ISSN 0022–9032

e-ISSN 1897–4279

September 2022, vol. 80, number 9

KARDIOLOGIA POLSKA

Polish Heart Journal

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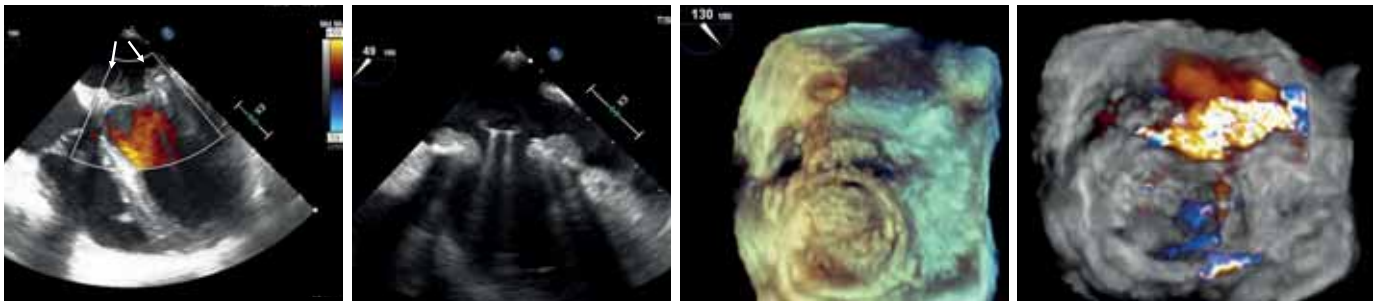

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ISSN 0022-9032
e-ISSN 1897-4279

Subscription rates: Paper subscription, 12 issues incl. package and postage individual 150€
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CLINICAL VIGNETTE

LETTER TO THE EDITOR

Cardiac magnetic resonance imaging as screening for cardiac sarcoidosis or not?

Vasileios Kouranos[1, 3], Rakesh Sharma[2, 3]

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Related article
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DOI: 10.33963/KP.a2022.0229

Received:
September 28, 2022

Accepted:
September 28, 2022

Early publication date:
September 30, 2022

In the last 2 decades, the wide use of cardiac magnetic resonance imaging (CMR) has revolutionized the diagnostic approach to patients with suspected cardiac sarcoidosis (CS). Several case series have shown that CMR alone was superior to the former (2007) Japanese Ministry of Health and Welfare (JMHW) guidelines on detecting myocardial involvement in patients with systemic sarcoidosis [1–8]. Furthermore, the identification of late gadolinium enhancement (LGE) on CMR; a marker for myocardial damage associated with cardiac sarcoidosis, was strongly associated with major adverse outcomes during follow-up [1–5]. As a result, CMR was considered a major diagnostic criterion in the Heart Rhythm Society expert consensus statement for diagnosis of CS in 2014 [9]. In that document, LGE on CMR in a pattern compatible with CS in patients with extra-cardiac sarcoidosis was consistent with at least probable cardiac involvement, when other causes were reasonably excluded. This was also acknowledged in the revised JMHW guidelines for diagnosis of CS [10].

While the role of CMR as a diagnostic tool has been widely accepted as the gold standard, its role as a screening tool in the general sarcoidosis population remains controversial. In the latest American Thoracic Society clinical practice guidelines in sarcoidosis, CMR was not recommended as part of the screening strategy [11]. Baseline evaluation of the general sarcoidosis population with cardiac symptoms and a 12-lead electrocardiogram (ECG) remain the recommended screening strategy [11]. Although CMR is expected to detect a higher prevalence of myocardial damage in the sarcoidosis population, clinical implications for an asymptomatic patient without rhythm or morphological abnormalities remain unclear. On the other hand, CMR was strongly recommended as the first-choice imaging modality in patients with suspected CS patients with cardiac symptoms and/or ECG abnormalities.

In this issue of the *Kardiologia Polska* (*Polish Heart Journal*), we read with interest the article regarding the role of CMR in the asymptomatic sarcoidosis population, which aims to shine light on the use of CMR in a subclinical setting [12]. In a cohort of 55 sarcoidosis patients with evidence of extra-cardiac disease, CMR managed to detect only 6% of cardiac involvement when used as a screening tool. None of the patients had cardiac symptoms, while all patients had no significant ECG abnormalities or morphological abnormalities on echocardiography or CMR at baseline. In addition, none of the patients was found to have elevated cardiac biomarkers such as troponin or BNP. Therefore, CS was an incidental finding in this population. No follow-up data were provided to evaluate the prognostic role of CS in this group of patients. A similar prevalence of CS (13%) was reported in a cohort of 61 Japanese sarcoidosis patients without any cardiac manifestations of CS [13]. In that study, the detection of LGE was not associated with any adverse events during follow-up. In a larger cohort of patients with extra-cardiac disease demonstrated by biopsy, CMR detected approximately 20% of CS in a subclinical

setting (lack of cardiac symptoms and/or ECG abnormalities) [3]. However, LGE on CMR was not associated with major adverse events during follow-up in the patients with subclinical disease in that study [3].

Current literature indicates that CMR has high sensitivity and specificity in identifying patients with CS and particularly those at higher risk of major arrhythmias during follow-up. CMR has clear superiority in evaluating cardiac morphology, in particular myocardial fibrosis, which has greater prognostic value than any other imaging modality in current use. In the study by Kouranos et al. [3], CMR was found to be superior to conventional tests such as 12-lead ECG, Holter monitoring, echocardiography, or a combination of those. What becomes crucial is identifying which suspected sarcoidosis patients should undergo CMR. Kysperska et al. [12] showed that it is unlikely to detect CS in the asymptomatic population without ECG or echocardiographic abnormalities, supporting the current guideline recommendations. However, we should acknowledge that the authors performed a comprehensive baseline assessment with all conventional tests such as 12-lead ECG, Holter monitoring, and echocardiography, as well as biomarker testing outside the guideline recommendations.

We support the measurement of serum biomarkers, such as NT-proBNP, and echocardiography for screening the sarcoidosis population. Modern echocardiographic techniques, such as speckle tracking, have been shown to be more sensitive in detecting myocardial involvement than conventional echocardiographic modalities. Such an approach in addition to the current strategy of assessment of cardiac symptoms and ECG abnormalities should be able to identify a higher number of patients suspected of CS. BNP and NT-proBNP are associated with both left and right ventricular strain, even at an early stage, and have been linked with CS [14]. Speckle tracking analysis is an echocardiographic technique that measures myocardial deformation and may be able to detect cardiac involvement of sarcoidosis earlier than conventional echocardiographic modalities [15]. In addition, regional wall motion abnormalities appear to be strongly associated with CS, which should be part of the routine echocardiographic assessment [15]. Finally, there was a weak association between elevated angiotensin converting enzyme levels and CS detection in the latest study presented in this issue of the *Kardiol Pol* [12]. This would raise suspicion as to whether the clinical impression of disease activity should be included in the screening strategy, and it should indicate the performance of CMR as a screening test. Further studies are warranted to identify the optimal screening strategy for CS. The association of CS with sudden cardiac death and high morbidity and mortality requires early and accurate diagnosis.

Article information

Conflict of interest: None declared.

Funding: None.

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Atrial fibrillation post-coronary or cardiac surgery: A transient inflammation-related event or the expression of a pre-existing arrhythmogenic atrial substrate?

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Related article
by Smukowska-Gorynia et al.

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DOI: 10.33963/KP.a2022.0212

Received:
September 4, 2022

Revision accepted:
September 5, 2022

Early publication date:
September 5, 2022

Atrial fibrillation (AF) is a common cardiac arrhythmia, occurring as a result of a complex interaction between cardiac substrate, triggers, precipitating factors, and altered autonomic nervous system activity [1]. AF may occur in the setting of patients undergoing both cardiac and non-cardiac surgery and may depend on several factors (Figure 1) [2–5]. Postoperative AF (POAF) usually occurs during the first postoperative week, more frequently after cardiac surgery than after non-cardiac surgery, and it is associated with worse outcomes as compared to patients who do not develop AF [2–5]. A recent systematic review and meta-analysis pooling data from six studies enrolling more than 2 000 000 patients showed that patients developing POAF after non-cardiac surgery had a four-fold higher risk of stroke and mortality as compared to controls during a median follow-up of 12 months [2]. In the setting of patients undergoing cardiac or coronary surgery, POAF usually occurs within the first 2 weeks, with a peak of incidence on the second and third postoperative day. POAF is considered the expression of an inflammatory process occurring at the cardiac level, which may be transient [5–7]. However, it is associated with lengthening of hospitalization, need for acute treatment, and need for anticoagulation [6].

In the current issue of *Kardiologia Polska* (*Polish Heart Journal*), Smukowska-Gorynia et al. [7] reported an interesting study on neopterin as a biomarker associated with the occurrence of AF following coronary artery bypass grafting (CABG). Neopterin is a marker of cellular inflammation linked to processes involving macrophages and dendritic cells, and its increase expresses increased oxidative stress [7]. The authors evaluated 101 consecutive patients with advanced coronary artery disease and without a history of AF undergoing CABG. They found that preoperative neopterin levels were associated with the occurrence of POAF, which was observed in 30% of patients. Other significant predictors of POAF were (1) higher body mass index, (2) history of pulmonary disease, (3) increased diastolic thickness of the interventricular septum, and (4) duration of operation. Most patients experienced POAF within the first 2–3 days after intervention and AF recurrence was observed in one-third of patients during the hospital stay. POAF required treatment with intravenous amiodarone in almost all cases, while only 1 patient was treated with electrical cardioversion. These findings suggest that preoperative neopterin levels may be a marker of AF occurrence, whose mechanism may be linked to the activation of inflammatory pathways. According to these interesting findings, this marker could be clinically helpful in discriminating between episodes of POAF elicited by transient inflammatory factors and episodes of POAF that are mainly an expression of a pre-existing arrhythmogenic atrial substrate, characterizing an "AF susceptibility" whereby patients are more prone to

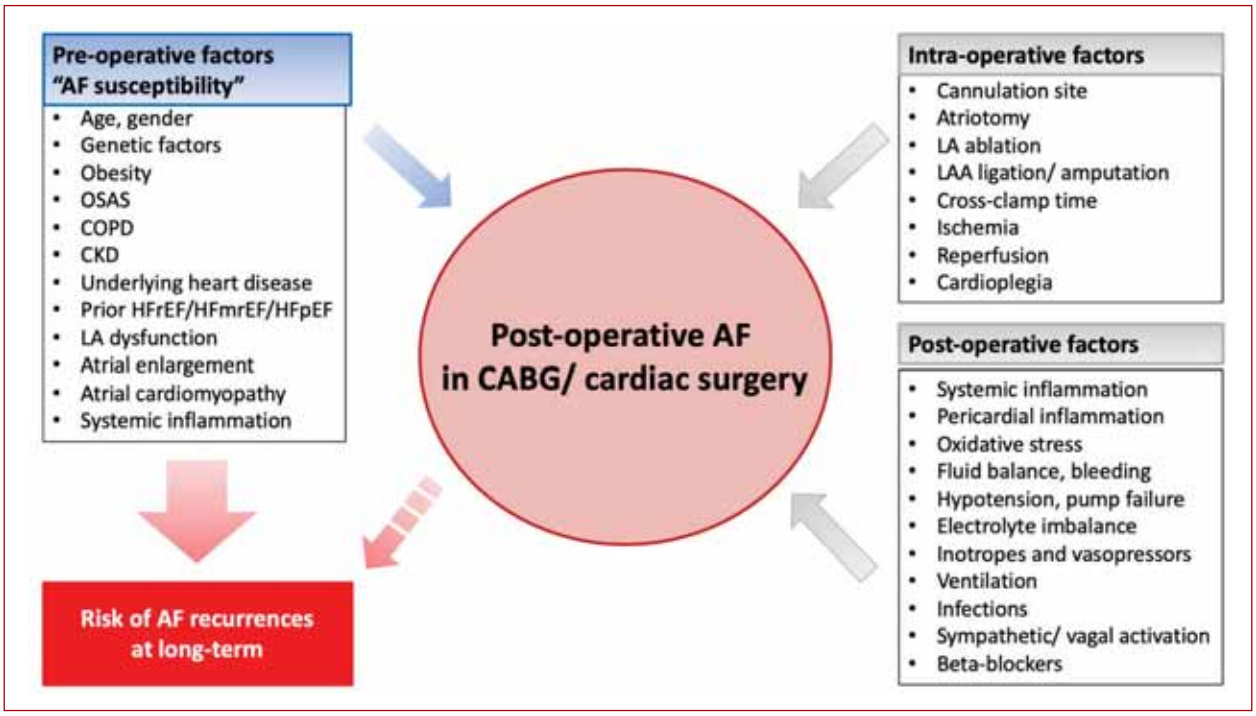

Figure 1. Pre, intra, and postoperative factors associated with postoperative atrial fibrillation after cardiac surgery and risk of long-term recurrences

Abbreviations: CABG, coronary artery bypass grafting; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LA, left atrial; LAA, left atrial appendage; OSAS, obstructive sleep apnea syndrome

develop AF in case of stressors typical of a post-operative phase, but also with a tendency to have recurrences of AF in the long term [2, 8] and AF progression. From a wider perspective, we could hypothesize that neopterin could be of clinical value in differentiating between the two conditions previously described and, therefore, help in better predicting the risk of AF recurrence in the long term after CABG, related to the underlying atrial substrate, independently of inflammation, thus contributing to improved knowledge in this complex field. Indeed, POAF has been traditionally considered as an event substantially linked to transient factors, therefore, with a limited risk of recurrences. However, recent long-term observational studies [2, 5] showed that both the risk of recurrences and the risk of stroke in the long term are much higher in patients with POAF (either after CABG or other types of surgery) as compared to controls. Unfortunately, no controlled study on the management of patients presenting with *de novo* AF in the postoperative phase is available, and also the guidelines [6] do not deliver evidence-based recommendations on how to manage patients with POAF in the long term. In the European Society of Cardiology guidelines [6], the recommendations for long-term oral anticoagulants (OAC) in POAF patients at risk of stroke (according to the CHA_2DS_2-VASc score) are of relatively low-grade: class IIb for patients in the setting of post-cardiac surgery and class IIa for non-cardiac surgery. In the setting of patients with AF treated with rhythm control, recent evidence-based recommendations suggest that early restoration of sinus rhythm is associated with a lower risk of adverse cardiovascular outcomes in the long term [9]. However, these recommendations are not strictly related to POAF and direct evidence is needed in this context. Indeed, no specific trial addressed the issue of cardioversion of recent-onset AF after surgery. We think that in POAF with no resumption of sinus rhythm within a few hours, a personalized approach to cardioversion should be advocated, including a"watchand-wait" approach, pharmacological cardioversion, or electrical cardioversion depending on the patient's profile (e.g.: hemodynamic status, presence of structural heart disease, symptoms, and fluid and electrolyte balance) and organizational issues [10].

We think that the findings of the study by Smukowska-Gorynia et al. [7] can help to characterize the occurrence of POAF as mainly related to transient inflammatory factors rather than linked to an underlying arrhythmogenic substrate prone to AF. This distinction can be of value for future prospective studies aiming to assess the risk of stroke and adverse outcomes in the long term and the effectiveness of OAC in POAF patients at risk. Unfortunately, the study by Smukowska-Gorynia et al. [7] did not provide information on long-term follow-up. Therefore, long-term clinical implications of high levels of neopterin and the real incidence of AF in the long-term in this cohort of patients remain at present unknown and deserve future prospective studies.

The issue of detecting POAF is particularly complex since AF may occur as an asymptomatic event, and the ability to identify this arrhythmia may strictly depend on the intensity of cardiac monitoring. This may vary and range from the duration of monitoring with telemetry, execution of 12-lead ECG at standardized time intervals after surgery, up to the planning of intermittent Holter recordings, or even continuous monitoring through implanted devices, further enhanced by remote monitoring functions [11]. In the latter context, indeed, it is known that episodes of atrial tachyarrhythmia lasting a few minutes are commonly detected by cardiac implantable electronic devices and may progress to clinical AF in up to 30% of patients at 2-year follow-up [12, 13]. Since AF is strictly linked to a variety of factors (Figure 1), such as patients' age and a variable combination of cardiac substrate, triggers, precipitating factors, and altered autonomic modulation, it appears that, in this context, individualized decision-making is needed also with regard to indication for long-term OAC and extent of monitoring for patients in whom anticoagulation is not established or is prescribed for a limited period after surgery [14]. In the future, improved and more specific diagnostic tools to better characterize the underlying cardiac substrate in terms of atrial cardiomyopathy will help to predict the risk of AF in the long term, independently of transient risk factors, and this is a field of increasing interest and research [15]. So far, clinical guidelines [6] have not specifically addressed in depth the complex scenario of POAF, either in coronary/cardiac surgery or non-cardiac surgery. Notably, it is still unclear how to optimally stratify the risk of recurrences and the risk of stroke in these patients [2, 6].

Finally, the findings by Smukowska-Gorynia et al. [7] can open the way to prospective studies evaluating the impact of interventions aimed to reduce inflammation in patients at higher risk of POAF, who could be identified by higher baseline neopterin levels. A baseline status prone to more intense activation of the inflammatory pathway may portend a higher risk of POAF and identify a subset of patients who may benefit from specific prophylactic interventions aiming at reducing peri-operative inflammation. In more general terms, improvement in risk stratification and effectiveness of treatments for AF patients, including patients with POAF, will depend on the close collaboration between basic scientists and physicians involved in clinical trials, trying to bridge the gap between bench and bedside.

Article information

Conflict of interest: GB received a small speaker fee from Bayer, Boehringer Ingelheim, Boston, Daiichi-Sankyo, and Janssen outside the present article. No fees are received personally. The other authors declare no conflict of interest.

Funding: None.

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REVIEW

A new approach to statin therapy in carotid atherosclerosis: Targeting indices of plaque vulnerability in addition to lipid-lowering. A narrative review

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DOI: 10.33963/KP.a2022.0155

Received:
May 31, 2022

Accepted:
June 10, 2022

Early publication date:
June 13, 2022

ABSTRACT

Novel imaging techniques and biomarkers have emerged as surrogate markers of carotid plaque vulnerability. In parallel, statin administration in patients with established carotid atherosclerosis not requiring revascularization has reduced the number of consequent cerebrovascular events. This reduction is not only attributed to the lipid-lowering properties of statins but also to their pleiotropic actions. The present literature review aimed to summarize the stabilizing effects of statins on carotid plaques based on imaging modalities and biomarkers and propose an alternative approach to their implementation. Moreover, we assessed the perioperative use of statins in patients undergoing carotid revascularization and the impact of aggressive vs. conventional statin therapy. Recent studies using: (1) ultrasound indices of plaque echogenicity; (2) fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) scans for plaque inflammation assessment; or (3) magnetic resonance imaging (MRI) scans quantifying intraplaque hemorrhage, and lipid-rich necrotic core (LRNC) have shown quite promising results in evaluation of carotid plaque vulnerability. Based on those imaging modalities, a growing number of studies have demonstrated a very modest carotid plaque regression due to/induced by statins, while their stabilizing impact is disproportionally higher. Other studies assaying several biomarkers (e.g. inflammation, etc.) have confirmed a statin-induced carotid plaque stabilization. All the aforementioned benefits followed a dose-dependent pattern of statins, on top of the low-density lipoprotein cholesterol (LDL-C) target in current guidelines. In the case of symptomatic patients with carotid atherosclerosis suitable for revascularization, robust evidence implicates a significant statin-related reduction of perioperative cardiovascular risk only in patients undergoing endarterectomy.

Key words: statins, carotid plaque vulnerability, pleiotropic effects, biomarkers

INTRODUCTION

Carotid atherosclerosis has been associated with acute ischemic cerebrovascular events and high morbidity and mortality in western countries [1]. It is undoubtful that symptomatic patients with carotid atherosclerosis should be treated with invasive methods. So far, the risk stratification of asymptomatic patients with established carotid atherosclerosis has been based on the degree of carotid artery lumen encroachment. However, such an approach cannot predict ischemic strokes or transient ischemic attacks (TIAs) that occur frequently in patients with more or less moderate carotid stenosis. The unstable carotid plaque, prone to rupture, is strongly related to cerebrovascular ischemic events and does not parallel the degree of carotid stenosis [2]. Unstable plaques have specific characteristics, like lipid accumulation, inflammatory cell infiltration, less calcification, thin fibrous cap, etc. [3]. The early detection of those plaques before symptoms occurrence remains a great challenge for imaging techniques. In the absence of a "gold standard" imaging modality, several imaging markers have been

proposed, such as low echogenicity on ultrasound, high inflammatory burden on positron emission tomography (PET) scans, and large lipid core or neovascularization on magnetic resonance imaging (MRI) views, monitoring the aforementioned pathophysiologic mechanisms. Despite the growing evidence, their application in current clinical decision-making and risk stratification of patients with carotid atherosclerosis is limited.

Moreover, the presence of vulnerable carotid plaques is associated with a high risk of not only ischemic strokes but also other atherosclerotic cardiovascular events implicating a systematic process in a "vulnerable" patient [4, 5]. As an adjunct to vascular imaging, a long list of circulating molecules, known as biomarkers, has been proposed for the detection of vulnerable plaques and "vulnerable" patients [6–8]. Among biomarkers, those depicting inflammation [9], vascular calcification [10], and neovascularization [11] have been more studied showing a strong relationship with histopathological features of carotid plaque vulnerability and cardiovascular events [12, 13].

The majority of patients with carotid atherosclerosis are asymptomatic, requiring close monitoring and intensive pharmaceutical therapy to prevent the destabilization of initially stable carotid plaques. Statins have long been the mainstay of treatment of patients with asymptomatic significant (>50%) carotid stenosis [14]. The current guidelines recommend a target of serum low-density lipoprotein cholesterol (LDL-C) <70 mg/dl or decreasing by ≥50% if the initial LDL-C level ranges between 70 and 135 mg/dl in patients with peripheral artery disease [15]. Such a pharmaceutical approach is associated with reduced all-cause and cardiovascular mortality and cerebrovascular morbidity [16, 17]. In the case of patients requiring carotid revascularization (symptomatic and asymptomatic), most, but not all, studies have shown favorable outcomes from the perioperative use of statins [18, 19].

In all aforementioned algorithms with statins, their prescription is entirely guided by LDL-C levels. However, their efficacy is dose-dependent, and it is attributed not only to their lipid-lowering effects but additionally to the pleiotropic actions leading to the improvement of carotid plaque texture and the reduction of the overall cardiovascular risk [20]. Therefore, it is wise to modify the therapeutic target of statin therapy to a composite endpoint combining LDL-C reduction with favorable changes in plaque stability and the patient's risk profile quantified by imaging techniques and biomarkers. The present literature review summarizes the stabilizing mechanisms of statins using imagingand biomarkers-based data in either asymptomatic patients with carotid atherosclerosis under pharmaceutical treatment or patients undergoing carotid revascularization, supporting an alternative target of their usage. We also comment on the perioperative manipulation of statins ending up with more aggressive therapy.

SEARCH STRATEGY

This is a traditional literature review with a more critical appraisal of the targets of lipid-lowering therapy in patients with carotid atherosclerosis. A literature search in the English language was conducted for publications in MEDLINE and EMBASE, Web of Science, Cochrane, and Google Scholar databases from 1990 to June 2021. The reference lists of the identified articles were checked for any additional relevant articles. The following search terms, in titles and abstracts, including Medical Subject Headings (MeSH) were used: carotid plaque, carotid artery stenosis, carotid atherosclerosis, carotid artery disease, lipid-rich necrotic core, magnetic resonance imaging, plaque imaging, carotid artery stenting (CAS), carotid endarterectomy (CEA), statins, and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor. Two investigators (NV and EK) independently performed the literature search. We further limited our literature search by setting the following inclusion criteria: randomized and non-randomized prospective studies, published only in the English language, enrolling at least 10 patients in each pharmaceutical arm. We excluded studies with retrospective or cross-sectional or review designs and those using animals, children, or adolescents. Applying several terms and inclusion and exclusion criteria, we attempted a more systematic approach to reviewing the existing literature. However, we did not follow the methodology of full systematic review, weakening the power of our review.

Based on abstracts and titles, we initially found 1649 potentially eligible studies. After full-text screening, we excluded another 1584 studies because they did not provide adequate information (conference abstracts, small samples, wrong design, etc.). We ended up with 65 clinical trials including five systematic reviews and meta-analyses for several aspects of our subject (Figure 1).

EFFECTS OF STATINS ON IMAGING-BASED ASSESSMENT OF CAROTID PLAQUE VULNERABILITY

Effects of statins on MRI-based carotid plaque vulnerability

High-resolution MRI has been recently proposed for the evaluation of atherosclerotic plaque vulnerability. MRI can illustrate in detail the components of the atherosclerotic plaque, arterial wall, and surrounding soft tissues [21–24]. Notably, it can adequately quantify the main features of the vulnerable plaque, IPH, ulceration, lipid-rich necrotic core (LRNC), calcification, intraplaque neovascularization (IPN), and inflammation [25–27]. Both intraplaque hemorrhage and LRNC have emerged as predictors of both cardiovascular and cerebrovascular events in patients with carotid atherosclerosis, indicating their clinical significance as indices of systemic, high cardiovascular risk [28, 29].

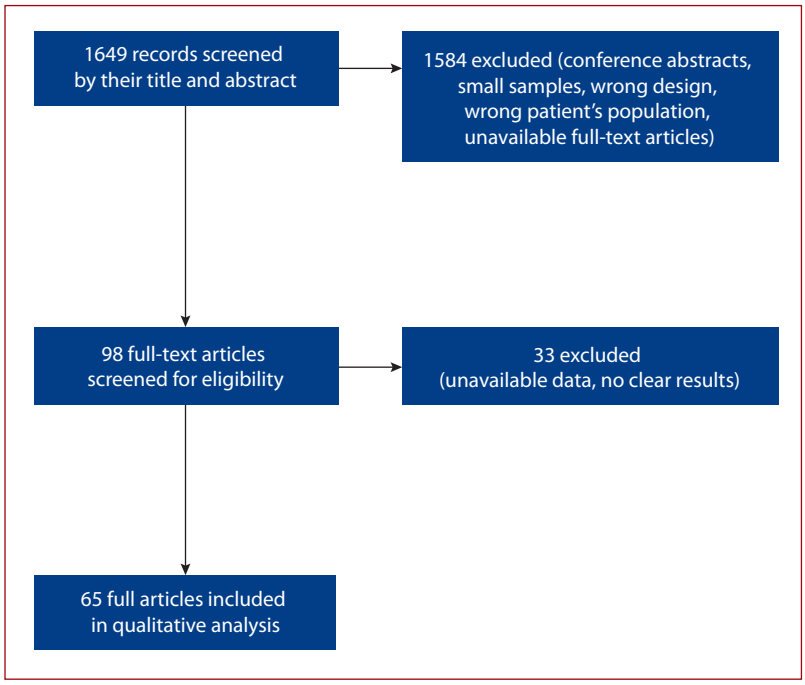

Figure 1. Flow chart showing a selection of studies in the literature review

Despite some integral technical limitations, such as being time-consuming, showing artifacts, and contrast-induced artifacts, MRI can assess non-invasively statin-induced changes in carotid plaque morphology [23, 30]. A recent systematic review [31] included seven prospective studies (a total of 361 patients with carotid atherosclerotic disease) and examined changes in LRNC volumes and lumen volumes after statin therapy for at least one year. The vast majority of prospective studies reported a significant reduction in LRNC volumes, without any significant change in plaque burden. The small sample size of included studies and their large heterogeneity in doses and types of statins were important limitations of that meta-analysis.

Lipid-core regression can be a representative mechanism of statin-induced plaque stabilization [32]. The latest prospective studies [22, 33] using 3T MRI imaging have confirmed the statin-induced reduction in lipid percentage and lipid volume within the carotid plaque after intensive statin therapy. Notably, MRI images showed a dose-dependent counterregulatory effect of pitavastatin (4 mg/d vs. 2 mg/d) on lipid core, plaque thickness, and lumen area [22]. In parallel, MRI can detect IPN, which is associated with a high risk of plaque rupture and consequent events [34–36]. A recent prospective study (Du et al. 2019 [34]) reported a significant reduction in adventitial and IPN over two years with rosuvastatin therapy. Notably, that effect peaked in the first 3 months after rosuvastatin initiation.

Therefore, MRI has the potential to quantify carotid plaque vulnerability and stabilizing effects of statin therapy by assessing the changes in lipid content and neovascularization [33, 34]. Future studies will clarify whether an MRI-based algorithm could tailor the optimal statin therapy in patients with carotid atherosclerosis.

Effects of statins on ultrasound-based carotid plaque vulnerability

Ultrasonography of the carotid arteries is an old, widely used imaging modality for the assessment of carotid plaque morphology. Carotid ultrasound constitutes a cost-effective, easily performed, non-invasive, reproducible technique for the evaluation of the degree of carotid stenosis and the vulnerability of carotid atheromatous plaques. Plaques rich in lipid and hemorrhagic content appear echolucent while those with fibrous or calcific content appear echogenic. Prospective studies have documented the strong association between low echogenicity and carotid plaque vulnerability, the latter clinically manifested with neurological symptoms and/or ipsilateral to plaques ischemic lesions on brain scans [12]. Moreover, plaque echolucency has been also associated with a high occurrence of adverse cardiovascular events, as an expanded measure of "vulnerable" patients[5]. The traditional role of ultrasound in this context is the estimation of the grayscale median (GSM) or the integrated backscatter. Both scales have been applied in carotid atherosclerosis, but their validation as prognostic modalities requires more evidence.

A meta-analysis of nine studies (566 patients) published in 2015, investigated the impact of statins on carotid plaque echogenicity [37]. The important finding of that meta-analysis was the statin-induced amelioration of carotid plaque echogenicity and other features of plaque stability, independently of changes in the plaque size (e.g.

thickness, area, volume). Most importantly, the authors described a dose-dependent pattern of statin-induced plaque echogenicity since it was more profound when higher doses were administered. Probably, the pleiotropic (e.g. anti-inflammatory) rather than lipid-lowering properties of statins, might provide a plausible explanation for this pattern. Since 2015, three more studies [38–40] have been published investigating the effect of statins on carotid plaque echogenicity. Those studies examined different statin class members (atorvastatin 20–80 mg/d, pitavastatin 2 mg/d, pravastatin 10 mg/d) in patients with already existing carotid plaques and stroke or hypercholesterolemia for 6–12 months. All three studies showed an increase in carotid plaque echogenicity. Notably, statin-related reduction in high-sensitivity C-reactive protein (hs-CRP) was inversely correlated with the increase of the GSM [38]. Advances in carotid ultrasound allow for the measurement of carotid total plaque area, which has been associated with a high rate of cardiovascular events (stroke/myocardial infarction/revascularization) [41]. Intensive pharmaceutical interventions, among them statin administration, reduce total plaque area, which results in a decline in clinical adverse events. Newer ultrasonographic techniques have also emerged, such as superb microvascular imaging (SMI), contrast-enhanced ultrasound (CEUS), and carotid plaque elasticity [42]. Preliminary data have suggested the association of statin therapy with less IPN, based on SMI and CEUS, but their diagnostic accuracy should be further tested [40]. Regarding the underlying mechanisms of statin-induced carotid plaque echogenicity (a higher GSM score), this probably derives from increased plaque calcification, usually observed with statins [10]. Hence, carotid ultrasound has the potential to easily assess changes in plaque composition, but more studies are required to validate the impact of statin therapy on ultrasound-based "vulnerable" plaques and clinical outcomes.

Effects of statins on fluorodeoxyglucose-positron emission tomography/computed tomography--based assessment of carotid plaque vulnerability

PET/computed tomography (CT) has been proposed as a useful tool for the detection of arterial wall inflammation implicating atherosclerotic plaque vulnerability [43]. In assessing the noninvasive quantification of inflammation--related plaque metabolism, 18-fluorodeoxyglucose (FDG) radiotracer accumulates in plaque macrophages, depicting the severity of atherosclerotic plaque inflammation [44]. In other words, PET/CT can detect even small changes in arterial wall inflammation, which is a unique property among other imaging techniques or biomarkers. So far, seven prospective studies have used scintigraphy to evaluate the impact of statins on carotid plaque inflammation by measuring target-to-background ratio (TBR) (n = 5 studies) [45–48] and/or standardized uptake value (SUV) (n = 3 studies) [39, 49, 50]. Most of them supported a significant reduction of arterial wall inflammation after either 3-month atorvastatin (10–80 mg/d)[46, 48–50] therapy, or 1-month atorvastatin (20 mg/d) [45] administration, or 6-month therapy with either simvastatin (10 mg/d), rosuvastatin (10 mg/d) [39], pitavastatin (2 mg/d), or pravastatin (10 mg/d) [39]. Only one study failed to show such an effect [46]. Although none of those studies co-evaluated the clinical outcomes along FDG-PET/CT scan findings, the results indirectly suggest that statin administration favorably changes plaque texture by suppressing intraplaque inflammation [48]. This could decide unambiguously the dosage of statins.

Table 1 summarizes the up-to-date data on statin--induced effects on novel imaging markers of carotid plaque vulnerability based on imaging modalities.

Limitation of imaging markers

Overall, the absence of cut-off values remains the great disadvantage of novel imaging markers for their clinical application in patients with carotid atherosclerosis. The favorable statin-induced changes in imaging parameters should be graded based on validation studies. Unambiguously, carotid ultrasound seems to be the most cost-effective among all imaging techniques; and it is also superior in terms of saving time, feasibility, and reproducibility. There is a plethora of prospective data supporting its accuracy, which makes it a first-line choice for monitoring patients with asymptomatic carotid atherosclerosis.

EFFECTS OF STATINS ON BIOMARKERS OF CAROTID PLAQUE VULNERABILITY

Inflammatory biomarkers

Inflammatory biomarkers play a key role in carotid artery disease, mediating plaque progression and vulnerability. In parallel, statins exert anti-inflammatory properties with potential stabilizing effects on atherosclerotic plaques [51]. Twenty-four prospective clinical trials have assessed the influence of statins on carotid plaque vulnerability concomitantly with the modulation of circulating inflammatory biomarkers. Based on imaging indices of plaque vulnerability, such as PET scans [47, 48–50, 52] and carotid plaque echogenicity [53, 54], most of those studies suggested an improvement in plaque stability after statin administration, accompanied by a significant reduction in inflammatory biomarkers. Those studies used the most known inflammatory biomarkers, like CRP [47–49, 53–59], interleukin (IL)-6 [53, 55–57, 59], tumor necrosis factor (TNF)-a [49, 54, 56, 59], and monocyte chemoattractant protein-1 [49]. Nevertheless, two studies[52,58] failed to demonstrate the stabilizing effects of statins despite their anti-inflammatory action while other studies failed to find any effect of statins on the aforementioned anti-inflammatory biomarkers at all. Using less-known inflammatory biomarkers such as tumor necrosis factor receptor (TNFR)-I and II [58], IL-2, -8, -10, -18, -23, interferon-γ, transforming growth factor (TGF)-β [59], pentraxin-3 [49], and others, statins have shown anti-inflammatory impact as well. The association

Table 1. Studies investigating the effects of statins on carotid plaque vulnerability based on novel imaging modalities

Authors	Population (number, underlying disease)	Protocol design (type, duration, groups, dose)	Novel imaging markers
MRI			
Feng T 2017 [22]	50 patients with carotid atherosclerosis	Randomized (48 weeks) • 26 patients PITA (2 mg/d) • 24 patients PITA (4 mg/d)	↓ Lipid core area ↓ Plaque thickness ↓ Wall area ↓ Normalized wall index ↓ Lumen area (dose-dependent effect of PITA)
Brinjikji W 2017 [31]	Systematic review: 7 studies (8 treatment arms), 361 patients with carotid atherosclerosis	Non-randomized (3–24 months) Various statins	↔ Wall volume ↔ Lumen volume ↓ LRNC volume
Alkhalil M 2018 [33]	21 statin-naive patients with ACS	Non-randomized (3 months) ATOR (80 mg/d)	↓ Carotid lipid (%) ↑ Carotid fibrous (%)
Du R 2019 [34]	43 statin-naive patients with asymptomatic carotid atherosclerosis underwent	Non-randomized (3, 12 and 24 months) ROSU (5–20 mg/d) & DCE-MRI	↓ Adventitial & plaque vascularity ↔ Adventitial & plaque vascular permeability
Carotid ultrasound			
Ibrahimi P 2015 [37]	Systematic review: 9 studies (11 treatment arms), 566 participants with carotid atherosclerosis	5 prospective open-label studies and 4 RCTs Mean follow up: 7.2 months ATOR, SIMVA, PRAVA, PITA, and ROSU	↑ Plaque echogenicity ↓ hs-CRP (dose-dependent statin effect)
Marchione P 2015 [38]	210 patients with recent symptomatic ischemic cerebrovascular event (TIA, minor stroke, major stroke)	Randomized (12 months) • 68 patients ATOR (80 mg/d) • 69 patients ATOR (40 mg/d) • 73 patients no statin	↑ Plaque echogenicity ↑ GSM score ↔ Plaque thickness ↔ Degree of stenosis ↓ hs-CRP
Zhu Y 2019 [40]	82 patients with carotid atherosclerosis	Randomized (6 months) • 39 patients ATOR (20 mg/d) • 43 patients control group	↓ Intraplaque neovascularization (CEUS and SMI)
F^{18}-FDG-PET			
Kim CJ 2020 [45]	Statin-naive patients with ACS and non-calcified carotid plaques	Non-randomized (1 month) ATOR (20 mg/d)	↓ TBR
Hoogeveen RM 2021 [46]	14 patients with CKD stage 3 or 4 (eGFR = 15–60 ml/min/1.73 m^2)	Non-randomized (12 weeks) ATOR (40 mg/d)	↔ TBR
Oh M 2019 [47]	50 patients with ACS	Randomized (6 months) • 25 patients Ezetimibe/SIMVA (10/10 mg/d) • 25 patients ROSU (10 mg/d)	↓ Plaque inflammation ↓ TBR
Tawakol A 2013 [48]	67 subjects with risk factors or established carotid atherosclerosis	Randomized (4 weeks and 12 weeks) • ATOR (10 mg/d) • ATOR (80 mg/d)	↓ TBR (dose-dependent reduction)
Komatsu T 2021 [49]	31 statin-naive patients w/ carotid atherosclerosis	Randomized (12 weeks) • 15 patients dietary management • 16 patients ATOR (10 mg/d)	↓ Arterial inflammation (carotid and thoracic aorta) ↓ 18-FDG uptake
Van der Valk F 2016 [50]	24 patients with AS 20 controls age- and sex-matched	Non-randomized (3 months) ATOR (40 mg/d)	↓ Carotid arterial wall inflammation ↓ 18-FDG uptake
F^{18}-FDG-PET + carotid ultrasound			
Watanabe T 2015 [39]	20 patients high risk of atherosclerosis or in need of statin treatment	Randomized (6 months) • 10 patients PITA (2 mg/d) • 10 patients PRAVA (10 mg/d)	↓ TBR (in the PITA group) ↓ CIMT (PITA group) ↑ CIMT (PRAVA group) ↓ SUV ↑ Plaque echogenicity

Abbreviations: ACS, acute coronary syndrome; AS, ankylosing spondylitis; ATOR, atorvastatin; CEUS, contrast enhanced ultrasound; CIMT, carotid intima-media thickness; DCE-MRI, dynamic contrast-enhanced MRI; FDG, fluorodeoxyglucose; GSM, gray scale median; hs-CRP, high-sensitivity C-reactive protein; LRNC, lipid-rich necrotic core; MRI, magnetic resonance imaging; PET, positron emission tomography; PITA, pitavastatin; PRAVA, pravastatin; RCTs, randomized controlled trials; ROSU, Rosuvastatin; SIMVA, simvastatin; SMI, superb microvascular imaging; SUV, standardized uptake value; TBR, target-to-background ratio; TIA, transient ischemic attack

between carotid plaque stabilization and suppressed inflammation after statins was observed across heterogeneous studies using a wide spectrum of statins, doses, and therapy duration. Nevertheless, the inhibition of inflammatory pathways remains among the predominant pleiotropic mechanisms of intensive statin therapy, leading to histopathologically stable carotid plaques and fewer cardiovascular events [60–62]. Provisionally, close monitoring of those biomarkers in statin-treated patients could predict atherosclerotic plaque destabilization and cardiovascular disease progression (Figure 2).

