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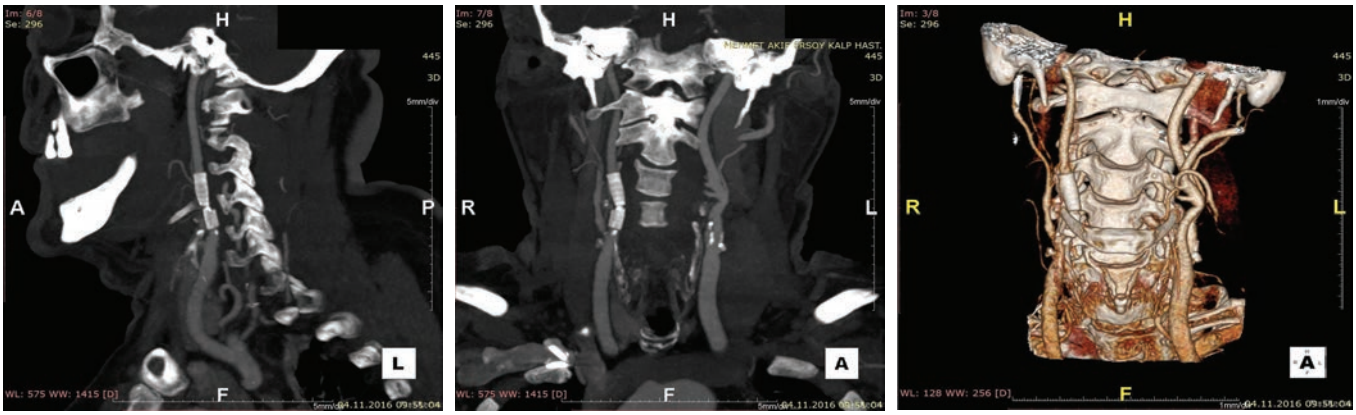

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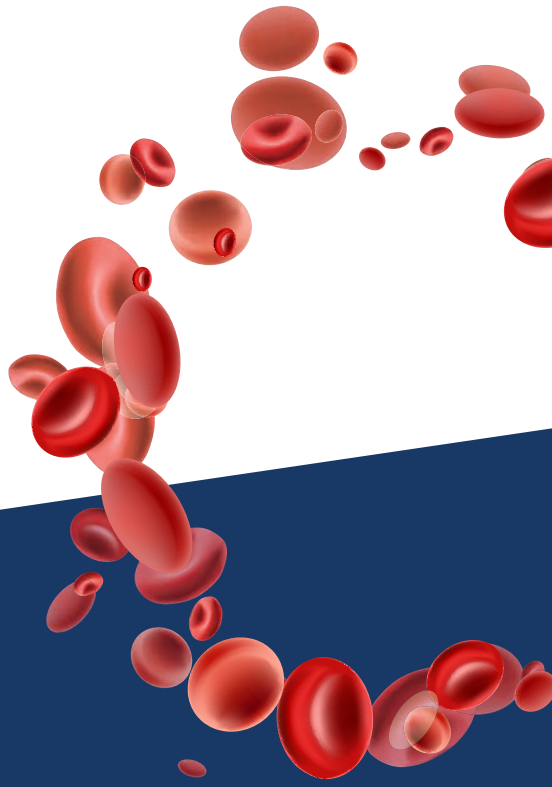

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KARDIOLOGIA POLSKA
Polish Heart Journal

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Is cardiac magnetic resonance ready for aortic regurgitation?

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Related article
by Haberka et al.,
see p. 965

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Current European Society of Cardiology and American Heart Association guidelines highlight the importance of echocardiography for the assessment of aortic regurgitation (AR), since it is widely available and allows for comprehensive evaluation of multiple factors in one exam, such as valve morphology, jet angle, pressure half time as well as quantification of regurgitant volume (RVol) and regurgitant fraction (RF), left ventricular (LV) dimensions and function [1, 2]. However, standard 2D echocardiography is often limited by anatomic coverage, and limited inter-, intra-observer, and sonographer variability. As a diagnostic alternative, cardiac magnetic resonance imaging (CMR) offers superior image contrast with flexible 2D or 3D image orientation and is considered the clinical reference standard for LV and right ventricular (RV) volumetry [3]. In addition, 2D phase-contrast CMR can reliably measure blood flow in the aorta and has been shown to provide reproducible AR RVol and RF, which are crucial metrics associated with the heart valve disease severity [4]. However, despite the benefits of CMR over transthoracic echocardiography (TTE), only limited data on the systematic comparison of both modalities have been presented.

In the current issue of *Kardiologia Polska* (*Polish Heart Journal*), Haberka et al. present an interesting and timely study comparing TTE and CMR for the assessment of AR in a group of 49 patients [5]. The study cohort included a broad range of AR severity determined by the quantitative and semiquantitative integrative approach described in American Society of Echocardiography guidelines [3]. AR severity for all patients was also assessed using RVol and RF quantified by 2D phase-contrast CMR with the same cutoffs for the grading used by TTE. In line with previous studies [4, 6, 7], the authors demonstrated that TTE overestimated AR severity, RVol, and RF in comparison to CMR. Further investigation revealed that factors associated with AR grading discrepancies between CMR and TTE were the presence of eccentric AR flow jets (≥40° deviation from the axis perpendicular to the aortic valve). This finding illustrates a well-known limitation of 2D Doppler echocardiography which can only quantify the AR flow jet velocity component parallel to the ultrasound beam. As a result, the increased eccentricity of the AR flow jets can compromise the accuracy of TTE. However, whether the presence of an eccentric jet leads to over- or underestimation by TTE was not discussed by the authors. In addition to AR assessment, the authors compared the diagnostic value of CMR vs TTE for detecting LV remodeling impacted by AR. Their study found that, for both modalities, LV end-diastolic volume (EDV) significantly correlated with RVol, which supports the potential benefit of using EDV as an indicator of LV dilatation associated with AR [8, 9]. Furthermore, LV EDV and ejection fraction (LVEF) were higher for CMR compared to TTE. Since LV EDV and LVEF are both used to determine (surgical) intervention, this finding implies that CMR might be preferable in monitoring the progression of AR.

There are a few limitations: As the authors mentioned, there were only 5 cases of severe AR, which limits the clinical transferability of results. Second, for this type of study, it is of importance to ensure the discrepancy of measurements is primarily driven by the difference

in the technique itself and not by physiological conditions between TTE and CMR examination. Blood pressure, heart rate, and time between the TTE and CMR exams would have been good indicators for changes in subject physiology but were not reported. Third, accurate flow quantification use of 2D phase-contrast CMR requires careful 2D analysis plane orientation [10] along the aorta [11], correction for eddy-current induced background phase offset [12], and the use of sufficiently high-velocity encoding sensitivity. Finally, only half of the study cohort (n = 24) were used to compare AR flow metrics between the two modalities due to the limited applicability of the proximal isovelocity surface area (PISA) method. PISA is less suitable for AR than mitral regurgitation as the visualization of flow convergence in color Doppler echocardiography is often restricted by thickening and/or calcification of the aortic valve which is also the case in this study cohort. As the focus was to compare TTE vs CMR, other indirect volumetric methods (e.g., subtracting mitral valve stroke volume from LV stroke volume) [3] available by TTE could have been an alternative to PISA in order to improve the statistical power of the study results.

Nonetheless, the data presented in this study by Haberka et al. adds valuable information to understand the differences between the two modalities in AR assessment. Further investigation is still required to demonstrate the prognostic value of CMR-based AR assessment. TTE will thus likely remain the first-choice imaging modality to evaluate and follow-up patients with AR in clinical practice due to its wide availability. Nevertheless, the advantages of CMR are evident in its ability to provide robust and reproducible aortic flow quantification and assessment of global LV and RV function metrics. CMR could thus serve as an important clinical tool for patients with severe AR who require an accurate and comprehensive diagnosis to determine the need and timing of intervention.

Article information

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REFERENCES

1. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017; 38(36): 2739–2791, doi: 10.1093/eurheartj/ehx391, indexed in Pubmed: 28886619.
2. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021; 143(5): e72–e7e227, doi: 10.1161/CIR.0000000000000923, indexed in Pubmed: 33332150.
3. Zoghbi W, Adams D, Bonow R, et al. Recommendations for noninvasive evaluation of native valvular regurgitation A report from the american society of echocardiography developed in collaboration with the society for cardiovascular magnetic resonance. J Indian Acad Echocardiogr Cardiovasc Imaging. 2020; 4(1): 58, doi: 10.4103/2543-1463.282191.
4. Cawley PJ, Hamilton-Craig C, Owens DS, et al. Prospective comparison of valve regurgitation quantitation by cardiac magnetic resonance imaging and transthoracic echocardiography. Circ Cardiovasc Imaging. 2013; 6(1): 48–57, doi: 10.1161/CIRCIMAGING.112.975623, indexed in Pubmed: 23212272.
5. Haberka M, Bałys M, Gąsior Z, et al. Aortic regurgitation and left ventricle remodeling on cardiac magnetic resonance and transthoracic echocardiography. Kardiol Pol. 2021; 79(9): 965–971, doi: 10.33963/KP.a2021.0047, indexed in Pubmed: 34176113.
6. Gelfand EV, Hughes S, Hauser TH, et al. Severity of mitral and aortic regurgitation as assessed by cardiovascular magnetic resonance: optimizing correlation with Doppler echocardiography. J Cardiovasc Magn Reson. 2006; 8(3): 503–507, doi: 10.1080/10976640600604856, indexed in Pubmed: 16755839.
7. Kammerlander AA, Wiesinger M, Duca F, et al. Diagnostic and prognostic utility of cardiac magnetic resonance imaging in Aortic regurgitation. JACC Cardiovasc Imaging. 2019; 12(8 Pt 1): 1474–1483, doi: 10.1016/j.jcmg.2018.08.036, indexed in Pubmed: 30448117.
8. Myerson SG, d'Arcy J, Mohiaddin R, et al. Aortic regurgitation quantification using cardiovascular magnetic resonance: association with clinical outcome. Circulation. 2012; 126(12): 1452–1460, doi: 10.1161/CIRCULATIONAHA.111.083600, indexed in Pubmed: 22879371.
9. Uretsky S, Argulian E, Supariwala A, et al. Quantification of left ventricular remodeling in response to isolated aortic or mitral regurgitation. J Cardiovasc Magn Reson. 2010; 12(11): 32–1088, doi: 10.1186/1532-429X-12-32, indexed in Pubmed: 20497540.
10. Tang C, Blatter DD, Parker DL. Accuracy of phase-contrast flow measurements in the presence of partial-volume effects. J Magn Reson Imaging. 1993; 3(2): 377–385, doi: 10.1002/jmri.1880030213, indexed in Pubmed: 8448400.
11. Iwamoto Y, Inage A, Tomlinson G, et al. Direct measurement of aortic regurgitation with phase-contrast magnetic resonance is inaccurate: proposal of an alternative method of quantification. Pediatr Radiol. 2014; 44(11): 1358–1369, doi: 10.1007/s00247-014-3017-x, indexed in Pubmed: 24939669.
12. Gatehouse PD, Rolf MP, Graves MJ, et al. Flow measurement by cardiovascular magnetic resonance: a multi-centre multi-vendor study of background phase offset errors that can compromise the accuracy of derived regurgitant or shunt flow measurements. J Cardiovasc Magn Reson. 2010; 12: 5, doi: 10.1186/1532-429X-12-5, indexed in Pubmed: 20074359.

Hypoxic induction of atrial natriuretic peptide (factor) secretion

An inflammatory interleukin-18 pathway is involved in the control of cardioprotective molecule

Mikko Nikinmaa

Department of Biology, University of Turku, Finland

Related article
by Li et al.,
see p. 972

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In 1985 a seminal article by Lang et al. [1] was published in *Nature*. It described an atrial factor, which is secreted in response to volume load. This changed the concept of the heart from being just a pump to also being an endocrine organ. The finding of atrial natriuretic peptide (ANP = ANF, atrial natriuretic factor) was followed by the discovery of other cardiac peptides such as brain-type cardiac peptide (BNP), which instead of atria is mainly secreted by ventricles, and C-type cardiac peptide (CNP). In addition, vertebrate groups other than mammals have a different repertoire of peptides. Natriuretic peptides or cardiac peptides (ANP, BNP, and CNP) play a role at least in volume regulation, hemodynamics and the control of heart function. They protect the heart, for example, during ischemia/reperfusion injury. In addition, the diuresis and increasing vascular permeability, which are effects exerted by cardiac peptides, decrease total blood volume. This, in turn, will increase the oxygen-carrying capacity of a unit volume of blood, as a constant number of erythrocytes is in a reduced plasma volume. Thus, cardiac peptides may also function in the control of oxygen transport.

The regulation of ANP secretion has been shown to depend on mechanical stress on the myocytes: the more you stretch the heart, the more pronounced the increase of cardiac peptide secretion is [1, 2]. Also hypoxia, i.e. decreased oxygen level, causes natriuretic peptide release [3]. The best known hypoxic or even anoxic condition of the heart is infarct, but reduced oxygenation in mammals also occurs at high altitudes. Hypoxia is caused by any mismatch between oxygen consumption and blood perfusion of the tissue or the animal: in heart infarct, the perfusion of cardiac cells is reduced because of impaired coronary circulation, at high altitude coronary circulation is not compromised, but the amount of oxygen it contains in a unit volume is decreased. It has initially been considered that also the hypoxia-induced increase in natriuretic peptide secretion would be the result of mechanical stretch occurring in hypoxic cardiac cells. However, accumulating evidence indicates that hypoxia can affect natriuretic peptide release even in the absence of stretch [4] (note that this editorial considers the secretion of both A- and B-type natriuretic peptides to be regulated similarly [5]). In this context, it is notable that virtually all the studies with isolated hearts or cardiac cells have been done with physiological saline, which has the oxygen capacity of ca. 1/30 as compared to blood. Consequently, the cells of perfused hearts may become hypoxic whenever they are, e.g. stretched, making it difficult to differentiate between stretch and hypoxia as the stimuli causing natriuretic peptide release [5]. Furthermore, provided that hypoxia is the stimulus for natriuretic peptide release, isolated heart preparation and the heart in an intact animal may behave differently, since the intact, blood-perfused heart is not experiencing hypoxia in conditions making the isolated heart hypoxic. In addition to the hypoxic increase of natriuretic peptide secretion, also their clearance from the circulation may be affected by hypoxia. There are natriuretic peptide receptors in diverse tissues, and the consensus is that they

are largely clearance receptors, which decrease in numbers in hypoxia leading to reduced clearance of the peptide.

The regulatory pathway of hypoxia-induced natriuretic peptide secretion has, up to now, remained poorly characterized [6]. It may involve the hypoxia-inducible factor (HIF), and could directly be controlled by it, as the genes encoding natriuretic peptides have hypoxia response elements in their promoter region [7] and as their transcription is increased by HIF [8]. In the current issue of *Kardiologia Polska (Polish Heart Journal)* Li et al. [9] presented studies showing that the Src-Interleukin-18 (Src-IL-18) pathway regulates ANP production in hypoxic rat atria. Subjecting atria to hypoxic conditions (oxygen tension around 55 mm Hg) they showed that hypoxia upregulated the expression of non-receptor tyrosine kinase Src, causing an increase in the expression of IL-18 and its two receptors through activation of RhoA signaling. The increase in IL-18 was followed by upregulated expression of ATF3, TCF3/LEF1, and TCF4/LEF1, leading to an induction of ANP secretion in hypoxia.

Overall, the effects of the inflammatory cytokine IL-18 on the heart are deleterious: it induces myocardial hypertrophy, loss of contractility of cardiomyocytes, and apoptosis leading to myocardial dysfunction [9, 10]. In contrast, those of natriuretic peptides are cardioprotective [3]. This may appear contradictory but is teleologically attractive. Whenever there is an inflammatory heart condition leading to reduced oxygenation in cardiac cells, the very agent, IL-18, involved in the inflammation, will promote natriuretic peptide secretion with a cardioprotective effect.

The whole pathway from hypoxia to IL-18 induction may involve the well-known hypoxic stimulation of ET-1 (endothelin 1) expression, which increases Src expression [9]. Reactive oxygen species (ROS) may be signaling molecules involved [11]. ROS also appear to be behind the ischemia/reperfusion injury: after the ischemic period, reperfusion causes a surge of ROS to the reperfused area. Although the authors did not address the question of whether HIF is involved also in the hypoxia response pathway they describe, this is quite possible. First, HIF is involved in inflammation [12]. Second, HIF is associated with the expression of both ET-1 and Src [13, 14]. Third, although the findings are somewhat controversial, ROS are also involved in the control of HIF [15].

The study by Li et al. [9] helps us in understanding the mechanisms of regulation of natriuretic peptide secretion in a hypoxic heart. Furthermore, as their results connect the deleterious IL-18 with the cardioprotective ANP, the findings have value for the treatment of heart conditions, which are associated with hypoxia. However, up to now, information on the pathways controlling the natriuretic peptide secretion in the hypoxic heart has been delivered in small fragments. Maybe the time would now be right to combine the bits and pieces in order to see the full picture of natriuretic peptide release in hypoxia?

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REFERENCES

1. Lang RE, Thölken H, Ganten D, et al. Atrial natriuretic factor — a circulating hormone stimulated by volume loading. Nature. 1985; 314(6008): 264–266, doi: 10.1038/314264a0, indexed in Pubmed: 3157062.
2. Ruskoaho H. Atrial natriuretic peptide: synthesis, release, and metabolism. Pharmacol Rev. 1992; 44(4): 479–602, indexed in Pubmed: 1480667.
3. Arjamaa O, Nikinmaa M. Hypoxia regulates the natriuretic peptide system. Int J Physiol Pathophysiol Pharmacol. 2011; 3(3): 191–201, indexed in Pubmed: 21941610.
4. Arjamaa O, Vuolteenaho O, Kivi E, et al. Hypoxia increases the release of salmon cardiac peptide (sCP) from the heart of rainbow trout (Oncorhynchus mykiss) under constant mechanical load in vitro. Fish Physiol Biochem. 2014; 40(1): 67–73, doi: 10.1007/s10695-013-9824-4, indexed in Pubmed: 23813187.
5. Anttila K, Streng T, Pispa J, et al. Hypoxia exposure and B-type natriuretic peptide release from Langendorff heart of rats. Acta Physiol (Oxf). 2017; 220(1): 28–35, doi: 10.1111/apha.12767, indexed in Pubmed: 27496203.
6. Arjamaa O, Nikinmaa M. Natriuretic peptides in hormonal regulation of hypoxia responses. Am J Physiol Regul Integr Comp Physiol. 2009; 296(2): R257–R264, doi: 10.1152/ajpregu.90696.2008, indexed in Pubmed: 19005014.
7. Chun YS, Hyun JY, Kwak YG, et al. Hypoxic activation of the atrial natriuretic peptide gene promoter through direct and indirect actions of hypoxia-inducible factor-1. Biochem J. 2003; 370(Pt 1): 149–157, doi: 10.1042/BJ20021087, indexed in Pubmed: 12413399.
8. Weidemann A, Klanke B, Wagner M, et al. Hypoxia, via stabilization of the hypoxia-inducible factor HIF-1alpha, is a direct and sufficient stimulus for brain-type natriuretic peptide induction. Biochem J. 2008; 409(1): 233–242, doi: 10.1042/BJ20070629, indexed in Pubmed: 17822384.
9. Li X, Wei CX, Wu CZ, et al. Src-IL-18 signaling regulates the secretion of atrial natriuretic factor in hypoxic beating rat atria. Kardiol Pol. 2021; 79(9): 972–979, doi: 10.33963/KP.a2021.0051, indexed in Pubmed: 34176112.
10. Doi T, Sakoda T, Akagami T, et al. Aldosterone induces interleukin-18 through endothelin-1, angiotensin II, Rho/Rho-kinase, and PPARs in cardiomyocytes. Am J Physiol Heart Circ Physiol. 2008; 295(3): H1279–H1287, doi: 10.1152/ajpheart.00148.2008, indexed in Pubmed: 18660453.
11. Wu CZ, Li X, Hong L, et al. NOX4/Src regulates ANP secretion through activating ERK1/2 and Akt/GATA4 signaling in beating rat hypoxic atria. Korean J Physiol Pharmacol. 2021; 25(2): 159–166, doi: 10.4196/kjpp.2021.25.2.159, indexed in Pubmed: 33602886.
12. Imtiyaz HZ, Simon MC. Hypoxia-inducible factors as essential regulators of inflammation. Curr Top Microbiol Immunol. 2010; 345: 105–120, doi: 10.1007/82_2010_74, indexed in Pubmed: 20517715.
13. Tipoe GL, Lau TYH, Nanji AA, et al. Expression and functions of vasoactive substances regulated by hypoxia-inducible factor-1 in chronic hypoxemia. Cardiovasc Hematol Agents Med Chem. 2006; 4(3): 199–218, doi: 10.2174/187152506777698290, indexed in Pubmed: 16842206.
14. Liu P, Gu Y, Luo J, et al. Inhibition of Src activation reverses pulmonary vascular remodeling in experimental pulmonary arterial hypertension via Akt/mTOR/HIF-1 signaling pathway. Exp Cell Res. 2019; 380(1): 36–46, doi: 10.1016/j.yexcr.2019.02.022, indexed in Pubmed: 30802452.
15. Görlach A, Kietzmann T. Superoxide and derived reactive oxygen species in the regulation of hypoxia-inducible factors. Methods Enzymol. 2007; 435: 421–446, doi: 10.1016/S0076-6879(07)35022-2, indexed in Pubmed: 17998067.

REVIEW

Mavacamten — a new disease-specific option for pharmacological treatment of symptomatic patients with hypertrophic cardiomyopathy

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ABSTRACT

Current pharmacotherapy for hypertrophic cardiomyopathy (HCM) is not disease-specific and has suboptimal efficacy, often necessitating interventional treatment. EXPLORER-HCM was a phase 3, randomized, double-blind, placebo-controlled, multicenter clinical trial investigating the effects of mavacamten, a first-in-class selective cardiac myosin inhibitor, in patients with HCM, left ventricular outflow tract obstruction (LVOTO) and New York Heart Association (NYHA) class II or III symptoms. The primary endpoint was defined as either a ≥1.5 ml/kg/min increase in peak oxygen consumption (pVO_2) and ≥1 NYHA class reduction or a ≥3.0 ml/kg/min pVO_2 increase without NYHA class worsening. Secondary endpoints evaluated changes in post-exercise LVOT gradient, pVO_2, NYHA class, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS), and Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath subscore (HCMSQ-SoB). A total of 251 patients were randomized to receiving mavacamten or placebo. The primary endpoint and all secondary endpoints were met significantly more frequently in the mavacamten arm versus placebo. The safety profile of mavacamten was similar to that of placebo. In conclusion, disease-specific treatment with mavacamten in patients with obstructive HCM led to reduced LVOTO and improvement in both objective functional parameters and patient-related health status.

Key words: hypertrophic cardiomyopathy, left ventricular outflow obstruction, mavacamten

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiomyopathy, with a 1:500 prevalence in the general population [1]. The diagnosis of HCM is based on demonstrating significant thickening of at least one myocardial segment of the left ventricle. Regardless of the imaging technique (echocardiography, magnetic resonance, computed tomography), a cut-off value of 15 mm in diastole has been adopted. Additionally, in first-degree relatives of patients with confirmed HCM, a wall thickness of ≥13 mm is deemed sufficient for diagnosis. The core pathomechanism of HCM is represented by the enhanced affinity between actin and myosin filaments leading to hypercontractility, left ventricular diastolic dysfunction, and in about 70% of patients, dynamic left ventricular outflow tract obstruction (LVOTO). So far, roughly 1500 mutations in about 11 genes encoding different proteins of the sarcomere were identified. Most frequently (>70%), genes encoding the beta-myosin heavy chain-7 and myosin-binding C3 proteins are affected. Recent investigations in understudied populations offer local and global verification of the genetic mutation underlying HCM [2, 3]. The key features of HCM are unexplained wall thickening, abnormal relaxation with increased filling pressures, myocardial fibrosis. Clinical manifestations are heart failure (HF), atrial fibrillation (AF), ventricular arrhythmia, potentially leading to sudden cardiac death, syncope, and angina. HCM can have a nonobstructive (no-HCM) or more frequent obstructive (oHCM) form. Dynamic LVOTO related to systolic anterior motion (SAM) of the mitral valve can be present

at rest or detected after proper physiological provocative test, i.e., exercise, especially in the upright position [4–7] in up to 70% cases (sum of resting obstructive and provoked obstructive gradients) [8, 9]. Medical treatment of the HCM with severe LVOTO (gradient of ≥50 mm Hg) has been challenging, with many patients experiencing poor quality of life and often drug side effects. As the disease-specific treatment for HCM is still lacking, the current therapeutic regimens are based on empiric use of drugs such as beta-blockers (BB), verapamil, or disopyramide. The medical therapy is effective, however often associated with drug side effects, in particular in the case of disopyramide. Patients with symptoms refractory to medical therapy usually require septal reduction therapies (SRTs) which remains the most effective treatment provided it is performed in experienced high-volume centers.

UNMET CLINICAL NEEDS IN OHCM WITH LVOTO

Based on the 2014 European Society of Cardiology (ESC) guidelines, pharmacotherapy aiming to relieve the LVOTO and improve symptoms encompasses BB, non-dihydropyridine calcium channel blockers (CCB), and disopyramide (unavailable in Poland). Similar medical management is recommended in recent American Heart Association/American College of Cardiology guidelines [10–12]. Such therapies often lead to a reduction of LVOT gradient and improvement of symptoms. Still, they are often associated with clinically significant side effects, especially if combination therapy is used (BB or CCB + disopyramide). Also, the use of CCB in patients with HF and very high LVOT gradients is problematic due to their vasodilatory effects.

In the presence of LVOTO, BB became the first-line pharmacotherapy [13, 14] preferred over verapamil, reducing LVOT gradient via a negative inotropic effect. Direct comparison between propranolol and verapamil revealed that propranolol was more effective in gradient reduction, but only verapamil was able to significantly decrease New York Heart Association (NYHA) class [15]. Verapamil utility in oHCM with high resting gradients is limited by its vasodilating effects that can, infrequently, worsen gradient and symptoms [16, 17]. As such, we tend to avoid it in patients with high gradients and severe HF symptoms [16].

In the European HCM center of excellence [13, 14] nadolol is the first choice drug, considering its good tolerability, favorable electrophysiological profile, potent effect on gradients, and adequate 24-h coverage. Conversely, in the American HCM center of expertise [16] bisoprolol is the first-choice BB due to the highest beta-1 selectivity. However, at high doses of BB needed for obstruction, relief might be poorly tolerated (hypotension, bradycardia, decreased atrio-ventricular conduction, chronotropic incompetence, exacerbation of the chronic obstructive pulmonary disease, or erectile dysfunction). Verapamil, but not BB, improved coronary endothelial dysfunction [18]. Overall, the efficacy and side effect profile of the current pharmacotherapy are not optimal. Established SRTs involve surgical septal myectomy (Morrow's operation) and transcatheter alcohol septal ablation. The first one is recommended in younger, active patients with a thicker interventricular septum (IVS), higher LVOT gradient, and concurrent structural heart disease warranting, e.g., simultaneous mitral valve repair or replacement. Alternatively, the percutaneous approach is considered more suitable in the elderly, with IVS thickness below 18 mm. Septal reduction therapies effectively reduce symptoms in the majority (>95% myectomy and >75% alcohol septal ablation) of patients, however, they must be performed in experienced high-volume centers and are not widely available.

All of the above are not targeting the underlying pathophysiology of the disease. The contractile apparatus is a promising target for novel drug development; therefore, investigation for a new drug reducing LVOT gradient was crucial. In 2016 a small-molecule allosteric inhibitor of myosin was discovered (initially coded MYK-461), currently named mavacamten [19]. In contrast to non-specific inotropic negative drugs, mavacamten is a specific compound targeting the primary molecular defect of the cardiomyocyte function [20–22].

MECHANISM OF ACTION

From the pathophysiological point of view, both oHCM and noHCM are characterized by hypercontractile left ventricular myocardium despite hypertrophy status. The molecular underpinnings of hypercontractility relate to an energetically inefficient myosin. Active myosin is a composite of two myosin heads with intertwined tails. During the myosin force production cycle, there is an autoinhibited state, sometimes referred to as a super-relaxed state. With certain myosin mutations, in the HCM sarcomere, this inhibited state is shortened, leading to hyperactivation and excess ATP utilization [23–25]. Mavacamten, a first-in-class oral small molecule, targets this process directly as an allosteric modulator of cardiac β-myosin, causing reversible inhibition of actin-myosin cross-bridging (Figure 1). In detail, mavacamten stabilizes this inhibited state, effectively lengthening the time that myosin is inactive [23–25]. Mavacamten binds to myosin, stabilizes the super-relaxed conformation, and shifts the kinetics of the actin-activated phosphate release step of myosin activation, thus decreasing ATPase activity and essentially slowing interaction of myosin with actin. Although there are multiple myosin forms, Mavacamten is specific for β-myosin heavy chain, expressed in the myocardium. Mavacamten demonstrated low clearance, a high volume of distribution, long terminal elimination half-life, and high bioavailability after oral intake cross-species. Simple four-species allometric scaling led to predicted plasma clearance, the volume of distribution, and half-life of 0.51 ml/min/kg; 9.5 l/kg, and 9 days, respectively, in humans [26]. Importantly this molecule is cardiac-selective and does not influence the function of skeletal muscles.

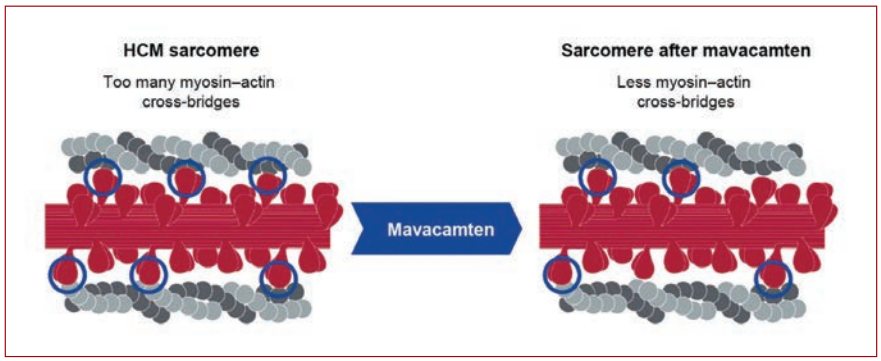

Figure 1. Mechanism of mavacamten action

STUDIES IN ANIMAL MODELS

Green et al. [19] demonstrated that chronic administration of MYK-461 during development suppresses the development of ventricular hypertrophy, cardiomyocyte disarray, myocardial fibrosis and attenuates hypertrophic and profibrotic gene expression in a mouse model of HCM. In the echocardiographic study in the feline genetic model of oHCM, treatment with mavacamten reduced contractility eliminated SAM, and relieved LVOTO [27]. The latest study assessed the effect of mavacamten on cardiac muscle contraction in two transgenic mouse lines expressing the human isoform of cardiac myosin regulatory light chain in their hearts [28]. Findings indicate that the drug reduces isometric tension and Ca^{2+}-sensitivity of contraction via decreased strong cross-bridge binding.

FIRST IN MAN STUDIES

In the first study in patients, mavacamten was evaluated in a subgroup of oHCM in the open-label PIONEER-HCM (Pilot Study Evaluating drug in Subjects With Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction) [29]. The PIONEER-HCM was a prospective, phase 2 study to evaluate the pharmacokinetics and pharmacodynamics of mavacamten. The inclusion criteria were resting LVOT gradient greater than 30 or provoked gradient greater than 50 mm Hg. The study included 21 patients. In subgroup A (n = 11), higher-dose mavacamten resulted in a significant and rapid reduction in the degree of post-exercise LVOTO (average ~90 mm Hg decrease in post-exercise LVOT gradient). In this subgroup, there was also a substantial (17%) improvement in exercise capacity (peak oxygen consumption [VO_2] + 3.5 ml/kg/min). Subgroup B (n = 10) received lower doses of mavacamten. While improvement in LVOT obstruction (average ~25 mm Hg decrease in post-exercise LVOT gradient) and exertional capacity (peak VO_2 + 1.7 ml/kg/min) were more modest, there was still significant symptom improvement. In both higher and lower doses of mavacantem, a substantial reduction in gradient was observed. Furthermore, eight participants had a decrease of LVOT gradient <30 mm Hg. Apart from positive hemodynamic changes, a beneficial lowering of serum N-terminal pro-brain natriuretic peptide (NT-proBNP) was also observed (biomarker representing myocardial wall stress). Importantly, the left ventricular ejection fraction declined by 6% to 15%, which corresponds with the expected mode of cellular action of the myosin inactivator. These positive findings set the stage for the recently presented EXPLORER-HCM (Clinical Study to Evaluate Mavacamten [MYK-461] in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy) study.

RANDOMIZED, MULTICENTER STUDIES

EXPLORER-HCM is a multicenter, phase 3, randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of mavacamten in treating symptomatic 220 patients with oHCM. EXPLORER-HCM trial enrolled adult patients with an established diagnosis of HCM, maximal LVOT gradient exceeding 50 mm Hg (at rest or provoked by Valsalva maneuver or exercise), preserved left ventricular ejection fraction (LVEF ≥55%), and NYHA class II or III HF symptoms. Moreover, patients had to be capable of performing upright cardiopulmonary exercise testing. Main exclusion criteria included a history of exercise-induced syncope or sustained ventricular tachyarrhythmia (VT) within 6 preceding months; QT interval corrected using Fridericia's formula >500 ms, AF present on screening electrocardiogram, and any AF without anticoagulation for at least 4 weeks or with insufficient rate control within 6 months before screening. Prior septal reduction therapy did not exclude a patient, provided it was performed more than 6 months before screening. Continuation of standard HCM pharmacotherapy with a BB or calcium channel blocker was allowed as long as the dosing remained unchanged for at least 2 weeks before the screening, and no modifications were expected throughout the study. The base dose of mavacamten was 5 mg qd and was individually up-titrated to a maximum of 15 mg at weeks 8 and 14 to achieve the target reduction of LVOT gradient <30 mm Hg and mavacamten plasma concentration between 350 ng/ml and 700 ng/ml. The primary composite endpoint was defined as an increase of pVO_2 by at least 1.5 ml/kg/min accompanied by at least one NYHA class reduction or an increase of pVO_2 by at least 3.0 ml/kg/min with no worsening of NYHA class. Among secondary endpoints, changes in post-exer-

cise LVOT gradient, pVO_2, percentage of patients with at least one NYHA class improvement, and cardiomyopathy questionnaires (KCCQ-CSS, HCMSQ-SoB) were evaluated.

Eligible adults with oHCM and NYHA were randomized 1:1 to receive once-daily, oral mavacamten, or matching placebo for 30 weeks [30]. 98% of patients enrolled completed the study. Of the 2% who dropped out, none was lost due to reduced LVEF or symptoms of HF. Overall rates of adverse events, serious adverse events, and cardiac adverse events, including AF, were comparable for patients treated with mavacamten and placebo. Safety and tolerability of the agent were similar to placebo. One patient died by sudden death in the placebo group.

Main results

The primary endpoint was achieved by 45 (37%) patients in the mavacamten group and 22 (17%) in the placebo group (+19.4%; 95% CI, 8.7–30.1; P = 0.0005). Additionally, in the mavacamten group, an increase of pVO_2 by at least 3.0 ml/kg/min together with at least one NYHA class improvement was noted in 45 (37%) patients, while the same effect in the placebo group was found in 10 patients (difference +12.5%; 95% CI, 4.0–21.0).

Secondary endpoints also pointed at the improvement associated with mavacamten administration. The decrease in post-exercise LVOT gradient in the treated group was greater by 35.6 mm Hg (95% CI, –43.2 to –28.1; P <0.0001) with a mean reduction from 86 mm Hg to 38 mm Hg vs 84 mm Hg to 73 mm Hg. The pVO_2 increase with mavacamten was 1.4 ml/kg/min greater than with placebo (95% CI, 0.6–2.1; P = 0.0006). 80 (65%) patients treated with mavacamten noted an improvement by at least one NYHA class vs 40 (31%) patients receiving placebo (difference 33.8%; 95% CI, 22.2–45.4; P <0.0001). Furthermore, in the mavacamten group 61 (50%) patients achieved NYHA class I, whereas, in the placebo group, there were 27 (21%) of them. Correspondingly, also patient-reported outcomes as assessed by KCCQ-CCS (positive change better) and HCMSQ-SoB (negative change better) favored treatment with mavacamten (KCCQ-CCS +9.1; 95% CI, 5.5–12.7; HCMSQ-SoB –1.8; –2.4 to –1.2; P <0.0001 for both). Complete response was defined as a reduction of LVOT gradient <30 mm Hg together with achieving NYHA class I. Such a result was noted in 32 (27%) patients treated with mavacamten, and only 1 (1%) receiving placebo (+26.6%; 95% CI, 18.3–34.8). Reduction of LVOT gradient below the standard cut-off value for interventional treatment that is <50 mm Hg was achieved by 53% more often in the mavacamten group (74.3% vs 20.8% [difference 53.5%; 95% CI, 42.0 to 65.0, P<0.001)].

Notably, a significant number of patients on placebo had improvement in the primary endpoint and NYHA class. This highlights the need for proper double-blinding in such studies, which evaluate the physical performance and HF symptoms. On the other hand, the reduction of the NT-proBNP observed in the mavacamten group supported the conclusion that the differences between the groups were truly significant. Also, the reduction of the LVOT gradient was by 35% greater on mavacamten than on placebo and all of the secondary endpoints were consistently showing the superiority of the drug over placebo. Another important issue is the variability of the LVOT gradients. The variability tends to be higher for resting gradients and less for gradients provoked by exercise. The post-exercise gradient was the secondary endpoint of the trial, which makes the variability less relevant.

The reduction of cardiac biomarkers concentrations was similarly rapid and sustained, parallel to the hemodynamic changes noted. At week 30 compared with baseline, the drop in NT-proBNP after mavacamten treatment was 80% greater than for placebo, and the decrease in hs-cTnI was 41% greater for mavacamten than for placebo.

NONOBSTRUCTIVE HCM

Another direction of investigation (MAVERICK-HCM study) was designed to evaluate the dosing of mavacamten in HCM without LVOTO since the drug has extended pharmacokinetic properties [31]. Fifty nine patients were enrolled and observed for over 16 weeks. Patients were subdivided into 3 subgroups (n = 19 allocated to serum drug concentration of ~200 ng/ml, n = 21 allocated to ~500 ng/ml, and n =19 to placebo), followed by an 8-week washout period. The MAVERICK-HCM study fulfilled its primary objective concerning safety and tolerability. The drug was well tolerated, with no differences in reported serious adverse events (SAE) between treatment groups (10% on mavacamten and 21% on placebo). A common SAE was AF (5% in both groups), and the majority of other side effects (>70%) were not clinically relevant. The main secondary outcome was a reduction in plasma biomarkers. In the pooled mavacamten groups, the NT-proBNP decreased by 53% vs 1% in the placebo group (–435 pg/ml vs –6 pg/ml; P = 0.0005). Similarly, the cardiac troponin I also decreased by 34% in the pooled-mavacamten group compared to a 4% increase in the placebo group (P = 0.009). The investigators evaluated exploratory functional endpoints, including peak VO_2 or NYHA functional class. Among a high-risk subgroup with elevated myocardial injury biomarkers (cardiac troponin I >99th percentile) or elevated diastolic filling pressures (average E/e' >14 on Doppler-echocardiogram), one-third of mavacamten treated patients met the composite functional endpoint defined as achieving: (1) an improvement of at least 1.5 ml/kg/min in peak VO_2 with a reduction of NYHA functional class; or (2) an improvement of 3.0 ml/kg/min or more in peak VO_2 with no worsening in NYHA functional class — compared with none in the placebo group (P = 0.03). The effect on the plasma level of both biomarkers is particularly beneficial given recent evidence demonstrating the unfavorable role of persistently high levels of these biomarkers in HCM [32, 33].

IMAGING STUDIES

The recent cardiac magnetic resonance substudy of EXPLORER [34] is the first to show the favorable influence of mavacamten on cardiac remodeling in HCM. Mavacamten was associated with a significant reduction in the total intracellular myocardial mass index as well as left ventricular (LV) mass index, maximum LV wall thickness, and left atrial volume index. Importantly, no changes in fibrosis level were observed over 30 weeks. Furthermore, the contractile function was maintained in the normal range. Reduction in hypertrophy and left atrial volume were demonstrated parallelly with a decrease in plasma levels of biomarkers of myocardial stress and injury.

ONGOING STUDIES

The findings of EXPLORER-HCM and MAVERICK-HCM studies are further confirmed in two ongoing long-term extension studies — A Long-term Safety Extension Study of Mavacamten (MYK461) in Adults with Hypertrophic Cardiomyopathy Who Have Completed the MAVERICK-HCM (MYK-461-006) or EXPLORER-HCM (MYK-461-005) Trials (MAVA-LTE).

The main goals of LTE are: (1) assessment of the long-term safety and tolerability of mavacamten in participants with HCM who completed the prior studies; (2) collection of data on the long-term outcomes in patients with symptomatic noHCM and oHCM; and (3) evaluation of the echo-guided mavacamten titration algorithm in symptomatic oHCM participants. The active treatment in both studies is 2 years, and all patients receive the drug.

VALOR-HCM (Evaluation of Mavacamten in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy who are Eligible for Septal Reduction Therapy) study will verify the hypothesis that in patients (n = 100) with symptomatic oHCM the course of mavacamten over 16 week will reduce the need for SRTs [35]. Until then SRTs remain the most effective treatment for drug-refractory oHCM [36].

CLINICAL PERSPECTIVE

Mavacamten seems to be a useful drug for the full spectrum of HCM presentations (obstructive and nonobstructive). Beneficial effects include LVOT gradient reduction, an increase of exercise tolerance, and a decreased level of biomarkers (reduction of wall stress and ischemia injury). Also, clinical status and quality of life tend to follow these hemodynamic changes. Mavacamten is the first in class drug targeting the key underlying molecular mechanisms of cardiomyocyte hypercontractility in HCM.

Article information

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REFERENCES

1. Maron BJ. Clinical course and management of hypertrophic cardiomyopathy. N Engl J Med. 2018; 379(7): 655–668, doi: 10.1056/NEJMra1710575, indexed in Pubmed: 30110588.
2. Lipari M, Wypasek E, Karpinski M, et al. Identification of a variant hotspot in MYBPC3 and of a novel CSRP3 autosomal recessive alteration in a cohort of Polish cases affected by hypertrophic cardiomyopathy. Pol Arch Intern Med. 2020; 130(2): 89–99, doi: 10.20452/pamw.15130, indexed in Pubmed: 31919335.
3. Walsh R, Bezzina CR. Research in understudied populations offers local and global insights into the genetics of hypertrophic cardiomyopathy. Pol Arch Intern Med. 2020; 130(2): 76–78, doi: 10.20452/pamw.15214, indexed in Pubmed: 32105245.
4. Dimitrow PP, Rajtar-Salwa R. Obstructive form of hypertrophic cardiomyopathy-left ventricular outflow tract gradient: novel methods of provocation, monitoring of biomarkers, and recent advances in the treatment. Biomed Res Int. 2016; 2016: 1575130, doi: 10.1155/2016/1575130, indexed in Pubmed: 27247935.
5. Smarż K, Zaborska B, Pilichowska-Paszkiet E, et al. Significant left ventricular outflow tract obstruction observed during postexercise verticalization in a symptomatic patient with hypertrophic cardiomyopathy. Kardiol Pol. 2019; 77(6): 655–656, doi: 10.33963/KP.14860, indexed in Pubmed: 31169812.
6. Dimitrow P, Rajtar-Salwa R, Tokarek T. Exercise stress test methodology and safety in hypertrophic cardiomyopathy. Eur J Prev Cardiol. 2020; 27(17): 1819–1820, doi: 10.1177/2047487319901059, indexed in Pubmed: 32013606.
7. Reant P, Dufour M, Peyrou J, et al. Upright treadmill vs. semi-supine bicycle exercise echocardiography to provoke obstruction in symptomatic hypertrophic cardiomyopathy: a pilot study. Eur Heart J Cardiovasc Imaging. 2018; 19(1): 31–38, doi: 10.1093/ehjci/jew313, indexed in Pubmed: 28329285.
8. Maron MS, Olivotto I, Zenovich AG, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation. 2006; 114(21): 2232–2239, doi: 10.1161/CIRCULATIONAHA.106.644682, indexed in Pubmed: 17088454.
9. Dimitrow PP, Cheng TO. Standing position alone or in combination with exercise as a stress test to provoke left ventricular outflow tract gradient in hypertrophic cardiomyopathy and other conditions. Int J Cardiol. 2010; 143(3): 219–222, doi: 10.1016/j.ijcard.2010.04.026, indexed in Pubmed: 20442001.
10. Elliott PM, Anastasakis A, Borger MA, et al. Authors/Task Force members. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014; 35(39): 2733–2779, doi: 10.1093/eurheartj/ehu284, indexed in Pubmed: 25173338.
11. Sherrid MV, Barac I, McKenna WJ, et al. Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2005; 45(8): 1251–1258, doi: 10.1016/j.jacc.2005.01.012, indexed in Pubmed: 15837258.
12. Sherrid MV, Shetty A, Winson G, et al. Treatment of obstructive hypertrophic cardiomyopathy symptoms and gradient resistant to first-line therapy with β-blockade or verapamil. Circ Heart Fail. 2013; 6(4): 694–702, doi: 10.1161/CIRCHEARTFAILURE.112.000122, indexed in Pubmed: 23704138.

13. Ammirati E, Contri R, Coppini R, et al. Pharmacological treatment of hypertrophic cardiomyopathy: current practice and novel perspectives. Eur J Heart Fail. 2016; 18(9): 1106–1118, doi: 10.1002/ejhf.541, indexed in Pubmed: 27109894.
14. Nistri S, Olivotto I, Maron MS, et al. β Blockers for prevention of exercise-induced left ventricular outflow tract obstruction in patients with hypertrophic cardiomyopathy. Am J Cardiol. 2012; 110(5): 715–719, doi: 10.1016/j.amjcard.2012.04.051, indexed in Pubmed: 22633205.
15. Kober G, Hopf R, Biamino G, et al. Long-term treatment of hypertrophic cardiomyopathy with verapamil or propranolol in matched pairs of patients: results of a multicenter study. Z Kardiol. 1987; 76(Suppl 3): 113–118, indexed in Pubmed: 3324526.
16. Sherrid MV. Drug therapy for hypertrophic cardiomypathy: physiology and practice. Curr Cardiol Rev. 2016; 12(1): 52–65, doi: 10.2174/1573403x1201160126125403, indexed in Pubmed: 26818487.
17. Epstein SE, Rosing DR. Verapamil: its potential for causing serious complications in patients with hypertrophic cardiomyopathy. Circulation. 1981; 64(3): 437–441, doi: 10.1161/01.cir.64.3.437, indexed in Pubmed: 7196300.
18. Dimitrow PP, Krzanowski M, Nizankowski R, et al. Comparison of the effect of verapamil and propranolol on response of coronary vasomotion to cold pressor test in symptomatic patients with hypertrophic cardiomyopathy. Cardiovasc Drugs Ther. 2000; 14(6): 643–650, doi: 10.1023/a:1007871032421, indexed in Pubmed: 11300365.
19. Green EM, Wakimoto H, Anderson RL, et al. A small-molecule inhibitor of sarcomere contractility suppresses hypertrophic cardiomyopathy in mice. Science. 2016; 351(6273): 617–621, doi: 10.1126/science.aad3456, indexed in Pubmed: 26912705.
20. Tuohy CV, Kaul S, Song HK, et al. Hypertrophic cardiomyopathy: the future of treatment. Eur J Heart Fail. 2020; 22(2): 228–240, doi: 10.1002/ejhf.1715, indexed in Pubmed: 31919938.
21. Fumagalli C, De Gregorio MG, Zampieri M, et al. Targeted medical therapies for hypertrophic cardiomyopathy. Curr Cardiol Rep. 2020; 22(2): 10, doi: 10.1007/s11886-020-1258-x, indexed in Pubmed: 31993794.
22. Alsulami K, Marston S. Small molecules acting on myofilaments as treatments for heart and skeletal muscle diseases. Int J Mol Sci. 2020; 21(24): 9599, doi: 10.3390/ijms21249599, indexed in Pubmed: 33339418.
23. Kawas RF, Anderson RL, Ingle SRB, et al. A small-molecule modulator of cardiac myosin acts on multiple stages of the myosin chemomechanical cycle. J Biol Chem. 2017; 292(40): 16571–16577, doi: 10.1074/jbc.M117.776815, indexed in Pubmed: 28808052.
24. Rohde JA, Roopnarine O, Thomas DD, et al. Mavacamten stabilizes an autoinhibited state of two-headed cardiac myosin. Proc Natl Acad Sci USA. 2018; 115(32): E7486–E7494, doi: 10.1073/pnas.1720342115, indexed in Pubmed: 30018063.
25. Anderson RL, Trivedi DV, Sarkar SS, et al. Deciphering the super relaxed state of human β-cardiac myosin and the mode of action of mavacamten from myosin molecules to muscle fibers. Proc Natl Acad Sci U S A. 2018; 115(35): E8143–E8152, doi: 10.1073/pnas.1809540115, indexed in Pubmed: 30104387.
26. Grillo MP, Erve JCL, Dick R, et al. In vitro and in vivo pharmacokinetic characterization of mavacamten, a first-in-class small molecule allosteric modulator of beta cardiac myosin. Xenobiotica. 2019; 49(6): 718–733, doi: 10.1080/00498254.2018.1495856, indexed in Pubmed: 30044681.
27. Stern JA, Markova S, Ueda Y, et al. A small molecule inhibitor of sarcomere contractility acutely relieves left ventricular outflow tract obstruction in feline hypertrophic cardiomyopathy. PLoS One. 2016; 11(12): e0168407, doi: 10.1371/journal.pone.0168407, indexed in Pubmed: 27973580.
28. Awinda PO, Watanabe M, Bishaw Y, et al. Mavacamten decreases maximal force and Ca sensitivity in the N47K-myosin regulatory light chain mouse model of hypertrophic cardiomyopathy. Am J Physiol Heart Circ Physiol. 2021; 320(2): H881–H890, doi: 10.1152/ajpheart.00345.2020, indexed in Pubmed: 33337957.
29. Heitner SB, Jacoby D, Lester SJ, et al. Mavacamten treatment for obstructive hypertrophic cardiomyopathy: a clinical trial. Ann Intern Med. 2019; 170(11): 741–748, doi: 10.7326/M18-3016, indexed in Pubmed: 31035291.
30. Olivotto I, Oreziak A, Barriales-Villa R, et al. EXPLORER-HCM study investigators. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2020; 396(10253): 759–769, doi: 10.1016/S0140-6736(20)31792-X, indexed in Pubmed: 32871100.
31. Ho CY, Mealiffe ME, Bach RG, et al. Evaluation of mavacamten in symptomatic patients with nonobstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2020; 75(21): 2649–2660, doi: 10.1016/j.jacc.2020.03.064, indexed in Pubmed: 32466879.
32. Rajtar-Salwa R, Hładij R, Dimitrow PP. Elevated level of troponin but not N-terminal probrain natriuretic peptide is associated with increased risk of sudden cardiac death in hypertrophic cardiomyopathy calculated according to the ESC guidelines 2014. Dis Markers. 2017; 2017: 9417908, doi: 10.1155/2017/9417908, indexed in Pubmed: 29358842.
33. Rajtar-Salwa R, Gębka A, Dziewierz A, et al. Hypertrophic cardiomyopathy: the time-synchronized relationship between ischemia and left ventricular dysfunction assessed by highly sensitive troponin I and NT-proBNP. Dis Markers. 2019; 2019: 6487152, doi: 10.1155/2019/6487152, indexed in Pubmed: 31320942.
34. Saberi S, Cardim N, Yamani M, et al. Mavacamten favorably impacts cardiac structure in obstructive hypertrophic cardiomyopathy: EXPLORER-HCM cardiac magnetic resonance substudy analysis. Circulation. 2021; 143(6): 606–608, doi: 10.1161/CIRCULATIONAHA.120.052359, indexed in Pubmed: 33190524.
35. Desai MY, Wolski K, Owens A, et al. Study design and rationale of VALOR-HCM: evaluation of mavacamten in adults with symptomatic obstructive hypertrophic cardiomyopathy who are eligible for septal reduction therapy. Am Heart J. 2021 -89. 3; 239: 80–89, doi: 10.1016/j.ahj.2021.05.007, indexed in Pubmed: 34038706.
36. Dorobantu L, Ticulescu R, Greavu M, et al. Current management and surgical advances in patients with hypertrophic obstructive cardiomyopathy. Kardiol Pol. 2019; 77(9): 829–836, doi: 10.33963/KP.14965, indexed in Pubmed: 31495825.

REVIEW

Left atrial strain — a current clinical perspective

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ABSTRACT

The speckle-tracking technique has become an easily accessible, quick-to-use, and straightforward tool for assessing advanced myocardial function. Achievements in the analysis of the left atrium have demonstrated that it plays an important role in the physiology and pathophysiology of the circulatory system. Deformation analysis allows the detection of even subtle functional abnormalities when atrial enlargement is not yet detected. Thus, left atrial strain has a documented diagnostic and prognostic value in many clinical scenarios. Furthermore, this technique is increasingly entering routine clinical practice. The analysis becomes possible thanks to new tools that simplify the speckle-tracking assessment. Left atrial strain improves diagnostic possibilities of standard echocardiographic examination, and its diagnostic and prognostic value is sometimes comparable with more advanced and less available techniques. In this review, we discuss the principles of performing strain analysis and the results of current research, and thus the potential possibilities of sophisticated atrial assessment application in various clinical scenarios.

Key words: atrial cardiomyopathy, left atrial strain, speckle tracking echocardiography

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FUNCTIONAL SIGNIFICANCE OF THE LEFT ATRIUM

Dysfunction and structural remodeling of the left atrium (LA) are significant components of cardiovascular pathology [1, 2]. Early detection of these abnormalities contributes to evaluating even preclinical diagnosis of ventricular dysfunction or valve disease. It can also corroborate the diagnosis of emerging atrial cardiomyopathy [3, 4].

Traditional echocardiographic evaluation of the LA used to be oversimplified and limited to the anteroposterior dimension and semi quantification of atrial component of ventricular filling, and only recently it was supplemented with standardized volumetry [5]. However, routine measures of atrial function have not been implemented yet [6].

LA function consists of three components, mainly: reservoir, conduit, and active pump [7]. In the case of normal diastolic function, the relative contribution of the particular LA phases into the left ventricular (LV) filling is as follows: reservoir 40%, conduit 35%, pump 25% [8].

LA contractility modulates LV filling and plays an essential role in maintaining cardiac output even in the setting of impaired relaxation or reduced compliance of LV [1, 7]. The importance of reservoir and pump phases increases, and the conduit phase's role decreases in patients with disturbed LV relaxation [8]. The impaired phasic function of the LA was described in many cardiovascular diseases, including atrial fibrillation (AF), stroke, cardiomyopathies, and valvular heart disease [2].

LEFT ATRIAL STRAIN ASSESSMENT

Speckle-tracking echocardiography (STE) has become an established method for quantifying myocardial function [9]. It provides reliable estimates of myocardial deformation with further accuracy, thanks to the recent advent of dedicated software packages. Measurements of atrial strain using STE are well-validated [10, 11] and, notably, correlated with the histologically proven fibrotic remodeling of the LA wall [12–14]. However, the results obtained with different echocardiographic machines and post-processing software packages should be interpreted with caution because vendor variability is not well studied yet.

In contrast to Doppler techniques, STE is independent of the angle of the ultrasound beam and cardiac translational movements. A two-dimensional speckle consisting of a group of pixels is traced in all directions within the imaging plane. The main limitation can be partial displacement of the speckles outside the imaging plane. Three-dimensional echocardiography may overcome this limitation by analysis within a volumetric dataset [15]. The most frequently used measurement based on the STE technique

is global longitudinal strain, describing the relative change in the muscle length averaged for visible segments [5]. The strain is a change in the distance between two points of the myocardium occurring in the cardiac cycle. When the distance decreases (shortening), the deformation has a negative value, and when the distance increases (lengthening), its value is positive. The strain rate reflects the rate of change of the mentioned distance [16, 17].

The majority of published studies on the LA strain (LAS) are based on the measurements performed with LV-dedicated software, but several dedicated tools are currently available. In addition, due to increasing interest in the functional assessment of the LA, the international expert group has recently published a document to standardize LAS evaluation [6].

LAS is measured from the apical 4- and 2-chamber views. For a reliable analysis, the apical views should be optimized to avoid foreshortening and to record a maximized cross-sectional view of the LA cavity. The assessment can involve only a 4-chamber view (6 LA segments) or both 4- and 2-chamber views to report the average value from 12 segments (Figure 1). The 3-chamber view should not be taken into account because of the proximity of the aortic valve and aorta, which could falsify LAS measurements [2, 6]. It is crucial to keep the frame rate above 60 [18, 19].

LAS measurements should be interpreted with caution for the definition of the reference point. In fact, for LAS, two possibilities were explored, using QRS-complex or P-wave as the starting points for LA border detection [16, 17, 20]. The software automatically indicates the upslope of the R-wave as the starting point and generates the frame for endocardial tracing. This timepoint is a surrogate for end-diastole [6]. The analysis, which is focused on other zero-reference points, such as the onset of QRS complex or P-wave, requires additional manipulations on the ECG curve [10]. The strain curve with different starting points is presented in Figure 2. Data from 26 expert centers (MASCOT HIT study, Multicentric Atrial Strain COmparison between Two different modalities) proved that both methods are characterized by similar reproducibility. Still, calculations using the QRS complex as a reference point were associated with better feasibility and shorter analysis time [10]. This convention is also more universal because it can be applied in AF. The strain curve generated using this method enables the assessment of:

- LA strain in the reservoir phase (LAS-r) corresponding to LA early diastole with maximum relaxation of its wall, also known as peak atrial longitudinal strain (PALS);
- LA strain in the conduit phase (LAS-cd) corresponding to LA mid-diastolic emptying with its passive shortening;
- LA strain in the contraction phase (LAS-ct) or peak atrial contraction strain (PACS) corresponding to LA systole with active myocardial shortening producing the atrial contribution to LV filling [21].

Thus, the total function of the LA is best reflected by reservoir strain expressed in percentage points, algebraically positive.

The LAS calculated using P-wave as the starting point is known as epsilon (ε). The generated strain curve allows to assess:

- peak negative ε corresponding to LA contractile;
- peak positive ε corresponding to LA conduit phase;
- total ε as the absolute value of both abovementioned peaks, reflecting the LA reservoir phase [22].

Recently available software dedicated to the LA, such as AutoStrain LA or LA Automated Function Imaging, allows for a quick assessment with a smooth transition between the P-wave and R-wave methods. For example, Figure 3 shows the results of the LA strain assessment with AutoStrain LA.

STE also enables the assessment of the LA strain rate by a curve with three peaks. In the analysis with R-wave set as a reference point, the first peak is positive and corresponds to the LA reservoir phase. The consecutive two peaks are negative. The first corresponds to the LA conduit phase (passive LA strain rate) and the second one to the LA contractile (active LA strain rate) [23, 24]. However, STE strain rate analysis is of less interest in the literature. A significant limitation is the temporal resolution of acquired images. The frame rate should be increased significantly in tachycardia. The strain rate as a time-dependent parameter requires higher temporal resolution, optimally >100 frames per second [25]. A recently developed novel imaging technique enabling the acquisition of images with 200 frames per second is a promising prospect [26].

The analysis of LAS dispersion is possible due to advanced assessment of regional data and is calculated as the standard deviation of regional values of time to the maximum peak of segmental strain curves normalized to the R-R interval [27, 28].

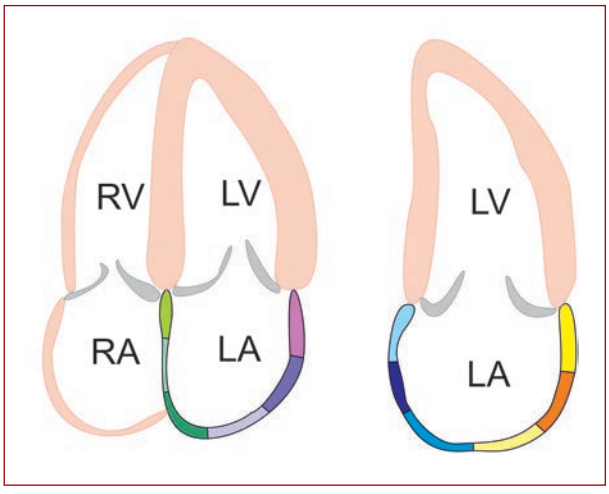

Figure 1. Segmental division of the left atrium in 4- and 2-chamber apical views using the speckle tracking echocardiography

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

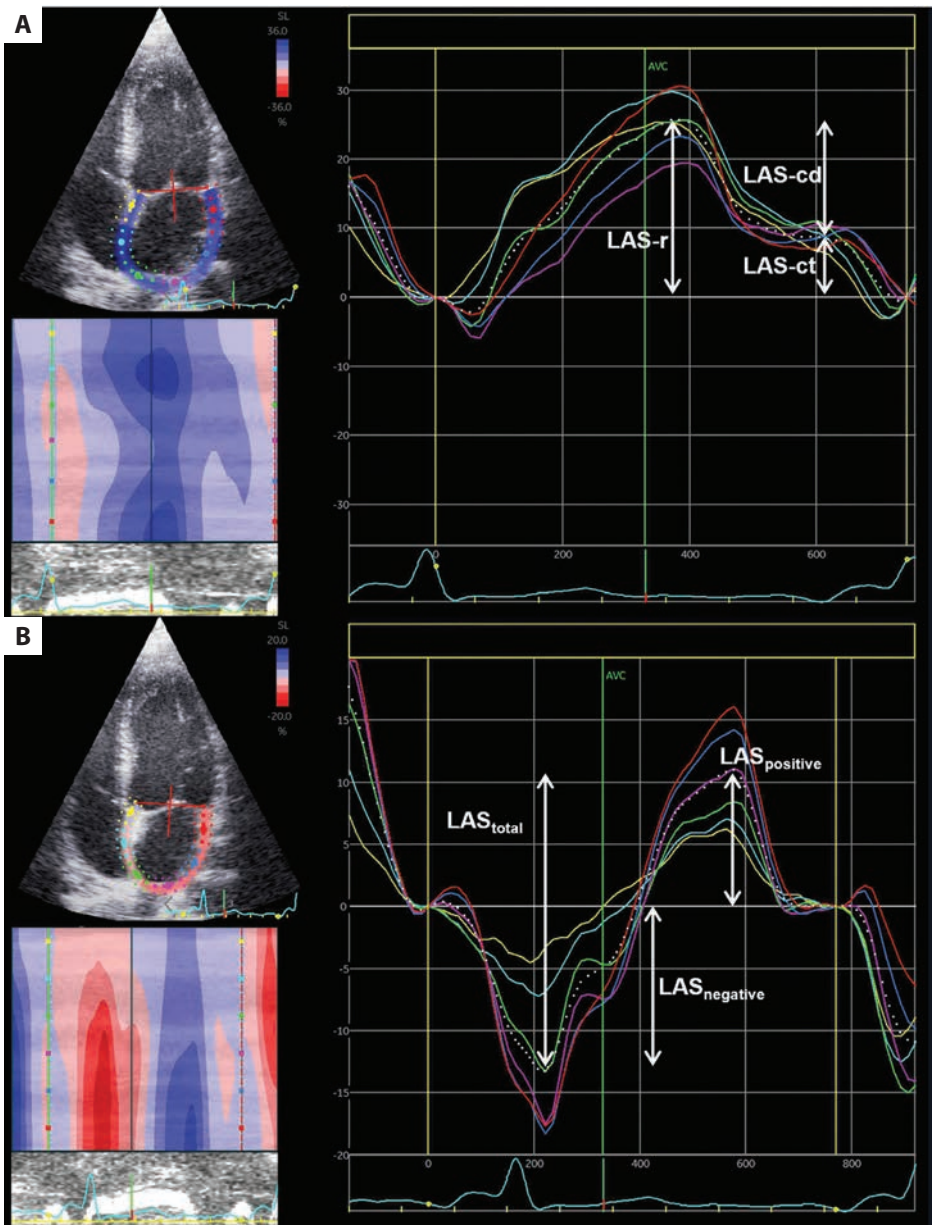

Figure 2. Left atrial strain (LAS) nomenclature depending on the choice of zero reference time-point — QRS-complex (panel **A**) and P-wave (panel **B**). When R-wave is set as the starting point, the first positive peak corresponds to the left atrium (LA) reservoir phase, the second peak characterizes LA contractile, and the difference between those peaks corresponds to the conduit phase. When P-wave is set as the reference, the first negative peak characterizes the LA contraction, positive peak — conduit phase, and their sum corresponds to the LA reservoir phase

Several parameters derived from LAS were proposed to describe the cardiac function better. The LA stiffness index reflecting decreased compliance of LA can be non-invasively calculated as the quotient of mitral E/E' ratio and LAS-r. This parameter can be used as a surrogate of invasively measured stiffness requiring pulmonary capillary wedge pressure assessment. The LA stiffness index was revealed to be useful for differentiating healthy controls, patients with diastolic dysfunction, and patients with heart failure (HF) and preserved and reduced ejection fraction [29]. Moreover, this parameter is related to collagen synthesis and predicts AF recurrence after pulmonary vein isolation [30]. Interestingly, the LA stiffness index is decreased in competitive athletes coexisting with the enlarged LA as physiological adaptation [31].

LA function should be interpreted in the context of LV, and it is interesting to analyze atrioventricular strain calculated as the sum of absolute LAS-r and LV strain. However, in patients with hypertension and/or diabetes mellitus without alteration of standard echo parameters, the best marker of subclinical abnormalities was LAS-r [32].

Experience with LAS calculated from 3D datasets is preliminary, but current software used for 4D LA analysis automatically calculates the strain curve with longitudinal and circumferential strain values (Figure 4).

NORMAL VALUES OF LEFT ATRIAL STRAIN

A meta-analysis of 40 studies conducted predominantly using EchoPAC software (General Electric Healthcare, Milwaukee, WI, USA) defined a range of normal values for atrial deformation (Table 1). The authors compiled data obtained both with tools provided by General Electric and other suppliers, without noting significant vendor-related differences [33].

