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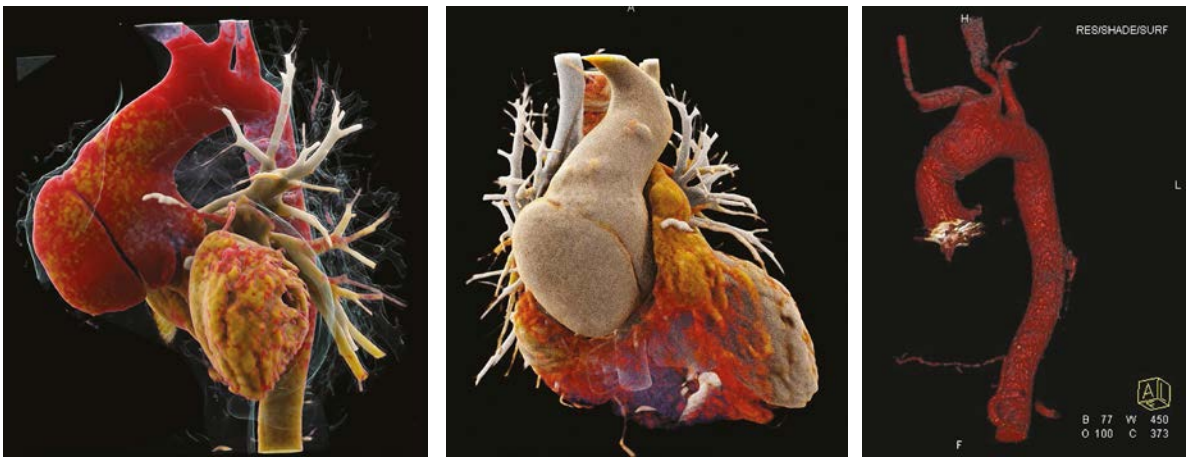

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Address
Kardiologia Polska
ul. Prądnicka 80, bud M–IX, p. 41
31–202 Kraków
phone: +48 126143004
e-mail: kardiologiapolska@ptkardio.pl
www.kardiologiapolska.pl

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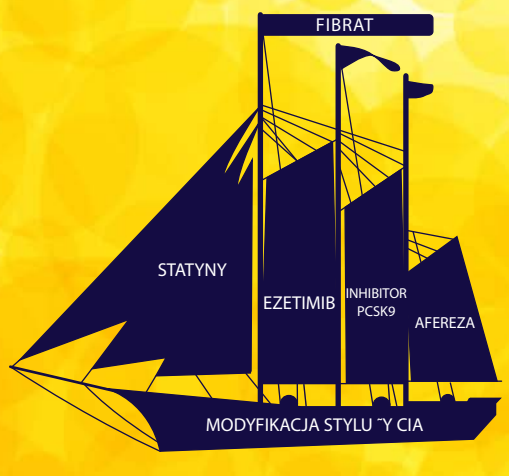

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CLINICAL VIGNETTE

MEMORIAL ARTICLE

Right coronary artery patency as a modulator for unprotected left main PCI risk: myth or reality?

Francesco Burzotta[1, 2], Mila Kovacevic[3, 4], Carlo Trani[1, 2]

[1]Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[2]Università Cattolica del Sacro Cuore, Rome, Italy
[3]Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia
[4]Institute of Cardiovascular Diseases of Vojvodina, Cardiology Clinic, Sremska Kamenica, Serbia

Related article
by Skorupski et al.,
see p. 631

Correspondence to:
Francesco Burzotta, MD, PhD, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore, L.go A. Gemelli 1, 00168 Rome, Italy, phone: +39 06 30154187, e-mail: francesco.burzotta@unicatt.it

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According to the evolving definition for high-risk percutaneous coronary intervention (PCI) [1], unprotected left-main (ULM) disease is recognized as one of the unfavorable features helping to identify high-risk PCI patients. Randomized trials made it possible to highlight the overall coronary artery tree involvement as a potent modulator of PCI efficacy [2] so that only patients with ULM disease and low (≤22) Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score have a class I recommendation for PCI. Nevertheless, remarkable progress in PCI techniques and devices facilitated offering PCI to many ULM patients with a wide spectrum of anatomic complexity [3].

The experience of interventionalists early started to consider the possible "protective" value of right coronary artery (RCA) flow during ULM PCI. Indeed, considering the large region of jeopardized myocardium in the absence of a patent RCA concern about the possible occurrence of hemodynamic deterioration during ULM PCI is justified.

The SYNTAX score provided numbers (proven to be useful for ULM patients) that are influenced by RCA dominance, RCA patency, and RCA disease pattern. For instance, RCA patency disease by itself does not imply a strong SYNTAX score rise. On the opposite, a long, calcified, chronic total occlusion (CTO) dominant RCA lesion has a major impact on the SYNTAX score.

When assessing the impact of RCA features on ULM PCI, the major focus of the past investigations was on RCA CTO. Of note, complex anatomy and CTO are the most frequent reasons for referring patients to CABG [4]. According to the early publication of Capodanno et al. [5], patients with concomitant LM and RCA disease had higher cardiac mortality after LM PCI (17.7% vs 6.7%; $P = 0.056$) than those without RCA disease. Importantly, mortality in patients with RCA CTO was extremely higher (30% vs 6.7%; $P = 0.015$) in comparison to the patients without RCA CTO. Similarly, Migliorini et al. [6] noticed significantly higher 6-month (12.8% vs 3.6%; $P < 0.02$) and 3-year mortality rates (23.6% vs 10.3%; $P < 0.03$) in patients with RCA CTO than in those without RCA CTO. Moreover, RCA CTO was recognized as an independent predictor of 3-year cardiac mortality (HR, 2.15 [1.02–4.05]; $P = 0.043$). In line with these results, Takagi et al. [7] reported that in patients undergoing ULM PCI, cardiac death rate was higher in the presence of residual RCA CTO (HR, 2.163 [1.018–4.597]; $P = 0.045$) at 1466 days of follow-up. Additionally, they showed that recanalization of RCA CTO significantly improves long-term survival ($P = 0.010$).

In such a context, Skorupski et al. [8] assessed the impact of the absent functional RCA support on prognosis of patients undergoing ULM PCI. They applied an original definition of no "RCA support" which included a broader spectrum of patients, not only with RCA CTO but also with significant stenosis or minor RCA. They concluded that long-term all-cause mortality at a median follow-up of 1149 days did not differ among the groups (23% vs 20%;

$P = 0.37$ in patients without and with RCA support, respectively). Moreover, RCA CTO (found in 14.3% of patients) did not increase all-cause mortality.

How to explain these conflicting results of Skorupski et al. [8] in comparison to the previous retrospective trials/registries?

A logical explanation might come from differences in the characteristics of the study population investigated in different studies. Indeed, the relevance of RCA support during ULM PCI is strongly modulated by:

- left ventricular ejection fraction;
- technical complexity of PCI on the left system;
- clinical conditions.

In these regards, the study population enrolled by Skorupski et al. [8] was characterized by a favorable combination of high ejection fraction (mean value around 55%), low SYNTAX score (mean value 21), and low incidence of 3-vessel disease (7.5%). Furthermore, most of the patients were stable and EuroSCORE II (a strong predictor of adverse clinical outcome after PCI as previously reported) [9] was as low as 1.45%. In other words, RCA support failed to impact the outcome of PCI in a "selected" subgroup of ULM patients exhibiting low risk of both acute hemodynamic compromise and late adverse outcome, as compared with other studies. Consequently, the reported findings cannot translate to other patient subsets.

Another important issue is related to the size of RCA (ranging between super-dominant and recessive) and the type of eventually present coronary lesions (ranging between plaques with borderline hemodynamic significance to sub-occlusions and collateralized chronic total occlusions). Skorupski et al. [8] tried to address this issue but the three categories they applied to RCA lesions (recessive, significant stenosis and CTO) cannot entirely describe the relevance of hemodynamic support provided during ULM PCI. According to a recent study [10], in patients with ULM PCI, the performance of PCI on significant (>70%) RCA stenosis during the same hospitalization might reduce 30-day cardiovascular death. All together, these observations call for patient-to-patient decisions which should take into account the feasibility of achieving reasonable levels of revascularization completeness (not to leave unrevascularized stenoses supplying large areas of ischemic myocardium [11]).

As a final remark, it is crucial to highlight the possibility to deal with patients exhibiting extreme challenges like complex, calcific ULM bifurcation disease and very low ejection fraction. In these circumstances:

- a patent RCA can provide minor support so that mechanical circulatory support can be considered to increase procedure safety (moving from high risk to "protected" PCI [12]);
- untreated proximal lesion in a large RCA may imply large residual jeopardized myocardium resulting in impaired late outcome despite successful protected PCI [13].

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Cardiology CathLab-based multispecialty stroke thrombectomy — Poland is moving on!

Iris Q Grunwald[1, 2], Anna Podlasek[2], Rafał Nizankowski[3]

[1]University of Dundee, Chair of Neuroradiology, Department of Radiology, Ninewells Hospital, Dundee, Scotland, United Kingdom
[2]Division of Imaging Science and Technology, School of Medicine, University of Dundee, Dundee, Scotland, United Kingdom
[3]Accreditation Council, National Centre for Health Quality Assessment, Kraków, Poland

Related article
by Pawłowski et al.
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Correspondence to:
Prof. Iris Grunwald, MD, PhD, Imaging Science and Technology, School of Medicine, University of Dundee Nethergate DD1 4HN, Dundee, Scotland, United Kingdom, phone: +44 01382 383000, e-mail: i.grunwald@gmx.net

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There is little doubt that mechanical thrombectomy (MT) is a breakthrough technology that can radically improve outcomes in a substantial fraction of stroke patients. Pawlowski and colleagues wisely stress that: "there is a large unmet need to deliver MT to LVO stroke patients in a timely manner" [1]. Consequently, one has to consider three major elements: LVO + MT + TIME. Introduction of MT to clinical practice raised a hot debate on who is able to perform the procedure and who should be "allowed" to do it. In Poland, but also in other countries, the small number of neuroradiology centers with 24/7 staff on-site was suddenly confronted with large numbers of stroke patients who would be eligible to receive MT [2, 3]. Many argued that other interventionists, namely cardiologists and angiologists, should be involved [4, 5], but uncertainty existed whether the quality of the thrombectomy procedures would be sufficient. The current body of evidence shows that MT results by cardiologist/angiologist do not differ from those in neuroradiology centers [1, 6, 7].

The paper by Pawłowski et al. [1] published in the current issue of *Kardiol Pol* bears excellent news for Poland. The results of their cardiology team, among the first group of 15 LVO patients, was better than required by international consensus — they achieved TICI 2b/3 in 93% of cases while >60% is required, embolization in only 7% while <15% is required and intracranial hemorrhage in 0%, with <10% required. Thus, the important message for health care system organizers is: a thrombectomy center based on a cardiac cath lab service could safely offer a high-quality MT service. Cardiology CathLab-based MT is a truly multispecialty endeavour, as beautifully coined into the "BRAIN Team" concept (Basic CathLab staff, Radiologist, Anaesthesiologist, Interventionalist, stroke Neurologist) by Pawlowski et al. [1].

Interventional cardiologists already provide a fully operational infrastructure with 24/7/365, large volume interventional service for patients with acute myocardial infarction and are highly skilled at reopening occluded arteries [8] — something neurointerventionists rarely do outside of AIS treatment [9], arguably making them better suited to perform safe and effective MTs. In the end, having proven skills and practical knowledge of performing mechanical thrombectomy is much more important than having a certain medical specialty degree, which was also echoed in the recent position paper on stroke thrombectomy by the Chamber of Physicians (Poland) of February 25, 2021 [10].

The concept of TIME is often misunderstood, with some research data showing, in highly selected patients, benefit from late MT procedures. Many neurologists argue that the best delivery of MT is limited to so-called neuroradiology centers of excellence with neurosurgical backup on-site and neuroradiologists that are highly experienced in the cerebral vasculature. However, the rationale and ethics of transporting patients to an outside hospital when MT is feasible locally are questionable, especially if we remind ourselves of the thrombolysis trials where every 6 min delay results in a 1% lesser chance of a good outcome [11]. Kunz et al. showed that expediting MT by

10 minutes is estimated to gain each patient a median of 106 additional days of functional independence [12]. Interfacility transport inevitably delays treatment and has been shown to be associated with worse neurological outcomes [7]. In the MR Clean Registry, every hour that passes from stroke onset to EVT start resulted in a 5.3% decreased probability of functional independence (modified Rankin Scale, 0–2) [13]. In the stent retriever arm of the SWIFT Prime trial, time from symptom onset to reperfusion of 150 minutes led to a 91% estimated probability of functional independence. This decreased by 10% over the next hour, and by 20% with every subsequent hour of delay [14].

LVO causes (focal) brain ischemia. This is in many ways analogue to global brain ischemia as a result of cardiac arrest. There is no doubt among specialists and lay people that, in case of a cardiac arrest, cardio-pulmonary resuscitation is needed as quickly as possible. No one in this scenario would suggest referring patients (with arrested blood flow to the brain) to regional resuscitation centers of excellence with the best-trained staff. Unfortunately, in LVO, where only a part of the brain suffers from impaired blood flow, the unfeasibility and unethical aspect of a remote center of excellence are not generally appreciated. It is difficult to understand why. Stroke thrombectomy is a cerebral resuscitation. Currently, the shortage of MT centers and operators results in a severe under-treatment of the Polish LVO stroke population. With about 0.5 thrombectomy-capable centers per 1 million population [2, 15], the MT rate in 2020 was only approximately 3.1%, compared to approximately 7.5%–8.1% in the neighboring Czech Republic and Germany (both systems have cardiologist participation) [6, 7, 16]. With a 38 million population, this difference translates into a shortage of approximately 1700 MTs and at least 800 disabilities that could have been prevented in Poland each year [2].

To answer the clearly unmet need to deliver effectively this level 1A-evidenced treatment to Polish patients, there is no doubt that more cardiac cath labs engaged in revascularization of LVO in stroke are needed today. Pawłowski and his team [1] show a progressive way forward that is beneficial for patients, the population and the healthcare system.

Article information

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REVIEW

Fatty acids and aortic valve stenosis

Oscar Plunde, Magnus Bäck

Translational Cardiology, Center for Molecular Medicine, Department of Medicine Solna, Karolinska Institutet and Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden

Correspondence to:
Prof. Magnus Bäck, MD, PhD, Karolinska University Hospital, Department of Cardiology, M85 141 86 Stockholm, Sweden, phone: +46858580000, e-mail: magnus.back@ki.se

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ABSTRACT

Aortic valve stenosis (AVS), a valvulopathy that threatens life quality and longevity, in particular in an aging population. Yet no medical treatment is to date available emphasizing the need for more mechanistic insight into the disease to provide future treatment targets. Obesity and genetic variants within genes involved in lipid metabolisms and lipoprotein (a) have emerged as risk factors for AVS as these variants have significant genome-wide associations. The metamorphosis of the aortic valve to severe calcification involves lipid infiltration, inflammation, and oxidative stress which promotes further calcification in a viscous cycle in tandem with biomechanical factors that trigger further recruitment of inflammatory cells. The resolution of inflammation is an active and regulated process which therefore offers new possible targets. Fatty acids serve as substrate for many lipid mediators involved in the resolution of inflammation which may counterbalance the inflammation by promoting macrophage-mediated healing leading to a dampened inflammatory response. Recent data have put fatty acids in the spotlight as an important mechanism in the development of aortic valve disease. This review discusses possible mechanisms exerted by fatty acids in the context of AVS to facilitate future search for therapeutic targets.

Key words: calcification, inflammation, lipid mediators, valvular heart disease

Kardiol Pol 2021; 79, 6: 614–621

INTRODUCTION

The most common indication for valve replacement is aortic valve stenosis [1] which affects over 10% of the population over 75 years of age [2]. Despite substantial advances, including reduced risks associated with surgical and catheter based techniques [3, 4], potential advantages for alternatives to aortic valve intervention are stressing the need for a hitherto undiscovered effective medical treatment.

Several factors pave the way to severe AVS including modifiable lifestyle risk factors, genetic predisposition and congenital development defects e.g., bicuspid aortic valve. Risk factors associated with increased AVS incidence include diabetes [5], renal disease [6] and obesity [7]. The importance of the latter as a causal factor for AVS is illustrated by results from Mendelian Randomization (MR), in which body mass and fat mass indexes exhibit stronger associations with AVS compared with other cardiovascular diseases [8]. The genetic variants located in proximity to LPA and FADS1 have a genome-wide association with AVS [9, 10] and coronary artery disease [11] and acting through affecting levels of lipoprotein (a) (Lp(a)) and fatty acids, respectively. Interestingly, MR studies have shown a stronger association of these genetically determined risk factors with AVS compared with other cardiovascular diseases [12, 13]. Each of these predisposing factors may influence the gradually fibrocalcific remodeling taking place locally in the aortic valve which ultimately may lead to a significant reduction in the aortic valve opening (Figure 1). The stenotic aortic valve has both hemodynamic and structural consequences to the left ventricle and if left untreated comes with a poor prognosis [14].

Given that obesity and specific lipids pathways are emerging as major risk factors for AVS, the present review aims to focus on fatty acids and their possible contribution to AVS development, by deciphering possible disease mechanisms affected by fatty acids and to evaluate the therapeutic potential within these pathways.

INFLAMMATION

Inflammation is a key component of the fibrocalcific remodeling in AVS and partakes throughout the continuum of the disease, driven by lipids. The commonly used inflammation marker C-reactive protein (CRP) is associated with AVS [15]. Calcified aortic valve tissue is a source for local production of cytokines e.g. interleukin-1β [16] and tumor necrosis

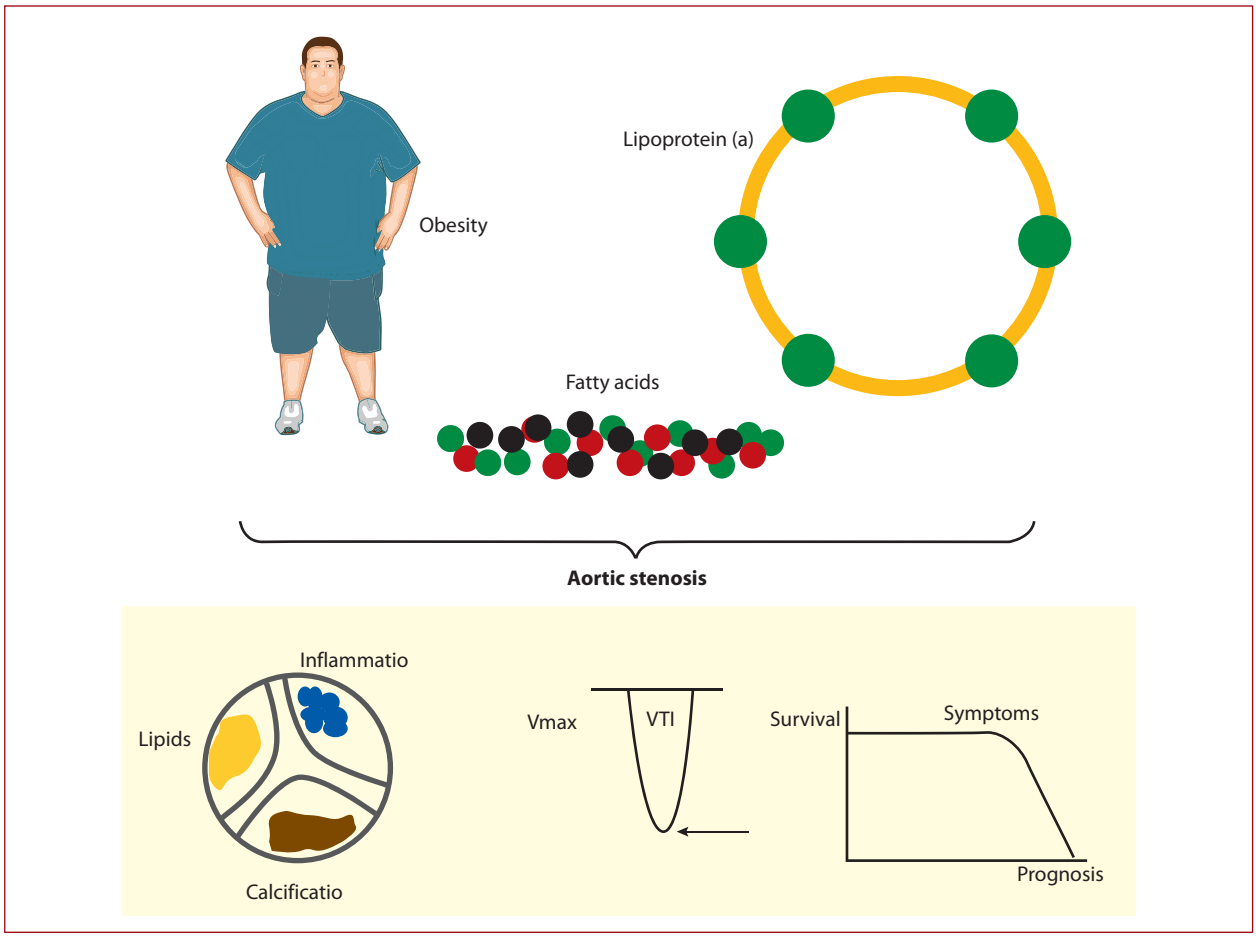

Figure 1. Key components paving the way to aortic valve stenosis. Obesity, lipoprotein (a) (Lp[a]) and fatty acids are risk factors for aortic valve disease. These factors influence the pathophysiology locally in the aortic valve and partake in the progressive fibrocalcific remodelling by lipid and fatty acid alterations and affect severally inflammatory pathways ultimately leading to calcification. Lp(a) and fatty acid desaturase (FADS) are under the influence of genetic variants located in proximity to LPA and FADS1 which have shown genome-wide associations with aortic valve stenosis. The calcified aortic valve progressively turns immobile resulting in reduced valve orifice leading to increased transaortic peak velocity and pressure gradients, measured by echocardiography. When severe, only aortic valve replacement may ease the poor prognosis otherwise encountered ahead

factor-α (TNF-α) [17], as well as the proinflammatory lipid mediators prostaglandins [18] and leukotrienes [19, 20]. Increased mechanical stress potentiates the inflammation by endothelial cell activation which further propagates the influx of inflammatory cells [21] and lipids [22].

Inflammatory mediators give rise to a disturbance in the balance of synthesis and degradation of extracellular matrix (ECM) [23]. Malfunctioning ECM and matrix vesicles play a role in the initial stage of calcification acting as the foundation for dystrophic microcalcification [24, 25]. In response to inflammatory stimuli, valvular interstitial cells express osteogenic genes like bone morphogenic protein 2 (BMP2), Runx2, in addition to intracellular adhesion molecule 1 (ICAM-1), which also suggest a tight link between inflammation and calcification [26]. The coupling between inflammation and AVS also involves increased oxidative stress [27, 28]. Finally, the initiation of the fibrocalcific process leads to increased mechanical stress, which acts to further propagate inflammatory pathways to drive the AVS disease forward.

Importantly, these processes are chronic, indicating a non-resolving aortic valve inflammation. The resolution of inflammation is a highly regulated process that balances the pro-inflammatory response by halting the influx of inflammatory cells, as well as promotes clearance of apoptotic polymorphonuclear leukocytes and immune cell efflux from sites of inflammation [29]. The balance between pro-inflammatory and pro-resolving mediators has gained great interest since it was found to be an actively regulated process and showed promise for future treatment targets [30]. In human aortic valves, the macrophage M2 phenotype is associated with the expression levels of proresolution mediating receptors [19] and pattern recognition receptors [31]. Fatty acids and in particular polyunsaturated fatty acids (PUFAs) are key components in this balance since they serve as substrates for lipid mediators exerting

contradictory proinflammatory and pro-resolving actions potentially promoting progression and healing, respectively, of the AVS pathological circuits.

FATTY ACIDS

Fatty acids have been of interest for decades since Danish scientists discovered the beneficial cardiovascular effects of a diet rich in marine omega-3 fatty acids [32, 33]. Greenland Inuits had lower mortality rates from myocardial infarction despite similar amount of total fat intake as Americans and Danes. The studies marked the beginning of the hypothesis that omega-3 PUFAs could be beneficial due to the favorable change in the ratio of downstream inflammatory and thrombotic mediators such as arachidonic acid (AA) and eicosapentaenoic acid (EPA). Following the release of AA (C20:4n6) from the membrane by phospholipase A2, AA acts as a substrate for classical pro-inflammatory mediators. Catalyzed by the constitutively expressed cyclooxygenase (COX)-1 and the inflammation induced COX-2, prostaglandins (PGs) and thromboxane A (TXA) are formed [34]. COX-derived products generally have pro-inflammatory and pro-thrombotic properties exemplified by TXA2 which facilitates clot formation. This is also supported by the effect of non-steroidal anti-inflammatory drugs (NSAIDs) [35]. AA also gives rise to leukotrienes via the 5-lipoxygenase (5-LO) pathway which promote inflammation in cardiovascular disease via leukotriene B4 (LTB4) among others [36]. Omega-3 EPA (C20:5n3), on the other hand, may act as a competing substrate for COX which results in the production of PGI3 with a similar beneficial profile as PGI2 produced with AA as substrate [37] and TXA3 which is less potent than TXA2 [38, 39]. In tandem, 5-LO catalyzed leukotriene production results in LTB5 which shows less activity compared to AA derived LTB4 and may therefore act as a competitive ligand for the common receptor resulting in a halted inflammatory response [40].

CIRCULATING PUFAS AS BIOMARKERS

High circulating levels of PUFAs measured as biomarkers have been associated with a higher chance of healthy aging [41]. Subjects within the highest quintile of docosapentaenoic acid (DPA), EPA and a composite of EPA, DPA and docosahexaenoic acid (DHA) concentration displayed significantly improved disease-free aging compared to the lowest quantile. This suggests that a relatively high concentration of omega-3 fatty acids is needed to achieve beneficial effects. Interestingly, alpha-linolenic acid (ALA) was neutral for any association with unhealthy aging which suggests that the consumption of fish rich in EPA, DPA and DHA rather than the precursor is needed. This could also be a result of diverse individual genetics since the downstream modification of ALA is dependent on catalytic enzymes affected by polymorphisms within the gene encoding those enzymes. However, ALA measured in extracted phospholipids from plasma or total plasma was inversely correlated with fatal coronary heart disease as was DHA and EPA (a trend in total plasma) [42]. Importantly, a diet rich in seafood has been associated with other factors considered included in a healthy lifestyle [43] and the risk for residual confounding can therefore not be neglected. Also, shifting the balance of the omega-3/omega-6 ratio was not interrogated and hence the results might have been impacted by lower omega-6 PUFAs rather than higher omega-3. However, a recent large meta-analysis suggested that higher circulating levels of the omega-6 PUFA linoleic acid (LA) associate with a lower risk of CVD and CVD mortality [44].

To our knowledge, associations of PUFAs in phospholipids extracted from plasma and AVS specifically only come from one genome-wide association study (GWAS) [10]. In pooled results from two previous studies, LA and ALA were inversely associated with aortic valve calcium (AVC), a predecessor of AVS. Furthermore, AA but not EPA was associated with AVC in addition to AVS.

PUFAS IN THE AORTIC VALVE

The pro-inflammatory and pro-resolution mediators can act locally making it reasonable to not only seek associations in the plasma but also locally in the valve. Indeed, lipids are present in aortic valves [45]. In calcified valves, higher amounts of oxidized lipids are found. The composition of PUFAs in aortic valves has been unknown until recently. Measured by gas chromatography as a percentage of total analyzed fatty acids, aortic valves contain high amounts of saturated palmitic acid (C16:0) and omega-9 oleic acid (C18:1n9). The most abundant PUFAs were linoleic acid (LA, C18:2n6), AA (C20:4n6) and DHA (C22:6n3) [46]. Interestingly, in a paired analysis comparing non-calcified and calcified parts within the same valve, the content of DHA was lower and gamma-linolenic acid (GLA) was higher in the calcified parts. This observation, which is summarized in Figure 3, strongly supports that aortic valve fatty acids are altered during AVS development.

GENETIC DETERMINATION OF AORTIC VALVE PUFA METABOLISM

Not only dietary intake determines the phospholipid composition but also genetic variants within genes encoding key enzymes in the metabolism of PUFAs. Of particular interest in the context of AVS are variants within the gene cluster in proximity to fatty acid desaturase (FADS) located on chromosome 11. FADS is a family of enzymes catalyzing the insertion of double bonds on PUFAs at specific positions. FADS1 encodes the delta-5-desaturase (D5D) activity enzyme that catalyzes the insertion of a double bond at carbon 5 yielding AA from dihomo-γ-linolenic acid (DGLA, C20:3n6) and EPA from eicosatetraenoic acid (ETA, C20:4n3). FADS2, located in the proximity of FADS1, encodes the delta-6-desaturase (D6D) activity enzyme that catalyzes the insertion of a double bond at carbon 6 yielding γ-linolenic acid (GLA, C18:3n6) from linolenic acid (LA, C18:2n6) and stearidonic acid (SDA, C18:4n3) from a-linolenic acid (ALA,

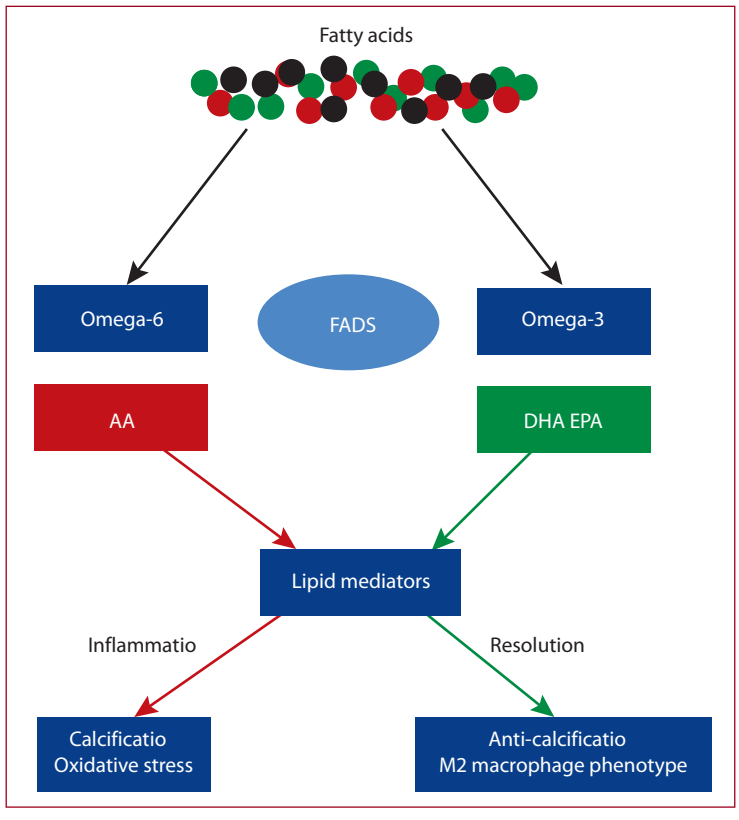

Figure 2. Metabolism of fatty acids by desaturase enzymes encoded by FADS. Rate-limiting enzymes encoded by fatty acid desaturase (FADS) 1/2 are important in the production of polyunsaturated fatty acids that may be used for the production of lipid mediators. The omega-6 fatty acid arachidonic acid (AA) gives rise to mediators prone to elicit a pro-inflammatory response which has been shown to increase the risk of calcification-related mechanisms in aortic valves. The omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) on the other and act in favor of a pro-resolution response through downstream lipid mediators. The latter have a beneficial profile in the context of aortic valve calcification by halting the influx of inflammatory cells, clearing apoptotic cells and immune cell efflux

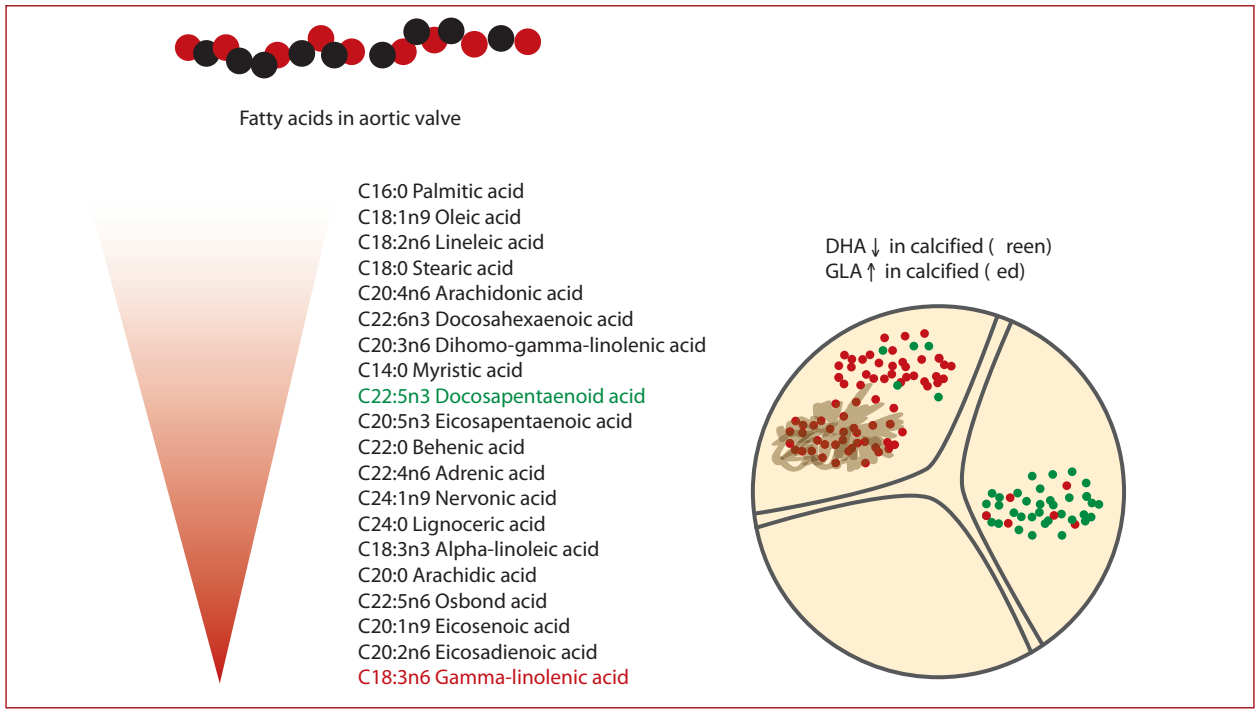

Figure 3. Fatty acids in the aortic valve and the implication in calcification. Levels of fatty acids in aortic valves (measured by gas chromatography as a percentage of total analyzed fatty acids) are presented with decreasing order. Aortic valves contain high amounts of saturated palmitic acid (C16:0) and omega-9 oleic acid (C18:1n9). The most abundant PUFAs are linoleic acid (LA, C18:2n6), AA (C20:4n6) and DHA (C22:6n3). Also, DHA is present in significantly higher levels in non-calcified tissue in contrast to gamma-linoleic acid with higher amounts in calcified tissue

C18:3n3) [47]. FADS3 function remains to be elucidated [48]. These rate-limiting enzymes in the metabolism of PUFAs provide the strongest genetic influence on both PUFA blood concentrations [49] and D5D/D6D activity measured by-product to precursor ratio [50, 51]. Single nucleotide polymorphism (SNP) rs174547 located in an intron within FADS1 demonstrated the most robust association with omega-6 [52] and with omega-3 PUFA ALA [49] in large GWAS studies. The minor C-allele was associated with lower D5D activity (low AA and high DGLA) and D6D activity (low GLA and high LA). SNP within the FADS cluster has further been implicated in several diseases including coronary artery disease [13, 53, 54], stroke [13], diabetes [55] and markers of inflammation in adipose tissue [56].

The minor FADS C-allele of the SNP rs174575 is associated with an approximately 10% decreased risk of AVS in a GWAS [10] and similar results in a Mendelian randomization study of the minor FADS C-allele of rs174547 [13]. In the latter study, genetically determined (not including FADS1/2 variants) increased levels of AA was associated with AVS. Importantly, since FADS1/2 variants have been associated with risk factors for AVS [57, 58], it might be difficult to fully account for pleiotropic effects even though rigorous efforts were made and the mechanisms behind these findings remain to be discovered. The genetic impact of FADS may be differently interpreted on a systemic and local level. Specifically, plasma levels of AA and the plasmatic AA to LA ratio were associated with both AVS and AVC [10], whereas neither EPA nor the EPA to ALA ratio exhibited significant associations with these phenotypes. In contrast, FADS-determined fatty acid levels in aortic valves showed the strongest associations with the omega-3 pathways [46].

OMEGA-6 FATTY ACIDS IN AORTIC VALVE STENOSIS

AA lipids are abundant in stenotic aortic valves [45]. Inhibiting the D5D in mice fed a western diet promotes amelioration of the atherosclerosis burden [59] which support the hypothesis that D5D-generated AA is indeed important for lipid-driven inflammation. Moreover, phospholipase A2 (PLA2) is responsible for making AA available for downstream metabolism. In aortic valves, PLA2 activity was associated with calcification and calcification-associated gene expression including BMP, osteopontin and alkaline phosphatase [60]. Also, COXs have been tightly linked to aortic valve calcification where upregulation of COX-2 leads to calcification [18, 60, 61]. Furthermore, upregulation of 5-lipoxygenase which catalyze the first step in the cascade of leukotriene biosynthesis is upregulated in calcified compared to non-calcified regions in aortic valves [20]. The cysteinyl-leukotriene LTC4 is a potent stimulator of in vitro calcification of human valvular cells [20]. Additionally, hyperlipidemic mice with abolished FADS1-expression by anti-sense treatment had increased atherosclerotic burden in tandem with a balance in favor of the pro-inflammatory leukotrienes [62]. This emphasizes that lipid-derived pro-resolution mediators indeed impact AVS related mechanisms and are strongly influenced by the FADS1 genetic variant (Figure 2).

Although most AA-derived lipid mediators are proinflammatory, AA metabolism into lipoxins may balance the AA-induced inflammatory regulation. AA-derived lipoxins exert beneficial effects in murine atherosclerosis [63] and abdominal aortic aneurysms [64] what remains to be explored in AVS. The intricate balance between PUFAs is indeed complex and remains to be completely understood.

In the context of AVS, much is still unexplored but in the search for new therapeutic opportunities, one may link previous work on the mechanisms underlying AVS and PUFAs separately to drive hypothesis. In future work, the diverse effects of omega-6 PUFAs in AVS should not be neglected. In addition to AA, its upstream PUFA DGLA alleviates atherosclerosis and aortic calcification after supplementation in apolipoprotein E deficient mice [65]. This was accompanied by a decreased mRNA expression of adhesion molecules ICAM-1, VCAM-1 and NADPH oxidase subunits, which have all previously been shown to contribute to aortic valve inflammation and oxidative stress-driven calcification [21, 27, 66]. The observed beneficial effect could be the result of increased metabolism of prostaglandin E2 (PGE2) or DGLA itself and should be further evaluated. More recent in vitro studies have shown that DGLA decreases TNF-α independently of COX, suggesting that PGE2 does not account for the whole effect seen in in vivo studies [67]. Furthermore, DGLA dampens interferon-γ induced adhesion molecules in macrophages in addition to increasing PGE1 concentration which itself partly attenuates IFN-γ mediated inflammation [68]. Of importance, IFN-γ has also been shown to partake in the aortic valve calcification [69].

The elongation product of AA Adrenic acid (AdA) shows beneficial pro-resolution effects in a murine peritonitis model [70]. Neutrophils may internalize AdA and when human primary neutrophils were stimulated, a significant reduction in LTB4 was found when AdA was administered. Interestingly, LTB4 is increased in calcified aortic valves [19, 71]. While the role of neutrophils in AVS is poorly understood [72, 73], macrophages, on the other hand, are key players in inflammation and aortic valve calcification. It is therefore important that AdA increases efferocytosis of apoptotic cells by macrophages [70] which could be of importance since apoptotic cells may serve as a nidus for calcification in aortic valves [74].

More studies are needed to fully appreciate the complete effects of the omega-6 fatty acids in valvular inflammation, the above-mentioned studies enlighten the complexity of the often simplified balance between omega-6-derived lipid mediators and raise a novel notion that future therapeutic opportunities of fatty acids may arise also from specific omega-6 PUFAs.

OMEGA-3 FATTY ACIDS IN AORTIC VALVE STENOSIS

AVS patients with a higher omega-3 index locally in the explanted tricuspid aortic valve have echocardiographic signs of a slower AVS disease progression in the retrospective analysis [19]. A possible causality behind these observational human data is supported by the slower progression of murine aortic valve disease when genetically introducing endogenous omega-3 production. These mice have not only increased systemic but also increased valvular omega-3-levels, which reduced valve calcification but also improved the echocardiographic parameters similar to humans with high valvular omega-3 content.

The D- and E-series of resolvins (Rv) derived from DHA and EPA, respectively, have been identified in human aortic valves and raised the notion of these mediators as key omega-3-derived components in the resolution of valvular inflammation. In human aortic valves, both DHA-derived RvD3 and EPA-derived RvE1 are abundant in non-calcified but scarcely found in calcified tissue [19]. The exploration of valvular expression of the receptors for omega-3-derived lipid mediators points showed high levels of mRNA encoding the ChemR23 receptor for RvE1 in human aortic valve tissue. In support of the importance of this, ChemR23-/- hyperlipidemic mice display aggravated aortic valve disease compared with wild type mice [19]. Mechanistic exploration in mouse models and human aortic valves have supported direct valvular effects both as calcification inhibitors and by favoring a pro-resolving immune response by M2 macrophages. Taken together, this emerging evidence points towards the EPA-RvE1-ChemR23 axis a crucial beneficial role of fatty acids in AVS, with possible therapeutic implications [75].

THERAPEUTIC OPPORTUNITIES

As AVS still stands without medical treatment, we encourage the scientific community to include studies on AVS outcome based on PUFA status and PUFA intervention. Future opportunities may arise from both purified PUFAs exemplified by the REDUCE-IT trial, in which the omega-3 fatty acid PUFA decreased all-cause mortality. In addition, future studies should further explore downstream lipid mediators, modifications of the receptors and enzymes in the fatty acid pathway may serve as therapeutic targets. To merely use diet as an intervention has a high risk of inconclusive data and will most likely be more sensitive to individual genetics. Therefore, considering that (i) aortic valves incorporate omega-3 PUFA (ii) high omega-3 fatty acids associate with slower progression av AVS (iii) EPA-derived RvE1 attenuates aortic valve disease in murine models and (iiii) high-dose EPA reduce all-cause mortality in high-risk individuals, provide a rationale for further clinical trials of high-dose EPA supplement as treatment for AVS.

Article information

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REVIEW

Laboratory assessment of the direct oral anticoagulants: who can benefit?

Imo J Akpan[1], Adam Cuker[2]

[1]Division of Hematology/Oncology, Department of Medicine, Columbia University Irving Medical Center, New York, NY, United States
[2]Department of Medicine and Department of Pathology & Laboratory Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States

Correspondence to:
Adam Cuker, MD, MS, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104, USA, phone: +1 (215) 615-6555, e-mail: adam.cuker@pennmedicine.upenn.edu

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ABSTRACT

Direct oral anticoagulants (DOACs), apixaban, dabigatran, edoxaban, and rivaroxaban, are widely used for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation as well as for prevention and treatment of venous thromboembolism. Although DOACs do not require routine laboratory monitoring of anticoagulant effect, there are special situations in which laboratory assessment may be warranted. Laboratory tests include quantitative assays, which measure plasma DOAC levels, and qualitative or semi-quantitative assays, which may be used to screen for the presence of clinically relevant DOAC levels. Indications for laboratory assessment include emergent indications (serious bleeding, urgent surgery, acute ischemic stroke with consideration of thrombolysis) and elective indications (extremes of bodyweight, renal hypo- or hyperfunction, liver disease, suspected drug-drug interactions, suspected gastrointestinal malabsorption). In general, quantitative assays that measure DOAC levels may be used for elective indications, whereas screening assays may be necessary for emergent indications if a quantitative assay with sufficiently rapid turnaround time is not available. Therapeutic ranges for DOACs have not been defined. In lieu of therapeutic ranges, data from pharmacokinetic studies may be used to determine whether a patient's plasma DOAC level falls within the expected range. If it does not, a change in therapy may be warranted. Depending on the clinical scenario, a change in therapy may involve adjustment of the DOAC dose, a change to a different DOAC, or a change to a different class of anticoagulant.

Key words: apixaban, dabigatran, edoxaban, laboratory measurement, rivaroxaban

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INTRODUCTION

Direct oral anticoagulant (DOAC) use has now outpaced vitamin K antagonists (VKAs) for various indications including non-valvular atrial fibrillation and treatment and prevention of venous thromboembolism (VTE) [1, 2]. There are four DOACs approved by the US Food and Drug Administration (FDA) that are available in the US, Europe, and other jurisdictions including the direct thrombin inhibitor, dabigatran, and the direct oral factor Xa inhibitors, rivaroxaban, apixaban, and edoxaban. The properties of these agents are summarized in Table 1.

DOACs have several advantages compared with VKAs. They are associated with lower risk of major bleeding including intracranial hemorrhage [3–7]. They also have a shorter half-life, quicker onset of action, and fewer dietary and drug-drug interactions [8, 9]. An additional advantage of DOACs is that they do not require routine laboratory monitoring of anticoagulant effect because they have a broad therapeutic window and more predictable pharmacokinetics than VKAs. Nevertheless, there are special situations in which DOAC laboratory assessment may be warranted. In this review, we discuss laboratory assays for DOAC assessment and their interpretation. We also describe circumstances in which such testing is warranted and how the results may be used to guide management.

LABORATORY ASSAYS FOR DOAC ASSESSMENT

Laboratory assays for DOAC assessment can be divided into quantitative tests used to measure plasma drug levels and qualitative or semi-quantitative tests used to screen for the presence of clinically relevant drug levels (Table 2).

Table 1. Properties of direct oral anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
References	[46, 47]	[48, 49]	[50]	[51]
Mechanism of action	Thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Bioavailability, %	3	80–100 (when taken with food)	50	62
Time to peak, hour	1–2	2–4	3–4	1–2
Protein binding, %	35	92–95	87	55
Half-life (normal renal function), hour	12–14	5–9	12	10–14
Metabolizers	Major substrate of P-gp	Major substrate of CYP3A4. Minor substrate of P-gp	Major substrate of CYP3A4. Minor substrate of P-gp	Major substrate of P-gp
Renal elimination, %	~80	~66	~27	~50

Abbreviations: CYP, cytochrome P450; P-gp, P-glycoprotein

Table 2. Laboratory assays for direct oral anticoagulants

	Dabigatran	Rivaroxaban, Apixaban, Edoxaban
Quantitative assays for measurement of drug levels	LC-MS/MS dTT ECT ECA	LC-MS/MS Chromogenic anti-Xa assay calibrated with drug of interest
Screening assays for excluding the presence of clinically significant drug levels[a]	TT[b] DOASENSE™[c]	Chromogenic heparin anti-Xa assay[d] DOASENSE™[c]

[a]"Clinically significant drug levels" refers to DOAC levels that may contribute to bleeding risk. The minimum DOAC level that may contribute to bleeding risk is unknown. The International Society on Thrombosis and Haemostasis suggests consideration of DOAC reversal in patients with serious bleeding and a DOAC level >50 ng/ml and in patients undergoing a surgical procedure with high bleeding risk and a DOAC level >30 ng/ml. [b]A normal TT excludes the presence of clinically significant dabigatran levels. A prolonged TT may suggest the presence of clinically significant or trivial levels of dabigatran. [c]A negative DOASENSE™ generally excludes the presence of clinically significant DOAC levels. A positive DOASENSE™ may suggest the presence of clinically significant or trivial DOAC levels. [d]A chromogenic heparin anti-Xa assay below the lower limit of quantitation generally excludes the presence of clinically significant levels of rivaroxaban, apixaban, or edoxaban.

Abbreviations: DOAC, direct oral anticoagulants; dTT, dilute thrombin time; ECA, ecarin chromogenic assay; ECT, ecarin clotting time; LC-MS/MS, liquid chromatography--tandem mass spectrometry; TT, thrombin time

Assays for measuring drug levels

Liquid chromatography with tandem mass spectrometry (LC-MS/MS) is the gold standard for measuring DOAC levels. However, it is not widely available in clinical practice, particularly when rapid turnaround is required [10, 11]. To meet the need for more rapid provision of results, simpler assays with greater availability have been developed for the measurement of dabigatran and direct oral factor Xa inhibitors that demonstrate close correlation with LC--MS/MS (Table 2).

Dabigatran

When the dilute thrombin time (dTT) is used in conjunction with a drug calibrator, there is a strong linear relationship between dabigatran levels across a wide range of concentrations with less accuracy at levels <50–100 ng/ml [10–12]. Ecarin is a metalloprotease from the venom of the saw-scaled viper (*Echis carinatus*) that cleaves prothrombin to the intermediate product meizothrombin, which is inhibited by dabigatran [10–12]. Ecarin-based assays including the ecarin clotting time (ECT) and ecarin chromogenic assay (ECA) demonstrate a strong linear correlation across a wide range of dabigatran concentrations with reduced accuracy at levels <50 ng/ml and >500 ng/ml [10, 12].

Oral factor Xa inhibitors (rivaroxaban, apixaban, edoxaban)

For measurement of rivaroxaban, apixaban, and edoxaban, chromogenic anti-Xa assays calibrated with the drug of interest show a linear correlation across a wide range of concentrations. However, the correlation is less precise at lower drug levels (rivaroxaban level <30 ng/ml, apixaban <15 ng/ml, edoxaban <10 ng/ml) and at levels >500 ng/ml [10–12].

Screening assays to determine whether clinically relevant drug levels are present

In many centers, assays for DOAC quantitation may not be available, particularly on a 24/7 basis. When such assays are not available, qualitative or semi-quantitative assays, which are more readily accessible, may be used to screen for the presence of clinically relevant drug levels (Table 2).

Dabigatran

The thrombin time (TT) is widely available and is exquisitely sensitive to even minor, clinically insignificant concentrations of dabigatran. Therefore, a normal TT excludes the presence of clinically significant levels of dabigatran, whereas a prolonged TT may indicate the presence of clinically significant or trivial levels of drug [13]. DOASENSE™ is a urine dipstick that provides a rapid qualitative assessment of the presence of dabigatran and is only available in Europe [11, 14]. Like the TT, a negative dipstick generally excludes the presence of clinically significant plasma drug levels but a positive result cannot distinguish between clinically relevant and trivial plasma levels of dabigatran.

Table 3. Expected steady-state peak and trough direct oral anticoagulants (DOAC) concentrations

DOAC	Dose	Peak (ng/ml) 5th–95th percentile	Trough (ng/ml) 5th–95th percentile	References
Dabigatran	150 mg bid	64–443[a]	31–225[a]	[52, 53, 54]
Rivaroxaban	2.5 mg bid	28–70[b]	6–37[b]	[48]
Rivaroxaban	20 mg daily	184–343[a]	12–137[a]	[53, 55]
Apixaban	5 mg bid	69–321[a]	34–230[a]	[53, 56]
Edoxaban	60 mg daily	91–321[a]	31–230[a]	[53, 57]

Adapted from Hindricks et al. [53].

[a]In patients taking a DOAC for atrial fibrillation. [b]In patients taking a DOAC for secondary prevention of acute coronary syndromes

Oral factor Xa inhibitors (rivaroxaban, apixaban, edoxaban)

Chromogenic anti-Xa assays calibrated with heparin show less linearity and are therefore not suitable for quantification of oral factor Xa inhibitors. However, a heparin anti-Xa level below the lower limit of quantitation is generally sufficient to exclude clinically relevant drug levels [10, 11]. As with dabigatran, DOASENSE™ can be used to screen for oral factor Xa inhibitors. A negative dipstick generally excludes the presence of clinically significant plasma drug levels whereas a positive result may indicate the presence of clinically relevant or trivial levels of oral factor Xa inhibitor.

Prothrombin time and activated partial thromboplastin time

Dabigatran and the oral factor Xa inhibitors prolong the prothrombin time (PT) and activated partial thromboplastin time (APTT) in a dose-dependent manner. In general, the APTT is more sensitive to dabigatran and the PT is more sensitive to oral factor Xa inhibitors. Among oral factor Xa inhibitors, the PT and APTT are more sensitive to rivaroxaban and edoxaban than they are to apixaban. However, neither the PT nor APTT shows sufficient linearity to be suitable for DOAC quantitation. Moreover, the PT and APTT may remain normal in the presence of clinically relevant DOAC levels, depending on the sensitivity of the reagent [13]. Therefore, the PT and APTT cannot be relied upon as screening tests to exclude the presence of clinically significant drug levels.