Neovascularization

Intraplaque neovascularization is a characteristic feature of vulnerable plaques, associated with carotid plaque rupture and stroke recurrence [63]. Unfortunately, only small-cohort studies have examined the impact of statins on IPN. Four previous studies have assessed IPN using

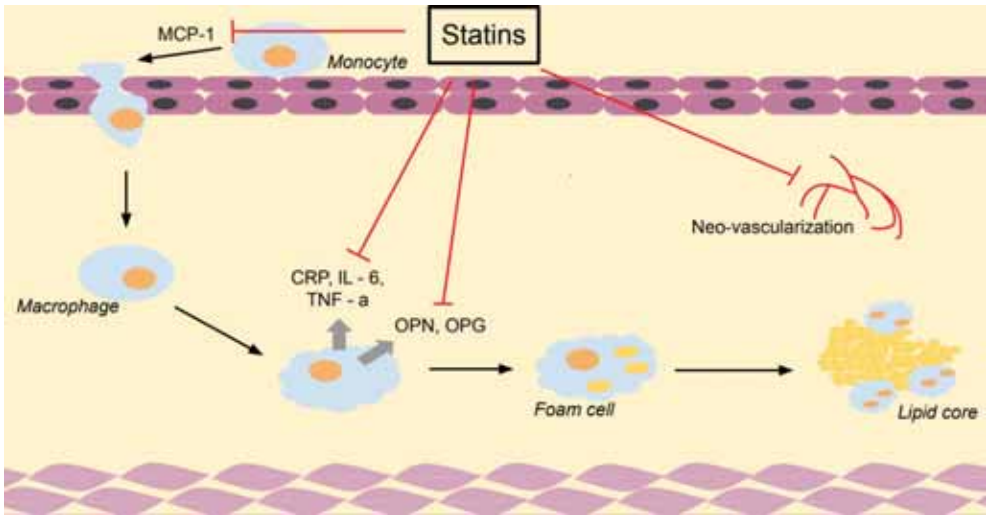

Figure 2. Stabilizing effects of statins on the carotid atherosclerotic plaque by suppressing inflammation and neovascularization

Abbreviations: CRP, C-reactive protein; IL, interleukin; MCP, monocyte chemoattractant protein; OPG, osteoprotegerin; OPN, osteopontin; TNF-a, tumor necrosis factor-a

CEUS. All of them suggested reduced IPN after either 6-month statin therapy [40, 64], or 24-month atorvastatin administration (20 mg/d) [65], or angiotensin-converting enzyme inhibitors and statins treatment [66]. Similarly, in 45 statin-naive patients with asymptomatic carotid atherosclerosis, 24-month rosuvastatin therapy (5–20 mg/d) reduced the MRI-based IPN[34]. The main limitations of the existing studies are the small number of participants and short duration of therapy [34]. To our knowledge, a single study [67] has reported an inverse relationship between the statin-induced regression of IPN within carotid plaques and stroke incidence. Those atheroprotective mechanisms of statins may be attributed to their favorable effects on endothelial cell proliferation and nitric oxide (NO) bioavailability [68–70]. Therefore, larger studies are needed to confirm the negative impact of statins on IPN, the underlying mechanisms, and the clinical relevance.

Calcification

Osteopontin (OPN) and osteoprotegerin (OPG) constitute potent inhibitors of osteoclastogenesis and vascular calcification and are secreted by a plethora of tissues, including endothelial cells, vascular smooth muscle cells, and macrophages [71–72]. OPN is a multifunctional phosphoprotein, and OPG is a member of the TNF-related family and part of the receptor activator of nuclear factor-B ligand (RANKL). Both of them have been involved in several inflammatory conditions, such as autoimmune diseases, atherosclerosis, and vascular calcification [73], and they have been associated with cardiovascular mortality [74, 75].

Scarce data support the influence of statins on blood regulators of vascular calcification [76].So far, only three studies have investigated the effect of statins on circulating levels of OPN and OPG in patients with carotid artery disease [77–79]. In particular, patients with symptomatic or asymptomatic established carotid atherosclerosis were treated with atorvastatin 10–80 mg/d for 6 to 12 months. Statin administration significantly reduced OPN and OPG levels in a dose-dependent manner. Simultaneously, the GSM score was inversely correlated to the atorvastatin-induced changes in OPN and OPG levels [77, 78]. That led to a mechanistic explanation of an inverse relationship between atherosclerotic calcification triggered by statins and carotid plaque vulnerability. Although this hypothesis seems attractive, it has two important drawbacks. First, it should be further tested in studies evaluating clinical outcomes and not only surrogate markers, like the GSM [10]. Second, the interplay between statins and vascular calcification is more complex. The latter comprises an essential part of atherosclerosis development but is a less common characteristic in advanced, vulnerable atherosclerotic plaques. Statins seem to exert a dual action. On the one hand, in developing atherosclerotic plaques, they can slow down or even inhibit atherogenic mechanisms, like calcium deposition [80]. On the other hand, in established and advanced atherosclerotic lesions, they may increase the calcification density [81]. This working hypothesis has been derived from extensive research about the interpretation of higher calcium scores in the coronary artery tree among statin users [82]. The calcium score is an unambiguous index of atherosclerosis progression, but the clinical meaning of its modification by statins is still complex. Extrapolating those results to carotid artery disease, more studies with a larger number of patients need to be conducted to verify the interplay between statin use, the serum levels of vascular calcification inhibitors, the stabilization process via calcification, and the net effect on the overall cardiovascular risk. Table 2 depicts the combined application of biomarkers and imaging techniques for the assessment of carotid plaque vulnerability.

Table 2. Studies investigating the effects of statins on carotid plaque vulnerability based on a combined assessment of biomarkers and imaging markers

Authors	Population (number, underlying disease)	Protocol design (type, duration, groups, dose)	Biomarkers	Novel imaging markers
Komatsu T 2021 [49]	31 statin-naive patients carotid atherosclerosis	Randomized (12 weeks): 15 patients dietary management 16 patients ATOR (10 mg/d)	↓ CRP ↓ S100A12 ↔ TNF-a ↔ MCP-1 ↔ Pentraxin 3	↓ Arterial inflammation (carotid and thoracic aorta) by FDG-PET/CT ↑ FMD
Oh M 2020 [52]	48 patients ACS	Randomized (6 months) ROSU (20 mg/d) Ezetimibe/ROSU (10 mg/5 mg/d)	↓ hs-CRP (ezetimibe/ /ROSU group)	↔ TBR (PET)
Oh M 2019 [47]	50 patients ACS	Randomized (6 months) 25 patients Ezetimibe /SIMVA (10/10 mg/d) 25 patients ROSU (10 mg/d)	↔ hs-CRP	↓ Atherosclerotic plaque inflammation ↓ TBR
Van der Valk F 2016 [50]	24 patients AS 20 age-, sex- matched controls	Non-randomized (3 months) ATOR (40 mg/d)	↓ CRP	↓ Carotid arterial wall inflammation (by FDG-PET/CT)
Watanabe T 2015 [39]	20 patients	Randomized (6 months) 10 patients PITA (2 mg/d) 10 patients PRAVA (10 mg/d)	↔ -CRP	↓ TBR (PITA group)
Tawakol A 2013 [48]	67 patients cardiovascular risk factors or established atherosclerosis	Randomized (4 weeks and 12 weeks) ATOR (10 mg/d) ATOR (80 mg/d)	↔ hs-CRP	↓ TBR (dose-dependent reduction)
Yamagami H 2008 [53]	81 patients hypercholesterolemia + carotid atherosclerosis	Non-randomized (12 months): 41 patients no statin 24 patients SIMVA (10 mg/d) 16 patients ATOR (5 mg/d)	↓ hs-CRP ↓ IL-18 ↔ IL-6	↓ Plaque thickness ↑ Plaque echogenicity
Nakamura T 2008 [54]	65 patients ACS + echolucent carotid plaque	Randomized (1 month): 33 patients PITA (4 mg/d) 32 patients placebo	↓ CRP ↓ VEGF ↓ TNF-a ↓ Total cholesterol ↓ Triglycerides ↓ LDL-C	↑ Plaque echogenicity
Kadoglou N 2008 [77]	97 patients with carotid atherosclerosis mot requiring intervention 52 age- and sex-matched controls	Non-randomized (6 months) 97 patients ATOR (10–80 mg/d) target LDL-C <100 mg/dl 52 controls no treatment	↓ hs-CRP ↓ OPG ↓ OPN	↑ GSM
Kadoglou N 2010 [79]	140 patients with symptomatic or asymptomatic moderate carotid atherosclerosis not requiring intervention	Randomized (12 months) 70 patients moderate therapy: ATOR (10–20 mg/d) target LDL-C <100 mg/dl 70 patients aggressive therapy: ATOR (80 mg/d) target LDL-C <70 mg/dl	↓ hsCRP ↓ OPG ↓ OPN (dose-dependent manner)	↑ GSM (significant increase after aggressive therapy)

Abbreviations: AS, ankylosing spondylitis; CT, computed tomography; FMD, flow-mediated dilatation; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; MCP, monocyte chemoattractant protein; OPG, osteoprotegerin; OPN, osteopontin; TBR, target-to-background ratio; TNF-a, tumor necrosis factor-a; VEGF, vascular endothelial growth factor; other — see Table 1

Thrombosis

A few other biomarkers have been targeted by statin interventions with regard to their correlation to carotid plaque vulnerability and cardiovascular morbidity and mortality. Tissue factor (TF) is a glycoprotein, derived from activated macrophages and T cells. It is highly expressed in unstable atheromatous plaques and relates to the coagulation cascade [83]. Two studies have examined the effect of statin use on TF expression in carotid plaques extracted from patients undergoing CEA. Both of them found less TF protein expression within carotid plaques from statin-treated patients, without any influence on tissue factor pathway inhibitor [84, 85]. Perhaps, this may lead to a suppressed thrombotic response to plaque rupture, and consequently to a reduced incidence of ipsilateral stroke.

Limitations of biomarkers

Biomarkers are easy to use, accessible, relatively cheap, and repeatable tools for the surveillance of many diseases and monitoring the efficacy of their therapeutic regimens. Numerous biomarkers can be easily assayed in blood samples, but their levels may be affected by co-morbidities or medications while their circulating levels do not exclusively express the local plaque destabilization process, confounding the interpretation of their changes. Moreover, their use at the moment is limited to research purposes.

PERIOPERATIVE TREATMENT WITH STATINS OF PATIENTS WITH CAROTID ATHEROSCLEROSIS

The systematic use of statins is increasing during the perioperative period of carotid revascularization, either CEA or CAS. Substantial evidence supports using statins before major vascular operations as a measure to reduce the perioperative incidence of major complications/death [86]. A meta-analysis of six studies (7 053 patients) undergoing CEA demonstrated a lower periprocedural death rate in statin-treated patients compared to statin-naive

patients, without affecting the risk of stroke [87]. A more recent systematic review analyzed seven studies of 21 387 CEA-treated patients and confirmed reduced mortality associated with statin treatment persistent for a longer mean follow-up period (62 months) [88]. That meta-analysis described also a lower incidence of periprocedural stroke as a result of statin administration. Lastly, a similar meta-analysis (four studies of 4 978 patients) showed better survival rates and decreased risk of stroke when statins were used before CEA [89]. In conclusion, in patients undergoing CEA, the early prescription of statins unambiguously reduces mortality and, possibly, stroke incidence, but more studies are needed.

In the case of patients undergoing CAS, a single meta-analysis including 11 studies and 4 088 patients documented lower rates of perioperative ischemic stroke and death in patients treated with statins before intervention [90]. However, the risk of perioperative TIAs was not affected by statins. Since then, one randomized control trial (RCT) and three retrospective studies have been published with controversial results. In particular, the RCT confirmed that patients receiving statins had a lower incidence of post-operative TIAs and stroke in comparison to placebo receivers [91]. However, the latest three retrospective studies did not detect any benefit from statin administration in terms of stroke incidence [92–94]. Thus, the evidence about the advantages of statins' use in patients undergoing CAS is still controversial. Further data, especially from powered RCTs are needed.

AGGRESSIVE VS. CONVENTIONAL STATIN THERAPY

The benefits of aggressive over conventional statin treatment in patients with carotid stenosis is a highly challenging topic. The term "aggressive" describes the prescription of the highest dose of statins independent of LDL-C levels, while the "conventional" approach determines the dose based on the achievement of LDL-C targets. We have previously demonstrated a dose-dependent increase in carotid plaque stability expressed by the GSM score in patients with carotid atherosclerosis receiving statins and not requiring revascularization [81]. Growing evidence supports the aggressive statin therapy over the conventional one with regard to its impact on plaque stability in asymptomatic patients with carotid atherosclerosis without the need for revascularization [95]. Most importantly, the higher doses of statins have been extensively shown as an effective measure to reduce morbidity and mortality in patients with other atherosclerotic manifestations at very low risk of adverse events [96, 97].

On the other hand, only a few retrospective and observational studies have comparatively evaluated aggressive versus conventional perioperative statin therapies in patients undergoing either CEA or CAS. The results regarding the perioperative stroke rates were contradictory [94, 98, 99]. Interestingly, the higher the dose of statins, the lower the frequency of new lesions on MRI after 48 hours of CAS. In a retrospective study of 21 277 individuals undergoing CEA, aggressive statin therapy did not further reduce the perioperative stroke rates [100]. As a result, RCTs with larger populations need to be conducted to clarify whether higher statin doses confer greater cardiovascular and cerebrovascular protection on patients with carotid stenosis undergoing revascularization. After aggressive statin therapy, a further decrease in LDL-C levels is expected. This is in line with the current recommendations of the scientific societies for very low LDL-C targets in patients with significant carotid atherosclerosis. However, the bottom LDL-C limit has not been yet established, maintaining "the lower LDL-C, the better for the patient" as a general rule. In this case, the therapeutic target should be re-considered from lipid-lowering to other indices of plaque vulnerability.

CONCLUSION

The current literature review recommends a multi-level guided statin therapy based on blood LDL-C levels, novel imaging modalities, and systematic biomarkers in patients with established asymptomatic carotid atherosclerosis not requiring revascularization. Such an approach, in addition to lipid-lowering, will assist in patient risk stratification and guide an aggressive statin therapy, with favorable effects on the clinical course. On the other hand, perioperative statin usage has not shown consistently beneficial results. Only the pre-operative commencement of statins in patients undergoing CEA has been shown to be beneficial independently of the dose. More unambiguous data are needed to alter the therapeutic targets of statins in patients with carotid atherosclerosis undergoing, or not, carotid revascularization.

Article information

Conflict of interest: None declared.

Funding: None.

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REVIEW

Mitral valve prolapse: From new mechanisms to diagnostic challenges

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DOI: 10.33963/KP.a2022.0147

Received:
June 10, 2022

Accepted:
June 15, 2022

Early publication date:
June 17, 2022

ABSTRACT

Mitral valve prolapse (MVP) is the most common primary valvular abnormality, associated with various degrees of incompetent function and sequelae, including heart failure and sudden cardiac death. Recent improvements in echocardiographic techniques and new insights into mitral valve anatomy and physiology have rendered the diagnosis of this condition more accurate and reliable. Here we review the genetic etiology, clinical significance, diagnosis, and treatment options for MVP patients.

Key words: echocardiography, genetics, heart valve, mitral valve prolapse

INTRODUCTION

Mitral valve prolapse (MVP) is a common cardiac valvular disorder occurring in 1.2%–3% of the general population. The characteristics of mid-systolic click were already described in 1887 by Cuffer and Barbillon [1]. In 1936, Barlow further attributed the physical finding to the mitral valve-chordal origin, describing mitral insufficiency in these patients [2]. The prolapse, as a distinct syndrome, was later described using surgical and autopsy specimens [3], and since then, it has remained a clinical and scientific challenge.

MVP has at least two histological types. The first MVP is caused by fibromyxomatous changes in the valve leaflets characterized by alterations in collagen organization and an increase in glycosaminoglycans causing thickening of the leaflets. This gives the valve the pathological appearance designated "myxomatous degeneration". The second, termed fibroelastic deficiency, is more prevalent in elderly people and is characterized by thickening of the spongiosa and accumulation of collagen [4]. These changes lead to biomechanically impaired leaflets, resulting in redundancy and prolapse into the left atrium (Figure 1) [5, 6]. This further creates abnormal strain on the chordae, which may lead to rupture and worsen the regurgitation.

ETIOLOGY

MVP genetics

MVP can be classified as sporadic (isolated cardiac presentation), familial or syndromic. Syndromic MVP, also referred to as secondary MVP, is the presence of MVP and other known disorders, most commonly, a connective tissue disease. The prominent related syndromes include Marfan syndrome [7], Loeys–Dietz syndrome, Ehlers–Danlos syndrome, and osteogenesis imperfecta, among others [8]. A summary of the main syndromes is presented in Table 1.

Familial MVP is diagnosed whenever MVP is present as an isolated malformation in a first-degree relative. About 35%–50% of MVP cases are familial, suggesting a strong genetic component in its etiology. The prevalence of MVP among first-degree relatives is higher than in the general population and is estimated at 5%–20%. Familial studies of non-syndromic MVP suggest an autosomal

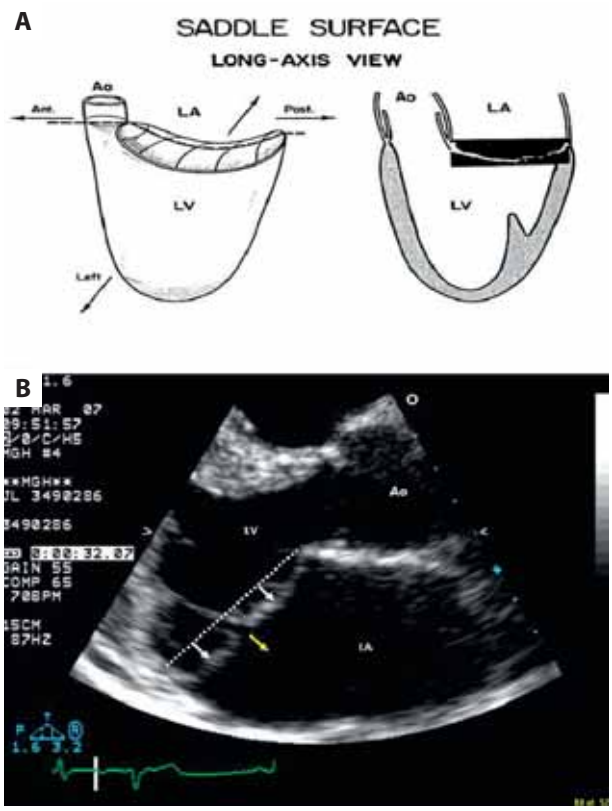

Figure 1. A. Mitral valve prolapse (MVP) is defined by the abnormal position of the mitral leaflets to their surrounding structures. Cardiac ultrasound is well suited for MVP phenotyping. **B.** Parasternal long-axis view of a human heart with MVP. The leaflets are above the annular line (the dotted line) during systole (the white arrows). The gap between the leaflets generates the potential for regurgitation (the yellow arrow). Adapted from [6]

Abbreviations: Ao, aorta; LA, left atrium; LV, left ventricle

dominant mode of inheritance with incomplete and age-dependent penetrance [9–12].

Genes that are associated with non-syndromic MVP are detailed in Table 2. The first genetic mutation for non-syndromic MVP has been successfully linked to *FLNA* (filamin A mutations) in the family with X-linked inheritance [13]. The *FLNA* gene encodes an actin-binding protein that crosslinks actin filaments and links them to membrane glycoproteins. Later on, mutations in the *DCHS1* gene were also identified as causing MVP [14]. *DCHS1* is a member of the cadherin superfamily that encodes calcium-dependent cell-cell adhesion molecules. Using zebrafish and mouse models, it has been demonstrated that mutated valves exhibit abnormal planar cell polarity architecture in the valve matrix resulting in myxomatous degeneration and prolapse. Six loci reached genome-wide statistical significance in a genome-wide association study (GWAS) of 1412 MVP cases and 2439 controls. Through functional analysis, clinical importance was demonstrated for two genes: *LMCD1* (LIM and cysteine-rich) and *TNS1* (tensin1) by altered valve phenotype in zebrafish. A recent study found that mutations in the DZIP (DAZ interacting zinc finger protein 1) gene, involved in primary cilia formation, can cause MVP. Combining analyses of mitral valve development in mice with human genetic data suggested that MVP can be caused by abnormal cilia function [15]. Recent studies have also found epigenetics involvement in the pathogenesis of MVP [16], such as evidence from *in vivo* and *in vitro* studies demonstrating a regulatory role for microRNAs (miRNAs) [17]. While these genetic findings point out potential mechanisms for myxomatous degeneration, they currently lack clinical implications.

Table 1. Genetics of syndromic mitral valve prolapse

	Genes	Gene's function	Presence of MVP	Inheritance mode	Main features
Marfan syndrome	FBN1	Structural component in the extracellular matrix	40%–80%	AD	MVP is one of the diagnostic criteria
Loeys–Dietz syndrome	TGF-β receptor 1 (*TGFBR1*); *TGFBR2*; *SMAD3*; *TGFB2*; *TGFB3*	TGF-β singling — well-established pathway for connective tissue disorders	25%	AD/AR	Lower rate of MVP in comparison to *FBN1*
Ehlers–Danlos syndrome	*COL5A1* or *COL5A2* or *COL1A1* and *TNXB*	Connective tissue components		AD	Mainly vascular phenotype, MVP in ~6%
Williams–Beuren syndrome	ELN	Encode major structural protein involved in organization of vascular smooth muscle	6%	AD	Cardiac phenotype includes supravalvular and pulmonary stenosis (45%–75%) and MVP (6%)
Osteogenesis imperfecta	*COL1A1*, *COL1A2*, *CRTAP*, and *P3H1*	Proteins involved in the extracellular matrix of connective tissues	5.4%	AD	Cardiac phenotype includes aortic root dilatation and aortic valve abnormalities
Trisomies	Trisomies in chromosomes 18, 13, and 15			Most cases are sporadic	Sever global phenotype (including growth retardation and cognitive impairment)
Stickler syndrome	*COL2A1*, *COL11A1*, *COL11A2*, *COL9A1*, *COL9A2*, *COL9A3*	Proteins involved in the extracellular matrix of connective tissues	4%	AD/AR	

The main syndromes which may present with MVP, their genetic origin, and the prevalence of MVP within each syndrome

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; TGF-β, transforming growth factor β; other — see Figure 1

Table 2. The main genes associated with non-syndromic mitral valve prolapse

Gene	Gene function	Genetic approach
DCHS1	Member of the cadherin superfamily that encodes calcium-dependent cell-cell adhesion molecules	Familial segregation study
FLNA	Promotes orthogonal branching of actin filaments and links actin filaments to membrane glycoproteins	Familial segregation study
TNS1	Encodes for tensin 1, actin-binding protein	GWAS
LMCD1	Transcription factor repressor of *GATA6*	GWAS
DZIP	Role in primary cilium formation	Familial segregation study
LMCD1, *NMB*, and *ALPK3*	Known to be involved in cardiomyopathies	GWAS
LTBP2, TGFB2,	Encodes an extracellular matrix protein involved in regulation of TGF-β signaling. *LTBP2* is associated with connective tissue disorders	
SPTBN1	Encodes β2-spectrin, a scaffold protein that connects the actin cytoskeleton to the plasma membrane	

Abbreviation: GWAS, genome-wide association study; other — see Table 1

Structural mechanisms

The mitral valve annulus has a characteristic saddle-shaped shape, with high anterior and posterior points and concave leaflets toward the left ventricle in the zone of coaptation. This determines the anatomical definition of MVP in which prolapse is defined when the leaflet or leaflets prolapse into the left atrium above the line connecting the two annular high points [6]. The practical aspect of this is that prolapse can only be safely diagnosed by echocardiography (such as in parasternal long-axis view on echocardiography) whenever both high points are in the image plane.

It has been suggested that structural and functional remodeling, as shown by cardiac magnetic resonance, may lead to early focal or diffuse fibrosis of the papillary muscles, which play a role in reentry circuits, leading to a high-risk MVP phenotype [18].

CLINICAL SIGNIFICANCE

MVP is a progressive disease, found with increased rates and severity with age [19]. It has a broad spectrum of clinical presentations, from silent disease to severe cardiac events. While incorrectly considered by many a benign condition, it often manifests from the fourth to sixth decades of life as a severe cardiac event [9]. Clinical symptoms may include atypical chest pain, exertional dyspnea, palpitations, and the classical sign is mid-systolic click. MVP is the most common cause of isolated mitral regurgitation requiring surgical repair. The lifelong serious adverse complication rate for MVP is 30% [20, 21]. MVP often results in mitral regurgitation, which can lead to cardiac chamber dilation, arrhythmias, bacterial endocarditis, and congestive heart failure [22].

Importantly, MVP has recently been recognized as a common cause of arrhythmias, including sudden cardiac death (SCD). This life-threatening phenotype is referred to as "arrhythmogenic" or "malignant" MVP [23], and its exact prevalence is unclear [24, 25]. In our preliminary results, 9.4% of the MVP families had a history of SCD (unpublished data). The risk of SCD in MVP is estimated to be 3-fold higher than in the general population (0.1% per year) [26]. Four percent of SCDs among young athletes are attributed to MVP [27]. Arrhythmogenic MVP has been associated with abnormalities of T-waves, which can be a result of the endocardial and mid-myocardial changes of the papillary muscles or the left ventricle [24]. Other factors include bileaflet involvement, polymorphic inferiorly triggering ventricular premature beats, mitral annular disjunction, Pickelhaube sign on tissue Doppler tracing of the mitral annulus, and female sex [28]. Mitral annulus disjunction (MAD) is an abnormal atrial displacement of the posterior mitral leaflet hinge point. This creates a separation of the mitral valve annulus-left atrial wall. Although MAD is a common finding in MVP and could also be found in normal hearts, it has recently been associated with ventricular arrhythmias and SCD [29]. Few studies have also evaluated the effect of the MAD length, suggesting a cut-off value of 6–8.5 mm on transthoracic echocardiography (TTE) for the predication of arrhythmia [30]. Pickelhaube sign is a high-velocity (usually >16 cm/s) mid-systolic spike in the tissue Doppler velocity profile of the mitral valve annulus in patients with bileaflet MVP.

The high morbidity of MVP leads to a significant economic burden for both the patient and the healthcare system. The annual hospitalization cost for treating mitral regurgitation in France only was €292 million, including surgical and non-surgical cases [31]. The yearly cost for surgical interventions only was estimated at €80 million.

Due to the described variability, further studies to develop a risk-stratification model for MVP are pertinent. This will allow personalized treatment that could address individual risks for adverse outcomes, saving unnecessary interventions.

DIAGNOSIS

The classic physical auscultatory findings of mid-systolic clicks and/or late systolic murmurs are associated with MVP but are not sufficient for diagnosis.

The first-line and most commonly used imaging modality for MVP is TTE. The seminal work by Robert Levine on the saddle shape of the mitral valve annulus informed the definition of MVP in the American Society of Echocardiography guidelines as displacement of 2 mm or more of

the valve leaflets above the annular line in the long-axis view during systole (Figure 1A). The European Society of Cardiology (ESC) guidelines refer to the superior displacement of the mitral valve coaptation point relative to the annulus [32, 33].

Transthoracic echocardiography is also the gold standard for assessing the grade of MR severity. Transesophageal echocardiography can define the abnormal position of the mitral leaflets to their surrounding structures based on specific and validated criteria (Figure 1B), and can further delineate MAD. Three-dimensional echocardiographic studies [5, 6] have significantly increased the specificity of diagnostic criteria for MVP.

In recent years, the role of structural imaging is becoming significant as it has the potential to identify patients at risk of complications. Risk features for arrhythmia include thickened leaflets, fibrosis of the papillary muscles and inferobasal wall, and MAD as described above. These may be used for early detection of arrhythmias allowing for appropriate preventative intervention.

Cardiac magnetic resonance for MVP evaluation is currently gaining popularity. It can facilitate diagnosis [34], and with the use of gadolinium, it can offer benefits in better characterizing the tissue, for example detecting myocardial and papillary muscle fibrosis and defining its pattern (macro or diffuse fibrosis). Cardiac magnetic resonance is the gold standard for left ventricular and right ventricular volumetric assessment and can accurately measure regurgitant volume and fraction.

MANAGEMENT

Currently, our arsenal for the management of MVP is mostly surgical. While it is customary to treat MVP with after-load reduction with medications such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, none of the pharmacologic treatments for MVP have ever been shown efficacious in slowing disease progression. The only treatments for MVP that are thought to be efficacious are surgical and thus palliative. The goal of surgical intervention for MVP is to relieve papillary muscle stretching and facilitate ventricular remodeling, which aims to reduce ventricular arrhythmias. The options include mitral valve repair or replacement, with continuous debate in the literature regarding the best method. These interventions carry a significant complication rate and up to 6.5% mortality rate in one study.

For arrhythmic events prevention and treatment, beta-blockers are the first-choice treatment for symptomatic or asymptomatic patients with non-sustained or sustained ventricular arrhythmias. However, high-risk features such as ventricular arrhythmias, hypercontractility, and fibrosis may prompt further electrophysiologic study investigations [23]. Some authors have considered ablation protocols to relieve the arrhythmia burden with high procedural success, although recurrence of ventricular arrhythmia was not uncommon [35].

Interestingly, higher levels of soluble suppression of tumorigenicity-2 serum levels were associated with MAD and ventricular arrhythmias. This biomarker was suggested to indicate myocardial stretch. It may have a potential in arrhythmogenic MVP diagnosis: the prolapsing leaflets in MVP lead to stretching of the papillary muscles and adjacent myocardium, which has been associated with ventricular arrhythmias.

One of the key questions in treating MVP is whether pharmacological interventions are effective in preventing complications, particularly given that MVP is seen as a structural disease. Recent advances in genetic and molecular techniques may enable the identification of genetic mechanisms leading to preventive treatment that reduces disease complications. Marfan syndrome is characterized by a high prevalence of mitral valve myxomatous degeneration leading to MVP [36]. Mice with a missense mutation in *FBN1* are known to phenocopy Marfan syndrome. In one study, both heterozygous and homozygous mice with a fully expressed missense mutation in *FBN1* were compared to wild-type mice. Adult heterozygous mutant mice were shown to have MVP by high-resolution echocardiography. Treatment with a TGFβ-neutralizing antibody successfully normalized morphologic characteristics of myxomatous degeneration in both the length and the thickness of the mitral valve leaflets [37]. These data suggest that in the future medical treatment will be used to modify disease progression.

Cascade screening

The familial presentation of MVP raises the question of "cascade screening" for first-degree relatives of the MVP index case. Cascade screening refers to the common practice of identifying individuals at risk of a genetic condition through the process of systematic screening. It is a common practice for MVP in many centers but has yet to be recommended in guidelines. There are several accepted criteria for screening methods, including clinical significance, cost-effectiveness, test acceptability, and options for early treatment. Screening for MVP by echocardiography is a simple procedure that does not involve risk for the patient or radiation exposure as in other imaging modalities. It has the benefit of detecting MVP or associated pathologies at an early stage. This allows appropriate follow-up and timely intervention. On the other hand, the emotional burden on the patient and his family should also be considered. Cost-effective data is also lacking in this preliminary stage for systematic screening implantation.

CONCLUSIONS

MVP clinical variability poses a great challenge to clinicians who aim to identify high-risk cases at an early stage. In addition to the basic thorough anamnestic, clinical, and echocardiographic examination, a deeper understanding of the disease development and mechanism may be achieved through combining information about genetics,

structural features on advanced imaging, and electrophysiological characteristics.

Article information

Conflict of interest: None declared.

Funding: None.

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Role of magnetic resonance in the detection of cardiac involvement in patients with newly diagnosed extracardiac sarcoidosis: A single-center experience

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Editorial
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DOI: 10.33963/KP.a2022.0163

Received:
May 15, 2022

Accepted:
June 21, 2022

Early publication date:
June 27, 2022

ABSTRACT

Background: Sarcoidosis is a systemic inflammatory disease of unknown etiology, which can affect almost any organ. Cardiac involvement determines the prognosis of the affected individuals. Its prevalence in patients with extracardiac sarcoidosis with the absence of cardiac symptoms remains unclear. Cardiac magnetic resonance (CMR) provides excellent diagnostic accuracy in the detection of heart involvement by sarcoidosis.

Aim: We sought to determine the prevalence of cardiac sarcoidosis in asymptomatic individuals with newly diagnosed extracardiac sarcoidosis using CMR.

Methods: We prospectively evaluated 55 consecutive patients including 23 women with newly diagnosed extracardiac sarcoidosis who underwent contrast-enhanced CMR and had no symptoms of heart disease. The mean (standard deviation) age of patients was 43 (11) years. The presence of myocardial late gadolinium enhancement (LGE) of non-ischemic etiology on CMR examination was considered diagnostic for cardiac sarcoidosis.

Results: In 3 (6%) patients, the LGE pattern consistent with cardiac sarcoidosis was detected. In all patients, preserved left ventricular systolic regional and global function was present, and in none of them, the elevation of blood biomarkers of myocardial injury or overload was found.

Conclusions: Our study suggests that the prevalence of cardiac involvement in patients with newly diagnosed extracardiac sarcoidosis and no symptoms of heart disease is very low as assessed by CMR. However, CMR may be considered as part of routine evaluation of patients with extracardiac sarcoidosis due to its higher diagnostic yield in comparison with echocardiography and electrocardiography, respectively.

Key words: cardiac sarcoidosis, cardiac magnetic resonance, late gadolinium enhancement

INTRODUCTION

Sarcoidosis is a systemic inflammatory disease of unknown origin characterized by epithelioid non-necrotizing granulomas, which can affect almost any organ. The most common form of the disease is pulmonary sarcoidosis. However, the presence of cardiac involvement determines the prognosis of affected individuals. The heart may be involved as part of the systemic disease or in an isolated form. Approximately only 5% of patients with systemic disease have symptoms of cardiac sarcoidosis [1]. However, the prevalence of heart involvement seems to be more frequent and

WHAT'S NEW?

Our study shows the prevalence of cardiac involvement in patients with newly diagnosed extracardiac sarcoidosis and no symptoms of heart disease. Our data suggest that the prevalence is very low as assessed by cardiac magnetic resonance. Nevertheless, based on the current knowledge the detection of heart involvement has significant impact on the management of these patients.

present in about 25% of patients with systemic sarcoidosis based on autopsy studies [2]. Nevertheless, the frequency of cardiac involvement in living subjects diagnosed primarily with extracardiac sarcoidosis remains unclear.

Cardiac sarcoidosis may remain asymptomatic or present as dilated or less frequently restrictive cardiomyopathy with symptoms of heart failure, or in the form of several types of arrhythmias. Conduction disorders, especially atrioventricular blocks and ventricular arrhythmias, are of great clinical importance. Furthermore, these life-threatening arrhythmias may be the first manifestation of the disease and lead to sudden cardiac death [3]. Echocardiography is typically used as a first-line method for the detection of cardiac sarcoidosis. However, its sensitivity is low for detection of the early stages of the disease. Cardiac magnetic resonance (CMR) has excellent diagnostic accuracy in the diagnosis of cardiac sarcoidosis including its subclinical forms [4]. Therefore, we aimed to prospectively assess the presence of cardiac involvement using contrast-enhanced CMR in patients with newly diagnosed extracardiac sarcoidosis and no symptoms of heart disease.

METHODS

In this prospective study, we included 55 consecutive patients with no symptoms of heart disease who were referred to our institution between August 2015 and November 2021 for evaluation of the presence of cardiac sarcoidosis. In all of them, the extracardiac form of sarcoidosis had been confirmed in the previous 12 months. The diagnosis of extracardiac sarcoidosis was based on the positive histology characterized by the presence of epithelioid, non-caseating, non-necrotizing granulomas with varying degrees of lymphocytic inflammation.

The diagnostic evaluation included physical examination, assessment of heart failure symptoms according to the New York Heart Association (NYHA) classification, standard 12-lead electrocardiogram (ECG), 24-hour ECG Holter monitoring, transthoracic echocardiography, blood analysis for biomarkers of myocardial injury and overload, creatinine and serum levels of angiotensin-converting enzyme (sACE), and performing CMR.

Transthoracic echocardiography imaging was performed using the GE Vivid 9 or GE Vivid E95 system (GE Healthcare, Chicago, IL, US), and all measurements were done according to the current recommendations of American Society of Echocardiography/European Association of Cardiovascular Imaging [5].

CMR imaging was performed using a 1.5 T system Philips Achieva (Philips Healthcare, Eindhoven, the Netherlands). Our protocol included a series of steady-state free precession images in the vertical, horizontal, short-axis, and four-chamber views. The sequence parameters were echo time (TE) — 1.46 ms, repetition time (TR) — 2.9 ms, flip angle — 60 degrees, matrix — 204 × 192, field of view (FOV) — from 320 to 440 mm with phase FOV — from 0.75 to 1.0 mm, and 8-mm slice thickness without any interslice gap. Left ventricular (LV) end-diastolic and end-systolic volumes, LV ejection fraction, right ventricular end-diastolic and end-systolic volumes, right ventricular ejection fraction, and cardiac output were analyzed. The presence of myocardial edema was evaluated on T2-weighted spectrally selective inversion recovery (SPIR) images. Late gadolinium enhancement (LGE) images were obtained from 5 to 15 minutes after intravenous administration of 0.2 mmol/kg gadoterate meglumine (Dotarem®, Guerbet, France) with segmented inversion recovery fast gradient echo sequences (TE, 1.19 ms; TR, 3.7 ms; flip angle, 15 degrees; matrix, 209 × 164; FOV, 310 mm). The presence of myocardial LGE of non-ischemic etiology on CMR examination was considered diagnostic for the presence of cardiac sarcoidosis as stated in the Heart Rhythm Society 2014 criteria for the diagnosis of cardiac sarcoidosis.

Signed informed consent was obtained from all patients in a format standardized by our institution. The study conformed to the principles outlined in the Declaration of Helsinki.

Statistical analysis

Data are expressed as mean and standard deviation (SD) or median and interquartile range (IQR), or as number and percentage of subjects. The normality of data was tested with the Shapiro-Wilk test. All analyses were performed using the STATISTICA version 12 software (Statsoft, Inc., Tulsa, OK, US).

RESULTS

The baseline characteristics of the study population are summarized in Table 1. The study cohort included 55 subjects, 23 (42%) were women. The mean age of the patients was 43 (11) years. Fifty-four (98%) patients had pulmonary sarcoidosis, and 34 (62%) patients had multiple organ involvement.

The elevated values of natriuretic peptides (brain natriuretic peptide [BNP] or N-terminal pro-BNP) were found in

Table 1. Clinical characteristics of patients

Number of subjects	55
Age, years, mean (SD)	43 (11)
Females, n (%)	23 (42)
Height, cm, mean (SD)	176 (11)
Weight, kg, mean (SD)	86 (19)
SBP, mm Hg, mean (SD)	129 (18)
DBP, mm Hg, mean (SD)	75 (14)
Arterial hypertension, n (%)	14 (25)
Diabetes mellitus, n (%)	5 (9)
Active smoking, n (%)	11 (20)
Dyslipidemia, n (%)	8 (15)
Coronary artery disease	0
Chronic renal insufficiency	0
Bronchial asthma, n (%)	6 (11)
Pulmonary sarcoidosis, n (%)	54 (98)
Cutaneous sarcoidosis, n (%)	5 (9)
Gastrointestinal sarcoidosis, n (%)	4 (7)
Ocular sarcoidosis, n (%)	6 (11)

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure

Table 2. Electrocardiographic and 24-hour Holter ECG monitoring parameters

Heart rate, min^{-1}, mean (SD)	77 (12)
Sinus rhythm, n (%)	55 (100)
PQ, ms, mean (SD)	150 (11)
QRS, ms, mean (SD)	88 (6)
QTc, ms, mean (SD)	414 (23)
PACs, median (IQR)	4 (0–13)
PVCs, median (IQR)	2 (0–14)
Interventricular conduction delay, n (%)	2 (4)
NSVT	0
PVC over 10% QRS	0
AV block first-degree, n (%)	2 (4)
AV block second-degree Wenckebach, n (%)	2 (4)
AV block second-degree Mobitz	0
AV block third-degree	0

Abbreviations: AV, atrioventricular; ECG, electrocardiogram; NSVT, non-sustained ventricular tachycardia; PAC, premature atrial contraction; PVC, premature ventricular complex

4 patients. In all subjects, normal values of troponin I were present. None of the patients had renal insufficiency. sACE levels were increased in 17 (31%).