The authors of the multicenter NORRE study (Normal Reference Ranges for Echocardiography) determined

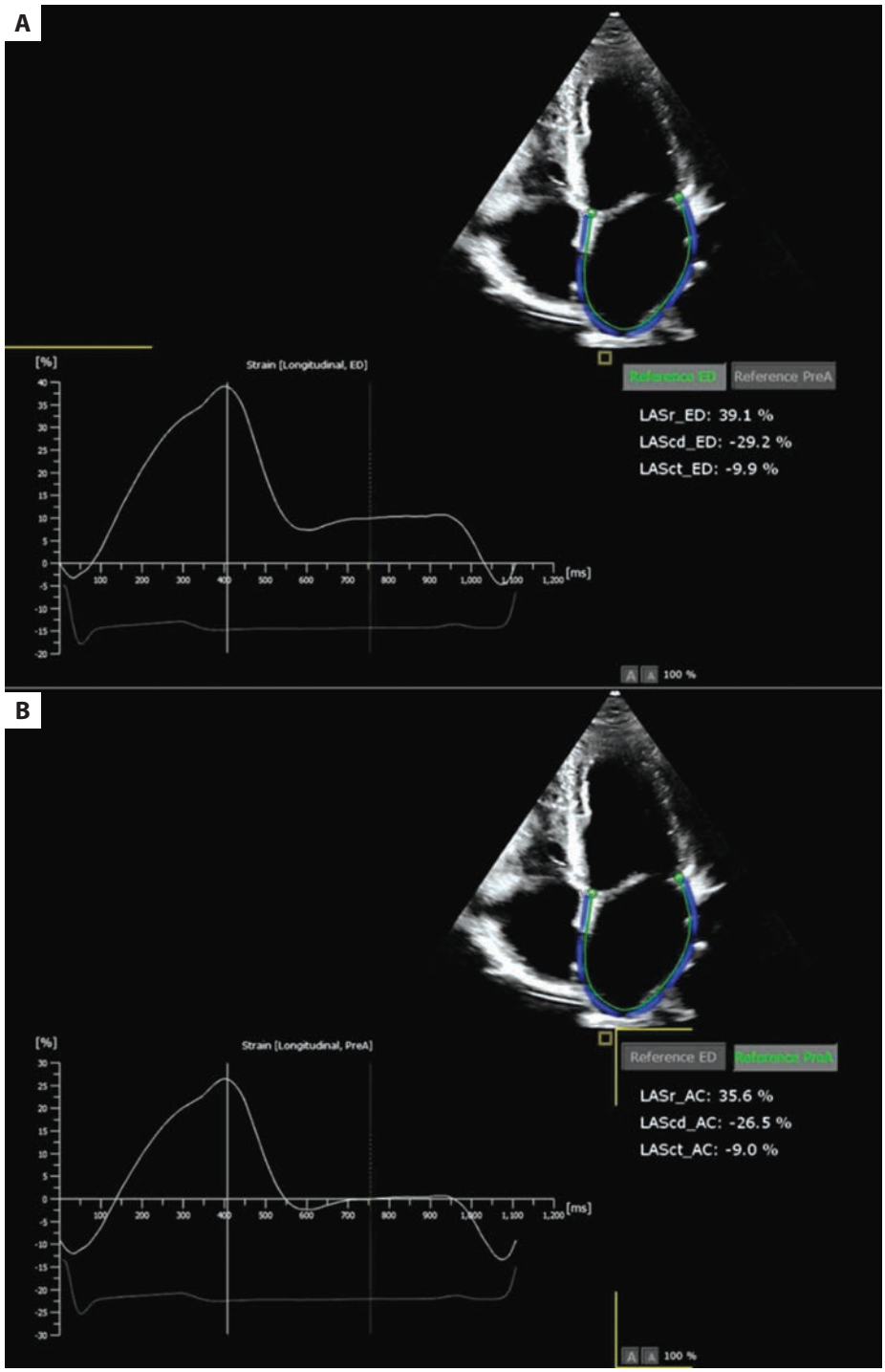

Figure 3. Left atrial strain derived left atrium (LA) dedicated software (AutoStrain LA). Strain curve generated depending on zero-reference timepoint — QRS-complex (panel **A**) and P-wave (panel **B**). Courtesy Philips Poland

a range of reference values for LAS and LA stiffness index using commercially available VIS — Vendor Independent Software (TomTec Imaging System, Unterschleißheim, Germany) (Table 2). The study included 371 healthy individuals. In the multivariate analysis, it turned out that age is independently related to the individual components of deformation, regardless of gender or an echocardiograph type used for registration [11].

Table 3 shows the strain values obtained in the MASCOT HIT study and derived from three study groups (healthy volunteers, patients with LV pressure overload, or LV volume overload). The median time needed for analysis with R-wave reference point was shorter (120 sec, interquartile range [IQR], 80–165 sec) than with P-wave set as a starting point (110 sec, IQR, 78–149 sec) [10].

ATRIAL CARDIOMYOPATHY

An important concept related to the LA is atrial cardiomyopathy, defined as a complex of changes in the structure, tissue architecture, contractility, or electrophysiological

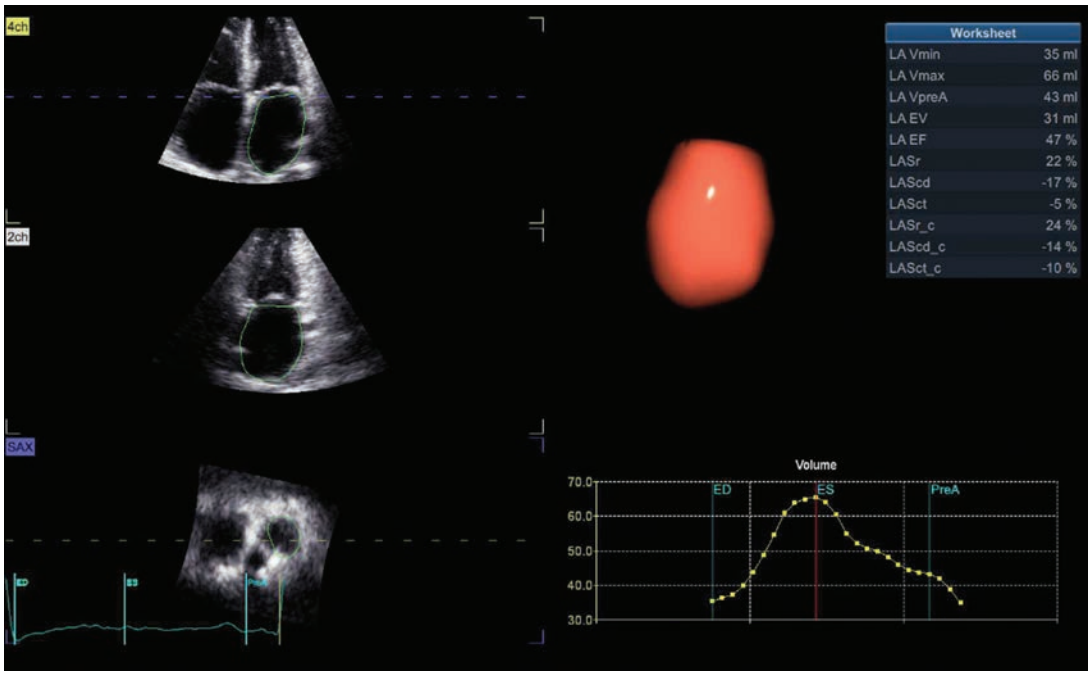

Figure 4. Left atrial assessment derived from 4D full volume data set enabling volumetric and strain analysis (Automated Function Assessment, Echopac, GE Healthcare, Chicago, IL, USA)

Abbreviations: LAScd, longitudinal strain during conduit phase; LASct, longitudinal strain during contraction phase; LASr, longitudinal strain during reservoir phase; LAScd_c, circumferential strain during conduit phase; LASct_c, circumferential strain during contraction phase; LASr_c, circumferential strain during reservoir phase

Table 1. Summary of the left atrial strain reference values obtained from the meta-analysis [33]

	Mean (95% CI)	Comments
LAS-r, %	39.4 (38–40.8)	40 studies (2542 subjects)
LAS-ct, %	17.4 (16–19)	18 studies (1005 subjects)
LAS-cd, %	23 (20.7–25.2)	14 studies (805 subjects)

Abbreviations: LAS-cd, left atrial strain — phase of conduit; LAS-ct, left atrial strain — phase of contraction; LAS-r, left atrial strain — phase of reservoir

Table 2. Reference values defined in the NORRE study for the individual components of left atrial deformation (lower limit of normal) and the stiffness index (upper limit of normal) [11]48.7%, and 41.4% for left atrial strain (LAS

Age range	20–40 years (n = 137)	40–60 years (n = 173)	>60 years (n = 61)
LAS-r, %	≥31.1	≥27.7	≥22.7
LAS-ct, %	≥7.2	≥9.3	≥7.7
LAS-cd, %	≥16.2	≥12	≥11.5
LA stiffness index	≤0.22	≤0.42	≤0.55

Abbreviations: LA stiffness index — ratio of E/E' to LAS-r (dimensionless parameter). Other — see Figure 1 and Table 1

Table 3. Summary of left atrial strain values obtained in the MASCOT HIT study for all subgroups: healthy individuals, patients with pressure overload (hypertension or aortic stenosis), and patients with left ventricular volume overload (heart failure or mitral regurgitation) [10]

	Healthy volunteers		LV pressure overload		LV volume overload	
	P-wave	R-wave	P-wave	R-wave	P-wave	R-wave
LAS-r, %	30.5 ± 8	33.5 ± 10.9	21.9 ± 6.8	23.0 ± 8.5	19.2 ± 7.4	18.9 ± 9.2
LAS-ct, %	Not published	15 ± 5.3	Not published	13.4 ± 5.7	Not published	10 ± 5.7

Abbreviations: see Figure 1 and Table 1

characteristics affecting the atria with the possibility of clinically significant manifestation [34]. LAS can be easily implemented to identify abnormalities in LA function corresponding to atrial fibrosis. Furthermore, STE detects LA dysfunction before anatomical changes occur [4, 35]. However, it should be emphasized that atrial cardiomyopathy is currently a pathophysiological concept rather than a clinical unit with specific diagnostic criteria and treatment rules, and further research is needed in this field.

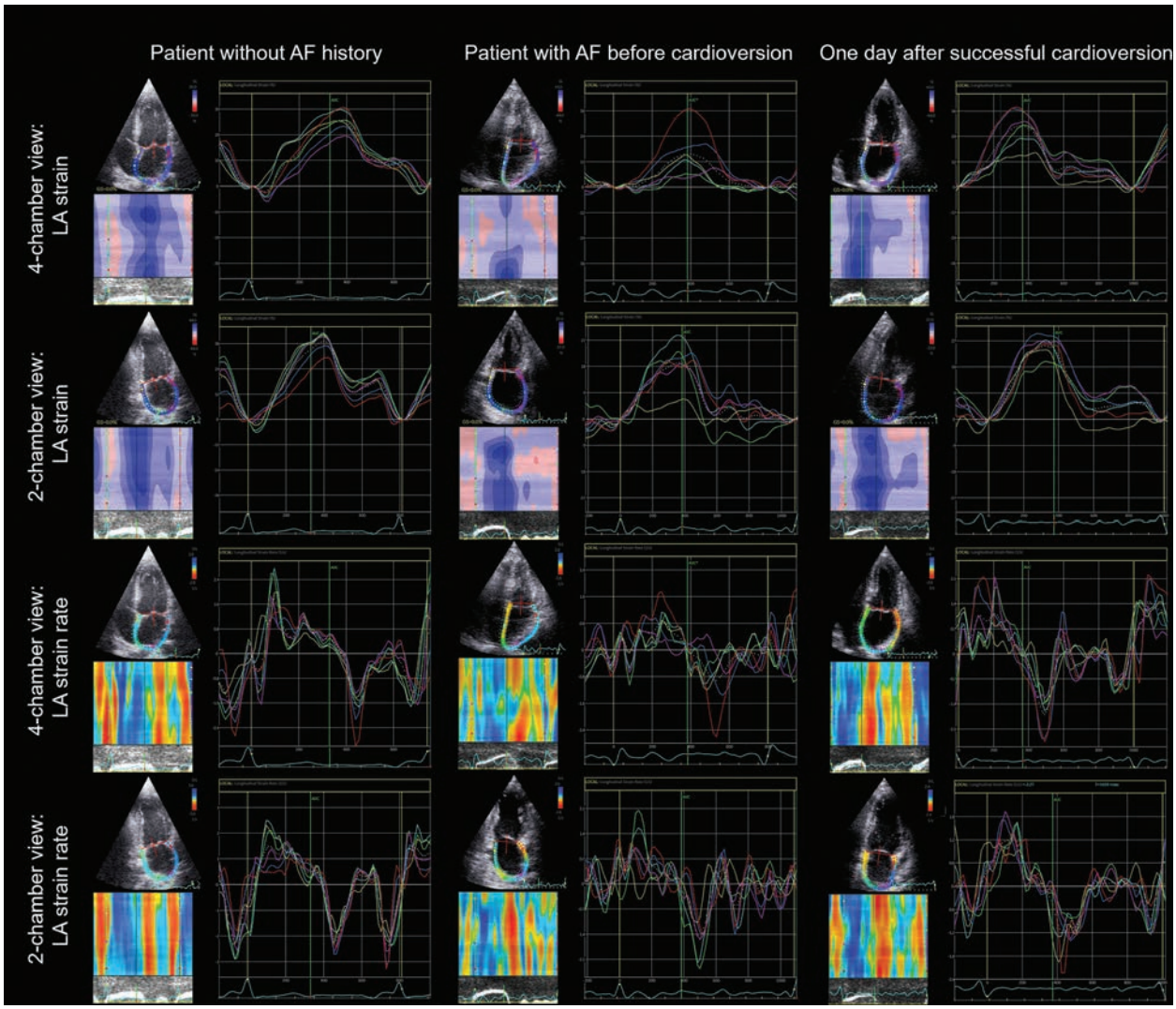

Figure 5. Left atrial strain and strain rate assessment in a patient without atrial fibrillation history (left panel), and in a patient with atrial fibrillation before and one day after successful electrical cardioversion (middle and right panels respectively)

ATRIAL FIBRILLATION

AF is a factor contributing to the development of atrial cardiomyopathy and its manifestation, which may explain the weak temporal relationship between episodes of AF and embolic stroke [36].

LAS both in the reservoir (optimal cut-off value LAS-r ≤19%) and contractile phase (LAS-ct ≤8.7%) enables the identification of patients with a history of AF in the population with hypertension [37].

Abnormal LAS is a proven predictor of AF occurrence, especially in patients after cryptogenic stroke [38, 39]. Recently, Kawakami et al. proposed an innovative approach, analyzing whether the assessment of LA strain brings additional benefits against well-established LV strain analysis. Based on the obtained results, the authors proposed an algorithm in which a patient with an increased 5-years risk of AF and normal LA volume should at first have LAS-ct assessed while in the case of increased LA volume, LV global longitudinal strain should be evaluated first [40].

Surprisingly few studies refer to LA deformation in the active phase of the pump as a prognostic factor [21]. However, this parameter assessed on the first day after successful electrical cardioversion showed a predictive role in maintaining sinus rhythm during a one-year follow-up. The value of LAS-ct >3.4% derived from the 4-chamber view analysis was an optimal cut-off. LAS-r >14.6% was a significant predictor of survival without AF recurrence [41]. Figure 5 shows the comparison of LA strain results in a patient without a history of AF and a patient with AF, before and after successful electrical cardioversion.

A LAS-r ≤10, 75% had a sensitivity of 85% and a specificity of 99% in predicting 6-months AF recurrence after electrical cardioversion carried out due to persistent and long-lasting persistent AF and was an independent marker in multivariate analysis [42].

Impaired LA function favors the formation of thrombi, especially in the LA appendage. Intra-atrial thrombus was related to LA dysfunction assessed during AF with the best discriminating power by a LAS dispersion >22% (sensitivity:

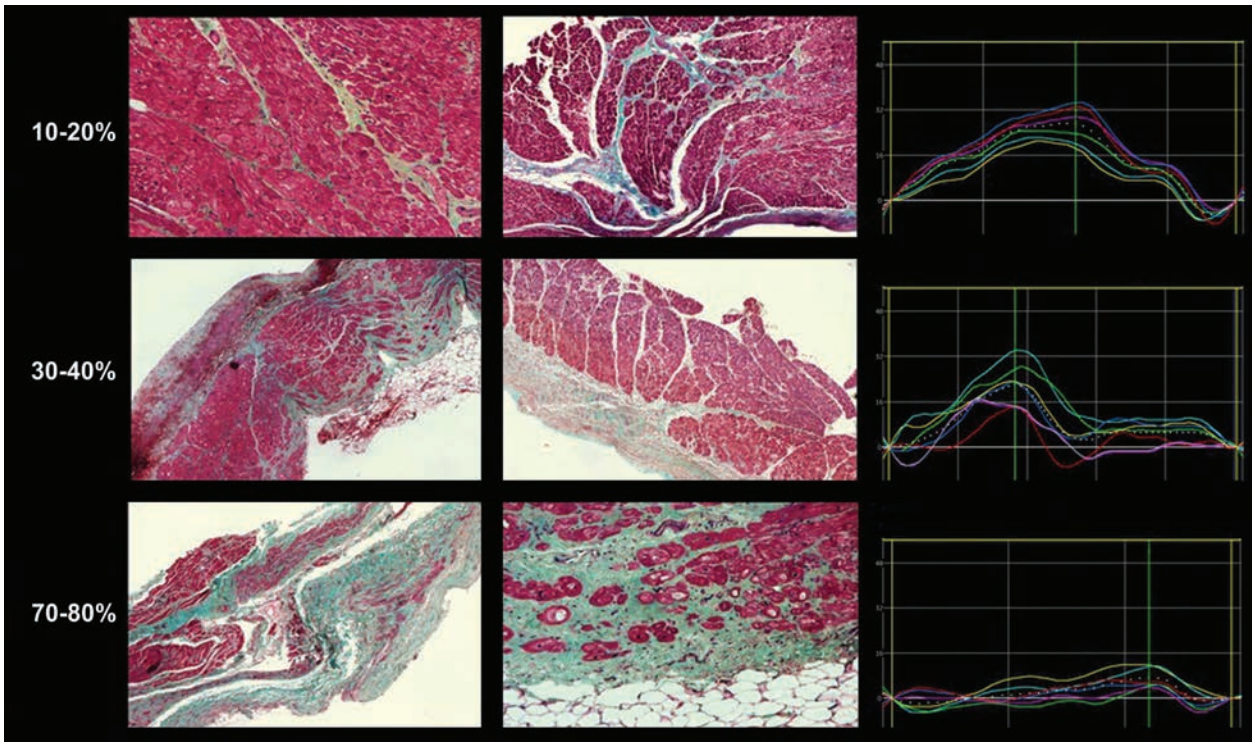

Figure 6. Left atrial strain correlates with fibrosis on atrial samples. Comparison between left atrial bioptic specimens (hematoxylin and eosin staining) with increasing amounts of wall myocardial fibrosis and corresponding left atrial strain curves, showing progressively reduced longitudinal deformation. Adapted from Lisi et al. [49]

45% and specificity: 89%) and LAS-r ≤11% (sensitivity: 74%, specificity: 65%) [27]. Moreover, both parameters were independent factors related to the presence of thrombi, even after adjustment for CHA_2DS_2-VASc score [27, 43], and LAS dispersion adjusted for LV ejection fraction or LV global longitudinal strain [27].

Similarly, Obokata et al. reported that LAS-r assessed in AF improved the predictive ability of the CHA_2DS_2-VASc score in the prediction of systemic embolism and was also an independent prognostic factor of mortality following stroke. The best criterion for discriminating between patients with stroke and a demographically and clinically matched control group with AF but without an embolic event was LAS-r <15.4%. In this study, LA roof segments were excluded from the analysis [44].

HEART FAILURE

The importance of LA assessment is demonstrated by including its enlargement as one of the diagnostic criteria in the current HF definition [45]. In addition to its prognostic significance, LA volume is also used to assess LV diastolic function and the diagnosis of HF with preserved LV ejection fraction (HFpEF) [46, 47]. However, LA function could be already abnormal even if LA size is preserved.

Patients with HFpEF had impaired LAS-r and LA passive and active strain rates compared to healthy controls. Moreover, HFpEF patients with LA enlargement or a history of AF had lower LA strain values [24].

Another study revealed in a group of 4312 consecutive patients with acute HF that LAS-r <18% identifies individuals who may develop new-onset AF within 5-year follow-up, both in the HF with reduced ejection fraction (HFrEF) subgroup and analyzed together HFpEF and HF with mid-range ejection fraction (HFmrEF) [48]. In advanced HFrEF, LAS-r strongly correlated with the amount of invasively analyzed fibrosis on LA bioptic samples (Figure 6) [49].

DIASTOLIC DYSFUNCTION

The quantification of LA volume is used to support the diagnosis of LV diastolic function. However, macroscopic changes in its structure are the late manifestation of dysfunction. Left atrial strain deteriorates along with the severity of diastolic dysfunction and is proposed as a helpful parameter to distinguish particular grades of diastolic dysfunction with good to excellent diagnostic ability. A LAS-r >35% allowed to differentiate patients with normal diastolic function with an accuracy of 72%. Moreover, a LAS-r ≤19% had the accuracy of 95% to identify patients with the 3rd grade of diastolic dysfunction [50]. The cut-off of LAS-r <20% was proposed to improve the diagnosis in case of an indeterminate degree of diastolic dysfunction [51].

CORONARY ARTERY DISEASE

The LA can also be affected by ischemic heart disease, mainly as a consequence of LV myocardial damage. Both LAS-r and LAS-ct were impaired in patients with acute myocardial infarction, with a circumflex artery identified as a culprit lesion [52]. LAS-r assessed within 48 hours after primary percutaneous coronary intervention for the first ST-segment elevation acute myocardial infarction was

the independent predictor associated with a lower risk of adverse LV remodeling (OR, 0.77; $P = 0.003$; optimal cut-off, 28.9%) and adverse clinical events (OR, 0.88; $P = 0.04$; optimal cut-off, 23.8%) during 6-month follow-up [53].

CARDIAC AMYLOIDOSIS

Cardiac amyloidosis, in the study by Nochioka et al., was associated with severe LA dysfunction. Mean LAS-r was significantly lower in the patients with amyloidosis than in healthy controls (18.8 ± 11.6% vs 40.6 ± 6.2%; $P < 0.001$). It should be mentioned that differences in LA function were identified between amyloid subtypes with most abnormal LAS-r in wild-type transthyretin amyloidosis [54].

VALVULAR HEART DISEASE

LA functional parameters decrease in valvular heart disease and have prognostic significance. In asymptomatic patients with pure mitral valve stenosis, LAS-r <17.4% showed a good predictive value to predict AF in 4-year follow-up [55]. In the study by Sugimoto et al., LA pump and reservoir function were impaired in patients with primary and secondary mitral regurgitation. The subgroup with primary, but not secondary, regurgitation had some exercise reserve in LA functional parameters, even in moderate to severe regurgitation. Patients with mild to moderate secondary mitral regurgitation had a higher stiffness index than patients with moderate to severe primary mitral regurgitation during exercise. Moreover, LAS-r >16% at peak exercise predicted a 3-year event-free survival [56]. A reduced basal LAS-r could also predict mid-term adverse events, including AF, stroke, acute HF, and cardiovascular death, in patients with asymptomatic moderate mitral regurgitation, helping identify a subpopulation of patients with a more advanced stage of the disease [57].

STE analysis of LA had very good predictive value for the prognosis of postoperative AF in patients with aortic stenosis undergoing surgical replacement. The LAS-r <16.9% had a sensitivity of 86% and specificity of 91% in predicting new-onset AF after implantation of biological aortic valve prosthesis [58].

ANTHRACYCLINE THERAPY

Recently published results proved the importance of LA strain assessment in monitoring the cardiotoxic effects of cancer chemotherapy. STE analysis enables early diagnosis of cardiac dysfunction and starting treatment. Significant reduction in LAS-r can be defined as a relative decrease of >10% or LAS-r <35%. LAS-r and LAS-cd, but not LAS-ct, showed a significant decline in patients with breast cancer during doxorubicin therapy [59].

CONCLUSIONS

The LA function assessment by STE is a relatively simple and robust tool allowing to disclose pathophysiological mechanisms in the broad spectrum of cardiovascular disease. The prognostic significance of LA strain has been demonstrated in many clinical scenarios, including the definition of diastolic dysfunction, cardioembolic risk, and even cardiovascular mortality in a selected patient population. The most actual diagnostic application includes heart failure and atrial cardiomyopathy (with emphasis on identifying AF episodes) and may influence clinical decision-making, refining the prediction of rhythm-control strategy success in AF.

Article information

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REFERENCES

1. Rosca M, Lancellotti P, Popescu BA, et al. Left atrial function: pathophysiology, echocardiographic assessment, and clinical applications. Heart. 2011; 97(23): 1982–1989, doi: 10.1136/heartjnl-2011-300069, indexed in Pubmed: 22058287.
2. Thomas L, Muraru D, Popescu BA, et al. Evaluation of left atrial size and function: relevance for clinical practice. J Am Soc Echocardiogr. 2020; 33(8): 934–952, doi: 10.1016/j.echo.2020.03.021, indexed in Pubmed: 32762920.
3. Donal E, Lip GYH, Galderisi M, et al. EACVI/EHRA expert consensus document on the role of multi-modality imaging for the evaluation of patients with atrial fibrillation. Eur Heart J Cardiovasc Imaging. 2016; 17(4): 355–383, doi: 10.1093/ehjci/jev354, indexed in Pubmed: 26864186.
4. Hirsh BJ, Copeland-Halperin RS, Halperin JL. Fibrotic atrial cardiomyopathy, atrial fibrillation, and thromboembolism: mechanistic links and clinical inferences. J Am Coll Cardiol. 2015; 65(20): 2239–2251, doi: 10.1016/j.jacc.2015.03.557, indexed in Pubmed: 25998669.
5. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015; 28(1): 1–39.e14, doi: 10.1016/j.echo.2014.10.003, indexed in Pubmed: 25559473.
6. Badano LP, Kolias TJ, Muraru D, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging. 2018; 19(6): 591–600, doi: 10.1093/ehjci/jey042, indexed in Pubmed: 29596561.
7. Matsuda Y, Toma Y, Ogawa H, et al. Importance of left atrial function in patients with myocardial infarction. Circulation. 1983; 67(3): 566–571, doi: 10.1161/01.cir.67.3.566, indexed in Pubmed: 6821898.
8. Callegari S, Macchi E, Monaco R, et al. Myocyte changes and their left atrial distribution in patients with chronic atrial fibrillation related to mitral valve disease. Hum Pathol. 2005; 36(10): 1080–1089, doi: 10.1016/j.humpath.2005.07.018, indexed in Pubmed: 16226107.
9. Szymczyk E, Lipiec P, Michalski B, et al. 2D and 3D acoustic marker tracking technique: clinical application [article in Polish]. Kardiol Pol. 2013; 71(1): 77–83.
10. Cameli M, Miglioranza MH, Magne J, et al. Multicentric atrial strain comparison between two different modalities: MASCOT HIT study. Diagnostics (Basel). 2020; 10(11), doi: 10.3390/diagnostics10110946, indexed in Pubmed: 33202837.
11. Sugimoto T, Robinet S, Dulgheru R, et al. NORRE Study. Echocardiographic reference ranges for normal left atrial function parameters: results from the EACVI NORRE study. Eur Heart J Cardiovasc Imaging. 2018; 19(6): 630–638, doi: 10.1093/ehjci/jey018, indexed in Pubmed: 29529180.

12. Cameli M, Lisi M, Focardi M, et al. Left atrial deformation analysis by speckle tracking echocardiography for prediction of cardiovascular outcomes. Am J Cardiol. 2012; 110(2): 264–269, doi: 10.1016/j.amjcard.2012.03.022, indexed in Pubmed: 22497676.
13. Mandoli GE, D'Ascenzi F, Vinco G, et al. Novel approaches in cardiac imaging for non-invasive assessment of left heart myocardial fibrosis. Front Cardiovasc Med. 2021; 8: 614235, doi: 10.3389/fcvm.2021.614235, indexed in Pubmed: 33937354.
14. Her AY, Choi EY, Shim CY, et al. Prediction of left atrial fibrosis with speckle tracking echocardiography in mitral valve disease: a comparative study with histopathology. Korean Circ J. 2012; 42(5): 311–318, doi: 10.4070/kcj.2012.42.5.311, indexed in Pubmed: 22701133.
15. Mor-Avi V, Lang RM, Badano LP, et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. J Am Soc Echocardiogr. 2011; 24(3): 277–313, doi: 10.1016/j.echo.2011.01.015, indexed in Pubmed: 21338865.
16. Hoit BD. Left atrial size and function: role in prognosis. J Am Coll Cardiol. 2014; 63(6): 493–505, doi: 10.1016/j.jacc.2013.10.055, indexed in Pubmed: 24291276.
17. Rimbaş RC, Mihăilă S, Vinereanu D. Sources of variation in assessing left atrial functions by 2D speckle-tracking echocardiography. Heart Vessels. 2016; 31(3): 370–381, doi: 10.1007/s00380-014-0602-8, indexed in Pubmed: 25388354.
18. Cameli M, Lisi M, Righini FM, et al. Novel echocardiographic techniques to assess left atrial size, anatomy and function. Cardiovasc Ultrasound. 2012; 10: 4, doi: 10.1186/1476-7120-10-4, indexed in Pubmed: 22296702.
19. Cameli M, Caputo M, Mondillo S, et al. Feasibility and reference values of left atrial longitudinal strain imaging by two-dimensional speckle tracking. Cardiovasc Ultrasound. 2009; 7: 6, doi: 10.1186/1476-7120-7-6, indexed in Pubmed: 19200402.
20. Hayashi S, Yamada H, Bando M, et al. Optimal analysis of left atrial strain by speckle tracking echocardiography: P-wave versus R-wave trigger. Echocardiography. 2015; 32(8): 1241–1249, doi: 10.1111/echo.12834, indexed in Pubmed: 25363348.
21. Pastore M, Mandoli G, Santoro C, et al. Left atrial strain in cardiovascular diseases : An overview of clinical applications. Cardiologia Hungarica. 2021; 51(1): 11–17, doi: 10.26430/chungarica.2021.51.1.11.
22. Saraiva RM, Demirkol S, Buakhamsri A, et al. Left atrial strain measured by two-dimensional speckle tracking represents a new tool to evaluate left atrial function. J Am Soc Echocardiogr. 2010; 23(2): 172–180, doi: 10.1016/j.echo.2009.11.003, indexed in Pubmed: 20152699.
23. Miśkowiec D, Kupczyńska K, Michalski BW, et al. Left atrial dysfunction assessed by two-dimensional speckle tracking echocardiography in patients with impaired left ventricular ejection fraction and sleep-disordered breathing. Echocardiography. 2016; 33(1): 38–45, doi: 10.1111/echo.12987, indexed in Pubmed: 26058894.
24. Santos ABS, Kraigher-Krainer E, Gupta DK, et al. Impaired left atrial function in heart failure with preserved ejection fraction. Eur J Heart Fail. 2014; 16(10): 1096–1103, doi: 10.1002/ejhf.147, indexed in Pubmed: 25138249.
25. Voigt JU, Pedrizzetti G, Lysyansky P, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging. 2015; 16(1): 1–11, doi: 10.1093/ehjci/jeu184, indexed in Pubmed: 25525063.
26. Fujikura K, Makkiya M, Farooq M, et al. Speckle-Tracking echocardiography with novel imaging technique of higher frame rate. J Clin Med. 2021; 10(10), doi: 10.3390/jcm10102095, indexed in Pubmed: 34068134.
27. Kupczynska K, Michalski BW, Miskowiec D, et al. Incremental value of left atrial mechanical dispersion over CHA DS -VASc score in predicting risk of thrombus formation. Echocardiography. 2018; 35(5): 651–660, doi: 10.1111/echo.13899, indexed in Pubmed: 29691894.
28. Dell'Era G, Rondano E, Franchi E, et al. Atrial asynchrony and function before and after electrical cardioversion for persistent atrial fibrillation. Eur J Echocardiogr. 2010; 11(7): 577–583, doi: 10.1093/ejechocard/jeq010, indexed in Pubmed: 20400765.
29. Kurt M, Wang J, Torre-Amione G, et al. Left atrial function in diastolic heart failure. Circ Cardiovasc Imaging. 2009; 2(1): 10–15, doi: 10.1161/CIRCIMAGING.108.813071, indexed in Pubmed: 19808559.
30. Machino-Ohtsuka T, Seo Y, Tada H, et al. Left atrial stiffness relates to left ventricular diastolic dysfunction and recurrence after pulmonary vein isolation for atrial fibrillation. J Cardiovasc Electrophysiol. 2011; 22(9): 999–1006, doi: 10.1111/j.1540-8167.2011.02049.x, indexed in Pubmed: 21457382.
31. D'Ascenzi F, Pelliccia A, Natali BM, et al. Increased left atrial size is associated with reduced atrial stiffness and preserved reservoir function in athlete's heart. Int J Cardiovasc Imaging. 2015; 31(4): 699–705, doi: 10.1007/s10554-015-0600-7, indexed in Pubmed: 25627780.
32. Cameli M, Mandoli GE, Lisi E, et al. Left atrial, ventricular and atrio-ventricular strain in patients with subclinical heart dysfunction. Int J Cardiovasc Imaging. 2019; 35(2): 249–258, doi: 10.1007/s10554-018-1461-7, indexed in Pubmed: 30251175.
33. Pathan F, D'Elia N, Nolan MT, et al. Normal ranges of left atrial strain by speckle-tracking echocardiography: a systematic review and meta-analysis. J Am Soc Echocardiogr. 2017; 30(1): 59–70.e8, doi: 10.1016/j.echo.2016.09.007, indexed in Pubmed: 28341032.
34. Goette A, Kalman JM, Aguinaga L, et al. Document Reviewers:. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: Definition, characterization, and clinical implication. Heart Rhythm. 2017; 14(1): e3–e40, doi: 10.1016/j.hrthm.2016.05.028, indexed in Pubmed: 27320515.
35. Yuda S, Muranaka A, Miura T. Clinical implications of left atrial function assessed by speckle tracking echocardiography. J Echocardiogr. 2016; 14(3): 104–112, doi: 10.1007/s12574-016-0283-7, indexed in Pubmed: 26951561.
36. Healey JS, Brambatti M, Gold MR, et al. Temporal relationship between subclinical atrial fibrillation and embolic events. Circulation. 2014; 129(21): 2094–2099, doi: 10.1161/CIRCULATIONAHA.113.007825, indexed in Pubmed: 24633881.
37. Petre I, Onciul S, Iancovici S, et al. Left atrial strain for predicting atrial fibrillation onset in hypertensive patients. High Blood Press Cardiovasc Prev. 2019; 26(4): 331–337, doi: 10.1007/s40292-019-00326-4, indexed in Pubmed: 31309456.
38. Deferm S, Bertrand PB, Churchill TW, et al. Left atrial mechanics assessed early during hospitalization for cryptogenic stroke are associated with occult atrial fibrillation: a speckle-tracking strain echocardiography study. J Am Soc Echocardiogr. 2021; 34(2): 156–165, doi: 10.1016/j.echo.2020.09.009, indexed in Pubmed: 33132019.
39. Sade LE, Keskin S, Can U, et al. Left atrial mechanics for secondary prevention from embolic stroke of undetermined source. Eur Heart J Cardiovasc Imaging. 2020 [Epub ahead of print], doi: 10.1093/ehjci/jeaa311, indexed in Pubmed: 33206942.
40. Kawakami H, Ramkumar S, Pathan F, et al. Use of echocardiography to stratify the risk of atrial fibrillation: comparison of left atrial and ventricular strain. Eur Heart J Cardiovasc Imaging. 2020; 21(4): 399–407, doi: 10.1093/ehjci/jez240, indexed in Pubmed: 31578558.
41. Wałek P, Grabowska U, Cieśla E, et al. Left atrial longitudinal strain in the contractile phase as a predictor of sinus rhythm maintenance after electrical cardioversion performed due to persistent atrial fibrillation. Kardiol Pol. 2021; 79(4): 458–460, doi: 10.33963/KP.15913, indexed in Pubmed: 33784038.
42. Moreno-Ruiz LA, Madrid-Miller A, Martínez-Flores JE, et al. Left atrial longitudinal strain by speckle tracking as independent predictor of recurrence after electrical cardioversion in persistent and long standing persistent non-valvular atrial fibrillation. Int J Cardiovasc Imaging. 2019; 35(9): 1587–1596, doi: 10.1007/s10554-019-01597-7, indexed in Pubmed: 30993507.
43. Kupczynska K, Michalski BW, Miskowiec D, et al. Association between left atrial function assessed by speckle-tracking echocardiography and the presence of left atrial appendage thrombus in patients with atrial fibrillation. Anatol J Cardiol. 2017; 18(1): 15–22, doi: 10.14744/AnatolJCardiol.2017.7613, indexed in Pubmed: 28559531.
44. Obokata M, Negishi K, Kurosawa K, et al. Left atrial strain provides incremental value for embolism risk stratification over CHA2DS2-VASc score and indicates prognostic impact in patients with atrial fibrillation. J Am Soc Echocardiogr. 2014; 27(7): 709–716.e4, doi: 10.1016/j.echo.2014.03.010, indexed in Pubmed: 24767972.
45. Seferovic PM, Ponikowski P, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure

of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016; 37(27): 2129–2200, doi: 10.1093/eurheartj/ehw128, indexed in Pubmed: 27206819.
46. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016; 29(4): 277–314, doi: 10.1016/j.echo.2016.01.011, indexed in Pubmed: 27037982.
47. Kapłon-Cieślicka A, Kupczyńska K, Dobrowolski P, et al. On the search for the right definition of heart failure with preserved ejection fraction. Cardiol J. 2020; 27(5): 449–468, doi: 10.5603/CJ.a2020.0124, indexed in Pubmed: 32986238.
48. Park JJ, Park JH, Hwang IC, et al. Left atrial strain as a predictor of new-onset atrial fibrillation in patients with heart failure. JACC Cardiovasc Imaging. 2020; 13(10): 2071–2081, doi: 10.1016/j.jcmg.2020.04.031, indexed in Pubmed: 32682715.
49. Lisi M, Mandoli GE, Cameli M, et al. Left atrial strain by speckle tracking predicts atrial fibrosis in patients undergoing heart transplantation. Eur Heart J Cardiovasc Imaging. 2021 [Epub ahead of print], doi: 10.1093/ehjci/jeab106, indexed in Pubmed: 34118154.
50. Singh A, Addetia K, Maffessanti F, et al. LA strain for categorization of LVdiastolic dysfunction. JACC Cardiovasc Imaging. 2017; 10(7): 735–743, doi: 10.1016/j.jcmg.2016.08.014, indexed in Pubmed: 28017389.
51. Cameli M, Mandoli GE, Mondillo S. Left atrium: the last bulwark before overt heart failure. Heart Fail Rev. 2017; 22(1): 123–131, doi: 10.1007/s10741-016-9589-9, indexed in Pubmed: 27873135.
52. Said KM, Nassar AI, Fouad A, et al. Left atrial deformation analysis as a predictor of severity of coronary artery disease. Egypt Heart J. 2018; 70(4): 353–359, doi: 10.1016/j.ehj.2018.09.004, indexed in Pubmed: 30591754.
53. Chu AA, Wu TT, Zhang Lu, et al. The prognostic value of left atrial and left ventricular strain in patients after ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. Cardiol J. 2021; 28(5): 678–689, doi: 10.5603/CJ.a2020.0010, indexed in Pubmed: 32037499.
54. Nochioka K, Quarta CC, Claggett B, et al. Left atrial structure and function in cardiac amyloidosis. Eur Heart J Cardiovasc Imaging. 2017; 18(10): 1128–1137, doi: 10.1093/ehjci/jex097, indexed in Pubmed: 28637305.
55. Ancona R, Comenale Pinto S, Caso P, et al. Two-dimensional atrial systolic strain imaging predicts atrial fibrillation at 4-year follow-up in asymptomatic rheumatic mitral stenosis. J Am Soc Echocardiogr. 2013; 26(3): 270–277, doi: 10.1016/j.echo.2012.11.016, indexed in Pubmed: 23261148.
56. Sugimoto T, Bandera F, Generati G, et al. Left atrial dynamics during exercise in mitral regurgitation of primary and secondary origin: pathophysiological insights by exercise echocardiography combined with gas exchange analysis. JACC Cardiovasc Imaging. 2020; 13(1 Pt 1): 25–40, doi: 10.1016/j.jcmg.2018.12.031, indexed in Pubmed: 30878440.
57. Mandoli GE, Pastore MC, Benfari G, et al. Left atrial strain as a pre-operative prognostic marker for patients with severe mitral regurgitation. Int J Cardiol. 2021; 324: 139–145, doi: 10.1016/j.ijcard.2020.09.009, indexed in Pubmed: 32920069.
58. Cameli M, Lisi M, Reccia R, et al. Pre-operative left atrial strain predicts post-operative atrial fibrillation in patients undergoing aortic valve replacement for aortic stenosis. Int J Cardiovasc Imaging. 2014; 30(2): 279–286, doi: 10.1007/s10554-013-0323-6, indexed in Pubmed: 24202403.
59. Laufer-Perl M, Arias O, Dorfman SS, et al. Left atrial strain changes in patients with breast cancer during anthracycline therapy. Int J Cardiol. 2021; 330: 238–244, doi: 10.1016/j.ijcard.2021.02.013, indexed in Pubmed: 33581179.

Aortic regurgitation and left ventricle remodeling on cardiac magnetic resonance and transthoracic echocardiography

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ABSTRACT

Background: Transthoracic echocardiography (TTE) is the first imaging modality used to assess aortic regurgitation (AR). However, it is not possible to provide precise quantification in all patients.

Aim: Our aim was to compare TTE and cardiovascular magnetic resonance (CMR) measurements in grading AR and left ventricle (LV) remodeling.

Methods: A total of 51 consecutive patients with AR in TTE (New York Heart Association I/II, 55%/38%) were enrolled into the study and 49 individuals (age, 57.1 [14]; 61% males) underwent a non-contrast CMR (2 patients excluded) obtained on 1.5 T system (GE Optima MR450w).

Results: The comprehensive quantitative grading with AR volume (AR vol) and regurgitant fraction (RF) were measurable in TTE in 24 cases and showed an association with CMR parameters (AR vol: r = 0.75; P <0.001 and RF: r = 0.55; P <0.01). CMR revealed larger LV end-diastolic volumes (EDV) (185.5 [61] vs 158.4 [61] ml; P = 0.03) and a trend towards higher left ventricular ejection fraction (59% [8] vs 56% [8]; P = 0.08). The association of AR vol and LV EDV was stronger in CMR (r = 0.85; P <0.0001) compared to TTE (r = 0.6; P = 0.001). The inter-modality agreement (TTE-CMR) in AR grading was low (κ = 0.15), with highly concordant grading in mild AR (91%).

Conclusions: CMR provides a comprehensive assessment of AR severity and LV remodeling with a weak or a moderate agreement with TTE.

Key words: aortic regurgitation, cardiovascular magnetic resonance, echocardiography

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INTRODUCTION

Transthoracic echocardiography (TTE) is the main imaging modality used to assess patients with chronic aortic regurgitation (AR). It is used for screening, grading, and monitoring patients with AR and mild symptoms. Current guidelines recommend aortic valve (AV) replacement or repair in patients with overt symptoms and/or severe left ventricle enlargement or systolic dysfunction [1]. The AR is usually well tolerated by most patients over several years and it is crucial to detect the optimal time to surgery and when the clinical prognosis is reduced. However, due to the limitations of ultrasound and the complex nature of AV disease, it is not possible to provide precise quantification of AR and dimensions of the left ventricle (LV) in all patients. Therefore, our aim was to compare TTE and cardiovascular magnetic resonance (CMR) measurements in grading AR and LV remodeling in patients with chronic AR.

METHODS

Study population

All the consecutive patients scheduled for routine TTE in the echocardiography laboratory were screened (2018–2019) and 51 patients were included in the study group after consideration of exclusion criteria. The chronic regurgitation of the native aortic valve (with or without concomitant stenosis) was the inclusion criterion.

WHAT'S NEW?

First, the study showed only a weak or moderate intermodality agreement between transthoracic echocardiography (TTE) and cardiovascular magnetic resonance (CMR) in quantitative aortic regurgitation (AR) grading. Second, the CMR-TTE compatibility was higher in patients with central jets with no associations with the degree of aortic valve (AV) degeneration or the Carpentier classification. Third, CMR provided significantly larger left ventricular end-diastolic volume (LV EDV) compared to TTE, which is especially important in patients with AR. Fourth, there was a significant association in LV EDV between the modalities, but CMR showed a stronger association between the quantitative AR parameters and LV EDV. The study supports better implementation of CMR into clinical practice, especially in patients with a moderate AR.

The main exclusion criteria were as follows: acute aortic regurgitation and/or endocarditis of any native valve, aortic valve prosthesis, any stenosis or more than mild mitral regurgitation, acute coronary syndrome or decompensated congestive heart failure in prior 1 month, infectious diseases in prior 1 month, significant anemia, and contraindications to CMR.

This was a prospective single-center study performed in accordance with the principles of the Declaration of Helsinki and the Bioethics Committee of the Medical University of Silesia. All patients signed the informed consent. This work was supported by the research non-commercial grant from the Medical University of Silesia (KNW-1-027/K/9/K).

Echocardiography

Echocardiography (TTE) was performed with a commercially available 2-dimensional imaging system (General Electric company Vivid e9, Milwaukee, WI, USA). All the patients were scanned in the left lateral decubitus position and each of the examinations followed the EACVI/ASE 2015 recommendations for cardiac chamber quantification by echocardiography in adults [2]. Left ventricular ejection fraction (LVEF) was calculated with the biplane Simpson method (without an ultrasound contrast) and LV mass was estimated using the linear method and Cube formula [2]. Given the main aim of the paper, the grading of the AR was based on the extensive multiparametric approach following the 2017 ASE recommendations for noninvasive evaluation of native valvular regurgitation [3]. The integrative AR measurements were obtained in all patients using qualitative, semi-quantitative (SQ) and quantitative (Q) parameters depending on the quality of the acoustic window and the type of AR itself. Each of the TTE followed the steps of the SQ and Q described in the guidelines [3]. The AR volume (AR vol) and AR regurgitant fraction (AR RF) were estimated using the Doppler method based on proximal isovelocity surface area (PISA). The final severity of AR was a multiparametric assessment with the focus on Q parameters or SQ, if PISA method was not measurable (acoustic window, asymmetric jet, multiple jets). The following quantitative criteria for the AR severity were used: severe (AR vol ≥60 ml; RF ≥50%; ERO ≥0.3 cm^2), moderate (AR vol = 30–59 ml; RF = 30%–49%; ERO = 0.1–0.29 cm^2) and mild (AR vol <30 ml; RF <30%; ERO <0.1 cm^2) [3]. The degree of AV calcifications was based on the subjective assessment, where „0" was for elastic leaflets with no calcifications and „3" was for hyperechogenic severe calcifications. The angle of AR was assessed manually by the single observer as the angle between the axis of the aortic root and the axis of the jet in the parasternal long-axis view. The AR jet angle 0 was central and the more asymmetric jet (in either of the sides) the larger the AR angle.

All the TTE images were obtained, stored anonymously, and then analyzed offline by a single observer (MB) blinded to patient clinical characteristics and CMR results.

Cardiovascular magnetic resonance imaging

The CMR images were acquired on 1.5T system (GE Optima MR450w, GE Healthcare, Wisconsin, WI, USA) with a dedicated phased-array cardiac coil. The study CMR protocol included a non-contrast examination with a multi-planar cine steady-state free precession (SSFP) acquisitions and flow visualization using phase-contrast (PC) flow imaging. Cardiac chambers volumes and functions were analyzed by SSFP in several planes, including 2-chamber, 4-chamber, orthogonal LV outflow track, and parallel short-axis planes covering both atria and ventricles. The typical scan parameters used were TE/TR (time to echo/time of repetition) 1.9/4.3 ms, slice thickness 4–8 mm (no interslice gap), and temporal resolution 30–40 ms. The SSFP planes for the aortic valve complex and ascending aorta were placed perpendicular to the aortic root. The through-plane PC flow imaging was obtained at the slices perpendicular to the axis of flow with the positions just above the valve and velocity encoding maximum values set at 200 cm/s. The PC imaging was repeated, and the position of the slice and maximum velocity values were modified to avoid aliasing or artifacts [4]. The severity of AR was based on AR vol and AR RF obtained in PC imaging and volumetric data calculated from cine images and manual endocardial tracings. The CMR grades of AR were defined according to the 2017 ASE guidelines and the criteria for AR vol and RF were similar as described above for echocardiography [3].

Statistical analysis

The results presented in the manuscript are expressed as means (standard deviation [SD]) for normally distributed

variables or medians (interquartile range [IQR]) for abnormal distribution. In the case of descriptive data, a number (percentage) was used. The distribution was tested for normality with the Kolmogorov-Smirnov test. Baseline clinical parameters and the measures were compared between the subgroups using the t-tests for the normally distributed continuous variable (Student's t-test); in case of abnormal distribution, the Mann-Whitney U test was used. Associations between parameters were assessed using Pearson correlation analysis (parametric variables). The Bland-Altman analysis was performed to measure the agreement between the main parameters of CMR and TTE (AR vol and AR RF). Intermodality agreement for AR severity classification was performed using κ statistics. The calculated kappa coefficients were graded as follows: 0–0.2 low, 0.2–0.4 fair, 0.4–0.6 moderate, 0.6–0.8 good, and >0.8 excellent [5]. A value P <0.05 was considered statistically significant. Statistical analysis was undertaken using Medcalc software (version 19.1, Osten, Belgium).

Table 1. Clinical characteristics of the study group

Age, years, mean (SD)	57.1 (14.2)
Female/male, n (%)	19 (39) / 30 (61)
Diabetes, n (%)	6 (12)
Dyslipidemia, n (%)	45 (91)
Hypertension, n (%)	41 (83)
Smoker or ex-smoker, n (%)	7 (14)
Ischemic heart disease, n (%)	22 (45)
Prior MI, n (%)	0 (0)
Body mass index, kg/m^2, mean (SD)	26.4 (3.6)
Overweight/obesity, n (%)	24 (48) / 8 (16)
Body surface area, m^{2a}, mean (SD)	1.93 (0.18)
NYHA class, n (%)	
I	27 (55)
II	19 (38)
III	3 (7)
IV	0
CCS class, n (%)	
0	39 (79.6)
I	1 (2)
II	6 (12.2)
III	3 (6.2)
IV	0
Aortic valve disease, n (%)	
Bicuspid aortic valve	14 (28.5)
Aortic valve stenosis	20 (40)
Aortic valve calcifications, n (%)	
0	14 (28)
1	16 (32)
2	15 (30)
3	4 (10)
Aortic valve regurgitation, n (%)	
Multiple jets in echocardiography	7 (14)
Central/eccentric jet	26 (53) / 23 (47)
Jet angle, n (%)	
0–30	23 (47)
31–60	16 (32)
61–90	10 (20)

Abbreviations: MI, myocardial infarction; NYHA, New York Heart Association

RESULTS

Clinical characteristics

A total of 51 consecutive patients with AR in TTE were enrolled into the study and finally 49 individuals (age: 57.1 [14]; 61% males) completed a non-contrast CMR (2 excluded for CMR contraindications).

The clinical characteristics, symptoms, and baseline parameters of AV disease are presented in Table 1. In brief, the study patients revealed cardiovascular risk factors, including dyslipidemia (91%), hypertension (83%), obesity (16%), or diabetes (12%). Ischemic heart disease was found in almost half of the patients (45%), and most subjects showed moderate symptoms (New York Heart Association I or II).

Most individuals had some degree of AV calcification (72%), which resulted in a mild (19 patients; 38%) or a moderate (1 patient; 2%) AV stenosis. Half of the subjects showed AR with eccentric jets, and multiple jets were found in 14% of cases.

Left ventricle remodeling

Left ventricle dimensions and systolic function were assessed in both modalities. The LV end-diastolic diameters (EDD) and end-diastolic volumes (EDV) measured in CMR were larger compared to TTE: 57.4 (7) mm vs 54 (6) mm (P = 0.02) and 185.5 (61) ml vs 158.5 (61) ml (P = 0.03). However, there were no differences in the LV end-systolic diameters (35.6 [8] mm vs 35.1 [6] mm; P = 0.7), end-systolic volumes (ESV) (78.5 [36] ml vs 71 [33.2] ml; P = 0.3) and there was a trend towards higher LV ejection fractions in CMR compared to TTE (59 [8] % vs 56.2 [8] %; P = 0.08). Despite some differences, there were significant associations between both modalities in LV EDV and ESV (Figures 1, 2), but not in LV EF. Moreover, LV mass calculated in TTE was overestimated compared to CMR (245 [84] g vs 152 [52] g; P <0.0001), but there was also an association between modalities (r = 0.8; P <0.0001).

Aortic regurgitation

The main SQ measures found in TTE were as follows: jet/LVOT ranged from 15% to 65% (31% [22–36]) and PHT was between 35 ms and 752 ms (404 ms [320–510]). The comprehensive quantitative assessment by the Doppler PISA method with AR vol and AR RF were measurable in TTE in 24 cases: AR vol 38 ml (26–57 ml) and AR RF 43% (33%–57%).

The CMR AR vol ranged from 5 ml to 92 ml (18 ml [6–39]) and AR RF ranged from 5% to 75% (21% [7–36]). In the subgroup of 24 cases, the TTE AR vol was larger compared to CMR AR: 38.5 ml (26–57) vs 18 ml (6–39) (P <0.01) and TTE AR RF was higher compared to CMR RF: 43% (33–57) vs 21% (7–36) (P <0.0001).

Both modalities showed significant associations in AR vol and AR RF (Figures 3, 4).

Both TTE and CMR provided the conclusions for AR grading, which were compared in all patients. The intermo-

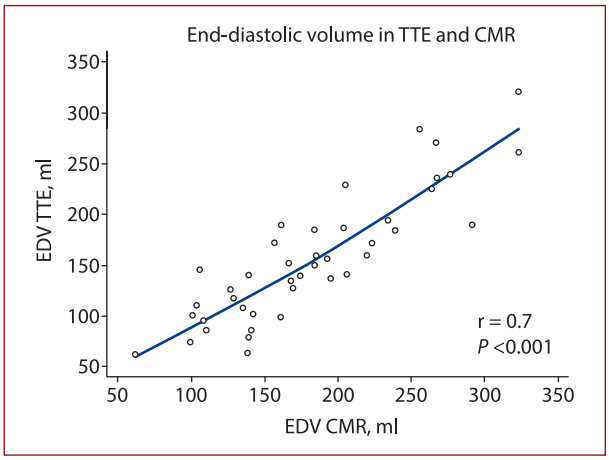

Figure 1. End-diastolic volume (EDV) on transthoracic echocardiography (TTE) and cardiovascular magnetic resonance (CMR). Pearson correlation

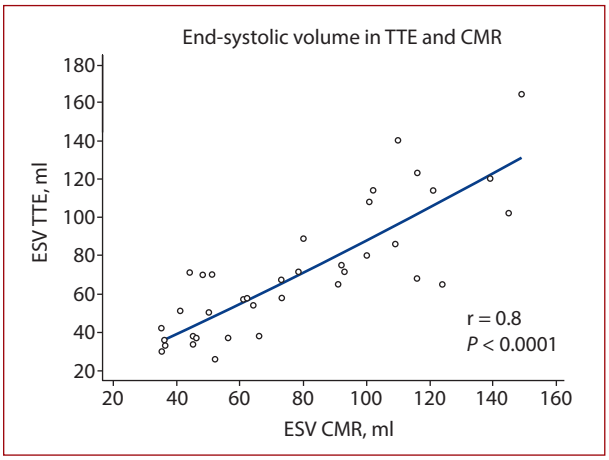

Figure 2. End-systolic volume (ESV) on transthoracic echocardiography (TTE) and cardiovascular magnetic resonance (CMR). Pearson correlation

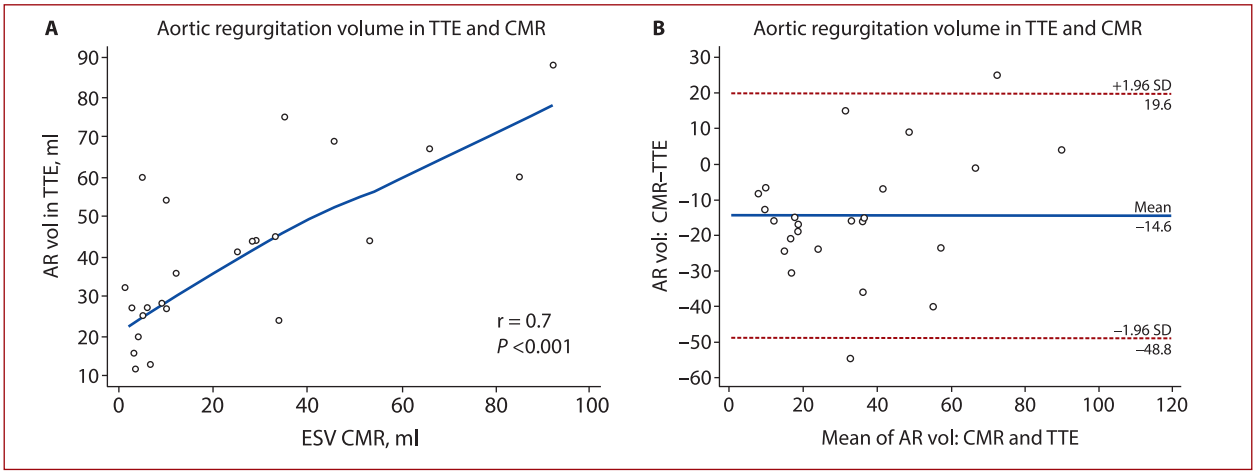

Figure 3. Aortic regurgitation volume (AR vol) on transthoracic echocardiography (TTE) and cardiovascular magnetic resonance (CMR) — Pearson correlation (**A**) and Bland-Altman plot (**B**)

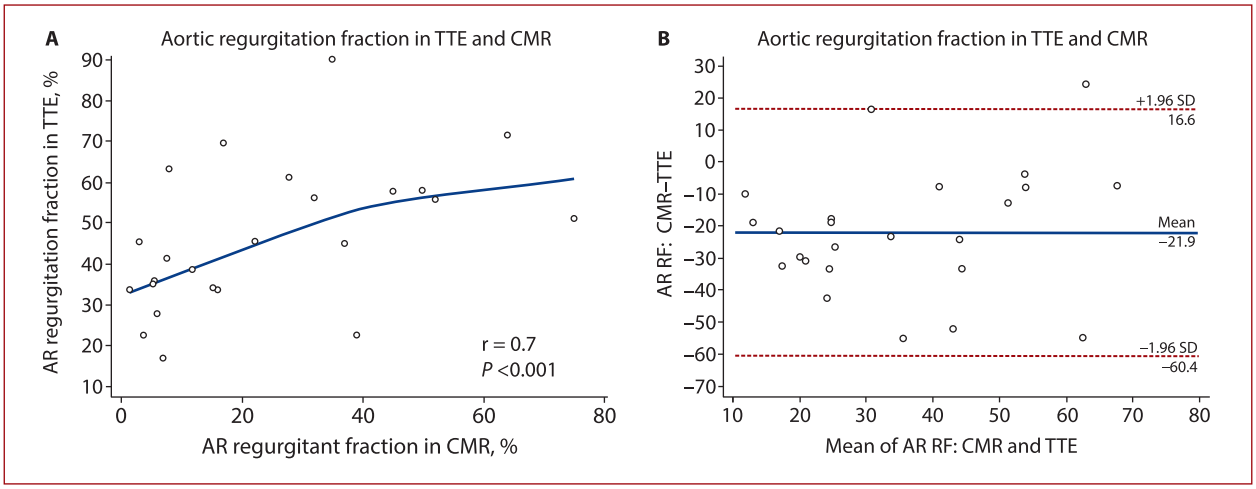

Figure 4. Aortic regurgitation — regurgitation fraction (AR RF) on transthoracic echocardiography (TTE) and cardiovascular magnetic resonance (CMR) — Pearson correlation (**A**) and Bland-Altman plot (**B**)

Table 2. Aortic regurgitation grading in transthoracic echocardiography and cardiovascular magnetic resonance

Transthoracic echocardiography	Mild	Moderate	Severe
Mild	9	0	0
Moderate	22	9	4
Severe	1	1	3

dality agreement (TTE-CMR) in AR grading across a mild, moderate and severe AR was low (κ = 0.15, SE = 0.08; 95% CI, –0.006–0.309) (Table 2). Both modalities provided similar conclusions mostly in mild AR (91%). TTE overestimated the grade of AR in 51% and underestimated the AR severity in 15% of patients (Figure 5).

The rate of concordant AR severity between both modalities was significantly higher in 32 patients with jet angle <40° compared to 17 subjects with asymmetric jet angle ≥40° (50% vs 35%; P <0.05). However, the degree of AV calcification or the mechanism of AR according to the Carpentier classification were not associated with the rate of concordant AR severity (P = ns).

The association of AR vol and LV EDV was stronger in CMR (r = 0.85; P <0.0001) compared to TTE (r = 0.6; P = 0.001).

Myerson et al. showed that CMR AR RF >33% or AR vol >42 ml have a high predictive value to identify patients who will develop symptoms and strong indication for surgery in the following years [4]. In our study group, 18 patients revealed at least one of the above parameters identifying those with worse prognoses. In this subgroup, TTE indicated a significant AR in 50% (severe or moderate-to-severe) and underestimated AR in another 50% of subjects (mild-to-moderate in 45% and even mild in 5%).

DISCUSSION

Our prospective study evaluated the incremental value of CMR over TTE for the assessment of patients with chronic AR. First, there was a moderate intermodality agreement between TTE and CMR in quantitative AR grading. Second, the CMR-TTE compatibility was higher in patients with central jets with no associations with the degree of AV degeneration or the Carpentier classification. Third, CMR provided significantly larger LV EDV compared to TTE, which is especially important in patients with AR. Fourth, there was a significant association in LV EDV between the modalities, but CMR showed a stronger association between the quantitative AR parameters and LV EDV.

Our results are based on the consecutive patients scheduled for the echocardiography lab and they are representative for clinical practice. There were patients with all the degrees of native AR, different AR mechanisms, and various severity of AV calcifications, including any grade of stenosis in 40% of cases. We found that the comprehensive quantitative grading by the Doppler PISA method was available in TTE only in half of the cases. While the PISA method is a major tool for mitral valve regurgitation [6], it is not well visualized in AR, except for significant regurgitations with preferably central jets, when a continuous wave Doppler may be used. Pirat et al. showed that regurgitant volumes in the 2D PISA method had a moderate correlation

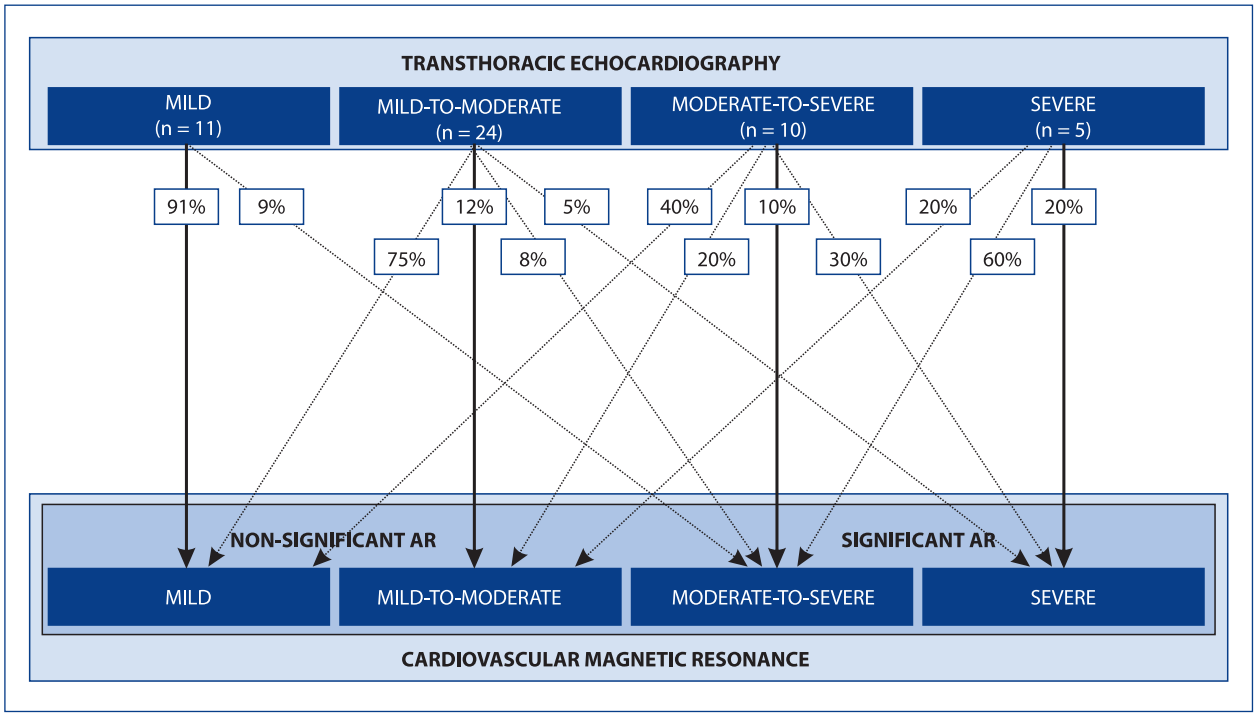

Figure 5. Flow chart — the primary grading of aortic regurgitation on transthoracic echocardiography (number of patients in brackets) and the final grading on cardiovascular magnetic resonance with the rates of patients (%)

Abbreviations: AR, aortic regurgitation

with the actual volumes in an in-vitro flow model for AR, with an accuracy dependent on the shape of the orifice [7]. The 3D PISA method would improve the accuracy of AR quantification, but it requires high-quality images available in transesophageal echocardiography. The other TTE method for quantification (the SV method) is prone to variability mainly due to a 3-dimensional complex and dynamic shape of the mitral annulus and LV outflow tract. The minor change in echocardiographic view is subject to a major change in diameters and estimated volumes and it has higher variability in measurements [4].

Our study showed that the AR vol and AR RF were significantly larger in TTE compared to CMR. Given that TTE showed systematically lower volumes of LV, it is expected that AR RF would be systematically overestimated compared to CMR. Moreover, AR RF obtained in TTE showed only a moderate association with a reference CMR, which suggests that it should not be used in clinical practice. The conclusions of both modalities obtained in all study groups were similar in patients with mild AR. The concordance among the other three grades of AR was moderate or low and, in general, TTE overestimated most cases. However, we had only 5 patients with a severe AR in TTE. Cawley et al. compared both modalities and they also found that TTE used in 31 patients (SV method) overestimated AR vol with no differences in AR RF [8]. There was also only a moderate association between modalities in AR volumes. Gelfand et al. showed a moderate agreement in final AR grading in a small group of patients with AR [9]. Our study is one of the largest among few papers comparing CMR with echocardiography in patients with a native AR [10].

Previous reports showed that the CMR AR grading and AR volumes revealed better predictive values for AV replacement (AVR) or heart failure and it showed a better correlation with an LV remodeling following AVR compared to echocardiography in a relatively small study groups [11, 12]. Given the cut-offs for AR vol and AR RF in CMR provided by Myerson et al. [4], we found that TTE would underestimate the clinical prognosis in half of our study group in a relation to the same cut-off values.

We have used the same cut-off values for quantitative parameters (AR vol and AR RF) in both TTE and CMR, which were recommended in the latest guidelines [3]. There are various cut-offs suggested for AR grading in CMR [13, 14]. The evidence on the appropriate values for CMR is still very scarce and we are awaiting the specific guidelines. We used the CMR PC as the primary method for AR grading as it was shown to have lower variability compared to the CMR RV-LV volume method [6]. Moreover, it was shown that this direct method of AR quantification has high accuracy and reproducibility [15–17].

LV remodeling and systolic function are the other key parameters for appropriate timing of cardiac surgery [1]. CMR is well evidenced to provide very accurate measurements of LV volumes, function, and mass [18, 19]. We found that CMR revealed significantly larger LV EDV compared to TTE. It is in line with previous studies [8, 10]. All our study patients had preserved LV systolic function and the relative differences were small. Therefore, our number of study patients might not have been large enough to provide statistical significance. Although there was an association between LV mass calculated in CMR and estimated in TTE, the linear method used in TTE led to a significant overestimation as it was found in previous reports [8]. Finally, our study showed that there was a stronger association between the quantification of AR and LV EDV in CMR compared to TTE, which is a similar result to the study by Uretsky et al. [20]. Aortic valve-sparing surgery is a recently evolving novel surgical therapeutic option with promising early effects and long-term clinical outcomes [21, 22]. However, it is a highly complex procedure requiring comprehensive imaging diagnostics and an experienced surgical team. Thus, CMR seems to be the best imaging modality for patients scheduled for AV repair.