HOW TO INTERPRET DOAC LEVELS

In order to interpret a DOAC level correctly, it is useful to know when the drug was last taken. When possible, a peak and trough level should be drawn because expected plasma drug levels have been defined for these time points (Table 3) [12]. However, there are situations in which it may be necessary to check a randomly timed level (e.g. in a patient with emergent bleeding) or in which it may not be possible to determine the time of last ingestion (e.g. in an unconscious patient).

Although several studies have demonstrated a relationship between DOAC levels and clinical outcomes [15], therapeutic ranges have not been defined for DOACs and a strategy of dose-adjustment to target certain drug levels has not been tested in clinical trials. In lieu of therapeutic ranges, it is useful to consider the expected steady-state peak and trough levels for a given DOAC at a given dose (Table 3), which are based on pharmacokinetic studies [10–12].

The minimal DOAC level that may contribute to bleeding is unknown. Guidance from the International Society on Thrombosis and Haemostasis (ISTH) suggests that reversal may be warranted in a bleeding patient with a level >50 ng/ml or in a preoperative patient with a level >30 ng/ml, but it is important to emphasize that these thresholds are based on expert opinion rather than clinical evidence [16].

INDICATIONS FOR LABORATORY ASSESSMENT OF DOACs

Indications for laboratory assessment of DOACs may be divided into emergent and elective indications. Laboratory assessment for emergent indications must yield results within minutes in order to inform management decisions. At many centers, assays that measure DOAC levels are not available with such a short turnaround time and the clinician must rely on screening assays (Table 2). Conversely, a longer turnaround time of hours to days is acceptable for elective indications, allowing for the use of assays that measure DOAC levels (Table 2), even if they need to be sent out to a reference laboratory.

Emergent indications

Serious bleeding

Patients on DOACs may experience serious or life-threatening bleeding. In such situations, the clinician must make a rapid determination about whether to use a reversal agent. DOAC laboratory assessment can be a useful tool in guiding this decision [17]. If the result of a quantitative assay can be obtained quickly, a drug level >50 ng/ml may be used to justify the administration of a reversal agent, consistent with ISTH guidance [16]. More often, a quantitative assay will not be available with sufficiently rapid turnaround and the clinician will need to rely on a screening assay. In a patient taking dabigatran, a normal TT or DOASENSE™ would be justification for withholding a reversal agent. Similarly, reversal would not be warranted

in a patient taking an oral factor Xa inhibitor with a negative DOASENSE™ or a heparin anti-Xa level below the lower limit of quantification (Table 2).

Incomplete or impermanent reversal has been reported with the DOAC reversal agents, idarucizumab and andexanet alfa. Uncommonly, repeat dosing of a reversal agent may be considered. In such cases, a quantitative assay to measure drug levels may be useful for determining the need for re-dosing [18].

Measurement of a DOAC level in a bleeding patient may also be useful for excluding drug concentrations above the expected range (Table 3), which could be due to accidental or intentional overdose or to a condition resulting in DOAC bioaccumulation (e.g. low body weight, renal or hepatic dysfunction, certain drug-drug interactions).

Urgent surgery

The Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) study showed that DOAC levels generally do not need to be measured before elective procedures. Moreover, some procedures can be performed safely without interruption of anticoagulation [19, 20]. Nevertheless, DOAC laboratory assessment may be helpful prior to certain unplanned, urgent surgeries [19], especially if there is consideration for delaying the surgery or administering a reversal agent [17].

If the result of a quantitative assay can be obtained quickly, a drug level >30 ng/ml may be used to justify postponement of a high bleeding risk procedure or administration of a reversal agent, consistent with ISTH guidance [16]. If a quantitative assay is not available with a sufficiently rapid turnaround, the clinician may need to rely on a screening assay. In a patient taking dabigatran, a normal TT or DOASENSE™ would justify withholding a reversal agent [17]. Similarly, reversal would not be warranted in a patient taking an oral factor Xa inhibitor with a negative DOASENSE™ or a heparin anti-Xa level below the lower limit of quantification (Table 2).

Acute ischemic stroke, consideration of thrombolysis

The American Heart Association/American Stroke Association 2018 guideline recommends against intravenous thrombolysis (IVT) in patients on DOACs who have taken their last dose within the previous 48 hours and have laboratory evidence of residual anticoagulant effect [21]. However, a recent expert review highlights that using time since the last dose of anticoagulation as a surrogate for DOAC activity is not always reliable due to pharmacokinetic variability among patients [22]. The authors recommend proceeding with IVT if at least 48 hours have elapsed since the last DOAC dose and the creatinine clearance is >50 ml/min. If the patient does not meet one or both criteria, DOAC laboratory assessment is recommended. For patients on dabigatran, IVT is only recommended if the dabigatran level is <30 ng/ml or the TT is normal. For patients on an oral factor Xa inhibitor, IVT is recommended if the drug level is <30 ng/ml and may be considered if the drug level is 30–100 ng/ml [22]. Clinical outcome data validating these recommendations are needed.

Measurement of a DOAC level in a DOAC-treated patient with stroke or other thromboembolic events may also be useful for excluding drug concentrations below the expected range (Table 3), which could be due to a condition resulting in low DOAC levels (e.g. high body weight, renal hyperfunction, certain drug-drug interactions, gastrointestinal malabsorption) or to non-adherence. It should be noted, however, that a DOAC level only indicates whether the patient took the prescribed drug in the last 12 to 24 hours. Owing to the short half-life of the DOACs (Table 1), the measurement of DOAC levels is not a useful tool for assessing longer-term adherence.

Elective indications

Extremes of body weight

Patients with extremes of body weight (e.g. <50 kg or >120 kg) had very limited representation in the pivotal trials that led to the approval of the DOACs. There is a theoretical concern that high body weight could be associated with subtherapeutic drug levels whereas low body weight could be associated with DOAC bioaccumulation. Based on these concerns, the ISTH has suggested that DOACs be avoided in patients weighing >120 kg or with a body mass index >40 kg/m^2. If DOACs are to be used in this population, the ISTH recommends measuring DOAC peak and trough levels to ensure that they fall within the expected range (Table 3) [23]. The ISTH has not offered guidance for patients with low body weight.

In spite of these cautions, clinical outcome evidence in patients with extremes of body weight, particularly high body weight, has been largely reassuring. In a meta-analysis and systematic review of 11 randomized controlled trials of DOACs in non-valvular atrial fibrillation and VTE, patients with high body weight did not have a greater risk of thrombosis than those with non-high body weight. Interestingly, patients with low body weight had an increased thrombotic risk, but not an increased bleeding risk compared with non-low bodyweight individuals [24]. In a retrospective analysis of 18,147 patients with VTE treated with DOACs, 6-month readmission for recurrent VTE was not increased in the 13% of patients weighing >120 kg [25]. Another 5-year retrospective study found no difference in VTE recurrence in 133 patients weighing ≥120 kg compared to 1063 patients weighing <120 kg (0.8% vs 1.1%; OR, 0.66; 95% CI, 0.09–5.14; $P = 0.69$) [26]. Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (n = 18,201), a randomized trial comparing apixaban with warfarin for the prevention of stroke in patients with atrial fibrillation, included 1,985 (10.9%) patients weighing ≤60 kg group and 982 (5.4%) patients weighing >120 kg. Apixaban was found to be efficacious and safe in both groups [27].

Although these studies suggest that DOAC laboratory assessment may not be necessary in most adults with low or high body weight, they included few patients weighing <50 kg or >150 kg. Thus, it may be reasonable to consider the measurement of steady-state trough and peak levels in such patients to confirm they are within the expected range (Table 3). If levels are outside the expected range, transition to a VKA should be considered.

Renal hypo- or hyperfunction

All 4 DOACs are partially cleared by the kidneys, with dabigatran being the most reliant (80%) on renal elimination (Table 1) [28]. DOAC levels are therefore inversely related to renal function. For example, in the pivotal trial of dabigatran for atrial fibrillation, subjects with a creatinine clearance of 30–50 ml/min had a 2.29-fold greater dabigatran trough concentration than those with creatinine clearance ≥80 ml/min [15]. Conversely, edoxaban was shown to be less efficacious in patients with atrial fibrillation and very robust renal function (i.e. creatinine clearance >95 ml/min), presumably due to lower plasma drug concentrations [28].

Dosing recommendations in the US FDA labels reflect the importance of renal function on DOAC levels and clinical outcomes [29–32]. Among patients with atrial fibrillation, edoxaban is contraindicated in patients with a creatinine clearance >95 ml/min. Dose-reduction is advised for edoxaban and rivaroxaban if the creatinine clearance is 15–50 ml/min, for dabigatran if the creatinine clearance is 15–30 ml/min, and for apixaban if the patient has at least two of three features (creatinine ≥1.5 ml/min, age ≥80, or weight ≤60 kg) that could contribute to reduced creatinine clearance [33].

While these dosing recommendations apply to patients with chronic kidney disease stages I through IV, there is greater controversy about anticoagulant selection and dosing in patients with stage V chronic kidney disease (creatinine clearance <15 ml/min or on dialysis) as well as in patients with rapidly changing renal function. In such patients, measurement of DOAC peak and trough levels may be useful in guiding management. For example, identification of levels above the on-therapy range (Table 3) may justify changing to a different DOAC that is less reliant on renal clearance, to an entirely different class of anticoagulant such as a VKA, or discontinuation of anticoagulation altogether depending on the clinical context and indication.

Liver disease

All 4 DOACs are variably metabolized by the liver with apixaban being the most reliant (75%) and dabigatran the least reliant (20%) on hepatic metabolism [34] Moreover, decreased albumin synthesis in patients with liver disease may affect levels of the free drug depending on the degree to which each agent is protein-bound (Table 1).

Evidence on the use of DOACs in patients with moderate or severe liver disease is limited. Such patients were excluded from the pivotal clinical trials. Small retrospective studies have been reported [35–37].

The US FDA recommends using the Child-Pugh score to guide dosing. Dose adjustment is not needed for any of the DOACs in patients with Child-Pugh class A (mild hepatic impairment). Caution or avoidance is advised for apixaban, edoxaban, and rivaroxaban in patients with moderate (Class B) or severe (Class C) liver disease [29–32, 34]. Prescribing instructions differ in other jurisdictions including Europe and Canada.

If a DOAC is to be used in a patient with moderate or severe liver disease, steady-state peak and trough levels may be useful for confirming that drug concentrations are within the expected range (Table 3). If a level is above the on-therapy range, it may be advisable to change to a different DOAC that is less reliant on the liver for its metabolism or to change to a different class of anticoagulant (e.g. VKA, low molecular weight heparin).

Suspected drug-drug interactions

An important advantage of DOACs over VKAs is that DOACs have fewer drug-drug interactions. Nevertheless, DOACs are substrates of cytochrome p450 (particularly CYP3A4) as well as p-glycoprotein (P-gp) and drugs that inhibit or induce these systems may affect plasma DOAC concentrations [33, 38, 39]. CYP3A4 is important for metabolizing apixaban (20%–25%) and rivaroxaban (50%), but not dabigatran or edoxaban. Dabigatran and edoxaban are major substrates and apixaban and rivaroxaban are minor substrates of P-gp [39] (Table 1).

Drug interactions can affect DOAC levels and, in turn, may influence clinical outcomes. A study of the Taiwanese national insurance database showed that concurrent use of dabigatran, rivaroxaban, or apixaban with amiodarone, fluconazole, rifampin, or phenytoin was associated with increased major bleeding [39, 40]. The FDA labels for DOACs acknowledge the risk posed by drug-drug interactions by recommending avoidance or dose-reduction with concomitant use of certain medications [29–32].

In addition to avoidance or dose-reduction, measurement of drug levels may serve as a useful strategy for guiding management. Steady-state peak and trough levels in the expected range (Table 3) may provide reassurance that it is safe to continue a given drug combination. Conversely, a drug level outside of the expected range may suggest the need to adjust the dose of the DOAC, change to another DOAC that is less likely to have a potent interaction with the concomitant medication, change to a different class of anticoagulant (e.g. VKA), or stop the concomitant medication.

Suspected gastrointestinal malabsorption

A number of conditions could potentially be associated with malabsorption of DOACs including bariatric surgery, short-gut syndrome, inflammatory bowel disease, and other disorders of the gastrointestinal tract.

In a study of 9 patients who had undergone roux-en-y gastric bypass, the median peak dabigatran concentration was only 34.6 ng/ml, well below the expected range (Table 3) [41]. Another study compared peak DOAC levels in 18 bariatric surgery patients and 18 controls. Five (28%) patients in the bariatric group and 0 in the control group had peak levels below the expected range. All 5 patients with low levels were taking rivaroxaban. Other pharmacokinetic studies suggest reduced rivaroxaban absorption after sleeve gastrectomy or gastric banding [42].

The aforementioned pharmacokinetic evidence notwithstanding, it remains uncertain whether reduced DOAC levels in bariatric surgery patients translate to inferior outcomes. A recent observational study of patients on oral anticoagulation for atrial fibrillation compared outcomes in 1,673 bariatric surgery patients with 155,619 non-bariatric patients. The incidence of ischemic stroke/systemic embolism (0.83 vs 1.32 per 100 person years; HR, 0.62, 95% CI, 0.31–1.22; $P = 0.17$) and major bleeding (5.30 vs 4.87 per 100 person years; HR, 1.05, 95% CI, 0.80–1.37; $P = 0.73$) was similar between the 2 groups [43].

There is scant information regarding DOAC absorption in other conditions. One small study demonstrated potentially reduced dabigatran and rivaroxaban levels in patients with short-gut syndrome [44]. We are not aware of evidence on DOAC levels in other malabsorptive disorders including inflammatory bowel disease, celiac disease, or small bowel bacterial overgrowth.

If a patient with suspected gastrointestinal malabsorption is treated with a DOAC, it may be reasonable to measure steady-state peak and trough levels. If the levels are below the expected range (Table 3), suggestive of DOAC malabsorption, a change to a different anticoagulant such as a VKA may be warranted [45].

CONCLUSION

Although DOACs do not require routine laboratory monitoring of anticoagulant level, there are special circumstances in which laboratory assessment may be helpful in guiding management. Indications for laboratory assessment of DOACs may be divided into emergent (serious bleeding, urgent surgery, acute ischemic stroke) and elective (extremes of bodyweight, renal hypo- or hyperfunction, liver disease, suspected drug-drug interaction, suspected gastrointestinal malabsorption).

Our approach to patients with an emergent indication for laboratory assessment is summarized in Figure 1. If available with sufficiently rapid turnaround time, a randomly timed quantitative assay that measures plasma DOAC levels should be ordered. If a quantitative assay is not available,

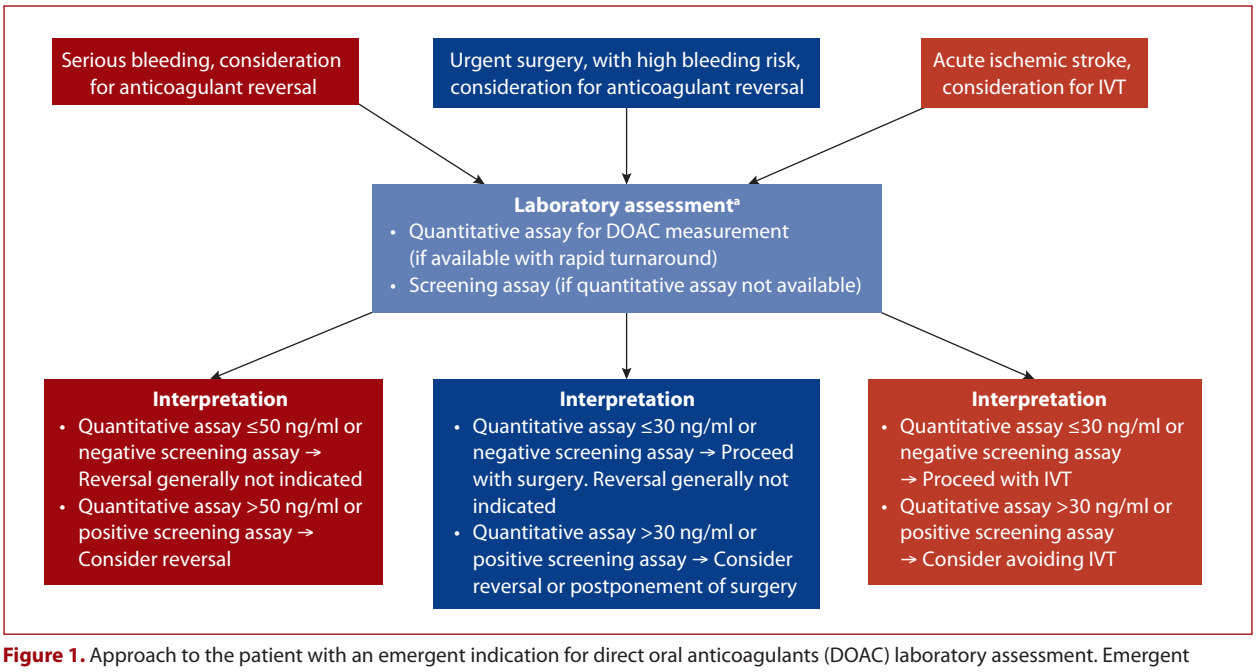

Figure 1. Approach to the patient with an emergent indication for direct oral anticoagulants (DOAC) laboratory assessment. Emergent indications for DOAC laboratory assessment include serious bleeding or urgent surgery with consideration for anticoagulant reversal or acute ischemic stroke with consideration for IVT. In a patient with an emergent indication for DOAC laboratory assessment, a randomly timed DOAC level should be measured using a quantitative assay. If a quantitative assay with sufficiently rapid turnaround time is not available, a screening assay should be used. In patients with serious bleeding and a DOAC level ≤50 ng/ml or a negative screening assay, anticoagulant reversal is generally not warranted. However, if the DOAC level is >50 ng/ml or a screening assay is positive, reversal should be considered depending on the type and severity of the bleed [16]. In patients who require urgent surgery with high bleeding risk, reversal is generally not warranted if the DOAC level is ≤30 ng/ml or a screening assay is negative. However, if the DOAC level is >30 ng/ml or a screening assay is positive, reversal or postponement of surgery should be considered depending on the nature and urgency of the surgery [16]. In patients with acute ischemic stroke and a DOAC level ≤30 ng/ml or a negative screening assay, IVT is likely to be safe. The maximum DOAC level at which IVT is safe is unknown. We suggest avoiding IVT if the DOAC level is >30 ng/ml or a screening assay is positive [21, 22]. [a]See Table 2 for a list of assays that may be used for laboratory assessment of DOACs.

Abbreviations: IVT, intravenous thrombolysis

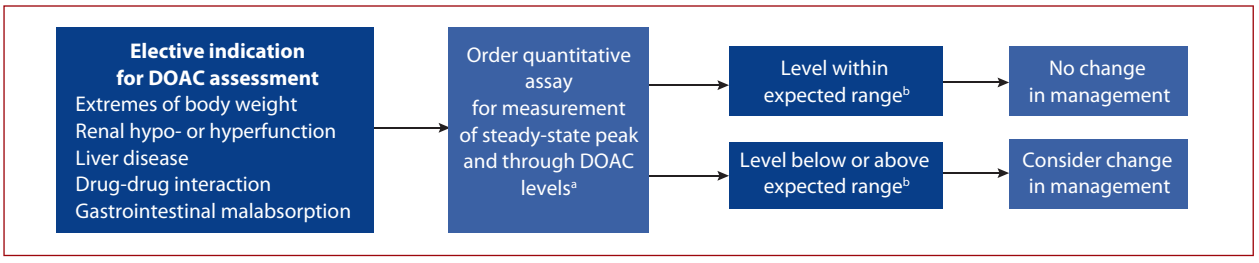

Figure 2. Approach to the patient with an elective indication for direct oral anticoagulants (DOAC) laboratory assessment. In a patient with an elective indication for DOAC laboratory assessment, steady-state peak and trough levels should be measured using a quantitative assay. Levels within the expected range support continuation of present management. A level outside the expected range should prompt consideration of a change in management. Depending on the clinical context, a change in management may include adjusting the DOAC dose, changing to a different DOAC, or changing to an anticoagulant of a different class (see text for further details). [a]See Table 2 for a list of assays that may be used for measurement of DOAC levels. [b]See Table 3 for expected ranges for DOACs taken at standard doses

a screening assay should be requested (Table 2). Threshold DOAC levels above which anticoagulant reversal or avoidance of IVT is warranted have been proposed [16, 21, 22] and are listed in Figure 1. These thresholds are based largely on expert opinion. Clinical outcomes research is needed to refine and validate these thresholds. Development of simple, rapid, point-of-care quantitative assays is also needed so that measurement of plasma DOAC levels for emergent indications can be made accessible to a greater number of patients.

Our approach to patients with an elective indication for laboratory assessment is depicted in Figure 2. Steady-state peak and trough plasma DOAC levels should be measured using a quantitative assay (Table 2). Levels that fall within the expected range (Table 3) support the continuation of current management. Levels that fall outside the expected range should prompt consideration of a change in management, which may include adjustment of the DOAC dose, changing to a different DOAC, or changing to a different class of anticoagulant, depending on the clinical scenario. Further research is needed to better understand the relationship between plasma DOAC levels and clinical outcomes.

While the development of improved assays and additional evidence linking DOAC levels and clinical outcomes is eagerly awaited, clinicians should be aware that laboratory assessment of DOACs using currently available methods may be used to guide the management of their patients in special situations.

Article information

Conflict of interest: AC has served as a consultant for Synergy, has received authorship royalties from UpToDate, and his institution has received research support on his behalf from Alexion, Bayer, Novartis, Novo Nordisk, Pfizer, Sanofi, Spark, and Takeda. IJA has no conflicts to declare.

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ORIGINAL ARTICLE

The impact of right coronary artery support on outcomes of patients with unprotected left main disease undergoing percutaneous coronary intervention

Wojciech Jan Skorupski, Marek Grygier, Aleksander Araszkiewicz, Włodzimierz Skorupski, Stefan Grajek, Małgorzata Pyda, Andrzej Siniawski, Przemysław Mitkowski, Maciej Lesiak, Marta Kałużna-Oleksy

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

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by Burzotta et al.,
see p. 609

Correspondence to:
Wojciech Skorupski, MD, 1st Department of Cardiology, Poznan University of Medical Sciences, Poznań, Poland, Długa 1/2, 61–848 Poznań, phone: +48 61 8549222, e-mail: wojtek.skorupski@wp.pl

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ABSTRACT

Background: Many operators are discouraged from performing left main (LM) percutaneous coronary interventions (PCI) in the absence of right coronary artery (RCA) support due to the increased procedure risk.

Aims: We aimed at assessing the impact of absent functional RCA on prognostic implications in patients undergoing unprotected LM PCI.

Methods: 613 patients underwent LM PCI in our department between 2015 and 2019. Consecutive 385 patients with unprotected LM and at least 1-year follow-up were included in the study. The study population comprosed 272 patients with unprotected left main coronary artery disease (ULMCAD) with dominant RCA, without any significant lesions (Group 1), and 113 ULMCAD patients and without RCA support (Group 2).

Results: In Group 2, 32.7% patients had a significant RCA stenosis, 48.7% had chronic total occlusion (CTO) of RCA, and 18.6% had recessive RCA. Patients in Group 2 were older and had higher prevalence of chronic obstructive pulmonary disease (COPD). SYNTAX Score (median [IQR] 26.0 [20.0–33.0] vs 19.0 [13.0–25.5]; P <0.001) was higher and left ventricular ejection fraction was lower (median [IQR] 50.0 [40.0–60.0]% vs 55.0 [45.0–60.0]%; P = 0.01) in this group. All periprocedural complications did not differ among the groups. Long-term all-cause mortality at a median follow-up of 1149 days did not differ significantly (23% vs 20%; P = 0.37). The long-term mortality in CTO-RCA group was also not significantly different.

Conclusions: Patients with ULMCAD who have undergone LM PCI in the absence of RCA support, compared with those with ULMCAD and RCA support, differed neither in the prevalence of periprocedural complications nor in long-term all-cause mortality.

Key words: left main, percutaneous coronary intervention, right coronary artery support

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INTRODUCTION

Significant left main coronary artery (LM) lesions are detected in about 4%–9% of patients referred for coronary angiography [1, 2]. Advances in the field of percutaneous coronary interventions (PCI) including proper patient selection, improvements in device technology, stenting techniques, and medical therapy post procedure have all made PCI a safe and effective alternative to coronary artery bypass graft (CABG) surgery for unprotected LM coronary artery disease (ULMCAD) [3–5].

PCI in ULMCAD has shown favorable results in large clinical trials and is being widely used worldwide [3, 5–10]. However, many operators are discouraged from performing PCI of the LM in the absence of right coronary artery (RCA) support to the left coronary circulation. This is due to a potentially increased risk of live-threatening periprocedural complications. It is a common belief, that in such cases occurrence of significant complications during PCI of LM can lead to complete deprivation of blood supply to the entire myocardium and may put the patient at an unacceptably high risk.

Chronic total occlusion (CTO) of the coronary artery is the most common reason for referring patients with LM stenosis requiring revascularization to CABG surgery [11–13]

WHAT'S NEW?

To the best of our knowledge, this is the first study presenting the issue of unprotected left main (LM) percutaneous coronary intervention (PCI) in the absence of functional right coronary artery (RCA) in the broad sense. Absence of RCA support was defined as presence of recessive RCA, significant stenosis of RCA or total occlusion of RCA. We found that patients with unprotected LM coronary artery disease PCI with absent RCA support had the same frequency of periprocedural complications and long-term all-cause mortality rate, as patients with unprotected LM coronary artery disease with RCA support. Therefore, PCI of LM could be a safe and effective procedure, also in patients with absence of RCA support.

which explains a relatively low incidence of CTO-RCA in previous randomized LM studies [14]. A similar issue also concerns the absence of RCA support, when a significant stenosis and/or an anatomically recessive variant of RCA is present. The impact of RCA support absence on the outcomes of patients undergoing PCI for unprotected LM disease continues to be of interest. The aim of the present study was to assess whether the absence of RCA circulation carries prognostic implications in patients undergoing unprotected LM PCI.

METHODS

Six hundred and thirteen patients who underwent PCI of LM in our department from January 2015 to June 2019 were included in the initial analysis. Consecutive 385 patients with unprotected LM and with at least 1-year follow-up were included in a prospective registry presented in this paper. Inclusion criteria were: presence of ≥50% diameter stenosis of unprotected LM with or without the involvement of the left anterior descending artery, ostial circumflex coronary artery (LCx), or both of the above. In patients with moderate lesions, the intravascular ultrasound imaging (IVUS) was used to confirm the significance of the stenosis, with a cut-off value of a minimal lumen area of 6.0 mm^2. Terminal patients whose expected survival was less than one year were excluded from the study. The invasive procedures were performed after a Heart Team Meeting with a cardiac surgeon, by an experienced invasive cardiologists, at a high volume referral center with Cardiac Surgery Department on site.

The study group consisted of 272 patients with ULMCAD with dominant RCA, without any significant lesions (Group 1), and 113 patients with ULMCAD and without RCA support (Group 2). Absence of RCA support was defined as the presence of recessive RCA, significant stenosis of RCA, or total occlusion of RCA. A coronary artery system was classified as right dominant when the posterior descending artery (PDA) originated from the right coronary artery, while left dominance was defined as PDA originating from the LCx.

The clinical and angiographic data of these patients, including short- and long-term outcomes were analyzed. Baseline clinical data were collected for each patient at the index procedure. The main procedural data with all periprocedural and in-hospital complications were collected and analyzed. Chronic kidney disease was defined as decreased kidney function established on the basis of glomerular filtration rate <60 ml/min for 3 months or more, calculated by the Cockcroft–Gault equation. All bifurcation lesions were classified angiographically according to the Medina classification [15]. Patients with LM equivalent disease, i.e., distal bifurcation Medina 0–1–1, who presented <70% stenoses of the ostial left anterior descending artery or LCx without any evidence of ischemia in its myocardial distribution, were not included in the study [5]. CTO-RCA was defined as complete occlusion of RCA with 0 flow lasting at least 3 months, regardless of the occlusion location. In patients with coexisting diseases of the LM and the RCA, the decision about the sequence of procedures was up to the operator's discretion. In the group with lack of RCA support the decision to treat LM prior to RCA was made. Patients were treated with the intention to achieve complete revascularization of all their major vessels bearing significant lesions; consequently they were scheduled for future procedures. The decision regarding CTO-RCA treatment was taken after PCI of LM. Therefore, all the analyzed patients in the CTO-RCA group at the time of analysis exhibited residual CTO. Some patients with LM lesions and concomitant RCA disease had RCA PCI prior to LM PCI and were not included in the group with lack of RCA support. Periprocedural myocardial infarction (type 4a) was diagnosed based on European Society of Cardiology Fourth Universal Definition of Myocardial Infarction (2018) [16]. A glycoprotein IIb/IIIa receptor blocker, IVUS, and optical coherence tomography (OCT) were used at the operator's discretion. However, IVUS or OCT imaging were used in 118 (30.65%) patients and were not analyzed in great detail. The antiplatelet regimens were low-dose aspirin (75 mg daily) and clopidogrel (75 mg daily) for a minimum of 6 months after PCI, with the intention of 12 months of dual antiplatelet therapy.

The primary short-term outcome of the study was the composite of in-hospital death or myocardial infarction. Whereas, the long-term study end point was all-cause mortality. The median follow-up was 1149 days (max: 1650 days, interquartile range: 541 days). The data were collected by telephone or based on the official records of the National Health Fund. The registry conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was granted ethics approval by the Institutional Review Board and the Bioethics Committee of the University.

Statistical analysis was performed using STATISTICA 12 (Tibco Software Inc., Palo Alto, CA, USA). A standard descriptive statistics are presented as medians (interquartile range, [IQR]). The normality distribution was analyzed using the Shapiro-Wilk test. The statistical significance of differences was tested with the nonparametric U Mann-Whitney test. Categorical variables were reported as counts or percentages and compared by tests for proportions. The Kaplan-Meier method was used to calculate the survival probability at follow-up. The survival curves were compared with the log-rank test. A two-sided *P*-value of <0.05 was considered significant for all the tests.

RESULTS

From the total cohort of 613 patients who underwent PCI of LM in our department, a total number of consecutive 385 unprotected LM PCI patients, with at least 1-year follow-up (median [IQR] age, 68.0 [62.0–76.0] years, 74.3% male), were included in this analysis. Patient baseline characteristics are presented in Table 1. Patients with absence of RCA support (Group 2) were older (median [IQR], 69.0 [64.0–78.0] vs 68.0 [61.0–74.0] years; *P* = 0.03) and had higher prevalence of COPD (15.0% vs 6.3%; *P* = 0.006). The groups did not differ in other cardiovascular risk factors. Left ventricular ejection fraction (LVEF) was significantly lower in Group 2 (median [IQR], 50.0 [40.0–60.0] vs 55.0 [45.0–60.0]; *P* = 0.01), with no significant differences in other echocardiographic parameters. Euroscore II was consequently higher in Group 2 (median [IQR], 2.01 [1.41–2.89] vs 1.20 [0.82–2.34]; *P* = 0.002).

Coronary artery disease characteristics are shown in Table 2. Of the 113 patients from Group 2, 37 (32.7%) had a significant stenosis of RCA, 55 (48.7%) chronic total occlusion (CTO) of RCA, and 21 (18.6%) recessive RCA. CTO of RCA with collateral circulation from left coronary artery (LCA) was described in 40 (35.4%) patients from Group 2. Moreover, more patients in the Group with absent RCA support had severe disease of the LCx (39.8% vs 27.2%; *P* = 0.02) and calcifications in LM (20.4% vs 11.4%; *P* = 0.02). SYNTAX Score was significantly higher in Group 2 (median [IQR], 26.0 [20.0–33.0] vs 19.0 [13.0–25.5]; *P* <0.001) and these patients more often required the use of two-stent techniques (29.2% vs 17.3%; *P* = 0.009). Patients in Group 2 had more advanced atherosclerotic disease

Table 1. Baseline characteristics by the study group

Variable	Total (n = 385)	Group 1 (n = 272)	Group 2 (n = 113)	*P*-value (Group 1 vs Group 2)
Age, years	68.0 (62.0–76.0)	68.0 (61.0–74.0)	69.0 (64.0–78.0)	0.03
Gender, male	286 (74.3)	198 (72.8)	88 (77.9)	0.30
BMI, kg/m^2	27.8 (24.9–30.8)	28.1 (25.1–31.1)	27.2 (24.3–30.2)	0.24
Hypertension	311 (80.8)	218 (80.2)	93 (82.3)	0.63
Hyperlipidemia	190 (49.4)	135 (49.6)	55 (48.7)	0.86
CKD	133 (34.5)	89 (32.7)	44 (38.9)	0.24
DM	139 (36.1)	101 (37.1)	38 (33.6)	0.51
Stroke/TIA	29 (7.5)	21 (7.7)	8 (7.1)	0.83
COPD	34 (8.8)	17 (6.3)	17 (15.0)	0.006
PVD	54 (14.0)	35 (12.9)	19 (16.8)	0.31
AF	48 (12.5)	35 (12.9)	13 (11.5)	0.71
Cigarette smoking (current)	143 (37.1)	98 (36.0)	45 (39.8)	0.48
Prior MI	181 (47)	127 (46.7)	54 (47.8)	0.84
Prior PCI LAD	91 (23.6)	69 (25.4)	22 (19.5)	0.22
Prior PCI LCx	55 (14.3)	36 (13.2)	19 (16.8)	0.36
Prior PCI RCA	116 (30.1)	101 (37.1)	15 (13.3)	<0.001
Prior CABG	26 (6.8)	17 (6.3)	9 (8.0)	0.54
Clinical presentation				
Stable angina	220 (57.1)	159 (58.5)	61 (54.0)	0.42
Unstable angina	113 (29.4)	80 (29.4)	33 (29.2)	0.97
NSTEMI	37 (9.6)	22 (8.1)	15 (13.3)	0.12
STEMI	11 (2.9)	8 (2.9)	3 (2.7)	0.88
LVEDD, mm	50.0 (47.0-55.0)	50.0 (47.0-55.0)	50.5 (46.0-56.0)	0.65
LVEF, %	55.0 (45.0–60.0)	55.0 (45.0–60.0)	50.0 (40.0–60.0)	0.01
EuroScore II	1.45 (0.88–2.44)	1.20 (0.82–2.34)	2.01 (1.41–2.89)	0.002
SYNTAX Score	21.0 (15.0–28.0)	19.0 (13.0–25.5)	26.0 (20.0–33.0)	<0.001
0–22 (low)	210 (54.5)	176 (64.7)	34 (30.1)	<0.001
23–32 (intermediate)	117 (30.4)	67 (24.6)	50 (44.2)	
≥33 (high)	58 (15.1)	29 (10.7)	29 (25.7)	

Data are presented as number (percentage) of patients or median (IQR) unless otherwise indicated.

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass graft; CKD, Chronic Kidney Disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; LAD, left anterior descending artery; LCx, left circumflex; LVEDD, left ventricular enddiastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RCA, right coronary artery; TIA, transient ischemic attack

Table 2. Coronary artery disease characteristics

Variable	Total (n = 385)	Group 1 (n = 272)	Group 2 (n = 113)	*P*-value (Group 1 vs Group 2)
LM distal	312 (81.0)	219 (80.5)	93 (82.3)	0.68
LM bifurcation	246 (63.9)	172 (63.2)	74 (65.5)	0.68
LM trifurcation	44 (11.4)	27 (9.9)	17 (15.0)	0.15
LM calcification	54 (14.0)	31 (11.4)	23 (20.4)	0.02
LAD disease (not ostial)	192 (49.9)	129 (47.4)	63 (55.8)	0.14
LCx disease (not ostial)	119 (30.9)	74 (27.2)	45 (39.8)	0.02
Protected LM	0 (0)	0 (0)	0 (0)	—
RCA recessive (a)	21 (5.5)	0 (0)	21 (18.6)	<0.001
RCA with significant stenosis (b)	37 (9.6)	0 (0)	37 (32.7)	<0.001
RCA total occlusion (c)	55 (14.3)	0 (0)	55 (48.7)	<0.001
Lack of RCA support (a + b + c)	113 (29.4)	0 (0)	113 (100)	<0.001
CTO of RCA with collateral circulation from LCA	40 (10.4)	0 (0)	40 (35.4)	<0.001
Extent of diseased vessels				
LM plus 2-vessel disease	93 (32.6)	47 (17.3)	46 (40.7)	<0.001
LM plus 3-vessel disease	29 (7.5)	0 (0)	29 (25.7)	<0.001
Bifurcation medina				
1-0-0	85 (22.1)	59 (21.7)	26 (23.0)	0.78
1-0-1	27 (7.0)	22 (8.2)	5 (4.4)	0.20
1-1-0	79 (20.5)	57 (21.0)	22 (19.5)	0.74
1-1-1	55 (14.3)	34 (12.5)	21 (18.6)	0.12

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

Abbreviations: CTO, chronic total occlusion; LAD, left anterior descending artery; LCA, left coronary artery; LCx, left circumflex; LM, left main; RCA, right coronary artery

Table 3. Left main percutaneous coronary intervention (PCI) procedure characteristics and periprocedural outcomes

Variable	Total (n = 385)	Group 1 (n = 272)	Group 2 (n = 113)	*P*-value (Group 1 vs Group 2)
PCI success	383 (99.5)	271 (99.6)	112 (99.1)	0.89
Number of stents	2.0 (1.0–2.0)	1.0 (1.0–2.0)	2.0 (1.0–2.0)	0.12
Total length of implanted stents, mm	33.0 (23.0–48.0)	32.0 (23.0–47.0)	39.0 (23.0–56.0)	0.07
Radiation time, min	15.0 (11.0–22.0)	14.0 (10.0–21.0)	17.0 (11.0–24.0)	0.02
Radiation dose, mGy	1237 (813–1886)	1237 (826–1838)	1238 (734–2161)	0.34
Contrast volume, ml	220 (180–300)	215 (180–300)	230 (180–300)	0.43
Arterial access site				
Radial	238 (61.8)	166 (61.0)	72 (63.7)	0.62
Femoral	147 (38.2)	106 (39.0)	41 (36.3)	
Stenting LM only	48 (12.5)	35 (12.9)	13 (11.5)	0.71
Stenting LM bifurcation				
One-stent technique	257 (66.8)	190 (69.9)	67 (59.3)	0.045
Two-stents technique	80 (20.8)	47 (17.3)	33 (29.2)	0.009
Two-stents techniques	Total, n = 80	n = 47	n = 33	
Crush	27 (33.8)	14 (29.8)	13 (39.4)	0.37
DK-Crush	11 (13.8)	7 (14.9)	4 (12.1)	0.98
Cullote	1 (1.3)	1 (2.1)	0 (0)	0.86
T-stenting	17 (21.3)	10 (21.3)	7 (21.2)	0.99
Provisional stenting	24 (30)	15 (31.9)	9 (27.3)	0.67
Periprocedural outcomes				
Myocardial infarction	18 (4.7)	14 (5.2)	4 (3.5)	0.50
In-hospital Death	2 (0.5)	2 (0.7)	0 (0)	0.36
Stroke	1 (0.3)	1 (0.4)	0 (0)	0.65
Tamponade	2 (0.5)	0 (0)	2 (1.8)	0.09
Pulmonary oedema	1 (0.3)	0 (0)	1 (0.9)	0.29
Dissection of aorta	1 (0.3)	0 (0)	1 (0.9)	0.29
Perforation of femoral artery	1 (0.3)	1 (0.4)	0 (0)	0.65
Contrast induced nephropathy	16 (4.2)	11 (4.0)	5 (4.4)	0.91

Data are presented as number (percentage) of patients or median (IQR) unless otherwise indicated.

Abbreviations: DK-Crush, double kissing crush technique; LM, left main; PCI, percutaneous coronary intervention

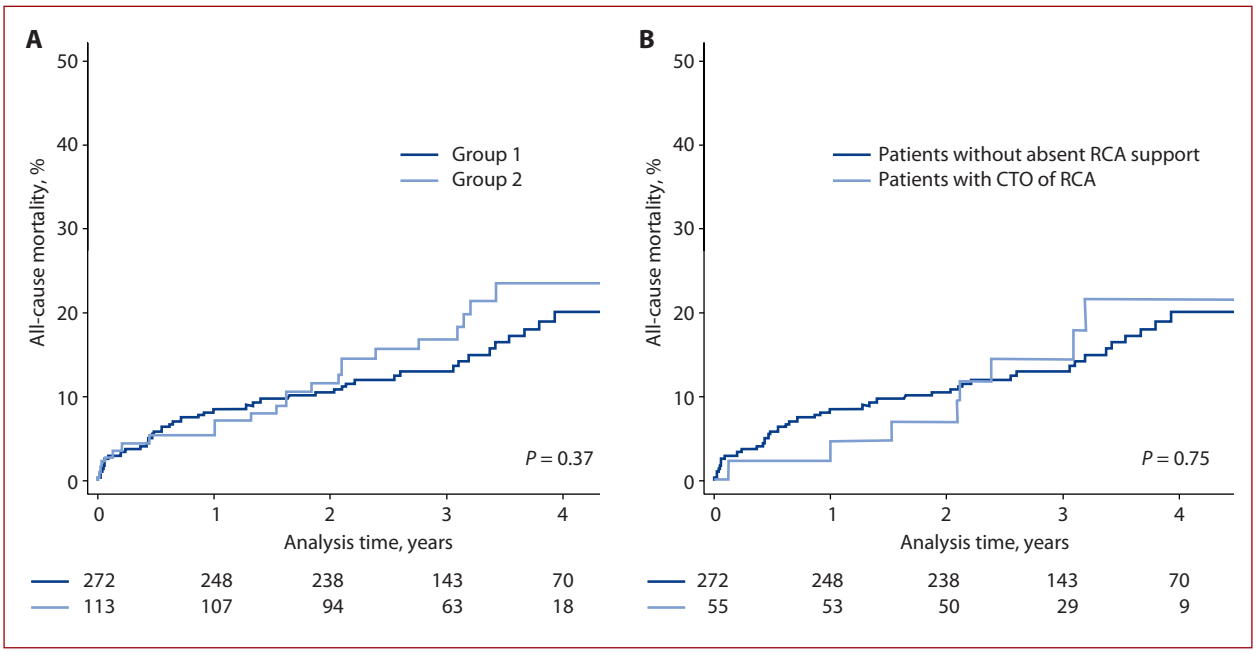

Figure 1. A. Kaplan-Meier analysis of all-cause mortality: Group 1 (patients with dominant RCA and without any significant lesions) vs Group 2 (patients with ULMCAD and absence of RCA support). **B.** Kaplan-Meier analysis of all-cause mortality: patients with RCA support vs patients with CTO of RCA. Abbreviations: see Table 1

and procedure radiation time was higher (median [IQR], 17.0 [11.0–24.0] min vs 14.0 [10.0–21.0] min; $P = 0.02$). Various stenting techniques were used. No significant differences in the frequency of use of selected stenting techniques were observed (Table 3). All LM lesions were stented with second-generation drug-eluting stents (DES). Number of stents and total length of implanted stents did not differ significantly between the two groups. Artery access was similar and it was more often radial approach in both groups. An early success rate was very high (99%) and did not differ between the groups. All LM procedures were carried out without left ventricular assist devices.

Periprocedural clinical outcomes are summarized at the end of Table 3. Frequency of all the perioperative complications (9.7% vs 8.1%; $P = 0.60$) was similar in both study groups. Periprocedural mortality and myocardial infarction (type 4a) did not differ between the groups. Long-term all-cause mortality did not differ significantly (23% vs 20%; $P = 0.37$) between the two study groups either (Figure 1A).

In subanalysis, long-term mortality in patients with CTO of RCA was not different compared to the patients without absent RCA support (22% vs 20%; $P = 0.75$) (Figure 1B). The incidence of perioperative complications in the group of patients with CTO-RCA, compared to the patients without absence of RCA support, was also not different (9.09% vs 8.09%; $P = 0.82$).

DISCUSSION

The main conclusion of the study is the fact that absence of RCA support during PCI of LM was not associated with an increased number of periprocedural complications and in-hospital mortality, and in the presence of such circumstances the procedure is still deemed safe. However, it should be highlighted that there exists a risk of complications and such complex procedures, especially in absence of RCA support, should be performed in high-volume reference centers with quick access to cardiac surgery and the eventual use of left ventricular assist devices [17, 18].

Several papers have been published showing long-term outcomes of PCI of LM in presence of CTO-RCA [19–21], however, they were restricted only to the patients with CTO. The papers did not deal with the lack of RCA support in a situation of recessive or significantly stenotic RCA. To the best of our knowledge, the present study is the first one which raises the issue of unprotected LM PCI in the absence of functional RCA in the broad sense.

The analysis of population from the EXCEL study shows that among 1753 patients included in the study, an occluded RCA at baseline was present in 130 patients (7.4%) [19], which was analogous to our analysis, where CTO-RCA was noted in 14.3% of the patients. In EXCEL, the patients with an occluded RCA more frequently had a peripheral vascular disease, prior PCI, lower LVEF, and a significantly higher SYNTAX Score [19]. However, the frequency of comorbidities in our real-life study was much higher than in the groups from the randomized EXCEL trial, where diabetes and renal insufficiency occurred in 33.6% vs 27.7% and 38.9% vs 14.4% respectively. It must be pointed out that frequency of periprocedural myocardial infarction was similar in both groups. Also, the success of LM angioplasty did not differ in both groups, despite an increased difficulty of the procedures in patients in Group 2.

Absence of RCA support (similarly to CTO-RCA) had no influence on long-term outcomes. The data from our

real-world cohort study are in line with the results obtained in the EXCEL trial, where the presence of occluded RCA was also not independently associated with a higher 30-day, or a 3-year MACCE risk (a composite of death from any cause, e.g. stroke or myocardial infarction) [19]. These results are, however, contrary to these presented by other authors. In the prospective registry (involving 78 patients with CTO-RCA and ULMCAD) that assessed the impact of CTO-RCA in patients undergoing unprotected LM PCI, Migliorini et al. [20] showed that the CTO-RCA is a significant predictor of mortality in patients with ULMCAD undergoing PCI. This major difference may result from older age (71 years vs 69 years) and more likely from lower LVEF (39.0% vs 45%) in the study by Migliorini et al. [20]. Similar findings to those by Migliorini et al. [20] were presented by Takagi et al. [21]. In their study (75 patients with CTO-RCA), cardiac death occurred more frequently in patients with residual CTO-RCA, as compared to those without residual CTO-RCA. Takagi et al. [21] also showed that recanalization of CTO-RCA had a significant impact on long-term cardiac-mortality in patients undergoing ULMCAD PCI, probably due to retrograde coronary circulation in these patients, in the event of LM stent restenosis. It is noteworthy that 5-year all-cause mortality in patients with residual CTO in the study by Takagi et al. [21] was relatively high, reaching up to 31% — this result, however, may be the consequence of a large proportion of patients with chronic kidney disease (60.9%) in this group and the use of first generation DES.

Our study focuses not only on CTO-RCA, which in an obvious way increases SYNTAX Score and correlates with a more severe clinical condition, but unlike other studies, it also deals with the issues of the absence ofthe RCA support and performing high-risk procedures in the presence of only functional left coronary artery. In some cases, the presence of significant stenosis in RCA only slightly affects the SYNTAX Score, but in real-life practice it significantly increases the risk of the procedure. Interestingly, in Group 2 in our study, significantly more frequent use of two-stent techniques was observed, which probably results from advanced atherosclerotic disease in all coronary arteries and higher percentage of LM plus 2- and 3-vessel disease. Higher incidence of diffuse coronary atherosclerosis may result in an incomplete revascularization PCI, and a large survey study in the DES era revealed that incomplete revascularization associated with CTO carries a worse prognosis and a higher risk of death, compared with complete revascularization [22]. In our study, we treated patients with the intention of achieving total revascularization, however, the decision to treat CTO-RCA, as well as severe stenosis of RCA, was undertaken after LM PCI and was performed at a later stage.

In summary, the most important conclusion of our study is that angioplasty in patients in the absence of RCA support is a safe procedure that does not significantly increase the incidence of complications. Our study includes real-life patients and proves that the absence of RCA support or CTO-RCA does not necessarily significantly increase long-term mortality.

Study limitations

The presented study is an analysis of a real-world cohort of patients. One limitation of the study involves the lack of a surgical group. However, the comparison of such a group with the CABG group was beyond the scope of this study. Secondly, although the presented study was a prospective registry, not all clinical data were available. Thirdly, the analyzed population was a population of patients treated in a real-word setting, therefore, many patients with ULMCAD had multivessel disease and PCI was not just about LM, which can influence the prognosis. Finally, the present study analyzed in-hospital, as well as long-term follow-up with the median observation time of over 3 years. However, the long-term follow-up assessed all-cause mortality and we were not able to show cardiovascular vs non-cardiovascular death rates analysis.

CONCLUSIONS

Patients with ULMCAD who have undergone LM PCI with absent RCA support, compared with patients with ULMCAD with RCA support, differed neither in the frequency of periprocedural complications nor in long-term all-cause mortality.

These findings suggest that PCI of LM could be a safe and effective procedure, also in patients without RCA support.

Article information

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The increase of the pulmonary blood flow inhigh-risk hypoxic patients with a bidirectional Glenn anastomosis

Jacek Kołcz[1], Mirosława Dudyńska[2], Aleksandra Morka[3], Sebastian Góreczny[4], Janusz Skalski[1]

[1]Department of Pediatric Cardiac Surgery, Jagiellonian University Medical College, Kraków, Poland
[2]Department of Pediatric Cardiac Surgery, University Children's Hospital in Krakow, Kraków, Poland
[3]Faculty of Health Sciences, Jagiellonian University Medical College, Kraków, Poland
[4]Department of Pediatric Cardiology, Jagiellonian University Medical College, Kraków, Poland

Correspondence to:
Jacek Kołcz, MD, PhD, FECTS, Department of Pediatric Cardiac Surgery, Jagiellonian University Medical College, Wielicka 265, 30–663 Kraków, Poland, phone: +40 12 658 20 11, e-mail: jacek.kolcz@uj.edu.pl

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ABSTRACT

Background: An additional shunt in single ventricle patients with Glenn anastomosis may increase pulmonary flow at the expense of ventricle volume overloading. The performance of the modification depends on pulmonary resistance, indicating better results in favorable hemodynamic conditions.

Aims: The study aims at analyzing the influence of precisely adjusted pulsatile shunt in borderline high-risk Glenn patients on early and late results.

Methods: The study involved 99 patients (including 21 children) with the bidirectional Glenn and accessory pulsatile shunt (BDGS group), and 78 patients with the classic bidirectional Glenn anastomosis (BDG group).

Results: There was 1 death in the BDGS group and 4 deaths in the BDG group. No difference in mortality ($P = 0.71$) was found. The Fontan completion was achieved in 69 (88.5%) children in the BDG group and 18 (85.7%) patients in the BDGS group, without fatalities. No intergroup differences in postoperative pulmonary artery pressure ($P = 0.10$), ventilation time ($P = 0.12$), the McGoon ratio ($P = 0.9$), or chylothorax frequency ($P = 0.14$) were observed. Intensive care unit ($P = 0.28$) and hospitalization ($P = 0.05$) times were comparable. Echocardiography revealed no significant differences in the ventricle and atrioventricular valve function between groups. In the BDGS group, higher blood oxygen saturation ($P = 0.03$) and increase of the McGoon index ($P = 0.002$) were noted.

Conclusions: Bidirectional Glenn anastomosis with precisely adjusted accessory pulmonary blood flow provides stable hemodynamics and adequate oxygen saturation in borderline, profoundly hypoxic patients. An advantageous pulmonary artery development before Fontan completion was observed.

Key words: bidirectional Glenn anastomosis, single ventricle, accessory pulmonary flow

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INTRODUCTION

The main concerns of staged treatment of single ventricle type congenital heart defects are low pulmonary artery (PA) resistance, adequate pulmonary microvasculature maturation, and the pulmonary arteries' growth [1]. Unfortunately, after initial palliative procedures some patients do not meet the criteria for successful Glenn or hemi-Fontan surgery and eventual Fontan completion, which is the treatment goal. Low energy non-pulsatile blood flow through the cavo-pulmonary connection significantly increases pulmonary resistance over that seen in pulsatile flow. It can cause preoperative underestimation of postoperative pulmonary resistance in borderline cases, leading to profound hypoxia and circulatory failure immediately after the Glenn procedure. In the long-term prognosis, non-pulsatile flow can contribute to the underdevelopment of pulmonary arteries and thromboembolic issues. Elimination of the hepatic bloodstream through the lungs contributes to developing pulmonary arteriovenous malformations and severe hypoxia [2, 3]. Lack of optimal preoperative risk stratification may extend the ultimate decision on the intraoperative period. Patients approaching borderline criteria are frequently disqualified from surgery. We present a group of high-risk borderline patients with hypoxia, increased pulmonary resistance, and marginal-sized pulmonary arteries in whom the lungs accessory blood flow was established and precisely adjusted during the Glenn procedure. The group of patients with pulsatile Glenn (BDGS) is compared to pa-

WHAT'S NEW?