The 12-lead ECG and 24-hour ECG Holter monitoring data are presented in Table 2. All patients were in sinus rhythm. The first-degree atrioventricular (AV) block was found in 2 (4%) patients, and second-degree AV block (Wenckebach type), was detected in other 2 (4%) patients. None of the individuals had second-degree AV block (Mobitz type) or third-degree AV block. ECG Holter monitoring did not document sustained or nonsustained ventricular tachycardia or a significant number of premature ventricular extrasystoles in any subject.

In patients who were subsequently diagnosed with CMR signs of cardiac sarcoidosis, no ECG changes including conduction defects or any significant arrhythmia on ECG Holter monitoring were detected.

Table 3. Echocardiographic parameters

IVS, mm, mean (SD)	9 (2)
LVEDD, mm, mean (SD)	48 (4)
LVEF, %, mean (SD)	63 (5)
LAVi, ml/m^2, mean (SD)	26 (7)
DD absent/grade I/grade II/grade III, n (%)	35 (63)/20 (37)/0/0
MR absent/mild/moderate/severe	3 (5)/52 (95)/0/0
RVEDD, mm, mean (SD)	33 (5)
PASP, mm Hg, mean (SD)	25 (5)
TAPSE, mm, mean (SD)	25 (3)
PEEF, n (%)	6 (11)

Abbreviations: DD, diastolic dysfunction; IVS, interventricular septum; LAVi, left atrial volume index; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PASP, pulmonary artery systolic pressure; PEEF, pericardial effusion; RVEDD, right ventricular end-diastolic diameter; TAPSE, tricuspid annular plane systolic excursion

Table 4. Cardiac magnetic resonance parameters

LVEDV, ml, mean (SD)	146 (32)
LVEF, %, mean (SD)	63 (4)
CO, l/min, mean (SD)	7 (2)
RVEDV, ml, mean (SD)	133 (37)
RVEF, %, mean (SD)	58 (7)
Myocardial edema	0
LGE, n (%)	3 (6)

Abbreviations: CO, cardiac output; LGE, late gadolinium enhancement; LVEDV, left ventricular end-diastolic volume; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; other — see Table 3

Echocardiographic and CMR data are shown in Tables 3 and 4, respectively. The LV was not dilated in any subject based on either echocardiographic or CMR measurements. The right ventricle was of a borderline size in one patient. None of the patients had reduced right or left ventricular global systolic function, and no regional wall motion abnormality was observed either. No moderate or severe valvulopathy was found in any patient. The values of estimated pulmonary artery systolic pressure were within the normal range in all individuals. A small pericardial effusion was found in 6 patients (11%). LGE of the pericardium was found in none of these 6 patients.

Myocardial edema was not present in any patient on CMR examination. In 3 patients (6%), the non-ischemic pattern of LGE was found, always involving basal segments of the LV. In more detail, isolated midmyocardial LGE in the basal segment of the interventricular septum was present in one subject, and in two individuals midmyocardial LGE in the interventricular septum together with subepicardial LGE in the lateral LV wall were seen (Figure 1). One of these patients had a very small pericardial effusion. The sACE level was increased in one subject with LGE positivity. In all LGE-positive patients, the levels of cardiac biomarkers were within the normal range.

DISCUSSION

CMR represents currently the preferred non-invasive method for the initial evaluation of patients with suspected cardiac sarcoidosis [6]. Its major advantage, in comparison

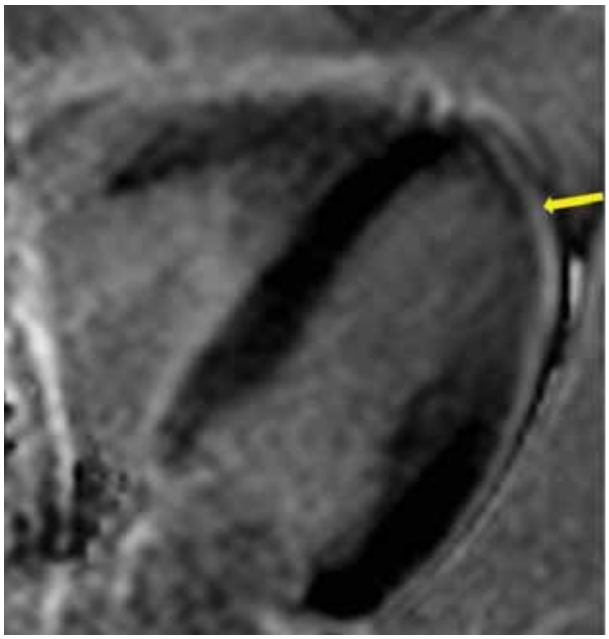

Figure 1. The presence of subepicardial late gadolinium enhancement (the arrow) in the lateral wall of the left ventricle detected by cardiac magnetic resonance

with the endomyocardial biopsy, is its sensitivity for detection of cardiac sarcoidosis, which is reported to be 90%–100% [7, 8], whereas the sensitivity of the endomyocardial biopsy is only about 25% [9]. The diagnosis of myocardial involvement based on the CMR study is traditionally based on the presence of LGE of non-ischemic etiology found in the subepicardial or midmyocardial segments of the LV walls, often involving the basal LV segments including the interventricular septum [10].

Based on the so far published studies using CMR in patients with known extracardiac sarcoidosis, the presence of myocardial involvement varies between 20% and 35% [11–14]. In our study, we detected clinically probable cardiac sarcoidosis based on the presence of LGE in only 6% of the study cohort. This lower prevalence could be explained by the fact that we screened patients with newly diagnosed extracardiac sarcoidosis who did not have any cardiac symptoms, including those that are suggestive of cardiac sarcoidosis, such as syncope, light-headedness, palpitations, or chest pain. In all the above-mentioned studies, the authors performed screening in mixed cohorts of individuals for the presence or absence of cardiac symptoms. On the other hand, our results are in concordance with a recently published study by Panovsky et al. [15]. Those authors screened only patients without known cardiovascular diseases and no cardiac symptoms, and detected possible myocardial involvement based on the presence of LGE in 7% of their study population. In contrast to our study, they found only questionable small LGE, which did not have the expected pattern of cardiac involvement in all cases. To our best knowledge, our study is the first to show the prevalence of clear myocardial involvement in patients with newly diagnosed extracardiac sarcoidosis lacking cardiac symptomatology.

An early diagnosis of cardiac sarcoidosis is of utmost importance because it makes it possible to administer immunosuppressive therapy. Moreover, the presence of LGE is well known to be associated with worse clinical outcomes including heart failure, arrhythmias, and sudden cardiac death [16].

Echocardiography, due to its wide availability, safety, and relatively low cost, still represents the first-line imaging method for screening for cardiac involvement in subjects with extracardiac sarcoidosis. However, its sensitivity in the early stages of cardiac sarcoidosis is very low and reaches only about 25% [17]. Following that, we were unable to detect any specific features of cardiac sarcoidosis, such as the presence of thinning of the basal segment of the interventricular septum or the presence of the phenotype of dilated or restrictive cardiomyopathy in our study subjects. We documented the presence of a small pericardial effusion in 11% of individuals. However, none of these subjects expressed pericardial LGE that would suggest pericardial involvement associated with sarcoidosis.

Twelve-lead ECG and ECG Holter monitoring are often used as screening tools in patients with extracardiac sarcoidosis. Unfortunately, none of these methods has satisfying accuracy in the detection of cardiac sarcoidosis [18]. In our study, we did not detect any second-degree AV block (Mobitz type), third-degree atrioventricular block, or sustained ventricular tachycardia, which are traditionally considered diagnostic for cardiac sarcoidosis in patients with a confirmed extracardiac form of the disease.

Study limitation

The main limitation of our study is the relatively small number of patients. Furthermore, newer CMR parametric techniques such as T1 or T2 mapping were not performed.

CONCLUSIONS

The prevalence of myocardial involvement in patients with newly diagnosed extracardiac sarcoidosis and the absence of obvious signs or symptoms suggesting cardiac disease seems to be very low as assessed by CMR. Nevertheless, we believe that CMR with its ability to detect the early stages of the disease may still be considered for routine evaluation of heart involvement in patients with extracardiac sarcoidosis.

Article information

Acknowledgment: The study was supported by the Charles University Research program Cooperatio Cardiovascular Science.

Conflict of interest: None declared.

Funding: None.

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Neopterin as a predictive biomarker of postoperative atrial fibrillation following coronary artery bypass grafting

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Editorial
by Boriani et al.

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DOI: 10.33963/KP.a2022.0143

Received:
January 26, 2022

Accepted:
June 10, 2022

Early publication date:
June 10, 2022

ABSTRACT

Background: The pathophysiology of postoperative atrial fibrillation (POAF) is multifactorial. Inflammation and increased oxidative stress play a significant role in POAF development. Neopterin, a biomarker of cellular immune response that enhances oxidative stress and increases the cytotoxic potential of activated macrophages and dendritic cells, was recently found as an independent predictive biomarker of non-operative atrial fibrillation. However, as far as we know, neopterin has never been investigated in POAF.

Aims: The study aimed to assess neopterin concentration as a prognostic biomarker of POAF following coronary artery bypass grafting (CABG).

Methods: One hundred one patients (80.2% males, 85% off-pump, 15% on-pump) were included. Blood samples were taken from patients for analysis of serum neopterin and high-sensitive C-reactive protein (hs-CRP) at three time points: (1) before operation (NP0); (2) on the first day after operation (NP1); and (3) between the fifth and eighth day after the procedure (NP5–8). All factors (preoperative, echocardiographic, and surgical), significant in univariate analysis, were included in a multivariable logistic regression analysis.

Results: POAF occurred in 30 patients (30%). In the analyzed multivariable logistic regression models, the independent predictors of POAF occurrence were: higher NP0 concentration (odds ratio [OR], 1.16; 95% confidence interval [CI], 1.02–1.38 for continuous and OR, 3.75; 95% CI, 1.39–10.1 for NP0 cut-off >8.7 nmol/l), higher body mass index (OR, 1.15; 95% CI, 1.02–1.29), history of pulmonary disease (OR, 6.72; 95% CI, 1.57–28), increased diastolic thickness of the interventricular septum (OR, 1.45; 95% CI, 1.14–1.83), and duration of operation (OR, 1.01; 95% CI, 1.03–1.36).

Conclusions: We found that elevated neopterin concentration before CABG may be a predictive biomarker of POAF.

Key words: coronary artery bypass grafting, inflammatory biomarker, neopterin, postoperative atrial fibrillation

WHAT'S NEW?

The study investigated the prognostic value of neopterin in postoperative atrial fibrillation occurrence following elective coronary artery bypass. Neopterin, a biomarker of inflammation, has been recently found as an independent predictive factor of non-operative atrial fibrillation. In the current study, for the first time, we have documented that elevated neopterin concentration can also be an useful prognostic biomarker in postoperative arrhythmia. Multivariable logistic regression analysis identified neopterin concentration before operation, adjusted for body mass index, age, total cholesterol concentration and left atrium diastolic diameter, echocardiographic factors, as well as operative factors, as independent predictors of postoperative atrial fibrillation.

INTRODUCTION

Most episodes of postoperative atrial fibrillation (POAF) occur within the first six days after cardiac operations, with a peak of incidence on the second and third postoperative days [1]. The occurrence of POAF is associated with not only postoperative complications, increased duration and costs of hospitalization [2], but also with higher late mortality and more frequent episodes of atrial fibrillation during long-term follow-up [3]. The pathophysiology of POAF is highly complex, and its development is a net result of numerous factors. Many of them enhance and promote an inflammatory process that is considered crucial in POAF development [4]. It was observed that POAF incidences reached a peak on the second and third postoperative days, simultaneously with the highest concentrations of C-reactive protein (CRP) [5], interleukin 2 [6], and interleukin 6 [7]. Interestingly, cardiopulmonary bypass (CPB) has also been documented as a factor associated with systemic inflammation through complement activation. However, CPB application was not a predictive factor of POAF in several studies [8, 9], while it was an independent POAF predictor in other studies (e.g., in the elderly with high surgical risk) [10, 11]. Furthermore, oxidative stress is known to be one of the mechanisms of POAF development [12–14].

Neopterin is a biological marker for cellular inflammation, generated by activated (stimulated *via* interferon γ) macrophages and dendritic cells. The principal mode of action for neopterin is to enhance cytotoxic activity of macrophages and dendritic cells [15] through intensifying oxidative stress and the the formation of reactive oxygen species. Neopterin generation at the cost of tetrahydrobiopterin synthesis, which is a cofactor of nitric oxide synthase (NOS), leads to tetrahydrobiopterin depletion and, in turn, to NOS uncoupling and creation of reactive oxygen (O_2) [16]. Increased concentration of neopterin has been observed in diseases that are characterized by inflammation and upregulated inflammatory response. Higher neopterin concentration was associated with ischemic heart disease [17], chronic heart failure with reduced [18] and preserved ejection fraction [19], pulmonary arterial hypertension, and inoperable chronic thromboembolic pulmonary hypertension [20]. Moreover, dedicated studies showed that higher neopterin concentration was a predictive biomarker of death and adverse events. Increased postoperative neopterin concentration was predictive of postoperative complications following cardiac surgery such as circulatory, respiratory, liver, and renal failure, as well as blood coagulation disorders [21, 22]. Similarly, a higher concentration of neopterin was associated with cognitive disorders in elderly patients after coronary artery bypass grafting (CABG) or CABG with valve replacement [23]. To our knowledge, the prognostic value of neopterin for POAF development after CABG has never been investigated.

In the current study, the predominant purpose was to evaluate neopterin concentration as a prognostic biomarker of POAF following CABG. In addition, the study was designed to determine if the preoperative or postoperative concentration was a better prognostic factor of POAF.

METHODS

Patients

One hundred one patients (80.2% males) with advanced coronary artery disease were found to be eligible for elective CABG by our Heart Team and recruited in a single-center prospective observational study. Detailed patient characteristics are shown in Tables 1 and 2.

Exclusion criteria included emergency operation, other operation than isolated CABG, history of atrial fibrillation or flutter, pacemaker implantation, clinical symptoms of infection (body temperature >38°, current antibiotic or systemic steroid therapy, acute or chronic renal failure on dialysis, current hyperthyroidism). Medical interview, physical examination, 12-lead electrocardiogram, and transthoracic echocardiography were performed on every patient. All subjects signed informed consent and the Ethics Committee of the University of Medical Sciences in Poznan, Poland, approved the study (no. 546/13).

Surgery

The method of CABG was a choice of the surgeon. Only operations done by surgeons with at least 5-year experience were taken into consideration.

On-pump operations were performed *via* median sternotomy, in moderate systemic hypothermia (27°–29°). CPB was conducted through an arterial cannula in the ascending aorta and a venous cannula in the right atrium. Cold cardioplegic (4°) arrest with the use of St. Thomas Hospital No. 2 solution, in an initial dose of 10 ml/kg, then

Table 1. Detailed baseline patient characteristics and comparison of preoperative factors in patients with postoperative atrial fibrillation (the POAF group) and without POAF (the non-POAF group)

	All patients (n = 101)	POAF group (n = 30)	Non-POAF group (n = 71)	*P*-value
Age, years, mean (SD)	62.6 (7.3)	65 (6)	62 (8)	0.03
Sex				0.59
Female, n (%)	19 (18)	7 (23)	13 (18)	
Male, n (%)	81 (82)	13 (77)	58 (82)	
Weight, kg, mean (SD)	83.3 (13)	86 (10)	82 (14)	0.15
Height, cm, mean (SD)	169.9 (9)	169 (8)	170 (9)	0.68
BMI, kg/m^2, median (IQR)	28.8 (26.8–30.9)	29.6 (27.8–32.8)	28.1 (25.8–30.7)	0.03
Heart failure with LVrEF, n (%)	17 (17)	7 (23)	10 (14)	0.26
Diabetes mellitus, n (%)	38 (38)	15 (50)	23 (32)	0.12
History of stroke or TIA, n (%)	10 (10)	5 (17)	5 (7)	0.15
History of AMI, n (%)	68 (68)	22 (73)	46 (65)	0.49
History of PCI, n (%)	33 (33)	11 (37)	22 (31)	0.64
Hypertension, n (%)	88 (87)	29 (97)	59 (83)	0.10
Pulmonary disease, n (%)	11 (11)	7 (23)	4 (6)	0.01
Hypothyroidism, n (%)	10 (10)	3 (10)	7 (10)	1.0
LM stenosis, n (%)	35 (35)	13 (43)	19 (27)	0.11
Two vessel-disease, n (%)	19 (19)	5 (16.7)	14 (19.7)	0.94
Three vessel-disease, n (%)	82 (81)	25 (83.3)	57 (80.3)	0.94
SYNTAX II score, mean (SD)	30.8 (4.5)	31.2 (4.5)	30.3 (5.9)	0.68
LAD stenosis, % of stenosis, median (IQR)	80 (60–95)	80 (60–90)	80 (70–95)	0.73
Cx stenosis, % of stenosis, median (IQR)	78 (20–90)	80 (70–90)	75 (20–90)	0.28
RCA stenosis, % of stenosis, median (IQR)	87 (60–100)	90 (80–100)	85 (60–100)	0.25
Peripheral artery stenosis, n (%)	22 (22)	8 (27)	14 (20)	0.29
Carotid artery stenosis, n (%)	8 (8)	3 (10)	5 (7)	0.69
Lower limb artery stenosis, n (%)	14 (14)	5 (17)	9 (13)	0.75
Atheromatic plaque in the aorta, n (%)	14 (14)	4 (13)	10 (14)	1.0
Cigarette smoking				
Active, n (%)	35 (35)	11 (37)	24 (34)	0.65
Within last 10 years, n (%)	6 (6)	1 (3)	5 (7)	0.67
>10 years ago, n (%)	35 (35)	10 (33)	25 (35)	1.0
Drugs				
ACEI, n (%)	73 (73)	23 (76)	50 (70)	0.63
ARB, n (%)	12 (12)	3 (10)	9 (13)	1.0
ASA, n (%)	97 (96)	27 (90)	70 (100)	0.08
β-blocker n (%)	83 (82)	24 (80)	59 (83)	0.78
Ca-blocker, n (%)	23 (23)	6 (20)	17 (24)	0.80
Spironol/eplerenone, n (%)	14 (14)	7 (23)	7 (10)	0.11
Statin, n (%)	100 (99)	30 (100)	70 (100)	1.0
Diuretics, n (%)	28 (28)	12 (40)	16 (23)	0.09

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; BMI, body mass index; Cx, circumflex artery; IQR, interquartile range; LAD, left descending coronary artery; LM, left main; PCI, percutaneous coronary intervention; POAF, postoperative atrial fibrillation; RCA, right coronary artery; LVrEF, left ventricular reduced ejection fraction; SD, standard deviation; TIA, transient ischemic attack

repeated every 30 minutes; infused antegrade to the aortic root was applied as a protective measure. Distal anastomoses were done during cardiac arrest, whereas proximal anastomoses were performed on the beating heart, with a partially clamped aorta.

Off-pump operations were also performed *via* median sternotomy but in normothermia. Distal anastomoses were done on the beating heart, using negative pressure-based stabilizers and intravascular shunts, while proximal anastomoses were done with a partially clamped aorta.

Blood sampling

Peripheral venous blood samples were taken from every patient at three time points: (1) before operation (NP0); (2) on the first day after operation, and (3) between the fifth and eighth day after operation for analysis of serum neopterin and hs-CRP. The blood samples for preoperative neopterin testing were obtained the day before operation. Then they were centrifuged at 10000 g (10 min) and preserved at –80°C for future analysis. Enzyme immunoassay Neopterin (ELISA, DRG International, Inc., Springfield, NJ, US) was used to assess serum neopterin concentration.

Heart rhythm analysis

Heart rhythm was monitored with continuous telemetry during the time from surgery to discharge from the hospital. Episodes of atrial fibrillation lasting at least 30 seconds were classified as POAF. When POAF occurred, short episodes that lasted less than one hour and that were well tolerated were managed without any antiarrhythmic

Table 2. Detailed baseline patient characteristics and comparison of preoperative, surgical, and postoperative factors in patients with postoperative atrial fibrillation (the POAF group) and without POAF (the non-POAF group)

	All patients (n = 101)	POAF group (n = 30)	Non-POAF group (n = 71)	*P*-value
Echocardiography				
EF, %, median (IQR)	55 (50–60)	55 (50–60)	57 (50–60)	0.42
LV, mm, median (IQR)	48 (43–52)	51 (43–55)	47 (43–51)	0.07
LA, mm, mean (SD)	38 (5)	39 (5)	37 (5)	0.06
RV, mm, mean (SD)	29 (4)	30 (4)	29 (4)	0.54
Ao asc., mm, mean (SD)	33 (6)	34 (7.5)	32 (6)	0.18
PWd, mm, mean (SD)	12 (3)	12.5 (2.3)	12 (2.5)	0.35
IVSd, mm, median (IQR)	13 (11–14)	13.5 (13–15)	12 (11–13)	<0.001
ECG				
Beats per minute, median (IQR)	62 (58–73)	63 (57–73)	62 (58–72)	0.95
Pathological Q or QS, n (%)	55 (54)	18 (60)	37 (52)	0.51
Laboratory parameters				
ESR, mm/h, median (IQR)	11 (5–18)	10 (5–13)	12 (5–18)	0.29
Hb, mmol/l, mean (SD)	8.9 (0.7)	9.0 (0.7)	8.9 (0.8)	0.54
WBC, 10^3/µl, mean (SD)	7.8 (1.9)	8.1 (2.2)	7.6 (1.7)	0.30
RDW, %, median (IQR)	13.8 (13.4–14.2)	14 (0.8)	13.7 (1.0)	0.29
T-chol, mmol/l, median (IQR)	3.8 (3.2–4.5)	3.4 (3.0–4.17)	4.0 (3.4–4.7)	0.02
LDL-cholesterol, mmol/l, median (IQR)	2.0 (1.6–2.6)	1.8 (1.5–2.4)	2.0 (1.6–2.7)	0.10
HDL-cholesterol, mmol/l, median (IQR)	1.13 (0.9–1.3)	1.1 (0.9–1.2)	1.2 (0.9–1.4)	0.25
TAG, mmol/l, median (IQR)	1.2 (0.9–1.7)	1.3 (0.9–1.6)	1.2 (0.9–1.8)	0.85
eGFR, ml/kg/1.73 m^2, mean (SD)	90.8 (24.5)	86 (23)	93 (25)	0.24
Off-pump, n (%)		26(86)	60 (85)	1.0
On-pump, n (%)		4 (14)	11 (15)	
Number of grafts, median (IQR)		3 (2–3)	2 (2–3)	0.24
Duration of operation, min, mean (SD)		191 (42)	165 (80)	0.08
IABP, n (%)		0 (0)	2 (3)	1.0
Red blood concentrate transfusions, median (IQR)		2 (0–2)	1 (0–2)	0.24

Abbreviations, Ao (asc.), dimension of the ascending aorta; ECG, electrocardiogram; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; HDL-cholesterol, high-density lipoprotein cholesterol; IABP, intra-aortic balloon pump; IVSd, diastolic interventricular septum dimension; LA, left atrium; LDL-cholesterol, low-density lipoprotein cholesterol; LV, left ventricle; PWd, posterior wall of the left ventricular diastolic dimension; RDW, red blood cell distribution width; RV, right ventricular dimension; TAG, triglycerides; T-chol, total cholesterol; WBC, white blood cells count; other — see Table 1

treatment. Longer episodes of POAF or POAF leading to hemodynamic worsening were treated with intravenous amiodarone; in cases of pharmacotherapy failure, electrical cardioversion was performed.

Postoperative period

All patients routinely received I generation cephalosporin intravenous for up to 48 hours as the infection prophylaxis. The following postoperative complications were recorded: postoperative wound infection, body temperature ≥38°C, *Clostridium difficile* infection, urinary tract infection, pleural abscess or pneumonia, several red blood cell concentrate transfusions, prolonged antibiotic therapy, cognitive impairment, pericardial effusion or tamponade, renal failure with the need of hemofiltration, pleural effusion, pneumothorax, acute heart failure, increased alanine transaminase (ALAT) or aspartate transaminase (ASPAT) >8 times the upper limit of normal (ULN), acute limb ischemia. Additionally, the duration of hospitalization was compared in the POAF and non-POAF groups.

Statistical analysis

The normality distribution of all variables was checked with the Shapiro-Wilk test. Data are presented as mean (standard deviation [SD]) or median values (interquartile range [IQR]) as appropriate. Group comparison was conducted using a t-test or Mann–Whitney U test for continuous data depending on distribution, and an exact Fisher test for categorical variables. A receiver operating characteristics (ROC) curve was plotted to establish a cut-off point of variables in the POAF group vs. the non-POAF group. The area under the curve (AUC) of the ROC curve of more than 0.60 was regarded as good discrimination. The univariable logistic regression was used to discriminate significant prognostic factors of POAF. The multivariable logistic regression analysis model included the variables with the *P*-value logistic regression (p[LR]) <0.2 and information value (IV) >0.3 in the univariable model. IV was derived by statistical quantitative analysis of data based on information theory. We used a combined model of IV and p(LR) to predict POAF occurrence. The multivariable models were divided into three models: preoperative, surgical, and echocardiographic. These results were shown as odds ratio (OR) with 95% confidence intervals (CI). Neopterin concentration was analyzed both as continuous and dichotomous variables (the cut-off value derived from ROC curve analysis). *P*-values <0.05 were considered statistically significant. Statistical analysis was performed using Statistica 12 and PQStat 1.6.6.

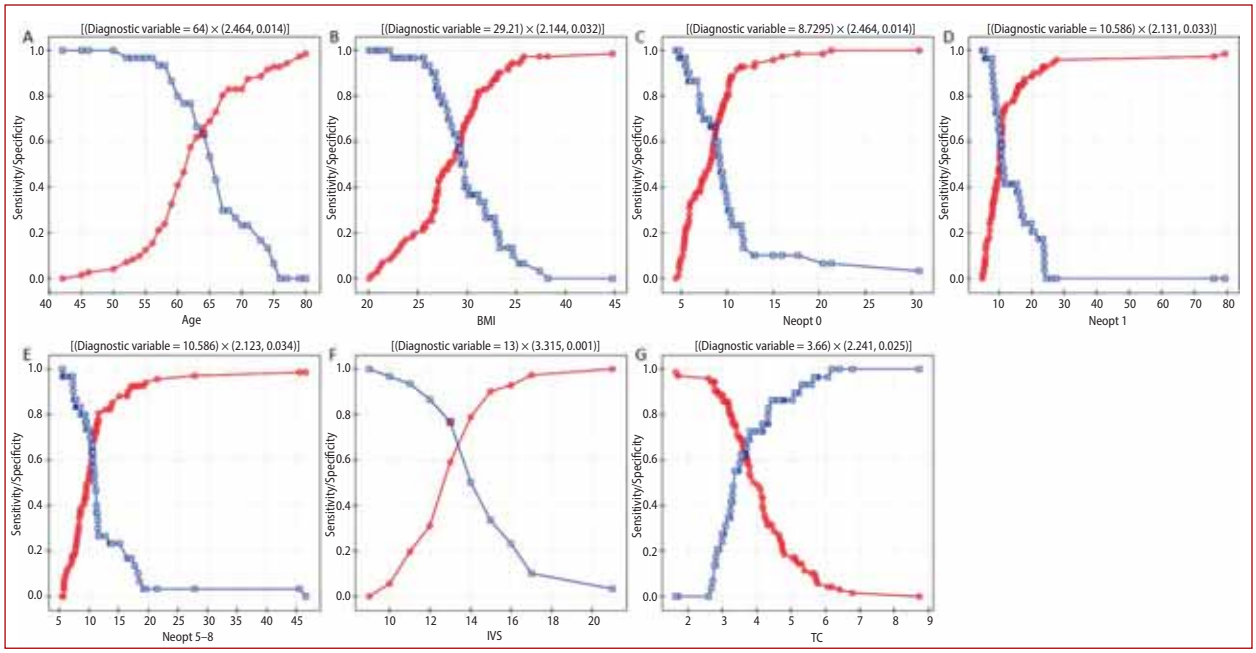

Figure 1. Cut-off values derived from receiver operating characteristic analyses. **A.** 64 years (area under the curve [AUC], 0.66; 95% confidence interval [CI], 0.54–0.77) for age; **B.** 29.2 kg/m^2 (AUC, 0.64; 95% CI, 0.52–0.75; $P = 0.03$) for body mass index; **C.** 8.7 nmol/l (AUC, 0.66; 95% CI, 0.54–0.77) for neopterin concentration before operation (Neopt0); **D.** 10.6 nmol/l (AUC, 0.64; 95% CI, 0.52–0.75) for neopterin concentration 1 day after operation (Neopt1); **E.** 10.6 (AUC, 0.64; 95% CI, 0.52–0.75) for neopterin concentration between 5 and 8 days after operation (Neopt5–8); **F.** 13 mm (AUC, 0.71; 95% CI, 0.6–0.82) for interventricular septum (IVS), and **G.** 3.7 nmol/l (AUC, 0.64; 95% CI, 0.52–0.77) for total cholesterol concentration (TC)

RESULTS

The mean age in the study group was 62.6 (7.3) years. POAF occurred in 30 patients (30%). Most patients experienced the onset of POAF on the second (n = 13, 43%) and third (n = 9, 30%) postoperative days, while in two patients (7%) POAF occurred on the fourth day, and on the first, sixth, seventh, ninth, tenth, and thirteenth day each in one patient (20%). In 10 patients (33.3%) recurrence of POAF was observed. The median duration time of POAF was 7 (2.5–18) hours. In four patients (13.3%), POAF lasted longer than 48 hours. In two of them (6%) oral anticoagulants (antagonists of vitamin K) were introduced. Twenty-seven (90%) patients with POAF received intravenous amiodarone; in three patients (10%), POAF resolved spontaneously without any additional treatment, and in one patient (3%), electrical cardioversion was successfully performed. No sustained ventricular arrhythmias were observed during the postoperative period. Fifteen (15%) patients underwent surgery with CPB. All patients were in sinus rhythm at the time of hospital discharge.

In the intergroup comparison (the POAF group vs. the non-POAF group), statistically significant factors associated with POAF included higher neopterin concentration before operation (NP0, Figure 1; Supplementary material, *Figure S1*), on the first day after operation (NP1, Figure 1; Supplementary material, *Figure S1*) and between the fifth and eighth day after operation (NP5–8, Supplementary material, *Figure S1*); older age, higher body mass index, lower total cholesterol concentration (T-chol), higher diastolic interventricular septum thickness (IVSd), pulmonary disease, left atrial (LA) diastolic dimension (Tables 1–3). Neither hs-CRP concentration before operation nor hs-CRP concentration after operation showed any difference in the POAF group vs. the non-POAF group (Table 3). There was no significant difference in neopterin concentration concerning the operation method: on-pump vs. off-pump (Table 3). Moreover, neither the number of coronary arteries involved nor SYNTAX Score II differed markedly between the POAF and non-POAF subset of surgically treated individuals (Table 2).

The cut-off value derived from ROC curve analysis was 8.7 nmol/l (AUC, 0.66; 95% CI, 0.54–0.77; $P = 0.01$) for NP0, 10.6 nmol/l (AUC, 0.64; 95% CI, 0.52–0.75; $P = 0.03$) for NP1, and 10.6 nmol/l (AUC, 0.64; 95% CI, 0.52–0.75; $P = 0.03$) for NP5-8; 64 years (AUC, 0.66; 95% CI, 0.54–0.77; $P = 0.01$) for age; 29.2 kg/m^2 (AUC, 0.64; 95% CI, 0.52–0.75; $P = 0.03$) for body mass index (BMI); 3.7 nmol/l (AUC, 0.64; 95% CI, 0.52–0.77; $P = 0.03$) for T-chol concentration; and 13 mm (AUC, 0.71; 95% CI, 0.6–0.82; $P < 0.001$) for IVSd (Figure 1).

In univariate logistic regression analysis significant predictive factors of POAF were: NP0, NP0 cut-off >8.7 nmol/l, BMI, age, T-chol, history of pulmonary disease, IVSd, left ventricular diastolic dimension (LVd), ascending aorta diameter (Ao asc), LA and duration of operation (Table 1; Supplementary material, *Figure S1*).

Stepwise multivariable logistic regression analysis, adjusted for BMI, age, T-chol, and pulmonary disease identified NP0 (OR, 1.19; 95% CI, 1.02–1.38 for continuous and

Table 4. Multivariable logistic regression models for postoperative atrial fibrillation (POAF) following coronary artery bypass grafting (CABG)

	NP0 continuous	NP0 dichotomous (>8.7 nmol/l)
	OR (95% CI)	OR (95% CI)
Preoperative factors		
NP0	1.19 (1.02–1.38)	3.75 (1.39–10.1)
BMI, kg/m^2	1.15 (1.02–1.29)	1.14 (1.02–1.29)
Pulmonary disease	6.72 (1.57–28.74)	6.52 (1.51–28.19)
Age, years	1.05 (0.97–1.13)	1.06 (0.98–1.15)
T-chol	0.73 (0.43–1.23)	0.74 (0.43–1.26)
Surgical factors		
NP0	1.18 (1.0–1.02)	3.5 (1.41–8.66)
Duration of operation	1.01 (1.03–1.36)	1.00 (0.99–1.02)
Echocardiographic factors		
NP0	1.13 (0.97–1.31)	3.26 (1.26–8.4)
IVSd	1.45 (1.14–1.83)	1.42 (1.11–1.81)
LVd	1.06 (0.97–1.16)	1.06 (0.97–1.16)
Ao (asc)	1.00 (0.93–1.09)	0.99 (0.91–1.07)
LA	1.04 (0.94–1.16)	1.06 (0.95–1.17)

Abbreviations: LVd, diastolic dimension of the left ventricle; NP0: concentration of neopterin before operation; OR, odds ratio; other — see Tables 1 and 2

Table 3. Comparison of neopterin and high sensitivity C-reactive protein (hs-CRP) concentrations before operation (NP0, hs-CRP0), on the first day (NP1, hs-CRP1), and between the fifth and eighth day after operation (NP5–8, hs-CRP5–8) in patients with postoperative atrial fibrillation (POAF) vs. without POAF and with cardiopulmonary bypass (CPB, on-pump) vs. without CPB (off-pump)

	POAF group (n = 30)	Non-POAF group (n=71)	*P*-value	On-pump group (n = 15)	Off-pump group (n = 86)	*P*-value
NP0, nmol/l, median (IQR)	9.2 (7.0–10.4)	8.0 (5.8–9.5)	0.01	6.5 (5.3–9.6)	8.5 (6.0–10.0)	0.18
NP1, nmol/l, median (IQR)	10.9 (9–17.5)	10.0 (7.1–11.7)	0.03	10.3 (7.2–15.0)	10.2 (8.2–15.2)	0.84
NP5-8, nmol/l, median (IQR)	11.0 (9.5–12.8)	9.6 (7.9–11.3)	0.03	9.3 (7.1–14.0)	10.5 (8.3–11.5)	0.22
hs-CRP, nmol/l, median (IQR)	1.4 (0.06–5.0)	1.4 (0.2–3.1)	0.69	1.1 (0.06–5.0)	1.5 (0.1–3.3)	0.32
hs-CRP1, nmol/l, median (IQR)	19.5 (15.6–33.2)	19.0 (15.1–26.0)	0.70	21.2 (17.1–41.1)	19.1 (15.1–26.0)	0.48
hs-CRP5-8, nmol/l, median (IQR)	17.1 (8.5–21.0)	15.5 (12.0–19.6)	0.79	14.6 (9.5–23.0)	15.8 (11.8–19.6)	0.92

Abbreviations: IQR, interquartile range; other — see Table 1

OR, 3.75; 95% CI, 1.39–10.1 for cut-off >8.7 nmol/l) as an independent predictor of POAF (Table 4). After adjustment for echocardiographic factors, NP0 >8.7 nmol/l was also an independent predictive factor (OR, 3.26; 95% CI, 1.26–8.4; Table 4), as well as after adjustment for surgical factors (OR, 1.18; 95% CI, 1.0–1.02 for NP0 continuous and OR, 3.5; 95% CI, 1.41–8.66 for NP0 >8.7 nmol/l, Table 4). Other independent predictors of POAF were BMI, pulmonary disease, IVSd, and duration of operation (Table 4).

In-hospital mortality was 0%. Postoperative complications occurred in 38 (38%) patients. The length of hospitalization was significantly longer in the POAF group (10 [7–13] days) vs. the non-POAF group (8 [7–9] days; P <0.01). The most common complication was postoperative wound infections (14% of patients). In the POAF group compared to the non-POAF group, all postoperative complications combined (P <0.001; OR, 9.5; 95% CI, 3.5–25.2), wound infections (P <0.001; OR, 8.4; 95% CI, 2.4–29.6), all infections combined (P <0.001; OR, 7.2; 95% CI, 2.38–21.9), and cognitive impairment (P = 0.02; OR, 6.9; 95% CI, 1.3–37.9) occurred significantly more frequently. All observed postoperative complications in the POAF and non-POAF groups are presented in Table 5.

