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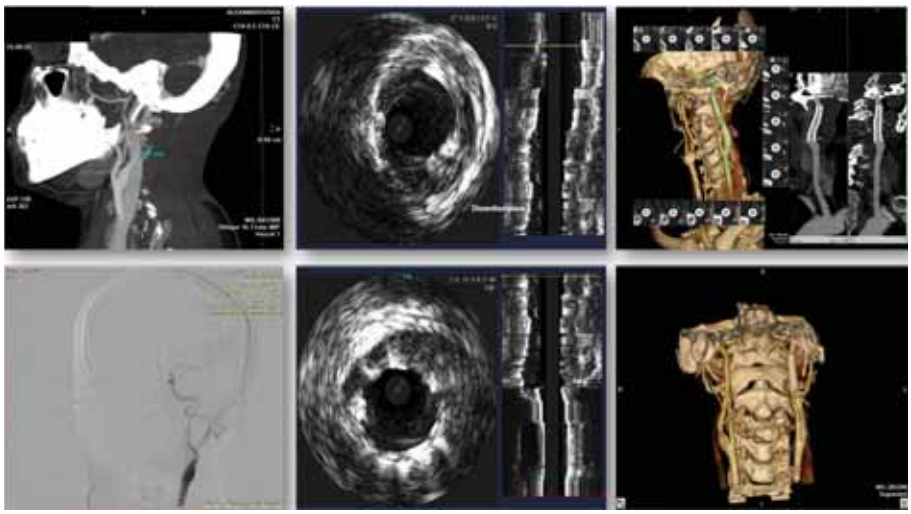

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31–202 Kraków
phone: +48 126 143 004
e-mail: kardiologiapolska@ptkardio.pl
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CLINICAL VIGNETTE

LETTER TO THE EDITOR

EXPERT OPINION

Distal radial access: No pain, no gain

Zoltan Ruzsa[1], Alexandru Achim[1, 2]

[1]Department of Internal Medicine, Division of Invasive Cardiology, University of Szeged, Szeged, Hungary
[2]"Nicolae Stancioiu" Heart Institute, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

Related article
by Momot et al.

Correspondence to:
Zoltán Ruzsa, MD, PhD,
Department of Internal Medicine,
Division of Invasive Cardiology,
University of Szeged,
Szeged Semmelweis Str 6, 6726,
Szeged, Hungary,
phone: +36 203 338 490,
e-mail: zruzsa25@gmail.com

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By 2021, both American and European guidelines aligned, endorsing transradial access (TRA) for all coronary procedures, stable or acute [1, 2]. With this momentum, the surging "radial-first" strategy gained increased attention, particularly on social media, pushing the boundaries of TRA in the anatomical snuffbox or the dorsal hand [3]. The metamorphosed distal radial access (DRA) was quickly adopted by many centers, in the absence of strong evidence, due to its clear advantages: less postprocedural occlusion, faster hemostasis, and better intraprocedural ergonomics [4–6]. Although smaller in diameter than its proximal surrogate, its versatility has been tested even in balloon aortic valvuloplasty, with large sheaths of 7–8 F, keeping its promised low occlusion rate (6%) [7]. However, with a more angled path and a smaller diameter, DRA cannulation may be more difficult and perhaps more painful. During access, vasoconstriction may occur in the vessel, and rupture of the elastic lamina and media layer may occur, resulting in complications such as bleeding, hematoma, and later, radial artery occlusion.

In this issue of *Kardiologia Polska* (*Kardiol Pol*, *Polish Heart Journal*) Momot et al. [8] looked at an interesting aspect of DRA, namely, if it produces more vascular injury than its predecessor and if this is being transmitted subjectively through the pain felt by the patient. On closer inspection, it remains to be seen whether this pain is caused by the operator, or objectively, strictly by the aggression of sheath insertion.

