin or placebo and treatment was started the day after MI. A non-MI pig group that was not treated with empagliflozin served as a control. The observation period lasted for 2 months. As anticipated, empagliflozin initiation after reperfusion did not reduce infarct size, but myocardial metabolism and function differed considerably between the three groups. Placebo-treated MI animals were characterized by a reduced myocardial uptake of free fatty acids, an increased uptake of glucose, and a net lactate production — typical patterns of anaerobic metabolism. Empagliflozin-treated MI animals showed a less pronounced reduction of myocardial free fatty acids uptake while there was no difference in the uptake

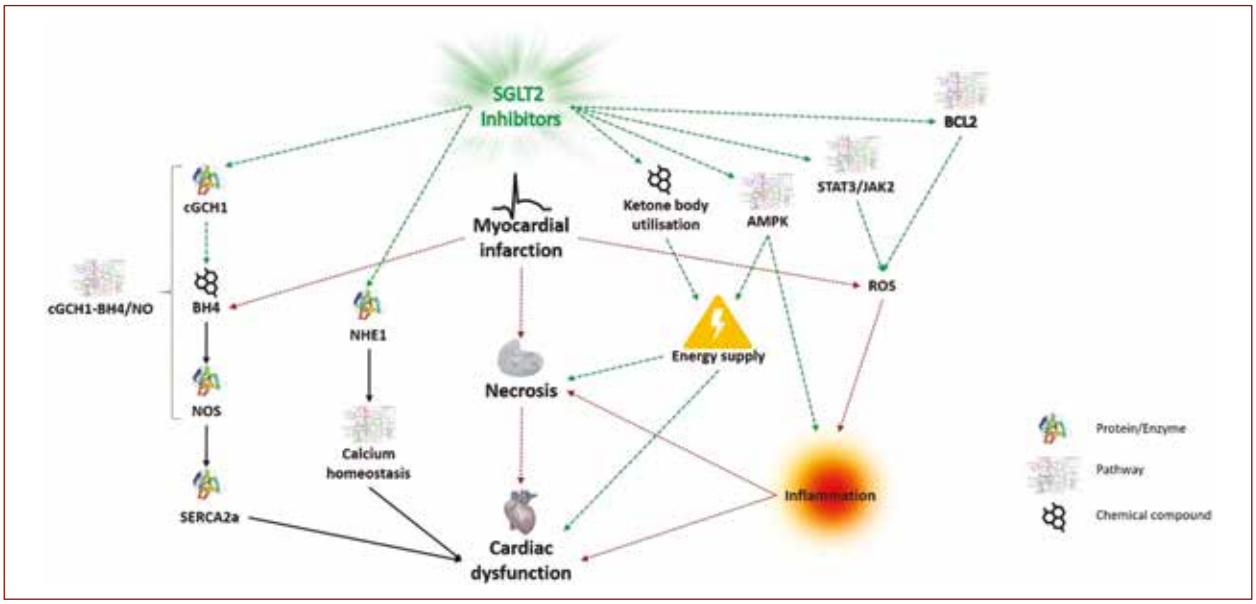

Figure 2. Interactions of sodium-glucose cotransporter 2 inhibitors (SGLT2i) and myocardial infarction (MI) on the homeostasis of cardiomyocytes in different species and on different biological levels (full animals, organs, tissue, and single cells). MI leads directly to tissue necrosis and indirectly via reactive oxygen species (ROS) and inflammation. Additionally, MI negatively influences the downstream pathway of tetrahydrobiopterin (BH4) leading to a dysfunction of calcium homeostasis via sarco/endoplasmic reticulum Ca2+-ATPase (SERCA2a) (dotted red lines). SGLT2i interacted with and via various proteins, pathways, and compounds that counteract the negative effects induced by MI (dashed green lines). The wide interactions with cardiomyocytes via miscellaneous second messengers are not shown.

Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; BCL2, B-cell lymphoma 2 gene; cGH1, cGH1 gene; JAK2, Janus kinase 2; NHE1, sodium-hydrogen antiporter 1; NOS, nitric oxide synthase; STAT3, signal transducer and activator of transcription 3 transcription factor

of glucose and lactate compared to non-MI animals. In conclusion, empagliflozin treatment preserves the aerobic metabolism after MI. Moreover, empagliflozin increased the myocardial uptake of ketone bodies resulting in an increased calculated myocardial work efficiency. Mechanistically, empagliflozin treatment leads to less reduced pAMPK/AMPK and PGC1α/glyceraldehyde 3-phosphate dehydrogenase (GAPDH) ratios as well as less reduced myocardial adenosine triphosphate (ATP) content compared to controls. This likely improves the energetic state of the cells. These data support the abovementioned findings of Lu et al. [35] on the murine single-cell level.

Finally, these beneficial metabolic changes translated into improved myocardial function analyzed by cardiac magnetic resonance imaging and three-dimensional echocardiography. Here, empagliflozin significantly attenuated left ventricle enlargement and significantly improved LVEF and longitudinal strain.

MYOCARDIAL PROTECTION BY PERSISTENT EFFECTS INDUCED BY SGLT2 INHIBITORS

The experimental evidence available clearly describes the beneficial effects of SGLT2i initiation after MI. Unfortunately, all these studies only used a small number of animals (4–6 animals per group), different treatment protocols, and different SGLT2 inhibitors. Therefore, only speculations and no final conclusions can be drawn from these observations. Examining hearts in Langendorff set-ups presume a crystalloid washout before the ischemia/reperfusion procedure can be induced. Data derived from these experiments are therefore likely unaffected by the metabolic effects or substrates originating from other organs such as liver-derived ketones. Next, the discrepancy of acute and chronic effects in ischemia/reperfusion damage speaks rather against a fast-acting membrane-based mechanism like the inhibition of the sodium-hydrogen antiporter 1 with consecutive alterations in the cellular calcium homeostasis reported earlier by Baartscheer et al. [42]. Of note, initiation of SGLT2i after ischemia/reperfusion damage cannot reduce infarct size per se too, therefore mechanisms to be addressed must positively influence cardiac remodeling.

As summarized in Figure 2, data derived from various experimental settings supports a persistent myocardial effect of SGLT2i with the best available evidence so far for the upregulation of the protective JAK/STAT3 [30, 40], the cGCH1-BH4/NO [31], the B-cell lymphoma 2 gene [36], and the AMPK [35, 41] pathway. Further pleiotropic mechanisms reducing oxidative stress [36] and inflammation as revealed by Koyani et al. [43] certainly play their part in this complex cascade of interactions too, although these pathways seem to be much more regulated and affected by SGLT2i treatment in the early phase after MI. Improved myocardial efficiency would obviously shift myocardial function towards a less energy-consuming mode of action which is likely delaying or preventing further cardiac deterioration. Increased myocardial ketone body consumption upon SGLT2i treatment [41, 44] supports this hypothesis. Finally,

structural decline as increased fibrosis typically observed in remodeling seems to be preventable by SGLT2i [40]. However, it remains unclear if a brief pretreatment can already mediate chronic metabolic or structural protective effects.

Regarding canagliflozin, another aspect must be kept in mind since this substance is less selective for SGLT2 compared to empagliflozin and dapagliflozin. Effects induced by canagliflozin might therefore also be attributed to SGLT1 mediated mechanisms. This might be of special importance in human myocardial tissue as SGLT2 is neither expressed in the atrial [45] nor in the ventricular myocardium [46].

FIRST CLINICAL DATA OF SGLT2 INHIBITORS AFTER MYOCARDIAL INFARCTION

Data from clinical trials specifically addressing acute MI patients is scarce. There is practically only a single study analyzing sympathetic and parasympathetic activity using heart rate variability and heart rate turbulence in 96 diabetic patients [47]. Patients were enrolled in the trial 2–12 weeks after MI. Average creatinine kinase was approximately 2200 IU/l and N-terminal pro–B-type natriuretic peptide was 1150 pg/ml indicating rather large MIs. The prescription rate of guidelines-recommended medication post-MI including β-blockers, renin–angiotensin–aldosterone system inhibitors, statins, and dual platelet inhibition was high. Follow-up of the patients was up to 24 weeks and the primary endpoint of heart rate variability was reported as the standard deviation of all 5-minute mean normal RR intervals. Low frequency to high frequency ratio was significantly changed only in the empagliflozin group but there was no significant difference compared to placebo. However, potentially even more interesting was the effect on average N-terminal pro-B-type natriuretic peptide levels. In the empagliflozin group, a reduction of 64% to baseline could be reached compared to a reduction of 53% in the placebo group. This data is in line with the known beneficial effects of SGLT2 i in HF.

CONCLUSIONS

Meta-analyses of clinical trials emphasize that SGLT2i treatment leads to a reduction of 10%–20% in the number of MI in diabetic patients. Experimental data highlights a reduction in infarct size and consecutively less remodeling and development of HF after MI in almost all experimental settings ranging from single cells to large animal models with and without diabetes. The reason for this finding is likely multifactorial, including delayed progression of diabetes, improved myocardial energetics, activation of cardioprotective downstream mechanisms counteracting remodeling processes, antifibrotic and antiapoptotic processes, potential anti-inflammatory mechanisms, and direct interaction with cardiomyocytes (Figure 2). Thereby, the heart may resist episodes of ischemia that would otherwise result in cell damage and MI. Importantly, experimental and first clinical data strongly point towards effects independent from the presence of diabetes. Therefore, it needs to be considered if treatment with SGLT2i irrespective of the diabetes status is reasonable to initiate in patients after MI. This claim is already heavily backed by experimental data and will soon be complemented by clinical data.

Article information

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Conflict of interest: The authors are investigators of the EMMY-trial, otherwise, no conflict of interest is declared.

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Cost-effectiveness of telerehabilitation in patients with heart failure in Poland: an analysis based on the results of Telerehabilitation in the Heart Failure Patients (TELEREH-HF) randomized clinical trial

Maciej Niewada[1, 2], Bernadetta Tabor[2], Ewa Piotrowicz[3], Ryszard Piotrowicz[4, 5], Grzegorz Opolski[6], Maciej Banach[7], Michał Jakubczyk[2, 8]

[1]Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, Warszawa, Poland
[2]HealthQuest, Warszawa, Poland
[3]Telecardiology Center, National Institute of Cardiology, Warszawa, Poland
[4]National Institute of Cardiology, Warszawa, Poland
[5]Warsaw Academy of Medicine Rehabilitation, Warszawa, Poland
[6]1st Department of Cardiology, Medical University of Warsaw, Warszawa, Poland
[7]Department of Hypertension, Medical University of Lodz, Łódź, Poland
[8]SGH Warsaw School of Economics, Warszawa, Poland

Correspondence to:
Ewa Piotrowicz, MD, PhD, FESC,
Telecardiology Center,
National Institute of Cardiology,
Alpejska 42, 04–628 Warszawa, Poland,
phone: +48 22 343 46 64,
e-mail: epiotrowicz@ikard.pl

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ABSTRACT

Background: Telerehabilitation in the Heart Failure Patients (TELEREH-HF) study showed a statistically significant improvement in the tertiary outcomes i.e. the New York Heart Association (NYHA) class after a 9-week follow-up, consistent with telerehabilitation-related benefits to quality of life (QoL) measured with the 36-item Short Form questionnaire (SF-36).

Aims: The study analyzed the cost-effectiveness of hybrid telerehabilitation compared to standard care in heart failure patients in the Polish setting using findings from the TELEREH-HF trial.

Methods: Cost-utility analysis was conducted from the perspective of a public payer (the Polish National Health Fund). The quality-adjusted life-year (QALY) measure was based on QoL, as survival benefit was not confirmed in the TELEREH-HF. Utility values were estimated based on NYHA improvement and a systematic review of NYHA-specific utility values. Alternatively, SF-36 results were translated into utility values. Telerehabilitation costs covered 8 weeks, 5 days/week, at a daily cost of 74 Polish zloty (PLN). Standard care costs resulted from extra in-patient and out-patient rehabilitation costs incurred for selected patients. A lifetime horizon was adopted, with an estimated average survival time of 3.9 years based on 2 years TELEREH-HF follow-up and subsequent literature-derived prognosis.

Results: Base case analysis yielded a 0.044 and 0.027 gain in QALY for the NYHA and SF-36-based approaches, corresponding to a cost per QALY of 58.7 and 96 thousand PLN, respectively. Sensitivity analysis confirmed that the cost per QALY value was likely below the official cost-effectiveness threshold in Poland.

Conclusions: The use of telerehabilitation was found cost-effective in Poland, i.e., the clinical benefits justify the additional costs.

Key words: cost-effectiveness, heart failure, telerehabilitation

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INTRODUCTION

Hybrid comprehensive telerehabilitation is the possibility of supervising and providing rehabilitation at a distance by using advanced medical and telecommunication technologies. Telerehabilitation can be combined with standard cardiovascular rehabilitation programs or used alone as a hybrid comprehensive procedure. High adherence to telerehabilitation may not only improve clinical outcomes but lower total treatment costs of heart failure.

WHAT'S NEW?

Telerehabilitation in the Heart Failure Patients (TELEREH-HF) randomized clinical trial showed a statistically significant clinical improvement in the tertiary outcomes i.e. the New York Heart Association class, and quality of life of heart failure patients. That benefit justifies the additional cost incurred, and telerehabilitation was found to be a cost-effective intervention in Polish settings.

Therefore telerehabilitation is a feasible and safe alternative to standard rehabilitation [1–3].

The aim of the study was to present a cost-utility analysis (CUA) of a hybrid telerehabilitation procedure in patients with heart failure compared to standard care based on the outcomes of the Telerehabilitation in Heart Failure Patients (TELEREH-HF) randomized clinical trial conducted in 5 Polish centers [4].

The hybrid telerehabilitation program was initiated during hospital stay and continued after discharge in the form of remotely supervised exercise training at home over 8 additional weeks combined with multi-parameter telemonitoring. Patients randomized to the standard care group received usual care appropriate for their clinical status and standardized within a particular center; some of them could participate in a rehabilitation program either in outpatient or inpatient settings [4, 5].

METHODS

Type of analysis

The TELEREH-HF trial demonstrated no significant differences between the two groups in overall and cardiovascular mortality [5]. However, there were statistically significant differences in the tertiary outcomes including the New York Heart Association (NYHA) class after 9 weeks in favor of telerehabilitation. This is particularly important as NYHA is more directly related to patients' functioning and quality of life (QoL). In contrast, only small changes in the NYHA class were observed after 9 weeks in those undergoing standard care, with a trend towards a deterioration of the NYHA (Table 1).

Consequently, telerehabilitation may positively impact QoL, even in absence of survival benefit. The outcome was confirmed in a direct comparison of QoL in both groups, which was measured with the 36-item Short Form questionnaire v2 (SF-36). The average score after 9 weeks of care was 91.7 in the telerehabilitation group and 89.3 in the control group (P <0.001).

Due to the QoL differences, a CUA is a suitable comparison technique. For the outcomes of CUA to be a valid basis for financial decisions on health technologies from a single budget, quality-adjusted life years (QALYs) are routinely used to measure the effects [6]. QALYs measure the length of life adjusted for its quality, resulting in what can be thought of as an equivalent of years of life in full health. For various health conditions, the conversion factor of a year spent in a given state to an equivalent of a year in full health is referred to as the health utility [7].

For the health utility to have a theoretical foundation and be economically interpretable, values must be determined through a preference-based method. Thus, the assessment of QoL with the SF-36 cannot be used, as the point values are assigned arbitrarily (e.g., assigning the values of 100, 75, 50, 25, 0 to the levels of a given attribute without checking if the differences between attribute levels are equidistant). Therefore, we converted the data describing a patient's health to a number interpreted as the health utility in order to calculate QALY.

Perspective

The analysis was conducted from the perspective of a public payer, the Polish National Health Fund (NHF), which seems to be most natural in the context of this study. The patients do not bear the medical costs related to both interventions. Although they can bear additional non-medical costs not covered by the NHF budget and not included in the adopted perspective. Meanwhile, from the perspective of a service provider, the emphasis is placed on the cost-effectiveness of procedure applications (i.e., the differences between the financing provided by NHF and the real costs incurred by the hospital), which are not suitable for making decisions at the level of the entire healthcare system.

Time horizon and discounting

The lifetime time horizon was selected. Estimation of the average life expectancy (i.e., the horizon under consideration) was performed. Two-year mortality in the TELEREH-HF trial

Table 1. The New York Heart Association (NYHA) classification at baseline and after 9 weeks

NYHA class	Telerehabilitation		Standard care	
	Baseline	9 weeks	Baseline	9 weeks
I	51 (13.0)	99 (25.2)	49 (14.2)	60 (14.9)
II	279 (71.0)	242 (61.6)	272 (67.7)	255 (63.4)
III	63 (16.0)	52 (13.2)	81 (20.1)	85 (21.1)
IV	0 (0)	0 (0)	0	2 (0.5)

Data are presented as number (percentage)

Table 2. Utility of New York Heart Association (NYHA) classes based on the studies used in the analysis and weighted according to the mean number of patients

	Berg 2015 [11]	Göhler 2009 [12]	Griffiths 2017 [13]	Mean
NYHA I	0.823	0.823	0.823	0.823
NYHA II	0.755	0.752	0.738	0.746
NYHA III	0.673	0.662	0.643	0.657
The number of patients	4147	1395	5313	—

was approximately 12.5% for each group, whereas available studies indicate approximate 75% 5-year mortality in a similar group of patients [8]. Assuming a constant mortality rate in the first 2 years (based on 2-year mortality) and another constant mortality rate in subsequent years (based on the relative probability of survival for 2 years and 5 years, i.e., the probability of surviving 5 years on condition of surviving 2 years), approximate 10-year survival curves were built (by extrapolating the annual risk of death from the 2–5 year to the 5–10 year period). The average survival time estimated (including half-cycle correction) is 3.9 years. This outcome corresponds well with median survival time in patients with heart failure and left ventricular ejection fraction (LVEF) reduced below 40% [8], especially with the assumption of a right-skewed lifetime distribution (i.e., the lifetime of many patients is below average and the lifetime of some patients is substantially above the average — in this case, the mean exceeds the median). Namely, this median is 3.6 years in patients aged 65–69 years and decreases in older age groups (e.g., 2.9 for patients aged 70–74 years and 2.3 for patients aged 75–79 years).

As the time horizon covered by the analysis exceeds one year, discounting was used. A discount rate of 3.5% was adopted [9, 10].

Population

The outcomes presented in this study refer to the clinical trial population [4]. The TELEREH-HF study was approved by the local Ethics Committee and each patient provided written informed consent.

The majority of patients included in the trial were men (approx. 89%), aged 62 years, and in the NYHA II class (approx. 68%; 20% in NYHA III and 12% in NYHA I).

In the context of the present analysis, it is important that the mean age at enrolment is less than 65–69 years, which is the interval for which the median survival data were presented above. In this sense, the assumption of 3.9 years life expectancy seems conservative, i.e., the actual average life expectancy may exceed 3.9 years.

Methods of assessing the effects

A CUA was performed, as the TELEREH-HF trial showed benefits of telerehabilitation for tertiary outcomes, suggesting an improvement in QoL. Two outcomes reported in the study were used in the present analysis: the NYHA class and SF-36 QoL assessment. One method was not chosen as a base case due to its complementary nature. The NYHA class can only take 4 values, which may adversely affect its ability to express the patient's health through the utility accurately. The SF-36 is a generically-used instrument; however, it is more complex, which may be considered a disadvantage as converting the health condition factor to the utility would require the use of more parameters.

Each outcome was converted into the utility. For the NYHA class, a literature review was carried out (see Supplementary material) to evaluate the utility difference between the NYHA classes I and II, I and III, or II and III. Three studies that reported (respectively) large numbers of patients with the LVEF <40% were chosen for the utility parametrization [11–13]. In two of the studies the results were given in the form of utility differences between the NYHA classes (e.g. II and I), not the levels; however, this does not affect the outcome of the CUA as it is only based on utility differences [11, 12]. Nevertheless, to compare the results between studies, the utility level for the NYHA class I was adopted as the value of 0.823 [13]. It is also worth noting that among the studies found in the review, in the present analysis we eventually used those with the largest number of patients. Additionally, the results are very consistent across these studies.

The final data used to assess the utility of the NYHA classes are presented in Table 2. The average baseline utility derived from the NYHA class structure is $13\% \times 0.823 + 71\% \times 0.746 + 16\% \times 0.657 = 0.7419$, and is 0.7538 after 9 weeks.

To convert the SF-36 into the utility, the following approach was used. Although state utility sets for the Polish population are available for the health states defined in the EuroQol-5-Dimensions-5-Level (EQ-5D-5L) questionnaire [7], there are currently no algorithms to assign this utility to the SF-36 questionnaire. Therefore, we used an algorithm developed for the United Kingdom [14].

By comparing the health utility calculated at baseline and after 9 weeks, we can estimate the change in the utility, which is then related to life expectancy, to calculate the therapeutic benefit in QALYs. The analysis assumed that the effect obtained during telerehabilitation lasts until the end of the patient's life. This does not mean that a constant QoL is assumed from telerehabilitation to the end of life, but that the difference in life utility between patients using telerehabilitation and those receiving standard care remains unchanged over the lifespan. Meanwhile, based on the TELEREH-HF trial, it was conservatively assumed that telerehabilitation does not translate into longer life

expectancy [5]. Finally, in the base case analysis, the further life expectancy adopted was 3.9 years. Considering the mean patient's age of 63 years, and the median reported life expectancy for those aged 65–69 years of 3.6 years, this assumption also seems to be conservative.

Methods of assessing the costs

The costs of the initial (i.e., diagnosis and the first week of hospitalization) and the final assessment were not included, as these were identical for telerehabilitation and standard care. For telerehabilitation, the costs covered 8 weeks (i.e., 5 days/week, excluding weekends, when no telerehabilitation sessions were conducted), with a daily cost of 74 Polish zloty (PLN) (according to Regulation No. 133/2019/DSOZ issued by the President of the NHF). Thus, the total cost of telerehabilitation was estimated at 2960 PLN per patient.

In those undergoing standard care, most did not generate extra costs. However, rehabilitation was also used in 12% (51/425) of patients, 24% (12/51) of whom were rehabilitated in the hospital, and the rest (76% [39/51]) in an outpatient setting. Inpatient rehabilitation (7 days/week for 5 weeks) was estimated at 218.40 PLN/day (according to Regulation No. 133/2019/DSOZ issued by the President of the NHF), resulting in a cost of 7644 PLN per patient. Outpatient rehabilitation (24 days) was estimated as 74 PLN/day (according to Regulation No. 133/2019/DSOZ issued by the President of the NHF), resulting in a cost of 1776 PLN per patient. Finally, the mean cost of standard care was calculated as: $12\% \times (12/51 \times 7644 + 39/51 \times 1776) = 378.80$ PLN.

Therefore, the cost difference between telerehabilitation and standard care is 2581.20 PLN. The costs are incurred in the first weeks after enrolment and are not discounted.

RESULTS

Base case analysis

Using the NYHA class shift approach, we obtained an average utility difference of 0.01187 between telerehabilitation and standard care. For the SF-36-based approach, the average change in utility in the telerehabilitation group during the ninth week was 0.01 (95% confidence interval [CI], 0.0016 to 0.0184) compared to 0.0028 (95% CI, –0.0056 to 0.0112) in the standard care group. This difference in the mean effect (i.e., 0.00726) was taken as the annual measure of telerehabilitation benefits. The cumulative effect difference over 3.9 years, at the discount rate of 3.5% per year, gives a total of:

- $3.71 \times 0.01187 = 0.044$ QALY for the NYHA-based approach, and
- $3.71 \times 0.00726 = 0.0269$ QALY for the SF-36-based approach.

The difference in the costs is 2581.20 PLN. Therefore, the ratio of the additional cost to the additional effect expressed in QALY, i.e., incremental cost-utility ratio (ICUR), is:

- 2581.20/0.044 = 58 663.42 PLN/QALY for the NYHA-based approach, and
- 2581.20/0.0269 = 95 955.39 PLN/QALY for the SF-36-based approach.

Incremental cost-utility ratio is interpreted as an average cost of getting an additional unit of the therapeutic effect when using the analyzed technology in place of the comparator. In Poland, the threshold differentiating cost-effective technologies from cost-ineffective technologies has been adopted by law and equals three times the annual gross domestic product per person, i.e., currently 155 514 PLN/QALY [15]. Therefore, in both approaches of calculating the effect in the form of utility, we found that telerehabilitation is cost-effective, i.e., the additional costs are justified by the outcomes gained.

Sensitivity analysis

Influence of lifespan and effect persistence

In the base case, a further life expectancy equal to 3.9 years, and the persistence of the effect difference between groups of patients throughout life was adopted. Supplementary material, Table 3 presents the impact of these assumptions on the results. Various variants concerning the number of years of the effect's persistence have been presented (the life expectancy itself is irrelevant in the model, but it exceeds the duration of the effect). The effects obtained during these years were discounted the same way as in the base case.

The longer the duration of the effect, the lower the ICUR value, which proves the higher cost-effectiveness of telerehabilitation. Importantly, when parameterizing the effect based on the NYHA, even when the effect endures for 2 years, it can already be concluded that it is cost-effective. With the SF-36 approach, a 3-year duration of the effect is needed.

Considering both approaches collectively, a 2-year period of the telerehabilitation effect is sufficient for cost-effectiveness.

Lack of discounting

No discounting in the base case resulted in:

- $3.9 \times 0.01187 = 0.0463$ QALY for the NYHA-based approach, and

Table 3. The impact of New York Heart Association (NYHA) classes and 36-item short form questionnaire (SF-36) effects duration

The number of years the benefit of the utility persists	ICUR (based on NYHA class) [PLN/QALY]	ICUR (based on SF-36) [PLN/QALY]
1	217 456	355 537
2	110 598	180 826
3	74 993	122 612
4	57 201	93 522
5	46 534	76 082

Abbreviations: ICUR, incremental cost-utility ratio, QALY, quality-adjusted life year, PLN, Polish zloty

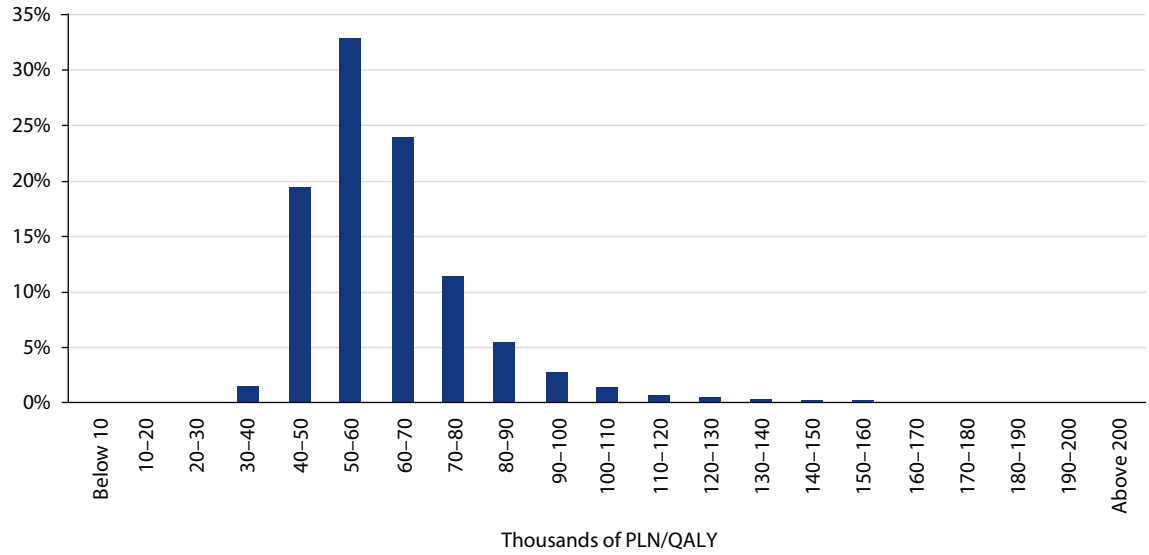

Figure 1. Distribution of the incremental cost-utility ratio (in thousands of Polish zloty per quality-adjusted life year [PLN/QALY]) for the New York Heart Association class-based approach considering the uncertainty of the New York Heart Association class distribution after telerehabilitation

- 3.9 × 0.00726 = 0.0283 QALY for the SF-36-based approach.

  In this case, the ICURs are:
- 2581.20/0.0463 = 55 757.89 PLN/QALY for the NYHA-based approach, and
- 2581.20/0.0269 = 91 63.38 PLN/QALY for the SF-36-based approach.

Probabilistic analysis

To determine the effect of stochastic uncertainty in the data on the results obtained, a probabilistic sensitivity analysis was performed using the Monte Carlo method. In terms of the NYHA-based approach, the impact of the target structure uncertainty of the NYHA classes was investigated. Ten thousand bootstrap samples were generated, and their ICUR values calculated, resulting from the observation of the population structure appropriate for a given sample after 9 weeks. As shown in Figure 1, for almost all Monte Carlo iterations, the ICUR value is below the applicable profitability threshold, which indicates a very high resistance of the obtained conclusions to the uncertainty associated with the use of random tryouts. Importantly, studies on the relationship between the NYHA class and utility cover a very large number of patients and are characterized by high convergence of the presented results. Therefore, this element of the model is not an important source of additional uncertainty.

Regarding the SF-36-based approach, the effect of uncertainty related to the value of the utility difference was examined for both subgroups of the TELEREH-HF study. The parametric bootstrap method was used. The mean and standard deviation of change in utility between baseline and week 9 were calculated for each group, yielding 0.00276 and 0.0846 for the control group, and 0.01 and 0.08375 for the telerehabilitation group. Based on the size of both groups (393 and 385 patients, respectively), a normal distribution was assumed to estimate the uncertainty of the mean: the standard error of the mean was approximately 0.0043 in both groups. The Monte Carlo simulation generated 10 000 utility difference values from this distribution. As shown in Figure 2, the uncertainty of the estimates using this approach is much greater; still, for approximately 68%, the ICUR value does not reach the profitability threshold in Poland, indicating the cost-effectiveness of telerehabilitation.

DISCUSSION

This study analyzed the economic viability of telerehabilitation in heart failure. When estimating health-related utility gain, two approaches were used: one based on the improvement in the NYHA class, and another based on QoL measured with SF-36. For both approaches, telerehabilitation was found cost-effective, i.e., the cost of one QALY gained is below the statutory threshold in Poland.

The specific results obtained for both approaches are different: such differences are expected in the case of instruments based on the subjective assessment of QoL. Additionally, for the NYHA and SF-36, different algorithms were used to convert their values into utility, as they are different instruments. Nonetheless, despite the quantitative differences, both approaches gave consistent findings.

Unfortunately, in the case of both the NYHA and SF-36, no Polish data was available that could be converted into utility values to specifically reflect societal preferences in Poland. In this context, it is important that the difference between the obtained ICUR coefficients and the statutory threshold is large and gives a large margin of freedom for the model parameters. For example, if we take 2.5 years instead of the assumed effect duration of 3.9 years, telerehabilitation remains a cost-effective option.

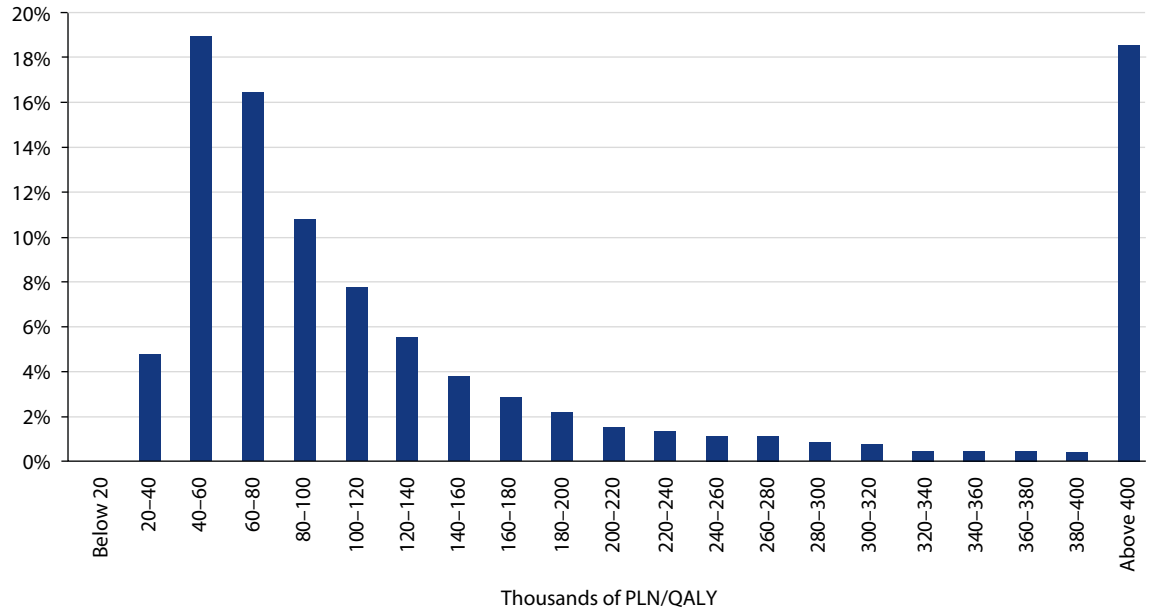

Figure 2. Distribution of the incremental cost-utility ratio (in thousands of Polish zloty per quality-adjusted life year [PLN/QALY]) for the 36-item short form questionnaire approach including the uncertainty in the distribution of the utility change in both groups

The greater uncertainty of the estimates based on the SF-36 is interesting. Perhaps this is due to the greater number of aspects covered by this instrument, leading to greater 'noise' in a given sample. Another reason may be that in the probabilistic analysis based on SF-36, uncertainty was considered for both the telerehabilitation and control groups, both in terms of the initial and target utility levels. For the NYHA-based approach, only the structure of the telerehabilitation group was considered uncertain, and only after 9 weeks of care. In conclusion, the results of both the base case analysis and the sensitivity analysis indicate the cost-effectiveness of telerehabilitation.

The compared groups were not homogeneous. In the telerehabilitation group, some patients did not follow the doctor's instructions. In the group of patients who did, the results expressed by SF-36 were slightly better (utility increases by 0.0107 vs 0.01), indicating a slightly larger difference in the change in utility between the telerehabilitation and standard care groups (by approx. 10%). Additionally, different results were reported for the participating centers, which could be interpreted in a future post-hoc analysis with corresponding limitations. Moreover, some patients in the control group received rehabilitation, and likely achieved better results; thus, the comparison is conservative for telerehabilitation. It should be noted the analysis also covered the costs of extra rehabilitation in the control group, so the overall impact on ICUR should not be significant.

The analysis assumed a constant difference in utility gain related to telerehabilitation over standard care, which might be perceived as a less conservative approach. To explore that assumption, we estimated the necessary duration of effects, both in the NYHA and SF-36, to maintain the cost-effectiveness of telerehabilitation. The estimated 2-year duration of the effects represents roughly half of anticipated mean survival.

Telerehabilitation has been shown to be cost-effective in Belgium [16]. In the randomized study of total 126 patients, a 6-month telerehabilitation resulted in QoL improvement, which translated into incremental QALY gain of 0.22. This stronger effect may be due to longer duration of telerehabilitation itself, longer follow-up period, greater sensitivity of the EQ-5D instrument, or the sensitivity of the utility attribution algorithm to various health conditions to telerehabilitation outcomes. Lower costs were additionally observed in the telerehabilitation group, mainly due to lower costs of rehospitalization. In the TELEREH-HF study, no such differences were observed.

Lower costs in the telerehabilitation group were also observed in an Australian study [17], although no improvement in the QoL was found, which may reflect its significantly shorter follow-up than in the Belgium study [16]. Telerehabilitation was reported cost-effective due to the savings generated. Similar results were reported for New Zealand [18].

In Denmark, an analysis of the effectiveness of telerehabilitation compared to traditional rehabilitation also showed that the additional costs generated were small (approx. 1700 EUR) [19]. However, the differences in QALY over the one-year horizon, although in favor of telerehabilitation, were not significant. This study used the SF-36 to measure QoL, which may suggest a low sensitivity of this instrument in the context of the considered intervention.

The economic modeling reported savings generated by telecare and an additional effect of approximately 0.03 QALY per year, although authors stressed that the

financial benefits may not apply to patients with low baseline risk [20].

The benefits of telerehabilitation not included in the present study should also be noted. Better health outcomes can lead to lower patient resource use and costs. Telerehabilitation may improve access to healthcare, as care can be provided regardless of whether a patient lives close to the rehabilitation center. Thus, telerehabilitation may increase the equity between patients. Telerehabilitation may also increase the possibilities of using the existing base by releasing resources in outpatient clinics and hospitals, which may motivate service providers to promote telerehabilitation care.

CONCLUSIONS

The telerehabilitation compared to standard care was found to be cost-effective, i.e., additional costs are justified by the clinical effects gained. The additional cost of gaining one year of healthy life is in the range of 58 000––96 000 PLN/QALY, depending on the adopted approach, clearly below the profitability threshold in Poland. The therapeutic benefits are driven by the improvement of the patients' clinical condition, the NYHA class, or their QoL as measured by the SF-36 questionnaire.

Article information

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ORIGINAL ARTICLE

Polish Multicenter Registry (Pol-LAS-SE registry). Stress echocardiography in low-gradient aortic stenosis in Poland: numbers, settings, results, complications and clinical practice

Edyta Płońska-Gościniak[1], Jarosław D Kasprzak[2], Tomasz Kukulski[3], Katarzyna Mizia-Stec[4], Maciej Haberka[5], Ludmiła Daniłowicz[6], Małgorzata Peregud-Pogorzelska[1], Janusz Kochanowski[7], Małgorzata Knapp[8], Mirosław Marciniak[9], Barbara Brzezińska[10], Piotr Gościniak[11], Grzegorz Skonieczny[12], Beata Zaborska[13], Ewa Flis-Zaremba[14], Dariusz Kosior[15], Wojciech Witkiewicz[1], Barbara Zawiślak[16], Danuta Sorysz[17], Wojciech Kosmala[18]

[1]Department of Cardiology, Pomeranian Medical University, Szczecin, Poland
[2]Department of Cardiology, Biegański Hospital, Medical University of Lodz, Łódź, Poland
[3]Department of Cardiology, Congenital Heart Disease and Electrotherapy, School of Health Sciences in Zabrze, Medical University of Silesia, Katowice, Poland
[4]Department of Cardiology, School of Medicine in Katowice, Upper-Silesian Medical Centre, Medical University of Silesia, Katowice, Poland
[5]Department of Cardiology, Medical University of Silesia, Katowice, Poland
[6]Department of Cardiology and Electrotherapy, Medical University of Gdansk, Gdańsk, Poland
[7]First Department of Cardiology, Warsaw Medical University, Warszawa, Poland
[8]Department of Cardiology, Medical University of Bialystok, Białystok, Poland
[9]Provincial Polyclinical Hospital, Cardiology Ward, Toruń, Poland
[10]Department of Cardiology, T. Marciniak Hospital, Wrocław, Poland
[11]Laboratory for Noninvasive Cardiac Diagnostics for Children and Adults, prof. Tadeusz Sokołowski Hospital, Szczecin, Poland
[12]Cardiology Department and Intensive Cardiac Unit, Provincial Polyclinical Hospital, Toruń, Poland
[13]Department of Cardiology, Centre of Postgraduate Medical Education, Grochowski Hospital, Warszawa, Poland
[14]Cardiology Department, Province Hospital, Zamość, Poland
[15]Department of Cardiology and Hypertension with Electrophysiological Lab, Central Research Hospital the Ministry of the Interior and Administration, Warszawa, Poland
[16]Intensive Cardiac Care Unit, University Hospital, Kraków, Poland
[17]Department of Cardiology and Cardiovascular Interventions, University Hospital, Kraków, Institute of Cardiology CMUJ, Kraków, Poland
[18]Department of Cardiology, Wroclaw Medical University, Wrocław, Poland

Correspondence to:
Danuta Sorysz, MD, PhD, Department of Cardiology and Cardiovascular Interventions, University Hospital in Kraków, Jakubowskiego 2, 30–688 Kraków, Poland, phone: +48 12 400 22 50, e-mail: dtsorysz@op.pl

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ABSTRACT

Background: The diagnostic workup of low-gradient aortic stenosis (LG AS) is a challenge in clinical practice.

Aims: Our goal was to assess the diagnostic value of stress echocardiography (SE) performed in patients with undefined LG AS with low and preserved ejection fraction (EF) and the impact of its result on therapeutic decisions in Polish third level of reference.

Methods: All the patients with LG AS and with SE performed were recruited in 16 Polish cardiology departments between 2016 and 2019. The main exclusion criteria were as follows: moderate or severe aortic or mitral regurgitation and mitral stenosis.

Results: The study group included 163 patients (52% males) with LG AS who underwent SE for adequate diagnostic and therapeutic decision. In 14 patients DSE was non-diagnostic. The mean aortic valve (AV) pressure gradient was 24.1 (7.3) mm Hg, while an AV area was 0.86 (0.2) cm^2. Among 149 patients with conclusive DSE, severe AS was found in 59.8%, pseudo-severe in 22%, and moderate AS in 18%. There were no cases of death or vascular events related to DSE. Among 142 patients 63 (44%) patients had an aortic valve intervention in a follow-up (median: 208 days; lower-upper quartile: 73–531 days). Based on the result of the DSE test, severe AS was significantly more often associated with qualification to interventional treatment compared to the moderate and pseudo-severe subgroups (P <0.0001).

Conclusions: The DSE test in severe AS is a valuable diagnostic tool in patients with LG AS in Poland.

Key words: aortic stenosis, dobutamine stress echocardiography, low gradient aortic stenosis, stress echocardiography

Kardiol Pol 2021; 79, 5: 517–524

WHAT'S NEW?

The Pol-LAS-SE registry was the first initiative in Poland investigating application of stress echocardiography (SE) in low-gradient aortic stenosis. Despite the time-consuming nature and the lack of reimbursement in Poland, SE is an important method used in the case of low gradient aortic stenosis. The dobutamine SE provided complete hemodynamic information that enabled the division of aortic stenosis into subgroups, however, the registry showed that in everyday practice advanced calculations, e.g. aortic valve projected area is not performed. Only 8.6% of exams were non-diagnostic. In doubtful cases, the final decision was additionally made taking into account the entire clinical presentation, which was reflected in the 2017 Valvular Heart Disease Guidelines, although the study was conducted in previous years. The survey has documented that SE has direct implications for clinical and therapeutic decisions. In our opinion, the observations are trustworthy and reflect current approaches to aortic stenosis in Poland.

INTRODUCTION

Low-flow low-gradient aortic stenosis (LFLG AS) is a frequent hemodynamic type of aortic valve disease, accounting for 30%–50% of all cases of severe aortic stenosis (AS) [1, 2]. The risk of adverse outcome in patients with LFLG AS has been reported to be even higher than in high-gradient AS patients [3]. Low-flow low-gradient aortic stenosis is defined by the coexistence of mean transvalvular gradient <40 mm Hg, effective aortic valve area (AVA) <1.0 cm^2 (0.6 cm^2/m^2 BSA) and stroke volume (SV) index <35 ml/m^2, and may occur with reduced or preserved left ventricular ejection fraction (LVEF): classical and paradoxical type, respectively. Given the discrepant values of valve area and gradient metrics that are a feature of the LFLG profile, a challenging part of the diagnostic process is to determine whether the stenosis is true-severe or pseudo-severe [4, 5]. Recent ESC guidelines endorse a practical stepwise approach for the assessment of AS severity, in which dobutamine stress echocardiography (SE) and CT calcium scoring help to identify candidates for surgery among patients with LFLG AS [5, 6]. According to these recommendations, dobutamine SE using a low-dose protocol plays a crucial role in stratifying the degree of valve stenosis in classical LFLG AS [2, 4, 5]. The inotropic stimulation of left ventricular (LV) myocardium with dobutamine by increasing aortic flow permits a distinction between true-severe and non-severe AS, which is possible in the presence of LV contractile reserve defined as >20% increase in LV stroke volume, as well as, in a proportion of cases not satisfying this criterion by calculating the projected valve area at a normal flow rate, i.e. 250 ml/s [8–10]. A recently published Polish registry of SE showed that dobutamine SE (DSE) was the most commonly used stress echo method, however, its use in non-coronary indications, including LFLG AS, was relatively rare [11].

The current study is the first registry of SE performed in patients with low-gradient aortic stenosis (LG AS) in Poland. This study aimed to evaluate indications, the diagnostic utility of SE, and the impact of information obtained from this test on therapeutic decisions in Polish cardiology centers.

METHODS

Patient population

A total of 163 patients were recruited by 16 Polish cardiology centers dedicated to heart valve disease between 2016 and 2019. Patients were included in the Pol-LAS-SE registry if they had aortic stenosis with mean aortic gradient (MPG) <40 mm Hg on a resting echocardiogram. Patients were excluded if they had more than mild aortic regurgitation, moderate and severe mitral regurgitation, or mild mitral stenosis, as assessed by the multiparametric integrative approach recommended in the current guidelines for native valve regurgitation and stenosis. The treatment (aortic valve replacement [AVR], transcatheter aortic valve implantation [TAVI] or medical management) was left to the discretion of the treating physician who was aware of the results of resting and stress echocardiogram. Based on hospital registries, clinical data were collected and included age, sex, body mass index, co-morbidities, symptoms, heart rate/rhythm, and blood pressure measurements.

Echocardiography

SE was performed using commercially available ultrasound systems. Dobutamine infusion protocol consisted of 5-min (including ca. 3 min for image recording) stages with increments of 10 μg/kg/min up to a maximum dosage of 20 μg/kg/min. Beta-blockers were not withdrawn before stress echo. Left ventricular outflow tract (LVOT) diameter was measured at rest and considered constant during stress echo. The following measurements were performed at rest and each SE stage:

- stroke volume (SV) was measured in the LV outflow tract (LVOT VTI × LVOT area);
- aortic valve area was calculated by the continuity equation;
- mean aortic gradient was obtained by the Bernoulli formula;
- left ventricular ejection fraction was measured using the biplane Simpson method. For all these parameters, we averaged the measures of 3 cycles in normal sinus rhythm and 5 cycles in the presence of irregular rhythm.

The image recordings performed at each stage could be subsequently displayed for offline analysis on quad

— 4 screen mode. The presence of flow reserve was assumed if ΔSV (i.e. peak SV–resting SV) was >20% of resting SV value. The non-diagnostic group includes tests whose technical quality or lack of data prevented being assigned to one of the categories. True severe AS was confirmed if stimulated values were as follow (increase of SV >20% and any increase of EF, MPG ≥40 mm Hg, AVA ≤1.0 cm^2) while pseudo severe AS was confirmed if (an increase of SV >20% and any increase of EF, MPG <40 mm Hg, AVA >1.0 cm^2) was observed. Patients without SV increase by more than 20%, stimulated MPG <40 mm Hg, any AVA change, any EF increase were considered as undefined AS (non-conclusive AS). Moderate AS was defined as AVA >1.0 cm^2 and MPG <40 mm Hg at baseline, and 1.5 cm^2 >AVA >1.0 cm^2 and MPG <40 mm Hg during dobutamine infusion.