DISCUSSION

In our series of patients, postoperative atrial fibrillation occurred in 30 subjects (30%), which is consistent with the incidence of POAF after elective CABG reported in other studies with continuous rhythm monitoring [2]. The use of CPB did not significantly affect the incidence of POAF, which may indicate that inflammation associated with surgical trauma itself, change of pressures in the atria, volume overloading, activation of the sympathetic nervous system, patient comorbidities, as well as atrial remodeling have a greater influence on POAF development than a surgical technique. This supports findings from the study by Kim et al. [13], in which no difference in nicotinamide adenine dinucleotide phosphate (NADPH) activity before and after CPB use was observed. In addition, in the current study, neopterin concentration also did not significantly differ

Table 5. Postoperative complications in the postoperative atrial fibrillation (POAF) group vs. the non-POAF group

	POAF group (n = 30)	Non-POAF group (n = 71)	*P*-value
All postoperative complications combined, number of patients (%)	22 (73)	16 (23)	<0.001
Length of hospitalization, days, median (IQR)	10 (7–13)	8 (7–9)	0.01
Packed red blood cell concentrate, median (IQR)	2 (0–2)	1 (0–2)	0.45
Temperature ≥38°C, n (%)	2 (7)	2 (3)	0.58
All infections combined, n (%)	12 (40)	6 (8)	<0.001
postoperative wound infection, n (%)	10 (33)	4 (6)	<0.001
other infections (*Clostridium difficile*, urinary tract infection, pleural abscess, or pneumonia), n (%)	2 (7)	2 (3)	0.58
Prolonged antibiotic therapy, n (%)	7 (23)	6 (8)	0.05
Cognitive impairment, n (%)	5 (17)	2 (3)	0.02
Pericardial effusion or tamponade, n (%)	3 (10)	2 (3)	0.15
Hemofiltration, n (%)	1 (3)	1 (1)	0.51
Pleural effusions, n (%)	4 (13)	4 (6)	0.23
Acute heart failure, n (%)	3 (10)	1 (1)	0.08
Other complications: increased ALAT or ASPAT >8 × ULN			
Acute limb ischemia, pneumothorax, n (%)	2 (7)	2 (3)	0.58

Abbreviations: ALAT, alanine transaminase; ASPAT, aspartate transaminase; ULN, upper limit of normal; other — see Table 1

in the on-pump group compared to the off-pump group. However, in the previous study, CPB use was shown to be associated with higher postoperative neopterin concentration when compared to the off-pump group [30]. In the literature, four studies were designed to evaluate neopterin concentration in relation to non-operative atrial fibrillation (AF) [31–34]. In these reports, a higher concentration of neopterin was found in patients with AF compared to those without arrhythmia. However, to the best of our knowledge, the association of neopterin concentration with POAF occurrence after CABG has never been investigated. In the current study, we have documented a higher concentration of neopterin (NP0, NP1, and NP5–8) in patients with the new onset of AF compared to patients without POAF development following elective CABG. Furthermore, a stepwise multivariable analysis adjusted for age, BMI, T-chol, history of pulmonary disease, echocardiographic parameters, and surgical factors, showed NP0 as a significant factor in the prediction of POAF. These results indicate that inflammation plays an important role in POAF development. Similarly, in a recent large cohort study, a higher neopterin concentration after adjustment for age, sex, BMI, creatinine, current smoking, diabetes mellitus, systemic hypertension, as well as hs-CRP level was an independent predictor of non–operative AF. The limitation of the mentioned study is that none of the echocardiographic nor electrocardiographic variables were included in the analysis [31]. In our study, apart from elevated preoperative neopterin concentration, significant independent factors of POAF included a thicker interventricular septum (IVS), higher BMI, and a history of pulmonary disease. In addition, the efficacy of electrical cardioversion of non-operative atrial fibrillation was higher in non-obese patients compared to the obese group [35]. While higher BMI and pulmonary disease are well-established predictive factors of POAF, a thicker IVS as a predictor of POAF has not been widely described in the literature [36, 37]. Thus, even though in the current study the diagnosis of systemic hypertension was not identified as a predictive factor of POAF, we speculate that a higher diastolic IVS dimension might be a marker of uncontrolled systemic hypertension and may be a better prognostic factor of the arrhythmia. Among surgical factors, in the univariate analysis, the duration of operation had the highest predictive value of POAF. Preoperative, as well as postoperative white blood cell (WBC) count, was found higher in patients with POAF in one study, but WBC count as a predictive factor of POAF was not confirmed in other studies [8]. Moreover, it has been found previously that CRP was a predictive factor of non-operative AF [9], while results of studies evaluating the impact of CRP concentration on POAF have been so far inconclusive [1, 10–12]. In the previous study, a synthesis-based review article, CRP and some other markers (e.g., BNP or interleukin 6) had controversial clinical utility in predicting POAF [13]. Thus, it should be stressed that of the laboratory parameters examined in the current study (such as hs-CRP, WBC, RDW, erythrocyte sedimentation rate, and creatinine concentration), only neopterin concentration (NP0, NP1, and NP5–8) was significantly higher in the POAF group compared to the non-POAF group, while T-chol concentration was lower in POAF group. According to the univariate analysis, NP0 concentration (continuous and cut-off >8.7) was the highest predictive value of POAF compared to NP1 and NP5–8 concentrations. The explanation why the preoperative concentration of neopterin was a better predictor of POAF than postoperative neopterin concentration, may be that other significant chronic factors existed before operation, such as age, left atrial or ventricular remodeling and patient comorbidities have a stronger influence on POAF occurrence than acute factors directly related to operation, such as CPB use or operation duration. All these chronic factors are potentially reflected by higher NP0 concentration. However, it is well known that blockade of the upregulated sympathetic nervous system during operation is of relevance too; therefore, in the current

study, most patients (82%) received beta-blockers before and after operation. According to our results, the POAF occurrence was associated with longer hospitalization, as well as postoperative complications. Interestingly, among them, the infective complications (P <0.001) and cognitive impairment (P = 0.02) were significantly more frequent in the POAF group compared to the non-POAF group, thus, we hypothesize these complications may be reflected by higher concentration of an inflammatory marker like neopterin. Contrary to the neopterin concentration, the concentration of CRP showed only a trend toward higher values in the POAF group but did not reach statistical significance, which indicates that neopterin may be a more accurate prognostic biomarker.

In summary, in terms of the multifactorial etiology of POAF and worse outcomes for patients who develop this type of arrhythmia, there is a great need to introduce a simple test to identify patients at the highest risk of POAF and implement additional preventive strategies such as administration of amiodarone. Thus, our findings have a clinical impact on the selection and further management of patients at the highest risk of POAF occurrence who should be treated with particular caution during the postoperative period. Therefore, we believe that a higher serum neopterin concentration before operation (cut-off value, 8.7 nmol/l) may help in the identification of patients at risk of POAF development.

Limitations

This study has several limitations that may have an impact on the findings. Firstly, the number of on-pump patients (15%) was relatively small, and any attempt to find detailed differences between coronary artery bypass grafting on the beating heart and in CPB would have been afflicted with likely bias. Therefore, it must be stressed that comparison between these groups was not the main purpose of our analysis. Secondly, evaluation of left atrial remodeling was presented exclusively as an anterior-posterior dimension of the left atrium measured on transthoracic echocardiography. We are aware of the fact that the left atrial volume is regarded to be a more specific parameter.

CONCLUSIONS

We found that neopterin concentration before operation adjusted for age, BMI, T-chol, pulmonary disease, echocardiographic parameters, and surgical factors may be POAF predictive. Regarding the highly complex pathophysiology of POAF, elevated preoperative serum neopterin concentration is one of the potential predictive factors of POAF.

Supplementary material

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

Article information

Conflict of interest: None declared.

Funding: None.

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Low-grade endotoxemia and NOX2 in patients with coronary microvascular angina

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DOI: 10.33963/KP.a2022.0130

Received:
February 18, 2022

Accepted:
May 17, 2022

Early publication date:
May 17, 2022

ABSTRACT

Background: Endothelial dysfunction and oxidative stress were hypothesized to be involved in the pathogenesis of coronary microvascular angina (MVA). NADPH oxidase-2 (NOX2) activation could provoke increased oxidative stress and endothelial dysfunction, but data on MVA have not been provided yet.

Aims: This study aimed to evaluate the interaction among NOX2 activation, serum lipopolysaccharide (LPS) levels, as well as oxidative stress production as potential causes of endothelial dysfunction in MVA patients.

Methods: In this study, we wanted to compare serum levels of soluble NOX2-dp (sNOX2-dp), H_2O_2 production, hydrogen peroxide breakdown activity (HBA), nitric oxide (NO) bioavailability, endothelin 1 (ET-1), serum zonulin (as intestinal permeability assay), and LPS in 80 consecutive subjects, including 40 MVA patients and 40 controls (CT), matched for age and sex.

Results: Compared with CT, MVA patients had significantly higher values of sNOX2-dp, H_2O_2, ET-1, LPS, and zonulin. Conversely HBA and NO bioavailability were significantly lower in MVA patients. Simple linear regression analysis showed that sNOX2 was associated with serum LPS, serum zonulin, H_2O_2, and ET-1. Furthermore, an inverse correlation between sNOX2, HBA, and nitric oxide bioavailability was observed. Multiple linear regression analysis showed that LPS and zonulin emerged as the only independent predictive variables associated with sNOX2.

Conclusions: This study provides the first report attesting that patients with MVA have high LPS levels, NOX2 activation, and an imbalance between pro-oxidant and antioxidant systems, in favor of the oxidizing molecules that could be potentially implicated in the endothelial dysfunction and vasoconstriction of this disease.

Key words: coronary microvascular angina, LPS, NADPH oxidase, NOX2, oxidative stress

WHAT'S NEW?

The role of oxidative stress and low-grade endotoxemia is unclear in patients with coronary microvascular angina (MVA). This study aimed to evaluate NADPH oxidase-2 activation, serum lipopolysaccharide levels, as well as oxidative stress production, and endothelial dysfunction in MVA patients and controls. The results of this study show that MVA patients have high circulating levels of serum lipopolysaccharide, oxidative stress, and endothelin 1. NADPH oxidase-2 activation could contribute to provoking an imbalance between pro-oxidant and antioxidant systems, which could determine endothelial dysfunction and vasoconstriction in MVA.

INTRODUCTION

Microvascular angina (MVA) is defined as microvascular dysfunction of the coronary arteries. It is characterized by typical chest pain, evidence of myocardial ischemia on an electrocardiogram, and the absence of obstructive coronary artery disease (CAD) [1]. MVA represents an increasingly growing problem when we consider that up to 50% of patients with angina who undergo coronary angiography have not any significant artery obstruction [2–4]. Despite the absence of significant coronary lesions, its prognosis is not benign, because MVA is an independent risk factor for major adverse cardiovascular events [5, 6].

Microvascular dysfunction is studied invasively with coronary angiography and use of pharmacological tests to evaluate the endothelial reactivity [7]. It has been demonstrated that it mainly embraces two aspects: firstly, inadequate vasodilatation to a stimulus, and secondly, exaggerated vasoconstriction (coronary microvascular spasm) [7]. Experimental studies suggested a major role of oxidative stress in the initiation and progression of microvascular dysfunction in MVA [8]. NADPH oxidase-2 (NOX2) is considered one of the main sources of superoxide anion in humans, a modulator of the arterial tone [9–12], and an enzyme directly implicated in microvascular dysfunction [13]. The role of NOX2 in MVA has not been yet elucidated.

Lipopolysaccharide (LPS) is an endotoxin derived from the membrane of gram-negative bacteria that, by binding to Toll-like receptor 4 (TLR4), activates intracellular transcription of several inflammatory mediators in the vessels [14]. An impairment of tight junction causes translocation of LPS from the gut to the systemic circulation where it initiates pro-inflammatory and pro-oxidant effects in the vessels [15]. Moreover, a recent experimental study showed that LPS from *Escherichia coli* was localized in human plaque and may contribute to atherosclerotic damage *via* TLR4-mediated oxidative stress and NOX2 activation [16, 17]. A relationship between LPS and NOX2 activation has been previously described in other clinical settings such as non-alcoholic fatty liver disease (NAFLD), pneumonia [18], and neurodegenerative disease [19], but no data have showed its role in MVA yet. Thus, in this study, we evaluated the potential role of low-grade endotoxemia by LPS in eliciting systemic Nox2 activation and the balance of pro-oxidant molecules, such as H_2O_2, and the antioxidant system, such as hydrogen peroxide breakdown activity (HBA), in MVA.

METHODS

The study was supported by the Sapienza University in cooperation with Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Republic of Moldova, to strengthen institutional competencies and the management of partner universities, finalized to cardiovascular prevention [20].

Forty consecutive Moldovan patients with coronary MVA and 40 controls (CT) matched for age and sex agreed to participate in the study, which was performed between July 2018 and December 2020. These patients were recruited at the Moldavian Research Institute of Cardiology, Chisinau, Republic of Moldova.

Coronary MVA was diagnosed according to the criteria suggested by the Coronary Vasomotion Disorders International Study Group [21]; these criteria include (1) presence of symptoms suggestive of myocardial ischemia; (2) objective documentation of myocardial ischemia, as assessed by currently available techniques; (3) absence of obstructive CAD (<50% coronary diameter reduction and/or fractional flow reserve >0.80) documented by CT coronary scan or coronary angiography, as in our case; (4) confirmation of a reduced coronary blood flow reserve and/or inducible microvascular spasm [21]. Microvascular disorder was confirmed by using the angiographic flow assessment criteria based on the thrombolysis in myocardial infarction (TIMI) flow grade or TIMI frame count (TFC/cTFC). TIMI-2 flow grade, which means partial perfusion (i.e. requiring three or more beats to opacify the distal vessel) or a corrected TIMI frame count >27 frames, in at least one major coronary vessel, have been frequently used and were, therefore, preliminarily assumed. The latter is based upon images acquired at 30 frames/second and a correction factor of 1.7 for the left anterior descending artery (LAD). The speed with which the dye reaches the distal bifurcation of LAD from the ostium is measured in frame counts. In right coronary artery, the flow was measured from the ostium to the origin of the first posterolateral branch. In the left circumflex, the flow was measured from the ostium to the most distal branch of the last OM. A correction factor of 1.7 was used for LAD (for corrected TFC). The normal count was considered 21 ± 3 frames.

Considering the COVADIS (Coronary Vasomotion Disorders International Study Group) criteria, our cohort of patients had a definitive diagnosis of MVA.

From all patients included in the study, blood samples for analysis of oxidative stress, LPS, and zonulin levels were collected after a fasting period of 8 hours.

Subjects were excluded from the study if they had liver insufficiency, advanced chronic kidney disease, acute cerebrovascular disease, acute myocardial infarction, recent abdominal surgery or were taking antioxidants. We also excluded patients with active cancer, uncontrolled blood pressure or diabetes, inflammatory bowel disease, and those taking or with a recent intake of antibiotics.

Informed written consent was obtained from all subjects: the study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethical Committee of the Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Republic of Moldova (no. 3-9-19/41/49).

Serum sNOX2-dp detection

NOX2 activation was measured as soluble NOX2-derived peptide (sNOX2-dp) with an ELISA method, as previously described [22]. Briefly, the peptide is recognized by binding to a specific monoclonal antibody against the amino acid sequence (224–268), the extra membrane portion of NOX2. Values were expressed as pg/ml; intra-assay and inter-assay coefficients of variation were 8.95% and 9.01%, respectively.

H_2O_2 production

The H_2O_2 was evaluated by a Colorimetric Detection Kit (ArborAssay, Ann Arbor, MI, US) and expressed as µM. Intra-assay and inter-assay coefficients of variation were 2.1% and 3.7%, respectively.

Determination of % HBA in serum

Serum hydrogen peroxide (H_2O_2) HBA was measured with an HBA assay kit (Aurogene, Rome, Italy; code HPSA-50). The percentage of HBA was calculated according to the following formula: % of HBA = [(Ac–As) / Ac] × 100, where Ac is the absorbance of H_2O_2 1.4 mg/ml, and As is the absorbance in the presence of the serum sample.

NO bioavailability

A colorimetric assay kit (Abcam, Cambridge, UK) was used to determine NO bioavailability as previously described [23]. Intra-assay and inter-assay coefficients of variation were 2.9% and 1.7%, respectively.

Serum zonulin

Serum zonulin was used as an intestinal permeability assay. Serum zonulin levels were measured using a commercial ELISA kit (Elabscience, Houston, TX, US). Antibody specific for zonulin has been pre-coated onto a microplate and 100 µl of standards, and patient sera samples were added and incubated for 90 min at 37°C. Then, a biotinylated detection antibody specific for zonulin and Avidin-Horseradish Peroxidase (HRP) conjugate was added to each microplate. Values were expressed as ng/ml; both intra-assay and inter-assay coefficients of variation were within 10%.

Serum LPS assay

LPS levels in serum were measured using a commercial ELISA kit (Cusabio, Houston, TX, US). The standards and samples were plated for 2 hours at room temperature into a micro-plate pre-coated with the antibody specific for LPS. After incubation, samples were read at 450 nm. Values were expressed as pg/ml; intra-assay and inter-assay coefficients of variation were <10%.

Serum endothelin 1 assay

Serum endothelin 1 (ET-1) levels were measured using a commercial ELISA kit (Thermo Fisher Scientific, Waltham, MA, US).

Statistical analysis

Statistical analyses were undertaken using SPSS 25.0 software for Windows (IBM, Armonk, NY, US). The Kolmogorov–Smirnov test was used to determine whether variables were normally distributed. Normally distributed data are described as means and standard deviations (SD). Between-group differences were analyzed by Student t-test. Differences between percentages were assessed by the χ^2 test. Bivariate analysis was performed by Spearman correlation; the variables with evidence of an association P <0.10 were included in a multivariable linear regression using an automated procedure. The results of the multivariable linear regression analysis were expressed as standardized coefficient beta (β) with standard error (SE). Moreover, the coefficient of determination was provided (R2). A P-value of <0.05 was considered statistically significant.

Sample size determination

We computed the minimum sample size with respect to a two-tailed, one-sample Student t-test considering, on the basis of data from a previous pilot study (data not shown): a difference of 7.3 pg/ml for sNOX2-dp levels between patients and controls (mean patients, 32; mean controls, 24.2 pg/ml), 10 as SD, 0.05 (α) as type-I error probability and 0.95 as power 1–β. The sample size was 40 patients/group.

RESULTS

Clinical characteristics of MVA patients and controls are reported in Table 1. There was no significant difference in age, sex, and classic cardiovascular risk factors between the two groups (Table 1).

LPS and zonulin

MVA patients had increased levels of LPS (mean [SD], 37.5 [12.9] pg/ml vs. 20.7 [10.1] pg/ml; P <0.001) and zonulin (3.0 [0.9] ng/ml vs. 1.57 [0.5] ng/ml; P <0.001) compared to the control group (Figure 1A and B).

Table 1. Clinical characteristics of the patients with and without microvascular angina

	Patients with microvascular angina (MVA) n = 40	Patients without microvascular angina (control group) n = 40	*P*-value
Age, years	62.7 (8.1)	61.7 (5.7)	0.56
Male sex	14 (35)	20 (50)	0.17
Diabetes	10 (25)	4 (10)	0.11
Dyslipidemia	36 (90)	38 (95)	0.39
Hypertension	37 (92)	36 (90)	0.69
Current smokers	6 (15)	8 (20)	0.46
Obesity	15 (37)	18 (45)	0.49
Anticoagulants	3 (7.5)	2 (5)	0.74
Beta-blockers	34 (85)	19 (47)	<0.01
Calcium antagonists	28 (70)	10 (35)	<0.01
ACE inhibitors	23 (57)	15 (37)	0.14
Renin-angiotensin-aldosterone system inhibitors	12 (30)	2 (5)	0.01
Statins	33 (82)	25 (62)	0.11
Diuretics	17 (42)	3 (7.5)	<0.01
Anti-platelet drugs	35 (87)	21 (52)	<0.01

Continuous variables are reported as mean (SD); categorical variables are expressed as n and percentage

Abbreviations: ACE, angiotensin-converting enzyme

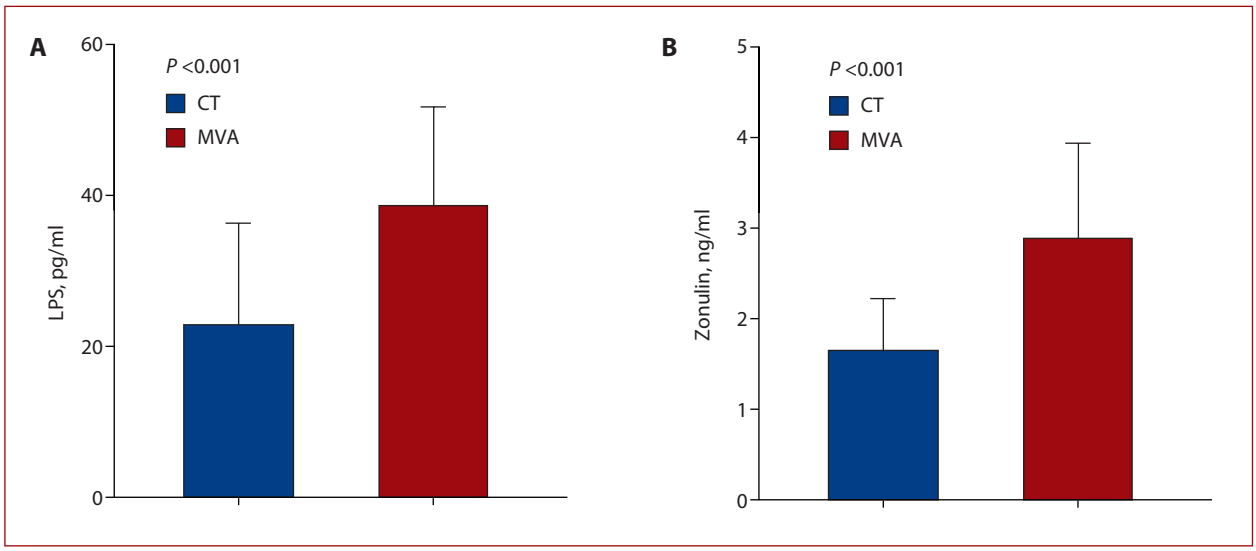

Figure 1. Gut-permeability analysis: serum lipopolysaccharide concentration (**A**) and serum levels of zonulin (**B**) in microvascular angina (MVA) patients (n = 40) and controls (CT) (n = 40)

Oxidative stress

Compared with CT, MVA patients had significant higher mean values of sNOX2-dp (57.4 [13.1] pg/ml vs. 27.4 [11.5] pg/ml; *P* <0.001) and H_2O_2 production (47.7 [21.4] µM vs. 22.1 [10.3] µM; *P* <0.001) (Figure 2A and B). Conversely HBA were significantly lower in patients with MVA compared to controls (27.8 [10.8] vs. 56.1 [21.2] %; *P* <0.001) (Figure 2C).

Endothelial dysfunction and NO bioavailability

MVA patients had significant lower NO bioavailability (28.1 [10.5] µM vs. 35.6 [14.4] µM; *P* = 0.01) and higher levels of ET-1 (15.6 [6.2] pg/ml vs. 10.2 [5.6] pg/ml; *P* <0.001) (Figure 3A and B).

Associations among the studied variables

Univariate analysis by Spearman correlation test showed that sNOX2 was associated with serum LPS (Rs = 0.629; *P* <0.001), serum zonulin (Rs = 0.641; *P* <0.001), H_2O_2 (Rs = 0.590; *P* <0.01), and ET-1 (Rs = 0.410; *P* <0.001). Furthermore, an inverse correlation between sNOX2 and HBA (Rs = –0.646; *P* <0.001) and nitric oxide bioavailability (Rs = –0.312; *P* <0.01) was observed. LPS was also associated with serum ET-1 (Rs = 0.243; *P* = 0.03), zonulin (Rs = 0.474; *P* <0.001), and oxidative stress, as shown by its correlation with H_2O_2 (Rs = 0.490; *P* <0.001) and HBA (Rs = –0.560; *P* <0.001).

Multiple linear regression analysis, adjusted for statins, beta-blockers, calcium antagonists, diabetes and hyperten-

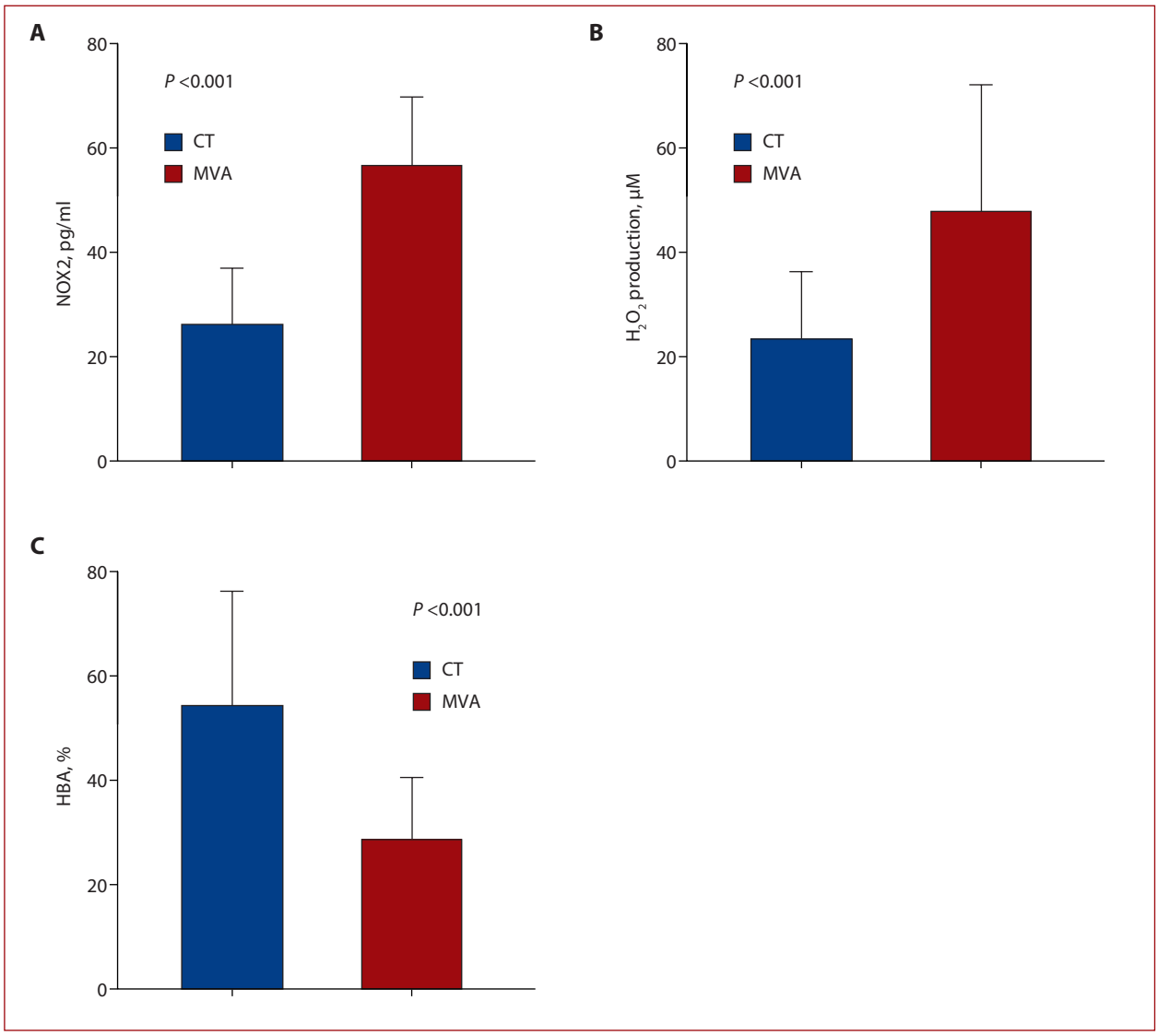

Figure 2. Oxidative stress production: serum sNOX2-dp levels (**A**), serum H_2O_2 production (**B**), and serum hydrogen peroxide breakdown activity (**C**) in microvascular angina (MVA) patients (n = 40) and controls (CT) (n = 40)

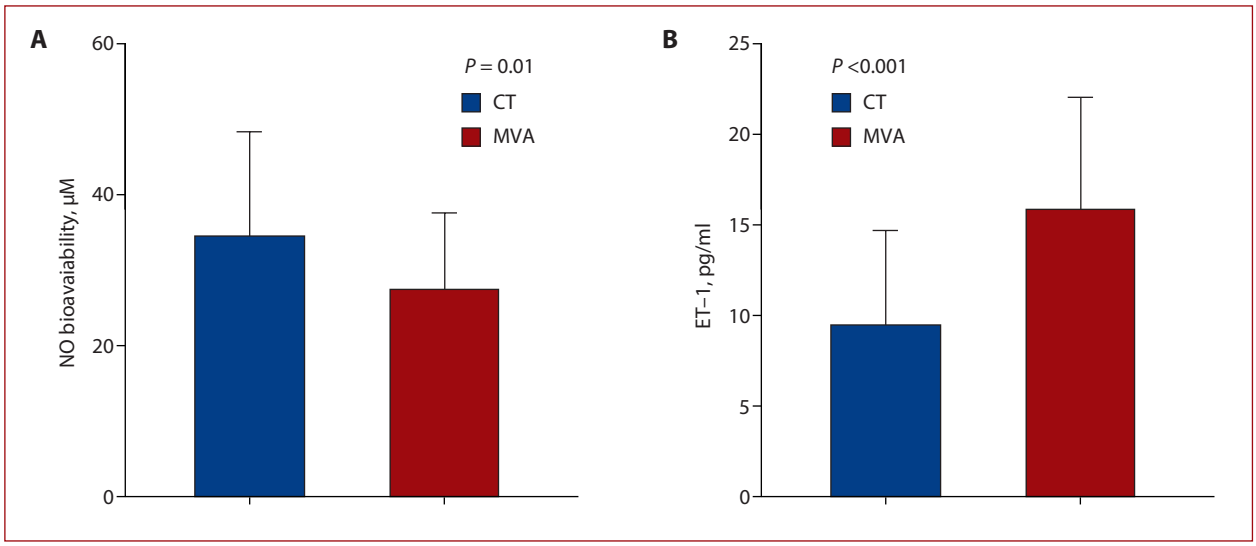

Figure 3. Endothelial dysfunction evaluation: serum NO bioavailability (**A**) and serum levels of endhotelin 1 (ET-1) (**B**) in microvascular angina (MVA) patients (n = 40) and controls (CT) (n = 40)

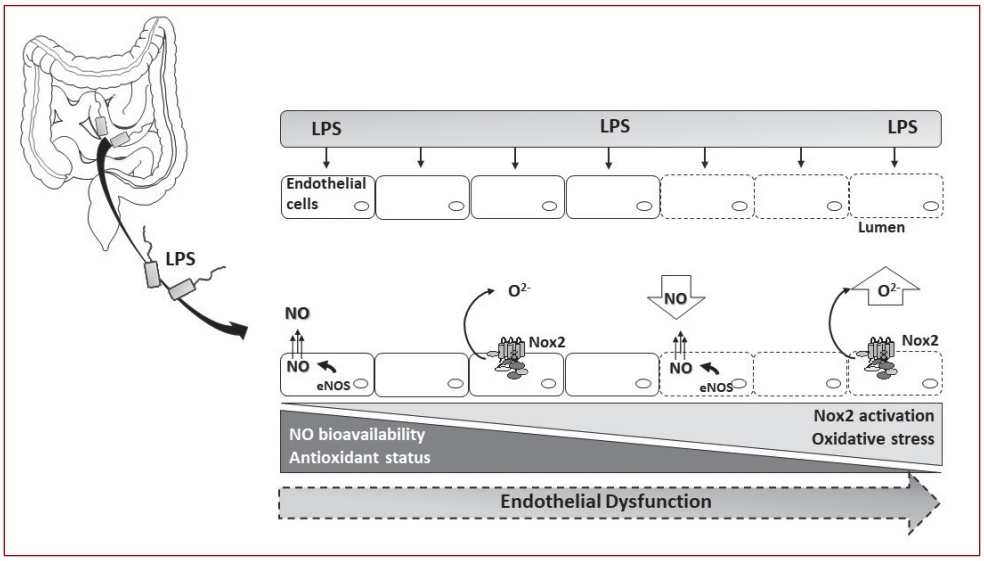

Figure 4. Low-grade endotoxemia could trigger activating NOX2, which increases oxidative stress and decreases antioxidant status and nitric oxide bioavailability, causing endothelial dysfunction in patients with microvascular angina (MVA)

sion, showed that LPS (SE, 0.129; standardized coefficient β, 0.335; P =0.001) and zonulin (standardized coefficient β, 0.279; SE, 1.828; P =0.006) emerged as the only independent predictive variables associated with sNOX2 (R^2 = 61%). Furthermore, sNOX2 (standardized coefficient β, 0.469; SE, 0.099; P = 0.001) and HBA (standardized coefficient β, –0.258; SE, 0.082; P = 0.04) were the independent predictive variables associated with LPS (R^2 = 44%).

DISCUSSION

The study shows for the first time that MVA patients have increased LPS serum levels. To find if gut permeability may account for LPS increase in patients with MVA, we measured the circulating levels of zonulin, which modulates gut permeability by disassembling the intercellular tight junctions [24]. Experimental and clinical studies demonstrated that zonulin up-regulation increases gut permeability [25]. The increased serum levels of zonulin in patients with MVA and its correlation with serum LPS could provide evidence that gut permeability is enhanced in this cohort and may be responsible for the high circulating levels of LPS.

LPS is a pro-inflammatory molecule that may favor endothelial dysfunction with an oxidative stress-mediated mechanism. In particular, LPS binds to TLR4 complex and activates a series of proteins and kinases in endothelial cells (as nuclear factor-kappa B [NF-κB]), interleukin 1 receptor-associated kinase (IRAK), tumor necrosis factor receptor-associated factor 6, NF-kB-inducing kinase, and inhibitor kappa B, which increase the production of proinflammatory molecules (as cytokines/chemokines) [26].

In accordance with this, LPS directly correlated with NOX2, suggesting a role for LPS as a trigger for oxidative stress [8]. The high levels of H_2O_2 and the close relation with sNOX2 observed in this study suggest that systemic oxidative stress in MVA could derive from LPS-induced NADPH oxidase activation as hypothesized by previous papers [8, 27].

NOX2 is considered an important modulator of artery vasodilation in endothelial cells; previous studies showed that NOX2 activation increases oxidative stress and impaired NO biosynthesis determining vasoconstriction [9, 11, 28].

No description of an association between LPS, NOX2, and endothelial dysfunction in MVA has been reported. Previously, in other settings, such as neurodegenerative diseases and neuropsychiatric disorders, associations among increased LPS, NOX2, oxidative stress, and endothelial dysfunction were reported [19, 29]. Experimental studies in animals showed that LPS could induce cardiac microvascular dysfunction [30]. Mice treated with LPS showed cardiac endothelial dysfunction and higher mortality that could be related to the loss of pericytes [30]. Other studies showed that LPS impaired endothelial dysfunction by reducing vasodilatory response to acetylcholine and eNOS phosphorylation [31, 32].

Our report supports and extends these previous findings in patients with MVA by demonstrating that NOX2 activation could increase oxidative stress and could determine endothelial dysfunction by reduction of NO bioavailability [33] and by increased ET-1 production. Reactive oxygen species generated by NOX2 activation could stimulate ET-1 secretion and provoke microvascular dysfunction [34]. In line with several previous studies, we found increased serum ET-1 levels in MVA patients [8, 35]; however, we cannot exclude that genetic dysregulation of ET-1 could be implicated [36].

The study has some limitations and implications. We did not perform all the invasive tests to evaluate the coronary function, including measurements of CFR, microvascular resistance, acetylcholine, or adenosine provocation

test. We did not evaluate other NADPH isoforms, such as NOX1 and NOX4, and other antioxidant systems such as catalase, SOD, and glutathione peroxidase that could also contribute to increased oxidative stress in MVA. The mechanism accounting for LPS translocation from the gut microbiota to systemic circulation was not addressed by the present study. However, changes in gut permeability might be a plausible mechanism as increased serum zonulin, which reflects enhanced gut permeability, is significantly correlated with blood LPS. Nevertheless, zonulin is an indirect marker of gut permeability, and we cannot exclude that serum LPS could also be derived from other sources, thereby a further study is necessary to elucidate this issue. Furthermore, some sources of chronic inflammation such as periodontitis [37] that may have affected LPS levels were not analyzed in this study.

Future studies are necessary to assess if improvement of gut permeability and eventually lowering of low-grade endotoxemia improve artery dysfunction in MVA.

In conclusion, this study provides the first report attesting that patients with MVA have high LPS levels, NOX2 activation, and an imbalance between pro-oxidant and antioxidant systems, in favor of the oxidizing molecules that could be potentially implicated in the endothelial dysfunction and vasoconstriction of this disease. These results could open new therapeutic strategies to modulate gut microbiota and oxidative stress to reduce the cardiovascular risk in MVA patients.

Article information

Conflict of interest: None declared.

Funding: This study was supported by a grant from the University of Rome "La Sapienza" (Università degli Studi di ROMA "la Sapienza" Progetti di COOPERAZIONE E SVILUPPO 2017 n.: 000324_18_RS; funds to LL).

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The cost of CIED infectious complications treatment in Poland from the perspective of Polish hospitals

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DOI: 10.33963/KP.a2022.0144

Received:
March 20, 2022

Accepted:
May 25, 2022

Early publication date:
June 14, 2022

ABSTRACT

Introduction: Cardiac implantable electronic devices (CIED) are a recognized form of therapy in cardiology. Apart from the benefits, the use of CIEDs is also associated with the risk of complications, and the most important ones influencing treatment results and prognosis are infectious complications.

Aim: This study aimed to calculate the cost of treatment of CIED-related infections, including transvenous lead extraction and device reimplantation, from the perspective of a Polish hospital.

Methods: A retrospective analysis of hospitalization costs of patients referred to transvenous lead extraction (TLE) for CIED infection was performed. The study covers cases from three Polish reference centers specializing in the comprehensive treatment of cardiac electrotherapy complications.

Results: It was shown that the average cost of treating a CIED infection is 34 000 PLN (8010 EUR) and is the highest in the cardiac resynchronization therapy with defibrillator function (CRT-D) group, where it amounts to almost 50 000 PLN (11 440 EUR). Thus, treatment of CIED infections is associated with an average loss of 3000 PLN for the healthcare provider and the length of hospitalization has a major influence on final outcomes.

Conclusions: The hospital cost of treatment of CIED-related infections was high and related mainly to the type of device and length of hospitalization. Despite the low utilization of costly extraction tools, the hospitalization was still likely to be unprofitable.

Key words: CIED-related infectious complications, healthcare costs, transvenous lead extraction

INTRODUCTION

Cardiac implantable electronic devices (CIEDs) have long been an important tool in the treatment of many cardiac diseases. Their use is associated with a significant improvement in the quality of life or better prognosis [1]. Continuous progress in this field and the development of electrotherapy have led to the implementation of more complex devices than standard pacemakers (PM), such as implantable cardioverter-defibrillators (ICD) and cardiac resynchronization therapy (CRT). Despite the benefits of CIEDs, there is a risk of complications. One of the most important problems is CIED-related infection, which leads to a number of consequences including an increased risk of death, the need for system removal and new implantation, or prolonged hospitalization [2].

Determining the prevalence of CIED infections is difficult due to the heterogeneity of the populations analyzed, the lack of a precise definition, and different methodologies used. There is a clear difference between the incidence of infection in prospective studies where a risk of 0.6%–1.3% [3, 4] is observed

WHAT'S NEW?

This was a multicenter Polish study that analyzed the contemporary real-world costs of treatment of cardiac implantable electronic device-related infections from the perspective of the healthcare provider and not the public payer. The results of the study analyses indicate a high cost of care despite low utilization of costly extraction tools, and that this cost may not be entirely covered by the dedicated National Health Fund tariffs.

compared to retrospective studies where the incidence of infection was 2.3%–3.4% [5, 6] within the first year of implantation. The most commonly isolated microorganisms are Staphylococcus aureus and coagulase-negative staphylococci [5]. Several risk factors for infectious complications have been identified such as renal failure, especially in the final stage with dialysis, history of device infections, diabetes, use of anticoagulants and antiplatelet agents, malnutrition, fever, and active infection before the procedure, temporary pacing, and long duration of the procedure [6, 7]. The cornerstone of CIED-related infection treatment is the extraction of the whole device together with leads (transvenous lead extraction [TLE]) and reimplantation of a new one after curing the infection. It seems that the best way to reduce the costs of treatment of infectious complications is their prevention [6, 8]. Preventive strategies with proven effectiveness include the creation of high-volume centers performing an appropriate number of procedures per center and operator, an appropriate surgical technique limiting the frequency of reinterventions, and the prevention of hemorrhagic complications [9]. In addition, the use of antibacterial envelopes, which reduce the risk of staphylococcal infections in high-risk patients, i.e. patients with *de novo* cardiac resynchronization therapy with defibrillator function (CRT-D) implantation and those undergoing device replacement procedures, has proved effective [10]. In scientific publications regarding cost analyses in cardiology in Poland, we can find single studies on the costs of outpatient treatment of patients with heart failure or the costs of treatment of patients with supraventricular arrhythmia [11, 12], and one single-center analysis of TLE costs, which showed an underestimation of the procedure's reimbursement TLE [13]. There is a general belief among Polish cardiologists that the reimbursement of these procedures based on diagnosis-related groups of patients (DRG) is underestimated and in most cases does not cover the costs of standard tools used during the procedure, thus discouraging the use of more modern and safer but more expensive techniques.

This study aimed to calculate the cost of treatment of CIED-related infections, including transvenous lead extraction and device reimplantation, from the perspective of a Polish hospital.