Study limitations

Our study group included only 5 individuals with a severe AR, which limits the strength of our conclusions. We do not have a clinical follow-up yet and we cannot relate our results to clinical prognosis. All the valve regurgitations have a physiological variability in loading conditions dependent on blood pressure or heart rate, which could affect the measurements. However, it affects both modalities and our study group included only chronic AR. We did not use 3-dimensional measurements of LV volumes, which would improve the compatibility in measurements between TTE and CMR. However, 3D TTE is measurable only in patients with a good acoustic window.

CONCLUSIONS

In our study, CMR provided a comprehensive assessment of AR severity and LV remodeling with a moderate agreement with TTE and a better clinical predictive value. In clinical practice, echocardiography is the most reliable in patients with mild or non-significant AR and central jets with good conditions for a PISA method quantification. However, a comprehensive quantitative assessment by the PISA method was measurable in less than half of the study patients. There is a clear underestimation of the degree of LV remodeling in TTE and systematical difference in quantitative parameters of AR between CMR and TTE. It suggests the need for new cut-off values in AR in both modalities. Our study supports also better implementation of CMR into clinical practice, especially in patients with a moderate AR.

Article information

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REFERENCES

1. Baumgartner H, Falk V, Bax JJ. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017; 38(36): 2739–2791, doi: 10.1093/eurheartj/ehx391, indexed in Pubmed: 28886619.
2. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015; 28(1): 1–39.e14, doi: 10.1016/j.echo.2014.10.003, indexed in Pubmed: 25559473.
3. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation – a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr. 2017; 30(4): 303–371, doi: 10.1016/j.echo.2017.01.007, indexed in Pubmed: 28314623.
4. Myerson SG, d'Arcy J, Mohiaddin R, et al. Aortic regurgitation quantification using cardiovascular magnetic resonance: association with clinical outcome. Circulation. 2012; 126(12): 1452–1460, doi: 10.1161/CIRCULATIONAHA.111.083600, indexed in Pubmed: 22879371.
5. Medvedofsky D, León Jiménez J, Addetia K, et al. Multi-parametric quantification of tricuspid regurgitation using cardiovascular magnetic resonance: A comparison to echocardiography. Eur J Radiol. 2017; 86: 213–220, doi: 10.1016/j.ejrad.2016.11.025, indexed in Pubmed: 28027750.
6. Sköldborg V, Madsen PL, Dalsgaard M, et al. Quantification of mitral valve regurgitation by 2D and 3D echocardiography compared with cardiac magnetic resonance a systematic review and meta-analysis. Int J Cardiovasc Imaging. 2020; 36(2): 279–289, doi: 10.1007/s10554-019-01713-7, indexed in Pubmed: 31664679.
7. Pirat B, Little SH, Igo SR, et al. Direct measurement of proximal isovelocity surface area by real-time three-dimensional color Doppler for quantitation of aortic regurgitant volume: an in vitro validation. J Am Soc Echocardiogr. 2009; 22(3): 306–313, doi: 10.1016/j.echo.2008.11.031, indexed in Pubmed: 19168322.
8. Cawley PJ, Hamilton-Craig C, Owens DS, et al. Prospective comparison of valve regurgitation quantitation by cardiac magnetic resonance imaging and transthoracic echocardiography. Circ Cardiovasc Imaging. 2013; 6(1): 48–57, doi: 10.1161/CIRCIMAGING.112.975623, indexed in Pubmed: 23212272.
9. Gelfand EV, Hughes S, Hauser TH, et al. Severity of mitral and aortic regurgitation as assessed by cardiovascular magnetic resonance: optimizing correlation with Doppler echocardiography. J Cardiovasc Magn Reson. 2006; 8(3): 503–507, doi: 10.1080/10976640600604856, indexed in Pubmed: 16755839.
10. Lee JC, Branch KR, Hamilton-Craig C, et al. Evaluation of aortic regurgitation with cardiac magnetic resonance imaging: a systematic review. Heart. 2018; 104(2): 103–110, doi: 10.1136/heartjnl-2016-310819, indexed in Pubmed: 28822982.
11. Neisius U, Tsao CW, Hauser TH, et al. Aortic regurgitation assessment by cardiovascular magnetic resonance imaging and transthoracic echocardiography: intermodality disagreement impacting on prediction of post-surgical left ventricular remodeling. Int J Cardiovasc Imaging. 2020; 36(1): 91–100, doi: 10.1007/s10554-019-01682-x, indexed in Pubmed: 31414256.
12. Harris AW, Krieger EV, Kim M, et al. Cardiac Magnetic Resonance Imaging Versus Transthoracic Echocardiography for Prediction of Outcomes in Chronic Aortic or Mitral Regurgitation. Am J Cardiol. 2017; 119(7): 1074–1081, doi: 10.1016/j.amjcard.2016.12.017, indexed in Pubmed: 28153348.
13. Gabriel RS, Renapurkar R, Bolen MA, et al. Comparison of severity of aortic regurgitation by cardiovascular magnetic resonance versus transthoracic echocardiography. Am J Cardiol. 2011; 108(7): 1014–1020, doi: 10.1016/j.amjcard.2011.05.034, indexed in Pubmed: 21784393.
14. Kutty S, Whitehead KK, Natarajan S, et al. Qualitative echocardiographic assessment of aortic valve regurgitation with quantitative cardiac magnetic resonance: a comparative study. Pediatr Cardiol. 2009; 30(7): 971–977, doi: 10.1007/s00246-009-9490-6, indexed in Pubmed: 19636486.
15. Dulce MC, Mostbeck GH, O'Sullivan M, et al. Severity of aortic regurgitation: interstudy reproducibility of measurements with velocity-encoded cine MR imaging. Radiology. 1992; 185(1): 235–240, doi: 10.1148/radiology.185.1.1523315, indexed in Pubmed: 1523315.
16. Honda N, Machida K, Hashimoto M, et al. Aortic regurgitation: quantitation with MR imaging velocity mapping. Radiology. 1993; 186(1): 189–194, doi: 10.1148/radiology.186.1.8416562, indexed in Pubmed: 8416562.
17. Søndergaard L, Hildebrandt P, Lindvig K, et al. Quantification of aortic regurgitation by magnetic resonance velocity mapping. Am Heart J. 1993; 125(4): 1081–1090, doi: 10.1016/0002-8703(93)90117-r, indexed in Pubmed: 8465731.
18. Bellenger NG, Burgess MI, Ray SG, et al. Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable? Eur Heart J. 2000; 21(16): 1387–1396, doi: 10.1053/euhj.2000.2011, indexed in Pubmed: 10952828.
19. Hudsmith LE, Petersen SE, Francis JM, et al. Normal human left and right ventricular and left atrial dimensions using steady state free precession magnetic resonance imaging. J Cardiovasc Magn Reson. 2005; 7(5): 775–782, doi: 10.1080/10976640500295516, indexed in Pubmed: 16353438.
20. Uretsky S, Supariwala A, Nidadovolu P, et al. Quantification of left ventricular remodeling in response to isolated aortic or mitral regurgitation. J Cardiovasc Magn Reson. 2010; 12: 32, doi: 10.1186/1532-429X-12-32, indexed in Pubmed: 20497540.
21. Gocoł R, Malinowski M, Bis J, et al. Long-term outcomes of aortic valve repair in over 500 consecutive patients: a single-center experience. Kardiol Pol. 2020; 78(9): 861–868, doi: 10.33963/KP.15406, indexed in Pubmed: 32486628.
22. Łukaszewski M, Bielicki G, Berezowski M, et al. Aortic valve-sparing procedures in patients with aortic valve insufficiency: a singlecenter experience. Kardiol Pol. 2020; 78(2): 158–160, doi: 10.33963/KP.15152, indexed in Pubmed: 31969551.

Src-IL-18 signaling regulates the secretion of atrial natriuretic factor in hypoxic beating rat atria

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ABSTRACT

Background: Interleukin (IL)-18 is produced mainly in the heart and can be associated with the development of cardiac hypertrophy that leads to cardiac dysfunction. However, the effects of hypoxia on IL-18 expression and atrial natriuretic factor (ANF) secretion remain largely unknown.

Aim: The aim of this study was to assess the effect of hypoxia on IL-18 production and its role in ANF secretion by using an isolated perfused beating rat atrial model.

Methods: The level of ANF in the perfusates was determined by radioimmunoassay, and the protein levels of Src, IL-18 and its receptors (IL-18-Rα and IL-18-Rβ), Rho guanine nucleotide exchange factor (RhoGEF) and RhoA, activating transcription factor 3 (ATF3), T cell factor (TCF) 3 and 4, and lymphoid enhancer factor (LEF) 1 in atrial tissue samples were detected by Western blotting.

Results: Hypoxia significantly upregulated the expression of the non-receptor tyrosine kinase Src, and this effect was blocked by endothelin-1 receptor type A (BQ123) and type B (BQ788) antagonists. Hypoxia also enhanced the expression of RhoGEF and RhoA concomitantly with the upregulation of IL-18, IL-18-Rα and IL-18-Rβ. The hypoxia-induced RhoGEF and RhoA were abolished by Src inhibitor 1 (SrcI), and the protein levels of IL-18 and its two receptors were also blocked by SrcI. Moreover, the hypoxia-induced expression levels of ATF3, TCF3, TCF4 and LEF1 were repealed by IL-18 binding protein, and the hypoxia-promoted secretion of ANF was also obviously attenuated by this binding protein.

Conclusions: These findings imply that Src-IL-18 signaling is involved in the release of ANF in hypoxic beating rat atria.

Key words: atrial natriuretic factor, endothelin-1, hypoxia, interleukin-18, non-receptor tyrosine kinase Src

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INTRODUCTION

Interleukin (IL)-18 is a proinflammatory cytokine that has been discovered from the serum of mice injected and infected with endotoxin and Mycobacterium bovis bacillus Calmette-Guérin, respectively [1]. Accumulating evidence has demonstrated that endothelial cells, infiltrated neutrophils, smooth muscle cells, resident macrophages, and cardiomyocytes can generate IL-18 in response to infection or injury [2, 3]. IL-18 is associated with the development of cardiomyocyte hypertrophy that leads to extracellular matrix remodeling and myocardial contractile dysfunction in different animal models of pressure overload, acute myocardial infarction, and lipopolysaccharide-induced dysfunction [4–6]. The overexpression of IL-18 is related to an increased risk of developing cardiovascular diseases and confer a poor prognosis in these patients [3]. Additionally, IL-18 upregulates the protein and mRNA expression of atrial natriuretic peptide (ANF) concomitantly with an increase in the expression of GATA4 through the phosphatidylinositol 3 kinase-Akt pathway [7, 8]. As a peptide hormone,

WHAT'S NEW?

In this study, hypoxia regulates atrial natriuretic factor (ANF) secretion by activating the Src-interleukin-18-activating transcription factor 3 signaling pathway. These effects were controlled by hypoxia-induced endogenous endothelin-1 (ET-1) via ET receptors in isolated beating rat atria. The findings reveal a new mechanism for the regulation of ANF secretion during hypoxia, which provides a new target for the treatment of myocardial ischemia/hypoxia-related diseases.

ANF is produced and released from the atrial myocytes in response to certain stimuli (e.g., stretch and hypoxia) [9]. It possesses beneficial effects on cardiovascular diseases such as natriuresis, diuresis, vasodilation, blood pressure regulation [10]. ANF secretion is strongly augmented by hypoxia, which can regulate cellular adaptation to hypoxia, protect cardiomyocytes against ischemia/reperfusion injury, decrease the risk of heart failure and prevent ventricular remodeling after dilated cardiomyopathy [11–13]. In our previous work [14], we found that hypoxia could stimulate the secretion of ANF by regulating endogenous endothelin-1 (ET-1) expression through activation of cyclooxygenase 2-lipocalin-type prostaglandin D synthase–peroxisome proliferator-activated receptor γ signaling pathway in beating rat atria, but the precise mechanisms by which hypoxia regulates atrial ANF secretion are still unclear. Other studies have demonstrated that the mRNA levels of IL-18 and pro-IL-18 are notably upregulated in the left ventricular myocardium after ischemia/reperfusion in the mouse model [15], while the levels of IL-18 in the circulation and myocardial tissue are also upregulated in heart failure patients [16, 17]. However, the effects of hypoxia on IL-18 expression and its role in ANF secretion remain largely unknown. This study aims to determine the effects and underlying mechanisms by which hypoxia regulates ANF secretion in beating rat atria.

METHODS

Reagents

Human and murine IL-18 binding protein (IL-18-BP) isoforms are active across species [18]. Thus, recombinant human IL-18-BP (100.0 ng/ml; CB99) was selected in this study and was purchased from Novoprotein (Shanghai, China). Endothelin receptor type A (ETA) antagonist BQ123 (0.3 μM; B150) and endothelin receptor type B (ETB) antagonist BQ788 (0.3 μM; B157) were supplied by Sigma-Aldrich (St. Louis, MO, USA). Src tyrosine kinase antagonist or Src inhibitor 1 (SrcI, 1.0 μM; HY-101053) and Rhosin hydrochloride (Rhosin) or Rho guanine nucleotide exchange factor (RhoGEF) inhibitor (10.0 μM; HY12646) were supplied by MedChemExpress (Monmouth Junction, NJ, USA).

Isolation and perfusion of beating rat atria

To avoid gender interference, 129 Sprague-Dawley rats of different sexes (62 male and 67 female; weight: 250–300 g; age: 18 weeks) were randomly selected to prepare the perfused beating rat atria. The rats were maintained under specific pathogen-free conditions at Yanbian University (Permit No.: SCXK [Ji] 2011–006) and fed a standard chow diet. All experiments were approved by the Animal Care and Use Committee of Yanbian University and were in accordance with the laboratory animal guidelines of the US National Institutes of Health. The perfused beating left atrium was isolated from each rat and prepared according to the previous methods [14, 19]. Transmural electrical field stimulation (30–40 V, 0.3 ms) was operated at a frequency of 1.5 Hz using a luminal electrode. To measure the changes in pulse pressure variation, atrial pacing was conducted by perfusing HEPES buffer solution into the atrium via a peristaltic pump (1.0 ml/min). An adequate amount of oxygen was supplied to the perfused atrium throughout the whole process. The HEPES buffer solution (pH 7.4) consisted of NaCl, $NaHCO_3$, HEPES, glucose, KCl, $CaCl_2$, $MgCl_2$, and bovine serum albumin (118, 25, 10, 10, 4.7, 2.5,1.2 mmol/l, and 0.1%, respectively).

Construction of the hypoxic atrial model

To establish a hypoxic atria model, O_2 was replaced with N_2 by substituting the standard HEPES buffer with an N_2-saturated HEPES buffer. The P_{O2} of N_2 saturated perfusates was 55 ± 2 mm Hg, indicating that the hypoxic condition has reached a severe level.

Determination of ANF levels

The concentrations of ANF in the perfusates were determined by the Iodine [^{125}I] Atrial Natriuretic Factor Radioimmunoassay Kit, according to the previous methods [14, 19]. The inter- and intra-assay coefficients of variation for this assay were <15% and <10%, respectively. The amounts of ANF secretion are presented as ng/min/g of atrial tissue wet weight.

Experimental procedures

The rats were randomly assigned to 8 groups (n = 6 in each group): (1) normoxia, (2) hypoxia, (3) IL-18-BP + hypoxia, (4) BQ123 + hypoxia, (5) BQ788 + hypoxia, (6) BQ123 + BQ788 + hypoxia, (7) SrcI + hypoxia, and (8) Rhosin + hypoxia groups.

To stabilize the atrial dynamic parameters, each atrium was subjected to perfusion over a period of 1 hour. Following two 12-minutes normoxia cycles, the perfusates were infused with hypoxic buffer for four cycles. Samples were collected at 4°C every 2 minutes to measure ANF levels. After perfusion, the atrial tissues were immediately frozen and kept at −80°C. Subsequently, another set of

experiments was conducted to elucidate the mechanisms of hypoxia-regulated ANF secretion. After one normoxia cycle, one treatment cycle was followed by four infusion cycles of hypoxia plus the treatment agent(s). The normoxia experiments were carried out with the infusion of normoxic buffer for 6 cycles.

Immunoblot analysis

Each left atrium tissue was rinsed with saline and transferred into RIPA buffer (Solarbio Institute of Biotechnology, Shanghai, China) containing 1.0 M protease inhibitor (Beyotime Biotechnology) and 1.0 M phosphatase inhibitor (Bestbio, Shanghai, China) for homogenization. Immunoblotting, quantitative autoradiography, and densitometric analysis were carried out according to the previous methods [14, 19]. Briefly, the equal amounts (40 μg) of protein samples were subjected to SDS-PAGE and subsequently transferred onto PVDF membranes. After blocking (5% BSA; SW3015; Solarbio) for 2 hours, the membranes were separately incubated with anti-IL-18 (1:000; bs-0529R; Bioss, Beijing, China), anti-IL-18-type α receptor (IL-18-Rα; 1:500; BS9268; Bioworld Technology, Nanjing, China), anti-IL-18-type β receptor (IL-18-Rβ; 1:1000; bs-2616R; Bioss), anti-Src (1:500; 04-889; Millipore, MA, US), anti-p115RhoGEF (1:1000; BS5901; Bioworld Technology), anti-RhoA (1:1000; 10749-1-AP; Proteintech, Wuhan, China), anti-activating transcription factor 3 (ATF3; 1:1000; DF6660; Affinity, Changzhou, China), anti-T cell factor (TCF) 3 (1:500; DF4573; Affinity), anti-TCF4 (1:500; DF7622; Affinity), anti-lymphoid enhancer factor 1 (LEF1; 1:1000; DF7570; Affinity), or anti-β-actin antibodies (1:1000; AP0060; Bioworld Technology) overnight at 4°C. The membranes were then washed and incubated again with a secondary antibody (1:3000; AP132P; Nachuan biotech, Changchun, China) for 1.5 hours at room temperature. Visualization of the protein bands was performed using ECL Western blotting substrate kit (Raybiotech, Atlanta, GA, USA) and a chemiluminescent detection system. Densitometric analysis of the protein blots was conducted using ImageJ software (NIH, Bethesda, MA, USA).

Statistical analysis

All data were normally distributed (Kolmogorov–Smirnov test) and presented as mean (standard error of the mean, SEM). IBM SPSS Statistics software ver. 19.0 (IBM Corp, Armonk, NY, USA) and GraphPad Prism ver. 9.1.2 software (San Diego, CA, USA) were employed for statistical analyses. The Student's t-test was used to compare the difference between two groups (Supplementary material, *Figure S1B*), while one-way

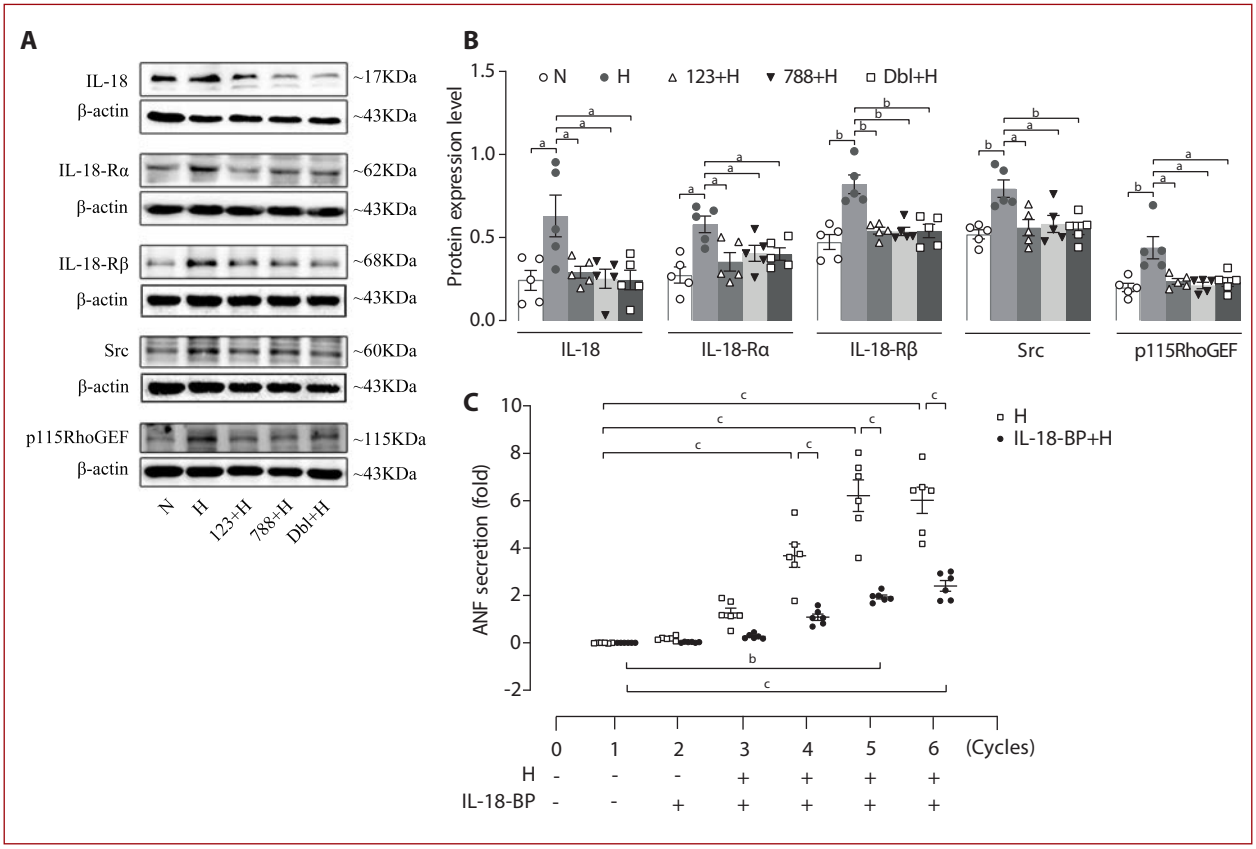

Figure 1. Effects of hypoxia on IL-18, IL-18-Rα, IL-18-Rβ, Src, and RhoGEF expression, and ANF secretion in isolated beating rat atria. **A.** Representative Western blot bands. **B.** Quantification of protein levels (n = 5, 3 male and 2 female/per group). **C.** Changes of ANF secretion (the values were represented the averages of each cycle, n = 6, 3 male and 3 female/per group). Data were expressed as mean (SEM). ^{a}P <0.05; ^{b}P <0.01; ^{c}P <0.0001. IL-18-BP, and hypoxia, respectively

Abbreviations: 123, BQ123, an ETA antagonist; 788, BQ788, an ETB antagonist; ANF, atrial natriuretic factor; Dbl, BQ123+BQ788; H, hypoxia; IL-18, interleukin-18; IL-18-BP, IL-18 binding protein, an IL-18 antagonist; IL-18-Rα, IL-18-type α receptor; IL-18-Rβ, IL-18-type β receptor; N, normoxia; RhoGEF, Rho guanine nucleotide exchange factor

ANOVA followed by Dunnett's multiple comparison (Figures 1B, 2B, 3B, 4B, and Supplementary material, *Figure S2B*). Two-way ANOVA followed by Bonferroni post hoc test was used for Figure 1C, 2C, and 3C. *P*-value <0.05 was considered statistically significant. The Bonferroni-corrected *P*-value thresholds were calculated as follows: for the study of associations between normoxia, hypoxia, and hypoxia plus the treatment agent (hypoxia + IL-18-BP, hypoxia + SrcI, hypoxia + Rhosin), a significance level of α = 0.05, so the corrected *P*-value threshold was 0.05/3 = 0.0167.

RESULTS

Effects of hypoxia on IL-18 expression and ANF secretion

To explore the roles of hypoxia in regulating IL-18 expression and ANF secretion, a series of experiments were conducted using the isolated atrial perfusates and tissue of a hypoxic rat model. The results demonstrated that hypoxia remarkably upregulated the expression of IL-18 ($P = 0.02$ vs normoxia) and its type α (IL-18-Rα) and β (IL-18-Rβ) receptors ($P = 0.03$, 0.001 vs normoxia, respectively, Supplementary material, *Figure S1A*). Corrected *P*-values were applied to multiple comparisons of ANF secretion using Bonferroni posthoc analysis. Posthoc analysis showed that hypoxia also significant increase ANF secretion ($P < 0.0001$ vs normoxia; Figure 1C), and the ANF secretion was obviously decreased by IL-18-BP, an IL-18 antagonist ($P < 0.0001$ vs hypoxia; Figure 1C), reaching the Bonferroni-corrected *P*-value threshold (<0.0167). In addition, the upregulated expression levels of IL-18 and its receptors, IL-18-Rα and IL-18-Rβ, induced by hypoxia were completely suppressed by BQ123 ($P = 0.03$, 0.02, 0.002 vs hypoxia) and BQ788 ($P = 0.03$, 0.04, 0.002 vs hypoxia), the ETA and ETB antagonists (Figure 1A, 1B). These findings indicated that IL-18 altered by endogenous ET-1 was involved in the release of ANF in beating rat hypoxic atria.

Effects of hypoxia on the expression of Src and RhoA as well as the secretion of ANF

In accordance with the role of Src in inflammatory actions and the relationship between RhoA and interleukins, we determined the effects of hypoxia on the protein levels of Src, RhoA, as well as the secretion of ANF. The results indicated that hypoxia markedly upregulated the expression of Src ($P = 0.002$ vs normoxia; Figure 1A, 1B), but such upregulation was entirely abolished by BQ123 ($P = 0.01$ vs hypoxia) and BQ788 ($P = 0.02$ vs hypoxia; Figure 1A, 1B). Hypoxia was also noticeably upregulated the expression of p115RhoGEF ($P = 0.01$ vs normoxia; Figure 1A, 1B) and RhoA ($P = 0.005$ vs normoxia; Figure 2A, 2B). However,

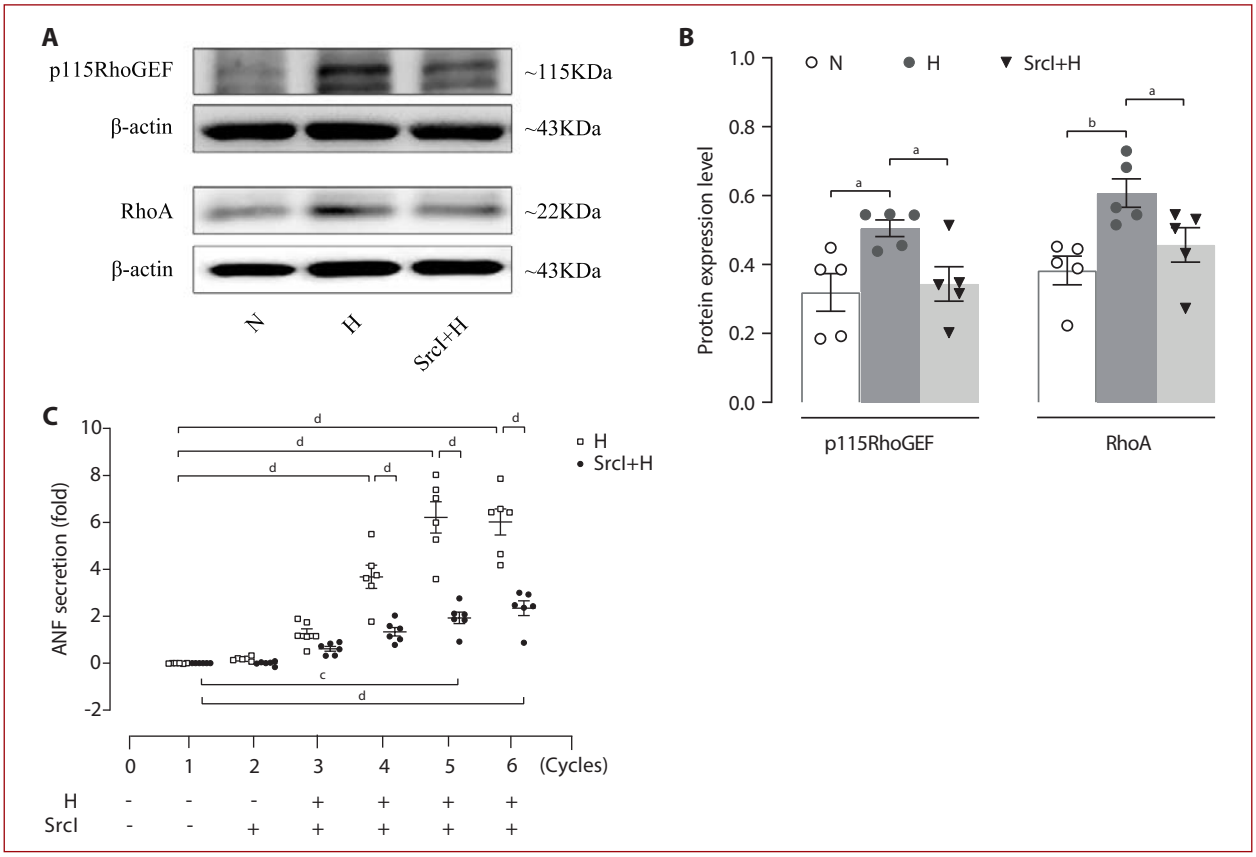

Figure 2. Effects of Src on RhoGEF and RhoA protein levels as well as the secretion of ANF in beating rat atria. **A.** Representative Western blot bands. **B.** Quantification of protein levels (n = 5, 3 male and 2 female/per group). **C.** Changes of ANF secretion (n = 6, 3 male and 3 female/per group). Data were expressed as mean (SEM). [a]$P < 0.05$; [b]$P < 0.01$; [c,d]$P < 0.0001$

Abbreviations: SrcI, Src inhibitor 1, a Src antagonist. Other — see Figure 1

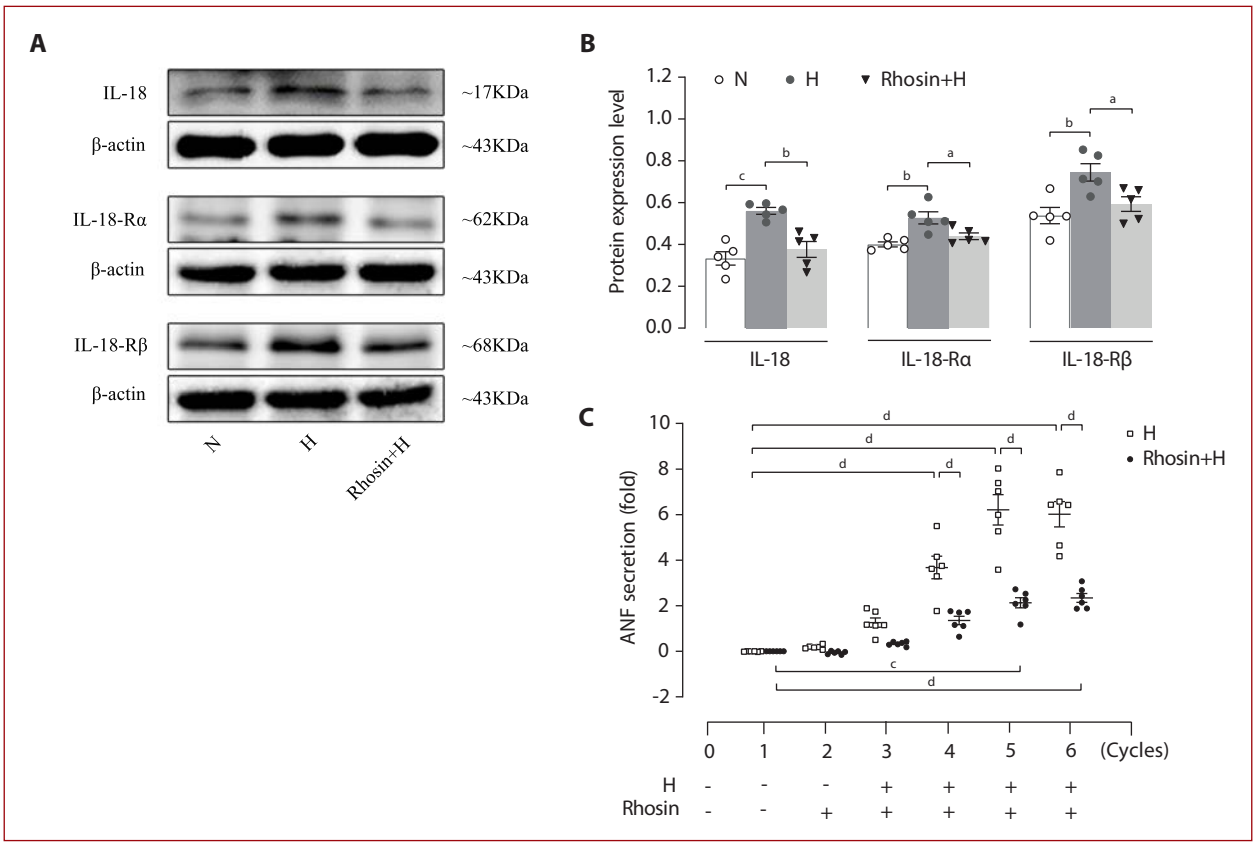

Figure 3. Effects of RhoGEF on the protein levels of IL-18 and its receptors, and the secretion of ANF in hypoxic beating rat atria. **A.** Representative Western blot bands. **B.** Quantification of protein levels (n = 5, 2 male and 3 female/per group). **C.** Changes of ANF secretion (n = 6, 3 male and 3 female/per group). Data were expressed as mean (SEM). ^{a}P <0.05; ^{b}P <0.01; ^{c}P <0.001; ^{d}P <0.0001

Abbreviations: Rhosin, a RhoGEF antagonist. Other — see Figure 1

the hypoxia-induced expression of p115RhoGEF was obviously reduced by BQ123 (P = 0.02 vs hypoxia) and BQ788 (P = 0.01 vs hypoxia; Figure 1A, 1B). Moreover, a Src antagonist SrcI also downregulated the expression of p115RhoGEF (P = 0.02 vs normoxia) and RhoA (P = 0.049 vs normoxia; Figure 2A, 2B). Moreover, posthoc analysis showed that the hypoxia-induced ANF secretion (P <0.0001 vs normoxia; Figure 2C, 3C) was remarkably decreased by SrcI (P <0.0001 vs hypoxia; Figure 2C) and Rhosin, a RhoGEF inhibitor (P <0.0001 vs hypoxia; Figure 3C), reaching the Bonferroni-corrected P-value threshold (<0.0167). These results demonstrated that Src induced by hypoxia-induced ET-1 could regulate the expression of RhoA through p115RhoGEF activation and mediate the hypoxia-induced release of ANF.

Effects of RhoA on hypoxia-induced expression of IL-18

To elucidate the role of RhoA in modulating the hypoxia-induced expression of IL-18 and its receptors, a series of experiments were performed using Rhosin. The hypoxia-induced upregulation of IL-18 (P = 0.0002 vs normoxia) and its receptors (IL-18-Rα and IL-18-Rβ, P = 0.004, 0.007 vs normoxia) were utterly blocked by Rhosin (P = 0.002, 0.03, 0.02 vs hypoxia, respectively; Figure 3A, 3B). These findings showed that RhoA controlled by Src could regulate the protein levels of IL-18, IL-18-Rα, and IL-18-Rβ under hypoxic conditions.

Effects of IL-18 on hypoxia-induced expression of TCF/LEF

To understand the mechanisms by which IL-18 mediates hypoxia-induced ANF secretion, the effect of IL-18 on TCF/LEF expression was determined using IL-18-BP. The results demonstrated that hypoxia markedly increased the protein levels of ATF3, TCF3, TCF4, and LEF1 (P = 0.01, 0.001, 0.03, 0.005 vs normoxia, respectively; Figure 4A and 4B), but such upregulation patterns were entirely abolished by BQ123 (P = 0.04, 0.03, 0.04, 0.02 vs hypoxia) and BQ788 (P = 0.02, 0.02, 0.03, 0.02 vs hypoxia; Supplementary material, *Figure S1A*, *S1B*). IL-18-BP also dramatically suppressed the hypoxia-induced expression of ATF3 (P = 0.048 vs hypoxia), TCF3 (P <0.001 vs hypoxia), TCF4 (P = 0.04 vs hypoxia) and LEF1 (P = 0.04 vs hypoxia; Figure 4A, 4B). These findings revealed that IL-18 could regulate the expression of ATF3, TCF3/LEF1, and TCF4/LEF1 in hypoxic beating rat atria.

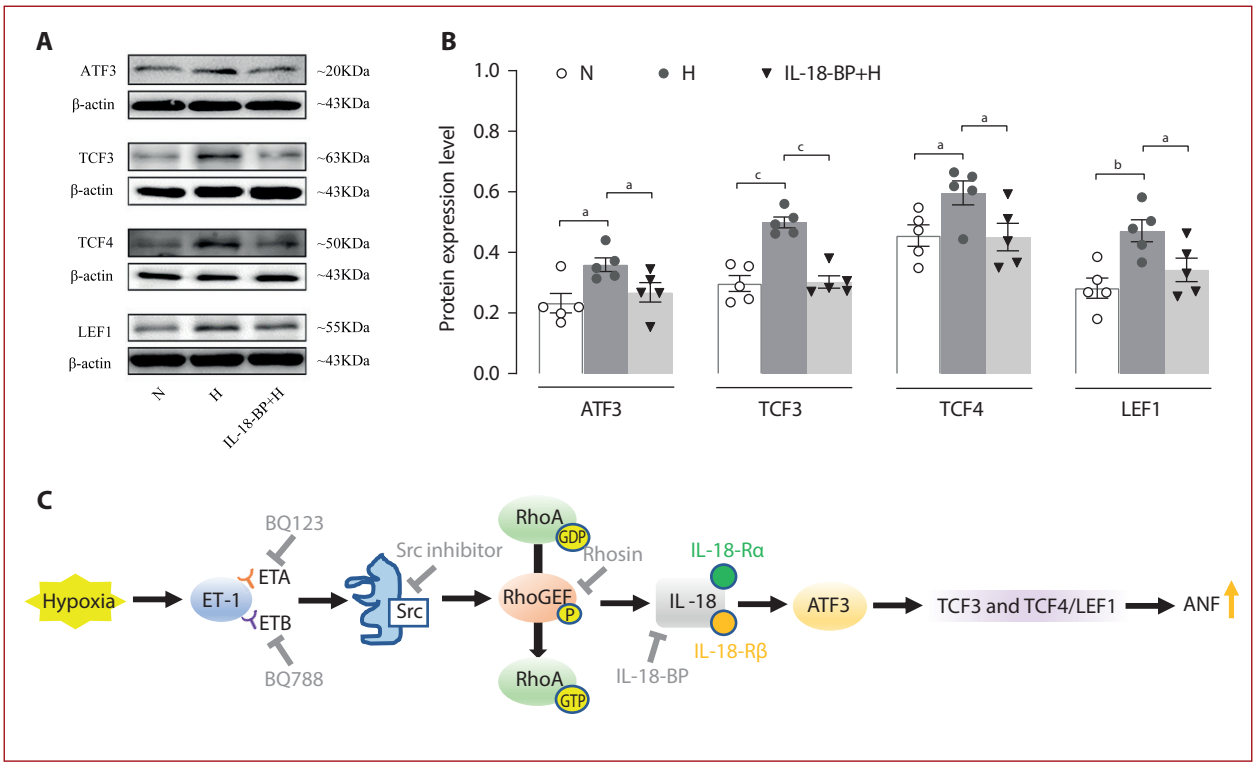

Figure 4. A, B. Effect of IL-18 on the protein levels of ATF3, TCF3, TCF4 and LEF1. **C.** Schematic mechanisms by which Src–IL-18 regulates ANF secretion during hypoxia. Representative Western blot bands and their quantification (n = 5, 2 male and 3 female/per group) were presented at **A** and **B** panels. Data were expressed as mean (SEM). ^{a}P <0.05; ^{b}P <0.01; ^{c}P <0.001

Abbreviations: ATF3, Activating transcription factor 3; TCF3, T cell factor 3; TCF4, T cell factor 4; LEF1, lymphoid enhancer factor 1

DISCUSSION

This study revealed that hypoxia upregulated the expression of non-receptor tyrosine kinase Src, which obviously increased the expression of IL-18 and its two receptors through activation of RhoA signaling. The increase in IL-18 subsequently upregulated the expression of ATF3, TCF3/LEF1, and TCF4/LEF1, which ultimately regulated hypoxia-induced ANF secretion. These effects were controlled by hypoxia-stimulated ET-1 expression via ET receptors in the isolated beating rat atria (Figure 4C).

Src, a non-receptor tyrosine kinase, is activated by hypoxia and plays a crucial role in triggering intracellular signaling cascades in cardiac myocytes. Additionally, Src is also involved in the processes of cardiovascular disorders induced by ET-1 [20]. Our results demonstrated that hypoxia remarkably upregulated the expression of Src concomitantly with a potent promotion of ANF secretion, while the expression of Src was completely abolished by ET receptor antagonists (BQ123 and BQ788). Moreover, hypoxia-induced ANF secretion was obviously attenuated by SrcI. These data indicated that Src controlled by ET-1 was involved in the atrial secretion of ANF under hypoxic conditions. These results were similar to the previous studies mentioned above and supported a previous study in which the increased Src activity in response to ET-1 treatment was involved in ET-dependent pathway activation of ANF promoter in cardiomyocytes [21].

Rho-kinase is an important downstream effector of RhoA and its activity often requires prior activation of RhoGEFs and subsequently enabling the activation of RhoA [22]. RhoA/Rho-kinase pathway plays a vital role in diverse cellular functions, while its excessive activity is involved in the development of cardiovascular diseases [23]. Results of this study further showed that p115RhoGEF and RhoA were markedly upregulated by hypoxia concomitantly with increased expression of IL-18 and its two receptors. Interestingly, the hypoxia-induced expression of p115RhoGEF was completely blocked by BQ123, BQ788, and SrcI, whereas Rhosin, an antagonist of RhoGEF, was entirely suppressed the expression of IL-18 and its two receptors. These results imply that Src controlled by endogenous ET-1 via its both antagonists could upregulate the protein levels of IL-18 and its receptors through activation of RhoA, which support a previous study showing that hypoxia- or G-protein-coupled receptor-induced ROS-dependent activation of Src led to the overexpression of RhoA via p115RhoGEF in rat intrapulmonary artery [24]. Moreover, our findings are also consistent with a previous report indicating that aldosterone-induced ET-1 upregulated the expression of IL-18 through activation of Rho-kinase via ETA in cultured rat neonatal cardiomyocytes [25]. However, the effect of ETB on IL-18 expression in this study is controversial with the earlier mentioned reports. This may be, at least in part, explained by the differences in experimental design, sub-

jects and conditions. However, evidence has implicated the potential role of *EdnrB* (ETB gene) in cardiovascular function, where this gene could be targeted by pharmacological agents under hypoxic conditions [26]. Additionally, *EdnrB*$^{-/+}$ heterozygote mice could tolerate different levels of hypoxia by stabilizing cardiac function and maintaining cardiac energy balance [27]. Data from this study also showed that an antagonist of ETB abolished the hypoxia-induced expression of IL-18, IL-18-Rα, and IL-18-Rβ, suggesting that it might be beneficial to alleviate inflammation and improve atrial tolerance to hypoxia.

TCF/LEF proteins act as the major downstream effectors of Wnt signaling and can be activated by ATF3, an adaptive-response gene in ATF/cyclic adenosine monophosphate responsive element-binding protein subfamily [28]. It has been shown that TCF/LEF1 binds directly to the ANF promoter via its binding site, thereby regulating ANF transcription in phenylephrine-induced hypertrophic rat cardiomyocytes [29]. Similarly, this study also confirmed that hypoxia dramatically increased the protein levels of ATF3 and TCF3/LEF1 as well as TCF4/LEF1, and such expression patterns were completely blocked by BQ123 and BQ788 concomitantly with an obvious attenuation of ANF secretion. Besides, IL-18-BP mimicked the effects of ET receptor antagonists on the expression of these transcription factors and hypoxia-induced secretion of ANF. Therefore, this study suggests that IL-18 regulated by ET-1-Src is involved in the atrial secretion of ANF in hypoxia beating rat atria through ATF3 as well as TCF3/LEF1 and TCF4/LEF1 signaling.

In summary, the increased expression of Src controlled by hypoxia-induced endogenous ET-1 could lead to the upregulated expression of IL-18 and its receptors through activation of RhoA, which ultimately regulate the atrial secretion of ANF via ATF3 as well as TCF3/LEF1 and TCF4/LEF1 signaling in hypoxic beating rat atria. The increase in ANF secretion during hypoxia might be one of the mechanisms for the inhibition of ET-1 and its downstream IL-18 signaling and exert a beneficial action on cardiovascular health.

Supplementary material

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

Article information

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REFERENCES

1. Nakamura K, Okamura H, Wada M, et al. Endotoxin-induced serum factor that stimulates gamma interferon production. Infect Immun. 1989; 57(2): 590–595, doi: 10.1128/iai.57.2.590-595.1989, indexed in Pubmed: 2492265.
2. Wang M, Markel TA, Meldrum DR. Interleukin 18 in the heart. Shock. 2008; 30(1): 3–10, doi: 10.1097/SHK.0b013e318160f215, indexed in Pubmed: 18562922.
3. O'Brien LC, Mezzaroma E, Van Tassell BW, et al. Interleukin-18 as a therapeutic target in acute myocardial infarction and heart failure. Mol Med. 2014; 20: 221–229, doi: 10.2119/molmed.2014.00034, indexed in Pubmed: 24804827.
4. Yu Q, Vazquez R, Khojeini EV, et al. IL-18 induction of osteopontin mediates cardiac fibrosis and diastolic dysfunction in mice. Am J Physiol Heart Circ Physiol. 2009; 297(1): H76–H85, doi: 10.1152/ajpheart.01285.2008, indexed in Pubmed: 19429811.
5. Bellora F, Castriconi R, Doni A, et al. M-CSF induces the expression of a membrane-bound form of IL-18 in a subset of human monocytes differentiating in vitro toward macrophages. Eur J Immunol. 2012; 42(6): 1618–1626, doi: 10.1002/eji.201142173, indexed in Pubmed: 22678914.
6. Takahashi M. NLRP3 inflammasome as a novel player in myocardial infarction. Int Heart J. 2014; 55(2): 101–105, doi: 10.1536/ihj.13-388, indexed in Pubmed: 24632952.
7. Chandrasekar B, Mummidi S, Claycomb WC, et al. Interleukin-18 is a pro-hypertrophic cytokine that acts through a phosphatidylinositol 3-kinase-phosphoinositide-dependent kinase-1-Akt-GATA4 signaling pathway in cardiomyocytes. J Biol Chem. 2005; 280(6): 4553–4567, doi: 10.1074/jbc.M411787200, indexed in Pubmed: 15574430.
8. Colston JT, Boylston WH, Feldman MD, et al. Interleukin-18 knockout mice display maladaptive cardiac hypertrophy in response to pressure overload. Biochem Biophys Res Commun. 2007; 354(2): 552–558, doi: 10.1016/j.bbrc.2007.01.030, indexed in Pubmed: 17250807.
9. Cho KW, Seul KH, Ryu H, et al. Characteristics of distension-induced release of immunoreactive atrial natriuretic peptide in isolated perfused rabbit atria. Regul Pept. 1988; 22(4): 333–345, doi: 10.1016/0167-0115(88)90110-3, indexed in Pubmed: 2973090.
10. McGrath MF, de Bold ML, de Bold AJ. The endocrine function of the heart. Trends Endocrinol Metab. 2005; 16(10): 469–477, doi: 10.1016/j.tem.2005.10.007, indexed in Pubmed: 16269246.
11. Arjamaa O, Nikinmaa M. Hypoxia regulates the natriuretic peptide system. Int J Physiol Pathophysiol Pharmacol. 2011; 3(3): 191–201, indexed in Pubmed: 21941610.
12. Hong L, Xi J, Zhang Y, et al. Atrial natriuretic peptide prevents the mitochondrial permeability transition pore opening by inactivating glycogen synthase kinase 3β via PKG and PI3K in cardiac H9c2 cells. Eur J Pharmacol. 2012; 695(1-3): 13–19, doi: 10.1016/j.ejphar.2012.07.053, indexed in Pubmed: 22975711.
13. Wang D, Gladysheva IP, Fan THM, et al. Atrial natriuretic peptide affects cardiac remodeling, function, heart failure, and survival in a mouse model of dilated cardiomyopathy. Hypertension. 2014; 63(3): 514–519, doi: 10.1161/HYPERTENSIONAHA.113.02164, indexed in Pubmed: 24379183.
14. Li X, Han ZN, Liu Y, et al. Endogenous ET-1 promotes ANP secretion through activation of COX2-L-PGDS-PPARγ signaling in hypoxic beating rat atria. Peptides. 2019; 122: 170150, doi: 10.1016/j.peptides.2019.170150, indexed in Pubmed: 31541683.
15. Woldbaek PR. Increased cardiac IL-18 mRNA, pro-IL-18 and plasma IL-18 after myocardial infarction in the mouse; a potential role in cardiac dysfunction. Cardiovascular Research. 2003; 59(1): 122–131, doi: 10.1016/s0008-6363(03)00339-0.
16. Oberholzer A, Steckholzer U, Kurimoto M, et al. Interleukin-18 plasma levels are increased in patients with sepsis compared to severely injured patients. Shock. 2001; 16(6): 411–414, doi: 10.1097/00024382-200116060-00001, indexed in Pubmed: 11770036.

17. Naito Y, Tsujino T, Fujioka Y, et al. Increased circulating interleukin-18 in patients with congestive heart failure. Heart. 2002; 88(3): 296–297, doi: 10.1136/heart.88.3.296, indexed in Pubmed: 12181230.
18. Banda NK, Vondracek A, Kraus D, et al. Mechanisms of inhibition of collagen-induced arthritis by murine IL-18 binding protein. J Immunol. 2003; 170(4): 2100–2105, doi: 10.4049/jimmunol.170.4.2100, indexed in Pubmed: 12574381.
19. Li X, Zhang Y, Zhang Bo, et al. HIF-1α-l-PGDS-PPARγ regulates hypoxia-induced ANP secretion in beating rat atria. Prostaglandins Other Lipid Mediat. 2018; 134: 38–46, doi: 10.1016/j.prostaglandins.2017.12.001, indexed in Pubmed: 29287795.
20. Seko Y, Takahashi N, Tobe K, et al. Hypoxia and hypoxia/reoxygenation activate Src family tyrosine kinases and p21ras in cultured rat cardiac myocytes. Biochem Biophys Res Commun. 1996; 226(2): 530–535, doi: 10.1006/bbrc.1996.1389, indexed in Pubmed: 8806668.
21. Kovacic B, Ilić D, Damsky CH, et al. c-Src activation plays a role in endothelin-dependent hypertrophy of the cardiac myocyte. J Biol Chem. 1998; 273(52): 35185–35193, doi: 10.1074/jbc.273.52.35185, indexed in Pubmed: 9857056.
22. Jaiswal M, Gremer L, Dvorsky R, et al. Mechanistic insights into specificity, activity, and regulatory elements of the regulator of G-protein signaling (RGS)-containing Rho-specific guanine nucleotide exchange factors (GEFs) p115, PDZ-RhoGEF (PRG), and leukemia-associated RhoGEF (LARG). J Biol Chem. 2011; 286(20): 18202–18212, doi: 10.1074/jbc.M111.226431, indexed in Pubmed: 21454492.
23. Shimokawa H, Sunamura S, Satoh K. RhoA/Rho-Kinase in the cardiovascular system. Circ Res. 2016; 118(2): 352–366, doi: 10.1161/CIRCRESAHA.115.306532, indexed in Pubmed: 26838319.
24. MacKay CE, Shaifta Y, Snetkov VV, et al. ROS-dependent activation of RhoA/Rho-kinase in pulmonary artery: Role of Src-family kinases and ARHGEF1. Free Radic Biol Med. 2017; 110: 316–331, doi: 10.1016/j.freeradbiomed.2017.06.022, indexed in Pubmed: 28673614.
25. Doi T, Sakoda T, Akagami T, et al. Aldosterone induces interleukin-18 through endothelin-1, angiotensin II, Rho/Rho-kinase, and PPARs in cardiomyocytes. Am J Physiol Heart Circ Physiol. 2008; 295(3): H1279–H1287, doi: 10.1152/ajpheart.00148.2008, indexed in Pubmed: 18660453.
26. Green DS, Rupasinghe C, Warburton R, et al. A cell permeable peptide targeting the intracellular loop 2 of endothelin B receptor reduces pulmonary hypertension in a hypoxic rat model. PLoS One. 2013; 8(11): e81309, doi: 10.1371/journal.pone.0081309, indexed in Pubmed: 24312288.
27. Stobdan T, Zhou D, Ao-leong E, et al. Endothelin receptor B, a candidate gene from human studies at high altitude, improves cardiac tolerance to hypoxia in genetically engineered heterozygote mice. Proc Natl Acad Sci U S A. 2015; 112(33): 10425–10430, doi: 10.1073/pnas.1507486112, indexed in Pubmed: 26240367.
28. Hrckulak D, Kolar M, Strnad H, et al. TCF/LEF transcription factors: an update from the internet resources. Cancers (Basel). 2016; 8(7), doi: 10.3390/cancers8070070, indexed in Pubmed: 27447672.
29. Zhang CG, Jia ZQ, Li BH, et al. Beta-Catenin/TCF/LEF1 can directly regulate phenylephrine-induced cell hypertrophy and Anf transcription in cardiomyocytes. Biochem Biophys Res Commun. 2009; 390(2): 258–262, doi: 10.1016/j.bbrc.2009.09.101, indexed in Pubmed: 19799869.

The prevalence and association of major ECG abnormalities with clinical characteristics and the outcomes of real-life heart failure patients — Heart Failure Registries of the European Society of Cardiology

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ABSTRACT

Background: Electrocardiogram (ECG) abnormalities increase the likelihood of heart failure (HF) but have low specificity and their occurrence is multifactorial.

Aim: This study aimed to investigate the prevalence and association of major ECG abnormalities with clinical characteristics and outcomes in a large cohort of real-life HF patients enrolled in HF Registries (Pilot and Long-Term) of the European Society of Cardiology.

Methods: Standard 12-lead ECG containing at least one of the following simple parameters was considered a major abnormality: abnormal rhythm; >100 bpm; QRS ≥120 ms; QTc ≥450 ms; pathological Q-wave; left ventricle hypertrophy; left bundle branch block. A Cox proportional hazards regression model was used to identify predictors of the primary (all-cause death) and secondary (all-cause death or hospitalization for worsening HF) endpoints.

Results: Patients with abnormal ECG (1222/1460; 83.7%) were older, more frequently were male and had HF with reduced ejection fraction, valvular heart disease, comorbidities, higher New York Heart Association class, or higher concentrations of natriuretic peptides as compared to those with normal ECG. In a one-year follow-up, the primary and secondary endpoints occurred more frequently in patients with abnormal ECG compared to normal ECG (13.8% vs 8.4%; $P = 0.021$ and 33.0% vs 24.7%; $P = 0.016$; respectively). Abnormal rhythm, tachycardia, QRS ≥120 ms, and QTc ≥450 ms were significant in univariable (both endpoints) analyses but only tachycardia remained an independent predictor of the primary endpoint.

Conclusions: HF patients with major ECG abnormalities were characterized by worse clinical status and one-year outcomes. Only tachycardia was an independent predictor of all-cause death.

Key words: tachycardia, electrocardiogram, QRS duration, left bundle branch block, heart rhythm

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INTRODUCTION

According to the heart failure (HF) guidelines of the European Society of Cardiology (ESC), an electrocardiogram (ECG) is the basic examination that should be performed routinely in patients with suspected or known HF [1]. ECG abnormalities increase the likelihood of HF (89% sensitivity) but have low specificity [1]. The presence of ECG abnormalities, especially in patients with HF, may depend on many

WHAT'S NEW?

Data from the heart failure registries of the European Society of Cardiology showed that major electrocardiogram (ECG) abnormalities (simple ECG parameters: abnormal rhythm; >100 bpm; QRS ≥120 ms; QTc ≥450 ms; pathological Q-wave; left ventricular hypertrophy; left bundle branch block) were present in the majority of real-life heart failure patients. What is more, these major ECG abnormalities were more common in patients with reduced left ventricular ejection fraction. Assessment of these simple major ECG abnormalities showed association with a worse general condition and one-year outcomes. Among others, tachycardia was the strongest predictor of all-cause death. Results of the ECG examination should not be overlooked as may provide important information in risk stratification.

factors (e.g. ischemia, HF etiology, electrolyte disturbances, pharmacotherapy) and is often observed. ECG abnormalities may be helpful in determining the HF etiology and making therapeutic decisions (e.g. anticoagulation in atrial fibrillation, pacing in bradycardia, cardiac resynchronization therapy [CRT] when QRS complex is prolonged). Several studies have also demonstrated that QRS duration or left bundle branch block (LBBB) can predict the risk of death in patients with chronic and decompensated HF [2–5]. Prolonged QTc (especially if genetically conditioned) may be associated with an increased risk of malignant ventricular arrhythmias, and ,in selected clinical situations, may be an indication for implantation of a cardioverter-defibrillator (ICD) [6]. The importance of ECG in clinical practice is undeniable, but particularly in the chronic setting of the disease, the results of this study are often overlooked. There is also insufficient data on the prevalence and role in risk stratification of major ECG abnormalities depending on the type of HF — HF with reduced (HFrEF), mid-range (HFmrEF) or preserved (HFpEF) ejection fraction.

The aim of the study was to analyze the prevalence and association of easily measured major ECG abnormalities with clinical characteristics and outcomes in a large cohort of real-life HF patients enrolled in HF Registries (Pilot and Long-Term) of the ESC.

METHODS

Study design

The analysis is based on data from two HF Registries (the ESC-HF Pilot and the ESC-HF Long-Term) of the ESC. These registries were multicenter, prospective, observational surveys conducted in 136 (including 29 centers from Poland) and 211 European cardiology centers (including 35 centers from Poland), respectively. A detailed study design was previously published [7, 8]. In short, the registries enrolled participants in outpatient and inpatient setting with chronic, worsening, or new-onset HF meeting diagnostic criteria for HF aged ≥18 years. There were no other specific exclusion criteria. The study protocol was approved by local ethics committees. All participating patients were provided with detailed information and signed written consent. The electronic Case Report Form contained data on past medical history, clinical characteristics, test results, HF management, and one-year follow-up.

The current analysis concerns 2019 Polish patients. Full data on ECG recordings were available for 1611 patients, 1460 patients had available data on the primary endpoint and were included in the final analysis. The prevalence of the major ECG changes was analyzed on a standard resting 12-lead ECG. ECG containing at least one of the following parameters was considered a major abnormality: abnormal rhythm; tachycardia (>100 bpm); duration of QRS complex ≥120 ms; QTc interval ≥450 ms (Bazett correction); pathological Q-wave; left ventricle hypertrophy; LBBB. Patients were divided into two groups according to the presence of ECG abnormalities and compared with regard to baseline clinical characteristics, type of HF (HFrEF, HFmrEF, and HFpEF), and one-year outcomes. The type of HF was defined by the authors based on baseline LVEF measurement. The primary endpoint was all-cause death at one year. The secondary endpoint was a composite of all-cause death and hospitalization for HF worsening at one year (follow-up available for 1326 participants). The New York Heart Association (NYHA) functional class with regard to the presence of ECG changes at baseline and 12-month was also evaluated. Data regarding participants' status were collected via telephone follow-up from patients or their close relatives. If the contact was not possible, then the primary endpoint was ascertained from the data of the Polish National Health Fund.

Additionally, we sought to determine whether major ECG abnormalities were independent predictors of the primary and secondary endpoints in the study cohort.

Statistical analysis

The results were presented as median and quartiles for continuous variables and as frequencies and percentages for ordinal variables. Fisher's exact test was used for comparison of categorical variables and a Mann-Whitney U test for continuous and ordinal variables. Cox proportional hazards regression models were used to identify predictors of the primary and secondary endpoints. All variables found to be statistically significant in univariable analyses ($p < 0.05$) were included in multivariable analyses. Kaplan-Meier survival curves were plotted for both study endpoints. A *P*-value below 0.05 was considered significant for all tests. All tests were two-tailed. Statistical analyses were performed using SPSS software, version 22 (IBM SPSS Statistics 22, New York, NY, USA).

Table 1. Prevalence of major ECG abnormalities according to types of heart failure

Variable	% of the total cohort; number of patients	HFrEF (n = 806)	HFmrEF (n = 279)	HFpEF (n = 375)	*P*-value
Abnormal ECG	83.7%; 1222	88.7%; 715	83.9%; 234	72.8%; 273	0.14[a] 0.003[b] <0.001[c]
Not sinus rhythm on ECG	36%; 526	34.9%; 281	34.1%; 95	40%; 150	0.18[d]
Tachycardia	5.8%; 85	6%; 48	6.1%; 17	5.3%; 20	0.91[d]
Pathological Q-wave	28.5%; 416	33%; 266	33%; 92	15.5%; 58	1.00[a] <0.001[b] <0.001[c]
LVH	19.5%; 285	19.7%; 159	24.7%; 69	15.2%; 57	0.27[a] 0.009[b] 0.21[c]
LBBB	12.3%; 180	16.7%; 135	10.4%; 29	4.3%; 16	0.042[a] 0.01[b] <0.001[c]
QRS complex ≥120 ms	28.1%; 410	37.3%; 301	20.1%; 56	14.1%; 53	<0.001[a] 0.17[b] <0.001[c]
QTc interval ≥450 ms	44.4%; 648	50.5%; 407	35.1%; 98	38.1%; 143	<0.001[a] 1.00[b] <0.001[c]

[a]*P*-value for HFrEF vs HFmrEF after Bonferroni correction; [b]*P*-value for HFmrEF vs HFpEF after Bonferroni correction; [c]*P*-value for HFrEF vs HFpEF after Bonferroni correction; [d]*P*-value for overall test

Abbreviations: ECG, electrocardiogram; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LBBB, left bundle branch block; LVH, left ventricular hypertrophy

RESULTS

Prevalence of ECG abnormalities

There were 1222 out of 1460 (83.7%) HF patients with major ECG abnormalities. The most frequent ECG abnormalities in the entire cohort were: prolonged QTc interval (44.4%) and abnormal heart rhythm (36.0%). Differences in the presence of major ECG abnormalities were observed across the HF types, with the most prevalent changes observed in HFrEF patients (Table 1).

Clinical characteristics

Patients with abnormal ECG were older (median, 67.2 vs 66 years; $P = 0.03$) and more often were male (68.1% vs 58.8%; $P = 0.007$) when compared with those with normal ECG. They were also more likely to have lower left ventricular ejection fraction (median, 35% vs 45%; $P < 0.001$), moderate or severe valvular heart disease, ischemic heart disease, a history of atrial fibrillation, and chronic kidney disease than the patients with normal ECG. The group with abnormal ECG findings also had a higher NYHA class, higher concentrations of natriuretic peptides and more frequently required treatment with diuretics, antiarrhythmic (amiodarone and digitalis) and anticoagulation than the patients with normal ECG. Detailed baseline clinical characteristics of both study groups are presented in Table 2.

Predictors of one-year outcomes

In a one-year follow-up the patients with abnormal ECG were more likely to reach the primary and secondary endpoints than those with normal ECG (13.8% vs 8.4%; $P = 0.021$ and 33% vs 24.7%; $P = 0.016$; respectively) (Table 2). The Kaplan-Meier curves for the primary and secondary endpoints for both subgroups are shown in Figure 1A, B, respectively.

Across the types of HF, HFrEF patients with abnormal ECG had worse one-year outcomes when compared with the HFmrEF and HFpEF groups (Table 3, Figure 1C, D).

In the total cohort, the presence of any ECG abnormality was a predictor of both the primary and secondary endpoints but only in the univariable analyses (Supplementary material, *Table S1*). The univariable analyses of specific ECG abnormalities revealed abnormal rhythm, tachycardia, QRS complex duration ≥120 ms, and QTc interval ≥450 ms (but not LBBB, pathological Q-wave, and left ventricular hypertrophy) to be predictors of both the primary and secondary endpoints (Supplementary material, *Table S1*). In the multivariable analysis, only tachycardia on ECG remained an independent predictor of the primary endpoint (hazard ratio 1.75; 95% CI, 1.06–2.87; $P = 0.03$) but not of the secondary endpoint (hazard ratio 1.33; 95% CI, 0.93–1.90; $P = 0.09$) (Table 4).

DISCUSSION

The results of this analysis provided important epidemiological data on the prevalence, associated patients' clinical characteristics, and relevance of basic ECG abnormalities in real-life HF patients. The study showed that ECG abnormalities were present in the majority of HF patients but were observed more frequently in HFrEF patients. What is more, these easily measured ECG parameters reflected patients in worse general condition, with multiple comorbidities, and were associated with poor one-year outcomes.