The bioethics committee approval was not required.

Statistical analysis

Results were expressed as numbers and percentages for categorical variables and as mean (SD) or median (interquartile range) for continuous variables. The distribution of continuous variables was tested for normality with the Shapiro-Wilk test. In cases of slight deviations, skewness determined the choice of tests. Non-parametric tests were used when the skewness was greater than <–1.7 or >1.7. Comparisons between frequencies were made using the chi-square test of independence or Fisher's exact test (when the number of expected events was less than 5). Differences between means were assessed using Student's t-tests or Satterthwaite's method — or by one-way analysis of variance (ANOVA) when the number of compared groups was greater than two — followed by the Tukey multiple comparison test. In the case of high skewness, the analyzes were performed with non-parametric Mann-Whitney or Kruskal-Wallis tests.

All statistical tests were performed at α = 0.05 (2-sided). Analyses were performed using SAS software version 9.4. Data with normal distribution are presented at mean (SD).

RESULTS

Characteristics of the study group

Clinical characteristics

The multicentre Pol-LAS-SE registry involved 163 patients, including 85 (52.1%) males, with LG AS who underwent SE for adequate diagnostic and therapeutic facilities.

Fourteen (8.6%) out of the 163 SE tests performed within the Pol-LAS-SE registry were non-diagnostic and did not allow the evaluation of LG AS severity (Figure 1). Of the 14 non-diagnostic tests, 13 were tests with dobutamine, and 1 was an exercise test. Based on the SE results, the remaining 149 patients were divided into three categories: 89 (59.8%) patients with severe AS (severe subgroup); 33 (22.1%) to pseudo-severe AS (pseudo-severe subgroup) and 27 (18.1%) to the moderate AS group (moderate subgroup).

Table S1 (Supplementary material, *Table S1*) summarises the clinical characteristics of the overall cohort and subgroups according to the LG AS category. The most common co-morbidities in all the study groups were arterial hypertension and coronary artery disease (CAD); 52 (32.9%) patients were diagnosed with atrial fibrillation. The vast majority of patients presented symptoms of heart failure (94%).

Parameters of resting and stress echocardiography test

Overall, stress echocardiography test was performed in 163 patients; 157 (96.3%) subjects underwent a dobutamine test, while 6 (3.7%) had an exercise stress test. The mean (SD) dobutamine maximal dose was 19.7 (2.8) μg/kg/min, while a mean (SD) exercise load was 58.3 (12.9) Watts. Table S2 (Supplementary material, *Table S2*) shows the hemodynamic data of the SE test conducted in the study cohort overall and three subgroups by the severity of the LG AS (severe, pseudo-severe, and moderate). There was no statistically significant difference in the dobutamine dose used in each study group; however, differences in the blood pressure (BP) values were found.

In the overall cohort, average mean pressure gradient value was 24.1 (7.3) mm Hg, while an AVA was 0.86 (0.2) cm^2. Overall, a mean (SD) SV index was 29.9 (8.8) ml/m^2. During a SE test, we have observed a significant increase in the transaortic Pmax, MPG, and SV as well as a significant shortening of the LV ejection time (ET) (P <0.0001). The mean (SD) relative increase in SV at peak stress was 27.8 (24.6),

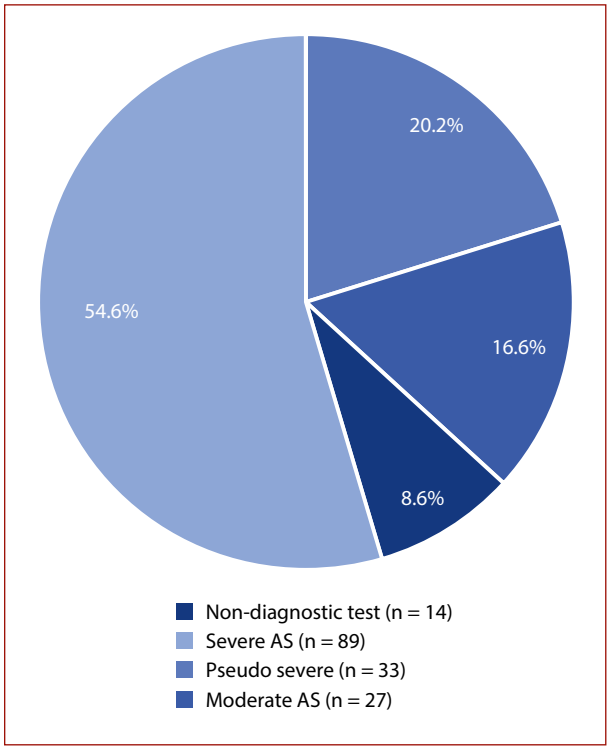

Figure 1. Results of the stress echo test in patients enrolled into Pol-LAS-SE registry.

Abbreviations: AS, aortic stenosis

Table 1. Differences in the echocardiographic and haemodynamic parameters between stress and resting tests by the severity of aortic stenosis (absolute deltas unadjusted for the baseline measurement)

	Moderate AS (n = 27)	Pseudo-severe AS (n = 33)	Severe AS (n = 89)	*P* — overall test	Moderate vs pseudo--severe	Moderate vs severe	Pseudo-severe vs severe
HR, mean (SD), bpm	31.2 (24.5)	23.1 (17.1)	23.5 (15.3)	0.14	—	—	—
SBP, mean (SD), mm Hg	8.5 (16.1)	15.0 (13.4)	11.1 (19.1)	0.39	—	—	—
DBP, mean (SD), mm Hg	–0.9 (12.8)	0.9 (8.6)	1.6 (11.8)	0.64	—	—	—
LVEF, mean (SD), %	7.8 (6.4)	8.8 (5.5)	8.7 (6.4)	0.82	—	—	—
Pmax, mean (SD), mm Hg	13.6 (14.2)	13.5 (9.6)	23.6 (13.0)	<0.001	0.99	0.001	0.001
MPG, mean (SD), mm Hg	9.5 (8.2)	8.3 (6.2)	15.3 (8.2)	<0.001	0.82	0.003	<0.001
VTI LVOT, mean (SD), cm	2.50 (2.4)	7.25 (5.32)	2.92 (4.14)	<0.001	0.003	0.92	<0.001
VTI LVOT / VTI AV, mean (SD)	0.04 (0.06)	0.08 (0.09)	0.02 (0.06)	0.001	0.21	0.47	0.001
AVA, mean (SD), cm^2	0.12 (0.22)	0.32 (0.14)	0.02 (0.13)	<0.001	<0.001	0.008	<0.001
SV, mean (SD), ml	11.7 (10.8)	20.3 (10.4)	13.8 (10.2)	0.002	0.005	0.64	0.007
ET, mean (SD), ms	–15.0 (33.4)	–38.8 (51.7)	–39.7 (46.5)	0.06	—	—	—

Abbreviations: AS, aortic stenosis; AV, aortic valve; AVA, aortic valve area; DBP, diastolic blood pressure; ET, ejection time; HR, heart rate; LVEF, left ventricle ejection fraction; LVOT, left ventricle outflow tract; MPG, mean transvalvular gradient; Pmax, maximal transvalvular gradient; SBP, systolic blood pressure; SV, stroke volume; VTI, time velocity integral

and the presence of a contractile (flow) reserve at 20% threshold was confirmed in 111 (68.5%) patients.

Table 1 summarises the differences in the hemodynamic data and the values of the echocardiographic parameters measured during the peak stage of SE compared to a resting echo test in three subgroups of patients defined by the severity of AS. Patients with severe AS had significantly higher changes in the transaortic gradient compared to the moderate and pseudo-severe subgroups. In the moderate and pseudo-severe subgroups, significantly higher changes in the aortic valve area were observed.

Reasons for the SE termination and complications of the SE test in the overall cohort

In all the patients, the main reason for the termination of the SE test was meeting the study's protocol requirements.

We did not observe any severe cardiovascular events (death, myocardial infarction, or cerebral stroke/TIA) during SE.

One subject developed a non-sustained ventricular tachycardia episode which resolved spontaneously.

In total, 143 patients (87.7%) did not experience any important symptoms during SE.

Mild symptoms (dyspnoea, fatigue, weakness, headache, mild arrhythmia) were reported during the SE only in 20 (12.3%) patients, however, they did not result in the cessation of the SE test and resolved spontaneously.

Characteristics of patients depending on haemodynamic type of aortic stenosis

The patients included in the registry (MPG at rest <40 mm Hg) were divided into subgroups depending on the hemodynamic type of the valve defect based on the resting SVI, LVEF and AVA measurements.

Group A involved LG AS with AVA <1 cm^2, including patients with SVI <35 ml/m^2 and EF <50%, SVI <35 ml/m^2 and LVEF >50% as well as SVI >35 ml/m^2 and LVEF >50%, that form the A1, A2 and A3 subgroups, respectively. The remaining LG AS patients with AVA above 1 cm^2 formed group B which comprised subjects with reduced LVEF <50%, and group C involving patients with LVEF >50% (Figure 2).

The A1 subgroup involved 81 (56.2%) patients with a classical LFLG AS.

The A2 subgroup involved 25 (17.4%) patients with a paradoxical LFLG AS.

The A3 subgroup involved 14 (9.7%) patients with normal flow, low gradient (NFLG) AS.

Group B was formed by 20 LG AS patients (13.9%) with an AVA above 1 cm^2 at rest (1.0 to 1.2 cm^2) and LV impairment.

The remaining patients, 4 (2.8%), with an LG AS and AVA above 1 cm^2 (1.1–1.2 cm^2) at rest and LVEF >50% represented group C.

Table 2 shows the differences in hemodynamic and echocardiographic parameters measured at rest and peak exercise in the groups/subgroups defined based on the haemodynamic type of aortic stenosis.

It was demonstrated that more patients with severe LG AS belonged to the A1 and A2 subgroups, while the B subgroup involved more patients with moderate AS (*P* <0.001). Of the patients with a hemodynamic type of severe LG AS (n = 120), 67.5% subjects presented classical LFLG AS (A1 subgroup); 21.3% had a paradoxical LFLG AS (A2); and 7.5% had NFLG AS (A3 subgroup) with an AVA <1 cm^2, while 3.7% of patients had a borderline AVA (1–1.2 cm^2).

Characteristics of patients according to the transaortic flow

Of the 163 AS patients, 128 subjects had a reduced SVI (LF AS group – SVI <35 ml/m^2); 35 patients had normal SVI (NF AS group; SVI >35 ml/m^2). The most common co-morbidities in both groups were arterial hypertension and CAD.

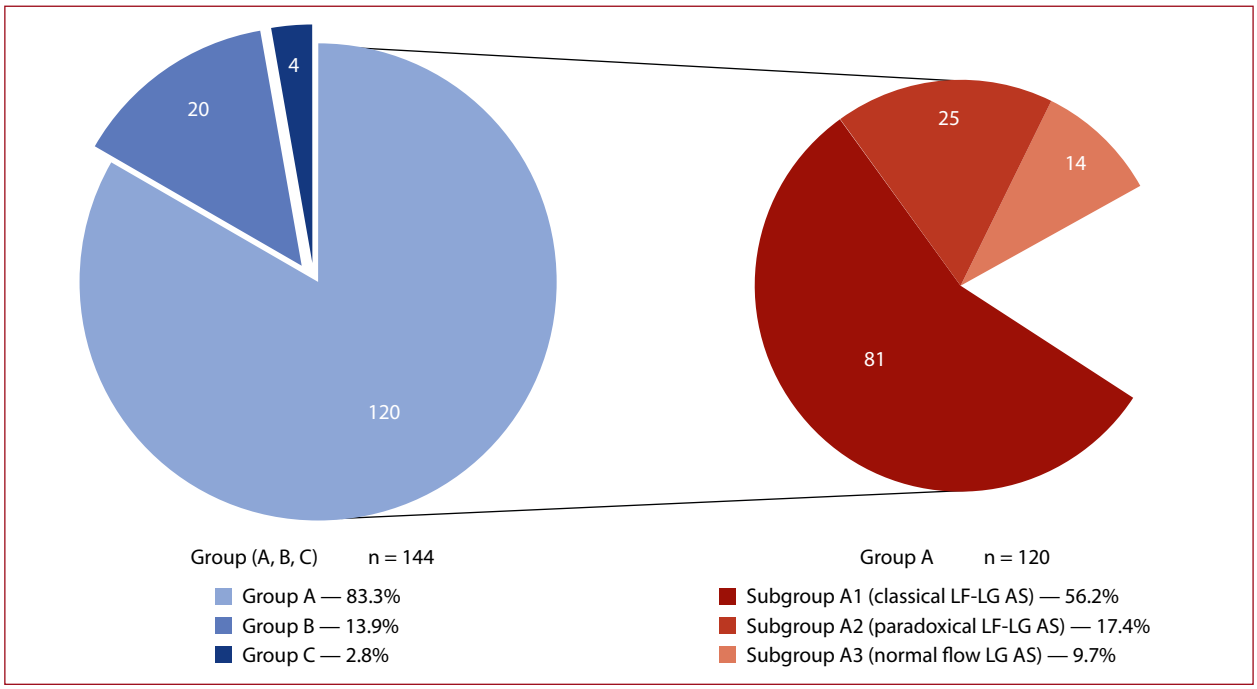

Figure 2. Distribution of low-gradient aortic stenosis patients by the haemodynamic type of the defect (n = 144). Group A: AVA <1.0 cm^2, Group B: AVA >1.0 cm^2, LVEF <50%. Group C: AVA >1.0 cm^2, LVEF >50%. Subgroup A1: classical LFLG AS. Subgroup A2: paradoxical LFLG AS. Subgroup A3: NFLG AS.

Abbreviations: AVA, aortic valve area; LF, low flow, NF, normal flow, LG, low gradient

Table 2. Differences in echocardiographic and haemodynamic measurements between the stress and resting conditions by the haemodynamic type of the low-gradient aortic stenosis (absolute deltas, unadjusted for the baseline)

	A1 (n = 81)	A2 (n = 25)	A3 (n = 14)	B (n = 20)	*P* overall test	A1 vs A2	A1 vs A3	A1 vs B	A2 vs A3	A2 vs B	A3 vs B
HR, mean (SD), bpm	22.5 (15.3)	26.2 (21.3)	26.7 (20.9)	35.3 (27.4)	0.09	—	—	—	—	—	—
SPB, mean (SD), mm Hg	11.4 (16.9)	17.1 (16.9)	4.5 (17.8)	3.3 (15.50	0.05	0.52	0.61	0.26	0.21	0.06	1.00
DBP, mean (SD), mm Hg	1.0 (11.6)	6.1 (7.2)	1.2 (12.1)	–2.1 (12.3)	0.13	—	—	—	—	—	—
LVEF, mean (SD), %	8.8 (6.1)	8.0 (6.9)	5.8 (9.2)	8.2 (4.1)	0.46	—	—	—	—	—	—
Pmax, mean (SD), mm Hg	17.5 (12.6)	23.5 (12.6)	26.6 (17.2)	13.8 (16.1)	0.01	0.22	0.10	0.71	0.90	0.09	0.040
MPG, mean (SD), mm Hg	11.5 (8.5)	14.0 (11.5)	13.6 (11.5)	10.6 (9.5)	0.45	—	—	—	—	—	—
VTI LVOT / VTI AV mean (SD)	0.03 (0.07)	0.07 (0.12)	0.02 (0.14)	0.05 (0.05)	0.32	—	—	—	—	—	—
AVA, mean (SD), cm^2	0.10 (0.20)	0.12 (0.29)	0.19 (0.14)	0.07 (0.21)	0.37	—	—	—	—	—	—
SV, mean (SD), ml	14.3 (11.7)	13.8 (9.8)	11.6 (10.8)	13.4 (10.1)	0.86	—	—	—	—	—	—
ET, mean (SD), ms	–32.5 (40.0)	–2.6 (47.3)	–74.6 (70.1)	–15.4 (25.3)	0.002	0.76	0.007	0.47	0.14	0.21	0.002

Abbreviations: see Table 1 and Figure 2

The LF AS group included more patients with a severe AS (78 [60.9%] vs 11 [31.4%] patients; *P* <0.002).

Table 3 shows the absolute differences in the hemodynamic and echocardiographic parameters measured in the resting and stress conditions in LF AS and NF AS groups.

Stress echocardiography test results and clinical interventions

Comparison of the severe, moderate and pseudo-severe subgroups by the intervention

In total, 142 patients were followed up for potential qualification to aortic valve interventions (AVI) including TAVI, BAV (balloon aortic valvuloplasty), AVR. Sixty-three (44.4%) patients underwent an aortic valve intervention. No intervention was performed in 79 (55.6%) patients. The median follow-up time in the overall cohort was 208 days (interquartile range, 73–531 days). However, all interventions were performed between 3-303 days after stress echo test.

During the follow-up, 63 (84%) patients from the severe group (n = 75), when defined based on the results of the stress echo test, qualified for the aortic valve procedures (TAVI, BAV, AVR); 52 (69.3%) underwent AVI; 5 (6.7%) patients were awaiting intervention; while 6 (8%) subjects did not consent to undergo AVI. Twelve (16%) patients from the severe group did not undergo aortic valve intervention.

In the moderate group (n = 26), aortic valve intervention (along with coronary arteries revascularisation) was

Table 3. Differences in the echocardiographic and haemodynamic measurements between stress and resting conditions by trans-aortic flow (absolute deltas)

	LF AS n = 128 (SVI <35 ml/m²)	NF AS n = 35 (SVI ≥35 ml/m²)	*P*
HR, mean (SD), bpm	26.2 (18.2)	24.8 (18.9)	0.69
SBP, mean (SD), mm Hg	8.4 (17.4)	11.8 (17.3)	0.35
DBP, mean (SD), mm Hg	–0.1 (12.3)	1.5 (11.3)	0.50
LVEF, mean (SD), %	7.2 (7.2)	8.7 (6.0)	0.24
Pmax, mean (SD), mm Hg	19.2 (14.7)	18.8 (13.4)	0.87
MPG, mean (SD), mm Hg	11.0 (8.5)	12.4 (8.5)	0.40
VTI LVOT/ VTI, mean (SD)	0.04 (0.10)	0.04 (0.08)	0.97
AVA, mean (SD), cm²	0.20 (0.18)	0.08 (0.22)	0.004
SV, mean (SD), ml	11.6 (11.8)	14.2 (11.2)	0.22
ET, mean (SD), ms	–48.3 (59.3)	–31.5 (41.5)	0.07

Abbreviations: LF, low flow; NF, normal flow. Other abbreviations: see Table 1

performed in as few as 4 patients (15.4%), while 22 (84.6%) did not undergo intervention.

During the follow-up, only 3 (10%) out of 30 patients in the pseudo-severe subgroup underwent intervention (TAVI) with associated revascularization of coronary arteries. One patient (3.3%) did not consent to intervention. In total, 27 (86.7%) of the patients in the pseudo-severe group did not undergo aortic valve intervention.

After exclusion non-conclusive results, the final diagnosis of severe AS based on the SE test result contributed to the appropriate selection of interventional treatment, much more frequent in this group of patients compared to the subgroups: with moderate or pseudo-severe AS (P <0.0001).

Regarding the SE test results, the patients with severe AS group were more often scheduled for the AVR procedure (25 patients; 33.3%; including one awaiting patient) compared to the pseudo-severe (0) and moderate subgroups (1 subject; 3.8%; P <0.0001).

Similarly, patients in the severe AS group, defined on the results of the SE test, were more often qualified for the TAVI procedure (31 patients; 41.3%; including 3 awaiting patients) compared to the pseudo-severe (3 patients; 9.7%) and moderate subgroups (2 subjects; 7.4%; P <0.003).

In total, only 7 patients underwent the BAV procedure, including 5 patients in the severe group, as a bridge therapy (P = 0.381).

DISCUSSION

This study demonstrated that in Polish hospitals, SE was performed in accordance with the European guidelines for valvular heart disease. The most common indication for SE was classical LFLG-AS. SE testing was safe, with a low rate of side-effects being reported. The information provided by SE was useful in decision-making on the interventional treatment of LG-AS.

Data obtained from a recent Pol-STRESS ECHO registry show that stress echocardiography performed in valvular heart diseases accounts for 4.4% of all echocardiographic stress tests in Poland, with low gradient AS and asymptomatic AS being the most frequent underlying reasons for this diagnostic approach [11]. Analogous data from the European Registry VHD II demonstrated similar numbers for Western Europe (5.4%, including 3.1% in AS), and a much lower proportion of stress echo with "valvular" indications in Eastern European countries reaching only 0.6% [13].

AS is the most common valvular heart disease leading to surgery or catheter intervention, and its prevalence has increased when comparing the results of VHD and VHD II registries [13, 14].

According to the guidelines, the indications for SE in AS are the verification of asymptomatic status in patients with no determined timing of surgery (exercise) or clarification of stenosis severity in the setting of a low-flow state (dobutamine) [2, 4, 5, 6, 11, 14].

Numbers, settings, safety of Pol-LAS-SE registry

The present registry included 163 patients from 16 centers in Poland. The most frequently used modality was stress with dobutamine, and only in the minority of cases (3.7%), an exercise test was conducted. It should be underscored that the collection of data for the registry started in 2016, i.e. before the publication of updated recommendations that limited the use of DSE to the classical LFLG-AS. Thus, this is the reason why a number of DSE tests were carried out in the paradoxical type of LFLG-AS. In the vast majority of patients (86%) SE was conclusive, significantly adding to the diagnostic process and facilitating subsequent decision making. Even though coronary artery disease was diagnosed in 63.6% of patients, including 36.8% with multivessel disease, the rate of SE-associated adverse events was low. In our report, 87.7% of patients completed the test without any complications, while serious arrhythmias in the form of unstable ventricular tachycardia occurred only in 0.6% of patients.

In our registry, the median time between DSE and invasive treatment was 208 days (interquartile range, 73–531 days). This result has several reasons: the beginning of the diagnostic pathway, the need for diagnosis and treatment of concomitant diseases (i.e. gastrointestinal

Table 4. Haemodynamic characteristics of pseudosevere aortic stenosis group at baseline and during the dobutamine stress echocardiography

Pseudo-severe AS	REST	STRESS	*P*
HR, mean (SD), bpm	73.9 (10.9)	97.0 (20.6)	<0.0001
SPB, mean (SD), mm Hg	131.5 (14.4)	146.5 (17.3)	<0.0001
DBP, mean (SD), mm Hg	78.0 (11.0)	78.9 (14.1)	0.587
Pmax, mean (SD), mm Hg	36.7 (13.5)	50.2 (14.3)	<0.0001
MPG, mean (SD), mm Hg	20.5 (6.6)	28.8 (8.5)	<0.0001
VTI AV, mean (SD), cm	63.4 (17.8)	68.3 (16.8)	0.032
VTI LVOT, mean (SD)	18.8 (4.7)	26.0 (8.0)	<0.0001
VTI LVOT / VTI AV, mean (SD)	0.305 (0.112)	0.383 (0.077)	<0.0001
AVA, mean (SD), cm^2	0.89 (0.09)	1.21 (0.17)	<0.0001
SV, mean (SD), ml	57.1 (15.8)	77.4 (19.4)	<0.0001
ET, mean (SD), ms	305.8 (39.7)	266.9 (53.7)	0.0002

Abbreviations: see Table 1

bleeding, hyperthyroidism, lower leg skin ulceration, etc.) and the initial refusal of surgical treatment, especially in patients with minor symptoms. However, the waiting time for TAVI is long.

Interpretation of SE results

A prerequisite for a reliable interpretation of DSE in LFLG-AS is the presence of contractility reserve. Its reduction due to LV scaring or fibrosis may complicate determining the degree of stenosis because of the inability to sufficiently increase SV, i.e. by >20%. In the current registry, the presence of flow (contractile) reserve was demonstrated in 111 subjects (68.5%). Despite the lack of adequate increase in LV flow in response to dobutamine, the test in the vast majority of remaining subjects was interpreted as diagnostic, and 75 patients were finally diagnosed with severe aortic stenosis and scheduled for interventional treatment. The final interpretation of AS severity in the group without contractility reserve was done arbitrarily by the echocardiographer based on the comprehensive patient assessment including both imaging and clinical data i.e. borderline gradient or SV, significant valvular calcification, presence of AF, age, etc. Eventually, severe low gradient AS requiring valvular intervention was diagnosed in 89 patients (54.6%). This registry showed that the calculation of projected AVA — an alternative approach permitting in some patients unable to increase SV by 20% a conclusive evaluation with DSE — is not a standard part of diagnostic strategies assessing AS severity in Poland.

There was no statistically significant difference in dobutamine dose among the groups identified on the basis of stenosis severity. However, the response of systolic and diastolic blood pressure to the administration of dobutamine was blunted in patients with severe AS, which is consistent with the progression of hemodynamic disturbances with an increasing stenosis degree.

The stress-assisted diagnosis of severe aortic stenosis was most common in the classical (67.5%) and paradoxical low-flow low gradient AS categories (21.3%). In recent years, the latter group has been of particular interest to clinicians because of the challenges associated with adequate quantification of AS severity and prognostic stratification. In our registry, the prevalence of paradoxical low flow severe AS diagnosed with stress echocardiography was higher than previously published rates of 3%–13% [16–18]. The reason for this difference might be the fact that the presented data from our registry were direct findings from DSE, with no further verification by other imaging modalities or intraoperative inspection as was the case with the above-referenced studies.

Pol-LAS-SE results and the decision for interventional treatment

The crucial importance of stress echocardiography is to help in the decision-making for interventional treatment. Accordingly, the final diagnosis of severe AS, being an indication for surgery or catheter intervention, was established in 84% of patients from our registry. Another contribution from SE to the diagnostic process was the distinction between trivial and moderate AS in patients undergoing surgical revascularization since in this case concomitant aortic valve replacement should be considered when confirming moderate AS [5]. In our registry, this scenario took place in 15.4% of patients diagnosed to have moderate AS.

The most interesting group is the pseudosevere AS. These patients are rarely referred for surgery after the stress test. However, SE in this subset might provide meaningful information by examining whether there is "stretch" in AVA (Table 4).

Limitations

The SE protocols used by the participating centers did not include some of the echocardiographic parameters proposed for the assessment of aortic valve hemodynamics, such as transvalvular flow rate and projected AVA, which might improve the accuracy of the diagnostic process. As all of 16 participating centers were recruited on a voluntary basis, the data may not be fully representative of the entire country, however, the majority of university centers in Poland were involved.

CONCLUSIONS

SE used in Polish cardiology centers proved to be a valuable diagnostic procedure in the evaluation of patients with LFLG-AS, delivering relevant information in the context of subsequent patient management, especially valvular interventions.

The proportion of non-diagnostic/inconclusive tests unable to stratify the severity of aortic stenosis was low.

The protocols of SE used in Polish cardiology centers were in line with the European guidelines for valvular heart disease.

The SE-related adverse events of the stress test in patients with aortic stenosis were rarely reported and SE did not require discontinuation.

Supplementary material

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

Article information

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ORIGINAL ARTICLE

Atrial fibrillation risk scores to evaluate left atrial substrate based on voltage analysis in long-standing persistent type of arrhythmia

Radosław Marek Kiedrowicz, Maciej Wielusiński, Andrzej Wojtarowicz, Jarosław Kaźmierczak

Cardiology Department, Pomeranian Medical University, Szczecin, Poland

Correspondence to:
Radosław Marek Kiedrowicz, MD, PhD, Pomeranian Medical University, Cardiology Department, Powstańców Wlkp. 72, 70–111 Szczecin, Poland, phone: +48 91 466 13 78, e-mail: radkied@wp.pl

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ABSTRACT

Background: Pre-ablation identification of left atrial (LA) low voltage areas (LVA) among long-standing persistent atrial fibrillation (LSPAF) population remains challenging.

Aims: The aim of the study was to analyze the potential of selected scores originally developed to assess arrhythmia recurrences, thromboembolic complications, or progression from paroxysmal to persistent AF to predict the presence of LA-LVA in LSPAF patients.

Methods: One hundred and fifty-two patients underwent pulmonary vein isolation followed by high-density-high-resolution LA voltage mapping. AF risk scores, such as APPLE, ATLAS, CAAP-AF, DR-FLASH, CHA2DS2-VASc, and HATCH were retrospectively calculated. A receiver operating characteristic curve analysis was performed to evaluate the ability of the scores to predict LVA.

Results: Low voltage areas were detected in 52% of the patients. 28% of the patients with LVA presented severe global LVA burden, whereas 56% of the patients showed a disseminated pattern of remodeling. CAAP-AF ≥7, DR-FLASH ≥4, and CHA2DS2-VASc ≥3 predicted the presence of LVA, whereas ATLAS ≤7 indicated the absence of LVA. ATLAS ≤8, CAAP-AF ≤9, DR-FLASH ≤4, and CHA2DS2-VASc ≤3 predicted the absence of severe LVA. APPLE ≤3 and CHA2DS2-VASc ≤2 predicted the absence of a LVA disseminated pattern. Among predictive scores, ATLAS (AUC, 0.633, 95% CI, 0.543–0.723, P = 0.004), DR-FLASH (AUC, 0.696; 95% CI, 0.594–0.81; P <0.001), and CHA2DS2-VASc (AUC, 0.644; 95% CI 0.518–0.77; P = 0.025) were the best predictors for the absence of LVA, severe LVA and a disseminated pattern of LVA, respectively.

Conclusions: Atrial fibrillation risk stratification with specific scoring systems can unmask the presence of LA-LVA in the LSPAF population.

Key words: atrial fibrillation, atrial fibrillation risk scores, long-standing persistent atrial fibrillation, low voltage areas, voltage mapping

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INTRODUCTION

Important variables associated with atrial fibrillation (AF) pathogenesis and commonly considered for fibrotic remodeling are low voltage areas (LVA) in the left atrium (LA), detected by bipolar voltage mapping [1]. The pre-ablation identification of LVA could essentially contribute to a choice of particular individualized AF therapy, unmasking patients who are unlikely to remain in sinus rhythm or require extensive substrate modification. However, parameters predicting LVA burden are yet to be established, especially among the long-standing persistent AF (LSPAF) population [2]. This study aimed to analyze the potential of selected, easily applicable clinical scores originally developed to assess arrhythmia recurrences after AF ablation, thromboembolic complications, or progression from paroxysmal to persistent AF to predict the presence of LVA in LSPAF patients.

METHODS

Patient selection

One hundred and sixty-six consecutive LSPAF patients who underwent RF point-by-point pulmonary vein isolation (PVI) were enrolled prospectively. Direct current cardioversion was applied to restore sinus rhythm in all patients following PVI. Only individuals able to maintain sinus rhythm (n = 152, 92% of the total study popula-

WHAT'S NEW?

This study aimed to analyze the potential of selected clinical scores to predict the presence of left atrial low voltage areas (LA-LVA), detected by invasive voltage mapping during catheter ablation in long-standing persistent AF patients. The study population included 152 patients who underwent pulmonary vein isolation (PVI), a widely accepted treatment strategy for AF. It was found that some AF risk scores significantly predicted LA-LVA before ablation. Among those scores, ATLAS, DR-FLASH, and CHA_2DS_2-VASc were the best predictors for the absence of LVA, severe LVA, and the disseminated pattern of LVA, respectively. These findings could help to identify individuals requiring both less and more extensive ablation to modify the LA-LVA substrate, in addition to PVI when an ablation strategy is chosen.

tion) were included in the analysis. To assess the large unselected LSPAF population, the only factors that might significantly alter the accuracy of LVA burden detection were taken into account as exclusion criteria. Therefore, only patients with a history of an AF ablation procedure or any cardiac surgery, severe valvular disease, or a mechanical valve were excluded. All antiarrhythmic drugs were discontinued for at least five half-lives before ablation. Beta-blockers were allowed throughout the study (n = 103). The study protocol was approved by a local institutional review board and all patients provided written informed consent.

AF risk scores selection and calculation

It was decided to only assess those AF risk scores that could be simply calculated. Only scores incorporating non-invasive parameters collected with widely available techniques and calculated without dedicated software were selected. In order to focus on the pre-ablation identification of LVA, risk scores requiring the assessment of post-ablation arrhythmia recurrence were excluded. Therefore clinical scores were applied as follows: APPLE (based on Age >65 years, Persistent AF, impaired glomerular filtration rate <60 ml/min/1.73 m^2, LA diameter ≥43 mm, Ejection fraction <50%) [3], ATLAS (based on Age >60 years, persistent AF Type, indexed Left Atrial volume, female Sex, and current Smoking) [4], CAAP-AF (based on Coronary artery disease, Atrial diameter, Age >70 years, Persistent or long-standing AF, number of Antiarrhythmic drugs failed and Female sex) [5] and DR-FLASH (based on Diabetes mellitus, Renal dysfunction, persistent AF type, LA diameter >45 mm, Age >65 years, female Sex, and Hypertension) [6], which were originally developed to assess arrhythmia recurrences after AF ablation. Moreover, the CHA_2DS_2-VASc score (based on Congestive heart failure, Hypertension, Age >75 years, Diabetes, previous Stroke or transient ischemic attack, Vascular disease, Age >65 years, and female Sex) [7] designed to predict thromboembolic AF complications and the HATCH score (based on Heart failure, Age >75 years, previous Transient ischemic attack or stroke, Chronic obstructive pulmonary disease, and Hypertension) [8] to predict a progression from paroxysmal to persistent AF, were included as general scores.

Detection of LVA

All patients underwent high density-high resolution LA bipolar voltage mapping using the CARTO®3 system fitted with a CONFIDENSE™ module (Biosence-Webster). This mapping protocol is described in detail elsewhere [2]. Briefly, this was performed during coronary sinus (CS) pacing with a Pentaray catheter. The voltage map was created during CS pacing to reduce the occurrence of spontaneous atrial ectopy and to facilitate the identification of incorrectly annotated points. To ensure detailed mapping, the distance filling threshold was set at 5 mm, the tissue proximity filter was always enabled and only mapping sites that were within a distance of 5 mm from the acquired shell contributed to the voltage map. Further discrete mapping using a Thermocool SmartTouch catheter (Biosence-Webster), which covered less than 10% of the total LA surface area (TSA) at sites presenting inadequate Pentaray-tissue contact, was performed if necessary. Electrograms (EGM) were only accepted if a contact force was ≥6 g. EGM amplitude ≥0.5 mV was defined as normal and <0.5 mV as diseased tissue. All points presenting low voltage were visually inspected and those incorrectly annotated were deleted from the map. An extension of all areas showing low voltage potentials at least 5 mm away from the ablation lesion set was measured with custom CARTO®3 system software. The global LVA burden was calculated as a sum of LVA and then expressed as a percentage of TSA. The part of the PV inside ablation encirclement, LA appendage and an area adjacent to the fossa ovalis were excluded from TSA calculations. The extent of global LVA burden >20% of TSA was arbitrarily considered as severe based on our observation that all detected LVA can be easily ablated if it occupies less than 20% of TSA [2]. The body of LA was segmented into 5 areas: septum, anterior, posterior, inferior, and lateral wall. If LVA were identified within 3 out of 5 LA segments it was considered a disseminated pattern of voltage-defined remodeling.

Statistical analysis

All continuous variables are expressed as a median and interquartile range [Q1-Q3] as not normally distributed. The categorical variables are presented as values and percentages. Comparisons between groups were performed with the Mann–Whitney U-test. A receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of

AF risk scores to predict LVA. The area under the ROC curve (AUC) was used to evaluate the accuracy of their prognostic values [9]. The sensitivity, specificity, positive predictive value and negative predictive value were calculated with corresponding 95% confidence intervals (CI). Optimal cut-off points were determined by an analysis of sensitivity and specificity values derived from ROC curve data, prioritizing high sensitivity values. Hanley and McNeil's method was used to compare AUC for LVA Statistical significance was accepted at P value < 0.05. The analysis was performed using Statistica software version 13.3 (StatSoft).

RESULTS

The baseline characteristics of the study population, which includes mean AF risk score values, are presented in Table 1. LVA (15 [7.5–31] cm^2) were detected in 52% (79/152) of the patients. Twenty-eight percent of the patients with LVA (22/79) presented a severe global LVA burden >20% of the total LA surface area, whereas 56% of the patients (44/79), a disseminated pattern of remodeling, as 3 out of 5 LA segments were affected. Among the patients with detected LVA, 48% (38/79) had documented LVA on the septum (8 [3–12] cm^2), 58% (46/79) on the anterior wall (6.5 [2–10.5] cm^2], 77% (61/79) on the posterior wall (7.5 [4–12] cm^2), 44% (35/79) on the inferior wall (6 [4–10] cm^2), and 25% (20/79) on the lateral wall (3.5 [1.5–6] cm^2). Patients with detected LVA and severe LVA pattern had higher values of ATLAS, CAAP-AF, DR-FLASH, and CHA_2DS_2-VASc scores than those without LVA (Table 2).

Predictive scores for LVA

On the ROC curve analyses, only the ATLAS, CAAP-AF, DR-FLASH, and CHA_2DS_2-VASc scores showed significant predictive values for LVA (Table 3, Figure 1). The CAAP-AF, DR-FLASH, and CHA_2DS_2-VASc score exhibited moderate positive results, whereas ATLAS offered a negative predictive ability for LVA. While comparing AUC among the predictive scores no significant difference was noted. There were 18% of the patients with ATLAS ≤ 7 (28/152), 32% (49/152) with CAAP-AF ≥ 7, 34% (52/152) with DR-FLASH ≥ 4, and 24% (37/152) with CHA_2DS_2-VASc ≥ 3 in the LVA cohort.

Table 1. Baseline characteristics of the study population (n = 152)

Parameters	Value
AF duration, months	24 (12–36)
Age, years	63 (58–67)
Females, n (%)	27 (18)
BMI, kg/m^2	30.1 (27.5–32)
Hypertension, n (%)	123 (81)
Moderate mitral regurgitation, n (%)	40 (26)
Moderate tricuspid regurgitation, n (%)	29 (19)
Chronic coronary syndrome, n (%)	34 (22)
Prior myocardial infarction, n (%)	11(7)
Heart failure, n (%)	38 (25)
eGFR <60 ml/min/1.73 m^2, n (%)	17 (11)
Diabetes, n (%)	32 (21)
Hyperthyroidism, n (%)	17 (11)
LVEF, %	60 (55–65)
LA antero-posterior diameter, mm	47 (44–50)
LAAI, cm^2/m^2	13.0 (11.6–15.5)
LAVI, ml/m^2	47.0 (37.7–59.4)
Enlarged LA (LAVI >34 ml/m^2), n (%)	124 (82)
Severely enlarged LA (LAVI >48 ml/m^2), n (%)	65 (43)
APPLE score	2 (2–3)
ATLAS score	8 (7–10)
CAAP-AF score	7 (6–8)
DR-FLASH score	4 (3–5)
CHA_2DS_2-VASc score	2 (1–3)
HATCH score	1 (1–2)

Abbreviations: AF, atrial fibrillation; BMI, body mass index; eGFR, estimated glomerular filtration rate; LA, left atrium; LAAI, left atrial area index; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction

Predictive scores for severe LVA

On the ROC curve analyses, only ATLAS, CAAP-AF, DR-FLASH, and CHA_2DS_2-VASc scores showed significant predictive values for severe LVA (Table 4, Figure 2). However, all scores presented a high negative association. Areas under the ROC-curve, which were ATLAS, CAAP-AF, DR-FLASH and CHA_2DS_2-VASc suggested moderate discriminative power, but in the case of CHA_2DS_2-VASc the highest values. In the comparison of AUC among the predictive scores no significant difference was observed. It was noted that 7% (10/152) of the patients with ATLAS ≤8, 12% (18/152) with CAAP-AF ≤9, 9% (13/152) with DR-FLASH ≤4, and 9% (13/152) with CHA_2DS_2-VASc ≤3 within the severe LVA cohort.

Table 2. Comparison of atrial fibrillation risk scores among different left atrial low voltage areas patterns

	LVA (+) n = 79	LVA (–) n = 73	P	Severe LVA (+) n = 22	Severe LVA (–) n = 130	P	Disseminated LVA pattern (+) n = 44	Disseminated LVA pattern (–) n = 108	P
APPLE	2 (2–3)	2 (2–3)	0.39	2 (2–3)	2 (2–3)	0.89	2 (2–3)	3 (3–4)	0.02
ATLAS	8 (7–11)	7 (6–10)	0.005	9 (8–11)	7 (6–10)	0.004	8 (6–10)	8 (7–11)	0.50
CAAP-AF	7 (6–8)	6 (5–8)	0.04	8 (6–9)	7 (5–8)	0.01	7 (6–8)	7 (6–8)	0.58
DR-FLASH	4 (3–5)	3 (3–4)	0.02	4 (4–5)	4 (3–4)	0.003	4 (3–5)	4 (3–5)	0.65
CHA_2DS_2-VASc	3 (2–3)	2 (1–3)	0.001	3 (2–4)	2 (1–3)	0.001	2 (1–3)	3 (2–3)	0.09
HATCH	1 (1–2)	1 (1–2)	0.36	1 (1–2)	1 (1–2)	0.66	1 (1–2)	1 (1–2)	0.95

Abbreviations: LVA, left atrial low voltage areas

Table 3. Receiver operating characteristic curve analysis to compare the ability of atrial fibrillation risk scores to predict the presence of absolute left atrial low voltage areas

	AUC	95% CI	*P*	Best cut-off value	Accuracy	Sensitivity	Specificity	PPV	NPV
APPLE	0.54	0.449–0.632	0.39	2	0.539	0.937	0.890	0.532	0.615
ATLAS	0.633	0.543–0.723	0.004	7	0.632	0.844	0.632	0.604	0.707
CAAP-AF	0.596	0.506–0.686	0.04	7	0.579	0.620	0.466	0.590	0.565
DR-FLASH	0.61	0.521–0.699	0.02	4	0.586	0.658	0.493	0.591	0.578
CHA_2DS_2-VASc	0.657	0.571–0.743	<0.001	3	0.618	0.506	0.260	0.678	0.581
HATCH	0.543	0.451–0.634	0.36	1	0.539	0.899	0.849	0.534	0.579

Abbreviations: AUC, area under the receiver operating characteristic curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value

Table 4. Receiver operating characteristic curve analysis to compare the ability of atrial fibrillation risk scores to predict the presence of severe left atrial low voltage areas

	AUC	95% CI	*P*	Best cut-off value	Accuracy	Sensitivity	Specificity	PPV	NPV
APPLE	0.491	0.359–0.623	0.89	5	0.859	0.045	0	1.0	0.858
ATLAS	0.693	0.58–0.8	<0.001	8	0.535	0.810	0.512	0.215	0.937
CAAP-AF	0.672	0.542–0.789	0.005	9	0.810	0.333	0.107	0.350	0.885
DR-FLASH	0.696	0.594–0.81	<0.001	4	0.528	0.875	0.529	0.20	0.950
CHA_2DS_2-VASc	0.748	0.653–0.878	<0.001	3	0.683	0.714	0.322	0.278	0.932
HATCH	0.529	0.413–0.644	0.62	1	0.275	1.0	0.851	0.169	1.0

Abbreviations: see Table 3

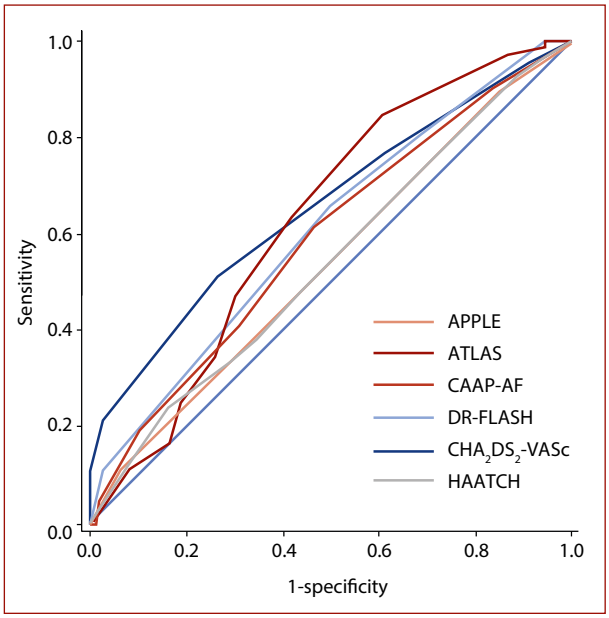

Figure 1. A comparison of atrial fibrillation risk scores for the prediction of low voltage areas

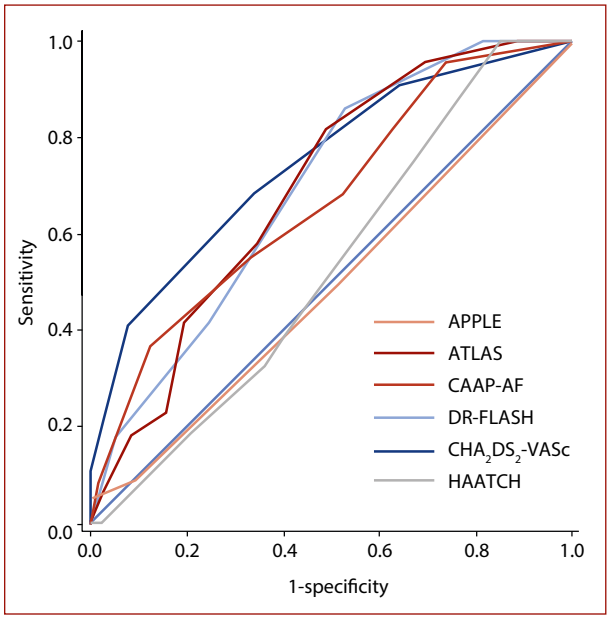

Figure 2. A comparison of atrial fibrillation risk scores for the prediction of severe low voltage areas

Predictive scores for a disseminated pattern of LVA

On the ROC curve analyses, only APPLE and CHA_2DS_2-VASc scores showed significant predictive values for a disseminated pattern of LVA (Table 5, Figure 3). Each score exhibited a moderately negative predictive ability for LVA. No significant difference was observed between the scores when AUC were compared. It was noted that 7% (10/152) of the patients with APPLE ≤3, and 3% (5/152) with CHA_2DS_2-VASc ≤2 in this group.