METHODS

A retrospective analysis of hospitalization costs of patients referred for TLE due to the CIED infection was performed. The study covers cases from three Polish reference centers specializing in comprehensive treatment of cardiac electrotherapy complications: Górnośląskie Centrum Medyczne im. prof. Leszka Gieca Śląskiego Uniwersytetu Medycznego w Katowicach, Szpital Kliniczny Przemienienia Pańskiego Uniwersytetu Medycznego im. Karola Marcinkowskiego w Poznaniu, and Kliniczny Szpital Wojewódzki Nr 2 im. Św. Jadwigi Królowej w Rzeszowie. As a case study, this analysis has no intent to mimic the whole population of patients with CIED infections. The analysis specifically covers patients hospitalized for CIED infections in the 2016–2018 period. Information on diagnostics, type of CIED, applied treatment and length of hospitalization was extracted from medical records. The extracted data were accompanied by information on the direct real gross costs of every good products and service contributing to patients' hospitalization outlays obtained from financial departments of individual centers. The financial data were then divided into the following cost categories: manhours (fixed cost of an hour of hospital stay), personnel, medical tests, total drugs and medical devices, antibiotics, CIED with leads, drugs and medical devices used either for extraction or implantation, as well as other drugs and medical devices. It needs to be borne in mind that, depending on how costs are calculated in a particular center, the category 'personnel' may not be consistent between analyzed centers, though the problem of inconsistency does not affect the total costs. Furthermore, the financial data on public payer reimbursement of each patients' therapy were also obtained, which made it possible to assess economic viability of CIED infection treatment in current systemic conditions.

In Poland, the treatment of CIED infections is reimbursed by the single central national insurer — the National Health Fund (NHF) based on the DRG — standard payment rates dependent on the diagnosis and treatment provided. This is the basic way of accounting for all hospitalizations in Poland. In exceptional cases, when the cost of hospitalization exceeds three times the valuation of the relevant DRG, the NHF may, but is not obliged, to cover the cost of hospitalization following a case-based decision. To maintain consistency and reproducibility of the results presented, hospitalizations financed in this way were excluded from the present analysis. Moreover, hospitalizations of patients who did not complete therapy in a given center and were subsequently transferred to other hospitals were excluded from the study, as in such cases the identification of the total cost of treatment was precluded. Our calculation does not take into account opportunity costs related to prolonged hospitalizations and

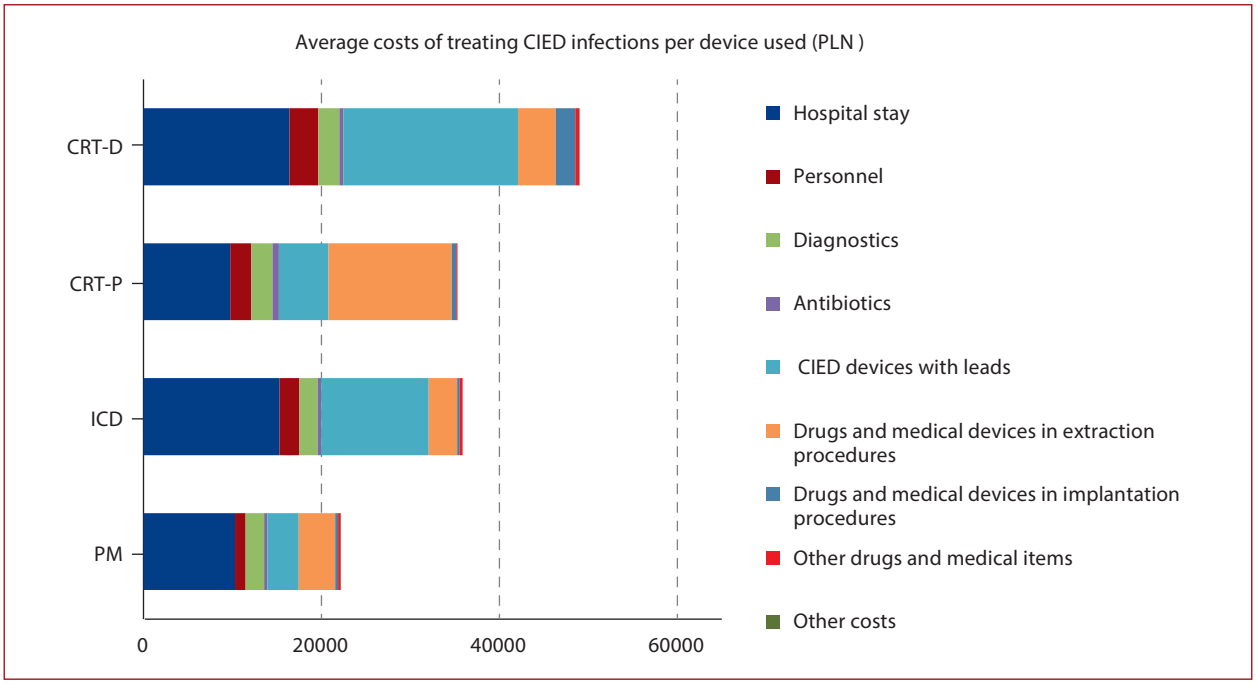

Figure 1. Average costs of treating CIED infections per device used (PLN)

Abbreviations: CIED, cardiac implantable electronic devices; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; ICD, implantable cardioverter-defibrillator; PM, pacemaker

additional costs of a cardiac surgery team being on alert in case of serious complications.

For each patient in the identified sample, the analysis included every cost element cataloged by a particular health center at their gross value in PLN. The costs were also presented in EUR, using the National Bank of Poland exchange rates from the end of each analyzed year (mean exchange rate 1 EUR = 4.3 PLN).

Statistical analysis

The cost elements were grouped in categories mentioned earlier while the results were presented using descriptive statistics for the analyzed sample in the form of the average cost of treating a patient with a CIED infection in the analyzed sample. Descriptive statistics were applied to investigate cost categories with the highest impact on the financial result of CIED infection treatment. Variables were summarized with mean (standard deviation [SD]) or as counts and percentages while the basic ones were also analyzed for their skewness using Pearson's formula. Additionally, median and quartile deviation was included for the variables that exhibit a relatively high skewness. The relatively high amount of data, which includes the type of CIED used, sex, age, types of extraction devices used, etc. allowed for further analysis in the form of statistical regressions, used specifically to identify factors influencing hospitals' financial results for each treatment. The statistical regression was used to analyze the relationship between the number of hospitalization days and the profit/loss per treatment. Standard significance level of 5% was applied, while the presented regression met the requirements of homoscedasticity, lack of residuals' autocorrelation, and normal distribution of the residuals. All calculations were performed using MS Office Excel and PSPP GNU.

RESULTS

Between 2016 and 2018, 169 patients with CIED infections were treated at three reference centers: 17 hospitalizations were billed individually and for a further 81 cases treatment data were incomplete (part of the treatment process was carried out at another center). The exclusion of these patients from the sample most probably results in the underestimation of treatment costs against the overall number of CIED infections treated in the chosen medical centers. Finally, data from 71 hospitalizations were included in the final analysis. In 80.3% of cases, pocket infection was diagnosed, whereas the remaining 19.7% of patients experienced systemic infection.

In the study group, the average cost of treatment of a CIED infection was 34 346 PLN; SD 17 342 (8010 EUR) and was the highest in the CRT-D group, where it reached 49 038 PLN; SD 11 583 (11 440 EUR) (Figure 1). Mean treatment cost in the case of pocket infection was 3206 PLN; SD 16 601, whereas in the case of systemic infection the cost amounted to 43 627 PLN; SD 17 794. There was no sign of total costs' distribution skewness.

Two categories of direct costs account for more than two-thirds of the total costs of treating CIED infections. These are hospital stay costs (39.1% of total costs) and CIED devices including leads (31.2% of total expenditure). The costs of the devices depend on the type of device

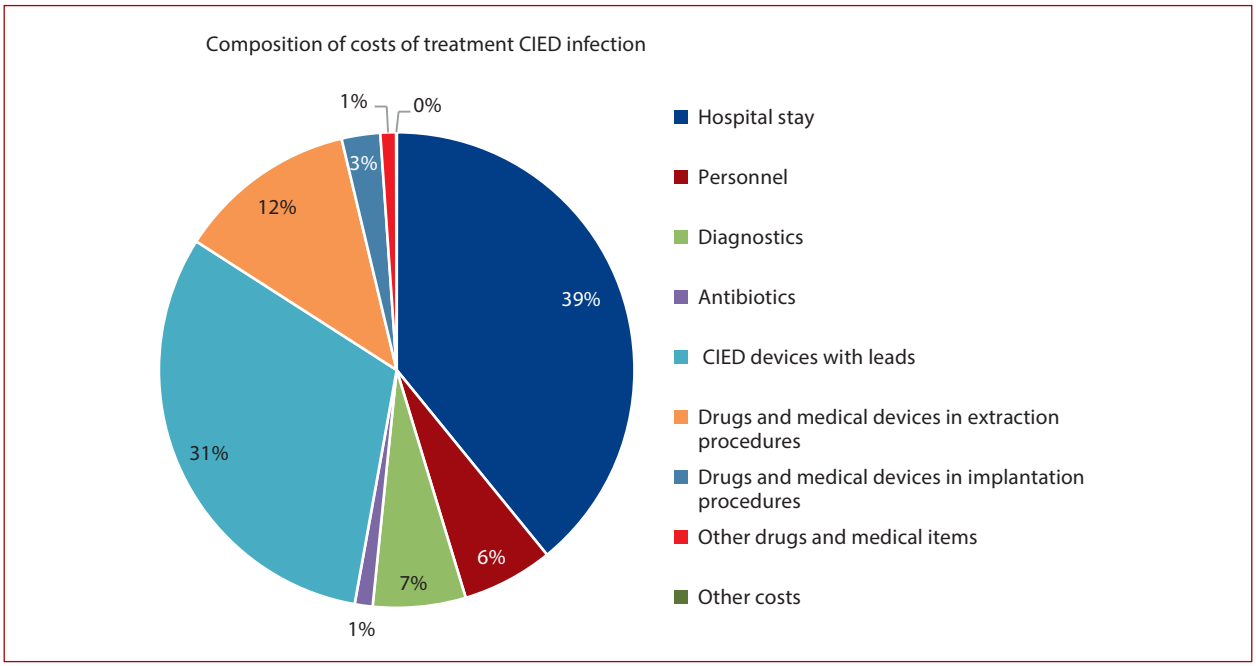

Figure 2. Composition of costs of treatment of CIED infections
Abbreviations: see Figure 1

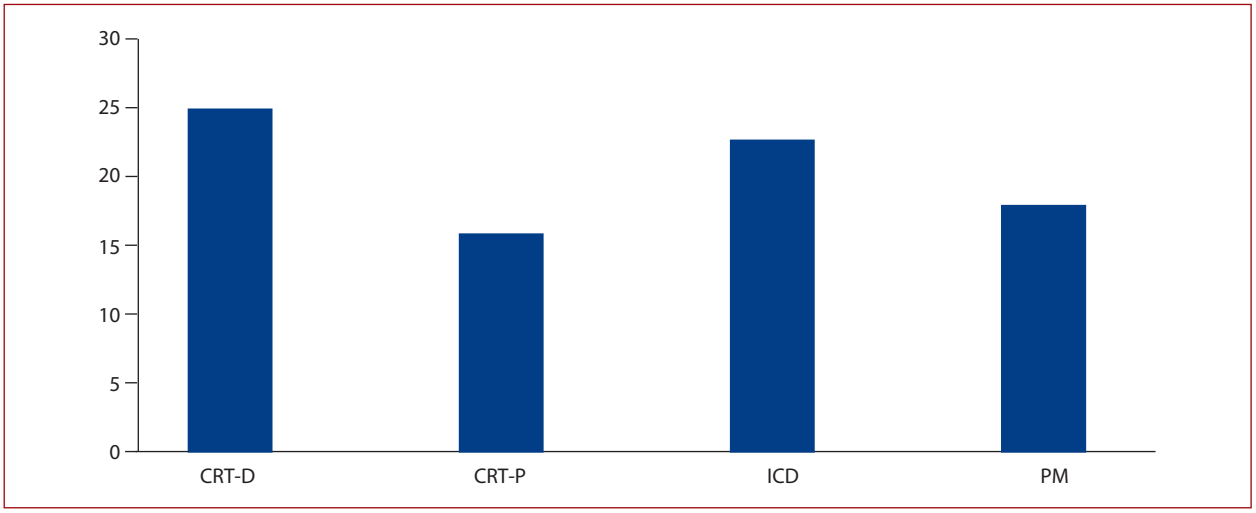

Figure 3. The average number of hospitalization days
Abbreviations: see Figure 1

used, with CRT-Ds being the most expensive devices on average (Figure 2).

The distribution of expenditures on patient treatment in the study group depended on the type of device. As only two patients underwent cardiac resynchronization therapy with peacemaker function (CRT-P) implantation, the interpretation of their treatment costs is highly dependent on case characteristics.

For PM and ICD systems, the largest cost category was hospital stay (Figure 2). Among patients with the relatively most complex CRT-D system, it was the device costs that had been highest when compared with other categories. Nevertheless, hospital stay costs were relatively high.

The cost of devices increased proportionally to their complexity while the cost of hospitalization depended on the length of hospital stay. The longest stays were for patients with the most complex systems and resulted from the need to treat infection before reimplantation. The average length of stay was 21 days: SD 11 for all patients.

Distribution of days spent in hospital in the study group (Figure 3).

The high cost of hospitalization resulted not only from the length of stay but also from the more frequent need

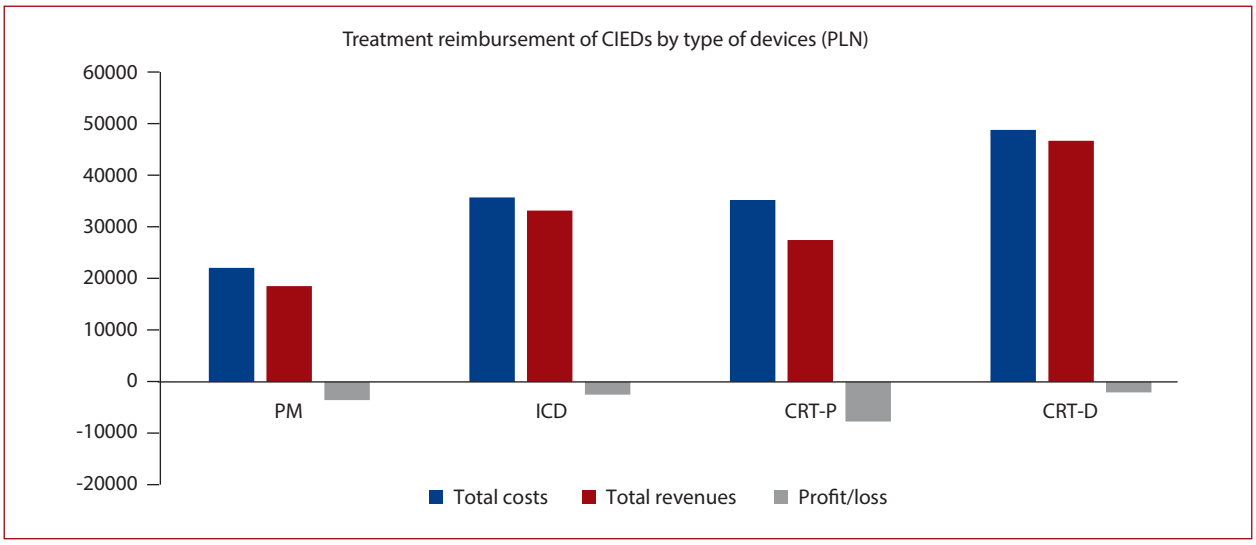

Figure 4. Treatment of reimbursement of cardiac implantable electronic devices (CIED) by type of devices
Abbreviations: see Figure 1

Table 1. Detailed breakdown of CIED infection treatment (PLN) costs

	PM	ICD	CRT-P	CRT-D	Average
Hospital stay	10 283.67	15 297.59	9764.72	16 400.15	13 435.43
Personnel	1194.96	2236.85	2354.54	3241.49	2125.90
Diagnostics	2068.88	2033.21	2373.28	2381.15	2165.17
Antibiotics	384.98	406.87	733.35	447.23	419.63
CIED devices with leads	3504.36	12 063.70	5 551.96	19 629.88	10 728.66
Drugs and medical devices in extraction procedures	4111.34	3205.96	13 863.16	4223.43	4191.24
Drugs and medical devices in implantation procedures	307.06	297.78	507.91	2 210.89	900.28
Other drugs and medical items	302.91	332.39	126.20	480.19	360.34
Other costs	22.91	—	—	23.80	16.73
Total costs	22 181.07	35 874.36	35 360.46	49 038.21	34 345.79
Total revenues	18 634.53	33 348.38	27 610.96	46 940.97	31 388.66
Profit/loss	–3546.54	–2525.98	–7749.50	–2097.25	–2957.13

Abbreviations: see Figure 1

for prolonged monitoring and longer stay in the intensive care unit. In most cases, it was not possible to discharge a patient before reimplantation.

Considering the aforementioned costs of hospitalization, the costs of devices used for reimplantation and other financial outlays, in many cases the treatment of CIED infection complications was a source of financial loss for the hospital. The average financial loss related to the treatment of CIED infections for all types of devices in the study sample amounted to 2957 PLN, while the median equaled 1090 PLN, with a quartile deviation of 6253 PLN. The profit and loss distribution exhibits negative skewness.

The highest cost burden on average was related to patients with an implanted CRT-P system, but the low number of cases does not allow for valid conclusions to be drawn on this basis. The distribution of revenues and costs per device is shown in Figure 4.

The regression analysis revealed that the number of days a patient spends in the hospital was a statistically significant factor influencing financial losses (PLN –871.86; 95% confidence interval [CI], –1091.48–[652.24]; *P*-value <1%). With each additional day of stay in the facility, the hospital's financial result decreases on average by more than 870 PLN — a number higher than the average cost of one-day hospitalization.

The third largest cost category is the equipment and drugs used in the TLE procedure. These costs constitute on average 12% of all expenditures and on average equaled 4191 PLN, while the median equaled 3183 PLN with a quartile deviation of 2332 PLN. However, extraction expenditures were curbed by the application of basic, low-cost solutions instead of more effective and expensive extraction methods, e.g. rotational sheaths were used only in 6% of cases. Table 1 shows a detailed cost breakdown.

DISCUSSION

The main outcomes of the study which calculated costs of CIED-related infection treatment from the hospital perspective are: (1) the average cost of treatment of a CIED-related infection was 34 000 PLN and was highest in CRT-D patients; (2) the cost of hospital stay and CIED-device, including leads, were two main factors driving the cost of hospital-

ization; (3) the average financial loss for the hospital due to treatment of CIED-related infection amounted to almost 3000 PLN; (4) the use of rotational extraction sheets in the study population was very low (6%).

The study is the first in Poland to analyze the real costs of treatment of CIED-related infections from the perspective of the healthcare provider and not the payer. The analysis shows that patients with the most complex devices, i.e. CTD-D, are hospitalized for the longest time, and also the cost of the reimplantation device in this group is the highest. Therefore, in this group, the treatment of infectious complications is the most costly, and, moreover, patients with the most complicated devices run the highest risk of infectious complications. Taking into account the total cost of CIED-related infection treatment in the analyzed period in Poland, it amounted to an average of 34 000 PLN, i.e. 8010 EUR.

Diagnosis and treatment of CIED-related infection is an expensive procedure usually involving many days of hospitalization and the need to remove the infected device. Procedures for transvenous removal of CIEDs require, especially in the case of multiple leads, the use of additional tools like rotational sheaths or excimer laser that uses external energy in the process of separating leads from the vessel wall. This entails additional costs as the procedure reimbursement does not take into account its complexity or the number of tools necessary to perform it. The cost of using a mechanical sheath alone exhausts the reimbursement for the whole procedure – transvenous lead removal. Nevertheless, it should be noted that such solutions increase the success rates of the procedure to over 95% while reducing its perioperative risk. In the study group, mechanical sheaths were used in only 6% of procedures, which was probably due to their price and concern for the economic calculation. Another problem associated with the procedure of lead extraction is the need to implant a new system on the contralateral side or epicardial lead placement. Solutions that broaden the spectrum of therapeutic options include using leadless pacemakers, in which the entire system is contained in a small capsule implanted directly into the lumen of the right ventricle, and using subcutaneous implantable cardioverter-defibrillators (S-ICDs) without intravascular access. Both in the case of subcutaneous cardioverter-defibrillators and leadless pacemakers, a reduction in the risk of infectious complications was observed [13–15], especially in the latter case. It must be stressed that a comprehensive strategy is needed to limit the incidence of infectious complications, starting with the provision of appropriate standards in the operating room, diagnostics and pre-implantation treatment of asymptomatic infections, preparation of the patient and the operating field (surgical field), appropriate personnel training, perioperative antibiotic prophylaxis and, finally, using absorbable mesh envelopes that locally release highly concentrated antibiotics: minocycline and rifampicin in high-risk populations. The cost-effectiveness of gentamycin-collagen sponge as part of a multicomponent prevention strategy has also been reported [16].

Analysis of all costs has shown that the treatment of CIED infection is associated with an average loss of 3000 PLN per case. An optimal solution would be to change the way of financing the treatment of CIED infections, bearing in mind the need for additional reimbursement in more complex cases. The cost estimation of a TLE procedure according to DRG does not differentiate the scale of difficulty of these procedures, does not include the cost of involving a cardiosurgical team, and finally, despite the constantly rising hospital operational costs, its amount is not subject to appropriate valorization. A previous study on the TLE procedures reimbursement in our country from 2012 also indicated the lack of proper valuation [13]. Studies on the treatment costs of CIED infections in other countries are largely based on the information from the public payer and show that the treatment of infectious complications doubles the cost of care for patients with CIED within a year [14]. In a prospective study in France, the average cost of treating a CIED infection was 23 000 EUR for *de novo* implantations and 21 000 EUR for reimplantations [4]. An interesting conclusion is provided by a study of the American population from 2016, which shows that an additional cost of treating such infections exceeded 45 000 USD over 12 months [18]. A disadvantage of these calculations is the fact that this estimation is from the payer's perspective and does not reflect the actual cost accrued by the center, while its advantage is a large database. Few data are available from studies on the cost of treating CIED infections from a provider's perspective. The results then relate to two different healthcare systems, small groups of patients, and different periods analyzed. For example, the cost of treating a pacemaker-related infection was estimated at 11 555 EUR according to an analysis performed in Germany in 2010 [19], while a study conducted in 2019 in Manchester revealed the cost of 8000 GBP in the case of pacemakers and 22 000 GBP for CRT-Ds [20]. In our country, we do not have a consistent database to determine the actual frequency of infectious complications in CIED patients and to estimate the cost of treatment. The paucity of such data does not allow us to conclude that the NHF reimbursement for therapies in this group of patients is realistic. In 2019, some progress was made in the availability of therapies for the treatment of infectious complications in patients with CIED. This concerns the NHF's reimbursement for S-ICD implantations. Both antimicrobial envelopes, which reduce the risk of pocket infection, especially in high-risk patients, and leadless pacemakers should become part of services financed by the NHF.

Limitations of the study

The study is conducted retrospectively and prone to typical biases of this methodology. The presented results of the study have some limitations such as a relatively small but homogenous group and the involvement of three

high-volume hospitals — the results may be different in less experienced centers. The standard of cost calculation for different cost categories may differ between individual centers, but the total cost of hospitalization is comparable.

CONCLUSIONS

The hospital cost of treatment of CIED-related infections was high and related mainly to the type of device and length of hospitalization. Despite the rare use of costly extraction tools, the hospitalization was still likely to be unprofitable.

Article information

Conflict of interest: None declared.

Funding: The study was supported by an unconditional grant provided by Medtronic Polska.

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Culprit plaque location within the left circumflex coronary artery predicts clinical outcomes in patients experiencing acute coronary syndromes with percutaneous coronary intervention: Data from the ORPKI registry

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DOI: 10.33963/KP.a2022.0150

Received:
October 13, 2021

Accepted:
June 20, 2022

Early publication date:
June 20, 2022

ABSTRACT

Background: The left circumflex (LCx) artery is the most diagnostically challenging of the coronary branches in terms of diagnostics because the clinical presentation and electrocardiography (ECG) do not always suggest critical occlusion despite its presence. Therefore, it is important to determine the factors contributing to the clinical manifestation and outcome, such as the culprit location.

Aims: To determine the relationship between the location of the culprit plaque and clinical outcomes in the LCx artery.

Methods: Data from the Polish Registry of Invasive Cardiology Procedures (ORPKI) from the years 2019–2020 concerning percutaneous coronary intervention (PCI) procedures were extracted and analyzed using appropriate statistical tests.

Results: 97 899 clinical records were analyzed. Patients with proximal occlusion received a worse grade using the Killip classification. Patients with Thrombolysis in Myocardial Infarction (TIMI) score 0 had worse clinical presentation in each of the occlusion locations. The periprocedural cardiac arrest and death rates were the highest among patients with proximal circumflex (Cx) occlusion. The death rate among patients with proximal occlusion and non-ST-segment elevation myocardial infarction (NSTEMI) was greater than among patients with distal occlusion and ST-segment elevation myocardial infarction (STEMI).

Conclusions: Among patients with proximal occlusions of the Cx artery and TIMI 0 grade flow on initial angiogram, a STEMI-like approach should be undertaken apart from initial ECG findings. This is driven by a higher rate of critical and fatal complications such as cardiac arrest and periprocedural death. Fatal complications occur more often in patients with proximal occlusion of Cx than in medial or distal occlusion. Grade IV according to the Killip classification can suggest a proximal culprit location.

Key words: acute coronary syndromes, clinical outcomes, culprit lesion, Killip classification, left circumflex artery

INTRODUCTION

Acute coronary syndromes (ACS) encompass ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA). When typical symptoms of myocardial infarction (MI) are associated with STEMI changes on baseline electrocardiography (ECG), cur-

WHAT'S NEW?

Data from the Polish Registry of Invasive Cardiology Procedures (ORPKI) have shown that the location of the culprit plaque has a great impact on the severity of myocardial infarction. Patients with proximal occlusion and non-ST-segment elevation myocardial infarction (NSTEMI) are at a greater risk than patients with distal occlusion and ST-segment elevation myocardial infarction (STEMI). This correlation indicates how important it is to consider other factors alongside the presence of ST-segment elevation, most importantly the Killip score, as a patient with NSTEMI may require more urgent and careful treatment than a patient with STEMI.

rent guidelines recommend urgent primary percutaneous coronary intervention (PCI) with a maximum reduction of door-to-balloon time [1]. In the NSTEMI subgroup, recommendations are not so strict and depend upon the clinical and hemodynamic condition of the patient [2]. Moreover, among MI patients, those with an occluded or critically stenosed left circumflex (LCx) coronary artery seem to be the most challenging group to identify and immediately qualify for urgent angiography due to non-conclusive ECG changes on admission and confusing clinical presentation [3–11]. Our investigation has gone further, and we focused on assessing whether a different localization of the culprit plaque (proximal vs. medial vs. distal segment) within the circumflex artery responsible for MI has any implications on procedural aspects and clinical outcomes for these patients. The present study aimed to assess the influence of culprit plaque location within the circumflex artery segments (proximal vs. medial vs. distal) on procedural characteristics and clinical outcomes in patients with ACS treated using primary PCI. The impact of the culprit plaque location within the ACS-related artery on the preliminary diagnosis (STEMI, NSTEMI, UA) in different Thrombolysis in Myocardial Infarction (TIMI) flow grade subgroups was also investigated.

METHODS

All data were obtained from the electronic database of the Polish Registry of Invasive Cardiology Procedures (ORPKI) operated by the Jagiellonian University Medical College in Kraków. The ORPKI is a national registry with data compiled from all cardiology percutaneous interventions performed in Poland. Data in the ORPKI registry have been gathered via electronic case report forms at the majority of interventional cardiology centers in Poland since 2004. No personal data is collected in the registry. The presented archive is a single-arm registry of PCIs performed at Polish cath labs within the years 2019–2020 [12–14]. Core lab assessment was not applied. The MI, STEMI, NSTEMI, and UA were defined according to the fourth universal definition of myocardial infarction (2018) [15]. The segmentation visual assessment was performed in accordance with the Coronary Artery Surgery Study (CASS) [16]. The Killip-Kimball classification was used to evaluate the stage of heart failure among patients with acute myocardial infarction [17]. The TIMI score was used to assess coronary artery flow [18].

In the study, the ORPKI patients who were included were admitted to a cath lab with ACS and underwent a primary PCI of a significant circumflex (Cx) artery occlusion. The exclusion criterion was a significant incomplete medical records. Patients were divided according to the culprit location in the Cx artery. Primary endpoints compared between the groups were the intra- and peri-procedural cardiac arrest and death rates.

The study complied with ethical principles for clinical research based on the Declaration of Helsinki and appropriate consent was obtained from the institutional review board.

Statistical analysis

Categorical variables are presented as numbers and percentages. The normality of quantitative variables was assessed *via* the Shapiro-Wilk test. As the distribution of all quantitative data was other than normal, they are expressed as median (interquartile range [IQR]) and were compared using the Kruskal-Wallis ANOVA with the *post hoc* Dunn tests. Categorical variables were compared with the Pearson χ^2 or Fisher exact tests if 20% of cells had an expected count of fewer than 5 (Monte Carlo simulation for tables larger than 2×2). The significance level (α) was set at 0.05. Based on the results of univariate analysis, multivariable logistic regression models were constructed to find predictors of periprocedural deaths, cardiac arrests, and all complications in the analyzed group of patients. In the multivariable analysis, we included indices with $P < 0.1$ based on the results of univariate analysis. The best model was obtained using the stepwise regression with minimization of the Bayesian Information Criterion as a target. Statistical analysis was performed using JMP, version 15.2.0 (SAS Institute Inc., Cary, NC, US).

RESULTS

Characteristics

Initially, 97 899 clinical records were analyzed. All patients were divided according to localization of the culprit plaque within the Cx artery: group A — proximal segment (n = 43 444); group B — medial segment (n = 45 363), and group C — distal segment (n = 9092), based on initial angiography. Patient characteristics and data concerning past medical history are presented in

Table 1. Demographics and characteristics of the analyzed populations

All patients					
Cx narrowing location	**Proximal — A**	**Medial — B**	**Distal — C**	**Total**	***P*-value**
Age, years	68 (61–76)	67 (60–75)	66 (60–75)	67 (60–76)	<0.001
Sex	F: 14029 (32.47) M: 29175 (67.53)	F: 14549 (31.11) M: 30759 (67.89)	F: 2659 (29.51) M: 6352 (70.49)	F: 31237 (32.93) M: 66286 (67.97)	<0.001
Weight, kg	80 (70–90)	80 (70–90)	80 (73–90)	80 (70–90)	<0.001
Diabetes	11209 (25.79)	10584 (23.32)	2356 (25.90)	24149 (24.66)	<0.001
Previous MI	13897 (31.98)	12682 (27.94)	2715 (29.85)	29294 (29.91)	<0.001
Previous PCI	15106 (34.76)	14767 (32.54)	3138 (34.50)	33011 (33.70)	<0.001
Previous CABG	3938 (9.06)	2324 (5.12)	477 (5.24)	6739 (6.88)	<0.001
Previous stroke	1663 (3.83)	1442 (3.18)	348 (3.83)	3453 (3.53)	<0.001
Smoking (overall)	9165 (21.09)	10301 (22.70)	2116 (23.26)	21582 (22.04)	<0.001
Psoriasis	175 (0.40)	208 (0.46)	46 (0.51)	429 (0.44)	0.27
Hypertension	30763 (70.78)	31945 (70.39)	6523 (71.71)	69231 (70.68)	0.03
Kidney disease (GFR <60 ml/min/1.73 m^2 or renal replacement therapy)	3164 (7.28)	2374 (5.23)	538 (5.91)	6076 (6.20)	<0.001
COPD	1102 (2.54)	991 (2.18)	204 (2.24)	2297 (2.35)	0.002
Initial TIMI 0 patients					
Cx narrowing location	**Proximal — A**	**Medial — B**	**Distal — C**	**Total**	***P*-value**
Age, years	65 (58–73)	65 (58–72)	65 (57–73)	65 (58–73)	<0.001
Sex	F: 3054 (30.95) M: 6814 (69.05)	F: 2631 (29.34) M: 6337 (70.66)	F: 697 (30.15) M: 1383 (69.85)	F: 6282 (30.18) M: 14534 (69.82)	0.06
Weight, kg	80 (70–90)	80 (70–90)	80 (72–91)	80 (70–90)	<0.001
Diabetes	2107 (21.28)	1780 (19.83)	449 (22.60)	4336 (20.78)	0.005
Previous MI	2005 (20.25)	1671 (18.61)	374 (18.82)	4050 (19.41)	0.01
Previous PCI	1873 (18.92)	1586 (17.67)	363 (18.27)	3822 (18.32)	0.09
Previous CABG	389 (3.93)	227 (2.53)	57 (2.87)	673 (3.23)	<0.001
Previous stroke	360 (3.64)	287 (3.20)	77 (3.88)	724 (3.47)	0.15
Smoking (overall)	2723 (27.50)	2694 (30.01)	571 (28.74)	5988 (28.70)	<0.001
Psoriasis	41 (0.41)	47 (0.52)	17 (0.86)	105 (0.50)	0.04
Hypertension	6305 (63.67)	5798 (64.58)	1349 (67.89)	13452 (64.47)	0.002
Kidney disease (GFR <60 ml/min/1.73 m^2 or renal replacement therapy)	508 (5.13)	367 (4.09)	107 (5.39)	982 (4.71)	0.001
COPD	203 (2.05)	175 (1.95)	43 (2.16)	421 (2.02)	0.79

Data presented as median (interquartile range [IQR]) or n (%)

Abbreviations: CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; Cx, circumflex branch of left coronary artery; F, female; GFR, glomerular filtration rate; M, male; MI, myocardial infarction; PCI, percutaneous coronary intervention

Table 1. On admission, patients were assessed according to the Killip-Kimball classification. The patients with proximal occlusion received, on average, the worst score. The results of the assessment on this scale are presented in Table 2.

Clinical status at baseline — whole group (independent of TIMI grade)

On admission, cardiac arrest was observed in 2.31% of patients. The highest rate of cardiac arrest was observed in group A — the proximal segment of Cx, followed by groups B and C (Table 2). This difference was concordant with the Killip classification — the percentage of grade IV in group A was twice as high as in groups B and C. The differences were statistically significant (Table 2).

Hypothermia was used extremely rarely in all groups — most commonly in group A, followed by groups B and C — proportionally to the differences in cardiac arrest in analyzed groups (Table 2). In all groups, direct transport to the Cath lab was relatively rare (8.03%).

Clinical status at baseline — patients with TIMI 0 on initial angiogram

On admission, cardiac arrest was observed in 4.89% of patients in the TIMI 0 subgroup, which was over 2 times higher than in the general comparison (Table 2). In the TIMI 0 subgroup, the highest rate of cardiac arrest was also observed in group A — the proximal segment of Cx, followed by groups B and C (Table 2). This difference was concordant with the Killip classification — the percentage of grade IV was the highest in group A, followed by groups B and C. The differences were statistically significant (Table 2).

Hypothermia was used extremely rarely in all groups – most commonly in group A, followed by groups B and C — proportionally to differences regarding cardiac arrest in analyzed groups (Table 2). In the TIMI 0 subgroup, direct

Table 2. Clinical characteristics of the groups

Initial diagnosis based on ECG and troponin level					
	Proximal — A	Medial — B	Distal — C	General	*P*-value
STEMI	11039 (25.41)	11214 (24.72)	2425 (26.67)	24678 (25.21)	<0.001
NSTEMI	15575 (35.85)	14802 (32.63)	2979 (32.76)	33356 (34.07)	
UA	16830 (38.74)	19347 (42.65)	3689 (40.57)	39866 (40.72)	
TIMI 0 without ST-segment elevation	4637 (51.67)	4084 (50.03)	893 (46.22)	9614 (50.59)	0.02
Cardiac arrest on admission	1234 (2.84)	903 (1.99)	132 (1.45)	2269 (2.32)	<0.001
Cardiac arrest on admission (TIMI 0)	575 (5.81)	390 (4.35)	55 (2.79)	1020 (4.89)	<0.001
Therapeutic hypothermia	52 (0.12)	32 (0.07)	1 (0.01)	85 (0.09)	0.001
Therapeutic hypothermia (TIMI 0)	28 (0.28)	11 (0.12)	1 (0.05)	40 (0.19)	0.01
Killip classification					
All patients					
Killip class	**Proximal — A**	**Medial — B**	**Distal — C**	**General**	***P*-value**
I	36814 (84.74)	40654 (89.62)	8145 (89.58)	85613 (87.45)	<0.001
II	3893 (8.96)	3248 (7.16)	706 (7.77)	7847 (8.02)	
III	1208 (2.78)	785 (1.73)	120 (1.32)	2113 (2.16)	
IV	1529 (3.52)	680 (1.50)	121 (1.33)	2330 (2.38)	
Initial TIMI 0					
Killip class	**Proximal — A**	**Medial — B**	**Distal — C**	**General**	***P*-value**
I	7711 (77.88)	7675 (85.52)	1729 (87.04)	17115 (82.04)	<0.001
II	1117 (11.28)	745 (8.30)	173 (8.70)	2035 (9.74)	
III	402 (4.06)	237 (2.64)	35 (1.76)	674 (3.22)	
IV	671 (6.78)	319 (3.55)	49 (2.49)	1039 (4.97)	

Data presented as n (%)

Abbreviations: ECG, electrocardiography; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; UA, unstable angina

transport to the cath lab was observed more frequently than in the whole cohort (16.11%).

Initial diagnosis based on ECG and troponin level (STEMI vs. NSTEMI vs. UA)

The most common reason for the procedure in all of the groups was UA. STEMI was most common in group C, followed by groups A and B.

Based on initial diagnosis, the cardiac arrest rate was significantly higher in patients with STEMI on the initial ECG, and considering segment division, more frequent in the proximal segments: 1.51% in group A; 0.75% in group B and 0.74% in group C (P <0.001). In NSTEMI patients, this totaled 0.56% vs. 0.24 % vs. 0.30%, respectively (P = 0.007), while in UA patients, this was 0.17% vs. 0.08% vs. 0.03% (P = 0.015).

Vascular access

The most frequently used access during the procedures in all of the groups was the right radial approach. More specific data concerning vascular access are presented in Supplementary material, *Table S1*.

Angiographic characteristics

Multivessel coronary artery disease (CAD) without left main coronary artery (LMCA) involvement was present in more than half of the performed procedures. Single-vessel CAD was the second most common finding. Specific data concerning the results of the angiograms are given in Table 3.

Advanced morphology and functional assessment

Additional assessments, such as intracoronary ultrasound (ICUS), plaque assessment with optical coherence tomography (OCT), or functional assessment with fractional coronary flow reserve measurement (FFR) were rarely performed in all groups. Further data are presented in Supplementary material, *Table S2*.

Procedural characteristics — the amount of contrast and radiation dose

In the whole group, the median contrast volume used during the procedure was 160 (120–210) ml. The smallest amount of contrast was used in group B (medial segment) followed by the C and A groups. In the TIMI 0 subgroup, the median general contrast usage was greater compared to the whole group: 170 (135–220) ml; with the same proportion between segments. It was significantly higher in group B (medial segment) in comparison to groups A and C. A detailed comparison is provided in Table 4.