A standard 12-lead ECG is an essential diagnostic tool in clinical cardiology and crucial for the management of

Table 2. Baseline characteristics and one-year outcomes of patients with abnormal or normal ECG

Variable	Abnormal ECG (n = 1222)	Normal ECG (n = 238)	*P*-value
Baseline characteristics			
Age, years	67.2 (58.2–77.0)	66.0 (54.8–76.6)	0.04
Male	68.1%; 832	58.8%; 140	0.01
BMI, kg/m^2	27.8 (25.0–31.2); [1169]	27.8 (24.5–31.8); [227]	0.81
LVEF, %	35 (25–46)	45 (30–55.8)	<0.001
HFrEF	58.5%; 715	38.2%; 91	<0.001
HFmrEF	19.1%; 234	18.9%; 45	0.80
HFpEF	22.3%; 273	42.8%; 102	<0.001
Previous HF hospitalization	75.4%; 921	68.1%; 162	0.03
Coronary artery disease	56%; 684	42.4%; 101	<0.001
Prior PCI or CABG	34.2%; 417	26.1%; 62	0.01
Moderate or severe mitral regurgitation	49.7%; 572/[1150]	30.7%; 67/[218]	<0.001
Moderate or severe aortic stenosis	10.2%; 90/[882]	4.0%; 6/[151]	0.01
Hypertension	63.9%; 780	63.0%; 150	0.75
History of atrial fibrillation	46.5%; 568	21.1%; 50	<0.001
Peripheral artery disease	11.9%; 145	8.8%; 21	0.24
Diabetes	33.6%; 411	27.7%; 66	0.20
Chronic kidney disease	19.1%; 233	13.4%; 32	0.07
COPD	18.3%; 223	15.5%; 37	0.44
Prior stroke or TIA	12.0%; 146	10.1%; 24	0.73
CHA2DS2-VASc score	4 (3–5)	4 (2–5)	0.11
Current malignant disease	3.7%; 45	3.4%; 8	0.85
Current or former smoking	57.9%; 700	56.8%; 133	0.71
Alcohol usage	56.8%; 674	58.7 %; 135	0.59
Pacemaker	7.1%; 87	3.8%; 9	0.07
ICD	17.4%; 213	12.2%; 29	0.13
CRT	5.9%; 72	0.4%; 1	<0.001
Clinical status			
Heart rate, bpm	80 (70–96)	76 (68–88.2)	0.01
SBP, mm Hg	130 (110–140)	130 (120–150)	0.003
DBP, mm Hg	80 (70–83)	80 (70–90)	0.03
NYHA class	3 (2–3); [1218]	2 (2–3); [237]	<0.001
Anemia	32.4%; 298/[921]	34.6%; 56/[162]	0.29
Pleural effusion/congestion (X-ray)	39.2%; 360/[918]	27.0%; 47/[174]	0.003
Hemoglobin, g/dl	13.4 (11.9–14.4); [1140]	13.2 (11.1–14.4); [220]	0.31
Serum creatinine, mg/dl	1.1 (0.9–1.4); [1158]	1.0 (0.8–1.3); [214]	0.001
Serum sodium, mmol/l	139 (136–141); [1157]	139 (136–141); [220]	0.92
Serum potassium, mmol/l	4.4 (4.1–4.8); [1158]	4.4 (4.1–4.7); [220]	0.46
BNP, pg/ml	576 (203–1386.8); [163]	364 (155–643.5); [24]	0.01
NT-proBNP, pg/ml	3048 (1352–7024); [315]	1580 (419.5–4959.5); [55]	0.01
Pharmacotherapy			
ACE-I	75.4%; 921/[1221]	75.6%; 180	0.93
ARB	10.2%; 124/[1219]	15.1%; 36	0.02
β-blocker	89.1%; 1088/[1221]	86.6%; 206	0.42
Diuretic	83.3%; 1016/[1220]	77.3%; 184	0.08
MRA	67.3%; 821/[1221]	58.6%; 139	0.01
Statins	65.9%; 805/[1221]	60.5%; 144	0.21
Oral Anticoagulant	45.4%; 554/[1221]	26.2%; 62	<0.001
Antiplatelets	60.0%; 732/[1221]	65.5%; 156	0.11
Digitalis	25.1%; 306[1221]	16.0%; 38	<0.001
Amiodarone	9.7%; 118/[1221]	5.9%; 14	0.16
Other Antiarrhythmic	6.1%; 75/[1221]	3.4%; 8	0.09
One-year outcomes			
NYHA class I or II	68.2% 690/[1011]	81.0% 171/[211]	<0.001
NYHA class III or IV	31.8% 321/[1011]	19% 40/[211]	
Death	13.8%; 169	8.4%; 20	0.02
Death or rehospitalization	33%; 367/[1111]	24.7%; 53/[215]	0.02

Continuous variables are presented as medians and interquartile ranges (IQR);
Available cases count in the respective variable are presented in square brackets.
Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; bpm, beats per minute; CABG, coronary artery bypass grafting; CHA2DS2VASc score, congestive heart failure, hypertension, age >75 years, diabetes mellitus, history of stroke or thromboembolism, vascular disease, age 65 to 74 years, female sex; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TIA, transient ischemic attack. Other — see Table 1

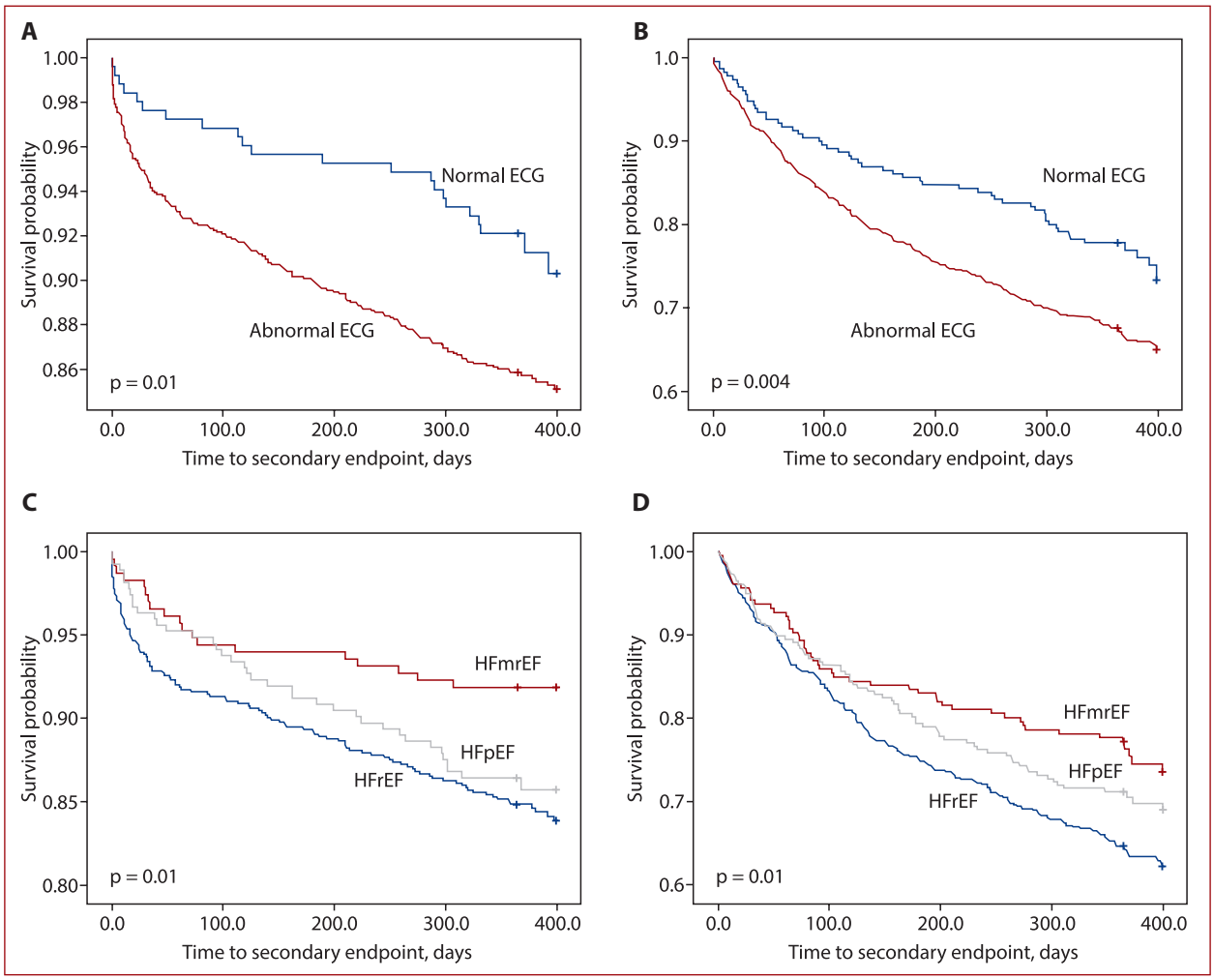

Figure 1. A. Kaplan-Meier curves for the primary endpoint of patients with abnormal or normal ECG. **B**. Kaplan-Meier curves for the secondary endpoint of patients with abnormal or normal ECG. **C**. Kaplan-Meier curves for the primary endpoint of patients with abnormal ECG regarding to the type of heart failure. **D**. Kaplan-Meier curves for the secondary endpoint of patients with abnormal ECG regarding to the type of heart failure

Abbreviations: see Table 1 and 2

Table 3. One-year outcomes of patients with abnormal or normal electrocardiogram regarding to the type pf heart failure

Type of HF	Abnormal ECG	Normal ECG	*P*-value
NYHA class			
HFrEF	3 (2–4); n = 719	2 (2–3); n = 91	<0.001
HFmrEF	3 (2–3); n = 234	3 (2–3); n = 45	<0.001
HFpEF	3 (2–3); n = 273	3 (2–3); n = 102	0.20
Death			
HFrEF	15.6%; 112/715	6.5%; 6/91	0.01
HFmrEF	8.1%; 19/234	6.6%; 3/45	1.00
HFpEF	13.9%; 38/273	10.7%; 11/102	0.49
Death or rehospitalization			
HFrEF	36.9%; 239/648	29.6%; 24/81	0.22
HFmrEF	24.8%; 51/206	26.8%; 11/41	0.84
HFpEF	30%; 77/257	19.4%; 18/93	0.06

Abbreviations: see Table 1 and 2

patients with most cardiovascular conditions, including patients with HF. The advantages of ECG are simplicity of implementation, non-invasive nature, low cost, and wide availability. ECG is routinely performed in most HF patients, but frequently not enough attention is paid to its results. A normal ECG is infrequently observed in patients with suspected HF but it has a low specificity [9]. Analysis of EuroHeart Failure survey data showed that ECG

Table 4. Multivariable analysis of predictors of the primary and secondary endpoints in heart failure patients at one-year

Variable	Primary endpoint (n = 189)			Secondary endpoint (n = 420)		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age	1.03	1.02–1.05	<0.001	1.01	0.99–1.02	0.20
Male	–	–	–	0.77	0.62–0.96	0.03
BMI	0.98	0.95-1.01	0.21	–	–	–
NYHA (class III or IV vs I or II)	1.91	1.50–2.43	<0.001	2.02	1.52–2.68	<0.001
CKD	1.66	1.19–2.34	0.003	1.40	1.11–1.76	0.005
COPD	1.25	0.88–1.78	0.22	1.20	0.95–1.52	0.11
Diabetes	1.37	0.98–1.93	0.07	1.26	1.03–1.55	0.04
AF history	0.88	0.59–1.31	0.53	–	–	–
HGB	0.97	0.89–1.05	0.46	0.96	0.91–1.01	0.09
Serum sodium	0.92	0.90–0.94	<0.001	0.96	0.94–0.98	<0.001
SBP	1.00	0.99–1.01	0.92	0.996	0.99–1.0001	0.05
B-blocker	0.47	0.31–0.70	0.001	0.70	0.52–0.93	0.01
ARB	0.52	0.26–1.02	0.06	–	–	–
ACE-I	0.72	0.49–1.06	0.1	0.76	0.61–0.95	0.02
Abnormal rhythm	1.08	0.72–1.63	0.70	0.98	0.80–1.22	0.88
Tachycardia (>100 bpm)	1.84	1.12–3.03	0.02	1.41	0.98–2.01	0.06
QRS ≥120 ms	1.34	0.94–1.91	0.11	1.21	0.97–1.51	0.10
QTc interval ≥450 ms	1.13	0.81–1.59	0.46	1.14	0.92–1.41	0.22
Digitalis	–	–	–	1.03	0.82–1.30	0.80
Amiodarone	1.66	1.06–2.62	0.03	1.19	0.87–1.62	0.29
Statins	0.76	0.54–1.08	0.12	–	–	–
HF type						
HFmrEF (reference)	1.00	1.00–1.00	1.00	1.00	1.00–1.00	1.00
HFrEF	2.04	1.21–3.44	0.01	1.27	0.95–1.71	0.10
HFpEF	1.42	0.82–2.46	0.22	0.86	0.61–1.20	0.36

Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; bpm, beats per minute; CI, confidence interval; CKD, chronic kidney disease; HGB, hemoglobin; HR, hazard ratio; SBP, systolic blood pressure. Other — see Table 1 and 2

abnormalities (including ventricular rate, PR, QRS and QTc intervals, left ventriclar hypertrophy, pathological Q-wave, ST-T-wave abnormalities, and interventricular conduction abnormalities) were observed in more than 98% of HF patients [9]. In our study, we focused on the predefined major ECG parameters, which can be assumed as being in line with the previous observations.

All of the ECG abnormalities (except abnormal heart rhythm and tachycardia) were more prevalent in HFrEF patients when compared with patients with HFmrEF and HFpEF. Although it is known that heart rhythm abnormalities (especially atrial fibrillation) are frequently present in patients with HFpEF [1, 10], the presence of ECG abnormalities was more commonly associated with a history of advanced heart valve disease, atrial fibrillation, chronic kidney disease, signs of HF decompensation (higher natriuretic peptides, pleural effusion, higher NYHA class) and use of diuretics and anticoagulants.

A standard resting 12-lead ECG may reveal signs of inherited disorders but also suggests underlying structural heart disease, electrolyte disturbances and may reflect patients at higher risk of poor prognosis. In our study, the presence of at least one of the major ECG abnormalities and associated worse general condition at baseline translated into a worse prognosis in a one-year observation (higher rate of all-cause death, death, or HF hospitalization and higher NYHA class than in the patients without such ECG abnormalities). Among all tested major ECG abnormalities only tachycardia (defined as >100 bpm) was an independent predictor of the primary endpoint but not the secondary endpoint. Important to note is that patients in the abnormal ECG group had significantly higher resting heart rates, despite the more frequent use of antiarrhythmic drugs (amiodarone, digitalis) and a high rate of β-blocker (89.2%) administration. A higher resting heart rate in HF patients was proven to be associated with higher long-term mortality [11, 12], particularly when above 110 bpm and with concomitant atrial fibrillation [13, 14].

It can be concluded that none of the other typical ECG parameters except tachycardia independently influenced the prognosis of patients with HF, regardless of the type of HF. However, it should also be emphasized that the presence of ECG abnormalities was a marker of patients in a worse clinical condition and with a worse one-year prognosis.

In our study, QTc prolongation was the most frequent abnormality (44.4% and 50.5% of the whole cohort and HFrEF patients, respectively) but it was not an independent predictor of worse outcomes. Similarly, it was previously presented that QTc interval was frequently prolonged in HF patients (70% of patients had QTc ≥440 ms) but it was not associated with increased long-term mortality [15].

There is evidence that both patients with reduced or mildly reduced left ventricular ejection fraction (35%–50%) and with LBBB are at higher risk of death and HF hospital-

izations [16–18], and in selected cases, CRT might be particularly beneficial [1]. Similarly, QRS complex prolongation due to right ventricular pacing was shown to be associated with an increase in HF hospitalization [19]. In our study, LBBB was observed in 12.3% of the total cohort but it was not a predictor of a worse prognosis. It is worth noting that CRT was implanted in 5.8% of patients with the ECG abnormalities and nobody in the normal ECG group. It should also be highlighted that there are no standardized LBBB criteria, hence the clinical trials and registries used various and divergent definitions of LBBB. As a consequence, this translates into different observed rates of LBBB occurrence and associated prognosis [20].

Despite years of investigations, knowledge on the risk stratification for sudden cardiac death (SCD) in patients with HF is incomplete. The primary prevention of SCD is based only on left ventricular ejection fraction, which translates into difficulty in choosing patients who will benefit from ICD implantation, particularly among patients with nonischemic HF. Several ECG parameters alone or in combination were shown to have prognostic relevance (e.g. LBBB, prolonged QRS complex, prolonged QTc interval) [6, 21]. However, despite certain clinical scenarios (CRT implantation, ICD implantation in secondary SCD prevention) they are used infrequently in risk stratification, particularly in patients with chronic HF, or at high risk of HF decompensation. Therefore, further research on better risk stratification in HF, including the risk of HF decompensation and mortality in different HF subgroups, is particularly warranted and is currently ongoing [22–24]. This might be an important strategy in guiding the HF therapy to reduce risk via further intensification of pharmacological treatment or closer monitoring [25].

Limitations

The inclusion of real-life patients followed by cardiologists is an important advantage of ESCHF Pilot and ESCHFLT registries, but drawbacks include the partial incompleteness of the data and the observational design. What is more, only the predefined ECG data in the Case Report Forms designed by the coordinators of the registries were available for analysis. The registries were not primarily focused on the ECG analysis, hence measurement errors are possible. There were no predefined definitions of the ECG parameters, including LBBB, pathological Q-wave, and left ventricular hypertrophy.

CONCLUSIONS

Results from a large real-world HF database of patients followed by cardiologists showed that ECG abnormalities were present in the majority of HF patients but more frequently in HFrEF patients. The patients with ECG abnormalities were characterized by a worse general condition and poor one-year outcomes when compared with thos without any abnormal ECG findings. Among other ECG abnormalities, only tachycardia was an independent predictor of all-cause mortality.

Supplementary material

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

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REFERENCES

1. Ponikowski P, Voors A, Anker S, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [in Polish]. Kardiol Pol. 2016; 74(10): 1037–1147, doi: 10.5603/kp.2016.0141.
2. Dhar R, Alsheikh-Ali AA, Estes NA, et al. Association of prolonged QRS duration with ventricular tachyarrhythmias and sudden cardiac death in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II). Heart Rhythm. 2008; 5(6): 807–813, doi: 10.1016/j.hrthm.2008.02.013, indexed in Pubmed: 18534364.
3. Bode-Schnurbus L, Böcker D, Block M, et al. QRS duration: a simple marker for predicting cardiac mortality in ICD patients with heart failure. Heart. 2003; 89(10): 1157–1162, doi: 10.1136/heart.89.10.1157, indexed in Pubmed: 12975406.
4. Agarwal SK, Singla I, Hreybe H, et al. Predictors of mortality amongst recipients of implantable cardioverter defibrillators for secondary prevention of cardiac arrest. Indian Pacing Electrophysiol J. 2007; 7(4): 218–224, indexed in Pubmed: 17957270.
5. Breidthardt T, Christ M, Matti M, et al. QRS and QTc interval prolongation in the prediction of long-term mortality of patients with acute destabilised heart failure. Heart. 2007; 93(9): 1093–1097, doi: 10.1136/hrt.2006.102319, indexed in Pubmed: 17395674.
6. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. ESC Scientific Document Group. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015; 36(41): 2793–2867, doi: 10.1093/eurheartj/ehv316, indexed in Pubmed: 26320108.
7. Maggioni AP, Dahlström U, Filippatos G, et al. Heart Failure Association of the European Society of Cardiology (HFA). EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). Eur J Heart Fail. 2013; 15(7): 808–817, doi: 10.1093/eurjhf/hft050, indexed in Pubmed: 23537547.
8. Balsam P, Ozierański K, Kapłon-Cieślicka A, et al. Differences in clinical characteristics and 1-year outcomes of hospitalized patients with heart failure in ESC-HF Pilot and ESC-HF-LT registries. Pol Arch Intern Med. 2019; 129(2): 106–116, doi: 10.20452/pamw.4418, indexed in Pubmed: 30648697.

9. Khan NK, Goode KM, Cleland JGF, et al. EuroHeart Failure Survey Investigators. Prevalence of ECG abnormalities in an international survey of patients with suspected or confirmed heart failure at death or discharge. Eur J Heart Fail. 2007; 9(5): 491–501, doi: 10.1016/j.ejheart.2006.11.003, indexed in Pubmed: 17218150.
10. Kapłon-Cieślicka A, Tymińska A, Peller M, et al. Diagnosis, clinical course, and 1-year outcome in patients hospitalized for heart failure with preserved ejection fraction (from the Polish Cohort of the European Society of Cardiology Heart Failure Long-Term Registry). Am J Cardiol. 2016; 118(4): 535–542, doi: 10.1016/j.amjcard.2016.05.046, indexed in Pubmed: 27374606.
11. Kapłon-Cieślicka A, Balsam P, Ozierański K, et al. Resting heart rate at hospital admission and its relation to hospital outcome in patients with heart failure. Cardiol J. 2014; 21(4): 425–433, doi: 10.5603/CJ.a2013.0147, indexed in Pubmed: 24142684.
12. Laskey WK, Alomari I, Cox M, et al. AHA Get With The Guidelines®-Heart Failure Program. Heart rate at hospital discharge in patients with heart failure is associated with mortality and rehospitalization. J Am Heart Assoc. 2015; 4(4): e001626, doi: 10.1161/JAHA.114.001626, indexed in Pubmed: 25904590.
13. Ozierański K, Kapłon-Cieślicka A, Balsam P, et al. Effect of β-blockers on 1-year survival and hospitalizations in patients with heart failure and atrial fibrillation: results from ESC-HF pilot and ESC-HF long-term registry. Pol Arch Intern Med. 2018; 128(11): 649–657, doi: 10.20452/pamw.4346, indexed in Pubmed: 30303491.
14. Simpson J, Castagno D, Doughty RN, et al. Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC). Is heart rate a risk marker in patients with chronic heart failure and concomitant atrial fibrillation? Results from the MAGGIC meta-analysis. Eur J Heart Fail. 2015; 17(11): 1182–1191, doi: 10.1002/ejhf.346, indexed in Pubmed: 26358762.
15. Breidthardt T, Christ M, Matti M, et al. QRS and QTc interval prolongation in the prediction of long-term mortality of patients with acute destabilised heart failure. Heart. 2007; 93(9): 1093–1097, doi: 10.1136/hrt.2006.102319, indexed in Pubmed: 17395674.
16. Sze E, Dunning A, Loring Z, et al. Comparison of incidence of left ventricular systolic dysfunction among patients with left bundle branch block versus those with normal QRS duration. Am J Cardiol. 2017; 120(11): 1990–1997, doi: 10.1016/j.amjcard.2017.08.003, indexed in Pubmed: 28958452.
17. Moss A, Hall W, Cannom D, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med. 2009; 361(14): 1329–1338, doi: 10.1056/nejmoa0906431.
18. Witt CM, Wu G, Yang D, et al. Outcomes with left bundle branch block and mildly to moderately reduced left ventricular function. JACC Heart Fail. 2016; 4(11): 897–903, doi: 10.1016/j.jchf.2016.07.002, indexed in Pubmed: 27614941.
19. Sweeney MO, Hellkamp AS, Ellenbogen KA, et al. MOde Selection Trial Investigators. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation. 2003; 107(23): 2932–2937, doi: 10.1161/01.CIR.0000072769.17295.B1, indexed in Pubmed: 12782566.
20. Jastrzębski M, Kukla P, Kisiel R, et al. Comparison of four LBBB definitions for predicting mortality in patients receiving cardiac resynchronization therapy. Ann Noninvasive Electrocardiol. 2018; 23(5): e12563, doi: 10.1111/anec.12563, indexed in Pubmed: 29806716.
21. Václavík J, Špinar J, Vindiš D, et al. ECG in patients with acute heart failure can predict in-hospital and long-term mortality. Intern Emerg Med. 2014; 9(3): 283–291, doi: 10.1007/s11739-012-0862-1, indexed in Pubmed: 23054408.
22. Jahmunah V, Oh SL, Wei JK, et al. Computer-aided diagnosis of congestive heart failure using ECG signals — a review. Phys Med. 2019; 62: 95–104, doi: 10.1016/j.ejmp.2019.05.004, indexed in Pubmed: 31153403.
23. Balsam P, Lodziński P, Tymińska A, et al. Study design and rationale for biomedical shirt-based electrocardiography monitoring in relevant clinical situations: ECG-shirt study. Cardiol J. 2018; 25(1): 52–59, doi: 10.5603/CJ.a2017.0102, indexed in Pubmed: 28840587.
24. Reichlin T, Abächerli R, Twerenbold R, et al. Advanced ECG in 2016: is there more than just a tracing? Swiss Med Wkly. 2016; 146: w14303, doi: 10.4414/smw.2016.14303, indexed in Pubmed: 27124801.
25. Grabowski M, Ozierański K, Balsam P, et al. The effect of sacubitril / valsartan on the occurrence of ventricular arrhythmia and the risk of sudden cardiac death in patients with chronic heart failure with reduced left ventricular ejection fraction. Expert opinion of the Heart Rhythm and Heart Failure Sections of the Polish Cardiac Society. Kardiol Pol. 2019; 77(10): 987–993, doi: 10.33963/KP.14972, indexed in Pubmed: 31527563.

Predictors and mid-term outcomes of nosocomial infection in ST-elevation myocardial infarction patients treated by primary angioplasty

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ABSTRACT

Background: Nosocomial infections (NI) are associated with high morbidity and mortality. Existing data on the impact of NI on patients with ST-elevation myocardial infarction (STEMI) is scarce.

Aim: Our aim was to determine the incidence, predictors, and prognosis of NI in a contemporary series of STEMI patients.

Methods: 1131 consecutive STEMI patients treated by primary percutaneous coronary intervention from January 2008 to December 2017 were analyzed. Binary logistic regression and Cox proportional hazard models were used to identify predictors of NI and major adverse cardio-cerebrovascular events (MACCE) at 1-year follow-up, respectively.

Results: Of all patients, 126 (11.1%) were diagnosed with NI (>48 hours from admission), mostly of respiratory (50.8%) and urinary (39.7%) tract origin. Insulin-treated diabetics were 3-fold more likely to develop NI. Other independent predictors were peripheral arterial disease, intra-aortic balloon pump insertion, age, lower systolic blood pressure, and higher peak creatine-kinase. Only pre-infarction angina was negatively related to NI. Age, peripheral arterial disease, femoral approach and larger infarct were related to MACCE at 1-year follow-up. NI in isolation was not independently related to MACCE (hazard ratio [HR], 1.24; 95% confidence interval [CI], 0.80–1.94; $P = 0.34$). However, we found a significant interaction between NI and smoking (HR, 2.33; 95% CI, 1.03–5.24; $P_{interc} = 0.04$).

Conclusion: Larger infarct size, hemodynamic instability, and co-morbidities were related to both NI and 1-year adverse events. Smokers who developed NI also had a higher 1-year risk of MACCE.

Key words: cross infection, myocardial infarction, outcomes, smoking ST-elevation myocardial infarction

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INTRODUCTION

The advent of reperfusion therapy, namely by percutaneous coronary intervention (PCI), has been critical for the decreased mortality of patients presenting with ST-elevation myocardial infarction (STEMI). However, in-hospital and mid-term adverse outcomes range from as low as 1% to more than 30% [1], emphasizing the need to identify and treat clinical features that may negatively impact patients' prognoses. In previous studies, nosocomial infections (NI) in STEMI patients have been related to higher mortality and longer hospital stay, along with higher health care costs [2, 3]. Mechanisms behind the adverse events of patients with STEMI patients complicated by NI may include the myocardial infarction-related inflammatory state, which might predispose to the development of sepsis, as well as the pro-thrombotic milieu induced by inflammation [4, 5].

Data about the incidence and impact of NI on prognosis following STEMI are scarce and vary according to definitions and the studied population. The reported incidence of infection in a recent octogenarian cohort undergoing primary PCI was nearly 30% [6], whereas another study found that 2.4% of STEMI patients included in a randomized trial developed a serious infection [2].

WHAT'S NEW?

Our study demonstrated that nosocomial infection is a relatively common complication of ST-elevation myocardial infarction, affecting more than 10% of the patients. Nosocomial infection was predicted by infarct size, hemodynamic instability, and co-morbidities. Pre-infarction angina was the only protective feature identified. Regarding nosocomial infection's impact at 1-year follow-up, we concluded that it does not constitute an independent predictor of major adverse cardio-cerebrovascular events (MACCE). However, smokers who complicate with nosocomial infection experience a higher 1-year MACCE incidence. Our study indicates that a continuous effort to treat STEMI patients early and to limit infarct size seems to be an effective way to prevent post-reperfusion nosocomial infections.

In this study, we aimed to address the prevalence and predictors of NI in a series of STEMI patients treated by PCI in a tertiary care center and to ascertain its impact on the incidence of major adverse cardio-cerebrovascular events (MACCE) at 1-year follow-up.

METHODS

Studied population and definitions

We conducted a retrospective study including consecutive adults (≥18 years old) with a diagnosis of STEMI treated with primary PCI, in a tertiary care center between January 1, 2008 and December 31, 2017. Considering our focus on NI, patients with a diagnosis of overt infection at the time of admission or <48 hours from admission were excluded, to assure that all infections included developed in the hospital setting and were not present at the time of admission [7].

All STEMI patients entered an anonymized prospective database which included demographic, clinical, and procedural characteristics. Data were obtained by medical chart review. According to the 4th Universal Definition of Myocardial Infarction, STEMI was defined as typical chest discomfort or other ischemic symptoms, associated with new ST-segment elevations in two contiguous leads or new bundle branch blocks with ischemic repolarization patterns. The ST-elevation cutpoints (measured at the J-point) were considered as follows: in leads V2–V3 ≥2 mm in men ≥40 years; ≥2.5 mm in men <40 years; ≥1.5 mm in women regardless of age, and ≥1 mm in all the other leads [8]. In addition, to be included in this study, all patients were required to have a culprit lesion identified and to have undergone PCI. Patients' treatment strategy followed per current guidelines [9].

NI was defined as an infection diagnosed 48 hours after hospital admission requiring antibiotics, which reflect infection's clinical impact with the need for specific treatment. Infection sites were grouped into the following main categories: "respiratory tract infection", "urinary tract infection", "catheter-related infection" and "other". Respiratory tract infection comprised both tracheobronchitis and pneumonia. Identification of a pathogen was not mandatory for diagnosis but was collected whenever possible. Urinary tract infection was defined in the presence of signs and symptoms and $>10^5$ CFU/ml on urine culture. A catheter-related infection required a positive tip culture and documentation of the same organism on peripheral blood. The "other" category included additional infection types in accordance with the Centers for Disease Control and Prevention/National Healthcare Safety Network (CDC/NHSN) criteria, that did not comprise enough patients to permit a separate category [7].

Clinical and demographic characteristics are detailed in Table 1. Pre-infarct angina (PIA) was diagnosed if a patient had arm, jaw, or chest pain in the preceding eight days before the diagnosis of STEMI. Total ischemic time and door-to-balloon time were the time elapsed from symptom onset (the time when chest pain became more intense and sustained) and presentation to the hospital or the passage of the coronary guidewire, respectively. Peripheral arterial disease (PAD) was considered if the patient had peripheral claudication and established aorto-iliac or peripheral disease.

Clinical follow-up was performed by record-linkage and ascertained by electronic records to check for the occurrence of a MACCE comprising death (any cause), a cerebrovascular accident (brain imaging was mandatory), new myocardial infarction in any vessel, or target lesion revascularization (TLR — new intervention on target lesion due to angina or ischemia), during the first year after the index STEMI. Patients having any of the aforementioned MACCE were censored. The study was approved by the hospital ethics committee (2019.128[108-DEFI/112-CE]), and the informed consent for the studied cohort was waived due to the retrospective nature of the analysis. The database was anonymized.

Statistical analysis

Categorical variables are expressed as absolute values and percentages, comparison was performed by Pearson chi-square or Fisher exact test, as appropriate. Continuous data are expressed as the median and interquartile range (IQR) and were compared using the Mann-Whitney U test. Normality of distribution was assessed from visual inspection of histograms and the Shapiro-Wilk test.

MACCE rates were plotted as Kaplan-Meier curves, and groups were compared using the log-rank test.

To identify the independent predictors of NI we ran a stepwise multivariable logistic regression that included variables with a P <0.1 in the univariable analysis. Cox proportional hazard models were used to identify predictors

Table 1. Baseline characteristics of STEMI patients

	All patients (n = 1131)	Infection (n = 126)	No infection (n = 1005)	*P*-value
Age, years, median (IQR)	62.0 (53.0–72.0)	70.0 (62.0–80.3)	61.0 (52.5–71.0)	<0.001
Men, n (%)	839 (74.2)	78 (75.7)	761 (61.9)	0.001
Pre-infarction angina, n (%)	356 (31.6)	24 (19.4)	332 (33.2)	0.002
BMI, kg/m^2, median (IQR)	26.0 (23.9–28.4)	26.0 (24.0–28.0)	26.0 (23.9–28.5)	0.74
Medical history				
Hypertension, n (%)	626 (55.6)	81 (64.8)	545 (54.4)	0.03
Dyslipidemia, n (%)	600 (53.3)	25 (53.2)	533 (53.6)	0.94
Peripheral arterial disease, n (%)	100 (8.9)	25 (11.0)	75(7.5)	<0.001
Smoker, n (%)	564 (50.0)	52 (41.6)	512 (51.1)	0.045
History of CABG, n (%)	15 (1.3)	2 (1.6)	13 (1.3)	0.68[a]
History of MI, n (%)	87 (7.8)	11 (8.9)	76 (7.6)	0.62
Diabetes mellitus				<0.001
No, n (%)	847 (76.0)	79 (63.7)	768 (77.5)	
Yes, without insulin, n (%)	221 (19.8)	29 (23.4)	192 (19.4)	
Yes, with insulin, n (%)	47 (4.2)	16 (12.9)	31 (3.1)	
Total ischemic time, hours, median (IQR)	4.0 (2.5–7.8)	4.0 (2.5–9)	4.0 (2.5–7.71)	0.76
Door-to-balloon time, hours, median (IQR)	1.3 (0.8–2.0)	1.5 (1.0–2.5)	1.3 (0.8–2.0)	0.11
Creatinine clearance, ml/min, median (IQR)	84.0 (60.1–110.0)	60.0 (42.7–85.0)	87.0 (64.0–111.4)	<0.001
Hemoglobin at admission, g/dl, median (IQR)	14.2 (12.9–15.2)	13.5 (12.0–14.9)	14.30 (13.0–15.3)	<0.001
Systolic pressure, mm Hg, median (IQR)	120 (103–136)	101(90–128)	120 (105–137)	<0.001
Staged PCI, n (%)	205 (18.3)	14 (11.4)	191 (19.2)	0.04
Killip class				<0.001
1, n (%)	845 (75.3)	53 (43.4)	792 (79.2)	
2, n (%)	122 (10.9)	13 (10.7)	109 (10.9)	
3, n (%)	38 (3.4)	9 (7.4)	29 (2.9)	
4, n (%)	117 (10.4)	47 (38.5)	70 (7.0)	
LAD, n (%)	477 (42.2)	50 (39.7)	427 (42.6)	0.54
TIMI score, median (IQR)	3 (2–5)	6 (4–8)	3 (2–5)	<0.001
Peak CK, U/l, median (IQR)	1667 (904–3017)	1972 (1010– 3812)	1649 (893–2914)	0.06
Radial approach, n (%)	772 (68.6)	71 (57.3)	701 (70.0)	0.004
Glycoprotein IIb/IIIa inhibitors, n (%)	236 (21.1)	26 (26.1)	210 (21.1)	0.98
IABP insertion, n (%)	31 (2.8)	9 (7.1)	22 (2.2)	0.005[a]
Length of hospital stay, days, median (IQR)	6 (5–8)	12 (7–20)	6 (5–7)	<0.001

[a]Fisher's exact test.

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; CK, creatine-kinase; IABP, intra-aortic balloon pump; IQR interquartile range; LAD, left anterior descending artery; MI, myocardial infarction

of MACCE during the follow-up, variables with a P <0.1 on univariable analyses were included in multivariable equations. The presence of possible interactions between NI and all the other variables was tested. Statistical analysis was conducted using Statistical Package for Social Sciences (SPSS version 25.0) and a two-tailed P <0.05 was considered significant for all tests.

RESULTS

From January 2008 to December 2017, of the 1150 STEMI consecutive patients screened, 12 were excluded for presenting an infection at the time of admission and 7 for developing an infection <48 hours after admission. From the 1131 patients included in the study, 126 (11.1%) developed a NI, mostly of respiratory (50.8%) and urinary (39.7%) tract origin (Figure 1). The median time until the diagnosis of NI was 3 days (IQR, 2–6).

Patients who developed a NI were older, more often men, non-smokers, and had more comorbidities. They also had lower hemoglobin, lower creatinine clearance, and lower systolic blood pressure on admission, as well as a higher Killip class during the hospital stay and a higher TIMI score for STEMI on arrival (Table 1). NI was also related

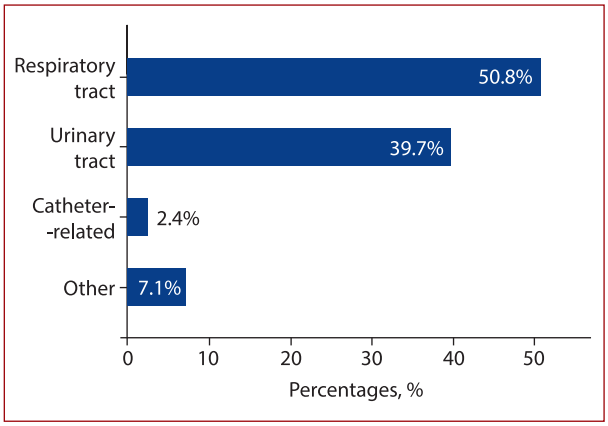

Figure 1. Nosocomial infection site

Table 2. Predictors of nosocomial infection during hospitalization

	Univariable		Multivariable	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age, years	1.05 (1.03–1.07)	<0.001	1.05 (1.02–1.07)	<0.001
Men vs women	0.52 (0.35–0.77)	0.001	0.68 (0.41–1.13)	0.14
Pre-infarction angina (yes vs no)	0.48 (0.30–0.77)	0.002	0.56 (0.33–0.95)	0.03
BMI, kg/m^2	0.98 (0.93–1.04)	0.51		
Medical history (yes vs no)				
Hypertension	1.54(1.05–2.27)	0.03	1.19 (0.73–1.94)	0.49
Dyslipidemia	1.01 (0.70–1.47)	0.94		
PAD	3.12 (1.90–2.14)	<0.001	2.74 (1.52–4.95)	0.001
Smoker	0.68 (0.47–0.99)	0.046	1.72 (0.99–3.00)	0.06
History of CABG	1.23 (0.28–5.52)	0.79		
History of MI	1.19 (0.61–2.31)	0.61		
Diabetes (vs no)				
Yes, without insulin	1.47 (0.93–2.31)	0.10	1.25 (0.73–2.15)	0.41
Yes, with insulin	5.02 (2.63–9.58)	<0.001	3.40 (1.53–7.56)	0.003
Total ischemic time, hours	1.01 (0.99–1.03)	0.38		
Door-to-balloon time, hours	1.04 (0.98–1.09)	0.25		
Creatinine clearance, ml/min	0.98 (0.97–0.99)	<0.001	0.99 (0.98–1.00)	0.08
Hemoglobin at admission, g/dl	0.82(0.74–0.90)	<0.001	0.99 (0.86–1.13)	0.83
Systolic pressure, mm Hg	0.99(0.98–0.99)	<0.001	0.99 (0.98–1.00)	0.002
Staged PCI (yes vs no)	0.54 (0.30–0.96)	0.04	0.54 (0.27–1.08)	0.08
LAD vs Non-LAD	0.89 (0.61–1.30)	0.54		
Peak CK, U/l ×10^3	1.10 (1.02–1.18)	0.01	1.12 (1.03–1.22)	0.01
Femoral vs Radial Approach	1.74 (1.19–2.54)	0.004	1.27 (0.81–2.01)	0.30
Glikoprotein IIb/IIIa inhibitors (yes vs no)	0.99 (0.62–1.57)	0.98		
IABP insertion (yes vs no)	3.42 (1.54–7.59)	0.003	3.09 (1.12–8.47)	0.03

Abbreviations: CI, confidence interval; OR, odds ratio; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention. Other — see Table 1

to the use of an intra-aortic balloon pump (IABP), whereas utilization of a radial approach and staged PCI for multivessel coronary disease were more prevalent in patients without NI. Length of hospital stay was significantly longer in patients with NI (median 6 vs 12 days). There were no other significant differences between groups.

Predictors of NI

Fourteen variables were eligible for multivariable analysis, as shown in Table 2. Diabetic patients on insulin therapy were approximately 3 times more likely to develop in-hospital infection (odds ratio [OR], 3.40; 95% confidence interval [CI], 1.53–7.56; $P = 0.003$), however, this association was not significant for non-insulin treated diabetes (OR, 1.25; 95% CI, 0.73–2.15; $P = 0.41$). Other predictors of NI were PAD (OR, 2.74; 95% CI, 1.52–4.95; $P = 0.001$) and the need for an IABP (OR, 3.09; 95% CI, 1.12–8.47; $P = 0.03$). NI was also statistically more prevalent in older patients (OR, 1.05 per year of age; 95% CI, 1.02–1.07; $P < 0.001$), those with lower systolic blood pressure on admission (OR, 0.99 per mm Hg rise; 95% CI, 0.98–1.00, $P = 0.002$) and those who had a higher peak creatine-kinase (CK) activity (OR, 1.12 per unit rise; 95% CI, 1.03–1.22; $P = 0.01$). On the contrary, PIA was negatively related to NI (OR, 0.56; 95% CI, 0.33–0.95; $P = 0.03$).

Impact of NI on outcomes

As observed on the Kaplan-Meier survival curve (Figure 2), in a 1-year follow-up, the occurrence of MACCE was more than twice as common in the NI group: 47 (37.3%) vs 193 (14.6%), log-rank $P < 0.001$, driven by a larger difference in the first month after STEMI. The statistically significant difference between patients with and without NI is consistent for all composite events of MACCE, except target lesion revascularization (Supplementary material).

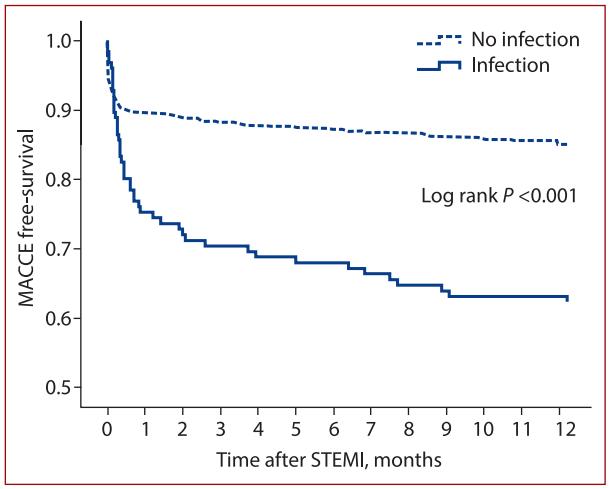

Figure 2. Kaplan-Meier survival curve showing the probability of a STEMI patient to remain free of a MACCE event according to nosocomial infection

Table 3 shows the proportional hazard Cox analysis for predictors of MACCE at 1-year follow-up. The strongest MACCE predictor was PAD (hazard ratio [HR], 3.16; 95%

Table 3. Predictors of MACCE at 1-year follow-up

	Univariable		Multivariable (without interaction)	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age, years	1.04 (1.03–1.05)	<0.001	1.02 (1.00–1.04)	0.04
Men vs women	0.67 (0.50–0.91)	0.009	1.15 (0.76–1.73)	0.52
Pre-infarction angina (yes vs no)	0.62 (0.44–0.86)	0.005	0.83 (0.56–1.23)	0.35
BMI, kg/m^2	0.98 (0.94–1.02)	0.34		
Medical history (yes vs no)				
Hypertension	1.82 (1.34–2.48)	<0.001	1.13 (0.76–1.68)	0.54
Dyslipidemia	0.82 (0.62–1.09)	0.17		
PAD	4.46 (3.23–6.15)	<0.001	3.16 (2.05–4.87)	<0.001
Smoker	0.55 (0.41–0.74)	<0.001	1.01 (0.65–1.56)	0.98
History of CABG	1.66 (0.62–4.46)	0.32		
History of MI	1.72 (1.11–2.66)	0.02	1.20 (0.69–2.07)	0.52
Diabetes (vs no)				
Yes, without insulin	1.36 (0.96–1.92)	0.09	1.16 (0.76–1.77)	0.49
Yes, with insulin	3.21 (1.98–5.20)	<0.001	1.23 (0.63–2.40)	0.54
Total ischemic time, hours	1.02 (1.01–1.03)	0.008	1.01 (0.99–1.04)	0.81
Door-to-balloon time, hours	1.04 (1.00–1.08)	0.07	1.03 (0.97–1.07)	0.32
Creatinine clearance, ml/min	0.98 (0.97–0.98)	<0.001	1.00 (0.99–1.00)	0.27
Hemoglobin at admission, g/dl	0.76 (0.71–0.82)	<0.001	0.85 (0.77–0.94)	0.002
Systolic pressure, mm Hg	0.98 (0.97–0.99)	<0.001	0.99 (0.98–1.00)	0.003
Staged PCI (yes vs no)	0.57 (0.40–0.90)	0.02	0.65 (0.38–1.10)	0.11
LAD vs Non-LAD	0.81 (0.60–1.08)	0.15		
Peak CK, U/l ×10^3	1.08 (1.02–1.15)	0.02	1.11 (1.04–1.19)	0.002
Femoral vs radial approach	3.18 (2.39–4.24)	<0.001	1.85 (1.30–2.64)	0.001
Glikoprotein IIb/IIIa inhibitors (yes vs no)	0.85 (0.59–1.23)	0.40		
IABP insertion (yes vs no)	4.04 (2.38–6.86)	<0.001	1.38 (0.62–3.09)	0.44
Nosocomial infection	2.73 (1.96–3.79)	<0.001	1.24 (0.80–1.94)	0.34

Abbreviations: see Table 1 and 2

CI, 2.05–4.87; *P* <0.001). Age (HR, 1.02; 95% CI, 1.00–1.04; *P* = 0.04), lower hemoglobin concentration (HR, 0.85; 95% CI, 0.77–0.94; *P* = 0.002), lower systolic blood pressure on admission (HR, 0.99; 95% CI, 0.98–1.00; *P* = 0.003), a higher peak CK activity (HR, 1.11; 95% CI, 1.04–1.19; *P* = 0.002), and the utilization of a femoral approach (HR, 1.85; 95% CI, 1.30–2.64; *P* = 0.001) were also found to be independent predictors of MACCE. NI was not found to be an independent predictor of MACCE (HR, 1.24; 95% CI, 0.80–1.94; *P* = 0.34). An interaction between NI and smoking was identified (HR, 2.33; 95% CI, 1.03–5.24; P_{interc} = 0.04). No more interactions were found between NI and other plausible variables. Furthermore, interaction with smoking was not significant when the infection site was considered (P_{interc} = 0.29). As seen in Figure 3, dividing patients into four groups according to the presence of NI and smoking habits, a significant difference between the incidence of MACCE at 1-year follow-up was observed (*P* <0.001), with smokers who have a NI being the most affected group (42.3%).

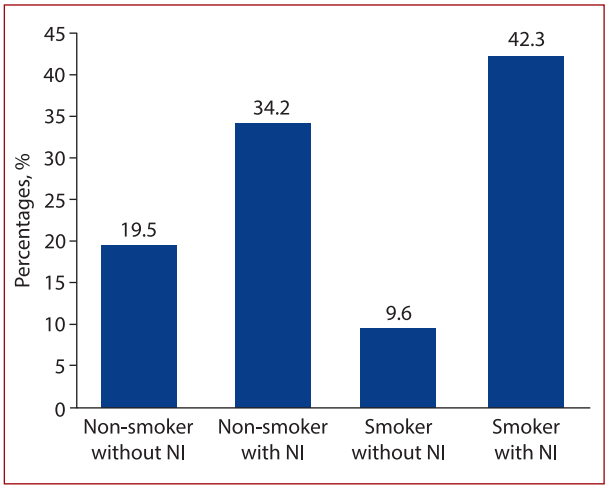

Figure 3. Incidence of MACCE at 1-year follow up according to the presence of nosocomial infection (NI) or smoking habits

DISCUSSION

Our study reveals that 11.1% of STEMI patients had a NI during the hospital stay, a prevalence lower than reported by some studies in mixed populations undergoing PCI (from 16% to nearly 30%) [6, 10, 11], but higher than others (from 2.4 to 5%) [2, 3, 12]. This may reflect the inhomogeneous definitions of hospital-acquired infection and various indications for PCI (from stable disease to STEMI).

Consistent with most studies [6, 10, 12], pulmonary and urinary tract infections were the most frequent NI site. Even though primary PCI carries vascular invasiveness, the incidence of bloodstream infections was low. As expected, we observed a prolonged hospital stay in infected patients compared to the non-infected group.

Age, diabetes on insulin therapy, PAD, insertion of an IABP, low blood pressure, and high peak CK were identified as factors that favor infection. This comes as no surprise, since it may reflect patients with larger infarcts, requiring more invasiveness, as well as those who are more prone to infections (the elderly, the diabetics, and those with established PAD). Insulin therapy most likely works as a marker of diabetes progression, signaling patients with aggravated immune, vascular, and neurological dysfunction, rather than representing a direct result of prior antidiabetic therapy on NI risk [13–15].

The insertion of an IABP can understandably lead to an increase in bacteremia, wound, respiratory, and urinary tract infections as these patients frequently require a prolonged stay in intensive care units. IABP's complications have a considerable discrepancy of prevalence reported in the literature (0.9% to 7%) [16–19]. Also, IABP's correlation to NI likely reflects STEMI's severity (hemodynamic instability or cardiogenic shock), rather than an effect of the IABP itself. According to previous reports, a femoral rather than radial approach is associated, not only with a higher rate of bleeding and vascular complications, but morbidity and mortality as well [20–22]. However, the correlation with NI reported in our study may likely be related to the operator's preference in patients who arrive unstable to the catheterization laboratory, and so the reasoning behind the cause-and-effect relationship to predict infection may be the same as for the IABP.

PIA was a protective characteristic. It is likely related to the smaller infarct size caused by preconditioning which limits the reperfusion-injury phenomenon [23, 24], rather than having a direct influence on the development of a NI.

At 1-year follow-up, MACCE was independently associated with age, PAD, low hemoglobin concentration and low systolic pressure on admission, a higher peak CK activity, and femoral approach. Despite the unadjusted statistically significant difference in MACCE's incidence between patients with and without infection, it was not an independent predictor of these events on multivariate Cox model analysis. This is probably explained by the overlap of risk factors for infection and MACCE, namely age, PAD, and larger infarctions. This signals that features that favor infection are similar to those favoring adverse events, undermining a cause-and-effect relationship. Nevertheless, NI could function as a marker of frailty, helping physicians identify STEMI patients who are more prone to deteriorate clinically and might benefit from close surveillance.

Our analysis also showed a significant interaction between infection and smoking, seemingly not related to the infection site (namely, respiratory or urinary). Since smoking contributes both to the development of infection and cardiovascular disease in the long term [25, 26], and mortality from infection was also reported to be higher in smokers [27], this signals a tendency for a synergic effect between infection and smoking on MACCE. However, it is also reasonable to speculate that a nosocomial infection is more a sign of an underlying lung dysfunction then aggravated by heart insufficiency translated in mid-term events, than a causal risk factor *per se*.

Notwithstanding our findings, some series had shown that infection was significantly associated with a 30 or 90-day mortality. These cohorts only addressed "serious" infections and only captured short-term follow-up [2, 3]. On the other hand, another series reported that only pneumonia, and not infection in other sites, was associated with an increased risk of adverse events for an elderly population who underwent PCI irrespective of the indication [6]. Hence, the association between smoking habits and NI could be related to respiratory tract infections and might not be the same for urinary tract infections. We believe this is a hypothesis that should be addressed in future studies.

Limitations

The 48 hour cutpoint used for the definition of nosocomial infection is debatable, however, it is widely accepted and utilized in the literature. A major limitation of our study is the relationship between common risk factors to predict adverse events and the risk of a NI. The relative impact of NI in follow-up is, therefore, difficult to filter, despite the confounding variables incorporated in the multivariate equation and interaction analysis. Another limitation is the well-known limitation of a retrospective analysis, with its inherent bias to assume a cause-and-effect relationship between NI and outcomes. Lastly, being a single-center cohort study, the results may not be representative of all patients with STEMI undergoing PCI.

CONCLUSION

Our study determined that NI is a relatively common complication of STEMI (11.1%), with most risk factors that predict NI also being related to mid-term adverse events. NI does not constitute an independent predictor of MACCE, however, its occurrence during the first year was more than two times higher in smokers who complicate with a NI.

Supplementary material

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

Article information

Conflict of interest: None declared.

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REFERENCES

1. Wayangankar SA, Bangalore S, McCoy LA, et al. Temporal trends and outcomes of patients undergoing percutaneous coronary interventions for cardiogenic shock in the setting of acute myocardial infarction: a report from the CathPCI registry. JACC Cardiovasc Interv. 2016; 9(4): 341–351, doi: 10.1016/j.jcin.2015.10.039, indexed in Pubmed: 26803418.
2. Truffa AAM, Granger CB, White KR, et al. Serious infection after acute myocardial infarction: incidence, clinical features, and outcomes. JACC Cardiovasc Interv. 2012; 5(7): 769–776, doi: 10.1016/j.jcin.2012.03.018, indexed in Pubmed: 22814783.
3. Piccaro de Oliveira P, Gonzales V, Lopes RD, et al. Serious infections among unselected patients with ST-elevation myocardial infarction treated with contemporary primary percutaneous coronary intervention. Am Heart J. 2016; 181: 52–59, doi: 10.1016/j.ahj.2016.08.005, indexed in Pubmed: 27823693.
4. Merx MW, Weber C. Sepsis and the heart. Circulation. 2007; 116(7): 793–802, doi: 10.1161/CIRCULATIONAHA.106.678359, indexed in Pubmed: 17698745.
5. Musher DM, Abers MS, Corrales-Medina VF, et al. Acute infection and myocardial infarction. N Engl J Med. 2019; 380(2): 171–176, doi: 10.1056/NEJMra1808137, indexed in Pubmed: 30625066.
6. Leistner DM, Münch C, Steiner J, et al. Effect on outcomes: infections complicating percutaneous coronary interventions in patients ≥80 years of age. Am J Cardiol. 2019; 123(11): 1806–1811, doi: 10.1016/j.amjcard.2019.03.003, indexed in Pubmed: 30910227.
7. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008; 36(5): 309–332, doi: 10.1016/j.ajic.2008.03.002, indexed in Pubmed: 18538699.
8. Thygesen K, Alpert J, Jaffe A, et al. Fourth universal definition of myocardial infarction (2018). Circulation. 2018; 138(20): e618–e651, doi: 10.1161/cir.0000000000000617.
9. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018; 39(2): 119–177, doi: 10.1093/eurheartj/ehx393.
10. Liu Y, Dai Y, Chen J, et al. Predictive value of the Canada Acute Coronary Syndrome risk score for post-acute myocardial infarction infection. Eur J Intern Med. 2020; 71: 57–61, doi: 10.1016/j.ejim.2019.10.012, indexed in Pubmed: 31732453.
11. Wang L, Huang G, Peng Q, et al. Risk predictive ability of ACEF score for infection in patients with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention. Eur J Prev Cardiol. 2020; 27(2): 220–222, doi: 10.1177/2047487319873142, indexed in Pubmed: 31619086.
12. Júnior LG, Caramelli B. Complicação infecciosa indica mau prognóstico no infarto agudo do miocárdio. Arq Bras Cardiol. 2006; 87(3): 267–274, doi: 10.1590/s0066-782x2006001600007.
13. Dryden M, Baguneid M, Eckmann C, et al. Pathophysiology and burden of infection in patients with diabetes mellitus and peripheral vascular disease: focus on skin and soft-tissue infections. Clin Microbiol Infect. 2015; 21(Suppl 2): S27–S32, doi: 10.1016/j.cmi.2015.03.024, indexed in Pubmed: 26198368.
14. Donnelly JP, Nair S, Griffin R, et al. Association of diabetes and insulin therapy with risk of hospitalization for infection and 28-day mortality risk. Clin Infect Dis. 2017; 64(4): 435–442, doi: 10.1093/cid/ciw738, indexed in Pubmed: 28174913.
15. Cooke FJ. Infections in people with diabetes. Medicine. 2015; 43(1): 41–43, doi: 10.1016/j.mpmed.2014.10.002.
16. Meharwal ZS, Trehan N. Vascular complications of intra-aortic balloon insertion in patients undergoing coronary reavscularization: analysis of 911 cases. Eur J Cardiothorac Surg. 2002; 21(4): 741–747, doi: 10.1016/s1010-7940(02)00034-9, indexed in Pubmed: 11932177.
17. Alvarez JM, Gates R, Rowe D, et al. Complications from intra-aortic balloon counterpulsation: a review of 303 cardiac surgical patients. Eur J Cardiothorac Surg. 1992; 6(10): 530–535, doi: 10.1016/1010-7940(92)90003-g, indexed in Pubmed: 1389234.
18. Wasfie T, Freed PS, Rubenfire M, et al. Risks associated with intraaortic balloon pumping in patients with and without diabetes mellitus. Am J Cardiol. 1988; 61(8): 558–562, doi: 10.1016/0002-9149(88)90764-3, indexed in Pubmed: 3344679.
19. Borges LHB, Camargo LFA, Strabelli TMV, et al. Contrapulsação em operação cardíaca: análise retrospectiva da incidência de infecção. Braz J Cardiovasc Surg. 1994; 9(2): 88–94, doi: 10.1590/s0102-76381994000200003.
20. Rao SV, Ou FS, Wang TY, et al. Trends in the prevalence and outcomes of radial and femoral approaches to percutaneous coronary intervention: a report from the National Cardiovascular Data Registry. JACC Cardiovasc Interv. 2008; 1(4): 379–386, doi: 10.1016/j.jcin.2008.05.007, indexed in Pubmed: 19463333.
21. Nardin M, Verdoia M, Barbieri L, et al. Radial vs femoral approach in acute coronary syndromes: a meta- analysis of randomized trials. Curr Vasc Pharmacol. 2017; 16(1): 79–92, doi: 10.2174/1570161115666170504125831, indexed in Pubmed: 28490313.
22. Valgimigli M, Gagnor A, Calabró P, et al. MATRIX Investigators. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. Lancet. 2015; 385(9986): 2465–2476, doi: 10.1016/S0140-6736(15)60292-6, indexed in Pubmed: 25791214.
23. Mladenovic ZT, Angelkov-Ristic A, Tavciovski D, et al. The cardioprotective role of preinfarction angina as shown in outcomes of patients after first myocardial infarction. Tex Heart Inst J. 2008; 35(4): 413–418, indexed in Pubmed: 19156234.
24. Ottani F, Galvani M, Ferrini D, et al. Prodromal angina limits infarct size. A role for ischemic preconditioning. Circulation. 1995; 91(2): 291–297, doi: 10.1161/01.cir.91.2.291, indexed in Pubmed: 7805230.
25. Arcavi L, Benowitz NL. Cigarette smoking and infection. Arch Intern Med. 2004; 164(20): 2206–2216, doi: 10.1001/archinte.164.20.2206, indexed in Pubmed: 15534156.
26. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol. 2004; 43(10): 1731–1737, doi: 10.1016/j.jacc.2003.12.047, indexed in Pubmed: 15145091.
27. Carter BD, Abnet CC, Feskanich D, et al. Smoking and mortality — beyond established causes. N Engl J Med. 2015; 372(7): 631–640, doi: 10.1056/NEJMsa1407211, indexed in Pubmed: 25671255.

Protamine sulfate during transcatheter aortic valve implantation (PS TAVI) — a single-center, single-blind, randomized placebo-controlled trial

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ABSTRACT

Background: Bleeding complications after transcatheter aortic valve implantation (TAVI) negatively affect the post-procedural prognosis. Routine use of protamine sulfate (PS) to reverse unfractionated heparin after TAVI was never assessed in a randomized controlled trial.

Aims: The aim of this study was to assess the impact of PS on bleeding complications after TAVI.

Methods: Between December 2016 and July 2020 311 patients qualified to TAVI in one academic center were screened. Patients that met the inclusion criteria were randomized to either PS or normal saline administration at the moment of optimal valve deployment. Baseline, procedural, and follow-up data for up to 30 days were collected and analyzed. The primary endpoint (PE) was a composite of life-threatening and major bleeding according to Valve Academic Research Consortium within 48 hours after the procedure.

Results: Overall, 100 patients (48 males, median age 82 years) met the inclusion criteria and were included in the study. Forty-seven subjects (47%) were randomized to PS. The primary endpoint occurred in 29% of the study population. Despite numerically lower rates of PE in patients randomized to PS, a statistical significance was not reached (21% in the PS group and 36% in the placebo group; odds ratio [OR], 0.48; 95% confidence intervals [CI] 0.2–1.2; $P = 0.11$). There were no significant differences in secondary endpoints.

Conclusions: Routine protamine sulfate administration did not significantly decrease the rate of major and life-threatening bleeding complications after TAVI. Larger studies are required to assess the impact of routine PS use.

Key words: aortic, implantation, protamine, sulfate, transcatheter, valve

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INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is an increasingly popular treatment method for patients with severe, symptomatic aortic stenosis (AS). In a plethora of studies either a clear benefit or non-inferiority was demonstrated in comparison to the gold standard — surgical aortic valve replacement — across almost all spectrums of AS patients [1]. Despite the fact, that many aspects of the antithrombotic treatment before and after TAVI have been studied, routine use of protamine sulfate (PS) to reverse the effect of the unfractionated heparin (UFH) was never included in those analyses.

Based on an expert consensus [2], UFH should be administered in every patient and should be reversed with PS after transapical and transfemoral TAVI except for transfemoral cases with minimal bleeding risk. The clinical practice, however, differs between centers [3, 4]. The impact of PS on bleeding and thromboembolic complications is unknown and reports of the pro-thrombotic effect of the PS have been published in different clinical settings [5–7]. Hemor-

WHAT'S NEW?

For the first time, the impact of routine administration of protamine sulfate (PS) in patients undergoing transcatheter aortic valve implantation was assessed in a randomized controlled trial (RCT). In this first, albeit a relatively small RCT, routine administration of PS did not significantly decrease the rate of major and life-threatening bleedings.

rhagic complications (at least major bleedings according to Valve Academic Research Consortium [VARC] criteria [8]) increase mortality after TAVI [9] and are relatively frequent ranging from 4.7% up to 77% [10–12]. No randomized trials assessing the influence of PS on bleeding rates after TAVI have been published to date. In order to comply with the rule of thumb — "when in doubt, randomize" — a clinical, placebo-controlled trial is required in order to properly assess the impact of protamine sulfate administration.

METHODS

Trial design and funding

The protamine sulfate during transcatheter aortic valve implantation (PS TAVI) is a single-center, single-blind randomized placebo-controlled trial in which routine PS administration to reverse UFH was compared to placebo. The study was investigator-initiated and did not receive any funding from the industry. Informed consent was obtained from all participating patients and the local ethics committee granted permission for the study (approval number KB/212/2016). The study protocol is available on ClinicalTrials.gov (NCT02974660). The study design is presented on Figure 1.

Patients, randomization, and procedures

The study aimed to include patients with severe, symptomatic aortic stenosis (aortic valve area [AVA] <1.0 cm^2 or indexed valve area less than 0.6 cm^2/m^2 or mean gradient >40 mm Hg or maximum jet velocity >4.0 m/s or velocity ratio <0.25), qualified by the Heart Team to a transfemoral TAVI with a planned application of pre-close devices such as Prostar® or Proglide®. The exclusion criteria were lack of informed consent, participation in another clinical trial, and known allergy to protamine sulfate.

Both mechanically- and self-expandable aortic valve prostheses of the second generation were used. In all cases, transfemoral access with at least two pre-close devices was applied. The procedures were performed in hybrid operating rooms under general anesthesia or local anesthesia with conscious sedation. After obtaining the vascular access, all patients received UFH at the dose of 100 IU/kg with the target activated clotting time (ACT) of 250–300 seconds.

At the moment of the optimal valve implantation, eligible patients were randomly assigned using the envelope method to either protamine sulfate or normal saline. The PS was administered in a slow bolus at the dose of 1 mg per 100 IU of unfractionated heparin administered within the last 30 minutes plus 0.5 mg per 100 IU of the UFH administered earlier. The successful reversal of heparin was confirmed by ACT measurements at baseline, after UFH boluses, before and after PS administration.

The type and number of preclose devices was noted as well as potential issues with the closure, including extravasation of the contrast in the final femoral angiography,

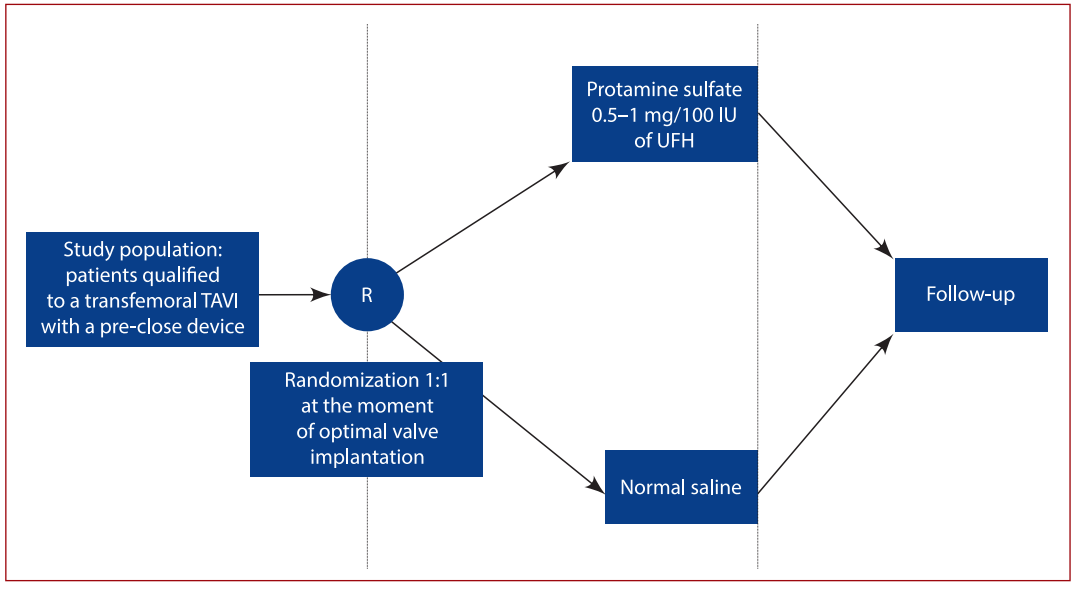

Figure 1. Study design

Abbreviation: TAVI, transcatheter aortic valve implantation; UFH, unfractionated heparin

device malfunction, need for balloon angioplasty, stent implantation, or emergent surgical cut-down.

In terms of antithrombotic treatment before and after TAVI, patients without indications for chronic oral anticoagulation (OAC) were given loading doses of 300 mg of aspirin and clopidogrel within 24 hours before TAVI, and then continued 75 mg daily after the procedure. In patients requiring chronic OAC, the treatment was stopped 2–3 days before the procedure in order to obtain an international normalized ratio of <2 in case of vitamin K antagonists (VKA) and 1–2 days before the procedure depending on the renal function in case of non-vitamin K antagonists. After TAVI the oral anticoagulation was restarted as soon as deemed safe, with additional bridging with low-molecular-weight heparin in patients receiving VKA.

Endpoints and definitions

The primary endpoint of the study was a composite of life-threatening and major bleeding complications according to VARC-2 at 48 hours after the procedure. The secondary endpoints were major and minor bleedings according to VARC-2 at 48 hours after the procedure, all-cause mortality at 30 days, a drop in hemoglobin concentration 48 hours after the procedure, the length of the hospitalization (the time from the index procedure to discharge), and thromboembolic events (stroke, transient ischemic attack, myocardial infraction) within 48 hours after the procedure. Coronary artery disease was defined as the presence of at least one lesion >70% in the epicardial coronary vessel >1.5 mm (>50% for left main), history of myocardial infarction, previous percutaneous coronary intervention, or coronary artery bypass grafting. Successful closure of the access artery was defined as obtaining proper hemostasis with no residual bleed, without device malfunction or a need for prolonged balloon inflation or covered stent implantation. Access-site and access-related vascular injury (ASARVI) was defined according to a modified classification by Sedaghat et al. [13]: type I, blush or minimal extravasation; type II, moderate extravasation (<5 mm); type III, major extravasation (>5 mm) including vessel perforation/rupture; and type IV, vessel dissection or occlusion.

Statistical analysis

Estimation was done based on the major and life-threatening bleeding rates from the historic material of the center (28%), that 100 patients are required to have a 90% chance of detecting a significant decrease in the primary outcome occurrence from 28% in the placebo group to 5% in the PS group. The primary analysis was performed in the intention-to-treat population.

Continuous variables, expressed as the median and interquartile range (IQR), were compared between the study and control groups using Mann-Whitney U-test. Shapiro-Wilk test was used to confirm or reject the normal distribution of each continuous variable. Categorical variables, expressed as counts and percentages, were compared using the Chi-square test or Fisher's exact test, as appropriate.

A uni- and multivariable backward likelihood ratio logistic regression model was used to identify predictors of the primary and secondary endpoints. Variables from the univariate analysis (with a *P* value of ≤0.20 difference) were included in the multivariable analysis. Results are presented as odds ratio (OR) with 95% confidence intervals (CI).

All probability values reported are 2-sided and a value <0.05 was considered to be significant. All data were processed using the SPSS software, version 22 (IBM SPSS Statistics, New York, NY, USA).

RESULTS

Population

Of the 311 consecutive patients screened between December 2016 and July 2020 in one academic center, 85 (27%) underwent TAVI via an other-than-transfemoral or transfemoral with surgical cut-down access, 78 (25%) participated in other clinical trials and 48 (15%) did not consent to participation in the study. The study flow-chart is presented in Figure 2. Overall, one hundred patients were included in the study. The median age was 82 years (IQR 77–85), there were 48 males (48%), almost 90% of patients had hypertension, 43% — diabetes, and approximately one-third (36%) was in New York Heart Association (NYHA) class III or IV. The median logistic EuroSCORE was 10.5 (IQR, 8–16). All the procedures were performed via transfemoral access and in all cases, a pre-close system was used. Detailed baseline data are shown in Table 1.

Protamine sulfate administration

Forty-seven subjects (47%) were randomized to protamine sulfate and 56 patients (56%) have received PS (cross-over: 9%; in all cases the reason for cross-over was due to operators' decision). Median PS dose was 35 mg or 0.5 mg per 100 IU of UFH. There were no major differences between the PS and placebo group, except for the presence of moderate or severe mitral regurgitation (49% vs 30%, PS and placebo respectively, $P = 0.07$) as well as pre- and post-dilatation (pre-dilatation: PS — 45%, placebo — 68%, $P = 0.03$; post-dilation: PS — 26%, placebo — 46%, $P = 0.04$).