The study presents the results of assisted Glenn anastomosis in high-risk single ventricle patients. An additional pulsatile pulmonary blood flow source was precisely constructed and adjusted intraoperatively in patients in whom otherwise it was impossible to win from by-pass. The results show that bidirectional Glenn anastomosis with an accessory pulsatile blood flow source can assure safe hemodynamics and satisfactory development of the pulmonary arteries as a preparation for Fontan completion. This option may be considered as a solution in borderline Fontan candidates or definitive palliation instead of Fontan completion.

tients with classic bidirectional Glenn anastomosis (BDG) as preparation for Fontan surgery. Although the concept has been known for decades, there is no evidence-based ground for routine leaving an additional pulmonary blood flow at Glenn surgery in all patients. The advantages and disadvantages of the modification are still debated, and the exact role of the procedure unknown [4–7].

METHODS

The study involved patients with single ventricle physiology who underwent the Glenn procedure at the Department of Pediatric Cardiac Surgery, Jagiellonian University, between 2008 and 2019. Jagiellonian University Ethics Committee approved the project, and the informed consent for the study was obtained from the patients' parents.

The BDG and BDGS groups were identified and compared (Table 1, Table 2). All children with Glenn anastomosis and biventricular physiology (e.g., Ebstein anomaly, one and a half ventricle repairs) were excluded from the study. Also, patients who needed extensive PA patch plasty treated with the hemi-Fontan procedure were excluded from the study (Table 1).

All surgeries were carried out using the previously described technique and methodology. During surgery, the superior vena cava was anastomosed to the PA in the end–to–side manner. All accessory sources of pulmonary blood flow were closed (including tightening of the native PA, if present) (Figure 1). An additional pulmonary blood flow source was created based on preoperative data, size of pulmonary arteries, and lung disease history. In patients in whom preoperative pulmonary resistance was higher (above 1.8 WU/m^2), a mean PA pressure elevated (13–15 mm Hg), or pulmonary arteries small-sized (z score –1.5 to –1.8), and/or there was no possibility of weaning from cardiopulmonary bypass (CPB) because of hypoxia (e.g., blood oxygen saturation below 70%, despite 20 ppm

Table 1. Procedures carried out in patients with single ventricle physiology in the 12 years. The numbers in brackets indicate patients who died

Year	No. of hemi-Fontas	No. of BDG	No. of BDGS	No. of Fontans after hemi-Fontan	No. of Fontans after BDG	No. of Fontans after BDGS
2008	12	5	2	15	0	0
2009	20 (3)	8 (1)	1	9	2	2
2010	18	9	3	13	8	1
2011	25 (1)	5	2	27	11	2
2012	15 (2)	3	1	18	6	3
2013	21	4	2	13	5	2
2014	28	5	2	7	6	2
2015	32 (2)	2	0	19	3	1
2016	17	13 (1)	0	25	4	0
2017	31 (2)	6 (1)	3	14	5	2
2018	12 (1)	8 (1)	3	26	12	2
2019	3	6	2 (1)	8	7	1
Total	234 (11)	74 (4)	20 (1)	194	69	18

Abbreviations: BDG, bidirectional Glenn; BDGS, bidirectional Glenn and shunt

Table 2. Patient's characteristics

Characteristics	BDGS (n = 21)	BDG (n = 78)	*P*-value
Age, months, mean (SD)	6.68 (3.93)	5.92 (4.40)	0.240
Body weight, kg, mean (SD)	7.12 (4.3)	8.3 (6.2)	0.34
Left ventricle morphology, n (%)	14 (66.7)	30 (38.4)	0.02
Right ventricle morphology, n (%)	7 (33.3)	48 (61.5)	
HLHS, n (%)	2 (9.5)	43 (55.1)	0.033
Tricuspid atresia, n (%)	7 (33.3)	20 (25.6)	0.012
DORV, n (%)	4 (19.0)	6 (7.6)	0.42
Pulmonary atresia, n (%)	3 (14.2)	7 (8.9)	0.38
Others, n (%)	5 (23.8)	2 (2.6)	0.43

Abbreviations: DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; SD, standard deviation. Other abbreviations: see Table 1

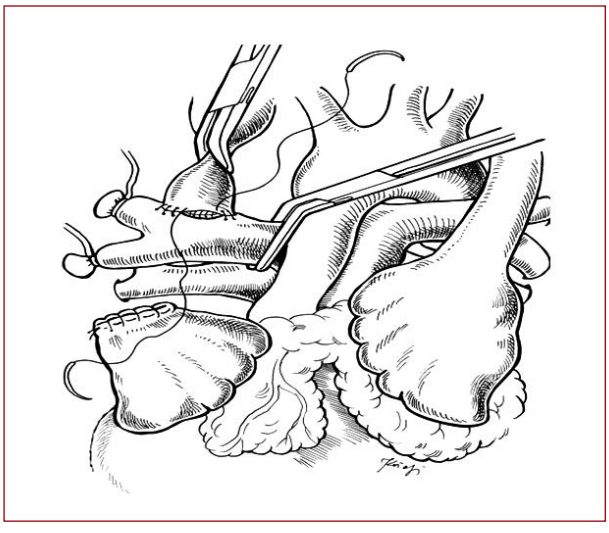

Figure 1. The surgical technique of creating a bidirectional Glenn shunt. The superior vena cava is cut of the right atrium and anastomosed to the pulmonary artery in the end to side

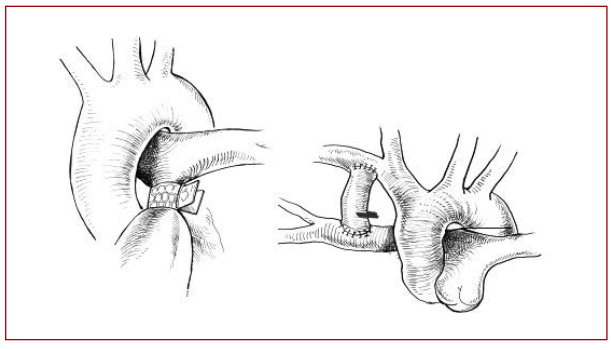

Figure 2. The technique of creation of additional pulmonary blood flow source. **A.** Pulmonary artery banding by narrowing of a distal portion of the pulmonary trunk with polytetrafluoroethylene (PTFE) band. **B.** Modified Blalock–Taussig shunt (diameter of 3.5–3.0 mm) with narrowing of distal part with vascular clip to 3.0 mm

of nitric oxide and FiO_2 1.0, appropriate pharmacologic support with catecholamines and milrinone), either a 3.5 Blalock–Taussig shunt (BTS) was created or a native pulmonary outflow tract was adjusted. The invasive measurement of the pressure in PA was done and, based on the measurements, the BTS was narrowed at the pulmonary end with a vascular clip (to the diameter of approximately 3 mm), or the native outflow tract was banded to a diameter of approximately 3 mm (Figure 2) to maintain mean PA pressure below 15 mm Hg by FiO_2 0.7, $ETCO_2$ 35–40, hemoglobin level 13–14 g/dl, and systemic oxygen saturation 75%–85%. The Fontan procedure was performed before 4 years of age. The total cavopulmonary connection was completed using an extracardiac or intra-extracardiac conduit with fenestration. Any residual accessory pulmonary blood flow source was eliminated at the time of Fontan surgery.

Details concerning preoperative data, diagnostic procedures (echocardiography, hemodynamic assessment), laboratory tests, early postoperative results, and follow-up data, including pre-Fontan clinical data, were gathered and statistically analyzed. Pulmonary artery size was analyzed using the McGoon ratio [8].

Systemic ventricular contractility and atrioventricular valve function were assessed with echocardiography by two experienced echocardiographers, and graded as normal, mildly decreased, moderately decreased, or severely decreased. Two different, previously described quantitative echocardiographic assessment methods of right ventricular function were consequently applied in all patients: the biplane pyramidal approximation method [9] and apical area fractional shortening [10]. The data concerning clinical characteristics and numbers of patients are presented in Table 1 and Table 2.

Statistical analysis

For statistical analysis, standard statistical methods were used. The nominal data were described using the following frequency measures: number count and percent group. Normally distributed quantitative variables were presented as the mean and standard deviation (SD). Non-normally distributed data were presented using the median and interquartile range (IQR). The normality of distribution of quantitative data was tested using the Shapiro–Wilk's test. The differences between the groups concerning normally distributed quantitative data were assessed using a paired or an unpaired t-test. Non-normally distributed data were compared using the Mann–Whitney test. The Fisher exact test was used to determine the differences between the groups concerning categorical data. The *P*-value <0.05 was considered statistically significant using STATISTICA data analysis software system, version 13.

RESULTS

Bidirectional Glenn anastomosis was carried out in 99 patients. In 21 (21.3%) of them, an accessory pulsatile shunt was created (the BDGS group) (Table 1). One (4.7%) patient in the BDGS group died after the procedure because of sepsis. In 78 patients the only pulmonary blood flow source was Glenn anastomosis (the BDG group). Four (5.1%) patients died in the BDG group. Two of them died because of thromboembolic complications and neurologic damage. One child died of sepsis, and one because of the single ventricle's severe dysfunction. There was no difference in the mortality rate between groups ($P = 0.71$).

The Fontan completion was achieved in 69 (88.5%) children in the BDG group and in 18 (85.7%) patients in the BDGS group (Table 1) without fatalities.

There were no differences in mean age (6.68 [3.93] vs 5.92 [4.40] years; $P = 0.24$) and mean weight of the patients (7.12 [4.3] vs 8.3 [6.2] kg; $P = 0.34$) before surgery. In the BDGS group, there was a prevalence of patients with a single left ventricle (14 [66.7%] vs 30 [38.4%]; $P = 0.02$)

and, consequently, a lower rate of hypoplastic left heart syndrome (2 [9.5%] vs 43 [55.1]; $P = 0.03$; Table 2).

There were no differences in a mean value of preoperative blood oxygen saturation (67.52% [5.66] vs 68.19% [4.65]; $P = 0.58$) or mean value of McGoon index (1.57 [0. 11] vs 1.68 [0.19]; $P = 0.30$). Before surgery, the mean value of PA pressure was higher (14.3 mm Hg [1.33]) in the BDGS group than in the BDG group (12.48 mm Hg [1.20]; $P = 0.04$). Also, a tendency was observed towards higher mean value of PA resistance (1.8 [0.9] vs 1.4 [0.70] WU/m^2; $P = 0.09$) before surgery and higher mean value of postoperative PA pressure (14.72 mm Hg [3.36] vs 13.10 mm Hg [1.26]; $P = 0.09$) in the BDGS group. There was no significant difference concerning median of postoperative time of respiratory support (5.62 h [IQR 3.6–12.8]) vs 7.23 h [IQR 4.8–18.5]; $P = 0.12$), mean McGoon ratio (1.59 [0.72] vs 1.64 [0.66]; $P = 0.90$), or chylothorax frequency (3 [14.2%] vs 4 [5.1%]; $P = 0.16$). A median of intensive care unit time (4.1 days [IQR 2.7–5.8] vs 5.83 days [IQR 3.2–8.42]; $P = 0.28$) and hospitalization time (7.20 days [IQR 5.3–16.7] vs 12.03 days [IQR 6.8–20.3]; $P = 0.05$) were comparable (Table 3). The mean value of postoperative blood oxygen saturation was higher in the BDGS group (81.72% [1.97] vs 78.32% [2.34]; $P = 0.032$).

Postoperative echocardiography revealed no significant differences in ventricular function or atrioventricular valve regurgitation (Table 4). There was no difference in the McGoon ratio and PA pressure between groups in pre-Fontan catheterization (Table 3). Patients from the BDGS group had a higher mean value of blood oxygen saturation (85.2% [4.3] vs 82.5% [3.9]; $P = 0.03$). There were no significant differences in the mean value of McGoon index within BDGS group (1.57 [0.11] vs 1.59 [0.72]; $P = 0.9$; 1.59 [0.72] vs 1.98 [1.62]; $P = 0.3$) and within BDG group (1.68 [0.19] vs 1.64 [0.66]; 1.64 [0.66] vs 1.91 [2.14]; $P = 0.3$). Looking however, at the rate of change of the McGoon index within groups (ΔMcGoon), a significant difference of the median of the increment was noted comparing the BDGS group and the BDG group (0.35 [IQR 0.29–0.42] vs 0.16 [IQR 0.11–0.25]; $P = 0.002$).

DISCUSSION

The bidirectional Glenn shunt or hemi-Fontan anastomosis are well-established, integral steps in a single ventricle treatment strategy. As a second step, these procedures are preceded by neonatal palliations such as Norwood surgery, PA banding, or systemic-to-PA shunt. Both stages aim to

Table 3. Comparison of data concerning clinical and laboratory characteristics of the patients in the investigated period

Characteristics	BDGS (n = 21)	BDG (n = 78)	*P* -value
Pre-operative PA pressure, mean (SD)	14.3 (1.43)	12.48 (2.20)	0.04
Pre-operative PA resistance, WU/m^2, mean (SD)	1.8 (0.9)	1.4 (0.7)	0.09
Pre-operative McGoon index, mean (SD)	1.57 (0.11)	1.68 (0.19)	0.29
Pre-operative O_2 saturation, mean (SD)	67.52 (5.66)	68.19 (4.65)	0.58
Duration of ventilation, hours, median (IQR)	5.62 (3.6–12.8)	7.23 (4.8–18.5)	0.124
Chylothorax, postoperative, n (%)	3 (14.2)	4 (5.1)	0.16
ICU stay, days, median (IQR)	4.1 (2.7–5.8)	5.83 (3.2–8.42)	0.28
Hospitalisation time, days, median (IQR)	7.20 (5.3–16.7)	12.03 (6.8–20.3)	0.05
Postoperative PA pressure, mm Hg, mean (SD)	14.72 (3.36)	13.10 (1.26)	0.09
Postoperative McGoon index, mean (SD)	1.59 (0.72)	1.64 (0.66)	0.90
Postoperative O_2 saturation, mean (SD)	81.72 (1.97)	78.32 (2.34)	0.032
Pre-Fontan PA pressure, mm Hg, mean (SD)	14.4 (2.8)	13.2 (3.8)	0.18
Pre-Fontan PA resistance, WU/m^2, median (IQR)	1.8 (1.4–2.6)	1.5 (1.3–1.8)	0.23
Pre-Fontan McGoon index, mean (SD)	1.98 (1.6)	1.91 (2.14)	0.91
Pre-Fontan O_2 saturation, mean (SD)	85.2 (4.3)	82.5 (3.9)	0.035
Δ of McGoon index, median (IQR)	0.35 (0.29–0.42)	0.16 (0.11–0.25)	0.002

Abbreviations: ICU, intensive care unit; IQR, interquartile range; PA, pulmonary artery; SD, standard deviation; WU, Wood unit. Other abbreviations: see Table 1

Table 4. Postoperative echocardiographic characteristic of heart and valve function

Parameters	BDGS (n = 21)	BDG (n = 78)	*P*-value
Ventricular function			
Normal, n (%)	14 (66.7)	51 (65.3)	0.56
Mildly depressed, n (%)	5 (23.8)	14 (17.9)	
Moderately depressed, n (%)	1 (4.7)	8 (10.2)	
Severely depressed, n (%)	1 (4.7)	5 (6.4)	
AV regurgitation			
None, n (%)	12 (57.1)	48 (61.5)	0.54
Mild, n (%)	3 (14.2)	16 (20.5)	
Moderate, n (%)	3 (14.2)	9 (11.5)	
Severe, n (%)	2 (9.5)	5 (6.4)	

Abbreviations: see Table 1

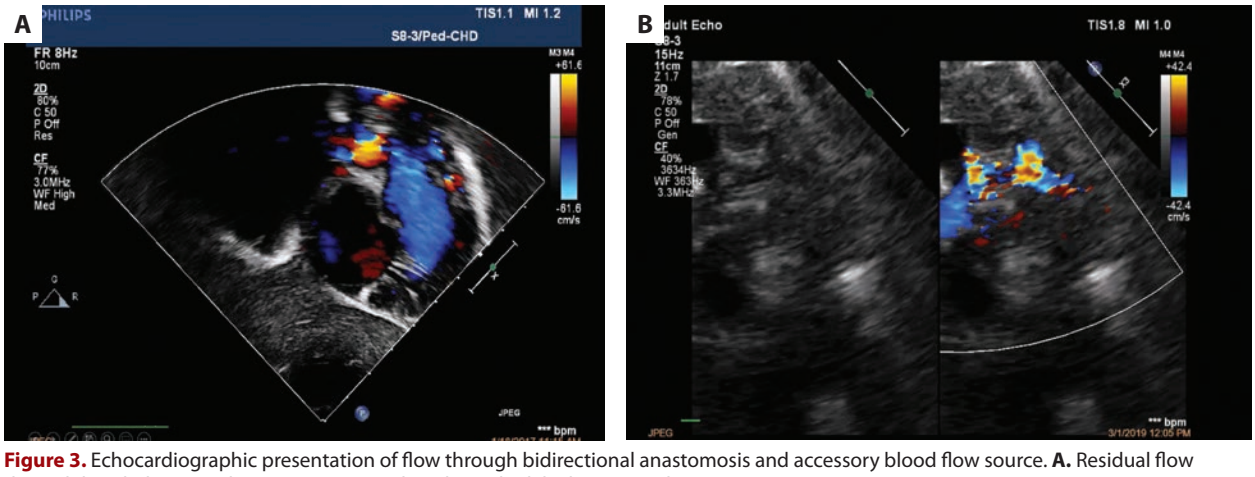

Figure 3. Echocardiographic presentation of flow through bidirectional anastomosis and accessory blood flow source. **A.** Residual flow through banded main pulmonary artery. **B.** Flow through Blalock–Taussig shunt

optimize the circulatory system for the third step, the Fontan procedure. After several decades of developing such a strategy, 2 of the initial 10 [11] necessary conditions of successful creation of Fontan circulation remained: the good functioning single ventricle and well-developed pulmonary arteries. These are the main goals of the initial stages of treatment. They ensure volume unloading, stepwise remodeling of the single ventricle, and PA development [12, 13]. Unfortunately, a group of patients in whom the criteria of creating cavo-pulmonary anastomosis are borderline imposes significantly increased risk on the second-stage procedure. Lack of perfect preoperative risk stratification causes disqualification of many of them from further treatment. In the present study, we looked at the borderline cavo-pulmonary anastomosis candidates in whom an additional blood flow source was created during surgery. The pulsatile shunt's influence on early and late postoperative results was shown compared to patients with classic BDG.

The population of single ventricle patients with hemodynamics not necessarily suited for creating Fontan circulation is growing. The elevated PA pressure and resistance, small PA branches, accessory vascular or lung defects, chronic lung disease, or single ventricle dysfunction may contribute to intolerance of Fontan physiology [11, 14]. Regrettably, there is no good alternative for such patients. Following neonatal palliative procedures, our approach was not to disqualify borderline patients, however, at the expense of higher perioperative risk. After weaning from CPB, all patients in the BDGS group experienced severe desaturation, despite appropriate pharmacological support. The alternative was to start extracorporeal membrane oxygenation support without a realistic perspective for a successful outcome. The ultimate decision to create an accessory pulsatile shunt was reached intraoperatively. Such an approach ensured a stable, reasonably safe clinical conditions with optimal systemic oxygen saturation and ventricular function. It also created additional possibility of long-term palliation if Fontan completion would be contraindicated [15].

The pulsatile shunt was constructed under the precise invasive pressure measurement within the cavo-pulmonary connection, putting accessory banding on the native pulmonary trunk or a vascular clip on the distal end of the BTS. Such a narrowing can significantly reduce pressure transition to the superior vena cava (SVC) and cause the "ejector pump effect". This approach was based on experimental hemodynamic studies and computational simulations indicating that optimal conditions were reached with the clipped distal shunt, anastomosed to the SVC. This model provided evidence that the energy of the systemic flow is partly transferred to the SVC flow and that it works as the ejector pump. It can increase pulmonary flow without significantly increasing SVC pressure [16, 17].

The reported mortality and morbidity in patients with BDGS differ in previous reports. A higher mortality rate in comparison to classic BDG was reported [18, 19]. In our group of higher-risk patients, only one patient died in the postoperative period because of sepsis, and the mortality rate did not differ between groups. Also, respiratory support time, intensive care time, and hospitalization time were not significantly different. The chylothorax frequency was higher in the BDGS group, although not significantly. Additionally, in the BDGS group, the systemic blood oxygen saturation was significantly higher than in the BDG group, which seems to be the most crucial benefit for patients' quality of life and physical efficiency.

Although there was no difference in the McGoon ratio before the second stage and before the third stage ($P = 0.91$, Table 3), there was a significant difference in the change (Δ) of the McGoon ratio with a substantial increment in the BDGS group ($P = 0.002$). The pulmonary branches' diameter, expressed as the McGoon ratio, is an important risk factor of creating Fontan circulation [20]. Although the time between the first and second stage coincides with intensive PA growth, classical Glenn physiology with a non-pulsatile blood flow through the lungs can profoundly affect PA development. In our material, it ensured significantly better development of pulmonary arteries. It contradicted

previous studies that revealed the absence of development or even regression of PA indices [21–23]. In most published works, the comparison between matched groups (classic Glenn anastomosis vs assisted Glenn shunt) and case-control studies, the comparison of absolute diameters, z-scores, and PA indices between groups were unable to reveal the increase of their size. In our study, the paired comparison of the McGoon index's mean values within matched groups between the surgical treatment stages also did not reveal significant differences. However, the comparison of the mean inside group increments (the mean Δ, the mean change) of the McGoon index between matched groups showed a significantly higher increment in the assisted Glenn (BDGS) group between the second and the third stage of treatment. A pulsatile flow in the vascular bed is a well-known factor influencing vascular development by appropriate shear stress regulation, the release of endothelium-derived factors (nitric oxide, endothelin), and reducing vascular resistance [24]. The additional advantage of such an approach is perfusion of the lungs supplied with blood containing angiogenesis inhibitors of the liver (e.g., endostatin, angiostatin), which were shown to regulate normal development and prevent the formation of arteriovenous fistulas [25–27].

Our data show higher blood oxygen saturation after BDGS than following the BDG ($P = 0.03$). It is related to slightly increased pulmonary blood flow, increased PA pressure, and increased ventricle volume load [28]. Before the second stage surgery, the PA resistance and pressure were higher in the BDGS group (Table 3). However, there was no difference in PA pressure and PA resistance in pre-Fontan catheterization. At the same time, the oxygen saturation and increase in the McGoon ratio were significantly higher in the BDGS group. The ventricular function and atrioventricular valve performance were comparable in both groups (Table 4). Given that the BDGS group contained borderline candidates for Glenn surgery, the results indicate a positive influence of pulsatile blood flow on central pulmonary arteries development in these high-risk patients by maintained atrioventricular valve and ventricle function.

CONCLUSIONS

In summary, bidirectional Glenn with precisely adjusted accessory pulmonary blood flow provides stable hemodynamics in the early postoperative period in borderline cavo-pulmonary anastomosis candidates. Adequate pulmonary blood flow and preserved ventricular function can provide appropriate PA development before Fontan completion with results comparable to outcomes in the group of low-risk patients.

Article information

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ORIGINAL ARTICLE

Revascularization approaches in patients with radiation-induced carotid stenosis: an updated systematic review and meta-analysis

Andreas Tzoumas[1], Dimitrios Xenos[1], Stefanos Giannopoulos[2], Marios Sagris[3], Damianos G Kokkinidis[4], Christos Bakoyiannis[5], Dimitrios Schizas[5]

[1]Aristotle University of Thessaloniki, Thessaloniki, Greece
[2]Division of Cardiology, Rocky Mountain Regional VA Medical Center, University of Colorado, Denver, CO, United States
[3]General Hospital of Nikaia, Piraeus, Athens, Greece
[4]Department of Medicine, Jacobi Medical Center, Albert Einstein College of Medicine New York, NY, United States
[5]1st Department of Surgery, National and Kapodistrian University of Athens, Laikon General Hospital, Athens, Greece

Correspondence to:
Stefanos Giannopoulos, MD, Division of Cardiology, Rocky Mountain Regional VA Medical Center, University of Colorado, Denver, 1700 N Wheeling St, Aurora, CO 80045, USA, phone: (303) 399-8020, e-mail: stefanosgiannopoulosmed@gmail.com

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ABSTRACT

Background: Ionizing radiation remains a well-known risk factor of carotid artery stenosis. The survival rates of head and neck cancer patients undergoing radiotherapy have risen owing to medical advancements in the field. As a consequence, the incidence of carotid artery stenosis in these high-risk patients has increased.

Aims: In this study we sought to compare the outcomes of carotid endarterectomy (CEA) vs carotid artery stenting (CAS) for radiation-induced carotid artery stenosis.

Methods: This study was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines. Eligible studies were identified through a comprehensive search of PubMed, Scopus and Cochrane Central until July 2020. A random-effects model meta-analysis was conducted, and odds ratios (ORs) were calculated. The I-square statistic was used to assess for heterogeneity.

Results: Seven studies and 201 patients were included. Periprocedural stroke, myocardial infarction (MI), and death rates were similar between the two revascularization approaches. However, the risk for cranial nerve (CN) injury was higher in the CEA group (OR, 7.40; 95% CI, 1.58–34.59; $I^2 = 0\%$). Analysis revealed no significant difference in terms of long-term mortality (OR, 0.41; 95% CI, 0.14–1.16; $I^2 = 0\%$) and restenosis rates (OR, 0.69; 95% CI, 0.29–1.66; $I^2 = 0\%$) between CEA and CAS after a mean follow-up of 40.5 months.

Conclusions: CAS and CEA appear to have a similar safety and efficacy profile in patients with radiation-induced carotid artery stenosis. Patients treated with CEA have a higher risk for periprocedural CN injuries. Future prospective studies are warranted to validate these results.

Key words: carotid stenosis, carotid artery stenting, carotid endarterectomy, endarterectomy, radiation

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INTRODUCTION

Carotid artery stenting (CAS) is a less invasive alternative approach to carotid endarterectomy (CEA) [1]. Currently, CEA remains the gold standard for treatment of both symptomatic and asymptomatic carotid atherosclerotic disease, whereas CAS is currently reserved for patients with high surgical risk, including those with post-radiation stenosis [2–5]. Proposed mechanisms for post-radiation carotid stenosis include de novo atherosclerotic lesion development or progression of existing plaques [6, 7]. These atherogenic properties of ionizing radiation have been attributed to pro-inflammatory reactions within the arterial wall that weaken endothelial cells barrier, leading to inflammatory cell recruitment, accumulation and eventually plaque formation [8, 9].

Significant carotid stenosis can cause devastating neurological complications, including disabling stroke and transient ischemic attacks (TIA) [9]. Considering the increasing survival rates of patients who undergo radiotherapy for head and neck cancer, the incidence of radiation induced

WHAT'S NEW?

Radiation-induced carotid stenosis is associated with an increased stroke risk and it is a challenging clinical entity. Carotid endarterectomy (CEA) and carotid artery stenting (CAS) are the two revascularization approaches. Prior work suggested that performing CEA in patients with radiation-induced carotid stenosis might be associated with a lower long-term mortality. The present study, including larger population, did not identify a statistically significant difference in the odds of long-term mortality between patients treated with CEA vs CAS, and confirmed a higher rate of cranial nerve injury with CEA. In addition, we now provide a subgroup analysis based on embolic protection device utilization along with suggestions for the design of future studies.

carotid artery stenosis has risen [10]. The time period from radiation exposure to the development of atherosclerotic carotid lesions causing significant stenosis varies across the literature [6, 11], with a recent systematic review suggesting that the yearly incidence of carotid stenosis >50% increases every year during the first three years after radiation treatment [12]. Interestingly, patients who received radiotherapy for head and neck malignancies are at higher risk for TIAs or strokes compared to patients with carotid stenosis who were not exposed to radiation therapy [13].

However, the optimal revascularization approach for this high-risk population is still debatable. CEA can be challenging to perform in patients with a history of radiation exposure in the neck due to extensive tissue scarring, whereas CAS has been related to poor long-term anatomic outcome and higher restenosis rates [13–15]. The aim of this systematic review and meta-analysis was to compare the safety and efficacy profiles of CEA and CAS for treatment of radiation-induced carotid stenosis.

METHODS

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [16]. Literature searches were systematically conducted in PubMed, Scopus, and Cochrane Central by two independent investigators. The following algorithm was utilized for PubMed dataset: ("radiotherapy" OR "irradiation" OR "radiation") AND ("cervical" OR "neck") AND "carotid" AND ("stenosis" OR "atherosclerosis" OR "restenosis") AND ("operation" OR "surgery" OR "surgical" OR "endarterectomy") AND ("stent" OR "stenting" OR "angioplasty" OR "balloon" OR "endovascular" OR "percutaneous"). Any disagreements were resolved with discussion and consensus was settled with the addition of a 3rd independent reviewer. Additionally, the references of the eligible articles were manually reviewed in order to identify potential additional studies.

Studies that fulfilled all the predefined inclusion criteria were eventually included in this meta-analysis. These were: (1) randomized controlled trials (RCT) or observational studies comparing CEA vs CAS for radiation-induced carotid stenosis; (2) studies reporting on relevant clinical outcomes (e.g. restenosis rate, death, stroke, transient ischemic attack, myocardial infarction, cranial nerve injury); (3) studies published up to July 2020. For this systematic review and meta-analysis of study level data no approval by a local institutional review board was required.

Data extraction and risk of bias assessment

Data extraction was performed by 2 independent investigators (AT, DX), blind to each other. All disagreements were discussed with a 3rd reviewer (SG) until consensus was settled. The incidence of stroke within 30 days was the primary endpoint. Secondary endpoints were TIA, cranial nerve (CN) injuries, myocardial infarction (MI) and death within 30 days, and long-term mortality and carotid artery restenosis. Risk of bias was assessed by 2 investigators with the Robins-I tool for non-randomized studies [17]. Additionally, publication bias was evaluated with the methods of the Egger's test and funnel plots.

Statistical synthesis and analysis

Odds ratios (ORs) with the corresponding 95% confidence intervals (CIs) were synthesized for the primary and secondary outcomes. A random-effects model was used to evaluate heterogeneity among studies with the Higgins I-square (I^2) statistic [18]. I^2 greater than 75% indicated significant heterogeneity [18]. The main results (i.e. effect size of each study and pooled estimates) were graphically displayed with a forest plot. A *P*-value <0.05 was considered significant. The statistical software used was STATA 14.1 (StataCorp, College Station, TX, USA).

RESULTS

Search results

Literature search yielded 191 potentially eligible records after duplicates were removed. Fifteen articles were retrieved for full-text evaluation after screening titles and abstracts. Overall, 7 comparative studies satisfied the predetermined search criteria and were included in this meta-analysis [19–25]. The PRISMA flow diagram is illustrated in Figure 1.

Characteristics of the studies and patients

In total, 201 patients undergoing procedures for radiation induced carotid artery stenosis were included in this study (CEA, 50.2% [n = 101/201] vs CAS, 49.8% [n = 100/201]). The mean weighted long-term follow up was 40.5 months as calculated from studies with available data. The average

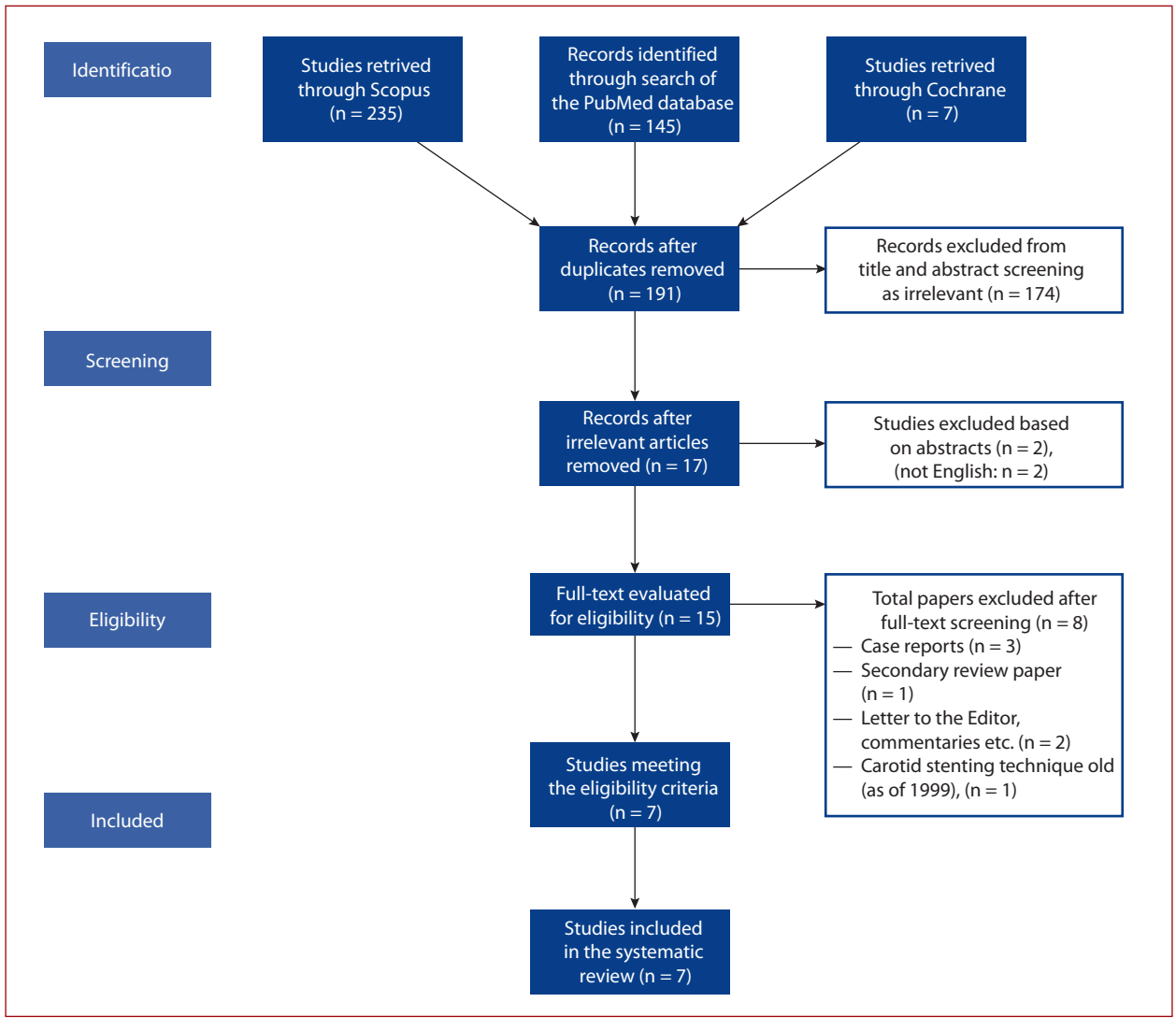

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram

Table 1. Important patient characteristics

Study	Country	Total number of patients, n	CEA, n	CAS, n	Mean age, years	Males, %	Symptomatic at baseline total, %	Symptomatic at baseline CEA, %	Symptomatic at baseline CAS, %
Carpenter 2018 [22]	USA	12	3	9	59.6	NR	0	0	0
Gaudry 2017 [24]	France	43	21	22	CEA: 66.9; CAS: 68.2	CEA: 81; CAS: 77	21	28.5	13.6
Massoni 2017 [23]	Italy	12	5	7	71	75	17	0	28
Sano 2015 [19]	Japan	21	11	10	71.6	95	59	NR	NR
Dorth 2014 [21]	USA	9	3	6	56	78	0	0	0
Tallarita 2011 [20]	USA	60	27	33	66.5	75	65	74	57
Hassen-Kohdja 2004 [25]	International	44	31	13	64.4	51	80	NR	NR

Abbreviations: CAS, carotid artery stenting; CEA, carotid endarterectomy; NR, not reported

time interval between carotid artery irradiation and carotid intervention among the individual studies is presented in Supplementary material, *Figure S1*. No studies with high risk of bias were identified. A detailed assessment of risk of bias can be found in Supplementary material, *Table S1*. Overall, 19.7% (n = 34/173) of the patients had diabetes, 25.4% (n = 44/173) had CAD, and 45.5% (n = 80/176) had a type of dyslipidemia. Important patient characteristics are summarized in Table 1, while details about comorbidities in the CEA and CAS group are presented in Supplementary material, *Table S2*.

Carotid artery duplex ultrasound was the most commonly used imaging study to evaluate the plaques' composition and the degree of stenosis. Additionally, computed

tomography angiography or magnetic resonance angiography were performed or reviewed pre-procedurally in order to identify more specific lesion characteristics, including but not limited to lesion length, degree of calcification, existence of thrombus, or ulceration. The most commonly utilized stents were bare metal stents including the PRECISE stent (Cordis [43.4%; n = 33/76]) and the Wallstent (Boston Scientific [51.3%; n = 39/76]). Carotid artery stenting was mainly performed through femoral access and with local anesthesia. An embolic protection device (EDP) was utilized in 81.6% (n = 62/76) of the CAS cases. This lower than expected percentage of EPD utilization was largely driven by the study by Tallarita et al. [20], which reported a 67.5% EPD utilization rate (n = 25/37). Three studies [21, 22, 25] did not report their EPD utilization rate while the rest reported >90% utilization.

Early periprocedural outcomes (within 30 days)

The two carotid revascularization techniques were comparable in terms of periprocedural stroke (CEA, 1.4%; n = 1/71 vs CAS, 3.4%; n = 2/58; OR, 0.64; 95% CI, 0.12–3.37; I^2 = 0%) (Figure 2). Of note, the study by Tallarita et al. [20] was not used in the analysis of stroke because of an EPD utilization rate that does not correspond to the current standard of care. In addition, no differences in terms of death (CEA, 1.9%; n = 2/101 vs CAS, 0%; n = 0/100; OR, 1.54; 95% CI, 0.34–6.91; I^2 = 0%) (Figure 3) and myocardial infarction (CEA, 4.6%; n = 2/43 vs CAS, 0%; n = 0/50; OR, 2.36; 95% CI, 0.30–18.60; I^2 = 0%) (Figure 4) were identified. However, patients undergoing CEA had a significantly higher incidence of CN injuries compared to patients undergoing CAS (CEA, 17.1%; n = 11/64 vs CAS, 0%; n = 0/72; OR, 7.40; 95% CI, 1.58–34.59; I^2 = 0%) (Figure 5). The most common

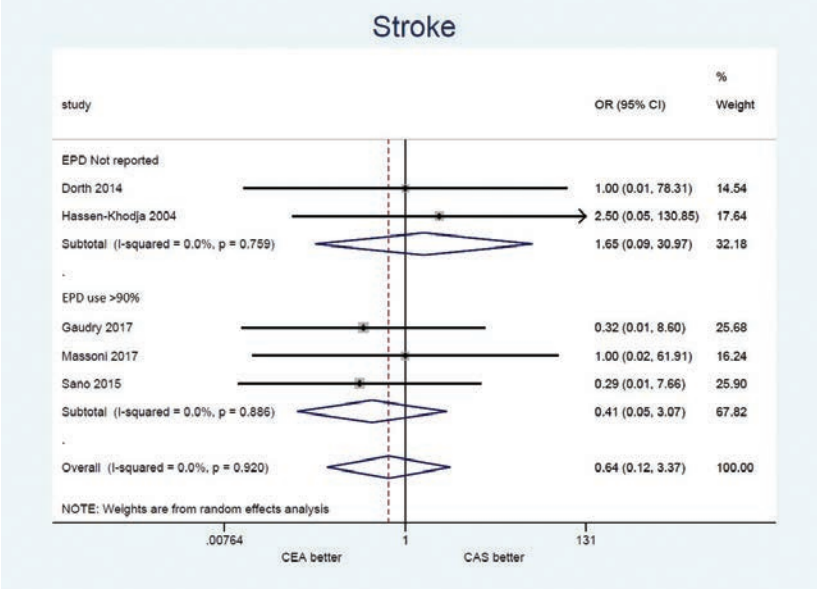

Figure 2. Comparison of 30-day stroke between carotid endarterectomy (CEA) and carotid artery stenting (CAS)

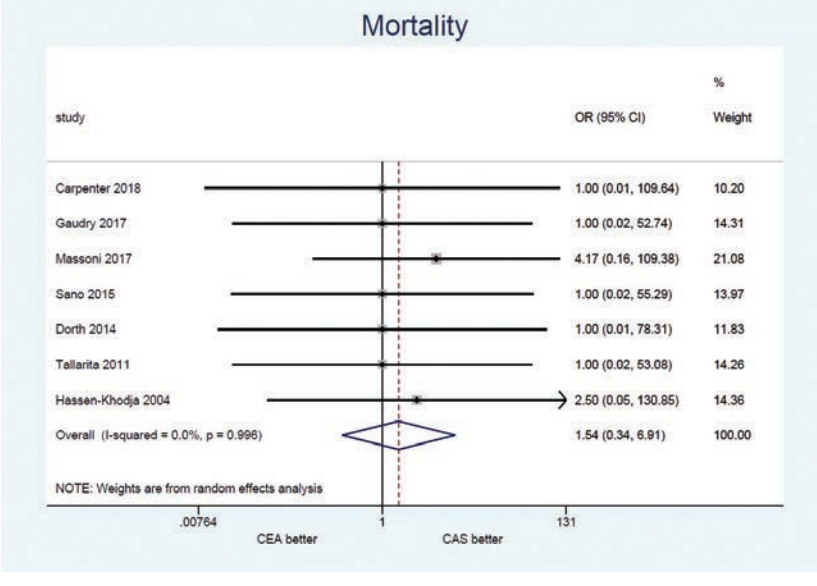

Figure 3. Comparison of 30-day mortality between carotid endarterectomy (CEA) and carotid artery stenting (CAS)

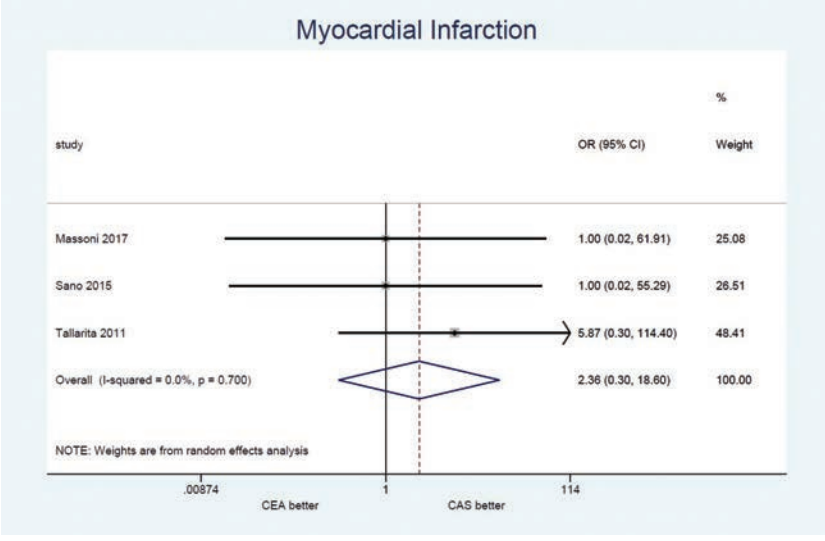

Figure 4. Comparison of 30-day myocardial infarction between carotid endarterectomy (CEA) and carotid artery stenting (CAS)

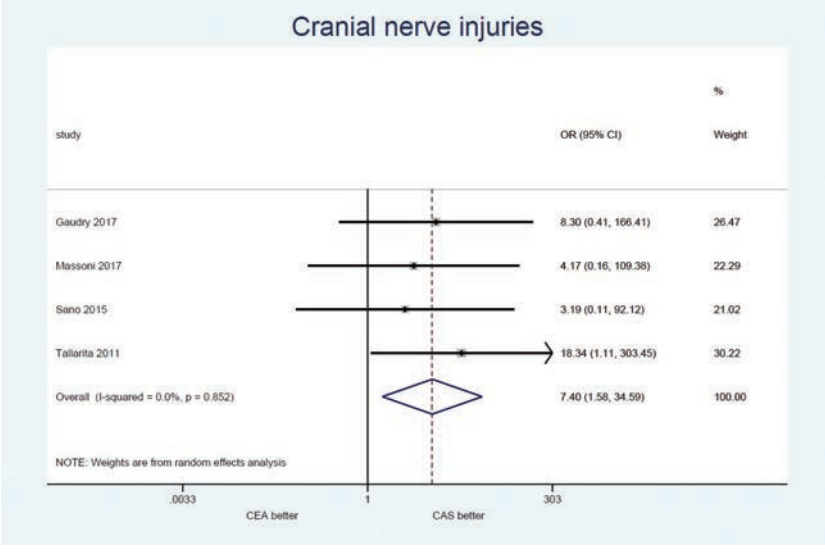

Figure 5. Comparison of cranial nerve injuries between carotid endarterectomy (CEA) and carotid artery stenting (CAS)

injuries affected the hypoglossal and vagus nerves. Two CN injuries were reported to cause permanent deficits. There was no obvious asymmetry in the funnel plots of all early periprocedural outcomes, which were validated by nonsignificant results following the Egger's test (stroke: $P = 0.10$; MI: $P = 0.06$; death: $P = 0.06$; CNI: $P = 0.07$) (Supplementary material, *Figure S2*).

Late outcomes

Long-term all-cause mortality (40.5 months average) was similar between the CEA and CAS groups (CEA, 7.1%; n = 5/70 vs CAS, 17.2%; n = 15/87; OR, 0.41; 95% CI, 0.14–1.16; $I^2 = 0\%$) (Figure 6). Similarly, no difference was detected in the incidence of carotid artery restenosis among patients undergoing CEA vs CAS (CEA, 10.9%; n = 10/101 vs CAS, 17%; n = 17/100; OR, 0.69; 95% CI, 0.29–1.66; $I^2 = 0\%$) (Figure 7). No evidence of publication bias was found for long-term outcomes based on the Egger's test (long-term all-cause mortality: $P = 0.14$; restenosis: $P = 0.53$) and funnel plots (Supplementary material, *Figure S2*).

Subgroup analysis

A subgroup analysis was performed for periprocedural stroke by pooling studies that have utilized >90% EPD use and those studies that have not reported any EPD utilization rate. Neither of the two subgroups showed any significant difference in terms of stroke (EPD not reported; OR, 1.65 [0.09–30.97] and EPD >90%; OR, 0.41 [0.05–3.07]) (Figure 2).

DISCUSSION

This was a systematic review and meta-analysis of seven studies comparing CEA vs CAS for the treatment of carotid stenosis associated with radiotherapy for head and neck cancer. In a previously published meta-analysis CEA yielded a significantly reduced risk of all-cause long-term mortality [4]. In the present study, the long-term mortality difference between the groups was not detected; this result could be attributed to the larger sample size of this study. In addition, we showed that patients undergoing CEA were at an increased risk for periprocedural CN injuries. However,

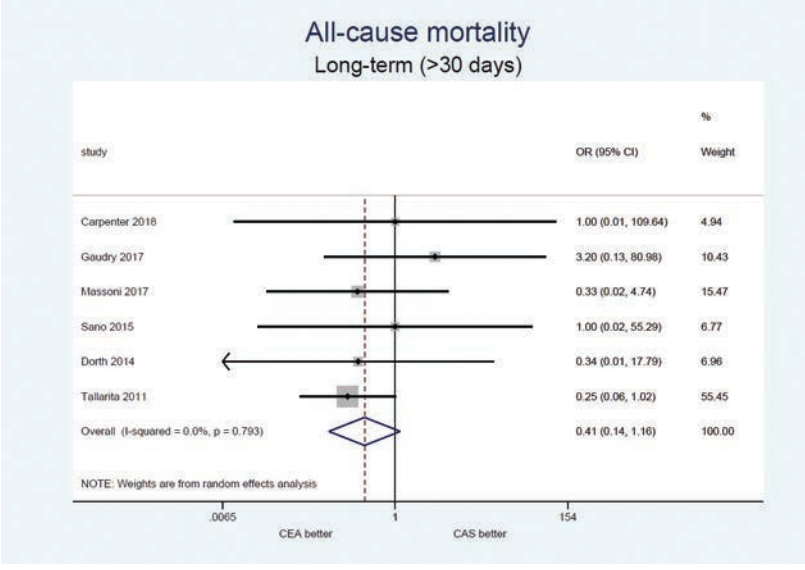

Figure 6. Comparison of late all-cause mortality between carotid endarterectomy (CEA) and carotid artery stenting (CAS)

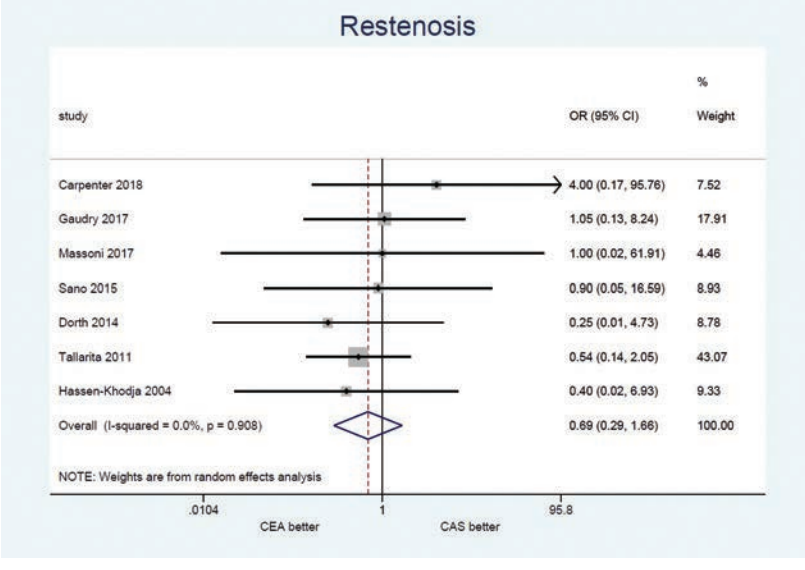

Figure 7. Comparison of late restenosis between carotid endarterectomy (CEA) and carotid artery stenting (CAS)

the incidence of periprocedural adverse events including stroke, myocardial infarction and short-term all-cause mortality were similar between the two groups. Additionally, our results demonstrated no differences in terms of late restenosis over an average follow up of 40.5 months between the two groups.

Medical advancements including the use of radiotherapy, chemotherapy, and surgery have led to increased survival rates in patients with head and neck malignancies. This increased survival has inevitably raised the overall incidence of post-radiation carotid artery stenosis which has been estimated to be 2%–22% [23, 26–28]. The development of radiation-induced arterial stenosis has been associated with several different pathogenic mechanisms, including injury and occlusion of the vasa vasorum feeding the arterial wall [29, 30], and endothelial cell dysfunction resulting from the effects of ionizing radiation itself [31–33]. Indeed, previous clinical studies have shown that radiation is an independent risk factor for the development of early atherosclerosis [34, 35]. This high-risk patient population often requires carotid revascularization for the prevention of neurologic sequelae, commonly with CEA or CAS. Intervention is challenging, since radiation-induced carotid lesions begin as fibrotic changes within the arterial wall, which convert into more unstable large necrotic lesions over time [19, 32]. This transformation makes them more prone to embolization [36]. Moreover, post-radiation lesions tend to affect more extensive segments of carotid arteries and have multifocal distribution compared to common atherosclerotic lesions; therefore, surgery in irradiated anatomy increases the difficulty of the procedure [37, 38]. Nonetheless, as comparative studies for the treatment of radiation induced carotid artery are sparse, the optimal revascularization approach for this entity is still under investigation.

Recent progress in the field of endovascular management of carotid stenosis have introduced novel second-generation carotid stents which yielded promising results in preventing distal embolization during CAS ("the cheese-grater effect" with older stents) [39, 40]. Additionally, current evidence suggests that dual layer embolic prevention stent systems have shown to be safe and effective in reducing stroke risk due to intraprocedural debris dislodgement from the target lesion and during the post-CAS period [40, 41]. However, the use of EPD can be affected by the operator experience and it has been related with certain complications during deployment or retrieval processes in cases of difficult anatomy and unstable ulcerative plaques [42].