When we evaluated the contrast volume between assessed segments and stratified it by differential diagnoses, we found that patients with STEMI were related to the greatest contrast volume use during the procedures and this concerned proximal and distal occlusion; while in NSTEMI — the greatest contrast volume was used in

Table 3. Angiographic characteristics of the groups — results of angiography

All patients					
Result of angiography	**Proximal — A**	**Medial — B**	**Distal — C**	**General**	***P*-value**
No significant stenosis	4 (0.01)	14 (0.03)	1 (0.01)	19 (0.02)	<0.001
No atherosclerotic changes	9 (0.02)	14 (0.03)	5 (0.05)	28 (0.03)	
Single-vessel CAD	12768 (29.39)	17624 (38.85)	3312 (36.43)	33704 (34.43)	
Multi-vessel CAD without LMCA involvement	24802 (57.09)	25576 (56.38)	5378 (59.15)	55756 (56.95)	
Multi-vessel CAD with LMCA involvement	5787 (13.32)	2096 (4.62)	387 (4.26)	8270 (8.45)	
Only LMCA disease	70 (0.16)	41 (0.09)	9 (0.10)	120 (0.12)	
Initial TIMI 0					
Result of angiography	**Proximal — A**	**Medial — B**	**Distal — C**	**General**	***P*-value**
No significant stenosis	0 (0.00)	5 (0.06)	0 (0.00)	5 (0.03)	<0.001
No atherosclerotic changes	2 (0.02)	4 (0.05)	2 (0.10)	8 (0.04)	
Single-vessel CAD	3139 (31.70)	3277 (36.51)	767 (38.61)	7183 (34.44)	
Multi-vessel CAD without LMCA involvement	5802 (58.60)	5241 (58.39)	1128 (56.78)	12171 (58.33)	
Multi-vessel CAD with LMCA involvement	946 (9.55)	441 (4.91)	87 (4.40)	1474 (7.06)	
Only LMCA disease	13 (0.13)	7 (0.08)	2 (0.10)	22 (0.11)	

Data presented as n (%)

Abbreviations: CAD, coronary artery disease; LMCA, left main coronary artery; other — see Table 2

proximal and distal occlusion; and in UA — the greatest contrast volume was used in proximal occlusion (Table 4).

The radiation dose received during the procedure was higher in the TIMI 0 subgroup than in the main comparison. In this subgroup, the radiation exposure was the greatest in group C, followed by groups A and B, whereas in the general comparison, it was greatest in group A, followed by groups C and B (Table 4).

Comparing the radiation dose according to initial diagnosis; in patients with STEMI, the highest dose of radiation was used during the procedures which concerned distal occlusion; in NSTEMI — distal occlusion; in UA — distal occlusion (Table 4).

COMPLICATIONS

Lesions in the proximal segment of the Cx artery resulted in significantly greater rates of intra-procedural cardiac arrests and death compared to other locations, both in the TIMI 0 subgroup and in the main comparison. There was no difference in terms of puncture-site bleeding (Table 4).

On division into subgroups according to the initial diagnosis, the results were concordant with the whole group comparison — the cardiac arrest and death rates were the highest in the A group (proximal occlusion), followed by the B and C groups. This relationship occurred in every subgroup (STEMI, NSTEMI, UA). The death rate in NSTEMI patients with proximal occlusion was comparable to that in STEMI patients with medial occlusion and was twice as high as the death rate in STEMI patients with distal occlusion (Table 4).

Procedural characteristics: time delays

Time from first contact to inflation or angiogram was the shortest in groups C and A, followed by group B, considering the whole group. In the TIMI 0 subgroup, the time from first contact to inflation or angiogram was the shortest in the C group (distal), followed by the A and B groups. The results were statistically significant (Table 5).

Regarding the initial diagnosis: in each occlusion location group, patients with STEMI had undergone an angiography much faster than patients with NSTEMI, and even faster than patients with UA. NSTEMI patients had undergone an angiography slightly faster than UA patients (Table 5).

Stenting

Stenting comparison was performed in the TIMI 0 subgroup. In each group, the most commonly used stent type was drug eluting stent. Bioresorbable vascular stent was used extremely rarely — in fewer than 0.5% of cases. Stents were implanted most commonly in the medial location. A substantial percentage of patients did not receive any implant (Supplementary material, *Table S3*).

Risk factors for periprocedural death and complications

Among risk factors influencing periprocedural death, there is the culprit location (the worst survival in the proximal location), the type of ACS (the worst survival in STEMI, followed by NSTEMI and UA), TIMI flow after the intervention (worse survival in cases of smaller flow) and the Killip class (worse survival in higher class) and others. The presence of multi-vessel disease also increased the risk of death. All risk factors found are presented in Figure 1.

When it comes to periprocedural cardiac death, similar risk factors have been determined. The risk factors include, among others: unsuccessful PCI (TIMI 0 vs. TIMI 3 after PCI), Killip class (worse survival in higher score), and initial diagnosis (STEMI worse than NSTEMI, followed by UA). Surprisingly, intervention on vessel bifurcation were found

Table 4. Contrast, radiation and complications

All patients					
	Proximal — A	**Medial — B**	**Distal — C**	**General**	***P*-value**
Contrast volume, ml	170 (130–220)	150 (120–200)	170 (130–220)	160 (120–210)	<0.001
Post hoc test	A vs. C: $P = 0.02$	B vs. A: $P < 0.001$	C vs. B: $P < 0.001$		
Radiation dose, mGy	956 (527–1630.50)	826 (459–1407)	908 (524–1557.50)	889 (493–1518)	<0.001
Post hoc test	A vs. C: $P < 0.001$	B vs. A: $P < 0.001$	C vs. B: $P < 0.001$		
Bleeding at the puncture site, %	70 (0.16)	68 (0.15)	18 (0.20)	156 (0.16)	0.45
Cardiac arrest during procedure, %	569 (1.31)	236 (0.52)	50 (0.55)	855 (0.87)	<0.001
Death during procedure, %	478 (1.10)	172 (0.38)	21 (0.23)	671 (0.69)	<0.001
Initial TIMI 0					
	Proximal — A	**Medial — B**	**Distal — C**	**General**	***P*-value**
Contrast volume, ml	180 (140–220)	170 (130–220)	180 (140–220)	170 (135–220)	<0.001
Post hoc test	A vs. C: $P = 0.81$	B vs. A: $P < 0.001$	C vs. B: $P < 0.01$		
Radiation dose, mGy	973 (543–1668)	920 (526–1547)	1000 (581.75–1675.50)	952 (540–1619)	<0.001
Post hoc test	A vs. C: $P = 0.85$	B vs. A: $P < 0.001$	C vs. B: $P < 0.01$		
Bleeding at the puncture site, %	18 (0.18)	19 (0.21)	4 (0.20)	41 (0.20)	0.90
Cardiac arrest during procedure, %	308 (3.11)	123 (1.37)	20 (1.01)	451 (2.16)	<0.001
Death during procedure, %	264 (2.67)	90 (1.00)	8 (0.40)	362 (1.73)	<0.001
Exposition compared according to initial diagnosis and location of narrowing					
Diagnosis		**Proximal — A**	**Medial — B**	**Distal — C**	***P*-value**
STEMI	Contrast volume, ml	170 (130–220)	150 (120–200)	170 (130–220)	<0.001
	Radiation dose, mGy	957 (530–1656)	825 (459–1404.50)	922 (529–1597.50)	<0.001
NSTEMI	Contrast volume, ml	175 (130–220)	160 (120–200)	175 (130–220)	<0.001
	Radiation dose, mGy	974 (544–1665.75)	850 (484–1439.25)	949 (553–1600)	<0.001
UA	Contrast volume, ml	170 (120–220)	150 (120–200)	160 (130–210)	<0.001
	Radiation dose, mGy	937.00 (505.75–1593.00)	806.00 (442.00–1391.00)	871.50 (498.00–1484.50)	<0.001
Complications compared according to initial diagnosis and location of narrowing					
Diagnosis		**Proximal — A Medial — B**	**Distal — C**	**General**	***P*-value**
STEMI	Bleeding at puncture site	26 (0.24) 17 (0.15)	6 (0.25)	49 (0.19)	0.27
	Cardiac arrest during procedure	317 (2.87) 132 (1.18)	25 (1.03)	476 (1.93)	<0.001
	Death during procedure	281 (2.54) 110 (0.98)	14 (0.58)	405 (1.65)	<0.001
NSTEMI	Bleeding at puncture site	25 (0.16) 27 (0.18)	3 (0.10)	55 (0.16)	0.61
	Cardiac arrest during procedure	187 (1.20) 75 (0.51)	18 (0.60)	280 (0.83)	<0.001
	Death during procedure	161 (1.03) 44 (0.30)	5 (0.17)	210 (0.62)	<0.001
UA	Bleeding at puncture site	18 (0.11) 22 (0.11)	11 (0.30)	51 (0.13)	0.01
	Cardiac arrest during procedure	66 (0.39) 27 (0.14)	7 (0.19)	100 (0.25)	<0.001
	Death during procedure	36 (0.21) 17 (0.09)	2 (0.05)	55 (0.14)	<0.001

Data presented as median (interquartile range [IQR]) or n (%)

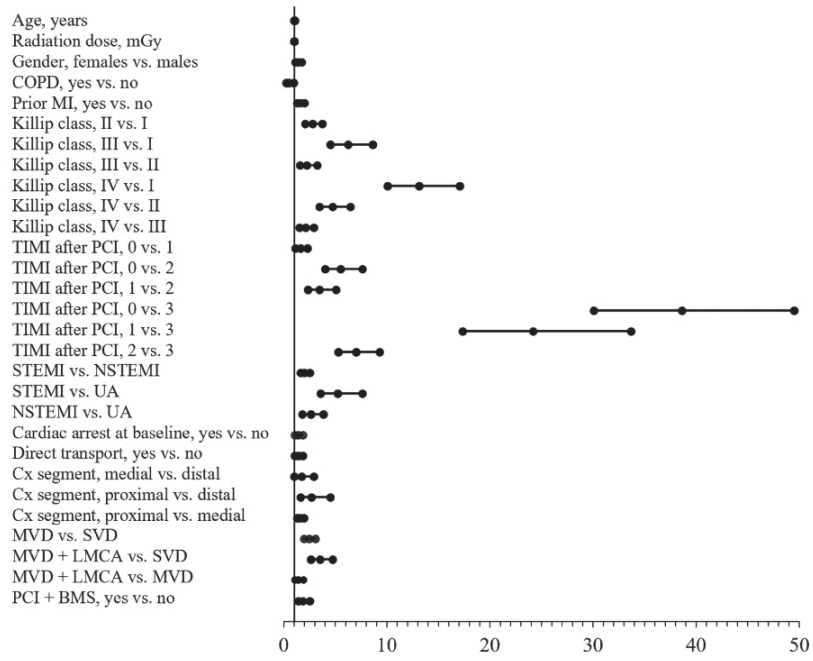
Abbreviations: see Table 2

to be a protective factor. All risk factors determined in this study were presented in Figure 2.

In terms of overall complications, the risk factors include, among others: unsuccessful PCI, Killip class (greater odds of complications in higher score), initial diagnosis, and application of non-standard vascular access (mostly brachial) instead of radial access. The access site was not a risk factor for previously mentioned outcomes (fatal complications). All risk factors determined in this study were presented in Figure 3.

DISCUSSION

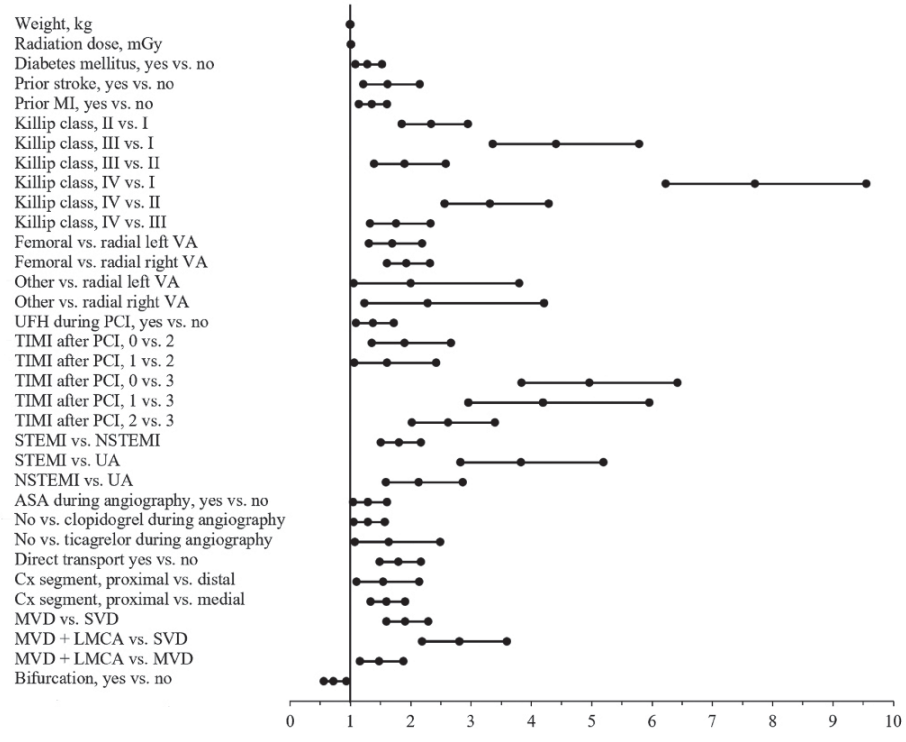
The study has shown that the culprit location in the Cx artery greatly impacts the clinical manifestation in patients with ACS. Patients with the proximal location of the culprit lesion are generally in a worse condition — considering



	OR	95% CI	P-value
Age, years	1.019	1.01-1.029	<0.001
Radiation dose, mGy	1.000098	1.000028-1.000169	0.008
Gender, females vs. males	1.383	1.121-1.706	0.002
COPD, yes vs. no	0.474	0.243-0.921	0.016
Prior MI, yes vs. no	1.595	1.284-1.981	<0.001
Killip class, II vs. I	2.771	2.061-3.726	<0.001
Killip class, III vs. I	6.221	4.493-8.614	<0.001
Killip class, III vs. II	2.244	1.561-3.225	<0.001
Killip class, IV vs. I	13.1	10.051-17.075	<0.001
Killip class, IV vs. II	4.726	3.469-6.438	<0.001
Killip class, IV vs. III	2.105	1.523-2.91	<0.001
TIMI after PCI, 0 vs. 1	1.596	1.117-2.28	<0.001
TIMI after PCI, 0 vs. 2	5.519	4.016-7.584	<0.001
TIMI after PCI, 1 vs. 2	3.456	2.356-5.071	<0.001
TIMI after PCI, 0 vs. 3	38.571	30.052-49.504	<0.001
TIMI after PCI, 1 vs. 3	24.155	17.342-33.643	<0.001
TIMI after PCI, 2 vs. 3	6.988	5.269-9.267	<0.001
STEMI vs. NSTEMI	1.984	1.581-2.489	<0.001
STEMI vs. UA	5.195	3.553-7.597	<0.001
NSTEMI vs. UA	2.618	1.799-3.811	<0.001
Cardiac arrest at baseline, yes vs. no	1.385	1.049-1.829	0.021
Direct transport, yes vs. no	1,385	1.049-1.829	0.002
Cx segment, medial vs. distal	1.714	1.01-2.908	0.045
Cx segment, proximal vs. distal	2.681	1.602-4.486	<0.001
Cx segment, proximal vs. medial	1.564	1.251-1.955	<0.001
MVD vs. SVD	2.44	1.945-3.06	<0.001
MVD + LMCA vs. SVD	3.499	2.601-4.706	<0.001
MVD + LMCA vs. MVD	1.432	1.071-1.92	0.015
PCI + BMS, yes vs. no	1.849	1.369-2.496	<0.001

Figure 1. Risk factors for periprocedural death

Abbreviations: BMS, bare metal stent; CI, confidence interval; MVD, multivessel disease; OR, odds ratio; SVD, single-vessel disease; other — see Tables 1–3



	OR	95% CI	P-value
Weight, kg	0.991	0.985-0.996	<0.001
Radiation dose, mGy	1.00013	1.00008-1.00019	<0.001
Diabetes mellitus, yes vs. no	1.277	1.075-1.518	0.005
Prior stroke, yes vs. no	1.612	1.21-2.147	0.001
Prior MI, yes vs. no	1.346	1.129-1.603	<0.001
Killip class, II vs. I	2.331	1.844-2.945	<0.001
Killip class, III vs. I	4.406	3.358-5.782	<0.001
Killip class, III vs. II	1.89	1.387-2.574	<0.001
Killip class, IV vs. I	7.704	6.216-9.549	<0.001
Killip class, IV vs. II	3.305	2.553-4.278	<0.001
Killip class, IV vs. III	1.748	1.318-2.319	<0.001
Femoral vs. radial left VA	1.69	1.306-2.186	<0.001
Femoral vs. radial right VA	1.924	1.603-2.31	<0.001
Other vs. radial left VA	1.996	1.051-3.79	0.03
Other vs. radial right VA	2.273	1.227-4.21	0.009
UFH during PCI, yes vs. no	1.365	1.087-1.713	0.007
TIMI after PCI, 0 vs. 2	1.896	1.349-2.664	<0.001
TIMI after PCI, 1 vs. 2	1.602	1.06-2.421	0.025
TIMI after PCI, 0 vs. 3	4.956	3.828-6.417	<0.001
TIMI after PCI, 1 vs. 3	4.187	2.948-5.948	<0.001
TIMI after PCI, 2 vs. 3	2.613	2.011-3.395	<0.001
STEMI vs. NSTEMI	1.797	1.495-2.161	<0.001
STEMI vs. UA	3.826	2.821-5.188	<0.001
NSTEMI vs. UA	2.128	1.582-2.861	<0.001
ASA during angiography, yes vs. no	1.287	1.037-1.598	0.021
No vs. clopidogrel during angiography	1.284	1.052-1.567	0.013
No vs. ticagrelor during angiography	1.627	1.065-2.486	0.024
Direct transport yes vs. no	1.787	1.477-2.162	<0.001
Cx segment, proximal vs. distal	1.532	1.532-2.14	0.012
Cx segment, proximal vs. medial	1.588	1.327-1.901	<0.001
MVD vs. SVD	1.905	1.588-2.285	<0.001
MVD + LMCA vs. SVD	2.799	2.18-3.592	<0.001
MVD + LMCA vs. MVD	1.469	1.151-1.875	0.002
Bifurcation, yes vs. no	0.715	0.551-0.927	0.011

Figure 2. Risk factors for periprocedural cardiac death

Abbreviations: ASA, acetylsalicylic acid; UFH, unfractionated heparin; VA, vascular access; other — see Figure 1 and Tables 1–3

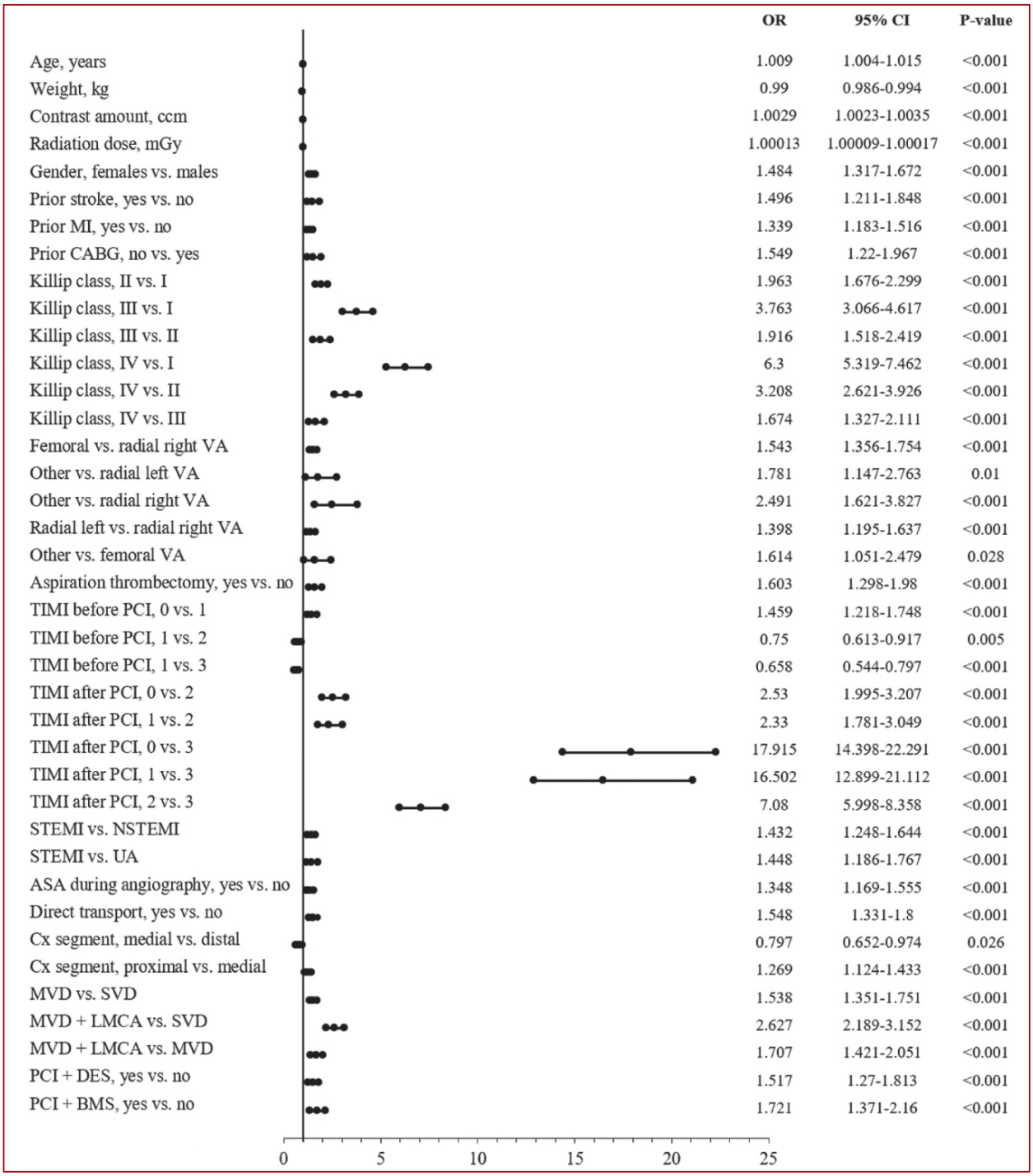


Figure 3. Risk factors for the overall periprocedural complications occurrence

Abbreviations: DES, drug-eluting stent; other — see Figures 1–2 and Tables 1–3

the Killip class upon admission — and suffer from higher periprocedural mortality. Further multifactorial investigation confirmed these findings, determining the culprit location and Killip classification upon admission as independent risk factors for periprocedural death. Other risk factors worth mentioning are the unsuccessful PCI and initial diagnosis (STEMI/NSTEMI/UA).

In comparison to other coronary arteries, the culprit location in the Cx artery remains the most difficult and challenging to properly diagnose in patients with acute myocardial infarction (AMI) [19]. This may be associated with the location on the lateral and posterior wall of the left ventricle and limited effectiveness of ECG to detect ischemia/infarction in this area [20, 21]. Time delays or failure in the case of the Cx artery occlusion diagnosis have serious clinical consequences because it supplies a significant area of the left ventricle myocardium [22]. This is extremely important when the left coronary artery is the dominant one

Table 5. Time from first healthcare contact to inflation or angiogram in minutes, excluding cases over 24 hours

Compared according to the location of narrowing					
	Proximal — A	**Medial — B**	**Distal — C**	**General**	***P*-value**
All patients	140.00 (70.00–345.00)	150.00 (75.00–355.00)	140.00 (70.00–346.75)	145.00 (72.00–350.00)	<0.001
Post hoc test	A vs. C: $P = 0.72$	B vs. A: $P < 0.01$	C vs. B: $P = 0.59$		
Initial TIMI 0	113.00 (60.00–240.00)	117.00 (63.00–240.00)	110.00 (60.00–229.50)	115.00 (60.00–240.00)	0.04
Post hoc test	A vs. C: $P = 0.60$	B vs. A: $P = 0.16$	C vs. B: $P = 0.10$		
Compared according to initial diagnosis and location of narrowing					
	Proximal — A	**Medial — B**	**Distal — C**	***P*-value**	
STEMI	85.00 (59.00–140.00)	90.00 (60.00–145.00)	89.00 (58.00–144.00)	0.002	
NSTEMI	240.00 (115.00–512.50)	260.00 (120.00–540.00)	270.00 (120.00–565.00)	<0.001	
UA	253.50 (148.50–825.00)	330.00 (72.00–426.00)	629.00 (37.00–1222.50)	0.79	

Data presented as median (interquartile range [IQR])

Abbreviations: see Table 2

[23]. Delayed treatment of the culprit artery located within Cx results in the worst clinical outcomes [3, 24].

The most serious periprocedural complications during primary PCI are cardiac arrest and death. Despite frequent lack of ischemic changes on ECG and less pronounced clinical symptoms, cardiac arrest and death are also observed in patients with AMI of the Cx artery, as in the case of AMI of the right coronary artery, left anterior descending artery, or bypass grafts. Our study revealed that when the culprit plaque is located in the proximal segment of the Cx artery, fatal complications occur more frequently — both on admission and during the procedure. The location of the culprit plaque within the proximal segment also results in a higher rate of left ventricular dysfunction, which could predispose these patients to further fatal complications. All these findings could be explained by the significantly larger mass of the left ventricle muscle affected by an infarct in the case of proximal segment occlusion compared to medial and distal ones.

Surprisingly, ST-segment elevation was present more frequently in patients with a distal plaque location. It is hard to explain this phenomenon, however, we suspect that this difference might be due to artery thrombosis or embolization, which occurs more likely in smaller vessel diameters, thus in the distal location [25]. This reduces the myocardial perfusion completely, contrary to proximal occlusions where total thrombosis is less likely, and additionally, the affected myocardium can be partially supplied by collateral circulation. However, the difference in the occurrence of STEMI between the groups was small, and we believe that significant result of the statistical test could be caused by the disproportion in the occurence of NSTEMI and UA in different culprit plaque locations, which was much greater than the disproportion in the occurence of STEMI. Moreover, as previously mentioned, the Cx artery supplies an area where ischemia is exceptionally difficult to detect on an ECG [20], which additionally impacts the results. Another consequence of these anatomical conditions was observed in this study, where total occlusion (TIMI 0) did not cause ST-segment elevation in a substantial percentage of patients, further proving that ST-segment elevation depends on many factors and its absence can be misleading in regard to the Cx area.

Considering the initial diagnosis (STEMI vs. NSTEMI vs. UA), the fatal complications were more frequently observed in patients with STEMI, which may be explained by higher intensification of ongoing ischemia in these subgroups. Regarding both serious complications: cardiac arrest and death — they were more frequently observed in patients with an initially occluded artery on index angiogram — TIMI 0 flow. This is probably justified by the earlier appearance of large-area total necrosis followed by serious rhythm disturbances in this case, compared to arteries with critical stenosis but still preserved flow in the coronary artery.

The median contrast volume in the whole group was high probably due to difficulties with the visualization caused by the spatial conditioning of the Cx artery. The larger contrast volume in the proximal segments could be explained by the larger diameter of the vessel and greater area of the distal vascular bed, as well as a more difficult procedure, often resulting in complications that prolong the procedure. In turn, almost the same median volume of contrast used during procedures within the distal segments is most likely due to the difficulties with the infero-basal area visualization despite smaller vessel diameters.

Regarding initial diagnosis in all comparable segments, the greatest volume of contrast was used in patients with NSTEMI. It was previously shown that total procedural time in NSTEMI is longer than in STEMI [26]. In this subgroup, a further difficulty is observed in identifying the culprit plaque in patients with multi-vessel coronary artery disease. Additional tools such as ICUS or OCT, were, unfortunately, applied too rarely during procedures in this registry.

Regarding radiation dose, a smaller dose was used during interventions on the medial segments of the Cx artery. Again, this is probably due to spatial conditioning as proximal and distal segments are more difficult to visualize in the Cx artery.

Regarding time delays, we observed greater delays in the whole group in comparison to the TIMI 0 subgroup when time delays were shorter. This could be explained by more significant clinical symptoms associated with the occluded infarct-related artery in the TIMI 0 group. This condition could influence medical staff to make quicker decisions when directing the patient to urgent angiography. Estimating time delays in different diagnoses, we observed smaller delays in STEMI patients in all analyzed segments similarly due to more pronounced ischemia and clinical symptoms in this situation.

In comparison to other coronary vessels (RCA and LAD), the percentage of patients who underwent PCI more than 24 hours from pain onset is higher in the case of the Cx artery: 30% vs. 20% vs. 17%, respectively, which was explained by the lower sensitivity of ST-segment elevation in the detection of acute Cx occlusion [3, 20]. This hypothesis is also consistent with an underrepresentation of the Cx artery as the culprit artery among patients with STEMI [8, 27].

Risk factors determined in this study indicate that vascular access do not have an impact on serious complications, and thus on clinical outcomes in patients with ACS. However, they do influence overall complications, probably due to the most common, mild complication — puncture-site hematoma, which occurs more often in brachial access [28].

Regarding therapeutic hypothermia, it was most commonly applied in patients with proximal lesions and TIMI 0. This can be again explained by greater ischemia, which was associated with a worse Killip score, and, therefore, a worse clinical condition of the patient. This may be an indication for therapeutic hypothermia due to its cardioprotective effect during transport to a cath lab [29, 30]. However, these cases were rare in our study, which can be explained by the fact that the network of cath labs in Poland is dense and highly developed, and the time of patient transport to a cath lab is relatively short [31].

The results show that patients with NSTEMI and proximal occlusion are at a greater risk than patients with STEMI and distal occlusion. However, according to the results of our study, which are concordant with the current guidelines, NSTEMI patients are treated less urgently than patients with STEMI [1, 2], as the initial ECG diagnosis greatly impacts time delay. Unfortunately, the location of the culprit plaque cannot be considered in initial diagnosis, as it is known only after performing a coronary angiogram. Therefore, apart from the initial ECG diagnosis, it is crucial to make decisions according to the whole clinical presentation, with special emphasis on the Killip score, as there is a group of patients with NSTEMI who require as urgent intervention as patients with STEMI.

Limitations

Considering major limitations, the leading one is the retrospective nature of the present study. Another one is due to the variability in the area that is supplied with blood by the Cx artery, which affects patients' characteristics and clinical outcomes. However, this random bias should be excluded thanks to the large number of patients that we assessed.

CONCLUSIONS

Among patients with culprit lesions located in the proximal segment of the Cx artery and TIMI 0 grade flow on the initial angiogram, a STEMI-like approach should be undertaken apart from initial ECG findings. This is caused by a higher rate of critical and fatal complications such as cardiac arrest and periprocedural death. Fatal complications occur more often in patients with proximal occlusion of Cx than in medial or distal occlusion. The location of the occlusion should be considered, alongside an ECG diagnosis, as a risk factor for periprocedural cardiac arrest and death. The Killip classification can be used to predict the suspected culprit location, as patients with proximal occlusion more often receive grade IV.

Supplementary material

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

Article information

Conflict of interest: None declared.

Funding: None.

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Atrial fibrillation and elevated heart rate: Independent prognostic factors of right ventricular dysfunction in patients with heart failure with reduced ejection fraction

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DOI: 10.33963/KP.a2022.0171

Received:
May 9, 2022

Accepted:
July 11, 2022

Early publication date:
July 25, 2022

INTRODUCTION

Heart failure with reduced ejection fraction (HFrEF) is diagnosed when left ventricular ejection fraction (LVEF) is less than 40% in patients with adequate symptoms and signs. As the disease progresses, atrial fibrillation (AF) occurs in up to 50% of patients [1, 2]. We have shown before that in patients with AF, right ventricular function (RV) is worse [3]. The current study aimed to search for independent prognostic factors of depressed RV function in patients with HFrEF and AF.

METHODS

This was an observational, case-control, two-center study. Patients were recruited in the years 2013–2016.

Patients with HFrEF of ischemic etiology, on optimal current heart failure medical therapy, the New York Heart Association (NYHA) class II–III, LVEF ≤40%, with sinus rhythm (SR) or permanent AF for at least one year, underwent echocardiography to assess RV. All the patients had two- and three-dimensional echocardiography (2DE and 3DE; sonograph Phillips iE33 xMATRIX; Phillips Medical Systems, Netherlands, transducer iE33 X5-1). Right ventricular ejection fraction (RVEF) was assessed on three-dimensional echocardiography (4 D RV-Function 2.0 TomTec Imaging Systems GmbH, Munich, Germany).

Independent prognostic factors of depressed RVEF <45% were searched. The following variables were analyzed: age, sex, body mass index, NYHA class, history of percutaneous intervention (PCI) and coronary by-pass grafting (CABG), diabetes, arterial hypertension, systolic and diastolic blood pressure, chronic kidney disease, thyroid disease, history of stroke or transient ischemic attack, left ventricular end-diastolic diameter, left ventricular ejection fraction, presence of significant mitral or aortic regurgitation, heart rate (HR), right ventricular pacing, and cardiac resynchronization therapy. The study was supported by the State Committee for Scientific Research grant (3/5/VII/2013). The design and protocol of the study were approved by the institutional Ethics Committee at the National Institute of Cardiology, Warsaw (IK-NP-0021-28/1365/13, IK-NP-0021-7/1365/14).

Statistical analysis

The results are presented as mean and standard deviation (SD) (continuous variables with normal distributions — the Shapiro–Wilk test) or counts and frequencies. Baseline characteristics are compared using the t-test, the χ^2 test, or the Fisher exact test. To identify independent factors of depressed right ventricular function (defined as RVEF <45%), multivariable logistic regression was performed. The stepwise variable selection procedure was used. Odds ratios with 95% confidence intervals (CI) were calculated. The statistical software package (SAS 9.4, Cary, NC, US) was used for the analysis.

RESULTS AND DISCUSSION

Clinical and echocardiographic characteristics of the study group (n = 126 patients) have been published before [3]. In the AF group (94 patients), the mean HR was higher than in the SR group (32 patients), 76.7 (13)

Table 1. Patients' characteristics stratified by right ventricular dysfunction. Results of univariable and multivariable logistic regression to identify independent prognostic factors of right ventricular ejection fraction <45%

	Univariable analysis				Multivariable analysis	
	RVEF <45% (n = 85)	RVEF ≥45% (n = 31)	OR (95% CI)[a]	*P*[b]	OR (95% CI)[a]	*P*[b]
Age, years, mean (SD)	72.9 (8.4)	71.6 (9.4)	1.019 (0.971–1.068)	0.44	—	
Male sex, n (%)	76 (89.4)	27 (87.1)	1.251 (0.356–4.397)	0.73	—	
BMI, kg/m^2, mean (SD)	27.8 (4.5)	27.2 (4.9)	1.031 (0.940–1.130)	0.52	—	
HF NYHA class III, n (%)	30 (35.3)	5 (16.1)	2.836 (0.987–8.149)	0.053	—	
History of PCI, n (%)	51 (60.0)	25 (80.6)	0.360 (0.134–0.970)	0.043	—	
History of CABG, n (%)	21 (24.7)	4 (12.9)	2.215 (0.694–7.065)	0.18	5.53 (1.341–2.80)	0.018
Diabetes, n (%)	25 (29.4)	11 (35.5)	0.758 (0.317–1.810)	0.53	—	
Arterial hypertension, n (%)	61 (71.8)	19 (61.3)	1.605 (0.677–3.806)	0.28	—	
Chronic kidney disease, n (%)	27 (31.8)	6 (19.3)	1.940 (0.713–5.279)	0.19	—	
Thyroid disease, n (%)	19 (22.3)	3 (9.7)	2.687 (0.736–0.913)	0.13	—	
History of stroke, n (%)	18 (21.2)	1 (3.2)	7.123 (0.958–52.96)	0.055	—	
LVEDD, cm, mean (SD)	6.1 (1.0)	5.7 (0.9)	1.610 (1.049–2.472)	0.029	—	
LVEF, %, mean (SD)	28.2 (8.5)	30.6 (7.3)	0.963 (0.914–1.015)	0.16	—	
MR (≥III), n (%)	25 (30.1)	6 (19.3)	1.796 (0.656–4.916)	0.25	—	
AF, n (%)	74 (87.1)	12 (38.7)	10.65 (4.07–7.84)	0.01	9.14 (3.20–6.12)	<0.001
HR, bpm, mean (SD)	77.2 (13.0)	69.4 (10.2)	1.058 (1.018–1.101)	0.005	1.07 (1.02–1.13)	0.006

The results are presented as mean values and standard deviations or counts and proportions or odds ratios with a 95% confidence interval. [a]Risk of right ventricular dysfunction for increasing the feature by one unit or for the category "yes" vs. "no". [b]*P*-value for the likelihood ratio test

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass grafting; HF, heart failure; HR, heart rate; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association class; PCI, percutaneous coronary intervention; RVEF, right ventricular ejection fraction

bpm vs. 70.2 (9.5) bpm, respectively; *P* = 0.003. In the AF group, more patients had significant mitral and tricuspid regurgitation, and mean right ventricular systolic pressure was higher (Supplementary material, *Table S1*). A reliable analysis of 3DE data was possible in 116 patients (30 in the SR group, 86 in the AF group). In the AF group, RVEF was worse than in SR group, 37.2% (7.3%) vs. 48.2% (7.5%), respectively; *P* <0.0001. Among other analyzed parameters of RV function, longitudinal strain of RV free wall acquired while analyzing 3DE data sets and s' in 2DE were worse in the AF group (Supplementary material, *Table S1*). Only a few correlations between 2DE and 3DE were found (Supplementary material, *Table S2*). RVEF <45% was found in 74 patients with AF (86.1%) and 11 patients with SR (36.7%). Multivariable analysis of the whole study group (both AF and SR patients) showed that AF, HR, and history of CABG were independent predictors of RVEF <45% (Table 1 and Supplementary material, *Figure S1*). Odds ratios (OR) were for AF — 9.14 (3.20–26.12); *P* <0.001; for HR (by one beat per minute) — 1.07 (1.02–1.13); *P* = 0.006; for CABG — 5.53 (1.34–22.80); *P* = 0.018. The area under the curve (AUC; 95% CI) for the model was 0.83 (0.74–0.92). An increase in HR by five beats per minute was associated with an OR of 1.42 (1.11–1.78); *P* = 0.006 of RVEF <45% in the whole study group (both AF and SR). Multivariable analysis made only in the patients with AF showed that only HR was an independent factor of RVEF <45%: OR (95% CI), 1.06 (1.003–1.12); *P* = 0.037; AUC (95% CI), 0.69 (0.53–0.84). An increase in HR by five beats per minute was associated with an OR of 1.35 (1.10–1.78); *P* = 0.037 in the AF group. In the SR group, the only prognostic factor of RVEF <45% was CABG, 7.08 (1.07–46.7); *P* = 0.042; AUC, 0.675 (0.505–0.844). In this group HR was not found to be a prognostic factor of RVEF <45% in univariable analysis: OR (95% CI), 1.02 (0.94–1.10); *P* = 0.62. However, the analysis could only be made in 30 patients who had a reliable 3DE, and only 11 of them presented RVEF <45%.

It is debatable what was a direct cause of right ventricular dysfunction in the AF group. In both AF and SR groups, direct damage due to ischemia or RV dysfunction as an effect of interventricular interdependence was possible. However, impaired RV function may be a marker of a more advanced stage of HFrEF, similarly to AF. Patients with HFrEF and AF may be more prone to volume and, subsequently, pressure overload. When its compensation capacity expires, the RV dilates, and its myocardial contractility deteriorates. An increase in HR maintains cardiac output but also increases myocardial strain and oxygen demand, which leads to decompensated RV failure [4]. RV dysfunction may also result from a primary reduction of myocardial contractility due to arrhythmia, which leads to impaired RV filling and increased right atrial pressures and tricuspid regurgitation [5]. RV failure has been repeatedly shown to compromise the prognosis in heart failure. In a recent study, it was confirmed to be an independent prognostic factor of all-cause mortality and rehospitalization for heart failure [6]. It underlines the need for the search for therapies focused on preserving RV function in heart failure. The patients in this study were recruited in the years 2013–2016. Since that time new therapeutic agents have been introduced to the standard treatment of heart failure. A few studies showing an RV function improvement

and clinical short-term outcomes in patients treated with sacubitril/valsartan have been published [7, 8]. Other agents are at the stage of clinical trials. We are aware of other study limitations — the small number of patients in the two-center study and the observational design of the study with no prospective assessment. Further research is needed to establish the clinical value of the presented observations.

Supplementary material

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

Article information

Conflict of interest: None declared.

Funding: None.