Primary endpoint

The primary composite endpoint of VARC-defined major and life-threatening bleeding was observed in 29 patients (29% of the study population, 21% of the PS cohort, and 36% of the control group, $P = 0.13$). Major bleeding occurred in 19 patients (19%, 13% of those randomized to PS, and 25% of the control group, $P = 0.2$). One disabling stroke (1%) and 2 transient ischemic attacks (2%) were reported. The 30-day all-cause mortality was 5%. A detailed list of study endpoints is presented in Table 1.

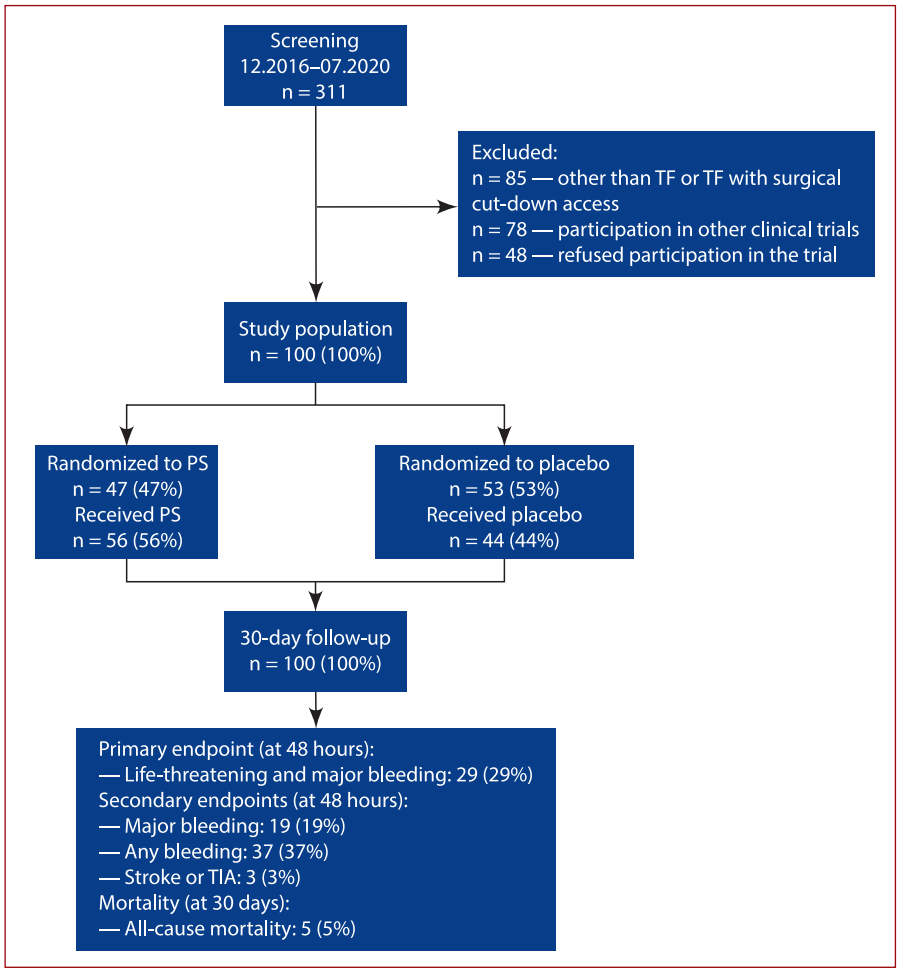

Figure 2. Study flowchart

Abbreviations: PS, protamine sulfate; TF, transfemoral; TIA, transient ischemic attack; other: see Figure 1

Table 1. Baseline and procedural characteristics of the study population along with endpoint rates

	Total (n = 100)	Protamine sulfate (n = 47, 47%)	Placebo (n = 53, 53%)	*P*-value
Demographics				
Female gender, n (%)	52 (52)	25 (53)	27 (51)	0.84
Age, years, median (IQR)	81.7 (77–85)	81.8 (77–85)	81 (75–86)	0.63
Baseline characteristics				
BMI, kg/m^2, median (IQR)	26.6 (23–28)	26 (23–29)	26.6 (23–28)	0.78
BSA, m^2, median (IQR)	1.79 (1.7–1.9)	1.79 (1.7–1.9)	1.78 (1.7–1.9)	0.84
LogEuroSCORE, %, median (IQR)	10.5 (7.9–16.3)	10.5 (7.8–16.3)	10.4 (8–16.9)	0.75
Hypertension, n (%)	87 (87)	41 (87)	46 (87)	1
Diabetes, n (%)	43 (43)	24 (51)	19 (36)	0.16
GFR <30 ml/min, n (%)	9 (9)	4 (9)	5 (9)	1
History of bleeding, n (%)	10 (10)	6 (13)	4 (8)	0.51
Coronary artery disease, n (%)	75 (75)	37 (79)	38 (72)	0.49
Prior cardiac surgery, n (%)	12 (12)	7 (15)	5 (9)	0.54
History of stroke/TIA, n (%)	12 (12)	4 (9)	8 (15)	0.37
Atrial fibrillation, n (%)	44 (44)	20 (43)	24 (45)	0.84
COPD, n (%)	16 (16)	9 (19)	7 (13)	0.59
Prior pacemaker implantation, n (%)	24 (24)	8 (17)	16 (30)	0.16
Oral anticoagulation, n (%)	46 (46)	22 (47)	24 (45)	1
NYHA class 3-4, n (%)	36 (36)	16 (34)	20 (38)	0.84
LVEF, %, median (IQR)	58 (53–63)	60 (55–64)	58 (53–62)	0.4
LVEF <30%, n (%)	10 (10)	6 (13)	4 (8)	0.51
Mean AV pressure gradient, mm Hg, median (IQR)	42 (34.5–50)	42 (38–50)	42 (34–50)	0.81
Aortic valve area, cm^2/m^2, median (IQR)	0.7 (0.6–0.8)	0.7 (0.6–0.8)	0.74 (0.6–0.8)	0.17

→

Table 1. cont. Baseline and procedural characteristics of the study population along with endpoint rates

	Total (n = 100)	Protamine sulfate (n = 47, 47%)	Placebo (n = 53, 53%)	*P*-value
Moderate or severe MR, n (%)	39 (39)	23 (49)	16 (30)	0.07
Serum creatinine, mg/dl, median (IQR)	1.22 (1–1.5)	1.22 (1.0–1.5)	1.21 (1–1.5)	0.97
Hemoglobin, g/dL, median (IQR)	12.5 (11.4–13.6)	12.6 (11–13.6)	12.4 (11.5–13.6)	0.9
Procedural and post-procedural data				
General anaesthesia, n (%)	5 (5)	3 (6)	2 (4)	0.66
Other than femoral access, n (%)	0 (0)	0 (0)	0 (0)	1
Self-expandable prosthesis, n (%)	92 (92)	42 (89)	50 (94)	0.47
Delivery system profile >16 French, n (%)	54 (54)	24 (51)	30 (57)	0.69
Predilation, n (%)	57 (57)	21 (45)	36 (68)	0.03
Postdilation, n (%)	36 (36)	12 (26)	24 (46)	0.04
Closure device, n (%)	100 (100)	47 (100)	53 (100)	1
Number of closure devices >2, n (%)	16 (16)	9 (19)	7 (13)	0.59
Successful closure, n (%)	91 (91)	43 (92)	48 (91)	1
ASARVI ≥3, n (%)	6 (6)	3 (6.4)	3 (5.7)	1
Need for peripheral angioplasty, n (%)	15 (15)	7 (15)	8 (15)	1
UFH, IU 10^3, median (IQR)	7 (6–8)	7 (6–8)	7 (6–8)	0.83
UFH/kg, IU, median (IQR)	100 (86–117)	100 (87–117)	100 (86–117)	0.9
LVEF, %, median (IQR)	60 (52–65)	60 (55–65)	57 (51–62)	0.17
Mean AV pressure gradient, mm Hg, median (IQR)	8 (6–10)	8.5 (5.8–11)	8 (6–10)	0.72
Aortic valve area, cm^2/m^2, median (IQR)	1.9 (1.8–2.1)	1.9 (1.7–2)	1.9 (1.8–2.1)	0.52
Serum creatinine, mg/dl, median (IQR)	1.28 (1–1.5)	1.27 (1–1.5)	1.3 (1–1.6)	0.68
Hemoglobin, g/dL, median (IQR)	9.8 (8.8–10.9)	9.8 (8.8–11.1)	9.8 (8.8–10.8)	0.83
Protamine sulfate				
Randomized to protamine, n (%)	47 (47)	—	—	—
Received protamine, n (%)	56 (56)	—	—	—
Protamine dose, mg, median (IQR)	—	35 (25–50)	—	—
Protamine dose per 100 IU of UFH, mg, median (IQR)	—	0.5 (0.4–0.6)	—	—
Endpoints				
30-day all-cause mortality, n (%)	5 (5)	3 (6)	2 (4)	0.66
Life threatening bleeding, n (%)	10 (10)	4 (9)	6 (11)	0.75
Major bleeding, n (%)	19 (19)	6 (13)	13 (25)	0.20
Minor bleeding, n (%)	8 (8)	4 (9)	4 (8)	1
Need for transfusion, n (%)	26 (26)	10 (21)	16 (30)	0.37
TIA, n (%)	2 (2)	0	2 (4)	0.5
Disabling stroke, n (%)	1 (1)	0 (0)	1 (2)	1
Need for permanent pacemaker, n (%)	24 (24)	11 (23)	13 (25)	1
Moderate or severe PVL, n (%)	16 (16)	6 (13)	10 (19)	0.43
Length of stay, days, median (IQR)	8 (6–15)	7 (6–15)	9 (6–14.5)	0.25
Any bleeding, n (%)	37 (37)	14 (30)	23 (43)	0.21
Major + life threatening bleeding , n (%)	29 (29)	10 (21)	19 (36)	0.13
Major + minor bleeding, n (%)	27 (27)	10 (21)	17 (32)	0.26

Abbreviations: AR, aortic regurgitation; ASARVI, access-site or access-related vascular injury; AV, aortic valve; BMI, body mass index; BSA, body surface area; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; PS, protamine sulfate; TIA, transient ischemic attack; UFH, unfractionated heparin

In a multivariable analysis of the primary endpoint occurrence, only serum creatinine (OR, 2.93 per 1 mg/dl increment; CI, 0.97–8.8; P = 0.06) has shown a trend towards statistical significance, while the remaining parameters included in the model: female gender (OR, 2.21; CI, 0.86–5.66; P = 0.1) and randomization to protamine sulfate administration (OR, 0.49; CI 0.92–1.2; P = 0.13) did not reach significance (Table 2).

Protamine sulfate and secondary endpoints and the per-protocol analysis

The impact of randomization to PS on VARC-defined major bleeding (OR, 0.45; CI, 0.2–1.3; P = 0.14, Table 3), any bleeding (OR, 0.55; CI 0.2–1.27; P = 0.16) as well as the remaining study endpoints also did not reach statistical significance (Table 4). Results of the per-protocol analysis are presented in the Supplementary material, *Tables S1, S2,* and *S3*.

DISCUSSION

Despite the long-lasting presence of protamine sulfate in the pharmacological arsenal of peri-procedural drugs in the field of interventional cardiology, it has never been studied in a randomized fashion in the setting of TAVI. Both bleeding and thromboembolic complications may potentially arise from PS administration, with the first being a result of potential rebound anticoagulation due to PS short half-life

Table 2. Uni- and multivariable logistic regression analysis of the composite of VARC-defined major and life-threatening bleeding occurrence

	Univariate		Multivariable	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Demographics				
Female gender	1.78 (0.74–4.31)	0.2	2.21 (0.86–5.66)	0.1
Age per 1 year	0.99 (0.93–1.06)	0.83		
Baseline characteristics				
BMI per kg/m^2	0.95 (0.84–1.07)	0.38		
Hypertension	1.42 (0.36–5.59)	0.62		
Diabetes	0.61 (0.25–1.49)	0.27		
GFR <30 ml/min	3.49 (0.87–14.1)	0.08	1.84 (0.31–10.8)	0.5
History of bleeding	0.58 (0.12–2.9)	0.51		
History of stroke/TIA	0.8 (0.2–3.17)	0.75		
Oral anticoagulation	0.77 (0.32–1.84)	0.55		
Serum creatinine per 1 mg/dl	2.35 (0.89–6.21)	0.09	2.93 (0.97–8.79)	0.06
Hemoglobin per 1 g/dl	1.1 (0.86–1.4)	0.45		
Procedural data				
General anaesthesia	1.68 (0.27–10.6)	0.58		
Delivery system profile >16 French	0.88 (0.37–2.09)	0.77		
Number of closure devices >2	2.19 (0.73–6.59)	0.16	2.27 (0.68–7.5)	0.18
Successful closure	0.47 (0.12–1.91)	0.29		
ASARVI ≥3	2.62 (0.5–13.8)	0.26		
Need for peripheral angioplasty	0.87 (0.25–3)	0.83		
UFH/kg per 1 IU	1 (0.99–1.02)	0.77		
Randomized to protamine	0.48 (0.2–1.19)	0.11	0.49 (0.92–1.2)	0.13
Received protamine	0.64 (0.27–1.54)	0.32		

Abbreviations: CI, confidence intervals; OR, odds ratio; other — see Table 1

Table 3. Uni- and multivariable logistic regression analysis of VARC-defined major bleeding occurrence

	Univariate		Multivariable	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Demographics				
Female gender	1.76 (0.63–4.92)	0.28	1.77 (0.51–5.14)	0.29
Age per 1 year	2 (0.9–1.1)	0.82		
Baseline characteristics				
BMI per kg/m^2	1.01 (0.9–1.1)	0.92		
Hypertension	0.75 (0.2–3)	0.69		
Diabetes	0.73 (0.26–2)	0.55		
GFR <30 ml/min	2.3 (0.5–10.4)	0.26	2.6 (0.57–12)	0.22
History of bleeding				
History of stroke/TIA				
Oral anticoagulation	1.1 (0.4–2.9)	0.89		
Serum creatinine per 1 mg/dl	1.5 (0.6–4)	0.39		
Hemoglobin per 1 g/dl	1.02 (0.8–1.4)	0.87		
Procedural data				
General anaesthesia	3.1 (0.5–19.8)	0.24	3.6 (0.53–24.5)	0.19
Delivery system profile >16 French	0.55 (0.2–1.5)	0.31		
Number of closure devices >2	1.5 (0.4–5.4)	0.51		
Successful closure	0.8 (0.2–4.2)	0.8		
ASARVI ≥3	0.84 (0.1–7.7)	0.88		
Need for peripheral angioplasty	0.62 (0.1–3)	0.55		
UFH/kg per 1 IU	1.01 (0.99–1.03)	0.58		
Randomized to protamine	0.45 (0.2–1.3)	0.14	0.45 (0.16–1.3)	0.14
Received protamine	0.5 (0.2–1.4)	0.18		

Abbreviations: see Table 1 and 2

Table 4. Impact of protamine sulfate administration on study endpoints occurrence

	OR (95% CI)	*P*-value
30-day all-cause mortality, n (%)	1.8 (0.3–10.8)	0.55
Life threatening bleeding, n (%)[a]	0.73 (0.2–2.76)	0.64
Major bleeding, n (%)[a]	0.45 (0.2–1.3)	0.14
Minor bleeding, n (%)[a]	1.14 (0.3–4.8)	0.86
Need for transfusion, n (%)[a]	0.63 (0.3–1.56)	0.31
TIA, n (%)[a]	—	—
Disabling stroke, n (%)[a]	—	—
Any bleeding, n (%)[a]	0.55 (0.2–1.27)	0.16
Major + life threatening bleeding, n (%)[a]	0.48 (0.2–1.19)	0.11
Major + minor bleeding, n (%)[a]	0.57 (0.2–1.42)	0.23

[a]At 48 hours.

Abbreviations: see Table 1 and 2

(7 minutes as compared to UFH's 60–90 minutes), while the latter occurring due to possible rebound thrombosis after sudden UFH reversal [14]. In a study assessing UFH reversal with PS after carotid endarterectomy, a trend towards thrombosis and stroke was reported [5].

To the best of our knowledge, our study reports the results of the first-ever randomized, clinical, placebo-controlled trial evaluating the impact of routine PS administration after TAVI. The trial design aimed to assess the impact of PS in the setting reflecting the majority of TAVI procedures performed worldwide — via transfemoral access with a pre-close device.

Despite a numerically lower rate of VARC-defined life-threatening and major hemorrhagic complications in patients randomized to protamine sulfate, the bleeding reduction did not reach statistical significance. Similarly, there were no differences in terms of stroke or transient ischemic attack (TIA) occurrence between the PS and the placebo group, however, the number of thromboembolic events was low in the study population.

Only 2 published papers focused on protamine sulfate administration after TAVI. In a recently published retrospective analysis of our own material (186 patients undergoing transfemoral TAVI, 44% via surgical cut-down, 21% received PS at operators' discretion) PS administration did not decrease the rate of bleeding complications [15]. Conversely, in a much larger (873 patients), single-center, prospective observational study, in which 677 patients undergoing TAVI received PS, protamine administration resulted in significantly lower rates of life-threatening and major bleeding complications while not increasing the occurrence of stroke and myocardial infarction [16]. That? study, however, was not randomized and the use of PS was left at operators' discretion in the initial phase of the study, whereas towards the end of the trial all patients received protamine, potentially introducing a selection bias as well as a confounding bias secondary to improvements in vascular access technics over time.

The reported rate of VARC-defined life-threatening and major bleeding complications (29%) remains high but is in line with the previously published results from large real-life populations of TAVI patients [4, 14, 17] — in a meta-analysis of 3519 patients, the rate of hemorrhagic sequelae ranged from 27% to 77% [12]. The tendency to suffer from bleeding complications is multifactorial in this elderly, often frail population with numerous comorbidities. Apart from obvious bleeding risks associated with the primary and secondary access sites, such as the diameter of the femoral and iliac arteries, the delivery sheath profile, and the quality of the puncture and the closure, additional blood loss may arise either from gastrointestinal and urinary tracts [12] or from acquired coagulopathies, such as acquired von Willebrand syndrome and heparin-induced thrombocytopenia [18]. The disproportionate rate of bleeding complications and ASARVI can potentially be explained by a blood loss occurring throughout the procedure, despite a successful hemostasis visualized during final angiography of the femoral access.

In terms of primary endpoint predictors, only a negative impact of serum creatinine was close to reaching statistical significance. Renal function-dependent increase in bleeding complications after TAVI is consistent with previous reports and may be a result of impaired metabolism of a variety of antithrombotic drugs administered before, during, and after TAVI. In a study in which ACT-guided heparin administration was assessed in 362 patients, baseline GFR was an independent predictor of 30-day bleeding with an odds ratio of 0.96 [19].

Lack of statistical significance precludes drawing unequivocal conclusions in regard to the usefulness of routine PS administration after TAVI. Perhaps, a larger, multi-center trial would provide a clear answer to whether the rich historical past of protamine sulfate can translate to a great future in the TAVI world.

Limitations

Despite the obvious advantages of the randomized placebo-controlled trial, our study has a number of limitations. First and most importantly, the small sample size precluded obtaining statistically significant differences between the groups. Secondly, the cross-over rate was almost 9%, and concerned patients randomized to placebo, who ended up receiving protamine. Thirdly, the endpoints were not independently adjudicated and the intervention was not blinded. On the other hand, only patients qualified for a transfemoral procedure with a pre-close device were included. This eliminated the potential bias of surgeon-dependent hemostasis present in cut-down approaches.

CONCLUSIONS

Routine protamine sulfate administration did not significantly decrease the rate of major and life-threatening bleeding complications after TAVI. Larger studies are required to assess the impact of routine PS use.

Supplementary material

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

Article information

Conflict of interest: None declared.

Trial registry and number: ClinicalTrials.gov; NCT02974660.

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REFERENCES

1. Mack MJ, Leon MB, Thourani VH, et al. PARTNER 3 Investigators. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med. 2019; 380(18): 1695–1705, doi: 10.1056/NEJMoa1814052, indexed in Pubmed: 30883058.
2. Holmes DR, Mack MJ, Kaul S, et al. 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement: developed in collabration with the American Heart Association, American Society of Echocardiography, European Association for Cardio-Thoracic Surgery, Heart Failure Society of America, Mended Hearts, Society of Cardiovascular Anesthesiologists, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. J Thorac Cardiovasc Surg. 2012; 144: e29–e84, doi: 10.1016/j.jtcvs.2012.03.001.
3. Gauthier C, Astarci P, Baele P, et al. Mid-term survival after transcatheter aortic valve implantation: Results with respect to the anesthetic management and to the access route (transfemoral versus transapical). Ann Card Anaesth. 2015; 18(3): 343–351, doi: 10.4103/0971-9784.159804, indexed in Pubmed: 26139739.
4. Borz B, Durand E, Godin M, et al. Incidence, predictors and impact of bleeding after transcatheter aortic valve implantation using the balloon-expandable Edwards prosthesis. Heart. 2013; 99(12): 860–865, doi: 10.1136/heartjnl-2012-303095, indexed in Pubmed: 23236027.
5. Fearn SJ, Parry AD, Picton AJ, et al. Should heparin be reversed after carotid endarterectomy? A randomised prospective trial. Eur J Vasc Endovasc Surg. 1997; 13(4): 394–397, doi: 10.1016/s1078-5884(97)80082-2, indexed in Pubmed: 9133992.
6. Levison JA, Faust GR, Halpern VJ, et al. Relationship of protamine dosing with postoperative complications of carotid endarterectomy. Ann Vasc Surg. 1999; 13(1): 67–72, doi: 10.1007/s100169900222, indexed in Pubmed: 9878659.
7. Cosgrave J, Qasim A, Latib A, et al. Protamine usage following implantation of drug-eluting stents: a word of caution. Catheter Cardiovasc Interv. 2008; 71(7): 913–914, doi: 10.1002/ccd.21439, indexed in Pubmed: 18383161.
8. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). Eur J Cardiothorac Surg. 2012; 42(5): S45–S60, doi: 10.1093/ejcts/ezs533.
9. Rodés-Cabau J, Dauerman HL, Cohen MG, et al. Antithrombotic treatment in transcatheter aortic valve implantation: insights for cerebrovascular and bleeding events. J Am Coll Cardiol. 2013; 62(25): 2349–2359, doi: 10.1016/j.jacc.2013.03.029, indexed in Pubmed: 23583252.
10. Gerckens U, Tamburino C, Bleiziffer S, et al. Final 5-year clinical and echocardiographic results for treatment of severe aortic stenosis with a self-expanding bioprosthesis from the ADVANCE Study. Eur Heart J. 2017; 38(36): 2729–2738, doi: 10.1093/eurheartj/ehx295, indexed in Pubmed: 28633375.
11. Meredith IT. Australia-New Zealand corevalve transcatheter aortic valve study. Paper presented at: transcatheter valve therapies: an advanced scientific and clinical workshop. Seattle, Washington, June 2–5, 2012.
12. Généreux P, Head S, Mieghem NV, et al. Clinical outcomes after transcatheter aortic valve replacement using valve academic research consortium definitions. J Am Coll Cardiol. 2012; 59(25): 2317–2326, doi: 10.1016/j.jacc.2012.02.022.
13. Sedaghat A, Neumann N, Schahab N, et al. Routine endovascular treatment with a stent graft for access-site and access-related vascular injury in transfemoral transcatheter aortic valve implantation. Circ Cardiovasc Interv. 2016; 9(8): e003834, doi: 10.1161/CIRCINTERVENTIONS.116.003834, indexed in Pubmed: 27512089.
14. Sergie Z, Lefèvre T, Van Belle E, et al. Current periprocedural anticoagulation in transcatheter aortic valve replacement: could bivalirudin be an option? Rationale and design of the BRAVO 2/3 studies. J Thromb Thrombolysis. 2013; 35(4): 483–493, doi: 10.1007/s11239-013-0890-3, indexed in Pubmed: 23553245.
15. Zbroński K, Grodecki K, Gozdowska R, et al. Use of protamine sulfate during transfemoral transcatheter aortic valve implantation - a preliminary assessment of administration rate and impact on complications. Postepy Kardiol Interwencyjnej. 2020; 16(3): 306–314, doi: 10.5114/aic.2020.99266, indexed in Pubmed: 33597996.
16. Al-Kassou B, Kandt J, Lohde L, et al. Safety and efficacy of protamine administration for prevention of bleeding complications in patients undergoing TAVR. JACC Cardiovasc Interv. 2020; 13(12): 1471–1480, doi: 10.1016/j.jcin.2020.03.041, indexed in Pubmed: 32553337.
17. Stortecky S, Stefanini GG, Pilgrim T, et al. Validation of the valve academic research consortium bleeding definition in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation. J Am Heart Assoc. 2015; 4(10): e002135, doi: 10.1161/JAHA.115.002135, indexed in Pubmed: 26408014.
18. Grodecki K, Zbroński K, Przybyszewska-Kazulak E, et al. Pre-procedural abnormal function of von Willebrand Factor is predictive of bleeding after surgical but not transcatheter aortic valve replacement. J Thromb Thrombolysis. 2019; 48(4): 610–618, doi: 10.1007/s11239-019-01917-7, indexed in Pubmed: 31359325.
19. Bernelli C, Chieffo A, Montorfano M, et al. Usefulness of baseline activated clotting time-guided heparin administration in reducing bleeding events during transfemoral transcatheter aortic valve implantation. JACC Cardiovasc Interv. 2014; 7(2): 140–151, doi: 10.1016/j.jcin.2013.10.016, indexed in Pubmed: 24556092.

ORIGINAL ARTICLE

Randomized clinical trials of patients with acute myocardial infarction-related cardiogenic shock: a systematic review of used cardiogenic shock definitions and outcomes

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ABSTRACT

Background: Cardiogenic shock (CS) is a critical complication to acute myocardial infarction (AMI), with short-term mortality rates exceeding 40%. However, no international consensus of a CS definition exists. This may compromise interstudy comparability.

Aims: The aim of the current study was to review differences and similarities of CS enrolment criteria in AMI-related CS randomized clinical trials (RCT).

Methods: From the electronic databases MEDLINE and EMBASE we identified all AMI-related CS trials.

Results: A total of 19 trials comprising a total of 2674 unique patients with CS were identified. Seven trials investigated left ventricular assist devices, eight investigated medical treatments, three percutaneous coronary intervention (PCI), and one trial investigated targeted temperature management. The inclusion criteria, baseline hemodynamics, endpoints, and mortality varied markedly between trials. Hypotension was the most frequent overall inclusion criterion (17 [90%] trials), and a systolic blood pressure <90 mm Hg (and/or need of vasopressors) was the most frequently used limit. Twelve (63%) trials had signs of impaired end-organ perfusion as an inclusion criterion and 10 (53%) signs of impaired cardiovascular function most frequently low cardiac index and reduced left ventricular ejection fraction. Ten (53%) trials included patients resuscitated from a cardiac arrest, three trials excluded cardiac arrest patients whereas six trials did not state whether cardiac arrest was an exclusion criterion. Mortality ranged from 8% to 73%.

Conclusions: The RCTs of AMI-related CS have marked heterogeneity in enrolment criteria and outcomes potentially hampering interstudy comparability. The overall consensus of CS enrolment criteria appears needed for future selection of patients.

Key words: acute heart failure, acute myocardial infarction, cardiac arrest, cardiogenic shock, randomized controlled trial

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INTRODUCTION

Mortality related to acute myocardial infarction (AMI) has declined dramatically during the past decades [1]. However, 5%–10% of AMI patients deteriorate to cardiogenic shock (CS), which is associated with in-hospital mortality rates exceeding 40% [1–3]. Cardiogenic shock is a low-cardiac output state with end-organ hypoperfusion and adequate ventricular filling [4]. Several advanced pharmacological therapies and devices are available, however, only limited data to support the use of these interventions are available and the patient selection seems crucial [5, 6]. CS can be defined as "a state in which ineffective cardiac output caused by a primary cardiac disorder results in both clinical and biochemical manifestations of inadequate tissue perfusion" [7] or "the inability of the heart, generally as a result of impairment of its pumping function, to deliver an adequate amount of blood to the tissues to meet resting metabolic demands" [8]. From these definitions, it can be deduced that CS is a syndrome of (1) low cardiac output caused by, (2) cardiac dysfunction, leading to (3) tissue hypoperfusion. CS patients encompass a broad spectrum of hemodynamic states with differing degrees of shock leading to substan-

WHAT'S NEW?

An international consensus with regards to patient enrolment criteria in randomized clinical trials of cardiogenic shock patients is lacking. In the current study we observed marked differences in used cardiogenic shock definitions between the existing randomized clinical trials. This also applied among ongoing studies currently enrolling patients. These varying definitions limit interstudy comparability. A future consensus of overall cardiogenic shock enrolment criteria appears needed and beneficial.

tial heterogeneity in CS study populations. In AMI-related CS, patients may begin with clinical signs of CS without increased lactate/hypoperfusion. Expert consensus has a novel CS classification categorizing patients with or at risk of CS into 5 worsening stages of CS. Hypotension necessitating vasoactive pharmacological treatment or mechanical circulatory support is often present [7, 9]. However, the clinical presentation can vary significantly between patients, possibly delaying the diagnosis and treatment [7]. Some trials mandate objective measures of reduced cardiac function [10], whereas others rely on clinical assessment combined with increased lactate [11]. So far, no international consensus on a CS definition has been established, why interstudy comparison remains challenging. Also, it is debated whether trials of CS should include patients successfully resuscitated from cardiac arrest [12], which make up approximately half of the patients in contemporary CS trials [11, 13]. Cardiogenic shock and cardiac arrest often occur together, however some aspects of pathophysiology etiologies and cause of in-hospital death (anoxic brain injury vs acute intractable cardiac failure) [14] differs substantially, suggesting that patients with concomitant cardiac arrest and CS possibly should be analyzed separately from patients with CS without cardiac arrest in clinical trials [12]. In this systematic review, inclusion criteria used in randomized controlled acute myocardial infarction-related CS trials have been described and critically appraised. Additionally, we provide an overview of endpoints used in existing and ongoing CS trials.

METHODS

Search strategy

Published studies

With the assistance of an expert scientific librarian, we developed search strategies and applied them to the electronic databases MEDLINE and EMBASE. All searches were run on September 10, 2020, and included all RCTs since 1999. The search strategy included Medical Subject Headings (MeSH) for MEDLINE and keywords related to CS and AMI. An overview of the complete search strategy is available upon request.

Study selection

Eligibility criteria for inclusion in this review required that studies were on human subjects conducted in adults with CS and were full-text articles written in English. We included studies without limitation on sample size. We excluded reviews, commentaries, editorials, letters to the editor, studies where only the abstract was available, case reports, case series, and studies of CS which were not prospective, randomized, controlled trials (RCTs). Furthermore, we excluded studies, in which CS patients were a subgroup of a larger study. References were checked from the included studies and included if relevant.

Each study abstract was assessed independently by two investigators (JJ and JG). We used the software package Covidence, which is an online tool for systematic reviews (*www.covidence.org*). The software allows upload and evaluation of searches of abstracts and full texts by each investigator blinded to the other evaluator's decision. Disagreements were marked for later evaluation. We resolved such cases using a third reviewer (MF). After screening abstracts, all the studies that met the inclusion criteria went through full-text screening by JJ and JG.

Data extraction

We then extracted data from each study using a standardized, pilot-tested form. Extracted data included study characteristics (study title, authors, year of publication, study design, number of included patients, inclusion and exclusion criteria, details of the intervention, and endpoints). Inclusion criteria were grouped into basic hemodynamics (heart rate, blood pressure), advanced hemodynamics/cardiac function (left ventricular ejection fraction [LVEF], cardiac index, pulmonic-capillary wedge pressure [PCWP], central venous pressure [CVP]), signs of end-organ hypoperfusion, and biomarkers (lactate). In cases of multiple publications of the same trial, the original publication would be given priority. If data seemed to be missing from a trial, we tried to acquire the data through correspondence with the trial authors. We contacted the corresponding authors of nine trials for missing data, of which five answered [5, 10, 15–17]. Data extraction was conducted by two reviewers (JJ and JG) and independently checked by one further reviewer (MF). Following the extraction of data, careful consideration was given to the suitability of conducting a meta-analysis. As the trials were too heterogeneous, the data were synthesized qualitatively.

Ongoing and future trials

A search for the overall term "Cardiogenic shock" was run on ClinicalTrials.gov on September 10, 2020. A total of 19 trials studying CS are currently registered, of which 8 are relevant for this systematic review. Data was extracted

similarly to the method described above and presented in the supplementary.

Ethics

The study was conducted in accordance with the national and institutional ethical guidelines.

Statistical analysis

The results are presented as percentages of the total number of published AMI-related CS RCTs.

RESULTS

The search strategy identified 513 studies and another three were identified through other sources. Of these, 73 were duplicates. After screening of titles and abstracts, 480 studies were excluded for not meeting our inclusion criteria. Two authors (JG and JJ) reviewed the full text of 35 studies, identifying 19 RCTs for inclusion in this review. Details are provided in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram shown in Figure 1.

Study characteristics

Seven trials investigated mechanical circulatory assist devices such as an intra-aortic balloon pump, TandemHeart®(LivaNova, London, UK) and Impella® (Abiomed, Danvers, MA, USA) [16, 18–22], 8 trials investigated pharmacological treatments [15, 17, 23–28], 3 investigated coronary interventions (PCI) [10, 13, 29], and 1 trial investigated targeted temperature management [16]. The trials were published from 1999 onwards. Two trials included more than 500 patients [11, 13]. Another two trials included 250–500 patients [10, 15]. However, the majority of trials were small and included less than 100 patients. A total of 2674 unique individual patients were randomized in the reviewed trials. Follow-up periods, as well as endpoints of the trials, differed markedly, with mortality being the most common primary endpoint or part hereof in 8 (42%) trials. Study characteristics, sample size, publication year, endpoints, and intervention investigated, are summarized in Table 1.

Definition of cardiogenic shock

A persisting systolic blood pressure (SBP) value <90 mm Hg and/or vasopressor requirements were the most frequent inclusion criteria and were used in 13 (68%) trials [10, 11, 13, 17–20, 22–24, 26, 29, 30]. Three (16%) trials used an SBP value <100 mm Hg [15, 25, 27] and 1 (5.3%) trial used SBP <80 mm Hg [21]. No trials used mean arterial or diastolic blood pressure, while 3 trials included heart rate [10, 17, 25]. A total of 12 (63%) trials required signs of impaired end-organ perfusion [10, 11, 15, 17, 19–23, 26, 30], with clinical assessment being a central part of which 10 trials required at least 1 of several possible symptoms; 11 trials (58%) included low urine output defined either as a urine output <30 ml/h or more unspecific as "oliguria" [10, 11, 13, 15, 19–23, 26, 30]. Altered mental status was used in 6 (32%) trials [11, 13, 22, 23, 26, 30] and clinically assessed cold and/or clammy skin and limbs was used in 12 trials (63%) [10, 11, 13, 15, 17, 19–23, 26, 30]. Elevated arterial

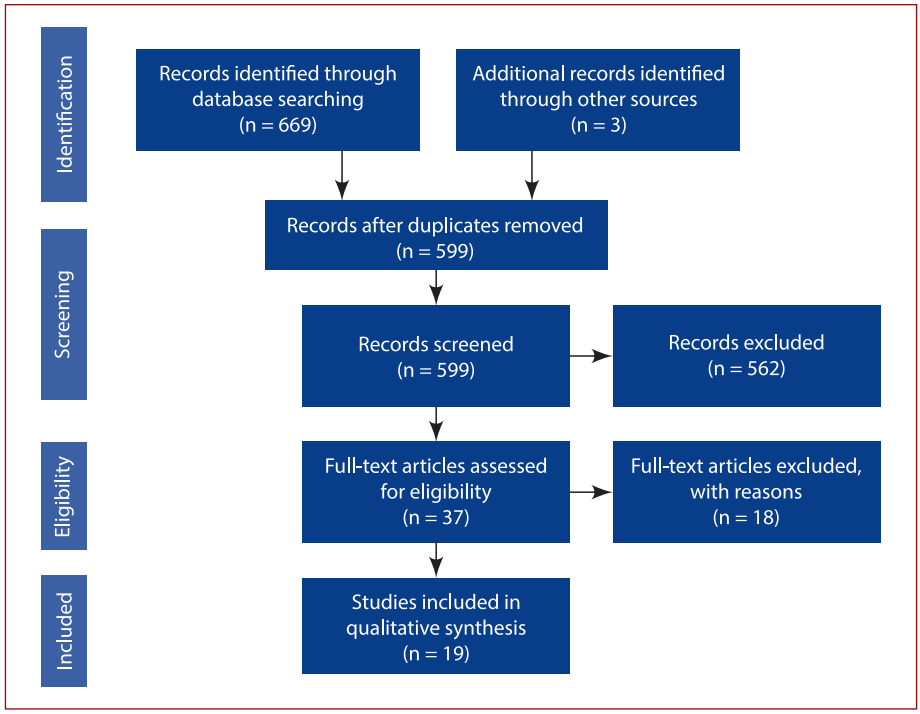

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of reviewed and included trials. Reasons for full text exclusion: substudy to already included study (n = 3), protocol future study (n = 1), not randomized controlled trial (n = 3), methods insufficiently described (n = 1), including other patients than cardiogenic shock (n = 3), including other patients than myocardial infarction (n = 5)

Table 1. Study characteristics

Author	Sample size	Intervention	Length of follow-up	Primary endpoint	Main secondary endpoints
Bochaton et al. 2019 [15]	15	IABP vs IABP + Impella 5.0	1 month	Cardiac power index 12 hours after implantation	Hemodynamic and metabolic variables over 96 hours; 30-day all-cause mortality; device-related complications; LVEF at 30 days
Fuernau et al. 2018 [29]	40	TTM at 33°C vs no TTM	24 months	Cardiac power index 24 hours after randomization	All-cause mortality after 30 days, 1 year, and 2 years
Thiele et al. 2017 [13]	686	Culprit PCI vs Multivessel PCI	30 days	Composite of death from any cause or severe renal failure leading to renal-replacement therapy within 30 days after randomization	Individual components of the primary endpoint; recurrent myocardial infarction; rehospitalization for congestive heart failure; and repeat revascularization
Pan et al. 2017 [13]	48	rhBNP vs no rhBNP	In-hospital	Changes in PCWP from baseline to 72 hours after randomization	In-hospital mortality; cardiac index, urine output
Ouweneel et al. 2017 [13]	48	IABP vs Impella CP	6 months	30-day all-cause mortality	6-month mortality
Yan-yan et al. 2016 [13]	60	IABP vs IABP + Shenfu	6 months	All-cause mortality	Major adverse cardiac and cerebrovascular events
Barilla et al. 2016 [13]	58	Ivabradine vs no ivabradine	6 months	Change in NT-proBNP from baseline to 1 week after randomization	Cardiovascular death; hospital re-admission for worsening heart failure; clinical and hemodynamic improvement
Thiele et al. 2012 [13]	600	IABP vs no IABP	30 days	30-day all-cause mortality	Serial assessments of serum lactate levels; creatinine clearance; C-reactive protein levels; and severity of disease as assessed with the use of the Simplified Acute Physiology Score II
Tousek et al. 2011 [16]	80	Abciximab vs no abciximab	30 days	30-day combined outcome (death/reinfarction/stroke/new severe renal failure)	Not reported
Prondzinsky et al. 2010 [16]	45	IABP vs no IABP	In-hospital	Change in APACHE II scores from baseline to 4 days after randomization	Cardiac index; plasma brain natriuretic peptide; and serum levels of interleukin-6
Fuhrmann et al. 2008 [16]	32	Levosimendan vs Enoximone	30 days	30-day all-cause mortality	Changes in invasively measured hemodynamic variables during the first 48 hours
Seyfarth et al. 2008 [16]	26	Impella vs IABP	30 days	Change in the cardiac index from baseline to 30 min after implantation	30-day all-cause mortality; device-related complications included; and MODS and SOFA score after 30 days
Alexander et al. 2007 [16]	398	Tilarginine vs Placebo	6 months	30-day all-cause mortality (overall and stratified by age)	New York Heart Association functional class at 30 days, and 6-month mortality
Dzavik et al. 2007 [16]	79	NOS vs Placebo	30 days	Change in MAP from baseline to 2 hours after initiation of study drug	Change in other hemodynamic variables at 15 minutes and 2 hours; overall 30-day mortality
Jin-Long et al. 2007 [16]	39	Prolonged IABP vs IABP	12 months	Long-term left ventricular function	Exercise-capacity
Garcia-Gonzalez et al. 2006 [16]	22	Levosimendan vs Dobutamine	Not reported	Change in cardiac power from baseline to 24 hours after initiation of therapy	Not reported
Thiele et al. 2005 [16]	41	IABP vs Tandem heart	30 days	Change in MAP from baseline to 2 hours after implantation	All other hemodynamic and metabolic parameters; 30-day mortality
Hochman et al. 1999 [16]	302	Revascularization vs Medical treatment	1 year	30-day all-cause mortality	Overall mortality 6 and 12 months after infarction
Urban et al. 1999 [16]	55	Acute CAG vs Initial medical management	30 days	Primary pump failure within the first 48 hours	

Abbreviations: APACHE, Acute Physiologic Assessment and Chronic Health Evaluation; BNP, brain natriuretic peptide; CAG, coronary angiograms; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; NT-proBNP, N-terminal prohormone BNP; PCI, percutaneous coronary intervention; PCWP, pulmonic-capillary wedge pressure; rhBNP, recombinant human BNP; TTM, targeted temperature management

lactate as a biochemical sign of hypoperfusion was used as an inclusion criterion in 5 (26%) trials [11, 13, 22, 23, 30]. A value of >2 mmol/l was used in all 5 trials. In total 10 (53%) trials mandated signs of circulatory impairment or reduced cardiac function [10, 15, 19, 20, 22, 24–27, 29], while the remaining trials did not use any criteria of hypoperfusion for inclusion. Low cardiac index (9 [47%]) and reduced LVEF (3 [16%]) were used as estimates of cardiac function. Cardiac index of <2.2 l/min/m^2 was the most frequent limit for inclusion, however one trial used a limit of

<1.8 l/min/m^2 [24] and another trial used <2.5 l/min/m^2 [26]. Pulmonary capillary wedge pressure (PCWP) was used in 9 (47%) trials [10, 15, 20, 22–24, 26, 27, 29], and a cut-off value of 15 mm Hg was used in 6 (32%) trials whereas 18 mm Hg was used in 3 (16%) trials [23, 24, 26]. One trial had a pragmatic selection process, which included STEMI with PCI within 24 hours, inotropic drugs, and an intra-aortic balloon pump [16]. Only 6 (32%) trials mandated both criteria for impaired cardiac function/low cardiac index and reduced end-organ perfusion [10, 15, 19, 20, 22, 26]. Overview of inclusion and exclusion criteria for each trial is presented in Table 2.

Resuscitated out-of-hospital cardiac arrest in cardiogenic shock trials

A total of 10 (53%) trials included patients resuscitated from a cardiac arrest [10, 11, 13, 17, 18, 20, 22, 24, 26, 29], 6 (32%) trials did not report whereas only 3 (16%) trials specifically excluded cardiac arrest patients [16, 23, 30]. Of the trials including cardiac arrest, the proportion of cardiac arrest patients were large ranging from 28%–91% [10, 18].

Outcomes

Eight (42%) trials used mortality as endpoints either as all-cause mortality rate alone [10, 11, 15, 18, 24, 26] or a combined endpoint where mortality was part of other variables [13, 17]. Six (32%) trials used measures of cardiac function at follow-up as the primary endpoint [16, 20, 21, 28–30], with cardiac index and cardiac power index being most frequent. Two (11%) trials used mean arterial blood pressure as an endpoint [22, 27]. One (5.3%) trial used the change in left ventricular preload, measured as the PCWP [23]. One trial used NT-proB-type Natriuretic Peptide [25] and 1 trial used the change in Acute Physiologic Assessment and Chronic Health Evaluation (APACHE)-score [19].

Ongoing trials

The CS definitions used in future trials show a similar heterogeneity as the already published trials (Supplementary material, *Tables S1–S2*).

DISCUSSION

We described and summarized the definitions, inclusion criteria, and outcomes used in RCTs of CS. Furthermore, we assessed differences and similarities of trials regarding inclusion criteria, which relates to how researchers define CS. We report that inconsistencies of inclusion criteria across different trials exist. Furthermore, a similar pattern is seen in ongoing trials. This could increase the heterogeneity of trial populations between studies, thus making interstudy comparisons, including meta-analyses, difficult in addition to limiting external validity. This and a low level of evidence for CS treatment may partly explain the wide variation of care delivered to CS patients [30]. It would be advantageous to have uniform criteria for inclusion in future CS trials as well as having comparable outcomes.

Blood pressure

The most frequent inclusion criterion identified in this review was low systolic blood pressure, followed by different signs of peripheral hypoperfusion and reduced cardiac function (Figure 2). It is remarkable that blood pressure is the most frequent inclusion criterion in CS trials, since blood pressure is not part of the definition of CS [7, 8] in contemporary recommendations. On the contrary, patients can have hypoperfusion and reduced cardiac output without hypotension [32]. However, hypoperfusion is often associated with low blood pressure and blood pressure is an easily obtainable parameter that can be measured by non-physicians already prehospitally without the need for invasive catheters. Furthermore, low blood pressure has been shown to be a prognostic factor in CS, with lower blood pressure being associated with worse outcome [9]. Consequently, the Acute Cardiovascular Care Association's (ACVC) position statement for AMI-related CS has included hypotension (systolic blood pressure <90 mm Hg for >30 min or use of vasopressors to maintain pressure >90 mm Hg during systole) as one of the criteria for CS [8]. It seems reasonable to use blood pressure as an inclusion criterion in CS trials, but research is needed to assess whether systolic, diastolic, or mean arterial blood pressure best reflects cardiovascular function. Low diastolic blood pressure can potentially be harmful and compromise coronary perfusion even with adequate systolic pressure [33].

End-organ hypoperfusion

Despite blood pressure being easily obtainable, a patient must fulfill other criteria such as tissue hypoperfusion to be considered in CS. Surprisingly, only 12 (63%) trials included in this review had signs of hypoperfusion in the inclusion criteria. Tissue hypoperfusion is often defined by a clinical assessment of extremities, skin, urine output, and mental status, which are susceptible to subjective assessment by the treating physician. However, a biomarker of tissue hypoperfusion such as lactate concentration could propose an easily obtainable and more objective measure [34]. Furthermore, higher lactate concentrations have been shown to be a prognostic marker of poor outcome in CS [35]. The Association for Acute CardioVascular Care has included a plasma lactate concentration >2.0 mmol/l. Whether this is the optimal cut-off value is speculative. One previous study has shown mortality to drastically increase when lactate levels surpass 2.5 mmol/l, which therefore may be a better cut-off value [35]. In our review, only 5 (26%) trials used lactate as an inclusion criterion. IABP-SHOCK II used a less restrictive threshold of serum lactate of >2 mmol/l compared to the ongoing DanGer-SHOCK, which excludes patients with <2.5 mmol/l. Moreover, one-third of the patients in the CULPRIT-SHOCK trial had a lactate level of ≤2 mmol/l. These inconsistencies are of importance when comparing CS trials, since the included populations will potentially differ substantially in disease severity, and

Table 2. Inclusion and exclusion criteria

Author	Inclusion criteria	Exclusion criteria	Including comatose out-of-hospital cardiac arrest patients?
Bochaton et al. 2019 [15]	Blood pressure: — Cardiac function: — End-organ perfusion: — Other: — STEMI — Treated with primary angioplasty within 24 hours of the index AMI, and — Required inotropic drugs and an IABP	— Resuscitation >30 min — Aortic valvulopathy or mechanical valve — Hypertrophic cardiopathy — Left ventricular thrombus — Refractory cardiogenic shock (INTERMACS 1 or 2) — Right ventricular failure — Sepsis	No
Fuernau et al. 2018 [29]	Blood pressure: — Systolic blood pressure <90 mm Hg for >30 minutes or catecholamines required Cardiac function: — End-organ perfusion: At least 1 of the following: — Altered mental status — Cold, clammy skin and limbs — Urine output <30 ml/h — Arterial lactate >2 mmol/l Other: — Signs of pulmonary congestion	— CS duration >12 hours — Prior CPR with an indication for TTM treatment	No
Thiele et al. 2017 [13]	Blood pressure: — Systolic blood pressure <90 mm Hg for >30 minutes or catecholamines required Cardiac function: — End-organ perfusion: At least 1 of the following: — Altered mental status — Cold, clammy skin and limbs — Urine output <30 ml/h — Arterial lactate >2 mmol/l Other: — Signs of pulmonary congestion	— Resuscitation >30 min — No intrinsic heart action — Expected severe deficit in cerebral function — Indication for urgent CABG — Mechanical cause of cardiogenic shock — Single vessel disease — CS duration >12 hours — Age >90 years — Massive pulmonary embolism — Known severe renal insufficiency — Life expectancy <6 months prior to admission	Yes
Pan et al. 2017 [13]	Blood pressure: — Systolic blood pressure <90 mm Hg for >30 minutes or catecholamines required Cardiac function: — End-organ perfusion: At least 1 of the following: — Altered mental status — Cold, clammy skin and limbs — Urine output <30 ml/h — Arterial lactate >2 mmol/l Other: — Signs of pulmonary congestion	— SBP <90 mm Hg within first hour post-intervention although 12 mg/kg × min dopamine and 1:1 IABP supporting — PCWP <18 mm Hg — Inferior, posterior and right ventricle AMI — Previous history of myocardial infarction; — Previous electrocardiogram suggesting an old myocardial infarction — Previous history of chronic heart failure or decreased LVEF — Hypertrophic cardiomyopathy — Severe valvular disease — Estimated glomerular filtration rate <15 ml/min per 1.73 m^2 — Known intolerance history to rhBNP	No
Ouweneel et al. 2017 [13]	Blood pressure: — Systolic blood pressure <90 mm Hg for >30 minutes or catecholamines required Cardiac function: — End-organ perfusion: — Other: — Mechanical ventilation (To select a patient population with even worse condition)	— Severe aorto-iliac arterial disease impeding placement of either IABP or percutaneous MCS — Known severe cardiac aortic valvular disease — Life expectancy < 12 months — CABG during the previous week	Yes
Yan-yan et al. 2016 [13]	Blood pressure: — Systolic blood pressure <90 mm Hg for >30 minutes or catecholamines required Cardiac function: — A reduction of cardiac index <1.8 l/min/m^2 End-organ perfusion: — Other: — PCWP >18 mm Hg	— Severe valvular diseases — Autoimmune diseases — Infection — Rheumatic activity — Chronic liver disease — Kidney disease — Cancer — Unable to be followed-up	Yes

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Table 2. cont. Inclusion and exclusion criteria

Author	Inclusion criteria	Exclusion criteria	Including comatose out-of-hospital cardiac arrest patients?
Barilla et al. 2016 [13]	Blood pressure: Systolic blood pressure <100 mm Hg Cardiac function: LVEF <40% End-organ perfusion: — Other: — Sinus rhythm — HR >75 beats/min	— Atrial fibrillation — II–III degree atrioventricular block	n/a
Thiele et al. 2012 [13]	Blood pressure: — Systolic blood pressure <90 mm Hg for >30 minutes or catecholamines required Cardiac function: — End-organ perfusion: At least 1 of the following: — Altered mental status — Cold, clammy skin and limbs — Urine output <30 ml/h — Arterial lactate >2 mmol/l Other: — Signs of pulmonary congestion	— Resuscitation >30 min — No intrinsic heart action — Expected severe deficit in cerebral function — Mechanical cause of shock — Duration >12 hours — Age >90 years — Massive pulmonary embolism — Severe peripheral artery disease precluding IABP insertion — Aortic regurgitation >grade II (on a scale of I to IV, with higher grades indicating more severe regurgitation); were older than 90 years of age — Life expectancy <6 months prior to admission	Yes
Tousek et al. 2011 [16]	At least 1 of the following: Blood pressure: — Systolic blood pressure <90 mm Hg and heart rate >90 beats/min — Catecholamine support to maintain systolic blood pressure >90 mm Hg Cardiac function: — End-organ perfusion: — Cold, wet, sweating skin, and heart rate >90 beats/min Other: —	— Contraindications for the use of abciximab — Severe valvular disease — Mechanical cause of shock — 10 000 IU of heparin in the previous 6 h — No indication for PCI	Yes
Prondzinsky et al. 2010 [16]	End-organ perfusion criteria + at least 1 of the following: Blood pressure: — Systolic blood pressure <90 mm Hg for >30 minutes or catecholamines required Cardiac function: — Cardiac index ≤2.2 l/min/m^2 End-organ perfusion: At least 1 of the following: — Cool extremities — Oliguria Other: —	— Severe peripheral artery disease precluding IABP insertion — Mechanical cause of CS — Severe valvular disease	n/a
Fuhrmann et al. 2008 [16]	Blood pressure: — Systolic blood pressure <90 mm Hg for >30 minutes or catecholamines required Cardiac function: — Cardiac index <2.5 l/min/m^2 End-organ perfusion: At least 1 of the following: — Altered mental status — Cold, clammy skin and limbs — Urine output <30 ml/h Other: — PCWP >18 mm Hg	— Duration of CS >24 hours — Mechanical cause of CS — Severe valvular disease — Sustained VT — Major bleeding — Severe hepatic failure — Sepsis	Yes
Seyfarth et al. 2008 [16]	Blood pressure: — Systolic blood pressure <90 mm Hg for >30 minutes or catecholamines required Cardiac function: At least 1 of the following: — Cardiac index <2.2 l/min/m^2 + PCWP >15 mm Hg — LVEF <30% + LV end-diastolic pressure <30 mm Hg End-organ perfusion: At least 1 of the following: — Cold, clammy skin and limbs — Urine output <30 ml/h Other: — Heart rate >60 beats/min	— Duration of CS >24 hours — Resuscitation >30 minutes — Mechanical cause of CS — Predominant RV failure — Massive pulmonary embolism — Severe valvular disease — Sepsis — Known cerebral disease — Thrombus in the LV — Hypertrophic obstructive cardiomyopathy	Yes

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Table 2. cont. Inclusion and exclusion criteria

Author	Inclusion criteria	Exclusion criteria	Including comatose out-of-hospital cardiac arrest patients?
Alexander et al. 2007 [16]	Blood pressure: — Systolic blood pressure <100 mm Hg despite vasopressor therapy for more than 1 hour Cardiac function: — LVEF <40% End-organ perfusion: — Mandatory but not specified Other: — Clinical or hemodynamic evidence of elevated left ventricular filling pressures	— Duration of CS >24 hours — Mechanical cause of shock — Indication for acute CABG — Severe valvular disease — Predominant RV failure — End-stage renal disease — Acute respiratory distress syndrome — Severe cerebral damage precluding survival — Recent thoracic or abdominal surgery — Primary pulmonary hypertension — Infection	n/a
Dzavik et al. 2007 [16]	Blood pressure: — Systolic blood pressure <100 mm Hg despite vasopressor therapy Cardiac function: — Cardiac index <2.2 l/min/m^2 if measured off IABP, or <2.5 l/min/m^2 on End-organ perfusion: — Other: — PCWP >15 mm Hg	— Mechanical cause of CS — Severe valvular disease — Predominant RV failure — Sepsis — Major bleeding — Preterminal profound shock — Anoxic brain damage — Primary pulmonary hypertension — Life expectancy <6 months prior to admission	n/a
Jin-Long et al. 2007 [16]	Blood pressure: — Systolic blood pressure <80 mm Hg or >20% reduction from baseline Cardiac function: — End-organ perfusion: — Peripheral cyanosis — Oliguria — Cold extremities Other: —	None mentioned	n/a
Garcia-Gonzalez et al. 2006 [16]	n/a	— Mechanical cause of CS — Severe valvular disease — Predominantly RV failure — Sustained VT — Stroke within last 3 months — II or III atrioventricular block — End-stage renal failure — Severe liver disease — Acute respiratory distress syndrome — Sepsis	n/a
Thiele et al. 2005 [16]	Blood pressure: — Systolic blood pressure <90 mm Hg for >30 minutes or catecholamines required Cardiac function: — Cardiac index <2.1 l/min/m^2 End-organ perfusion: At least 1 of the following: — Altered mental status — Cold, clammy skin and limbs — Urine output <30 ml/h — Arterial lactate >2 mmol/l Other: — PCWP >15 mm Hg	Resuscitation >30 minutes — Duration >12 hours — Mechanical cause of CS — Right ventricular failure — Age >75 years — Sepsis — Severe aortic regurgitation — Severe cerebral damage — Severe peripheral vascular disease — Diseases with reduced life expectancy	Yes
Hochman et al. 1999 [16]	Blood pressure: — Systolic blood pressure <90 mm Hg for >30 minutes or catecholamines required Cardiac function: — Cardiac index <2.2 l/min/m^2 End-organ perfusion: At least 1 of the following: — Cold, clammy skin and limbs — Urine output <30 ml/h Other: — Heart rate >60 beats/min — PCWP >15 mm Hg	— Duration of CS >12 hours — Mechanical cause of CS — Severe valvular disease — Dilated cardiomyopathy	Yes
Urban et al. 1999 [16]	Blood pressure: — Systolic blood pressure <90 mm Hg or catecholamines required Cardiac function: — Cardiac index <2.2 l/min/m^2 End-organ perfusion: — Other: — PCWP >15 mm Hg	— Mechanical cause of CS — Severe valvular disease — Ongoing CPR — Expected severe deficit in cerebral function — Serious non-cardiac disease	Yes

Abbreviations: AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CPR, cardiopulmonary resuscitation; CS, cardiogenic shock; LV, left ventricle; MCS, mechanical circulatory support; RV, right ventricle; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction; TTM, targeted temperature management; VT, ventricular tachycardia; other — see Table 1

Table 3. Cohort characteristics

Author	Age, years	Blood pressure, mm Hg	Heart rate, bpm	Proportion resuscitated from CA, %	Proportion of mechanical ventilation, %	STEMI, %	LVEF, %	Cardiac Index, %	PCWP, %	CVP, %	Lactate, %	Mortality, %	Death of hypoxic brain injury, %
Bochaton et al. 2019 [15]	57	69 (MAP)	101	0	31	n/a	30	2.3	16	10	1.5	15	n/a
Fuernau et al. 2018 [29]	76	84 (SBP)	n/a	0	100	52	n/a	n/a	n/a	n/a	3.4	55	n/a
Thiele et al. 2017 [13]	70	100 (SBP)	91	54	81	62	31	n/a	n/a	n/a	5.0	47	11
Pan et al. 2017 [13]	64	104	98	0	n/a	100	39	1.7	27	n/a	n/a	33	0
Ouweneel et al. 2017 [13]	58	82 (SBP)	82	91	100	100	46	n/a	n/a	n/a	8.2	48	23
Yan-yan et al. 2016 [13]	58	77 (SBP)	n/a	n/a	n/a	100	45	n/a	n/a	n/a	n/a	8.3	n/a
Barilla et al. 2016 [13]	55	84 (SBP)	96	n/a	38	100	34	n/a	n/a	n/a	n/a	10	0
Thiele et al. 2012 [13]	70	90 (SBP)	92	45	82	69	35	n/a	n/a	n/a	4.2	41	n/a
Tousek et al. 2011 [16]	66	97 (SBP)	90	25	46	75	n/a	n/a	n/a	n/a	n/a	30	n/a
Prondzinsky et al. 2010 [16]	64	n/a	n/a	n/a	52	64	38	2	18	n/a	n/a	33	n/a
Fuhrmann et al. 2008 [16]	68	69 (MAP)	105	62	87	84	24	2.2	21	n/a	5.4	53	0
Seyfarth et al. 2008 [16]	66	103 (SBP)	96	77	92	0	27	1.7	22	n/a	6.5	46	n/a
Alexander et al. 2007 [16]	67	88 (SBP)	n/a	n/a	86	77	27	n/a	n/a	n/a	n/a	45	n/a
Dzavik et al. 2007 [16]	69	71 (SBP)	90	n/a	n/a	n/a	27	1.7	22	n/a	n/a	39	n/a
Jin-Long et al. 2007 [16]	66	77 (SBP)	115	n/a	n/a	n/a	30	2	27	n/a	n/a	n/a	n/a
Garcia-Gonzalez et al. 2006 [16]	64	76 (MAP)	85	n/a	n/a	100	29	1.7	26	n/a	n/a	n/a	n/a
Thiele et al. 2005 [16]	64	64 (MAP)	117	54	98	n/a	27	1.6	24	12	4.2	44	n/a
Hochman et al. 1999 [16]	66	88 (SBP)	101	28	n/a	n/a	31	1.7	24	n/a	n/a	51	n/a
Urban et al. 1999 [16]	65	77	103	31	54	80	n/a	1.7	24	n/a	7.7	73	n/a

Abbreviations: CA, cardiac arrest; CVP, central venous pressure; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction; other: see Table 1 and 2

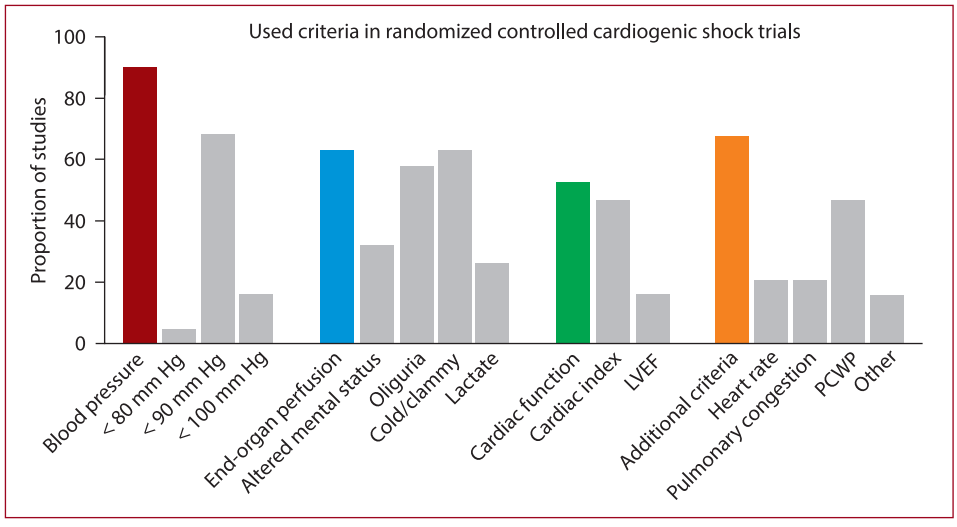

Figure 2. Bar chart depicting proportions of existing trials using different overall inclusion criteria (red, blue, green, and orange columns) and sub-criteria (grey columns) in the definition of cardiogenic shock

Abbreviations: LVEF, left ventricular ejection fraction; PCWP, pulmonic-capillary wedge pressure

possibly extrapolation of results from one trial may be limited [11, 13, 36].

Assessment of cardiac output and cardiac function in the CS-definition

Per definition, true CS represents an extreme degree of acute heart failure whereby cardiac output is insufficient to meet basic metabolic requirements. These organ-level perturbations may occur at different levels of cardiac output, which varies from individual to individual [37]. As such, no universal cardiac output cut-off can be used to define CS from a theoretical point of view. Furthermore, it has been proven difficult to relate low cardiac output with poor outcomes in critically ill patients [40, 41]. In this review, eight trials used cardiac index to include patients, and values varied from <1.8 l/min/m^2 [24] to <2.5 l/min/m^2 [26]. When including patients with hyperacute, severe illness in trials it may, however, be difficult to obtain a valid measure of cardiac output prior to randomization if an invasive procedure is needed [40].

An alternative measure of cardiac performance is an echocardiographic assessment. Three (16%) trials in this review used LVEF to include patients. Two trials used LVEF <40% [15, 25] and one trial used LVEF <30% [20]. Echocardiography has several advantages, being easily accessible, if trained personnel are present, and not having the adverse effects of an invasive procedure. Echocardiography should be performed in all patients with suspected CS and AMI for rapid assessment of differential diagnoses and rule-out of mechanical complications [8]. LV dysfunction is a marker of CS, whereas small heart cavities with normal function may suggest hypovolemic shock. It may, therefore, be problematic to consider a patient for a CS trial without echocardiographic evidence of reduced cardiac function. However, the optimal cut-off value of LVEF is unknown.

There are several limitations to LVEF and cardiac index as estimates of cardiac function. In dilated hearts, stroke volume and cardiac output may be normal despite reduced LVEF, and further LVEF is often unprecise, especially when estimating LVEF in bedridden, intubated patients. Only 6 (32%) trials had defined requirements for both inadequate tissue perfusion and low cardiac output/impaired cardiac function. Lastly, CS can be caused by predominantly RV failure, which has previously been shown to be the primary cause of CS of approximately 7% of the patients [41]. In such cases echocardiographic assessment of RV function plays a key role, as the typical sign of LV failure usually is absent.

Pulmonary capillary wedge pressure

The cardiac index can be reduced because of insufficient preload when filling pressures are low despite preserved cardiac function. Thus, hypovolemia is a differential diagnosis to CS. Therefore, adequate filling of the failing ventricle is required for the diagnosis of CS. If PCWP is low, CS is unlikely unless caused by right heart failure [42]. When PCWP is elevated, it is an estimate of backward LV failure, thus giving an index of poor LV function. In this review, 9 trials used elevated PCWP (>15 mm Hg or >18 mm Hg) as an inclusion criterion, and 1 trial used low/normal PCWP (<18 mm Hg) as an exclusion criterion. A PCWP >15 mm Hg in the supine position is used by guidelines as a diagnostic for left-sided heart failure. This corresponds to a value of 2 mm Hg higher than the 98th percentile of the healthy [43]. Yet, PCWP in heart failure has a poor negative predictive value (52%), because PCWP is often elevated only during exercise in chronic heart failure [44]. In this context, it is meaningful to use low PCWP to exclude CS. However, high PCWP is not necessarily associated with CS and is a highly invasive technique.

Outcomes

The outcomes of patients included in trials as well as the outcomes definitions and endpoints differ significantly between trials. Most frequently, all-cause mortality was used, which is a robust endpoint but limited to larger trials with sufficient power. Since CS patients are rare compared to for example myocardial infarction patients, it is to be expected that some trials use other outcome measures than mortality, which enables smaller sample sizes. Underlining the point, that CS trials lacks comparability, it is striking that multiple different hemodynamic endpoints have been chosen in different trials. Cardiac index, cardiac power index, as well as blood pressure, change in ventricular preload, PCWP, and biomarkers have all been used as endpoints. A discussion and consensus among experts regarding relevant endpoints should be published for the guidance of future trialists. So far no discussion of outcomes has been made in published consensus documents [8].

What to do with CS patients with cardiac arrest?

CS frequently occur together with cardiac arrest due to shared etiology, being acute or chronic myocardial injury. Comatose patients successfully resuscitated from a cardiac arrest often require vasopressors to maintain blood pressure, have decreased urine output (acute kidney injury), have cold skin/extremities (targeted temperature management), have markedly elevated lactate levels due to cessation of circulation, and have reduced myocardial function with low cardiac output and reduced LVEF (myocardial stunning) [38, 45]. Therefore, a large proportion of resuscitated cardiac arrest patients fulfill the criteria used in CS trials [12] and this may explain the large proportion of cardiac arrest patients in the CS trials, which we found in this review.

However, low blood pressure in cardiac arrest is often a consequence of vasoplegia due to systemic inflammation, and not always a consequence of low cardiac output [46]. Cardiac arrest and CS also often differ regarding sequelae (i.e., anoxic brain injury vs multisystem organ failure) and anoxic brain injury is unlikely to improve with cardiovascular therapies.