But perhaps, we should see first if the insertion of a sheath into an artery causes so much endothelial injury that we should be concerned about its clinical impact if any. The fact that using radial conduits is not recommended in coronary artery bypass grafting (CABG) after coronary angiography and catheter manipulation shows that this topic is relevant [2]. The quality of the radial artery is accounted for by an inadequate endothelial (vasodilation) response and arterial remodeling, which may restrict its usage as a bypass graft or as a dialysis shunt [2, 9]. Boos et al. [10] observed significant increases in three endothelial markers (circulating endothelial cells [CECs], von Willebrand factor, and soluble E selectin) with elective percutaneous coronary intervention (PCI), but not coronary angiography. On the other hand, Dinat-George et al. [11] noted a significant increase (approximately 13-fold) in CECs following primary coronary angioplasty in 10 patients using larger 7 F femoral catheters. In an older study, Sbarbati et al. [12] noted a threefold to fourfold increase in CEC counts after coronary angiography (no PCI/stenting), but through the femoral approach only and using large 8 F sheaths. It is understood, therefore, that these biomarkers increase even more in the femoral approach or when working on the coronary arteries. In terms of flow-mediated dilatation, the radial artery's function is suppressed immediately after coronary angiography, but it recovers after 2–3 months [13]. In fact, a study by Kis et al. [14], DRA showed significantly less affected vasomotor functions the day after the procedure, compared to the conventional TRA. This was also confirmed by Soydan et al. [15]. The slower decrease in flow-mediated dilation after DRA was assumed to be connected with higher preservation of endothelial functions than the other access sites. The possible explanation for this preservation could lie in the fact

that the distal radial artery is one of the distal branches of the main radial artery and that the insertion of the radial sheath towards the endothelium could be less aggressive than introducing it directly into the main radial artery [3].

TRA remains, therefore, the most harmless procedure as confirmed by the Polish team. In their study, no differences were found between endothelin 1, interleukin 8, and levels of soluble vascular cell adhesion molecule-1 in conventional TRA vs. DRA although accessing the distal radial artery was subjectively more painful [8]. Several comments are worth discussing. First, if the basal venous blood had been collected before the puncture and compared to the levels after the procedure, it would have brought more value to the dispute over how aggressive TRA is in general. Second, DRA, like any technique, involves a learning curve, which can be challenging at first; only after 100 cases, stability in the success rate was observed [4]. Momot et al. [8] did not provide us with details about the experience of operators with DRA, which turns out to be different compared to TRA. Moreover, we do not know the number of puncture attempts while endeavoring DRA. Logically, with the number of attempts, the pain increases exponentially. But we have indirect signs that obtaining DRA was more difficult: longer access time with DRA (81 vs. 50 seconds), more hematomas (12 vs. 5), and a lower success rate (84% vs. 100%) [8]. It is almost clear then why DRA was more painful. As soon as appropriate skills are acquired, such as insertion of a small (5–6 F) sheath into a lumen that can easily accommodate it (a 6 F sheath has an outer diameter of approximately 2.4–2.5 mm while the mean distal radial artery diameter is 2.5–2.6 mm [4, 5]), and the reasonable steps of local anesthesia, nitroglycerin, hand positioning, careful device manipulation, etc., the cannulation should come with low levels of pain perceived by the patient. Third, the relevance of this topic is reflected in the low reactivity of biomarkers for endothelial dysfunction. Even with theoretically higher concentrations, radial access remains the safest of all, and its distal neighbor refines it further, reducing the rate of vascular complications and enhancing both patient and operator's comfort. What concentrations of biomarkers would we have in vascular surgery, where the arteries are sectioned and cauterized? The benefit of using TRA (and DRA) for all types of percutaneous interventions is indisputably greater than the risk of endothelial injury without a clinical impact. As for the pain, both the operator and the patient must go through it, on the way to success.

Article information

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Distal radial access: A better way to the heart?

Emmanouil S Brilakis, Bahadir Simsek, Spyridon Kostantinis

Minneapolis Heart Institute and Minneapolis Heart Institute Foundation, Minneapolis, MN, United States

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Correspondence to:
Emmanouil S Brilakis, MD, PhD, Minneapolis Heart Institute, 920 E 28th Street 300, 55407 Minneapolis, MN, United States, phone: +612 863 39 00, e-mail: esbrilakis@gmail.com

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In both the European [1] and the American [2] coronary revascularization guidelines, radial access is given a class I recommendation for coronary angiography and percutaneous coronary intervention (PCI) because it reduces the risk of vascular access complications and bleeding. Increasing evidence shows favorable outcomes with radial access even for highly complex PCI [3], such as chronic total occlusion PCI [4] or PCI in patients with prior coronary artery bypass graft surgery (CABG) [5]. However, radial access also has limitations, such as the risk of compartment syndrome and radial artery occlusion. Radial access can cause radial artery injury, potentially preventing the use of the radial artery as a conduit for CABG. Moreover, left radial access can be uncomfortable for both the patient and the operator.