DISCUSSION

Many studies have demonstrated that there is a strong association between LVA and AF duration and adverse ablation outcomes [1]. Therefore, the persistence of AF is a common component of scores to assess arrhythmia recurrences following AF ablation, including APPLE, ATLAS, CAAP-AF, and DR-FLASH scores. However, as noted here, LSPAF diagnosis does not necessarily equate to extensive voltage-derived LA remodeling. The present study focused on the evaluation of multiple AF risk scores, and whether they have any predictive ability to detect voltage-based LA substrate among large, unselected LSPAF cohort. It was found that:

- CAAP-AF ≥7, DR-FLASH ≥4, and CHA_2DS_2-VASc ≥3 predicted the presence of LVA whereas ATLAS ≤7, the absence of LVA. Among the scores, the ATLAS score showed the highest sensitivity and specificity;

Table 5. Receiver operating characteristic curve analysis to compare the ability of AF risk scores to predict the presence of a disseminated pattern of left atrial low voltage areas

	AUC	95% CI	*P*	Best cut-off value	Accuracy	Sensitivity	Specificity	PPV	NPV
APPLE	0.69	0.526–0.864	0.02	3	0.572	0.769	0.446	0.139	0.963
ATLAS	0.557	0.397–0.717	0.48	7	0.342	0.923	0.712	0.108	0.976
CAAP-AF	0.546	0.378–0.715	0.59	8	0.638	0.462	0.346	0.111	0.969
DR-FLASH	0.539	0.367–0.71	0.66	6	0.868	0.154	0.065	0.182	0.922
CHA_2DS_2-VASc	0.644	0.518–0.77	0.03	2	0.388	0.923	0.662	0.115	0.979
HATCH	0.506	0.335–0.676	0.95	2	0.632	0.385	0.345	0.094	0.919

Abbreviations: see Table 3

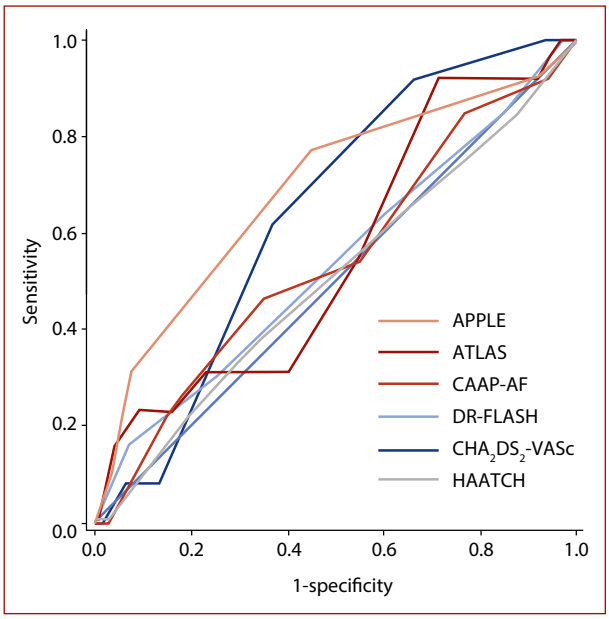

Figure 3. A comparison of atrial fibrillation risk scores for the prediction of a disseminated pattern of low voltage areas

- The ATLAS ≤8, CAAP-AF ≤9, DR-FLASH ≤4, and CHA_2DS_2-VASc ≤3 predicted the absence of severe LVA. Among the scores, the DR-FLASH score showed the highest sensitivity and specificity;
- The APPLE ≤3 and CHA_2DS_2-VASc ≤2 predicted the absence of a disseminated pattern of LVA. Among the scores, the CHA_2DS_2-VASc score showed the highest sensitivity and specificity;
- The HATCH score neither predicted LVA, nor severe or the disseminated pattern of LVA.

To date, only the DR-FLASH score has been developed primarily to directly predict LVA in AF patients [6]. This has been also recently verified [10]. The most notable increase in the dimension of LVA was observed in patients with DR-FLASH scores >3 [6] and a mean DR-FLASH score of 5 was observed among patients with LVA [10]. Moreover, it was recently shown that the APPLE score can be useful to detect LVA [10, 11]. A mean APPLE score of 5 was observed among patients with LVA [10]. Of note, all of the abovementioned research included paroxysmal and persistent, but not long-standing persistent AF patients [6, 10, 11]. This seems to be a main cause for the diverse or discrepant results achieved in our study. The predictive ability of other AF risk scores, such as ATLAS, CAAP-AF, CHA_2DS_2-VASc, and HATCH for the estimation of the electro-anatomical substrate was yet to be used to date.

All assessed AF risk scores, excluding the HATCH score, were useful to detect voltage-based LA remodeling. However, individual scores applying distinct components were able to detect the various extent of LVA. In addition, many of these presented high negative predictive values, meaning that they perform better as part of a "rule-out" test. It seemed clear that such variations between the scores, in terms of their predictive value, show that the development and progression of LVA are most likely multifactorial with a potential interplay between contributing factors. That is the reason why there is no universal risk score to predict the presence and extent of LVA. The only common parameter included in all 6 scores was patient age (60–75 years).We believe that a major reason that resulted in a HATCH score was the unhelpful fact of unmasking patients with LVA, which did not include female sex and/or LA size, which were integral components of the other scoring system (however, female sex was not incorporated into the APPLE score). Female sex was recently considered a strong risk factor in the development of LA substrate in AF patients. Females might probably present with clinical AF at a later state of fibro-fatty infiltration, which could explain the higher presence of electro-anatomical substrate among them [2].

In the current study, we found that some AF risk scores significantly predicted LA LVA before catheter ablation among LSPAF patients. This could help to identify individuals who require PVI alone, minor substrate modification, or extensive substrate modification in addition to PVI when an ablation strategy is chosen. This finding may essentially contribute to tailored AF therapy when considering a catheter ablation as a potential treatment strategy.

Limitations

The accuracy of LA voltage mapping might have been influenced by several factors, such as mapping during CS pacing, following PVI, using voltage cut-off values <0.5 mV, or due to functional voltage reduction related to the electrical stunning caused by long-lasting AF.

We cannot exclude the possibility that the overall LVA burden might have been altered due to the exclusion

of patients unable to maintain sinus rhythm, presenting LAA thrombus, or if another method of LVA detection had been applied.

Women were underrepresented in this study.

CONCLUSIONS

Atrial fibrillation risk stratification with specific scoring systems can noninvasively unmask the presence of voltage-derived LA remodeling and lead to more tailored management in the LSPAF population. Among several predictive scores, ATLAS, DR-FLASH, and CHA_2DS_2-VASc scores were the best predictors for the absence of LVA, severe LVA, and the disseminated pattern of LVA, respectively.

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Is the extent of left atrial fibrosis associated with body mass index in patients undergoing pulmonary vein isolation for atrial fibrillation?

Janko Szavits Nossan[1], Igor Šesto[1], Krešimir Štambuk[1], Tomislav Šipić[1], Robert Bernat[2, 5], Ivan Gudelj[3], Luka Rotkvić[1], Marinko Žulj[4], Jure Mirat[5]

[1]Magdalena Clinic for Cardiovascular Disease, Krapinske Toplice, at Faculty of Medicine, JJ Strossmayer University in Osijek, Osijek, Croatia
[2]Westpfalz-Klinikum, Kaiserslautern, Germany
[3]Genos Glycoscience Research Laboratory, Zagreb, Croatia
[4]Faculty of Dental Medicine and Health Osijek, University of Osijek, Osijek, Croatia
[5]Faculty of Medicine, J.J. Strossmayer University in Osijek, Osijek, Croatia

Correspondence to:
Janko Szavits Nossan, MD, Magdalena Clinic for Cardiovascular Disease, 49217 Krapinske Toplice, Croatia,
phone: +385 49 244 000,
e-mail: janko.szavitsnossan@gmail.com

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ABSTRACT

Background: Left atrial (LA) fibrosis is associated with a higher rate of recurrence of atrial fibrillation (AF) after pulmonary vein isolation (PVI). Body mass index (BMI) is strongly associated with the prevalence of AF, but there is insufficient data about the association between BMI and LA fibrosis.

Aims: The aim of the study was to examine the association between LA fibrosis and BMI in patients with AF undergoing PVI.

Methods: In 114 patients an electro-anatomical voltage map was created using the CARTO 3 three-dimensional system before PVI. The total fibrosis area (voltage criteria ≤0.5 mV), percentage, and the number of fibrotic areas were calculated. A general linear model was used to determine the differences in BMI with confounders between groups of patients with differing extents of fibrosis and numbers of focuses.

Results: Advanced fibrosis was found in 53 (47%) patients, in up to 9 areas with a median of 2 and an interquartile range (IQR) of 0–3. The median total fibrotic area was 27.3 cm^2 with an IQR of 0.1–30.3 cm^2. Patients were stratified by percentage of fibrotic area: <5%, 5%–20%, 20%–35%, and above 35%; no significant difference in mean BMI was found between the groups ($P = 0.57$). When stratified by the number of fibrotic areas (0, 1, 2, and ≥3 fibrotic areas), no difference in BMI was noted between the groups ($P = 0.67$).

Conclusions: Fibrosis of the LA, as the strongest predictor of AF recurrence after PVI, does not correlate with BMI in patients with AF where PVI is indicated.

Key words: atrial fibrillation, body mass index, fibrosis, pulmonary vein isolation, recurrence

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INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia with a prevalence in the general population of 2.3%–3.4% [1]. AF impairs quality of life and may increase the risk of stroke, heart failure, and cardiovascular mortality [1]. The pathogenesis of AF includes initiation triggers, such as rapid firing of ectopic foci located within the pulmonary veins and perpetuating substrate, and abnormal tissue of the left atrium (LA) [2]. Microfibrosis of the myocardium resulting in loss of side-to-side cell connections (coupling) and consequent anisotropic electrical conduction has been proposed as a major mechanism for the initiation and perpetuation of AF [3, 4]. Increased fibrosis has been found in surgically obtained left atrial specimens of patients with AF [5, 6].

Fibrosis and scarring of the myocardial tissue result in a reduced voltage of the electrical signals from the affected area. Electro-anatomical voltage mapping (EAVM) shows a good correlation between pathological findings and the electrophysiological characteristics of fibrosis [7]. Several studies have shown a strong correlation between left atrial fibrosis and AF recurrence using EAVM. Verma et al. [8] used EAVM to measure the extent of LA fibrosis (<0.5 mV)

WHAT'S NEW?

Left atrial (LA) fibrosis is associated with a higher rate of recurrence of atrial fibrillation (AF) following pulmonary vein isolation (PVI), but does not correlate with age, hypertension, diabetes, or the clinical type or duration of AF. Excess body weight is strongly associated with the prevalence of AF, but its association with LA fibrosis has not yet been established. This study is the first to investigate the association between excess body weight and LA fibrosis in humans. The main result of this study was that no association was found between the prevalence or the extent of LA fibrosis and body mass index in patients with AF undergoing PVI. Further studies comparing the AF burden, presence and extent of LA fibrosis, AF recurrence after PVI, and different indices of obesity are needed to clarify if PVI could be routinely planned regardless of body mass index.

and its prognostic value for AF recurrence after pulmonary vein isolation (PVI) in 700 patients. LA scarring was the only predictor associated with higher AF recurrence [8]. Another study using EAVM prior to PVI provided strong evidence that LA fibrosis can be found in a significant proportion of patients with paroxysmal AF [9]. The presence and extent of atrial fibrosis did not correlate with any other potential risk factor (clinical type, LA diameter, age, duration of AF, etc.) in these studies. Kottkamp et al. suggested a new entity — fibrotic atrial cardiomyopathy (FACM) [10–12]. FACM is described as a specific preexisting chronic progressive disease of the LA predisposing patients to AF in the presence of modulators (inflammation, hypertension, obesity) and triggers (pulmonary vein foci). The authors suggested 5 stages of severity of fibrosis based on EAVM, defining normal voltage as above 1.5 mV: FACM 0 without any fibrosis; FACM I with moderate fibrosis (1.0–1.5 mV); FACM II with one area of severe fibrosis (<0.5 mV); FACM III with at least two areas of severe fibrosis, and FACM IV with severe diffuse fibrosis of the LA.

Advanced age, hypertension, diabetes, obesity, obstructive sleep apnoea, and excessive alcohol consumption are all well-established risk factors for the development of AF [13]. Together with hypertension and diabetes, cigarette smoking, and vigorous or low physical activity are also associated with the risk of AF and its recurrence after PVI or electrocardioversion [14]. Moreover, structured weight reduction, abstaining from alcohol, and treatment of obstructive sleep apnoea significantly reduce new-onset and recurrence of AF after PVI [15]. Age is the strongest risk factor for AF. However, the histopathological study of the specimens from different parts of the LA collected during autopsies of 30 patients with AF showed no correlation between age and extent of fibrosis [16]. No difference in the extent of atrial fibrosis using late enhancement magnetic resonance could be found between lone AF patients and those with AF and co-morbidities [17].

Excess weight is strongly associated with the prevalence of AF. Wong et al. [18] estimated a 3.5%–5.3% excess risk of AF for every unit of body mass index (BMI) increase, based on a meta-analysis of 51 studies. The association of BMI with AF was found to be independent of hypertension, diabetes, and myocardial infarction [19]. Body mass index is a predictor of progression from paroxysmal to permanent AF [20]. Conversely, weight loss was found to be associated with greater freedom from AF, as well as with reversal of the type and progression of AF [21]. Several mechanisms of AF development in obese patients have been investigated so far. Could LA fibrosis also play a role? This cross-sectional study examined the extent of LA fibrosis in patients undergoing PVI and explored cross-sectional associations with BMI. The prevalence and extent of atrial fibrosis and its role in the AF burden in overweight and obese patients have not been investigated so far.

METHODS

Patients

All patients with a history of symptomatic paroxysmal or persistent AF who met the inclusion and exclusion criteria were consecutively included in this prospective observational study immediately before the planned PVI procedure. The exclusion criteria included: permanent AF, previous PVI, left ventricular ejection fraction <50% measured by echocardiography, history of myocardial infarction, acute or chronic inflammatory disease, history of malignant neoplasm, and hypo- or hyperthyroidism. In the period between March 2019 and June 2020, a total of 125 patients in whom PVI was performed were initially included. Subsequently, 11 patients who did not have an adequate electro-anatomical map of the LA according to the protocol described here were excluded from the study. The research was approved by the ethics committee at the University of Osijek Faculty of Medicine (KLASA: 602-04/19-08/04; URBROJ: 2158-61-07-19-09). All patients signed their informed consent.

Clinical parameters

The following clinical parameters were examined: age, sex, BMI, type of AF (paroxysmal, persistent), drugs and preparations taken (including antiarrhythmics and anticoagulants), as well as history of hypertension, coronary heart disease, diabetes, and cerebrovascular stroke. BMI was determined according to the definition of the World Health Organization: normal weight patients with BMI <25 kg/m^2, overweight patients with BMI between 25 and 30 kg/m^2, and obese patients with BMI ≥30 kg/m^2. Left atrial volume measures were assessed by standard echocardiography.

Assessment of left atrial fibrosis

A detailed anatomical map (fast anatomical mapping [FAM]) and a voltage map (EAVM) of the LA were created using a three-dimensional mapping system and an ablation catheter with a Biosense Webster Smart Touch contact force sensor (CARTO 3, Biosense Webster) [10, 11]. The map was created exclusively in sinus rhythm, taking a minimum of 400 individual points evenly distributed throughout the LA. Points with catheter contact force of less than 5 g and more than 20 g were excluded. The program displays surfaces of the same voltage in the same color. Surfaces with a voltage criterion of ≤0.5 mV (low voltage zones [LVZ]) are shown in red, which indicates advanced tissue fibrosis. Areas with moderate fibrosis of voltage criterion between 0.5 and 1.5 mV are shown in blue and green. Healthy tissue of voltage criteria above 1.5 mV is shown in purple. The density of the points, defined by the distance between two points, is set at a minimum of 5 mm. The system is programmed to take only points at the end of expiration that meet the criteria for a minimum contact force of 5 g and adequate catheter stability. As a result of the EAVM, the following parameters were calculated using Biosense Webster CARTO 3 software: the volume of the LA, the total surface area of the LA, the number and total surface area of LVZs (described by voltage points ≤0.5 mV) and the share of LVZs in the surface of the LA.

Data analysis

Data was analyzed and visualized using the Python programming language (version 3.8.3) and Jupyter Notebooks [22]. Percentages of fibrosis were assigned first to two groups (NO group if fibrosis was less than 5%, and YES group if it was above 5%), then to four groups (NO for fibrosis <5%, I 5%–20%, II 20%–35%, and III above 35%). Areas of fibrosis were divided into four groups (NO if a patient was without fibrosis, I for 1 fibrotic area, II for 2 fibrotic areas, and III for 3 and more fibrotic areas). The dependent variable was tested for normality using the Shapiro–Wilk test of normality before performing ANCOVA to determine the differences in BMI between groups of patients with age, sex, hypertension, diabetes, and persistent AF as confounders. T-test and Mood's median test, as appropriate, were used to assess differences between groups stratified by the presence of fibrosis in quantitative variables, while Fisher's exact test was employed to examine respective differences in qualitative characteristics. All the tests were performed using SciPy, statsmodels, and pandas packages. Quantitative data are reported as mean (standard deviation [SD]) for normally distributed variables or median (interquartile range [IQR]) for not normally distributed data, while categorical variables are presented as the number of individuals (% of total).

RESULTS

The population of the study consisted of 114 patients (65% male and 35% female). The baseline characteristics of all patients, as well as the two groups of patients when stratified by the presence of significant LA fibrosis, are described in Table 1. No significant differences were observed, apart from more frequent use of antiarrhythmic medication in

Table 1. Patient characteristics stratified by the presence of significant left atrial fibrosis

Variable	All patients (n = 114)	No fibrosis group (n = 52)	Fibrosis group (n = 62)	*P* value
Age, years (SD)	61.5 (8.7)	62.5 (9)	62.6 (8.3)	0.135[a]
Male	74 (65)	36 (69)	37 (60)	0.330[b]
BMI, kg/m^2, mean (SD)	29.1 (4.4)	29.3 (4.5)	28.9 (4.3)	0.690[a]
Normal BMI	21 (19)	9 (18)	12 (19)	0.813[b]
Overweight	46 (40)	22 (42)	24 (39)	0.706[b]
Obesity	47 (41)	21 (40)	26 (42)	1.0[b]
Persistent AF	30 (27)	12 (23)	18 (29)	0.526[b]
History of hypertension	68 (60)	31 (60)	37 (60)	1.0[b]
History of diabetes mellitus	9 (8)	4 (8)	5 (8)	1.0[b]
History of cerebrovascular accident	6 (5)	4 (8)	2 (3)	0.409[b]
History of asymptomatic CAD	14 (12)	6 (12)	8 (13)	1.0[b]
CHA2DS2-VASc score, median (IQR)	2 (1–3)	1 (0–2.75)	2 (1–3)	0.876[c]
Antiarrhythmic use				0.02[b]
None	30 (27)	20 (39)	10 (16)	
Class I	44 (39)	15 (29)	29 (47)	
Class III	39 (34)	17 (32)	22 (35)	
Anticoagulant use				0.23[b]
None	2 (2)	2 (4)	0	
VKA	24 (21)	9 (17)	15 (24)	
NOAC	87 (77)	41 (79)	47 (76)	
Other medication use				
ACE/ARB	67 (59)	24 (46)	43 (69)	0.013[b]
Statins	42 (37)	20 (38)	22 (35)	0.845[b]

Data are presented as number (percentage) of patients unless otherwise indicated.
[a]Student t-test. [b]Fisher's exact test. [c]Mood's median test.
Abbreviations: ACEI, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; IQR, interquartile range; NOAC, non vitamin K antagonists oral anticoagulants; SD, standard deviation; VKA, vitamin K antagonist

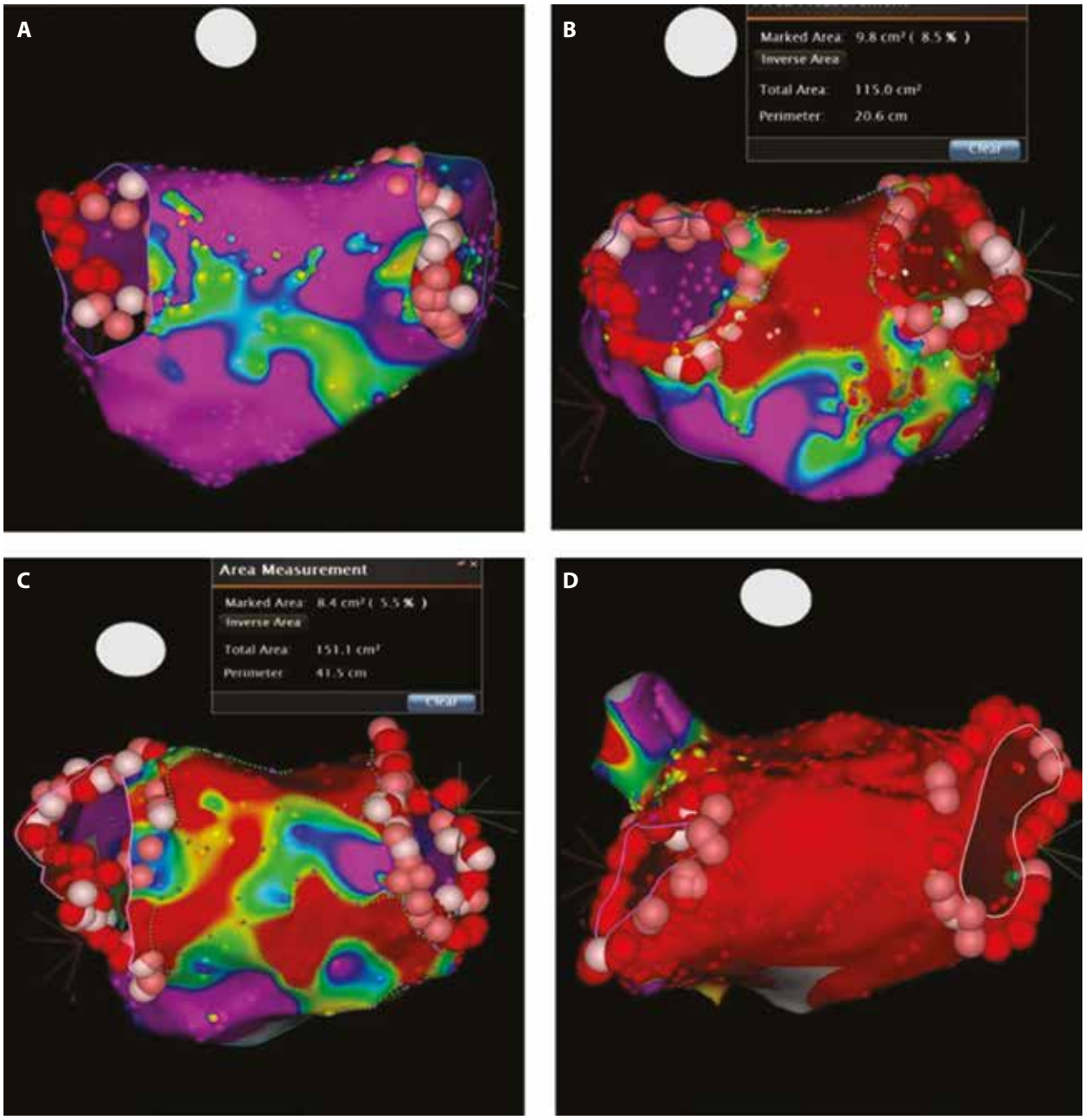

Figure 1. Examples of left atrium electro-anatomical voltage maps from 4 patients with different extent of fibrosis. **A.** No significant fibrosis. **B.** One area of severe fibrosis. **C.** Two areas of severe fibrosis. **D.** Diffuse severe fibrosis

patients with apparent fibrosis. The mean (SD) LA body volume, measured by standard two-dimensional echocardiography, was 56 (19) cm^3 in the no fibrosis group and 62 (22) cm^3 in the fibrosis group, but when measured by three-dimensional mapping software it was 127 (3) cm^3 in the no fibrosis group and 128 (2) cm^3 in the fibrosis group. The mean (SD) LA surface area was 149.8 (27) cm^2 in the no fibrosis group and 151.6 (35) cm^2 in the fibrosis group. LVZs were found in 86 (76%) patients, though 62 (54%) patients had LVZs in ≥5% of the LA surface which is usually considered to be significant. Patients with LVZs had up to 9 areas, with a median of 2 and an IQR of 0–3. In 15 (13%) patients, LVZs were found in 100% of the LA body surface indicating advanced atrial fibrosis. The median total LVZ area for all patients was 27.3 cm^2 with an IQR of 0.1–30.3 cm^2 (0.1%––19.9%). Examples of EAVM from 4 patients with different extent of left atrial fibrosis are shown in Figure 1.

Association of LVZs and BMI

In the current cohort we assessed the association between BMI and groups of patients with and without significant (<5%) fibrosis (Figure 2). Patients without significant fibrosis had a mean BMI (SD) of 29.3 (4.5) kg/m^2, while patients with significant fibrosis had a mean BMI (SD) amounting to 28.9 (4.3) kg/m^2. After adjusting for age, sex, hypertension, diabetes, and persistent AF, we found that no association remained statistically significant (P = 0.84). We further assessed the association between BMI and four groups of

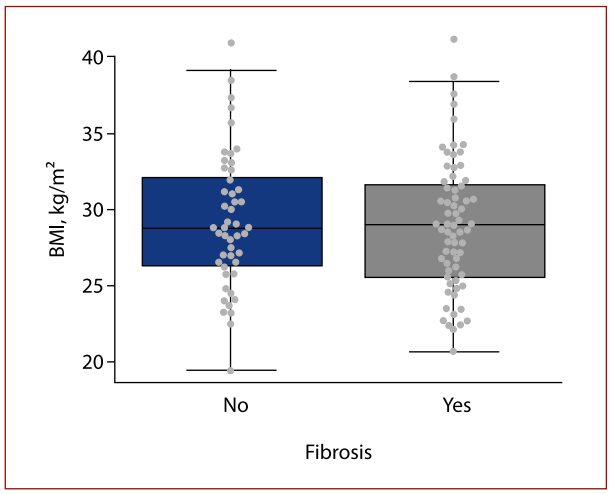

Figure 2. Box plot showing the distribution of body mass index (BMI) in two groups of patients based on the presence of significant fibrosis: NO — a group of patients in whom fibrosis was less than 5%; YES — a group of patients in which fibrosis was above 5%. The lower and upper boundaries of the boxplots indicate the first and third quartile, the middle notch indicates the median, and whiskers include all data points that fall within 1.5 × interquartile range. ANCOVA adjusted for age, sex, and the presence of hypertension, diabetes and persistent atrial fibrillation showed no difference between groups ($P = 0.84$)

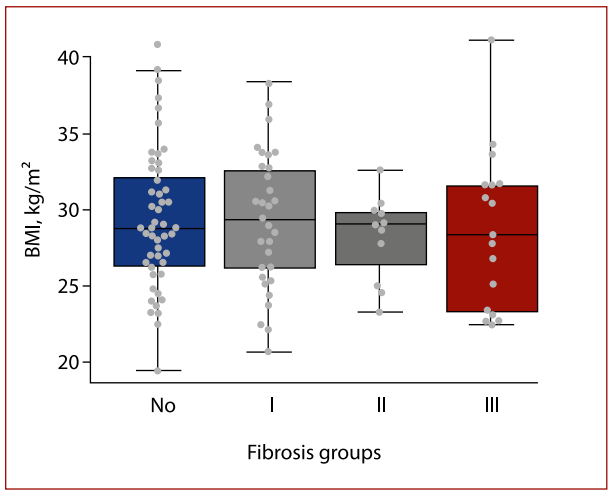

Figure 3. Box plot showing the distribution of body mass index (BMI) in four groups of patients stratified by percentage of fibrotic area: NO — group of patients in which fibrosis was less than 5%; I — group of patients in which fibrosis was 5%–20%; II — group of patients in which fibrosis was 20%–35%; III — group of patients in which fibrosis was above 35%. The lower and upper boundaries of the boxplots indicate first and third quartile, the middle notch indicates the median, and whiskers include all data points that fall within 1.5 × interquartile range. ANCOVA adjusted for age, sex, and the presence of hypertension, diabetes, and persistent atrial fibrillation showed no difference between groups ($P = 0.57$)

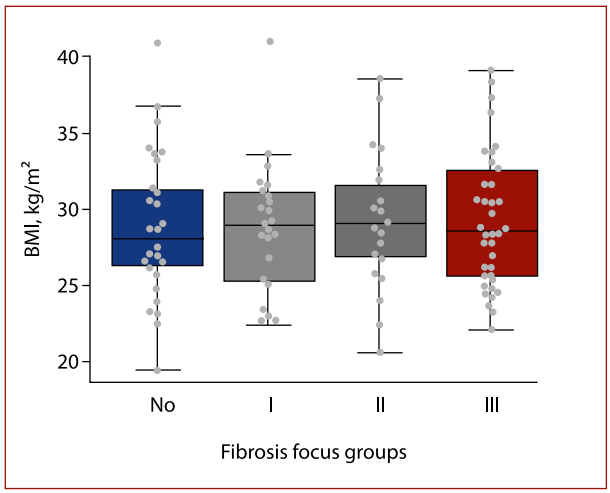

Figure 4. Box plot showing the distribution of body mass index (BMI) in four groups of patients based on the number of fibrotic areas: NO — a group of patients with no fibrotic areas; I — a group of patients with 1 fibrotic area; II — a group of patients with 2 fibrotic areas; III — a group of patients with 3 and more fibrotic areas. The lower and upper boundaries of the boxplots indicate the first and third quartile, the middle notch indicates the median, and whiskers include all data points that fall within 1.5 × interquartile range. ANCOVA adjusted for age, sex, and the presence of hypertension, diabetes, and persistent atrial fibrillation showed no difference between groups ($P = 0.64$)

patients stratified by percentage of fibrotic area: NO for fibrosis <5%, I 5%–20%, II 20%–35%, and III above 35%. The mean (SD) BMI in these four groups was 29.2 (4.5) kg/m^2, 29.3 (4.4) kg/m^2, 28.2 (2.8) kg/m^2, and 28.7 (5.2) kg/m^2, respectively (Figure 3). After adjusting for age, sex, hypertension, diabetes, and persistent AF, BMI was not significantly different between the groups ($P = 0.57$).

Similarly, no association was found between BMI and four groups of patients stratified by the number of fibrotic areas: NO if a patient was without fibrosis, I for 1, II for 2 and III for 3 and more (Figure 4). Mean BMI (SD) in the four groups was 28.8 (4.7) kg/m^2, 28.6 (4.3) kg/m^2, 29.3 (4.4) kg/m^2, and 29.5 (4.4) kg/m^2, respectively ($P = 0.64$).

A subgroup of 21 (18%) patients with normal BMI was additionally analyzed. In this group, 14 (67%) patients had significant fibrosis of the LA. Patients with normal BMI and significant LA fibrosis had a median CHA_2DS_2-VASc score of 2.5 with IQR 2–3. Persistent AF was found in 4 (29%) patients, arterial hypertension in 9 (64%) patients, and 7 (50%) patients had diffuse LVZ covering ≥90% of the LA surface.

DISCUSSION

To our knowledge, this study is the first to investigate the association between excess body weight and LA fibrosis in humans. The main result of this study is that no association was found between the prevalence and the extent of LA fibrosis and BMI in patients undergoing PVI.

In our study, only 18% of patients were of normal weight, while 41% of patients were obese. The high prevalence of obesity in the investigated cohort could partly explain why 60% of patients had hypertension, 8% had diabetes, 12% had asymptomatic coronary artery disease, and 5% had a history of cerebral vascular incidents. There is no evidence of any association between these co-morbidities and atrial fibrosis. Weight loss results in a significant reduction of the AF burden, comparable with PVI results.

However, we found no correlation between obesity and atrial fibrosis, which is the strongest risk factor for AF recurrence after PVI, suggesting other possible mechanisms for the higher AF burden in obese and overweight patients. There is strong evidence of a correlation between LA fibrosis and a worse prognosis for AF in terms of the progression of the disease and ineffective invasive therapy. Previous studies showed a strong correlation between AF and risk factors such as advanced age, hypertension, diabetes, obesity, and obstructive sleep apnoea. However, studies investigating some of these factors and the presence of left atrial fibrosis showed no correlation, suggesting a new idiopathic entity — fibrotic atrial cardiomyopathy.

There are some indications of a possible pro-inflammatory, thus a profibrotic effect of obesity on left atrial tissue, but no correlation has been established. Important findings from the ovine model have been published by Abed et al. [23]. In this study, animals were on a high-calorie diet that resulted in weight gain. The animals underwent electrophysiological studies, cardiac magnetic resonance imaging, and histology at baseline, 4- and 8-monthly intervals. Weight gain resulted in progressive remodeling characterized by conduction heterogeneity, bi-atrial enlargement, and increased pericardial fat volumes. Histology showed increased atrial interstitial fibrosis and inflammation [23].

Apart from the role of cardio-metabolic factors associated with obesity in promoting AF, several other factors have been observed and investigated. Diastolic function impairment has a strong correlation with the risk for AF onset [24, 25]. Possible mechanisms include enlargement of the LA area with consequent changes in the electrical properties of the tissue that promotes re-entry. Cardiac fat deposits overlying the LA also seem to be an important factor in promoting AF in obese patients. Investigators from the Framingham Heart Study Offspring and Third Generation Cohorts analyzed 2317 patients and showed an association of total pericardial fat volume measured by computed tomography and prevalence of AF [26]. Wong et al. [27] showed that pericardial fat, measured by magnetic resonance in this study, is also a predictor of AF recurrence after PVI. Possible mechanisms are local inflammation mediated by paracrine mediators and the arrhythmogenicity of interpolated fat tissue [28].

Strengths and limitations of the study

A high number of patients with excess body weight was included in this study, giving strength to evidence on LA fibrosis within this population. However, the proportion of these patients is not consistent with other studies investigating the extent of LA fibrosis. Body mass index is strongly correlated with the development of AF [19], progression from paroxysmal to persistent AF, [20] and with AF burden, [21] and was the only parameter of general obesity used in this study. Epicardial adipose tissue (EAT) emerged as an important factor in AF pathogenesis in recent studies. Metaanalysis showed a highly significant correlation between BMI and EAT, but the correlation was even greater between EAT and waist circumference and between EAT and visceral adipose tissue [29]. These indices of obesity should also be included in future research on left atrial fibrosis. This study investigated the extent of LA fibrosis only in patients with AF, therefore the results could not be extrapolated to the healthy population. Although a correlation between low voltage zones in the LA and histological findings of fibrosis has been confirmed, exact voltage cut-off values have not been established yet. Commonly used voltage cut-off values in most of the studies for normal tissue, moderate fibrosis, and severe fibrosis are ≥1.5 mV, 0.5–1.5 mV, and ≤0.5 mV, respectively. In this study, we observed only areas of severe fibrosis (≤0.5 mV). Areas of moderate fibrosis were not analyzed in this study but might also play an important role in the development of FACM.

Electro-anatomical voltage mapping can give inconsistent results. Various catheters are used in studies to collect voltage points within the body of the LA. Multi-polar catheters can collect a greater number of voltage points over the same period of time than bipolar catheters, resulting in more detailed EAVM. Multipolar catheters use tissue impedance for contact assurance, while new generation bipolar catheters use contact force criteria (≥5 g/mm^2).

In this study, 76% of patients had LVZs and 54% of the patients had fibrosis in more than 5% of the LA surface, which was considered significant in most previous studies. The exact proportion of left atrial fibrosis significant for developing AF has not been established. It is also not clear whether the number of LVZs would be a better predictor of AF recurrence after PVI than the proportion of LA fibrosis. Therefore, we decided to investigate if there was a difference in BMI between patients with and without fibrosis, and also with different proportions of fibrotic areas and with different numbers of fibrotic areas. This multiple hypothesis approach would lessen the strength of scientific proof in case of a positive result, but in our study the results were negative — we found no difference in BMI among the groups of patients. This study aimed to investigate only the correlation between BMI and LA fibrosis. Obesity has other well-established links with AF independent of LA fibrosis including associated co-morbidities such as arterial hypertension, diabetes mellitus, coronary artery disease, and obstructive sleep apnea, together with ventricular adaptation, diastolic dysfunction, and epicardial adipose tissue.

CONCLUSIONS

In conclusion, our study did not find a correlation between fibrosis of the LA, as the strongest predictor of AF recurrence after PVI, and BMI. There was no significant difference in BMI between groups of patients stratified by the presence and the extent of LA fibrosis, and the number of fibrotic areas. Further studies comparing the AF burden, the presence and the extent of LA fibrosis, and AF recurrence

after PVI including different indices of obesity, particularly abdominal obesity, are needed to clarify if PVI could be routinely planned regardless of BMI. The exact criteria for measurement of LA fibrosis and the clinical significance of different stages, proportions, and numbers of fibrotic areas should be set by future research.

Article information

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ORIGINAL ARTICLE

Longitudinal assessment of cardiac function in extremely low birth weight children at 7 and 11 years of age: implications for adult medicine

Andrzej Grudzień, Mateusz Jagła, Małgorzata Klimek, Anna Knapp, Przemko Kwinta

Department of Pediatrics, Jagiellonian University Medical College, Kraków, Poland

Correspondence to:
Prof. Przemko Kwinta, MD, PhD, Department of Pediatrics, Jagiellonian University Medical College, Wielicka 265, 30–663 Kraków, Poland, phone: +48 12 333 90 36, e-mail: przemko.kwinta@uj.edu.pl

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ABSTRACT

Background: The long-term impact of extreme prematurity on cardiac structure and function has not been fully evaluated.

Aims: The aim of the study was to assess cardiac condition at 11 years of age in a local cohort of extremely low birth weight (ELBW) children born between 2002 and 2004 and to compare it to a previous study in the same group at 7 years of age.

Methods: Sixty-four children with ELBW (median birth weight of 890 g) and 36 children born at full term underwent echocardiography and physical examination.

Results: M-mode echocardiography parameters, expressed as z-scores for body surface area (mean [SD]), showed significant differences in left ventricular end-diastolic dimension (–1.01 [0.91] vs 0.35 [0.71]; P <0.001), left ventricular end-systolic dimension (–0.29 [0.92] vs 0.57 [0.65]; P <0.001), aorta dimension (0.63 [1.14] vs 1.63 [1.30]; P <0.001), and left atrial dimension (–1.75 [0.97] vs –0.01 [0.86]; P <0.001) between the study group and controls at 11 years of age. Fractional shortening (FS) and ejection fraction (EF) were higher in the ELBW children than in their full-term counterparts (33.6 [5.5] vs 30.8 [4.34]; P = 0.009 and 0.63 [0.07] vs 0.58 [0.06]; P = 0.005, respectively) at a mean age of 11 years.

Conclusions: The ELBW children had smaller hearts than full-term controls at both 7 and 11 years of age. The FS and EF were elevated in the group of 11-year-old ELBW children. We observed comparable progress in cardiac growth (approximately 20%) in premature and full-term children over a 4-year study period.

Key words: cardiac index, extremely low birth weight, left ventricular hypertrophy, preterm infants, stroke volume

Kardiol Pol 2021; 79, 5: 539–545

INTRODUCTION

Continuous improvements in perinatal medical services and neonatal intensive care have resulted in an increasing number of surviving extremely low birth weight (ELBW) infants. This particular patient population suffers the highest risk of early and late complications of prematurity. There are a growing number of studies evaluating the long-term side effects of perinatal disorders. Since some published reports show increased cardiovascular mortality in adults who were born preterm [1, 2], a number of researchers have investigated the impact of extreme prematurity on cardiac structure and function during extended periods of time.

The aim of this study was to identify any potential late cardiac complications in a group of 11-year-old children whose birth weight was less than 1000 g and who had already undergone similar examinations at the age of 6–7 years (results published previously in *Neonatology* in 2013 [3]). In particular, the results of the echocardiographic investigations were compared. The results made it possible to perform a detailed evaluation of cardiac functional and structural variability together with an assessment of overall cardiac development. It was hypothesized that cardiac lesions in the ELBW group occurred mostly in the perinatal period. The general heart development of the ELBW children and their healthy counterparts was comparable during their preschool and early school years.

METHODS

Patients

A cross-sectional observational study was conducted in the Outpatient Pediatric Department of the University

WHAT'S NEW?

Extremely low birth weight children had smaller hearts than full-term controls at both 7 and 11 years of age. The observation that the heart growth rate during preschool age and school age in extremely premature infants is comparable to that in full-term controls suggests that the most critical cardiac lesions occurred in early postnatal life. Despite their normal heart development during school age, preterm infants require repeated monitoring to diagnose possible cardiac complications later in life.

Children's Hospital in Krakow, Poland, between December 30, 2013, and April 30, 2015. The study cohort comprised ELBW survivors recruited at birth and term control participants enrolled in the study at 6–7 years of age.

During the study period, 169 newborns with birth weights <1000 g were born alive in the southeast district of Poland (Malopolska Region). All these children were hospitalized in one of 3 tertiary-care neonatal intensive care units in southeastern Poland. Ninety-one infants were discharged home, and they were further monitored on an outpatient basis. Eighty-one children took part in the follow-up assessment at 6–7 years of age. The control group for the study included forty age- and gender-matched children with birth weights >2500 g who were recruited at a single general practitioner's office between 2009 and 2010. Details on the methodology and results of the follow-up performed at 6–7 years of age have already been published [3].

All the participants of the study at 6–7 years of age were invited to the present follow-up at 10–11 years of age. Ultimately, 64 (79%) children from the study group and 36 (90%) children from the control group returned for the second follow-up assessment (Figure 1).

The study was approved by the Jagiellonian University Bioethical Committee and adheres to the tenets of the Declaration of Helsinki. The parents and caregivers signed informed consent before the children were included in the study.

Follow-up at 10–11 years of age

All the study participants underwent physical examinations, height and weight measurements, and standard two-dimensional echocardiography tests. The parents completed questionnaires on their children's demographic data and health status. The whole procedure was completed during a single visit to the Pediatric Outpatient Department of the University Children's Hospital of Krakow.

Echocardiography

The same echocardiographic analyses, as in a previously published study, were performed using the same ultrasound device — the Philips EnVisor HD (Philips, Amsterdam, The Netherlands) with a 2- to 4-MHz transducer and simultaneous heart rate (HR) measurement [3]. The measurements were performed twice by the same echocardiographers as in the previous study. Left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), interventricular septal thickness at end diastole (IVSd) and end systole (IVSs), left ventricular posterior wall thickness at end diastole (LVPWd) and

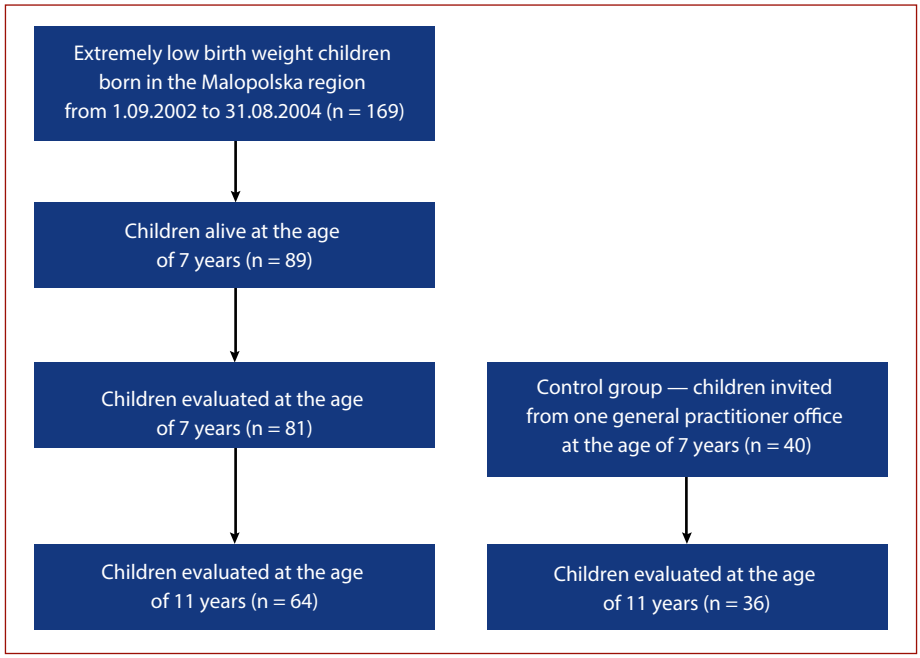

Figure 1. Protocol of the study — flow diagram

end systole (LVPWs), right ventricular end-diastolic dimension (RVDD), and left atrial dimension (LAD) were measured using 2-dimensional guided M-mode echocardiography with the parasternal shortaxis view at the midpapillary level.

Diameters and thickness were corrected for body surface area (BSA), and normal ranges were assessed according to values published by Kampmann et al. [4].

When the z-scores of RVDD, LVEDD, and the LAD were >2, right ventricle (RV), left ventricle (LV), or left atrium (LA) enlargement was diagnosed.

The following parameters were calculated from M-mode measurements: LV volumes at end diastole (EDV) and end systole (ESV) according to the method described by Tortoledo et al. [5] and ejection fraction (EF), fractional shortening (FS), and stroke volume (SV).

Left ventricular mass (LVM) was calculated according to the formula described by Devereux et al. [6]. The LVM z-score for height was calculated using the method described by Foster et al. [7]. The LVM index (LVMI) was obtained by dividing LVM by height$^{2.7}$ to normalize and linearize the relationship between LVM and height [8]. Left ventricular hypertrophy (LVH) was based on the reference values published by Diaz et al. [9]. For the purpose of this study, HR was evaluated. Original data were converted into z-scores.

Moreover, the cardiac index was calculated. The cardiac index was the normalized value of cardiac output calculated for BSA.

Outcome variables

The primary outcome variable was the identification of a cardiac complication. Cardiac complications were diagnosed if at least one of the following abnormalities was detected: (1) LVH; (2) systolic dysfunction, defined as abnormal EF and/or FS; and (3) RV, LV or LA enlargement. The secondary outcome variables included absolute and relative values of LVEDD, LVESD, IVSd, IVSs, LVPWd, LVPWs, RVDD, LAD, EF, FS, LVM, LVMI, and cardiac index.

Statistical analysis

The groups were compared using Student's t-test, the Mann–Whitney U test, the χ^2 test, or Fisher's exact test, as appropriate. The Shapiro–Wilk test was used to check the normality of the distribution of quantitative variables. Based on the obtained results, the hypothesis of normal distribution in the case of variables such as birth weight, gestational age, and age at evaluation was rejected. For the remaining variables, parametric tests were used in the further part of the analysis. The analysis of HR rates utilized an ANOVA of HR adjusted for BSA. The comparison of selected echocardiographic measurements between children aged 7 and 11 years was performed with a paired t-test.

The study compared multiple echocardiographic variables and required corrections for multiple testing. The Sidak correction for correlated variables was used. The corrected alpha level based on a mean correlation factor of 0.251 between different measurements equaled 0.0107. Based on this calculation, if the unadjusted *P* value was <0.0107, then the risk of type I error was <5%. Finally, statistical significance in the presented paper for M-mode measurements was defined as $P = 0.01$ on a 2-sided test; in all other analyses, statistical significance was defined as $P = 0.05$ on a 2-sided test.

Sample size estimations were based on the assumption that the follow-up rate among ELBW children would be as high as 90% (80 children). The presumed frequency of the primary endpoints was adopted from previously published studies that evaluated healthy Polish children aged 6–7 years whose LVH incidence ranged from 2% to 3.3%. Assuming that the risk of type I error equaled 5% (1-sided test) and the control group would include 40 children, a study with a power of 80% should demonstrate a 15% difference in the incidence of the primary endpoints between the ELBW and control groups.

The birth weight, gestational age, and age at evaluation were presented as a median and 25th–75th percentile, other quantitative variables as mean and standard deviation (SD) values. The qualitative variables were presented as number (n) and percentage (%).

Data were analyzed using SPSS statistical software, version 25 (2020 by IBM, USA).