In the trial by Thiele et al. [11], 598 CS patients were randomized to receive Intraaortic Balloon Pump vs control. Almost half were resuscitated from cardiac arrest. Overall, the use of an Intraaortic Balloon Pump did not improve outcome. However, a subgroup-analyses showed that the point estimate for mortality of the intervention showed numeric divergent results when stratified for the presence of cardiac arrest. This interaction was not statistically significant, though. However, the findings highlight the need for a discussion of whether to include cardiac arrest patients in CS trials. At least, analyses stratifying for cardiac arrest should be performed. Surprisingly, in this review, eight trials did not even report whether they included patients resuscitated from cardiac arrest.

Another important issue to consider when including cardiac arrest-patient in CS trials, is whether the patient is expected to recover neurologically. Therefore, cardiac arrest patients with early signs of poor prognosis, such as a long time to ROSC or non-shockable primary rhythm, should be considered excluded for CS trials [47].

Where to go from here?

Future CS trials should use uniform inclusion criteria based on consensus by a relevant international group of experts in the field, including relevant measures of acute LV and RV dysfunction and tissue hypoperfusion and particularly consensus of whether to include patients resuscitated from cardiac arrest, would be of value. Furthermore, a relevant measure to exclude patients in hypovolemic shock should be determined. Assessing PCWP with an invasive approach is one possibility, however, research in the acute setting cannot wait for the insertion of a pulmonary artery catheter, which is time-consuming and has not been shown to improve outcomes in shock [48]. Signs of pulmonary congestion, such as rales or a chest X-ray with pulmonary edema could be alternatives, as well as echocardiographic measures of elevated LV preload. Tissue hypoperfusion with at least one of the following: altered mental status, cold, clammy skin, or low urine output combined with increased arterial lactate (possibly >2.5 mmol/l). Low blood pressure can be used to raise suspicion of CS, but the optimal cut-off has not been determined. Specific cut-off values should be discussed internationally, and consensus guidelines should be published in order to increase comparability of future CS trials. The number of cardiac arrest patients included should be reported, and subgroup analyses on this group performed.

In septic shock, which is equally difficult to define, a data-driven approach has been undertaken and a possible septic shock definition with clinical criteria was generated through meetings, Delphi processes, and voting, followed by feedback from international professional societies [49]. Inspired by the current septic shock definition, a more pragmatic approach in CS RCTs could leave out invasive signs of reduced cardiac function and include all patients with AMI and signs of hypoperfusion (vasopressor requirements and elevated lactate). In this case, it is assumed that AMI-patients with shock most frequently have cardiogenic shock, but this approach will likely result in the inclusion of non-cardiogenic shock patients. However, a brief and focused transthoracic echocardiographic examination could quickly rule in or rule out a cardiac etiology and should be mandatory in every case where acute heart failure is suspected.

CONCLUSIONS

In conclusion, significant heterogeneity of inclusion criteria exists between CS trials. Differences are mainly related to objective measures of cardiac function such as LVEF or cardiac index and whether to include comatose patients after cardiac arrest. Uniform inclusion criteria in the future would be beneficial for interstudy comparisons, and we suggest an international consensus of overall CS enrolment criteria for future trials.

Supplementary material

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

Article information

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REFERENCES

1. Virani SS, Alonso A, Benjamin EJ, et al. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. Circulation. 2020; 141(9): e139–e596, doi: 10.1161/CIR.0000000000000757, indexed in Pubmed: 31992061.
2. Goldberg RJ, Makam RC, Yarzebski J, et al. Decade-Long trends (2001-2011) in the incidence and hospital death rates associated with the in-hospital development of cardiogenic shock after acute myocardial infarction. Circ Cardiovasc Qual Outcomes. 2016; 9(2): 117–125, doi: 10.1161/CIRCOUTCOMES.115.002359, indexed in Pubmed: 26884615.
3. Helgestad OKL, Josiassen J, Hassager C, et al. Temporal trends in incidence and patient characteristics in cardiogenic shock following acute myocardial infarction from 2010 to 2017: a Danish cohort study. Eur J Heart Fail. 2019; 21(11): 1370–1378, doi: 10.1002/ejhf.1566, indexed in Pubmed: 31339222.

4. Lindholm M, Køber L, Boesgaard S. Cardiogenic shock complicating acute myocardial infarction Prognostic impact of early and late shock development. Eur Heart J. 2003; 24(3): 258–265, doi: 10.1016/s0195-668x(02)00429-3.
5. Schrage B, Ibrahim K, Loehn T, et al. Impella support for acute myocardial infarction complicated by cardiogenic shock. Circulation. 2019; 139(10): 1249–1258, doi: 10.1161/CIRCULATIONAHA.118.036614, indexed in Pubmed: 30586755.
6. Poulidakis E, Spaulding C. Cardiac assist devices in cardiogenic shock. Circulation. 2019; 139(10): 1259–1261, doi: 10.1161/CIRCULATIONAHA.118.038855, indexed in Pubmed: 30865480.
7. van Diepen S, Katz JN, Albert NM, et al. American Heart Association Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Mission: Lifeline. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. Circulation. 2017; 136(16): e232–e268, doi: 10.1161/CIR.0000000000000525, indexed in Pubmed: 28923988.
8. Zeymer U, Bueno H, Granger CB, et al. Acute Cardiovascular Care Association position statement for the diagnosis and treatment of patients with acute myocardial infarction complicated by cardiogenic shock: A document of the Acute Cardiovascular Care Association of the European Society of Cardiology. Eur Heart J Acute Cardiovasc Care. 2020; 9(2): 183–197, doi: 10.1177/2048872619894254, indexed in Pubmed: 32114774.
9. Burstein B, Tabi M, Barsness GW, et al. Association between mean arterial pressure during the first 24 hours and hospital mortality in patients with cardiogenic shock. Crit Care. 2020; 24(1): 513, doi: 10.1186/s13054-020-03217-6, indexed in Pubmed: 32819421.
10. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK investigators. Should we emergently revascularize occluded coronaries for cardiogenic shock. N Engl J Med. 1999; 341(9): 625–634, doi: 10.1056/NEJM199908263410901, indexed in Pubmed: 10460813.
11. Thiele H, Zeymer U, Neumann FJ, et al. IABP-SHOCK II Trial Investigators. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med. 2012; 367(14): 1287–1296, doi: 10.1056/NEJMoa1208410, indexed in Pubmed: 22920912.
12. Jentzer JC, van Diepen S, Henry TD. Understanding how cardiac arrest complicates the analysis of clinical trials of cardiogenic shock. Circ Cardiovasc Qual Outcomes. 2020; 13(9): e006692, doi: 10.1161/CIRCOUTCOMES.120.006692, indexed in Pubmed: 32862695.
13. Thiele H, Akin I, Sandri M, et al. CULPRIT-SHOCK Investigators. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. N Engl J Med. 2017; 377(25): 2419–2432, doi: 10.1056/NEJMoa1710261, indexed in Pubmed: 29083953.
14. Josiassen J, Lerche Helgestad OK, Møller JE et al. Hemodynamic and metabolic recovery in acute myocardial infarction-related cardiogenic shock is more rapid among patients presenting with out-of-hospital cardiac arrest. PLoS One. 2020; 23; 15(12): e0244294, doi: 10.1371/journal.pone.0244294, indexed in Pubmed: 33362228.
15. Alexander JH, Reynolds HR, Stebbins AL, et al. TRIUMPH Investigators. Effect of tilarginine acetate in patients with acute myocardial infarction and cardiogenic shock: the TRIUMPH randomized controlled trial. JAMA. 2007; 297(15): 1657–1666, doi: 10.1001/jama.297.15.joc70035, indexed in Pubmed: 17387132.
16. Bochaton T, Huot L, Elbaz M, et al. IMPELLA-STIC investigators. Mechanical circulatory support with the Impella® LP5.0 pump and an intra-aortic balloon pump for cardiogenic shock in acute myocardial infarction: The IMPELLA-STIC randomized study. Arch Cardiovasc Dis. 2020; 113(4): 237–243, doi: 10.1016/j.acvd.2019.10.005, indexed in Pubmed: 31740272.
17. Tousek P, Rokyta R, Tesarova J, et al. Routine upfront abciximab versus standard periprocedural therapy in patients undergoing primary percutaneous coronary intervention for cardiogenic shock: The PRAGUE-7 Study. An open randomized multicentre study. Acute Card Care. 2011; 13(3): 116–122, doi: 10.3109/17482941.2011.567282, indexed in Pubmed: 21526919.
18. Ouweneel DM, Eriksen E, Sjauw KD, et al. Percutaneous mechanical circulatory support versus intra-aortic balloon pump in cardiogenic shock after acute myocardial infarction. J Am Coll Cardiol. 2017; 69(3): 278–287, doi: 10.1016/j.jacc.2016.10.022, indexed in Pubmed: 27810347.
19. Prondzinsky R, Lemm H, Swyter M, et al. Intra-aortic balloon counterpulsation in patients with acute myocardial infarction complicated by cardiogenic shock: the prospective, randomized IABP SHOCK Trial for attenuation of multiorgan dysfunction syndrome. Crit Care Med. 2010; 38(1): 152–160, doi: 10.1097/CCM.0b013e3181b78671, indexed in Pubmed: 19770739.
20. Seyfarth M, Sibbing D, Bauer I, et al. A randomized clinical trial to evaluate the safety and efficacy of a percutaneous left ventricular assist device versus intra-aortic balloon pumping for treatment of cardiogenic shock caused by myocardial infarction. J Am Coll Cardiol. 2008; 52(19): 1584–1588, doi: 10.1016/j.jacc.2008.05.065, indexed in Pubmed: 19007597.
21. Li JI, Xue H, Wang Bs, et al. Effect of prolonged intra-aortic balloon pumping in patients with cardiogenic shock following acute myocardial infarction. Med Sci Monit. 2007; 13(6): CR270–CR274, indexed in Pubmed: 17534233.
22. Thiele H, Sick P, Boudriot E, et al. Randomized comparison of intra-aortic balloon support with a percutaneous left ventricular assist device in patients with revascularized acute myocardial infarction complicated by cardiogenic shock. Eur Heart J. 2005; 26(13): 1276–1283, doi: 10.1093/eurheartj/ehi161, indexed in Pubmed: 15734771.
23. Pan Y, Lu Z, Hang J, et al. Effects of low-dose recombinant human brain natriuretic peptide on anterior myocardial infarction complicated by cardiogenic shock. Braz J Cardiovasc Surg. 2017; 32(2): 96–103, doi: 10.21470/1678-9741-2016-0007, indexed in Pubmed: 28492790.
24. Jin YY, Gao H, Zhang XY, et al. Shenfu Injection inhibits inflammation in patients with acute myocardial infarction complicated by cardiac shock. Chin J Integr Med. 2017; 23(3): 170–175, doi: 10.1007/s11655-016-2749-x, indexed in Pubmed: 28028723.
25. Barillà F, Pannarale G, Torromeo C, et al. Ivabradine in patients with st-elevation myocardial infarction complicated by cardiogenic shock: a preliminary randomized prospective study. Clin Drug Investig. 2016; 36(10): 849–856, doi: 10.1007/s40261-016-0424-9, indexed in Pubmed: 27312076.
26. Fuhrmann JT, Schmeisser A, Schulze MR, et al. Levosimendan is superior to enoximone in refractory cardiogenic shock complicating acute myocardial infarction. Crit Care Med. 2008; 36(8): 2257–2266, doi: 10.1097/CCM.0b013e3181809846, indexed in Pubmed: 18664782.
27. Dzavík V, Cotter G, Reynolds HR, et al. SHould we inhibit nitric Oxide synthase in Cardiogenic shocK 2 (SHOCK-2) investigators. Effect of nitric oxide synthase inhibition on haemodynamics and outcome of patients with persistent cardiogenic shock complicating acute myocardial infarction: a phase II dose-ranging study. Eur Heart J. 2007; 28(9): 1109–1116, doi: 10.1093/eurheartj/ehm075, indexed in Pubmed: 17459901.
28. García-González MJ, Domínguez-Rodríguez A, Ferrer-Hita JJ, et al. Cardiogenic shock after primary percutaneous coronary intervention: effects of levosimendan compared with dobutamine on haemodynamics. Eur J Heart Fail. 2006; 8(7): 723–728, doi: 10.1016/j.ejheart.2006.01.007, indexed in Pubmed: 16492404.
29. Urban P, Stauffer JC, Bleed D, et al. A randomized evaluation of early revascularization to treat shock complicating acute myocardial infarction. The (Swiss) Multicenter Trial of Angioplasty for Shock-(S)MASH. Eur Heart J. 1999; 20(14): 1030–1038, doi: 10.1053/euhj.1998.1353, indexed in Pubmed: 10383777.
30. Fuernau G, Beck J, Desch S, et al. Mild hypothermia in cardiogenic shock complicating myocardial infarction. Circulation. 2019; 139(4): 448–457, doi: 10.1161/CIRCULATIONAHA.117.032722, indexed in Pubmed: 30026282.
31. Lobo AS, Sandoval Y, Henriques JP, et al. Cardiogenic shock management: international survey of contemporary practices. J Invasive Cardiol. 2020; 32(10): 371–374, indexed in Pubmed: 32999090.
32. Menon V, Slater J, White H, et al. Acute myocardial infarction complicated by systemic hypoperfusion without hypotension: report of the SHOCK trial registry. Am J Med. 2000; 108(5): 374–380, doi: 10.1016/s0002-9343(00)00310-7.
33. Danzi G, Cuspidi C. Diastolic blood pressure and myocardial damage. J Am Coll Cardiol. 2017; 69(12): 1645–1646, doi: 10.1016/j.jacc.2016.11.086.
34. Vincent JL, Quintairos E Silva A, Couto L, et al. The value of blood lactate kinetics in critically ill patients: a systematic review. Crit Care. 2016; 20(1): 257, doi: 10.1186/s13054-016-1403-5, indexed in Pubmed: 27520452.

35. Frydland M, Møller JE, Wiberg S, et al. Lactate is a prognostic factor in patients admitted with suspected ST-elevation myocardial infarction. Shock. 2019; 51(3): 321–327, doi: 10.1097/SHK.0000000000001191, indexed in Pubmed: 30286032.
36. Udesen NJ, Møller JE, Lindholm MG, et al. DanGer Shock investigators. Rationale and design of DanGer shock: Danish-German cardiogenic shock trial. Am Heart J. 2019; 214: 60–68, doi: 10.1016/j.ahj.2019.04.019, indexed in Pubmed: 31176289.
37. Verbrugge FH, Guazzi M, Testani JM, et al. Altered hemodynamics and end-organ damage in heart failure: impact on the lung and kidney. Circulation. 2020; 142(10): 998–1012, doi: 10.1161/CIRCULATIONAHA.119.045409, indexed in Pubmed: 32897746.
38. Grand J, Kjaergaard J, Bro-Jeppesen J, et al. Cardiac output, heart rate and stroke volume during targeted temperature management after out-of-hospital cardiac arrest: association with mortality and cause of death. Resuscitation. 2019; 142: 136–143, doi: 10.1016/j.resuscitation.2019.07.024, indexed in Pubmed: 31362081.
39. Grand J, Bro-Jeppesen J, Hassager C, et al. Cardiac output during targeted temperature management and renal function after out-of-hospital cardiac arrest. J Crit Care. 2019; 54: 65–73, doi: 10.1016/j.jcrc.2019.07.013, indexed in Pubmed: 31362189.
40. Wetterslev M, Møller-Sørensen H, Johansen RR, et al. Systematic review of cardiac output measurements by echocardiography vs. thermodilution: the techniques are not interchangeable. Intensive Care Med. 2016; 42(8): 1223–1233, doi: 10.1007/s00134-016-4258-y, indexed in Pubmed: 26932349.
41. Josiassen J, Helgestad OKL, Møller JE et al. Cardiogenic shock due to predominantly right ventricular failure complicating acute myocardial infarction. Eur Heart J Acute Cardiovasc Care. 2021; 10(1): 33–39, doi: 10.1093/ehjacc/zuaa010, indexed in Pubmed: 33620420.
42. Ma TS, Paniagua D, Denktas AE, et al. Usefulness of the sum of pulmonary capillary wedge pressure and right atrial pressure as a congestion index that prognosticates heart failure survival (from the evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness trial). Am J Cardiol. 2016; 118(6): 854–859, doi: 10.1016/j.amjcard.2016.06.040, indexed in Pubmed: 27474338.
43. Yancy CW, Jessup M, Bozkurt B, et al. WRITING COMMITTEE MEMBERS, American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013; 128(16): e240–e327, doi: 10.1161/CIR.0b013e31829e8776, indexed in Pubmed: 23741058.
44. Obokata M, Kane GC, Reddy YNV, et al. Role of diastolic stress testing in the evaluation for heart failure with preserved ejection fraction: a simultaneous invasive-echocardiographic study. Circulation. 2017; 135(9): 825–838, doi: 10.1161/CIRCULATIONAHA.116.024822, indexed in Pubmed: 28039229.
45. Bro-Jeppesen J, Hassager C, Wanscher M, et al. Targeted temperature management at 33°C versus 36°C and impact on systemic vascular resistance and myocardial function after out-of-hospital cardiac arrest: a sub-study of the target temperature management trial. Circ Cardiovasc Interv. 2014; 7(5): 663–672, doi: 10.1161/CIRCINTERVENTIONS.114.001556, indexed in Pubmed: 25270900.
46. Bro-Jeppesen J, Johansson PI, Hassager C, et al. Endothelial activation/injury and associations with severity of post-cardiac arrest syndrome and mortality after out-of-hospital cardiac arrest. Resuscitation. 2016; 107: 71–79, doi: 10.1016/j.resuscitation.2016.08.006, indexed in Pubmed: 27523954.
47. Jentzer JC, van Diepen S, Barsness GW, et al. Cardiogenic shock classification to Predict mortality in the cardiac intensive care unit. J Am Coll Cardiol. 2019; 74(17): 2117–2128, doi: 10.1016/j.jacc.2019.07.077, indexed in Pubmed: 31548097.
48. Richard C, Warszawski J, Anguel N, et al. French Pulmonary Artery Catheter Study Group. Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: a randomized controlled trial. JAMA. 2003; 290(20): 2713–2720, doi: 10.1001/jama.290.20.2713, indexed in Pubmed: 14645314.
49. Singer M, Deutschman C, Seymour C, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016; 315(8): 801–810, doi: 10.1001/jama.2016.0287.

Evolution of implantation technique and indications for a subcutaneous cardioverter-defibrillator: over 7 years of experience in Poland

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INTRODUCTION

Implantation of a subcutaneous cardioverter-defibrillator (S-ICD) may be used to prevent sudden cardiac death (SCD) due to ventricular arrhythmias in patients not requiring permanent cardiac pacing or antitachycardia pacing [1, 2]. That method of treatment was first applied in Poland in 2014 [3, 4]. However, it took several years before in 2019 S-ICD became reimbursed to the extent necessary to cover all costs incurred by implant centers. That, in turn, led to an increase in the number of procedures performed in Poland [5]. Currently, there is no report available on how that updated reimbursement regulations might have influenced the qualification procedure, implantation technique, and results in comparison to the preceding period.

The aim of our analysis was to investigate, whether there was any change to indications for S-ICD implantation, operational technique, and patient outcomes over 7 years of S-ICD utilization in Poland.

METHODS

We compared data collected at two registries in different time intervals: Registry A (September 2014 to December 2015) and Registry B (May 2020 to May 2021). Registry A was a multicenter query reporting data of 18 patients from 5 centers that pioneered S-ICD implantations in Poland [6]. Registry B is a nationwide initiative held by the Heart Rhythm Section of the Polish Cardiac Society [7], and 16 centers performing S-ICD implantations report data on subsequent patients undergoing implantation or exchange of the device. The analysis comprised only 144 patients from Registry B undergoing the first-time implantation of the system. We compared the data describing the general characteristics of patients, underlying diseases, implantation techniques, as well as reasons for the choice of a subcutaneous, instead of a transvenous cardioverter-defibrillator.

Table 1. Comparison of clinical characteristics of patients in both registries. Registry A — September 2014 to December 2015; Registry B — May 2020 to May 2021

	Registry A	Registry B	*P*-value
General information			
Total number of patients	18	144	—
Age, years, median (IQR)	39 (32–62)	41 (31–55)	0.79
Male sex, n (%)	10 (56)	108 (75)	0.1
Sinus rhythm, n (%)	14 (78)	135 (94)	0.04
Primary prevention, n (%)	4 (22)	94 (65)	<0.001
LVEF, %, median (IQR)	52.5 (45–60)	35 (25–60)	0.005
Underlying disease			
Dilated cardiomyopathy, n (%)	3 (17)	68 (47)	0.02
Ischemic cardiomyopathy, n (%)	6 (33)	40 (28)	0.59
Hypertrophic cardiomyopathy, n (%)	2 (11)	7 (5)	0.26
Arrhythmogenic right ventricular dysplasia, n (%)	1 (6)	0	0.11
Long QT syndrome, n (%)	1 (6)	5 (3)	0.51
Brugada snyndrome, n (%)	1 (6)	3 (2)	0.38
Short QT syndrome, n (%)	0 (0)	2 (2)	1
Left ventricular non-compaction, n (%)	0 (0)	1 (1)	1
Catecholaminergic polymorphic ventricular tachycardia, n (%)	0 (0)	1 (1)	1
Mitral annular disjunction, n (%)	0 (0)	1 (1)	1
Congenital heart disease, n (%)	1 (6)	2 (1)	0.3
Primary ventricular fibrillation, n (%)	3 (17)	15 (10)	0.43
Reason for choice of S-ICD vs T-ICD			
Young age, n (%)	4 (22)	109 (76)	<0.001
Risk of infective endocarditis, n (%)	11 (61)	33 (23)	0.001
Recurrent lead failure, n (%)	1 (6)	10 (7)	1
Lack of venous access, n (%)	8 (44)	7 (5)	<0.001
Other, n (%)	1(6)	6 (4)	0.57
Implantation procedure			
General anesthesia, n (%)	18 (100)	107 (74%)	0.01
Intramuscular pocket, n (%)	13 (72)	144 (100)	<0.001
2-incision technique, n (%)	2 (11)	80 (56)	<0.001
Defibrillation test performed, n (%)	18 (100)	119 (83)	0.08
Defibrillation test successful, n (%)	18 (100)	119 (100)	—
Complications, n (%)	0 (0)	3 (2)	1

Abbreviations: IQR, interquartile range; LVEF, left ventricular ejection fraction; S-ICD, subcutaneous cardioverter-defibrillator; T-ICD, transvenous implantable cardioverter-defibrillator

Statistical analysis

Continuous variables were presented as the median and interquartile range (IQR) due to non-normal distribution confirmed with the Shapiro-Wilk test. The Mann-Whitney U test was used to compare continuous variables. Categorical parameters were presented as numbers and percentages, and Fisher's exact test was used for comparisons. A *P*-value of below 0.05 was considered statistically significant. Statistical analysis was performed with the use of Statistica 13.1 software (StatSoft, Tulsa, OK, USA).

RESULTS AND DISCUSSION

Detailed data of the patients in both groups are presented in Table 1. Inter-group comparisons revealed that during the early period of S-ICD implementation in Poland it was less often implanted in primary prevention of SCD (22% vs 65%; $P < 0.001$), and dilated cardiomyopathy was less frequently the main underlying disease (17% vs 47%; $P = 0.02$). Patients in the early group had higher left ventricular ejection fraction (LVEF) (median value, 52.5% vs 35%; $P = 0.005$), whereas the main indications prompting the choice of S-ICD were lack of venous access (44%) and high risk of infective complications (61%). In the more recent group, young age was the main reason for the choice of S-ICD (76%). The change in operational technique over time was expressed as a significant increase in the percentage of procedures performed without general anesthesia (0% vs 26%; $P = 0.01$). The 2-incision technique has become more frequently applied instead of the 3-incision one (11% vs 56%; $P < 0.001$), and now the device pocket is more frequently intramuscular than before (72 vs 100%; $P < 0.001$). Defibrillation test tends to be less frequently performed nowadays (100% vs 83%; $P = 0.08$). In the patients from Registry B, 3 cases of postoperative complications were reported: pocket hematoma treated conservatively, inadequate shock possibly due to air entrapment in the device connector or pocket, and unilateral lower limb paresis (with no lesions found on imaging of the central nervous system).

During the initial years of S-ICD use in Poland, the number of implanting centers and procedures was limited. It resulted from the high cost of the system and troublesome reimbursement procedure. Therefore, S-ICD implantation

was reserved for secondary prevention of SCD and patients not eligible for a transvenous system (either with limited vascular access or high risk of infective complications) because only in such cases the implanting center was certain it would be fully reimbursed. Once complete reimbursement was introduced, the method became more applicable in the primary prevention of SCD, and the patient's young age might have become an indication for the choice of S-ICD. That selection factor became dominant, which brought Polish data closer to European reports [8]. Novel operational techniques reported in the literature, such as regional anesthesia, 2-incision technique, and intramuscular pocket [9–12], have been introduced in Polish centers ever since. Those techniques have become most common, and our results suggest that general anesthesia may be replaced by local and regional anesthetic techniques soon. Our analysis shows that in many cases (17% in the Registry B) the defibrillation test is currently waived. It may result from the high efficacy of S-ICD in the termination of ventricular fibrillation, which reached 100% of performed tests in both registries. Alternatively, it may be due to the concerns about the safety of inducing ventricular fibrillation in patients with more reduced LVEF, as a tendency to implant S-ICD in patients with more severe LVEF impairment was observed in Registry B, as compared to Registry A (median LVEF 35% vs 52.5%, respectively). Notably, that did not significantly increase the complication rate, which remains below 2% in our data and is lower than reported by other groups [13].

Our analysis confirms the increasing role of S-ICD as a method of primary prevention of SCD in Poland. Recent administrative regulations resulted in a change of profile of patients qualified for the procedure. Currently, the main reason for the choice of S-ICD is the young age of a patient. A tendency to incorporate new operational techniques used in European centers is observed, with no increase in the perioperative complication rate. The influence of updated reimbursement regulations on the use of S-ICD in Poland suggests that other modern methods might be successfully introduced on condition that they are accompanied by clear regulations covering all the costs borne by the implanting centers.

Article information

Conflict of interest: MK received proctoring and lecturer fees from Boston Scientific. AP received lecturer's fees from Medtronic Polska, Biotronik Polska and consultancy fees from Medtronic Polska. KK received proctoring, and lecturer fees from Boston Scientific. MO: proctorship agreement with Boston Scientific. PS received lecturer's fees for Abbott, Biotronik, Boston Scientific, Medtronic, and consultancy fees for Biotronik, Boston Scientific. ASo: consultancy agreement with Boston Scientific. MG received consultant and lectures fees from Medtronic, Biotronik, Abbott and Boston Scientific. DJ received lecturer fees from Boston Scientific. ST received consultancy fee from Boston Scientific. SB, WK, MG, JR, MJ, ZO, JZK, ASt, MO declared no conflict of interest.

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REFERENCES

1. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015; 36(41): 2793–2867, doi: 10.1093/eurheartj/ehv316, indexed in Pubmed: 26320108.
2. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Executive summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Society. Heart Rhythm. 2018; 15(10): e190–e252, doi: 10.1016/j.hrthm.2017.10.035, indexed in Pubmed: 29097320.
3. Kaczmarek K, Kempa M, Grabowski M, et al. A subcutaneous implantable cardioverter-defibrillator - the first implantation in Poland. Kardiol Pol. 2015; 73(1): 62–771, doi: 10.5603/KP.2015.0010, indexed in Pubmed: 25625342.
4. Kempa M, Budrejko S, Sławiński G, et al. Subcutaneous implantable cardioverter-defibrillator (S-ICD) for secondary prevention of sudden cardiac death. Arch Med Sci. 2016; 12(5): 1179–1180, doi: 10.5114/aoms.2016.61921, indexed in Pubmed: 27695509.
5. Regulation of the Minister of Health of 9 January 2019 amending the regulation on guaranteed services in the field of hospital treatment. The Journal of Laws of the Republic of Poland: item 77 [text in Polish].
6. Kaczmarek K, Kempa M, Grabowski M, et al. Multicentre early experience with totally subcutaneous cardioverter-defibrillators in Poland. Arch Med Sci. 2020; 16(4): 764–771, doi: 10.5114/aoms.2019.83817, indexed in Pubmed: 32542076.
7. Kempa M, Przybylski A, Budrejko S, et al. Multicenter Registry of Subcutaneous Cardioverter-Defibrillator Implantations — preliminary report. Kardiol Pol. 2021; 79(6): 697–699, doi: 10.33963/KP.a2021.0002, indexed in Pubmed: 34013514.
8. Jędrzejczyk-Patej E, Boveda S, Kalarus Z, et al. Factors influencing the use of subcutaneous or transvenous implantable cardioverter-defibrillators: results of the European Heart Rhythm Association prospective survey. Europace. 2018; 20(5): 887–892, doi: 10.1093/europace/euy009, indexed in Pubmed: 29432525.
9. Droghetti A, Basso Ricci E, Scimia P, et al. Ultrasound-guided serratus anterior plane block combined with the two-incision technique for subcutaneous ICD implantation. Pacing Clin Electrophysiol. 2018; 41(5): 517–523, doi: 10.1111/pace.13318, indexed in Pubmed: 29493802.
10. van der Stuijt W, Baalman SWE, Brouwer TF, et al. Long-term follow-up of the two-incision implantation technique for the subcutaneous implantable cardioverter-defibrillator. Pacing Clin Electrophysiol. 2020; 43(12): 1476–1480, doi: 10.1111/pace.14022, indexed in Pubmed: 32720398.
11. Quast AFBE, Baalman SWE, Brouwer TF, et al. A novel tool to evaluate the implant position and predict defibrillation success of the subcutaneous implantable cardioverter-defibrillator: The PRAETORIAN score. Heart Rhythm. 2019; 16(3): 403–410, doi: 10.1016/j.hrthm.2018.09.029, indexed in Pubmed: 30292861.
12. Kempa M, Sterliński M, Mitkowski P, et al. Safety issues in selected patients implanted with Boston Scientific EMBLEM subcutaneous cardioverter defibrillator systems. Kardiol Pol. 2021; 79(2): 223–224, doi: 10.33963/KP.15833, indexed in Pubmed: 33635036.
13. Boersma LV, El-Chami MF, Bongiorni MG, et al. Understanding outcomes with the EMBLEM S-ICD in primary prevention patients with low EF study (UNTOUCHED): clinical characteristics and perioperative results. Heart Rhythm. 2019; 16(11): 1636–1644, doi: 10.1016/j.hrthm.2019.04.048, indexed in Pubmed: 31082539.

Clinical and linguistic validation of a Polish version of the Pulmonary Embolism Quality of Life Questionnaire: a disease-specific quality of life questionnaire for patients after acute pulmonary embolism

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INTRODUCTION

Acute venous thromboembolism involving deep vein thrombosis and/or pulmonary embolism (PE) has a broad array of early and long-term complications including recurrent episodes, bleeding complications related to anticoagulant treatment, persisting dyspnea or poor physical capacity, post-thrombotic syndrome, and chronic thromboembolic pulmonary hypertension. The underestimated sequala is decreased quality of life (QoL) [1–3]. Questionnaires for assessing QoL after an episode of acute PE were developed in several languages, however, there is none in Polish. The Pulmonary Embolism Quality of Life Questionnaire (PEmb-QoL) fits very well in the modern approach to the holistic management of PE and was proven to be a good instrument to detect and measure the intensity of symptoms and physical functioning. PEmb-QoL was first developed in Dutch and translated into English (2009). It was later validated in several languages: French (2014), German (2015), Norwegian (2015), and Chinese (2018) [4–8]. In this paper, we report the results of the validation of this questionnaire in Polish.

METHODS

The Pulmonary Embolism Quality of Life Questionnaire

The Pulmonary Embolism Quality of Life Questionnaire questionnaire consists of 9 questions (40 items) clustered into 6 dimensions: frequency of complaints (FO) — Q1; activities of daily living limitations (AD) — Q4; work-related problems (WR) — Q5; social limitations (SL) — Q6; intensity of complaints (IO) — Q7, Q8; emotional complaints (EC) — Q9. Questions Q2 and Q3 provide descriptive information and are not used to calculate scores. Higher scores indicate a worse outcome. Questions Q1, Q4, Q5, Q9 are reversely scored. Scores of a given dimension are calculated by averaging scores of all items in that dimension. Transformed dimensions score is calculated in a two-step process. The score of each item is rescaled in such a way that 100 corresponds to a possible maximal score and 0 corresponds to a minimal score. We take a mean of items that constitute a given dimension.

We performed a forward-backward translation of the English version of the PEmb-QoL questionnaire into Polish according to previously published recommendations [9]. The final Polish version is provided in the Supplementary material.

Patients sample

The inclusion criteria included age above 18 years, the history of acute PE confirmed objectively with computed tomography angiography of pulmonary arteries, ventilation/perfusion scintigraphy, angiography of pulmonary arteries or with transthoracic or transesophageal echocardiography with the detection of thrombi in the pulmonary arteries.

The exclusion criteria were the refusal to participate in the survey, chronic thromboembolic pulmonary hypertension, severe dementia, residence in a nursing facility, problems with using the Polish language. The median time

from an episode of PE to completing the questionnaire was 21 months (interquartile range [IQR], 13–31).

Data collection

The patients who were enrolled in the study were invited by a phone call to have an appointment at the cardiologist outpatient office at the hospital where they received a PEmb-QoL questionnaire and the Polish version of the 36-Item Short-Form Health Survey (SF-36) [10]. Patients were asked to complete and return both questionnaires. Patients who were not willing to visit the office, were asked to complete and return both questionnaires using a pre-stamped return envelope. The same scenario was used 14 days later.

Ethical issues

The study protocol was approved by the Bioethics Committee of the Regional Medical Chamber in Tarnow, Poland (No. 3/0177/2019).

Statistical analysis

Statistical analysis was performed using R software, version 4.0.2 with the "Psych" package. All tests were two-sided with a 5% significance level.

A detailed description of the statistical analysis can be found in the supplementary material.

RESULTS AND DISCUSSION

The final sample involved 103 patients. Included patients were 67 years old (IQR 67.00–72.50). The youngest participant was 22 and the oldest one was 87 years old. Sixty-four patients (62.14%) were aged ≥65 years, 63 (61.17%) of them were male. Clinical characteristics are presented in the Supplementary material, *Table S1*.

Scores of 6 dimensions of PEmb-QoL

The median score was 2 for FO (IQR 1.38–2.50), 1.92 for AD (IQR 1.31–2.42), 1.5 for WR (1–2), 2 for SL (IQR 1–3), 2.5 for IO (IQR 1.5–3.5), 2.3 for EC (1.5–2.95). Scores of aspects (0 indicates lowest possible score and 100 indicates maximal possible score) are shown in supplementary material, *Figure S1*.

Floor and ceiling effect

All dimensions had floor effects ranging from 8.74% for EC to 37.86% for SL, for four dimensions the floor effect was substantial. Three dimensions had a non-zero ceiling effect AD, WR, and SL with 7.77%, 30.1%, 6.8%, respectively (Supplementary material, *Table S2*).

Factor analysis

Factor analysis supported the underlying dimensions in general. The screen test identified four factors with eigenvalues greater than 2 (17.57; 3.26; 2.70; 2.15). They accounted for 29%; 17%; 12% and 10% of total variance. Factor 1 included items — Q4, Q6, Q8; Factor 2 included most of Q9; Factor 3 included most of Q1, Q7; Factor 4 included Q5 (Supplementary material, *Table S3*).

Reliability and reproducibility

A half of Cronbach's alpha coefficients were >0.9 except for FO 0.81; WR 0.89; IO 0.67; indicating high internal consistency. Items were positively related to each other, with all average inter-item correlations >0.3 (Supplementary material, *Table S4*). The values of item total correlations were ranging from 0.30 to 0.87.

PEmb-QoL dimensions were mostly moderately or well correlated between themselves ($0.37 \leq r \leq 0.82$), with the strongest correlation between the intensity of complaints and frequency of complaints (0.82) (Supplementary material, *Table S5*).

Intraclass correlation coefficients (ICCs) for test-retest analysis were high, ranging between 0.58 for SL (Q6) and 0.92 for FO (Q1) (Supplementary material, *Table S6*).

Construct validity

For correlations between aspects of PEmb-QoL and SF-36 Spearman's correlation coefficient ranged between –0.93 (for AD [Q4] and physical functioning) and –0.12 (for SL [Q6] and general health). The PEmb-QoL dimensions: AD (Q4), WR (Q5), SL (Q6), IO (Q7, Q8), EC (Q9) showed higher correlations with the SF-36 physical component summary, whereas FO (Q1) showed a higher correlation with the SF-36 mental component (Supplementary material, *Table S7*). Overall, these correlations supported good convergent validity.

PEmb-QoL dimension scores were mostly weakly correlated with clinical characteristics (Supplementary material, *Table S8*). The factor that influenced PEmb-QoL the most was the presence of cardiovascular disease. This indicates adequate discriminant validity.

Floor and ceiling effects

A substantial ceiling effect occurs only in one dimension — WR as in most previous studies [4–7]. A substantial floor effect was observed in four dimensions. As it was pointed out in the aforementioned studies [5], high floor and ceiling effects in particular aspects may be an effect of: a small number of items per dimension (Q6 — SL); a small range of possible answers per item (Q5 — WR). It is possible that the range of the scale is not large enough to accommodate the distribution of the data, or there is social desirability bias.

Factor analysis

There were different approaches to the factor analysis in the previous validations of PEmb-QoL. We chose to preserve clinical defined factors as in the primary English version. Preserving clinically defined factors had practical advantages. It makes it plausibly easier to extrapolate clinical outcomes from studies in most countries. Furthermore, it allows us to use foreign software to compute

PEmb-QoL scores. Clinically defined dimensions have the same number of answers per item and make computing scores easier. Clinical definitions were designed to be intuitive and easy. Factor analysis performed in our study can suggest a different structure of dimensions from the one in the English version of the questionnaire.

Test-retest reliability

There are no clear guidelines about the exact duration of the time gap before reassessment when test-retest reliability is verified [11]. We chose a 2-week period to retest our patients. ICC value was low only for SL, which is similar to other studies' results. SL had the lowest ICC in those publications [4, 5]. ICC of similar value had been accepted in previous studies [5]. All other ICC values were over 0.7. This indicates good overall reproducibility. To sum up, all exceptions to strict psychometric norms are not specific for the Polish version of this tool and were accepted in previous validations. The questionnaire has been proved to be a valid tool with adequate reliability and reproducibility.

CONCLUSIONS

The Polish version of the PEmb-QoL questionnaire is a valid tool in estimating disease-specific QoL.

Supplementary material

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

Article information

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REFERENCES

1. Konstantinides SV, Meyer G, Becattini C, et al. The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Respir J. 2019; 54(3): 543–603, doi: 10.1183/13993003.01647-2019, indexed in Pubmed: 31473594.
2. Roik M, Wretowski D, Łabyk A, et al. Initial experience of pulmonary embolism response team with percutaneous embolectomy in intermediate-high- and high-risk acute pulmonary embolism. Kardiol Pol. 2019; 77(2): 228–231, doi: 10.5603/KP.a2018.0239, indexed in Pubmed: 30566224.
3. Sławek-Szmyt S, Jankiewicz S, Smukowska-Gorynia A, et al. Implementation of a regional multidisciplinary pulmonary embolism response team: PERT-POZ initial 1-year experience. Kardiol Pol. 2020; 78(4): 300–310, doi: 10.33963/KP.15230, indexed in Pubmed: 32165606.
4. Rochat M, Méan M, Limacher A, et al. Quality of life after pulmonary embolism: validation of the French version of the PEmb-QoL questionnaire. Health Qual Life Outcomes. 2014; 12: 174, doi: 10.1186/s12955-014-0174-4, indexed in Pubmed: 25464821.
5. Frey PM, Méan M, Limacher A, et al. Quality of life after pulmonary embolism: Prospective validation of the German version of the PEmb-QoL questionnaire. Thromb Res. 2015; 135(6): 1087–1092, doi: 10.1016/j.thromres.2015.03.031, indexed in Pubmed: 25887632.
6. Klok FA, Cohn DM, Middeldorp S, et al. Quality of life after pulmonary embolism: validation of the PEmb-QoL Questionnaire. J Thromb Haemost. 2010; 8(3): 523–532, doi: 10.1111/j.1538-7836.2009.03726.x, indexed in Pubmed: 20025645.
7. Sun X, Li J, Shi J, et al. Validating the Chinese version of the PEmb-QoL questionnaire: A measure for quality of life assessment after pulmonary embolism. Thromb Res. 2018; 166: 86–91, doi: 10.1016/j.thromres.2018.04.020, indexed in Pubmed: 29704766.
8. Tavoly M, Jelsness-Jørgensen LP, Wik HS, et al. Quality of life after pulmonary embolism: first cross-cultural evaluation of the pulmonary embolism quality-of-life (PEmb-QoL) questionnaire in a Norwegian cohort. Qual Life Res. 2015; 24(2): 417–425, doi: 10.1007/s11136-014-0779-4, indexed in Pubmed: 25120017.
9. Beaton DE, Bombardier C, Guillemin F, et al. Guidelines for the process of cross-cultural adaptation of self-report measures. Spine (Phila Pa 1976). 2000; 25(24): 3186–3191, doi: 10.1097/00007632-200012150-00014, indexed in Pubmed: 11124735.
10. Tylka J, Piotrowicz R. Cardiac rehabilitation. Quality of life SF-36 questionnaire – the Polish version. Kardiol Pol. 2009; 67(10): 1166–1169.
11. Fayers PM, Machin D. Quality of life: the assessment, analysis and interpretation of patient-reported outcomes (2nd ed.). Wiley, Chichester 2007.

Characteristics of hospital admissions and invasive cardiology procedures in the Silesian Voivodeship in 2019 and 2020

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INTRODUCTION

The rapid spread of the coronavirus disease (COVID-19) has imposed significant changes for health care systems [1]. In order to provide care for patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and to reduce the risk of viral transmission, the work of many cardiology departments and outpatient clinics had to be reorganized, while many wards have been repurposed to facilitate care for patients infected with SARS-CoV-2 [2, 3]. Many planned hospital admissions have been postponed or canceled, while some patients resigned from a planned admission [4].

Due to the fear of becoming infected, many patients were reluctant to present in the hospital or call for an ambulance, which often resulted in a delay in the contact with healthcare in acute cases.

The purpose of the present analysis was to summarize the causes of hospital admissions and the major procedures performed in cardiology departments in the Silesian Voivodeship in 2020, with reference to the respective data from 2019.

METHODS

The analysis was based on data acquired from the questionnaires provided annually by the cardiology wards in the Silesian Voivodeship to the provincial consultant in cardiology. The response to the questionnaires is obligatory for every unit in the Voivodeship. The questionnaires contain information regarding the number of hospital admissions with the main diagnoses, along with the data on the procedures performed during these admissions. In the present study, the data regarding the years 2019 and 2020 were analyzed. It should be noted that the study encompassed the entire years and the detailed data for specific months, as well as the short- or long-term outcomes of the treated patients, were not available for the purpose of this analysis.

The approval of the ethics committee, and patient informed consent were not required for the purpose of this study.

Statistical analysis

The results presented in the manuscript were expressed as numbers and percentages. The comparison of the analyzed variables for each year was presented as relative differences.

RESULTS AND DISCUSSION

In 2019, there were 61 537 hospital admissions to the cardiology departments, which decreased by 22.4% to 47 734 in 2020. The

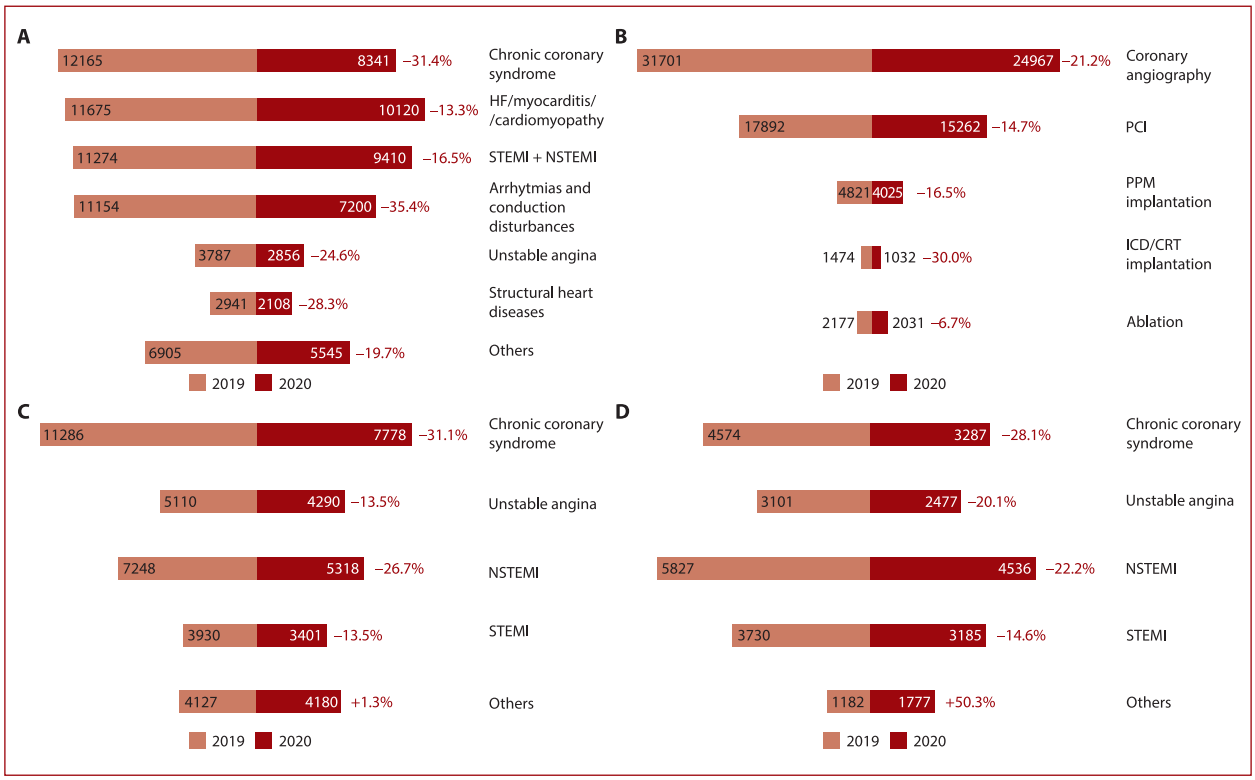

Figure 1. Data regarding the number of hospital admissions and invasive cardiology procedures in 2019 and 2020 in the Silesian Voivodeship. **A.** The primary causes of admissions. **B.** The number of invasive procedures. **C.** The number of coronary angiographies with regard to the indication. **D.** The number of percutaneous coronary interventions with regard to the indication. The percentage changes between the respective values are described in red

Abbreviations: CRT, cardiac resynchronization therapy device; HF, heart failure; ICD, implantable cardioverter-defibrillator; NSTEMI, non-ST-segment-elevation myocardial infarction; PCI, percutaneous coronary intervention; PPM, permanent pacemaker; STEMI, ST-segment-elevation myocardial infarction

major diagnoses in the respective years are summarized in Figure 1A. The primary causes of admissions in 2019 were chronic coronary syndromes (CCS) (19.8%; n = 12 165) and heart failure (HF), myocarditis, or cardiomyopathies (19.0%; n = 11 675). In 2020 the most prevalent cause of admission was HF, myocarditis or cardiomyopathies (21.2%; n = 10 120) followed by myocardial infarction (MI) (19.7%; n = 9 410).

There was a reduction in the number of all analyzed invasive procedures between 2020 and 2019, as presented in Figure 1B. The number of coronary angiography procedures decreased by 21.4%, while the number of percutaneous coronary interventions (PCI) decreased by 14.6%. The numbers of cardiac ablations or implantations of a permanent pacemaker, implantable cardioverter defibrillator, or cardiac resynchronization therapy devices were also reduced when compared with 2019.

As demonstrated in Figure 1C, in 2019 patients underwent coronary angiography most frequently due to CCS (35.6%; n = 11 286) and non-ST-segment elevation myocardial infarction (NSTEMI) (22.9%; n = 7248), which remained the most prevalent indications in 2020 (31.2%; n = 7778 and 20.6%; n = 5138, respectively). In 2019 the majority of PCIs were performed due to NSTEMI (32.6%; n = 5827) and CCS (25.6%; n = 4574), as described in Figure 1D. In 2020 the most prevalent indications for PCI were NSTEMI (29.7%; n = 4536), followed by ST-segment elevation myocardial infarction (STEMI) (20.9%; n = 3185).

In the Silesian Voivodeship, the number of patients admitted to the cardiology departments has seen a major reduction, which has also exerted a drop in the number of invasive procedures performed from the outbreak of the pandemic. A similar trend has been observed in Europe and the United States, where in the initial phase of the SARS-CoV-2 spread, the number of acute cardiovascular hospitalizations was reduced by almost 45% [1, 5–7].

The decrease in the number of admissions in the analyzed period has been observed regardless of the cause and diagnosis but was numerically most prominent in patients with CCS (by 31.4%, a reduction of 3824 admissions). The necessity to reorganize the cardiology departments, the redistribution of ward employees and the division of the departments to separate the patients with regard to their infectious status could play a role in this decrease.

Moreover, similarly to the specialties, the reduction in the number of planned admissions has been recommended in order to secure hospital beds for patients with life-threatening conditions.

A major reduction has also been observed in the numbers of patients with acute coronary syndromes, which corresponds with similar observations from Europe and the United States [5–9]. It is worth mentioning that the percentage of patients with MI undergoing invasive diagnostics and treatment remained similar, as 82.0% of patients with MI in 2020 and 84.8% in 2019 underwent PCI.

Finally, despite an absolute reduction in the numbers of admissions when compared with 2019, HF, myocarditis, or cardiomyopathy became the primary cause of hospital admissions in 2020, constituting more than 20% of all hospitalizations. One of the hypotheses explaining the increase in the relative frequency of admissions due to HF could be limited access to ambulatory care, provided mostly as the telehealth visits, or the apprehension of patients of becoming infected when seeking medical advice. Moreover, although the stay-at-home campaigns aimed to substantially reduce the social risk of viral transmission, the tendency to isolate at home could potentially lead to patients deferring seeking medical contact.

An effective HF treatment is based on dynamic responses to the patients' conditions, for instance using day-care units, which significantly reduced the risk of recurrent hospitalizations in patients with HF before the pandemic [10]. After the outbreak of COVID-19, the extensiveness of the functioning of these facilities has been reduced or even suspended.

Taking into consideration the absolute decrease in the number of hospital admissions due to HF and the previously published data on the increase of life-threatening arrhythmias in remotely monitored patients with HF, one can speculate that the fear of seeking medical care could have resulted in more pronounced development of HF, potentially leading to the death of some patients before arrival to the hospital [11, 12].

It is worth noting that an approximate 16% reduction in the number of admissions due to HF or acute coronary syndrome is lower than in the prior analyses [5–9]. However, the results of this analysis encompass the entire years, including the first months of 2020 before the pandemic, when the healthcare system has functioned similarly as in 2019.

In conclusion, in 2020 in the Silesian Voivodeship, there has been a decline in the number of hospital admissions to cardiology departments regardless of the condition, which has been followed by a reduction in the number of invasive procedures performed when compared with 2019. Unfortunately, the number of patients referred to the cardiology departments with acute coronary syndromes decreased in comparison with 2019, however, their treatment remained similar as before the pandemic.

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REFERENCES

1. Sokolski M, Gajewski P, Zymliński R, et al. Impact of coronavirus disease 2019 (COVID-19) outbreak on acute admissions at the emergency and cardiology departments across Europe. Am J Med. 2021; 134(4): 482–489, doi: 10.1016/j.amjmed.2020.08.043.
2. Her M. Repurposing and reshaping of hospitals during the COVID-19 outbreak in South Korea. One Health. 2020; 10: 100137, doi: 10.1016/j.onehlt.2020.100137, indexed in Pubmed: 32373705.
3. Świerad M, Dyrbuś K, Szkodziński J, et al. Telehealth visits in a tertiary cardiovascular center as a response of the healthcare system to the severe acute respiratory syndrome coronavirus 2 pandemic in Poland. Pol Arch Intern Med. 2020; 130: 700–703.
4. The number of admissions in respective months of 2020 with reference to 2019 obtained from the National Health Fund. https://zdrowedane.nfz.gov.pl/course/view.php?id=139 (March 8, 2021).
5. De Filippo O, D'Ascenzo F, Angelini F, et al. Reduced rate of hospital admissions for ACS during Covid-19 outbreak in Northern Italy. N Engl J Med. 2020; 383(1): 88–89, doi: 10.1056/NEJMc2009166, indexed in Pubmed: 32343497.
6. Bhatt AS, Moscone A, McElrath EE, et al. Fewer hospitalizations for acute cardiovascular conditions during the COVID-19 pandemic. J Am Coll Cardiol. 2020; 76(3): 280–288, doi: 10.1016/j.jacc.2020.05.038, indexed in Pubmed: 32470516.
7. Gąsior M, Gierlotka M, Tycińska A, et al. Effects of the coronavirus disease 2019 pandemic on the number of hospitalizations for myocardial infarction: regional differences. Population analysis of 7 million people. Kardiol Pol. 2020; 78(10): 1039–1042, doi: 10.33963/KP.15559, indexed in Pubmed: 32820878.
8. Hawranek M, Grygier M, Bujak K, et al. Characteristics of patients from the Polish Registry of Acute Coronary Syndromes during the COVID-19 pandemic: the first report. Kardiol Pol. 2021; 79(2): 192–195, doi: 10.33963/KP.15756, indexed in Pubmed: 33463992.
9. Metzler B, Siostrzonek P, Binder RK, et al. Decline of acute coronary syndrome admissions in Austria since the outbreak of COVID-19: the pandemic response causes cardiac collateral damage. Eur Heart J. 2020; 41(19): 1852–1853, doi: 10.1093/eurheartj/ehaa314, indexed in Pubmed: 32297932.
10. Gąsior M, Niedziela JT, Sikora J, et al. Improved prognosis in patients with recurrent hospitalizations for heart failure after day-care management. Kardiol Pol. 2019; 77(10): 975–977, doi: 10.33963/KP.14987, indexed in Pubmed: 31553331.
11. Tajstra M, Kurek A, Pyka Ł, et al. The increased rate of life-threatening interventions in remotely monitored patients with heart failure during the coronavirus disease 2019 pandemic. Pol Arch Intern Med. 2020; 130(10): 913–914, doi: 10.20452/pamw.15505, indexed in Pubmed: 32643914.
12. Marijon E, Karam N, Jost D, et al. Out-of-hospital cardiac arrest during the COVID-19 pandemic in Paris, France: a population-based, observational study. Lancet Public Health. 2020; 5(8): e437–e443, doi: 10.1016/S2468-2667(20)30117-1, indexed in Pubmed: 32473113.

Subcutaneous implantable cardioverter-defibrillator and the two-incision intermuscular technique in pediatric patients — a single center experience

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INTRODUCTION

For the past decade, the subcutaneous implantable cardioverter-defibrillator (S-ICD) has provided a safe and effective option to prevent sudden cardiac death for selected patients [1, 2]. This alternative to transvenous implantable cardioverter-defibrillator (TV-ICD) is superior for patients with difficult vascular access, high risk of infection, and expected lead failure in patients with anticipated life-long therapy [3, 4]. However, it is not appropriate for patients who need bradycardia-, antitachycardia- or resynchronization pacing [3–5]. With these limitations, the S-ICD has shown itself to be non-inferior to TV-ICD in several studies in adults [1–3]. There are few publications regarding S-ICD implantation in pediatric patients, probably due to a smaller subject population [3, 4, 6]. Investigators emphasize the importance of safety offered by S-ICD comparing with TV-ICD in adolescent patients [7]. We report our initial experience with 8 children referred for S-ICD implantation to our institution.

METHODS

Patients were considered for ICD implantation according to the current guidelines [5, 8]. Preimplant screening is routinely required to ensure appropriate sensing and to reduce the risk of inappropriate shocks. The aim of this procedure is to assess the accuracy of QRS discrimination at least in 1 of the 3 sensing vectors. The screening was performed in a supine and standing position using an automatic screening tool (Boston Scientific™ ZOOM programmer, Marlborough, MA, USA). In addition to the standard protocol, we tested all patients lying on the left and the right side. In case of inappropriate screening results with the standard device and electrode positions, we changed the lead position from the left sternum border to the right, and/or the can more posteriorly and repeated screening. We believe screening pass with not one positive sensing vector, as recommended by the producer of the hardware, but with 2 is justified by the specificity of the children population. Because of faster heart rate and higher motoric activity, we may observe more difficult and variable sensing conditions. Testing with an electrode positioned also on the right sternum border is reasonable considering child chest anatomy: child's heart is proportionally bigger in the chest. This should provide better sensing and effective shock vectors.

In 7 patients who passed screening, an S-ICD was implanted. Prior to the procedure in the operation room, screening was again confirmed using fluoroscopy. The final lead and can position, and skin incisions were marked. All implantations were performed by one operator (MJ).

Under general anesthesia, the device (Boston Scientific Emblem™ A219, Marlborough, MA, USA) was implanted intermuscularly between the anterior surface of serratus anterior and the posterior surface of latissimus dorsi [9]. To avoid a third superior parasternal incision the lead (model 3501) was tunneled subcutaneously from a subxiphoid incision parallel to the sternum using an 11F delivery system. At the end of the procedure, VF was induced by a 50 Hz burst and terminated in all patients with the first 65 J standard polarity shock. All children had individually programmed two-zone shock set

Table 1. Patient characteristics

Patient number	Age at implantation, years /sex	Body weight, kg	Body height, cm	BMI, kg/m²	Diagnosis	Indication	Screenig result/Sensing vector used	Shock zone (conditional) obligatory	Lead position	Follow-up, months
1	13/F	44	158	17.86	Andersen-Tawil S.	Secondary prevention	Positive/ /Alternate	(210) 240	Left parasternal	40
2	9/M	39	136	21.08	HOCM	Primary prevention	Positive/ /Primary	(210) 240	Right parasternal	17
3	17/F	59	165	21.67	Idiopathic VF	Secondary prevention	Positive/ /Primary	(210) 240	Left parasternal	17
4	9/M	32	134	17.68	HNOCMP	Primary prevention	Positive/ /Primary	(210) 240	Right parasternal	14
5	12/M	49	163	18.63	HOCMP	Primary prevention	Positive/ /Primary	(210) 240	Right parasternal	14
6	17/F	60	173	20.04	HOCMP	Secondary prevention	Positive/ /Secondary	(200) 240	Right parasternal	14
7	9/M	45	148	20.50	Danon S.	Primary prevention	No vector avaliable	(210) 240	—	—
8	14/F	40	160	15.60	LV tumor	Secondary prevention	Positive/ /Primary	(210) 240	Left parasternal	3

Abbreviations: BMI, body mass index; HNOCM, hypertrophic non-obstructive cardiomyopathy; HOCMP, hypertrophic obstructive cardiomyopathy; LV, left ventricle; VF, ventricular fibrillation

up: conditional shock zone 200–210 bpm and shock zone 240 bpm SMART PASS filter on. The patients were seen in the outpatient clinic 1 month after the procedure and after that every 6 months. The study was approved by the local ethics committee according to the Declaration of Helsinki.

The distribution of patient characteristics was done by presenting data ranges and median values for quantitative data and number count for qualitative data. Microsoft Excel© version 16.50 was used for calculations.

RESULTS AND DISCUSSION

Between January 2018 and February 2021, 8 children met ICD implantation criteria. Patients' data are presented in Table 1. Seven patients passed screening in two vectors and an S-ICD system was implanted. In patient no. 7 with Danon syndrome, hypertrophic cardiomyopathy (HCMP), and pre-excitation syndrome, initial screening failed. We performed radiofrequency ablation of the accessory pathway. Despite narrowing of QRS, this patient failed the screening again.

Patients' age at implantation was between 9 and 17 years (median, 12.5); body weight between 32 and 60 kg (median, 44.5); body height between 134 and 173 cm (median, 159); body mass index (BMI) 15.60–20.02 kg/m² (median, 19.33). Follow-up ranged from 3 to 40 months (median, 14).

Throughout the implantation procedure, no technical problems occurred. Regardless of patients' anatomy, even in the youngest patient, all were successfully implanted using the 2-incision intermuscular technique. Sensing vectors remained stable in all children.

We chose standard lead and device can position in 3 patients, whereas 4 children with HCMP had appropriate sensing only in a modified lead and can position. In the latter cases, we implanted the lead right parasternal and the can posterior to the mid-axillary line.

Any pocket complication, erosion of the lead tip, or incisional infection occurred. With good cosmetic effect, even in the youngest patients, the device did not cause any discomfort or mobility restriction.

At follow-up, neither appropriate nor inappropriate shocks were observed in any patient. Sensing vectors remained stable in all patients and no T wave oversensing occurred.

Implantable cardioverter-defibrillator in sudden cardiac death prevention remains a challenging therapy in young patients with long life expectancy. Lead failure is the main issue for both transvenous and epicardial lead systems [9]. The highest complication rates were observed in pediatric patients [10, 11]. As observational studies show, the risk of lead failure in a 5-year follow-up reaches 40% in TV-ICD [12]. Venous obstruction, system infections and thromboembolism, high-risk lead extraction are frequent complications. When various cohorts of patients were compared, complication rates did not differ significantly and remained comparable [13].

The answer to such issues may be the S-ICD. The S-ICD eliminates the need for the endovascular or epicardial placement of leads. The well-known problems of transvenous leads are avoided. Subcutaneous lead longevity needs further investigations, but current data are encouraging [1, 2].

The S-ICD system is limited by the lack of bradycardia, antitachycardia, and resynchronization pacing, being a simple shock box. Careful preoperative selection of the patients is therefore mandatory.

Accurate QRS sensing remains challenging in S-ICD systems. Inappropriate shocks are the most frequent complications in subcutaneous systems [14]. In our cohort, we were able to show that these concerns can be overcome by proper patient selection, extended screening, and careful implantation techniques. We believe that we did not observe any inappropriate shock due to our rigorous screening and device implantation under fluoroscopy. We

encountered preoperatively difficulties in obtaining proper sensing vectors in patients with HCMP, probably due to oversensed high-voltage T, wide and fragmented QRS. The solution was the right parasternal lead position and dorsal device position behind the mid-axillary line [15].

Another point is a large device size: Emblem™ A219: volume 59.5 ml, and size 83.1 × 69.1 × 12.7 mm. With the intermuscular two-incision technique we obtained excellent functional and cosmetic results. There was no restriction in arm and shoulder mobility. We preferred the 2-incision technique to the 3-incision technique to avoid lead tip erosion and subsequent local infections. The 2-incision technique minimizes the risk associated with the traditional 3-incision technique, especially with children [6].

This technique enables S-ICD implantation in children under 10 years of age. Current outcomes are promising in terms of lack of lead and pocket-related complications and excellent sensing accuracy.

Article information

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REFERENCES

1. Knops R, Nordkamp LO, Delnoy PP, et al. Subcutaneous or transvenous defibrillator therapy. N Engl J Med. 2020; 383(6): 526–536, doi: 10.1056/nejmoa1915932, indexed in Pubmed: 32757521.
2. Gold MR, Lambiase PD, El-Chami MF, et al. UNTOUCHED Investigators*. Primary results from the understanding outcomes with the S-ICD in primary prevention patients with low ejection fraction (UNTOUCHED) trial. Circulation. 2021; 143(1): 7–17, doi: 10.1161/CIRCULATIONAHA.120.048728, indexed in Pubmed: 33073614.
3. McLeod CJ, Boersma L, Okamura H, et al. The subcutaneous implantable cardioverter defibrillator: state-of-the-art review. Eur Heart J. 2017; 38(4): 247–257, doi: 10.1093/eurheartj/ehv507, indexed in Pubmed: 28182222.
4. Bordachar P, Marquié C, Pospiech T, et al. Subcutaneous implantable cardioverter defibrillators in children, young adults and patients with congenital heart disease. Int J Cardiol. 2016; 203: 251–258, doi: 10.1016/j.ijcard.2015.09.083, indexed in Pubmed: 26519678.
5. Brugada J, Blom N, Sarquella-Brugada G, et al. European Heart Rhythm Association, Association for European Paediatric and Congenital Cardiology. Pharmacological and non-pharmacological therapy for arrhythmias in the pediatric population: EHRA and AEPC-Arrhythmia Working Group joint consensus statement. Europace. 2013; 15(9): 1337–1382, doi: 10.1093/europace/eut082, indexed in Pubmed: 23851511.
6. Silvetti MS, Pazzano V, Verticelli L, et al. Subcutaneous implantable cardioverter-defibrillator: is it ready for use in children and young adults? A single-centre study. Europace. 2018; 20(12): 1966–1973, doi: 10.1093/europace/euy139, indexed in Pubmed: 29939256.
7. Lewandowski M, Syska P, Kowalik I. Children and young adults treated with transvenous and subcutaneous implantable cardioverter-defibrillators: a 22-year single-center experience and new perspectives. Kardiol Pol. 2020; 78(9): 869–874, doi: 10.33963/KP.15469, indexed in Pubmed: 32631024.
8. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. ESC Scientific Document Group. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Eur Heart J. 2015; 36(41): 2793–2867, doi: 10.1093/eurheartj/ehv316, indexed in Pubmed: 26320108.
9. Winter J, Shin D-I, Siekiera M, et al. Abstract 14479: first experiences in children and young adults with a totally subcutanous implantable cardioverter defibrillator system. Circulation. 2012; 126(Suppl 21): A14479.
10. van Rees JB, de Bie MK, Thijssen J, et al. Implantation-related complications of implantable cardioverter-defibrillators and cardiac resynchronization therapy devices: a systematic review of randomized clinical trials. J Am Coll Cardiol. 2011; 58(10): 995–1000, doi: 10.1016/j.jacc.2011.06.007, indexed in Pubmed: 21867832.
11. Link MS, Hill SL, Cliff DL, et al. Comparison of frequency of complications of implantable cardioverter-defibrillators in children versus adults. Am J Cardiol. 1999; 83(2): 263–266, A5-6, doi: 10.1016/s0002-9149(98)00834-0, indexed in Pubmed: 10073833.
12. Maisel WH, Moynahan M, Zuckerman BD, et al. Pacemaker and ICD generator malfunctions: analysis of Food and Drug Administration annual reports. JAMA. 2006; 295(16): 1901–1906, doi: 10.1001/jama.295.16.1901, indexed in Pubmed: 16639048.
13. Bogush N, Espinosa RE, Cannon BC, et al. Selecting the right defibrillator in the younger patient: Transvenous, epicardial or subcutaneous? Int J Cardiol. 2018; 250: 133–138, doi: 10.1016/j.ijcard.2017.09.213, indexed in Pubmed: 29169751.
14. Brisben A. How the S-ICD (subcutaneous implantable cardiac defibrillator) senses cardiac signals to minimize cardiac over-sensing and maximize rhythm discrimination. J Electrocardiol. 2018; 51(6S): S38–S43, doi: 10.1016/j.jelectrocard.2018.08.022, indexed in Pubmed: 30220546.
15. Kaczmarek K, Kałowski M, Krzysztof Wranicz J, et al. Conventional and alternative preimplantation ECG screening for subcutaneous ICD in high risk hypertrophic cardiomyopathy patients. J Electrocardiol. 2020; 58: 68–73, doi: 10.1016/j.jelectrocard.2019.11.044, indexed in Pubmed: 31770668.

Hypertrophic obstructive cardiomyopathy and cor triatriatum sinistrum. A casuistic coexistence

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Hypertrophic cardiomyopathy (HCM) is characterized by increased thickness of the left ventricular myocardium, not explained by abnormal loading conditions. Up to 70% of HCM patients have either resting or easily provoked left ventricle outflow tract (LVOT) obstruction-hypertrophic obstructive cardiomyopathy (HOCM).