Radial access has traditionally been obtained in the proximal radial artery above the styloid process of the radius. To improve the safety of radial access, distal radial access was developed at the anatomic snuffbox or more distally in the first intermetacarpal space [6, 7]. The use of distal radial access has been increasing [8], but the comparative efficacy and safety of distal vs. proximal radial access remains controversial [9].

In this issue of the *Kardiologia Polska* (*Polish Heart Journal*), Momot et al. [10] report the findings of a randomized controlled trial that assigned 200 patients scheduled for elective coronary angiography or PCI to either distal or proximal radial access in a 3:2 ratio. Twenty-two of the 120 patients assigned to distal radial access were converted to proximal radial access because of no palpable distal radial pulse (n = 4) or because of failure to cannulate the distal radial artery (n = 18). Blood was collected from the cephalic vein after removal of the pressure dressing in 40 random patients (20 from the distal and 20 from the proximal radial group), and several markers of endothelial injury (endothelin 1 [ET-1], interleukin 8 [IL-8], soluble vascular cell adhesion molecule-1 [sVCAM-1]) were measured. The time to obtain access was longer in the distal radial group. Moreover, patients in the distal radial access group had more discomfort. There was no difference in hematoma or radial artery occlusion, although the study was not powered for clinical endpoints. There was no difference in radiation dose and contrast volume. Finally, there was no difference in the plasma levels of ET-1, IL-8, sVCAM-1.

The authors should be congratulated for advancing our understanding of distal radial access. How do the study findings affect our current understanding of this field and what are the practical implications (Table 1)?

First, the present study confirms that distal radial access is more difficult and less predictable than proximal radial access: it required a longer time (111 vs. 50 seconds) and was associated with higher crossover to another access point (18% vs. 0%). These findings are very similar to the findings of the largest randomized controlled trial performed to date (n = 1042) comparing distal and proximal radial access [11] that reported 78.7% vs. 94.8% successful sheath insertion (P <0.001) and 120 vs. 75 seconds to insert the sheath (P <0.001) [11]. To what extent the higher failure and longer time required to obtain access via the distal radial artery is related to operator experience and access technique remains to be seen. Increasing experience and

Table 1. Comparison of distal vs. proximal radial access for cardiac catheterization

		Distal radial	Proximal radial
Success	Obtaining access		Better
	Crossover to femoral		Better
Efficiency	Time to obtain access		Better
	Difficulty in obtaining access		Better
	Able to insert a larger sheath		Better
	Time to hemostasis	Better	
	Ease of coronary engagement	No difference	
Comfort	Operator comfort — right radial	No difference	
	Operator comfort — left radial	Better	
	Patient comfort — right radial	No difference	
	Patient comfort — left radial	Better	
Complications	Compartment syndrome	Better	
	Hand ischemia	Better	
	Bleeding	No difference	
	Radial artery occlusion	Better	
	Radial artery injury	No difference	

consistent use of ultrasound [12] could help improve the success rate and reduce the time required for obtaining distal radial access.

Second, distal radial access was less comfortable for the patient, likely due to the longer time required to obtain access and multiple needle passes. Higher success and efficiency in obtaining radial access with increasing operator experience could improve the patient's experience. The right radial artery was used in the present study, but distal radial access may be particularly useful for left radial access, as it allows a more natural position for the patient's hand and easier operator access to the radial artery.

Third, the current study did not examine the impact of distal radial access on the time required to achieve hemostasis, as all patients received a pressure dressing for 120 minutes. This was required to prevent confounding of the endothelial damage markers. In the study by Tsigkas et al. [11], time to hemostasis was shorter with distal radial access (60 vs. 120 minutes; P <0.001). Shorter hemostasis time could increase patient comfort and potentially "counterbalance" some of the discomfort experienced while obtaining access.

Fourth, the risk of complications was similar with distal and proximal radial access, but the study was underpowered for clinical endpoints. Three randomized controlled trials have demonstrated lower rates of radial artery occlusion with distal radial access [11, 13, 14]. The distal radial artery may decrease the risk of compartment syndrome that could be a catastrophic complication. Moreover, maintaining radial artery patency would allow its repeat use for cardiac catheterization and possibly as a conduit for CABG.

Fifth, endothelial injury markers were similar with distal and proximal radial access, suggesting similar radial artery injury with the two approaches. Therefore, distal radial access does not alleviate concerns for radial artery injury in case the patient requires CABG using radial grafts. According to the 2022 American revascularization guidelines [2], "the decision to use the transradial approach should be tempered with the possibility that the radial artery may be needed for bypass grafting in the future. In patients for whom there is a high likelihood of future CABG, the choice of vascular access may require discussion with the patient and the cardiac surgeon".