RESULTS

Characteristics of the studied groups

Sixty-four children born as ELBW infants, who constituted 79% of the cohort evaluated at the age of 7 years during the first follow-up assessment, entered the current study at a mean age of 11 years. Their median birth weight was 875 g (25th–75th percentile, 750 g–960 g), and their median gestational age was 27 weeks (25th–75th percentile, 25–28 weeks). Nineteen of them had been small for their gestational age (30%), a majority of them had received surfactant (49 participants, 77%), and almost all of them had required mechanical ventilation (58 participants, 91%). Nineteen infants had been treated surgically for patent ductus arteriosus (30%), and 26 children had been receiving oxygen at 36 weeks of postmenstrual age (41%). The control group consisted of 36 full-term children, corresponding to 90% of the same group from the previous study 4 years earlier.

There were no significant demographic differences at the age of 7 years between the returning participants in the current study and the children who failed to return after the first follow-up study (data available on request).

The children from the ELBW group had lower birth weights (median, 875 g vs 3570 g; $P < 0.001$) and younger gestational ages (median, 27 weeks vs 40 weeks; $P < 0.001$) than the control group. They were also less likely to have been born via vaginal delivery (20% vs 86%; $P < 0.001$). The incidence of multiple pregnancy in the ELBW group was

Table 1. Comparison of selected demographic and clinical variables in the study groups and their control groups

	Study group (n = 64)	Control group (n = 36)	*P* value
Demographic variables			
Female	43 (67)	17 (47)	0.06[a]
Birth weight, g, median (25th–75th percentile)	875 (750–960)	3570 (3395–3880)	<0.001[b]
Gestational age, weeks, median (25th–75th percentile)	27 (25–28)	40 (39–40)	<0.001[b]
Vaginal delivery	13 (20)	31 (86)	<0.001[a]
Multiple pregnancy	9 (14)	0 (0)	0.02[a]
Small for gestational age	19 (30)	2 (6)	0.004[a]
First follow-up			
Age at evaluation, years, median (25th–75th percentile)	6.5 (6.4–6.8)	6.9 (6.4–7.4)	0.04[b]
Height, cm, mean (SD)	116 (6.3)	124 (7.4)	<0.001[c]
Height, z-score, mean (SD)	–1.08 (1.3)	0.21 (1.0)	<0.001[c]
Weight, kg, mean (SD)	19.5 (3.8)	25.2 (5.3)	<0.001[c]
Weight, z-score, mean (SD)	–0.92 (1.3)	0.26 (1.2)	<0.001[c]
Second follow-up			
Age at evaluation, years, median (25th–75th percentile)	11 (10.8–11.3)	10.7 (10.2–11.1)	0.01[b]
Height, cm, mean (SD)	141 (8)	146 (8)	0.003[c]
Height, z-score, mean (SD)	–0.88 (1.2)	0.20 (1.1)	<0.001[c]
Weight, kg, mean (SD)	33.7 (8.2)	40.4 (9.9)	<0.001[c]
Weight, z-score, mean (SD)	–0.92 (1.3)	0.24 (1.2)	<0.001[c]

Data are presented as the number (percentage) of patients unless otherwise indicated.

P value: [a]Fisher's exact test, [b]Mann–Whitney U test, [c]Student's t-test

significantly higher (14% vs 0%; $P = 0.02$), and there were significantly more infants who were small for gestational age (30% vs 6%; $P = 0.004$). In the current study, the 11-year-old children in the ELBW group were significantly smaller (mean, 141 cm vs 146 cm; $P = 0.003$) and weighed less than those in the control group (mean, 33.7 vs 40.4 kg; $P < 0.001$). The same significance was found when those values were converted into z-scores. A detailed comparison of the selected demographic and clinical variables in the ELBW and control groups is presented in Table 1.

Echocardiography

In the current study of 11-year-old children, we identified only one ELBW child with LVH. None of the other children who were studied, whether premature or fullterm, fulfilled the criteria for the diagnosis of LV and RV enlargement. We also diagnosed only one ELBW child with LA enlargement.

Absolute and relative M-mode measurements are presented in Table 2. All the results expressed as z-scores for BSA for all the analyzed parameters, except for RVDD, were 0.5 to 1 SD lower in the group of ELBW children than in the controls at both time points, 7 and 11 years of age. There was no difference in RVDD between ELBW and fullterm children at 11 years of age. Statistically significant differences between the studied and control groups were observed for RVDD, LVEDD, aortic diameter (AoD), and LAD in 7-year-old children and for LVEDD, LVESD, AoD, and LAD in 11-year-old children.

The comparisons of LVM, LVMI, diastolic parameters, and LV function variables between the two follow-up groups (at the ages of 7 and 11 years) are summarized in Table 3. LVM was consistently smaller in the ELBW children than in the control children at 7 and at 11 years of age. However, the rate of LVM increase in the ELBW group was comparable to that in the control group, equaling approximately 20% for both of those groups during the 4-year observation period. The LVMI differences were not statistically significant for either 7-year-old or 11-year-old children. The mean difference between the LVMI of the ELBW children and full-term controls was 4.1 g/m$^{2.7}$ at the age of 7 years and 6.2 g/m$^{2.7}$ 4 years later. Stroke volume remained lower in the prematurely born children at ages of 7 and 11 years. No significant differences were found in cardiac indexes in the analyses of 7-year-old and 11-year-old children.

The FS and EF did not differ significantly between the ELBW participants and their controls at the age of 7 years. However, we found higher values of FS and EF in the ELBW children than in the control children four years later.

There were only two 11-year-old ELBW children with fractional shortening <25% (absolute values 23.6% and 23.8%). Left ventricular ejection fraction <55% was diagnosed in two prematurely born children and two fullterm participants (absolute values from 50% to 55%) at the age of 11 years.

A comparison of the results for mean differences between selected echocardiographic measurements, presented as paired t-tests for two time points (7 and 11 years of age) in both analyzed groups of children, is shown in Table 4. Data were presented as z-scores. The mean differences in z-score values in the presented echocardiographic measurements were approximately 0.5 SD for the majority of presented variables in the two analyzed groups, and the confidence intervals were entirely above 1.

Heart rate assessment

The mean value of HR, whether presented as an absolute value or a z-score, was significantly higher in the ELBW chil-

Table 2. Comparison of M-mode echocardiographic measurements in 7- and 11-year-old extremely low birth weight newborns and their controls

	First follow-up (at the age of 7 years)			Second follow-up (at the age of 11 years)		
	Study group (n = 64)	Control group (n = 36)	*P* value[a]	Study group (n = 64)	Control group (n = 36)	*P* value[a]
Absolute values, cm, mean (SD)						
RVDD	1.20 (0.34)	1.66 (0.38)	0.001	1.66 (0.36)	1.74 (0.47)	0.35
IVSd	0.56 (0.16)	0.58 (0.13)	0.78	0.59 (0.28)	0.66 (0.18)	0.21
LVEDD	3.17 (0.42)	3.65 (0.39)	<0.001	3.79 (0.38)	4.14 (0.39)	<0.001
LVPWd	0.52 (0.10)	0.59 (0.12)	0.02	0.56 (0.12)	0.62 (0.13)	0.03
IVSs	0.83 (0.21)	0.92 (0.14)	0.02	0.93 (0.17)	1.02 (0.19)	0.01
LVESD	2.36 (0.29)	2.67 (0.37)	<0.001	2.51 (0.33)	2.86 (0.30)	<0.001
LVPWs	0.73 (0.13)	0.90 (0.31)	0.003	0.95 (0.19)	0.97 (0.16)	0.64
AoD	1.44 (0.18)	1.65 (0.20)	<0.001	1.75 (0.22)	1.99 (0.26)	<0.001
LAD	1.79 (0.29)	2.13 (0.29)	<0.001	2.1 (0.33)	2.33 (0.33)	0.002
Relative values, cm Expressed as z-score for body surface area (SD)						
RVDD	–1.51 (1.23)	–0.35 (0.94)	0.001	–0.62 (0.85)	–0.60 (1.25)	0.95
IVSd	0.04 (1.19)	–0.10 (1.06)	0.54	–0.47 (1.36)	–0.08 (1.16)	0.16
LVEDD	0.27 (0.98)	0.47 (1.02)	0.001	–1.01 (0.91)	–0.35 (0.79)	<0.001
LVPWd	–0.63 (1.29)	0.24 (0.86)	0.35	–0.23 (1.06)	0.08 (0.99)	0.16
IVSs	0.16 (1.09)	0.52 (0.87)	0.11	–0.23 (1.06)	0.07 (0.99)	0.19
LVESD	0.19 (0.95)	0.66 (1.05)	0.035	–0.29 (0.92)	0.57 (0.65)	<0.001
LVPWs	–1.78 (1.14)	–1.1 (1.26)	0.15	–0.99 (1.27)	–1.11 (1.02)	0.67
AoD	0.25 (1.27)	0.89 (0.99)	0.01	0.63 (1.14)	1.63 (1.30)	<0.001
LAD	–1.01 (1.10)	–0.07 (0.92)	<0.001	–1.75 (0.97)	–0.01 (0.86)	<0.001

Data are presented as the mean (SD).
[a]In order to correct for multiple testing, the Sidak adjustment for correlated variables was used. Significance was defined as a 2-sided $P \leq 0.01$.
Abbreviations: AoD, aortic diameter; IVSd, thickness of the intraventricular septum at end diastole; IVSs, thickness of the intraventricular septum at end systole; LAD, left-atrial dimension; LVEDD, left ventricular dimension at end diastole; LVESD, left ventricular dimension at end systole; LVPWd, left ventricular posterior wall thickness at end diastole; LVPWs, left ventricular posterior wall thickness at end systole; RVDD, right ventricular end-diastolic dimension

Table 3. Analysis of the selected left ventricle parameters in the study and control groups at 7 and 11 years of age

	First follow-up (at the age of 7 years)			Second follow-up (at the age of 11 years)		
	Study group (n = 64)	Control group (n = 36)	*P* value[a]	Study group (n = 64)	Control group (n = 36)	*P* value[a]
LVM, g	47.7 (15.3)	65.6 (15.6)	0.001	56.8 (42.7)	78.8 (31.4)	0.008
LVMI, g/m$^{2.7}$	31.9 (9.5)	36 (8.5)	0.04	21.9 (16)	28.1 (17.4)	0.04
Fraction of shortening	32.1 (7.0)	33.0 (6.9)	0.23	33.6 (5.5)	30.8 (4.34)	0.009
Ejection fraction	0.61 (0.10)	0.62 (0.09)	0.33	0.63 (0.07)	0.58 (0.06)	0.005
EDV, mL	52 (17)	72 (19)	<0.001	68 (29)	77 (30)	0.02
ESV, mL	20 (6.5)	27 (9.3)	<0.001	34 (15.6)	40.1 (15.9)	0.004
SV, mL	32 (13.6)	45 (14)	<0.001	39 (10.1)	45.2 (11.4)	0.01
Cardiac index, L/m^2	3.34 (1.96)	3.18 (1.74)	0.37	2.81 (0.89)	2.95 (0.69)	0.46
Mean HR, per min	93 (8.1)	86 (7.4)	0.001	86 (7.2)	82 (8.2)	0.05
Mean HR z-score	1.25 (1.34)	0.58 (1.45)	0.01	1.19 (1.2)	0.62 (1.6)	0.03

Data are presented as the mean (standard deviation).
[a]In order to correct for multiple testing, the Sidak adjustment for correlated variables was used. Significance was defined as a 2-sided $P \leq 0.01$.
Abbreviations: EDV, left ventricular volume at end diastole; ESV, left ventricular volume at end systole; HR, heart rate; LVM, left ventricular mass; LVMI, left ventricular mass index; SV, stroke volume

Table 4. Results of paired t-tests for selected echocardiographic measurements

	Study group (n = 64)	*P* for paired t-test[a]	Control group (n = 36)	*P* for paired t-test[a]
RVDD	0.96 (0.55 to 1.37)	0.001	–0.23 (–0.68 to 0.21)	0.29
IVSd	–0.44 (–0.94 to 0.05)	0.08	–0.07 (–0.52 to 0.38)	0.75
LVEDD	–0.42 (–0.80 to 0.04)	0.03	–0.65 (–1.07 to –0.13)	0.03
LVPWd	–0.49 (–0.88 to 0.09)	0.08	–0.34 (–0.85 to 0.18)	0.20
IVSs	–0.06 (–0.39 to 0.27)	0.72	–0.24 (–0.66 to 0.17)	0.23
LVESD	–0.52 (–0.79 to –0.24)	0.001	–0.08 (–0.58 to 0.42)	0.74
LVPWs	0.58 (–0.02 to 1.19)	0.07	0.03 (–0.53 to 0.59)	0.91
AoD	0.54 (0.11 to 0.97)	0.02	0.63 (0.12 to 1.09)	0.01
LAD	0.52 (0.03 to 1.01)	0.04	–0.09 (–0.41 to 0.23)	0.56

Data are presented as the mean difference (95% confidence interval for difference).
[a]In order to correct for multiple testing, the Sidak adjustment for correlated variables was used. Significance was defined as a 2-sided $P \leq 0.01$.
Abbreviations: see Table 2

dren than in the controls at age 7. The HR values remained higher in 11-year-old ELBW children, but the differences between the study group and fullterm controls were smaller at this point than at 7 years of age.

DISCUSSION

The study presented here is a follow-up to the one performed 4 years earlier that evaluated heart structure and function in 7-year-old children born prematurely as ELBW infants [3].

As in the previous study [3], we did not find any significant differences in the development of cardiac complications between the ELBW children and full-term participants. Previous studies reported similar observations [10, 11].

The cardiac dimensions, such as LV, LA, and AoD, were smaller in the 11-year-old ELBW children, as shown in the M-mode analysis. The results were comparable to those of our previous study, in which the same group of 7-year-old ELBW patients was diagnosed in a similar fashion. Other echocardiographic studies reported similar observations in such groups of patients [12, 13]. From 7 to 11 years of age, there was no decrease in the ratio of average RV dimensions between ELBW children and their full-term counterparts that was observed 4 years earlier in the same population. We believe that one possible explanation is the specificity of the M-mode and its use in the evaluation of RV dimensions, which were assumed to be the least precise and objective.

The LV of the ELBW children remained smaller than that of the controls over the 4 years between the two studies. However, there was no significant difference in the cardiac index, calculated as cardiac output adjusted for BSA, between the studied groups and the control groups of children at 7 or 11 years of age. One possible explanation for the unchanged value of the cardiac index could be faster HR compensating for the smaller SV in the ELBW participants, as previously reported in a number of studies [10, 13]. The differences in the evaluated parameters regarding LVM were the same at ages 7 and 11 in the two groups. However, the absolute value of the LVM and the LVMI adjusted for the child's height were significantly smaller in the ELBW children than in control children at 11 years of age.

A number of studies have reported a significant association between extreme prematurity and cardiovascular complications. Mohlkert et al. [13] demonstrated structural cardiac changes in this particular group of patients that resulted in evident systolic and diastolic dysfunction of the LV. Altered myocardial function was also described in infancy [14, 15]. Hoki et al. [16] studied a group of almost 500 children hospitalized in infancy due to apparent life-threatening events to identify potential predictors of cardiac disease. During 7 years of observation, the only clinical parameter indicating future heart problems was prematurity. In another study, Bolton et al. [17] demonstrated impaired hemodynamics of the large vessels in children born extremely prematurely. Echocardiography of those patients when they were 11 years old clearly showed an increased augmentation index, reflecting higher systemic arterial stiffness as calculated from the ascending aortic pressure waveform. However, some studies speculated that fetal growth restriction played a larger role than prematurity in cardiac morphology and/or postnatal cardiac adaptation [18, 19]. A cardiac evaluation of prematurely born adults showed some serious structural and functional changes in their hearts, including LVH and systolic and diastolic dysfunction of the LV [12].

One of the most important findings of our present study was the verification that the ELBW and control groups have the same rate of heart growth. We recorded a 20% increase in the LVM in both populations, with the difference in heart mass remaining unaltered at 7 and 11 years of age. Therefore, we hypothesized that the decreased heart size of the ELBW children resulted mostly from damage in the early perinatal period of life, whereas their further development was similar to that of healthy full-term children. The transition process from fetal to neonatal circulation in preterm infants is complex, and it can be more challenging in extremely low birth weight infants with hemodynamic instability [20]. This hypothesis could be also supported by the results of the study by Bokiniec et al. [21]. Compared with term neonates on the 28th day of life, preterm neonates evaluated at week 40 of postconceptional age had reduced myocardial thickness already at that age.

We further supported the above conclusions of comparable development of the hearts in ELBW and full-term children with a unique paired t-test for selected echocardiographic measurements expressed as z-scores for the two time points (7 and 11 years of age). Our results showed similar intensities of heart growth in both the studied and control groups over the 4 years between follow-up studies. The z-score differences in the majority of the echocardiographic parameters evaluated with the paired t-test were less than 0.5 SD in the ELBW children. Hence, we could assume that the hearts of these children were developing harmoniously, without overgrowth or involution.

The results of two studies of 7-year-old children in 2013 [3] and a recent study of 11-year-old children indicated that the most serious impact on ELBW children's heart lesion development occurred in the fetal and early postnatal age, when cardiomyocyte hyperplasia plays a pervasive role [22]. Our results indicated that the later development of extremely premature children's hearts remained stable and balanced, similar to the heart development of their full-term peers.

However, although our studies showed that the structural and functional cardiac changes in extremely prematurely born children did not constitute a clinical problem during infancy or school age, we recommend further echocardiographic follow-up investigations to monitor for potential cardiovascular complications in adulthood.

The strengths of our study included its multicenter, population-based design and the objectivity of the ob-

servations, which were based on standardized echocardiographic assessments. In the follow-up evaluation at 11 years, we enrolled satisfactory numbers of representatives for both the study and control groups, which justified and substantiated our conclusions.

Limitations

The main limitation of our study was the lack of a parallel clinical evaluation to determine whether the observed structural cardiac findings and faster HR in ELBW children affected their daily lives/routines. Moreover, there was no formal test of interrater reliability; however, post hoc analysis did not reveal any statistically significant differences in the measurements between the two echocardiographers.

CONCLUSIONS

The analyzed ELBW children had smaller heart sizes than the full-term controls at both the ages of 7 and 11 years. Almost all of their echocardiographic parameters, expressed as z-scores normalized for BSA, were 0.5–1 SD lower in the two follow-up assessments over 4 years of observation. We observed that the heart growth of the ELBW group was comparable to that of the full-term controls, and it increased by approximately 20% in both groups during the 4-year observation period. We believe that the most critical cardiac lesions occur in the fetal and early postnatal life of extremely premature children; therefore, despite their normal cardiac development up to this point during school age, they would require repeated monitoring to diagnose possible cardiac complications later in life.

Article information

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ORIGINAL ARTICLE

Neuron-specific enolase concentrations for the prediction of poor prognosis of comatose patients after out-of-hospital cardiac arrest: an observational cohort study

Robert Ryczek[1], Przemysław J Kwasiborski[2], Jolanta Dymus[3], Agata Galas[1], Anna Kaźmierczak-Dziuk[1], Anna M Karasek[1], Marta Mielniczuk[1], Małgorzata Buksińska-Lisik[2], Paweł Krzesiński[1]

[1]Department of Cardiology and Internal Diseases, Military Institute of Medicine, Warszawa, Poland
[2]3rd Department of Internal Diseases and Cardiology, Second Faculty of Medicine, Medical University of Warsaw, Warszawa, Poland
[3]Department of Laboratory Diagnostics, Military Institute of Medicine, Warszawa, Poland

Correspondence to:
Robert Ryczek, MD, PhD, Department of Cardiology and Internal Diseases, Military Institute of Medicine, Szaserów 128, 01–141 Warszawa, Poland
phone: +48 261 816 372, +48 691 380 560,
email: rryczek@wim.mil.pl

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ABSTRACT

Background: Neuron-specific enolase (NSE) is a biomarker for neurological outcomes after cardiac arrest with the most evidence collected thus far; however, recommended prognostic cutoff values are lacking owing to the discrepancies in the published data.

Aims: The aim of the study was to establish NSE cutoff values for prognostication in the environment of a cardiac intensive care unit following out-of-hospital cardiac arrest (OHCA).

Methods: A consecutive series of 82 patients admitted after OHCA were enrolled. Blood samples for the measurement of NSE levels were collected at admission and after 1 hour, 3, 12, 24, 48, and 72 hours. Neurological outcomes were quantified using the cerebral performance category (CPC) index. Each patient was classified into either the good (CPC ≤2) or poor prognosis (CPC ≥3) group.

Results: Median NSE concentrations were higher in the poor prognosis group, and the difference reached statistical significance at 48 and 74 hours (84.4 ng/ml vs 22.9 ng/ml at 48 hours and 152.1 ng/ml vs 18.7 ng/ml at 72 hours; P <0.001, respectively). Moreover, in the poor prognosis group, NSE increased significantly between 24 and 72 hours (P <0.001). NSE cutoffs for the prediction of poor prognosis after OHCA were 39.8 ng/ml, 78.7 ng/ml, and 46.2 ng/ml for 24, 48, and 72 hours, respectively. The areas under the curve were significant at each time point, with the highest values at 48 and 72 hours after admission (0.849 and 0.964, respectively).

Conclusions: Elevated NSE concentrations with a rise in levels in serial measurements may be utilized in the prognostication algorithm after OHCA.

Key words: biomarkers of brain injury, hypoxic brain injury, ischemic encephalopathy, neurologic prognostication, neuron-specific enolase

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INTRODUCTION

Cardiac arrest is one of the leading causes of death in high-income countries. Only one-third of out-of-hospital cardiac arrest (OHCA) patients, who have reached emergency medical services, survive until hospital admission [1]. Mortality rates for those admitted comatose to hospitals after (OHCA) remain high depending on the mechanism of cardiac arrest and quality of care and usually exceed 50% [2, 3]. Most deaths are caused by ischemic brain injury [4], and therefore, adequate neurological prognostication is an important part of the therapeutic process. Establishing a poor prognosis allows medical personnel to avoid inappropriate treatment, justify the withdrawal of life-sustaining therapy, and provide important information to the patients' families. Clinical examination and brain computed tomography (CT) are commonly used for this purpose; however, both lack appropriate diagnostic accuracy, especially at an early stage of hospitalization. Given that the gravity of decisions in this medical context is extremely high and to minimize the possibility of false-positive results (FPR), it is a commonly accepted strategy to use a multimodal prognostic

WHAT'S NEW?

Determining the concentrations of neuron-specific enolase (NSE) in patients admitted to the hospital following cardiac arrest is a method to assess the neurological prognosis of such patients. Since 2015, the European Resuscitation Council has recommended the use of NSE levels as a component in a multimodal prognostication algorithm for this group of patients. The main limitation of NSE levels, as reported by several authors, is the discrepancies in the cutoff thresholds for a poor prognosis. Therefore, the European Resuscitation Council recommends that such thresholds be set by local laboratories. To our knowledge, this study is the first to assess the use of NSE concentrations for the prognosis of patients following cardiac arrest at a Polish hospital. Setting cutoff values for poor prognosis of cardiac arrest patients may promote the application of this prognostic tool in Polish intensive care units, especially in centers cooperating with laboratories that can assess NSE levels.

algorithm for that purpose. Such algorithm includes the results of the neurological assessment and brain CT, but also short-latency somatosensory evoked potentials, electroencephalography, and biomarkers for brain injury [5].

Next to the glial S-100B protein, neuron-specific enolase (NSE) is the biomarker in ischemic brain injury that is most supported by the clinical evidence collected so far. NSE is an intracellular glycolytic enzyme that is mostly present in neurons, tissues of neuroectodermal origin, and erythrocytes. Following cardiac arrest, NSE is released from ischemic brain tissue, and its serum concentrations correlate with the extent of neurological injury. Many authors have proven that high NSE concentrations after cardiac arrest and its rise in serial measurements may predict poor neurologic outcomes. However, NSE concentration cutoff thresholds vary between studies, ranging from 33 ng/ml to 85 ng/ml for different time points, with the most discriminative being from 48 hours to 72 hours post-OHCA [5, 6].

The European Resuscitation Council (ERC) recommends incorporating NSE levels into a multimodal prognostication strategy algorithm, but at the same time, they advise that each laboratory establish its own values and cutoff levels for poor prognoses based on the assay used [7].

We intended to address these recommendations and for this purpose, we conduct the current study. Our aim was to define NSE cutoff values, at a few time points within the first 72 hours after admission, that have a high specificity for a poor prognosis prediction after cardiac arrest in settings specific to our center.

METHODS

Patient recruitment took place in the Cardiac Intensive Care Unit of the Military Institute of Medicine, Warsaw, Poland, between September 2016 and July 2019. The study had an observational, prospective design in the cohort of consecutive patients admitted after OHCA who remained unconscious at first presentation with a Glasgow Coma Scale score ≤8. In addition to standard care, blood samples for evaluation of NSE levels were collected at the time of admission and then after 1 hour, 3, 6, 24, 48, and 72 hours.

This study was approved by the Ethics Committee of the Military Institute of Medicine (no. 39/WIM/2013). Informed consent was obtained from relatives and all participants who regained consciousness.

Blood samples for the measurement of NSE levels were analyzed in a local laboratory using the Cobas e601 system and an electrochemiluminescence immunoassay (ECLIA) kit (Roche Diagnostics, Mannheim, Germany; reference number 12133113 122). The normal value for NSE concentration was <17 ng/ml, functional sensitivity was 0.25 ng/ml, and the range of measurements was 0.05–370 ng/ml.

A neurologist evaluated all patients 72 hours (standard deviation 24 h) after admission and at discharge. Each participant was classified using the cerebral performance category (CPC) scale: CPC 1, good cerebral performance; CPC 2, minor neurological deficit; CPC 3, severe neurological impairment and dependence for everyday activities; CPC 4, coma; and CPC 5, brain death [8]. Clinical outcomes were evaluated at discharge using the CPC classification. CPC 1–2 were considered as good clinical outcomes, and CPC 3–5, including death, were considered as poor clinical outcomes.

Statistical analysis

Data distributions were analyzed for each continuous variable. Non-Gaussian variables were presented as medians with an interquartile range. Comparison of the patients' clinical characteristics was conducted using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. Changes in NSE concentrations over time and between CPC groups were tested for significance using the Friedman rank test, nonparametric variant of ANOVA test with post hoc analysis. Bonferroni correction was applied to address the multiple comparisons issue. At each time point, a receiver operating characteristic curve was plotted, and the area under the curve was determined to evaluate the predictive power of NSE concentrations on CPC. Cutoff values were determined by maximizing the Youden index and using values providing 95% specificity. Sensitivity and specificity values were corrected using bootstrap internal validation. When possible, a normal approximation was used to obtain confidence intervals. Survival analyses and Kaplan–Meier curves were calculated for the four 4-quartiles of NSE concentrations and generalized log-rank test was used to compare the

Table 1. Basic demographic and selected clinical data for the cerebral performance category 1–2 and cerebral performance category 3–5 patient groups admitted after out-of-hospital cardiac arrest

	CPC 1–2 (n = 22)	CPC 3–5 (n = 60)	*P* value
Male	15 (68.2)	41 (68.3)	0.98
Age, years, median (IQR)	60 (45–70)	67 (62–76.5)	0.008
Time to CPR, min, median (IQR)	0 (0–0)	5 (0–10)	<0.001
Time to ROSC, min, median (IQR)	15 (10–25)	28 (19–45)	<0.001
Bystander CPR	20 (90.9)	31 (51.7)	0.002
Shockable rhythm	20 (90.9)	34 (56.7)	0.004
Lactate, mmol/l, median (IQR)	3.3 (2.8–5.1)	7.6 (4.6–12.25)	<0.001
Time to ROSC, min, median (IQR)	4.5 (3–6)	3 (3–3)	<0.001
SOFA, median (IQR)	8 (6–10)	12 (9–14)	<0.001
APACHE II, median (IQR)	19.5 (18–24)	29 (25–38)	<0.001
Hospitalization time, days, median (IQR)	16 (12–22)	9 (2–26)	0.09
Targeted temperature management	14 (63.6)	35 (58.3)	0.8

Data are presented as number (percentage) of patients unless otherwise indicated.
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; GCS, Glasgow Coma Scale; IQR, interquartile range; ROSC, return of spontaneous circulation; SOFA, Sequential Organ Failure Assessment Score

proportion of survival with good clinical outcome in analyzed groups. A *P* value <0.05 was considered significant for all tests performed. All statistical analyses were performed using Statistica 13.0 (StatSoft, Tulsa, OK, USA).

RESULTS

Eighty-two consecutively admitted adult OHCA patients were enrolled in this study. Overall, 450 serum samples were analyzed. The patients' basic clinical and demographic characteristics are shown in Table 1. Of the 82 patients, 22 were classified into the CPC 1–2 group and 60 were placed in the CPC 3–5 group. Except for sex, hospitalization time, and frequency of targeted temperature management (TTM) utilization, most parameters differed significantly between the groups.

The median (IQR) plasma NSE concentrations for the CPC 1–2 groups vs the CPC 3–5 groups, respectively, were as follows: at admission, 22.8 ng/ml (19.7–34.4) vs 37.65 ng/ml (29.4–51.0); $P = 0.7$; at 1 hour, 28.7 ng/ml (22.6–45.7) vs 38 ng/ml (29.5–60.5); $P = 0.9$; at 3 hours, 29.2 ng/ml (21.7–37.6) vs 44.55 ng/ml (31.4–87.6); $P = 0.6$; at 12 hours, 25.4 ng/ml (21.0–32.8) vs 46.55 ng/ml (30.9–87.7); $P = 0.1$; at 24 hours, 23 ng/ml (18.7–34.5) vs 55.9 ng/ml (34.1–134.1); $P = 0.1$; at 48 hours, 22.9 ng/ml (15.1–33.5) vs 84.4 ng/ml (42.0–192.0); $P < 0.001$; and at 72 hours, 18.7 ng/ml (14.1–29.0) vs 152.1 ng/ml (62.3–264.4); $P < 0.001$. In the poor prognosis group, NSE levels increased significantly between 24 and 72 hours ($P < 0.001$). In the good prognosis group, the NSE levels were constant within the first 72 hours ($P = 0.3$). Both groups tended to differ significantly in terms of NSE levels starting from 48 hours after the OHCA ($P < 0.001$), and at 72 hours, the difference increased (Figure 1).

Receiver operating characteristic analyses were carried out for NSE levels at each time point to predict CPC at discharge (Figure 2). The area under the curves for NSE levels in the CPC prediction were all significant, with the highest area under the curve value at 72 hours after OHCA (detailed data are shown in Supplementary material, *Table S1*). The cutoff values for NSE that maximized the Youden index, as well as those with FPR of 5% at each time point, are shown in Table 2. In the analyzed cohort the cutoff values for the concentrations of NSE calculated for a specificity of 95% (FPR <5%) at the time points during the first 24 hours had low sensitivity (14%–37%). The sensitivity of these cutoffs calculated to maximize the Youden index at the same time points was more eligible (71%–81%). The range of those cutoffs was from 27.2 ng/ml at admission to 39.8 ng/ml at 24 hours. The NSE concentration thresholds calculated for a 5% of FPR at subsequent time points had acceptable sensitivity exceeding 53%; these cutoff points were 78.7 ng/ml at 48 hours and 46.2 ng/ml at 72 hours.

The survival analysis indicated that the higher the NSE levels, the higher the probability of a poor neurological outcome. Kaplan–Meier curves (Figure 3) show that high NSE levels early after OHCA significantly increase the probability of a poor prognosis. The probability of a good prognosis would be >60% for the first NSE quartile at admission, in contrast to patients with higher NSE levels, where the probability of a good prognosis would be approximately 20% (Figure 3).

DISCUSSION

To our knowledge, this study presents the first attempt to test NSE levels as a predictor of poor clinical outcomes in comatose patients admitted to the hospital after OHCA in a Polish population. We identified the NSE cutoffs highly specific to ischemic brain damage. We also confirmed the negative prognostic value of the rise of NSE concentrations in serial measurements within the first 3 days after OHCA.

The prognostic usefulness of NSE concentrations as a neurologic outcome predictor after OHCA has been confirmed in diverse populations in the past [5] and in the era of TTM treatment [9]. Thus, based on the strongest evidence, NSE has been incorporated as a biomarker in

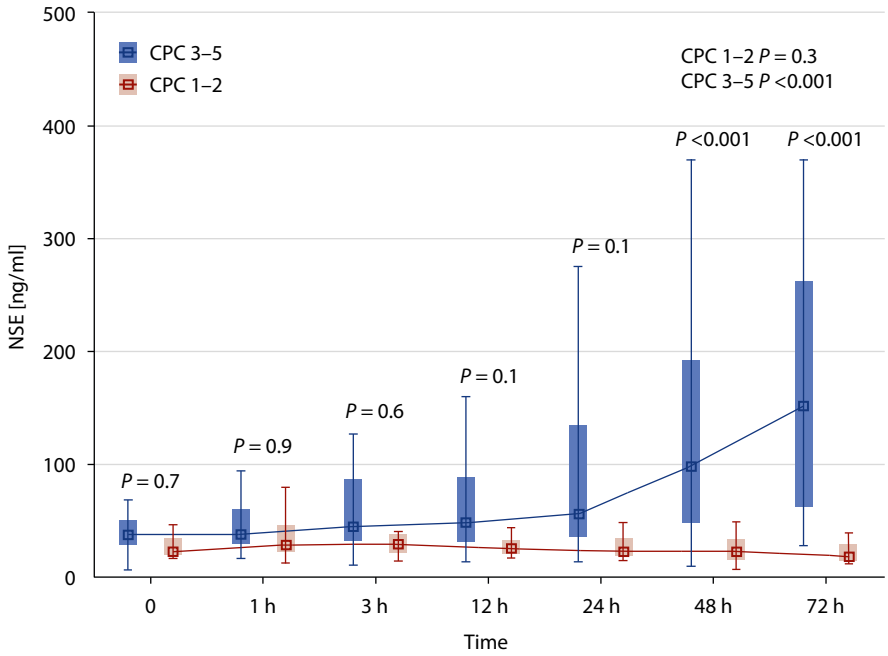

Figure 1. Neuron-specific enolase (NSE) concentrations at admission and 1, 3, 12, 24, 48, and 72 hours after admission in both groups.
Abbreviations: see Table 1

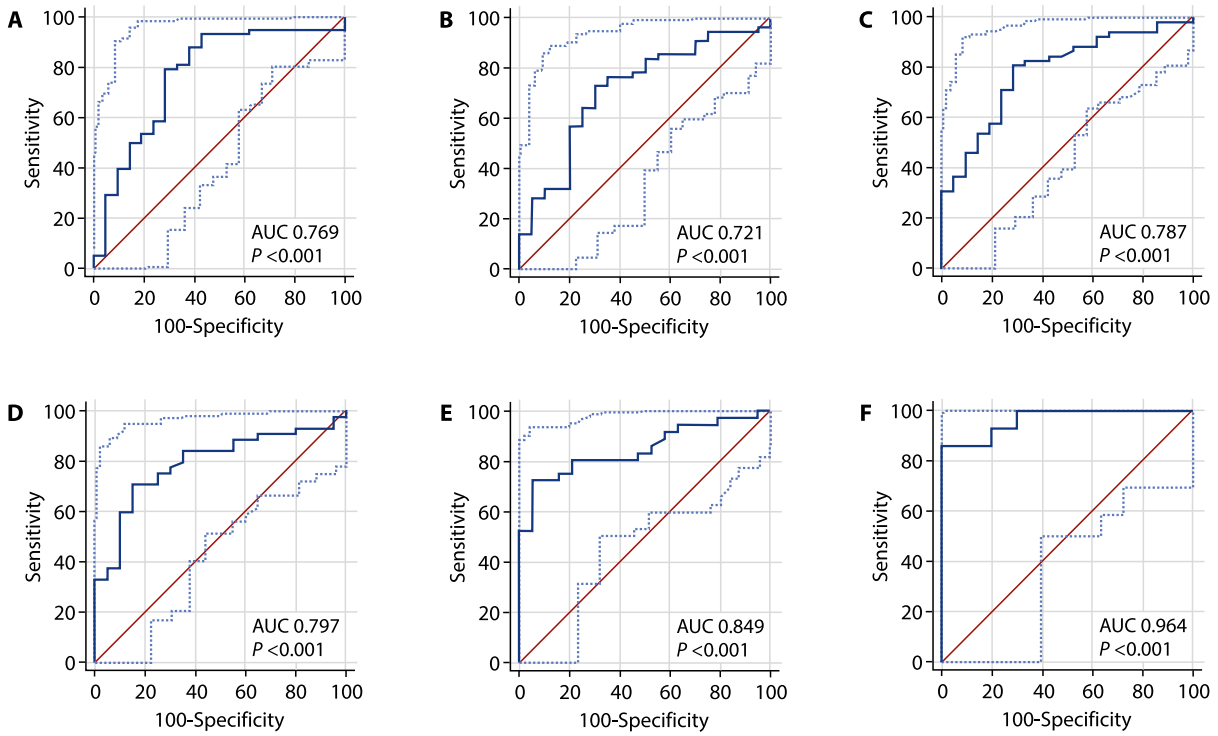

Figure 2. Receiver operating characteristic curves for the capacity of neuron-specific enolase at each time point to predict cerebral performance category at discharge. **A.** At admission; **B.** After 3 hours; **C.** After 12 hours; **D.** After 24 hours; **E.** After 48 hours; **F.** After 72 hours

brain injury and an important element of a multimodal prognostic algorithm for comatose patients admitted to the hospital after OHCA [7]. The advantages of NSE are that it is a simple and widely available laboratory measurement as it is utilized for monitoring the treatment of tumors of the neuroectodermal origin or small cell lung cancer. Further, the results of the measurements are quantitative and independent of the sedative and neuromuscular blockade effects that may influence the outcomes of a neurological examination. However, the continuous nature of the

Table 2. Neuron-specific enolase (NSE) concentration cutoff values for poor neurological prediction at each time point. Cutoff values are calculated to maximize the Youden index and at a fixed false-positive rate level of 5%

NSE, hours	Cutoff, ng/ml	Sensitivity, %	95% CI	Specificity, %	95% CI
0					
Youden	27.2	79	67–89	71	48–89
FPR <5	46.6	29	2–59	95	95–100
1					
Youden	28.9	77	64–87	57	34–78
FPR <5	79.7	16	4–37	95	95–100
3					
Youden	31.8	73	60–84	70	46–88
FPR <5	106.1	14	2–27	95	95–100
12					
Youden	28.2	81	68–90	71	48–89
FPR <5	62.5	37	21–62	95	95–100
24					
Youden	39.8	71	56–84	85	62–97
FPR <5	81.8	33	16–56	95	95–100
48					
Youden	48.9	72	55–86	95	74–100
FPR <5	78.7	53	28–69	95	95–100
72					
Youden	52.9	86	57–98	100	69–100
FPR <5	46.2	86	57–100	95	95–100

Abbreviations: CI, confidence interval; FPR, false-positive rate

numerical results implies the need to determine a cutoff value for a poor prognosis with the lowest risk of an FPR. The main reason why the evaluation of NSE levels cannot be implemented in routine clinical practice is that the reported threshold values differ among studies. In a recently published meta-analysis [10], the proposed cutoff values for predicting a poor neurological outcome varied from 13.3 ng/ml [11] to 47.6 ng/ml [12] for early periods of up to 24 hours of observation and from 22.4 ng/ml [13] to 97 ng/ml [14] for 48 hours to 72 hours after admission. Thus, the ERC, in its latest Guidelines for Post-Resuscitation Care has advised that ideally "every hospital laboratory assessing NSE should create its own normal values and cutoff levels based on the test kit used" [7]. It has also been emphasized that those thresholds should optimally minimize the risk of an FPR below 5%.

In the analyzed cohort, the cutoffs for the concentrations of NSE calculated for a specificity of 95% (FPR <5%) at the time points during the first 24 hours had an unacceptably low sensitivity. Therefore, in case of intention to predict bad outcome basing on the measurements done at first 24 hours we propose to use cutoffs that compromise sensitivity and specificity (calculated to maximize the Youden index). The range of those cutoffs was 27.2–39.8 ng/ml. So, to avoid FPR we propose to use the most conservative value — 39.8 ng/ml as a predictor of a poor outcome in the first 24 hours of observation.

The tools for evaluating the neurological prognoses of OHCA patients during the first 24 hours after admission are very scarce. Only the lack of pupillary or corneal reflexes [15] and the absence of somatosensory evoked potentials [16, 17] allow the prediction of poor outcomes with a high likelihood. However, both tests have low sensitivity as the observation of reflexes is highly subjective and the assessment of somatosensory evoked potentials requires expertise and is vulnerable to artifacts [18]. The possibility of utilizing the patient's NSE level, an observer-independent marker, in the prognostication process, seems a very valuable addition for this period of treatment, even if prognostic accuracy does not meet the assumed accuracy criteria.

On subsequent days of hospitalization, the sensitivity of NSE concentration thresholds calculated for a 5% FPR exceeded 53%; thus, we suggest using the following cutoff points calculated for 95% specificity: 78.7 ng/ml at 48 hours and 46.2 ng/ml at 72 hours.

It is interesting to compare our results with those obtained by the Target Temperature Management After Cardiac Arrest (TTM) Trial investigators [6], as they have been using the same test to determine NSE levels. The subpopulation of the TTM Trial with NSE concentration testing is the largest cohort analyzed so far (686 participants) that has dealt with the problem of establishing the role of NSE levels as a neurological outcome predictor after OHCA. Our cutoff points were higher than those obtained by the TTM Trial investigators: 39.8 ng/ml vs 27 ng/ml for a maximized Youden index 24 hours after admission, 78.7 ng/ml vs 42 ng/ml for 48 hours, and 46.2 ng/ml vs 33 ng/ml for 72 hours, with an FPR of 5%, respectively. These discrepancies can be explained by differences in the study population. Patients with unwitnessed cardiac arrest with asystole as the initial rhythm were excluded from the TTM Trial but not from our study. This may explain why we noted a higher percentage of non-shockable rhythms in our population than in the TTM Trial (34% vs 19%). The TTM Trial included only patients with a presumed cardiac cause of OHCA, while in our cohort, 18% of cases were defined as noncardiac or of unknown origin. In our population, 60% of the patients had TTM implemented, as compared

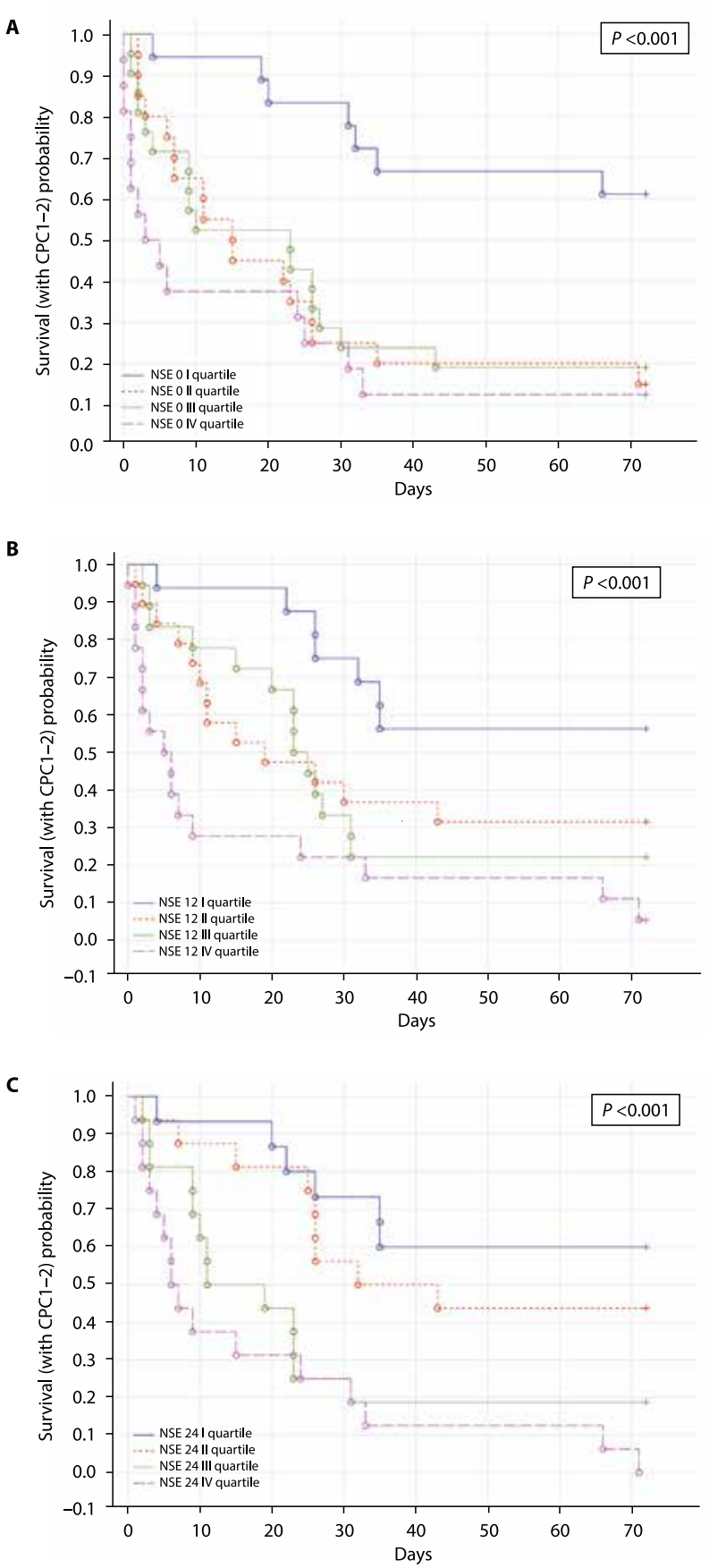

Figure 3. Kaplan–Meier curves showing the probability of a good outcome in relation to the quartile of neuron-specific enolase (NSE) level. **A.** At admission; **B.** After 12 hours; **C.** After 24 hours.

Abbreviations: see Table 1

with 100% in the TTM Trial. Nevertheless, the observed differences in cutoff levels support the relatively cautious position of the ERC and prove the necessity for establishing diagnostic thresholds at each center in order to use NSE levels for neurological prognosis.

While NSE concentrations remain constant in patients with a good prognosis, patients with poor neurologic outcomes typically have elevated NSE levels, and in serial measurements, there is also a significant rise in NSE concentrations [6, 19]. This observation was also confirmed by our results, showing an increase in NSE concentrations over time and, therefore, providing additional prognostic value.

Our results seem to have important clinical implications. The use of proposed NSE cutoffs, highly specific to poor neurological outcome, could be useful in determining therapeutic strategy. Objective, biochemical confirmation of serious brain injury may facilitate the withdrawal of life-sustaining therapy. We hope that our results will encourage other Polish cardiac intensive care unit teams to implement NSE assessment in their prognostication algorithms for patients after OHCA.

Limitations

The main limitation of NSE testing is that NSE may also have extracerebral origins. Hemolysis is the main cause of false-positive results, and even if undetectable, it may affect NSE concentration test results [20]. There is also a low risk that some of the individuals in our cohort may have had undiagnosed neuroendocrine tumors. The possibility of non-neuronal sources of NSE affecting NSE levels can be avoided by testing concentrations directly in the cerebrospinal fluid. NSE determined in the cerebrospinal fluid may have more diagnostic accuracy than serum measurements [21]. However, the technically demanding procedure for obtaining cerebrospinal fluid for diagnostic purposes makes this approach highly impractical.