Optimized neuroprotection during CAS with conventional stents may minimize intraprocedural cerebral embolism [43], albeit the problem of early or delayed postprocedural embolism can be better addressed with second generation stents which can maximize plaque coverage and prevent prolapse between the stent struts [44]. This is a great advantage of dual layer stents, since plaque protrusion has been associated with high-risk of ischemic complications during the 30-day post-CAS follow up period [40]. Moreover, proximal occlusion devices using flow arrest or reversal systems shown promising results in preventing post-CAS stroke [45]. Interestingly, the use of a proximal neuroprotection device in combination with new generation mesh stents has been described successfully during the endovascular treatment of challenging cases [46]. Future prospective studies should evaluate the introduction of these novel stents and techniques in the treatment of patients with radiation-induced carotid lesions, which constitute by definition a high-risk subset of patients.

Traditionally CEA has been associated with higher rates of CN injuries and local wound complications (e.g. infection, poor wound healing) [11, 47]. Moreover, there is evidence that history of radiotherapy for head and neck malignancies may have an additive effect to this higher risk for CN deficits owing to fibrotic remodeling in the perivascular soft tissue [48]. Our meta-analysis demonstrated that patients in the CEA group experienced CN injuries more frequently than the patients from the CAS group. However, previous studies are in agreement with the current meta-analysis showing that these cranial nerve deficits are rather transient and of low clinical significance [11, 49]. Furthermore, as our study did not detect any significant differences in the rates of periprocedural stroke, death, and MI between the two approaches, it could be concluded that both procedures seem to be equally safe in terms of periprocedural complications. It should be noted, however, that even though statistical significance was not reached for periprocedural stroke, its respective absolute incidence rates in CEA and CAS were 1.4% and 3.4%, which can raise the point of low statistical power to detect this difference. Future prospective cohorts and large registries should be designed to compare the two approaches and validate our results.

Despite the non-inferiority of CAS compared to CEA in terms of periprocedural adverse events, the former has been associated with higher rates of long-term restenosis and poor anatomic outcome in patients with radiation exposure; however, results are inconclusive in the literature. The pooled estimates of our meta-analysis did not show any significant differences in the rates of late restenosis between the two groups. However, it should be noted that the absolute incidence of restenosis in the present study was 9.7% and 16.3% in the CEA and CAS groups respectively, which raises the concern of low statistical power to detect this difference. In accordance with our results, a previous systematic review reported a 9.7% and 18.2% long-term restenosis rate; however this study was not a meta-analysis and head to head comparisons were not made [50]. Also, a prospective study investigating the long-term outcomes of CAS among patients that received radiotherapy vs patients being at high risk for surgery but without a history of head and neck radiation showed that radiation exposure was associated with lower freedom from restenosis during a mean follow up of 14.4 months; however a comparison between CEA and CAS was not made in that study [14]. In conclusion, current available evidence is insufficient to draw conclusions and thus, prospective studies with standardized follow-up intervals are warranted to investigate and compare restenosis rates in the two groups.

Limitations

This study was a systematic review and meta-analysis of comparative observational studies. However, there are several limitations that should be acknowledged. EPD use was not consistently reported by all studies and for this reason we conducted a subgroup analysis of stroke based on EPD reporting, which showed no differences. Importantly, however, future studies should always report the use of EPD during CAS as this is considered standard of care and is important information to the reader. Moreover, data regarding radiation dose regimen were inconsistently reported and varied widely among the included studies. The dose of external neck irradiation can affect the severity and extent of radiation-induced vasculopathy and lack of this information might have affected our outcomes. Furthermore, as patient-level data was not available, adjusted OR utilizing patients' comorbidities and procedural characteristics could not be provided. Additionally, data regarding the anti-platelet therapy and statin prescription during follow up were sparse. Furthermore, the data in each treatment arm regarding specific outcomes for symptomatic or asymptomatic carotid disease were inconsistently reported. Lastly, the follow-up intervals were not standardized across the included studies and a consistent definition for restenosis was not provided.

CONCLUSIONS

This meta-analysis demonstrated that CEA is associated with higher periprocedural CN injuries compared to CAS, although the periprocedural death, stroke and MI rates were not different between the two groups. Additionally, no significant differences were detected in terms of late all-cause mortality and restenosis between CEA and CAS. Further prospective studies are needed in order to eliminate bias and identify the optimal therapeutic approach for radiation-induced carotid stenosis.

Article information

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Machine learning versus classical electrocardiographic criteria for echocardiographic left ventricular hypertrophy in a pre-participation cohort

Daniel YZ Lim[1], Gerald Sng[1], Wilbert HH Ho[1], Wang Hankun[1], Ching-Hui Sia[1–3], Joshua SW Lee[1], Xiayan Shen[1, 2], Benjamin YQ Tan[1, 4, 5], Edward CY Lee[1], Mayank Dalakoti[1, 2], Wang Kang Jie[1, 5], Clarence KW Kwan[1], Weien Chow[4], Ru San Tan[6], Carolyn SP Lam[6], Terrance SJ Chua[6], Tee Joo Yeo[1, 2], Daniel TT Chong[1, 6]

[1]Medical Classification Centre, Central Manpower Base, Singapore Armed Forces, Singapore
[2]Department of Cardiology, National University Heart Centre Singapore, Singapore
[3]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[4]HQ Medical Corps, Singapore Armed Forces, Singapore
[5]University Medicine Cluster, National University Health System, Singapore
[6]Department of Cardiology, National Heart Centre Singapore, Singapore

Correspondence to:
Daniel YZ Lim, MBBS, MRCP, Outram Rd, Singapore 169608, phone: +65 97307915, e-mail: daniel.lim@mohh.com.sg

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ABSTRACT

Background: Classical electrocardiographic (ECG) criteria for left ventricular hypertrophy (LVH) are well studied in older populations and patients with hypertension. Their utility in young pre-participation cohorts is unclear.

Aims: We aimed to develop machine learning models for detection of echocardiogram-diagnosed LVH from ECG, and compare these models with classical criteria.

Methods: Between November 2009 and December 2014, pre-participation screening ECG and subsequent echocardiographic data was collected from 17 310 males aged 16 to 23, who reported for medical screening prior to military conscription. A final diagnosis of LVH was made during echocardiography, defined by a left ventricular mass index >115 g/m^2. The continuous and threshold forms of classical ECG criteria (Sokolow–Lyon, Romhilt–Estes, Modified Cornell, Cornell Product, and Cornell) were compared against machine learning models (Logistic Regression, GLMNet, Random Forests, Gradient Boosting Machines) using receiver-operating characteristics curve analysis. We also compared the important variables identified by machine learning models with the input variables of classical criteria.

Results: Prevalence of echocardiographic LVH in this population was 0.82% (143/17310). Classical ECG criteria had poor performance in predicting LVH. Machine learning methods achieved superior performance: Logistic Regression (area under the curve [AUC], 0.811; 95% confidence interval [CI], 0.738–0.884), GLMNet (AUC, 0.873; 95% CI, 0.817–0.929), Random Forest (AUC, 0.824; 95% CI, 0.749–0.898), Gradient Boosting Machines (AUC, 0.800; 95% CI, 0.738–0.862).

Conclusions: Machine learning methods are superior to classical ECG criteria in diagnosing echocardiographic LVH in the context of pre-participation screening.

Key words: biostatistics, electrocardiography, electronic medical records, myocardial disease

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INTRODUCTION

Left ventricular hypertrophy (LVH) is a clinically significant condition where there is an increased thickness of the left ventricular wall. It may be secondary to conditions such as athlete's heart, hypertension, valvular heart disease, and hypertrophic cardiomyopathy [1]. These conditions may need further evaluation, and may adversely impact fitness for participation in athletic endeavours and military training. Various electrocardiographic (ECG) criteria (Sokolow–Lyon [2], Cornell [3] etc.) have been proposed as markers of LVH, and are well studied in Western populations, particularly in hypertensive patients [4]. In our study, we examined ECG

WHAT'S NEW?

This large retrospective study examined the utility of machine learning algorithms in detecting echocardiographic left ventricular hypertrophy, when applied to screening electrocardiograms (ECG) of a young pre-participation cohort. Classical ECG criteria are not recommended in these individuals due to poor correlation with anatomic pathology, and no alternative algorithms currently exist. The machine learning algorithms applied showed good predictive power and performed better than classical criteria, whether clinical and anthropometric data were included as predictors or not. They also identified as important less recognized ECG parameters predictive of left ventricular hypertrophy, such as the mean QT interval, mean QRS duration, and R wave in lead I.

LVH criteria as predictors of LVH detected on transthoracic echocardiography, as defined by a left ventricular mass index (LVMI) >115 g/m^2.

Since 2008, it has been recognized that isolated electrocardiographic LVH may not apply to young athletic cohorts [5], and no specific recommendation exists for pre-participation cohorts. Referral for further cardiac investigations is no longer recommended by subsequent guidelines, such as the European Society of Cardiology (ESC) 2010 criteria [6], Seattle Criteria (2013) [7], Refined Criteria (2014) [8] and most recently the International Criteria for ECG interpretation in Athletes (2017) [9]. This was based on data showing no correlation between positive ECG LVH criteria and actual pathological LVH on cardiac imaging [10]. Nevertheless, detection of actual anatomic LVH remains a clinical outcome of interest. This is especially so in the context of fitness certification before participation in military training or sport, where patients with pathologic conditions (e.g. hypertrophic cardiomyopathy) should be excluded [11].

The main limitation of classical ECG criteria (e.g. Sokolow–Lyon, Cornell, Romhilt–Estes) is low sensitivity overall [4], and more so in younger populations [12]. This may stem from their statistical formulation, as most classical models assume each predictive factor is related in a linear fashion to LVH. For example, the Sokolow–Lyon criteria involve direct summation of S wave height in V_1, plus the larger of the R wave height in V_5 or V_6. This is an oversimplification of the overall information contained in an ECG. In addition, most current ECG criteria for LVH do not take into account demographic parameters, such as age, or anthropometric parameters, such as body mass index, body fat percentage, and presence of pectus excavatum.

Machine learning, or artificial intelligence, is an alternative approach that may improve the prediction of true LVH based on ECG parameters [13]. It can identify complex relationships between predictive parameters, and combine these in a non-linear fashion. This has the potential to improve prediction of clinical outcomes, and has been studied elsewhere for outcomes such as cardiovascular risk prediction [14]. There is limited literature on machine learning techniques to predict LVH from ECG parameters in adult cohorts [15, 16], but none in younger pre-participation cohorts.

Our objective in this study was to develop machine learning algorithms to predict LVH from resting ECG, as well as routine demographic, clinical, and anthropometric data in a cohort of young pre-participation individuals. All machine learning models were compared to classical ECG criteria for LVH. Machine learning models were first trained on ECG data alone, for a fair comparison with classical ECG criteria (which do not contain anthropometric data). They were also separately trained on the full set of predictors, including all ECG, demographic, clinical, and anthropometric data, to determine if this would improve the accuracy of predictions.

METHODS

Study population

The Singapore Armed Forces have conducted universal pre-participation screening before military enlistment for all young male Singaporeans [17]. Universal ECG screening was implemented since 2008, based on an Italian pre-participation cardiovascular screening system proposed by Corrado et al. [18], with referral for echocardiography if Sokolow–Lyon criteria for LVH were met. Echocardiography was performed within a year of referral to the national cardiology tertiary center, with all studies reported by a cardiology specialist. Our patient population comprised of 17 310 prospective male military recruits who had undergone transthoracic echocardiography from November 2009 to December 2014, as part of determination of their fitness to enlist into military service.

Approval for collection and use of data was granted by the Singapore Armed Forces Joint Medical Committee, and ethical approval was obtained from the local institutional review board.

Variables

For all individuals, demographic, anthropometric, and clinical parameters were collected, as well as a baseline resting 12 lead ECG. Resting ECGs were performed by trained personnel using the Philips Pagewriter TC70 ECG machine, which recorded at a sampling rate of 500 Hz. The electronic ECG readouts were analyzed using a proprietary Philips TM TraceMasterVue modular ECG analysis system

with automatic measurement of the ECG parameters. The full list of parameters collected are included in Supplementary material, *Table S1*.

The primary outcome was LVH, as assessed by LVMI on transthoracic echocardiography. Echocardiographic assessment was used as the determinant in view of operational considerations precluding general use of advanced imaging (such as cardiac magnetic resonance imaging [CMRI]) or histological diagnosis. A cutoff of LVMI >115 g/m^2 was used in this male population, based on the American Society of Echocardiography guidelines [19].

Prediction algorithms

For the machine learning algorithms, we employed a 70:30 train-test split (i.e. using 70% of the data to train the machine learning model, and the remaining 30% to assess accuracy). Continuous variables were scaled and normalized. Fivefold cross validation was used to tune the model parameters. We implemented some commonly used types of supervised machine-learning algorithms. We included regression based methods, namely conventional Logistic Regression and GLMNet (penalized logistic regression with the ElasticNet penalty) [20], as well as tree based methods, which were Random Forests [21] and Gradient Boosting Machines [22]. All machine learning models were trained first on ECG parameters only, and separately on the full set of predictive parameters (including demographic, clinical, and anthropometric data).

The machine learning models were compared with classical ECG criteria. We examined the commonly used Sokolow–Lyon, Romhilt–Estes, Modified Cornell, Cornell Product, and Cornell methods for assessing LVH on ECG, and calculated both their continuous and threshold forms. We summarize the different classical criteria being compared in Supplementary material, *Table S2*.

Statistical analysis

Summary statistics for anthropometric and ECG parameters were calculated, including counts and proportions for categorical data, as well as medians and interquartile ranges for continuous data.

The performance of the machine learning algorithms was assessed using the test cohort. We calculated receiver operating characteristic (ROC) curves for each algorithm, as well as the area under the curve (AUC). The 95% confidence interval (CI) for each AUC was determined using a bootstrap method. Likewise, we calculated the ROC and AUCs for the continuous versions of the various classical ECG methods. For machine learning models, variable importance was assessed using the final tuned coefficients for regression based models, and using the weighted average improvement in node impurity for tree based models. Analysis was performed using RStudio with R version 3.6.1, and using the packages caret, glmnet, randomForest, and pROC.

RESULTS

Study population characteristics

Our study included a total of 17 310 young men aged 16 to 23 years, of which 143 (0.82%) had LVH. The characteristics of the population stratified by LVH status are included in Table 1. Categorical variables are tabulated as frequencies with their respective percentages, and continuous variables are tabulated as means with standard deviation.

Performance of the various models

The predictive accuracy of the classical and machine learning models was assessed by the AUC. The values for the various models are tabulated in Table 2, with the bootstrapped 95% CIs. Other evaluation parameters are tabulated in Supplementary material, *Table S3*.

All machine learning models showed superior predictive accuracy compared to classical models, regardless of whether electrocardiographic (ECG) parameters alone were considered, or if all available predictive parameters were included. In particular, GLMNet, Random Forests, and Logistic Regression had excellent predictive accuracy with AUC surpassing 0.8. This can be seen in the numerical AUC values, as well as the ROC plots in Figure 1. The machine learning models which included ECG parameters only performed similarly to those with all predictive parameters included, as evidenced by the numerically similar AUC values as well as the overlapping 95% CIs.

Important variables

To interpret the machine learning models and compare them to classical criteria, the top ten most important variables for each machine learning model were ranked and listed in Table 3. Weight, height, body fat percentage, and systolic blood pressure were anthropometric parameters not used in the classical ECG criteria, but were deemed important to the machine learning algorithms. Mean QT interval, mean QRS duration and R wave in lead I were ECG parameters not used in the classical criteria, but were deemed important to the machine learning algorithms, both when ECG parameters alone were included, and when all predictive parameters were included.

DISCUSSION

General discussion

To the best of our knowledge, this is one of the few studies to employ machine learning to detect LVH. In our large, pre-participation cohort, we found that all 4 machine learning algorithms tested were superior to classical ECG criteria in identifying echocardiographic LVH. The high AUC values [23] of above 0.8 derived from the machine learning models are excellent and at a level which would generally be acceptable for clinical use. Other classical algorithms

Table 1. Population characteristics stratified by left ventricular hypertrophy (LVH) status

Variables	Overall (n = 17 310)	No LVH (n = 17 167)	Presence of LVH (n = 143)
Demographic and anthropometric parameters			
Age, years	18.0 (17.0–19.0)	18.0 (17.0–19.0)	18.0 (17.0–19.0)
Smoking	2921 (17)	2898 (17)	23 (16)
Urine dipstick blood (present)	33 (0)	33 (0)	0 (0)
Urine dipstick glucose (present)	28 (0)	28 (0)	0 (0)
Urine dipstick protein (present)	19 (0)	19 (0)	0 (0)
Pectus excavatum (present)	139 (1)	139 (1)	0 (0)
Hemoglobin, g/dl	15.6 (14.9–16.2)	15.6 (15.0–16.2)	15.3 (14.7–15.8)
Height, cm	172 (168–177)	172 (168–177)	172 (168–176)
Weight, kg	61 (54.5–69.5)	61 (54.5–69.4)	68 (60.4–75.35)
Body fat percentage, %	18.2 (14.5–23)	18.2 (14.5–23)	20.1 (17.3–24.3)
Systolic blood pressure, mm Hg	115 (105–125)	115 (105–125)	117 (108–127)
Diastolic blood pressure, mm Hg	66 (58–73)	66 (58–73)	64 (57–71)
Electrocardiogram parameters			
Mean PR interval, ms	144 (132–157)	144 (132–157)	148 (136.5–160.5)
Mean PR segment, ms	41 (31–51)	41 (31–51)	44 (33.5–54)
Mean QRS duration, ms	95 (89–102)	95 (89–102)	98 (92–105.5)
Mean QTc interval, ms	410 (395–425)	410 (395–425)	411 (394–427)
Mean QT interval, ms	364 (345–385)	364 (345–385)	388 (360.5–415.5)
Mean ventricular rate, bpm	43 (28–76)	43 (28–76)	54 (32–99.5)
QT interval dispersion, ms	76 (66–87)	76 (66–87)	68 (58–78)
R wave height in aVF, mV	1.4 (0.8–1.9)	1.4 (0.8–1.9)	1.6 (0.9–2.1)
R wave height in aVL, mV	0.2 (0.1–0.2)	0.2 (0.1–0.2)	0.2 (0.1–0.4)
R wave height in aVR, mV	0.1 (0.1–0.3)	0.1 (0.1–0.3)	0.1 (0–0.2)
R wave height in I, mV	0.5 (0.3–0.7)	0.5 (0.3–0.7)	0.7 (0.4–0.9)
R wave height in II, mV	1.5 (1–2.1)	1.5 (1–2.1)	1.9 (1.2–2.3)
R wave height in III, mV	1.2 (0.7–1.8)	1.2 (0.7–1.8)	1.3 (0.6–1.9)
R wave height in V1, mV	0.3 (0.2–0.5)	0.3 (0.2–0.5)	0.4 (0.2–0.5)
R wave height in V_2, mV	0.7 (0.5–1)	0.7 (0.5–1)	0.8 (0.6–1.1)
R wave height in V_3, mV	1 (0.7–1.4)	1 (0.7–1.4)	1.2 (0.9–1.6)
R wave height in V_4, mV	1.8 (1.3–2.4)	1.8 (1.3–2.4)	2.3 (1.6–2.9)
R wave height in V_5, mV	1.8 (1.3–2.3)	1.8 (1.3–2.2)	2.2 (1.6–2.6)
R wave height in V_6, mV	1.4 (1–1.8)	1.4 (1–1.8)	1.7 (1.3–2)
S wave depth in aVF, mV	0.1 (0–0.3)	0.1 (0–0.3)	0.1 (0–0.3)
S wave depth in aVL, mV	0.5 (0.2–0.8)	0.5 (0.2–0.8)	0.5 (0.2–0.9)
S wave depth in aVR, mV	0 (0–1.1)	0 (0–1.1)	0 (0–1.4)
S wave depth in I, mV	0.2 (0.1–0.4)	0.2 (0.1–0.4)	0.2 (0–0.3)
S wave depth in II, mV	0.2 (0–0.3)	0.2 (0–0.3)	0.1 (0–0.3)
S wave depth in III, mV	0.1 (0–0.2)	0.1 (0–0.2)	0.1 (0–0.3)
S wave depth in V_1, mV	1.1 (0.6–1.5)	1.1 (0.6–1.5)	1.3 (0.8–1.8)
S wave depth in V_2, mV	1.7 (1.1–2.3)	1.7 (1.1–2.3)	1.8 (1.4–2.7)
S wave depth in V_3, mV	1.5 (1.0–2.0)	1.5 (1.0–2.0)	1.6 (1.1–2.3)
S wave depth in V_4, mV	0.6 (0.3–1.0)	0.6 (0.3–1.0)	0.7 (0.4–1.1)
S wave depth in V_5, mV	0.3 (0.1–0.5)	0.3 (0.1–0.5)	0.3 (0.1–0.5)
S wave depth in V_6, mV	0.1 (0–0.3)	0.1 (0–0.3)	0.1 (0–0.3)
Ventricular activation time in aVL, ms	31 (20–62)	31 (20–62)	34 (22–60)
Ventricular activation time in V_5, ms	44 (37–49)	44 (37–49)	47 (39–51)
Ventricular activation time in V_6, ms	44 (38–48)	44 (38–48)	47 (42–52)

Values are expressed as counts (percentages) or median (interquartile range) as appropriate

based on ECG data were less discriminatory and had a lower predictive accuracy for LVH.

The machine learning models identified non-traditional ECG parameters that had predictive value for LVH. The approaches of the machine learning models were mathematically different, with Logistic Regression and GLMNet being regression type models, whereas Random Forest and Gradient Boosting Machines were decision tree-based models. We noted that some parameters that are less recognized and/or not included in all classical models, were instead consistently identified as important by the different machine learning modeling approaches. They are thus highly likely to represent true sources of predictive information about the underlying pathology, echocardiographic LVH. These included limb lead parameters (R wave in lead I) and parameters involving the duration of ventricular activity (such as mean QT interval and mean QRS duration). This suggests that electrical manifestations of LVH go beyond anteriorly directed depolarization forces in the precordial leads, but also involve abnormalities in depolarization and

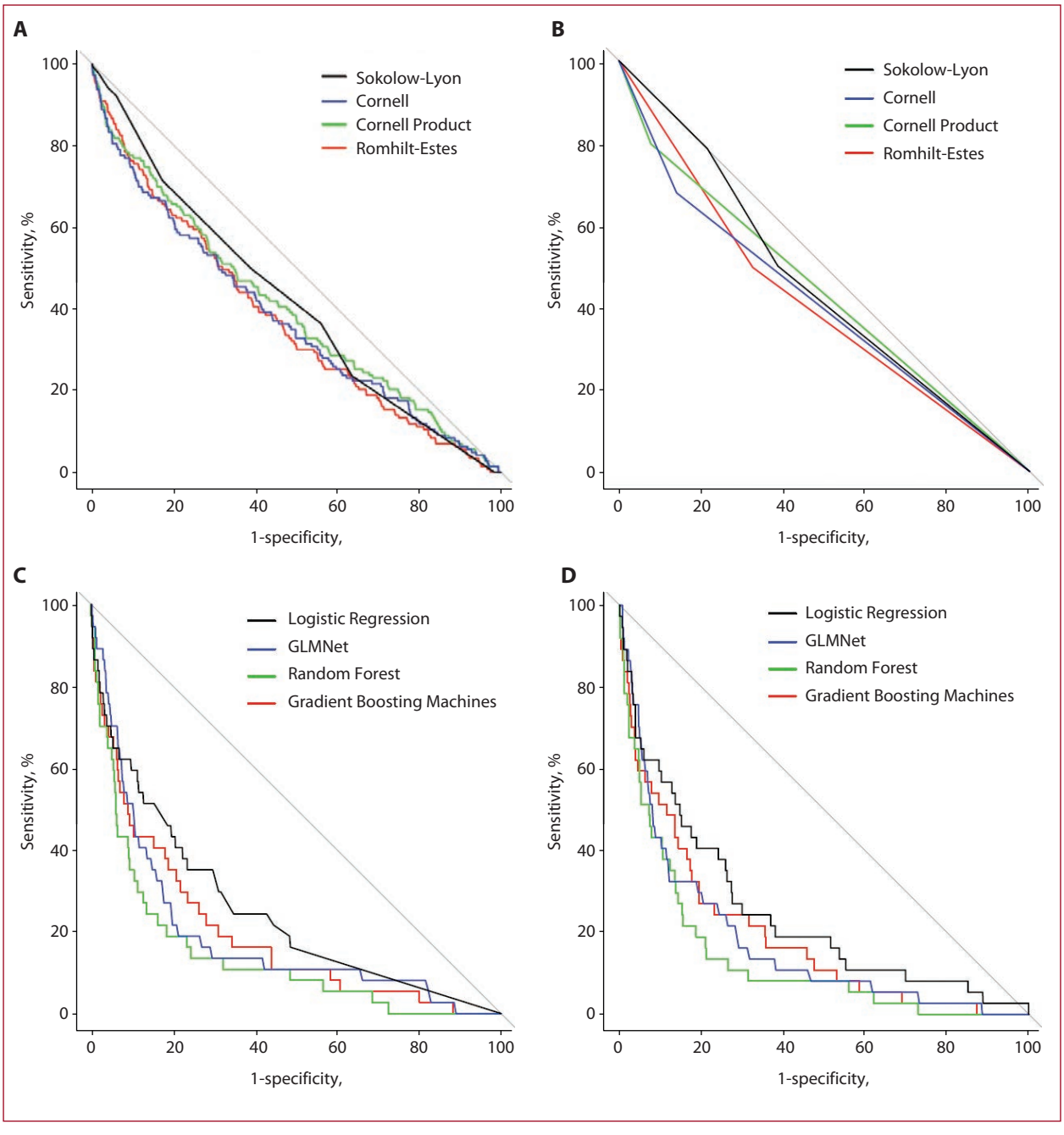

Figure 1. Composite plots of receiver operating characteristic curves for classical and machine learning models. **A.** Receiver operating characteristic plots for classical criteria (continuous). **B.** Receiver operating characteristic plots for classical criteria (thresholds). **C.** Receiver operating characteristic plots for machine learning models (with electrocardiogram parameters only). **D.** Receiver operating characteristic plots for machine learning models (with all predictive parameters)

repolarization. The left laterally directed depolarization forces may also be better represented by lead I, rather than the traditional precordial leads (such as V_5–V_6).

When trained on all available predictive parameters, the machine learning models were also able to integrate non-ECG data into their predictions, as evidenced by weight and body fat percentage being important variables identified. This suggests that the algorithms were able to learn adjustments for body habitus, an important factor that is not taken into account by classical models, but which prior studies have shown to improve diagnostic accuracy once included [24–26]. It is known that a person's habitus can affect the sensitivity and specificity of classical ECG criteria, and this is one factor that limits the accuracy of classical ECG criteria [27]. However, it is notable that the machine learning models which integrated non-ECG data had similar performance to those including ECG parameters only. This suggests that the machine learning algorithms are able to infer some of information about body habitus from the other ECG parameters, and that our models can still be applied even in cases where anthropometric information is not available.

Table 2. Area under receiver operating characteristic curve (AUC) of classical criteria and machine learning models

Predictive model		AUC (95% CI)
Classical criteria (continuous)	Sokolow–Lyon	0.629 (0.581–0.676)
	Cornell	0.599 (0.549–0.650)
	Cornell product	0.625 (0.575–0.675)
	Romhilt–Estes	0.582 (0.536–0.628)
Classical criteria (thresholds)	Sokolow–Lyon	0.589 (0.548–0.630)
	Cornell	0.562 (0.529–0.596)
	Cornell product	0.591 (0.552–0.629)
	Romhilt–Estes	0.544 (0.503–0.585)
Machine learning models (with electrocardiogram parameters only)	Logistic Regression	0.811 (0.738–0.884)
	GLMNet	0.873 (0.817–0.929)
	Random Forests	0.824 (0.749–0.898)
	Gradient Boosting Machines	0.800 (0.738–0.862)
Machine learning models (with all predictive parameters)	Logistic Regression	0.815 (0.745–0.885)
	GLMNet	0.864 (0.804–0.924)
	Random Forests	0.826 (0.756–0.897)
	Gradient Boosting Machines	0.793 (0.723–0.863)

Table 3. Table of important predictive variables for each machine learning model

Trained with electrocardiogram parameters only				Trained with all predictive parameters			
Logistic Regression	GLMNet	Random Forest	Gradient Boosting Machines	Logistic Regression	GLMNet	Random Forest	Gradient Boosting Machines
Mean QRS duration	R wave in I	Mean QT interval	Mean QT interval	Weight	Mean QT interval	Mean QT interval	R wave in I
S wave in V_4	Mean QT interval	R wave in I	R wave in V_4	Mean QRS duration	R wave in I	Weight	R wave in V_6
R wave in I	S wave in V_4	R wave in V_5	R wave in V1	Height	Weight	R wave in I	R wave in V_1
R wave in aVF	Mean QRS duration	R wave in aVL	S wave in aVR	S wave in V_4	R wave in V_4	Body fat percentage	Mean QT interval
Mean QT interval	R wave in V_4	R wave in V_4	R wave in V_6	Systolic blood pressure	S wave in V_4	R wave in V_4	R wave in V_4
R wave in III	S wave in V_3	Mean ventricular rate	R wave in I	R wave in aVF	Mean QRS duration	Mean ventricular rate	R wave in III
R wave in V_4	S wave in V_2	R wave in V_3	Mean QRS duration	R wave in III	S wave in V_3	R wave in V_3	S wave in aVR
S wave in I	R wave in II	Mean QRS duration	R wave in aVL	R wave in V_4	Systolic blood pressure	R wave in V_5	Mean ventricular rate
S wave in V_2	R wave in V_3	S wave in V_3	Mean ventricular rate	S wave in I	S wave in I	Mean QRS duration	S wave in V_3
S wave in V_5	S wave in aVR	R wave in II	R wave in V_3	S wave in V_6	S wave in V_2	R wave in aVL	R wave in V_3

A study by Kwon et al. [15] in an adult hospital cohort used a neural network based approach to improve on classical ECG criteria, with the best model (ensemble neural network) having an AUC of 0.868. Neural networks are a machine learning method which can accept unstructured data, such as an unprocessed ECG signal. They are able to use intensive computing methods to utilize information available in the signal that is not captured by conventional ECG parameters, but conversely, may be difficult to interpret (i.e. more "black-box") because the contributing information is not pre-defined as a parameter. In contrast, our study was done on a screening pre-participation cohort, and used machine learning methods which accepted only predefined parameters measured from the ECG, thus finding the most optimal ways that they could be mathematically combined. This approach also allowed identification of the most important conventional ECG parameters, for easier interpretability. Although we had a different approach, the best model in our study (GLMNet) achieved a comparable AUC of 0.873. We believe that both strategies are equally valid, and that combined strategies may be able to achieve further gains in predictive performance.

Strengths and limitations

The strength of our study is its large sample size, utilizing the data of 17 310 subjects. Furthermore, our dataset contained anthropometric variables, including body fat percentage, which are seldom collected systematically. However, we acknowledge that our study was performed in a pre-participation screening cohort, with a low incidence of actual LVH. The low number of true cases will limit gains to predictive accuracy, as subtle differences between true cases and controls will be harder to detect [28]. Further data collection with more pathological cases will help to increase the robustness of machine learning algorithms in this context.

Our study was performed exclusively in males, and there may be sex-specific differences in ECG-derived parameters or anthropometric findings. Further studies can be performed in populations of both sexes, but we believe that the techniques will be similarly applicable. We also recognize that CMRI derived LVH is the gold standard of diagnosis [29], whereas we used echocardiography to diagnose LVH. It is possible that classical criteria may perform better with CMRI as a diagnostic endpoint, as recent literature has showed that novel combinations of classical criteria can have good discriminatory power for CMRI derived LVH [30]. Nevertheless, this provides insight into the possibility of performing a similar analysis with CMRI data in the future.

One other potential limitation is that machine learning algorithms are by nature less interpretable than traditional predictive models [31]. Although it is possible to determine which variables are of importance to the algorithm, the underlying mathematical relationship to other variables is difficult to elucidate. This makes it challenging to check for problems such as overfitting [32]. Steps may be taken to guard against this, such as cross validation and separation of training and test sets [33, 34]. However, classical methods involving regression are just as susceptible to similar statistical problems, and are more likely to oversimplify the relationship between the variables. In general, all statistical models cannot determine the underlying pathophysiological reasons that make a variable predictive for pathology. For the novel predictive variables identified by our machine learning models, further studies will be needed to elucidate the underlying mechanism.

Future work

The gains in predictive accuracy found in our cohort using machine learning models should be validated in other large, external cohorts. It is possible that the novel parameters identified by our cohort will have applicability in older adults as well, and this may be explored by clinicians managing other cohorts where LVH prediction is clinically important, such as older adults, hypertensive patients and patients with cardiomyopathy.

Current consensus criteria recommend against the use of classical ECG criteria in determination of LVH from pre-participation ECGs [35], because their poor performance can lead to unnecessary investigation or exclusion from physical activities. However, no alternative criteria exists, and this may conversely lead to underdiagnosis of true LVH. More accurate machine learning models developed in this study suggest a renewed role for ECG detection of LVH, which can contribute to safer recommendations for pre-participation screening

CONCLUSIONS

Classical ECG criteria perform poorly in our young, pre-participation cohort with a low prevalence of LVH. Machine learning methods show superior predictive performance and accord high importance to less recognized predictors of LVH from ECG. Addition of anthropometric data did not improve performance of machine learning models. Further research is required to improve the predictive ability of machine learning models, to implement these models in clinical care, and to understand the underlying pathology of the novel ECG predictors identified.

Supplementary material

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

Article information

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ORIGINAL ARTICLE

A simplified acute kidney injury predictor following transcatheter aortic valve implantation: ACEF score

Begum Uygur, Omer Celik, Ali Riza Demir, Ahmet Anil Sahin, Ahmet Guner, Yalcin Avci, Umit Bulut, Omer Tasbulak, Gokhan Demirci, Fatih Uzun, Ali Kemal Kalkan, Mehmet Erturk

Cardiology Department, University of Health Sciences Turkey Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, Istanbul, Turkey

Correspondence to:
Begum Uygur, MD, İstasyon Mah. Turgut Özal Bulvarı No. 11, Küçükçekmece-Istanbul, Turkey,
phone: +90533 434 4881,
e-mail: uygurbegum@gmail.com

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ABSTRACT

Background: Transcatheter aortic valve implantation (TAVI) is an effective, less invasive treatment alternative for symptomatic severe aortic stenosis (AS). Acute kidney injury (AKI) following TAVI is a common complication and is associated with worse outcomes. The age, creatinine, ejection fraction (ACEF) score is a simple scoring method, including only three parameters: age, creatinine, and ejection fraction (EF). The score was well established in predicting AKI after coronary interventions.

Aims: We aimed to evaluate whether this simple scoring method, ACEF, may predict a development of AKI in patients who underwent TAVI.

Methods: A total of 173 consecutive patients with symptomatic severe AS who underwent TAVI were included retrospectively. The primary endpoint of the study was the development of AKI. Study population was divided into two groups according to the presence of AKI. The ACEF score was calculated with the formula: age/EF + 1 (if baseline creatinine >2 mg/dl).

Results: Twenty-nine patients developed AKI. The median (interquartile range) ACEF score was 1.36 (1.20–1.58). The ACEF score was found to be an independent predictor of AKI (P <0.001). The ACEF score ≥1.36 predicted AKI development with a sensitivity of 96.6% and specificity of 58.8%. Moreover, hypertension, hemoglobin levels, contrast volume, and aortic valve area (AVA) were found to be independent predictors of AKI.

Conclusions: Our study revealed that the ACEF score was an independent predictor of AKI. A simple and objective score might be very useful in predicting AKI development in patients undergoing TAVI.

Key words: ACEF score, acute kidney injury, transcatheter aortic valve implantation

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INTRODUCTION

Severe aortic stenosis (AS) is a common heart valve disease, especially in the elderly population and the most common treatment method used in these patients is surgical aortic valve replacement (SAVR) [1]. Transcatheter aortic valve implantation (TAVI) has emerged as a new and innovative approach to the treatment of severe AS [2, 3]. TAVI has become an effective, less invasive, and safe alternative treatment option for patients with severe AS who are not suitable for SAVR or who are considered to be at high surgical risk, and in patients with old age and some comorbidities [2, 3]. Recently, several trials have reported that TAVI can be considered an important alternative to SAVR even in patients with low and intermediate surgical risk. A surgical replacement and transcatheter aortic valve implantation trial focused on intermediate risk patients and revealed that TAVI is not inferior to SAVR [4], PARTNER 3 and Evolut Low Risk trials investigated the low-risk patients, and presented that TAVI is not inferior [5] or is even superior [6] to SAVR in terms of clinical outcomes.

Acute kidney injury (AKI) occurs after TAVI due to several factors including comorbidities of the patients, hemodynamic alterations during the procedure, and pre- or periprocedural contrast media usage [3]. Several studies investigated the utility of baseline, procedural characteristics or risk scores in predicting AKI following TAVI. These studies revealed that the development of AKI was closely associated with the patients' poor clinical outcome [7–10]. The age, creatinine, ejection fraction (ACEF) score is a simple scoring method that includes only three parameters and was originally developed to predict mortality in patients undergoing elective coronary

WHAT'S NEW?

In this manuscript, we presented that the age, creatinine, ejection fraction (ACEF) score is an independent predictor of acute kidney injury (AKI) in patients who underwent transcatheter aortic valve implantation (TAVI). A simple and objective score can be very useful in predicting AKI development. To the best of our knowledge, our study is the first that focuses on the relationship between the ACEF score and AKI development in TAVI patients.

artery bypass graft surgery [11]. Also, some investigators have examined ACEF, predicting mortality and clinical outcomes in patients undergoing percutaneous coronary intervention (PCI) [12–15]. The ACEF score has been previously studied for predicting mortality in patients who underwent TAVI but has not been fully investigated in predicting AKI. In the present study, we aimed to evaluate the utility of the ACEF score in predicting AKI in patients who underwent TAVI.

METHODS

Study population

This retrospective cohort study enrolled a total of 188 consecutive patients with symptomatic severe AS who underwent TAVI between December 2017 and June 2020 in the University Of Health Sciences Istanbul Mehmet Akif Ersoy Thoracic And Cardiovascular Surgery Training and Research Hospital, Turkey. Data was obtained after a systematic review of the patients' hospital records. The decision of TAVI was rendered with the consensus of a heart team involving cardiovascular surgeons, cardiologists, anesthesiologists, and pulmonologists. The preoperative risk was assessed with the European System for Cardiac Operative Risk Evaluation (EuroSCORE) or Society of Thoracic Surgeons (STS) risk calculator systems. Symptomatic severe AS patients who met transthoracic echocardiographic criteria at rest or with a dobutamine stress test in case of left ventricular impairment were included in study. Severe AS was defined as mean gradient >40 mm Hg, velocity >4.0 m/s, aortic valve area (AVA) <1 cm^2 or Indexed AVA <0.6 cm^2/m^2. Exclusion criteria were the absence of all medical records, already on the treatment of dialysis, patients who died during the procedure or within 72 hours after the procedure. 10 patients who were already on the hemodialysis treatment before the procedure and 5 patients who died during the procedure or in the first 72 hours were excluded from the study, and, finally, 173 patients were included in this study. The study protocol was approved by the Local Ethics Committee and the study conforms to the principles outlined in the Declaration of Helsinki.

Procedural details

The TAVI procedures were performed in a sterile environment in the catheterization laboratory under conscious sedation or general anesthesia. A transfemoral or transapical approach was used during the procedure. After the procedures, the patients were taken to the intensive care unit and followed up with non-invasive tests (including transthoracic echocardiographic, electrocardiography, and laboratory tests).

Clinical assessment and procedural complications

Transient ischemic stroke was defined as brief episodes of neurological dysfunction resulting from focal cerebral ischemia not associated with permanent cerebral infarction [16]. Moreover, ischemic stroke was defined as an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction [17]. These embolic events, the presence of clinical signs was confirmed by imaging modalities (magnetic resonance imaging with or without computed tomography angiography). The clinical diagnosis of a transient ischemic stroke, stroke, and hemorrhage was made by a neurologist. Vascular complications were categorized according to Valve Academic Research Consortium modified classification as major and minor vascular complications. Thoracic aortic dissection, access site-related vascular injury (including dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma >5 cm, irreversible nerve injury or compartment syndrome requiring >3 red blood cell units transfusion, peripheral embolization requiring surgical intervention or amputation, and left ventricular perforation were considered as major complications. Among the vascular complications, those not suitable for major complications were defined as minor complications.

Clinical histories, physical examinations, cardiovascular risk factors, pre-and post-procedural non-invasive laboratory studies, catheterization data such as implanted valve type and size, contrast volume used in the procedure, and procedural complications of the patients were reviewed and recorded. Serum creatinine levels (mg/dl) were measured within 24 hours before the procedure, immediately after the procedure, and daily until the patient was discharged. The ACEF score was calculated according to the following formula: ACEF = age/left ventricular ejection fraction (%) + 1 (if creatinine was >2.0 mg/dl).

Study endpoint

The primary endpoint of the study was the development of AKI. The AKI was defined according to Valve Academic Research Consortium-2 standardized endpoint definitions as a change in serum creatinine ≤72 hours postprocedure [18].

AKI diagnosis was made according to the following 3 major criteria: 1) increase in serum creatinine ≥1.5 times

compared with baseline, or 2) increase of ≥0.3 mg/dl (≥26.4 mmol/l), or 3) urine output <0.5 ml/kg/h for >6 h.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences, version 24.0 (SPSS Inc., Chicago, Illinois, USA). Whether the variables show normal distribution; visual (histograms, probability curves) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk) were evaluated. Numerical variables showing normal distribution were mean (standard deviation [SD]), numerical variables not showing normal distribution were expressed as median (interquartile range), and categorical variables as a percentage (%). Numerical variables were evaluated using Student t-tests and the Mann-Whitney U-test between the two groups. The chi-square or Fisher exact test were used to comparing categorical variables. Covariates including all baseline and procedural characteristics exhibiting significant *P*-value in the univariable analysis were included in a logistic regression analysis to determine the predictive factors of the incidence of AKI. Receiver operating characteristic curve analysis and Youden index (max [sensitivity + specificity – 1]) were used to determine the ideal ACEF cut-off value for predicting AKI. Throughout the present study, a *P*-value of <0.05 was considered significant.

RESULTS

We identified a total of 173 patients (mean age [SD]: 78.2 [7.4] years, male: 64) who underwent TAVI and met the inclusion criteria of the study. Patients were divided into two groups according to the presence of AKI as AKI (+) and AKI (–) groups. Twenty-nine patients were in AKI (+) group and 144 patients were in AKI (–) group. Except for age, demographic parameters were not significantly different between the two groups (P <0.001). However, hypertension rate was significantly higher (P = 0.04), and glomerular filtration rate was significantly lower in AKI (+) group (P <0.001). Also, hemoglobin levels were significantly lower in AKI (+) group (P = 0.005). AKI (+) group had significantly lower left ventricular EF (LVEF) (P <0.001) and higher STS score (P <0.001). The median (IQR) ACEF score was 1.36 (1.20–1.58) and AKI (+) group had significantly higher ACEF score (AKI [–]: 1.29 [1.15–1.46] vs AKI [+]: 1.64 [1.44–1.98], P <0.001) (Supplementary material, *Figure S1*). There was no significant difference in terms of mean aortic valve gradient; however, AVA was significantly lower in AKI (+) group (P = 0.01). Table 1 shows the demographic, clinical, echocardiographic, and laboratory characteristics of the patients.

There was no difference between the groups in terms of the type (balloon or self-expandable) and sizes of the implanted valves. The contrast volume used during the procedure was significantly higher in AKI (+) group (P = 0.001). There was no statistically significant difference between the two groups in terms of minor vascular complications and stroke; however, major vascular complications were significantly higher in the AKI (+) group (P = 0.003). AKI (+) group had a higher rate of predilation before valve implantation (P = 0.002), no significant differences were found in terms of postdilatation, access site, and rapid ventricular pacing between groups. Procedural information is presented in Table 2.

The parameters which were found to be significant in univariable analysis were taken into multivariable logistic regression analysis to determine independent associates AKI. Although age, LVEF, and STS score were found to be

Table 1. Comparison of basal demographic, clinical, echocardiographic and laboratory characteristics of the patients

	All patients (n = 173)	AKI (–) (n = 144)	AKI (+) (n = 29)	*P*-value
Age, years, mean (SD)	78.2 (7.4)	77.1 (7.3)	83.5 (5.8)	<0.001
Sex (male), n (%)	64 (37.0)	55 (38.2)	9 (31.0)	0.47
Diabetes mellitus, n (%)	58 (33.5)	49 (34.0)	9 (31.0)	0.76
Hypertension, n (%)	89 (51.4)	69 (47.9)	20 (69.0)	0.04
CAD, n (%)	115 (66.5)	96 (66.7)	19 (65.5)	0.91
PAD, n (%)	48 (27.7)	38 (26.4)	10 (34.5)	0.37
PH, n (%)	51 (29.5)	40 (27.8)	11 (37.9)	0.27
COPD, n (%)	78 (45.1)	65 (45.1)	13 (44.8)	0.98
CVE, n (%)	4 (2.3)	2 (1.4)	2 (6.9)	0.13
STS score	7.8 (5.8–9.2)	7.1 (5.3–9.0)	9.7 (7.8–12.0)	<0.001
ACEF score, median (IQR)	1.36 (1.20–1.58)	1.29 (1.15–1.46)	1.64 (1.44–1.98)	<0.001
LVEF, %	60 (55–65)	60 (55–65)	50 (40–58)	<0.001
Mean gradient, mm Hg, mean (SD)	48.4 (10.0)	47.8 (9.6)	51.3 (11.5)	0.09
AVA, cm^2, mean (SD)	0.75 (0.13)	0.76 (0.13)	0.69 (0.14)	0.010
Hemoglobin, g/dl, mean (SD)	11.0 (1.6)	11.2 (1.6)	10.3 (1.4)	0.005
Creatinine, mg/dl, median (IQR)	1.00 (0.83–1.20)	0.98 (0.82–1.15)	1.04 (0.90–1.30)	0.06
GFR, ml/min, mean (SD)	65.9 (18.9)	68.8 (18.5)	51.7 (14.1)	<0.001

Data is presented as percentage, mean (SD) or median (IQR).
Abbreviations: ACEF, age, creatinine, ejection fraction; AKI, acute kidney injury; AVA, aortic valve area; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVE, cerebrovascular event; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; PAD, peripheral artery disease; PH, pulmonary hypertension; STS, Society of Thoracic Surgeons

Table 2. Comparison of the groups according to the procedural features

	All patients (n = 173)	AKI (–) (n = 144)	AKI (+) (n = 29)	*P*-value
Balloon expandable	86 (49.7)	73 (50.7)	13 (44.8)	0.56
Self-expandable	87 (50.3)	71 (49.3)	16 (55.2)	0.56
Valve size, median (IQR)	27 (26–29)	27 (26–29)	29 (26–29)	0.72
Contrast volume, ml, median (IQR)	125 (100–160)	120 (95–154)	150 (130–193)	0.001
Major vascular complication	11 (6.4)	5 (3.5)	6 (20.7)	0.003
Minor vascular complication	38 (22.0)	33 (22.9)	5 (17.2)	0.50
Stroke	8 (4.6)	6 (4.2)	2 (6.9)	0.62
Post-op blood transfusion	40 (23.1)	29 (20.1)	11 (37.9)	0.04
Predilatation	75 (43.4)	55 (38.2)	20 (69.0)	0.002
Postdilatation	48 (27.7)	40 (27.8)	8 (27.6)	0.98
Rapid pacing	139 (80.3)	117 (81.3)	22 (75.9)	0.51
Access site (apical)	6 (3.5)	5 (3.5)	1 (3.4)	1.0

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

Abbreviations: see Table 1

Table 3. Univariable and multivariable analysis for detecting the predictors of acute kidney injury following transcatheter aortic valve implantation

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age,	1.140 (1.068–1.218)	<0.001		
Hypertension	5.217 (1.886–14.432)	0.001	15.310 (3.283–71.398)	0.001
Creatinine	2.745 (0.843–8.942)	0.09		
STS	1.316 (1.153–1.503)	<0.001		
LVEF	0.927 (0.893–0.962)	<0.001		
ACEF score	7.142 (2.648–19.264)	<0.001	22.911 (5.104–102.84)	<0.001
AVA	0.018 (0.001–0.413)	0.01	0.009 (<0.001–0.957)	0.048
Hemoglobin	0.560 (0.491–0.889)	0.006	0.388 (0.242–0.622)	<0.001
Contrast volume	1.006 (1.000–1.012)	0.04	1.016 (1.007–1.026)	0.001
Predilatasyon	3.596 (1.529–8.460)	0.003	2.373 (0.787–7.633)	0.15

Abbreviations: see Table 1

significant in the univariable analysis, they were not included in the multivariable analysis because age and LVEF are the components of ACEF score, and the ACEF score parameters exists in the STS score. Hypertension (OR, 15.31; 95% CI, 3.28–71.40; $P = 0.001$), ACEF score (OR, 22.91; 95% CI, 5.10–102.84; $P < 0.001$), hemoglobin levels (OR, 0.39; 95% CI, 0.24–0.62; $P < 0.001$), contrast volume (OR, 1.016; 95% CI, 1.007–1.026; $P = 0.001$), and AVA (OR, 0.009; 95% CI, <0.001–0.957; $P = 0.048$) were found to be independent predictors of AKI (Table 3).

Receiver operating characteristic analysis was generated to detect the optimal cut-off value of the ACEF score in predicting AKI (Supplementary material, *Figure S2*). The ACEF score higher than 1.36 predicted AKI with a sensitivity of 96.6%, specificity of 58.8%, positive predictive value of 34.1%, negative predictive value of 98.7%, and accuracy of 65.6% (area under curve [AUC]: 0.821; 95% CI, 0.752–0.891; $P < 0.001$).

DISCUSSION

In the present study, we evaluated the effect of the ACEF score and other traditional AKI risk parameters on AKI development in patients who underwent TAVI. Three major findings of the current study are: 1) an ACEF score was an independent predictor of AKI in TAVI patients; 2) an ACEF score ≥1.36 predicted AKI with the sensitivity of 96.6% and specificity of 58.8%; 3) hypertension, hemoglobin levels, contrast volume, and AVA were also found to be independent predictors of AKI following TAVI.

The ACEF score is a very simple scoring system that includes only 3 parameters: age, creatinine, and LVEF. Previously, it was found to be associated with AKI following primary PCI [15, 19] and coronary catheterization [20]. The ACEF score has previously been studied in patients undergoing TAVI, but most of these studies focused on predicting mortality from the ACEF score [21, 22]. In addition, previously, some studies showed the relationship between increasing age and AKI development in TAVI patients [23], nevertheless, some studies revealed that there was no statistically significant relationship between age and AKI development [9, 10, 24]. Although low LVEF has previously been reported to be an important predictor of AKI development [23, 24], Pyxaras et al. [25] indicated that low LVEF is not associated with the development of AKI after TAVI. Moreover, Elhmidi et al. showed that preprocedural creatinine level was a predictor of AKI [26]; however, some

investigators revealed no relation between creatinine levels and AKI development [25]. In our study, we found that age and LVEF were associated with AKI in TAVI patients, whereas creatinine level was not associated with the development of AKI. Based on the results of previous studies and our study, the effects of these three parameters on AKI development after TAVI are still controversial. The combination of multiple parameters increases the accuracy of risk models; however, including too many parameters will be difficult in daily clinical use. The main benefit of the ACEF score is its easy accessibility, three parameters, and simple calculability. Our study showed that the ACEF score was an independent predictor of AKI in patients undergoing TAVI. In the current literature, several studies were reported on the short and long-term mortality after TAVI procedure or comparison of the ACEF score with the other scores. In addition to our research, only Arai et al. [27] investigated the development of AKI in this patient population. However, they investigated the development of AKI with a modified ACEF score, which included creatinine clearance instead of creatinine. They also found that the modified ACEF score is an independent predictor of AKI. Gender, age, weight, and creatinine values are used in the calculation of creatinine clearance. Creatinine clearance is a better predictor of AKI when compared to serum creatinine in the patients who underwent coronary artery bypass graft surgery [28, 29] and the modified ACEF score has been reported to increase the accuracy of the original ACEF score among PCI patients [30–32]. However, there is no study comparing modified ACEF and original ACEF in TAVI patients. In our study, we can comment that both original and modified ACEF scores predict AKI in patients undergoing TAVI. To the best of our knowledge, there is no study which focuses fully on the role of ACEF score in predicting AKI in TAVI patients.