Sixth, the feasibility/safety of large (7 or 8 F) catheter insertion via distal radial access requires further study. In the present study, only 6 F sheaths and catheters were used, but larger sheaths and guide catheters may facilitate treatment of highly complex coronary lesions. Several studies have shown encouraging results with the use of low-profile 7 F sheaths *via* distal radial access [15]. Alternatively, sheathless guide catheters could be used.

In summary, distal radial access is here to stay and should become part of the armamentarium of all interventional cardiologists, but it is not a panacea. Increasing clinical experience and additional well-powered clinical studies will help further clarify the optimal application of distal radial access in contemporary cardiac catheterization.

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REVIEW

Severe maternal morbidity and risk of cardiovascular disease: Recent advances

Ugochinyere Vivian Ukah[1, 2], Nathalie Auger[1–4]

[1]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada
[2]Institut national de santé publique du Québec, Montreal, Quebec, Canada
[3]University of Montreal Hospital Research Center, Montreal, Quebec, Canada
[4]Department of Social and Preventive Medicine, School of Public Health, University of Montreal, Montreal, Quebec, Canada

Correspondence to:
Nathalie Auger, MD, Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, 190 Cremazie Blvd E, Montreal, Quebec H2P 1E2, Canada, phone: 514 864 1600 ext. 3717, e-mail: nathalie.auger@inspq.qc.ca

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ABSTRACT

Pregnancy complications including severe maternal morbidity have been linked with an increased risk of cardiovascular disease, and provide opportunities to identify women who would benefit from prevention. Severe maternal morbidity comprises life-endangering complications around the time of pregnancy and delivery. Literature on the relationship between severe maternal morbidity and cardiovascular disease is increasing at a rapid pace. Studies have shown that severe preeclampsia or eclampsia and severe hemorrhage are associated with cardiovascular disease later in life. Proposed pathways include endothelial damage, hypercoagulability, and impaired cardiac function that are induced or exacerbated by severe pregnancy complications that elevate cardiovascular risks. However, less is known about other types of severe maternal morbidity that may influence the risk of cardiovascular disease. Other research gaps include a need to better understand the pathways and mechanisms linking severe maternal morbidity with cardiovascular disease, the potential for cardiovascular recovery after severe cardiovascular events during pregnancy, and disparities in the occurrence of cardiovascular disease after severe maternal morbidity.

Key words: cardiovascular disease, heart disease, maternal near-miss, pregnancy complications, severe maternal morbidity

INTRODUCTION

Adverse pregnancy outcomes, including severe maternal morbidity, are receiving increasing attention for their potential link with cardiovascular disease [1, 2]. Pregnancy complications such as preeclampsia, gestational diabetes, and stillbirth have been associated with more than 1.5 times greater risk of cardiovascular disease in several studies [1–4]. There is a growing push for research to identify pregnancy-specific characteristics that may be targeted to improve cardiovascular outcomes, particularly since women are more likely to have advanced sequelae than men or die after myocardial infarction and other acute cardiovascular incidents [5, 6]. Pregnancy provides opportunities to detect women at risk of adverse cardiovascular outcomes and deliver tailored interventions to prevent disease.

Severe maternal morbidity is the most recent pregnancy complication that has garnered notice from obstetrical and cardiovascular epidemiologists [7]. Severe maternal morbidity includes events such as eclampsia, amniotic fluid embolism, and obstetric shock, which are considered life-threatening during pregnancy. The incidence of severe maternal morbidity appears to be increasing in several countries owing to advanced maternal age and an increasing prevalence of predisposing risk factors [8, 9]. A number of studies are beginning to document associations between severe maternal morbidity and cardiovascular disease [7, 10]. A comprehensive review of existing literature is warranted to summarize current evidence of the relationship between severe maternal morbidity and cardiovascular disease and identify potential research gaps that need to be filled.