Cor triatriatum sinistrum (CTS) is a rare congenital anomaly in which the left atrium (LA) is divided into proximal and distal chambers by a fibromuscular membrane. It constitutes only 0.1% to 0.4% of congenital heart defects. CTS is frequently associated with the tetralogy of Fallot, septal defects, or anomalous pulmonary vein return. Nonetheless, a coexistence of HCM and CTS is a casuistic finding. Pellaton et al. [1] most probably described the first HCM case with CTS. Bahlmann et al. [2] reported on CTS and apical-HCM. Uemura et al. [3] reported on the prenatal diagnosis of the Costello syndrome expressed by CTS and HCM. Finally, Tatco [4] presented cardiac magnetic resonance (CMR) images of a female adult with both anomalies.

A 59-year-old male HOCM-patient with metabolic syndrome, atrial fibrillation, and chronic heart failure, after implantation of implantable cardioverter-defibrillator for secondary prevention of sudden cardiac death, was admitted for further treatment. Both transthoracic echocardiography (TTE) and CMR showed asymmetrical hypertrophy of the interventricular septum (25 mm). The systolic anterior motion of the mitral leaflets with moderate mitral regurgitation was visualized. Maximal LVOT-gradient was 80–90 mm Hg. Moreover, right ventricular systolic pressure was elevated to 57 mm Hg. The systolic function of both ventricles was preserved. Assessment of the enlarged LA by TTE and CMR was somehow ambiguous (Figure 1), thus chest computed tomography was done and showed non-restrictive CTS: LA was divided by a fibrous and fibromuscular membrane with duplication of the right part of the membrane. Wide communication between proximal and distal LA chambers was present in the lower LA part. All four pulmonary veins drained into the proximal LA chamber. Alcohol septal ablation was considered for the reduction of LVOT obstruction. However, inappropriate anatomy of the septal branch precluded alcohol septal ablation. Surgical treatment was considered, however, due to increased perioperative risk (body mass index [BMI], 36.1 kg/m^2) conservative treatment strategy was chosen.

TTE is a first choice tool for diagnosis of CTS (providing satisfactory imaging quality) and diagnosis of CTS in adulthood is rarer. A systematic review revealed that the median age of diagnosis was 43 years [5], as opposed to 59 years of our patient. Multimodality imaging is advisable in suspicious LA appearance and recommended in HCM patients. Next, LVOT obstruction (which was visible in our patient) was most probably reported only once [5] among the HCM-CTS population.

Finally, CTS may lead to the obstruction of LA flow and create pulmonary hypertension (PH). The pathophysiology is similar to that of mitral stenosis namely, PH may result from backward transmission of the increased LA pressure. In the context of our patient no significant gradient across the LA membrane was observed (Supplementary material, *Figure S1*). Thus, PH is likely to be post-capillary due to significant LVOT obstruction, mitral regurgitation, diastolic dysfunction, or their combination. Nonetheless, the method of choice to definitely differentiate between the pulmonary artery hypertension and post-capillary PH is the right heart catheterization (not performed in our patient).

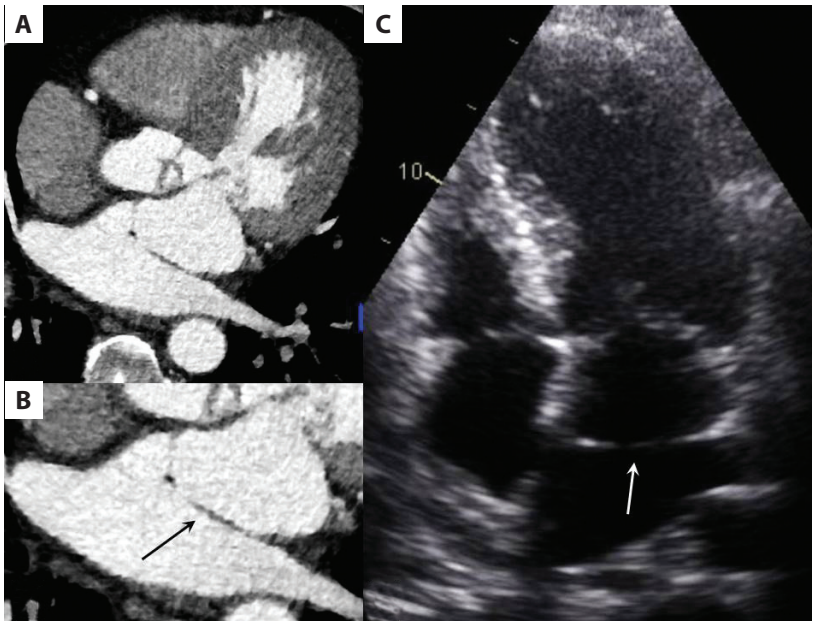

Figure 1. A. Computed tomography angiography. **B.** Magnification of the panel "A" with focus on the left atrium — white arrow indicates the fibromuscular membrane. **C.** Transthoracic echocardiography — apical view. The white arrow shows the linear echogenic structure across the left atrium

In conclusion, this report adds to the very limited literature on HOCM coexisting with CTS.

Supplementary material

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

Article information

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REFERENCES

1. Pellaton C, O'Mahony C, Ludman AJ, et al. Cor triatriatum and hypertrophic cardiomyopathy. J Cardiovasc Med (Hagerstown). 2016; 17(Suppl 2): e141–e143, doi: 10.2459/JCM.0000000000000078, indexed in Pubmed: 25000250.
2. Bahlmann E, van de, Dreher A, et al. Cardiac arrest in a fitness trainer with apical hypertrophic cardiomyopathy associated with cor triatriatum sinister [article in German]. Med Klin Intensivmed Notfmed. 2018; 113(5): 426–429, doi: 10.1007/s00063-017-0335-4, indexed in Pubmed: 28852773.
3. Uemura R, Tachibana D, Kurihara Y, et al. Prenatal findings of hypertrophic cardiomyopathy in a severe case of Costello syndrome. Ultrasound Obstet Gynecol. 2016; 48(6): 799–800, doi: 10.1002/uog.15888, indexed in Pubmed: 26916728.
4. Tatco V. Hypertrophic cardiomyopathy with cor triatriatum. https://radiopaedia.org/cases/hypertrophic-cardiomyopathy-with-cor-triatriatum (May 12, 2021).
5. Rudienė V, Hjortshøj CMS, Glaveckaitė S, et al. Cor triatriatum sinistrum diagnosed in the adulthood: a systematic review. Heart. 2019; 105(15): 1197–1202, doi: 10.1136/heartjnl-2019-314714, indexed in Pubmed: 31171629.

Homozygous familial hypercholesterolemia due to *APOB* genetic variant with unusual clinical course

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A 29-year-old patient was admitted to our center with suspected familial hypercholesterolemia (FH). The patient had no comorbidities, nor was she taking any medications. Her lipid profile was: total cholesterol 248 mg/dl, low-density lipoprotein cholesterol (LDL-C) 191 mg/dl, high-density lipoprotein cholesterol (HDL-C) 44 mg/dl, and triglycerides 64 mg/dl. Physical examination showed no relevant abnormalities. Mean carotid intima-media thickness was 0.37 mm and 0.49 mm in the left and right internal carotid arteries and coronary calcium score was 2. The patient scored 4 on the Dutch Lipid Clinic Network scale which is a diagnostic tool for FH. Next-generation sequencing revealed a homozygous variant in the apolipoprotein B (*APOB*) gene (c.10580G>A p.[Arg3527Gln]). Moreover the heterozygous APOE rare variant, denoted as c.460C>T p. (Arg154 Cys), was present in the patient. In the course of the cascade screening, we acquired data concerning the proband's family (Figure 1). Detailed analysis of family history revealed that the parents of the proband were 2nd line cousins. Dietary consultation and rosuvastatin 20 mg daily with ezetimibe 10 mg daily were prescribed with LDL-C reduction to 62 mg/dl by 67%.

According to WOBASZ II (*Wieloośrodkowe Badanie Stanu Zdrowia Ludności*, Multi-center National Population Health Examination Survey), lipid disorders and unsatisfactory treatment efficacy remain a major problem in the Polish population [1]. Inherited lipid abnormalities referred to as FH is genetically heterogeneous and the most common are variants within LDL receptor (*LDLR*), *APOB*, and proprotein convertase subtilisin/kexin type 9 (*PCSK9*) genes. Hypercholesterolemia

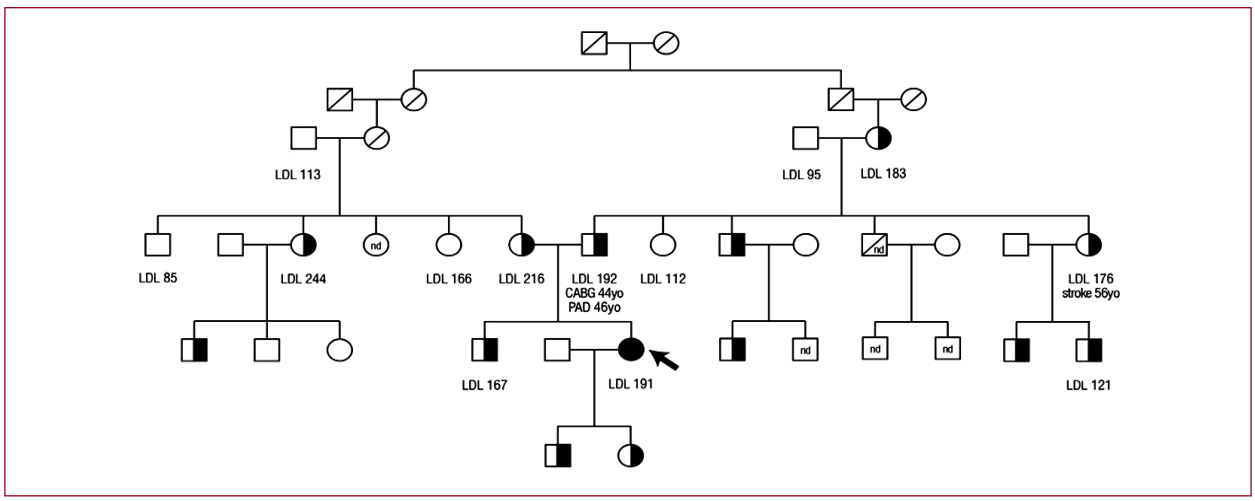

Figure 1. Pedigree of family. Numbers indicate low-density lipoprotein cholesterol (LDL-C) in mg/dl
Arrow — proband. Abbreviations: CABG, coronary artery bypass grafting; PAD, peripheral artery disease; nd, no data; yo, years old

due to APOB defect (FDB, familial defective APOB) is rare with a prevalence of 1:1000 and 1:4 000 000 for heterozygous and homozygous, respectively [2]. Homozygotes were observed in populations with the founder effect as well as in descendants of consanguineous parents, which is probably the case [3]. The most common pathogenic variant detected in the *APOB* gene results in reduced LDLR binding capacity, up to 25%, which leads to an accumulation of LDL-C [4]. Only a few cases of patients with homozygous FDB have been described in the literature and this is the first *APOB* homozygote case in the Polish population [2]. Homozygous FH (HoFH) is characterized by severe clinical presentation and classically is defined by LDL-C levels of ≥500 mg/dl in untreated patients, and ≥300 mg/dl in treated subjects with cutaneous or tendinous xanthoma occurring at less than 10 years of age [2]. Patients with pathogenic variants in *APOB* may have a milder clinical presentation, and the present case constitutes a documented example of this. As described in the literature, the average LDL-C concentrations found in cases of homozygous FDB were 265–331 mg/dl, and were lower in younger individuals, which may, at least partially, explain the proband's surprisingly low level of LDL-C [2, 5]. Causes of the relatively low LDL-C levels are sought in the apolipoprotein-E-dependent increased clearance of LDL-C precursor particles and the mechanism of up-regulation of the LDLR [3, 4]. Patients with HoFH do not attain satisfactory results of standard treatment and therapy must often be extended to include PCSK9 inhibitors or LDL-apheresis. The fact that the therapeutic objective is not achieved in patients with HoFH is particularly significant, as they are in the group of very high cardiovascular risk.

The described case of HoFH presented an unusual clinical course, even for FDB individuals, and underlines the necessity of a critical and individual assessment of all subjects with suspected FH.

Article information

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REFERENCES

1. Niklas A, Marcinkowska J, Kozela M, et al. Blood pressure and cholesterol control in patients with hypertension and hypercholesterolemia: the results from the Polish multicenter national health survey WOBASZ II. Pol Arch Intern Med. 2019; 129(12): 864–873, doi: 10.20452/pamw.15013, indexed in Pubmed: 31596271.
2. Foody JM, Vishwanath R. Familial hypercholesterolemia/autosomal dominant hypercholesterolemia: Molecular defects, the LDL-C continuum, and gradients of phenotypic severity. J Clin Lipidol. 2016; 10(4): 970–986, doi: 10.1016/j.jacl.2016.04.009, indexed in Pubmed: 27578130.
3. Gallagher JJ, Myant NB. The affinity of low-density lipoproteins and of very-low-density lipoprotein remnants for the low-density lipoprotein receptor in homozygous familial defective apolipoprotein B-100. Atherosclerosis. 1995; 115(2): 263–272, doi: 10.1016/0021-9150(94)05528-q, indexed in Pubmed: 7661885.
4. Schaefer JR, Scharnagl H, Baumstark MW, et al. Homozygous familial defective apolipoprotein B-100. Enhanced removal of apolipoprotein E-containing VLDLs and decreased production of LDLs. Arterioscler Thromb Vasc Biol. 1997; 17(2): 348–353, doi: 10.1161/01.atv.17.2.348, indexed in Pubmed: 9081691.
5. Andersen LH, Miserez AR, Ahmad Z, et al. Familial defective apolipoprotein B-100: a review. J Clin Lipidol. 2016; 10(6): 1297–1302, doi: 10.1016/j.jacl.2016.09.009, indexed in Pubmed: 27919345.

Changing appearance of lipomatous hypertrophy of the interatrial septum on positron emission tomography scan

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We present a rare imaging case of the lipomatous hypertrophy of the interatrial septum (LHIS), which may be correlated with arrhythmia and sudden death. We discuss the possible presence of brown adipose tissue within LHIS.

A 70-year-old female, with pancreatic cancer, underwent a positron emission tomography (PET/CT) examination during follow-up to evaluate the presence of metastases. Two months before the scan, the patient was treated with a pancreatoduodenectomy, which was complicated by an abscess. The PET/CT showed some post-operative inflammatory lesions in the area of surgery and no metastases were found. However, some unusual increased cardiac ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake was noted (Figure 1). The focus was located in the area of the interventricular septum. The area had a density of adipose tissue and the following dimensions: 27 × 14 × 36 mm. The ^{18}F-FDG uptake was relatively high (maximum standard unit value = 5.7).

Until now, the patient did not suffer from any cardiovascular disease, the echocardiogram did not reveal any pathologies of the heart. Due to the unusual finding, the patient was referred to a cardiologist. The patient underwent the 24-hour monitoring of the electrocardiogram,

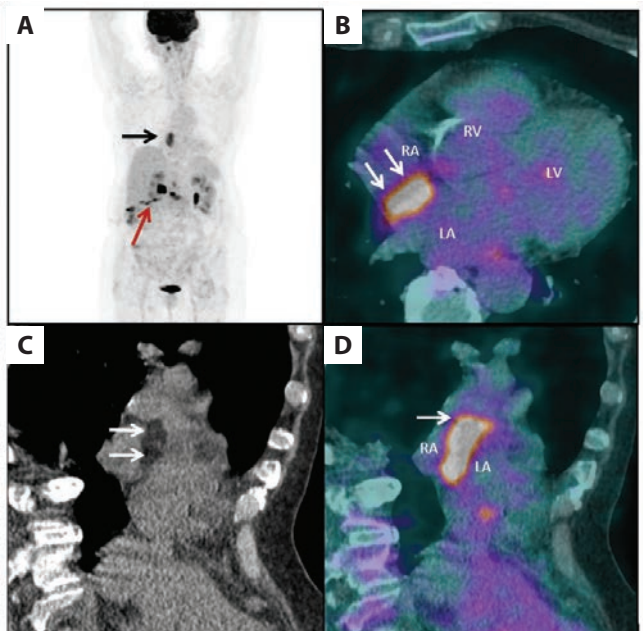

Figure 1. The positron emission tomography (PET/CT) images with increased activity of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) in the interatrial septum. The whole-body PET. **A.** Post-operative lesions in the abdomen (red arrow) and unusual cardiac activity (black arrow). **B.** and **D.** In the PET/CT fused images (B, transaxial image; D, sagittal image) the focal cardiac uptake (white arrows) corresponds to the area of fat density in the interatrial septum. **C.** Sagittal CT image, white arrows

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

which did not show any significant arrhythmia. In order to exclude an intracardiac malignancy, the patient was referred to cardiac magnetic resonance (CMR), since it can characterize the cardiac tissue and indicate malignancies [1]. The CMR examination consisted of: the cine imagines, T1-, T2-, T2*-weighted images with or without fat suppression, T1-mapping, and late gadolinium enhancement (LGE) 10–15 minutes after intravenous gadolinium contrast injection [2, 3]. The CMR images showed hyperintense signal on T1-weighted sequences before and after contrast injection and on LGE. Native T1-maps of the mass was 174 ms which confirmed the lipomatous tissue.

Based on the CMR, the LHIS was diagnosed. Further management of the pancreatic cancer in this patient included chemotherapy. A follow-up PET/CT scan performed seven months later confirmed complete cancer remission. Interestingly, there was no increased ^{18}F-FDG uptake in the interventricular area on the follow-up scan.

The lipomatous hypertrophy of the interatrial septum is usually a benign disease and appears as diffused thickening of the septum extending from fossa ovalis to the posterior wall of the right atrium and between great vessels [1]. It is rarely diagnosed, usually unintentionally, on echocardiography, CMR, or autopsy. Adipose tissue is physiologically present around the heart, however, in LHIS, there is a relevant idiopathic increase of the adipose tissue mass. LHIS may stay asymptomatic or cause a supraventricular arrhythmia or even sudden cardiac death [4]. Fortunately, our patient was free from life-threatening arrhythmia throughout the observation period. Further observation is still needed.

The conflicting results of two PET/CT scans in an individual patient are relatively common and the mechanism of ^{18}F-FDG uptake in LHIS is controversial [2, 5]. It may indicate the presence of metabolically active brown adipose tissue (BAT) within the LHIS. BAT presents different metabolic activities depending on body temperature. BAT is activated by exposure to cold and is associated with thermogenesis. Some studies demonstrated the different ^{18}F-FDG uptake, caused by BAT metabolic activity in some adults [5].

Article information

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REFERENCES

1. Fussen S, De Boeck BWL, Zellweger MJ, et al. Cardiovascular magnetic resonance imaging for diagnosis and clinical management of suspected cardiac masses and tumours. Eur Heart J. 2011; 32(12): 1551–1560, doi: 10.1093/eurheartj/ehr104, indexed in Pubmed: 21498848.
2. Baffour FI, Wenger DE, Broski SM. F-FDG PET/CT imaging features of lipomatous tumors. Am J Nucl Med Mol Imaging. 2020; 10(1): 74–82, indexed in Pubmed: 32211221.
3. Stojanovska J, Attili AK. AJR teaching file: fat-containing mass in the interatrial septum. AJR Am J Roentgenol. 2010; 195(Suppl 6): S73–S75, doi: 10.2214/AJR.09.7173, indexed in Pubmed: 21098164.
4. Fatma A, El-Sabbagh A, Muzaffar R, Osman M. Lipomatous hypertrophy of the inter-atrial septum: FDG PET/CT appearance and clinical correlation. J Nucl Med. 2017; 58 (Suppl. 1): 964.
5. Frontini A, Cinti S. Distribution and development of brown adipocytes in the murine and human adipose organ. Cell Metab. 2010; 11(4): 253–256, doi: 10.1016/j.cmet.2010.03.004, indexed in Pubmed: 20374956.

Acute coronary syndrome due to extrinsic left main compression

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Left main (LM) compression syndrome is defined as the LM stenosis due to extrinsic compression, triggering symptoms of myocardial ischemia. The prevalence is 5%–44% in patients with pulmonary arterial hypertension (PAH) [1]. The diagnostics and treatment algorithms in LM compression syndrome are not clearly defined.

We report here a 49-year-old male with atrial septal defect (ASD) type 2 and PAH, who was admitted to the emergency department because of typical symptoms of the acute coronary syndrome (ACS). The electrocardiogram revealed features of myocardial ischemia. Echocardiography showed a reduced ejection fraction (30%), enlarged right ventricle (52 mm) and left atrium (46 mm), elevated systolic pulmonary pressure (80 mm Hg), and bidirectional flow in ASD type 2 (Figure 1A). Coronary angiography raised suspicion of significant stenosis in the proximal segment of LM (Figure 1B). Intravascular ultrasound (IVUS) demonstrated the elliptical shape of LM without atherosclerotic lesions (Figure 1C, Supplementary material, *Video S1*). Computed tomography revealed significant dilation of the pulmonary trunk compressing the LM, hence confirming the diagnosis (Figure 1D–E). Due to the symptoms of overt heart failure, a decision to pursue invasive treatment was made. An intra-aortic balloon pump was implanted and IVUS-guided LM percutaneous coronary intervention was performed (bare-metal stent 4.5/15 mm; Figure 1F). Post-intervention IVUS showed good stent expansion and no features of LM compression. Further clinical course was uneventful. During a follow-up hospitalization, right heart catheterization confirmed the Eisenmenger syndrome. The 5-year follow-up was uneventful regarding recurrent ACS.

Considering the non-specific symptoms of LM compression, the diagnosis is challenging. The most effective non-invasive imaging methods are cardiac computer tomography and cardiac magnetic resonance imaging [2]. If the imaging suggests abnormalities, it is necessary to perform coronary angiography followed by intravascular imaging [2]. In our case, since IVUS clearly demonstrated the extrinsic LM compression, and given a strong correlation between IVUS and fraction flow reserve, the latter was not performed. Considering that LM compression syndrome is not common, there is insufficient research to establish the gold standard treatment. Some authors suggest that coronary artery bypass grafting should be performed [3]. However, surgical treatment is associated with the high risk of mortality in severe PAH patients, and our patients had previously rejected the proposed surgical treatment of ASD [4]. There have been several reports of successful percutaneous coronary intervention (PCI) with either bare-metal stents (BMS) or drug-eluting stents in LM compression, showing comparable results regardless of stent type up to 3 years [2, 5]. Considering the large vessel diameter, no evidence of atherosclerotic plaque, the risk of hemoptysis, and potential treatment with prostacyclin agonist or anticoagulants due to Eisenmenger syndrome, BMS was selected, with a good clinical result during 5-year follow-up.

In conclusion, LM compression syndrome is a rare entity that can lead to ACS, acute heart failure, and sudden cardiac arrest. The non-invasive medical imaging in conjunction with angiography and IVUS/FFR makes diagnosing it possible. The line of treatment has not been clearly defined, but our case demonstrates that LM compression syndrome can be successfully managed by percutaneous treatment of the compressed vessel.

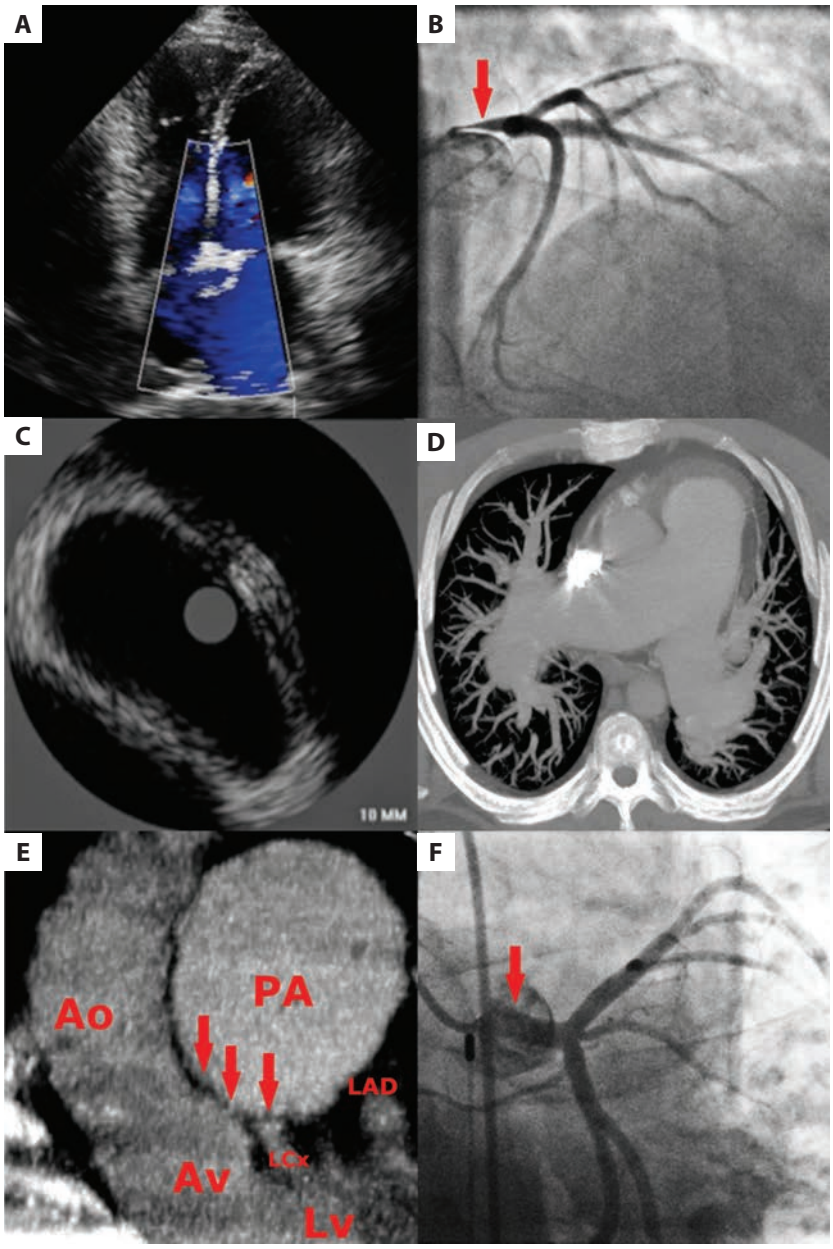

Figure 1. A. Echocardiography with color Doppler showing right ventricle enlargement and bidirectional flow in atrial septal defect type 2. **B.** Coronary angiography which raised suspicion of significant stenosis in the proximal part of the left main coronary artery (red arrow). **C.** Intravascular ultrasound demonstrating the elliptical shape of LM without atherosclerotic lesions. **D.** Computed tomography revealed enlargement of the pulmonary trunk (56 mm) and both pulmonary arteries (left 36 mm; right 51 mm). **E.** Computed tomography showing compression of the left main coronary artery against the sinus of Valsalva by the right pulmonary artery (red arrows) resulting in a subtotal occlusion, underlying acute coronary syndrome. **F.** Post-percutaneous coronary intervention angiography showing no features of left main compression (red arrow)

Abbreviations: Ao, aorta; AV, aortic valve; LAD, left anterior descending artery; LCx, left circumflex artery; LM, left main; LV, left ventricle; PA, pulmonary artery

Supplementary material

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REFERENCES

1. Albadri K, Jensen JM, Christiansen EH, et al. Left main coronary artery compression in pulmonary arterial hypertension. Pulm Circ. 2015; 5(4): 734–736, doi: 10.1086/683690, indexed in Pubmed: 26697183.
2. Lindsey JB, Brilakis ES, Banerjee S. Acute coronary syndrome due to extrinsic compression of the left main coronary artery in a patient with severe pulmonary hypertension: successful treatment with percutaneous coronary intervention. Cardiovasc Revasc Med. 2008; 9(1): 47–51, doi: 10.1016/j.carrev.2007.07.003, indexed in Pubmed: 18206638.
3. Varela SG, Orbe PM, Villa JA, et al. Stenting in primary pulmonary hypertension with compression of the left main coronary artery. Rev Esp Cardiol. 2004; 57(7): 695–698, doi: 10.1016/s1885-5857(06)60294-6.
4. Batra K, Saboo SS, Kandathil A, et al. Extrinsic compression of coronary and pulmonary vasculature. Cardiovasc Diagn Ther. 2020, doi: 10.21037/cdt-20-155.
5. Ikegami R, Ozaki K, Ozawa T, et al. Percutaneous coronary intervention for a patient with left main coronary compression syndrome. Intern Med. 2018; 57(10): 1421–1424, doi: 10.2169/internalmedicine.9534-17, indexed in Pubmed: 29321426.

Internal carotid artery stent fracture likely caused by hyoid bone compression

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A 70-year-old male patient visited the clinic for a regular check-up. Targeted medical history included a history of carotid artery stenting (CAS) (Xact carotid stent, Abbott Vascular, Lake Bluff, IL, USA) (Figure 1A). The carotid intervention was not complicated by dissection, oversized stent, or stent fracture. A routine Duplex ultrasonography follow-up indicated that the patient had the right internal carotid artery (ICA) asymptomatic restenosis (peak systolic velocity [PSV]: 360 cm/s, ICA/common carotid artery [CCA] PSV ratio >4.15). Residual, mixed plaque without calcification was present outside the stent. Computed tomography angiography (CTA) demonstrated a fractured right ICA stent (Figure 1B–C). Notably, it showed that the tip of the greater horn of the hyoid bone (HoB) passes between the right ICA and the right external carotid artery. A three-dimensional image reconstruction of CTA indicated that the right ICA traverses between the greater horn of the HoB and the transverse process of the C4 vertebra. The fractured stent was compressed by the HoB at its origin (Figure 1D). In contrast, the left carotid bifurcation and ICA were lateral to the HoB. Moreover, CTA did not show tortuosity and calcification in the right ICA. Cinefluoroscopic examination indicated a type-4 stent fracture (i.e., a complete transverse linear fracture with stent displacement) [1] in the right ICA (Figure 1E). Surgery was recommended because ICA stenosis due to extrinsic compression was contraindicated for endovascular therapy. Hence, the patient was scheduled for right carotid endarterectomy under general anesthesia. Vascular structures were clamped after intravenous injection of 5000 units of unfractionated heparin. The carotid endarterectomy was performed (Figure 1F). A fractured and thrombosed stent was revealed and excised (Supplementary material, *Figure S1*), and the reconstruction of the right ICA segment required a poly-patch use. The patient was discharged on the 6th day without any adverse clinical events. At the 20th-month follow-up, Duplex ultrasonography showed normal findings (right ICA PSV <125 cm/s, right ICA/CCA PSV <2).

Anatomically, the carotid arteries are located in a fibrous layer on the neck, which allows them to follow muscle movements properly [1]. The elongation and excessive tortuosity of the ICA can change the vessel route in this layer, causing it to be close to the HoB and consequently undergo mechanical stress [2]. Mechanical stress of the carotid artery by bone structures — HoB — is an extremely rare clinical entity. Three factors must take place to cause this mechanical pressure: (1) a long HoB horn protruding dorsally from the larynx; (2) a lower level of separation of the ICA from CCA; (3) kinking of ICA, which tends to deform stents placed in the vascular structure [3, 4]. Moreover, this mechanical compression can cause endothelial damage and consequently atheromatous plaque formation and thromboembolic events. Previously, Mori et al. [5] reported an ischemic cerebrovascular event with the occlusion and recanalization of a non-atherothrombotic ICA due to HoB compression. Extrinsic compression of the carotid artery was the contraindication to the endovascular treatment of ICA stenosis. Hence, two main treatment options can be considered in this pathology: (1) hyoid bone resection plus re-CAS [4]; (2) carotid endarterectomy, which includes removing surgically the fractured stent and then closing it with the poly-patch.

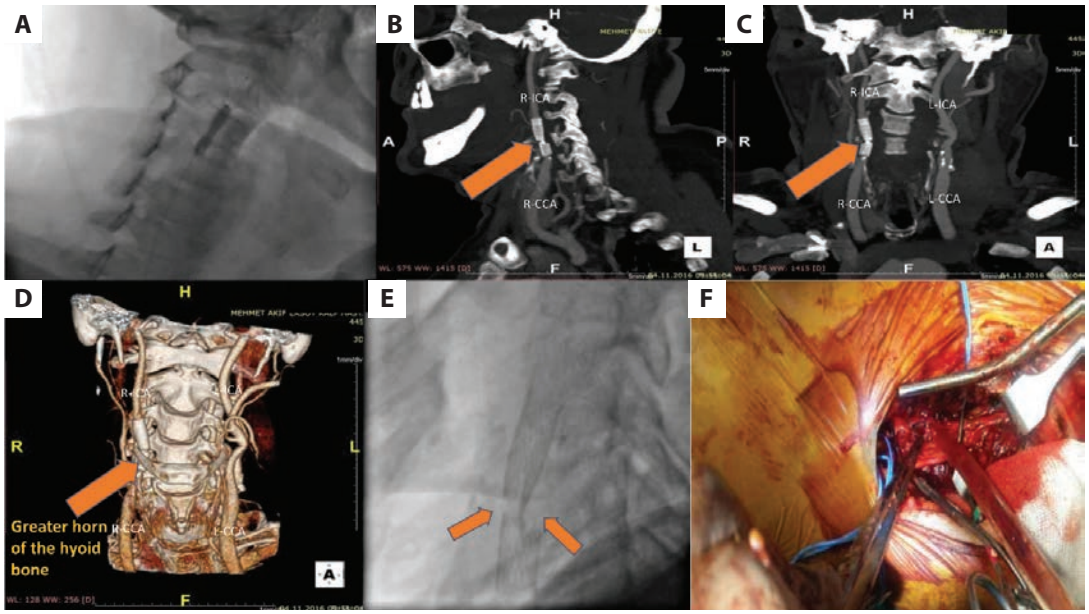

Figure 1. A. Conventional carotid angiography shows an 80%–90% stenotic lesion in the right internal carotid artery and successful stent implantation. **B.** and **C.** Coronal and sagittal images show the fractured right internal carotid stent. The tip of the greater horn of the hyoid bone passes between the right internal carotid artery and right external carotid artery (arrowhead). **D.** The three-dimensional image shows the medialized right internal carotid artery, traversing between the greater horn of the hyoid bone and the transverse process of the C4 vertebra (the red arrow points at that the greater horn of hyoid bone between external and internal carotid arteries). The left carotid bifurcation and internal carotid artery pass laterally to the hyoid bone (arrowhead). **E.** Cinefluoroscopic image indicates the fracture of the right internal carotid artery stent (arrowheads). **F.** The intraoperative image indicates that the internal carotid artery was explored

Abbreviations: L-CCA, left common carotid artery; L-ICA, left internal carotid artery; R-CCA, right common carotid artery; R-ICA, right internal carotid artery

Supplementary material

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REFERENCES

1. Sfyroeras GS, Koutsiaris A, Karathanos C, et al. Clinical relevance and treatment of carotid stent fractures. J Vasc Surg. 2010; 51(5): 1280–1285, doi: 10.1016/j.jvs.2010.01.050, indexed in Pubmed: 20347546.
2. Gray H. Anatomy of the Human Body. 39th edition. Churchill Livingstone, London 2000.
3. Martinelli O, Fresilli M, Jabbour J, et al. Internal carotid stenosis associated with compression by hyoid bone. Ann Vasc Surg. 2019; 58: 379.e1–379.e3, doi: 10.1016/j.avsg.2018.09.043, indexed in Pubmed: 30684622.
4. Tekieli Ł, Musiałek P, Kabłak-Ziembicka A, et al. Severe, recurrent in-stent carotid restenosis: endovascular approach, risk factors. Results from a prospective academic registry of 2637 consecutive carotid artery stenting procedures (TARGET-CAS). Postępy Kardiol Interwencyjnej. 2019; 15(4): 465–471, doi: 10.5114/aic.2019.90221, indexed in Pubmed: 31933663.
5. Mori M, Yamamoto H, Koga M, et al. Hyoid bone compression-induced repetitive occlusion and recanalization of the internal carotid artery in a patient with ipsilateral brain and retinal ischemia. Arch Neurol. 2011; 68(2): 258–259, doi: 10.1001/archneurol.2010.371, indexed in Pubmed: 21320995.

Immediate mechanical thrombectomy with DynaCT evaluation after percutaneous coronary intervention complicated by acute ischemic stroke

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The incidence of acute ischemic stroke secondary to percutaneous coronary intervention (PCI) ranges from 0.1% to 0.6% [1]. Furthermore, strokes related to PCI happen also as a result of reversible occlusions of large arteries [2]. Various predictors of acute ischemic stroke during PCI have been established, one of them being the radial access site [3, 4]. Mechanical thrombectomy is a rapid, safe, and feasible treatment option for acute ischemic stroke and has become the standard of care [2, 5]. The neurological outcome depends on the time from the onset of symptoms to treatment, and even a few-minute delay can critically influence the outcome. Thus, establishing a diagnosis of acute stroke without the need to transfer the patient from the catheterization laboratory to the computed tomography (CT) facility and later to the interventional radiology department for treatment might significantly shorten the time to reperfusion [1, 2, 5].

A 64-year-old Caucasian male with a history of prior ST-segment elevation myocardial infarction treated with PCI in the left anterior descending coronary artery (LAD), arterial hypertension, type 2 diabetes mellitus, and hypercholesterolemia was admitted to our department with a non-ST-segment elevation myocardial infarction. Transthoracic echocardiography showed decreased left ventricular ejection fraction (35%) with disturbed contractility in several segments. The patient was rushed to the catheterization laboratory where coronary angiography revealed a multivessel disease with critical stenosis in the right coronary artery (RCA) and the diagonal branch (Dg) of the left coronary artery (Figure 1A, B). A radial access site was established and PCI of RCA with stent implantation was performed. No periprocedural complications were observed. The patient was planned for delayed coronary intervention in LAD and Dg, again via radial access. During stent implantation, a neurological deterioration with focal deficits was observed (motor weakness of the left upper limb and motor aphasia). After consultation with the neurologist, the patient underwent immediate DynaCT (angiographic CT) (Siemens, Medical Solutions, Erlangen, Germany) followed by an immediate direct cerebral digital subtraction angiogram (cDSA) via the right femoral artery. Intracranial hemorrhage was ruled out (Supplementary material, *Video S1*). Thrombotic occlusion of the right vertebral and basilar arteries was confirmed (Figure 1C). Immediate aspiration thrombectomy and *stent retriever* technique were used to remove the thrombus and restore blood flow. The control angiography confirmed the patency of previously occluded arteries (Figure 1D–F). A control CT one day later excluded further ischemic or hemorrhagic events. The neurological assessment confirmed a good clinical outcome with no focal neurological deficits (2 points on the National Institutes of Health Stroke Scale). Dual antiplatelet therapy was continued.

Our case suggests that immediate direct cerebral digital subtraction angiogram (cDSA) followed by immediate mechanical thrombectomy reduces delay to treatment and might be a safe and feasible treatment option for acute ischemic stroke secondary to PCI. Quick and safe access to this treatment option should be widely provided [2, 5].

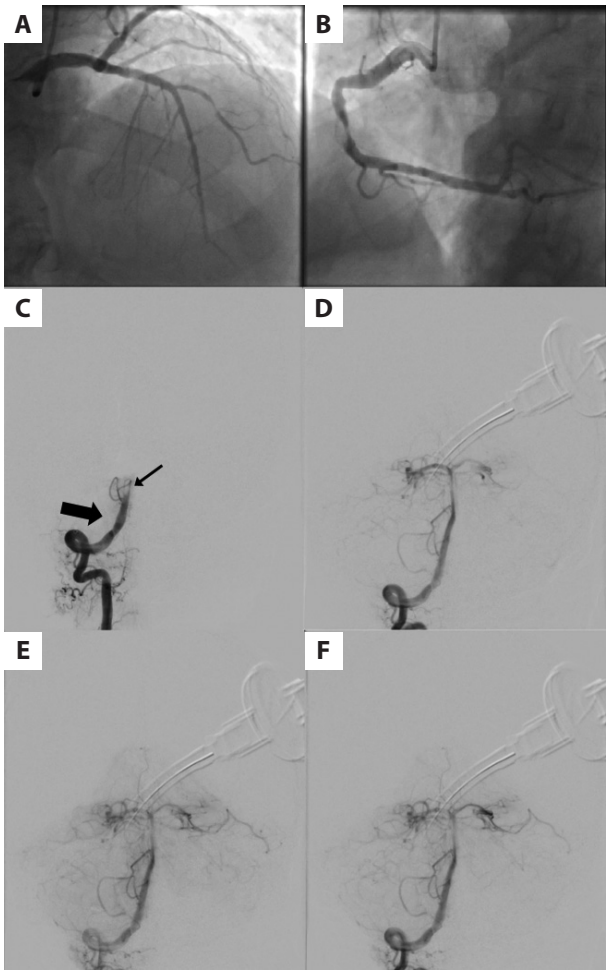

Figure 1. A, B. Coronary angiography and cerebral digital subtraction angiography. **C.** Thick arrow indicates the right vertebral artery. Thin arrow points at thrombus occlusion of the right vertebral and basilar artery. **D**–**F.** The final angiography after mechanical thrombectomy

Supplementary material

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REFERENCES

1. Werner N, Bauer T, Hochadel M, et al. Incidence and clinical impact of stroke complicating percutaneous coronary intervention: results of the Euro heart survey percutaneous coronary interventions registry. Circ Cardiovasc Interv. 2013; 6(4): 362–369, doi: 10.1161/CIRCINTERVENTIONS.112.000170, indexed in Pubmed: 23899872.
2. Hopkins LN. Mechanical thrombectomy for ischemic stroke: a role for cardiology! Kardiol Pol. 2020; 78(7–8): 798–799, doi: 10.33963/KP.15565, indexed in Pubmed: 32844614.
3. Tokarek T, Dziewierz A, Plens K, et al. Radial approach expertise and clinical outcomes of percutanous coronary interventions performed using femoral approach. J Clin Med. 2019; 8(9): 1484, doi: 10.3390/jcm8091484, indexed in Pubmed: 31540442.
4. Dziewierz A, Siudak Z, Tokarek T, et al. Determinants of stroke following percutaneous coronary intervention in acute myocardial infarction (from ORPKI Polish National Registry). Int J Cardiol. 2016; 223: 236–238, doi: 10.1016/j.ijcard.2016.08.214, indexed in Pubmed: 27544594.
5. Goyal M, Menon BK, van Zwam WH, et al. HERMES collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016; 387(10029): 1723–1731, doi: 10.1016/S0140-6736(16)00163-X, indexed in Pubmed: 26898852.

Sacubitril/valsartan as first-line therapy in anthracycline-induced cardiotoxicity

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A 69-year-old female patient was admitted to the cardiology department due to a diagnosis of acute heart failure (AHF). She had a history of chemotherapy due to diffuse large B-cell lymphoma. The patient received the total anthracycline dose of 450 mg/m^2. The last anthracycline chemotherapy was administered two months ago. The patient had no previous history of cardiovascular diseases. On admission, N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and high-sensitivity troponin I (hsTnI) levels were elevated (NT-proBNP: 5987 pg/ml; reference range <125 pg/ml; hsTnI: 74 pg/ml; reference range <14 pg/ml). Coronary angiography excluded vessel narrowing. Echocardiography showed moderate functional mitral regurgitation and severe left ventricular systolic dysfunction. Left ventricular ejection fraction (LVEF) was 24%, and global longitudinal strain (GLS) was 8.1% (Figure 1A). A preliminary diagnosis of anthracycline-induced cardiotoxicity was made. The patient was treated initially with intravenous catecholamines and diuretics. After hemodynamic improvement catecholamines were stopped and intravenous diuretics were switched to oral torasemide 40 mg once daily (OD). Sacubitril/Valsartan (S/V) 24/26 mg twice a day (BID) and bisoprolol 2.5 mg OD were started. During the next few days, hypotension was observed. Bisoprolol was switched to ivabradine 5 mg BID, and diuretics were reduced. Enhanced superveillance including control of diuresis, creatinine, and potassium levels, allowed to maintain the S/V treatment (Table 1). The patient was discharged home with the diagnosis of heart failure with reduced ejection fraction (HFrEF) associated with anthracycline-induced cardiotoxicity. At discharge the patient was in New York Heart Association (NYHA) class III; a 6-minute walk test (6MWT) was 192 m.

After one month, the patient's status was stable and S/V was increased to 49/51 mg BID. At the third-month follow-up the patient was in NYHA class II, and 6MWT distance increased to 384 m. The creatinine and potassium levels were stable, while NT-proBNP and hsTnI levels decreased to 865 pg/ml and 23 pg/ml, respec-

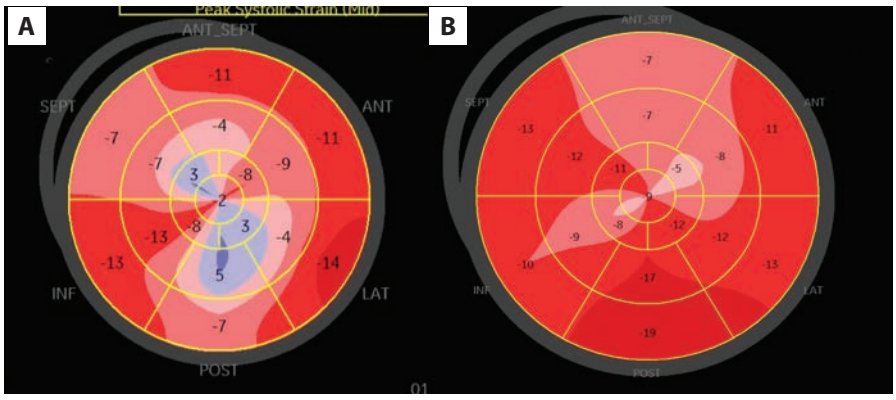

Figure 1. Global longitudinal strain — bull's-eye presentation. **A.** Baseline. **B.** Follow-up

Table 1. Pharmacological treatment, hemodynamics, and laboratory results of the patient during the hospitalization

	Admission	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Discharge
Treatment										
Catecholamines IV	Start			Stop						
Furosemide IV	Start			Stop						
Torasemide 40 mg OD				Start	Reduced (20 mg OD)					
Sacubitril/Valsartan 24/26 mg BID				Start						
Ivabradine 5 mg BID						Start				
Bisoprolol 2.5 mg OD			Start		Stop					
Hemodynamics										
Blood pressure, mm Hg										
Morning	92/78	109/81	111/69	106/73	87/54	93/69	99/67	97/58	101/71	102/61
Evening	102/76	104/78	103/77	97/62	91/62	92/65	92/68	91/52	97/59	
Heart rate, beats/min										
Morning	107	80	85	79	99	79	76	82	60	73
Evening	104	101	88	78	88	89	69	74	72	71
Laboratory investigations										
Potassium, mmol/l	5.1	4.6	3.9	4.1	4.6		4.3		4.5	
Creatinine, µmol/l	97.3	132.6	123.8	123.8	88.4		97.3		88.4	
eGFR, ml/min/1.73m^2	50.2	37.8	39.6	38.4	58.0		50.2		58.0	
Diuresis, ml/24 h		2500	2800	2600	2700	2900	3200	2300		

Abbreviations: BID, twice daily; IV, intravenous; OD, once daily

tively. The left ventricular systolic function improved (LVEF, 42%, GLS, –10.2%; Figure 1B), and mitral regurgitation was only mild.

Our clinical vignette concerns the problem of anthracycline-induced myocardial injury. Cardiotoxicity due to anthracyclines may be acute, early, or late [1]. In our case, we observed the early type (i.e. <1 year since the anthracycline chemotherapy). The previous retrospective studies considered both — early and late types of anthracycline-induced cardiotoxicity as irreversible [2]. However, recent studies showed that early detection and adequate, guideline-directed heart failure treatment could stop or even reverse the progression of cardiac dysfunction [3, 4].

Our case demonstrates that S/V can be initiated immediately after achieving the patient's hemodynamic stability. S/V was administered as the first-line therapy in our patient, instead of angiotensin-converting enzyme inhibitors. The essence of our observation is compliant with the results of the PIONEER-HF trial , which proved the safety and feasibility of early initiation of S/V therapy in hospitalized patients after the AHF episode [5]. Importantly, our case addresses also the central issue of S/V treatment — hypotension. We demonstrated that it could be effectively managed by reducing diuretics dose and switching from beta-blocker to ivabradine. We can conclude that S/V could be safely started as the first-line therapy in patients with anthracycline-induced cardiotoxicity.

Article information

Conflict of interest: AS, WS and RD received lecture honoraria from Novartis.

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REFERENCES

1. Semeraro GC, Lamantia G, Cipolla CM, et al. How to identify anthracycline-induced cardiotoxicity early and reduce its clinical impact in everyday practice. Kardiol Pol. 2021; 79(2): 114–122, doi: 10.33963/KP.15782, indexed in Pubmed: 33506661.
2. Steinherz LJ, Steinherz PG, Tan CT, et al. Cardiac toxicity 4 to 20 years after completing anthracycline therapy. JAMA. 1991; 266(12): 1672–1677, indexed in Pubmed: 1886191.
3. Cardinale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation. 2015; 131(22): 1981–1988, doi: 10.1161/CIRCULATIONAHA.114.013777, indexed in Pubmed: 25948538.
4. Słowik A, Jagielski P, Potocki P, et al. Anthracycline-induced cardiotoxicity prevention with angiotensin-converting enzyme inhibitor ramipril in women with low-risk breast cancer: results of a prospective randomized study. Kardiol Pol. 2020; 78(2): 131–137, doi: 10.33963/KP.15163, indexed in Pubmed: 31995035.
5. Velazquez EJ, Morrow DA, DeVore AD, et al. PIONEER-HF Investigators. Angiotensin-neprilysin inhibition in acute decompensated heart failure. N Engl J Med. 2019; 380(6): 539–548, doi: 10.1056/NEJMoa1812851, indexed in Pubmed: 30415601.

Recurrent pulmonary embolism in a patient after COVID-19 treated with percutaneous and surgical approach

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Evidence shows an increased prevalence of venous thromboembolism (VTE) after coronavirus disease 2019 (COVID-19) [1]. Pulmonary embolism (PE) with acute pressure overload may lead to death. An early diagnosis and therapy are crucial [2].

Catheter-directed therapy (CDT) is a promising alternative to the systemic thrombolysis (ST) pathway (class C/IIa recommendation by the European Society of Cardiology guidelines), but still needs research [3, 4].

A 48-year-old man with a history of arterial hypertension and COVID-19 infection was admitted due to dyspnea and syncopal episodes. He had no history of deep vein thrombosis (DVT), but one day prior to admission he was driving a long distance. Laboratory tests revealed elevated concentrations of D-dimer, cardiac troponin I (cTnI), and N-terminal B-type natriuretic peptide (NT-proBNP). Computed tomography (CT) angiography revealed a massive PE. Echocardiography showed right ventricular (RV) enlargement, shortening of pulmonary acceleration time, flattening of the interventricular septum, and McConnell's sign. Ultrasonography confirmed right popliteal vein thrombosis. Initial treatment with low- molecular-weight heparin (LMWH) was administered. However, 24 hours later, due to symptom worsening, progressing RV failure, and increasing cTnI and NT-proBNP levels, still without cardiogenic shock, the decision to start CDT (as preferred over ST) was made by the multidisciplinary pulmonary embolism response team (PERT). The PERT in our center includes interventional cardiologists, cardiac surgeons, cardiac intensive care cardiologists, and anesthesiologists. CTD was a unanimous decision. The procedure was performed under local anesthesia, via the left femoral vein access. Several passages with the Indigo Aspiration System (Penumbra Inc., Alameda, CA, USA) were done. The system utilizes an aspiration catheter connected to the engine generating negative pressure, and a retractable separator device to clear the thrombus from the catheter tip. Five thousand international units of unfractionated heparin were administered, activated clotting time was above 250 seconds. CDT resulted in a partial thrombus removal but was complicated by wire perforation of a subsegmental branch of the left PA, resulting in hemoptysis. Protamine sulfate was administered and no bleeding site was detected by angiography. After the procedure, LMWH was initially reduced but reintroduced at a full therapeutic dose over the next 24 hours since no signs of active bleeding occurred. The patient's condition and RV function were improving. However, four days later, the patient developed symptoms of cardiogenic shock with tachycardia, hypotension, and hypoxemia, with a need for inotropic and vasopressor support, and echocardiographic signs of PE recurrence. The PERT decided on surgical embolectomy and subsequently inferior vena cava (IVC) filter implantation and excluded ST due to bleeding risk. The periprocedural course was uncomplicated. The therapeutic dose of LMWH was maintained. Laboratory, genetic, and imaging testing ruled out cancer, inherited thrombophilia, antiphospholipid syndrome, autoimmune diseases, but confirmed methylenetetrahydrofolate reductase gene mutation (*677C>T*), which in addition to COVID-19 might provoke DVT. Echocardiography showed improved RV function. The six-month follow-up was free of VTE events.

In our opinion, the PERT-guided approach improves communication between specialists who provide complex care and facilitates difficult decisions making, including risk stratification, and therefore rapid redirection of therapeutic strategies. In patients with bleeding due to CDT and subsequent anticoagulation

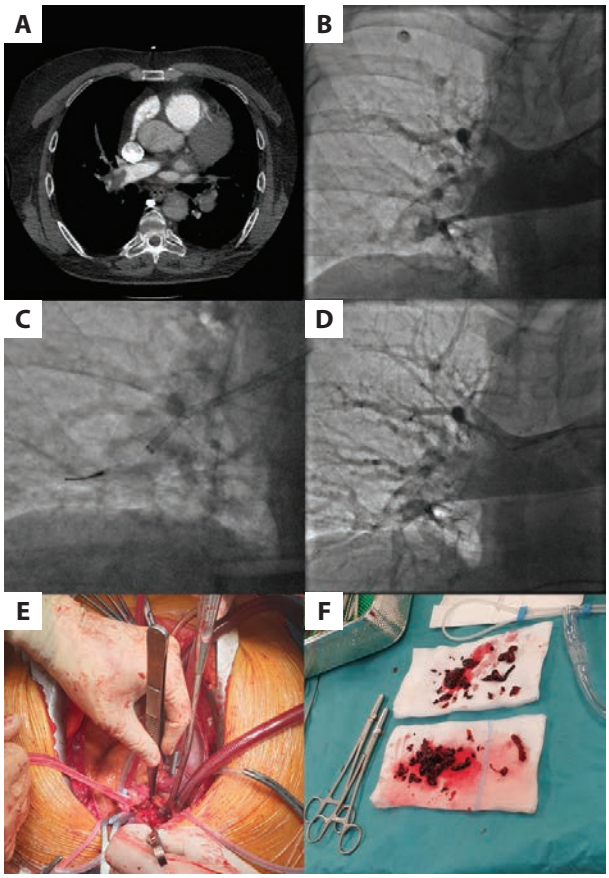

Figure 1. A. Computed tomographic pulmonary angiography. **B.** Pulmonary angiography prior to thrombectomy. **C.** Pulmonary thrombectomy — Indigo Aspiration System. **D.** Pulmonary angiography after thrombectomy. **E–F.** Surgical embolectomy

stopping, IVC filter implantation may be considered to avoid recurrence of PE.

Article information

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REFERENCES

1. Sakr Y, Giovini M, Leone M, et al. Pulmonary embolism in patients with coronavirus disease-2019 (COVID-19) pneumonia: a narrative review. Ann Intensive Care. 2020; 10: 124, doi: 10.1186/s13613-020-00741-0, indexed in Pubmed: 32953201.
2. Dilektasli AG, Demirdogen Cetinoglu E, Acet NA, et al. Catheter-directed therapy in acute pulmonary embolism with right ventricular dysfunction: a promising modality to provide early hemodynamic recovery. Med Sci Monit. 2016; 22: 1265–1273, doi: 10.12659/msm.897617, indexed in Pubmed: 27081754.
3. Avgerinos ED, Abou Ali A, Toma C, et al. Catheter-directed thrombolysis versus suction thrombectomy in the management of acute pulmonary embolism. J Vasc Surg Venous Lymphat Disord. 2019; 7(5): 623–628, doi: 10.1016/j.jvsv.2018.10.025, indexed in Pubmed: 30902560.
4. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): the task force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Heart J. 2019; 54(3): 1901647, doi: 10.1183/13993003.01647-2019, indexed in Pubmed: 31473594.

Percutaneous coronary intervention of a tortuous and complex circumflex lesion using the robotic CorPath GRX system

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Robotic-assisted percutaneous coronary interventions (R-PCI) dramatically reduce physician radiation exposure and potential musculoskeletal injuries [1]. In addition, accumulating evidence has demonstrated R-PCI safety and efficacy in a broad range of lesion types [2, 3].

We report the first case of R-PCI performed in Poland using the CorPath GRX (Corindus Vascular Robotics) system (Supplementary material, *Figures S1* and *S2*) to treat a complex tortuous lesion of the left circumflex (Cx) artery.

A 47-year-old male with previous PCI to the left anterior descending artery (LAD) was referred with worsening typical angina (Canadian Cardiovascular Society class III). Echocardiography revealed hypokinesia in the basal and mid-segments of the inferior and posterior wall. Diagnostic angiography revealed a short left main stem (LMS) and a tortuous circumflex (Cx) artery with a critical lesion in the mid-vessel (Figure 1A) associated with a separate critical lesion in the 1st obtuse marginal (OM) branch (Figure 1B). The right coronary artery was hypoplastic and the LAD stent was patent with no significant other lesions. A provisional strategy was planned to treat the disease in the Cx/OM1.

Six Fr right radial access was secured and the operator manually cannulated the LMS with a 6 Fr AL1 guiding catheter. Following successful and stable cannulation, the guiding catheter was connected to the robotic arm, and the rest of the procedure was completed from the remote workstation (Supplementary material, *Figure S3*). A Runthrough NS Floppy wire (Terumo systems, Somerset, NJ, USA) was selected and robotically advanced to the distal vessel, with the tortuosity and diseased segment successfully navigated using a combination of manual joystick controls and pre-set automation techniques (Figure 1C). A 2.5 × 27 mm non-compliant (NC) balloon was used to pre-dilate the lesion. Precise measurement (1 mm precision) of the lesion length was performed using the robotic system and accordingly a 3.0 × 38 mm drug-eluting stent (Promus PREMIER, Boston Scientific, Marlborough, MA, USA) was advanced and successfully implanted at the intended site (Figure 1D). Post-dilatation of the proximal portion of the stent was performed with a 3.5 × 15 mm NC balloon. Following main vessel stenting, the main vessel wire was retracted and robotically advanced into the OM1 branch which was treated with balloon-only angioplasty using a 2.0 × 12 mm NC inflated at 10 atm (Figure 1E).

Final angiography revealed a good angiographic result, optimal stent expansion with no complications (Figure 1F). Fluoroscopy time was 22 minutes, radiation dose was 943 mGy and total contrast volume was 150 ml.

This case demonstrates how the R-PCI system can be used to safely and successfully treat complex lesions. Despite the lack of haptic feedback, wiring of this tortuous vessel was achieved using the joystick controls manually aided by the built-in automated robotic movements. The CorPath GRX system can accommodate multiple coronary wires and devices simultaneously. In such instances, one wire and one device are allocated to the active

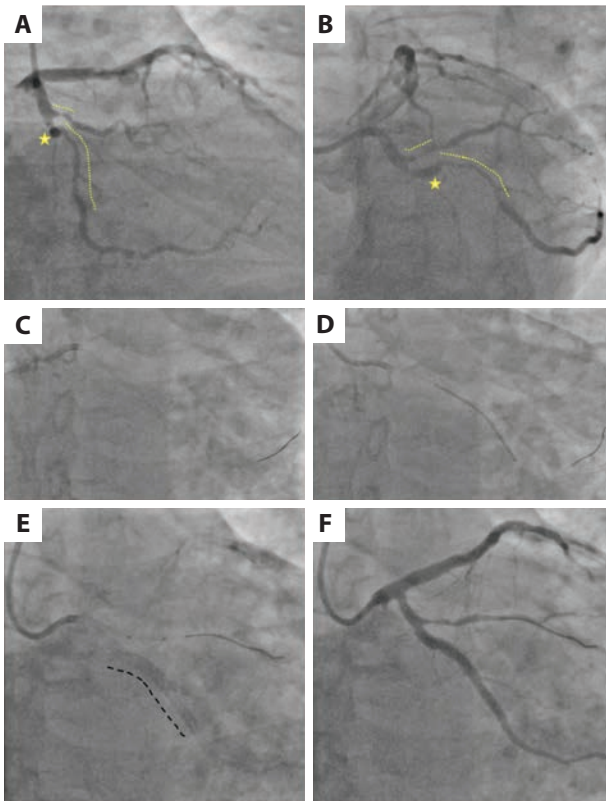

Figure 1. Robotic-assisted percutaneous coronary interventions (R-PCI) of the tortuous complex circumflex lesion. Baseline angiography (**A–B**) demonstrates the critical lesions (yellow dotted lines) in the mid circumflex artery and proximal segment of the 1st marginal branch. The tortuous segment of the vessel (yellow star) arises just before the critical lesion in the mid-vessel. Through a 6 Fr amplatz left guiding catheter a 0.014" coronary wire was advanced distally (**C**) using the robotic controls and following pre-dilatation, the stent was advanced and deployed (**D–E**) in the intended position (dashed black line). The marginal lesion was wired and treated with balloon angioplasty (**E**) using the robotic controls. The final result (**F**) was optimal without any angiographic complications

drive and can be controlled from the console, whilst the remaining wires and devices cannot be maneuvered but remained fixed in the passive drive. This can enable operators to treat complex lesions including bifurcations and perform final kissing inflations when required. The presence of a short LMS required repeated repositioning and stabilization maneuvers of the guiding catheter, which were all performed using the guide catheter joystick control. During initial wiring, the guide catheter disengaged into the aorta with subsequent loss of wire position. With the robotic controls, the guide catheter was safely manipulated back into a more stable position achieving semi-selective cannulation of the Cx artery.

Worldwide experience with R-PCI systems is growing, enabling increasingly complex coronary lesions to be treated safely and effectively, without compromising procedural time, and with improved operator safety [4, 5]. In our case, the primary operator completed the entire procedure without wearing any radioprotection sat at the robotic console, which was located within the operating room.

Supplementary material

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

Article information

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REFERENCES

1. Maor E, Eleid MF, Gulati R, et al. Current and future use of robotic devices to perform percutaneous coronary interventions: a review. J Am Heart Assoc. 2017; 6(7): e006239, doi: 10.1161/JAHA.117.006239, indexed in Pubmed: 28739860.
2. Weisz G, Metzger DC, Caputo RP, et al. Safety and feasibility of robotic percutaneous coronary intervention: PRECISE (Percutaneous Robotically-Enhanced Coronary Intervention) Study. J Am Coll Cardiol. 2013; 61(15): 1596–1600, doi: 10.1016/j.jacc.2012.12.045, indexed in Pubmed: 23500318.
3. Caputo R, Lesser A, Fischi M, et al. Safety and feasibility of robotic PCI utilizing radial arterial access. J Am Coll Cardiol. 2015; 65(10): A203, doi: 10.1016/s0735-1097(15)60203-0.
4. Kapur V, Smilowitz NR, Weisz G. Complex robotic-enhanced percutaneous coronary intervention. Catheter Cardiovasc Interv. 2014; 83(6): 915–921, doi: 10.1002/ccd.25271, indexed in Pubmed: 24167108.
5. Naghi J, Harrison J, Ang L, et al. Robotic versus manual percutaneous coronary intervention: effect on procedure time for simple and complex lesions. J Am Coll Cardiol. 2016; 67(13): 229, doi: 10.1016/s0735-1097(16)30230-3.

When Takayasu mimics pulmonary hypertension — severe pulmonary artery stenosis — what to do?

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A 27-year-old female, without a history of cardiac diseases, with increasing fatigue and dyspnea, up to class IV of New York Heart Association (NYHA) during the previous two weeks, was admitted to the cardiology department with suspicion of pulmonary arterial hypertension (PAH).

On admission, the patient presented resting dyspnea, tachycardia 120 bpm, and blood pressure 100/60 mm Hg. Capillary blood oxygen saturation was 80%. A loud systolic murmur was present over the entire chest. Physical examination did not reveal peripheral edema nor features of venous thromboembolism in the lower extremities.

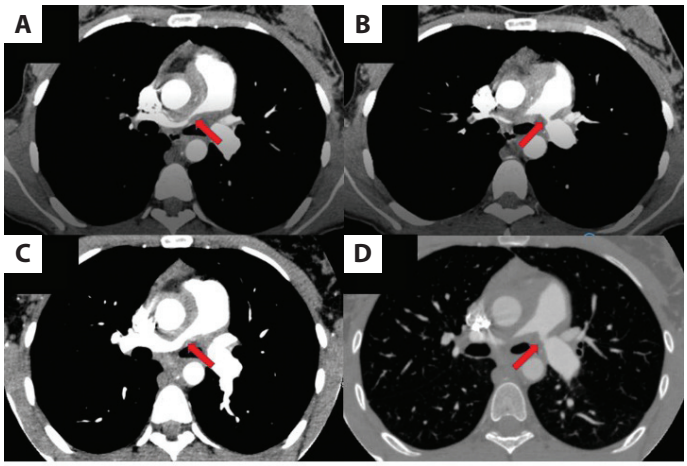
Laboratory tests revealed amino-terminal pro-brain natriuretic peptide of 10745 pg/ml (n = 0–125 pg/ml), increased inflammatory parameters (C-reactive protein 25 mg/l; white blood cells 13 × 10^3/μl), serum concentration of IgG4 of 60 mg/dl. Echocardiography showed the overload of the right ventricle, tricuspid annulus dilatation with torrential regurgitation. Calculated systolic pulmonary artery pressure was 110 mm Hg. Computed tomography angiography (angio-CT) scan revealed inflammatory infiltration of the pulmonary trunk, involving the pulmonary arteries and causing critical stenoses (Figure 1A–B). No embolic material was found on the scan.

Based on clinical and angiographic criteria proposed by the Japanese Research Committee on Vasculitis Syndromes [1], the initial diagnosis of Takayasu arteritis (TA) was stated. These criteria included: (1) angiographic evidence of narrowing or occlusion of the aorta or large arteries on CT or magnetic resonance imaging; (2) early age of onset; (3) presence of inflammatory markers; and (4) exclusion of atherosclerosis, other inflammatory diseases, or congenital vascular abnormalities.

The patient received 15 mg of prednisone per day and two intravenous infusions of 400 mg cyclophosphamide, achieving resolution of resting dyspnea. During the next 6 months, the patient received a total dose of 4.8 g cyclophosphamide and achieved total remission of clinical symptoms. Control angio-CT scan showed substantial regression of stenosis (Figure 1C–D). Figure 1E shows control parameters. Further hospitalizations were planned to perform imaging examinations and evaluate the effects of the treatment.

TA is a large-vessel vasculitis affecting the aorta and its primary branches: subclavian artery (33.7%), the renal artery (25.3%), and the common carotid artery (21.7%); the pulmonary artery comprised only 0.8%. Inflammatory processes in the acute phase cause thickening of the arterial wall. The chronic phase causes vascular fibrosis, stenosis, and occlusion, resulting in congestive heart failure and pulmonary hypertension [1].