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Correlation between sigmoid interventricular septum angle and presence of Q waves on the electrocardiogram

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DOI: 10.33963/KP.a2022.0175

Received:
May 12, 2022

Accepted:
July 22, 2022

Early publication date:
July 27, 2022

INTRODUCTION

Nowadays, the widespread use of transthoracic echocardiography (TTE) as a routine checkup test, especially amongst the elderly population, has increased the prevalence of incidental findings, with one of the most frequent being the sigmoid interventricular septum (SIVS). According to data from the Framingham Heart study, the overall prevalence of SIVS in the general population is only 1.5% and significantly increases to 18% in the eighth decade [1, 4]. Furthermore, observational studies show a prevalence of 50%–80% of arterial hypertension in the SIVS population, proving their strong correlation [2, 3]. As far as the electrocardiogram (ECG) is concerned, SIVS can be indicated by abnormal Q waves, especially in V1–V2 precordial leads, voltage criteria for ventricular hypertrophy, and ST/T wave changes. Our study aimed to determine the echocardiographic features of SIVS that predispose the appearance of Q wave in V1–V2 leads of the surface ECG in a group of hypertensive and normotensive patients diagnosed incidentally with SIVS.

METHODS

Study population

Our study was conducted in the Department of Cardiology of the General Hospital of Chios, Greece. The study population included adult patients with an incidental finding of SIVS during a routine TTE. Both hypertensive and normotensive patients were studied. Patients with a history of hypertrophic cardiomyopathy, infiltrative heart disease, cardiac surgery, aortic/subaortic stenosis, or prior myocardial infarction with fibrosis/scar of the ventricular septum were excluded. Informed written consent was obtained from all patients, and the study was approved by the local ethics committee.

Echocardiographic analysis

The presence of SIVS was defined as a hypertrophied proximal focal area within the first third of the ventricular septum, with thickness >13 mm in men and >12 mm in women and a proximal-to-mid/distal septal thickness ratio of 1.3–1.5 [1, 2]. The mid-ventricular septum thickness (Mid IVS), the maximum thickness of the proximal part of the sigmoid septum (Max IVS sigmoid), as well as the thickness of the posterior wall of the left ventricle (LVPW) were measured from the parasternal long axis view at end-diastole. The aortoseptal angle (Asep), defined as the angle between the long axes of the aorta and the left ventricle, was also measured. Considering that the latter is highly dependent on the position of the transducer and thus is poorly reproducible, the aortosigmoid angle (Asig), which is less position dependent, was measured. It was defined as the angle between the long axis of the aorta and the tangent of the distal part of the sigmoid septum (Figure 1A). All angles were measured, as described in Figure 1, on the Digital Imaging and Communications in Medicine (DICOM) echo images of each patient with the use of the RadiAnt DICOM Viewer software (v.2021.2, Medixant, Poznań,

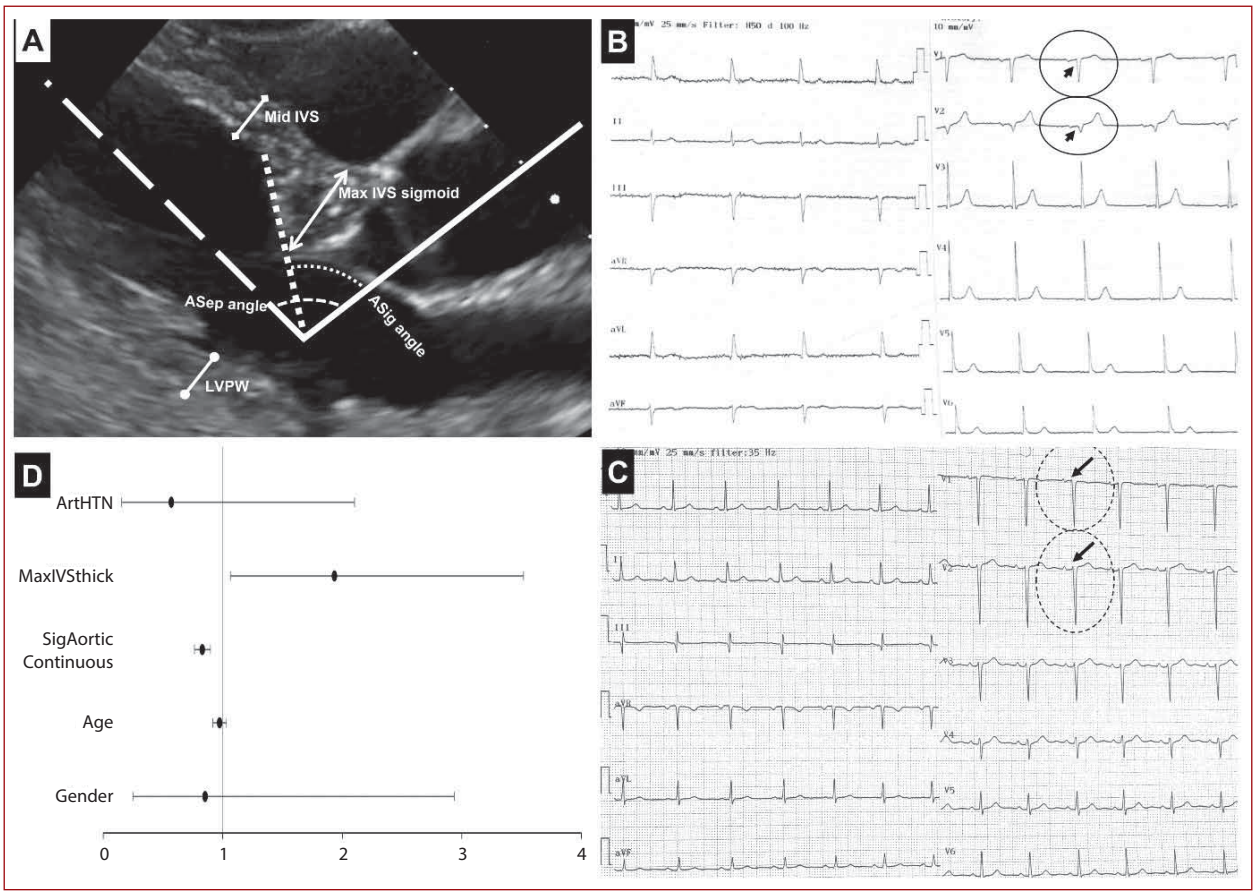

Figure 1. A. Measurements of angle and thickness on the echocardiographic image. All measurements performed at end-diastole. **B.** 12-lead surface electrocardiography (ECG) of a patient with sigmoid septum and Q waves in V1 and V2 leads. **C.** 12-lead surface ECG of a patient with sigmoid septum and non-Q waves in V1 and V2 leads (small initial r wave). **D.** Association between the aortosigmoid angle and the Q wave presence in V1–V2 leads, as analyzed in the second model. The odds ratio and 95% confidence interval are presented

Abbreviations: IVS, interventricular septum; LVPW, posterior wall of the left ventricle

Poland). The Max/Mid IVS ratio, Max/Posterior IVS ratio, Mid/Posterior IVS ratio, the Asig/Asep ratio, and the Asep-Asig subtraction were also calculated.

ECG analysis

All patients underwent a 12-lead surface ECG and were divided into the Q and non-Q groups based on the presence of Q waves in V1–V2 precordial leads (Figure 1 B, C).

Statistical analysis

Categorical variables were compared with the χ^2 test. Continuous variables were compared with the t-test or Mann–Whitney U test if normally or non-normally distributed, respectively. Statistical significance was defined as $P < 0.05$. Multivariable regression analysis was performed to find the significant predictors of the presence of Q waves in leads V1 and/or V2 on 12-lead surface ECG. The analysis was performed with the IBM SPSS Statistics v.23 software. The Mann–Whitney test was not conducted.

RESULTS AND DISCUSSION

A total of 103 patients at a mean age of 68.5 (10.7) years were included in the analysis (52 male and 51 female).

Sixty patients (58.3%) were included in the Q group (36 males and 24 females), and 43 patients (41.7%) were included in the non-Q group (16 males and 27 females).

There were statistically significant differences betweent the two groups in terms of sex, Mid IVS, Max IVS, and LVPW thickness, Asep and Asig, Asep-Asig subtraction, the Asig/Asep ratio, and presence of arterial hypertension (Supplementary material, *Table S1*).

To confirm the last observation, a binomial logistic regression was performed to ascertain the effects of sex, age, Asig ≤90º, Max IVS thickness, and arterial hypertension (HTN) on the likelihood that patients display Q waves in leads V1 and/or V2 on 12-lead surface ECG. The logistic regression model was statistically significant, $P < 0.0001$ and correctly classified 83.5% of cases. Sensitivity was 96.7%, specificity was 65.1%, positive predictive value was 79.5%,

and negative predictive value was 93.3%. Of the five predictor variables, only two were strongly correlated with the presence of Q waves in V1–V2 ECG leads: Asig ≤90° (odds ratio [OR], 30.07; 95% confidence interval [CI], 5.97–151.43; *P* <0.001) and Max IVS thickness (OR, 1.99; 95% CI, 1.17–3.39; *P* = 0.011). An Asig ≤90° increased the likelihood of presenting a Q wave in leads V1 and/or V2 more than 30 times compared to an obtuse angle. Similarly, Max IVS thickness increased by 1 mm raising that likelihood by almost 2 times (Supplementary material, *Table S2*).

A second model was created to assess the effect of the Asig as a continuous variable, with all other variables remaining the same as in the previous model. This model was also statistically significant (*P* <0.0001) correctly classifying 80.6% of cases. Sensitivity was 85%, specificity was 74.4%, positive predictive value was 82.3% and negative predictive value was 78%. Of the five predictor variables, only two were strongly correlated with the presence of Q waves in V1–V2 ECG leads: Max IVS thickness (OR, 1.93; 95% CI, 1.06–3.52; *P* = 0.031) and Asig (OR, 0.8; 95% CI, 0.76–0.88; *P* <0.001) (Figure 1D). In the Q group, the mean Asig was 74.5 (10.5) degrees, and the Max IVS thickness was 14.7 (1.3) mm. In the non-Q group, these measurements were 94.6 (11.9) degrees and 13.5 (0.9) mm, respectively. An increase in the Max IVS thickness by 1 mm and a decrease in the Asig by 1 degree were associated with a higher likelihood, by 1.9 and 1.2 times respectively, of presenting a Q wave in leads V1 and/or V2. Age, arterial HTN, and sex were not independent predictors of Q waves on the ECG (Supplementary material, *Table S3*).

When comparing the OR between the two models, we observed that the Asig when assessed with a cut-off value of ≤90° (Model 1), resulted in a higher OR (and higher likelihood) of Q wave presence in V1–V2 leads than when assessed as a continuous variable (Model 2) (OR, 30.07 vs. 1.2 between the two models). On the other hand, the OR for the Max IVS thickness was quite similar in the two models (OR, 1.99 vs. 1.93).

SIVS is one of the most frequent incidental findings during TTE in asymptomatic populations. Most studies correlate SIVS and its relevant echocardiographic features with the presence of arterial HTN or subclinical hypertrophied cardiomyopathy/subaortic stenosis, with cardiac magnetic resonance imaging being the best diagnostic tool for further evaluation [4–6]. Thus, based on the lack of data from the existing literature our study aimed to highlight the predisposing clinical and echocardiographic parameters for the appearance of Q waves in leads V1 and/or V2 of the ECG in subjects with SIVS.

In our study, the Asig was an additional parameter that was measured in comparison to previous studies, making our results more dependent on SIVS characteristics. The latter, along with the Max IVS thickness, were the main predictive factors of the appearance of Q waves on the ECG. It is important that an Asig ≤90° increased the likelihood of presenting a Q wave in leads V1 and/or V2 more than 30 times compared to an obtuse angle as it was ascertained by the statistical analysis, making the acute Asig a strong predictor of the presence of Q waves on the surface ECG. This was highlighted by the fact that every decrease of the Asig by one degree increased the likelihood of the appearance of the Q waves in leads V and V2 by 1.2 times, so the presence of more acute angles resulted in a higher probability of appearance of Q waves on the ECG.

In conclusion, the measurement of the Max IVS thickness, and especially the finding of an acute Asig ≤90°, is a widely available and reproducible diagnostic tool for the evaluation of patients with incidental finding of SIVS. In clinical practice, it could assist cardiologists in distinguishing in which patients the presence of Q waves in V1 and V2 leads of the ECG are not associated with characteristics of the SIVS, so alternative etiologies should be sought.

Supplementary material

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

Article information

Conflict of interest: None declared

Funding: None.

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Gastrointestinal bleeding as a symptom of failing Fontan circulation

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DOI: 10.33963/KP.a2022.0137

Received:
May 2, 2022

Accepted:
May 23, 2022

Early publication date:
May 27, 2022

Fontan procedure is a standard surgical palliation for single ventricle congenital heart defects. As a result of the procedure, systemic venous return is directly connected to pulmonary circulation without the interposition of the ventricle which leads to chronic venous hypertension. There are many widely known late consequences of Fontan physiology [1] such as the development of plastic bronchitis, protein-losing enteropathy, Fontan-associated liver disease, portal hypertension with esophageal varices, splenomegaly, and hypersplenism. We present a case that demonstrates a different manifestation of failing Fontan circulation.

A 10-year-old girl with a congenital heart disease including a double-outlet right ventricle, hypoplastic aortic arch, subvalvular aortic stenosis, and large ventricular septal defect was admitted to the hospital with symptoms of heart failure and acute lower gastrointestinal bleeding. She had undergone surgical palliation at 6 years of age: nonfenestrated extracardiac Fontan operation (with an additional source of pulmonary blood flow from the ventricle).

Laboratory investigations showed hypoalbuminemia, hypoproteinemia, and elevated stool alpha-1-antitrypsin level. Technetium labeled albumin scintigraphy was performed and confirmed protein-losing enteropathy.

Cardiac imaging was planned to assess the anatomy of Fontan circulation. Computed tomography angiography showed endothelial hyperplasia causing left pulmonary artery in-stent restenosis. The patient underwent successful percutaneous stent redilatation.

Although the signs of active gastrointestinal bleeding diminished, the patient suffered from severe recurrent anemia that required repetitive blood transfusions and during the hospital stay, melena was present. Abdominal ultrasound showed portal hypertension. There were no endoscopic signs of active or recent bleeding, but esophageal varices were found in gastroscopy. Bone marrow biopsy analysis showed normal hematopoietic function. Due to persistent positive fecal occult blood test (FOBT) — technetium labeled erythrocyte scintigraphy was scheduled and localized the source of bleeding.

Both scintigraphy examinations (Figure 1A — with albumin and 1B — with erythrocytes) show leakage in a similar region of the small intestine. After excluding other causes of intestinal bleeding, regarding the same localization of protein and erythrocyte leakage, failing Fontan circulation was identified as the most probable underlying cause of enteric erythrocyte loss [2, 3].

Treatment in our patient involved optimization of Fontan hemodynamics and pharmacotherapy: propranolol, lisinopril, spironolactone, low-fat high-protein diet, and enoxaparin (as data are showing good effects on intestinal epithelial cells of heparin therapy in protein-losing enteropathy [4]). Surgical segmental resection of the abnormal region of the small bowel was considered. One month later, as soon as laboratory assessment showed no anemia with negative FOBT, serum albumin, and protein levels within a normal range; any surgical intervention was postponed. The patient remained stable in a one-year follow-up.

Chronically elevated central venous pressure in Fontan physiology has a significant impact on subdiaphragmatic hemodynamics. Potentially, the same mechanism may play a role in erythrocyte enteric loss causing in-

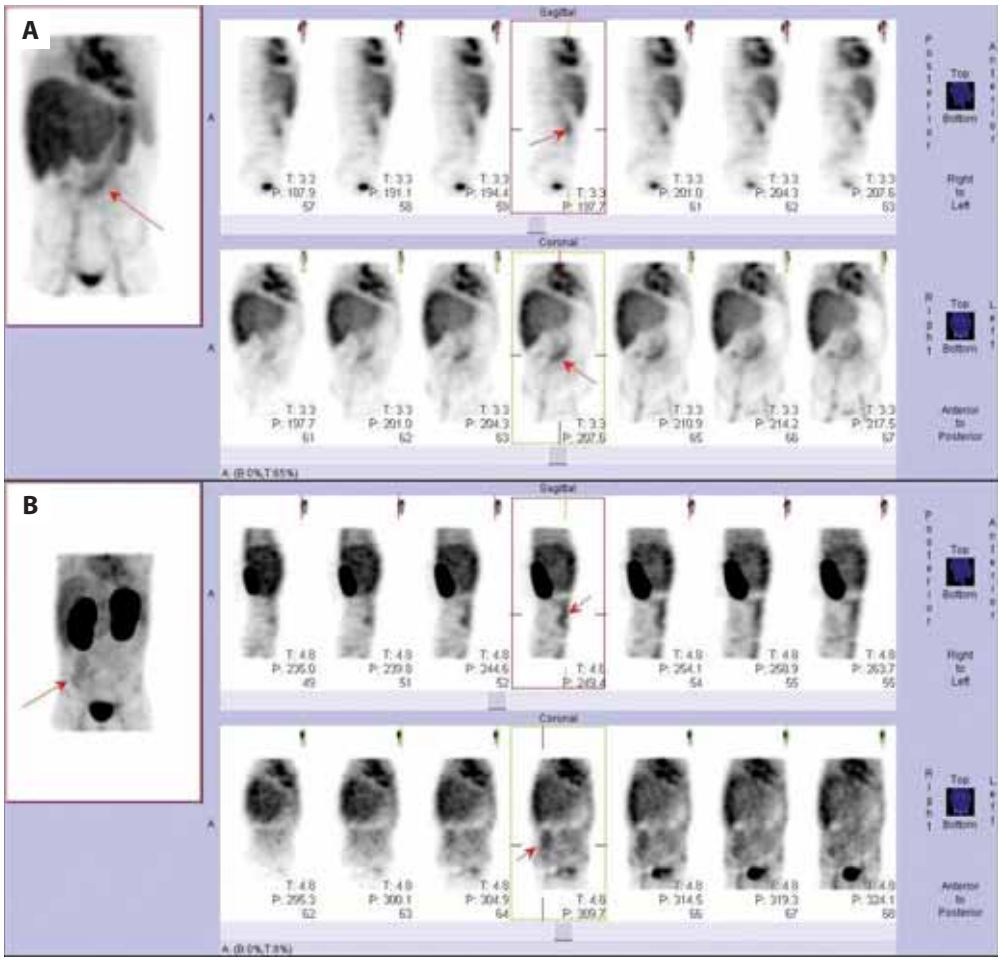

Figure 1. A. Technetium 99m-labeled human serum albumin scintigraphy (the arrows show leakage of albumin in the region of the small intestine). **B.** Technetium 99m-labeled erythrocytes scintigraphy, the arrows show leakage of erythrocyte in the region of the small intestine

creased vascular permeability for larger cells or molecules: lymphocytes, erythrocytes, serum albumin, and protein. Recurrent anemia resulting from enteric erythrocyte loss may be another significant complication related to Fontan palliation. Future studies are needed to confirm that.

Article information

Conflict of interest: None declared.

Funding: None.

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A complicated course of Salmonella endocarditis leading to heart transplantation

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DOI: 10.33963/KP.a2022.0176

Received:
June 20, 2022

Accepted:
July 20, 2022

Early publication date:
July 28, 2022

A 39-year-old woman with symptomatic severe mitral regurgitation due to myxoid valve disease was admitted to the cardiac surgery department (Figure 1A– B; Supplementary material, *Video S1*). She underwent mitral valve repair (posterior leaflet P2 segment resection followed by annuloplasty). Preoperative left ventricular ejection fraction (LVEF) was 65%. The perioperative course was uneventful.

Due to a prolonged fever (with no other symptoms), 6 weeks after the surgery, transthoracic and transesophageal echocardiography revealed a giant, mobile vegetation attached to the mitral annulus (Figure 1C; Supplementary material, *Video S2*). Furthermore, a smaller vegetation and perforation of the non-coronary cusp of the aortic valve were observed. The blood cultures revealed *Salmonella enterica* ssp. The patient initially did not give consent for reoperation and was treated with ceftriaxone and trimethoprim/sulfamethoxazole based on an antibiogram. The fever resolved, however, despite 6 weeks of antibiotic treatment, vegetations persisted and an acute spleen embolism was diagnosed. Finally, urgent reoperation was performed — mechanical mitral and aortic valves were implanted with the aorto-mitral curtain reconstruction using CorMatrix (commando procedure). Blood cultures repeated after surgery revealed persistent infection with the same bacteria, and antimicrobial treatment was continued. Despite that, a series of transesophageal echocardiography studies revealed recurrent vegetations on the mitral valve prosthesis (Figure 1D; Supplementary material, *Video S3*) and a significant paravalvular leak caused by laceration of the CorMatrix patch (Figure 1E–F; Supplementary material, *Video S4–5*). LVEF was 45%.

Three months after the second surgery, due to persistent endocarditis and significant paravalvular leak, the Heart Team decided on the third operation — this time biological mitral valve and aortic homograft were implanted. The periprocedural period was complicated by acute heart failure, treated with temporary extra corporeal membrane oxygenation (ECMO) support, inotropic therapy (dobutamine, milrinone), and intravenous loop diuretics. Immediately after cardiac surgery, LVEF severely decreased to 20% with an improvement to 40% at discharge, but persistent severe right ventricular failure was observed.

After several weeks, normalization of inflammatory markers and negative blood cultures were observed. The patient was qualified for a heart transplant and received the graft several months later. Two years after the heart transplantation she remains stable, with functional New York Heart Association class II.

Cardiovascular complications of salmonellosis are rare and occur in fewer than 5% of patients with Salmonella bacteremia. There are only a few reports in the literature describing myocarditis, pericarditis, or mycotic aneurysm [1–5]. Most of them are caused by immune deficiency in the course of lupus erythematosus, corticosteroid therapy, or human immunodeficiency virus (HIV) infection. None of the above risk factors were found in our patient. Nonetheless, the course was very severe with massive destruction of cardiac

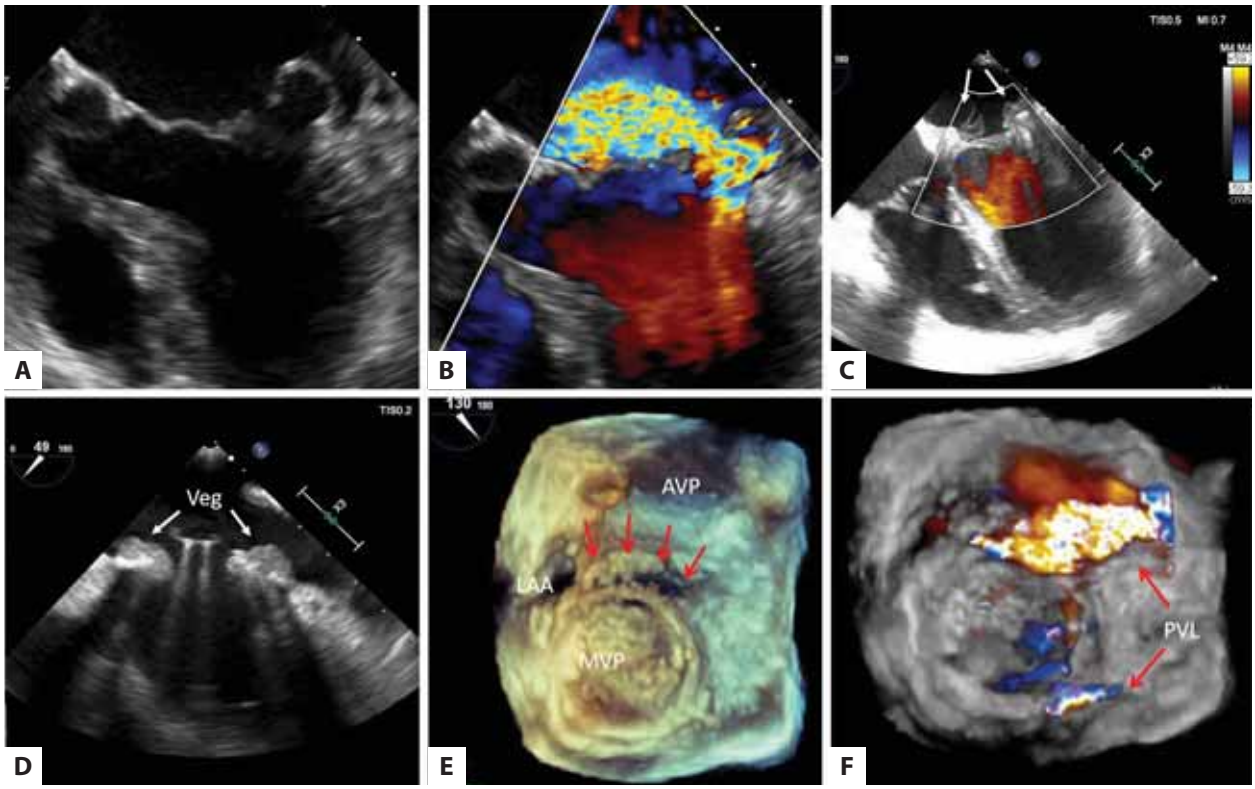

Figure 1. Transesophageal echocardiography: **A–B.** Preoperative study showing posterior mitral leaflet prolapse with severe MR; **C.** Control study post mitral valve repair — there is no MR but massive vegetations (Veg) are visible (the white arrows); **D–F.** Next study after AVP and MVP implantation and CorMatrix reconstruction of the aorto-mitral curtain — recurrence of endocarditis and PVLs are visible (the red arrows)

Abbreviations: AVP, aortic valve prosthesis; LAA, left atrium appendage; MR, mitral regurgitation; MVP, mitral valve prosthesis; PVL, paravalvular leak

tissues, several reoperations, mechanical support, and cardiac transplantation.

Supplementary material

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

Article information

Conflict of interest: None declared.

Funding: None.

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Large field-of-view intravascular ultrasound for periprocedural cross-sectional assessment of right ventricular outflow tract anatomy offering a detailed tomographic perspective

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DOI: 10.33963/KP.a2022.0177

Received:
April 20, 2022

Accepted:
July 25, 2022

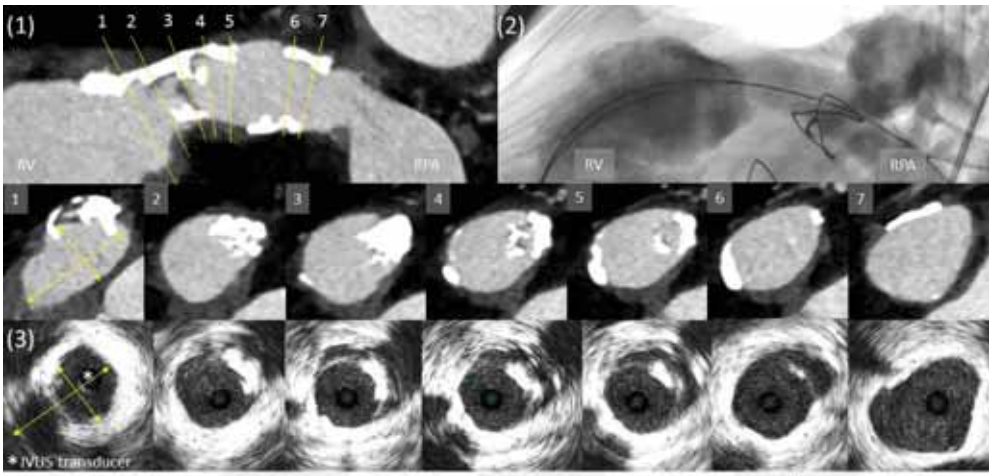
Early publication date:
July 29, 2022

A 35-year-old male born with tetralogy of Fallot with total surgical correction at the age of 3 years and reoperation at the age of 15 years with homograft insertion in the right ventricular outflow tract (RVOT) was admitted due to deterioration in exercise tolerance and arrhythmia. Echocardiography showed severe pulmonary insufficiency and stenosis (pressure half-time of 89 ms with maximal/mean gradient of 67/44 mm Hg). Pulmonary regurgitant volume measured in cardiac magnetic resonance was 13 ml with a regurgitant fraction of 16% and a substantially increased right ventricular end-diastolic volume (219 ml/m^2). Multi-slice computed tomography (MSCT) angiography (384-row SOMATOM® Definition Flash, Dual Source, SIEMENS, Forchheim, Germany) showed diffusely calcified and narrowed RVOT with minimal lumen cross-sectional area (CSA) of 1.89 cm^2 measured in systole (Figure 1, panels 3 and 4). Lumen CSAs measured in systole at the proximal and distal references were 2.99 and 3.15 cm^2, respectively (Figure 1, panels 1 and 7) with calculated stenosis area of 40% (1.89 cm^2/3.07 cm^2). Given our recent experiences documenting a unique 60-mm periprocedural tomographic imaging perspective offered by a Vision PV035 10 MHz intravascular ultrasound (IVUS, Philips North America Corporation, Andover, MA, US), novel imaging instrumentation was used to verify its diagnostic performance in the highly calcified RVOT (Figure 1, panel 3, the white arrow indicates the transducer location) [1–4]. Intravascular ultrasound cross-sectional visualization measured lumen dimensions that corresponded closely with those made in angio-MSCT (Figure 1, the lower row). Contrast-free cross-sectional imaging using a large field of view IVUS is feasible even in highly calcified RVOT anatomy, offering an understanding of the target zone anatomy and its dimensions that are crucial for planning transcatheter intervention.

Article information

Conflict of interest: None declared.

Funding: None.



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angio-MSCT	11.6	29.9	2.99	12.9	17.0	1.99	12.3	16.0	1.92	12.2	16.1	1.91	12.7	15.6	2.24	15.3	21.0	2.81	16.2	24.3	3.15
IVUS	**10.4**	**25.2**	**2.86**	**13.4**	**17.0**	**1.95**	**12.6**	**16.8**	**1.89**	**12.0**	**16.4**	**1.89**	**11.7**	**17.4**	**2.09**	**14.9**	**22.2**	**2.80**	**17.8**	**24.3**	**3.23**

Figure 1. Baseline RVOT anatomy in: angio-MSCT (panel 1: longitudinal and cross-sectional views seen in the upper and middle row, respectively), angiography (panel 2: corresponding longitudinal view), and parallel IVUS (panel 3: cross-sectional view). Corresponding relevant dimensions of RVOT lumen measured in angio-MSCT and parallel IVUS cross-sections presented are in the lower row

Abbreviations: angio-MSCT, multi-slice computed tomography angiography; IVUS, intravascular ultrasound; RPA, right pulmonary artery; RV, right ventricle; RVOT, right ventricular outflow tract

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Simultaneous use of implantable cardioverter-defibrillator in a patient with a preexisting deep brain stimulator: A proposed protocol of implantation to avoid dangerous interactions

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DOI: 10.33963/KP.a2022.0178

Received:
June 27, 2022

Accepted:
July 20, 2022

Early publication date:
August 1, 2022

Recently, the number of implantations of cardiac implantable electronic devices (CIED) has increased. Similarly, the field of extracardiac stimulation devices including deep brain stimulation (DBS) in medically refractory Parkinson's disease or essential tremor has also expanded. The DBS stimulator delivers continuous pacing of the subthalamic nucleus or internal globus pallidus with a frequency range of 130–185 Hz, a target amplitude typically 1.0–3.5 V, and a pulse width of 60–120 µs (depending on symptoms). Simultaneous indications for both types of the device may cause CIED malfunction induced by electromagnetic interference, namely inhibition of cardiac pacing, asynchronous pacing, inadequate high voltage therapy, or mode switch. Likewise, the high voltage therapy of implantable cardioverter-defibrillator (ICD) may cause damage to DBS or reset its programming [1–3]. Thus, proper programming (including bipolar configuration of pacing pulse if possible) of both devices, patient education, and testing for the "worst case" scenarios diminish the risk of interactions [1, 3–5]. It is also important to separate both devices by more than 20 cm. Close cooperation of a multidisciplinary team (including a cardiologist, neurologist, technicians, and nurses) is mandatory during preparation, implantation, and follow-up.

A 73-year-old male was referred for a single chamber cardioverter-defibrillator (VVI-ICD) implantation procedure as secondary prophylaxis of sudden death. This patient had a DBS implanted in the left subclavian region to treat tremors of the right upper extremity resistant to standard medications. The neurostimulator was programmed to deliver 2.6 V/60 µs unipolar impulses with a frequency of 130 Hz. Additionally, we checked the device for the minimal energy of DBS at which the neurological side effects of the stimulation occurred (the setting of 4.0 V/60 µs revealed a slow speech and muscle spasticity).

Due to the localization of the DBS can (left subclavian region), we decided to implant a VVI-ICD system (dual coil, active fixation, DF4 RV-HV Medtronic 6947 — 62 cm lead and Medtronic Visia AF MRI S VR SureScan generator) on the contralateral side using the right subclavian vein access and keeping the maximal possible distance (above 20 cm) between both devices.

The first check-up of the ICD system was performed after the lead implantation and before attaching it to the generator. It followed a routine protocol (impedance, sensing, pacing threshold), and it included a gradual increase of the neurostimulator impulse energy from 2.6 V to 4.0 V with the sensing at 0.3 mV, which did not provoke any artifacts in the V-EGM record. After attaching the lead to the generator and suturing the pocket, the second check-up was performed (R wave amplitude, 9.9 mV; pacing threshold, 0.5 V/0.4 ms; impedance, 399/55/55 Ohm). Again, the neurostimulator impulse energy was gradually increased and did not provoke any artifacts in the V-EGM record. Some far-field can-coil artifacts were

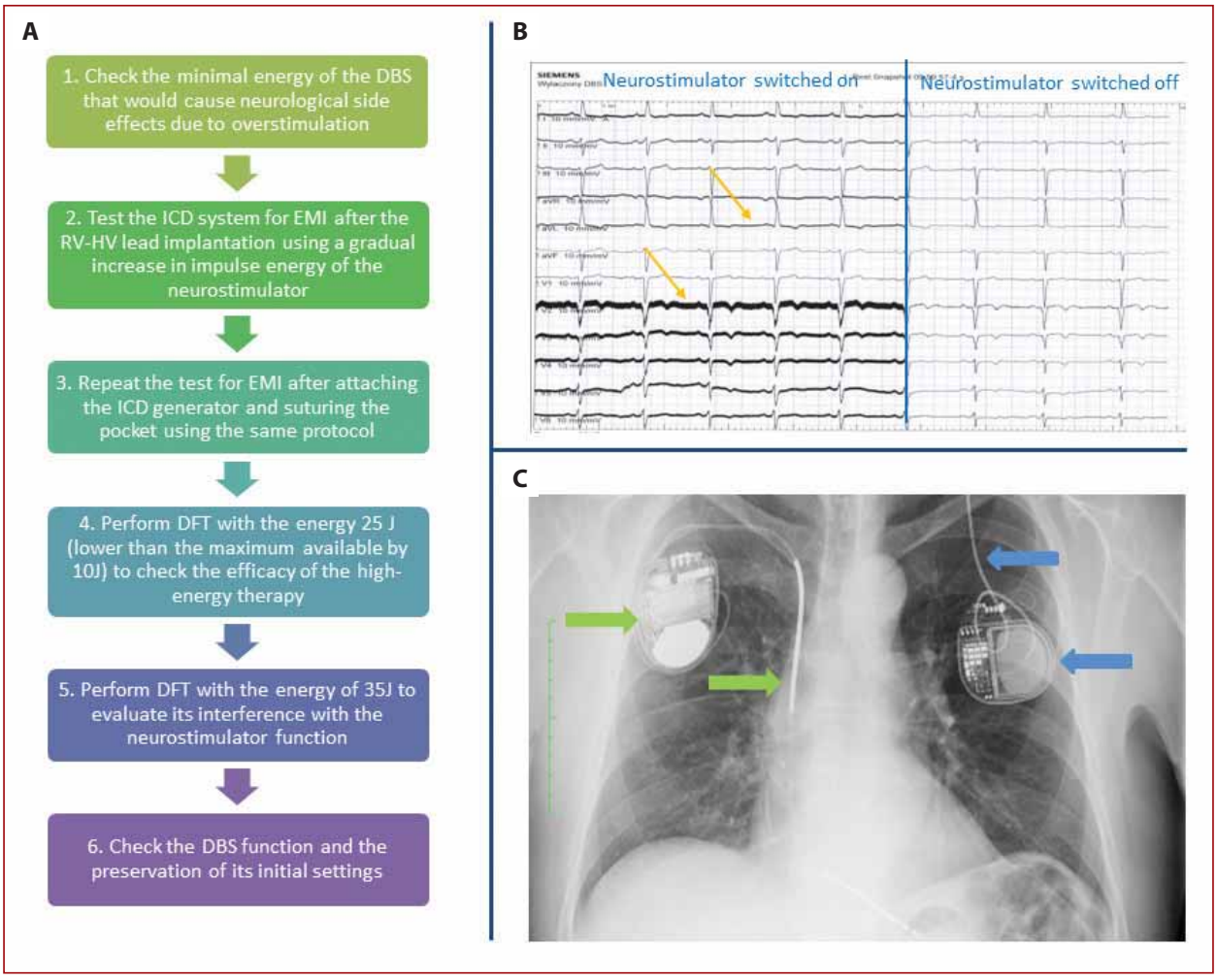

Figure 1. A. A protocol proposed to be followed during the procedure of ICD implantation in patients with preexisting neurostimulator. **B.** Our patient's electrocardiogram with the neurostimulator switched on (cycles 1 to 6) and off (cycles 7 to 9). The artifacts seen on all leads caused by EMI (the orange arrows). **C.** Our patient's chest X-ray after the procedure depicting the ICD generator with the RV-HV lead (the green arrows) and the DBS generator with the lead (the blue arrows)

Abbreviations: DBS, deep brain stimulator; DFT, defibrillation test; EMI, electromagnetic interference; ICD, implantable cardioverter-defibrillator; RV-HV, right ventricle-high voltage lead

observed, albeit they did not disturb the proper sensing of QRS complexes. The setting of the ICD was as follows: sensing 0.3 mV (standard programming), ventricular tachycardia, and fibrillation detection thresholds: 171–200 bpm and >200 bpm, respectively. The defibrillation vector was set between the superior vena cava and right ventricular coil, omitting the can of ICD ("cold can").

Subsequently, defibrillation tests (DFT) were performed. Firstly, we tested the energy of 25 J (lower than the maximum energy by 10 J). The DFT confirmed the efficacy of defibrillation delivered with the programmed vector by the ICD implanted in the right subclavian region. Secondly, the maximal energy of 35 J was delivered to evaluate its potential effect on the neurostimulator's function. Both energies effectively restored the sinus rhythm. Notably, the DBS function was re-checked, and we confirmed that its initial settings were preserved.

We found no dysfunction in either device during the 2-year follow-up.

Article information

Conflict of interest: PM declares support from Medtronic Company. Other authors have no conflicts to disclose.

Funding: None.

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A rare but challenging iatrogenic complication after radiofrequency ablation of atrial fibrillation could be worse than the original disease: The role of multimodal imaging

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DOI: 10.33963/KP.a2022.0179

Received:
June 20, 2022

Accepted:
July 29, 2022

Early publication date:
August 1, 2022

Pulmonary vein stenosis (PVS) is a rare complication of radiofrequency ablation (RFA) in atrial fibrillation (AF). Significant stenosis of all 4 pulmonary veins (PV) could lead to pulmonary hypertension (PH), which, if treated improperly, is associated with poor prognosis. It is essential to be aware of that dangerous complication.

A 65-year-old man with a history of AF and triple RFA (12, 9, and 4 years earlier) was admitted with significant dyspnea, which had progressed over the last 6 months. Transthoracic echocardiography (TTE) showed right ventricular (RV) enlargement and features of pressure overload (Figure 1A–B). The RV systolic pressure was estimated at 80 mm Hg. There was prominent turbulent flow across the right superior PV with increased velocity (Supplementary material, *Video S1*). Secondary PH resulting from the post-ablative PVS was the initial diagnosis. Transesophageal echocardiography (TEE) confirmed turbulent flow through PV (Figure 1C). In a three-dimensional reconstruction, the significantly narrowed PV ostium was visualized (Figure 1D). Computed tomography (CT) showed significantly stenotic PV (Figure 1E), which eventually confirmed the diagnosis. The patient was qualified for invasive treatment, which was performed in three PV (balloon angioplasty) with a satisfactory outcome (Supplementary material, *Video S2–S7*, *Figure S1*). A reduction in right ventricular systolic pressure (52 mm Hg), disappearance of the D-shape, and a complete resolution of the patient's symptoms were observed within two weeks. An RV catheterization with a further decision on CT is scheduled within the next three months.