Table 1. Common definitions of severe maternal morbidity

Organization	Definition of severe maternal morbidity
World Health Organization	Maternal near-miss based on clinical, laboratory, and management criteria: shock, hysterectomy, transfusion of ≥5 units of red cells, intubation, and ventilation Potential life-threatening conditions: severe hemorrhage, hypertensive disorders of pregnancy, intensive care unit admission
Centers for Disease Control and Prevention, jointly with the American College of Obstetricians and Gynecologists	21 indicators: acute myocardial infarction, aneurysm, acute renal failure, adult respiratory distress syndrome, amniotic fluid embolism, cardiac arrest/ventricular fibrillation, conversion of cardiac rhythm, disseminated intravascular coagulation, eclampsia, heart failure/arrest during surgery or procedure, puerperal cerebrovascular disorders, pulmonary edema/acute heart failure, severe anesthesia complications, sepsis, shock, sickle cell disease with crisis, air and thrombotic embolism, blood product transfusion, hysterectomy, temporary tracheostomy, ventilation
Canadian Perinatal Surveillance System	13 broad types (44 subtypes): Severe preeclampsia/eclampsia, severe hemorrhage, intensive care unit admission, hysterectomy, surgical complications, sepsis, embolism/shock/disseminated intravascular coagulation, assisted ventilation, cardiac and cerebrovascular conditions, severe uterine rupture, acute renal failure, other (sickle cell anemia, hepatic failure, acute abdomen, adult respiratory distress syndrome, and similar disorders)

DEFINITION

Severe maternal morbidity is a composite term for unexpected complications occurring around pregnancy and delivery that are serious and threaten a woman's life [11]. Up to 88% of maternal deaths are attributed to severe maternal morbidity [12]. Conditions such as stroke, acute renal failure, and myocardial infarction are all examples of severe maternal morbidities. Severe maternal morbidity is sometimes termed a maternal "near-miss", as a high proportion of women may die without early intervention [11, 13]. More than 30% of cases of severe maternal morbidity are considered preventable through early identification and treatment [14]. The World Health Organization and obstetric institutions such as the American College of Obstetricians and Gynecologists recommend ongoing surveillance of severe maternal morbidity to identify areas for improvement in maternal healthcare [11, 13, 14].

There is a lack of consensus on the definition of severe maternal morbidity between international bodies (Table 1). The World Health Organization defines a maternal near-miss as a case in which a woman survives serious acute complications around delivery [13]. The Centers for Disease Control and Prevention and Canadian Perinatal Surveillance System define severe maternal morbidity as pregnancy-related conditions associated with significant sequelae, prolonged hospitalization, and high case fatality [15, 16]. Most definitions of severe maternal morbidity include severe preeclampsia or eclampsia, stroke, hysterectomy, and intensive care unit admission [13, 15, 16]. The consensus is that severe maternal morbidity includes life-threatening conditions occurring up to 6 weeks postpartum [13, 15, 16].

PREVALENCE

For each maternal death, it is estimated that there are 20 or more cases of severe maternal morbidity [17]. The incidence of severe maternal morbidity is approximately 1.6% in North America, 1.2% in Australia, and 0.7% in the Netherlands [16, 18–20]. Variation in incidence is partly due to differences in the definition and measurement of severe maternal morbidity.

While the number of maternal deaths has decreased in high-income countries, the incidence of severe maternal morbidity appears to have remained stable or risen in some regions [16, 20, 21]. In the US, greater use of blood transfusion for pregnancy hemorrhage appears to account for most of the increase in severe maternal morbidity [15, 21]. On the other hand, increasing rates of severe maternal morbidity in Canada are thought to be due to a rise in the prevalence of cerebrovascular accidents, acute renal failure, and hysterectomy [16]. Some of the observed increases may be due to better measurement and surveillance of severe maternal morbidity with time. Regardless of the reason for the increase, rising trends in severe maternal morbidity have implications for pregnant women and are an economic burden for public healthcare.

RISK FACTORS

Risk factors for severe maternal morbidity include obesity, Black race, advanced maternal age, cesarean delivery, and pre-existing comorbidities such as chronic hypertension [8, 9, 15]. The rise in severe maternal morbidity is partly attributed to increasing rates of obesity, advanced maternal age, use of artificial reproductive techniques, and cesarean delivery [15, 22, 23]. Pregnant women over 40 years of age have a 1.6 to 2.7 times higher risk of severe maternal morbidity while infertility treatment is associated with a 1.4 times higher risk [22, 23]. Other risk factors for severe maternal morbidity include mental health disorders and disability [24, 25]. As some of these risk factors continue to be prevalent, severe maternal morbidity will likely remain an important item on the research agenda in the immediate future.