CONCLUSIONS

Our results revealed that in the environment of our center the NSE cutoffs measured at 48 hours and 72 hours may be useful in the prediction of poor prognosis after OHCA. The concentrations at first 24 hours are also of prognostic value, however, lower than those at 48 hours and 72 hours. The elevation of NSE levels and their rise in serial measurements are confirmed to be a valuable prognostic tool in patients after OHCA and should be considered in everyday clinical practice.

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Platelet function in patients undergoing surgical and transcatheter aortic valve replacement: a comparative study

Anna Komosa[1], Bartłomiej Perek[2], Piotr Rzymski[3, 4], Barbara Poniedziałek[3], Marek Grygier[1], Andrzej Siniawski[1], Katarzyna Szabatowska[1], Jolanta Siller-Matula[5, 6], Marek Jemielity[2], Marcin Misterski[2], Maciej Lesiak[1]

[1]1st Department of Cardiology, Poznan University of Medical Sciences, Poznań, Poland
[2]Department of Cardiac Surgery and Transplantology, Poznan University of Medical Sciences, Poznań, Poland
[3]Department of Facial Malformation, Poznan University of Medical Sciences, Poznań, Poland
[4]Integrated Science Association (ISA), Universal Scientific Education and Research Network (USERN), Poznań, Poland
[5]Department of Cardiology, Medical University of Vienna, Vienna, Austria
[6]Department of Experimental and Clinical Pharmacology, Center for Preclinical Research and Technology CEPT, Medical University of Warsaw, Warszawa, Poland

Correspondence to:
Anna Komosa, MD, PhD, 1st Department of Cardiology, Poznan University of Medical Sciences, ul. Długa 1/2, 60–848 Poznań, Poland, phone: +48 61 854 91 46, e-mail: komosa.ania@ump.edu.pl

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ABSTRACT

Background: Intervention-induced platelet hypercoagulability may pose a risk of serious adverse events for patients.

Aims: This study aimed to assess whether surgical and transcatheter aortic valve replacement (SAVR and TAVR) differ in periprocedural platelet activity.

Methods: The total number of 24 patients with a mean age (SD) of 71 (13) years who underwent SAVR (n = 12) or TAVR (n = 12) were recruited for the study. The following parameters were evaluated at 4 time-points: (i) platelet indices: total platelet count (PLT), platelet distribution width (PDW) and mean platelet volume (MPV), (ii) MPV/PLT ratio, (iii) platelet level of lipid peroxidation: malondialdehyde (MDA) content and MDA/PLT ratio. Eventually, percentage variations of PLT, PDW, and MPV in relation to the baseline values were determined.

Results: MPV/PLT ratio increased significantly after procedures in both groups ($P = 0.01$ in TAVI and $P = 0.01$ in SAVR). MDA concentrations were significantly higher when assessed directly post-procedure ($P = 0.04$) as well as 24 hours later ($P = 0.01$) in the SAVR and TAVI groups. The indirect parameter of platelet activity indexed for platelet counts (MDA/PLT) was comparable between both groups before and 48 hours after procedures, but was significantly higher in SAVR patients, particularly after 24 hours after interventions ($P = 0.04$; medians TAVR vs SAVR, respectively).

Conclusions: Standard surgical aortic valve replacement is associated with a more pronounced platelet reaction to intervention-induced injury, as compared to the transcatheter-based procedure. The importance of these laboratory findings requires further investigation focused on early and late clinical outcomes.

Key words: human platelets, lipid peroxidation, surgical aortic valve replacement, transcatheter aortic valve implantation

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INTRODUCTION

Aortic stenosis (AS) is the most common valvular heart disease among elderly patients [1]. Symptomatic severe AS is associated with a survival rate of 50% if untreated [2]. Thus, to improve a patient's prognosis it is crucial to undertake invasive treatment on time. Currently, there are two therapeutic options for patients with severe AS: surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR). SAVR is the treatment of choice in symptomatic patients with severe AS [3]. However, TAVR has lately become less invasive although valuable alternative to manage symptomatic patients at intermediate or high risk of surgical procedure [4, 5]. It has already been proven that TAVR is non-inferior to surgery when performed in experienced centers, with respect to the risk of death or stroke within 5 years of follow-up [6, 7]. The estimation has been made that the number of SAVR procedures is expected to decrease significantly due to the growing number of TAVR procedures [8].

WHAT'S NEW?

Intervention-induced platelet hypercoagulability may pose patients to potentially serious adverse events. This study aimed to assess whether surgical and transcatheter aortic valve replacement (SAVR and TAVR), differ in periprocedural platelet activity caused by iatrogenic injury due to intervention. Demonstrating the significance of parameters regarding platelets number and function such as total platelet count (PLT), platelet distribution width (PDW) and mean platelet volume (MPV), MPV/PLT ratio, platelet level of lipid peroxidation measured by means of its final major product, malondialdehyde (MDA) content and MDA/PLT ratio, and the percentage variation of PLT, PDW and MPV in relation to the baseline values, may be valuable in our understanding the effect of heart procedures on platelet dysfunction. We demonstrated that standard surgical aortic valve replacement is associated with a more pronounced platelet reaction to iatrogenic injury due to intervention, as compared to transcatheter-based technique.

Pathophysiology of AS is an overly complex issue. Impaired fibrinolysis, pronounced calcification, coagulation, and platelet activation abnormalities contribute to the progression due to increased fibrin deposition and inflammation [9–11]. Platelet activity has an impact on the development of atherosclerosis. Platelets contribute to the early stage of vascular pathology, such as endothelial dysfunction and rupture of vulnerable plaque [12]. Platelet activation caused by atherosclerotic plaque rupture or erosion of the endothelium contributes to the formation and progression of the atherothrombotic disease [13]. These processes lead to clinically relevant consequences — adverse cardiovascular events such as myocardial infarction or stroke [14, 15]. The influence of platelet activity on the course of AS has been investigated, but results remain unequivocal [16].

Intervention-induced platelet hypercoagulability may pose patients to potentially serious adverse events. It has already been proven that platelets play a significant role in reparation after injury, wound healing, and organ regeneration [17]. The coagulation cascade is initiated at the injured endothelial surface, where platelets migrate and a fibrin-rich clot is formed. Progressive postinjury thrombocytosis induces a hypercoagulable state associated with an increased risk of thromboembolic complications [18]. Postinjury thrombocytosis seems to be an underestimated factor of a hypercoagulable state causing platelet hyperactivity.

As reported in the previous study, both TAVR and SAVR can induce systemic oxidative stress, although the former is associated with a significantly lower redox imbalance and faster recovery of antioxidant capacity [19]. As established experimentally and through observational studies, increased levels of endo- and exogenous reactive oxygen species are important factors triggering platelet activation [20–22]. It is therefore important to understand whether there is an association between platelet-related oxidative stress and platelet function following TAVR and SAVR procedures. In this regard, malondialdehyde (MDA) in platelets appears to be a feasible marker and a link between oxidative stress and platelet activity, since it is a hallmark of lipid peroxidation, a common outcome of cellular redox imbalance [23]. Moreover, it correlates with platelet aggregation in response to arachidonic acid, epinephrine, and collagen [24], and it is, besides thromboxane A2, a product of prostaglandin H_2 conversion by thromboxane synthase [25, 26].

This study aimed to assess whether two available methods of AS treatment differ in periprocedural platelet activity caused by iatrogenic injury due to intervention. To this end, the platelet indices and platelet MDA were compared in patients undergoing TAVR and SAVR during the hospital stay.

METHODS

The total number of 24 patients with a mean age (SD) of 71 (13) years who underwent SAVR (n = 12) or TAVR (n = 12) procedures between May 2016 and March 2017 were recruited for the study. The baseline characteristics of the studied group are summarized in Table 1. Written informed consent was obtained from each patient before participating in the research. The study protocol was approved by the Ethical Committee of the Medical University in Poznan (No. 968/15). All of the studied individuals fulfilled the criteria for high-gradient AS defined according to the current European Societ of Cardiology guidelines [27].

The following parameters were evaluated in all studied patients: (i) platelet indices: total platelet count (PLT), platelet distribution width (PDW) and mean platelet volume (MPV), (ii) MPV/PLT ratio, (iii) platelet level of lipid peroxidation measured by means of its final major product, MDA content and MDA/PLT ratio, and (iv) the percentage variation of PLT, PDW and MPV in relation to the baseline values were also determined [28]. All parameters were measured at 4 time-points: pre-procedure, immediately post-procedure, then 1 and 2 days after the procedure. Subsequently, all values were compared between the two groups at each of the measured time-points: functional parameter (MDA) vs platelet morphological indicators (PLT, MPV, PDW, PLT/MPV). Additionally, the percentage variation of MDA vs PLT values, MDA vs PDW, MDA vs MPV, and MDA vs PLT/MPV ratio, in relation to the baseline values, were calculated.

Malondialdehyde concentration

The content of MDA was measured in isolated platelets. Firstly, the platelet-rich plasma was obtained from the patient's blood samples by centrifugation at 200 g for 12 minutes. Platelet-rich plasma was then transferred to

Table 1. Baseline characteristics of studied patients (n = 24)

Variable	SAVR (n = 12)	TAVR (n = 12)	*P* value
Gender (male), n (%)	7 (58)	6 (50)	0.7
Age, years, mean (SD)	63 (10)	80 (3)	0.001
Height, m, mean (SD)	1.67 (0.11)	1.64 (0.06)	0.43
Weight, kg, mean (SD)	78.8 (13.2)	74.2 (12.3)	0.39
BMI, kg/m^2, mean (SD)	28.2 (3.9)	27.5 (4.7)	0.73
Obesity (BMI >30 kg/m^2), mean (SD)	4 (33)	5 (42)	0.69
Prior medical history			
Arterial hypertension, n (%)	8 (67)	5 (42)	0.24
Atrial fibrillation, n (%)	2 (17)	3 (25)	0.63
PCI, n (%)	3 (25)	5 (42)	0.41
Myocardial infarction, n (%)	0 (0)	3 (25)	0.08
Diabetes mellitus, n (%)	3 (34)	6 (50)	0.43
CABG, n (%)	1 (8)	2 (17)	0.56
COPD, n (%)	1 (8)	2 (17)	0.56
Stroke/TIA, n (%)	0 (0)	2 (17)	0.17

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; TIA, transient ischemic attack

polypropylene tubes, 1/10 vol acid citrate dextrose was added, centrifuged again at 900 g for 15 minutes. Plasma was aspirated and platelets were suspended in 200 µl of distilled water. The platelet MDA level was assessed using the TBARS Assay kit (Cayman Chemicals, Ann Arbor, MI, USA). The platelets were treated with 300 ml of RIPA Buffer (50 mM Tris-HCl, pH 7.4, 1% Triton X-100, 150 mM NaCl, 1% Tergitol type NP-40, 0.5% sodium deoxycholate, 0.1% sodium dodecyl sulfate) to conduct the lysis of cellular components. The butylated hydroxytoluene was added to the RIPA Buffer to prevent artificial lipid peroxidation during platelet lysis. The samples were then centrifuged at 1600 g for 10 minutes and the resulting 100 µl of supernatants were transferred to new tubes. The 800 µl of thiobarbituric acid was added to generate an MDA-thiobarbituric acid adduct. The reaction was conducted at 95°C for 60 minutes, samples were then placed for 10 minutes on an icebath for inhibition and centrifuged at 1600 g for 10 minutes. The absorbance of the final product was measured at 532 nm using a SynergyHTX multi-mode plate reader (BioTek Instruments, Winooski, VT, USA). The MDA content, given as µM, was calculated by comparing the absorbance values to a calibration curve (r^2 = 0.99) prepared using the MDA standard (Cayman Chemicals, Ann Arbor, MI, USA).

Surgical aortic valve replacement

All operations were performed from full median sternotomy with the use of cardio-pulmonary bypass (CPB) in moderate hypothermia (28°C) and cardioplegic cardiac arrest according to St. Thomas Hospital II formula [29]. CPB was conducted through an arterial cannula introduced to the ascending aorta and a two-staged venous cannula to the right atrium. After the ascending aorta was opened, the aortic valve was completely removed and the aortic prosthesis using 2-0 sutures with Teflon pledges was implanted. After aortotomia was closed with 5-0 monofilament suture and de-airing of the left heart was completed, ascending aorta was de-clamped and reperfusion phase of CPB initiated. Successful weaning from CPB was followed by removal of all cannulas, protamine administration, careful hemostasis, and closure of the chest.

Percutaneous aortic valve implantation

Patients were eligible for TAVR based on the institutional heart team's decision (interventional cardiologist, cardiac surgeon, and echocardiography specialist).

The pre-procedural evaluation included: coronary angiography, transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE); contrast-enhanced computed tomography (CT) with off-line reconstruction to evaluate the aortic valve, and access site (femoral and iliac arteries). The final decision regarding the route of the vascular approach was made based on the results of the CT scan. General anesthesia or deep sedation was used during the procedures. The TTE monitoring was performed and a temporary pacemaker was inserted from the femoral vein for rapid pacing and as a backup in case of iatrogenic atrioventricular block consequences [30].

In patients with the percutaneous femoral approach, two Proglides™ were introduced before insertion of the vascular sheath. The Medtronic CoreValve Evolut R prosthesis was implanted in all cases. Once the prosthesis was correctly positioned, expanded, and deployed, the contrast injection was performed to assess the presence and degree of paravalvular leak. Control angiography of the access site was performed to assess vessel patency and possible bleeding [31].

Data presentation and statistical analysis

First, all continuous variables were checked for normality by means of the Shapiro–Wilk W test. Those meeting the

Table 2. The results of non-parametric tests of multiple comparisons of platelet count

	TAVI			
SAVR	'0'	'1'	'2'	'3'
'0'		0.624	0.239	0.010
'1'	0.022		1.000	0.777
'2'	0.020	1.000		1.000
'3'	0.003	1.000	1.000	

Abbreviations: SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; '0', baseline; '1', immediately post-procedure; 2', 24 hours after procedure; 3', 48 hours after procedure

Table 3. Distribution of mean values and standard deviation (SD) of mean platelet volume (MPV) and platelet distribution width (PDW) depending on sampling time after transcatheter aortic valve implantation (TAVI) and surgical aortic valve replacement (SAVR)

	Sampling time							
	0'		1'		2'		3'	
	MPV, fl	PDW, %	MPV, fl	PDW, %	MPV, fl	PDW, %	MPV, fl	PDW, %
TAVI, mean (SD)	8.83 (0.91)	54.6 (5.4)	8.96 (1.05)	58.8 (5.2)	8.99 (0.86)	59.0 (6.5)	9.27 (0.98)	60.8 (7.0)
SAVR, mean (SD)	8.62 (1.04)	55.1 (5.7)	9.05 (1.17)	60.2 (6.0)	9.31 (1.36)	60.1 (6.6)	9.61 (1.24)	59.7 (6.1)
P value	0.04	0.70	0.30	0.49	0.80	0.48	0.70	0.75

criteria of normal distribution were presented as means with standard deviations and then compared with the use of unpaired Student t-test (between TAVI and SAVR groups) or repeated-measures ANOVA followed by post hoc Tukey HSD test (for time-related changes within groups). Otherwise (i.e., for not normally distributed continuous variables), they were expressed as the medians with interquartile range (IQR: first to third quartile) and then analyzed statistically by non-parametric tests such as Friedman test followed by Dunn's multiple comparisons of ranks. Qualitative variables were compared by means of Yates' corrected χ^2 test. *P*-value <0.05 was considered as statistically significant. Analyses were performed with the use of Statistica 10.0 for the Windows package (StatSoft, Tulsa, OK, USA).

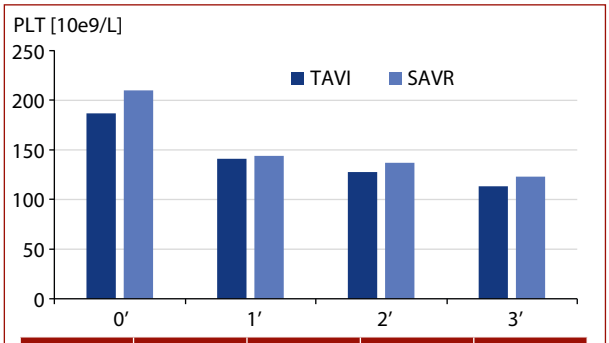
RESULTS

PLT count

In both groups, PLT decreased significantly following procedures (*P* <0.001). However, this drop was more pronounced in the SAVR group (*P* = 0.02 vs TAVI) because in all postoperative analyses (samples '1' to '3') PLT count was markedly lower than before surgery, whereas in the TAVI group only between two points, before procedure vs 48 hours after it (Table 2). Interestingly, the intergroup comparison did not show any statistical significance (Figure 1).

MPV and PDW

In both groups, these platelet parameters did not change during the periprocedural period (MPV, *P* = 0.67 and *P* = 0.26; PDW, *P* = 0.05 and *P* = 0.16; respectively for TAVI and SAVR in ANOVA) (Table 3). Of note, MPV before the procedure was significantly lower in SAVR than in the TAVI group.



Median with IQR	0'	1'	2'	3'
TAVI	175 (157–231)	141 (117–182)	137 (117–156)	112 (99–137)[a]
SAVR	210 (169–230)	144 (102–164)	137 (98–172)[a]	123 (11–140)[a]
P value	0.600	0.470	0.862	0.624

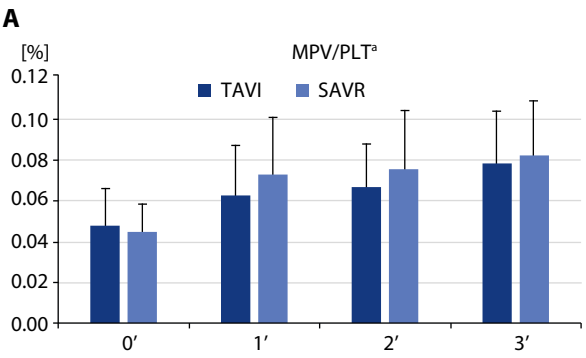
Figure 1. Platelet counts in the periprocedural period.

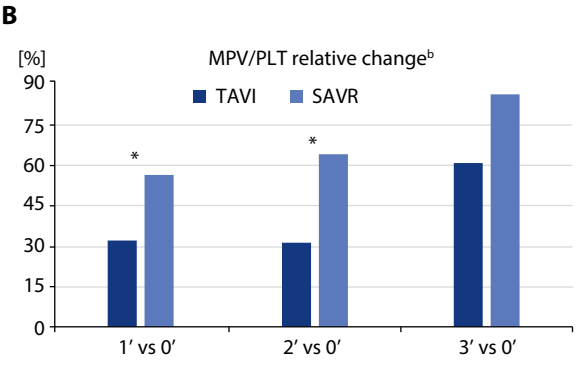
[a]*P* <0.05 after ('1'–'3') vs before procedure ('0') in multiple comparisons of ranks.
Abbreviations: PLT, platelet counts; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation

MPV/PLT

MPV/PLT ratio increased significantly after procedures in both groups (*P* = 0.01 in TAVI and *P* = 0.01 in SAVR), although its value did not differ between groups (Figure 2A).

Post-hoc analysis disclosed that marked increase in MPV/PLT ratio between baseline vs both 24 (*P* = 0.04) and 48 hours (*P* = 0.01) after valve implantations in the SAVR group whereas in the TAVI group only between baseline and 48 hours after (*P* = 0.01) the procedures. These findings encouraged us to perform a more detailed analysis of this parameter. In the next step, a relative increase of this ratio was compared between groups and was found to be more pronounced 24 hours after procedures (Figure 2B).





[%]	'1' vs '0'	2' vs '0'	3' vs '0'
TAVI	31.4 (17.2–39.8)	30.5 (20.4–58.1)	60.4 (47.9–81.9)
SAVR	56.2 (42.0–86.6)	63.2 (31.0–94.3)	85.4 (62.8–114.6)
P value	0.09	0.04	0.34

Figure 2. MPV/PLT ratio (**A**) and its relative changes (**B**) after procedures.

Data are presented as the means with standard deviations ([a]) or the medians ([b]). *$P < 0.05$ TAVI vs SAVR.
Abbreviations: MPV, mean platelet volume; others: see Figure 1

MDA and MDA/PLT

Multiple comparisons of ranks test revealed that platelet levels of MDA were significantly higher soon after procedures ($P = 0.046$) and 24 hours ($P = 0.02$) later in the SAVR group than in the TAVI group (Figure 3A).

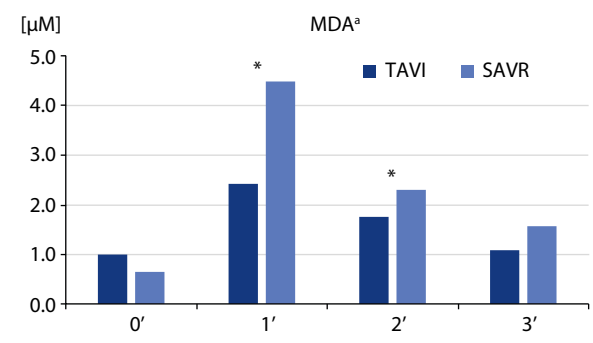
The parameter of single platelet activity (i.e., MDA/PLT) was comparable between groups before and 48 hours after procedures but in the other sampling points its value was significantly higher in SAVR patients (Figure 3B).

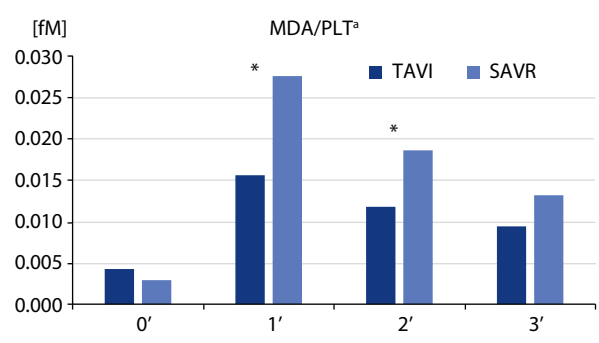
Multiple comparisons of MDA-to-PLT ratios within groups showed differences both in TAVI and SAVR patients. In the SAVR group, significant differences were noted not only after surgery ('1' vs '0'; $P < 0.001$) but also 24 hours later ('2' vs '0'; $P = 0.01$) whereas in TAVI one only soon after procedures ('1' vs '0'; $P = 0.02$).

DISCUSSION

Certain laboratory tests are done routinely in everyday clinical practice. The present study aimed to find out whether any of the available platelet-related indices such as PLT, MPV, PDW have importance in perioperative care in patients after TAVI and SAVR.

The decrease in PLT after procedures was observed in both studied groups. Platelet count was significantly lower in patients after SAVR at each time point after the operation. It is worth mentioning that none of the investigated patients had severe thrombocytopenia that would require blood or platelet transfusion following the procedure. Reasons behind the decrease in PLT after SAVR have been studied before. Aortic valve replacement operation was carried out using cardio-pulmonary bypass in moderate hypothermia (28°C). According to previously published data, hemodilution and destructive effect of CPB often cause secondary thrombocytopenia [32]. Moreover,





[μM]	0′	1′	2′	3′
TAVI	1.00 (0.67–1.25)	2.41 (1.92–2.79)	1.72 (1.17–1.88)	1.10 (0.93–1.51)
SAVR	0.63 (0.52–1.59)	4.48 (1.87–5.11)	2.27 (2.03–2.78)	1.54 (1.11–2.14)
P value	0.57	0.046	0.02	0.28

[fM]	0′	1′	2′	3′
TAVI	0.004 (0.003–0.007)	0.016 (0.011–0.020)	0.012 (0.008–0.015)	0.009 (0.007–0.013)
SAVR	0.003 (0.002–0.006)	0.027 (0.019–0.047)	0.019 (0.014–0.027)	0.013 (0.010–0.018)
P value	0.31	0.048	0.045	0.24

Figure 3. Total malondialdehyde (MDA) concentration (**A**) and its content in a single platelet (**B**).

[a]Non-parametric continuous variables are presented as medians. *$P < 0.05$ TAVI vs SAVR.
Abbreviations: see Figure 1

preoperative use of antiplatelet agents and hypothermia aggravate thrombocyte dysfunction [33].

Platelet count drop has already been observed after SAVR but also following percutaneous interventions. It has been postulated that it is due to the use of low-osmolar contrast agents and unfractionated heparin administration during the procedure [34–36]. The decrease in PLT is also a consequence of blood loss during (although minimally but still invasive) intervention. Unsurprisingly, classical aortic valve replacement generates more pronounced blood loss than TAVI, which is a transcatheter procedure. However, in the present study, the PLT was significantly lower 48 hours after TAVI in comparison to baseline. There is evidence that patients who have a decrease in PLT following transcatheter aortic valve implantation are at increased risk of adverse events [37]. However, the exact mechanisms for the condition and its consequences require further investigation.

Other possible reasons for PLT decrease include damage to the endothelium caused by prosthesis implantation and tissue injury. Moreover, shear stress modifications may play an important role in the platelet activation [38].

Large size platelets have increased metabolic and enzymatic activity profile and high prothrombotic potential [39]. It has been proven that increased MPV has an impact on myocardial infarction and cardiovascular death occurrence and thus is associated with worse outcome [40]. There is an inverse relationship between PLT and MPV observed in the physiological and pathophysiological state. The goal is to maintain hemostatic balance by the sustenance of constant platelet mass. The inflammatory process with enhanced thrombopoiesis is a clear example of this mechanism. The number of circulating platelets increases and many reactive large-sized platelets flow to the inflammatory site [41].

However, in the present study, no significant correlation with MPV levels was observed among investigated patients. Only a trend towards an increase of MPV after invasive procedures was noted, probably due to the low number of subjects included in this study.

Further study on a large group of patients is necessary to reveal whether any platelet-related laboratory test could serve as prediction markers and would be useful in the perioperative assessment of patients after SAVR or TAVI. Demonstrating the significance of parameters regarding platelet number and function may be valuable in understanding the effect of heart procedures on platelet dysfunction.

The aim of our study was also to use the levels of MDA in platelets in the assessment of oxidative stress. The present study has indicated that TAVR induced significantly lower redox imbalance as the platelet MDA content, the marker of lipid peroxidation, was lower than that in patients undergoing SAVR. These findings have important implications — they support the observations of previous research in which oxidative stress was measured using several different oxidative-stress biomarkers in the patient's serum [42]. Clearly, redox imbalance is less pronounced in the case of TAVI compared to SAVR, in which serum MDA levels increase significantly right after the surgical procedure [43]. Lower MDA in platelets not only highlights less cellular injury but also relates to how the MDA can affect platelet reactivity. Previous research has indicated the detrimental activation of platelets in some patients after SAVR [44]. Although platelet reactivity can be due to numerous factors and can be triggered via various pathways, reactive oxygen species are known to play their role as important mediators. For example, hydrogen peroxide supports platelet activation depending on arachidonic acid and collagen and triggers tyrosine phosphorylation of β3 [45, 46]. In turn, superoxide anion can enhance platelet activation by ADP, arachidonic acid, collagen, and thrombin, but also through scavenging endothelium- or platelet-derived nitric oxide [47, 48]. Therefore, reactive oxygen species can both induce oxidative stress in platelets and trigger their activation. Furthermore, MDA can be produced enzymatically by the thromboxane synthase in amounts equimolar to thromboxane A2 [49]. This further indicates that increased intraplatelet MDA content, more profoundly seen in patients undergoing SAVR, may also relate to the modification of thrombocyte function. Importantly, other studies suggest that suppression of platelet MDA levels can normalize arachidonate- and collagen-induced aggregation [50]. In SAVR patients, the post-procedural increase in this marker was higher than in TAVR, but a decreasing trend towards the baseline level was seen within 48 hours. This indicates that the potential effects of MDA on platelet activity were most likely ameliorated.

Limitations

The limitations of the present study should also be highlighted. Firstly, the research encompassed a small sample size. It is an effect of the complex protocol including the performance of surgical procedures requiring many preparations, precise timing of blood sample collection at 4 accurate time-points and a proper sample transfer to the experimental laboratory for determination of MDA levels. Furthermore, there is a need to emphasize a significant difference in the age of patients in both studied groups (TAVI vs SAVR; mean 80 years vs 63 years, respectively). It is a consequence of the qualification process by the heart team according to European Society of Cardiology guidelines on the management of patients with severe symptomatic AS. TAVR is a method preferred in elderly and high-risk patients. The findings of the present study cannot be used to modify the antiplatelet therapy, although they lay a foundation for further investigations encompassing larger groups and additional platelet-related parameters.

CONCLUSIONS

Standard surgical aortic valve replacement is associated with a more pronounced platelet reaction to intervention-induced injury, as compared to the transcathe-

ter-based technique. The importance of these laboratory findings warrants further investigation focused on early, as well as late, clinical outcomes. Whether these findings are of any significance in terms of selecting the appropriate antiplatelet therapy after SAVR and TAVI requires further investigations.

Article information

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Patients with heart failure and an implanted cardioverter--defibrillator during the coronavirus disease 2019 pandemic: insights from a multicenter registry in Poland

Mateusz Tajstra[1], Adam Wojtaszczyk[1, 2], Maciej Sterliński[3], Ewa Świerżyńska[3, 4], Łukasz Szumowski[3, 5], Mikołaj Tomasiuk[6], Marcin Grabowski[7], Łukasz J Januszkiewicz[7], Janusz Romanek[8], Andrzej Przybylski[8], Przemysław Mitkowski[9], Aneta Klotzka[9], Andrzej Szafranek[10], Mariusz Gąsior[1], Zbigniew Kalarus[6], Oskar Kowalski[6, 11]

[1]3rd Department of Cardiology, School of Medicine with the Division of Dentistry in Zabrze, Medical University of Silesia, Silesian Center for Heart Diseases, Zabrze, Poland
[2]Department of Electrocardiology, Medical University of Lodz, Łódź, Poland
[3]Department of Arrhythmia Institute of Cardiology, Warszawa, Poland
[4]1st Department of Cardiology, Doctoral School, Medical University of Warsaw, Warszawa, Poland
[5]Cardinal Stefan Wyszynski University in Warsaw, Warszawa, Poland
[6]Department of Cardiology, Congenital Heart Diseases and Electrotherapy, Silesian Center for Heart Diseases, Zabrze, Poland
[7]1st Chair and Department of Cardiology, Medical University of Warsaw, Warszawa, Poland
[8]Cardiology Department with the Acute Coronary Syndromes Subdivision, Clinical Provincial Hospital No. 2, Faculty of Medicine, University of Rzeszow, Rzeszów, Poland
[9]1st Department of Cardiology, Poznan University of Medical Sciences, Poznań, Poland
[10]Computer Science Laboratory, Silesian Center for Heart Diseases, Zabrze, Poland
[11]Department of Dietetics, School of Public Health in Bytom, Medical University of Silesia, Katowice, Poland

Correspondence to:
Mateusz Tajstra, MD, PhD, Silesian Center for Heart Diseases, Skłodowskiej-Curie 9, 41–800 Zabrze, Poland, phone: +48 32 373 36 74, e-mail: mateusztajstra@wp.pl

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INTRODUCTION

The outbreak of the coronavirus disease 2019 (COVID-19) has spread into a pandemic affecting more than 76 million people worldwide and causing nearly 1.7 million deaths so far and has become a disaster for healthcare systems around the world. Moreover, similar to other pandemics of the past, it is forcing preponderant alterations in many fields of medicine.

According to current practice guidelines, a significant portion of patients with heart failure (HF) receive implantable cardioverter-defibrillators (ICDs) with or without cardiac resynchronization therapy (CRTs) due to well-evidenced clinical benefits which include a long-term improvement of prognosis [1]. In patients hospitalized for COVID-19, the presence of HF is a powerful independent predictor of mortality and in-hospital complications [2].

While a follow-up is a strongly recommended element of care in patients with HF and ICD/CRT, including in many cases an in-person visit for clinical and technical evaluation of the implanted device, the pandemic has limited patient's contact with the medical staff in order to obtain rigorous isolation and reducing a human-to-human possible virus transmission.

In accordance with the Heart Rhythm Society Guidance, direct medical visits should be limited as much as possible in favor of the use of telehealth solutions [3]. Furthermore, teleconsultations have been approved by the Polish National Health Fund and implemented countrywide. However, prior to the spread of the pandemic, the use of telemedical services for patients with HF and ICD/CRTs was not widely implemented in everyday clinical practice.

Although over the last years, the introduction of remote monitoring (RM) of ICD/CRTs has significantly improved the prognosis in HF-patients [4] and its role may be even more significant in the current difficult reality, it is well known that RM can be clinically effective when RM care is based on the experienced medical staff. This requires logistic solutions, such as developing a model of alert-triggered clinical reactions, which requires ample time to achieve [5]. Moreover, mainly due to reimbursement issues, the use of RM in Poland is restricted. Besides some initial data regarding their clinical efficacy [6], teleconsultations, as the only pattern of supervision in patients with HF and ICD/CRT to date, have not been widely examined. Therefore, there are some legitimate concerns about the safety of such a model of

supervision, especially regarding potentially lethal and clinically silent events (arrhythmic events, lead integrity defects, premature battery depletion, or device-related infections).

Taking into consideration the above-mentioned issues, the purpose of the present study was to analyze the landscape of follow-up in patients with HF and implanted ICD/CRTs during the first 2 months of the outbreak of COVID-19 in Poland. We strongly believe that the study may be a cornerstone for assessing the impact of the change in supervision related to the pandemic on long-term clinical outcomes in patients with HF and ICD/CRTs in the future.

METHODS

We performed an analysis in consecutive patients with HF and implanted ICD/CRTs included in the multicenter registry from 6 tertiary, academic, high-volume cardiovascular hospitals in Poland. The study compared follow-up routines from the 2-month observation period starting with the beginning of the COVID-19 epidemic in Poland (March 14th, 2020) and the corresponding period of 2019. We investigated baseline characteristics, types of visits, ICD/CRT interventions, arrhythmic events, and clinical interventions. The percentage of individual forms of visits was calculated in relation to the number of all visits in the observation periods. At the same time, the number of interventions is presented in relation to the overall number of patients included in the analysed groups. The study was approved by an appropriate institutional review board and — given the retrospective nature of the analysis — a written informed consent to participate in the study was not required.

Statistical analysis

The qualitative variables were expressed as absolute number and percentage and were analyzed with the χ^2 test (where numbers were anticipated to be less than 5, Yates' correction for continuity was implemented). The distribution of continuous variables was verified using the Shapiro–Wilk test. Continuous variables were expressed as median and interquartile range (IQR). The significance of differences between median values was tested with the U-Mann–Whitney test. A *P* value of less than 0.05 was regarded as significant. Statistical analysis was performed using SPSS software version 25.0 (IBM Corp., Armonk, New York, United States).

RESULTS AND DISCUSSION

We recorded a reduction (16.5%) in the number of patients included in the study and in the control period (1259 and 1508, respectively), which provided a basis for the analysis. The baseline clinical and device characteristics were similar between the study groups (Table 1). During the coronavirus pandemic, a landscape shift in the follow-up care was observed, with a 16.8% reduction in all follow-up visits (1343 vs 1615), a higher rate of cancelled scheduled visits (15.8% vs 0.7%; *P* <0.001), scheduled telephone visits (66.7% vs 0%; *P* <0.001), and scheduled visits using only remote monitoring (14.4% vs 0%; *P* <0.001), as well as a lower rate of scheduled outpatients visits (20.1% vs 87.6%; *P* <0.001).

Despite the fact that significantly more patients with ICD/CRTs were supervised remotely (RM or teleconsultations), the rate of diagnosed appropriate ICD interventions (anti-tachycardia pacing or shock) due to life-threatening ventricular arrhythmias and the detection of *de-novo* atrial fibrillation remained similar in both groups (5.1% vs 4.4%; *P* = 0.43 and 2.62% vs 2.4%; *P* = 0.7, respectively). Equally, a proportion of diagnosed ICD/CRT technical dysfunctions were comparable in both analyzed time periods (3.5% vs 2.65%; *P* = 0.7). However, a significantly lower rate of inappropriate ICD interventions, and any arrhythmia detections and clinical reactions, mainly due to a pharmacotherapy change, were recorded in 2020 (Table 1). Possible reasons for this appear to include the organizational changes in the health care system and the greater level of stress among patients [7, 8]. However, which is noteworthy, this was not related to urgent or scheduled hospitalization recommendations (Table 1).

The study shows a significant change in the rate and types of follow-up visits, inappropriate ICD interventions, any arrhythmia findings, and clinical reactions in patients with HF and implanted with ICD/CRTs during the first 2 months of the COVID-19 pandemic in 6 high-volume cardiovascular centers in Poland. It is possible that the impact, particularly on long-term clinical outcomes, requires further evaluation.

The study has been a retrospective analysis and it involves all the limitations related thereto.

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Table 1. A comparison of baseline and device characteristics, type of visits, and clinically important interventions in patients with heart failure and implantable cardioverter-defibrillators (with or without resynchronization). The study period is defined as the time between the state of epidemic introduced by the Polish government (March 14, 2020) and May 14, 2020. The control period was from March 14, 2019 to May 14, 2019

Variable	Study period	Control period	*P* value
Patients	**1259**	**1508**	
Baseline characteristics			
Male	1003 (79.7)	1185 (78.6)	0.81
Age, years, median (IQR)	68 (15)	68 (15)	0.92
Ischemic aetiology	827 (65.7)	939 (62.3)	0.71
Implantation due to secondary prevention of SCD	189 (15)	256 (17)	0.61
RM	475 (37.7)	525 (34.8)	0.64
Device type			0.92
Single chamber ICD	464 (36.9)	558 (37.0)	
Dual chamber ICD	326 (25.9)	404 (26.8)	
Subcutaneous ICD	1 (0.1)	3 (0.2)	
CRT	467 (37.1)	543 (36)	
Device manufacturers			0.03
Abbott/St. Jude	244 (19.4)	332 (22)	
Biotronik	235 (18.7)	302 (20)	
Boston	410 (32.6)	398 (26.4)	
Medtronic	369 (29.3)	476 (31.6)	
Follow-up visits			
All follow-up visits	1343	1615	
Cancelled scheduled visits[a]	212 (15.8)	11 (0.7)	<0.001
Scheduled outpatient visits[a]	270 (20.1)	1415 (87.6)	<0.001
Scheduled telephone visits[a]	896 (66.7)	0 (0)	
Scheduled visits using only RM[a]	194 (14.4)	0 (0)	<0.001
Unscheduled outpatient visits[a]	35 (2.6)	19 (1.2)	0.02
Unscheduled telephone visits[a]	11 (0.8)	0 (0)	0.001
Unscheduled visits triggered by patient or alert using only RM[a]	118 (8.8)	144 (8.9)	0.91
Appropriate ICD intervention[b]	64 (5.1)	67 (4.4)	0.43
VT	59 (4.7)	63 (4.2)	0.35
ATP during VT	55 (4.4)	56 (3.7)	0.65
Shock during VT	15 (1.2)	19 (1.3)	0.46
VF	12 (0.9)	17 (1.1)	0.42
Shock during VF	12 (0.9)	16 (1.1)	0.25
Electrical storm	9 (0.7)	5 (0.3)	0.42
Inappropriate ICD intervention[b]	12 (1.0)	24 (1.6)	0.03
AF *de-novo* episode[b]	33 (2.6)	36 (2.4)	0.72
Any arrhythmia[b]	107 (8.4)	201(13.3)	<0.001
ICD/CRT dysfunction[b]	44 (3.5)	40 (2.7)	0.70
Any clinical reaction[b,c]	206 (16.4)	321 (21.3)	<0.001
Phone contact	111 (8.8)	104 (6.9)	0.57
Pharmacotherapy change	82 (6.5)	137 (9.1)	<0.001
Urgent hospitalization	41 (3.2)	47 (3.1)	0.52
Scheduled hospitalization	23 (1.8)	30 (2.0)	0.33

Data are presented as the number (percentage) of patients unless otherwise indicated.
[a]Percent of all visits in the analyzed period. [b]Percent of all patients included in the analyzed period. [c]Due to clinical and/or arrhythmic event.
Abbreviations: AF, atrial fibrillation; ATP, anti-tachycardia pacing; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; IQR, interquartile range RM, remote monitoring; SCD, sudden cardiac death; VT, ventricular tachycardia; VF, ventricular fibrillation

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Impact of diabetes mellitus on the dimensions of normal atherosclerosis-free coronary arteries

Jarosław Skowroński[1], Gary S Mintz[2], Ilona Michałowska[1], Emilia Szudejko[1], Min Jae Cha[3], Cezary Kępka[1], Mariusz Kruk[1], Jacek Kwieciński[1], Łukasz Kalińczuk[1], Zbigniew Chmielak[1], Adam Witkowski[1], Michał Ciszewski[1], Sang-Wook Kim[3], Jerzy Pręgowski[1]

[1]National Institute of Cardiology, Warszawa, Poland
[2]Cardiovascular Research Foundation, New York, United States of America
[3]Chung-Ang University Hospital, College of Medicine, Chung-Ang University, Seoul, Korea

Correspondence to:
Jarosław Skowroński, MD, PhD, National Institute of Cardiology, Alpejska 42, 04–628 Warszawa, Poland, phone: +48 22 3434127, e-mail: jskowronski@ikard.pl

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INTRODUCTION

In diabetic patients the coronary arteries appear angiographically smaller [1–5]. This is typically seen in the reference segments and may influence stent size selection. The possible explanations for this appearance in diabetics include: (1) more diffuse disease, (2) less pronounced remodeling, or (3) authentically smaller vessel size. The aim of our study was to use coronary computed tomography angiography (CCTA) in order to compare the dimensions of normal coronary arteries in patients with and without diabetes mellitus.

METHODS

The current study is a subgroup analysis of a larger study focused on the anatomy of normal coronary arteries [6]. The study conduct complied with the Helsinki Declaration and was performed with agreement of institutional review board. Written consent was not required due to the retrospective character of the study. Demographic characteristics and patient risk factors were collected retrospectively by hospital chart review. The risk factor definitions have been described previously [6]. Patients with diabetes mellitus were case-control matched in a 1:3 ratio with non-diabetics, exactly according to sex and coronary dominance pattern and within 0.1 m^2 maximal allowance of freedom for body surface area (BSA) calculated with the Du-Bois formula [7].

In all patients CCTA was performed after administration of sublingual nitroglycerin (0.8 mg). If necessary, intravenous boluses of metoprolol were given to reduce heart rate below 75 bpm. The CCTA studies were performed with the use of a dual-source computed tomography scanner (Somatom Definiton; Siemens Healthcare, Forchheim, Germany) as described previously [6].

The normal coronary artery was defined by CCTA as free of any calcification and detectable atherosclerosis. CCTA measurements were performed by a single reader at a dedicated workstation (Syngovia software, Siemens, Forchheim, Germany). The coronary artery dominance pattern and segmentation were defined according to the SYNTAX study criteria [8]. The distal coronary segments were excluded from the analysis. Lumen diameters (LD) and lumen areas (LA) were measured in all coronary segments. Mean values were computed using minimal and maximal dimension and then were used for the analyses.

The statistical analyses were performed with MedCalc 9.3.8.0 (MedCalc, Marierkerke, Belgium). The categorical data are presented as numbers and percentages and analyzed with the χ^2 test. The Shapiro-Wilk test was performed to assess the normality of data distribution. Continuous variables are presented as mean and standard deviation and compared with the t-test, or in the case of non-parametric distribution median with first and third quartile and compared with the Mann–Whitney U test. The Spearman test was used for the correlation analysis.

RESULTS AND DISCUSSION

The population of 201 consecutive subjects without CCTA-detected coronary atherosclerosis was described previously in an article focused on the influence of sex and coronary artery dominance pattern on the coronary segments dimensions [6]. Overall, in the cur-

rent sub-analysis, there were 14 (7%) diabetic patients (4 males, mean [SD] age 58 [6] years) and 42 matched control subjects (12 males, mean [SD] age 51 [12] years). All diabetic patients had type 2 diabetes and were on oral antidiabetic medication (8 patients treated with metformin, 1 patient with glyclaside, 2 patients with inhibitors of dipeptidyl peptidase-4), except for 2 patients treated with insulin and 1 patient with newly diagnosed diabetes with diet-controlled disease. The median duration of diagnosed diabetes was 5.5 years (Q1 = 2; Q3 = 9 years). Diabetic patients were older (58 [6] years vs 51 [12] years; $P = 0.046$), more often had arterial hypertension (100% vs 62%; $P = 0.005$), and their mean (SD) body mass index was higher (31.9 [5.6] kg/m^2 vs 27.9 [3.3] kg/m^2; $P = 0.002$). There were no differences in any coronary segments with regards to the LA or LD comparing the two groups (Table 1). We did not find any correlation between the duration of diabetes and coronary dimensions including the left main coronary artery LA (r = -0.2; $P = 0.48$) and LD (r = -0.3; $P = 0.38$) and proximal right coronary artery LA (r = -0.5; $P = 0.13$) and LD (r = -0.5; $P = 0.16$).

Interobserver variability for appropriate measurements was reported previously [6].

The main finding of our study is that diabetes mellitus *per se* does not influence the dimensions of coronary arteries in the absence of atherosclerosis.

The coronary arteries in diabetics with coronary artery disease (CAD) appear angiographically smaller than in CAD patients without diabetes [1–5]. By excluding any influence of diabetes mellitus on non-atherosclerotic coronary artery dimensions, the most probable explanations for this finding are either more diffuse atherosclerosis in diabetics or impairment of compensatory remodeling.

Coronary angiography can identify reduction of lumen size, but cannot explain its pathophysiological background. Moseri et al. [1] found that angiographically normal coronary arteries in diabetic patients were smaller as compared with matched controls. The authors claimed that their findings represented the earliest phase of CAD. However, invasive angiography cannot exclude mild atherosclerotic lesions that can be identified by CCTA.