Severe PVS due to RFA is a rare complication encountered in ca. 0.5% of RFA procedures due to AF [1]. The frequency of mild or moderate PVS, whose long-lasting effects are unknown, could be significantly higher, reaching even 20.8% [2]. At the same time, the benefits of treating AF with RFA significantly outweigh the risk of possible PV.

The stenosis of only one or two PV may be asymptomatic for a long time, whereas significant stenosis of all four PV could lead to PH. Quick diagnosis and treatment are crucial for preventing total occlusion of the PV.

The clinical symptoms of PVS are not specific, and this complication can be easily misdiagnosed [3]. Therefore, clinicians should evaluate the possibility of PVS in patients with a history of RFA. The role of TTE is limited, whereas TEE, CT, and cardiac magnetic resonance are recommended to confirm that diagnosis. Fusion imaging, possible during PV recanalization, is associated with lower contrast and radiation exposure compared to 2D angiography [4]. As first-line therapy, all symptomatic patients with confirmed PVS should be considered for PV stenting [5]. Interventional treatment of even one vessel may be sufficient to reduce pulmonary pressure and relieve the symptoms significantly, and if performed in specialized centers, it is associated with promising results and a low

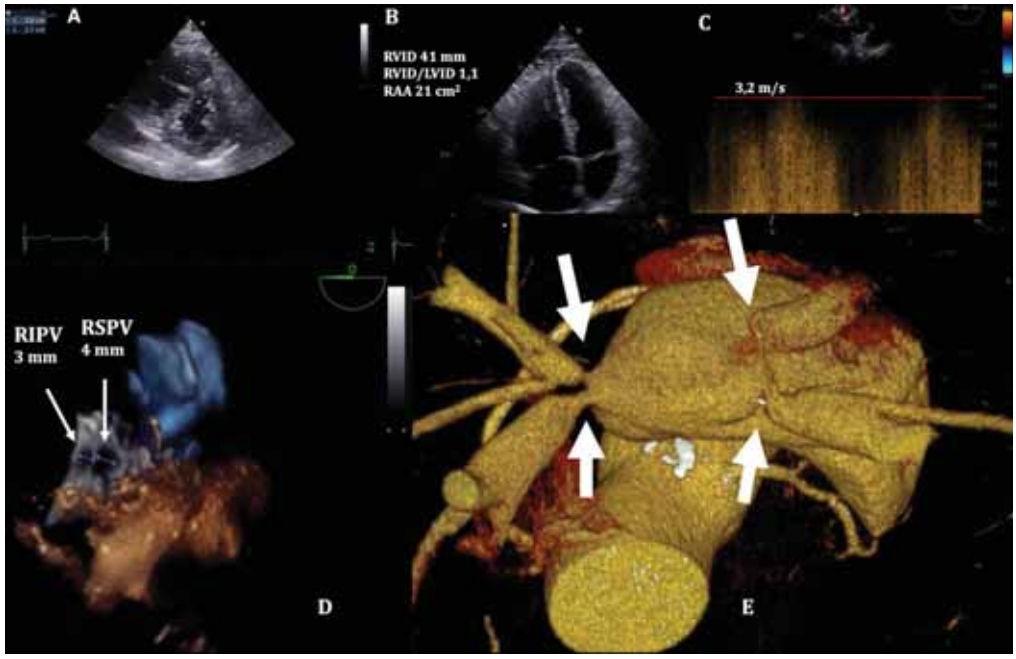

Figure 1. A. D-shape of the RV during systole when assessed in the parasternal short-axis view (TTE); **B.** A 4-chamber view showing dilated right heart cavities (TTE); **C.** Significantly increased flow velocity in CW in the PV (up to 3.2 m/s, pressure gradient 41 mm Hg) (TEE); **D.** The significantly narrowed PV ostium (3-dimensional TEE reconstruction); **E.** Confirmation of the diagnosis of PVS — sites of narrowing marked with the white arrows (CT)

Abbreviations: CT, computed tomography; CW, continuous wave; PV, pulmonary vein; PVS, pulmonary vein stenosis; RAA, right atrial area; RSPV, right superior pulmonary vein; RVID, right ventricular internal diameter; RV, right ventricle; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography

risk of complications. Balloon angioplasty is considered to be a method with a higher risk of restenosis; however, in our patient, that decision was made by a very experienced operator due to the large caliber of the PV.

As the number of RFA performed due to AF increases, so will the number of PVS cases. Delayed diagnosis and untreated pathology can lead to secondary PH with poor prognosis. The non-specific symptoms and challenging diagnosis of PVS in TTE make it necessary to be especially vigilant in the case of patients monitored after RFA procedures. A multimodality approach should be considered for proper diagnosis.

Supplementary material

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

Article information

Conflict of interest: None declared.

Funding: None.

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Coincidence of cor triatriatum sinistrum and bicuspid aortic valve in an adult patient

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DOI: 10.33963/KP.a2022.0180

Received:
June 22, 2022

Accepted:
July 29, 2022

Early publication date:
August 2, 2022

A 58-year-old female with uncontrolled arterial hypertension and obesity (body mass index [BMI], 35 kg/m^2) was admitted to the emergency department with elevated blood pressure (180/100 mm Hg) with concomitant dyspnea at rest. The patient had a 6-month history of worsening exertional dyspnea along with non-adherence to antihypertensive therapy which included ramipril 5 mg/day, nebivolol 5 mg/day, and doxazosin 4 mg/day. The patient discontinued amlodipine 5 mg/day due to intolerance. Upon admission to the hospital, physical examination showed mild lower extremity edema and a diastolic murmur on aortic valve auscultation. Lung auscultation was normal. The B-type natriuretic peptide and serum troponin I levels were within the normal range. Electrocardiogram presented sinus rhythm 75/min without ST-T changes. Blood pressure lowering therapy was administrated, and the patient was transferred to the Department of Cardiology for further assessment. Transthoracic and transesophageal echocardiography demonstrated preserved ejection fraction (60%) without left ventricle wall motion abnormalities, bicuspid aortic valve (BAV) with a fusion of non-coronary cusp and right-coronary cusp (Figure 1B and D; Supplementary material, *Video S2*, *Video S4*) with moderate central regurgitation jet (vena contracta width <0.4 cm, pressure half-time 380 ms), without any visible valve calcifications. The ascending aorta was dilated to 45 mm, while the size of the sino-tubular junction was 34 mm and the aortic root diameter at the Valsalva level was 38 mm. Left ventricular diastolic and systolic diameters were 51 mm and 44 mm, respectively. The left atrium (LA) was slightly enlarged (43 mm) and divided by a membrane into two parts with pulmonary veins draining into the "accessory" superior chamber of LA. The LA appendage without thrombus was connected with the "true" inferior chamber of LA (Figure 1A and D; Supplementary material, *Video S1*, *Video S3*). A wide single large opening in the intra-atrial membrane (Group 3 of Loeffler cor triatriatum classification [1]) was present in the inferomedial part of LA. Continuous wave Doppler across the orifice in the intra-atrium membrane did not reveal flow acceleration. Multislice computed tomography confirmed an intra-atrial membrane and a moderate dilatation of the aorta (Figure 1C and F). As coronary arteries were not sufficiently visible, coronary angiography was performed showing no coronary lesions. During the hospital stay, anti-hypertensive pharmacotherapy was optimized with good clinical response. It was assumed that the main pathology that was not sufficiently treated was hypertension, and other abnormalities were not responsible for the symptoms. At discharge, the patient was prescribed ramipril 10 mg/day, nebivolol 5 mg/day, doxazosin 4 mg/day, torsemide 5 mg/day, and spironolactone 25 mg/day for anti-hypertensive treatment. A periodic check of the aortic diameter and aortic regurgitation was scheduled. The 1-year follow-up was uneventful.

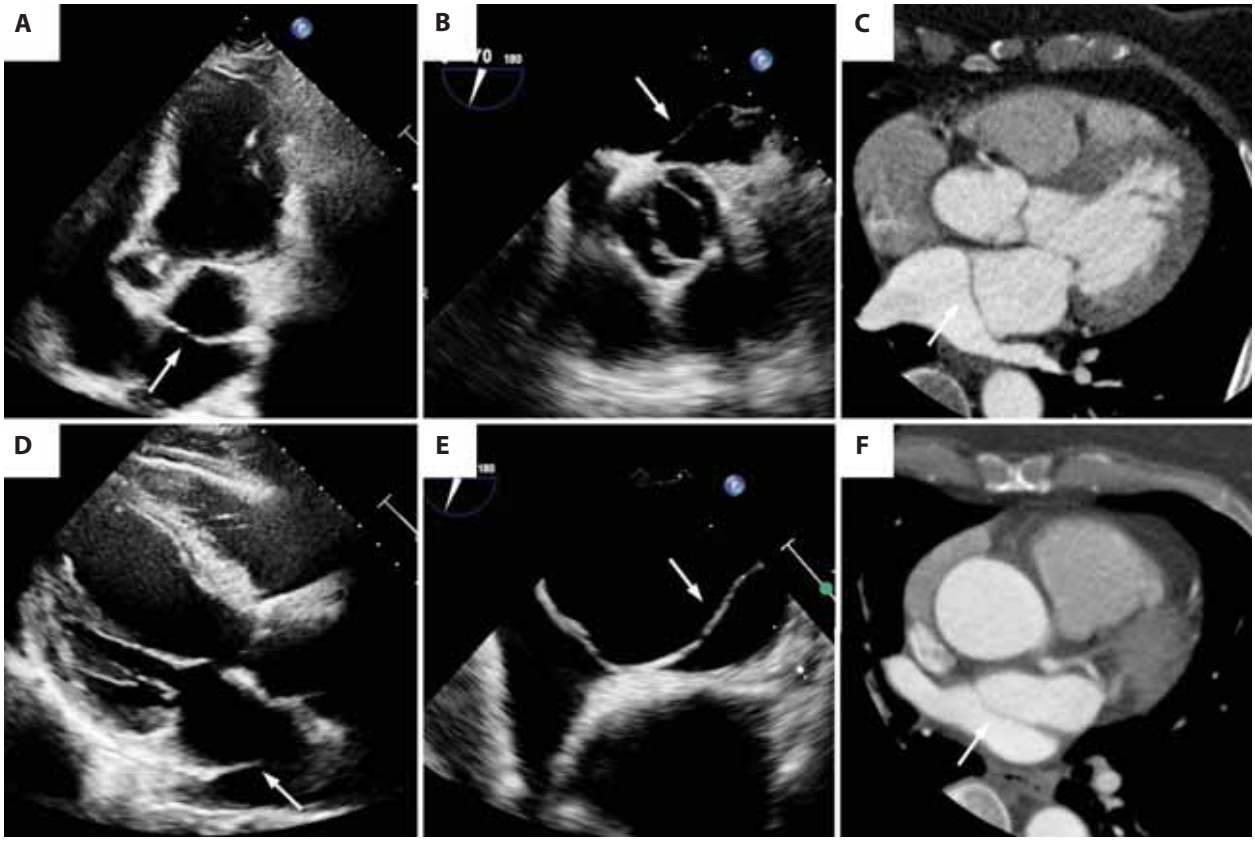

Figure 1. A. Transthoracic echocardiography — apical view. **B.** Transesophageal echocardiography — the bicuspid valve and left atrium membrane. **C.** Computed tomography angiography. **D.** Transthoracic echocardiography — long axis view. **E.** Transesophageal echocardiography — the left atrium membrane. **F.** Computed tomography angiography. The white arrow in all panels indicates the left atrium membrane

Cor triatriatum sinistrum (CTS) is a unique congenital abnormality with prevalence of 0.1%–0.4% in congenital heart disease [1]. It is usually corrected in childhood either surgically or percutaneously in highly symptomatic CTS group 1 (no connection between chambers) and 2 (small connection between chambers) according to the Loeffler classification [2]. It is incidentally recognized in adults in CTS group 3 (wide connection) [3]. The clinical presentation of CTS is similar to mitral stenosis. The coincidence of CTS with BAV is a unique finding — with only a few reports in adult patients available so far [4, 5].

Supplementary material

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

Article information

Conflict of interest: None declared.

Funding: None.

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Lightning 12: A new player in the field of pulmonary percutaneous mechanical thrombectomy

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DOI: 10.33963/KP.a2022.0181

Received:
June 28, 2022

Accepted:
July 26, 2022

Early publication date:
August 2, 2022

A 32-year-old male professional driver with a few days' dyspnea was admitted to our department. Physical examination revealed a heart rate (HR) of 110 bpm, respiratory rate (RR) of 31/min, and blood pressure (BP) of 114/62 mm Hg. Laboratory tests showed elevated troponin I (0.6 ng/ml; normal value <0.01 ng/ml) and low arterial saturation (SaO_2) — 89% despite oxygen supplementation through a mask with a reservoir bag (12 l/min). Computed tomography pulmonary angiography showed a large thrombus burden in both right (RPA) and left pulmonary artery (LPA). Echocardiography demonstrated right ventricular (RV) overload (increased RV/left ventricular [LV] ratio, 1.2) and decreased tricuspid annular plane systolic excursion (TAPSE), 18 mm (Figure 1A). The Pulmonary Embolism Severity Index indicated intermediate risk (102 points — class III). Initial therapy with low-molecular-weight heparin (LMWH) in a weight-adjusted dose for 24 hours was ineffective, with symptoms worsening (increase of HR and oxygen demand, without hypotension) and further RV failure progression (RV/LV, 1.3; TAPSE, 16 mm). Thus, our institutional Pulmonary Embolism Response Team (PERT) qualified the patient for catheter-directed mechanical thrombectomy (CDMT).

The procedure was performed *via* right internal jugular venous access obtained with a 12 F vascular sheath. In a first step, selective angiography of RPA and LPA was performed and revealed large central thrombi bilaterally

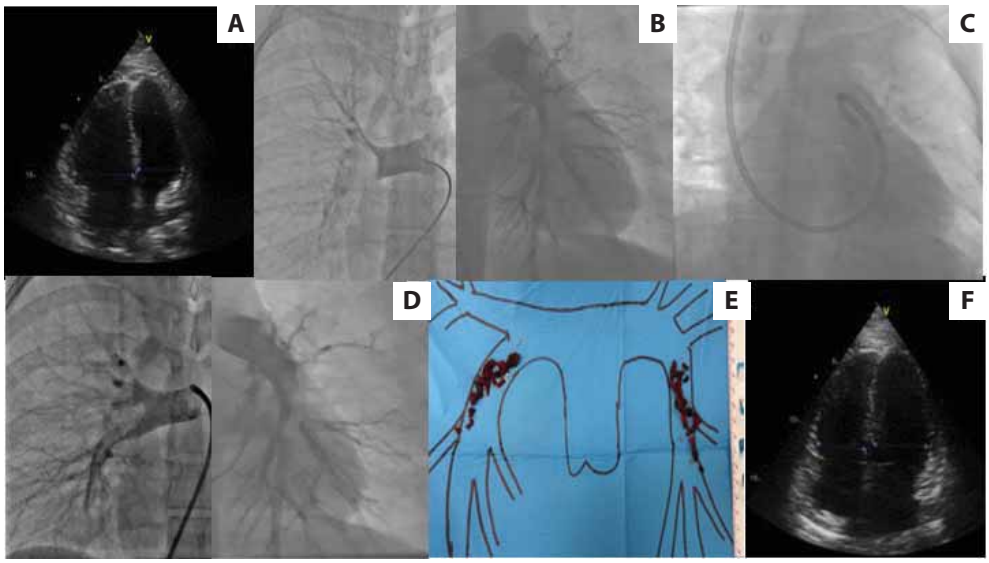

Figure 1. A. Echocardiography (apical four-chamber view) showing enlargement of the right ventricle (RV) before the procedure. **B.** Selective angiography of the right (RPA) and left pulmonary artery (LPA) before the procedure. C. The catheter-directed mechanical aspiration thrombectomy procedure with the Lightning 12 system in the LPA. **D.** Selective angiography of the RPA and LPA after the procedure. **E.** An image of the removed clots. **F.** Echocardiography (apical four-chamber view) showing normalization of the RV dimension after the procedure

mainly in the RPA and left lobar pulmonary arteries (Figure 1B). Subsequently, a 115 cm CAT12 HTORQ 12 F catheter of the Lightning 12 system (Penumbra, Alameda, CA, US) was inserted (the first use in Poland) through a 90-cm, 12 F Flexor sheath (Cook Medical, Bloomington, IN, US). Several repeated aspirations were performed in branches of the RPA and LPA with separator-wire-facilitated thrombus fragmentation (Figure 1C, E). The procedure resulted in significant bilateral thrombus burden reduction and a drop in mean pulmonary artery pressure from 28 mm Hg to 22 mm Hg, with no complications. However, increased stiffness of the device (due to a larger diameter of the catheter) resulted in worse maneuverability. The periprocedural blood loss was 300 ml. Twenty-four hours after CDMT, the patient's HR was 84 bpm, RR was 22/min, and SaO_2 was 94% on nasal cannula with a flow rate of 3 l/min, respectively. Echocardiography showed significant RV function improvement (RV/LV ratio, 0.9; TAPSE, 24 mm) (Figure 1F), and troponin I decreased to 0.08 ng/ml. LMWH was continued 48 hours after CDMT, and then warfarin was introduced (the patient was diagnosed with antiphospholipid syndrome).

The recent development of advanced endovascular therapies aims to reduce PE-related morbidity and mortality [1, 2]. CDMT involves devices for mechanical thrombus fragmentation and aspiration to quickly relieve the blockage and restore pulmonary blood flow with a subsequent improvement in the hemodynamic status in intermediate or high-risk PE [3, 4]. The key innovations of the novel Lightning 12 system are the new CAT12 catheter, with a large 0.131" lumen and angled tip for an additional circumferential sweep, and the lighting control unit with a pressure/flow sensor system and high-frequency valves. These innovations aim to efficiently regulate aspiration and prevent excessive blood loss [5]. Our case showed that CDMT with the use of the Lightning 12 system was well tolerated and effective.

Article information

Conflict of interest: None declared.

Funding: None.

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Sacubitril-valsartan: Hope or hype in the battle against cardiotoxicity due to cancer treatment?

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DOI: 10.33963/KP.a2022.0166

Received:
July 8, 2022

Accepted:
July 10, 2022

Early publication date:
July 14, 2022

In cardio-oncological practice, the term "cardiotoxicity" is defined as a new-onset myocardial injury/dysfunction mostly in response to a variety of chemotherapeutic regimens including anthracyclins and trastuzumab, etc. [1–3]. In their recently published article, Sławiński et al. [1] have reported the favorable impact of sacubitril-valsartan (an angiotensin receptor-neprilysin inhibitor) on the recovery of left ventricular (LV) systolic dysfunction associated with cancer treatment in a patient with breast cancer. Accordingly, we would like to have further information regarding that interesting case and make a few comments on cardiotoxicity and its management with sacubitril-valsartan in cancer survivors.

In particular, "early (incipient) cardiotoxicity" due to cancer treatment denotes an emerging subclinical myocardial dysfunction characterized by a persistent elevation in a variety of conventional markers, including cardiac troponins, natriuretic peptides along with subtle abnormalities in echocardiographic parameters (presenting with a fall in global longitudinal strain [GLS] and occasionally a slight reduction in the left ventricular ejection fraction [LVEF] value) [2–4]. However, when these initial changes go unnoticed following a cardiotoxic regimen, "early cardiotoxicity" generally progresses to "overt cardiotoxicity" that usually emerges as a form of late cardiomyopathy (universally characterized by a 10% reduction in the LVEF value from baseline to an ultimate value of <53% [or 50]) [2–4]. Apparently, the patient [1] initially seemed to have a pattern of "early cardiotoxicity" (presenting with slight reductions in LVEF and GLS values) that ultimately ended up with overt cardiotoxicity in the later stages. However, the diagnosis of "cardiotoxicity" traditionally needs also to be substantiated with persistent increases (mostly weeks apart) in troponins and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels [2, 3]. Accordingly, we are interested in the levels and elevation patterns of these biomarkers (and other markers, if any) in the patient, particularly during the "early cardiotoxicity" stage.

Importantly, timely initiation of cardioprotective agents (statins, β-blockers, etc.) might have the potential to block or slow down the progression of "early cardiotoxicity" [2–4]. However, despite the initiation of these agents (all were previously documented to have significant favorable effects in this context [4]), the patient was reported to ultimately progress to late cardiomyopathy [1]. Accordingly, we are interested in the dosages and duration of the use of these cardioprotective agents.

More interestingly, sacubitril-valsartan seemed to induce a substantial LV reverse remodeling leading to a significant increase in the LVEF value of the patient with overt cardiomyopathy [1]. This might imply that this agent might be even more efficacious when initiated during the stage of "early cardiotoxicity" and might potentially prevent transition to late cardiomyopathy. Therefore, LVEF [1] might have been already stabilized and preserved if the patient had received sacubitril-valsartan much earlier. Specifically, we also wonder whether the LV reverse remodeling, besides presenting with an increase in LVEF, also constituted a significant reduction in LV volumes and diameters, which potentially suggests that the improvement in LV systolic functions might be more likely due to the permanent effects of sacubitril-valsartan on LV morphology at the myocellular level rather than its favorable impact on preload and af-

terload. Notably, side effects of this agent (including severe hypotension) might be more prevalent in fragile cancer survivors with a reduced physiological reserve and need close monitoring. Did the patient report any side effects regarding sacubitril-valsartan?

Finally, cardiotoxicity in the patient might have been primarily due to trastuzumab therapy [1] which is well known to trigger a completely reversible form of cardiomyopathy in this context [2, 3]. Therefore, there also exists a potential possibility that LV reverse remodeling in the patient might have been a spontaneous and coincidental phenomenon rather than a consequence of sacubitril-valsartan therapy.

In conclusion, the authors [1] should be commended for their didactic case. However, further studies are needed to establish the value of sacubitril-valsartan in the prevention and management of cardiotoxicity due to cancer treatment.

Article information

Conflict of interest: None declared.

Funding: None.

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Sacubitril-valsartan: Hope or hype in the battle against cardiotoxicity due to cancer treatment? Authors' reply

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DOI: 10.33963/KP.a2022.0196

Received:
August 18, 2022

Accepted:
August 18, 2022

Early publication date:
August 18, 2022

We read with interest the letter to the editor entitled "Sacubitril-valsartan: Hope or hype in the battle against cardiotoxicity due to cancer treatment?" by Yalta et al. [1]. It emphasizes the importance of the problem we are discussing and contains several important remarks and comments, which we will try to address below.

The authors rightly emphasize the role of biomarkers, such as cardiac troponins and N-terminal pro-B-type natriuretic peptide (NT-proBNP), in diagnosing cardiotoxicity of oncological treatment (especially early cardiotoxicity). In our patient, both biomarkers remained normal throughout the therapeutic process, which could have a calming effect but is not a reason for not using cardioprotection in the case of worsening left ventricular (LV) systolic function [2]. The presence of elevated levels of troponin suggests that myocardial cell death has already occurred, raising questions about its role as an effective early marker of cardiotoxicity. Therefore, also the new European Society of Cardiology recommendations on the definition of cardiotoxicity mainly focus on echocardiographic parameters [3].

Our patient was initially treated with ramipril 5 mg twice daily, bisoprolol 2.5 mg twice daily, and atorvastatin 20 mg daily. Such treatment was used for 3 months before the implementation of mineralocorticoid receptor antagonist (MRA) and angiotensin receptor-neprilysin inhibitor (ARNI).

The question of whether the earlier use of sacubitril-valsartan could have prevented the deterioration of left ventricular ejection fraction (LVEF) remains unanswered for the time being, as it would require a study on this subject. However, it remains a possibility because the drug has a hemodynamic effect — it relieves LV by reducing the afterload, as well as the effect on myocellular level, as evidenced in our patient by the significant reduction in LV end-systolic and end-diastolic dimensions, along with its volumes. Fortunately, the patient tolerated ARNI well, which was accompanied by reduced blood pressure values (about 100/60 mm Hg), but it did not cause any discomfort.

The patient was treated for breast cancer with doxorubicin and cyclophosphamide, then paclitaxel, and finally trastuzumab. Yalta et al. [1] indicate that the decrease in LVEF could be caused mainly by trastuzumab, which is well known to induce a completely reversible form of cardiomyopathy, therefore, the improvement observed in our patient was spontaneous after temporarily withholding trastuzumab, and not after administration of sacubitril-valsartan.

We agree with this and, based on one clinical case, we would not dare to state that it was certainly only an ARNI effect. Even in our conclusions, we emphasize that ARNI may be a valuable component of cardioprotective regimens.

This has been indirectly confirmed by the observations of Canale et al. [4], who used ARNI in a group of patients in whom, due to the cardiotoxicity of various chemotherapy regimens, it was necessary to use the wearable cardioverter defibrillator (WCD) [4]. It resulted in protecting patients against life-threatening ventricular tachyarrhythmias in the period of low LVEF, as well as in significant improvement in LVEF seen in the long term. As a result, the patients did not require implantation of an implantable cardioverter-defibrillator (ICD).

Perhaps we will see the results of randomized trials on this subject conducted in numerically appropriate groups of patients. Until

then, we believe that our clinical vignette provides valuable data on the complex problem of cardiotoxicity.

Answering the title question of Yalta et al. [1], on the basis of the research conducted so far, by paraphrasing the words of Camilli et al. [5] we can say that "In ®Entresto we trust".

We hope that further research will confirm our expectations, which will contribute to better prognosis in cancer patients.

Article information

Conflict of interest: None declared.

Funding: None.

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Hypereosinophilic syndrome and eosinophilic granulomatosis with polyangiitis: Eosinophilic-associated inflammatory conditions with a challenging diagnosis and treatment

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DOI: 10.33963/KP.a2022.0172

Received:
July 19, 2022

Accepted:
July 20, 2022

Early publication date:
July 22, 2022

In their recently published clinical vignette, Gil and Zaręba [1] reported an interesting case of hypereosinophilic syndrome (HES) with Loeffler's endocarditis in a 60-year-old female with a medical history of eosinophilia, asthma, allergic rhinitis, chronic obstructive pulmonary disease, hypertension, coronary artery disease, and embolic stroke, presenting with hemorrhagic stroke and persistent hypoxemia. As eosinophilic-associated inflammatory conditions are an extremely rare heterogeneous group of diseases characterized by high tissue infiltrating and/or circulating eosinophils, which potentially affect multiple organs without a recognized cause [2], we would like to write a short comment.

Allergic bronchopulmonary aspergillosis may present with an elevated eosinophil count, and the diagnosis does not require positive *Aspergillus spp.* cultures and can be based on immediate skin test reactivity to *Aspergillus* antigens and elevated levels of serum IgG and IgE antibodies [3]. However, multiple organ damage combined with eosinophilia should trigger a search for an alternative diagnosis, as was done in the reported case [1].

Hypereosinophilic syndrome is a collection of disorders characterized by chronic hypereosinophilia (circulating eosinophil count $>1.5 \times 10^9$/ml documented on at least 2 occasions) or marked tissue eosinophilia, as well as clinical manifestations specifically related to or assumed to be the result of eosinophilia for which no other cause can be found. This is a broad definition that includes all patients with clinical manifestations of eosinophilia regardless of the underlying etiology. In patients with suggestive symptoms, the diagnostic "step-by-step" procedure for HES begins with screening for the various secondary causes of (reactive) eosinophilia (secondary HES), followed by a careful investigation of primary, clonal subtypes (primary or myeloid HES). The latter investigation is based mainly on a variety of molecular and cytogenetic analyses. The prognosis of the disease varies depending on the HES variant and the availability of targeted therapy [2].

The diagnosis of HES requires differentiation from eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg–Strauss syndrome. This is another uncommon primary systemic necrotizing vasculitis of the small vessels that frequently affects the skin and other organ systems and manifests as eosinophilia, asthma, and pulmonary infiltrates. Eosinophilic granulomatosis with polyangiitis typically manifests itself in three partially overlapping phases: a prodromal phase dominated by respiratory tract symptoms, asthma, and rhinosinusitis; a second phase characterized by blood eosinophilia, tissue infiltration of eosinophils, and organ inflammation; and a third phase characterized by systemic necrotizing vasculitis. Palpable purpura, peripheral nervous system involvement (e.g., mononeuritis multiplex), scleritis, alveolar hemorrhage, glomerulonephritis, pulmonary infiltrates, pleural effusion, urticarial papules, eosinophilic tubulointerstitial nephritis, and eosinophilic myocarditis are the main clinical manifestations of EGPA. Anti-neutrophil cytoplasmic antibodies (ANCA) are often directed against myeloperoxidase and can be found in up to 40% of patients with EGPA [2].

Clinical signs and symptoms of HES and EGPA greatly overlap. In the analysis by Maino

et al. [4] arterial thrombosis was more common in HES than in EGPA. On the contrary, in EGPA there was a predominance of venous thrombosis. It should be noted that, especially in young patients, thrombophilia tests should be performed. Furthermore, the occurrence of asthma is less common in EGPA, while splenomegaly and lymph node enlargement are more frequent in HES [2]. We wonder if the patient [1] presented other signs and symptoms suggestive of HES and EGPA, and if she had ANCA, molecular or cytogenetic tests performed.

We would also like to draw attention to the damage to the cardiac structure caused by eosinophils. Unfortunately, despite great improvements in management and survival, some patients continue to develop severe cardiomyopathy and heart failure [2, 5]. We would like to emphasize that cardiologists play a fundamental role in the early detection and treatment of these conditions. Loeffler's endocarditis is the cardiac manifestation of HES, which is usually diagnosed by transthoracic and/or transesophageal echocardiography. These imaging modalities are also used later in follow-up for prognostic stratification and to assess response to treatment. New imaging modalities, such as strain imaging and particularly cardiac magnetic resonance imaging sequences, give the possibility of identifying minor changes and discriminating between inflammatory and fibrotic processes. Endomyocardial biopsy can be useful in problematic situations, but it may be ineffective due to sampling difficulties, eosinophil degranulation, or fibrosis replacement and must always be performed after a careful assessment of the risk-benefit balance [5]. The nature of clinical manifestations arising from eosinophil-related organ dysfunction should influence the choice of treatment [2].

In conclusion, eosinophilic-associated inflammatory conditions should be treated by experienced physicians; however, cardiologists are crucial in the early diagnosis and management of the accompanying cardiomyopathy. We would also like to emphasize the importance of ANCA, molecular or/and cytogenetic testing.

Article information

Conflict of interest: None declared.

Funding: None.

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Differential diagnosis in a patient with eosinophilia, hypoxemia, and heart failure. Author's reply

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DOI: 10.33963/KP.a2022.0185

Received:
August 3, 2022

Accepted:
August 3, 2022

Early publication date:
August 5, 2022

We have read with great interest a recent article by Konsek-Komorowska et al. [1] entitled "Hypereosinophilic syndrome and eosinophilic granulomatosis with polyangiitis: Eosinophilic-associated inflammatory conditions with a challenging diagnosis and treatment". The letter was a response to our clinical vignette discussing a female patient with a history of eosinophilia, asthma, allergic rhinitis, chronic obstructive pulmonary disease, hypertension, coronary artery disease, embolic and hemorrhagic strokes, persistent hypoxemia, and heart failure. Based on this constellation of findings, the patient was diagnosed with hypereosinophilic syndrome (HES) with Loeffler's endocarditis.

The authors of the commentary discussed in detail the clinical presentation and differential diagnosis in eosinophilic-associated inflammatory conditions. The overlap of HES and eosinophilic granulomatosis with polyangiitis (EGPA) syndromes was brought up. In that context, several questions have been raised regarding other signs and symptoms presented by that patient.

The initial differential diagnosis included allergic bronchopulmonary aspergillosis, eosinophilic pneumonia, and EGPA. An infectious work-up was performed, and pulmonology, hematology, allergy, and rheumatology specialists were consulted. Rheumatologic studies were negative. A bone marrow biopsy was not performed, but molecular studies of the peripheral blood were negative for myeloproliferative neoplasms. Eosinophilic pneumonia was excluded based on the absence of eosinophils in the bronchoalveolar lavage. EGPA appeared less likely due to a lack of other clinical signs or symptoms of the disease. There was no evidence of venous thrombosis or systemic vasculitis; kidney function was preserved and thrombophilia tests, as well as anti-neutrophil cytoplasmic antibodies, were negative. Computed tomography showed significant mediastinal and hilar lymphadenopathy without splenomegaly.

Subsequently, the patient was diagnosed with allergic bronchopulmonary aspergillosis. The final diagnosis of HES with Loeffler's endocarditis was made after performing cardiovascular magnetic resonance that demonstrated left ventricular systolic dysfunction, as well as extensive fibrosis and fatty infiltration of the left ventricle.

In conclusion, diagnosing and treating eosinophilic-associated inflammatory conditions is challenging and requires a multidisciplinary approach [1]. Since cardiac involvement, common both in HES and EGPA, is associated with adverse outcomes, early detection is of utmost importance [3, 4]. Cardiac magnetic resonance imaging with its recent development in myocardial tissue characterization appears essential in this process [5].

Article information

Conflict of interest: None declared.

Funding: None.

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Fetal echocardiography is not only used to detect congenital heart disease but also to monitor fetuses, especially those with different pathologies

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DOI: 10.33963/KP.a2022.0159

Received:
June 21, 2022

Accepted:
June 21, 2022

Early publication date:
June 27, 2022

We have read with great interest the article by Buczyński et al. [1] entitled "Life-threatening congenital hydropericardium in a newborn with Down syndrome, transient abnormal myelopoiesis, Hirschsprung disease, and a ventricular septal defect". We would like to congratulate the authors on detecting prenatally a congenital heart defect and on their effort to publish such an interesting case. It is worth commending the authors' clinical experience with successful neonatal pericardial drainage. On the other hand, we would like to point out that some procedures described as "urgent" could have been predicted and "planned".

The authors presented the case of a neonate with prenatally diagnosed ventricular septal defect (VSD) with hydropericardium, who was delivered by Cesarean section at 37 weeks of gestation. Unfortunately, the manuscript lacks basic data, as mentioned below: gestational age at diagnosis of the congenital heart defect, more detailed description of fetal cardiovascular function during gestation, number of fetal echocardiographic examinations and strategy of fetal monitoring, fetal cardiovascular physiology changes with gestation, and indication for Cesarean section. As recommended by the Polish Society of Prenatal Cardiology, every congenital heart defect detected prenatally should be monitored using fetal echocardiography [2]. Contemporary fetal echocardiography focuses not only on the analysis of the heart structure but also on the assessment of its function. The evaluation of the fetal heart function is most valuable in the third trimester of pregnancy, just before delivery [2]. If the fetus, especially with a congenital heart defect or functional anomalies, is monitored for several weeks using fetal echocardiography, and the last examination is performed shortly before delivery, the condition of the newborn in the first hours and days of extrauterine life can be reliably predicted [2, 3]. Life-threatening congenital hydropericardium is an extremely rare condition and may be caused by infection, cardiac masses like tumors, and other chronic diseases, as mentioned by the authors. In each case, the cause of hydropericardium should be thoroughly searched. Hydropericardium could also occur along with genetic disorder such as Down syndrome. More detailed serial echocardiographic monitoring could have also had additional advantages — abnormal results of echocardiographic examination could be the indication for expanded "genetic ultrasonography", and other signs (VSD was noticed) of trisomy 21 could have been detected earlier. Any congenital heart defect detected prenatally should be closely examined, even during the COVID-19 pandemic [4]. In the current era of dynamic development of prenatal cardiology [5], the absence of at least two echocardiographic examinations in the case of timely prenatal detection of a congenital heart defect should be highlighted and reconsidered next time. Probably, we should pay more attention to the prenatal period of human life. Maybe in this case the postnatal tachycardia, central cyanosis, and transient hypoxia could have been avoided.

Article information

Conflict of interest: None declared.

Funding: None.

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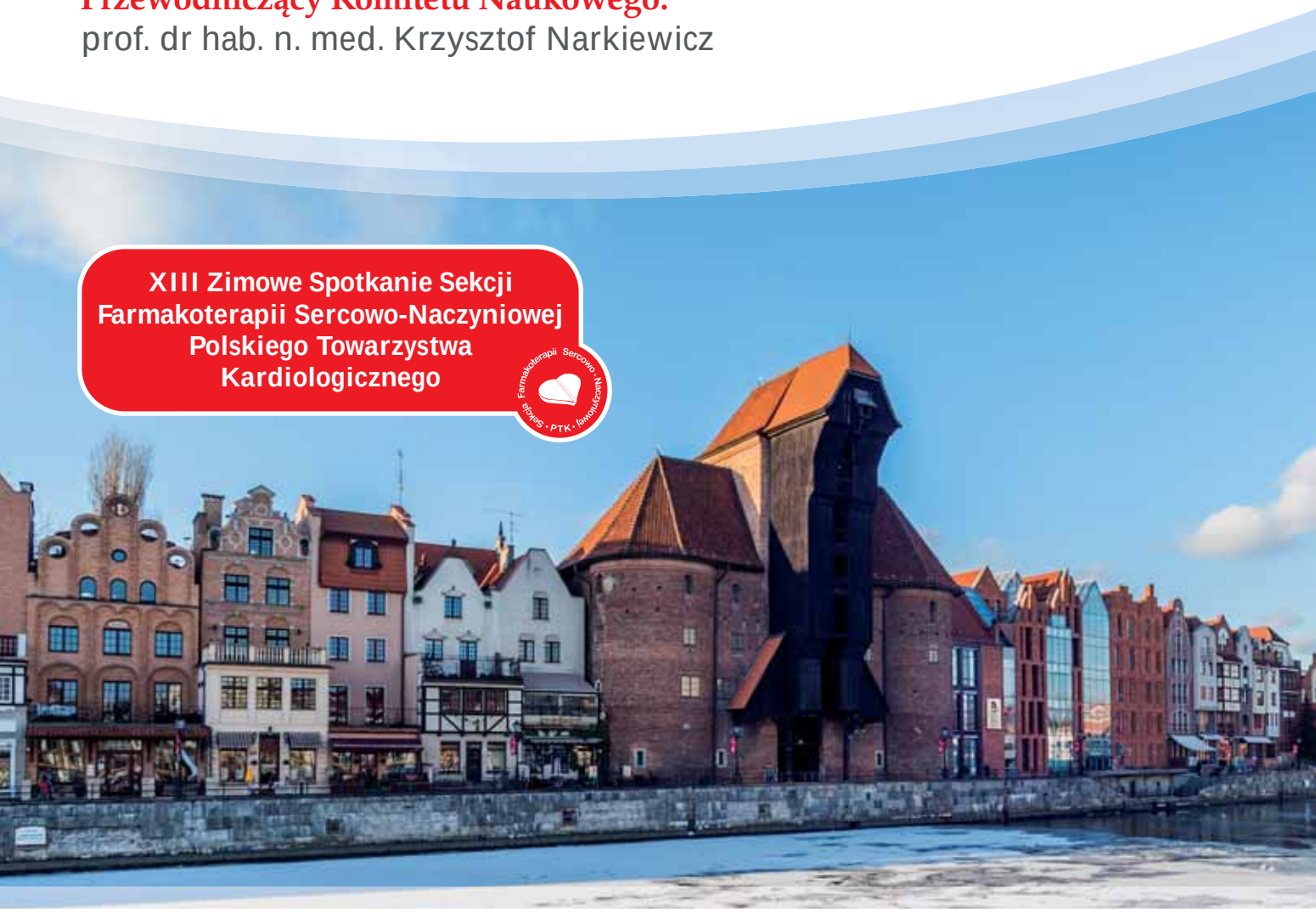

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