PROGNOSIS

Overall, women with severe maternal morbidity have lengthier postpartum hospital stays and approximately double the risk of hospital readmission within the first year of delivery, compared with no morbidity [12, 26–28]. Severe maternal morbidity is linked with adverse mental health, including post-traumatic stress disorder and other psychiatric illnesses within one year of birth [29–31]. Studies beyond the first year are scarce, but a few have reported that women with severe maternal morbidity have a lower perceived quality of life up to five years

Table 2. Summary of studies examining the risk of cardiovascular disease after severe maternal morbidity

Author, publication year	Type of severe maternal morbidity	Outcome; length of follow-up	Country; data source	Sample size	Adjusted risk estimate (95% CI)
Behrens, 2016	Severe preeclampsia	Cardiomyopathy; 34 years	Denmark; National Patient Register and Medical Birth Register (1978–2012)	2 067 633 pregnancies	HR, 2.22 (1.47–3.36) for cardiomyopathy 5 years after the latest delivery HR, 2.20 (1.50–3.23) for cardiomyopathy >5 months after the first delivery
Cartus, 2021	Any severe maternal morbidity following conditions listed by the Centers for Disease Control and Prevention	Atrial fibrillation, heart failure, ischemic heart disease (including acute myocardial infarction), stroke, transient ischemic attack, and a composite outcome of any of these events; 26 months	US; Pennsylvania Medicaid administrative claims data (2016–2018)	137 140 deliveries	RD, 27.9 (18.6–37.2)
Cho, 2021	Postpartum hemorrhage requiring transfusion	Any cardiovascular hospitalization; 8 years	Korea; Korea National Health Insurance claims, National Health Screening Examination and National Health Screening Program for Infants and Children (2007)	150 381 deliveries	HR, 1.60 (1.25–2.06)
Kestenbaum, 2003	Severe preeclampsia/ /eclampsia	Hospitalizations for acute myocardial infarction, acute stroke or coronary artery revascularization procedure, including coronary artery bypass graft; 13 years	US; Washington State Birth Events Record Database (1987–1998)	124 141 deliveries	HR, 3.3 (1.7–6.5)
Lykke, 2010	Severe preeclampsia/ /eclampsia	Death from cardiovascular causes; 30 years	Denmark; National Patient Registry (1978–2007)	782 287 deliveries	HR, 2.89 (1.93–4.33)
Ukah, 2020	Any hemorrhage requiring transfusion	Any cardiovascular hospitalization; 30 years	Canada; Maintenance and Use of Data for the Study of Hospital Clientele registry, Quebec (1989–2016)	1 224 975 deliveries	HR, 1.47 (1.23–1.76) for any hemorrhage with transfusion HR, 1.85 (1.28–2.68) for antenatal hemorrhage with transfusion HR, 1.85 (0.95–3.58) for placenta praevia with transfusion HR, 1.41 (0.58–3.43) for peripartum hemorrhage with transfusion HR, 1.38 (1.13–1.68) for postpartum hemorrhage with transfusion
Ukah, 2022	Any severe maternal morbidity following conditions listed by the Canadian Perinatal Surveillance System	Any cardiovascular hospitalization; 31 years	Canada, Maintenance and Use of Data for the Study of Hospital Clientele registry, Quebec (1989–2019)	1 224 975 deliveries	HR, 1.77 (1.72–1.82)
Wikstrom, 2005	Severe preeclampsia/ /eclampsia	Ischemic heart disease; 15 years	Sweden; Swedish Medical Birth Register (1973–1982)	403 550 deliveries	IRR, 2.8 (2.2–3.7)
Yeh, 2014	Eclampsia	Any cardiovascular hospitalization; 12 years	Taiwan; Taiwan National Health Insurance database (1997–2009)	6 300 deliveries	HR, 1.38 (0.28–6.83)

Abbreviations: CI, confidence interval; HR, hazard ratio; IRR, incidence rate ratio; RD, risk difference

after delivery and an increased risk of mortality in the long term [32–35].

Recent studies are beginning to show an association with cardiovascular disease (Table 2) [7, 10]. In an analysis of Medicaid administrative claims data from Pennsylvania in the US, it was demonstrated that severe maternal morbidity was associated with an increased risk of adverse cardiovascular outcomes in the first two years following pregnancy [10]. The investigators assessed the association with cardiovascular events such as stroke, transient ischemic attack, heart failure, and ischemic heart disease using the Centers for Disease Control and Prevention's definition of severe maternal morbidity [15]. Among 137 140 deliveries, the cumulative incidence of severe maternal morbidity was 4.2% [10]. After accounting for ethnicity, age, parity, mode of delivery, Medicaid eligibility, substance use disorders, and a range of maternal comorbidities, severe maternal morbidity was associated with an excess of 2.7 cardiovascular events per 1000 deliveries at one month postpartum (95% CI, 1.6–3.8) and 27.9 cardiovascular events per 1000 deliveries at 26 months postpartum (95% CI, 18.6–37.2). Severe maternal morbidity was most strongly associated with heart failure, with 12.1 excess cases per 1000 deliveries at 26 months postpartum (95% CI, 6.2–18.0).