Coronary stenoses develop either due to plaque accumulation that outstrips the capacity of the coronary artery to adapt (limitation of positive remodeling) or due to inadequate or negative vessel remodeling with limited plaque accumulation. These two processes can be visualized with intravascular ultrasound (IVUS) studies or non-invasively with CCTA. Vavuranakis et al. [5] showed with IVUS that compensatory vessel response to atherosclerosis is impaired in diabetic patients which may explain earlier and accelerated disease progression. Jansen et al. [4] found blunted remodeling response to atherosclerosis accumulation in reference segments of diabetic subjects. A pooled analysis of 5 prospective IVUS studies showed inadequate compensatory remodeling in diabetics, especially insulin-dependent subjects [9]. Typically, the development of type 2 diabetes mellitus is proceeded by several years of hyperinsulinemia [10]. Moreover, the diagnosis of type 2 diabetes is usually delayed by 2 years and 7% of patients are unaware of the disease for up to 7 years [11]. In response to insulin, the smooth muscle proliferates; and the amount of fibrous tissue increases which together with endothelial dysfunction may impact the ability of the arterial wall to expand [12]. However, it has been unclear whether negative remodeling (i.e. vessel shrinkage) in diabetic patients may occur independently and prior to the plaque accumulation. The results of the current study of diabetic patients without any plaque accumulation suggest that negative remodeling does proceed the plaque formation

Table 1. Comparison of lumen area and diameter in diabetic and control subjects

Segment	Diabetic group (n = 14)	Control group (n = 42)	*P* value
LMCA LA, mm^2, median (IQR)	21.7 (19.6–27.1)	21.3 (17.4–28.3)	0.64
LMCA LD, mm, mean (IQR)	5.4 (0.6)	5.3 (0.8)	0.60
Prox LAD LA, mm^2, median (IQR)	11.8 (10.1–13,9)	11.5 (9.8-14.4)	0.81
Prox LAD LD, mm, median (IQR)	3.9 (3.6–4.2)	3.9 (3.6–4.3)	0.87
Mid LAD LA, mm^2, mean (SD)	7.3 (2.5)	6.9 (2.1)	0.53
Mid LAD LD, mm, mean (SD)	2.9 (0.5)	2.9 (0.5)	0.57
OM LA, mm^2 median, (IQR)	3.6 (2.9–4.0)	2.9 (2.4–3.9)	0.19
OM LD, mm, mean (SD)	2.0 (0.3)	1.8 (0.3)	0.14
IM LA, mm^2, median (IQR)	2.0 (1.9–4.2)	3.3 (2.2–4.1)	0.33
IM LD, mm, median (IQR)	1.5 (1.4–2.1)	1.9 (1.6–2.1)	0.31
Prox LCX LA, mm^2, mean (SD)	12.6 (4.2)	10.4 (4.1)	0.09
Prox LCX LD, mm, mean (SD)	3.9 (0.7)	3.6 (0.7)	0.09
Mid LCX LA, mm^2, mean (SD)	12.9 (4.3)	10.7 (4.1)	0.44
Mid LCX LD, mm, mean (SD)	4.0 (0.7)	3.7 (0.7)	0.45
Prox RCA LA, mm^2, mean (SD)	13.1 (4.6)	12.5 (4.2)	0.66
Prox RCA LD, mm, mean (SD)	4.0 (0.6)	3.9 (0.7)	0.68
Mid RCA LA, mm^2, mean (SD)	11.1 (4.9)	9.4 (4.1)	0.20
Mid RCA LD, mm, mean (SD)	3.7 (0.9)	3.4 (0.8)	0.26

Abbreviations: IM, intermediate artery; LA, lumen area; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LD, lumen diameter; LMCA, left main coronary artery; mid, middle; OM, obtuse marginal branch; IQR, interquartile range; prox, proximal; RCA, right coronary artery; SD, standard deviation

and that the reduction of luminal diameters only begins with the start of plaque accumulation.

All the diabetics and control patients routinely received sublingual nitroglycerin prior to CCTA. It is possible that the size of coronary arteries in diabetic patients was smaller at baseline, due to lower levels of nitric oxide mediated vasodilation (i.e.. endothelial dysfunction) [13].

The current study has some limitations. The study is retrospective, and the population is small. However, diabetes is one of the strongest risk factors of the CAD and the diabetic patients with coronary tree virtually free from atherosclerosis are not common. The median duration of diabetes was 5.5 years. However, as stated above the pre-diabetic state and even undiagnosed diabetes could have been present for much longer period.

Article information

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Implementation of laser equipment in a center experienced in lead extraction: safety and efficacy within 1-year follow-up

Agnieszka Katarzyńska-Szymańska, Maciej Grymuza, Lidia Chmielewska-Michalak, Jacek Migaj, Mikołaj Barczyński, Romuald Ochotny, Maciej Lesiak, Przemysław Mitkowski

1st Department of Cardiology, Poznan University of Medical Sciences, Poznań, Poland

Correspondence to:
Agnieszka Katarzyńska-Szymańska, MD, PhD, 1st Department of Cardiology, Poznań University of Medical Sciences, Długa 1/2, 61–848 Poznań, Poland, phone: +48618549146, e-mail: agnieszka.katarzynska@skpp.edu.pl

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INTRODUCTION

As the use of cardiac implantable electronic devices (CIEDs) increases, so does the number of indications for their removal. Advancements in transvenous lead extraction (TLE) have brought physicians to use a variety of methods, including laser-assisted lead extraction (LALE) [1, 2].

The LALE procedure offers a potentially higher efficacy and the complication rate comparable to other TLE techniques. However, implementation of a new method is always associated with the risk of complications (learning curve) even in experienced teams [3].

METHODS

In this single-center registry we evaluated the safety and efficacy of LALE in our center that is highly experienced in TLE using a mechanical telescopic sheath. The study period involved two parts: June 27, 2009 through November 26, 2011, when the equipment was rented, and January 5, 2018 throgh January 29, 2019, when it was bought. It was a retrospective, observational study, and patients were treated according to the guidelines, hence there was no necessity to obtain consent from patients to take part in the study, nor to gain the approval of the Ethics Committee [1, 4]. All patients admitted to the hospital were eligible for TLE on elective judgement or as a bailout.

Before the surgery, informed written consent for the procedure was obtained, blood samples were collected for basic laboratory tests and for securing blood in case of transfusion, and also chest X-rays were taken in all patients. Transthoracic echocardiography (TTE) exams were performed using the GE *Vivid 6* on admission in the echocardiography examination room and during the procedure, with sterile probe cover, in the electrophysiology room. TLE surgeries were performed in the electrophysiology room equipped with high quality stationary fluoroscopy and medical gas supplies where in case of emergency on-site rescue procedures can be implemented. The cardio-surgical and anesthetic back-up, as well as transesophageal echocardiography were immediately available. Basic vital signs (heart rhythm, blood pressure, pulse oximetry) were continuously monitored during the procedure and for at least 4 hours after surgery. Transvenous temporary pacing lead was inserted through the femoral vein, if needed. LALE was the technique of choice, although conversion from mechanical extraction was necessary in 5 cases. The extraction technique is described in Supplementary material.

Endpoints were classified according to the guidelines [1, 4]. Complete procedural success was defined as the removal of all targeted leads from the vascular space, without any permanently disabling complications or procedure-related deaths. Clinical success in cases in which a small portion of the lead (less than 4 cm) remained in a vascular space and is not detrimental to the clinical outcome. Failure was defined as the inability to achieve either complete procedural or clinical success, or the occurrence of a major complication or procedure-related death.

Statistical analysis

Continuous variables are expressed as median values and 1st and 3rd quartiles (Q1–Q3) and categorical data are reported as frequencies and percentages. Statistics were completed using Statistica 13 software (Statistica, TIBCO Software Inc., Palo Alto, California, USA). The groups were compared using the Mann–Witney U test (W Shapiro–Wilk test showed non-nor-

mally distributed data), and a P <0.05 was considered to be significant.

RESULTS AND DISCUSSION

Laser-assisted lead extraction procedures were performed in 33 patients (24 men) at a median age of 64 years (57–74). We attempted to remove 49 leads. Detailed patient, lead and device characteristics are described in *Table S1* and *Table S2* in Supplementary material. Indications for lead extraction were: lead failure (15 [45.5%]), pocket infection (9 [27.3%]), cardiac device-related infective endocarditis (CDRIE) (5 [15.2%]), elective lead replacement (2 [6%]), and dislocation of the lead (2 [6%]).

Clinical success was achieved in 31 (94%) patients, whereas complete lead removal was achieved in 92% of lead extraction (45 leads). Complete procedural success appeared in 30 (91%) patients. TLE failure occurred in 3 patients with a dual-chamber pacemaker and was caused by inability to remove targeted leads from the vascular space in 2 cases and procedure-related death in 1 case. As a result, we noticed 4 failures of lead extraction (8%) in 3 patients. The mean lead dwell time of the failed extraction leads was 13.6 years (163 months [9–17 months]). The clinical success of the first 2 cases was confirmed during follow-up, and overall clinical success was 97% (32 out of 33 patients).

In-hospital complications related to procedure were divided, according to guidelines, into major (including death in 1 [3%] patient and cardiac avulsion in 2 [6%] patients) and minor (pericardial effusion not requiring surgical intervention in 2 [6%] patients and blood transfusion related to blood loss during surgery in 1 [3%] patient) [1, 4].

In 4 cases, a second procedure in the same patient was necessary to achieve procedural success, and in one situation, surgical removal of the lead was necessary.

It is worth noting that the last 9 out of all patients who underwent LALE did not have any complications. Those procedures were performed after purchase of the laboratory's own laser generator and after implementing the rule that a laser sheath was used only if the locking stylets reached the tip of the lead. Another factor that could have influenced that observation was the team's experience which had increased since the first use of LALE procedures.

During the follow-up, 11 out-of-hospital deaths were reported. There were three deaths between first and twelfth months after the procedure. The median time of death after 1 year was 53 months (range, from 17 to 86 months).

We performed an analysis of all-cause mortality, and the patients who died were older and had higher creatinine levels (Table 1).

The demographics, lead data, groups of indications for TLE are mostly comparable with other studies; however, there were some differences, for example the number of patients with pacemakers (45.4% vs 70%) [5, 6]. Also proportions of certain indications were different. In our study, the main indication for TLE was lead failure. The ELECTRa registry shows the same frequency of infectious and noninfectious indications in Europe [7]. Similarly, in the study by Ząbek et al. [8], both CDRIE and pocket infection together did not account for 20% of TLE indications.

In our study, the clinical success was achieved in 94% of cases, while Kennergren et al. [6] achieved an efficacy of 97.6% leads. Wazni et al. [9] described efficacy of 92.2% in operated patients, while Byrd et al. [10] reported complete success in 90% of leads. In our study, the mean lead dwell time was 150 months. In other studies it was much shorter, e.g. 91 months [6]. Byrd et al. [10] observed that removal of lead implanted more than 10 years prior to the procedure was a predictor of procedural failure. Kennegren et al. [6] also reported that a longer time from implanta-

Table 1. Comparison of survivors and non-survivors in the studied patients

	All-cause one-year mortality		
	Deaths (n = 13), median (IQR)	Alive (n = 20), median (IQR)	*P* value
Age, years	68 (64–77)	59.5 (50.5–70)	0.02
BMI, kg/m^2	25 (24–28)	28 (24.5–30.5)	0.12
WBC, k/µl	8.1 (6.3–8.9)	7.9 (6.7–9.1)	0.87
RBC, M/µl	4.3 (3.4–4.7)	4,5 (4.2–4.8)	0.74
Hemoglobin, mmol/l	8.4 (8.0–8.9)	8.9 (7.9–9.4)	0.59
Hematocrit, %	41.5 (37–43)	41.8 (38–44)	0.99
Platelets, K/µl	188.5 (161–219)	201 (172–245)	0.25
CRP, mg/l	7.8 (1.3–16.1)	4.7 (1.4–17.2)	0.84
Creatinine, µmol/l	122 (93–135.4)	90.1 (74.6–124.8)	0.03
LVEDD, mm	50 (43–70)	53.5 (47–58)	0.95
LA, mm	48.5 (39–52)	44.5 (38–47)	0.13
Ejection fraction, %	45 (25–60)	55 (35–60)	0.20
Age of the lead, years	7 (4–15)	8 (6–10)	0.91
Age of the oldest lead, years	7 (4–15)	8 (6–10)	0.57
Age of all extracted leads, years	14 (5–17)	9.5 (7–16.5)	0.61

Abbreviations: IQR, interquartile range; BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LA, left atrium dimension; LVEDD, left ventricular end diastolic diameter; RBC, red blood cell count; WBC, white blood cell count

tion to removal was associated with a higher incidence of procedure failure, although it did not reach a level of statistical significance.

In the presented study the rate of major complications was 6%, while in other studies it ranged from 4% in the Wazni et al. [9] study, through 2.5% in the laser group in the PLEXES trial [11], through 2.1% in the Byrd et al. [10] study, to 1.7% in the ELECTRa Registry [7].

The analysis of all-cause mortality shows that older age and a higher creatinine level are predictors of a worse outcome of TLE. This result is similar to the study by Brunner et al. [12]. Also Jacheć et al. [13] demonstrated that heart failure, chronic kidney disease, and pacemaker infections together with minor complications influenced 30-day mortality.

CONCLUSIONS

It is unlikely to prove that introducing new procedures like the new method of lead extraction is safe and effective. The implementation of new surgical methods should be initiated in centers that are already highly experienced, and which initiate contemporary practice. It is important to apply a risk-benefit analysis, especially in patients with class II TLE indications, taking into consideration risk factors such as older age and kidney impairment, which are proven to worsen outcomes of patients after TLE.

Supplementary material

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

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Hospitalizations and interventional procedures in cardiology departments in the region of 2.5 million inhabitants during the SARS-CoV-2 pandemic

Jarosław Drożdż[1], Grzegorz Piotrowski[2, 3], Marzenna Zielińska[4], Jerzy Krzysztof Wranicz[5], Andrzej Lubiński[6], Jan Krekora[1], Michał Krejca[7], Paweł Ptaszyński[5], Jarosław Kaźmierczak[8], Jarosław D Kasprzak[9]

[1]2nd Department of Cardiology, Central University Hospital, Medical University of Lodz, Łódź, Poland
[2]Department of Cardiooncology, Medical University of Lodz, Łódź, Poland
[3]Department of Cardiology, Kopernik Hospital, Łódź, Poland
[4]Department of Interventional Cardiology, Central University Hospital, Medical University of Lodz, Łódź, Poland
[5]Department of Electrocardiology, Central University Hospital, Medical University of Lodz, Łódź, Poland
[6]Department of Interventional Cardiology and Electrocardiology, Medical University of Lodz, Łódź, Poland
[7]Department of Cardiac Surgery, Central University Hospital, Medical University of Lodz, Łódź, Poland
[8]Department of Cardiology, Pomeranian Medical University, Szczecin, Poland
[9]1st Department of Cardiology, Medical University of Lodz, Łódź, Poland

Correspondence to:
Jarosław Drożdż, MD, PhD, 2nd Department Cardiology, Medical University of Lodz, Pomorska 251, 92–213 Łódź,
phone: +48 42 201 43 08,
e-mail: jaroslaw.drozdz@umed.lodz.pl

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INTRODUCTION

The COVID-19 pandemic has affected many aspects of our lives. This applies in particular to healthcare, and it is important to understand that it is not only restricted to aspects that are directly related to the diagnosis and treatment of SARS-CoV-2 infection. Other medical specialties face a number of barriers and everyday difficulties in carrying out their work and the consensus is that the care of patients with other diseases has deteriorated recently, thus a term of a syndemic has been coined to reflect collateral damage to non-communicable diseases care. It is disturbing that this also applies to cardiovascular diseases, which are the most common cause of death in Poland [1, 2].

A multicenter study from 15 European countries shows a 32% decrease in the number of patients hospitalized in cardiology departments [3]. The reduction in the number of acute coronary syndromes in the analysis was 32% in ST-segment elevation myocardial infarction (STEMI), 44% in non-ST-segment elevation myocardial infarction (NSTEMI), and 21% in unstable angina (UA) [3]. Recent data published by the National Registry of Interventional Cardiology Procedures in Poland, the respective percentages are 36%, 39%, and 58%, with an accompanying 74% decrease in the number of procedures in chronic coronary syndromes [4]. The number of coronary angiography and angioplasty in high-volume interventional cardiology centers in Poland decreased 44% and 36%, respectively [5] with significant regional disparities [6].

The main goal of this publication is to compare quantitative data of cardiac hospitalizations and coronary interventions in years 2019–2020 from all cardiology departments that provide care to the population of 2.5 million inhabitants of the Lodz Voivodship.

METHODS

Every year, the National Cardiology Consultant and regional representatives send a questionnaire to all heads of cardiology departments in Poland. The results of the questionnaire include the number of performed cardiological procedures, predominantly coronary interventions and electrocardiology. The analysis of the data is used by the National Cardiology Consultant in planning activities as part of his professional duties and it is the subject of joint discussions at annual meetings.

In order to calculate the actual impact of the COVID-19 pandemic on the work of cardiology departments, the 2020 questionnaire was sent to all 22 cardiology departments in Lodz Voivodship, referring to the same areas of activity of the centers, but divided into consecutive quarters of 2020. The date of hospital discharge (before or after April 1st, 2020) was adopted as a decisive factor for assigning a given procedure to the prepandemic quarter. As the Ministry of Health declared the national state of epidemics

on March 20, 2020, we assumed that the consequences in terms of numbers of procedures could be detected starting from the second quarter of 2020.

The scope of the analysis included the number of beds, the composition of the medical staff, the number of hospitalizations and coronary interventions in each center, divided into the following categories: coronary angiography (CORO), coronary angioplasty (PTCA), STEMI, NSTEMI, UA and chronic coronary syndromes (CCS). Data on the procedures performed in the field of electrocardiology will be analyzed separately.

Statistical analysis

For that statistical analysis the hospital administrative data was used, therefore the Ethics Committee agreement was not required. The Wilcoxon's test was carried out in order to determine whether the paired sets of data collected by the 22 cardiology departments were statistically different. Statistical analysis was performed in STATISTICA 13.1 software (TIBCO Palo Alto, CA, USA) and *P* values at the level of 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

The total number of beds in cardiology departments did not change significantly (561 in 2019 vs 580 in Q1 2020, $P = 0.47$; 561 in 2019 vs 564 in Q2 2020, $P = 0.80$; 561 in 2019 vs 533 in Q3 2020, $P = 0.62$; 561 in 2019 vs 577 in Q4 2020, $P = 0.62$). This includes similar numbers of Intensive Cardiology Unit beds (149 in 2019 vs 152 in Q1 2020 $P = 0.19$; 149 in 2019 vs 150 in Q2 2020, $P = 1.00$; 149 in 2019 vs 144 in Q3 2020, $P = 0.42$; 149 in 2019 vs 149 in 4Q 2020, $P = 1.00$), with similar numbers of working cardiologists (216 in 2019 vs 214 in Q1 2020, $P = 0.61$; 216 in 2019 vs 216 in Q2 2020, $P = 0.58$; 216 in 2019 vs 227 in Q3 2020, $P = 0.31$; 216 in 2019 vs 228 in Q4 2020, $P = 0.31$). The following total numbers of beds (with numbers of Intensive Cardiology Units beds in parentheses) were dedicated to COVID-19 patients in the consecutive quarters of 2020: Q1, 0 (0); Q2, 20 (8); Q3 14 (8); Q4, 60 (20).

The relative numbers of hospitalizations and coronary procedures in 2019 and consecutive quarters of 2020 are presented in Figure 1. The Supplementary material presents all 22 heads of cardiology departments, all numerical data, statistical analysis, as well as the original survey.

The key information resulting from the presented data is a statistically significant decrease in a total of hospitalizations and a noticeable but statistically insignificant decrease in the number of interventions in NSTEMI patients in the pandemic quarters of 2020 compared to the quarterly average of 2019. In addition, there is only a modest decrease in the number of interventions in STEMI patients with a statistically significant difference detected only between the average value in 2019 quartely and in the first quarter of 2020 (the average value of 508 in 2019 vs 522, 447, 493, 442 in consecutive quarters of 2020). There is also a statistically significant decrease in the total number of

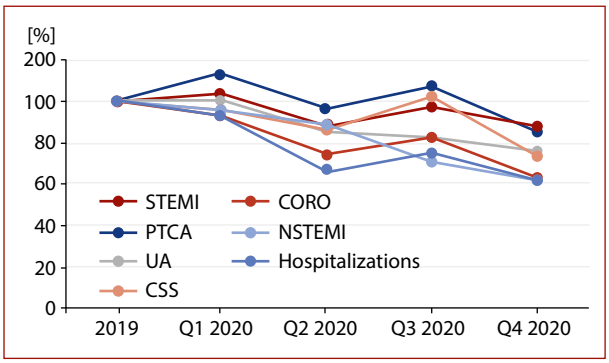

Figure 1. Hospitalizations and coronary procedures in all cardiology departments in Lodz Voivodship in years 2019–2020, shown as a percentage of the mean numbers in the corresponding quarters (Q) of 2019. The list of items was ranked from the highest percentage in Q4 2020.

Abbreviations: CCS, chronic coronary syndrome; CORO, coronary angiography; NSTEMI, non-ST-segment elevation myocardial infarction; PTCA, coronary angioplasty; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina

PTCAs between the first and third quarter of 2020 and the quarterly average of 2019 (2019 in the year 2019 vs 2283, 1946, 2131, 1717 in consecutive quarters of 2020).

These observation indicate a good adaptation of the guidelines of the European Society of Cardiology [7], the Polish Cardiac Society [8], at least regarding the number of coronary procedures in the emergency states. The lack of significant decrease in the number of STEMI patients who underwent interventional treatment seems to confirm the high efficacy of the teams' work.

On the other hand, a significant reduction of interventional revascularization procedures in NSTEMI is likely to generate heart failure patients in the future. Additionally, the significant decrease in the total number of hospitalizations not aimed at coronary interventions is worrying.

Supplementary material

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

Article information

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Left ventricular mass mimicking ST-segment elevation myocardial infarction: an initial manifestation of squamous cell carcinoma

Şahhan Kılıç, Tufan Çınar, Vedat Çiçek, Mehmet Uzun, Murat Selçuk, Ahmet Lütfullah Orhan

Department of Cardiology, Health Sciences University, Sultan II. Abdülhamid Han Training and Research Hospital, Istanbul, Turkey

Correspondence to:
Tufan Çınar, MD,
Health Sciences University,
Sultan II. Abdülhamid,
Han Training and Research
Hospital,
Department of Cardiology,
Tibbiye Street, 34668,
Uskudar, Istanbul, Turkey,
phone: +90 216 542 2020,
e-mail:
drtufancinar@gmail.com

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Although secondary cardiac metastases are mostly asymptomatic and often occur in patients with a history of malignancy, they can manifest as acute coronary syndrome, including ST-segment elevation myocardial infarction (STEMI) [1, 2]. Here, we present the first case of an adult patient diagnosed with a left ventricular (LV) mass due to squamous cell carcinoma (SCC) of unknown origin following STEMI.

A 76-year-old male patient presented to our emergency department with chest pain persisting for 2 hours. His medical history was not remarkable. Electrocardiography (ECG) performed at the emergency department revealed an ST elevation in V2–V6, I, and aVL leads (Figure 1A). The patient was immediately transferred to the catheterization laboratory for primary percutaneous coronary intervention. Coronary angiography revealed total occlusion of the proximal part of the diagonal artery (Figure 1B, Supplementary material, *Video S1*). The occlusion could not be crossed despite the use of multiple guidewires and balloon support (Figure 1C, Supplementary material, *Video S2*). During hospitalization, ST elevations persisted. Bedside transthoracic echocardiography revealed a mass in the apical and lateral segments of the LV (Figure 1D, Supplementary material, *Video S3*). Initially, the mass was thought to be a thrombus due to its appearance and accompanying persistence of ST elevation. Besides, there was no history of malignancy, therefore metastases were considered highly unlikely. Following consultation of cardiac surgeons, the patient underwent emergency surgery. The mass was found to be solid and fibrous by nature and involving the myocardium and endocardium. The mass was resected, and the LV was repaired using the sandwich technique (Figure 1E). However, the patient died of cardiogenic shock on the first postoperative day. Microscopic and immunohistochemical examinations confirmed the diagnosis of SCC of the LV myocardium (Figure 1F).

In the case of the patient, since we thought that there was no myocardial involvement and the characteristics of the mass would not affect the decision on surgery, we left the final diagnosis of the mass for the intraoperative and postoperative period and did not perform any advanced imaging modality, such as positron emission tomography, cardiac magnetic resonance imaging (MRI), or computed tomography. Perhaps the absence of a coronary lesion that could explain such an extensive ST elevation should have suggested a myocardial involvement, which is the main conclusion for cardiologists. Besides that, if performed, the cardiac MRI would accurately assess whether it was a thrombus or a malignant tumor.

Due to the lack of estimation of the size and possible origin of the tumor in the cardiac MRI or computed tomography imaging tests, the extent of the LV tumor resection was probably too large and the remaining LV volume too small to ensure cardiac output, resulting in cardiogenic shock [3]. If imaging tests were performed, there was a chance to identify the primary tumor and to qualify the patient for oncological treatment without cardiac surgery.

In conclusion, what we have learned from this case is that every patient with a cardiac mass should undergo imaging modalities that could reveal the presence of the mass, and, if present, the extent of myocardial involvement before making decision on surgery.

Supplementary material

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

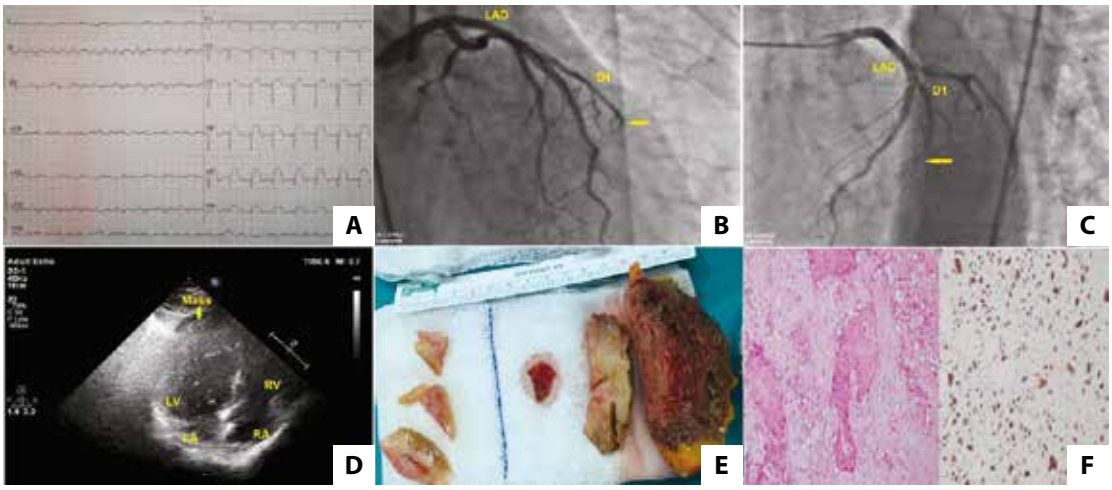

Figure 1. A–F. Electrocardiographic, coronary angiographic, and pathological findings in the patient. **A.** Electrocardiographic findings. **B.** Coronary angiographic image showing total occlusion (arrow) of the proximal diagonal artery. **C.** Recanalization could be achieved in the infarct-related artery despite the use of multiple guidewires and balloon support (arrow). **D.** Transthoracic echocardiographic image showing a mass (arrow) in the apical and lateral parts of the left ventricle in an apical 4-chamber view. **E.** Gross pathology of the mass. **F.** Hematoxylin–eosin staining of the tumor; immunohistochemical analysis revealed that the tumor was p40 (+)

Article information

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Severe cardiovascular involvement in a patient with rheumatoid arthritis

Damla Yalcinkaya[1], Mikail Yarlioglues[1], Elif Ergun[2], Ibrahim Etem Celik[1], Fatih Oksuz[1], Gokhan Cicek[1], Mustafa Duran[1], Sani Namik Murat[1]

[1]Department of Cardiology, Ankara Education and Research Hospital, Ankara, Turkey
[2]Department of Radiology, Ankara Education and Research Hospital, Ankara, Turkey

Correspondence to:
Assoc. Prof. Mikail Yarlioglues, MD, Department of Cardiology, Ankara Education and Research Hospital, Altindag, 06340 Ankara, Turkey, phone: +90 5454766320, e-mail: drmikailyar@gmail.com

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A 57-year-old female patient was admitted to the emergency department with angina pectoris. Her past medical history included hypertension and rheumatoid arthritis (RA). Electrocardiography revealed diffuse ST segment depression. She was hospitalized with a diagnosis of the acute coronary syndrome. Diffuse aortic calcification was detected on posteroanterior and lateral chest radiography (Figure 1A and 1B). Echocardiography revealed severe aortic regurgitation and aortic root calcification (Supplementary material, *Figure S1A* and *S1B*). In addition, moderate mitral regurgitation and mitral annular calcification were observed (Supplementary material, *Figure S1C* and *S1D*). The left ventricular ejection fraction was normal. Coronary angiography revealed calcification of the left main coronary artery without evident obstructive coronary artery disease (Supplementary material, *Figure S1E*). We investigated the patient for widespread calcification of major vessels and viscera. Pathologic parenchymal punctate calcifications and nodular choroid plexus calcification were observed in the cerebrum on computed tomography (CT) images (Supplementary material, *Figure S1F*). Carotid artery Doppler ultrasound demonstrated atherosclerotic plaques in the left carotid artery and complete occlusion of the right carotid artery. Diffuse atheromatous plaques were detected in the aorta on sagittal and axial plane conventional thoracic CT images (Figure 1C and 1D) and three-dimensional reconstruction thoracic CT images, indicating porcelain aorta (PA) (Figure 1E). It was observed that episodes of bradycardia and tachycardia, detected by bedside monitoring, resulted in severe dyspnea and chest discomfort. She was symptom free other than these attacks during hospitalization. Severe bradycardia led to frequent premature ventricular contractions with long compensatory pauses. Twenty-four hour Holter monitoring recordings were compatible with sick sinus syndrome.

The underlying pathogenesis of cardiovascular disease in RA involves diffuse subclinical atherosclerosis and atherosclerotic plaque calcification caused by chronic inflammation [1]. The extent of systemic inflammation is a predictor of poor cardiovascular outcomes [2]. Aorta is the one of the main target tissue in most of autoimmune diseases [3]. Patients with RA have a higher risk of developing calcification in the aorta, and carotid and coronary arteries [4]. PA is detected incidentally on chest radiography or CT images as extensive calcification of the aorta. It is associated with increased morbidity and mortality. The atherosclerotic PA is associated with RA and seen in individuals with hypertension, hyperlipidemia, and other autoimmune diseases [5]. Chronic inflammatory response leads to immunological vascular damage, which triggers microinfarctions and contributes to dystrophic calcification of soft tissues.

We diagnosed valvular heart disease as mitral and aortic valve regurgitation, cardiac conduction disorder as sick sinus syndrome, and diffuse arterial calcification as PA in our patient. We detected the complete occlusion of the right carotid artery, and dystrophic cerebral and cardiac calcifications. We attributed severe dyspnea, and chest discomfort attacks to increased aortic insufficiency during bradycardia episodes and increased mitral insufficiency to tachycardia episodes. We implanted a dual-chamber pacemaker in the patient to prevent bradycardia episodes. To prevent tachycardia attacks, we administered the maximum well-tolerated dose of a beta-blocker to the patient, which resulted in evident clinical improvement in 1 week.

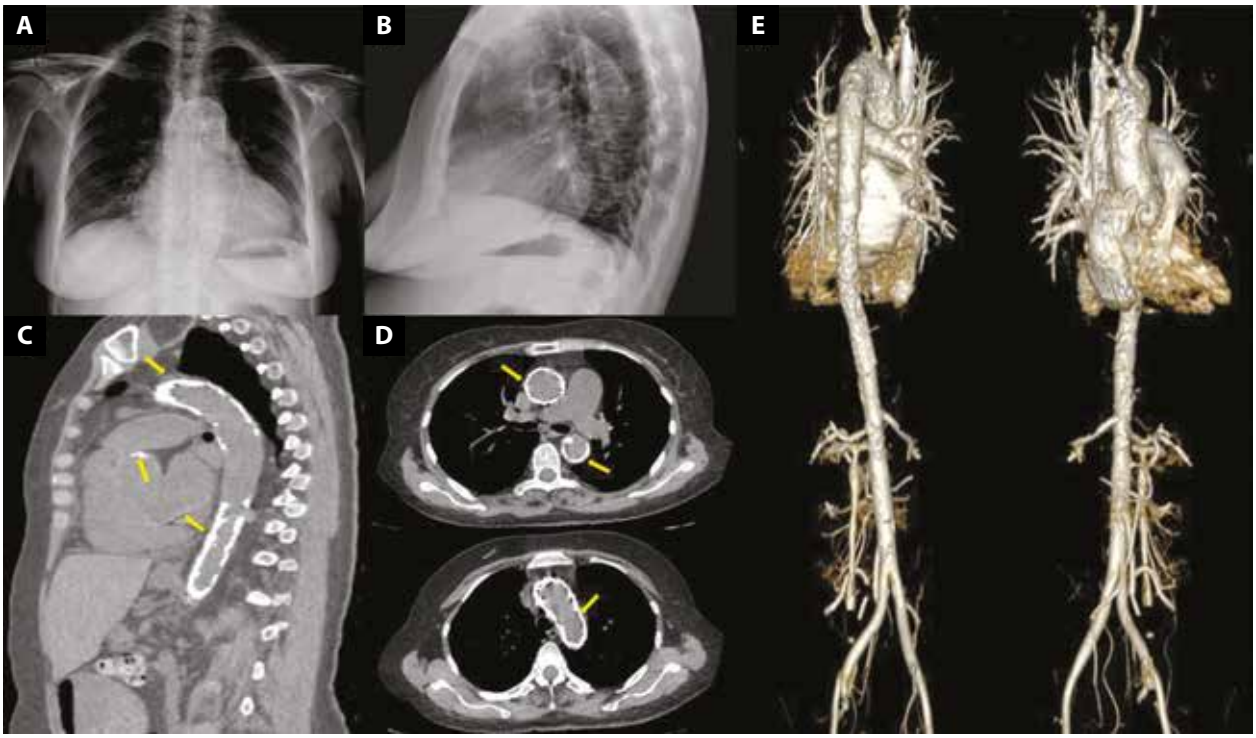

Figure 1. A, B. Chest radiography demonstrating diffuse aortic calcification. **C, D.** Conventional thoracic computed tomography images demonstrating diffuse aortic calcification. **E.** Three-dimensional reconstruction computed tomography images of the porcelain aorta

In conclusion, advanced cardiovascular and cerebral investigations should be performed during the clinical evaluation of patients with RA.

Supplementary material

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

Article information

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Surgical revascularization in STEMI patient after failed percutaneous coronary interventions with broken angioplasty wire protruding into the aortic root

Tomasz Urbanowicz[1], Bartłomiej Perek[1], Anna Olasińska-Wiśniewska[1], Włodzimierz Skorupski[2], Marek Jemielity[1]

[1]Cardiac Surgery and Transplantology Department, Poznan University of Medical Sciences, Poznań, Poland
[2]1st Cardiology Department, Poznan University of Medical Sciences, Poznań, Poland

Correspondence to:
Tomasz Urbanowicz, MD, PhD, Cardiac Surgery and Transplantology Department, Poznan University of Medical Sciences, Długa 1/2, Poznań, Poland, e-mail: tomasz.urbanowicz@skpp.edu.pl

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Percutaneous coronary interventions (PCI) have an established position in the management of patients presenting with acute coronary syndromes [1]. Rare, but serious adverse events may be related to stents/wire distortions [2, 3].

We present a case of a 67-year-old male who was admitted to a hospital with anterior wall ST-elevation myocardial infarction. Urgent coronary catheterization revealed left anterior descending artery (LAD) occlusion close to diagonal branch origin (Figure 1A). Middle segments of circumflex (CX) and right coronary (RCA) arteries were also significantly stenotic (Figure 1B). The heart team decided to perform emergent LAD angioplasty.

The bolus of 7.9 ml of INN-eptifibatide was administrated and followed by continuous infusion with a 14 ml/h rate. The drug-eluting sent (Xience 3.0 × 28 mm) was implanted into LAD. The drug-eluting sent (Xience 3.0 × 28 mm) was implanted into LAD. After stent implantation, a part of the wire was entrapped in the coronary artery. The metallic coil covering the core of the angioplasty wire was left in the proximal part of LAD and protruded into the aortic root.

The patient was referred for emergency surgery. The procedure was performed through median sternotomy in cardiopulmonary bypass. After transverse aortotomy, the aortic root lumen was inspected, and the metallic coil was localized (Figure 1C). As the foreign body of 7 cm in length was irremovable, it was transected and left in the proximal portion of the left main coronary artery (Figure 1D). The operators decided to perform revascularization of LAD, CX, and RCA. The saphenous vein bypass grafts (SVBG) were performed into CX and RCA and the left internal mammary (LIMA) was anastomosed into LAD with continuous 7-0 monofilament suture. The estimated blood flow was 7 ml/min with pulsation index (PI) of 3.4 in LIMA-to-LAD 39 ml/min with PI 1.3 in SVBG-to-CX and 43 ml/min with PI 1.1 in SVBG-to-RCA grafts, respectively.

The surgical approach allows achieving complete revascularization in acute coronary syndromes. Postoperative bypass blood flow measurements provide significant information about the quality of performed anastomoses.

Article information

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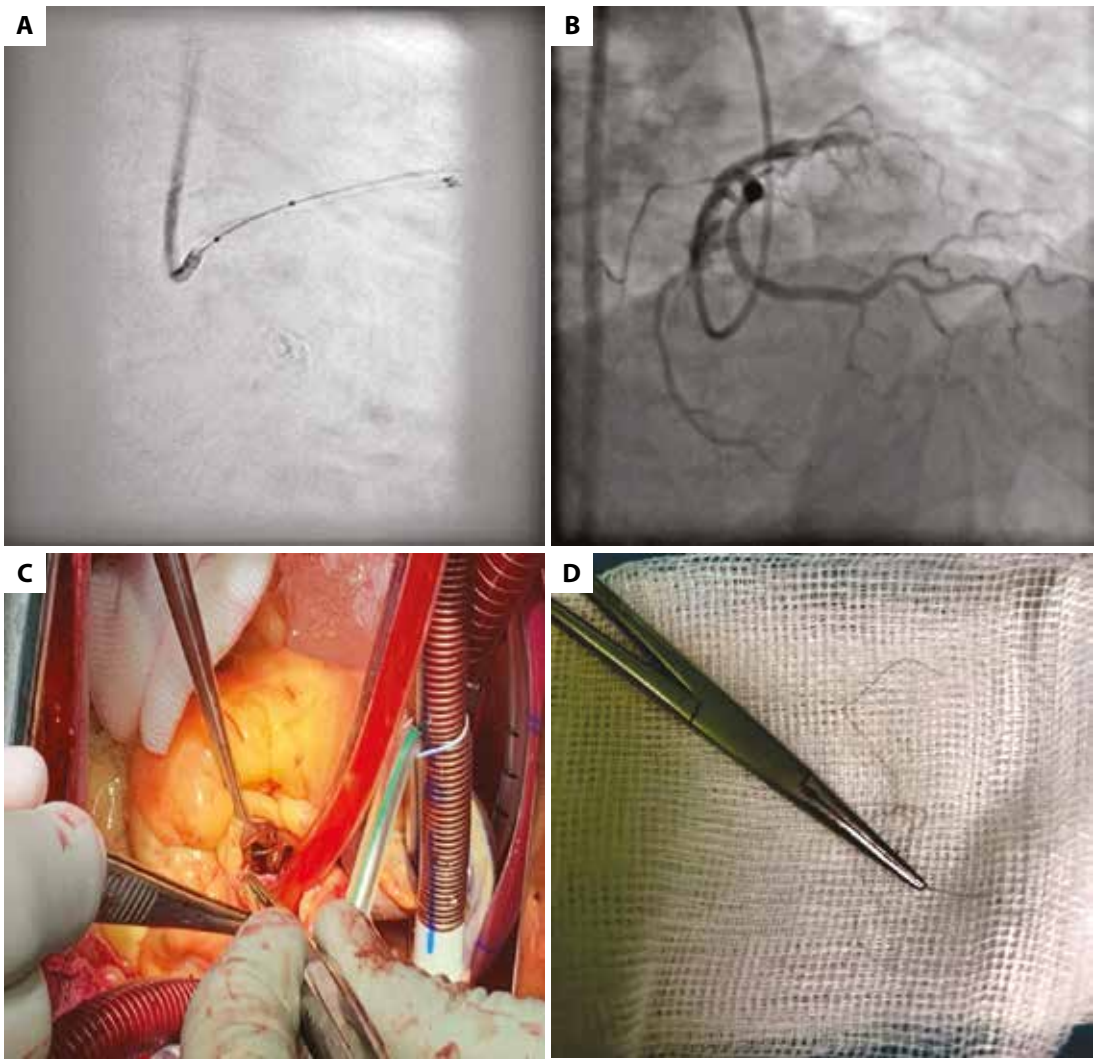

Figure 1. A. Angiography of acute left descending artery occlusion with metallic coil of the guidewire left in the proximal part. **B.** Right coronary artery angiography. **C.** Intraoperative view into aortic root with metallic coil. **D.** 7 cm long metallic coil removed from the aortic lumen

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Mitral annulus disjunction as an incremental risk factor for ventricular arrhythmia in young patient

Marcin Książczyk, Małgorzata Lelonek

Department of Noninvasive Cardiology, Medical University of Lodz, Łódź, Poland

Correspondence to:
Marcin Książczyk, MD, Department of Noninvasive Cardiology, Żeromskiego 113, 90–549 Łódź, Poland, phone: +48 42 639 35 71, e-mail: marcin_ksiazczyk@interia.pl

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Mitral annulus disjunction (MAD) is an abnormality defined as the distance of ≥2 mm between the mitral valve leaflet insertion point into the left atrial wall and the left atrium's connection point to the ventricular myocardium measured in systole in transthoracic echocardiography (TTE) or any distance between the abovementioned points in cardiac magnetic resonance (CMR) or coronary computed tomography angiography [1, 2]. MAD was found in 20%–32.6% of patients with mitral valve prolapse (MVP) [1, 3, 4]. On the contrary, MVP was found in 78% of patients with MAD [5].

A 23-years-old female patient was referred to our department with palpitations and presyncope recurring for a few months. There was no coronary artery disease, cardiomyopathies, channelopathies, arrhythmias, or sudden cardiac death in her family history. Resting electrocardiogram showed normal sinus rhythm without any specific abnormalities observed in channelopathies, corrected QT (QTc) 440 ms (Supplementary material, *Figure S1*). TTE revealed MVP with moderate mitral regurgitation (Figure 1A). 24-hour Holter recorded non-sustained ventricular tachycardia (VT) of frequency 140 bpm, variating in cycle length, lasting 4.2 seconds, preceded by bradycardia 50 bpm with normal QTc 402 calculated with Bazett's formula for the last sinus evolution before arrhythmia at night (Figure 1B), 27 premature ventricular contractions per hour, and median QTc interval 414 ms. Due to the strong suspicion of MAD, CMR was performed. CMR confirmed MAD and showed a longitudinal MAD distance of 5.2 mm (Figure 1C–E), posterior mitral valve leaflet billowing up to 7 mm, and moderate mitral regurgitation with a regurgitant fraction of 21%; there was no late gadolinium enhancement in the left ventricle wall as well as papillary muscles, and left ventricle ejection fraction (LVEF) was as much as 54%. Clinical presentation, resting electrocardiogram, and 24-hours Holter allowed excluding common channelopathies as potential risk factors for VT. Besides, according to Schwartz et al. diagnostic criteria for congenital LQTS, the patient was of low probability of LQTS. In contrast, TTE and CMR allowed excluding cardiomyopathies.

Mitral annulus disjunction arrhythmic syndrome is a clinically significant diagnosis evidenced by several clinical studies. In the study by Dejgaard et al. [5], ventricular arrhythmias (VA) (non-sustained VT, sustained VT, or aborted cardiac arrest) are postulated to occur in 34% of patients with MAD. In the same study, 71% of patients reported palpitations, 41% demonstrated presyncope, and 13% experienced syncope [5]. Young age, lower LVEF, papillary muscle fibrosis [5], and disjunction distance >8.5 mm [3] are markers for the prediction of VA. Sudden cardiac death might occur in up to 3.8% of patients with MAD [4]. MAD should be considered in younger patients with no other cause for VA or presyncope/syncope of uncertain etiology [5]. Our patient VA occurred despite preserved LVEF, absence of papillary muscles late gadolinium enhancement, and MAD distance ≤8.5 mm. We administered metoprolol succinate 25 mg once a day in VT prevention and referred the patient for subcutaneous loop recorder implantation. In further studies, in patients with the MAD arrhythmic syndrome, pharmacological or device therapies should be evaluated [5].

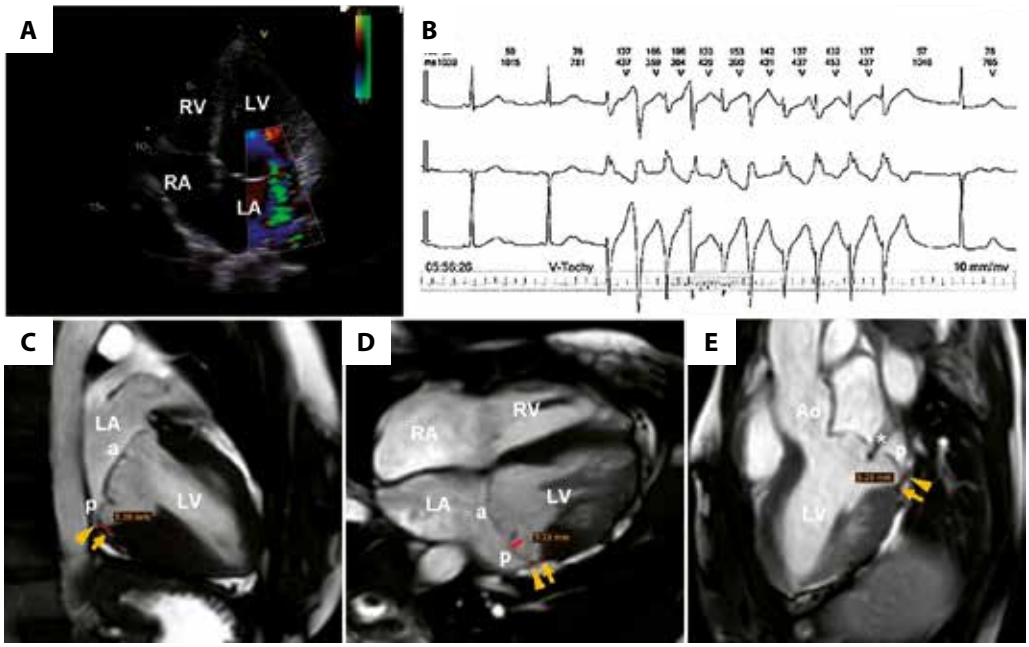

Figure 1. A. Transthoracic echocardiography presenting moderate mitral regurgitation and mitral valve posterior leaflet prolapse in apical four-chamber view. **B.** Non-sustained ventricular tachycardia, variating in cycle length, preceded by bradycardia with normal corrected QT recorded at night in 24-hour Holter. **C–E.** Cinematographic sequences of cardiac magnetic resonance in **C.** vertical long axis (two chambers) view; **D.** horizontal long axis (four chambers) view, and **E.** sagittal left ventricle outflow tract (three chambers) view showing mitral annulus disjunction distance of 5.2 mm measured between mitral valve posterior leaflet insertion point into the left atrial wall (orange arrowhead) and the left atrium's connection point to the ventricular myocardium (orange arrow), mitral valve posterior leaflet billowing of 7 mm (red two-headed arrow in panel E) and moderate mitral regurgitation jet (white asterisk in panel F).