The relationship between contrast volume and AKI development is also controversial. Previously, Barbash et al. reported that there was no statistical difference in the contrast volume used during the procedure between the groups with and without AKI (117 ± 88 ml vs 98 ± 46 ml, $P = 0.13$) [26]. In another study, it was shown that there was no statistical difference between AKI stages and contrast volume (103.84 ± 58.53 ml vs 122.61 ± 96.79 ml, $P = 0.78$) [33]. In 2012, Madershahian et al. [34] evaluated the risk of AKI after TAVI and reported a significantly increased risk of AKI when comparing patients who received a contrast volume of >100 ml vs <100 ml of contrast volume. A recent metaanalysis by Thongprayoon et al. [35] demonstrated no association between high contrast media volume and the risk of AKI following TAVI. Hence, the dose of contrast media may not play a significant role in the pathogenesis of TAVI-related AKI. This finding will likely impact the direction of future studies for TAVI-related AKI prevention. In contrast to the findings, Yamamoto et al. [24] indicated that a relationship between contrast volume increment and high prevalence of AKI. Although contrast volume was not identified as an independent predictor of AKI after TAVI in previous reports [26, 33–35], it is still of utmost importance to establish whether contrast volume should be limited in TAVI procedures carried out in an elderly and high risk cohort [36]. Similar to the findings of Yamamoto et al. [24], in the present study, we found that contrast volume was an independent predictor of AKI development in TAVI patients. In a review article, Legnazzi et al. [37] reported how to prevent contrast induced AKI in the patients undergoing PCI in detail. These approaches might be applied to the TAVI patients to avoid AKI development, however it should be supported with large prospective studies. We also found that hypertension was one of the independent predictors of AKI, which is consistent with the current literature [23, 36].

In the present study, AKI (+) group had significantly lower hemoglobin levels, and lower hemoglobin levels were found to be the independent predictors of AKI. Previously, Nuis et al. [38] revealed that periprocedural anemia was not associated with AKI after TAVI procedures. Hence, the relationship between hemoglobin levels and the development of AKI is still controversial. Larger randomized studies are needed to confirm the relationship between hemoglobin levels and AKI development.

The present study has several limitations. First of all, this was a single-center, retrospective study, and included a relatively small patient population. Thus, large prospective cohort studies are needed to fully appreciate and validate our findings. Second, there was no standard pre- and post-hydration regimen for patients who underwent TAVI.

In conclusion, our study showed that a simple and objective score, ACEF, may predict AKI development in patients who underwent TAVI.

Supplementary material

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

Article information

Conflict of interest: None declared.

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ORIGINAL ARTICLE

Association between calcifications of mitro-aortic continuity and mitral regurgitation in patients undergoing transcatheter aortic valve replacement

Małgorzata Ryś[1], Tomasz Hryniewiecki[1], Adam Witkowski[2], Ilona Michałowska[3], Karina Zatorska[1], Patrycjusz Stokłosa[1], Małgorzata Nieznańska[1], Piotr Szymański[4]

[1]Department of Valvular Heart Disease, National Institute of Cardiology, Warszawa, Poland
[2]Department of Interventional Cardiology and Angiology, National Institute of Cardiology, Warszawa, Poland
[3]Department of Radiology, National Institute of Cardiology, Warszawa, Poland
[4]Center for Non-Invasive Cardiovascular Diagnostic Services, Central Clinical Hospital of MSWiA and Center for Postgraduate Medical Education, Warszawa, Poland

Correspondence to:
Prof. Piotr Szymański, MD, FESC, Center for Non-Invasive Cardiovascular Diagnostic Services, Central Clinical Hospital of MSWiA, Wołoska 137, 02–507 Warszawa, Poland, phone: +477721830, e-mail: pszymanski@ptkardio.pl

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ABSTRACT

Background: The presence of mitral annular calcification (MAC) affects prognosis in patients undergoing transcatheter aortic valve implantation (TAVI). MAC frequently coexists with calcifications of mitro-aortic continuity (CMAC).

Aims: We aimed at qualitative and semi-quantitative analysis of calcifications of the mitral complex — MAC and CMAC in multi-slice computed tomography, in order to assess their impact on the occurrence and dynamics of mitral regurgitation (MR) following TAVI.

Methods: The study group consisted of 94 patients (mean [SD] age was 79.9 [8.02] years; 67.1% female). Agatston scale — Calcium Score was used for quantitative analysis. MAC and CMAC were also assessed semi-quantitatively as either non-severe or severe. MR following TAVI was defined as unchanged, improved or worsened by at least one degree.

Results: Patients with MAC (59.6%) had higher mean aortic gradients ($P = 0.02$) and smaller left ventricular diastolic diameter ($P = 0.002$). Patients with CMAC (48.9%) had higher Calcium Score aortic valve ($P = 0.006$). After TAVI MR improved in 17 (18.1%) patients and worsened in 7 (7.5%) patients. In multivariable logistic regression analysis MR worsening was associated with higher CMAC (OR, 1.092; 95% CI, 1.006–1.185; $P = 0.03$), as well as bicuspid aortic valve (OR, 6.348; 95% CI, 1.048–38.436; $P = 0.04$).

Conclusions: CMAC was associated with MR worsening following TAVI. This is of relevance in procedural planning in patients with severe aortic stenosis (AS) and coexisting MR in whom arguments for and against surgical repair of concomitant mitral insufficiency are considered.

Key words: aortic stenosis, calcification of mitro-aortic continuity, mitral annular calcification, mitral regurgitation, transcatheter aortic valve implantation

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INTRODUCTION

Mitral annular calcification (MAC) occurs as a result of a chronic degenerative process of the fibrous support structure of the mitral valve. MAC is present in approximately 8%–15% of the general population, more often in women [1–3]. MAC commonly coexists with aortic stenosis (AS) [4, 5] and may have similar etiology and pathophysiological mechanism [6, 7]. About one-fifth of patients with mild to moderate AS and half with severe AS have at least some degree of MAC [4, 8]. Half of all patients undergoing transcatheter aortic valve implantation (TAVI) have MAC, and approximately 20% have severe MAC [8–11]. The latter is associated with increased all-cause and cardiovascular mortality and with conduction abnormalities in patients undergoing TAVI [10, 11]. Several studies assessed the role of mitral regurgitation (MR) following TAVI [12, 13], but only few examined the influence of MAC on its changes after TAVI [8, 11, 14, 15]. MAC frequently coexists with calcification of mitro-aortic continuity (CMAC) [16]. The latter may influence the results of TAVI, especially in the case of deeper implantation, protruding to left ventricular outflow tract (LVOT). To the best of our knowledge, the role of CMAC on

WHAT'S NEW?

Aortic valve calcifications in patients with aortic stenosis (AS) undergoing transcatheter aortic valve implantation (TAVI) are frequently accompanied by calcifications of mitro-aortic continuity (CMAC). Their presence is frequently disregarded and not included in the qualitative and semi-quantitative analyses of calcifications of the aortic-mitral complex. We have demonstrated that the presence of CMAC was associated with mitral regurgitation (MR) worsening after TAVI. This is a novel finding, which may be of relevance for procedural planning, in particular in patients with severe AS and coexisting MR in whom arguments for and against surgical repair of concomitant mitral insufficiency are considered, as opposed to isolated aortic valve procedure.

the occurrence and dynamic changes of MR during TAVI procedure has never been examined.

In the present study we aimed at qualitative and semi-quantitative analysis of calcifications of the mitral complex — MAC and CMAC in multi-slice computed tomography (MSCT) in patients qualified to TAVI, in order to assess their impact on the occurrence and dynamics of MR following aortic valve implantation.

METHODS

Study group

We retrospectively examined 94 consecutive patients with severe AS who underwent TAVI procedure at the Institute of Cardiology in Warsaw, between January 2016 and December 2017. The study protocol was approved by the local Bioethics Committee. All examined patients presented severe symptomatic AS and had been disqualified from surgical aortic valve replacement by an institutional Heart Team. Informed consent for diagnostic and treatment procedures was obtained from all patients.

Before TAVI, all patients underwent routine laboratory testing, transthoracic echocardiography (TTE), coronary angiography, MSCT as well as angio-MSCT of iliac and femoral arteries [17]. Aortic valve anatomy and diameter were evaluated by TTE and MSCT [18]. These studies were used for proper planning of the valve implantation in terms of selection of access route, valve size, and complication risk assessment.

Multi-slice computed tomography

Before TAVI procedure, all patients underwent MSCT with and without contrast. MSCT was performed using a dual-source third generation scanner, Somatom Force (Siemens Healthcare, Forchheim, Germany). CT acquisition parameters were: slice collimation $2 \times 192 \times 0.6$ mm, 384 layers, gantry rotation time 250 ms, tube voltage 80–120 kV, tube current 320–500 mAs (depending on the patient body mass).

A prospective ECG gated non-contrast scan was performed to measure the Calcium Score of the aortic valve and mitral annulus. MAC and CMAC were evaluated in MSCT after contrast administration.

MSCT with contrast was routinely performed in patients before TAVI for evaluation of coronary arteries and access to TAVI (entire aorta and iliofemoral arteries). A bolus of 70 to 100 ml (depending on the patient body mass) of iodinated contrast media (Ultravist 370 Bayer Pharma AG) was administered through an antecubital vein at a rate of 4.0 ml/s.

Quantitative assessment of aortic valve calcifications was done using the Agatston scale — Calcium Score aortic valve [19, 20]. MAC was evaluated quantitatively and semi-quantitatively and CMAC was assessed semi-quantitatively.

MAC was defined as the presence of dense calcium deposits at the base of mitral leaflets at the level of the mitral annulus. The quantitative assessment of calcifications — Calcium Score mitral annulus — was done using the Agatston scale based on the maximum X-ray absorption coefficient measured in Hounsfield units (HU) and the measurement of the calcium deposits size. The absorbing structures were considered to be 130 HU and more.

MAC was assessed in cross-sectional view parallel to the plane of the mitral annulus and rated in the semi-quantitative scale, depending on the degree of annular involvement, in the following way: 0, no calcifications; 1, mild calcifications (less than one-third of the circumference of the annulus involved); 2, moderate calcifications (between one-third and half of the annulus circumference); 3, severe calcifications (more than half of the annulus circumference), according the methodology adopted by others [11, 21].

CMAC was defined as the presence of calcifications localized in the posterior aspect of LVOT — in the continuity between the base of anterior mitral leaflet/mitral annulus and non-coronary aortic cusp. Calcifications localized in the posterior (CMAC) and anterior aspect of LVOT are shown on Figure 1.

CMAC was evaluated semi-quantitatively in sagittal oblique view and assessed along the maximum length of calcification. CMAC was rated depending on the length of calcifications in the largest dimension the following way: 0, no calcifications; 1, mild calcifications (less than 3 mm); 2, moderate calcifications (3–8 mm); 3, severe calcifications (over 8 mm); according the methodology adopted by others [10].

Subsequently, patients were classified in a dichotomous manner as having non-severe or severe MAC and CMAC (grades 0, 1, and 2 versus grade 3). Classification was performed by a single observer, experienced in the

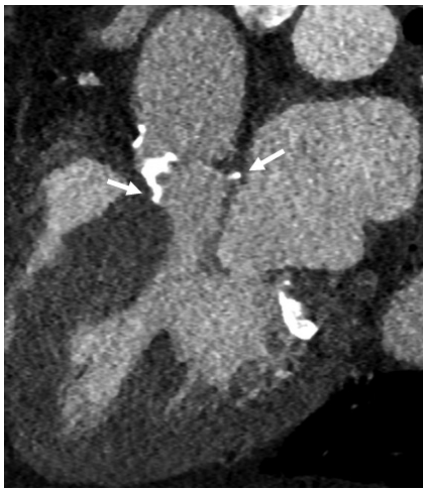

Figure 1. Comparison of calcifications localized in the anterior and posterior aspect of the left ventricular outflow tract in oblique sagittal projection on multislice computed tomography

assessment of pre-TAVR CT scans, blinded to the clinical and other imaging data.

Echocardiography

All patients underwent TTE (Vivid E95, Vivid S70) prior to the procedure, either during the same or preceding hospitalization, as part of diagnostic routine assessment. The follow-up transthoracic echocardiographic examination was routinely performed before discharge following TAVI procedure and up to 30 days after TAVI.

MR was evaluated in an integrated manner, according to a current standard, based on color Doppler jet area, vena contracta, proximal isovelocity surface area, effective regurgitant orifice [22, 23], and graded as: 0, no MR; 1, mild MR; 2, moderate MR; 3, severe MR; with significant MR defined as grade ≥2. Changes of MR severity following TAVI were defined as no change, improvement, or worsening by at least one degree.

Statistical analysis

Continuous variables with normal distribution were presented as means with their standard deviations, and in the case of non-normally distributed variables (as confirmed by the Kolmogorov-Smirnov test), in the form of the median and the interquartile range. Categorical variables were expressed as percentages. Patients were divided into groups with severe vs non-severe/absent MAC and CMAC, as previously defined. Comparative analyzes of continuous variables were done using the Student t-test or the Mann-Whitney tests, and of discrete variables using the chi-square test.

In order to evaluate if the degree of calcification of mitral complex affects MR in patients undergoing TAVI, single- and multi-variable logistic regression analyses were used.

A univariate logistic regression analysis was performed to obtain the odds ratio for worsening MR after TAVI.

The following variables were used in univariate models: age, female sex, clinical factors (hypertension, coronary artery disease**,** diabetes mellitus, atrial fibrillation, chronic renal failure, estimated glomerular filtration rate [eGFR]), echocardiographic parameters (left ventricular diastolic diameter, left ventricular systolic diameter, interventricular septal, ejection fraction, LVOT, aortic root, maximum aortic gradient, mean aortic gradient), bicuspid aortic valve (BAV), Calcium Score aortic valve, Calcium Score mitral annulus, CMAC and MAC.

Thereafter, a multivariable logistic regression analysis was performed using the variables with *P*-values <0.10 in the univariate analyses, to examine their independent association with MR worsening after TAVI. Results of the regression model were presented as odds ratios, with 95% confidence intervals. A *P*-value <0.05 was considered statistically significant. All analyses were performed using SAS 9.2.

RESULTS

The study group consisted of 94 patients (63 female [67.1%]), undergoing TAVI. The mean (SD) age of patients was 79.9 (8.02) years. Clinical characteristics and echocardiographic parameters of the studied patients are presented in Table 1. Examples of MAC and CMAC in MSCT are shown in Figure 2 and Figure 3.

Table 1. Baseline characteristics of the study group

Characteristics of patients (n = 94)	
Age, years, mean (SD)	79.86 (8.02)
Female sex, n (%)	63 (67.1)
Hypertension, n (%)	76 (80.8)
Diabetes mellitus, n (%)	34 (36.2)
Coronary artery disease, n (%)	52 (55.3)
Chronic lung disease, n (%)	15 (16.0)
Atrial fibrillation, n (%)	39 (41.5)
NYHA functional class III, n (%)	28 (29.8)
NYHA functional class IV, n (%)	3 (3.2)
eGFR, ml/min, mean (SD)	58.30 (18.67)
BAV, n (%)	23 (25.6)
Pacemaker before TAVI, n (%)	16 (17.2)
LVDD, mm, mean (SD)	48.14 (7.90)
LVDS, mm, mean (SD)	31.11 (9.54)
IVDS, mm, mean (SD)	14.53 (2.42)
EF, %, mean (SD)	55.12 (13.27)
Maximum aortic gradient, mm Hg, mean (SD)	83.58 (22.67)
Mean aortic gradient, mm Hg, mean (SD)	51.13 (14.33)
AVA, cm^2, mean (SD)	0.66 (0.18)
Aortic annulus TTE, mm, mean (SD)	22.99 (2.15)
Aortic root, mm, mean (SD)	31.53 (4.00)
Calcium Score mitral annulus, HU, median (IQR)	161 (0–3016)
Calcium Score aortic valve, HU, median (IQR)	3416 (856.8–8868)

Abbreviations: AVA, aortic valve area; BAV, bicuspid aortic valve; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HU, Hunsfield units; IVDS, interventricular septal; LVDD, left ventricular diastolic diameter; LVDS, left ventricular systolic diameter; NYHA, New York Heart Association; SD, standard deviation; TAVI, transcatheter aortic valve implantation; TTE, transthoracic echocardiography

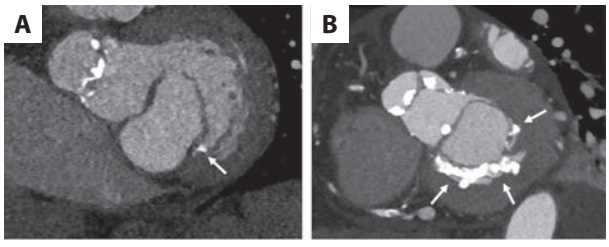

Figure 2. Comparison of reconstruction views showing non-severe mitral annular calcification (**A**) and severe mitral annular calcification (**B**) in sectional view parallel to the mitral annular on multislice computed tomography

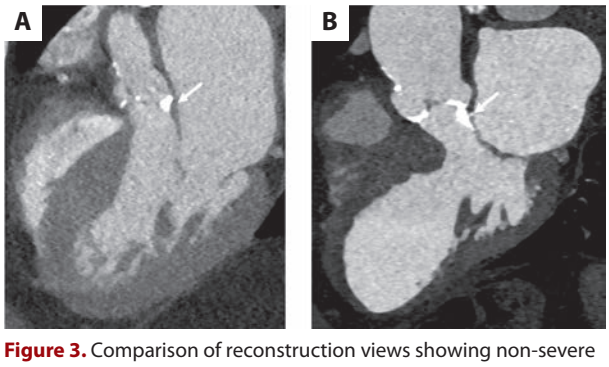

Figure 3. Comparison of reconstruction views showing non-severe calcifications of mitro-aortic continuity (**A**) and severe calcifications of mitro-aortic continuity (**B**) in sagittal oblique view on multislice computed tomography

MAC

Median and the interquartile range of Calcium Score mitral annulus was 161 (0–3016) HU. Fifty six (59.6%) out of 94 patients had MAC. Mild MAC was present in 25 patients (26.7%), moderate MAC in 10 patients (10.6%), and severe MAC in 21 patients (22.3%).

MAC was more prevalent in females (82.1% vs 44.7%; P <0.001) compared to patients without MAC. Patients with MAC had higher mean aortic gradients (mean [SD] 54.07 [13.62] mm Hg vs 46.79 [14.42] mm Hg; P = 0.02) and smaller left ventricular diastolic diameter (mean [SD] 46.09 [6.86] mm vs 51.19 [8.42] mm; P = 0.002) and trend to older patients (mean [SD] 81.09 [7.56] years vs 78.05 [8.42] years; P = 0.07) compared to patients without MAC. Comparison of selected variables in patients with no/non-severe MAC versus severe MAC is presented in Table 2.

CMAC

Almost half of the patients (46 [48.9%]) had CMAC. Mild CMAC was present in 21 patients (22.3%), moderate CMAC in 13 patients (13.8%), and severe CMAC in 12 patients (12.8%). Patients with CMAC had higher Calcium Score aortic valve (mean [SD] 3773.67 [1734.02] HU vs 2875.1 [1352.76] HU; P = 0.006) and a trend to smaller aortic valve area (AVA) (mean [SD] 0.59 [0.16] cm^2 vs 0.66 [0.20] cm^2; P = 0.05) compared to patients without CMAC.

Table 2. Baseline characteristic of patients with and without severe mitral annular calcification, as well as with and without severe calcification of mitro-aortic continuity (n = 94)

	Non severe MAC (n = 73)	Severe MAC (n = 21)	*P*-value	Non severe CMAC (n = 82)	Severe CMAC (n = 12)	*P*-value
Age, years, mean (SD)	78.79 (8.01)	83.57 (7.00)	0.01	80.32 (7.65)	76.75 (9.99)	0.15
Female sex, n (%)	46 (63.0)	17 (80.9)	0.12	52 (63.4)	11 (91.7)	0.09
Hypertension, n (%)	58 (79.4)	18 (85.7)	0.75	66 (80.5)	10 (83.3)	1.00
Coronary artery disease, n (%)	39 (53.4)	13 (61.9)	0.49	48 (58.5)	4 (33.3)	0.10
Diabetes mellitus, n (%)	29 (39.7)	5 (23.8)	0.18	30 (36.6)	4 (33.3)	1.00
Atrial fibrillation, n (%)	33 (54.8)	6 (28.6)	0.17	35 (42.7)	4 (33.3)	0.76
Chronic lung disease, n (%)	13 (17.8)	2 (9.5)	0.51	14 (17.1)	1 (8.3)	0.68
eGFR, ml/min, mean (SD)	57.57 (19.12)	60.84 (17.22)	0.48	58.73 (18.62)	55.4 (19.59)	0.57
BAV, n (%)	21 (30.0)	2 (10.0)	0.07	16 (20.2)	7 (63.6)	0.005
LVDD, mm, mean (SD)	49.35 (8.05)	44.05 (5.82)	0.006	48.41 (8.06)	46.18 (6.57)	0.38
LVDS, mm, mean (SD)	32.25 (10.17)	26.57 (4.50)	0.04	30.79 (9.73)	36.5 (2.12)	0.42
IVDS, mm, mean (SD)	14.17 (2.07)	15.80 (3.12)	0.04	14.51 (2.31)	14.64 (3.23)	0.87
EF, %, mean (SD)	53.75 (14.20)	59.76 (8.14)	0.02	55.35 (13.70)	53.45 (9.81)	0.66
LVOT, mm, mean (SD)	21.54 (2.08)	20.25 (1.48)	0.01	21.43 (2.06)	20.17 (1.40)	0.01
Aortic annulus TTE, mm, mean (SD)	23.20 (2.25)	22.00 (1.45)	0.006	23.09 (2.21)	21.92 (1.38)	0.02
Aortic root, mm, mean (SD)	31.79 (3.88)	30.63 (4.41)	0.27	31.47 (3.87)	32.00 (5.10)	0.69
AVA, cm^2, mean (SD)	0.80 (0.15)	0.66 (0.05)	0.01	0.78 (0.14)	0.63 (0.04)	0.008
Maximum aortic gradient, mm Hg, mean (SD)	82.48 (22.42)	87.38 (23.68)	0.39	83.52 (23.78)	83.96 (13.49)	0.92
Mean aortic gradient, mm Hg, mean (SD)	50.42 (14.09)	53.60 (15.24)	0.37	50.86 (14.97)	52.97 (9.11)	0.64
RVSP, mm Hg, mean (SD)	47.15 (14.73)	40.92 (8.81)	0.06	46.80 (14.03)	39.43 (12.80)	0.19
Pulmonary hypertension, n (%)	33 (45.2)	8 (38.1)	0.56	38 (47.8)	3 (25.0)	0.16
Calcium Score mitral annulus, HU, median (IQR)	0 (0–460.7)	5661 (4008–7598)	<0.0001	139.4 (0–2324)	689.7 (149–4040)	0.18
Calcium Score aortic valve, HU, mean (SD)/median (IQR)	3330.5 (1518.4)	3260.4 (1926.3)	0.86	3113 (1982–4000)	3960 (3371–4474)	0.02

Abbreviations: AVA, aortic valve area; BAV, bicuspid aortic valve; CMAC, mitro-aortic continuity; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HU, Hunsfield units; IVDS, interventricular septal; LVDD, left ventricular diastolic diameter; LVDS, left ventricular systolic diameter; LVOT, left ventricular outflow tract; MAC, mitral annular calcification; RVSP, right ventricular systolic pressure; SD, standard deviation; TTE, transthoracic echocardiography

Comparison of selected variables in patients with no/non-severe CMAC versus severe CMAC is presented in Table 2.

Association between MAC/CMAC and mitral regurgitation following TAVI

Before TAVI 64.9% of patients had mild or no MR (grades 1 or 0) and 35.1% of the patients had more than mild MR (grades 2 or 3). After TAVI 77.6% of patients had mild or no MR (grades 1 or 0). Patients with higher degrees of MR before TAVI had lower ejection fraction (EF) (mean [SD] 49% [15.12%] vs 58.38% [10.96%]; $P = 0.003$) as well as more frequent pulmonary hypertension (60.6% vs 34.3%; $P = 0.01$).

Calcium Score mitral annulus ($P = 0.34$), Calcium Score aortic valve ($P = 0.59$), MAC ($P = 0.15$) and CMAC ($P = 0.70$) were similar in patients with and without significant MR at baseline. MR improved by at least one grade following TAVI in 17 (18.1%) patients and worsened by at least one grade in 7 (7.5%).

Patients in whom MR improved after TAVI had diabetes mellitus more frequently (58.8% vs 31.2%; $P = 0.03$) and had a trend to lower baseline EF (mean [SD] 49.71% [12.92%] vs 56.35% [13.13%]; $P = 0.06$). Patients in whom MR worsened after TAVI more frequently had BAV (71.4% vs 21.7%; $P = 0.01$) and CMAC ($P = 0.03$).

The results of univariate logistic regression analysis of factors influencing MR worsening following TAVI are presented in Table 3. In multivariable logistic regression analysis, MR worsening was associated with higher CMAC (OR, 1.092; 95% CI, 1.006–1.185; $P = 0.03$), as well as the presence of BAV (OR, 6.348; 95% CI, 1.048–38.436; $P = 0.04$).

Table 3. Univariable logistic regression analysis: factors independently associated with MR worsening after TAVI

Variables	Univariable logistic regression analysis	
	OR (95% CI)	*P*-value
Age, years	0.96 (0.88–1.05)	0.41
Female sex	1.58 (0.33–7.54)	0.68
Hypertension	0.56 (0.10–3.17)	0.62
Coronary artery disease	0.58 (0.12–2.76)	0.69
Diabetes mellitus	1.35 (0.28–6.45)	0.70
Atrial fibrillation	1.98 (0.42–9.34)	0.44
eGFR, ml/min	0.99 (0.95–1.03)	0.71
BAV	9.03 (1.64–50.46)	0.01
LVDD, mm	1.03 (0.94–1.13)	0.52
LVDS, mm	0.97 (0.83–1.12)	0.65
IVDS, mm	1.12 (0.82–1.52)	0.49
EF, %	0.99 (0.93–1.04)	0.64
LVOT, mm	0.89 (0.60–1.34)	0.59
Aortic annulus TTE, mm	1.08 (0.77–1.52)	0.65
Aortic root, mm	1.148 (0.966–1.363)	0.11
Maximum aortic gradient, mm Hg	1.01 (0.98–1.05)	0.54
Mean aortic gradient, mm Hg	1.02 (0.96–1.08)	0.49
Calcium Score mitral annulus, HU	0.94 (0.76–1.16)	0.55
Calcium Score aortic valve, HU	2.47 (0.46–13.27)	0.29
CMAC ≥2, 3[a]	1.10 (1.02–1.19)	0.01
MAC ≥2[a]	0.56 (0.06–4.92)	1.00

[a]Grades of calcifications: 1, mild; 2, moderate; 3, severe.

Abbreviations: BAV, bicuspid aortic valve; CI, confidence interval; CMAC, mitro-aortic continuity; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HU, Hunsfield units; IVDS, interventricular septal; LVDD, left ventricular diastolic diameter; LVDS, left ventricular systolic diameter; LVOT, left ventricular outflow tract; MAC, mitral annular calcification; OR, odds ratio; TTE, transthoracic echocardiography

DISCUSSION

MAC and CMAC are frequent in severe aortic valve stenosis. In our study, MAC and CMAC were present in approximately half of the patients undergoing TAVI. In our series, MR severity changed following TAVI, as also described by others [8, 11–13, 24, 25].

Female sex, higher transvalvular gradient, and older age were more frequently present in patients with MAC, which is consistent with previous reports [4, 26]. Anatomic features, important from diagnostic and procedural point of view, such as narrower aortic annulus and LVOT and thicker interventricular septum, were associated with severe MAC. Conversely, other conditions frequently reported as risk factors for MAC (e.g, hypertension, diabetes mellitus, advanced kidney disease, atrial fibrillation) were not independent predictors in our population, perhaps due to smaller numbers and preselection of patients with AS [2, 27]. Only few studies examined the influence of MAC on the degree of MR after TAVI, with discordant results [8, 11, 14, 15]. In some series MAC was associated with worsening of MR [8, 14, 15]. Other authors did not report such relationship [11]. We did not observe differences in the degree of MR after TAVI in patients with and without MAC; however, the number of patients in whom the MR worsened was small.

In contrast to the relatively well defined role of MAC in patients with AS, including those undergoing TAVI, little is known about the potential role of CMAC in these patients. We demonstrated a correlation between CMAC and higher Calcium Score aortic valve, thicker ventricular septum, narrower aortic annular and LVOT diameters, smaller AVA, as well as female sex. These are important endpoints, relevant both to the diagnosis of severe AS, and to procedural issues, such as valve sizing, as well as prognosis [28]. A closer look at CMAC in larger datasets is necessary in order to better establish its influence on the procedure and its long term results.

The presence or absence of CMAC in patients with MAC may offer explanation to the discordant results of the studies examining the influence of MAC on the degree of MR after TAVI. Previous studies did not clearly distinguish between MAC and CMAC. In our study however, in contrast to MAC, the presence of CMAC was an independent predictor of worsened MR. To the best of our knowledge, this study is the first in which the role of CMAC in MR development was assessed. This is an important and novel finding, that may have implications in clinical practice. CMAC influences both LVOT geometry and mitral valve function. Theoretically, the presence of CMAC, working as a rigid scaffold, may limit potentially favorable reverse remodeling of mitral valve apparatus related to improved left ventricular function following TAVI.

The presence of CMAC may also influence prosthetic valve positioning and expansion, indirectly affecting also anterior mitral valve leaflet movement restriction. This is probably especially relevant in case of self-expandable valves protruding to a greater extend to LVOT, as valve implantation depth is related to the presence of MR [29].

In our series, lower LV ejection fraction predicted MR improvement. This was also observed by others [15, 30, 31]. Apart from reduced retrograde transmitral gradient, improvement of MR in patients with lower EF (also within normal limits) may be partially explained by the removal of afterload mismatch following TAVI [32], as acute improvement in MR reported following TAVR was related to immediate post-procedural changes in left ventricular hemodynamics and improved mitral leaflet tethering, resulting from reduced afterload [33]. In our patients, as in the other series, MR worsened following TAVI only in a minority of patients [34–37].

Study limitations

The main limitation of the present study is that it represents a retrospective, single-center experience. The relatively small population, allowed only for hypothesis generating results.

CONCLUSIONS

The study demonstrated that CMAC was prevalent in patients undergoing TAVI and associated with MR worsening. This is a novel finding, which may be of relevance for procedural planning and prevention of implantation failure. Its presence is of particular importance in patients with severe AS and coexisting MR in whom arguments for and against surgical repair of concomitant mitral insufficiency are considered, as opposed to isolated aortic valve procedure. Severe CMAC may be an additional argument to consider bivalvular cardiac surgery in patients with equivocal MR accompanying AS, rather than isolated percutaneous aortic procedure.

Article information

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ORIGINAL ARTICLE

Use of T-wave duration and Tpeak-Tend interval as new prognostic markers for patients treated with cardiac resynchronization therapy

Songül Usalp[1], Ramazan Gündüz[2]

[1]Department of Cardiology, Sancaktepe Sehit Profesor Ilhan Varank Education and Research Hospital, Istanbul, Turkey
[2]Department of Cardiology, Manisa City Hospital, Manisa, Turkey

Correspondence to:
Songül Usalp, MD, Department of Cardiology, Sancaktepe Sehit Profesor Ilhan Varank Education and Reaearch Hospital, Namık Kemal Street No 7, Sarıgazi Emek, Istanbul, Turkey, phone: +90 216 606 33 00, e-mail: dr.songulusalp@hotmail.com

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ABSTRACT

Background: The use of electrocardiography (ECG) is a practical method to evaluate the response to cardiac resynchronization therapy (CRT) implantation, as it is easily performed and saves time.

Aim: This study aimed to assess the predictive value of the T-wave duration and Tpeak-Tend (Tp-e) interval following the CRT implantation administered to heart failure patients.

Methods: Sixty-seven patients with left ventricular ejection fraction ≤35, New York Heart Association (NYHA) class II–III, ambulatory class IV, normal sinus rhythm, who have complete left bundle branch block on ECG and treated with CRT were included in this study. Patients who have manifested a ≥10% improvement in ejection fraction following CRT implantation, were categorized as "responders", and the remaining patients were categorized as "non-responders". ECGs and echocardiograms were evaluated both six months before and after CRT implantation.

Results: The post-CRT QRS duration ($P = 0.01$), cQT interval ($P = 0.005$), T-wave ($P < 0.001$), and Tp-e interval ($P < 0.001$) were found to be significantly reduced in the responder group compared to the non-responder group. The receiver operating characteristics curve analyses revealed that the predictive optimal cut-off of the T-wave was <182 ms ($P < 0.001$), and that of the Tp-e interval was <92 ms ($P < 0.001$).

Conclusions: T-wave and Tp-e interval may be independent predictors of a favorable CRT response in heart failure patients.

Key words: cardiac resynchronization therapy, electrocardiography, heart failure, T-wave, Tpeak-Tend interval

Kardiol Pol 2021; 79, 6: 676–683

INTRODUCTION

Heart failure with reduced ejection fraction (HFrEF) is a syndrome that is still associated with high mortality and morbidity rates, despite the advancements in the relevant diagnostic and therapeutic methods [1]. The mortality rate of the patients admitted to the hospital with the said diagnosis is approximately 20%, which goes up as high as 40% in patients over the age of 75 despite the administration of medical treatments [2]. The V-Heft (Veterans Heart Failure Trial) study revealed that the average life expectancy in HF patients receiving pharmacological treatment was 3.5 years [3], whereas the CARE-HF (Cardiac Resynchronisation in Heart Failure) study revealed that the addition of cardiac resynchronization therapy (CRT) to the treatment increased the average life expectancy by more than 8 years [2–4].

CRT improves the symptoms of HFrEF patients by reducing the prolonged conduction time, accelerating the myocardial contraction duration, and decreasing mitral regurgitation [2]. However, this response is not observed in all HFrEF patients that undergo CRT, and unfortunately, an adverse clinical course may be experienced in some patients. The favorable predictors of CRT responders are still a matter of investigation. Following the CRT implantation, narrowing of the QRS duration and the QT interval are known to be effective prognostic markers. However, only a limited number of studies available in the literature on the relationship between the post-implantation CRT response and T-wave and Tpeak-Tend (Tp-e) interval. Therefore, this study aimed to investigate the predictive value of T-wave and Tp-e interval in patients with HFrEF and left bundle branch block (LBBB) and who underwent CRT implantation.

WHAT'S NEW?

This study revealed that narrowing of Tpeak-Tend interval following the cardiac resynchronization therapy (CRT) implantation is associated with favorable response to CRT implantation and has predictive potency in the same range as QRS duration and QT interval, paving the way for the use of electrocardiography to easily evaluate the response to CRT implantation in daily clinical practice without the need for complex computer programs and other imaging tools.

METHODS

Study population

A total of 72 consecutive patients were admitted to the hospital between January 2017 and February 2020 with HFrEF ([left ventricular ejection fraction (LVEF) ≤35], New York Heart Association [NYHA] class II–III, ambulatory class IV, normal sinus rhythm) and complete LBBB (QRS ≥ 120 ms) was included in the study. Five of these patients were excluded from the study since they have developed atrial fibrillation during the follow-up. Demographic and clinical, laboratory data of patients were accessed from their medical records. All the patients received optimal HFrEF treatment dosage (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [ACEI/ARB], acetylsalicylic acid [ASA], ivabradine, β-blockers, mineralocorticoid antagonists, and loop diuretics).

Patients were categorized as "responders" and "non-responders" on the basis of the LVEF values, as per the previously published studies. A "responder" was described as a patient with an absolute LVEF recovery ≥of 10% as demonstrated by echocardiography six months after the CRT implantation, whereas a "non-responder" was described as any patient who did not meet the above-mentioned criterion [5, 6].

The exclusion criteria were as follows; revascularization due to acute coronary syndrome in the last 6 months, severe mitral and aortic valve diseases, development of atrial fibrillation, having undergone dialysis, cardiorenal syndrome, severe right heart failure, and development of ischemic hepatitis.

Ethics committee approval (no: 116.2017.178, date: July 2, 2020) was obtained from the Non-Interventional Clinical Research Ethics Committee of Istanbul Süreyyapasa Chest Disease and Chest Surgery Training and Research Hospital, before the initiation of the study. Written and verbal consents were obtained from all participants. Declaration of Helsinki was followed in the ethical principles of the study.

CRT device implantation

CRT devices (Boston Scientific, Natick, MA, USA) were placed in all patients by experienced electrophysiologists in accordance with current guidelines [1, 2]. The right atrial lead was inserted in the right atrium appendix, left ventricular lead was placed in the posterolateral coronary sinus vein, and right ventricular lead was implanted in the septal regions of the right ventricle.

Electrocardiography

All patients received 12-lead electrocardiography (ECG) in the supine position after resting for at least 15 minutes (GE MAC 1200, USA). Each ECG was taken at a paper rate of 25 mm/s, a gain of 10 mV, and a paper report format of 4 × 2.5R1. Before and after the CRT implantation ECG was interpreted by two different cardiologists independently. Patients that have met strict LBBB criteria (QS or rS in leads V1 and V2, and mid-QRS notching/slurring in ≥ 2 out of leads V1, 2, 5, 6, I and aVL, QRS duration ≥140 ms [men] or ≥130 ms [women]) were included in the study [7]. QRS duration was described as the time interval from the onset to the end of the QRS complex (Figure 1). Paced QRS duration was measured after CRT implantation from the peak to the end of the QRS complex (Figure 2). QT interval was measured from the onset of the QRS complex to the end of the T-wave (Figure 1). The QTc (corrected QT) interval was measured using Bazett's formula [8]. T-wave duration was described as the time interval from the onset to the end of the T-wave (Figure 1). The interval from the peak of the T-wave to the end of the T-wave was denoted as the Tp-e interval (Figure 3). The peak of the T-wave was defined as the maximum positive or the maximum negative amplitude taking the isoelectric line as the reference. The end of the T-wave was described as the intersection of the tangent with the descending part of the T-wave and the isoelectric line [9] (Figure 3). The QRS, T-wave and Tp-e interval values were obtained from the average of all precordial leads as exactly observed on the ECG [9].

Echocardiography

Echocardiography was performed in all patients within one week before and six months after CRT implantation. In accordance with the recommendations of the American Society of Echocardiography, all patients underwent a transthoracic echocardiographic examination with a commercially available device using 4 MHz probes (Vivid 9 Pro, GE Vingmed, Milwaukee, WI, USA) in the left lateral decubitus position [10]. All conventional measurements were performed on the parasternal long-axis and apical four-chamber views. LVEF was calculated by Simpson's method [10].

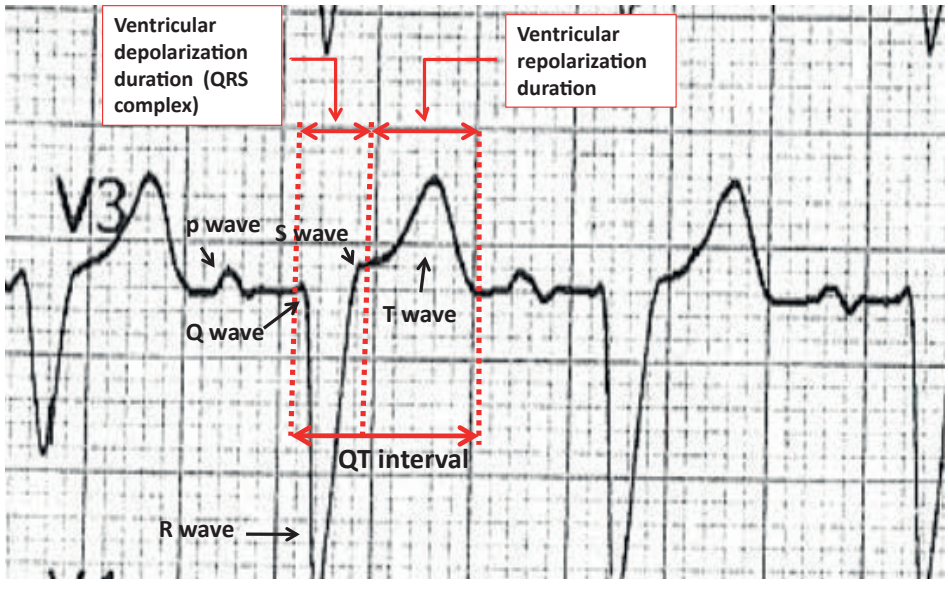

Figure 1. The illustrations of ventricular depolarization and repolarization duration on an electrocardiographic example

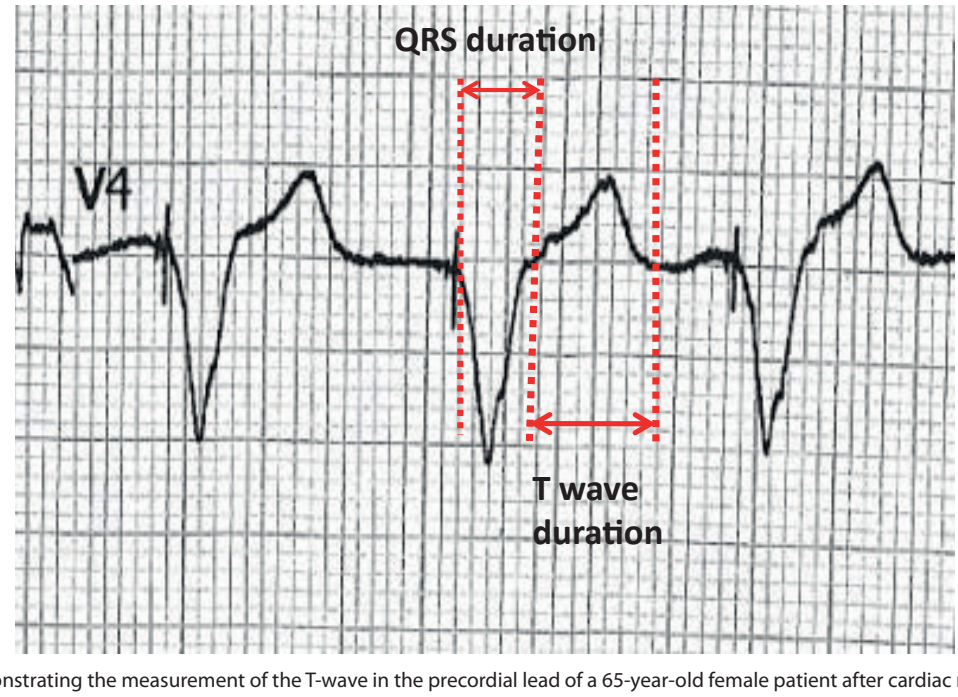

Figure 2. Demonstrating the measurement of the T-wave in the precordial lead of a 65-year-old female patient after cardiac resynchronization therapy

Chest radiography

Posteroanterior and lateral chest radiographs were taken for the location of the right and left ventricle leads after CRT implantation. The right ventricular lead was placed in the apical regions of the right ventricle in all patients.

Follow-up

All patients were followed by their cardiologists over the phone or in-person during their hospital visits. During the follow-up, their heart rhythm and functional capacity data as well as their ECGs and echocardiograms were recorded. The deaths of the patients who died during the follow-up period were investigated as to whether the deaths were due to a cardiovascular cause, and the relevant finding was included in the patient records.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM Corporation, Armonk, NY, USA) software package. Continuous variables were expressed as mean standard deviation (SD) values or median interval interquartile (IQR) values, whereas categorical variables were expressed as proportions. Shapiro-Wilk and Kolmogorov-Smirnov tests were performed to determine whether the research data had conformed to normal distribution. The baseline characteristics of the

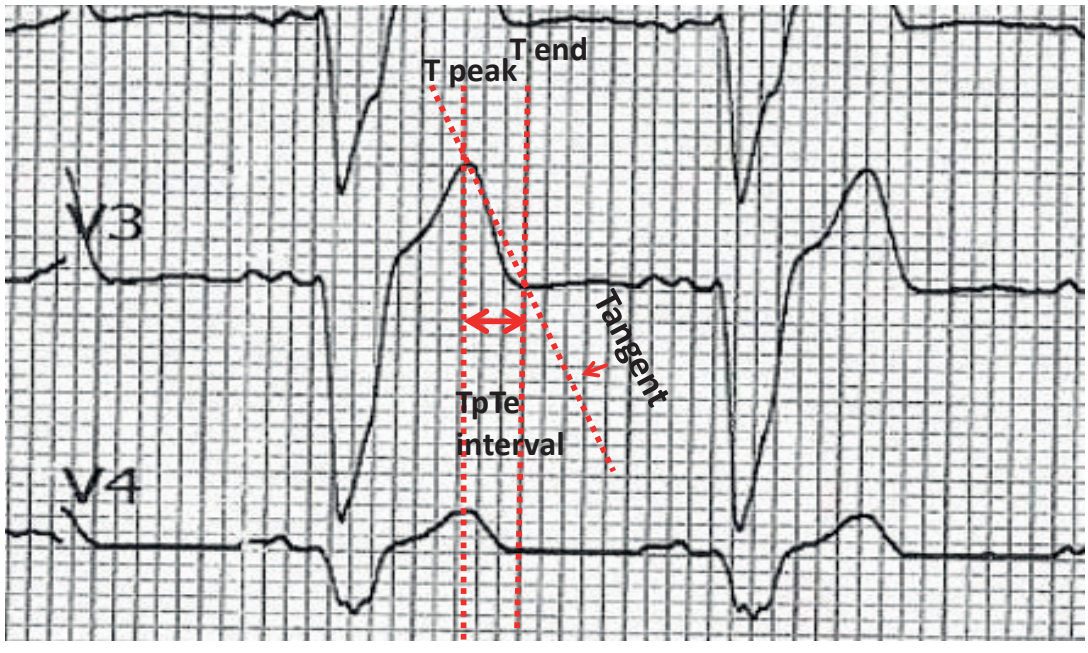

Figure 3. An example of the measurement of Tpeak-Tend interval from 12-lead surface electrocardiography

CRT patients were compared using the student's t-test for continuous variables and normal distribution and the χ2 Pearson's test for categorical variables. In cases where it was found that the data were not distributed normally, Mann-Whitney U test was used to compare the two independent groups. Univariable analysis was performed to identify potential risk factors for responder CRT. Multivariable logistic regression analysis was performed to determine independent predictors of responder CRT [11, 12]. The receiver operating characteristics (ROC) curve analysis was used to evaluate the optimal cut-off of the QRS, QT, T-wave and Tp-e interval prediction model for CRT responder. A 2-tailed *P*-value below 0.05 was considered to be significant in all statistical analyses performed.

RESULTS

The mean (SD) age of patients was 63.5 (10.0) years, most of the patients were men (n = 44, 65.7%), and had non-ischemic cardiomyopathy (74.2%). The median follow-up duration was 32 (IQR 9–41) months. The mean (SD) ejection fraction of pre-implantation and post-implantation were found to be 28.2(4.3)% and 38.9(6.8)%, respectively. In accordance with the recommendations set forth in the most recent guidelines, patients were determined to have used ACEI/ARB (95.5%) and β-blockers (92.5%). The majority of patients admitted to the hospital were those diagnosed with NYHA class III (59.7%), class II (26.8%), and class IV (13.4%) (Table 1).

No significant difference was found between the responder and non-responder groups in terms of age, body mass index, hypertension, diabetes mellitus, medications taken, and duration of follow-up period. There was no difference between the two groups in terms of pre-implantation ECG parameters, such as heart rate, P duration, PR interval, QRS duration, QT interval, cQT interval, T-wave, and Tp-e interval (Table 2).

The percentage of females (45.9% vs 6.0%; $P = 0.02$), and the number of NYHA class III patients (64.8% vs 53.3%; $P = 0.01$, respectively) were higher in the CRT responder group (Table 1).

Furthermore, post–implantation mean (SD) QRS duration (143.3 [18.6] vs 160.1 [29.2] ms; $P = 0.01$), QTc interval (474.8 [43.4] vs 502.7 [49.6] ms; $P = 0.005$), T-wave (165.6 [25.7] vs 192.1 [25.0] ms; $P < 0.001$) and Tp-e interval (82.9 [13.2] vs 98.1 [13.3] ms; $P < 0.001$) values were found to be substantially shorter in the CRT-responder group (Table 2).

The univariable regression analyses were revealed that shortening of QRS duration (OR, 0.976; 95% CI, 0.958–0.995; $P = 0.01$), cQT interval (OR, 0.983; 95% CI, 0.971–0.996; $P = 0.01$), T-wave duration (OR, 0.952; 95% CI, 0.928–0.976; $P < 0.001$), and Tp-e interval (OR, 0.905; 95% CI, 0.860–0.952; $P < 0.001$) was a potential risk factors for the CRT response, whereas multivariable logistic regression analysis was revealed that only the reduced Tp-e interval was the independent predictor of the CRT-response (Table 3).

The ROC analysis revealed that the optimal cut-off value of the Tp-e interval was <92 ms, with 80% sensitivity and 79% specificity (AUC, 0.82; 95% CI, 0.725–0.926; $P < 0.001$) (Figure 4).

DISCUSSION

In this study, it was found that the QRS duration, QT interval, T-wave duration, and Tp-e interval were significantly reduced in those who responded to CRT implantation. In addition, patients with NYHA class III and of female

Table 1. Demographic, clinical features of patients receiving cardiac resynchronization therapy with the responder and non-responder group

Variables	Overall (n = 67)	Responder (n = 37)	Non-responder (n = 30)	*P*-value
Age, years, mean (SD)	63.5 (10.0)	61.8 (10.4)	66.2 (8.9)	0.06
Female gender, n (%)	23 (34.3)	17 (45.9)	6 (20.0)	0.02
BMI, kg/m^2, mean (SD)	29.5 (14.5)	28.2 (15.6)	29.8 (13.8)	0.35
Hypertension, n (%)	26 (38.8)	15 (40.5)	11 (36.6)	0.78
Diabetes mellitus, n (%)	14 (20.9)	8 (21.6)	6 (20.0)	0.49
Ischemic CMP, n (%)	24 (35.8)	11 (29.7)	13 (43.3)	0.24
Follow-up, months, median (IQR)	32 (9–41)	33 (7-45)	20 (7–44)	0.06
Preimplantation LVEF, %, mean (SD)	28.2 (4.3)	28.9 (4.1)	27.4 (4.4)	0.15
Post implantation LVEF, %, mean (SD)	38.9(6.8)	40.5 (5.1)	28.0 (7.5)	<0.001
Pharmacological therapy				
ACEI/ARB, n (%)	64 (95.5)	36 (97.2)	28 (93.3)	0.38
Beta-blockers, n (%)	62 (92.5)	35 (95.6)	27 (90.0)	0.24
Loop diuretics, n (%)	50 (74.6)	28 (75.6)	22 (73.3)	0.93
Aldesterone antagonist, n (%)	15 (22.3)	9 (24.3)	6 (20.0)	0.73
ASA, n (%)	29 (43.2)	15 (40.5)	14 (46.6)	0.67
Ivabradine, n (%)	19 (28.3)	11 (29.7)	8 (26.7)	0.62
NYHA class, n (%)				
Class II	18 (26.8)	9 (24.3)	9 (30.0)	0.01
Class III	40 (59.7)	24 (64.8)	16 (53.3)	
Class IV	9 (13.4)	4 (10.8)	5 (16.6)	

Quantitative variable was presented as mean (SD) and median (IQR).

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; ASA, acetylsalicylic acid; BMI, body mass ındex; CMP, cardiomyopathy; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association

Table 2. Electrocardiographic evaluation of patients receiving cardiac resynchronization therapy with the responder and non-responder group

Variables	Overall (n = 67)	Responder (n = 37)	Non-responder (n = 30)	*P*-value
Pre CRT ECG parameters				
Heart rate, bpm	73.1 (15.1)	72.0 (15.8)	75.3 (13.8)	0.45
P duration, ms	96.4 (16.0)	93.8 (17.3)	101.5 (11.9)	0.09
PR interval, ms	178.3 (46.4)	177.4 (42.9)	181.5 (52.9)	0.75
QRS duration, ms	151.5 (18.8)	150.5 (18.1)	153.6 (12.9)	0.51
QT interval, ms	441 (46.7)	449.2 (52.8)	433.5 (43.7)	0.07
cQT interval, ms	481.2 (33.4)	482.7 (32.6)	478.5 (35.7)	0.66
T-wave duration, ms	193.6 (30.6)	197.9 (31.9)	185.1 (26.7)	0.14
Tp-e interval, ms	96.5 (15.4)	100.9 (16.9)	93.3 (14.8)	0.10
Post CRT ECG parameters				
Heart rate, bpm	78.4 (14.9)	76.8 (15.7)	81.2 (14.6)	0.31
P duration, ms	91.6 (14.4)	89.3 (13.4)	93.1 (16.3)	0.37
PR interval, ms	138.6 (28.2)	141.0 (26.8)	134.8 (27.7)	0.42
QRS duration, ms	155.6 (27.2)	143.3 (18.6)	160.1 (29.2)	0.01
QT interval, ms	438.6 (48.2)	432.7 (47.2)	448.7 (49.4)	0.18
cQT interval, ms	488.4 (45.9)	474.8 (43.4)	502.7 (49.6)	0.005
T-wave duration, ms	179.5 (24.7)	165.6 (25.7)	192.1 (25.0)	<0.001
Tp-e interval, ms	88.9 (13.1)	82.9 (13.2)	98.1 (13.3)	<0.001

The distribution of quantitative variable was presented as mean (SD).