A second study used hospital data from Canada in which pregnant women had up to three decades of follow-up [7]. The investigators followed 1.3 million women who delivered in Quebec to identify subsequent cardiovascular admissions over time [7]. Severe maternal morbidity occurred in 5% of women in the cohort and included conditions specified by the Canadian Perinatal Surveillance System [16]. A range of cardiovascular outcomes was examined including heart disease, cerebrovascular disease, pulmonary vascular disease, and cardiovascular interventions in the thirty years following delivery. Compared with no morbidity, severe maternal morbidity was associated with 1.8 times higher risk of any cardiovascular disease (95% CI, 1.72–1.82) and more than double risk of heart failure, cardiomyopathy, and pulmonary vascular conditions. Results were adjusted for confounders including maternal age at delivery, socioeconomic deprivation, comorbidity, substance use disorders, multiple gestation, and time.

In addition to examining severe maternal morbidity as a composite exposure, the investigators assessed the association of individual types of severe maternal morbidity with the risk of cardiovascular disease. Most types of severe maternal morbidity were associated with an elevated risk of cardiovascular disease, but serious cardiac complications during pregnancy were associated with the greatest risk (hazard ratio 5.37; 95% CI, 4.65–6.20). Assisted ventilation, cerebrovascular accidents, and admission to the intensive care unit were associated with more than triple the risk of cardiovascular disease. Furthermore, the investigators were able to demonstrate that associations differed depending on the length of time after delivery [7]. Severe maternal morbidity was associated with cardiovascular disease throughout follow-up, but the risks were greatest in the immediate period after delivery and declined slowly with time.

PATHWAYS TO CARDIOVASCULAR DISEASE

These novel findings have led to speculation about the pathways linking severe maternal morbidity with cardiovascular disease. Pathways may vary. Patients with severe maternal morbidity may have an underlying predisposition to cardiovascular disease [36]. Conditions such as severe preeclampsia, severe hemorrhage, and peripartum cardiomyopathy share common risk factors with cardiovascular disease, including smoking, obesity, hypertension, and Black race [36–38]. Similarly, preeclampsia is associated with an increased risk of renal disease, an additional risk factor for cardiovascular disease [37, 39]. Proposed mechanisms include insufficient spiral artery remodeling, oxidative stress, endothelial cell dysfunction, and exaggerated inflammatory responses in conditions such as preeclampsia, acute renal failure, and sickle cell crises [7, 36, 37, 40, 41].

There is ample literature on the risk of cardiovascular disease following preeclampsia, with most of this work summarized in literature reviews [42, 43]. However, only a few studies have investigated severe preeclampsia or eclampsia as components of severe maternal morbidity (Table 2) [7, 44–48]. The studies had sample sizes ranging from 6300 to over 2 million pregnancies from Denmark [45, 47], Sweden [48], the US [44], and Taiwan [46]. Severe preeclampsia and eclampsia were found to be associated with a 1.4 to 3.3-fold increase in the risk of cardiovascular disease and mortality, compared with uncomplicated pregnancies. In one systematic review [1], the pooled odds ratio was 2.74 (95% CI, 2.48–3.04) for the association of severe preeclampsia with cardiovascular disease. In patients with preeclampsia, an imbalance in levels of placental growth factor and sFlt-1 may result in endothelial or vascular damage [36, 37]. Severe maternal morbidity, including severe preeclampsia, is often marked by hypercoagulability and elevated C-reactive protein levels that may exacerbate an inflammatory response [37]. Both hypercoagulability and excessive inflammatory reactions have been linked with cardiovascular disease [36, 37].