Abbreviations: a, mitral valve anterior leaflet; Ao, ascending aorta; LA, left atrium; LV, left ventricle; p, mitral valve posterior leaflet; RA, right atrium; RV, right ventricle

Article information

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Acute heart failure in the course of fulminant myocarditis requiring mechanical circulatory support in a healthy young patient after coronavirus disease 2019

Kamil Marcinkiewicz[1], Joanna Petryka-Mazurkiewicz[2, 4], Michał M Nowicki[1], Jarosław Kuriata[3], Zofia Dzielińska[2], Marcin Demkow[2], Anna Konopka[1]

[1]Department of Intensive Cardiac Therapy, The Cardinal Stefan Wyszynski Institute of Cardiology, Warszawa, Poland
[2]Department of Coronary and Structural Heart Diseases, The Cardinal Stefan Wyszynski Institute of Cardiology, Warszawa, Poland
[3]Department of Cardiac Surgery and Transplantology, The Cardinal Stefan Wyszynski Institute of Cardiology, Warszawa, Poland
[4]Magnetic Resonance Unit, The Cardinal Stefan Wyszynski Institute of Cardiology, Warszawa, Poland

Correspondence to:
Kamil Marcinkiewicz, MD, Department of Intensive Cardiac Therapy, The Cardinal Stefan Wyszynski Institute of Cardiology, Alpejska 42, 04–628 Warszawa, phone: +48 22 343 43 14, e-mail: marcinkiewicz.kamil@gmail.com

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The novel coronavirus (SARS-CoV-2) responsible for coronavirus disease 2019 (COVID-19) not only affects the respiratory system but may have significant cardiovascular effects as well, causing arrhythmias, heart failure, myocarditis, and coagulation abnormalities [1].

A 20-year-old male with no prior cardiac medical history was admitted to our hospital with fever and dyspnea. Six weeks before admission he suffered from diarrhea shortly after his 10-year-old brother presented similar symptoms. Echocardiography performed 5 months earlier was unremarkable.

After admission, the patient deteriorated due to acute heart failure. Both NT-proBNP (26000 pg/ml [n <125 pg/ml]) and troponin T (850 ng/l [n <14 ng/l]) levels were significantly elevated on admission. Echocardiography revealed a severely lowered left ventricular ejection fraction (LVEF) of 15%. The patient required norepinephrine and dobutamine in increasing doses. Real-time PCR of his nasopharyngeal swab for the presence of SARS-CoV-2 RNA returned negative.

A blood test showed elevated inflammatory markers. Multiple tests were performed in search for the origin of the infection — however, both bacterial and viral causes were excluded.

Shortly after, an intra-aortic balloon pump (IABP) was implanted with mild improvement. The following day, due to complete cardiovascular insufficiency, veno-arterial extracorporeal membrane oxygenation (ECMO) was implanted. The patient improved quickly with this treatment and on the fourth day from ECMO implantation his LVEF increased to 48% and myocardium thickness increased to 20–21 mm, suggesting edema (Figure 1). Both ECMO and IABP were explanted after 6 days of therapy.

Magnetic resonance imaging revealed a small left ventricular cavity without regional wall motion abnormalities and a dynamic LVEF of 69% (Figure 1). On T2-weighted imaging, the myocardial signal was globally increased. Delayed late gadolinium imaging showed diffuse fibrosis in the anteroseptal and inferior walls. These findings were in keeping with acute myocarditis.

The diagnosis of fulminant myocarditis due to COVID-19 infection was confirmed (serological tests were positive for IgG and negative for IgM 8 weeks after first gastrointestinal tract symptoms).

Involvement of the cardiovascular system may occur in patients suffering from COVID-19 despite the absence of upper respiratory tract infection (URTI) symptoms. Several possible mechanisms of myocardial injury during COVID-19 infection have been discussed [2]. Surprisingly, myocarditis and other cardiovascular symptoms appear in COVID-19 patients after a prolonged period (up to 10–15 days) counting from the initial onset of URTI symptoms [3]. At this point, no viral particles may be detected. Myocarditis may be due to both plain viral invasion and an exaggerated secondary immune response. We hypothesize that the latter may be the pathomechanism of our patient's fulminant myocarditis.

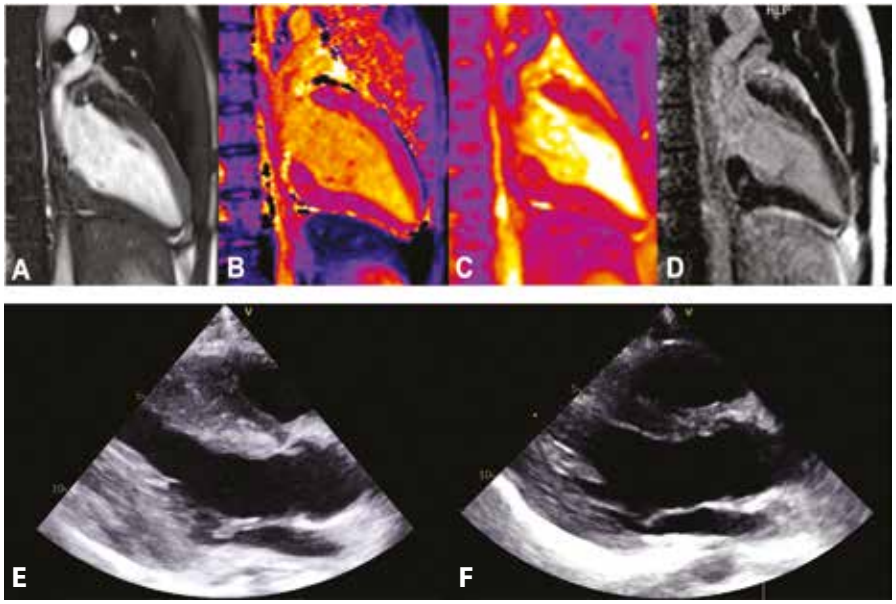

Figure 1. A–D. Post COVID-19 myocarditis on cardiac magnetic resonance — two-chamber images: **A.** cine; **B.** T1-mapping; **C.** T2-mapping; **D.** late gadolinium imaging. Images **B–D** show increased mid-wall signal in the basal inferior segment and increased subepicardial signal in the basal anterior segment. **E–F.** Wall thickness dimensions in the parasternal LAX view by TTE. **E.** Thickened LV wall (during hospitalization). **F.** Normal LV thickness (at discharge). The time difference between those two images is 13 days

SARS-CoV-2 induced fulminant myocarditis is an uncommon clinical presentation, with a mortality rate of approximately 40%–70% [4]. Nonetheless, the application of circulatory support systems, including IABP, Impella implantation, or ECMO might be beneficial for these patients. The hemodynamic rule of unloading the inflamed myocardium, which reduces wall stress and decreases myocardial oxygen requirements, supports myocardial recovery and is a viable treatment option in patients with fulminant myocarditis [5].

Our case report provides a unique insight into the traits of acute heart failure caused by fulminant myocarditis after a SARS-CoV-2 infection highlighting the value of mechanical circulatory support in these patients.

Article information

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Informed consent: The authors certify that they have obtained the appropriate patient consent form. In the form, the patient has given his consent for his clinical information to be reported in the journal.

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Multimodality imaging results of neointimal healing after magnesium scaffold implantation in an acute coronary syndrome setting

Magdalena Łanocha[1], Adrian Włodarczak[2], Marek Szudrowicz[2], Artur Jastrzębski[2], Maciej Pęcherzewski[2], Maciej Lesiak[3]

[1]St. Adalbert's Hospital, Poznań, Poland
[2]Department of Cardiology, MCZ Hospital, Lubin, Poland
[3]Department of Cardiology, Poznan University of Medical Sciences, Poznań, Poland

Correspondence to:
Magdalena Łanocha, MD, PhD, St. Adalbert's Hospital, Bolesława Krzywoustego 114, 61–144 Poznań, Poland, phone: +48 616 233 111, e-mail: drlanocha@gmail.com

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Treatment with bioresorbable magnesium scaffolds (Magmaris, Biotronik AG, Bülach, Switzerland) is recommended only for stable angina pectoris [1]. Confirmation of promising results using Magmaris in acute coronary syndrome (ACS) can be found in recently published registries [2].

A 57-year-old woman with typical risk factors (hypertension, hyperlipidemia) was admitted to the CathLab because of non-ST-segment elevation ACS. Coronary angiography showed a severe lesion at the proximal part of the left anterior descending artery (Figure 1A). The lesion characteristics (focal, concentric, smooth contour without calcification and thrombus) were encouraging for bioresorbable magnesium scaffolding. The lesion was predilated with a 3.5 mm at 16 atm non-compliant balloon, followed by implantation of a 3.5 × 20.0 mm bioresorbable magnesium scaffold at 16 atm; post-dilation was performed with a 3.5 mm at 16 atm non-compliant balloon. Optimal results (device expansion, struts apposition, no edge dissection) were confirmed on the final angiography (Figure 1B) and optical coherence tomography (OCT) assessment (Figure 1D). Three days later, the patient was discharged on aspirin and ticagrelor.

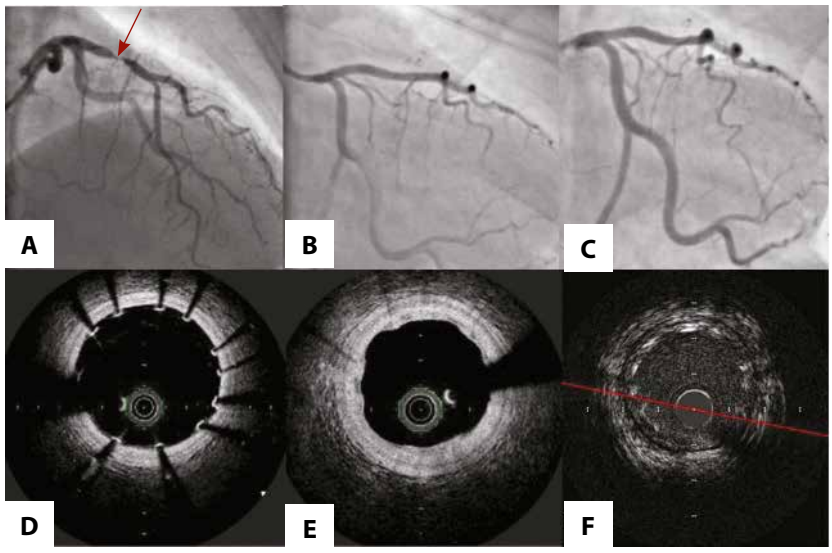

Figure 1. A. Coronary angiography: baseline lesion at the proximal part of the left anterior descending artery (arrow). **B.** Optimal results after Magmaris implantation. **C.** Control 12-month follow-up. **D.** Optical coherence tomography assessment: baseline after Magmaris implantation **E.** and control 12-month follow-up. **F.** Control 12-month follow-up intravascular ultrasound

Control coronary angiography performed 12 months later showed perfect angiographic results (Figure 1C). Neointimal healing was evaluated by OCT and intravascular ultrasound, confirming almost completed the scaffold bioresorption process. The magnesium scaffold or its footprint was no longer discernible by OCT (Figure 1E). Only intravascular ultrasound IVUS images contain the visible healing bright spots (amorphous calcium phosphate) within the neointima (Figure 1F).

At that time, DAPT was discontinued. Four-year clinical follow-up confirmed a further uneventful course of coronary artery disease.

Multimodality intracoronary imaging confirmed the 95% magnesium alloy resorption at 12 months. Presented magnesium scaffold images confirmed superiority over the polymeric scaffold regarding neointimal healing during the first year after scaffold implantation.

The second generation of bioresorbable scaffolds with their unique properties that 'do their job and disappear' may also be a promising therapeutic option for ACS patients.

Article information

Conflict of interest: MŁ and ML have received speaking fees from Biotronik AG. The other authors have no conflicts of interest to declare.

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Reaching the left bundle branch pacing area within 36 heartbeats

Marek Jastrzębski, Paweł Moskal

1st Department of Cardiology, Interventional Electrocardiology and Hypertension, Jagiellonian University, Medical College, Kraków, Poland

Correspondence to:
Prof. Marek Jastrzębski, MD, PhD,
1st Department of Cardiology, Interventional Electrocardiology and Hypertension, Jagiellonian University, Jakubowskiego 2, 30–688 Kraków, Poland,
e-mail: mcjastrz@cyf-kr.edu.pl

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Left bundle branch (LBB) area pacing has emerged as a promising method of physiological pacing both for bradycardia and heart failure indications [1]. This method addresses some limitations of the His bundle pacing technique [2]. One of the critical aspects of LBB lead implantation is monitoring the depth of penetration into the interventricular septum. This is necessary to reach the LBB area while avoiding perforation into the left ventricle. Several measures to monitor lead depth were proposed, including fulcrum sign, sheath angiography, impedance monitoring, changes in the QRS notch in V1 lead, pacing from the ring electrode, monitoring of the endocardial signal, and observation of fixation beats, that is, premature ventricular contractions induced mechanically by the penetrating lead tip [3]. The presented ECG was obtained from a 65-year-old woman with heart failure and atrial fibrillation in whom atrio-ventricular node ablation and permanent pacing were planned to achieve rate control. The purpose of the report is to illustrate a novel LBB lead implantation technique, developed in our electrophysiological laboratory, based on continuous pacemapping during screwing in the LBB lead.

During lead progression from the right to the left side of the septum the paced QRS changes: QRS gradually narrows, R wave in V1 appears and V6 R-wave peak time (RWPT) shortens. The technique of continuous pacemapping, similarly to the premature beats method [3] is a practical application of this phenomenon. Instead of waiting for mechanically induced ectopic beats, however, local depolarizations are forced by continuous pacing from an external pacemaker that remains connected to the distal pin of the lead during the whole process of lead rotation/implantation.

Figure 1 illustrates a smooth transition from right ventricular capture to LBB capture during uninterrupted pacing at 120 bpm during lead rotation; it is a collage of 18 out of 36 consecutive QRS complexes (for unedited continuous tracing see Supplementary material, *Video S1*). A revolving connector for the distal pin of the LBB lead is a prerequisite for the presented technique. Preparation and use of a simple model of such connector are presented in Supplementary materials: *Video S1* and *Figure S1*.

The ability to monitor in real-time the paced QRS morphology is very valuable. Continuous change of paced QRS morphology ensures the operator that the lead is advancing into the septum and the appearance of R wave in lead V1 indicates that the LBB area was just reached. At this moment the lead rotations should be stopped to test for LBB capture. Conversely, lack of QRS morphology change is a sign that the lead is not making any forward movement but rotating in the same position ("drill behavior" [4]) — indicating that the lead support/forward pressure should be increased or the implantation site changed.

In contrast to the popular implantation method of interrupted pacing, the novel continuous pacemapping technique enables real-time monitoring of lead behavior and depth, facilitates reaching the LBB capture area with one lead rotation episode, allows detailed analysis of V6 RWPT change, and has the potential to limit the risk of septal perforation. We believe that such LBB lead implantation method is superior and might become a standard technique soon.

Supplementary material

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

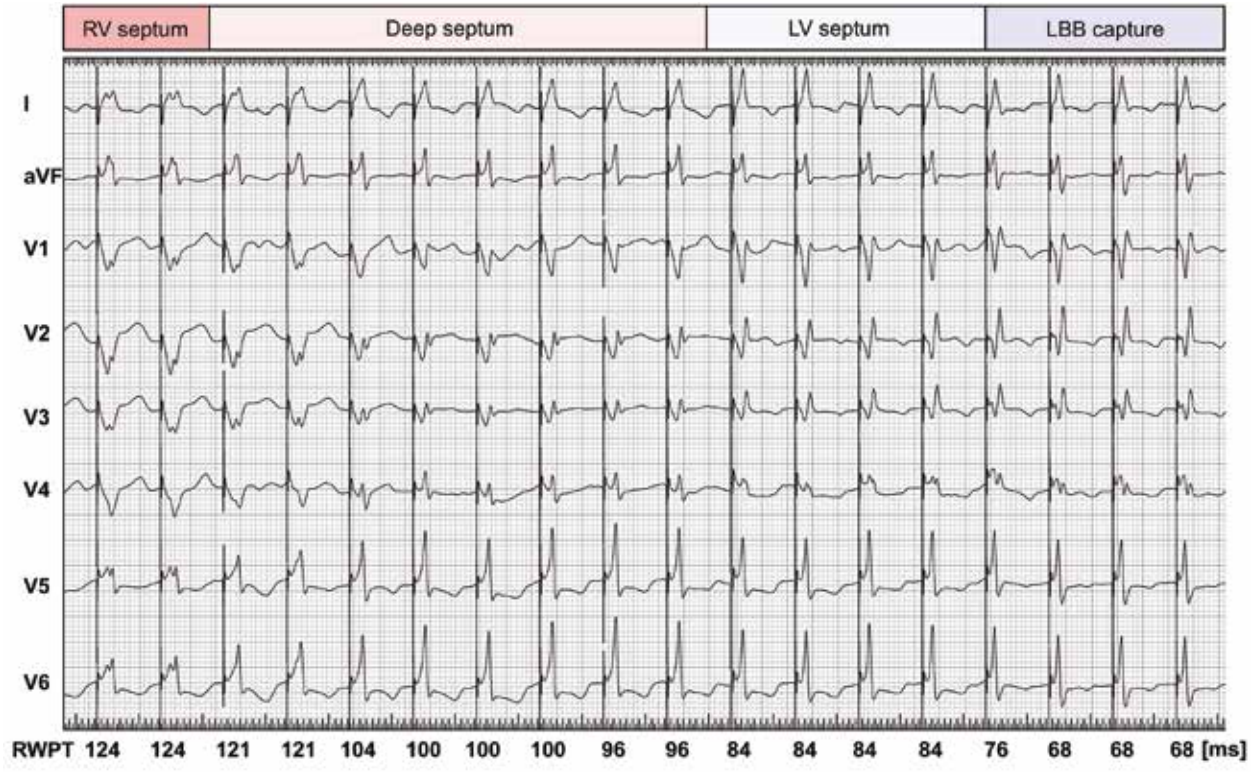

Figure 1. Continuous pacing during intraseptal lead deployment enables monitoring the continuous change of paced QRS complex morphology and lead depth in the septum. The right ventricular (RV septum) paced QRS is characterized by notches in lateral leads, "W" morphology in V1, and time to R-wave peak (RWPT) in V6 of >120 ms. Deep septal paced QRS is narrower, loses notches in lateral leads, the notch in V1 moves towards the end of QRS, and V6 RWPT is usually in the range of 120–95 ms. Pacing close to the left bundle branch area (LV septum) QRS is characterized by a positive terminal component in lead V1, the pseudo delta in leads V5-V6 and V6 RWPT of 95–80 ms. LBB capture paced QRS is characterized by deeper S wave in leads I, V5–V6, more prominent R in V1–V3 and V6 RWPT usually <80 ms. LBB capture in the current case was assured both by V6 RWPT <74 ms and transition to selective capture (not shown) [5]

Article information

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Hemoptysis as the first sign of angiosarcoma — an extremely aggressive cardiac tumor

Aleksandra Ciepłucha[1], Aleksandra Różycka[2], Deanna Rudiak[2], Supasin Watcharintrawut[2], Mehul Sharma[2], Aneta Klotzka[1], Adrian Gwizdała[1], Daria Keller[1], Agnieszka Katarzyńska-Szymańska[1], Przemysław Mitkowski[1]

[1]1st Department of Cardiology, Poznan University of Medical Sciences, Poznań, Poland
[2]1st International Student Scientific Group on Cardiovascular Medicine, Poznan University of Medical Sciences, Poznań, Poland

Correspondence to:
Aleksandra Ciepłucha, MD, PhD, FESC, 1st Department of Cardiology, Poznan University of Medical Sciences, Długa 1/2, 61–848 Poznań, Poland, phone: (+48) 618 549 146, e-mail: ola.cieplucha@gmail.com

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A 19-year-old male was admitted to the hospital with a two-month history of hemoptysis. Previously healthy, with no significant family history, he was initially examined for lung pathology. On admission, a chest X-ray showed disseminated consolidations in the lungs. Computed tomography showed subpleural opacities and multiple, bilateral solid nodules with ground-glass opacities (Figure 1A, 1B). The nodules were more dispersed in the peripheral lobules, which is suggestive of neoplastic spread [1]. The chest scans also showed an irregular mass in the right atrium. The patient was transferred to the cardiac surgery department. Transthoracic echocardiography (TTE) revealed a 70 × 45 mm heterogeneous lobulated tumor in the right atrium infiltrating the free wall of the right atrium, right ventricle, and tricuspid valve, suggestive of malignancy. Cardiac magnetic resonance demonstrated inhomogeneous late gadolinium enhancement of the mass infiltrating the pericardium (Figure 1C, 1D). Laboratory tests showed elevated D-dimer concentration, liver enzymes, and fibrinogen. Cancer biomarkers were within reference ranges. The most probable diagnosis was a primary cardiac neoplasm with metastatic spread; pulmonary lesions were highly suggestive of metastases of angiosarcoma. Surgical treatment was precluded due to the anatomical location and infiltration of the tumor. Biopsy of the lesion was necessary to implement any systemic treatment. Nevertheless, the patient refused this procedure and asked for discharge.

The patient was readmitted to the cardiology department two weeks later with severe dyspnea, weakness, and excessive hemoptysis. TTE confirmed enlargement of the tumor to 80 × 70 mm (Figure 1E, 1F). Due to hemoptysis the patient required numerous blood transfusions and intensified pain therapy. Biopsy of the tumor was eventually performed and poorly differentiated angiosarcoma cells classified as G3 were found. The patient was immediately transferred to the oncological center to undergo palliative chemotherapy. During transport, his condition got worse and he was admitted directly to the Intensive Care Unit with a suspicion of pulmonary embolism. After 2 days the patient died due to multiple organ dysfunction and septic shock.

Cardiac angiosarcomas are a rare pathology with an average survival period of 7 months if diagnosed in the metastatic stage [2]. Lesions of the right heart have a poorer prognosis compared to those on the left. They are described as infiltrative, bulky, heterogeneous lobulated masses with areas of hemorrhage and necrosis on echocardiography [3]. Surgical resection is essential, and both complete and partial resection contribute to longer survival. Adjuvant chemotherapy is used due to frequent metastases and their efficacy in reducing tumor tissue. Combining surgical resection, chemotherapy and radiotherapy can extend survival time up to 3 years [4].

If the tumor is not resectable, biopsy and histopathological analysis are crucial to implementing systemic treatment. This case exemplifies that if angiosarcoma is suspected, the biopsy must not be postponed. The course of the disease is very aggressive with extensive progression in tumor mass seen after two weeks. A prompt diagnostic workup is of vital importance for the rapid implementation of targeted therapy and requires the involvement of a multi-specialist team [4, 5].

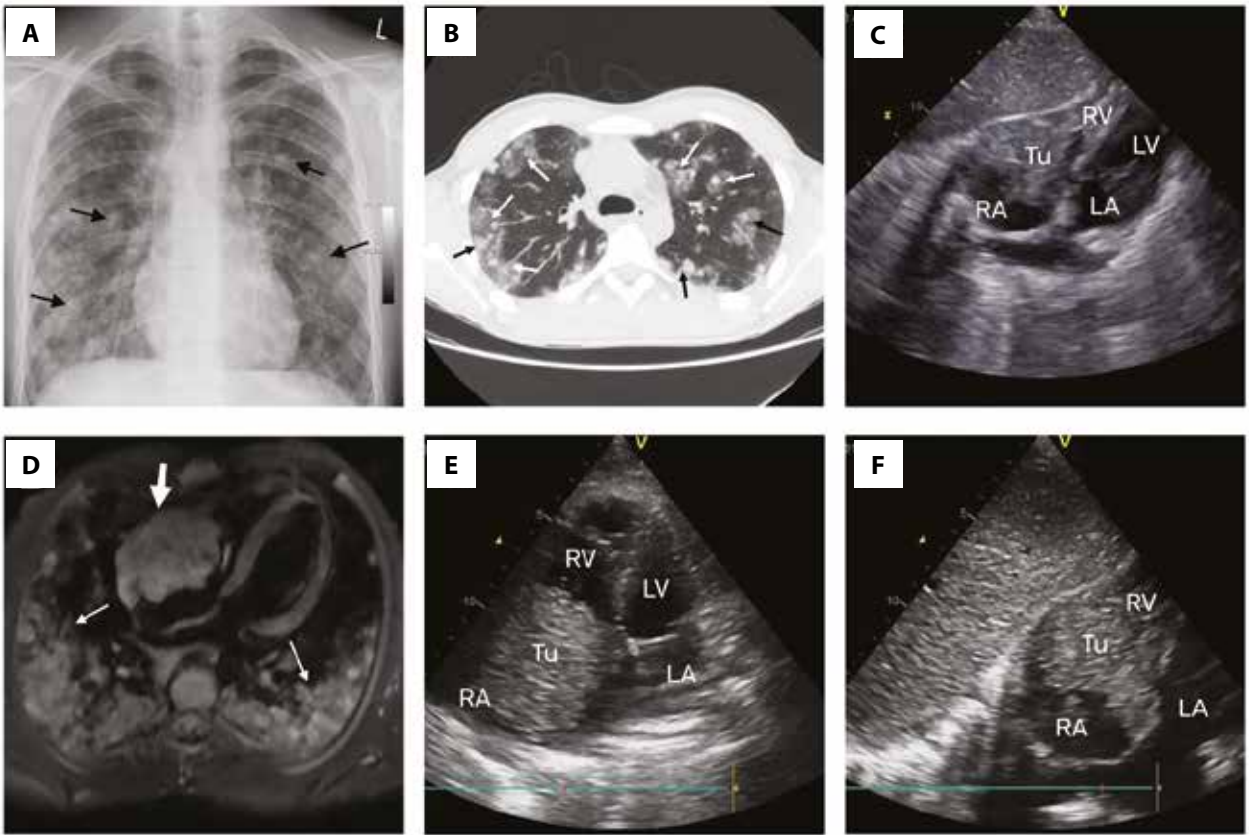

Figure 1. Multimodality imaging of cardiac angiosarcoma. **A.** X-ray of the lungs showing diffuse ground-glass opacities (black arrows). **B.** Computed tomography of the lungs showing ground-glass opacities in the center and periphery (white arrows) and subpleural opacifications (black arrows). **C.** Initial TTE, subcostal view showing a large right atrial tumor with a possible thrombus on the periphery. **D.** T1-weighted magnetic resonance imaging showing lesion in the right atrium of the heart (thick arrow) and metastatic lesions in both lungs (thin arrows). **E.** TTE after 2 weeks, apical 4-chamber view showing the tumor mass encroaching RA and infiltrating the free wall. **F.** TTE after 2 weeks, subcostal view, showing the enlargement of the tumor mass.

Abbreviations: LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; TTE, transthoracic echocardiogram

Article information

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Emergency mechanical thrombectomy to treat embolic stroke complicating catheter ablation of cardiac arrhythmia

Szymon Budrejko, Tomasz Królak, Maciej Kempa, Grzegorz Raczak

Department of Cardiology and Electrotherapy, Medical University of Gdansk, Gdańsk, Poland

Correspondence to:
Szymon Budrejko, MD, PhD, Department of Cardiology and Electrotherapy, Medical University of Gdansk Dębinki 7, 80–211 Gdańsk, Poland, e-mail: budrejko@gumed.edu.pl

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A 75-year old male patient with a complex medical history (myocardial infarction, diabetes mellitus, heart failure with ejection fraction of 35%, renal transplant, and resynchronization therapy cardioverter-defibrillator) was transferred to our clinic due to an electrical storm. His symptoms persisted for a month. Device interrogation revealed 42 episodes of ventricular tachycardia (VT) with a heart rate of 185 bpm, terminated with antitachycardia pacing. No antiarrhythmic treatment had been used before. He had no history of neurologic deficits.

Echocardiography confirmed the presence of lateral, inferior and infero-basal scar. No thrombus was found in the left ventricle (LV). The patient was referred for transaortic catheter ablation of VT substrate with the use of a 3-dimensional mapping system. In local anesthesia, the right femoral artery was cannulated, and an ablation catheter was introduced without any difficulty to the LV. Intravenous heparin (100 U/kg) was administered as soon as the arterial sheath was inserted, and the first activated clotting time was 314 seconds. Electroanatomical mapping of the LV was started, and soon we observed deterioration of the patient condition — loss of contact and symptoms of right-sided hemiparesis, however, with no signs of hemodynamic instability. The consulting neurologist found the patient to be conscious, in mixed type aphasia, and right hemianopsia, hemiplegia, and hemihypoesthesia. A stroke of the left (dominant) cerebral hemisphere was diagnosed and the arrhythmia ablation procedure was aborted. Due to prior administration of heparin, the patient was disqualified from thrombolysis. However, he still met the criteria for mechanical thrombectomy because 1) computed tomography (CT) angiography revealed a large-vessel occlusion (segments M1 and M2 of the left middle cerebral artery); 2) cerebral plain CT excluded cerebral bleeding; 3) the time from stroke onset was <6 hours; 4) ASPECTS score was >6 (10 in that case), NIH Stroke Scale was >6 (21 in that case) [1]. The patient was then transferred to the interventional radiology laboratory (within the radiology unit in our hospital). Emergency mechanical thrombectomy of the left middle cerebral artery was performed, using the existing vascular access (8 F sheath) with optimal angiographic effect (TICI 3). Angiographic scans pre- and post-procedure are shown in Figure 1. Embolic material macroscopically consistent with ruptured atherosclerotic plaque was removed from the occluded artery with stent-retriever. During the following days, the patient experienced the withdrawal of all neurologic deficits. Follow-up CT scan showed no ischemic lesions. Antiarrhythmic treatment with amiodarone was initiated, with no further episodes of sustained VT during hospitalization. The patient was referred to the rehabilitation department, with the possible ablation in stand-by. He was discharged home with no neurologic deficit. Three months later the patient experienced heart failure exacerbation and severe pneumonia and died in a local hospital due to sepsis and multiorgan failure.

Our experience proves that emergency mechanical thrombectomy in such a setting is feasible. It may be treated as a bailout option in patients experiencing thromboembolic complications during ablation procedures of ventricular arrhythmias, as in our patient, or other interventions [2–4]. Importantly, arterial access may be preserved during patient's transfer for easy vascular access to mechanical thrombectomy. Pre-set logistic workflow that shortens the time to cerebral reperfusion, should be prepared in advance. Multi-specialty collaboration is fundamental in optimizing stroke thrombectomy pathways and outcomes [5].

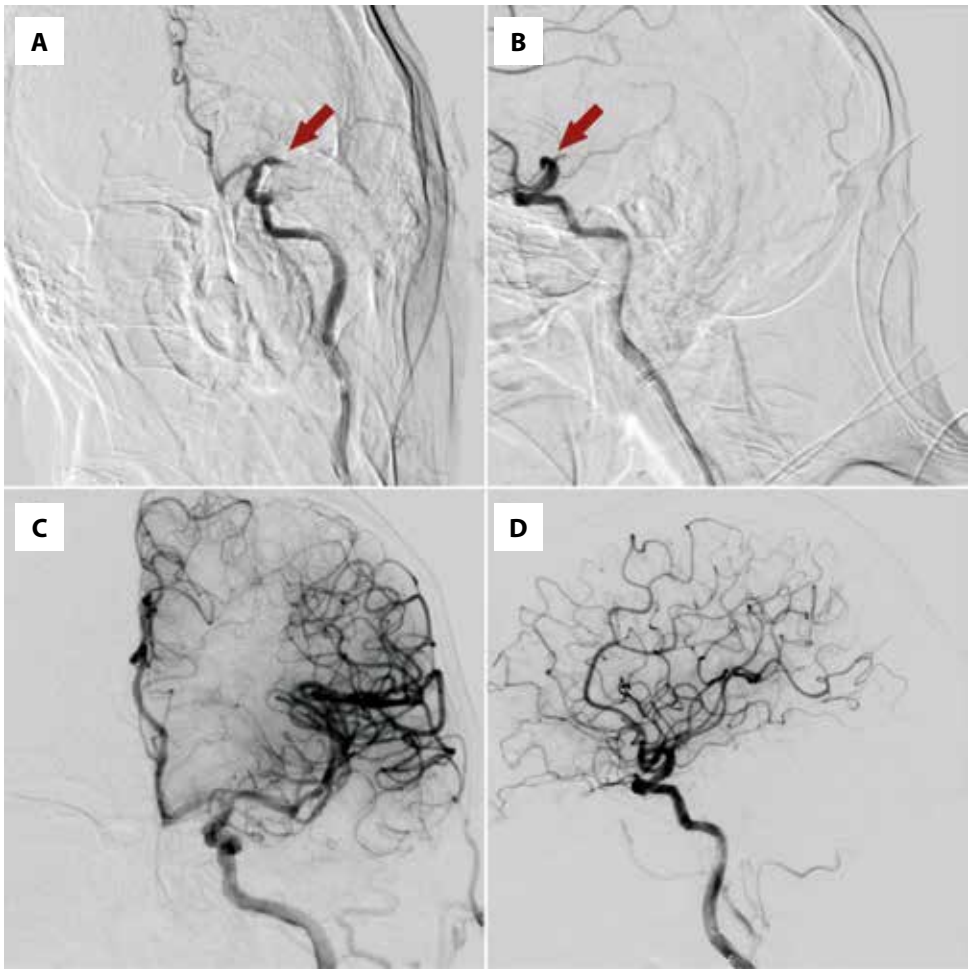

Figure 1. Angiographic scans of the cerebral flow. **A.** Initial postero-anterior view, no contrast is passing to the left middle cerebral artery. **B.** Initial lateral view, no contrast is passing to the left middle cerebral artery. **C.** Final postero-anterior view, complete reperfusion of the left middle cerebral artery. **D.** Final lateral view, complete reperfusion of the left middle cerebral artery. Arrows on panels indicate the site of occlusion

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Left bundle branch block as a sign of coexisting left main and right coronary artery occlusion, successfully treated with percutaneous coronary intervention

Adrian Włodarczak[1], Piotr Rola[2], Mateusz Barycki[2], Jan Jakub Kulczycki[1], Marek Szudrowicz[1], Barbara Engel[2], Adrian Doroszko[3], Maciej Lesiak[4]

[1]Department of Cardiology, The Copper Health Centre, Lubin, Poland
[2]Department of Cardiology, Provincial Specialized Hospital in Legnica, Legnica, Poland
[3]Department of Internal Medicine, Hypertension and Clinical Oncology, Wroclaw Medical University, Wrocław, Poland
[4]1st Department of Cardiology, Poznan University of Medical Sciences, Poznań, Poland

Correspondence to:
Piotr Rola, MD, PhD, Department of Cardiology, Provincial Specialized Hospital in Legnica, Iwaszkiewicza 5, 59–220 Legnica, Poland, phone: +48 888 272 007, e-mail: piotr.rola@gmail.com

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A 53-year-old male, active smoker with hypertension, hyperlipidemia, history of stroke and type 2 diabetes mellitus, was admitted to the hospital with symptoms of dyspnea and chest pain (class IV in the Canadian Cardiovascular Society scale).

Physical examination revealed cachexia, dyspnea with rales and crackles on auscultation (Killip–Kimball II). Transthoracic echocardiography showed enlarged, whole-hypokinetic left ventricle (left ventricular end-diastolic dimension/left ventricular end-systolic dimension = 68 mm/59 mm) with reduced ejection fraction (20%–25%) and coexisting moderate functional mitral regurgitation, without other mechanical complications. Additionally, a moderate amount of fluid in the right pleural cavity was diagnosed. Electrocardiogram showed sinus rhythm of 90/min conducted with the left bundle branch block (LBBB). The serum troponin I was positive.

In the emergency department, intravenous loop-diuretic, unfractionated heparin (5000 IU) were administered, following the prior loading doses of clopidogrel (600 mg) and acetylsalicylic acid (300 mg) given in the ambulance.

Coronary angiogram revealed chronic-total-occlusion of the right coronary artery with coexisting occlusion of the left main (LM) as a culprit lesion (Figure 1A, 1B). Due to advanced atherosclerosis, initial double-intravenous bolus of eptifibatide was administered (followed by the 24-h IV-infusion at the dose of 2 μg/kg/min) and a rescue percutaneous coronary intervention was performed using the left-radial approach with EBU3.5-Guide-Catheter (6 F) (Medtronic Ireland, Galway, Ireland). During the procedure we used: BMW Universal-II (Abbott-Vascular, Santa-Clara, California, US), Sion (Asahi-INTECC Co. Aichi, Japan), and Fielder XT (Asahi) guidewires. After LM opening with a 2 mm balloon-catheter (Figure 1C), we revealed a critical stenosis including: the LM, ostium of the left anterior descending (LAD), circumflex (Cx), and the intermediate artery (IM) without signs of residual thrombus (Figure 1D). Due to significant calcification, we performed a high pressure (24 atm) pre-dilatation of the LM alongside with LAD and Cx with a non-compliant balloon 3.0 × 15 mm. Using the Culotte technique, we implanted two coronary drug-eluting stents Orsiro 3 × 18 mm (Medtronic) into Cx and XiencePRO 3.5 × 18 mm (Abbott) into LAD. Afterwards, we performed optimization of: Cx/IM and LM/LAD/Cx with the kissing balloon technique using 3 × 5 mm and 3.5 × 15 mm (14 atm) catheters and subequal proximal-optimization technique in the LM using the non-compliant 4 × 8 mm (18 atm) balloon. During the procedure catecholamines were used to obtain hemodynamic stabilization, without need for additional mechanical left ventricle function support. The patient was discharged after 13 days of hospitalization with mild improvement of the left ventricle function, previously switched to ticagrelor from clopidogrel. Due to persistent LBBB, an implantation of cardiac resynchronization therapy with defibrillator was scheduled, following the ejection fraction assessment after 3 months of an optimal medical treatment.

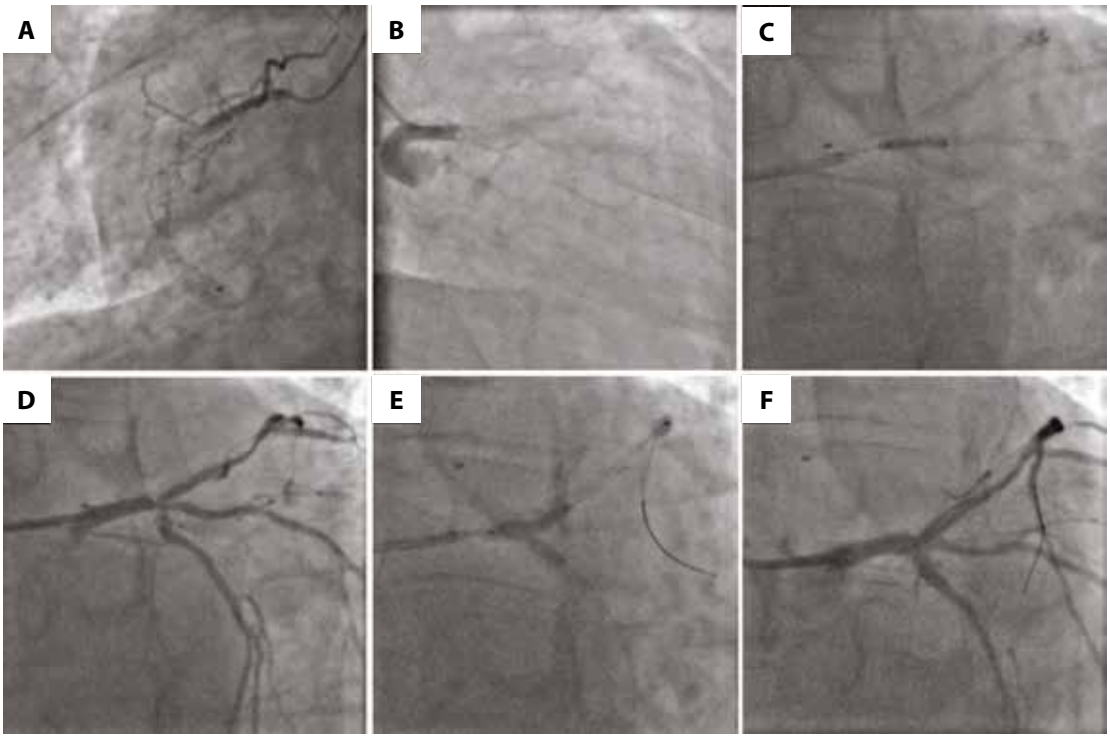

Figure 1. A. Coronary angiography of the right coronary artery. **B.** Coronary angiography of the left main. **C.** Lesion crossing with a 2 mm balloon. **D.** Left main after pre-dilation. **E.** Kissing balloon optimization of the left main trifurcation. **F.** Final result of the procedure

Acute coronary syndrome due to the LM occlusion is characterized by relatively high mortality [1, 2]. This location of the culprit lesion is associated with a suggestive electrocardiogram pattern, including the widespread ST depression in the precordial leads, accompanied by the ST segment elevation in the aVR and V1 and rarely ST elevation myocardial infarction [3]. In this case, the electrocardiogram revealed the LBBB, which is rather uncommon. While some data suggests that the one-stent technique can be suitable for dealing with the LM bifurcation [4, 5], we used the two-stent Culotte technique, with the multiple kissing-balloon inflation (Figure 1E). Such an approach made it possible to obtain optimal angiographic results (Figure 1F). The presented case demonstrates that even extremely advanced coronary artery disease can be successfully treated with the two-stent technique by 6 F radial access without additional mechanical circulatory support.

Supplementary material

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

Article information

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Echocardiography during the coronavirus disease 2019 pandemic — the impact of the vaccination program. A 2021 update of the expert opinion of the Working Group on Echocardiography of the Polish Cardiac Society

Piotr Szymański[1], Andrzej Gackowski[2], Katarzyna Mizia-Stec[3], Jarosław D Kasprzak[4], Magdalena Lipczyńska[5], Piotr Lipiec[6]

Review Committee/Collaborators: Olga Trojnarska[7], Paulina Wejner-Mik[4], Danuta Sorysz[8], Bożena Sobkowicz[9], Zofia Oko-Sarnowska[7], Andrzej Wysokiński[10], Andrzej Szyszka[11], Edyta Płońska-Gościniak[12], Zbigniew Gąsior[13], Michał Ciurzyński[14]*, Tomasz Pasierski[15]*, Piotr Hoffman[5]

[1]Clinical Cardiology Center, Central Clinical Hospital of the Ministry of the Interior in Warsaw and Center of Postgraduate Medical Education, Warszawa, Poland
[2]Jagiellonian University, Medical College, Institute of Cardiology, Department of Coronary Disease and Heart Failure, Noninvasive Cardiovascular Laboratory, John Paul II Hospital, Kraków, Poland
[3]1st Department of Cardiology, Medical University of Silesia in Katowice, Katowice, Poland
[4]1st Department of Cardiology, Medical University of Lodz, Bieganski Hospital, Łódź, Poland
[5]Department of Congenital Heart Disease, National Institute of Cardiology, Warszawa, Poland
[6]Department of Rapid Cardiac Diagnostics, Medical University of Lodz, Łódź, Poland
[7]1st Department of Cardiology, Poznan University of Medical Sciences, Poznań, Poland
[8]Department of Cardiology and Cardiovascular Interventions, University Hospital, Kraków, Poland
[9]Department of Cardiology, Medical University in Bialystok, Białystok, Poland
[10]Department of Cardiology, Pomeranian Medical University, Szczecin, Poland
[11]2nd Department of Cardiology, Poznan University of Medical Sciences, Poznań, Poland
[12]Department of Cardiology, Medical University of Lublin, Lublin, Poland
[13]Department of Cardiology, Medical University of Silesia in Katowice, Katowice, Poland
[14]Department of Internal Medicine and Cardiology Medical University of Warsaw, Warszawa, Poland
[15]Department of Medical Ethics and Palliative Medicine, Warsaw Medical University, Warszawa, Poland
*Reviewer on behalf of the Polish Cardiac Society

Correspondence to:
Prof. Piotr Szymański, MD, PhD, FESC, Central Clinical Hospital of the Ministry of the Interior in Warsaw, Center of Postgraduate Medical Education, Wołoska 137, 02–507 Warszawa, Poland, phone: +48 22 508 11 00, e-mail: pszymanski@ptkardio.pl

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic resulted in an urgent need to reorganize the work of echocardiography laboratories in order to ensure the safety of patients and the protection of physicians, technicians, and other staff members. In the previous Expert Opinion of the Working Group on Echocardiography of Polish Cardiac Society we provided recommendations for the echocardiographic services, in order to ensure maximum possible safety and efficiency of imagers facing epidemic threat. Now, with much better knowledge and larger experience in treating COVID-19 patients and with introduction of vaccination programs, we present updated recommendations for performing transthoracic and transesophageal examinations, including information on the potential impact of personnel and the patient vaccination program, and growing numbers of convalescents on performance of echocardiographic laboratories, with the goal of their ultimate reopening.

Key words: COVID-19, echocardiography, echocardiographic laboratories, vaccination

Kardiol Pol 2021; 79, 5: 595–603

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic resulted in an urgent need to reorganize the work of echocardiography laboratories in order to ensure the safety of patients and protection of physicians, technicians, and other staff members. In the previous Expert Opinion of the Working Group on Echocardiography of Polish Cardiac Society we provided recommendations for the echocardiographic services, in order to ensure maximum possible safety and efficiency of imagers facing epidemic threat [1].

Restrictions imposed on transthoracic (TTE) and transesophageal (TEE) examinations due to the pandemic resulted in significant limitation of access of patients with cardiovascular diseases to services. Currently, a year after the initial document, there is a need to provide updated information on the current knowledge on the COVID-19 pandemic as well as, perhaps even more importantly, on the potential impact of the vaccination program and growing numbers of convalescents on everyday practice of echocardiographic laboratories. Moreover, with much better knowledge and larger experience in treating COVID-19 patients, and with the introduction of vaccination programs, recommendations for TTE or TEE adopted for epidemic conditions, and health requirements need to be updated. This update is especially appropriate now when a substantial proportion of medical personnel in Poland are vaccinated with two doses of a mRNA vaccine and when, despite the current peak of the pandemic, we must think about the goal of restoring full capacity of echocardiographic laboratories, once the pandemic is under control [2].

For the purpose of this document we define the latter as the low and decreasing number of cases; the number of positive tests/number of all tests below 5%; contact tracing system is active and fully operational; at least 70% of personnel and general adult population are vaccinated; no new viral strains escaping from acquired immunity are detected.

Importantly, while certain regulators accept fully vaccinated people gathering indoors without wearing masks, we propose that until the end of the pandemic also vaccinated personnel and patients should wear masks during echocardiographic examinations, both in the in-patient and out-patient settings [3]. This recommendation may change as knowledge about the efficacy of vaccination programs expands.

COVID-19 AND CARDIOVASCULAR DISEASE

The COVID-19 pandemic has numerous cardiovascular implications. Firstly, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may adversely affect the cardiovascular system of infected patients. The proposed underlying pathophysiological mechanisms include hypoxemia, systemic inflammatory response, hypercoagulability, sympathetic stimulation, direct myocardial and vascular infection and myocyte necrosis. Myocardial injury detected by elevated cardiac biomarkers has been observed in 5% to 38% of hospitalized patients, depending on the criteria used. The most frequently described clinical manifestations of cardiovascular involvement include thromboembolism, arrhythmia, myocarditis, acute coronary syndrome, stress cardiomyopathy and heart failure, but the autopsy data suggest that their incidence may be underestimated [4, 5].