Abbreviations: CRT, cardiac resynchronization therapy; Tp-e, Tpeak to Tend interval

gender demonstrated predominantly favorable response to the CRT.

The objective of CRT is to reduce the cardiac conduction time, normalizing the duration of depolarization and repolarization and providing effective myocardial contractions as a result. In the light of the data reported in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) and CARE-HF studies, CRT significantly reduces all-cause mortality or hospitalization in patients with an HFrEF (LVEF ≤35) and a QRS duration of ≥150 ms [4, 11]. Along the same lines, it was demonstrated in many studies that reduced QT and QTc intervals following CRT implantation have been associated with improved LVEF and decreased mortality and morbidity in patients with HFrEF [4, 13–15]. Similarly, in this study, the QRS duration was found to have been shortened in patients with

Table 3. The association between cardiac resynchronization therapy responders and electrocardiographic parameters with logistic regression analysis

Variables	Univarable analysis		Multivariable analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Female gender	3.40 (1.127–1.253)	0.03		
PI LVEF, %	1.50 (1.052–2.351)	0.02		
NYHA class III	0.43 (0.104–1.819)	0.25		
PI QRS duration	0.97 (0.958–0.995)	0.01		
PI cQT interval	0.98 (0.971–0.996)	0.01		
PI T-wave duration	0.95 (0.928–0.976)	<0.001		
PI Tp-e interval	0.90 (0.860–0.952)	<0.001	0.90 (0.860–0.952)	<0.001

Abbreviations: PI, post implantation; other abbreviations: see Table 1 and 2

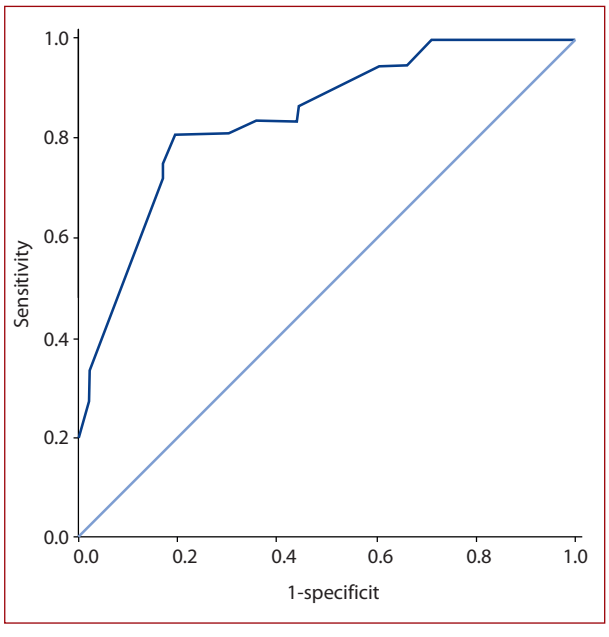

Figure 4. Receiver operating characteristic (ROC) curves for detecting patients with favourable responders to cardiac resynchronization therapy, the optimal cut-off Tpeak-Tend interval was <92 ms, with 80% sensitivity, 79% specificity and the area under the curve (AUC) of 0.82 (95% CI, 0.725–0.926; P <0.001)

CRT-response, and particularly in those with a QRS duration below 149 ms and with better outcomes. In sum, shortened QRS duration is currently a widely accepted marker in the determination of a favorable CRT-response [16, 17].

The main objective of this study was to investigate whether the use of repolarization shortening can be as effective as the use of depolarization shortening. For this reason, the T-wave and Tp-e interval, easily measurable ECG parameters, were taken into consideration. Despite the fact that there is no certain evidence that the increased T-wave duration implies an unfavorable CRT response, it was reported in the literature that the T-wave area and its morphology have been associated with prognosis in patients with HFrEF who underwent CRT [18, 19]. In addition, new measurement methods that utilize automatic ECG programs such as absolute T-wave residuum, T-wave morphology dispersion and T-wave loop area, are effective in predicting the CRT response [19]. Nonetheless, these complex measurement methods need special computer programs and are difficult to be performed during the daily clinical practice when evaluating the CRT response at the bedside. Hence, the aim of this study has been to come up with a method that can be easily measured and does not take much time, and which is as accurate and precise as the shortening of QRS duration as a predictor. In conclusion, significant results were achieved with regards to T-wave duration and Tp-e interval, as easily measurable predictors of CRT response.

Different types of cells in the myocardium such as epicardial, endocardial, and M cells take part in the generation of the T-wave, which is an indicator of ventricular repolarization. Complete repolarization of epicardial cells concurred with the peak of the T-wave, while repolarization of M cells complied with the end of the T-wave. Tp-e interval shows transmural repolarization (TMR), which corresponds to the last part of repolarization [20].

In patients with HF and LBBB, structural changes in myocardial cells (remodeling in calcium and ion channels, increases in fibrosis and myocardial cell volume changes) cause both electrical and mechanical desynchronization and prolong the depolarization and repolarization process. Prolonged duration of repolarization may result in worsening of HF through impaired cardiac relaxation. The objective of CRT implantation is to provide cardiac conduction within normal physiological limits with biventricular pacing. CRT assists the myocardial contraction and relaxation functions of the heart via subendocardial stimulation through right ventricular pacing and simultaneous epicardial stimulation with the left ventricular lead. In subjects without structural heart disease, the pacemaker causes a significant increase in the depolarization-repolarization process. In this context, Fuenmajor et al. have demonstrated that in subjects without heart disease, there was no difference in pacemakers compared to the right or left univentricular pacing, however that biventricular stimulation produced less variation in the depolarization-repolarization process [21]. Furthermore, a meta-analysis by Duan et al. revealed that biventricular pacing did not disturb repolarization functions, and it was only the left ventricular pacing that prolonged the Tp-e

interval in patients with heart failure and who underwent CRT implantation [22]. Engels et al. demonstrated that in patients with LBBB morphology, a larger baseline T-wave area is a significant independent predictor of LVEF increase following CRT [18]. Huang et al. demonstrated that HF patients with LBBB, larger T-wave morphology dispersion, larger T-wave loop area, and more negative QRS-to-T angle had a better echocardiographic response to CRT [19]. Flore et al. found that the absence of any changes in QRS duration and broader electrical remodeling (including the measurements of the angles between spatial QRS and T vectors before, during, and after CRT) are associated with notably better survival rates [23].

The common point of all the aforementioned studies is that the favorable effects of biventricular pacing on repolarization duration were implied in all, whereas in the study by Medina-Ravel et al. the QT and JT intervals reflecting repolarization were found to be longer in biventricular and left ventricular pacing compared to right ventricular pacing [24].

To sum up, CRT mimics normal cardiac physiology by biventricular pacing, providing the improvement of depolarization and repolarization time, which reflects the contraction and relaxation function of the heart, thereby increasing the functional capacity and improving LVEF in the patient with heart failure. In most of the above-mentioned studies as well as in this study, the favorable response to CRT implantation was evaluated on the basis of whether there was an increase in LVEF or not.

One of the important findings of this study was female gender had a higher rate of favorable response to CRT. The results were comparable to those reported in the Multicenter Automatic Defibrillator Implantation Trial — Cardiac Resynchronization Therapy (MADIT-CRT) trial [25]. All patients included in our study had LBBB and the majority of the female patients had a favorable CRT response, which supports the results of the previously published studies. Another outcome of this study was that the NYHA class III patients were found to have benefited more from CRT treatment, which is a comparable result to those reported in the MADIT, CARE-HF, COMPANION and AL-FINE CRT risk score studies [4, 13, 25–27].

Nevertheless, it is still not yet clear why only a certain number of patients were found to have benefited from CRT while others of similar characteristics have not. The fact that the heart construction and the electrophysiological conduction is different in every patient, irrespective of whether the patients had any structural heart disease or not, as well as any unidentified molecular or genetic differences might have affected the CRT response.

In this study, the importance of the background T-wave and Tp-e interval has been emphasized in assessing the CRT response. Normalization of the myocardial relaxation time as well as of the myocardial contraction is an important step in determining the response to CRT implantation. However, it may not be the right approach to arrive at a conclusion about the CRT response just based on the ECG parameters. Nevertheless, ECG is a very practical and simple method, and it does not take up much time in daily clinical practices.

Limitations

The first and foremost limitation of this study was that it was carried out as a single-center and retrospective study. Secondly, the number of patients included in the study was limited as only the patients with normal sinus rhythm and LBBB could be included in the study in order to achieve homogenization. Thus, the results of this study cannot be generalized to all patients with heart failure. In this study, an increase in LVEF values demonstrated by echocardiography was deemed to be the sign for a favorable CRT response. Another advanced technology such as cardiac magnetic resonance imaging (MRI) may also be employed to assess the CRT response in addition to echocardiographic imaging.

CONCLUSION

In conclusion, the current study shows that the Tp-e interval is an independent predictor of a favorable CRT response in symptomatic patients with ischemic and nonischemic cardiomyopathy. The use of T-wave duration and Tp-e interval together with QRS duration and QTc interval would prove to be useful in assessing favorable CRT response.

Article information

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Cardiac CathLab-based stroke thrombectomy routine service by the BRAIN team in a recently established Thrombectomy-Capable Stroke Center in Poland

Krzysztof Pawłowski[1], Jacek Klaudel[2], Artur Dziadkiewicz[3], Alicja Mączkowiak[3], Marek Szołkiewicz[1]

[1]Kashubian Center for Heart and Vascular Diseases, Pomeranian Hospitals, Wejherowo, Poland
[2]Department of Invasive Cardiology, St. Adalbert's Hospital, Copernicus PL, Gdańsk, Poland
[3]Department of Neurology and Stroke, Pomeranian Hospitals, Wejherowo, Poland

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Correspondence to:
Krzysztof Pawłowski, MD, Kashubian Center for Heart and Vascular Diseases, Pomeranian Hospitals, Jagalskiego 10, 84–200 Wejherowo, Poland, phone: +48 585727434, e-mail: krzysztof.pawlowski@wp.pl

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INTRODUCTION

There is level 1a evidence for mechanical thrombectomy (MT) in the management of large-vessel occlusion (LVO), as it reduces stroke-related disability [1]. In Poland, there is a large unmet need to deliver MT to LVO stroke patients in a timely manner. Poland; a country of 38 million inhabitants where the MT service is presently limited to 20 Comprehensive Stroke Centers (MT-CSC), which equates to 0.5 centers per 1 million population [2, 3]. Indeed, the shortage of MT centers and operators results in a severe under-treatment of the Polish LVO stroke patient population (MT rate in 2020 of only about 3.1% ischaemic strokes, compared to about 8.1% in neighboring Germany [4]). Furthermore, the Polish MT-CSC sparsity results in transportation-related significant MT delays and MT treatment denials [2, 3].

We provide a practical description of how to set up a cardiology cathlab-based Thrombectomy-Capable Stroke Center (TCSC) using the existing facilities and local multi-specialty collaboration centered around stroke neurology as the heart of the service [5–7]. We have coined the term the "BRAIN team" (Basic cathlab staff, Radiologist, Anesthesiologist, Interventionalist, stroke Neurologist). Here, we share our experience with regard to interdisciplinary cooperation, staff training, service organization and treatment protocols. The report includes treatment results in our initial series of unselected MT-eligible patients, with emphasis on intra-hospital times and radiologic and clinical outcomes.

METHODS

Kashubian Center for Heart and Vascular Diseases provides comprehensive cardiovascular services to the northern Pomerania region (2.3 million inhabitants). There is a strong in-house neurology department committed to top-level stroke care (European Stroke Organization highest — Diamond — Angels Quality Award status).

As the hospital does not possess a dedicated neuroradiology department, we have followed the World Federation for Interventional Stroke Treatment (WIST) structured training in stroke MT [8]. WIST emphasizes the role of simulator and team training along with the operator hands-on training, requires the results to be available for audit, promotes quality control and promotes a competence-based rather than time-based approach [8] that is consistent with Polish legal regulations [2, 3].

Along with other forms of MT training, the Kashubian Center stroke interventionists rotated into a level 1 stroke center (CSC) to gain practical skills and operator procedural requirements in MT. In-house standard operating procedures and checklists were developed in collaboration with the local stroke neurology team. MT-eligible consecutive patients were identified according to the international stroke and neuroradiology guidelines.

In statistical analysis, categorical variables are presented as numbers and percentages, and continuous variables are expressed as means ± standard deviation. Due to a small sample size, only descriptive statistics have been performed.

RESULTS AND DISCUSSION

The baseline clinical and procedural characteristics of the initial case series (n = 15) are provided, along with individual patient outcomes, in Supplementary material, *Tables S1–S3*. All target vessels were completely occluded (TICI 0) on initial angiograms, despite the background thrombolytic treatment in 86.7% of patients (Supplementary material, *Table S1*). To optimize the first-pass effect, we routinely adopted the SAVE (Stent-retriever Assisted Vacuum-locked Extraction) technique; the principal technique that we learned while on CSC rota. Figure 1 shows typical examples of the angiographic efficacy of the procedure.

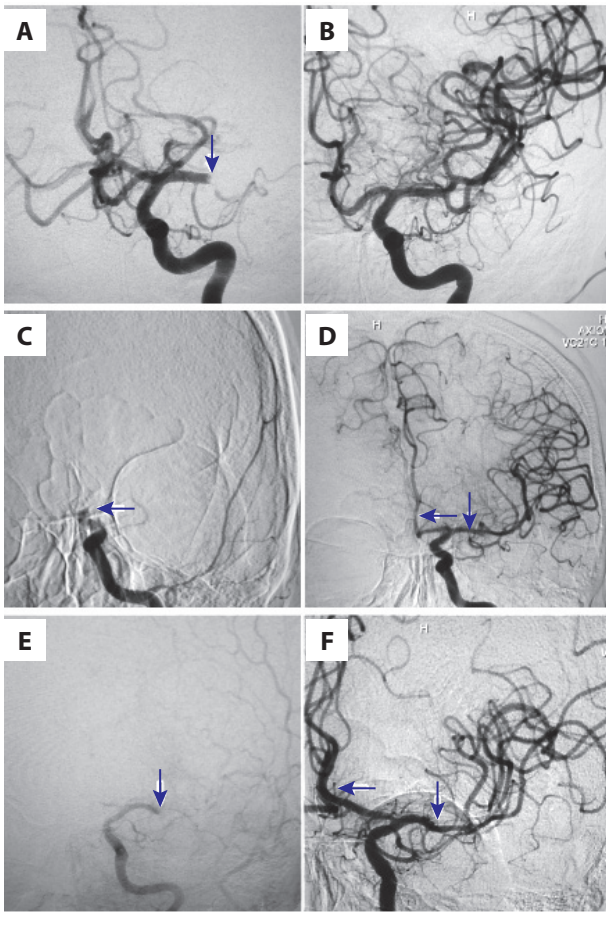

Figure 1. Typical angiographic images of brain-saving procedures performed by a multidisciplinary BRAIN team in our stroke thrombectomy center. **A.** Proximal occlusion of the left middle cerebral artery (L-MCA, arrow). **B.** Final result after mechanical thrombectomy (right, two passes) in a 67-year-old woman presenting with a large left haemispheric stroke (NIHSS 24) and contraindications to thrombolytic therapy. Discharge NIHSS was 3 (mRS 2). This was the first patient treated in our center**. C.** Carotid T-occlusion (left, arrow). **D**. Final result (arrows indicate good flow in both ACA and MCA) after mechanical thrombectomy (single-pass effect) in an 83-year old woman presenting with a large left hemispheric stroke (NIHSS 26). The patient received thrombolysis. Discharge NIHSS was 9 (mRS 3). **E.** Left MCA occlusion (arrow) in a 67-year-old man with NIHSS of 6 and severe aphasia. The patient received thrombolysis. A tandem lesion was identified. The L-MCA occlusion was treated first. **F.** Final result (arrows indicate good flow in both ACA and MCA). Carotid stenting was performed after thrombectomy (not shown). Discharge NIHSS was 2 (mRS 1)

Our mean door-to-computed tomography time was only 11 (±7) minutes, LVO diagnosis-to-groin 109 (±32) minutes, door-to-groin 133 (±37) minutes, groin-to-first-pass 49 (±26) minutes, and groin-to-recanalization 93 (±55) minutes. A balloon guide-catheter was used in all but one cases. Femoral approach was our default, brachial access was used twice. TICI 2b/3 was achieved in 93% of cases, TICI 0 rate was 0%. Embolism to a new territory rate was 6.7%. No intracranial hemorrhage occurred. The only serious, procedure-related complication was retroperitoneal hematoma, which resolved with conservative management. There were three in-hospital deaths unrelated to the procedure and no further deaths by 30 days. Functional independence (mRS ≤2) was 30% at 30 days.

The fundamental finding from this work is that it is feasible and safe to establish a much needed regional MT service (TCSC; level 2 stroke center) in Poland within a high-volume cardiac cath-lab that is equipped to meet the requirements for intracranial procedures. Such a service should be based on local multi-specialty collaboration between expert stroke neurologists and expert interventional cardiologists with supra-aortic artery skills and MT training as per legal requirements. Even though our report includes the center's learning curve (zero MT procedures outside the present report), our MT outcomes have been well within the safety margins. In particular, TICI 2b/3 was achieved in 93% (required >60%), embolization to new territories was 7% (required <15%) and intracranial hemorrhage was 0% (required <10%) [9].

There is irrefutable evidence that delays in MT treatment due to long inter-hospital transport times have a significant negative effect on clinical outcomes. Unnecessary patient transportation should be avoided and if MT can be performed on-site, transporting LVO stroke patients to other centers for MT may be considered unethical [10–12].

At the beginning of this project, our multidisciplinary team set clear objectives for the formation of a TCSC and a two-year comprehensive plan that included detailed training steps and the design of standard operating procedures.

If recent international estimates [13] are applied for Poland, the introduction of a truly operational MT network, inclusive of level 2 MT centers like ours, would result in a clinically significant reduction in stroke-related disability for 1700 additional Polish citizens each year [2, 13].

Mechanical thrombectomy centers based in cardiology cathlabs operate effectively worldwide including North and South America and Poland's European neighbours such as Germany or Czech Republic [7, 10, 12, 14]. We could demonstrate that the concept of cardiology-cathlab-based MT centers can be adopted safely and effectively in Poland and can increase population access to level 1 evidenced stroke care, thus reducing stroke-related disability and misery to patients, relatives and the economic impact on society [2, 3, 15].

Article information

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Impact of the coronavirus disease 2019 pandemic on atrial fibrillation and atrial flutter ablation rates. The analysis of nearly 5 million Polish population

Krzysztof Myrda[1], Aleksandra Błachut[1], Piotr Buchta[1], Michał Skrzypek[2], Anna-Maria Wnuk-Wojnar[3], Andrzej Hoffmann[3], Seweryn Nowak[3], Oskar Kowalski[4], Patrycja Pruszkowska[4], Adam Sokal[4], Krystian Wita[3], Katarzyna Mizia-Stec[3], Mariusz Gąsior[1,5], Zbigniew Kalarus[4]

[1]3rd Department of Cardiology, Silesian Center for Heart Diseases, Zabrze, Poland
[2]Department of Biostatistics, School of Health Sciences in Bytom, Medical University of Silesia, Katowice, Poland
[3]1st Department of Cardiology, Medical University of Silesia, Katowice, Poland
[4]Department of Cardiology, Congenital Heart Diseases and Electrotherapy, Division of Medical Sciences in Zabrze, Medical University of Silesia, Zabrze, Poland
[5]Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland

Correspondence to:
Aleksandra Błachut, MD, 3rd Department of Cardiology, Silesian Center for Heart Diseases, M. Curie-Skłodowskiej 9, 41–800 Zabrze, Poland, phone: +48 604 193 615, e-mail: ola.blachut@gmail.com

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INTRODUCTION

The pandemic of coronavirus disease 2019 (COVID-19), which is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has contributed to significant changes in the organization of public healthcare. Since hospitals had to be prepared for an increased number of infected patients, most elective procedures were postponed. A reduction in hospital admissions for acute coronary syndromes in association with a decreased number of cardiac catheterizations was observed in Poland [1]. These limitations, which were introduced to avoid unexpected outbreaks in hospitals, potentially also affected patients with atrial flutter (AFl) or atrial fibrillation (AF). According to expert recommendations, the exception should be applied to therapeutic procedures, including ablation in the cases of hemodynamically significant, severely symptomatic, drug and/or cardioversion refractory AF or AFl or in the case of pre-excited AF with syncope or cardiac arrest [2]. The detailed instruction of the arrangement of electrophysiology procedures was published by the Heart Rhythm Section of the Polish Cardiac Society at the very beginning of the pandemic [3]. In the current analysis, the aim is to demonstrate the impact of the COVID-19 pandemic on the number of AFl and AF ablations and clinical characteristics of patients who underwent ablation in the Silesian Province during the lockdown imposed in Poland in 2020.

METHODS

The analysis was based on the data from the Silesian Cardiovascular Database (SILCARD), which collected information on all patients hospitalized for cardiovascular diseases in the Silesian Province, which is the most urbanized region in Poland inhabited by 4.57 million people, constituting approximately 12% of the total population of Poland. All data for the registry have been provided by the National Health Fund (NHF) since 2006. Detailed information on the SILCARD registry was previously reported [4]. The SILCARD registry was approved by the local Ethics Committee. Only patients below 18 years of age at the time of admission or those who lived outside the Silesian Province were excluded from the registry. The collected data included information on initial hospitalization with a diagnosis of cardiovascular disease (CVD) with a potential transfer to another department or hospital, other hospitalizations, and data from outpatient visits. If the patient was hospitalized again due to CVD within 24 hours, both hospitalizations were considered one admission. According to the applicable rules, hospitals are obliged to report to the NHF on the principal diagnosis with up to two comorbidities as defined by the International Classification of Disease, 10th revision (ICD-10), and medical procedures defined by the ICD-9 classification. CVD was defined as R52, J96, or any "I" code based on the ICD-10. The hospital registry number and national identifi-

cation number (PESEL) were used to match the information to each patient. All data were anonymized.

For the purposes of the study, patients with diagnosed AF or AFl (ICD-10 code I48) who underwent ablation procedures (ICD-9 codes for ablation: 37.341, 37.342, for 3D mapping: 37.272 and for electrophysiological studies: 37.26) between weeks 12 and 22 of 2019 and weeks 12 and 22 of 2020 were selected for the analysis from the SILCARD registry. Baseline characteristics of the included patients and the number of ablation procedures were analyzed and compared between the time periods. Additional exclusion criterion comprised a simple ablation procedure (e.g., AV-node ablation) or electrophysiological studies without ablation defined by the following codes by the NHF, i.e., 5.06.00.0000969, 5.51.01.0005044, and 5.06.00.0000970.

Statistical analysis

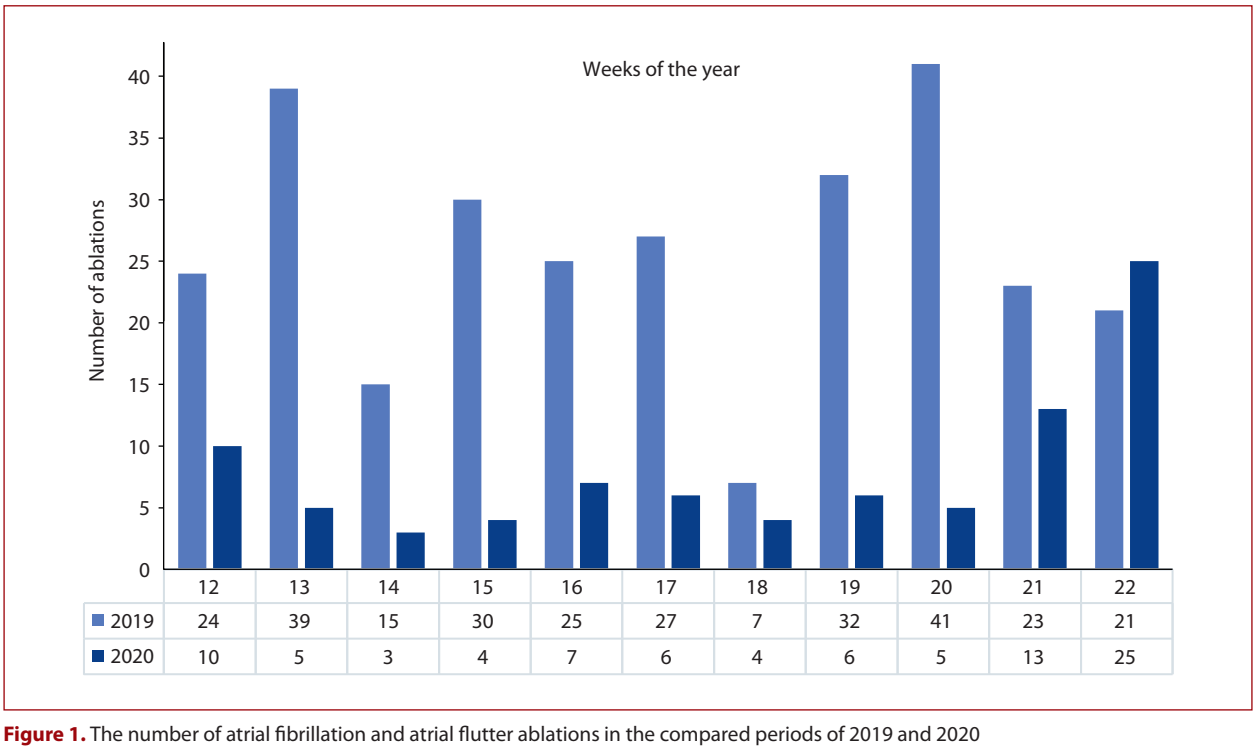
Statistical analysis was performed using STATISTICA PL version 13.3 (TIBCO, Palo Alto, USA). The normality of distribution was verified using the Shapiro-Wilk test. Continuous variables were summarized using median with interquartile range for non-normal distribution and were compared using the Mann-Whitney U test. Categorical variables were summarized using frequency tables. For the comparison of categorical data, the chi-square test was used. The results were considered statistically significant for two-sided $P < 0.05$.

RESULTS AND DISCUSSION

The COVID-19 pandemic had a significant impact on the treatment of patients, including AF and AFl therapy. During the lockdown imposed in Poland from 12th March to 31st May 2020, the number of patients hospitalized for elective cardiac procedures and heart surgery, including the treatment of the above arrhythmias, decreased significantly compared to the same period in 2019 [5, 6]. The previously observed upward trend in the number of ablation procedures in the Silesian Province [7] was also disturbed by the pandemic. We found a decreased number of percutaneous ablation procedures compared to 2019 (Figure 1).

The impact of the COVID-19 pandemic on the number of electrophysiological procedures varied across countries and regions, depending on the availability of hospital beds or necessary changes in healthcare management. Li et al. [8] found a significant decrease in the number of electrophysiological procedures performed in various countries, which was related to the time of occurrence of the first wave of the disease. Based on Italian data, Boriani et al. [9] indicated diverse numbers of procedures performed in different regions of the country, depending on the number of patients infected with the SARS-CoV-2. Contrary to other observations, a decrease in the number of ablation procedures was not documented in Shanghai, which is a municipality under the direct administration of the central Chinese government, after the implementation of an efficient pandemic management system [10]. Furthermore, in that analysis, the performed procedures were not related to the increased number of COVID-19 infections in the medical personnel.

Based on the previously published data, a large reduction in elective procedures could be noticed. However, urgent procedures such as electrical storm ablation or treat-



	12	13	14	15	16	17	18	19	20	21	22
2019	24	39	15	30	25	27	7	32	41	23	21
2020	10	5	3	4	7	6	4	6	5	13	25

Figure 1. The number of atrial fibrillation and atrial flutter ablations in the compared periods of 2019 and 2020

ment of arrhythmias, including AF, causing hemodynamic instability, were treated with adequate prophylaxis without undue delay, regardless of the result of the SARS-CoV-2 test [8, 10]. Additionally, patients eligible for ablation were older, mostly male, and presented with comorbidities (such as diabetes, hypertension, or heart failure), which increased the risk for an unfavorable course of infection [8, 10]. These data are consistent with our observations. We found that patients with a higher percentage of comorbidities such as heart failure ($P = 0.03$), diabetes ($P < 0.001$), or coronary heart disease ($P < 0.001$) were more often enrolled for ablation during the pandemic time. Interestingly, in the past, most patients had already undergone cardioversion ($P < 0.01$) or ablation, regardless of the prior invasive treatment ($P < 0.001$) (Supplementary material, *Table S1*). This treatment strategy was in line with the current recommendations of cardiology societies [2, 11, 12].

Limitations

This study has some limitations. The data used for the analysis were based on the electronic database of a single healthcare provider and consisted of core variables, such as demographic characteristics, comorbidities, and in-hospital events. Furthermore, the classification often does not specify the subcodes of individual diseases and comorbidities. Therefore, the available data may be imprecise. Based on the electronic database, it was impossible to distinguish cavotricuspid ablation for AFl from pulmonary vein isolation for AF due to the fact that the same codes (ICD-10 and ICD-9) are applied to both procedures.

CONCLUSIONS

Imposing the lockdown due to the COVID-19 pandemic provoked a reduction in the number of AFl and AF ablations in the Silesian Province. During the lockdown period, invasively treated patients presented with a greater number of comorbidities compared to the pre-COVID-19 era.

Supplementary material

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

Article information

Data were collected as part of the Silesian Cardiovascular Database (SILCARD) — ClinicalTrials.gov identifier, NCT02743533. https://clinicaltrials.gov/ct2/show/NCT02743533

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Quality analysis of chest compression during cardiopulmonary resuscitation performed by firefighters with physical effort

Łukasz Dudziński[1], Marcin Glinka[2], Dominik Wysocki[3], Piotr Leszczyński[4], Mariusz Panczyk[5]

[1]State Fire Service Lublin, Lublin, Poland
[2]State Fire Service Warsaw, Warszawa, Poland
[3]Provincial Headquarters of State Fire Service Lublin, Lublin, Poland
[4]Institute of Health Sciences, Faculty of Medical and Health Sciences, Siedlce University of Natural Sciences and Humanities, Siedlce, Poland
[5]Department of Education and Research in Health Sciences, Faculty of Health Sciences Medical University of Warsaw, Warszawa, Poland

Correspondence to:
Łukasz Dudziński, PhD, State Fire Service Lublin, Szczerbowskiego 6, 20–012 Lublin, Poland, phone: +48 81 535 13 20, e-mail: lukasz_dudzinski@o2.pl

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INTRODUCTION

The medical activities of firefighters in the State Fire Service (SFS) are based on 22 advanced first aid procedures (FAP). The procedures apply to both traumatic and non-traumatic health and life-threatening conditions [1, 2]. The most demanding FAP procedures concern cardiopulmonary resuscitation (CPR) broken down by age groups of victims [3]. They are concerned with the management of cardiac arrest in adults, children, infants, and newborns [4, 5]. The medical firefighter training system and the adult CPR procedure used in SFS are described in Supplementary material, *Figure S1*.

Successful CPR management and the chance of a return to spontaneous circulation (ROSC) depend on various factors. One of them are correct chest compressions in line with the European Resuscitation Council (ERC) guidelines for basic life support (BLS). For an adult, effective action is obtained by compressing in the right place (center of the chest), at a rate of 100–120 per minute, to a depth of 5–6 cm, as well as correct relaxation [6, 7]. Among the factors that influence the quality of compressions are practice, experience, mental state (stress load, acting in a public place), and physical conditions (weather conditions, overexertion). The study attempts to evaluate the effect of rescuer (firefighter) fatigue on the quality of adult chest compressions as an important part of CPR.

METHODS

The study involved compressing the Rescue Anne QCPR training manikin in a situation of physical and thermal stress of the rescuers. The fatigue effect was obtained by completing the test in a smoke chamber. Officers compressed the manikin's chest before the physical exercise for 2 minutes. Then the firefighters started the test in a smoke chamber (training path and chamber passage), where they obtained significant fatigue. For statistical analysis, the exercise time with the manikin (chest compressions) was presented in seconds (t. max = 120 seconds). The study was randomized, and participation depended on the schedule of tests in the smoke chamber.

The next sessions increasing the study population were scheduled for 2020, but the state of the SARS-CoV-2 epidemic made it impossible to increase the research sample. The study was approved by the Bioethics Committee at UPH Siedlce (No. 7/2019), and gained the consent of the Provincial Commander of the State Fire Service in Lublin. Each study participant gave their informed consent.

Statistical analysis

Statistical analysis is presented in Supplementary material.

Test parts to be assessed (parts I and III)

Part I — 2-minute rest cycle of chest compressions — assessed in the study. A firefighter dressed in special clothing, no respiratory protection (RP) kit, no helmet. After completing the 2-minute compressions cycle, the study subject puts on the RP set and proceeds to part II.

Part II — physical effort — training path lasting 15 minutes with the RP worn but not

connected, and the smoke chamber path with the RP on and connected. The passage time of the chamber path varies for each officer. The maximum passage time of the smoke chamber is limited by the air consumption in the cylinder. The smoke chamber path must be completed on the contents of one air cylinder. The average range of ventricular transit times is 6–10 minutes and depends on the individual characteristics of the exercising people. The exercise part was not assessed in the study, but it was necessary for the next part of the study.

Part III — a 2-minute cycle of chest compressions after exercise — assessed in the study. After leaving the smoke chamber, a firefighter approaches the CPR station, disconnects and takes off the RP kit, mask, and helmet, and starts compressing the manikin's chest. This part simulates the real conditions of rescue and firefighting operations (evacuating an unconscious person from the danger zone, finding no signs of circulation, starting CPR without being able to rest). Flow chart of the study stages is shown in *Figure S2* in Supplementary material.

RESULTS AND DISCUSSION

In total, 72 firefighters at a mean (SD) age of 34.14 (6.67) participated in the study. The mean (SD) length of service was 9.6 years (4.27). The full-time task planned in the study (all 3 parts) was completed by 64 officers. Parts I and II were completed by all 72 officers. Eight firefighters did not complete part III. Five completed compressions on the manikin's chest after 85, 90, 94, 101, 105 seconds out of the scheduled 120 seconds, respectively, and three did not take this part declaring too much fatigue. The parameters important for the study are presented in Table 1. Additional data are described in Supplementary material in the Results section.

Due to the lack of publication and results of similar studies on the assessment of the quality of chest compressions before and after exercise among PSP officers, reference was made to other results assessing the quality of chest compressions, and the impact of resuscitation on prognosis, survival and health after an episode of sudden cardiac arrest (SCA).

Table 1. Descriptive statistics of quantitative variables

Variable	Mean (SD)	W	*P*-value[a]
Age, years	34.14 (6.67)	0.972	0.106
Length of service, years	9.60 (4.27)	0.977	0.201
Depth of chest compressions at rest, mm	47.85 (3.98)	0.968	0.069
Variable	**Median (IQR/2)**	**W**	***P*-value[a]**
Frequency of chest compressions at rest, comp./min	110.75 (5.88)	0.961	0.025
Frequency of chest compressions after exercise, comp./min	120.00 (6.50)	0.879	0.00001
Depth of chest compressions after exercise, mm	47.00 (5.00)	0.914	0.00016

[a]Shapiro–Wilk test.

Abbreviations: IQR/2, Semi-interquartile range; SD, standard deviation; W, statistic value

Function (n)		Frequency of chest compressions, comp./min				t[a]/z[b]	*P*-value
		At rest		After exercise			
		M	SD	M	SD		
Commanders	(14)	109.04	9.58	124.18	11.48	3.965	0.001[a]
Function (n)		**Mdn**	**IQR/2**	**Mdn**	**IQR/2**		
Rescuers	(41)	112.25	4.75	120.50	6.13	3.139	0.002[b]
Drivers	(9)	108.00	3.75	109.75	10.75	1.013	0.311[b]
All group	(64)	110.75	5.69	120.00	6.56	3.354	0.001[b]

[a]Matched-pairs t-test. [b]Wilcoxon signed-rank test, t or z — statistic value.

Abbreviations: IQR/2, semi-interquartile range; M, mean; Mdn, median; SD, standard deviation

Function (n)		Depth of chest compressions, mm				t[a]/z[b]	*P*-value
		At rest		After exercise			
		M	SD	M	SD		
Drivers	(9)	47.46	3.64	47.42	3.65	0.312	0.760[a]
Function (n)		**Mdn**	**IQR/2**	**Mdn**	**IQR/2**		
Rescuers	(41)	48.50	1.75	44.00	5.00	3.813	<0.001[b]
Commanders	(14)	48.00	3.75	47.00	4.75	0.908	0.363[b]
All group	(64)	48.00	2.50	47.00	4.63	3.476	0.001[b]

[a]Matched-pairs t-test. [b]Wilcoxon signed-rank test, t or z — statistic value.

Abbreviations: IQR/2, semi-interquartile range; M, mean; Mdn, median; SD, standard deviation

Dąbrowski [8] in 2012 raised that the implementation of high-quality chest compressions without ventilation in the absence of equipment or safety. The 2015 CPR guidelines also addressed the issue of high-quality chest compressions as important for the further process of saving lives [9].

A similar topic of research was undertaken in 2014. In the cited work, the authors compared 3 methods of chest (device and non-device) compressions. Moreover, they described that the correct location of the chest compression point, pressure depth and frequency influenced the effectiveness of indirect heart massage and caused the correct compression of the heart muscle [10]. Similar results were presented in our study — firefighters' fatigue had a similar effect on lowering the quality of actions.

The authors also presented research on the quality of chest compression during CPR in the 2018 publication. A study comparing instrument and non-instrument operation had shown that the quality of manual chest compression performed during simulated adult resuscitation was lower than when using the chest compression system [11].

In another study from 2019, researchers cited data from the American Heart Association (AHA), according to which over 359 000 out-of-hospital cardiac arrest (OHCA) incidents are registered in the United States every year. The update of the guidelines for cardiopulmonary resuscitation, taking place every few years, on the basis of the latest scientific reports, leads to an increase in patient survival. The quality of life after cardiac arrest is closely related to careful and effective CPR [12].

Chomoncik [13] presents that good knowledge of rescue procedures and continuous training have an impact on the quality and speed of advanced first aid activities, also during CPR.

In the 2018 analysis, Iskrzycki et al. [14] demonstrated that the use of a real-time visual external feedback device (CPRMeter) significantly improved the quality of chest compressions in rescuers with little experience. Comparing the conclusions obtained by the authors of the study to the own results, it can be assumed that the use of real-time CPR quality monitoring devices may have a beneficial effect not only in the case of inexperienced but also tired rescuers.

CONCLUSIONS

Rescuer fatigue has a statistically significant impact on the frequency and depth of chest compressions during CPR. Consider implementing a cyclical evaluation of resuscitation activities in the fire service as part of professional development. CRP results after physical effort suggest changing rescuers more frequently than every 2 minutes.

Supplementary material

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

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SHORT COMMUNICATION

Clinical characteristics of patients with arrhythmic mitral valve prolapse in a single tertiary center: prevalence of electrocardiographic and myocardial abnormalities

Agnieszka Zienciuk-Krajka[1], Ludmiła Daniłowicz-Szymanowicz[1], Karolina Dorniak[2], Radosław Owczuk[3], Damian Kaufmann[1], Dariusz Zacharek[1], Alicja Dąbrowska-Kugacka[1], Monika Figura-Chmielewska[1], Radosław Nowak[1], Maciej Kempa[1], Piotr Kuźmiński[4], Grzegorz Raczak[1]

[1]Department of Cardiology and Electrotherapy, Medical University of Gdansk, Gdańsk, Poland
[2]Department of Noninvasive Cardiac Diagnostics, Medical University of Gdansk, Gdańsk, Poland
[3]Department of Anaesthesiology and Intensive Therapy, Medical University of Gdansk, Gdańsk, Poland
[4]Cardiology Unit, Hospital of the Ministry of Internal Affairs, Gdańsk, Poland

Correspondence to:
Agnieszka Zienciuk-Krajka, MD, PhD, Department of Cardiology and Electrotherapy, Medical University of Gdansk, Dębinki 7, 80–952 Gdańsk, phone: +48 583493910, e-mail: agzien@gumed.edu.pl

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INTRODUCTION

Mitral valve prolapse (MVP) related sudden cardiac death (SCD) occurs with an estimated annual risk of 0.2%–1.9% and affects also young and otherwise healthy MVP patients with trivial or absent mitral regurgitation (MR) [1–3]. Several characteristics of the arrhythmogenic MVP (AMVP) were found, including bileaflet MVP, female sex, T-wave inversions (TWI), mitral annular disjunction (MAD), focal fibrosis of papillary muscles (PMs) and adjacent inferobasal LV wall, and frequent/complex ventricular arrhythmias (VA) [1, 3, 4]. The cohorts studied in the MVP series included SCD victims [2, 4, 6], survivors of cardiac arrest (CA) [3], patients with frequent and complex VA referred for catheter ablation [7, 8], or imaging studies for MR [9]. Little is known, however, about the characteristics of patients diagnosed with AMVP in real-life settings. Given the paucity of data, we aimed to characterize consecutive patients from our institution, in whom features of AMVP were found.

METHODS

Patients referred to our tertiary center between October 2016 and March 2020 were screened for the presence of AMVP defined as MVP, MAD, curling, and frequent and/or complex VA. Patients underwent a cardiovascular evaluation that included history, physical examination, 12-lead ECG, transthoracic echocardiography, 24-hour Holter monitoring, exercise testing, and LGE-CMR unless contraindicated. Additionally, all patients implanted with an ICD and diagnosed with idiopathic ventricular fibrillation (IVF), i.e., negative for ischemia, cardiomyopathy, and channelopathy, were systematically re-screened, and included in the study group, if signs of AMVP were present. The patients were divided into two groups based on the occurrence of CA in the past medical history and followed prospectively. The institutional review board approved the study and all patients gave informed consent.

Statistical analysis

All calculations were done using Statistica 13PL (StatSoft, Tulsa, OK, USA). Continuous data were presented either as median (range) or median (IQR); categorical data were given as n (%). The normality of continuous data was tested with W Shapiro-Wilk test. U Mann-Whitney test was used for intergroup comparisons. Fisher's exact test was used for categorical data comparisons. P <0.05 was adopted as significant.

RESULTS AND DISCUSSION

Twenty-six patients met the study criteria (Table 1). Twelve (46%) patients were diagnosed with MVP and/or VA in childhood, at the median age of 9 years. A total of 23 (89%) patients reported symptoms such as palpitations, dizziness, and fatigue. Among 23 patients implanted with an ICD due to IVF, in 7 (30%, 2 males) AMVP was subsequently diagnosed. The median age of CA was 28 (range 17–37) years. In all patients, the sentinel VF event occurred while not on

β-blockers: at leisure activity (n = 7), and night (n = 1). In men, CA occurred in the daytime and was not associated with stress/exercise. In 3 women CA occurred in relation to pregnancy or postpartum period, i.e., in the 8th week of pregnancy, two and six months post-delivery. Noteworthy, all but one CA patient were consulted by a cardiologist for a median period of 7 (range 0–16) years before CA. Upon observation, in 3 patients (two males) appropriate ICD therapies occurred, with recurring electrical storms in one.

In the non-CA group the most common referral diagnoses were: frequent /complex VA (n = 14/18, 78%), either alone (n = 7) or with MVP (n = 5) and/or a suspicion of NC cardiomyopathy (n = 2), a suspicion of the long QT syndrome (n = 1); a cardiac murmur and palpitations (n = 1), syncope (n = 1), or arterial hypertension (n = 1).

All patients had bileaflet MVP with curling, MAD and preserved LVEF. In 13 (50%) mild/minimal MR, in 12 (46.2%) moderate, and one patient (3.8%) severe MR was found. CMR was performed in 12 (46%), and in 8/12 (67%) patients criteria for LVNC were fulfilled, with a median NC/C ratio of 3.2 (range 1.4–5.5). The NC pattern was associated with thinning of the compact myocardial layer to 2–4 mm in the anterior and/or lateral wall**,** and an abnormal structure/fragmented (trabeculated) base of PMs. In 9/12 (75%) subtle dispersed LGE was identified in the basal inferolateral wall and/or mid-inferolateral segments or PMs.

In all patients complex VA was recorded with >1 (median 3) PVCs morphology predominantly of the RBBB pattern from the posterior PM. In 15/26 (58%) patients three-beat nonsustained VT (nsVT), and in 14/26 patients nsVT lasting >3 beats occurred. In Holter recordings, PVCs occurred predominantly at night in two, and during the daily activity in the remaining patients. Of the 19 individuals who underwent exercise stress treadmill testing, an increase in frequency and VA complexity was observed in 3, resolution of VA in 6, VA onset in recovery stage in 3, and persistent VA with no/minimal change in 4 patients.

TWI was observed in the inferior leads in 20 (77%) patients, in 15 (58%) both normal ECGs and TWI were found. Among a total of 165 ECGs (6 strips/patient), 87 (53%) ECGs were normal, the remaining showed TWI in different configurations in ≥2 inferior leads. Only one CA survivor presented with normal ECG in all strips when compared to 5/18 nonCA patients (12.5% vs 28%; $P = 0.378$).

Twenty-four (92%) patients were treated with betablockers (bisoprolol, metoprolol, nadolol), which did not prevent malignant VA in ICD patients. Class Ic antiarrhythmics (propafenone or flecainide) alone or with betablocker were used in 2 patients with modest efficacy. One patient underwent mitral valve repair for significant MR 3 years after CA, with no VTA during follow-up.

The CA and non-CA patients differed for heart rate 68 (64–71) vs 76 (64–85) bpm; $P = 0.04$, E/e'ratio — 7.7 (6.5–9.2) vs 5.9 (5.4–6.7); $P = 0.04$, and the fastest rate of nsVT — 220 (181– 279) vs 178.5 (150–200) bpm; $P = 0.04$ (Table 1).

The presence of LV non-compaction in AMVP patients seems to contrast with the results of the studies reporting MVP as the only cardiac abnormality in SCD or out-of-hospital CA series [2–4]. In these studies, however, patients with any cardiomyopathy were *a priori* excluded. Recently, Garbi et al. showed that 81% of SCD cases with „lone" MVP had microscopic LV fibrosis associated with hypertrophy and degeneration of the myocytes, and 11% also had RV fibrosis [10]. The diffuse LV fibrosis was also demonstrated in AMVP by reduced post-contrast T1 times on CMR imaging [11]. Lastly, in MVP patients, VA arise from fascicles, LV outflow tract or septal aspect of the mitral annulus, RV outflow tract and free wall [3, 7] indicating the presence of more extensive arrhythmogenic substrate. In this context higher E/e'ratio, which is a noninvasive insight into diastolic LV pressures, might reflect more extensive disease (fibrosis) in CA patients. Various mechanisms for VA in the setting of MVP were postulated, with focal fibrosis (positive LGE) and consequent regions of conduction block promoting re-entry arrhythmia, and interstitial fibrosis (abnormal T1) resulting in spontaneous diastolic depolarization and abnormal automaticity [11]. To the best of our knowledge, E/e' ratio was not previously discussed in AMVP patients in the context of SCD risk.

Interestingly, inferior TWI was present in 77% of patients, with intermittent TWI in 58% of AMVP cases. This finding is of importance since TWI is considered a part of the diagnostic tetrad in AMVP [3, 4, 9]. The observed variability, however, may be also related to cardiac memory.

Our study showed that almost all patients were consulted by a cardiologist before CA, moreover, half of them was supervised since childhood/adolescence. Thus, patients with malignant MVP are under the specialist care for a long time, while their SCD risk goes unrecognized. In this context, the observed differences between CA and nonCA patients with regard to the rate of nsVT and E/e'ratio seem to be interesting, however, they need to be validated in larger groups of AMVP patients, preferably the multi-center registry, to establish risk stratification algorithms for SCD in MVP.

Finally, in women CA tends to occur in pregnancy or after delivery, pointing to a possible relation of hormonal status to VA. Similarly, Syed et al. found that in 2 of 6 females, pregnancy and a menstrual cycle were triggers for appropriate ICD shocks [7].

CONCLUSIONS

AMVP is a clinical syndrome characterized by intermittent TWI and myocardial abnormalities, such as LV non-compaction. AMVP patients after CA differ by faster rates of nonsustained VT and higher E/e' ratio from non-CA patients. We support the view that patients with IVF should be systematically reassessed for the presence of new arrhythmogenic conditions, including AMVP, which may constitute 30% of IVF cases.

Table 1. Characteristics of the study patients and group comparisons

Variables	Overall AMVP group (n = 26)	Non-CA group (n = 18)	CA group[a] (n = 8)	*P*-value
Age, years, median (IQR)	36 (33.5–46)	36.5 (35–48)	36.5 (29.5–44)	0.44
Women, n (%)	18 (69)	12 (67)	6 (75)	0.523
Follow-up, months, median(IQR)	27.5 (21–103)	24.5 (18–64)	108 (40–177)	0.009
Weight, kg, median (IQR)	65 (60–71)	64 (56–71)	65 (63–75)	0.36
Height, cm, median (IQR)	173 (170–179)	174 (170–180)	168.5 (166–178)	0.08
Body mass index, kg/m^2, median (IQR)	21 (20–23)	20.5 (20–23)	22.4 (22–25.5)	0.08
Age of first symptoms, years, median (IQR)	18 (9–28)	18 (8–26)	17.5 (9.5–29.5)	0.98
Symptomatic PVCs, n (%)	23 (89)	16 (89)	7 (88)	0.686
Syncope, n (%)	4 (15)	3 (17)	1 (13)	0.64
β-blockers, n (%)	24 (92)	16 (89)	8 (100)	0.471
Pacemaker, n (%)	1 (4)	0	1 (12.5)	0.31
ICD, n (%)	9 (35)	2 (11)	7 (88)	0.0004
ECG data				
No of PVCs, median (IQR)	3250 (1803–8675)	3000 (1800–9200)	3250 (1737–4500)	0.98
The shortest coupling interval, ms, median (IQR)	400 (360–440)	420 (370–440)	360 (330–440)	0.11
The longest coupling interval, ms, median (IQR)	480 (480–543)	520 (480–550)	480 (460–516)	0.11
Max VT rate, bpm, median (IQR)	188 (170–207)	178.5 (150–200)	220 (181–279)	0.04
HR, bpm, median (IQR)	75 (65–85)	75.5 (64–85)	67.5 (64–71)	0.04
PR, ms, median (IQR)	150 (130–160)	150 (130–160)	170 (150–195)	0.13
QRS, ms, median(IQR)	90 (90–110)	100 (90–100)	95 (85–100)	0.86
QT, ms, median (IQR)	400 (380–420)	400 (360–430)	420 (380–440)	0.43
QTc, ms, median (IQR)	437 (420–455)	440 (420–456)	439 (427–452)	0.98
Inferior TWI, n (%)	20 (77)	13 (72)	7 (88)	0.38
Intermittent TWI, n (%)	14 (54)	9 (50)	5 (63)	0.44
Echocardiographic data				
Curling distance, mm, median (IQR)	6 (5–7)	6 (4–7)	7 (5–8)	0.35
MAD, mm, median (IQR)	11 (9–12)	10 (9–12)	11 (8–13)	0.97
LVEF, %, median(IQR)	60 (55–60)	60 (55–60)	58 (53–63)	0.93
GLS, %, median (IQR)	–21 (–22.5–[–20])	–21.5 (–24.5–[–20])	–20.5 (–22–[–19])	0.26
LVESD, mm, median(IQR)	32 (28–35)	32 (30–35)	29.5 (26–37)	0.68
LVEDD, mm, median (IQR)	51 (47–55)	51 (49–55)	50 (46–55)	0.74
LA diameter, mm, median (IQR)	37 (34–42)	37 (35–43)	36(32–42)	0.52
LAVI, ml/m^2, median (IQR)	31 (23–40)	27 (23–41)	36 (22–45)	0.9
e', median (IQR)	0.11 (0.1–0.12)	0.11(0.1–0.12)	0.11 (0.09–0.14)	0.97
E/e', median (IQR)	6.2 (5.6–6.8)	5.9 (5.4–6.7)	7.7 (6.5–9.2)	0.04

[a]The patient with symptomatic polymorphic VT/VF and DDD pacemaker was also included in this group.