We present a rare case of TA involving pulmonary arteries that clinically mimicked signs of severe PAH. Clinical presentation: age, sex, symptoms, amino-terminal pro-brain natriuretic peptide (NT-proBNP) level, and echocardiographic signs suggested PAH. Detailed echocardiographic assessment and the CT-scan allowed to reveal that the PAH-like features of right ventricular overload were due to severe pulmonary arteries stenosis. In the differential diagnosis, it was essential to exclude another inflammatory artery stenosis, mainly giant cell arteritis (GCA). While TA is seen in young females, GCA affects older patients. In GCA, inflammation processes often involve the external carotid artery, which is not seen in TA. Arterial wall thickening can be due to retroperitoneal fibrosis and therefore mimics TA, but TA lacks peritoneal diffusion [2]. IgG4 related



E

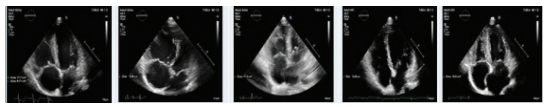
	Initial hospitalization	Control after 1 month	Control after 2 months	Control after 4 months	Control after 6 months
NYHA class	IV	III/IV	II	I	I
NT-proBNP, pg/ml	10749→4946	11087→3138	1326	607	496
RVOT, mm	48	46→40	32	26	30
RVID, mm	44	47→44	39	34	33
LVEDD, mm	38	37→40	36	41	44
LVESD, mm	18	17→23	21	23	26
RVSP, mm Hg	110	131→94	80	52	30
AcT, ms	77	78→87	95	110	150
Pericardial effusion, mm	6	4	0	0	0
6-MWT distance, m	0	110	320	440	500
Total dose of cyclophosphamide, mg	800	1800	2800	3800	4800
Echocardiography					

Figure 1. Contrast-enhanced computed tomography (CT). The initial angio-CT scan showed critical stenosis in pulmonary arteries, causing 99% narrowing of the lumen of the right pulmonary artery (RPA) (**A**, red arrow) and 95% of the left pulmonary artery (LPA) (**B**, red arrow). Control angio-CT scan after 6 months showed substantial regression of stenosis in both RPA (**C**, red arrow) and LPA (**D**, red arrow). **E.** Clinical, laboratory, and echocardiography parameters according to the total dose of cyclophosphamide in subsequent hospitalizations

Abbreviations: 6-MWT, 6-minute walking test; AcT, acceleration time; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; NT-proBNP, amino-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association class; RVIT, right ventricular inflow tract; RVOT, right ventricular outflow tract; RVSP, right ventricular systolic pressure

disease was also taken into consideration. With a serum concentration of IgG4 of 60 mg/dl, it was unlikely (96% negative predictive value) [3].

The first line of treatment for TA is glucocorticoids. Half of the patients require second-line agents: cyclophosphamide, methotrexate, or biologic drugs [4]. Endovascular or surgical interventions in artery stenosis may be necessary once irreversible stenosis starts to develop. Since the rates of complications are the highest in patients with acute inflammatory lesions, interventional therapy should be avoided during the acute phase of the disease [5].

Article information

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REFERENCES

1. Keser G, Aksu K, Direskeneli H. Takayasu arteritis: an update. Turk J Med Sci. 2018; 48(4): 681–697, doi: 10.3906/sag-1804-136, indexed in Pubmed: 30114347.
2. Zhang YH, Song WM, Wu M, et al. Initial isolated Takayasu's arteritis of bilateral pulmonary artery branches. Rev Bras Reumatol. 2017; 57(6): 626–629, doi: 10.1016/j.rbr.2015.10.002, indexed in Pubmed: 26920538.
3. Carruthers MN, Khosroshahi A, Augustin T, et al. The diagnostic utility of serum IgG4 concentrations in IgG4-related disease. Ann Rheum Dis. 2015; 74(1): 14–18, doi: 10.1136/annrheumdis-2013-204907, indexed in Pubmed: 24651618.
4. Bartczak-Rutkowska A, Trojnarska O, Ciepłucha A, et al. Enlarging aneurysm of the ascending aorta in a pregnant woman with Takayasu arteritis. Kardiol Pol. 2020; 78(1): 82–83, doi: 10.33963/KP.15059, indexed in Pubmed: 31724561.
5. Duan Y, Zhou X, Su H, et al. Balloon angioplasty or stent implantation for pulmonary vein stenosis caused by fibrosing mediastinitis: a systematic review. Cardiovasc Diagn Ther. 2019; 9(5): 520–528, doi: 10.21037/cdt.2019.09.14.

Cardiovascular drug therapy and surrogate COVID-19 outcomes: which is the impact of the "miraculous" sodium--glucose co-transporter-2 inhibitors?

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TO THE EDITOR

We really appreciated the results of the observational study conducted by Terlecki et al. [1], who demonstrated that, in a total of 1729 patients admitted to hospital due to coronavirus disease 2019 (COVID-19), history of diabetes mellitus significantly increased the odds of in-hospital death by 53%, while those patients with concomitant heart failure (HF) experienced a two-fold increase in the corresponding odds. Researchers have also shown in their cohort that prior treatment with renin-angiotensin-aldosterone system blockers, statins, antiplatelet drugs, or beta-blockers was associated with a significant decrease in the odds of in-hospital death, confirming a protective role of these drug classes against the most surrogate COVID-19 outcome [1].

Recently, there has been a vivid and ongoing discussion concerning the place of sodium--glucose co-transporter-2 (SGLT-2) inhibitors in the therapeutic management of patients with COVID-19 [2]. This drug class has an established role in the treatment of type 2 diabetes mellitus, while it has gained significant ground in the treatment armamentarium against HF, especially in patients with HF with reduced ejection fraction (HFrEF), even without concomitant type 2 diabetes mellitus [3].

According to a recently published nationwide cohort study from the National Diabetes Audit in England, prescription of SGLT-2 inhibitors is associated with a significant decrease in the risk for COVID-19 related death by 18% [4]. However, relevant data remain scarce and conflicting, as far as pathophysiologic background is concerned, and thus, further research on this field is required [5].

Therefore, it would be very interesting and would increase a value of the initial report, if Terlecki et al. [1] could provide data concerning the usage rates of SGLT-2 inhibitors in their cohort and the association with crude outcomes, such as mechanical ventilation and in-hospital death, since this "miraculous" drug class has attracted scientific interest, with an established role in the secondary prevention of cardiovascular disease. Data from such real-world studies may influence decision-making and improve therapeutic strategy if we confront another COVID-19 pandemic wave in the near future.

Article information

Conflict of interest: None declared.

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REFERENCES

1. Terlecki M, Wojciechowska W, Klocek M, et al. Association between cardiovascular disease, cardiovascular drug therapy, and in-hospital outcomes in patients with COVID-19: data from a large single-center registry in Poland. Kardiol Pol. 2021; 79(7–8): 773–780, doi: 10.33963/KP.15990, indexed in Pubmed: 33926173.
2. Scheen AJ. SGLT2 inhibition during the COVID-19 epidemic: Friend or foe? Diabetes Metab. 2020; 46(5): 343–344, doi: 10.1016/j.diabet.2020.06.003, indexed in Pubmed: 32562762.
3. Nessler J, Siniarski A, Leszek P, et al. Expert opinion of the Heart Failure Working Group of the Polish Cardiac Society on the use of dapagliflozin in the treatment of heart failure with reduced ejection fraction. Kardiol Pol. 2021; 79(3): 363–370, doi: 10.33963/KP.15859, indexed in Pubmed: 33687868.
4. Khunti K, Knighton P, Zaccardi F, et al. Prescription of glucose-lowering therapies and risk of COVID-19 mortality in people with type 2 diabetes: a nationwide observational study in England. Lancet Diabetes Endocrinol. 2021; 9(5): 293–303, doi: 10.1016/S2213-8587(21)00050-4, indexed in Pubmed: 33798464.
5. Patoulias D, Papadopoulos C, Katsimardou A, et al. Sodium-glucose cotransporter 2 inhibitors and major COVID-19 outcomes: promising mechanisms, conflicting data, and intriguing clinical decisions. Diabetes Ther. 2020; 11(12): 3003–3005, doi: 10.1007/s13300-020-00942-7, indexed in Pubmed: 33052538.

Cardiovascular drug therapy and surrogate COVID-19 outcomes: which is the impact of the "miraculous" sodium--glucose co-transporter-2 inhibitors? Author's reply

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We would like to thank for the interest in our article. It has been confirmed in numerous studies that COVID-19 can lead to increased risk of a poor outcome, which is particularly expressed in patients with older age and co-existing cardiometabolic comorbidities [1]. We confirmed in our study that older age, type 2 diabetes mellitus (DM), and heart failure were associated with worse in-hospital prognosis in patients hospitalized for COVID-19 [2].

We must admit that still there is a lack of specific therapy for COVID-19, despite the fact that numerous drugs have been studied. Since the beginning of the pandemic, the safety and efficacy of drugs dedicated to patients with cardiometabolic comorbidities have attracted interest. In our analysis, we confirmed that in patients hospitalized for COVID-19, prior treatment with renin-angiotensin system blockers, statins, antiplatelet drugs, or beta-blockers was associated with a significant decrease in the odds of in-hospital death [2], however, due to the observational nature of the study, it does not prove the causal association.

During several months of the pandemic, we have witnessed the change in the treatment standards of COVID-19 which have resulted in lower rates of complications (i.e. low-molecular-weight heparin in the prevention of thromboembolic events, steroids in patients requiring oxygen therapy, etc.). However, there is still a profound need to improve the standard of care in order to achieve faster and more complete recovery with an additional reduction of cases with fatal outcomes.

We agree with Patoulias et al. that theoretically there might be a place for sodium-glucose co-transporter-2 (SGLT-2) inhibitors in the management of patients with COVID-19 [3]. SGLT-2 inhibitors are not only antidiabetic drugs but it has been proven that this group improves prognosis in populations similar to those at risk for COVID-19 worse outcome, i.e. patients with DM and in subjects with heart failure, chronic kidney disease, and atherosclerotic cardiovascular disease [1, 4]. Treatment using SGLT-2 inhibitors is recommended by the latest 2021 Acute and Chronic Heart Failure Guidelines of the European Society of Cardiology. Therefore, investigation of the efficacy and safety profile of these agents in patients with COVID-19 is warranted.

In our study, we analyzed clinical data from 1729 patients. In this cohort, there were only 26 patients (1.5% of the entire cohort) with prior treatment with SGLT-2 inhibitors. We must acknowledge that it is insufficient to draw reliable conclusions. However, currently, we have available data of a larger group, i.e., 3391 patients hospitalized in our hospital for COVID-19. In this cohort, there were 65 patients (1.9%) treated with SGLT-2 inhibitors. In this group: 60 (92.3%) patients had DM, 9 (13.8%) had heart failure, 13 (30.0%) had ischemic heart disease, and 2 (3.1%) had chronic kidney disease.

If we take into consideration the highly beneficial impact of SGLT-2 inhibitors in patients with pre-existing cardiometabolic disorders, we must acknowledge that the prescription rate of these drugs in real life was lower than should have been expected. Of note, a low proportion of patients with diabetes on SGLT-2 inhibitors should be attributed mainly to a very limited reimbursement of these drugs in Poland, thus,

most type 2 diabetes patients have to pay for them out of pocket. At the beginning of the pandemic there was a concern about the safety profile of SGLT-2 inhibitors in patients with COVID-19, however, currently, there are data confirming their satisfactory safety profile in patients infected with SARS-CoV-2 [5].

In our cohort, we observed better outcomes among patients treated with SGLT-2 inhibitors (n = 65), as compared to non-treated (n = 3326). There were no in-hospital deaths in patients treated with SGLT-2, while in the rest of the cohort 354 (10.4%) patients died. We found lower frequency of need for mechanical ventilation (2 [0.1%] vs 351 [10.3%]; $P = 0.027$) in patients treated with SGLT-2 inhibitors. There was no significant difference in the need for intensive care unit hospitalization between SGLT-2 inhibitors users and non-users (5 [0.2%] vs 402 [11.8%]; $P = 0.19$). The low number of patients treated by SGLT2 inhibitors, the retrospective, observational nature of our analysis makes it prone to typical methodological problems, for example, selection bias related to higher eGFR among SGLT2 inhibitor users due to the SPC details in 2020 and beginning of 2021. Thus, the presented results should be treated with caution.

However, looking at our results, we should at least consider the continuation of SGLT-2 inhibitors in subjects with pre-existing indications for those medications. The mechanism of SGLT-2 inhibitor's action, the results of prior studies, and our findings indicate that further exploration is needed to fully establish the role of SGLT-2 inhibitors on COVID-19 course and outcome.

Article information

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REFERENCES

1. Grasselli G, Zangrillo A, Zanella A, et al. COVID-19 Lombardy ICU Network. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA. 2020; 323(16): 1574–1581, doi: 10.1001/jama.2020.5394, indexed in Pubmed: 32250385.
2. Terlecki M, Wojciechowska W, Klocek M, et al. Association between cardiovascular disease, cardiovascular drug therapy, and in-hospital outcomes in patients with COVID-19: data from a large single-center registry in Poland. Kardiol Pol. 2021; 79(7–8): 773–780, doi: 10.33963/KP.15990, indexed in Pubmed: 33926173.
3. Patoulias D, Papadopoulos C, Katsimardou A, et al. Sodium-glucose cotransporter 2 inhibitors and major COVID-19 outcomes: promising mechanisms, conflicting data, and intriguing clinical decisions. Diabetes Ther. 2020; 11(12): 3003–3005, doi: 10.1007/s13300-020-00942-7, indexed in Pubmed: 33052538.
4. Lopaschuk GD, Verma S. Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors: a state-of-the-art review. JACC Basic Transl Sci. 2020; 5(6): 632–644, doi: 10.1016/j.jacbts.2020.02.004, indexed in Pubmed: 32613148.
5. Kosiborod M, Berwanger O, Koch GG, et al. Effects of dapagliflozin on prevention of major clinical events and recovery in patients with respiratory failure because of COVID-19: design and rationale for the DARE-19 study. Diabetes Obes Metab. 2021; 23(4): 886–896, doi: 10.1111/dom.14296, indexed in Pubmed: 33319454.

Spontaneous coronary artery dissection: practical considerations in management

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TO THE EDITOR

Over recent years, spontaneous coronary artery dissection (SCAD) has gained a substantial reputation as a specific form of coronary artery disease affecting mostly young females [1–3]. Pathologically, it is defined as a separation between the intima and media layers in epicardial coronary arteries (mostly the left anterior descending [LAD] artery) in the absence of traumatic and iatrogenic triggers [1–3]. On invasive coronary angiogram (CAG), this phenomenon might present with a variety of patterns including characteristic dissection flap (type-1), intramural hematoma (type-2 and 3), and a total occlusion (type-4) [1]. In their recently published expert opinion paper, Kądziela et al. [1] have presented a didactic overview of current information on SCAD and its management. In this context, we would like to place more emphasis on certain aspects of SCAD management, based on our perspectives and experiences.

First, we agree with the authors that management of SCAD with invasive strategies (mostly percutaneous coronary interventions [PCIs]) should be the preferred option in the case of high-risk features, including hemodynamic instability, malignant arrhythmias, and persistent ischemia [1, 2]. However, the existing high-risk anatomy features (for instance, SCAD involving the proximal LAD), unlike other high-risk features, might not be regarded as an indication for urgent management. Accordingly, a 'deferred PCI' strategy (planned a few days or a week later following an admission) might arise as a viable option, particularly in the case of challenging type-1 SCAD (spiral or long dissection, etc.), involving anatomically high-risk coronary segments. This delayed strategy might significantly enhance the success of PCI, and it significantly diminishes complication rates due to the partially regressed false lumen at the time of deferred intervention. Importantly, strict control of blood pressure and heart rate, along with the administration of glycoprotein IIb/IIIa inhibitors, heparin, and dual antiplatelet therapy (DAPT), generally prevent potential complications (SCAD thrombosis or propagation) [1, 2] until the time of deferred PCI. However, SCAD involving the left main coronary artery (LMCA), even if clinically silent, should be regarded as an exception that requires urgent intervention due to its life-threatening risks [1, 2].

Second, SCAD might occasionally extend to the proximal aorta during coronary interventions [4] or spontaneously. Notably, the absence of atherosclerosis generally facilitates retrograde SCAD propagation [2], potentially leading to an extensive aortic involvement. Importantly, patients with SCAD involving the LMCA or the osteal right coronary artery (RCA) should be particularly evaluated in terms of co-existing aortic dissection with further imaging modalities (computed tomography [CT], etc.). In this context, extensive involvement of aorta and/or aortic dilatation strongly favor urgent aortic repair and coronary artery bypass grafting rather than PCI [4]. More alarmingly, the use of glycoprotein IIb/IIIa inhibitors or thrombolytic therapy in SCAD patients with a missed aortic dissection might result in catastrophic complications (including an aortic rupture). Taken together, a high index of suspicion for aortic involvement is mandatory in the setting of SCAD, particularly involving the LMCA or the osteal RCA.

Third, preferential use of cutting balloons might be regarded as a routine strategy in the case of type-2 and type-3 SCADs [5]. Technically,

cutting balloons potentially allow drainage of intramural hematoma [1] into the true lumen (through the creation of intimal microfenestrations), and generally obviate the need for subsequent stent implantation with lifetime complication risks in this young population [5]. This is of paramount importance particularly in the case of type-2 SCAD that requires long or multiple stent implantations.

Finally, severe degrees of myocardial wall motion abnormalities (including akinesia, etc.) might potentially be attributable to post-ischemic myocardial stunning [3] that might persist for variable durations even after complete recovery of SCAD and eventually vanish in time. Therefore, an assessment of myocardial viability with nuclear imaging, etc. might differentiate between myocardial necrosis and reversible stunning in severely affected myocardial segments associated with SCAD. It might help guide subsequent management strategies (including decision-making for cardiac device implantation).

More interestingly, takotsubo syndrome (TTS) might potentially co-exist with SCAD, mostly due to the common trigger of these entities including severe stressors [3]. Moreover, this co-existence might have prognostic and therapeutic implications (attributable to more severe adrenergic discharge, etc.) [3]. For instance, SCAD in association with TTS might be particularly prone to vascular complications, including dissection propagation, and hence it warrants an early intervention, even in the absence of high-risk features [3].

In summary, SCAD management might be regarded as a multi-faceted phenomenon. Notably, meticulous evaluation of clinical details might significantly impact the management and prognosis of patients with SCAD.

The authors chose not to respond.

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REFERENCES

1. Kądziela J, Kochman J, Grygier M, et al. The diagnosis and management of spontaneous coronary artery dissection — expert opinion of the Association of Cardiovascular Interventions (ACVI) of Polish Cardiac Society. Kardiol Pol. 2021; 79(7–8): 930–943, doi: 10.33963/KP.a2021.0068, indexed in Pubmed: 34292564.
2. Giacoppo D, Capodanno D, Dangas G, et al. Spontaneous coronary artery dissection. Int J Cardiol. 2014; 175(1): 8–20, doi: 10.1016/j.ijcard.2014.04.178, indexed in Pubmed: 24861255.
3. Yalta K, Ucar F, Yilmaztepe M, et al. Tako-tsubo cardiomyopathy and spontaneous coronary artery dissection: A subtle association with prognostic implications? Int J Cardiol. 2016; 202: 174–176, doi: 10.1016/j.ijcard.2015.08.152, indexed in Pubmed: 26397404.
4. Hayashi Y, Taoka M, Osaka S, et al. Iatrogenic acute aortic dissection caused by intervention for spontaneous coronary artery dissection: a surgical case report. J Cardiothorac Surg. 2020; 15(1): 280, doi: 10.1186/s13019-020-01333-6, indexed in Pubmed: 32993807.
5. Sharma H, Vetrugno V, Khan SQ. Successful treatment of a spontaneous right coronary artery dissection with a 4-mm diameter cutting balloon: a case report. Eur Heart J Case Rep. 2019; 3(4): 1–6, doi: 10.1093/ehjcr/ytz212, indexed in Pubmed: 31912001.

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Polfenon®

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Polfenon *(Propafenonum)*. **Skład i postać:** Każda tabletka powlekana zawiera 150 mg lub 300 mg propafenonu chlorowodorku oraz substancję pomocniczą o znanym działaniu, odpowiednio: 1,43 mg lub 2,86 mg laktozy jednowodnej. **Wskazania:** Objawowe tachyarytmie nadkomorowe: częstoskurcz węzłowy; częstoskurcz nadkomorowy u pacjentów z zespołem Wolfa-Parkinsona-White'a (WPW); napadowe migotanie przedsionków. Zagrażająca życiu, ciężka, objawowa tachyarytmia komorowa. **Dawkowanie i sposób podawania:** Leczenie tachyarytmii komorowych powinno przebiegać w warunkach szpitalnych. Lek należy podawać po posiłku, popijając niewielką ilością płynu. Dawkę należy ustalać indywidualnie dla każdego pacjenta, zależnie od jego potrzeb i odpowiedzi terapeutycznej. Należy podawać najmniejszą skuteczną dawkę leku. Dorośli W okresie ustalania dawki oraz w leczeniu podtrzymującym u pacjentów o masie ciała około 70 kg, zalecana dawka dobowa propafenonu chlorowodorku wynosi 450 do 600 mg, podawana w 2 lub 3 dawkach podzielonych. Niekiedy może być konieczne zwiększanie dawki dobowej propafenonu chlorowodorku, nie częściej niż co 3 - 4 dni, do 900 mg, pod warunkiem ścisłej kontroli kardiologicznej. U pacjentów z mniejszą masą ciała stosować mniejsze dawki dobowe. W razie wystąpienia znacznego poszerzenia zespołu QRS lub bloku przedsionkowo-komorowego II°lub III° należy rozważyć zmniejszenie dawki. Indywidualną dawkę podtrzymującą należy ustalać pod kontrolą kardiologiczną, obejmującą monitorowanie zapisu EKG i wielokrotny pomiar ciśnienia tętniczego krwi (faza ustalania dawki). Dzieci i młodzież Nie ustalono bezpieczeństwa i skuteczności stosowania produktu leczniczego u dzieci i młodzieży poniżej 18 lat. Ze względu na moc, produktu nie należy stosować u dzieci i młodzieży. Pacjenci w podeszłym wieku U pacjentów w podeszłym wieku oraz u pacjentów z istotnymi zaburzeniami czynności lewej komory (frakcja wyrzutowa <35%) lub z uszkodzeniem mięśnia sercowego leczenie należy rozpocząć od małych dawek, zwiększając dawkę ze szczególną ostrożnością, stopniowo i o małe ilości. Tak samo należy postępować w tracie leczenia podtrzymującego. Zwiększenia dawki, jeśli to konieczne, można dokonywać nie wcześniej niż po 5 do 8 dniach leczenia. Niewydolność nerek i (lub) wątroby U pacjentów z niewydolnością nerek i (lub) wątroby po podaniu standardowych dawek leczniczych dojść może do kumulacji leku. U tych pacjentów indywidualne ustalanie dawki propafenonu chlorowodorku wymaga kontroli zapisu EKG i stężenia propafenonu w osoczu. **Przeciwwskazania:** Nadwrażliwość na substancję czynną, soję, orzeszki ziemne lub na którąkolwiek substancję pomocniczą. Rozpoznany zespół Brugadów. Istotna klinicznie strukturalna choroba serca, taka jak: zawał mięśnia sercowego w ciągu ostatnich 3 miesięcy, niewyrównana zastoinowa niewydolność serca, z frakcją wyrzutową lewej komory poniżej 35%, wstrząs kardiogenny, z wyłączeniem wstrząsu wywołanego niemiarowością, objawowa ciężka bradykardia, zaburzenia czynności węzła zatokowego, zaburzenia przewodzenia przedsionkowego, blok przedsionkowo-komorowy II° lub wyższego stopnia, blok odnóg pęczka Hisa lub blok dystalny u pacjentów bez stymulatora serca, ciężkie niedociśnienie tętnicze. Objawy zaburzeń równowagi wodno-elektrolitowej (np. zaburzenia metabolizmu potasu). Ciężka obturacyjna choroba płuc. Miastenia. Jednoczesne stosowanie rytonawiru. **Ostrzeżenia i zalecane środki ostrożności:** U każdego pacjenta przed rozpoczęciem leczenia propafenonu chlorowodorkiem i w jego trakcie, należy wykonać badanie EKG, ciśnienia krwi i ocenę stanu klinicznego, aby ustalić czy reakcja na propafenon potwierdza konieczność jego stosowania. Ekspozycja na propafenon może doprowadzić do ujawnienia zespołu Brugadów lub wywołać przypominające zespół Brugadów zmiany w zapisie EKG u nosicieli zespołu, u których nie obserwowano wcześniej objawów. Po rozpoczęciu leczenia propafenonem należy wykonać badanie EKG, aby wykluczyć zmiany wskazujące na zespół Brugadów. Leczenie propafenonu chlorowodorkiem może wpływać na próg stymulacji i czułość wszczepionego stymulatora serca. Należy zatem podczas terapii sprawdzać działanie stymulatora i w razie potrzeby ponownie zaprogramować. Podobnie jak w przypadku stosowania innych leków przeciwarytmicznych klasy IC, u pacjentów z istotną klinicznie chorobą strukturalną serca wystąpić mogą ciężkie działania niepożądane i dlatego propafenonu chlorowodorek jest przeciwwskazany u tych pacjentów. Istnieje możliwość przejścia napadowego migotania przedsionków w trzepotanie przedsionków z towarzyszącym blokiem przewodzenia w stosunku 2:1 lub 1:1. Ze względu na działanie blokujące receptory β-adrenergiczne, należy zachować ostrożność stosując propafenonu chlorowodorek u pacjentów z astmą. Należy zachować ostrożność u pacjentów z niewydolnością wątroby i nerek. Produkt zawiera laktozę, dlatego nie powinien być stosowany u pacjentów z rzadko występującą dziedziczną nietolerancją galaktozy, niedoborem laktazy (typu Lapp) lub zespołem złego wchłaniania glukozy-galaktozy. **Działania niepożądane:** Objawy niepożądane, takie jak nieostre widzenie, zawroty głowy, zmęczenie i hipotonia ortostatyczna mogą wpływać na szybkość reakcji i upośledzać zdolność do prowadzenia pojazdów i obsługiwania maszyn. Skrócony profil bezpieczeństwa - najczęściej występującymi działaniami niepożądanymi związanymi z leczeniem propafenonu chlorowodorkiem są zawroty głowy, zaburzenia przewodzenia i kołatanie serca. Zestawienie działań niepożądanych - poniżej przedstawiono działania niepożądane zgłoszone w badaniach klinicznych oraz po wprowadzeniu propafenonu do obrotu. Działania uznane za mające co najmniej możliwy związek ze stosowaniem propafenonu chlorowodorku przedstawiono według klasyfikacji układów i narządów oraz częstości występowania: bardzo często (≥1/10), często (≥1/100 do <1/10), niezbyt często (≥1/1 000 do <1/100) oraz częstość nieznana (działania niepożądane zgłoszone po wprowadzeniu propafenonu do obrotu, częstość nie może być określona na podstawie dostępnych danych). Częstość występowania działania niepożądanego, w każdej kategorii, przedstawiono według zmniejszającej się ciężkości wtedy, gdy można ją było określić. Zaburzenia krwi i układu chłonnego: niezbyt często: trombocytopenia; częstość nieznana: agranulocytoza, leukopenia, granulocytopenia. Zaburzenia układu immunologicznego: częstość nieznana: nadwrażliwość (może się objawiać zastojem żółci, nieprawidłowym składem krwi i wysypką). Zaburzenia metabolizmu i odżywiania: niezbyt często: zmniejszone łaknienie. Zaburzenia psychiczne: często: niepokój, zaburzenia snu; niezbyt często: koszmary nocne; częstość nieznana: stan splątania. Zaburzenia układu nerwowego: bardzo często: zawroty głowy (z wyjątkiem zawrotów głowy obwodowych); często: zaburzenie smaku, ból głowy; niezbyt często: omdlenie, ataksja, parestezje; częstość nieznana: drgawki, objawy pozapiramidowe, niepokój ruchowy. Zaburzenia oka: często: nieostre widzenie. Zaburzenia ucha i błędnika: niezbyt często: zawroty głowy obwodowe. Zaburzenia serca: bardzo często: zaburzenia przewodnictwa (w tym blok zatokowo-przedsionkowy, blok przedsionkowo-komorowy i blok śródkomorowy), kołatanie serca; często: bradykardia zatokowa, bradykardia, tachykardia, trzepotanie przedsionków; niezbyt często: tachykardia komorowa, zaburzenia rytmu serca (stosowanie propafenonu może się wiązać z działaniami proarytmicznymi objawiającymi się zwiększeniem częstości akcji serca (tachykardia) lub migotaniem komór. Niektóre z tych zaburzeń rytmu serca mogą zagrażać życiu i wymagać resuscytacji, aby zapobiec zgonom); częstość nieznana: migotanie komór, niewydolność serca (może dojść do nasilenia występującej wcześniej niewydolności serca), zmniejszenie częstość akcji serca. Zaburzenia naczyniowe: niezbyt często: niedociśnienie tętnicze; częstość nieznana: niedociśnienie ortostatyczne. Zaburzenia układu oddechowego, klatki piersiowej i śródpiersia: często: duszność. Zaburzenia żołądka i jelit: często: ból brzucha, nudności, wymioty, biegunka, zaparcia, suchość w jamie ustnej; niezbyt często: rozdęcie brzucha, wzdęcia z oddawaniem gazów; częstość nieznana: odruchy wymiotne, zaburzenia żołądkowo-jelitowe. Zaburzenia wątroby i dróg żółciowych: często: nieprawidłowa czynność wątroby (określenie to dotyczy nieprawidłowych wyników testów wątrobowych, takich jak zwiększenie aktywności aminotransferazy asparaginianowej, zwiększenie aktywności aminotransferazy alaninowej, zwiększenie aktywności gamma-glutamylotransferazy oraz zwiększenie aktywności fosfatazy zasadowej we krwi); częstość nieznana: uszkodzenie komórek wątroby, zastój żółci, zapalenie wątroby, żółtaczka. Zaburzenia skóry i tkanki podskórnej: niezbyt często: pokrzywka, świąd, wysypka, rumień. Zaburzenia mięśniowo-szkieletowe i tkanki łącznej: częstość nieznana: zespół toczniopodobny. Zaburzenia układu rozrodczego i piersi: niezbyt często: zaburzenia erekcji; częstość nieznana: zmniejszenie liczby plemników (zmniejszenie liczby plemników jest odwracalne po zaprzestaniu stosowania propafenonu). Zaburzenia ogólne i stany w miejscu podania: często: ból w klatce piersiowej, osłabienie, zmęczenie, gorączka. Zgłaszanie podejrzewanych działań niepożądanych: Po dopuszczeniu produktu leczniczego do obrotu istotne jest zgłaszanie podejrzewanych działań niepożądanych. Umożliwia to nieprzerwane monitorowanie stosunku korzyści do ryzyka stosowania produktu leczniczego. Osoby należące do fachowego personelu medycznego powinny zgłaszać wszelkie podejrzewane działania niepożądane za pośrednictwem Departamentu Monitorowania Niepożądanych Działań Produktów Leczniczych Urzędu Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych; Al. Jerozolimskie 181C, 02-222 Warszawa; tel.: +48 22 49 21 301; faks: +48 22 49 21 309; e-mail: ndl@urpl.gov.pl. Działania niepożądane można zgłaszać również podmiotowi odpowiedzialnemu. **Podmiot odpowiedzialny:** Zakłady Farmaceutyczne Polpharma S.A. Pozwolenie na dopuszczenie do obrotu leku Polfenon: 150 mg, 300 mg odpowiednio nr: R/0341, R/0342 wydane przez MZ Lek wydawany na podstawie recepty. Cena urzędowa detaliczna leku Polfenon 150 mg x 20 tabl. powl. wynosi w PLN: 7,21. Kwota dopłaty pacjenta (We wszystkich zarejestrowanych wskazaniach na dzień wydania decyzji) wynosi w PLN: 4,93. ChPL: 2020.01.10.

POLFE/273/12-2020

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HFrEF – niewydolność serca z obniżoną frakcją wyrzutową.
* Dorośli pacjenci z przewlekłą niewydolnością serca (klasy II, III lub IV wg NYHA) i zredukowaną frakcją wyrzutową (LVEF ≤ 40%)[2].

1. Charakterystyka produktu leczniczego JARDIANCE® z dnia 17.06.2021 r. 2. Packer M. i wsp. N Engl J Med. 2020; 383 (15): 1413-1424. (Wyniki badania EMPEROR-Reduced® oraz dodatek uzupełniający do publikacji). 3. McDonagh T, Metra M, Adamo M, Gardner R, Baumbach A, Bohm M, Burri H, Butler J, Celutkiene J, Chioncel O, Cleland J, Coats A, Crespo-Leiro M, Farmakis D, Gilard M, Heymans S. Hoes W, Jaarsma T, Jankowska E, Lainscak M, Lam C, Lyon A, McMurray, Mebazaa A, Mindham R, Muneretto C, Piepoli M, Price S, Rosano G, Ruschitzka F, Skibelund A. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2021; 00, 1-128. doi:10.1093/eurheartj/ehab368.

Skrócona informacja o leku JARDIANCE®

Nazwa produktu leczniczego, dawka i postać farmaceutyczna: Jardiance® 10 mg, 25 mg tabletki powlekane. Każda tabletka zawiera 10 mg empagliflozyny lub 25 mg empagliflozyny. Jardiance® 10 mg okrągła tabletka powlekana barwy bladożółtej, obustronnie wypukła, o średnicy 9,1 mm ze ściętą ostro krawędzią, z wytłoczonym symbolem „S10" na jednej stronie oraz logo Boehringer Ingelheim na drugiej. Każda tabletka zawiera ilość laktozy jednowodnej odpowiadającą 154,3 mg laktozy bezwodnej. Każda tabletka zawiera mniej niż 1 mmol (23 mg) sodu, to znaczy lek uznaje się za „wolny od sodu". Jardiance® 25 mg owalna, bladożółta, obustronnie wypukła tabletka powlekana z wytłoczonym symbolem „S25" na jednej stronie oraz logo Boehringer Ingelheim na drugiej (długość tabletki: 11,1 mm, szerokość: 5,6 mm). Każda tabletka zawiera ilość laktozy jednowodnej odpowiadającą 107,4 mg laktozy bezwodnej. Każda tabletka zawiera mniej niż 1 mmol (23 mg) sodu, to znaczy lek uznaje się za „wolny od sodu". **Wskazania do stosowania:** Cukrzyca typu 2 Produkt leczniczy Jardiance® jest wskazany do stosowania w leczeniu dorosłych z niewystarczająco kontrolowaną cukrzycą typu 2 łącznie z dietą i aktywnością fizyczną: w monoterapii, kiedy nie można stosować metforminy z powodu jej nietolerancji, w skojarzeniu z innymi produktami leczniczymi stosowanymi w leczeniu cukrzycy. Wyniki badań dotyczące różnych skojarzeń, wpływu na kontrolę glikemii i zdarzenia sercowo-naczyniowe oraz badane populacje, patrz punkt Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania. Niewydolność serca Produkt leczniczy Jardiance® jest wskazany do stosowania u dorosłych w leczeniu objawowej przewlekłej niewydolności serca ze zredukowaną frakcją wyrzutową. **Dawkowanie i sposób podawania:** Dawkowanie Cukrzyca typu 2 Zalecana dawka początkowa wynosi 10 mg empagliflozyny raz na dobę w monoterapii oraz w terapii skojarzonej z innymi produktami leczniczymi stosowanymi w leczeniu cukrzycy. U pacjentów tolerujących dawkę 10 mg empagliflozyny raz na dobę z wartością eGFR ≥ 60 ml/min/1,73 m² i w wymagających ściślejszej kontroli glikemii, dawkę można zwiększyć do 25 mg raz na dobę. Maksymalna dawka dobowa wynosi 25 mg (patrz poniżej i punkt Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania). Niewydolność serca Zalecana dawka to 10 mg empagliflozyny raz na dobę. Wszystkie wskazania Podczas stosowania empagliflozyny w skojarzeniu z pochodną sulfonylomocznika lub z insuliną, konieczne może być zmniejszenie dawki pochodnej sulfonylomocznika lub insuliny, aby zmniejszyć ryzyko wystąpienia hipoglikemii (patrz punkt Działania niepożądane). W razie pominięcia dawki pacjent powinien ją zażyć niezwłocznie po przypomnieniu sobie o tym; nie należy jednak przyjmować podwójnej dawki tego samego dnia. *Szczególne grupy pacjentów Upośledzenie czynności nerek* U pacjentów z cukrzycą typu 2 skuteczność empagliflozyny w kontrolowaniu glikemii zależy od czynności nerek. Patrz tabela 1, aby uzyskać informacje dotyczące dostosowywania dawki w zależności od wartości eGFR lub CrCl.

Tabela 1: Zalecenia dotyczące dostosowywania dawki[a]

Wskazanie	eGFR [ml/min/1,73 m²] lub CrCL [ml/min]	Całkowita dawka dobowa
Cukrzyca typu 2	≥60	Rozpocząć od dawki 10 mg empagliflozyny. U pacjentów tolerujących dawkę 10 mg empagliflozyny i wymagających dodatkowej kontroli glikemii dawkę można zwiększyć do 25 mg empagliflozyny.
	45 do <60	Nie rozpoczynać stosowania empagliflozyny. Kontynuować stosowanie dawki 10 mg empagliflozyny u pacjentów, którzy już przyjmują produkt leczniczy Jardiance®.
	<45	Nie zaleca się stosowania empagliflozyny.
Niewydolność serca (z cukrzycą typu 2 lub bez cukrzycy typu 2)	≥20	Zalecana dawka dobowa to 10 mg empagliflozyny.
	<20	Nie zaleca się stosowania empagliflozyny.

[a] Patrz punkty Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania, Działania niepożądane Z uwagi na mechanizm działania empagliflozyny, jej skuteczność w odniesieniu do kontroli glikemii zależy od czynności nerek. Nie ma konieczności dostosowania dawki u pacjentów z wartością eGFR ≥ 60 ml/min/1,73 m² lub CrCl ≥ 60 ml/min. W przypadku leczenia cukrzycy typu 2 nie należy rozpoczynać leczenia empagliflozyną u pacjentów z wartością eGFR < 60 ml/min/1,73 m² lub z CrCl < 60 ml/min. U pacjentów tolerujących empagliflozynę, u których wartość eGFR obniżyła się i utrzymuje się poniżej 60 ml/min/1,73 m² lub z CrCl poniżej 60 ml/min, dawkę empagliflozyny należy dostosować lub utrzymywać na poziomie 10 mg raz na dobę. Należy przerwać leczenie empagliflozyną u pacjentów, których wartość eGFR utrzymuje się poniżej 45 ml/min/1,73 m² lub CrCl utrzymuje się poniżej 45 ml/min (patrz punkty Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania, Działania niepożądane). W przypadku leczenia niewydolności serca u pacjentów z cukrzycą typu 2 lub bez cukrzycy typu 2 stosowanie dawki 10 mg empagliflozyny można rozpocząć lub kontynuować leczenie do wartości eGFR równej 20 ml/min/1,73 m² lub wartości CrCl równej 20 ml/min. Nie należy stosować empagliflozyny u pacjentów ze schyłkową niewydolnością nerek (SNN), ani u pacjentów dializowanych. Nie ma wystarczających danych, aby uzasadnić stosowanie w tej grupie pacjentów (patrz punkt Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania). *Upośledzenie czynności wątroby* Nie ma konieczności dostosowania dawki u pacjentów z upośledzeniem czynności wątroby. U pacjentów z ciężkim upośledzeniem czynności wątroby ekspozycja na empagliflozynę jest zwiększona. Doświadczenie w leczeniu pacjentów z ciężkim upośledzeniem czynności wątroby jest ograniczone, w związku z czym nie zaleca się stosowania empagliflozyny w tej populacji pacjentów. *Pacjenci w podeszłym wieku* Nie ma konieczności dostosowania dawki w zależności od wieku pacjenta. U pacjentów w wieku 75 lat i starszych należy wziąć pod uwagę zwiększone ryzyko zmniejszenia objętości płynów (patrz punkty Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania i Działania niepożądane). Z uwagi na ograniczone doświadczenie w leczeniu pacjentów w wieku 85 lat i starszych, nie zaleca się rozpoczynania leczenia empagliflozyną w tej grupie wiekowej (patrz punkt Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania). *Dzieci i młodzież* Nie określono dotychczas bezpieczeństwa stosowania ani skuteczności empagliflozyny u dzieci i młodzieży. Dane nie są dostępne. Sposób podawania Tabletki mogą być przyjmowane jednocześnie z posiłkiem lub niezależnie od niego. Tabletki należy połykać w całości popijając wodą. **Przeciwwskazania:** Nadwrażliwość na substancję czynną lub na którąkolwiek substancje pomocniczą wymienioną w punkcie Wykaz substancji pomocniczych ChPL. **Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania:** Kwasica ketonowa U pacjentów z cukrzycą leczonych inhibitorami SGLT2, w tym empagliflozyną, zgłaszano rzadkie przypadki kwasicy ketonowej, w tym przypadki zagrażające życiu i zakończone zgonem. W niektórych przypadkach obraz kliniczny był nietypowy, tylko z umiarkowanym zwiększeniem stężenia glukozy we krwi, poniżej 14 mmol/l (250 mg/dl). Nie wiadomo, czy zastosowanie większych dawek empagliflozyny zwiększa ryzyko kwasicy ketonowej. Należy uwzględnić ryzyko kwasicy ketonowej w razie wystąpienia niespecyficznych objawów, takich jak: nudności, wymioty, jadłowstręt, ból brzucha, silne pragnienie, zaburzenia oddychania, splątanie, niezwykłe zmęczenie lub senność. W razie wystąpienia takich objawów należy niezwłocznie zbadać pacjentów, czy nie występuje u nich kwasica ketonowa, niezależnie od stężenia glukozy we krwi. Należy natychmiast przerwać leczenie empagliflozyną u pacjentów z podejrzeniem lub rozpoznaniem kwasicy ketonowej. Należy przerwać leczenie u pacjentów hospitalizowanych z powodu dużych zabiegów chirurgicznych lub ostrych ciężkich chorób. U tych pacjentów zaleca się monitorowanie stężeń ciał ketonowych. Preferowane jest oznaczanie stężenia ciał ketonowych we krwi, niż w moczu. Leczenie empagliflozyną można wznowić, gdy stężenie ciał ketonowych będzie prawidłowe, a stan pacjenta ustabilizuje się. Przed rozpoczęciem leczenia empagliflozyną należy rozważyć czynniki w wywiadzie predysponujące pacjenta do kwasicy ketonowej. Do pacjentów ze zwiększonym ryzykiem kwasicy ketonowej zalicza się osoby z małą rezerwą czynnościową komórek beta (np. pacjenci z cukrzycą typu 2 i małym stężeniem peptydu C lub późno ujawniającą się cukrzycą autoimmunologiczną dorosłych – ang. latent autoimmune diabetes in adults – LADA lub pacjenci z zapaleniem trzustki w wywiadzie), pacjentów ze stanami prowadzącymi do ograniczenia przyjmowania pożywienia lub z ciężkim odwodnieniem pacjentów, którym zmniejszono dawkę insuliny oraz pacjentów ze zwiększonym zapotrzebowaniem na insulinę z powodu ostrej choroby, zabiegu chirurgicznego lub nadużywania alkoholu. U tych pacjentów należy ostrożnie stosować inhibitory SGLT2. Nie zaleca się wznawiania leczenia inhibitorem SGLT2 u pacjentów, u których wcześniej wystąpiła kwasica ketonowa podczas stosowania inhibitora SGLT2, chyba że zidentyfikowano i usunięto inną wyraźną przyczynę. Produktu leczniczego Jardiance® nie należy stosować w leczeniu pacjentów z cukrzycą typu 1. Dane z programu badań klinicznych u pacjentów z cukrzycą typu 1 wykazały zwiększone, częste występowanie kwasicy ketonowej u pacjentów leczonych empagliflozyną w dawce 10 mg i 25 mg jako uzupełnienie insuliny w porównaniu z placebo. Niewydolność nerek Nie należy stosować empagliflozyny u pacjentów ze schyłkową niewydolnością nerek (SNN) ani u pacjentów dializowanych. Nie ma wystarczających danych, aby uzasadnić stosowanie w tej grupie pacjentów (patrz punkt Dawkowanie i sposób podawania). *Cukrzyca typu 2* Ponieważ kontrola glikemii zależy od czynności nerek, nie należy rozpoczynać leczenia produktem Jardiance® u pacjentów z wartością eGFR poniżej < 60 ml/min/1,73 m² lub z CrCl < 60 ml/min. U pacjentów tolerujących empagliflozynę, których wartość eGFR utrzymuje się poniżej 60 ml/min/1,73 m² lub CrCl < 60 ml/min, dawkę empagliflozyny należy dostosować lub utrzymywać na poziomie 10 mg raz na dobę. Nie zaleca się stosowania empagliflozyny u pacjentów, których wartość eGFR utrzymuje się poniżej 45 ml/min/1,73 m² lub CrCl utrzymuje się poniżej 45 ml/min (patrz punkty Dawkowanie i sposób podawania, Działania niepożądane). *Niewydolność serca* Nie zaleca się stosowania produktu leczniczego Jardiance® u pacjentów z wartością eGFR <20 ml/min/1,73 m². Monitorowanie czynności nerek Zaleca się ocenę czynności nerek w następujący sposób: przed rozpoczęciem leczenia empagliflozyną i okresowo podczas leczenia, tzn. co najmniej raz na rok (patrz punkty Dawkowanie i sposób podawania, Działania niepożądane); przed rozpoczęciem leczenia jakimkolwiek innym jednoczesnie stosowanym produktem leczniczym, który może mieć niekorzystny wpływ na czynność nerek. Ryzyko zmniejszenia objętości płynów Z uwagi na mechanizm działania inhibitorów SGLT-2, diureza osmotyczna towarzyszaca glukozurii może spowodować nieznaczne zmniejszenie ciśnienia krwi. W związku z tym należy zachować ostrożność u pacjentów, dla których taki spadek ciśnienia krwi spowodowany przez empagliflozynę mógłby stanowić zagrożenie, takich jak pacjenci z rozpoznaną chorobą układu krążenia, pacjenci stosujący leczenie przeciwnadciśnieniowe z epizodami niedokrwienia w wywiadzie lub pacjenci w wieku 75 i więcej lat. W przypadku stanów, które mogą prowadzić do utraty płynów przez organizm (np. choroba przewodu pokarmowego) zaleca się dokładne monitorowanie stanu nawodnienia (np. badanie przedmiotowe, pomiar ciśnienia krwi, testy laboratoryjne włącznie z oznaczeniem hematokrytu) i stężenia elektrolitów u pacjentów przyjmujących empagliflozynę. Należy rozważyć tymczasowe wstrzymanie leczenia empagliflozyną do czasu wyrównania utraty płynów. Pacjenci w podeszłym wieku Wpływ empagliflozyny na wydalanie glukozy z moczem związany jest z diurezą osmotyczną, co może mieć wpływ na stan nawodnienia. Pacjenci w wieku 75 i więcej lat mogą być w większym stopniu zagrożeni wystąpieniem zmniejszenia objętości płynów. Większa liczba takich pacjentów leczonych empagliflozyną miała działania niepożądane związane ze zmniejszeniem objętości płynów w porównaniu z pacjentami otrzymującymi placebo (patrz punkt Działania niepożądane). W związku z tym należy zwracać szczególną uwagę na przyjmowanej objętość płynów w razie jednoczesnego podawania z produktami leczniczymi mogącymi prowadzić do zmniejszenia objętości płynów (np. leki moczopędne, inhibitory ACE). Doświadczenie dotyczące leczenia pacjentów w wieku 85 i więcej lat jest ograniczone. Nie zaleca się rozpoczynania leczenia empagliflozyną w tej grupie wiekowej (patrz punkt Dawkowanie i sposób podawania). Powikłane zakażenia dróg moczowych U pacjentów otrzymujących empagliflozynę zgłaszano przypadki powikłanych zakażeń dróg moczowych, w tym odmiedniczkowe zapalenie nerek i posocznicę moczopochodną (patrz punkt Działania niepożądane). Należy rozważyć tymczasowe wstrzymanie leczenia empagliflozyną u pacjentów z powikłanym zakażeniem dróg moczowych. Martwicze zapalenie powięzi krocza (zgorzel Fourniera) Zgłaszano przypadki martwiczego zapalenia powięzi krocza (znanego także jako zgorzel Fourniera) u pacjentów płci żeńskiej i męskiej z cukrzycą przyjmujących inhibitory SGLT2. Jest to rzadkie, ale ciężkie i mogące zagrażać życiu zdarzenie, które wymaga pilnej interwencji chirurgicznej i antybiotykoterapii. Pacjentom należy zalecić, aby zgłosili się do lekarza, jeśli wystąpi u nich zespół objawów, takich jak ból, wrażliwość na dotyk, rumień lub obrzęk w okolicy zewnętrznych narządów płciowych lub krocza, z jednoczesną gorączką lub uczuciem rozbicia. Należy pamiętać o tym, że martwicze zapalenie powięzi może być poprzedzone zakażeniem narządów układu moczowo-płciowego lub ropniem krocza. Jeśli podejrzewa się wystąpienie zgorzeli Fourniera, należy przerwać stosowanie produktu Jardiance® i niezwłocznie rozpocząć leczenie (w tym antybiotykoterapię oraz chirurgiczne opracowanie zmian chorobowych). Amputacje w obrębie kończyn dolnych W długoterminowych badaniach klinicznych innego inhibitora SGLT2 zaobserwowano zwiększoną częstość przypadków amputacji w obrębie kończyn dolnych (szczególnie palucha). Nie wiadomo, czy jest to „efekt klasy leków". Podobnie jak w przypadku wszystkich chorych na cukrzycę, ważna jest edukacja pacjentów dotycząca profilaktycznej pielęgnacji stóp. Uszkodzenie wątroby W badaniach klinicznych obejmujących empagliflozynę zgłaszano przypadki uszkodzenia wątroby. Nie ustalono związku przyczynowo-skutkowego pomiędzy empagliflozyną a uszkodzeniem wątroby. Zwiększenie wartości hematokrytu Obserwowano zwiększenie wartości hematokrytu podczas leczenia empagliflozyną (patrz punkt Działania niepożądane). Laboratoryjna analiza moczu Z uwagi na mechanizm działania produktu Jardiance®, pacjenci przyjmujący go będą mieć dodatni wynik testu na zawartość glukozy w moczu. Wpływ na badanie stężenia 1,5-anhydroglucitolu (1,5-AG) Nie zaleca się monitorowania kontroli glikemii za pośrednictwem badania stężenia 1,5-AG, ponieważ oznaczanie stężenia 1,5-AG nie jest miarodajne w ocenie kontroli glikemii u pacjentów przyjmujących inhibitory SGLT2. Zaleca się stosowanie innych metod monitorowania kontroli glikemii. Laktoza Tabletki produktu leczniczego zawierają laktozę. Produkt leczniczy nie powinien być stosowany u pacjentów z rzadko występującą dziedziczną nietolerancją galaktozy, brakiem laktazy lub zespołem złego wchłaniania glukozy-galaktozy. **Działania niepożądane:** Podsumowanie profilu bezpieczeństwa *Cukrzyca typu 2* Łącznie 15 582 pacjentów z cukrzycą typu 2 wzięło udział w badaniach klinicznych oceniających bezpieczeństwo stosowania empagliflozyny, z czego 10 004 pacjentów otrzymywało empagliflozynę w monoterapii lub w skojarzeniu z metforminą, pochodną sulfonylomocznika, pioglitazonem, inhibitorami DPP-4 lub insuliną. W 6 badaniach przeprowadzonych z kontrolą placebo trwających od 18 do 24 tygodni wzięło udział 3534 pacjentów, z których 1183 otrzymywało placebo, a 2351 – empagliflozynę. Ogólna częstość występowania zdarzeń niepożądanych u pacjentów leczonych empagliflozyną była podobna do częstości w grupie otrzymującej placebo. Najczęściej obserwowanym działaniem niepożądanym była hipoglikemia przy stosowaniu w skojarzeniu z pochodną sulfonylomocznika lub insuliną (patrz opis wybranych działań niepożądanych). *Niewydolność serca* Do badania EMPEROR-Reduced włączono 3 730 pacjentów z niewydolnością serca i zmniejszoną frakcją wyrzutową, którzy otrzymywali leczenie 10 mg empagliflozyny lub placebo. U około połowy pacjentów występowała cukrzyca typu 2. Najczęściej zgłaszanym działaniem niepożądanym było zmniejszenie objętości płynów (10 mg empagliflozyny: 10,6%; placebo: 9,9%). Ciężką hipoglikemię (zdarzenia wymagające interwencji) obserwowano wyłącznie u pacjentów z cukrzycą. Ogólny profil bezpieczeństwa stosowania empagliflozyny był zasadniczo spójny w badanych wskazaniach. W badaniu niewydolności serca EMPEROR-Reduced nie zidentyfikowano żadnych nowych działań niepożądanych. Wykaz działań niepożądanych w postaci tabeli W poniższej tabeli przedstawiono działania niepożądane – sklasyfikowane według grup układowo-narządowych oraz według preferowanych terminów MedDRA – zgłaszane u pacjentów, którzy otrzymali empagliflozynę w badaniach prowadzonych z kontrolą placebo (Tabela 2). Działania niepożądane są wymienione według bezwzględnej częstości występowania. Częstość występowania zdefiniowana jest następująco: bardzo często (≥ 1/10); często (≥ 1/100 do < 1/10); niezbyt często (≥ 1/1000 do < 1/100); rzadko (≥ 1/10 000 do < 1/1000), bardzo rzadko (< 1/10 000), nieznana (częstość nie może być określona na podstawie dostępnych danych).

Tabela 2: Wykaz działań niepożądanych (MedDRA) obserwowanych w badaniach prowadzonych z kontrolą placebo i zgłoszonych po wprowadzeniu produktu do obrotu, w postaci tabeli

Klasyfikacja układów i narządów	Bardzo często	Często	Niezbyt często	Rzadko
Zakażenia i zarażenia pasożytnicze		kandydoza pochwy, zapalenie pochwy i sromu, zapalenie żołędzi i inne zakażenia narządów płciowych[a] zakażenie dróg moczowych (w tym odmiedniczkowe zapalenie nerek i posocznica moczopochodna)[a]		martwicze zapalenie powięzi krocza (zgorzel Fourniera)[b,*]
Zaburzenia metabolizmu i odżywiania	hipoglikemia (przy stosowaniu w skojarzeniu z pochodną sulfonylomocznika lub insuliną)[a]	pragnienie		cukrzycowa kwasica ketonowa*
Zaburzenia żołądka i jelit		zaparcie		
Zaburzenia skóry i tkanki podskórnej		świąd (uogólniony) wysypka	pokrzywka obrzęk naczynioruchowy	
Zaburzenia naczyniowe	zmniejszenie objętości płynów[a]			
Zaburzenia nerek i dróg moczowych		zwiększone oddawanie moczu[a]	dyzuria	
Badania diagnostyczne		zwiększenie stężenia lipidów w surowicy[a]	zwiększenie stężenia kreatyniny we krwi i (lub) zmniejszenie współczynnika filtracji kłębuszkowej[a] zwiększenie hematokrytu[a]	

[a] patrz dodatkowe informacje podane poniżej [b] W badaniu niewydolności serca EMPEROR-Reduced obserwowano jeden przypadek (<0,1%) martwiczego zapalenia powięzi krocza (zgorzeli Fourniera) u pacjenta z niewydolnością serca i cukrzycą leczonego empagliflozyną. * patrz punkt Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania

Opis wybranych działań niepożądanych *Hipoglikemia* Częstość występowania hipoglikemii zależała od leczenia podstawowego stosowanego w poszczególnych badaniach i była podobna jak po zastosowaniu placebo u pacjentów stosujących empagliflozynę w monoterapii, jako leczenie skojarzone z metforminą, jako leczenie skojarzone z pioglitazonem w skojarzeniu z metforminą lub bez niej, jako leczenie skojarzone z linagliptyną i metforminą, jako leczenie dodane do terapii standardowej oraz w razie stosowania skojarzenia empagliflozyny z metforminą u nieleczonych uprzednio pacjentów w porównaniu z pacjentami leczonymi osobnymi lekami empagliflozyną i metforminą. Zwiększoną częstość zaobserwowano w przypadku stosowania jako leczenie skojarzone z metforminą i pochodnymi sulfonylomocznika (10 mg empagliflozyny: 16,1%; 25 mg empagliflozyny: 11,5%; placebo: 8,4%), jako leczenie skojarzone z insuliną podstawową w skojarzeniu z metforminą lub bez niej oraz w skojarzeniu z pochodną sulfonylomocznika lub bez niego (10 mg empagliflozyny: 19,5%; 25 mg empagliflozyny: 28,4%; placebo: 20,6% w ciągu pierwszych 18 tygodni leczenia, gdy nie można było dostosowywać dawki insuliny; 10 mg i 25 mg empagliflozyny: 36,1%; placebo: 35,3% w ciągu 78 tygodni badania) i jako leczenie skojarzone z insuliną MDI w skojarzeniu z metforminą lub bez niej (empagliflozyna 10 mg: 39,8%, empagliflozyna 25 mg: 41,3%, placebo: 37,2% podczas pierwszych 18 tygodni leczenia, gdy nie można było dostosować dawki insuliny; empagliflozyna 10 mg: 51,1%, empagliflozyna 25 mg: 57,7%, placebo: 58% w ciągu 52 tygodni badania). W badaniu niewydolności serca EMPEROR-Reduced obserwowano podobną częstość występowania hipoglikemii podczas stosowania w skojarzeniu z sulfonylomocznikiem lub insuliną (10 mg empagliflozyny: 4,2%; placebo: 4,6%). *Ciężka hipoglikemia (zdarzenia wymagające interwencji)* Nie zaobserwowano zwiększenia częstości występowania ciężkiej hipoglikemii przy stosowaniu empagliflozyny w porównaniu do placebo, w monoterapii, w leczeniu skojarzonym z metforminą, w leczeniu skojarzonym z metforminą i pochodną sulfonylomocznika, w leczeniu skojarzonym z pioglitazonem w skojarzeniu z metforminą lub bez niej, w leczeniu skojarzonym z linagliptyną i metforminą, jako leczenie dodane do terapii standardowej oraz w razie stosowania skojarzenia empagliflozyny z metforminą u nieleczonych uprzednio pacjentów w porównaniu z pacjentami leczonymi osobnymi lekami empagliflozyną i metforminą. Zwiększoną częstość zaobserwowano w przypadku stosowania jako leczenie skojarzone z insuliną podstawową w skojarzeniu z metforminą lub bez niej oraz w skojarzeniu z pochodną sulfonylomocznika lub bez niego (10 mg empagliflozyny: 0%; 25 mg empagliflozyny: 1,3%; placebo: 0% w ciągu pierwszych 18 tygodni leczenia, gdy nie można było dostosowywać dawki insuliny; 10 mg empagliflozyny: 0%; 25 mg empagliflozyny: 1,3%; placebo: 0% w ciągu 78 tygodni badania) i jako leczenie skojarzone z insuliną MDI w skojarzeniu z metforminą lub bez niej (empagliflozyna 10 mg: 0,5%, empagliflozyna 25 mg: 0,5%, placebo: 0,5% podczas pierwszych 18 tygodni leczenia, gdy nie można było dostosować dawki insuliny; empagliflozyna 10 mg: 1,6%, empagliflozyna 25 mg: 0,5%, placebo: 1,6% w ciągu 52 tygodni badania). W badaniu dotyczącym niewydolności serca EMPEROR-Reduced ciężką hipoglikemię obserwowano tylko u jednego pacjenta z cukrzycą podczas stosowania w skojarzeniu z sulfonylomocznikiem lub insuliną (10 mg empagliflozyny: 1,2%, placebo: 1,5%). *Kandydoza pochwy, zapalenie pochwy i sromu, zapalenie żołędzi i inne zakażenia narządów płciowych* Kandydoza pochwy, zapalenie pochwy i sromu, zapalenie żołędzi i inne zakażenia narządów płciowych były obserwowane częściej u pacjentów leczonych empagliflozyną (10 mg empagliflozyny: 4,0%; 25 mg empagliflozyny: 3,9%) w porównaniu z pacjentami otrzymującymi placebo (1,0%). Zakażenia takie obserwowano częściej u kobiet leczonych empagliflozyną w porównaniu z placebo. Różnica ta była mniej wyraźna w przypadku mężczyzn. Zakażenia narządów płciowych miały nasilenie łagodne lub umiarkowane. W badaniu dotyczącym niewydolności serca EMPEROR-Reduced częstość występowania tego typu zakażeń była większa u pacjentów z cukrzycą (10 mg empagliflozyny: 1,9%; placebo: 0,4%) niż u pacjentów bez cukrzycy (10 mg empagliflozyny: 1,4%; placebo: 0,9%) w trakcie leczenia empagliflozyną w porównaniu z placebo. *Zwiększone oddawanie moczu* Zwiększone oddawanie moczu (obejmujące określone wcześniej takie terminy jak częstomocz, wielomocz i oddawanie moczu w nocy) były obserwowane częściej u pacjentów leczonych empagliflozyną (10 mg empagliflozyny: 3,5%; 25 mg empagliflozyny: 3,3%) w porównaniu z pacjentami otrzymującymi placebo (1,4%). Zwiększone oddawanie moczu miało przeważnie nasilenie łagodne lub umiarkowane. Obserwowana częstość oddawania moczu w nocy była podobna dla empagliflozyny i dla placebo (< 1%). W badaniu niewydolności serca EMPEROR-Reduced zwiększone oddawanie moczu obserwowano z podobną częstością występowania u pacjentów leczonych empagliflozyną i placebo (10 mg empagliflozyny: 0,7%, placebo 0,4%). *Zakażenie dróg moczowych* Ogólna częstość występowania zakażeń dróg moczowych zgłaszanych jako zdarzenie niepożądane była podobna u pacjentów otrzymujących 25 mg empagliflozyny i placebo (7,0% i 7,2%), i wyższa u pacjentów otrzymujących 10 mg empagliflozyny (8,8%). Podobnie jak w przypadku placebo, zakażenia dróg moczowych były zgłaszane częściej u pacjentów leczonych empagliflozyną z przewlekłymi lub nawracającymi zakażeniami dróg moczowych w wywiadzie. Nasilenie (łagodne, umiarkowane, ciężkie) zakażenia dróg moczowych było podobne u pacjentów otrzymujących empagliflozynę i placebo. Zakażenia dróg moczowych były zgłaszane częściej u kobiet leczonych empagliflozyną w porównaniu z placebo; nie było takiej różnicy w przypadku mężczyzn. *Zmniejszenie objętości płynów* Ogólna częstość występowania zmniejszenia objętości płynów (obejmującego określone wcześniej takie terminy jak spadek ciśnienia krwi (określony ambulatoryjnie), spadek skurczowego ciśnienia krwi, odwodnienie, niedokrwienie, hipowolemia, hipotonia ortostatyczna oraz omdlenie) była podobna u pacjentów otrzymujących empagliflozynę (10 mg empagliflozyny: 0,6%; 25 mg empagliflozyny: 0,4%) i placebo (0,3%). Częstość występowania zmniejszenia objętości płynów była zwiększona u pacjentów w wieku 75 lat i starszych leczonych empagliflozyną (10 mg empagliflozyny: 2,3%; 25 mg empagliflozyny: 4,3%) w porównaniu z pacjentami otrzymującymi placebo (2,1%). *Zwiększenie stężenia kreatyniny we krwi i (lub) obniżenie współczynnika filtracji kłębuszkowej* Ogólna częstość występowania przypadków zwiększenia stężenia kreatyniny we krwi i obniżenie współczynnika filtracji kłębuszkowej była podobna u pacjentów otrzymujących empagliflozynę lub placebo (zwiększenie stężenia kreatyniny: empagliflozyna 10 mg 0,6%, empagliflozyna 25 mg 0,1%, placebo 0,5%; zmniejszenie szybkości filtracji kłębuszkowej; empagliflozyna 10 mg 0,1%, empagliflozyna 25 mg 0%, placebo 0,3%). Występujące początkowo zwiększenie stężenia kreatyniny we krwi i (lub) obniżenie współczynnika filtracji kłębuszkowej u pacjentów leczonych empagliflozyną jako terapią uzupełniającą leczenie metforminą zwykle ustępowało w trakcie ciągłego leczenia lub było odwracalne po zakończeniu leczenia tym lekiem. Konsekwentnie w badaniu EMPA-REG OUTCOME u pacjentów leczonych empagliflozyną obserwowano występujący początkowo spadek eGFR (średnia: 3 ml/min/1,73 m²). Następnie wartość eGFR utrzymywała się w czasie trwania leczenia. Średnia wartość eGFR powracała do wartości początkowej po zakończeniu leczenia, co sugeruje, że w patogenezie tych zmian czynnościowych nerek mogą odgrywać rolę ostre zmiany hemodynamiczne. *Zwiększenie stężenia lipidów w surowicy* Średnie zwiększenie procentowe od punktu początkowego dla 10 mg i 25 mg empagliflozyny w porównaniu z placebo wynosiło odpowiednio dla cholesterolu całkowitego 4,9% i 5,7% w porównaniu z 3,5%; dla cholesterolu HDL 3,3% i 3,6% w porównaniu z 0,4 %; dla cholesterolu LDL 9,5% i 10,0% w porównaniu z 7,5%; dla triglyceryd ów 9,2% i 9,9% w porównaniu z 10,5%. *Zwiększenie wartości hematokrytu* Średnia zmiana wartości hematokrytu od punktu początkowego wynosiła odpowiednio 3,4% i 3,6% dla 10 mg i 25 mg empagliflozyny w porównaniu z 0,1% dla placebo. W badaniu EMPA-REG Outcome wartości hematokrytu powróciły do wartości wyjściowych po 30-dniowym okresie kontroli po zakończeniu leczenia. Zgłaszanie podejrzewanych działań niepożądanych Po dopuszczeniu produktu leczniczego do obrotu istotne jest zgłaszanie podejrzewanych działań niepożądanych. Umożliwia to nieprzerwane monitorowanie stosunku korzyści do ryzyka stosowania produktu leczniczego. Osoby należące do fachowego personelu medycznego powinny zgłaszać wszelkie podejrzewane działania niepożądane za pośrednictwem Departamentu Monitorowania Niepożądanych Działań Produktów Leczniczych Urzędu Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych: Al. Jerozolimskie 181C, 02-222 Warszawa, tel.: +48 22 49-21-301, faks: +48 22 49-21-309, strona internetowa: https://smz.ezdrowie.gov.pl. Działania niepożądane można zgłaszać również podmiotowi odpowiedzialnemu. **Podmiot odpowiedzialny:** Boehringer Ingelheim International GmbH, Binger Str. 173, 55216 Ingelheim am Rhein, Niemcy. **Numery pozwoleń na dopuszczenie do obrotu:** Jardiance® 10 mg tabletki powlekane: EU/1/14/930/013 (28 tabletek), Jardiance® 10 mg tabletki powlekane: EU/1/14/930/014 (30 tabletek) wydane przez Komisję Wspólnot Europejskich. **Data zatwierdzenia lub częściowej zmiany tekstu ChPL:** 17.06.2021. **Kategoria dostępności:** Produkt leczniczy wydawany na receptę – Rp. **Cena urzędowa detaliczna:** Jardiance® 10 mg x 28 tabl. – 170,38 zł. Wysokość dopłaty pacjenta: 54,00 zł we wskazaniu: Cukrzyca typu 2, u pacjentów przed włączeniem insuliny, leczonych co najmniej dwoma doustnymi lekami hipoglikemizującymi od co najmniej 6 miesięcy, z HbA1c ≥ 8 % oraz bardzo wysokim ryzykiem sercowo-naczyniowym rozumianym jako: 1) otwierdzona choroba sercowo-naczyniowa, lub 2) uszkodzenie innych narządów objawiające się poprzez: białkomocz lub przerost lewej komory lub retinopatię, lub 3) obecność 3 lub więcej głównych czynników ryzyka spośród wymienionych poniżej: -wiek ≥ 55 lat dla mężczyzn, ≥ 60 lat dla kobiet, -dyslipidemia, -nadciśnienie tętnicze, -palenie tytoniu, -otyłość – na podstawie obwieszczenia Ministra Zdrowia z dnia 21 czerwca 2021 r. w sprawie wykazu refundowanych leków, środków spożywczych specjalnego przeznaczenia żywieniowego oraz wyrobów medycznych na 1 lipca 2021 r. (DZ. URZ. Min. Zdr. 2021.44).

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Produkt leczniczy JARDIANCE® jest wskazany do stosowania u dorosłych w leczeniu objawowej, przewlekłej niewydolności serca ze zredukowaną frakcją wyrzutową*,[1]

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