Secondly, one should consider adverse cardiovascular effects of drugs prescribed to treat SARS-CoV-2 and post-viral complications, such as pediatric inflammatory multisystem syndrome. Thirdly, pre-existing cardiovascular diseases are the most common comorbidities in infected patients, with hypertension being the most common one. Of note, both cardiac involvement during SARS-CoV-2 infection and preexisting cardiovascular disorders have been shown to be associated with more severe clinical course of COVID-19 and worse prognosis [6].

ACUTE AND LONG-TERM ECHOCARDIOGRAPHIC FINDINGS IN COVID-19 PATIENTS

COVID-19 is a primarily respiratory infection, with common cardiovascular involvement in severe and critical stages of the disease. Echocardiography represents a versatile diagnostic procedure requiring high level of physician-patient interaction, thus posing a risk for infection. This is especially true for transesophageal studies (also most of stress-echo protocols) which are highly aerosol-generating. The policies of use of TTE in COVID-19 healthcare facilities may vary, but the general indication depends on potential impact of findings upon the management of the patient. Both the evidence of cardiovascular involvement during COVID-19 and precise identification of preexisting cardiovascular conditions may contribute to proper management.

Cardiac dysfunction present prior to the SARS-CoV-2 infection can influence the findings, the clinical course of the infection and the prognosis. Therefore, prior to interpretation of the echocardiographic study, an attempt should be made to determine the preexisting cardiac pathology based on the history and available medical records. Symptoms reported during COVID-19 are nonspecific and can result from other organ damage (i.e., lungs, skeletal muscles, kidneys, nervous system, etc.) or from psychological reasons and stress. Therefore, TTE is crucial to detect and differentiate the cardiac and non-cardiac reasons.

The most important cardiac complications of COVID-19 are myocardial injury and cardiovascular thrombosis [7–9]. Myocardial damage is more frequently found in patients with abnormal electrocardiogram or elevated biomarkers (troponin or natriuretic peptides) and these patients should undergo TTE. It is probably more common in hospitalized patients. Nearly half of patients with elevated troponins had at least moderate left ventricular (LV) dysfunction, which was associated with doubled risk of death, comparing to patients with no LV wall motion abnormalities. Myocardial function impairment can be reversible or irreversible. Both left and right ventricular

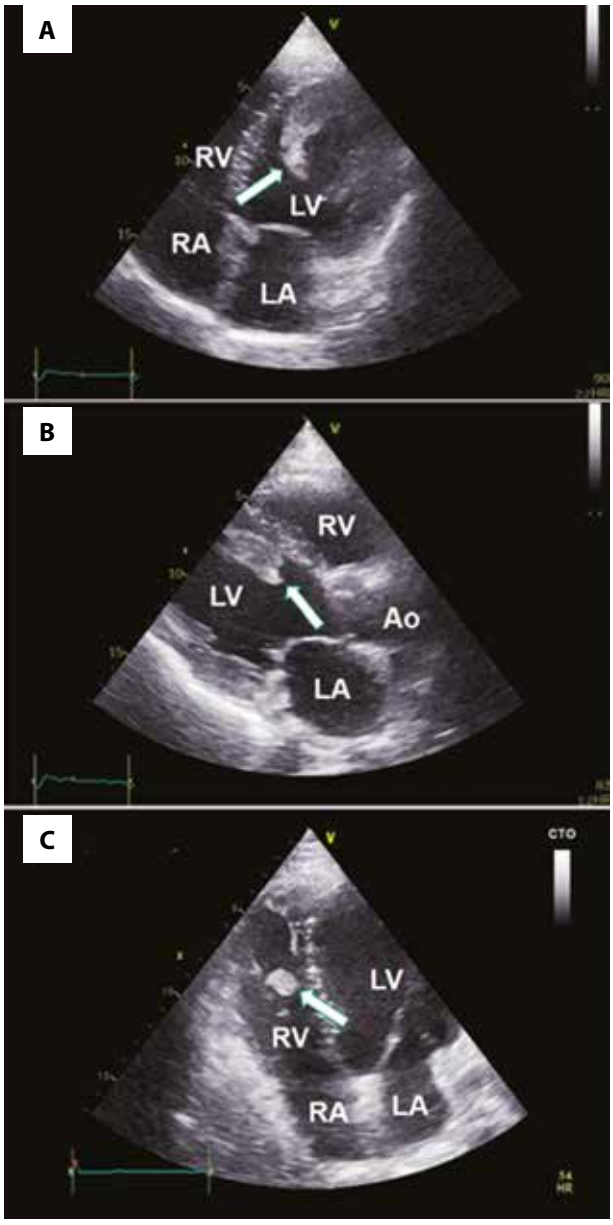

Figure 1. Transthoracic echocardiography in patients with COVID-19 — thrombi (arrows) in the left ventricle (**A**, **B**) and in the right ventricle (**C**).

Abbreviations: Ao, aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle

dilatation are associated with poor prognosis. Global or regional myocardial injury visible on echocardiography can be detected in up to 25% of hospitalized patients with COVID-19 and is associated with an increased risk of mortality. Intracardiac clots forming on the damaged cardiac endothelium or migrating from the veins to the pulmonary circulation may be observed (Figure 1). Pericardial or pleural fluid initially reported as rare in COVID-19 patients, has been recently more frequently described in the context of perimyocarditis [10]. In a study at least mild pericardial effusion was found in 7.2% of severely ill patients with myocardial dysfunction [10]. Cardiac tamponade was also reported in a case study [11].

Most common clinical indications for TTE in the acute COVID-19 are hemodynamic assessment (including fluid status), rising cardiac biomarkers, suspicion of pulmonary embolism, acute coronary syndrome, heart failure, or myocarditis [13]. Other indications include history of cardiac disease, suspicion of endocarditis, and evaluation for cardioembolic source of stroke [14]. In practice, many TTE tests are performed in mechanically ventilated subjects hospitalized due to COVID-19. Thus, in patients with clinical deterioration, TTE exams (optionally combined with lung ultrasound [LUS] tests and 4-point venous compression ultrasound [CUS]) may be needed to document myocardial dysfunction or other complications indicating the need for early intensive treatment. It is particularly important in patients with preexisting heart disease or comorbidities. In most patients simplified protocols are preferred to limit personnel exposure to infected patients. Advanced analysis (e.g., strain imaging), if considered essential, can be performed offline to document subtle ventricular dysfunction.

Recovery of the myocardial damage is variable and long-term sequelae may persist, depending on the baseline status, the severity of viral or inflammatory damage, and the speed and completeness of recovery phase.

Some patients may never recover completely following acute COVID-19. Symptom-free convalescents do not require cardiac imaging, however lack of complete recovery is an indication for the control TTE. In most cases, echocardiography should be performed when there is no further risk of infecting the personnel. Subclinical myocarditis may be of some concern, especially in patients with innate or acquired immune deficits. As data is conflicting further studies are needed to assess the long-term cardiac consequences of SARS-CoV-2 infection.

Last but not least, abnormalities detected in COVID-19 or post-COVID-19 patients include also the results of delayed cardiac care, like myocardial infarction (untreated or treated late or without reperfusion) that can be complicated with classical mechanical complications [12]. Delayed diagnosis due to the pandemic can result in late detection of decompensated chronic conditions, such as valvular disease (predominantly aortic stenosis, mitral and tricuspid regurgitations) or heart failure of any origin.

LUNG ULTRASOUND

Radiography and computed tomography remain the mainstay for evaluation of COVID-19 pneumonia. Although LUS has proven its diagnostic value and capability in COVID-19 patients, it lacks standardization and suffers from the absence of quantitative approaches. Importantly, LUS findings are nonspecific for COVID-19. A diffuse pattern of B-lines, irregular pleural lines, and subpleural consolidations affecting mainly the lower lobe and posterior lung segments, which show a bilateral, patchy, and peripheral pattern, represent typical LUS findings in COVID-19 pneumonia [15].

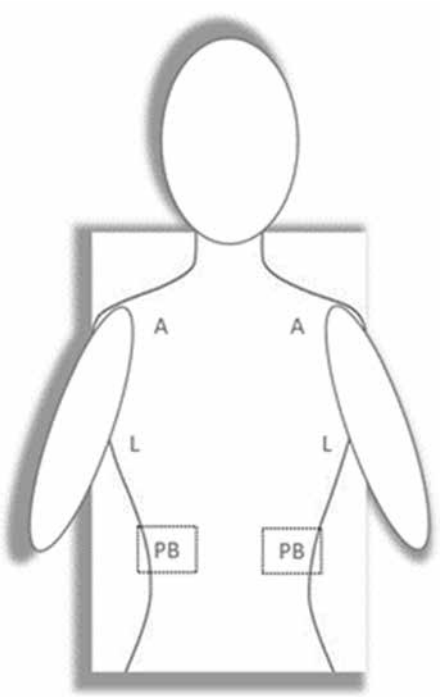

Figure 2. Simplified 3-zone protocol for bilateral lung ultrasound examination for cardiologists. Anterior (A), lateral (L), and postero-basal (PB) lung zones are examined

There is still great variability regarding the optimal technique, including different proposed scanning protocols and scoring algorithms. For this reason, Italian texperts proposed standardization for international use of LUS for the management of patients with COVID-19 [16]. Fourteen standard areas (7 areas per lung) are suggested for scanning in each patient, using landmarks on chest anatomic lines (3 posterior — paravertebral line; 2 lateral — mid-axillary line; 2 anterior — mid-clavicular line). In the absence of a standardized score for COVID-19 patients, Italian experts proposed to use a previously validated scoring system. The final score is obtained by summing up the scores of each area. Some studies suggested that a higher LUS score indicating a poorly aerated lung and a more severe pulmonary involvement may thus be useful for predicting adverse outcomes in patients with COVID-19, and important for risk stratification in COVID-19 patients [17]. Canadian experts described the 6-zone (3 zones per lung) protocol aimed at speeding up and simplifying the examination dedicated for cardiologists (posterior basal, lateral and anterior — for each lung), and we propose to use this protocol (Figure 2) [18].

According to the experience and reports of many groups throughout the world, even with a rather empirical approach, LUS seems to be an useful, radiation-free, bedside method which can be applied after the TTE examination. Current enthusiasm for LUS should lead to high-quality controlled studies which can determine its real utility among COVID-19 patients.

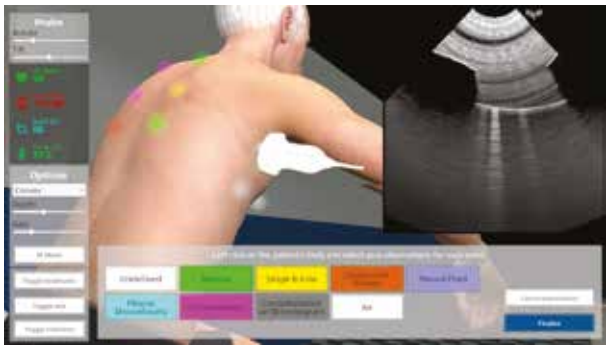

Figure 3. Web-based lung ultrasound simulator (www.lus.mstech.eu). The probe is dragged over the chest with a computer mouse. The user recognizes typical artifacts (here B-lines), which are then assigned to the standard lung ultrasound points. The findings are then verified and corrected in case of errors

Despite the fact that currently there is no clear data showing that LUS improves outcomes, the COVID-19 era poses unprecedented challenges, but also learning opportunities. Web based ultrasound simulators are available for training (Figure 3) [19].

COLLATERAL DAMAGE TO CARDIOVASCULAR HEALTHCARE

The COVID-19 pandemic has significantly impacted healthcare systems around the world, including echocardiography laboratories. A large portion of available resources has been repurposed towards fighting the pandemic. The remaining available cardiology departments and personnel have been often advised to defer scheduled elective procedures, especially those associated with increased risk of SARS-CoV-2 transmission, such as transesophageal echocardiography [1]. Moreover, patients' fear of infection and the desire to not overburden the healthcare system have also been keeping them from seeking medical care in case of symptoms unrelated to COVID-19, both in urgent and chronic clinical scenarios [20]. Thus, the COVID-19 pandemic has adversely influenced the care and treatment of cardiovascular patients. The full scope and the long-term consequences of this "collateral damage" are yet to be determined, but the data published so far is already alarming, even though the exact extent of observed detrimental effects varies greatly between reports and affected regions. To date, most studies have concentrated on patients with acute myocardial infarction, indicating lower number of their hospital admissions, higher rate of delayed presentations and a significant reduction in coronary angiographies and percutaneous coronary interventions [21, 22]. However, the hospitalizations for heart failure and cardiac arrhythmias, as well as the cumulative number of hospitalizations for acute and chronic cardiovascular conditions have also markedly decreased during the pandemic [23]. Similarly, a substantial drop in the number of outpatient cardiovascular visits has been reported, although it was partly compensated using telehealth

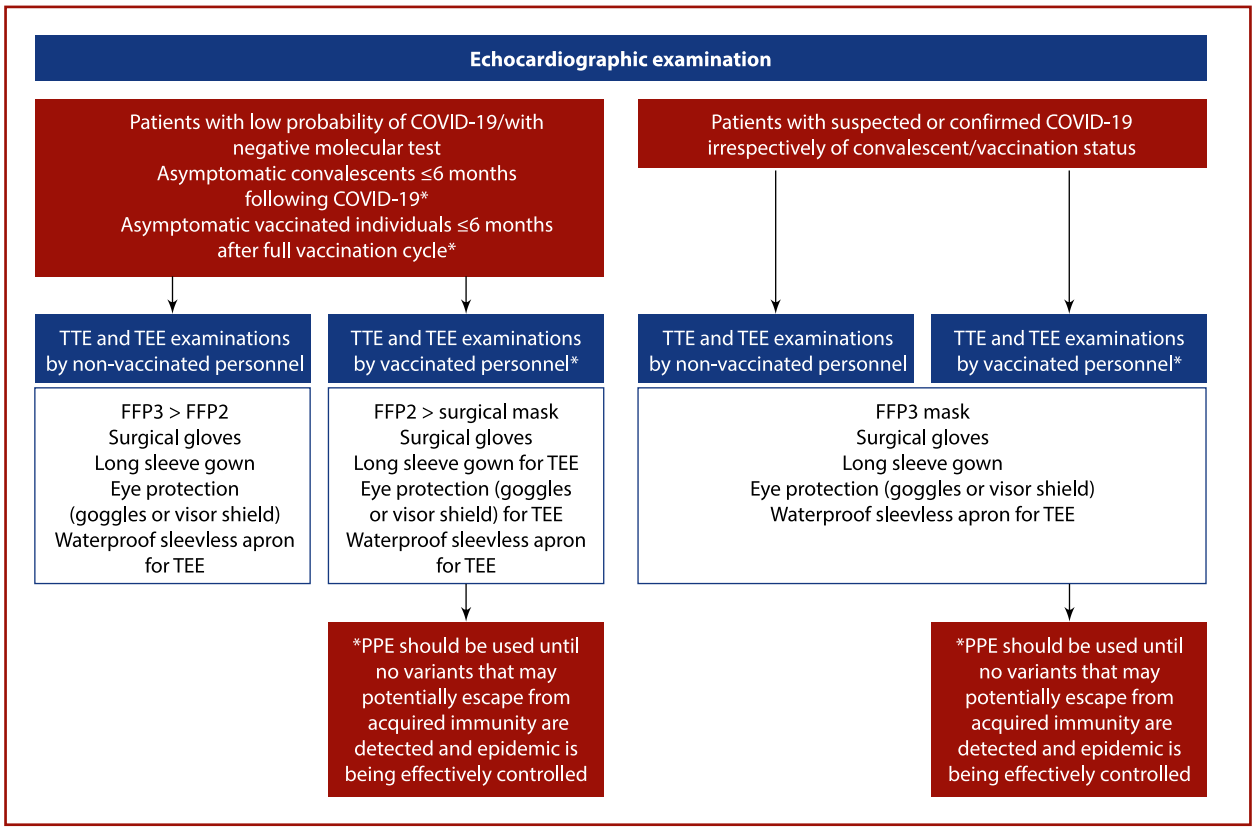

Figure 4. Suggested personal protection equipment, according to the probability of COVID-19, type of echocardiographic examination, patient and personnel vaccination/convalescent status.

Abbreviations: TEE, transesophageal echocardiography; TTE, transthoracic echocardiography

[24]. There also has been a considerable reduction in the number of inpatient and outpatient cardiac procedures and investigations [25, 26].

With regard to echocardiography, preliminary analysis of the survey study performed by the Working Group on Echocardiography of the Polish Cardiac Society suggests that the vast majority of centers have been performing significantly fewer examinations than before the pandemic. The drop has been most evident in TEE, in case of which indications for examination have been often reevaluated and narrowed, and a negative COVID-19 test prior to the procedure was required in the laboratories on non-COVID-19 wards. Most of the laboratories have also reported temporary shortages of staff due to COVID-19, quarantine or dispatching them to work in infectious disease departments. As a result, there even have been instances of temporary cessation of any activities. Moreover, a significant number of centers have been at least partially transformed to diagnose and treat COVID-19 patients. Thus, waiting times for both scheduled echocardiographic examinations and elective surgical and percutaneous procedures recommended for patients after echocardiographic examinations have been extended. Therefore, it comes as no surprise that a significant increase in out-of-hospital cardiac arrests and deaths was noted in the affected regions [27–29], and was accompanied by substantial overall excess mortality, which could not be explained by the number of COVID-19 fatalities [30, 31]. All these data call for urgent reintroduction of widely available echocardiography services.

REACTIVATION OF ECHOCARDIOGRAPHIC LABORATORIES

Despite the current peak of the pandemic, there is an urgent need for restoring full capacity of echocardiographic laboratories. It may be feasible in near future, as an increasing number of staff and patients are already either vaccinated or have recovered from COVID-19. Distinct separation of laboratories providing services for COVID-19 infected or COVID-free patients should be instituted, if logistically possible. Echocardiographic laboratories that are not directly involved in the care of COVID-19 patients should attempt to return to their full pre-pandemic activity and perform all study types, according to standard protocols, as well as try to alleviate collateral damage to the services caused by COVID-19. Waiting lists for echocardiographic examinations should be verified as prolonged waiting period for echocardiography examination has become a serious issue. Urgent patients for whom further delays may be life-threatening should be placed on a priority list (e.g., decompensated heart failure, severe aortic stenosis).

Although access to echocardiographic services should be urgently facilitated, all essential restrictive precautions and

Table 1. Recommendations for echocardiographic laboratory organization

Laboratories providing services for COVID-19 and non-COVID-19 patients should be separated, if logistically possible
Echocardiographic laboratories providing services for non-COVID-19 patients should return to their pre-pandemic level of activity
Patients with urgent indications for whom further delays may be life-threatening should be prioritized

Table 2. Recommendations for non-COVID-19 in-patient echocardiographic services

In-patient echocardiographic laboratories in non-COVID-19-dedicated wards should return to their pre-pandemic activity and perform all test types according to standard protocols
Decisions on the reinstitution of "lockdowns" of regular echocardiographic services should be made on the local basis rather than national basis
With regard to COVID-19 testing, echocardiography laboratories should follow local hospital policies and existing legal requirements
When/if the pandemic is under control (as defined above), preventive measures may be eased
We do recommend however that appropriate personal protective equipment should be always available/used during echocardiographic examinations in hospital settings until the end of the pandemic

safety measures should be preserved, to minimize the risk of infecting other patients and medical personnel at the peak of the pandemic. Decrease of the number of cases following an effective vaccination program may however enable to modify some protective measures or get away from them in the future. It is therefore strongly recommended that every member of an echo team be vaccinated against SARS-CoV-2.

Echocardiographic protocols should be differentiated according to the location of the echocardiographic laboratory (in-patient vs outpatient, COVID-19 vs non-COVID-19 services) and the epidemiologic status of the patients examined. When separation of COVID-19 and non-COVID-19 patients is impossible for logistic reasons, patient management should include isolation of infectious patients and case grouping, possibly at the end of the day, to ensure appropriate personnel protection and disinfection of the facilities. For recommendations see also Table 1, Figure 4.

Recommendations for non-COVID-19 in-patient echocardiographic services

Echocardiography laboratories in COVID-19-free wards should perform full range of examinations, following standard protocols. Intraprocedural TTE and TEE monitoring should also be reinstituted. At the peak of the pandemic, SARS-CoV-2-free status of non-vaccinated patients without COVID-19 symptoms should be confirmed through appropriate institutional screening procedures, including *reverse-transcription polymerase* chain reaction (RT-PCR) testing for the presence of SARS-CoV-2 immediately prior to admission and at the wards, according to local hospital policy and existing legal requirements. Surgical gloves and FFP2 masks (if available) should be used at all times during echocardiographic examinations in hospital settings.

Vaccinated patients without symptoms of infection, may be considered as having minimal probability of being infectious, at least for the 6 months after an index event. Therefore, when/if the pandemic is under control (as defined above), preventive measures may be relaxed. However we do recommend that appropriate personal protective equipment should be always available/used during echocardiographic examinations in hospital settings until the end of the pandemic. Exceptions may be considered only for contacts between fully vaccinated individuals. For recommendations see also Table 2, Figure 4.

In-patient COVID-19 echocardiographic services

The rules and procedures concerning echocardiography examination in COVID-19 wards do not change. Full personal protection must be available for every test (TTE, TEE), including those of potentially infected patients awaiting definite diagnostic test result. Minimum standards of personal protection as proposed below may be locally tightened up, according to local policies and pandemic situation. Complete disinfection of the lab and equipment should be performed on a regular basis as per local standards. Due to intense personal contact, every test ordered should have the potential to influence the management. The duration of TTE examination should be minimized and focused protocols are recommended to obtain the most important and clinically useful information quickly. If possible, analyses and measurements should be performed off-line to focus on problem-oriented examinations, facilitate therapeutic decisions, and minimize the risk of infecting medical personnel. Performing stress-testing during acute COVID-19 is contraindicated. It is the responsibility of hospital administration to ensure digital data transfer to reading lab with workstations to ensure analysis quality and safety. For recommendations see also Table 3 and Figure 4.

Out-patient echocardiographic services

Access to echocardiographic services is of key importance to ascertain reinstitution of routine care, especially for heart failure and structural heart disease patients. Out-patient echocardiographic services should therefore remain open; however, in patients with suspected COVID-19 (based either on their symptoms or contact history) or other respiratory infection, routine echocardiography should be postponed until COVID-19 diagnosis is excluded by the RT-PCR test or until the risk of transmission is considered minimal (usually no less than 10 days after symptom onset).

Until the pandemic is under control, both vaccinated and unvaccinated patients without clinically suspected COVID-19 should wear face mask in echo lab. Enhanced

Table 3. Recommendations for COVID-19 in-patient echocardiographic services

Recommendations for the COVID-19 patients and patients with unknown SARS-CoV-2 status remain unchanged, and all TTE and TEE studies must be performed with full personal protection, regardless of the vaccination status of the personnel
Indications for tests should remain restrictive with predictable influence upon clinical management
Echocardiographic protocols should be shortened
Whenever possible analyses and measurements should be performed off-line, outside the infectious zones and digital data transfer and analysis is encouraged

Abbreviations: TEE, transesophageal echocardiography; TTE, transthoracic echocardiography

Table 4. Recommendations for out-patient echocardiographic services

Out-patient echocardiographic laboratories should return to their pre-pandemic activity and perform all test types, according to the standard protocols
Stress echocardiography services should be reinstituted, and most of the protocols (except for rapid pacing) must be considered as aerosol-generating and personnel protection level should equal to that proposed for TEE
In patients with suspicion of COVID-19 (based either on their symptoms or contact history) or ongoing respiratory infection routine echocardiography should be postponed until COVID-19 diagnosis is excluded by the RT-PCR test or until the risk of transmission is considered minimal (usually no less than 10 days after symptom onset)
Vaccinated patients and convalescents without symptoms of infection should be considered as SARS-CoV-2 negative, at least for 6 months after an index event, unless new SARS-CoV-2 variants with demonstrated vaccine resistance are present in the community;
Routine screening of asymptomatic individuals using RT-PCR tests before TTE is not recommended;
Routine screening of asymptomatic individuals using RT-PCR tests before TEE may be considered, based on the local prevalence of COVID-19 cases;
Antigen testing for screening asymptomatic patients is not recommended;
Face masks should be worn by patients and medical personnel during TTE
Transducers must undergo disinfection after each study

Abbreviations: RT-PCR, reverse-transcription polymerase chain reaction; other abbreviations: see Table 3

personal protection is suggested in personnel prior to full vaccination, in cases of immune deficiencies or in case of emergent virus variants that may reduce vaccination efficacy. During TTE the echocardiographic laboratory staff should wear FFP2 or surgical masks (as per local policy) and probes must be disinfected between tests.

Transesophageal echocardiography during the SARS-COV-2 pandemic is recognized as a high-risk aerosol-generating procedure. In the early stages of the pandemic, indications were limited to emergency, in which test findings were crucial for the diagnostic and therapeutic processes. Currently it is recommended to reestablish full TEE echocardiographic services in patients without COVID-19, including patients with indications for structural interventions, catheter ablation, and other procedures. However RT-PCR tests must be obligatory for patients with suspected respiratory infection, as per general testing strategy, to avoid contamination of laboratories remaining in COVID-free status, while personnel protection for TEE should be implemented regardless of patients' status. At the peak of the pandemic, elective TEEs should be preceded by negative COVID-19 results also in apparently asymptomatic non-vaccinated patients. Medical personnel should always use personal protective equipment against airborne infections during TEE, irrespectively of the patient's status. Full protective gear including FFP3 face mask, eye protection (goggles or shields), and full barrier uniform is prerequisite when TEE is performed in an infected patient. When/if the pandemic is under control (as defined above), TEE examinations in asymptomatic patients need not be proceeded by RT-PCR COVID-19 testing. We do recommend, however, that surgical gloves and FFP2 (or FFP3) masks should be always used, until the end of the pandemic. Exceptions may be considered only for contacts between fully vaccinated individuals.

Stress echocardiography is a valuable option in non-COVID patients and services must be also reintroduced. Most types of stress echo (except for pacemaker rapid stress-testing) carry the risk of hyperventilation and aerosol generation, and, therefore, should be performed according to sanitary standards, like TEE in non-COVID facilities. Therefore, until the pandemic is under control, in non-pacemaker stress tests medical personnel should always use personal protective equipment against airborne infections, including FFP2 (optimally FFP3) face masks, disposable insulating gowns, protective eyewear and gloves.

Once the pandemic is under control, exceptions may be considered for contacts between fully vaccinated individuals. For recommendations see also Table 4 and Figure 4.

Impact of vaccination on echocardiographic services

The efficacy of both mRNA vaccines has been confirmed in pivotal randomized clinical trials with over 70 000 participants, including 40.9% and 42% high risk individuals and demonstrating over 95% efficacy [32, 33]. Real life data from United Kingdom (UK) and Israel, where effective vaccination programs were launched, confirm mRNA (UK and Israel) and adenoviral vaccine (UK only) efficacy. Vaccination programs proved their effectiveness also among healthcare workers [34]. Therefore, given confirmed efficacy and safety of mRNA vaccines as well as high morbidity and mortality associated with COVID-19 infections [35], we recommend universal vaccination of medical personnel and patients.

Table 5. Recommendation for vaccination of medical personnel

Experts recommend that ALL medical personnel working in the echocardiographic laboratories should be vaccinated against COVID-19 as soon as possible, regardless of antibody status or previous COVID infections, unless absolute contraindications exist (see relevant Summaries of Product Characteristics)
Time between the first and the second dose of the vaccine should be as short as possible (in case of two-dose vaccination schemes)

There is limited data about the durability of protection from the vaccines therefore this recommendation may be updated based on the available new data, but currently it is reasonable to assume that immune memory to SARS-CoV-2 lasts longer than 6 months. This may be assumed provided that no mutation is present that reduces acquired convalescent immunity and/or vaccine efficacy. For recommendations see also Table 5.

The use of personal protective equipment in the context of vaccination programs and the presence of convalescents

This paper builds upon previous authors' position statements, as far as personnel protection equipment (PPE) is concerned, but with some important modifications. Patients were previously classified into three groups:

- with confirmed COVID-19;
- with suspected COVID-19 (either symptomatic or identified by contact tracing but with unknown PCR), and
- with low probability of COVID-19 (no signs of respiratory infection and/or other early COVID symptoms, including those with recent negative molecular test).

Two groups are added to this classification:

- convalescents within 6 months following COVID-19 and
- vaccinated individuals within 6 months following a completed vaccination, at least 7 days after the second dose (recommendations may be extended over the next 6-month period once more complete data on the mid-term vaccine efficacy is available).

Recommendations regarding personal protective equipment use in the echocardiographic laboratories

Non-vaccinated healthcare professionals (including those who received only one dose of the vaccine) should keep on wearing previously recommended adequate PPE including FFP3 masks or equivalent respirators, appropriate gown and eye protection while performing examinations in groups 1 and 2. If PPE supplies are adequate, healthcare professionals examining group 3 patients should wear FFP2 masks rather than surgical masks (changed recommendation) until the pandemic is under control. The same recommendations apply to vaccinated healthcare professionals. In the case of asymptomatic patients belonging to groups 4 and 5 the following recommendations apply:

- non-vaccinated healthcare professionals (including those who received only one dose of the vaccine) should continue wearing previously recommended adequate PPE including FFP2 or FFP3 masks or equivalent respirators;
- vaccinated healthcare professionals (only those who received full cycle) should wear previously recommended, adequate full PPE for TEE with FFP2 mask rather than surgical mask, until the pandemic is under control;
- for TTE, FFP2 masks rather than surgical masks should be worn, together with disposable gloves, until the pandemic is under control;
- recommendations may be eased, when the pandemic is under control, but despite the fact that some regulators accept fully vaccinated people gathering indoors without masks, we propose that until the end of the pandemic also vaccinated personnel and patients should wear face masks, especially during aerosol-generating procedures like echocardiographic examinations.

It is important to note that current recommendations have been issued at a time of uncontrolled spread of the infection and in the absence of robust national systems for emergent virus variants tracking, and the lack of sufficient knowledge about the efficacy of the vaccines towards these variants. Therefore, authors recommend echocardiographic laboratory directors to regularly update their knowledge about the COVID-19 pandemic.

Article information

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Expert opinion of a Working Group on Leadless Pacing appointed by the National Consultant in Cardiology and the Board of the Heart Rhythm Section of the Polish Cardiac Society

Maciej Kempa[1], Przemysław Mitkowski[2], Oskar Kowalski[3], Maciej Sterliński[4], Andrzej Przybylski[5, 6], Jarosław Kaźmierczak[7]

Reviewers: Jerzy Krzysztof Wranicz[8], Marcin Grabowski[9]

[1]Department of Cardiology and Electrotherapy, Medical University of Gdansk, Gdańsk, Poland
[2]1st Department of Cardiology, Chair of Cardiology, Karol Marcinkowski University of Medical Sciences, Poznań, Poland
[3]Department of Human Nutrition, School of Public Health in Bytom Silesian Medical University in Katowice, Silesian Center of Heart Disease in Zabrze, Zabrze, Poland
[4]1st Arrhythmia Department National Institute of Cardiology, Warszawa, Poland
[5]Medical College, University of Rzeszow, Rzeszów, Poland
[6]Cardiology Department with the Acute Coronary Syndromes Subdivision, Clinical Provincial Hospital No 2, Rzeszów, Poland
[7]Department of Cardiology, Pomeranian Medical University, Szczecin, Poland
[8]Department of Electrocardiology, Central University Hospital, Medical University of Lodz, Łódź, Poland
[9]1st Chair and Department of Cardiology, Medical University of Warsaw, Warszawa, Poland

Correspondence to:
Maciej Kempa, MD, PhD, Department of Cardiology and Electrotherapy, Medical University of Gdansk, Dębinki 7, 80–211 Gdańsk, Poland, phone: +48 58 349 39 10, e-mail: kempa@gumed.edu.pl

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ABSTRACT

Permanent cardiac pacing is a recognized method of treatment of patients with sick sinus syndrome and/or atrioventricular conduction disturbances. Implantation of a traditional pacing system with transvenous leads is associated with a risk of complications, such as pneumothorax perforation of cardiac wall or cardiac device-related infection. An alternative method that may be used for permanent cardiac pacing is represented by the leadless pacemaker, implanted directly into the target cardiac chamber. Such devices have been implanted in Poland since 2016, but the number of procedures is limited due to the lack of clear reimbursement rules.

The expert panel appointed by the National Consultant in Cardiology and the Executive Board of the Heart Rhythm Section of the Polish Cardiac Society presents a statement on the use of a leadless pacemaker in Polish conditions. The statement present streatment method and results of clinical studies that confirm its safety and efficacy, indications and contraindications for its use, and precise requirements to be fulfilled by the implanting centers.

Key words: leadless pacemaker, expert opinion

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INTRODUCTION

Permanent cardiac pacing is a method of treatment commonly used in patients with bradycardia due to sinus node disease and/or atrioventricular conduction disturbances [1]. A pacemaker (PM) consists of a device can, containing the battery and the processor controlling its operation, and the lead or leads, routed transvenously into the target cardiac chambers. Implantation of a PM with endocardial leads is associated with a risk of complications during the procedure. Those complications include pneumothorax, perforation of heart chambers and dislocations [2]. The use of endocardial leads also increases the risk of lead-dependent endocarditis [3]. Last but not least, the leads are the main source of problems leading to malfunction of pacing systems, mainly due to their mechanical damage. Infections of the PM pocket, developing in the postoperative period or later, as a result of progressive skin damage or developing decubitus, constitute another crucial problem

of electrotherapy. Due to those reasons, the development of a leadless cardiac pacemaker (LCP), implanted directly into the cardiac chambers, has been carried out for many years now [5]. Currently, the PM produced by Medtronic company (Micra Transcatheter Pacing System) is the only available LCP, and therefore the majority of publications presenting the outcomes of this method are based on the analyses of the use of that particular system. One might expect though, that in the course of time other manufacturers will also introduce their own devices of that type.

CONSTRUCTION AND OPERATION OF THE LCP

The currently available LCP weighs 1.75 g, has a volume of 0.8 cm^3 and 26 mm of length. The implantation procedure involves the introduction of a vascular sheath of an outer diameter of 27 Fr through the femoral vein into the right ventricle. In the next step, having confirmed the appropriate placement of the sheath, the pacemaker's body is released from its end and fixed in the interventricular septum by means of special nitinol tines. Once stimulation threshold and appropriate sensing have been confirmed, the device is finally separated from the guiding catheter and left in the cardiac chamber. The operating parameters of the pacemaker are entirely programmable, both sensing and pacing current (energy and the pulse width), which makes the device operation identical to the PM system with transvenous leads. Adaptation of pacing rate to the physical activity is also available (rate-responsive mode). Magnetic resonance imaging is also possible in patients with that type of pacing system [6].

The leadless pacemaker is currently available in two versions the VR version — performing pacing in VVI(R) mode and the AV version — offering a possibility of ventricular pacing triggered by atrial activity (the VDD mode). This is acquired by using an accelerometer that effectively senses vibrations associated with blood flow through the tricuspid valve. Research data show that atrio-ventricular synchrony may be acquired in nearly 90% of heart beats [7–9]. The limitation of this device is, however, the relatively low upper sinus rate tracked in VDD mode, and above that rate, the device automatically switches into VVIR mode. The device life is estimated at 8–12 years, depending on the percentage of paced beats and pacing threshold.

CURRENT KNOWLEDGE ABOUT THE SAFETY OF USE AND EFFICACY OF LCP

The research data collected so far confirm the safety of use and efficacy of LCP. A procedural success rate of 99.2% was reported for the very first study of 725 patients who underwent PM implantation. During the follow-up of 6 months, serious complications were observed in 25 patients, resulting mainly from mechanical damage to the heart wall or femoral vein, that occurred during the implantation procedure [10]. During follow-up prolonged up to 12 months, 96% of patients were free from serious complications of the therapy, and thus the rates of serious complications were reduced by 48% in comparison with patients having transvenous systems, as reported in earlier studies [11]. It has been thereby confirmed that the incidence of complications during implantation of LCP is lower compared to a traditional PM, the reoperation rate is lower, and final pacing and sensing parameters are stable. In another study, including 795 patients, LCP was successfully implanted in 99.6% of cases and serious complications occurred in 1.5% of patients during 1-month follow-up [12]. In the follow-up period extended to 12 months, altogether including 1817 patients, serious complications were reported in 2.7% of patients, which equals to 63% reduction in comparison with the patients undergoing PM implantation with transvenous leads [13].

Although the leadless pacemaker offers a valuable alternative for the commonly used transvenous systems, is not free from certain limitations. Implantation technique, small size, and healing into the heart wall may result in significantly more difficult removal of the device if such a necessity occurs [14–16]. LCP cannot be used in patients with a filter in the inferior vena cava, with mechanical tricuspid valve, or in the case of femoral vein anatomy precluding the introduction of a sheath size required for LCP implantation. The procedure is also contraindicated if there is any risk of potential interference with other previously implanted devices or intolerance of materials that the device is made of. Nonetheless, LCP is a cardiac pacing modality for patients without vascular access needed for traditional PM implantation, or patients with skin lesions that increase risk of infection of a transvenous system. Moreover, LCP may be a safe therapeutic option for patients with infective complications of previously implanted transvenous systems, or at high risk of such events [17]. Of note, in an obvious manner, the use of LCP eliminates the risk of endocardial lead-related complications, as well as local complications affecting the PM pocket, which have always been the weak point of traditional permanent cardiac pacing.

Leadless cardiac pacemaker implantations have been performed in Poland since January 2016, however, its use is limited by the lack of clear rules for reimbursement, and it follows individual applications to the National Health Fund or is performed as part of clinical trials.

A working group appointed by the National Consultant in Cardiology and the Board of the Heart Rhythm Section of the Polish Cardiac Society, having analyzed the available data and related it to participants' personal experience, issues an opinion on the use of leadless pacing systems in Polish conditions.

RECOMMENDATIONS FOR IMPLANTATION OF A LCP

A. Implantation of a leadless cardiac pacemaker should be considered (class IIA of recommendations) in the following clinical settings in patients qualified for permanent cardiac pacing:

1. Lack of vascular access or other reasons precluding or significantly limiting the possibility of performing a standard transvenous implantation

This recommendation applies to the damage of the vascular system, both the subclavian vein and superior vena cava, resulting from an illness, iatrogenic causes, the use of vascular ports and other similar situations, as well as congenital abnormalities and anomalies in the cardiovascular system, and the history of their treatment (e.g. the history of tricuspid valve repair or implantation of a tricuspid bioprosthesis).

2. Recurrent or permanent focal or systemic inflammation, that may lead to (or led in the past) infective endocarditis

This recommendation, for example, includes patients with infected orthopedic or other implants, in whom infection of the implant is difficult to control and radical treatment is not planned. It also applies to patients with chronic inflammatory disorders of the skin or other organs, that increase the risk of infective endocarditis.

3. Comorbidities (or necessary medical interventions) that led to infective endocarditis, and therefore to the extraction of the traditional cardiac pacing system

This recommendation applies to patients undergoing dialysis or other analogous therapeutic interventions requiring permanent vascular access, as well as patients on long-term immunosuppressive treatment, or with other comorbidities that significantly and permanently impair the immunity.

4. Comorbidities (or medical interventions) that led to local damage within the pocket of the implanted pacemaker, resulting in its removal, or conditions in which the implanted device restricts or precludes the use of specific oncologic therapeutic interventions (e.g. radiotherapy)

This recommendation applies to patients undergoing radiotherapy in the course of oncologic treatment if it overlaps the pocket of the traditionally implanted pacemaker.

B. Implantation of a leadless cardiac pacemaker may be considered (class IIB of recommendations) in the following clinical settings in patients qualified for permanent cardiac pacing:

1. Comorbidities (or medical interventions) leading to an increased risk of infective endocarditis

This recommendation applies to patients undergoing dialysis or other analogous therapeutic interventions requiring permanent vascular access, as well as patients on long-term immunosuppressive treatment, or with other comorbidities that significantly and permanently impair the immunity.

2. Comorbidities or clinical situations (or medical interventions) possibly leading to local damage of the pacemaker pocket or the leads

This recommendation applies to patients undergoing radiotherapy or in whom radiotherapy is considered in the course of oncologic treatment if it overlaps the traditional pacemaker pocket, and implantation of a traditional pacemaker is planned. This recommendation also applies to patients potentially or chronically pacemaker dependent, in whom the risk of mechanical damage to the transvenous lead(s) is increased due to the nature of their work or limited supervision because of other socio-medical factors.

3. Comorbidities (or medical interventions) requiring permanent or periodical vascular access

This recommendation applies to patients, in whom there is an increased probability that vascular access may be needed for reasons other than implantation of a cardiac pacemaker.

4. Anticipated small percentage of pacing in young patients with a long life expectancy

This recommendation applies to young patients, requiring only ventricular pacing or with only occasional atrioventricular conduction disturbances. In such cases, the possible risks and benefits of the procedure should be evaluated with special care.

C. Leadless cardiac pacemaker should be avoided (class III of recommendations) in the following clinical situations in patients qualified for permanent cardiac pacing:

1. Sick sinus syndrome, especially with maintained retrograde ventriculoatrial conduction, in case of chronic bradycardia, when a high percentage of ventricular pacing is anticipated

This contraindication applies to patients with chronic (non-paroxysmal) sinus bradycardia, in whom, due to the

high percentage of pacing and maintained retrograde conduction, atrial contraction occurs nearly simultaneously with ventricular contraction (when atrioventricular valves are closed), causing the symptoms of pacemaker syndrome.

In all of the abovementioned recommendations, in case of maintained sinus rhythm, implantation of a leadless pacemaker capable of ventricular pacing triggered by atrial rhythm should be preferred.

REQUIREMENTS FOR CENTERS IMPLANTING LCP

Apart from the centers that have already performed implantation of LCP systems, cardiology centers that have the most considerable experience in performing cardiac electrophysiology and electrotherapy procedures, as well as in the treatment of early and late complications of such procedures, including transvenous lead extractions should be preferred. The availability of cardiac surgery in the center is essential. The possibility of performing outpatient follow-up visits of patients after electrotherapy and electrophysiology procedures is indispensable.

It is recommended to introduce the national registry of leadless pacemaker implantations and regular supervision from appropriate regulatory boards over the centers performing such procedures.

SUMMARY

Leadless pacemaker implantation is an important therapeutic option for patients requiring permanent cardiac pacing, in whom the use of a transvenous system is impossible or is associated with a high risk of complications. The possibility of maintaining vascular access intact for the purpose of future treatment and interventions is an important merit. It should be noted that the number of Polish centers utilizing this method is small, and their experience limited, which is mainly due to the current reimbursement regulations. The authors of that statement believe that introduction of clear reimbursement rules and fees covering entirely the costs of the procedure will result in increased availability of that method to fully satisfy the demand in Poland, which is estimated at approximately 300 procedures annually.

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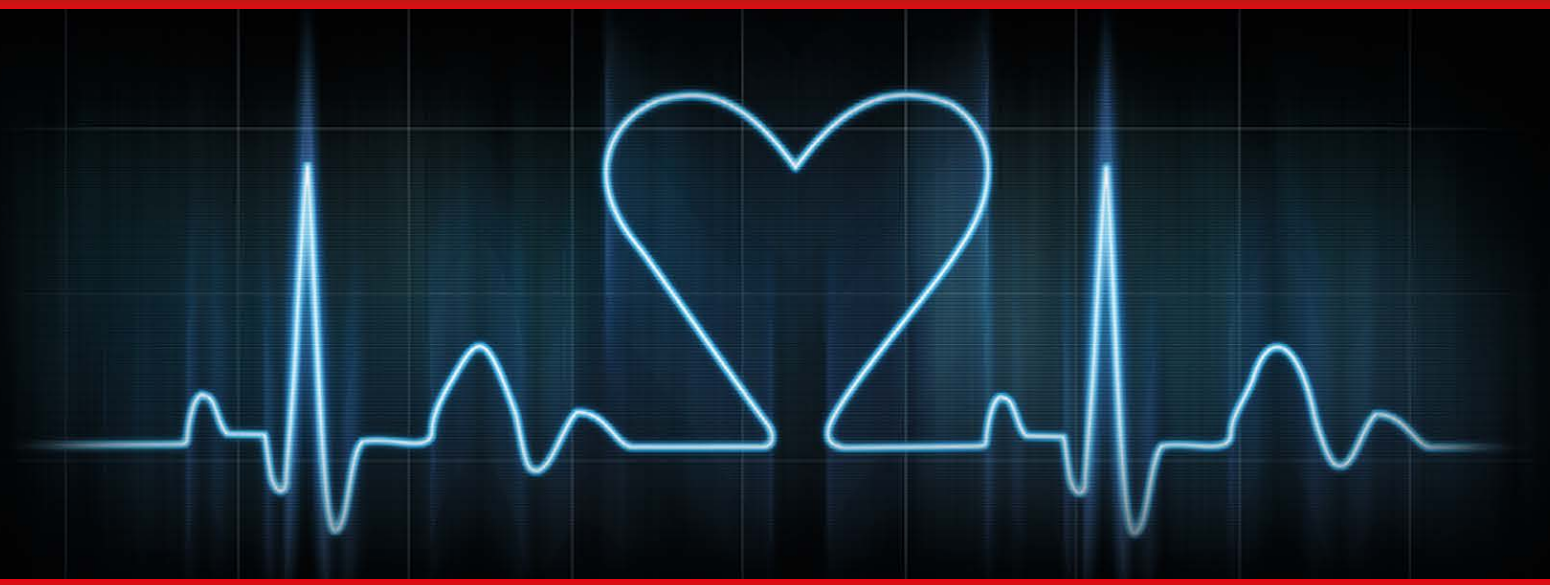

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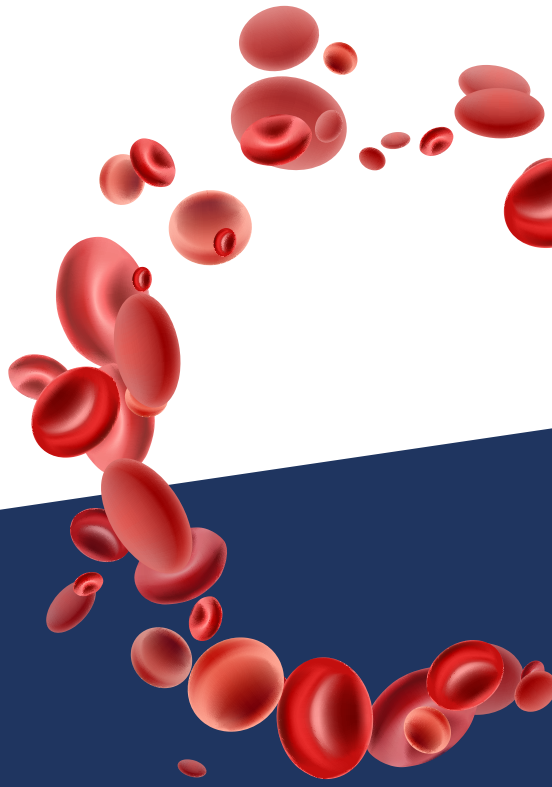

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