Abbreviations: GLS, global longitudinal strain; HR, heart rate; ICD, implantable cardioverter-defibrillator; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic diameter LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MAD, mitral annular disjunction; MVP, mitral valve prolapse; PVCs, premature ventricular contractions; TWI, T-Wave inversion; VT, ventricular tachycardia

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Multicenter Registry of Subcutaneous Cardioverter--Defibrillator Implantations: a preliminary report

Maciej Kempa[1], Andrzej Przybylski[2, 3], Szymon Budrejko[1], Wojciech Krupa[4], Krzysztof Kaczmarek[5], Anna Kurek[6], Paweł Syska[7], Adam Sokal[8], Marcin Grabowski[9], Dariusz Jagielski[10], Maciej Grymuza[11], Piotr Szafarz[2], Stanisław Tubek[12], Zbigniew Orski[13], Joanna Zakrzewska-Koperska[14], Jakub Machejek[15], Wojciech Kwaśniewski[16]

[1]Department of Cardiology and Electrotherapy, Medical University of Gdansk, Gdańsk, Poland
[2]Cardiology Department with the Acute Coronary Syndromes Subdivision, Clinical Provincial Hospital No. 2, Rzeszów, Poland
[3]Medical College, University of Rzeszow, Rzeszów, Poland
[4]Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland
[5]Department of Electrocardiology, Medical University of Lodz, Łódź, Poland
[6]3rd Department of Cardiology, School of Medicine with the Division of Dentistry in Zabrze, Silesian Centre for Heart Diseases, Medical University of Silesia, Katowice, Poland
[7]2nd Department of Arrhythmia, National Institute of Cardiology, Warszawa, Poland
[8]1st Department of Cardiology and Angiology, Silesian Centre of Heart Diseases, Zabrze, Poland
[9]1st Chair and Department of Cardiology, Medical University of Warsaw, Warszawa, Poland
[10]Department of Cardiology, Centre for Heart Diseases, 4th Military Hospital, Wrocław, Poland
[11]1st Department of Cardiology, Chair of Cardiology, Karol Marcinkowski University of Medical Sciences, Poznań, Poland
[12]Department of Heart Diseases, Wroclaw Medical University, Wrocław, Poland
[13]Department of Cardiology and Internal Diseases, Military Institute of Medicine, Warszawa, Poland
[14]1st Department of Arrhythmia, National Institute of Cardiology, Warszawa, Poland
[15]Department of Electrocardiology, John Paul II Hospital, Kraków, Poland
[16]1st Department of Cardiology, Upper-Silesian Medical Centre of the Silesian Medical University in Katowice, Katowice, Poland

Correspondence to:
Szymon Budrejko, MD, PhD, Department of Cardiology and Electrotherapy, Medical University of Gdansk, Dębinki 7, 80–211 Gdańsk, Poland, phone: +48 58 349 39 10, e-mail: budrejko@gumed.edu.pl

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INTRODUCTION

Implantation of a subcutaneous cardioverter--defibrillator (S-ICD) is a well-established method for prevention of sudden cardiac death due to ventricular arrhythmias. It may be applied in patients with indications for an implantable cardioverter-defibrillator (ICD) not requiring permanent cardiac pacing nor antitachycardia pacing [1]. First implantation procedures in Poland were performed in 2014 [2, 3]. Due to the lack of clear rules for reimbursement of the procedure in the early days, the total number of implantations performed in Poland at that time was low. Reimbursement rules were changed in 2019 to the level allowing for complete coverage of the costs. It led to an increase in the number of implantations, but the total cumulative number of implantations in Poland has not yet exceeded 450.

Although the Heart Rhythm Section of the Polish Cardiac Society has published an expert opinion on the use of S-ICD in Poland, there is currently no report available that would summarize the Polish experience with S-ICD [4]. Therefore, the Executive Board of the Heart Rhythm Section appointed the Multicenter Registry of Subcutaneous Cardioverter-Defibrillator Implantations. The registry has been approved by Bioethical Committee at the Regional Medical Board in Rzeszow, Poland (decision number 35/B/2020), and launched on the 1st of May 2020.

METHODS

The Multicenter Registry of Subcutaneous Cardioverter-Defibrillator Implantations is an open registry run by the Heart Rhythm Section of the Polish Cardiac Society. Centers implanting S-ICD devices add data of consecutive patients undergoing implantation or exchange of the S-ICD system. Participation in the registry does not influence the clinical routine in any way. All data are introduced when the hospitalization is finished, and include age, gender, underlying disease, reasons for indications for S-ICD, electrocardiographic parameters, technique of implantation, and complications during the in-hospital period. The analysis included data reported between May 2020 and January 2021, regarding the periprocedural period, whereas follow-up data will be collected onwards and reported accordingly.

Statistical analysis

Continuous variables were reported as a range, mean and standard deviation, and categorical variables as numbers and percentages. Due to the type of our analysis, only descriptive statistics was used.

RESULTS AND DISCUSSION

During the initial 8 months, 15 centers reported 123 patients (Supplementary material, *Table S1*), 90 men, aged 15–79. Most patients were in NYHA II class. Left ventricular ejection fraction (LVEF) was 10%–80%. In 78 patients S-ICD was indicated for primary prevention. The most frequent underlying disease (54 patients, 44%) was nonischemic cardiomyopathy (Table 1). The most frequent reason for the choice of S-ICD (76%) was the patient's young age (Supplementary material, *Table S2*).

In 114 patients (93%) the reported procedure was the first-time implantation of S-ICD, and in the remaining 9 cases (7%) — device exchange. The procedure was performed most often by cardiologists and in general anesthesia — 89 procedures (72%). Local anesthesia was used in 19 cases (15%), and regional anesthesia or blockade — in 15 cases (12%). Three procedures (2%) were assisted by a cardiac surgeon. The 2-incision technique was slightly more prevalent (63 cases, 51%). The device pocket was intermuscular in all cases but one. In 102 cases, the defibrillation test was performed immediately following the surgical part of the procedure, and the 65 J shock was effective in all those patients. In 2 patients no sustained ventricular tachyarrhythmia could be induced. In the remaining 19 patients, the test was abandoned due to contraindications, specifically the risk of thromboembolic complications (10 patients) or extremely low LVEF (4 patients). The mean (SD) procedural time was 75 (32) minutes (range 18–150 min). Mean post-procedural hospitalization continued for 3 days. Complications were observed in 2 patients (pocket hematoma treated conservatively, and unilateral paresis of the lower limb with no apparent pathology on the CT and MRI scans).

Table 1. Clinical characteristics of the study group

General information	
Total number of patients	123 (100)
Age, years, mean (SD)	43 (15)
Gender: male	90 (73)
Sinus rhythm	114 (93)
LVEF, %, mean (SD)	40 (17)
NYHA class	
NYHA I	56 (46)
NYHA II	52 (42)
NYHA III	15 (12)
NYHA IV	0 (0)
Indication	
Primary prevention	78 (63)
Secondary prevention	45 (37)
Underlying disease	
NICM	54 (44)
ICM	34 (28)
HCM	5 (4)
LQTS	5 (4)
BrS	3 (2)
SQTS	2 (2)
Myocarditis	2 (2)
LVNC	1 (1)
CPVT	1 (1)
MAD	1 (1)
ToF	1 (1)
Primary VF	14 (11)

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

Abbreviations: BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; HCM, hypertrophic cardiomyopathy; ICM, ischemic cardiomyopathy; LQTS, long QT syndrome; LVEF, left ventricle ejection fraction; LVNC, left ventricular non-compaction; MAD, mitral annular disjunction; NICM, nonischemic cardiomyopathy; SQTS, short QT syndrome; ToF, tetralogy of Fallot; VF, ventricular fibrillation

S-ICD systems have been implanted in Poland since 2014, but the total number of procedures remains relatively low, due to the high cost of the device and lack of clear rules for reimbursement during the early days of the method. Guidelines for S-ICD implantation in Poland and specified requirements for implantation centers, may potentially limit the access of patients to that method of treatment, but they enforce appropriate experience of implanting teams. Our analysis is based on the results of 123 patients, representing 90% of the total number of procedures performed in Poland between May 2020 and January 2021. According to the yearly report of the National Consultant in Cardiology, 9298 cardioverters-defibrillators were primarily implanted in Poland in 2019 (unpublished data, both ICD and CRT-D). Having taken into account the data from our eight-month period, it could be estimated that S-ICD represented about 2% of cardioverter-defibrillator implantations in our country.

In our study group, 73% of patients were men. That percentage is slightly higher than in other European centers (68.4%) but lower than in American groups (77%) [5, 6]. The mean age was 43 years, and it was lower in comparison with other studies [7].

Data concerning indications for S-ICD in our registry are also different from other reports. In our population, ischemic cardiomyopathy was diagnosed only in 28% of patients, whereas in other reports that percentage was definitely higher, reaching 48%–46% [7, 8]. The main reason for the choice of S-ICD in our study was concurrent with other studies, and it was young age in 76% of patients [9].

In clinical studies, S-ICD successfully terminated ventricular arrhythmias with 65 J test shock in over 90% of cases [10, 11]. In our population, the 65 J test shock was effective in 100% of the 102 tests performed. It may be related to the fact that the device pocket was dissected beneath the latissimus dorsi muscle in all cases of de novo implantations, which led to a dorsal final location of the can. Such a technique may be associated with higher efficacy of defibrillation test shock, due to the low impedance of defibrillation [12]. Implementation of the 2-incision technique in most cases (51%) and regional anesthesia in many

cases (28%) indicate the tendency to implement modern implantation techniques in Polish centers [13, 14].

The incidence of surgical complications of S-ICD implantation is currently estimated at approximately 3% during the first month [15]. In our study group, such complications have not been observed.

The most frequent reason for the choice of S-ICD was the patient's young age, similarly to other reports, but our observations revealed also some differences with regard to qualification for S-ICD implantation between Poland and other countries. High efficacy and lack of surgical complications in the post-operative period confirmed the appropriate selection of centers performing implantation procedures (according to the regulations issued by the National Health Fund, regarding requirements for reimbursement), and satisfactory level of training of implanting teams. The results of our study encourage further promotion of that modality of treatment in our country.

Article information

Conflict of interest: MK received consultancy fees from Boston Scientific. AP received lecturer's fees from Medtronic Polska, Biotronik Polska; consultancy fees from Medtronic Polska. KK received proctor/trainer and lecturer fees from Abbott Poland, Medtronic Poland and Boston Scientific Poland. PS received lecturer's fees from Abbott, Biotronik, Boston Scientific, Medtronic; consultancy fees from Biotronik, Boston Scientific. AS received consultancy agreement with Boston Scientific. MG received honoraria from Boston Scientific. DJ received honorarium from Boston Scientific for a lecture during Webinar. ST received a consultancy fee from Boston Scientific. The remaining authors declared no conflict of interest.

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Hypertrophic cardiomyopathy, non-compaction cardiomyopathy or non-compaction phenotype — another diagnosis, other further treatment

Anna Bednarek[1], Maria Stec[2], Magdalena Mizia-Szubryt[1], Małgorzata Cichoń[1], Wiktoria Kuczmik[2], Katarzyna Mizia-Stec[1]

[1]1st Department of Cardiology, Medical University of Silesia, Katowice, Poland
[2]Students Scientific Society, First Department of Cardiology, Medical University of Silesia, Katowice, Poland

Correspondence to:
Prof. Katarzyna Mizia-Stec, MD, PhD, 1st Department of Cardiology, School of Medicine in Katowice, Medical University of Silesia, Ziołowa 47, 40–635 Katowice, Poland, phone: +48 32 359 88 90, e-mail: kmiziastec@gmail.com

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Cardiomyopathy phenotype established using imaging methods determinates a diagnosis and further treatment in patients with cardiomyopathies. Hypertrophic cardiomyopathy (HCM) has been clearly defined whereas characterization of left ventricular non-compaction cardiomyopathy (LVNC) is still debated [1]. Apart from LVNC, a non-compaction pattern may accompany other cardiomyopathies, acute myocarditis, and athlete's heart [1, 2].

According to the recent data, HCM and LVNC are diseases with potent overlapping genetic defects as well as phenotypes [3, 4]. We present an atypical patient with a baseline diagnosis of HCM converted after a 3-month follow-up into the diagnosis of LVNC. Re-evaluation was crucial both for the final diagnosis, pharmacotherapy, and sudden cardiac death (SCD) risk re-assessment.

A 51-year-old man with hypertension and prior ischemic stroke was hospitalized due to atypical chest pain. Laboratory tests did not show any abnormalities. Resting ECG showed persistent ST-segment elevations up to 2 mm on the lateral wall leads. Transthoracic echocardiography (TTE) revealed increased thickness of the left ventricle (LV) wall (intraventricular septum [IVS] up to 17 mm, the maximal thickness of LV wall up to 24 mm) without LV gradient and with normal LV ejection fraction (LVEF, 55%) (Figure 1A–B); left atrial area 29.5 cm^2. There was no stenosis on coronary angiography. In 48-hour Holter monitoring several episodes of nsVT (max. 8 QRS) were recorded. His family history of SCD was positive. Family TTE screening allowed to recognize HCM in the patient's son (max. LV wall thickness, 29 mm; SCD risk score, 5.1%) (Figure 1C). Finally, HCM was diagnosed. The calculated SCD risk score was 7.8% and the patient was qualified for cardioverter-defibrillator (ICD) implantation. After three months an ambulatory cardiac magnetic resonance showed LVNC with LVEF 33%. In the 3rd month after the 1st assessment patient was re-hospitalized for ICD implantation. The control TTE showed: the maximal thickness of LV wall up to 15 mm, abnormal LV endocardial trabeculation with the index of spongy/compacted layers 2.0 and LVEF of 35% (Figure 1D–E). The baseline HCM diagnosis was verified by recognizing LVNC. Regardless of the other diagnosis, the patient still had the indications for ICD implantation, which was performed. Pharmacotherapy was optimized according to the heart failure guidelines and because of low LVEF, LV trabeculations and the ischemic stroke incident, anticoagulation was administered.

As it was mentioned, HCM and LVNC may present potent overlapping genetic defects as well as phenotypes [3, 4], therefore simultaneous screening for both HCM and LVNC is necessary. Until now, the overlapping phenotypes have been observed in different family members [3, 4]. Only two cases of coincident non-compacted myocardium and HCM were reported [5]. Based on our case, it might be speculated that the phenotype may change over time. The classical form of HCM has been either converted to LVNC or non-compaction pattern of HCM. Due to a short 3-month follow-up, it is unlikely that the presented asymptomatic patient demonstrated the decompensated HCM. Finally, the re-evaluation was necessary not to overlook details essential for the current

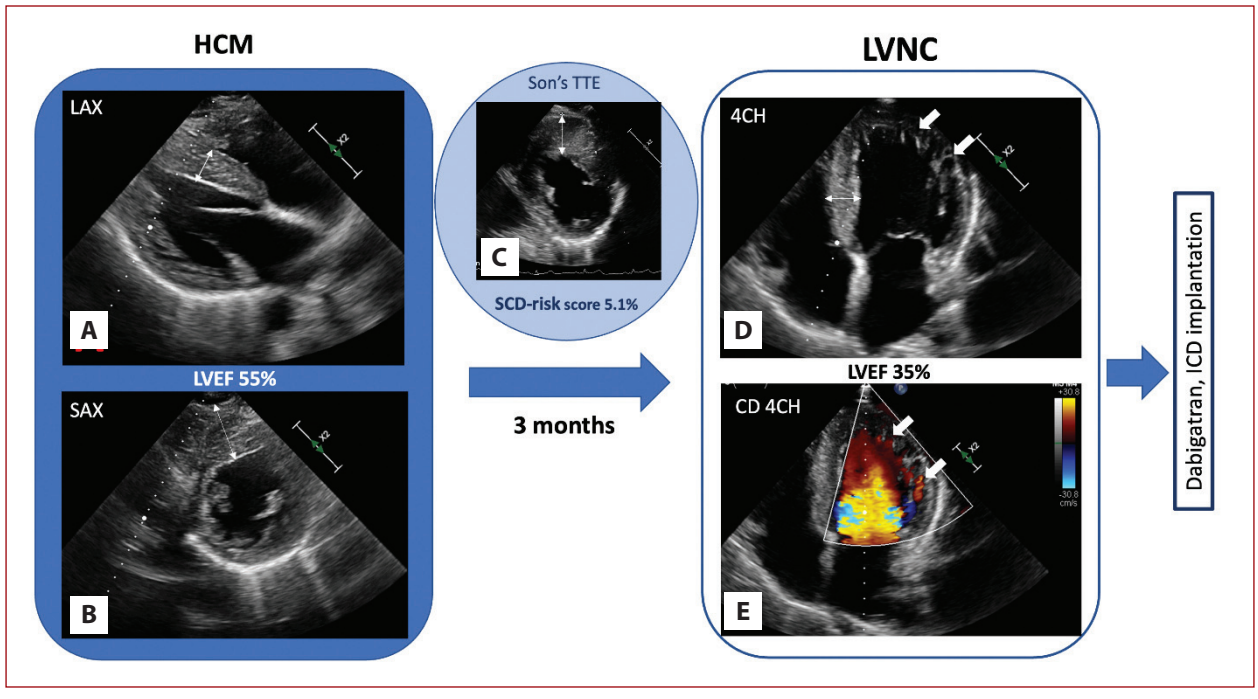

Figure 1. Transthoracic echocardiography (thin arrows — maximal thickness of LV segments). **A.** Long parasternal axis: hypertrophy of the LV wall (IVS thickness, 17 mm). **B.** Short parasternal axis: hypertrophy of the LV wall (maximal LV wall thickness, 24 mm). **C.** Short parasternal axis (echocardiography of the patient's son): hypertrophy of the LV wall (maximal LV wall thickness, 29 mm). **D.** Four-chamber view: the LV trabeculations (IVS thickness, 15 mm; thick arrows — trabeculations). **E.** Four-chamber view, color doppler: blood flow between the LV trabeculations (arrow — blood flow through trabeculations).

Abbreviations: HCM, hypertrophic cardiomyopathy; IVS, intraventricular septum; LV, left ventricle; LVEF, left ventricular ejection fraction; LVNC, left ventricle non-compaction cardiomyopathy; SCD, sudden cardiac death; TTE, transthoracic echocardiogram

approach. That prompts further clinical surveillance supported by genetic tests.

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Aortic dissection after the Ross procedure

Hanna Siudalska[1], Mariusz Kuśmierczyk[1], Jacek Różański[1], Joanna Petryka-Mazurkiewicz[2], Magdalena Kumor[3], Anna M Michałowska[4], Ilona Michałowska[5]

[1]Department of Cardiac Surgery and Transplantology, National Institute of Cardiology, Warszawa, Poland
[2]Department of Coronary and Structural Heart Diseases, National Institute of Cardiology, Warszawa, Poland
[3]Congenital Heart Disease Department, National Institute of Cardiology, Warszawa, Poland
[4]National Institute of Cardiology, Warszawa, Poland
[5]Department of Radiology, National Institute of Cardiology, Warszawa, Poland

Correspondence to:
Ilona M Michałowska, MD, PhD, Department of Radiology, National Institute of Cardiology, Alpejska 42, 04–628 Warszawa, Poland, phone: +48 22 3434167, e-mail: imichalowska@ikard.pl

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The Ross procedure is performed for the treatment of aortic valve disease in children and young adults. The diseased aortic valve is removed and replaced with the patient's pulmonary valve, and a pulmonary homograft is implanted in the pulmonary position.

The Ross procedure due to outstanding hemodynamic parameters and no need for anticoagulation provides the patients with a better quality of life compared to the patients who have undergone the mechanical aortic valve replacement. The implantation of the autograft in the subcoronary position was first described by Donald Ross. Then the Ross procedure has been modified and shifted toward a full root replacement technique. However, the implantation of pulmonary autograft as a full root may be complicated by dilatation of the autograft caused by systemic pressure higher than pulmonary pressure [1]. In cases of concomitant aortic valve stenosis with a very small aortic annulus or with a narrowed left ventricular outflow tract, the Ross-Rastan-Konno procedure is an option of surgical treatment [2].

We present here a 49-year-old male patient who was admitted to the hospital due to dissection of the aneurysm of the autograft which had been found on follow-up magnetic resonance imaging (Figure 1A) 15 years after the Ross procedure. The indication for the cardiac magnetic resonance imaging was pulmonary autograft widening to 53 mm identified five months earlier by echocardiography. Implantation of the pulmonary autograft in the aortic position was performed using the root replacement technique. The indication for the Ross procedure was bicuspid aortic valve stenosis. On admission to the hospital, the patient was asymptomatic, in good condition without complaints of chest pain or worsening of physical capacity. Lately, increased blood pressure was observed. Transthoracic echocardiography revealed a left ventricular dilatation to 65 mm, the left ventricular ejection fraction of 55%, dilatation of the autograft to 66 mm with dissection (Figure 1B–C), moderate autograft valve insufficiency and normal functioning of the pulmonary homograft. Cardiac computed tomography was performed to assess coronary arteries before surgery and showed normal vessels without significant stenosis, a dissection limited to the aneurysm of the autograft (Figure 1D–E) and a normal aortic arch with the descending aorta. The patient was referred for emergency surgery and underwent the Bentall procedure (the autograft and the valve were replaced with a conduit of the aorta and a mechanical valve, Figure 1F). Another option of surgical treatment for pulmonary autograft aneurysm can be one of the aortic valve-preserving procedures — the reimplantation of the native valve within a vascular graft or aortic remodeling of the root with valvuloplasty [3, 4]. These options were not considered because of degeneration and prolapse of the right coronary cusp of the pulmonary autograft valve. It was not possible to perform repair of autograft valve. The patient's postoperative course was uneventful.

Aortic root or ascending aorta dilatation and aortic regurgitation are relatively common consequences of the Ross procedure, which occur in 20%–30%, but dissection of the autograft is a rare complication [5]. To our knowledge, only a few cases of post-Ross procedure aortic dissection have been reported.

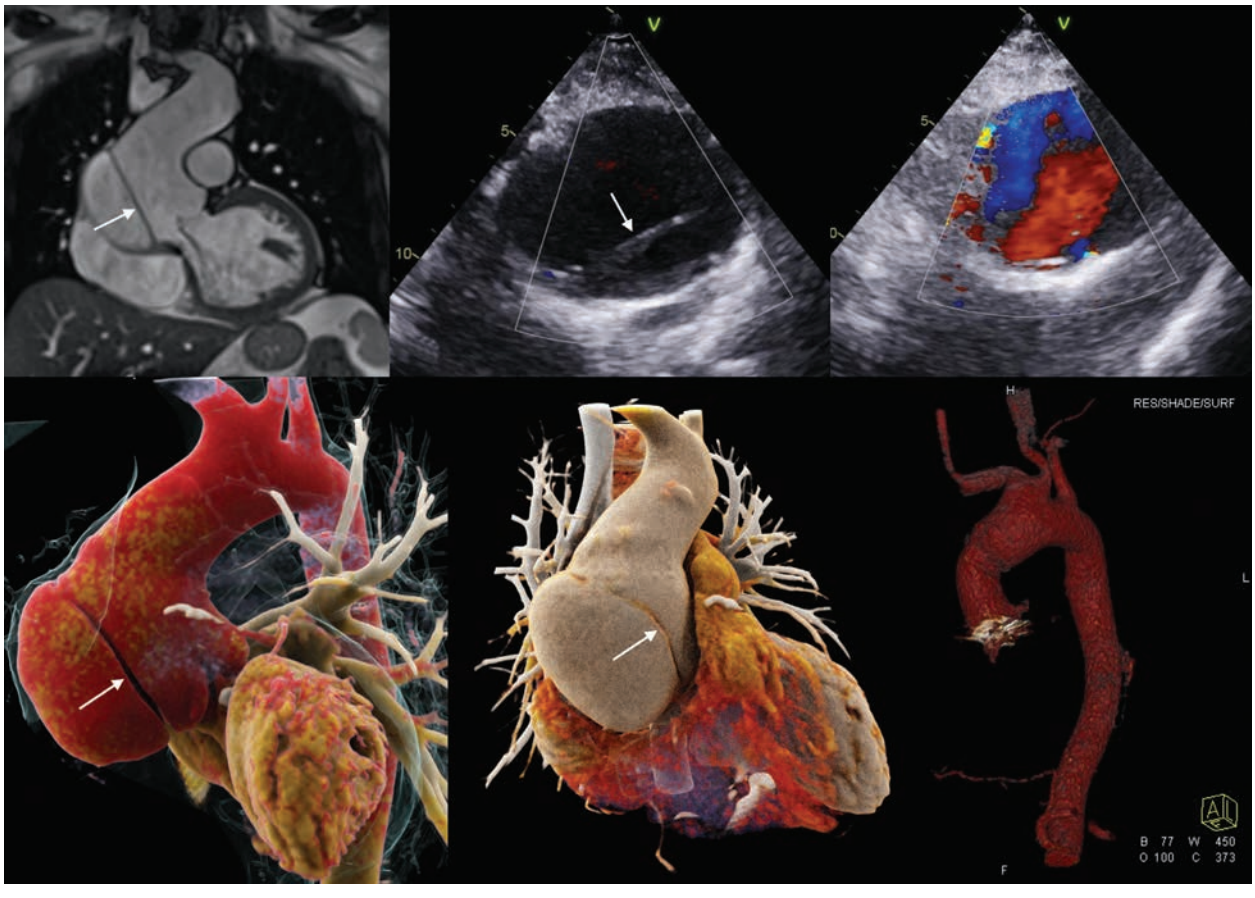

Figure 1. A. Magnetic resonance imaging, balanced steady-state free precession image, orthogonal to left ventricular outflow tract view shows dissection of the aneurysm of the autograft (arrow) and aortic regurgitation jet. **B, C.** Echocardiography imaging, a modified right parasternal short axis plane of the autograft above the neoaortic valve with dissection (arrow) (**B**), with color Doppler (**C**). **D, E.** Computed tomography angiography, a cinematic rendering reconstruction shows dissection of the aneurysm of the autograft (arrow). **F.** Computed tomography angiography, volume rendering reconstruction visualizes the thoracic aorta after Bentall procedure

Article information

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Unusual finding during screening for intracardiac thrombus in patients referred for percutaneous left atrial appendage closure

Vilhelmas Bajoras[1–3], Niels Grove Vejlstrup[1], Ivan Wong[1], Lars Søndergaard[1], Ole De Backer[1]

[1]The Heart Center, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[2]Center of Cardiology and Angiology, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania
[3]Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania

Correspondence to:
Prof. Ole De Backer, MD, PhD, FESC, The Heart Center, Rigshospitalet — University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen, Denmark, phone: +45 3545 7086, e-mail: ole.debacker@gmail.com

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A 65-year-old female, with a history of non-valvular atrial fibrillation and lower gastrointestinal bleeding while on oral anticoagulant therapy, was referred for percutaneous left atrial appendage (LAA) closure at the Heart Center, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. Transthoracic echocardiography revealed a preserved left ventricular ejection fraction, mild mitral regurgitation, moderately enlarged left atrium and no intracardiac thrombi.

Pre-procedural cardiac computed tomography (CT) showed an anatomically suitable LAA for catheter-based closure and excluded thrombus in the left atrium and LAA. Percutaneous LAA closure under local anesthesia with intracardiac echocardiography (ICE) guidance was, therefore, planned [1]. During the procedure, before transseptal puncture, ICE at the right ventricle position revealed there was a hypermobile, thrombus-like structure adhered to the calcified posterior mitral leaflet (Figure 1A–B; Supplementary material, *Video S1–S2*). Differential diagnosis of this intracardiac mass included thrombus or vegetation. Infective endocarditis was highly unlikely given negative blood culture and the absence of clinical signs of sepsis. Consequently, the procedure was interrupted, and a therapeutic dose of a low-molecular-weight heparin was initiated. Transesophageal echocardiography (TEE) was scheduled 6 weeks later to review the progression or resolution of the intracardiac mass. Retrospectively, this intracardiac mass adhered to the mitral valve could have been suspected at the pre-procedural cardiac CT scan (Figure 1C–D). In addition, other authors have previously reported routine TEE 24 hours before the LAA closure to exclude the presence of intracardiac thrombi [2].

Cardiac CT is increasingly adopted as the preferred imaging modality in the planning of catheter-based LAA closure [3, 4]. This report illustrates that screening for intracardiac thrombus should not only include the left atrium and LAA but all cardiac structures. Importantly, the essential role of intraprocedural echocardiography — either ICE or TEE — in the setting of percutaneous LAA closure should also be emphasized.

Supplementary material

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

Article information

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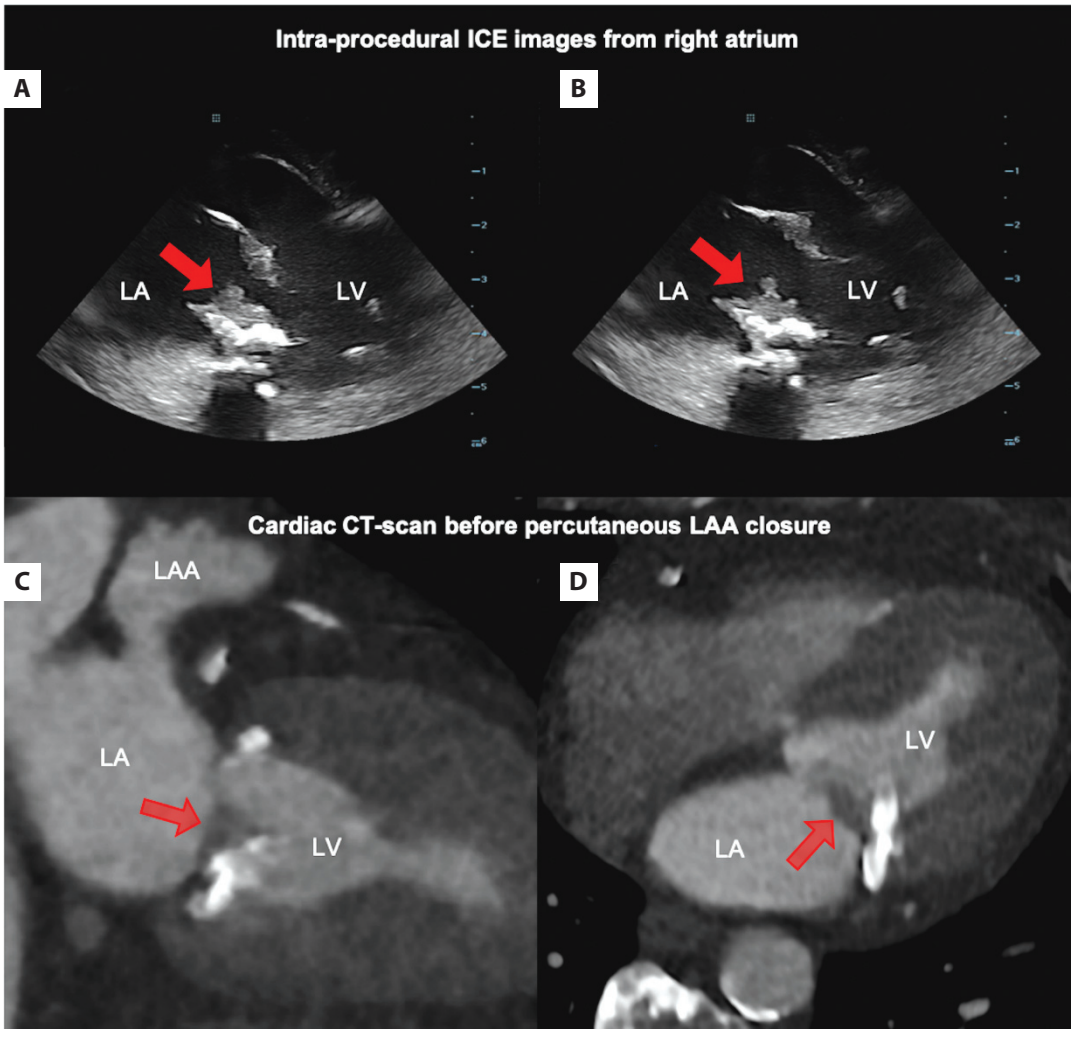

Figure 1. Intra-procedural intracardiac echocardiography and pre-procedural cardiac CT images. **A, B.** A thrombus-like structure (red arrow) shown by intra-procedural intracardiac echocardiography from the right atrium. **C, D.** Shady masses (red arrow) attached to the mitral valve as seen on the pre-procedural cardiac CT scan.

Abbreviations: CT, computed tomography; ICE, intracardiac echocardiography; LA, left atrium; LAA, left atrial appendage; LV, left ventricular

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Iatrogenic pulmonary embolism with cyanoacrylate — to remove, or to leave?

Arkadiusz Pietrasik[1], Aleksandra Gąsecka[1], Dominika Chojecka[1], Jakub Pytlos[1], Bartosz Rymuza[1], Renata Główczyńska[1], Marta Banaszkiewicz[2], Szymon Darocha[2], Marcin Kurzyna[2]

[1]1st Chair and Department of Cardiology, Medical University of Warsaw, Warszawa, Poland
[2]Department of Pulmonary Circulation, Thromboembolic Diseases and Cardiology, Centre of Postgraduate Medical Education, European Health Center, Otwock, Poland

Correspondence to:
Aleksandra Gąsecka, MD, PhD, 1st Chair and Department of Cardiology, Medical University of Warsaw, Banacha 1A, 02–097, Warszawa, Poland, phone: +48 22 599 19 51, e-mail: aleksandra.gasecka@wum.edu.pl

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A 46-year-old female with autoimmune hepatitis and liver cirrhosis presented with the symptoms of upper gastrointestinal bleeding. Gastroduodenoscopy revealed active hemorrhage from a huge duodenal varix and endoscopic injection sclerotherapy with cyanoacrylate was performed. Since the bleeding continued, the patient underwent a successful surgical ligation of bleeding varix the following day.

Twenty days later the patient was re-admitted due to dyspnea, cough and pleuritic chest pain. On physical examination, she was tachypneic and hypoxic. Computed tomography angiography revealed the presence of disseminated, hyperdense deposits in segmental and subsegmental branches of both pulmonary arteries (Figure 1A; Supplementary material, *Video S1*), confirming the previously suspected diagnosis of pulmonary embolism (PE) with cyanoacrylate. A single-photon-emission computed tomography revealed bilateral wedge-shaped perfusion defects matching several bronchopulmonary segments of both lungs (Figure 1B; Supplementary material, *Video S2*). Echocardiography showed no embolic material in heart chambers and no features of right ventricle overload (TAPSE, 22 mm), yet pericardial effusion (Figure 1C–D). The cardiac troponin I and natriuretic peptide concentrations were within the reference range .

In contact with blood, cyanoacrylate undergoes rapid polymerization. Large varix size and injected volume increase the risk of embolization via the varix efferent vein into the inferior vena cava, right heart chambers and pulmonary arteries. The nature of PE with cyanoacrylate rules out any form of pharmacological therapy, including anticoagulation. The range of surgical treatment options is wide but choosing an optimal therapy for an individual patient is truly challenging [1]. Hitherto, no consensus regarding the best way of clinical management of iatrogenic cyanoacrylate emboli has been established [2]. For this patient, the accurate management of the PE episode was crucial since it could impact her overall condition and potentially disqualify her from liver transplantation. To facilitate immediate decision making by experts, she was consulted by the local Pulmonary Embolism Response Team (PERT) [3].

Given the hemodynamic stability, the patient was at low risk of death. The danger of further thromboembolic and septic complications was also identified as unlikely. Consequently, PERT members assessed the risk of interventional therapy to be higher than the risk of death. A decision was made to continue with the conservative therapy, which was followed by a control computed tomography angiography a month after the episode and a series of endoscopies with varices ligation every 2 months, without further complications. A favourable outcome during the 12-month follow-up period confirmed that the right path of management had been taken.

This report highlights the challenges in the management of iatrogenic PE. Recently, an interesting case of acute PE and right atrial thrombus was presented, which was due to central venous access chemotherapy port migration and required surgical excision [4]. In contrast, our patient did not undergo interventional treatment, but only a 12-month follow-up assured us of the patient's recuperation. Hence, in every patient, the treatment should be based on the individualized risk stratification to determine whether the interventional or conservative approach is more beneficial. Consultation in a multidisciplinary team is an important part

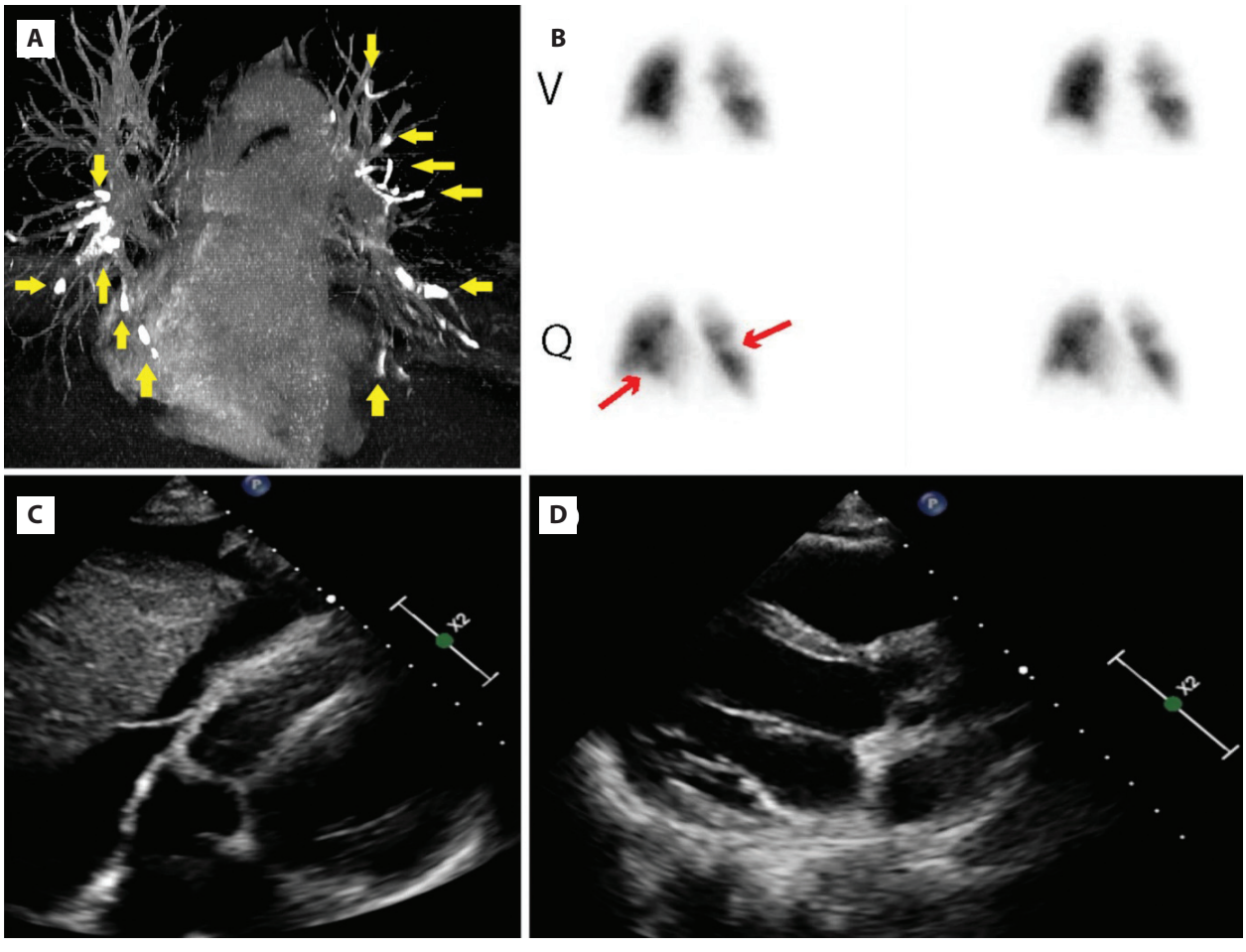

Figure 1. A. Coronal maximum intensity projection showing disseminated, hyperdense cyanoacrylate deposits within the segmental and subsegmental branches of pulmonary arteries to the middle and lower lobe in the right lung and the upper and lower lobe in the left lung (yellow arrows); there are no residual deposits visible within the right heart. **B.** Ventilation (V) and perfusion (Q) single-photon-emission computed tomography slices with multiple mismatched defects in the right and left lung (red arrows). **C, D.** Echocardiography showing no embolic material in the heart chambers and no features of right ventricular pressure overload

of the decision-making process to ensure optimal clinical management [5].

Supplementary material

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

Article information

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Transseptal implantation of HighLife self-expandable mitral valve in a patient with severe secondary mitral regurgitation and heart failure

Wojciech Wojakowski[1], Grzegorz Smolka[1], Nicolo Piazza[2], Radosław Gocoł[3], Damian Hudziak[3], Marek Jędrzejek[1], Piotr Pysz[1]

[1]Department of Cardiology and Structural Heart Diseases, Medical University of Silesia, Katowice, Poland
[2]Division of Cardiology, Department of Medicine, McGill University Health Centre, Faculty of Medicine, McGill University, Montreal, Quebec, Canada
[3]Department of Cardiac Surgery, Department of Cardiac Surgery, Medical University of Silesia, Katowice, Poland

Correspondence to:
Prof. Wojciech Wojakowski, MD, PhD,
Division of Cardiology and Structural Heart Diseases, Medical University of Silesia,
Ziołowa 45, 40–635 Katowice, Poland,
phone: +48 604188669,
e-mail: wwojakowski@sum.edu.pl

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The report presents the initial Polish experience with trans-septal transcatheter mitral valve implantation using the HighLife valve, specifically developed, for a patient with moderate-severe to severe functional mitral regurgitation. HighLife is a trans-septal self-expandable valve consisting of a nitinol frame with bovine pericardial leaflets and a post-implant mitral annular diameter of 28 mm. The patient was a 70-year-old male with *New York Heart Association* (NYHA) III class heart failure. He had a history of coronary artery disease (16 years after coronary artery bypass grafting [CABG]), atrial fibrillation, pacemaker implantation, hypertension, diabetes mellitus, and obesity (body mass index [BMI], 35 kg/m^2). Echocardiography showed left ventricular (LV) enlargement (end-diastolic diameter [EDD], 70 mm, end-diastolic volume [EDV], 211 ml) with mildly depressed LV ejection fraction (52%) and severe functional mitral regurgitation (Supplementary material, *Figure S1*). The Heart Team deemed the patient inoperable. Preprocedural multislice computed tomography showed a proper size of the mitral annulus and a low risk of LV outflow tract obstruction. The procedure was performed under general anaesthesia. The procedural steps consisted of the retrograde crossing of the aortic valve and introducing the loop placement catheter below the aortic valve and creating a loop with a guidewire encircling the chordae tendineae. Using the ring delivery catheter in the LV the subannular ring was advanced and closed after confirmation of proper positioning. The ring formed a landing zone for the valve. The interatrial septum was punctured and balloon septostomy with 10 mm balloon performed. A stiff Lunderquist wire was placed across the interatrial septum and the transeptal valve delivery system introduced into the LV. The LV portion of the valve was gradually deployed within the subannular ring, the valve is pulled against the ring, pushing the ring against the native mitral annulus, then the atrial portion is released (Figure 1). The transesophageal echocardiograpy (TEE) confirmed the proper function of the valve with no mitral regurgitation and no paravalvular regurgitation (Supplementary material, *Figure S2*). The arterial access site was closed with Manta 18 F device and venous access with an „8" suture. The patient was extubated in the hybrid room and ambulated the next day. He initially reported alleviation of heart failure symptoms, but at 1 month FU presented overt signs of right ventricular decompensation. TEE visualized significant right to left shunt across persistent iatrogenic atrial septal defect (ASD; oblong-shaped with max. dimension of 2.95 cm and an area of 2.15 cm^2) which was subsequently closed using the ASD Amplatzer plug (Supplementary material, *Figure S3–S4*). Further course was uneventful and the patient remains stable in NYHA class II at 5 months post-TMVR. This case is one of the first 15 transseptal HighLife valves implanted worldwide. Previous clinical data showed the feasibility and safety of the earlier transapical version of this device [1]. The possibility of a transseptal approach is the advantage of this technology and as a less invasive technique, it is a goal of the progress of the transcatheter mitral valve implantation field [2]. The key features of the HighLife valve is a stable landing zone formed by the subannular ring

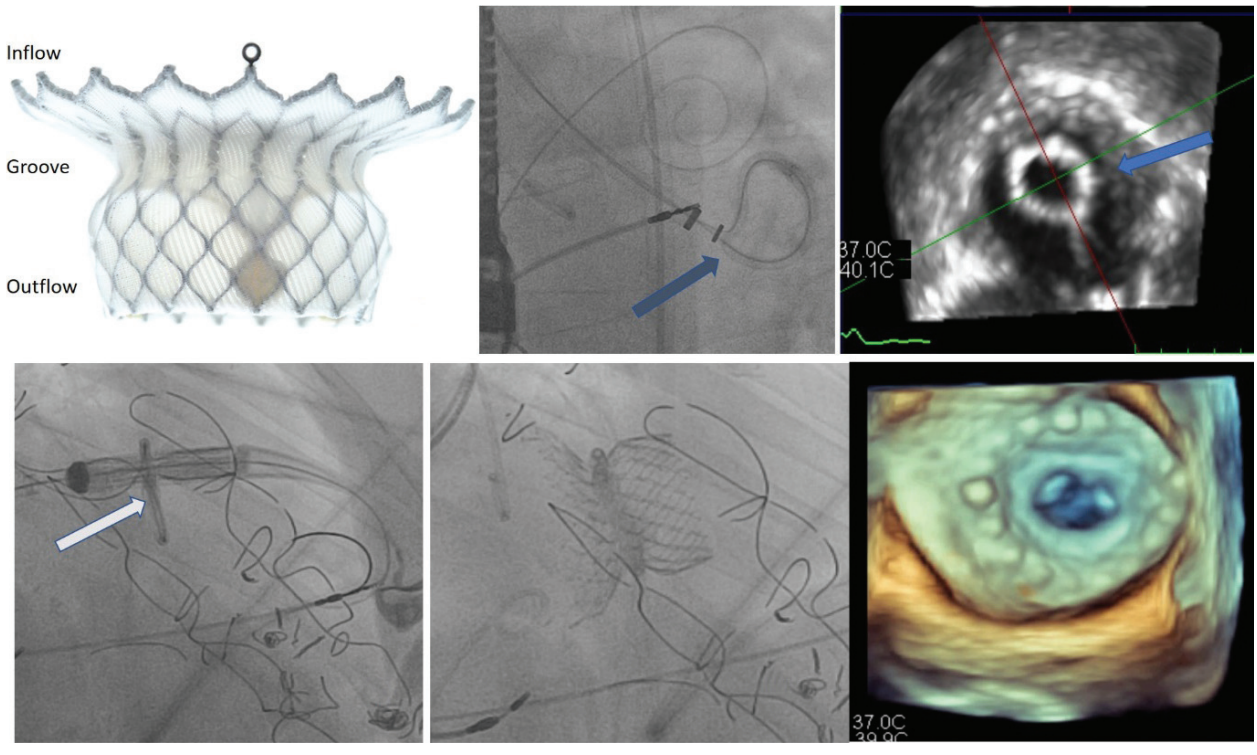

Figure 1. Fluoroscopy and transoesophageal echocardiography depicting the steps of High Life valve implantation. **A.** 28 mm HighLife self-expandable valve. **B.** Fluoroscopic image of loop placement catheter across the aortic valve with a closed ring encircling the mitral valve chords. **C.** Echocardiographic short-axis view showing the ring (arrow) and loop placement catheter. **D.** Fluoroscopic view of the valve in the capsule positioned to match the groove with the subvalvular ring. **E.** Deployed valve. **F.** 3D atrial view in transoesophageal imaging of the valve

controlled deployment and fully percutaneous access. The most important anatomic requirements currently are not over-large mitral annulus and no evidence of LV outflow tract obstruction on pre-procedure computed tomography review and adequate arterial vascular access.

Supplementary material

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Article information

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Ultrasound-assisted thrombolysis for a giant right atrial thrombus and pulmonary embolism in a COVID-19 patient

José Roberto Victoria-Nandayapa[1], Cuitláhuac Arroyo-Rodríguez[1], Salvador Leopoldo Franco-Rodríguez[2], Fausto Miguel Pérez-Méndez[3], Alan Humberto Soto-Gaxiola[4]

[1]Cardiology Department, Hospital San José Hermosillo, Sonora, México
[2]Radiology Department, Hospital San José Hermosillo, Sonora, México
[3]Pulmonology Department, Hospital San José Hermosillo, Sonora, México
[4]Infectious Diseases Department, Hospital San José Hermosillo, Sonora, México

Correspondence to:
Cuitláhuac Arroyo-Rodríguez, MD, Morelos No. 340, Colonia Bachoco, CP 83148 Hermosillo, Sonora, México,
phone: +52 6441678937,
e-mail: cuitla88@hotmail.com

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A 51-year-old male with type-2 diabetes and hypertension was admitted because of SARS-CoV-2 pneumonia (confirmed by real-time polymerase chain reaction). Physical examination revealed tachypnea, room air oxygen saturation 70%, body temperature 37.8°C, blood pressure 137/89 mm Hg, and a pulse of 100 bpm. Chest computed tomography (CT) showed extensive interstitial pneumonia affecting upper lobes with ground-glass opacities and crazy-paving pattern in lower lobes (Figure 1A). Global CT-score was 19 (severe involvement) [1].

Initial D-dimer was 333 ng/ml (reference range <500 ng/ml), troponin I was 0.003 ng/ml (reference range <0.03 ng/ml). Thromboprophylaxis with enoxaparin 60 mg daily was initiated.

Two days after admission he progressed to severe acute respiratory distress syndrome and hemodynamic instability requiring invasive mechanical ventilation and vasopressors. D-dimer peaked at 30994 ng/ml, and troponin I reached 0.046 ng/ml. Transthoracic echocardiogram (TTE) showed a large, multilobular, highly mobile mass in the right atrium protruding into the right ventricle (Figure 1B; Supplementary material, *Video S1*). Right ventricular systolic function was impaired (shortening fraction 27%, tricuspid annular plane systolic excursion 15 mm).

Pulmonary CT angiography revealed a 51 × 25 mm filling defect in the right atrium (thrombus) (Figure 1C) and pulmonary embolus in the posterior basal segmental artery (right lung) (Figure 1D). The right ventricular to left ventricular diameter ratio was 1.30.

Hemodynamic instability, a recent self-limited inadvertent subclavian arterial puncture (relative contraindication for systemic thrombolysis) and concerns about possible incomplete lysis with systemic thrombolysis due to the large size thrombus led to the decision of performing ultrasound-assisted thrombolysis. Before the procedure pulmonary arterial systolic/diastolic/mean pressure was 44/17/26 mm Hg. Invasive pulmonary angiography showed a hypoperfused area in the right lower pulmonary lobe (Figure 1E). The longest EKOS catheter (135 cm length) was chosen, targeting the treatment zone in the right atrium and right pulmonary artery (Figure 1F; Supplementary material, *Video S2*). Eighteen mg of alteplase (0.75 mg/h) were infused over 24 hours. Unfractionated heparin with a target activated partial thromboplastin time of 46 to 70 seconds was given simultaneously to alteplase. Enoxaparin 60 mg twice daily was administaered afterward. The patient improved soon thereafter and was extubated 2 days later. A 24-hour post-procedure TTE showed a 9 × 2 mm remnant thrombus in the right atrium. Repeated TTE 5 days post-procedure showed thrombus resolution (Supplementary material, *Video S3*). The patient was discharged on day 10 post-procedure with apixaban. At 1 month follow-up, he fully reintegrated. to previous life and working activities. However, lung parenchymal damage, incomplete resolution of pulmonary embolism, and endothelial dysfunction might cause persistent pulmonary hypertension [2], and as recommended by international guidelines, screening for chronic thromboembolic pulmonary hypertension will be performed at month 3.

This case highlights the prothrombotic state of patients with SARS-CoV-2 infection and

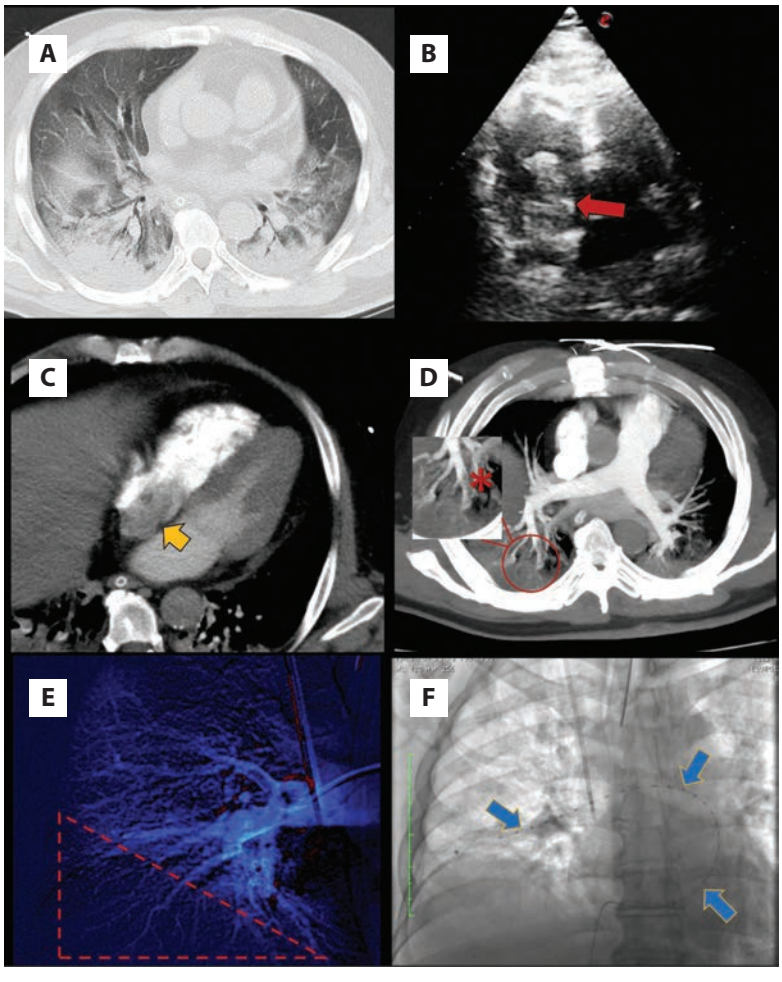

Figure 1. A. Chest computed tomography scan showing ground-glass opacities and crazy paving pattern in lower lobes associated with posterior basal consolidations. **B.** Transthoracic echocardiogram signalling the thrombus (red arrow). **C.** Four-chamber computed tomography signalling the thrombus (yellow arrow). **D.** Computed tomography pulmonary angiography demonstrating the pulmonary embolus (red asterisk). **E.** Pulmonary angiography demonstrating a hypoperfused area (dotted triangle). **F.** EKOS catheter inside the right atrium and right pulmonary artery (blue arrows)

demonstrates that ultrasound-assisted thrombolysis is an effective therapy for the treatment of concomitant right atrial thrombus and pulmonary embolism.

Advantages of ultrasound-assisted thrombolysis include the use of lower thrombolytic dose and lower bleeding risk compared with systemic thrombolysis [3]. Additionally, it is less invasive and more rapidly available compared with surgery [4], likely reducing the risk of exposure to a greater number of health personal in the operating and post-surgical care rooms. Potential benefits of a multidisciplinary pulmonary embolism response team strategy are improved outcomes, offering the most optimal strategy across a full range of advanced therapeutic options [5].

Supplementary material

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

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Rotational atherectomy and intravascular lithotripsy — two methods versus single lesion

Adrian Włodarczak[1], Jan Kulczycki[1], Łukasz Furtan[2], Piotr Rola[3], Mateusz Barycki[3], Magdalena Łanocha[4], Marek Szudrowicz[1], Maciej Lesiak[5]

[1]Department of Cardiology, MCZ Hospital, Lubin, Poland
[2]Department of Internal Medicine, District Hospital in Olawa, Oława, Poland
[3]Department of Cardiology, Regional Specialist Hospital, Legnica, Poland
[4]St. Adalbert's Hospital, Poznań, Poland
[5]1st Department of Cardiology, University of Medical Sciences, Poznań, Poland

Correspondence to:
Jan Kulczycki,
Department of Cardiology,
MCZ Hospital,
Skłodowskiej-Curie 52,
59–300 Lubin, Poland,
phone: +48 885 169 245,
e-mail: jan.jakub.kulczycki@gmail.com

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Intravascular lithotripsy (IVL) and rotational atherectomy are two different device designs dedicated to overcome their common enemy — heavily calcified lesions. Percutaneous coronary interventions in this kind of lesions are associated with a higher risk of periprocedural complications, such as dissection or perforation of the vessel, distal embolization, or device entrapment [1]. Rotational atherectomy is a well-established procedure with proven superiority over scoring balloons [2]. Intravascular lithotripsy is a relatively novel approach to heavily calcified lesions [3, 4], recently approved by Food and Drug Administration (FDA) in this indication.

An 81-year-old woman with a history of hypothyreosis, and persistent atrial fibrillation, on rivaroxaban treatment, was admitted to the Cardiology Department to undergo urgent percutaneous coronary interventions of the heavily calcified left anterior descending artery (LAD). Initially, the patient had been admitted to a remote hospital due to non-ST-segment elevation myocardial infarction. Coronary angiography revealed chronic total occlusion of the recessive right coronary artery and significant LAD stenosis (Figure 1A). High pressure predilatations (22 atm) with non-compliant (NC) balloons (2 × 18 mm; 2.5 × 20 mm) were unsuccessful. After the first procedure, bleeding from the lower gastrointestinal tract occurred.

Subsequently, the patient was referred to the Cardiac Intervention Unit capable of performing IVL and rotational atherectomy procedures. Laboratory tests on admission revealed severe anemia (hemoglobin, 7.1 g/dl) and coagulopathy (international normalized ratio [INR], 15.27). After blood transfusions and vitamin K administration, due to persistent angina symptoms, the patient underwent angioplasty within 24 hours after the occurrence of first symptoms.

The procedure was performed via the left radial artery with a 7F guide catheter. An initial attempt to cross the lesion with lithotripsy catheter ShockWave IVL 4 × 12 mm (Shockwave Medical Inc., Santa Clara, California, United States), was unsuccessful, therefore rotablation with 1.5 mm burr (Boston Scientific Marlborough, Massachusetts, USA) was performed to facilitate device delivery (Figure 1B–C). Afterwards, due to underexpansion of a 3.5 mm NC balloon, lithotripsy was performed (1 × 20 application) (Figure 1D). Before stent implantation, NC balloon TREK Abbott 3.5 × 20 mm was used for predilatation. Two Onyx drug eluting stents (Medtronic, Santa Rosa, California, United States), 3.5 × 38 mm and 4.0 × 34 mm, were implanted. Postdilatation was performed with NC balloons 3.5 × 15 mm and 4 × 20 mm. An optimal angiographic effect with TIMI 3 flow was achieved (Figure 1E–F). No adverse events including recurrence of bleeding were noted during hospitalization.

Appropriate lesion preparation is essential for optimal stent expansion and is challenging in heavily calcified lesions. Rotational atherectomy is suitable, in case of NC balloon expansion or IVL balloon delivery failure. IVL can be used for optimization of lesions, when suboptimal balloon or stent expansion is suspected.

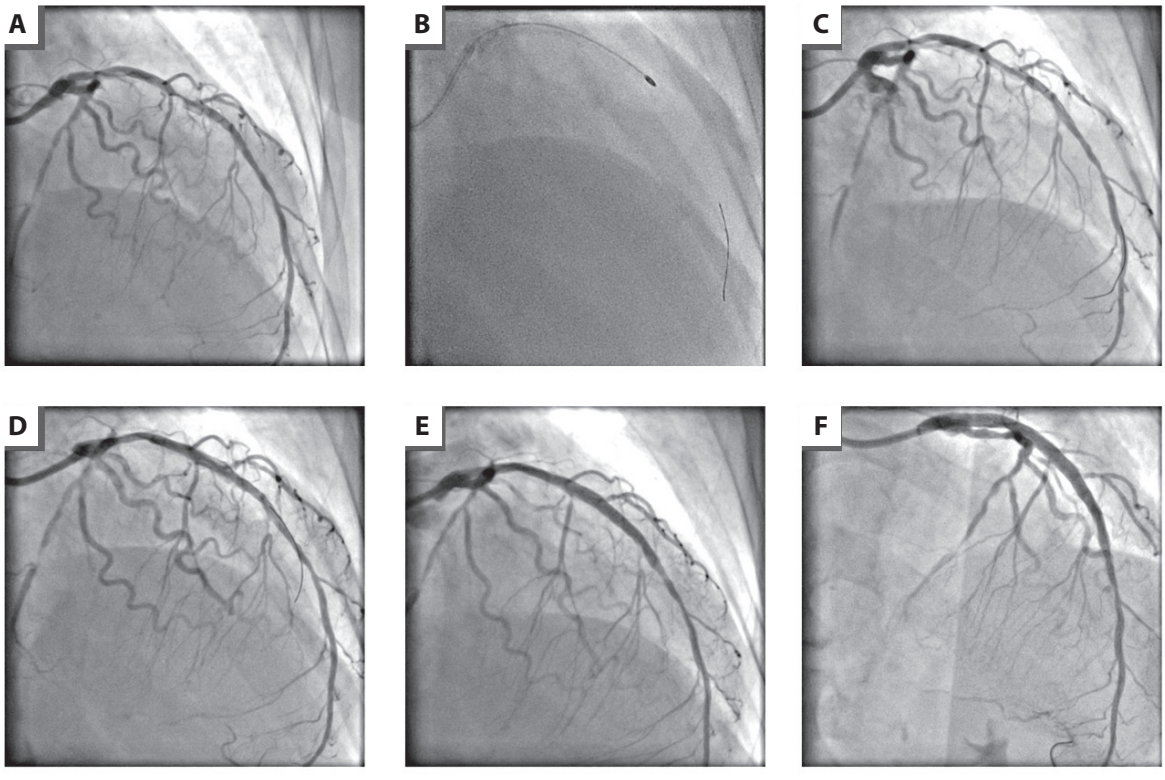

Figure 1. A. Angiography of the left anterior descending artery. **B.** Rotablation with 1.5 mm burr. **C.** Angiographic effect after rotablation. **D.** Angiographic effect after lithotripsy **E.** and **F.** final angiographic effect

Article information

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Giant right atrial tumor in three-dimensional echocardiographic imaging

Radosław Piątkowski, Monika Budnik, Michał Konwerski, Krzysztof Ozierański, Janusz Kochanowski

1st Chair and Department of Cardiology, Medical University of Warsaw, Warszawa, Poland

Correspondence to:
Monika Budnik, MD, PhD, 1st Chair and Department of Cardiology, Medical University of Warsaw, Banacha 1A, 02–097 Warszawa, Poland, phone: +48 22 599 26 12, e-mail: moni.budnik@gmail.com

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A 73-year-old woman was admitted to the hospital due to weakness, shortness of breath, and ankle edema. Symptoms had manifested one month before. She had a history of hypertension.

Transthoracic echocardiography revealed a dilated right atrium (RA) with an extremely large tumor occupying the entire RA. The mass did not extend into the inferior vena cava and it appeared to infiltrate the right wall and visceral pericardium. Moreover, pericardial and bilateral pleural effusions were present (Figure 1A).

We performed transesophageal echocardiography (TEE) which showed that the diameter of the tumor was about 80 × 66 mm (Figure 1B; Supplementary material, *Video S1*). Using three-dimensional imaging, we could see in detail that the mass was immobile, inhomogeneous, and non-pedunculated (Figure 1C; Supplementary material, *Video S2*). The tricuspid valve was not involved but inflow to the right ventricle was significantly reduced (Figure 1D; Supplementary material, *Video S3*). The tumor infiltrated the superior vena cava (Figure 1E–F; Supplementary material, *Video S4, S5*). Color Doppler study documented vasculature of the tumor indicating it is malignant nature (Supplementary material, *Video S6*). Computed tomography ruled out the presence of a tumor in other organs.

Primary cardiac tumors are extremely rare [1]. Most of them are benign and only approximately 25% [2] are malignant. The general prognosis is poor and the mean survival is about three months to one year after radical resection [3]. However, resection is often impossible. Unfortunately, the patient had a sudden cardiac arrest from pulseless electrical activity and died. The result of the histopathological exam was angiosarcoma.

Echocardiography is the method of choice in diagnosis cardiac masses and 3D TEE allows to add exact information about the location, mobility, attachment and wall infiltration of the tumor [4].

Supplementary material

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

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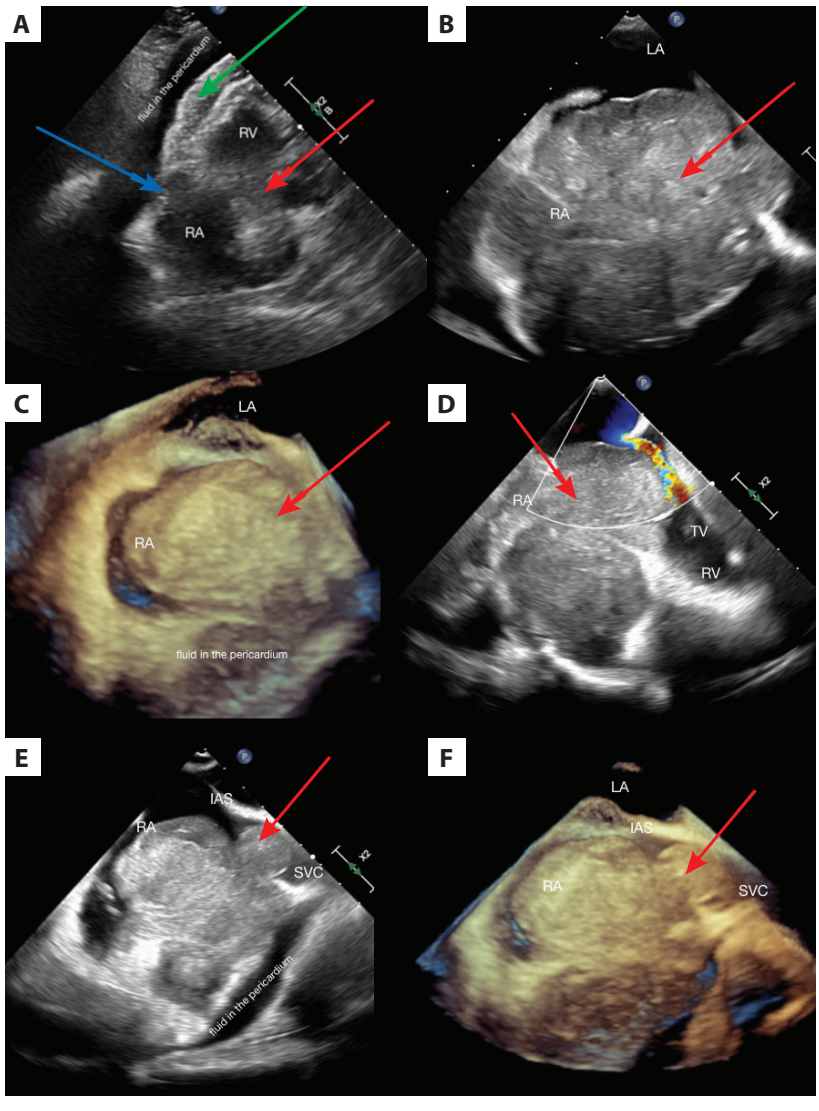

Figure 1. A. 2D transthoracic echocardiography, subcostal modified 4-chamber view. **B.** 2D TEE, modified bicaval view. **C.** 3D TEE, modified bicaval view. **D.** 2D TEE, modified 4-chamber view. **E.** 2D TEE, bicaval view. **F.** 3D TEE, bicaval view. Red arrow shows mass in the RA, green arrow shows tumor infiltration of the visceral pericardium, blue arrow shows tumor infiltration of the RA wall.

Abbreviations: IAS, interatrial septum; LA, left atrium; RA, right atrium; RV, right ventricle; SVC, superior vena cava; TEE, transesophageal echocardiography; TV, tricuspid valve

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Left ventricle non-compaction with a dilative phenotype and novel genetic mutations

Monika Shumkova[1], Dobrin Vassilev[1], Kiril Karamfiloff[1], Raya Ivanova[1], Teodora Yaneva-Sirakova[1], Kristina Stoyanova[1], Tsenka Boneva[1], Radka Kaneva[2], Robert J Gil[3]

[1]Department of Cardiology, Alexandrovska University Hospital, Sofia, Bulgaria, Faculty of Medicine, Medical University of Sofia, Sofia, Bulgaria
[2]Department of Medical Chemistry and Biochemistry, Molecular Medicine Center, Faculty of Medicine, Medical University of Sofia, Sofia, Bulgaria
[3]Mossakowski Medical Research Centre, Polish Academy of Sciences, Poland Department of Invasive Cardiology, Central Clinical Hospital of the Ministry of the Interior, Warszawa, Poland

Correspondence to:
Assist. Prof. Monika Shumkova, MD, Department of Cardiology, Alexandrovska University Hospital, Faculty of Medicine, Medical University of Sofia, Sveti Georgi Sofiyski 1, 1431, Sofia, Bulgaria, phone: +359883475726, e-mail: monika_shumkova@yahoo.com

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We present a case of a 46-year-old man with decompensated heart failure, class III New York Heart Association (NYHA) classification. The patient had a history of severe pneumonia two months ago when left ventriclar (LV) systolic dysfunction was diagnosed. There was no medical or family history of cardiac diseases, no alcohol or narcotics use.

Electrocardiogram was performed (Figure 1A). The echocardiography revealed LV systolic dysfunction with a massively trabeculated LV apex (Figure 1B–C). The standard laboratory tests and cardiac enzymes were in the normal range, the level of B-type natriuretic peptide was 2335 pg/ml (reference range <125 pg/ml).

Given the initial clinical presentation, history of pneumonia, and echocardiographic findings at admission, we should differentiate between the most common types of dilative cardiomyopathy (DCM): post myocarditis, idiopathic cardiomyopathy, LV non-compaction (LVNC), or ischemic heart disease.

A positron emission tomography scan (PET) was performed to assess myocardial perfusion and viability. PET findings were very similar to those of ischemic cardiomyopathy (Figure S1). Coronary angiography revealed normal coronary anatomy. The left ventriculography confirmed the diagnosis of DCM. To clarify the etiology of cardiomyopathy endomyocardial biopsy was performed. Histology showed diffuse cardiac fibrosis, typical of DCM. Myocardial tissue samples were tested for the presence of enteroviral sequences by a polymerase chain reaction, yielding negative results. Cardiovascular magnetic resonance (Figure 1D–F) was done for further evaluation of cardiac function and volume.

Genetic and family screening is important for the correct diagnosis and prognosis. Genetic analysis was performed with a new generation sequencing techniques and showed two missense mutations in the titin gene c.54703C>T (p.Arg18235Cys), and c.47090G>C (p.Arg15697Pro) — a novel variant, not described in the literature, and a dominant missense mutation in the Filamin C gene 5071G>A (p.Asp1691Asn). Titin has been recently reported to be associated with LVNC. Titin truncating variants are prevalent, but there are data for pathogenic missense variants [1]. Mutations in these genes were associated with DCM and hypertrophic cardiomyopathy [2, 3]. This is the first reported clinical case with these variants of mutations and LVNC. Screening echocardiography of the patient's relatives was done, showing no signs of cardiomyopathy.

The patient was treated following the recommendations for heart failure management [4].

At the follow-up visit on the third month, he still had persistent LV systolic dysfunction yet without any signs of heart failure.

LVNC is an uncommon myocardial disorder. Clinical presentation with a classical triad (heart failure, arrhythmias, and thromboembolism) is very rare [5]. This case is an example of the heterogeneity and overlapping between the different types of cardiomyopathies. This was a patient with symptoms of decompensated heart failure, with a history of a recent severe inflammatory disease (differential diagnosis: DCM after myoraditis) and imaging tests specific for the DCM with LVNC. Even if an accurate diagnosis does not lead to improvement of patients prognosis currently, the detection of

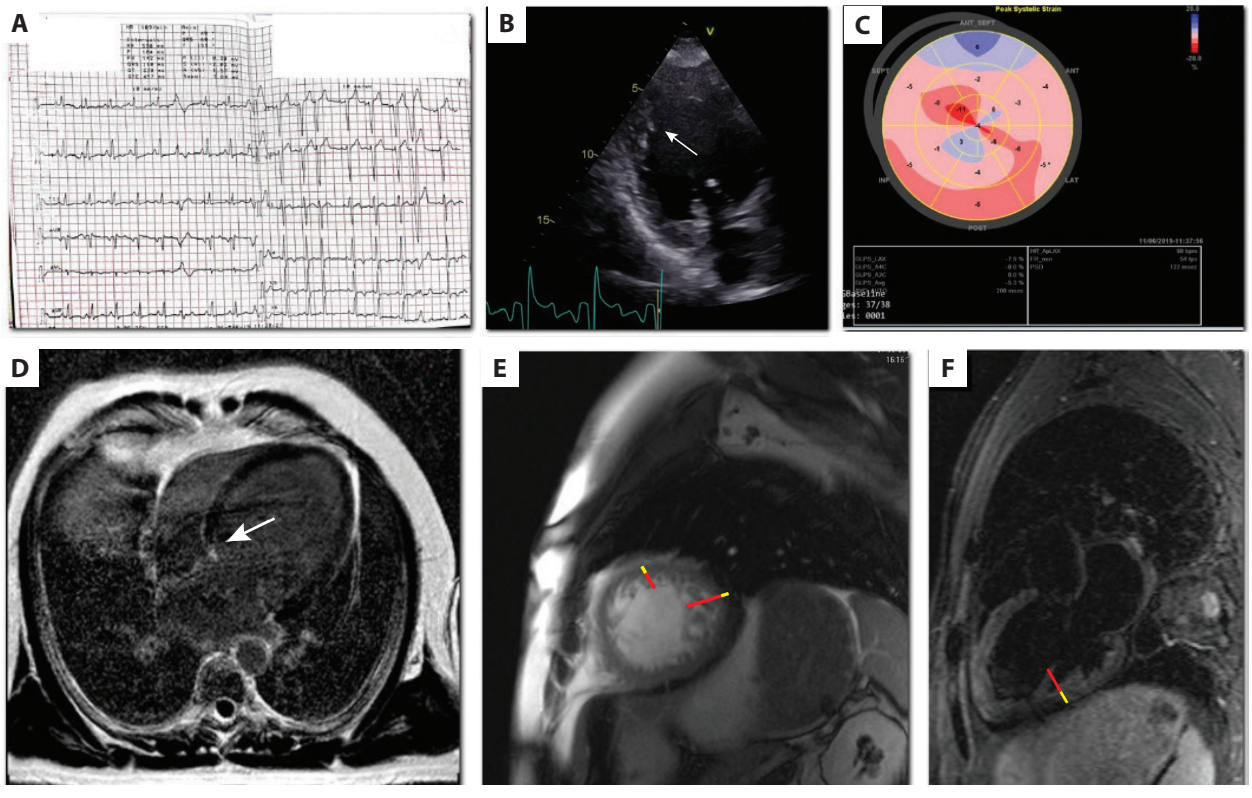

Figure 1. A. Electrocardiogram — sinus tachycardia, normal axis deviation, heart rate 109/min, poor R wave progression with nonspecific ST-T wave changes, and premature atrial and ventricular beats. **B.** Echocardiography — 2-chamber view. Massively trabeculated LV apex (white arrow). **C.** „Bull's-eye" representation of global left ventricle (LV) longitudinal strain measurements. Left ventriclar longitudinal function is reduced in all segments, average LV global longitudinal strain, GLS "–5.3%", typical for dilative cardiomyopathy. **D–F.** Cardiovascular magnetic resonance — late intramural gadolinium enhancement **(D)**; short-axis view **(E)**; and long-axis view **(F)** in end-diastole. End-diastolic volume 415 ml, end-systolic volume 318 ml, LV ejection fraction 23%. In addition, areas of non-compacted myocardium (red arrows), particularly in the free wall of the LV and most of the apex. The ratio of maximum thickness of non-compacted myocardium to compacted myocardium (yellow arrows) is 2.5/1. Late intramural gadolinium enhancement **(D)** in basal segments of the septum. The right ventricle was considered normal

a hereditary component of the disease and subsequent screening of relatives can help identify first-line relatives at risk.

Article information

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The role of temporary mechanical circulatory support in an effective surgical treatment of a left ventricular aneurysm and a ventricular septal defect in a patient after anterior wall myocardial infarction

Krzysztof Wróbel[1], Karolina Żbikowska[1, 4], Ryszard Wojdyga[1], Ewelina Pirsztuk[3], Marcin Zygier[1], Katarzyna Kurnicka[2]

[1]Department of Cardiac Surgery, Medicover Hospital, Warszawa, Poland
[2]Department of Internal Medicine and Cardiology, Medical University of Warsaw, Warszawa, Poland
[3]Department of Anesthesia and Intensive Care, Medicover Hospital, Warszawa, Poland
[4]Department of Cardiac Surgery, Medical University of Warsaw, Warszawa, Poland

Correspondence to:
Karolina Żbikowska, MD, Department of Cardiac Surgery, Medical University of Warsaw, Stefana Banacha 1A, 02–097 Warszawa, Poland, phone: +48 22 599 2161, e-mail: karolina_zbikowska@wp.pl

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Referring to the discussion on effective methods of treatment for patients with a post-infarction left ventricular aneurysm and a ventricular septal defect (VSD) [1], we present the case of a 57-year-old man with hypertension, chronic renal failure, and Crohn's disease who was admitted to the cardiac surgery department due to cardiogenic shock in the course of acute ST-segment elevation myocardial infarction of the anterior wall, complicated by rupture of the interventricular septum (IVS) and large left ventricular aneurysm within the apex. In the patient's history, an acute cardiac pain occurred six days before hospitalization in the department of cardiology. Coronary angiography revealed the left anterior descending artery with a very narrow 8th segment and a significantly stenosed marginal artery treated with one drug-eluting stent implantation. Transthoracic echocardiography showed akinesis with the thinning of apical segments of the left ventricle (LV) walls and the mid-anterior part of IVS (Figure 1A), dyskinesis of the apex and hyperkinesis of hypertrophied basal segments. LV ejection fraction was approximately 36%. In the apical segment of the IVS a 5 mm VSD with the left-right shunt was exposed (Figure 1B). The patient was qualified for a delayed surgical treatment after day 12 with femoral veno-arterial extracorporeal membrane oxygenation (VA-ECMO), instituted 8 hours after admission, as well as CRRT (renal failure, metabolic acidosis). He was extubated next morning. His hemodynamic and metabolic status improved in the next few days. On day 19 after the first symptoms of myocardial infarction, in a stable patient's condition, LV repair and VSD closure were performed using 2 goretex patches (Figure 1C). VA-ECMO was continued for the next 4 days. In the early postoperative phase, the patient required bedside dialysis and inotropic support. On day 3, levosimendan was administered. Two weeks after the surgery, the patient was discharged home in a good general condition. Almost 3 months after the surgery, a follow-up transthoracic echocardiography revealed no shunt between ventricles (Figure 1D) and showed an improved LV shape (Figure 1E–F). The LV end-diastolic volume was 180 ml, SV 60 ml and EF 35%.

VSD of the apical IVS segment develops typically in the course of a transmural anterior infarction, frequently in the absence of reperfusion therapy or delayed reperfusion [2, 3]. Surgery is an effective method of treatment, but with a high risk of complications, often due to the patient's hemodynamic instability and post-infarction fragility of tissues associated with increased activity of metalloproteinases and myocardial remodeling. Reports of recent years have drawn attention to the role of a delayed surgical treatment with the use of mechanical circulatory support devices [4]. Temporary VA-ECMO support may significantly contribute to the achievement of good therapeutic results by stabilizing the patient, maintaining adequate tissue oxygenation [4], obtaining time for myocardial remodeling, and elimination of the effect of antiplatelet therapy and further therapeutic decisions [5]. In patients

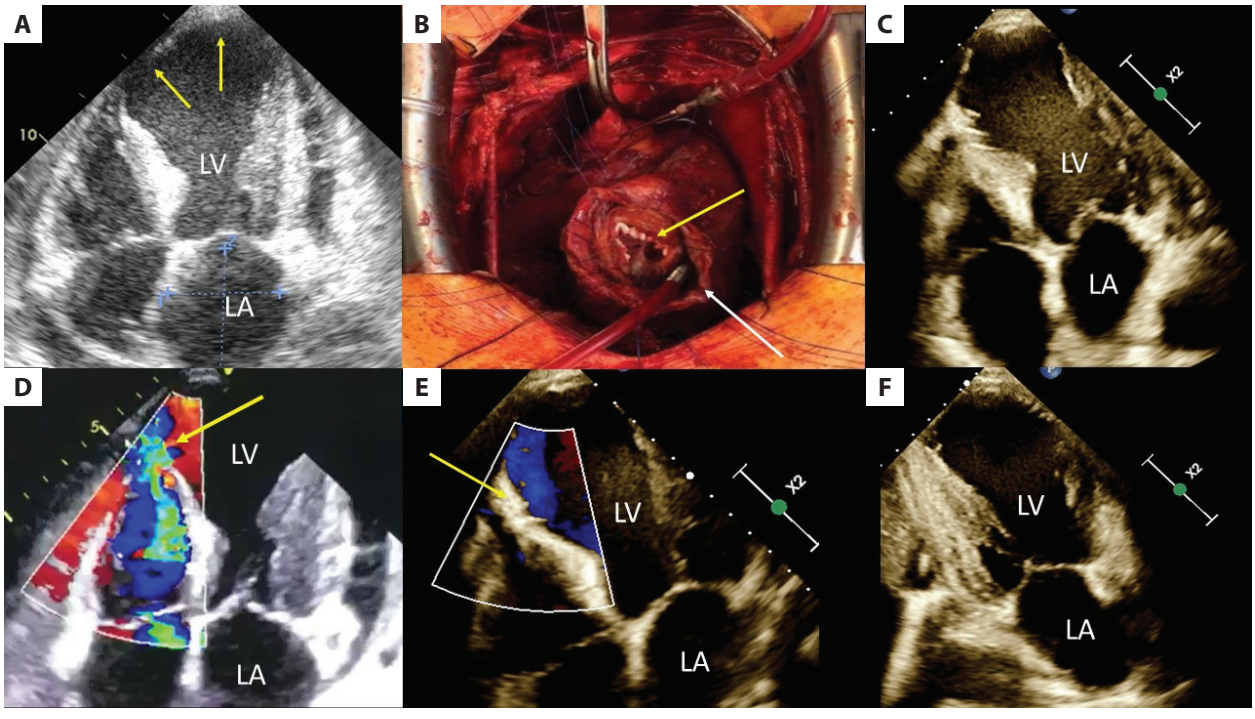

Figure 1. A. A large apical left ventricular aneurysm (arrows); two-dimensional transesophageal echocardiography, a four-chamber view. **B.** Ventricular septal defect in the apical segment of the interventricular septum (arrow); two-dimensional transesophageal echocardiography, color Doppler, a four-chamber view. **C.** Left ventricle aneurysm opened (white arrow). Ventricular septal defect with single pledgeted sutures (yellow arrow); an intraoperative view. **D.** Apical segment of the interventricular septum without the shunt between ventricles; ventricular septal defect patch (arrow); two-dimensional transesophageal echocardiography, color Doppler, a four-chamber view. **E.** An improved shape and volume of the left ventricle on follow-up echocardiography in a four chamber view. **F.** Two-chamber view.

Abbreviations: LA, left atrium; LV, left ventricle

without cardiogenic shock ECMO should be considered individually in order to unload the ventricles and prevent hemodynamic deterioration (large VSDs and impending deterioration, severe RV infarction, progressive dilatation of cardiac chambers).

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Artur Pietrucha (1964–2020)

Richard Sutton[1], Artur Fedorowski[2], Michele Brignole[3], Angel Moya[4]

[1]National Heart & Lung Institute, Imperial College, Hammersmith Hospital, Department of Cardiology, Du Cane Road, London, W12 OHS, United Kingdom
[2]Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden
[3]IRCCS Istituto Auxologico Italiano, Faint & Fall Programme, Ospedale San Luca, Milano, Italy
[4]Cardiology and Arrhythmia Unit, University Hospital Dexeus, Barcelona, Spain

Correspondence to:
Prof. Artur Fedorowski, MD, PhD, FESC, Department of Cardiology, Karolinska University Hospital, Eugeniavägen 3, 171 64 Solna, Stockholm, Sweden,
phone: +46 8 517 700 00.
e-mail: artur.fedorowski@med.lu.se

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In these brief memories, we, from among the authors of current European syncope guidelines, would like to honour the memory of our late colleague, Dr. Artur Pietrucha (Figure 1), whose life deeply impacted ours.

* * *

In Artur's short life, he became a world name in syncope care and research. He was denied the opportunity to contribute so much more of what he had to the field by the tragic intervention of COVID-19 in 2020.

I first met Artur in Dubai at the 2012 World Congress of Cardiology where we both presented on syncope in the same session. He had two abstracts to my one. I was immediately impressed with his innovative ideas and the warmth of his personality. We came to know each other after that session. Three months later, I visited Krakow, Poland at his invitation to address the medical community at the John Paul II hospital where Artur worked. My wife travelled with me. We received generous hospitality from Artur and his paediatric cardiologist wife, Beata.

Artur and I kept up from 2012 and met at numerous scientific meetings. He never failed to produce ideas that were unique and original. He repeatedly invited me to return to Krakow but, unfortunately, shortage of time prevented me from going. Nevertheless, we kept in close contact even during his illness trying to give him support. We are very happy to include Beata among our close friends.

The world has lost a fine physician, a great thinker and a very kind person. Long may his memory endure.

Richard Sutton

***

I met Artur for the first time around ten years ago while visiting prof. Jadwiga Nessler in Krakow. He made a deep impression on me by sharing his ideas on the use of cerebral oximetry in syncope evaluation, neuroendocrine changes in cardiovascular autonomic dysfunction, and hypercoagulability in syndromes of orthostatic intolerance. Most of these ideas created a solid ground for our future research, now recognized all over the world. We met again many times and, most spectacularly, during our session on syncope at the 22nd International Congress of the Polish Cardiac Society in Krakow in 2018, when we were joined by Michele Brignole and Angel Moya (Figure 1). However, my last memory of Artur is the most emotional one. In November 2020, I was sitting on a train from Malmo to Stockholm while Artur was lying on a hospital bed in Warsaw. We talked for 2 hours on the phone, about everything, his condition, our common research projects, his family – he did not want me to stop. Then, in the end, Artur said, "As soon as I feel better again, I will be back at my office to take care of my patients. I can't wait to see them again". I could not say a word. Artur was a real doctor, the one that you would wish to be yours.

Artur Fedorowski

* * *

I met Artur for the first time around 25 years ago when he visited my Syncope Unit at Lavagna Hospital, Italy. At that time, his Director of Cardiology Department in Krakow, prof. Wieslawa Piwowarska, wanted to start a similar unit and she found an enthusiastic junior doc-

Figure 1. A photograph of (left to right) Artur Fedorowski, Angel Moya, Michele Brignole and Artur Pietrucha from Department of Coronary Disease and Heart Failure, Medical College of Jagiellonian University, Krakow, Poland, in front of Collegium Novum in Krakow in September 2018, during the 22nd International Congress of the Polish Cardiac Society

tor, Artur Pietrucha, to assign to that task. Since then, I met Artur regularly during international meetings always finding him enthusiastic and passionate about syncope. Last time I met him was during the 22nd International Congress of the Polish Cardiac Society in Krakow in 2018, together with Artur Federowski and Angel Moya (Figure 1). We spent a couple of happy days receiving generous hospitality from Artur, his wife Beata, and his son Wojciech, to whom go my sincere condolences and friendship.

Michele Brignole

* * *

I had the opportunity to meet Artur in 2018, when he invited me, together with Artur Fedorowski and Michele Brignole, to participate in the 22nd International Congress of the Polish Cardiac Societyin Krakow.

I was so impressed by his enthusiasm in developing a well-structured syncope unit in his hospital, for the organization of the syncope session at the congress, and for his warm welcome to Krakow.

I have a great memory of the days we spent visiting Krakow, with his enthusiasm and erudition with his wife Beata and his son Wojciech. I have at home the painting of Krakow that he gave us with great generosity.

I was deeply saddened by the loss of a friend so young and so enthusiastic about medicine, life, and his city. I will always keep a very fond and vivid memory of him.

May I express my warmest condolences and friendship to his family.

Angel Moya

Article informations

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Leczenie skojarzone z innymi lekami przeciwnadciśnieniowymi: Leki blokujące receptory beta-adrenergiczne mogą być stosowane w monoterapii lub w skojarzeniu z innymi lekami przeciwnadciśnieniowymi. Jak dotąd, addycyjne działanie przeciwnadciśnieniowe obserwowano jedynie podczas jednoczesnego stosowania leku Nedal z hydrochlorotiazydem w dawce 12,5-25 mg. Pacjenci z niewydolnością nerek: Zalecana dawka początkowa dla pacjentów z niewydolnością nerek wynosi 2,5 mg na dobę. W razie konieczności dawkę dobową można zwiększyć do 5 mg. Pacjenci z niewydolnością wątroby: Dane dotyczące pacjentów z niewydolnością wątroby lub zaburzeniami czynności wątroby są ograniczone. Dlatego stosowanie leku Nedal u tych pacjentów jest przeciwwskazane. Pacjenci w podeszłym wieku: U pacjentów w wieku powyżej 65 lat zalecana dawka początkowa wynosi 2,5 mg na dobę. W razie potrzeby dawkę dobową można zwiększyć do 5 mg. Jednocześnie, ze względu na ograniczone doświadczenie u osób w wieku powyżej 75 lat, należy zachować ostrożność i ściśle obserwować pacjentów. Dzieci i młodzież: Nie przeprowadzono badań u dzieci i młodzieży. Dlatego nie zaleca się stosowania u dzieci i młodzieży. Przewlekła niewydolność serca: Leczenie stabilnej przewlekłej niewydolności serca należy rozpocząć poprzez stopniowe zwiększanie dawki, aż do uzyskania optymalnej dawki podtrzymującej, określonej dla każdego pacjenta. Pacjenci powinni mieć stabilną przewlekłą niewydolność serca bez ostrej niewydolności przez ostatnie sześć tygodni. Zaleca się, aby lekarz prowadzący miał doświadczenie w leczeniu przewlekłej niewydolności serca. U pacjentów otrzymujących leki działające na układ sercowo-naczyniowy, w tym leki moczopędne i (lub) digoksynę, i (lub) inhibitory ACE, i (lub) antagonistów receptora angiotensyny II, dawkowanie tych leków powinno być ustabilizowane podczas ostatnich dwóch tygodni przed rozpoczęciem leczenia lekiem Nedal. Dawkę początkową należy zwiększać co 1-2 tygodnie w zależności od tolerancji leku przez pacjenta: 1,25 mg nebiwololu, zwiększyć do 2,5 mg nebiwololu raz na dobę, następnie do 5 mg raz na dobę i następnie do 10 mg raz na dobę. Maksymalna zalecana dawka wynosi 10 mg nebiwololu raz na dobę. Rozpoczęcie leczenia i każde zwiększenie dawki powinno być wykonane pod nadzorem doświadczonego lekarza, trwającym co najmniej 2 godziny, dla upewnienia się, że stan kliniczny pacjenta pozostaje stabilny (zwłaszcza ciśnienie tętnicze krwi, częstość akcji serca, zaburzenia przewodzenia, objawy nasilenia niewydolności serca). Występowanie działań niepożądanych może uniemożliwiać leczenie maksymalną zalecaną dawką leku. W razie konieczności dawkę podtrzymującą można również stopniowo zmniejszać i ponownie zwiększać, jeżeli jest to wskazane. Podczas stopniowego zwiększania dawki, w przypadku nasilenia niewydolności serca lub nietolerancji leku, najpierw zalecane jest zmniejszenie dawki nebiwololu lub, w razie konieczności, natychmiastowe przerwanie leczenia (w przypadku ciężkiego niedociśnienia tętniczego, nasilenia niewydolności serca z ostrym obrzękiem płuc, wstrząsu kardiogennego, objawowej bradykardii lub bloku przedsionkowo-komorowego). Leczenie stabilnej przewlekłej niewydolności serca nebiwololem jest zwykle leczeniem długotrwałym. Nie zaleca się nagłego przerywania leczenia nebiwololem, ponieważ może to prowadzić do przejściowego nasilenia niewydolności serca. Jeśli przerwanie leczenia jest konieczne, dawka powinna być zmniejszana stopniowo, o połowę co tydzień. Pacjenci z niewydolnością nerek: Nie jest wymagane dostosowanie dawki w przypadku łagodnej do umiarkowanej niewydolności nerek, gdyż dawkę zwiększa się stopniowo do dawki maksymalnej tolerowanej przez pacjenta. Brak doświadczenia u pacjentów z ciężką niewydolnością nerek (stężenie kreatyniny w surowicy ≥ 250 µmol/l). Dlatego stosowanie nebiwololu u tych pacjentów nie jest zalecane. Pacjenci z niewydolnością wątroby: Dane dotyczące pacjentów z niewydolnością wątroby są ograniczone. Dlatego stosowanie leku Nedal u tych pacjentów jest przeciwwskazane. Pacjenci w podeszłym wieku: Nie jest wymagane dostosowanie dawki, gdyż dawkę zwiększa się stopniowo do dawki maksymalnej tolerowanej przez pacjenta. Dzieci i młodzież: Nie przeprowadzono badań u dzieci i młodzieży. Dlatego nie zaleca się stosowania u dzieci i młodzieży. Choroba wieńcowa: Dorośli - Leczenie stabilnej choroby wieńcowej należy rozpocząć poprzez stopniowe zwiększanie dawki, aż do uzyskania optymalnej dawki podtrzymującej określonej dla każdego pacjenta. Dawkę początkową należy zwiększać co 1-2 tygodnie w zależności od tolerancji leku przez pacjenta: 1,25 mg nebiwololu, zwiększyć do 2,5 mg nebiwololu raz na dobę, następnie do 5 mg raz na dobę i następnie do 10 mg raz na dobę. Maksymalna zalecana dawka wynosi 10 mg nebiwololu raz na dobę. Pacjenci z niewydolnością nerek - Nie jest wymagane dostosowanie dawki w przypadku łagodnej do umiarkowanej niewydolności nerek, gdyż dawkę zwiększa się stopniowo do dawki maksymalnej tolerowanej przez pacjenta. Brak doświadczenia u pacjentów z ciężką niewydolnością nerek (stężenie kreatyniny w surowicy ≥ 250 µmol/l). Dlatego stosowanie nebiwololu u tych pacjentów nie jest zalecane. Pacjenci z niewydolnością wątroby - Dane dotyczące pacjentów z niewydolnością wątroby są ograniczone. 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Dodatkowo, podobnie jak inne leki beta-adrenolityczne, Nedal jest przeciwwskazany w zespole chorej zatoki, w tym bloku zatokowo-przedsionkowym; bloku serca drugiego i trzeciego stopnia (bez rozrusznika); skurczu oskrzeli i astmie oskrzelowej w wywiadzie; nieleczonym guzie chromochłonnym nadnerczy; kwasicy metabolicznej; bradykardii (czynność serca < 60 uderzeń na minutę przed rozpoczęciem leczenia); niedociśnieniu tętniczym (skurczowe ciśnienie tętnicze krwi < 90 mmHg); ciężkich zaburzeniach krążenia obwodowego. **Ostrze˝enia i˚zalecane ˙rodki ostro˝no˙ci:** Poniższe ostrzeżenia i środki ostrożności dotyczą wszystkich leków blokujących receptory beta-adrenergiczne. Znieczulenie ogólne: Utrzymująca się blokada receptorów beta-adrenergicznych zmniejsza ryzyko arytmii w czasie wprowadzenia do znieczulenia oraz intubacji. Jeśli blokada receptorów beta-adrenergicznych jest przerywana w celu przygotowania pacjenta do zabiegu chirurgicznego, należy przerwać podawanie beta-adrenolityków co najmniej na 24 godziny przed zabiegiem. Należy zachować ostrożność podczas stosowania niektórych środków znieczulających, wpływających depresyjnie na mięsień sercowy. Można zapobiec wystąpieniu reakcji ze strony nerwu błędnego poprzez dożylne podanie atropiny. Układ sercowo-naczyniowy: Nie należy stosować leków beta-adrenolitycznych u pacjentów z nieleczoną zastoinową niewydolnością serca, aż do ustabilizowania się ich stanu. U pacjentów z chorobą niedokrwienną serca leczenie beta-adrenolitykami należy przerywać stopniowo, tj. przez ponad 1-2 tygodnie. W razie konieczności należy w tym samym czasie rozpocząć leczenie zastępcze, aby zapobiec zaostrzeniu dławicy piersiowej. Leki blokujące receptory beta-adrenergiczne mogą wywoływać bradykardię: jeśli częstość tętna wynosi poniżej 50-55 uderzeń na minutę w spoczynku i (lub) pacjent odczuwa objawy wskazujące na bradykardię, dawkę należy zmniejszyć. Należy zachować ostrożność w przypadku stosowania leków beta-adrenolitycznych: u pacjentów z zaburzeniami krążenia obwodowego (choroba lub objaw Raynauda, chromanie przestankowe), ponieważ może wystąpić zaostrzenie tych zaburzeń; u pacjentów z blokiem serca pierwszego stopnia, z powodu wydłużenia przez beta-adrenolityki czasu przewodzenia; u pacjentów z dławicą piersiową typu Prinzmetala z powodu ryzyka niehamowanego skurczu tętnic wieńcowych za pośrednictwem receptorów alfa: leki blokujące receptory beta-adrenergiczne mogą zwiększać liczbę i czas trwania napadów dławicowych. Zwykle nie zaleca się jednoczesnego podawania nebiwololu z antagonistami wapnia typu werapamilu i diltiazemu, z lekami przeciwarytmicznymi klasy I oraz z lekami przeciwnadciśnieniowymi działającymi ośrodkowo. Metabolizm/układ endokrynologiczny: Nedal nie wpływa na stężenie glukozy u pacjentów z cukrzycą. Mimo to należy zachować ostrożność u tych pacjentów, ponieważ nebiwolol może maskować niektóre objawy hipoglikemii (tachykardia, kołatanie serca). Leki blokujące receptory beta-adrenergiczne mogą maskować objawy tachykardii w nadczynności tarczycy. Nagłe odstawienie produktu może nasilić objawy. Układ oddechowy: U pacjentów z przewlekłymi obturacyjnymi chorobami płuc leki blokujące receptory beta-adrenergiczne należy stosować ostrożnie, ponieważ leki te mogą nasilać zwężenie dróg oddechowych. Inne: Pacjenci z łuszczycą w wywiadzie powinni przyjmować beta-adrenolityki jedynie po dokładnym rozważeniu. Leki blokujące receptory beta-adrenergiczne mogą zwiększać wrażliwość na alergeny oraz ciężkość reakcji anafilaktycznych. Rozpoczęcie leczenia przewlekłej niewydolności serca nebiwololem wymaga regularnej obserwacji. Nie należy nagle przerywać leczenia, chyba że jest to wyraźnie zalecone. Produkt leczniczy zawiera laktozę. Produkt leczniczy nie powinien być stosowany u pacjentów z rzadko występującą dziedziczną nietolerancją galaktozy, brakiem laktazy lub zespołem złego wchłaniania glukozy-galaktozy. **Działania niepo˝˜dane:** Oddzielnie wymieniono objawy niepożądane występujące podczas leczenia nadciśnienia tętniczego i przewlekłej niewydolności serca ze względu na różnice pomiędzy chorobami podstawowymi. Nadciśnienie tętnicze Zgłoszone działania niepożądane, które w większości przypadków miały nasilenie od łagodnego do umiarkowanego, wymieniono poniżej według klasyfikacji układowo-narządowej oraz częstości występowania: często (≥1/100 do <1/10); niezbyt często (≥1/1000 do <1/100); bardzo rzadko (<1/10000); nieznana (częstość nie może być określona na podstawie dostępnych danych). Zaburzenia układu immunologicznego: Częstość nieznana: obrzęk naczynioruchowy, nadwrażliwość; Zaburzenia psychiczne: Niezbyt często: koszmary senne, depresja; Zaburzenia układu nerwowego: Często: bóle głowy, zawroty głowy, parestezje; Bardzo rzadko: omdlenia; Zaburzenia oka: Niezbyt często: zaburzenia widzenia; Zaburzenia serca: Niezbyt często: bradykardia, niewydolność serca, spowolnienie przewodzenia przedsionkowo-komorowego/blok przedsionkowo-komorowy; Zaburzenia naczyniowe: Niezbyt często: niedociśnienie tętnicze, chromanie przestankowe (lub jego nasilenie); Zaburzenia układu oddechowego, klatki piersiowej i śródpiersia: Często: duszność, Niezbyt często: skurcz oskrzeli; Zaburzenia żołądka i jelit: Często: zaparcia, nudności, biegunka, Niezbyt często: niestrawność, wzdęcia, wymioty; Zaburzenia skóry i tkanki podskórnej: Niezbyt często: świąd, wysypka rumieniowa, Bardzo rzadko: nasilenie łuszczycy; Częstość nieznana: pokrzywka. Zaburzenia układu rozrodczego i piersi: Niezbyt często: impotencja; Zaburzenia ogólne i stany w miejscu podania: Często: zmęczenie, obrzęk. Podczas stosowania niektórych leków blokujących receptory beta-adrenergiczne obserwowano także następujące działania niepożądane: omamy, psychozy, splątanie, oziębienie/zasinienie kończyn, objaw Raynauda, suchość oczu i zespół oczno-śluzówkowo-skórny typowy dla praktololu. Przewlekła niewydolność serca Dostępne są dane dotyczące działań niepożądanych występujących u pacjentów z przewlekłą niewydolnością serca pochodzące z jednego kontrolowanego placebo badania klinicznego z udziałem 1067 pacjentów otrzymujących nebiwolol i 1061 pacjentów otrzymujących placebo. W badaniu tym działania niepożądane, których związek z leczeniem oceniano jako możliwy, zostały zgłoszone łącznie przez 449 pacjentów otrzymujących nebiwolol (42,1%) w porównaniu do 334 pacjentów otrzymujących placebo (31,5%). Najczęściej zgłaszanymi działaniami niepożądanymi u pacjentów otrzymujących nebiwolol były bradykardia i zawroty głowy, oba wystąpiły u około 11% pacjentów. Częstość występowania wśród pacjentów otrzymujących placebo wynosiła odpowiednio około 2% i 7%. Stwierdzono następujące częstości występowania działań niepożądanych (których związek z lekiem oceniano przynajmniej jako możliwy), które uznano za specyficznie związane z leczeniem przewlekłej niewydolności serca: nasilenie niewydolności serca wystąpiło u 5,8% pacjentów otrzymujących nebiwolol w porównaniu do 5,2% pacjentów otrzymujących placebo; ortostatyczne niedociśnienie tętnicze odnotowano u 2,1% pacjentów otrzymujących nebiwolol w porównaniu do 1,0% pacjentów otrzymujących placebo; nietolerancja leku wystąpiła u 1,6% pacjentów otrzymujących nebiwolol w porównaniu do 0,8% pacjentów otrzymujących placebo; blok przedsionkowo-komorowy pierwszego stopnia wystąpił u 1,4% pacjentów otrzymujących nebiwolol w porównaniu do 0,9% pacjentów otrzymujących placebo; obrzęki kończyn dolnych odnotowano u 1,0% pacjentów otrzymujących nebiwolol w porównaniu do 0,2% pacjentów otrzymujących placebo. Zgłaszanie podejrzewanych działań niepożądanych Po dopuszczeniu produktu leczniczego do obrotu istotne jest zgłaszanie podejrzewanych działań niepożądanych. Umożliwia to nieprzerwane monitorowanie stosunku korzyści do ryzyka stosowania produktu leczniczego. Osoby należące do fachowego personelu medycznego powinny zgłaszać wszelkie podejrzewane działania niepożądane za pośrednictwem Departamentu Monitorowania Niepożądanych Działań Produktów Leczniczych Urzędu Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych; Al. Jerozolimskie 181C, 02-222 Warszawa; tel.: +48 22 49 21 301; faks: +48 22 49 21 309; strona internetowa: https://smz.ezdrowie.gov.pl Działania niepożądane można zgłaszać również podmiotowi odpowiedzialnemu. **Podmiot odpowiedzialny:** Polfa Warszawa S.A. Pozwolenie na dopuszczenie do obrotu nr 14542 wydane przez MZ. Lek wydawany na podstawie recepty. Cena urzędowa detaliczna leku Nedal 5 mg x 28 tabl. wynosi w PLN: 17,95. Kwota dopłaty pacjenta (We wszystkich zarejestrowanych wskazaniach na dzień wydania decyzji) wynosi w PLN: 10,05. ChPL: 2020.03.16.

* Obwieszczenie Ministra Zdrowia z dnia 21 kwietnia 2021 r. w sprawie wykazu refundowanych leków, środków spożywczych specjalnego przeznaczenia żywieniowego oraz wyrobów medycznych na 1 maja 2021 r.

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Polfa Warszawa S.A. GRUPA polpharma

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