Severe maternal morbidity including hemorrhage may harm the cardiovascular system directly [36]. Severe hemorrhage can lead to hemorrhagic shock that impairs cardiac function [49, 50]. Excessive loss of blood has been linked with hemodynamic instability and end-organ damage [50]. Transfusion of blood, even in the absence of hemorrhage, is associated with venous thromboembolism, which may confer further cardiovascular risks [50, 51]. Some patients may not completely recover cardiac function in the postpartum period, leading to the development of long-term cardiovascular pathology [7, 52]. A growing number of studies have examined hemorrhage-related conditions during pregnancy and the risk of cardiovascular disease [45, 53–55]. Three studies have shown that severe postpartum hemorrhage requiring blood transfusion was associated with 1.4 to 1.6 times higher risk of subsequent cardiovascular disease, compared with no hemorrhage [7, 49, 50]. Antenatal hemorrhage requiring blood transfusion was associated with 1.9 times higher risk of cardiovascular disease in one analysis [50]. In another study, severe antepartum, intrapartum, and postpartum hemorrhage were associated with 1.5 times higher risk of developing cardiovascular disease [7].

Patients may also have undiagnosed cardiovascular disease at the time of pregnancy [36]. In patients with already existing cardiovascular conditions, the normal physiological changes of pregnancy, including increased cardiac output, elevated heart rate, and decreased vascular resistance [56], may overburden the cardiovascular system. In such situations, preexisting cardiovascular conditions may worsen and appear for the first time as a complication of pregnancy, including severe cardiac morbidity that exacerbates subsequent cardiovascular risks.

FUTURE RESEARCH FOCUS

Despite growing awareness that women with pregnancy complications may be at risk of cardiovascular disease, literature on severe maternal morbidity remains sparse. The scarcity of studies on how specific types of severe maternal morbidity are associated with cardiovascular disease remains a key knowledge gap. Studies so far have mostly reported on severe maternal morbidity as a composite exposure or focused only on severe preeclampsia and hemorrhage. Examining additional types of severe maternal morbidity may help identify patients more at risk of cardiovascular disease. There is also a need for a uniform definition of severe maternal morbidity. Concordance on the definition of severe maternal morbidity is necessary to replicate studies in different settings and enable comparisons between regions.

Mechanisms by which severe maternal morbidity affects the cardiovascular system also need further study. The extent to which pregnant women recover after cardiovascular incidents requires attention, including women with preexisting heart disease. None of the published studies reviewed were conducted in low and middle-income countries or populations most vulnerable to severe maternal morbidity, including women of African ethnicity or with disabilities. Greater effort is needed to assess cardiovascular risks associated with severe maternal morbidity in high-risk groups.

CONCLUSION

Current literature, although scarce, suggests that women with severe maternal morbidity have an elevated risk of cardiovascular disease. However, more research is needed in this area to identify the pathways linking severe maternal morbidity with cardiovascular disease and the types of severe maternal morbidity associated with a greater risk. Improved surveillance of women with severe maternal morbidity offers opportunities to identify, prevent, and treat future cardiovascular diseases in coming years.

Article information

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REVIEW

Cerebral embolic protection in patients undergoing transcatheter aortic valve implantation: Recent advances

Ines Richter, Mohamed Abdel-Wahab, Steffen Desch, Holger Thiele

Heart Center Leipzig at University of Leipzig, Leipzig, Germany

Correspondence to:
Prof. Holger Thiele, MD, FESC, Department of Cardiology, Heart Center Leipzig at University of Leipzig, Struempellstrasse 39, 04289 Leipzig, Germany, phone: +49 341 865 14 28, e-mail: holger.thiele@medizin.uni-leipzig.de

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ABSTRACT

Despite major advances in transcatheter aortic valve implantation (TAVI) technology during the last years, stroke remains one of the most serious complications of TAVI, tremendously increasing mortality and the loss of neurocognitive function. Since TAVI is expected to further spread into lower-risk patient groups, there will be greater emphasis to obviate such serious complications. One possible technique for preventing stroke is using cerebral embolic protection devices (CEPDs). CEPDs are designed for capturing or deflecting emboli that are en route to the brain and hence to protect the brain from embolism. Although their clinical utilization is increasing, the evidence for using CEPDs is not yet clear. Since this is a rapidly growing field with recent advances, and the impact of CEPD on preventing neurological events is still limited, there is an urgent need for understanding the role of CEPD in preventing clinically significant strokes. In this review, we present an overview of the available literature on CEPDs in patients undergoing TAVI and outline recent advances within this field.

Key words: aortic stenosis, cerebral embolic protection, stroke, transcatheter aortic valve implantation

INTRODUCTION

Despite the technical progress in transcatheter aortic valve implantation (TAVI) and the steadily increasing operator experience, stroke remains one of the main complications limiting the life expectancy and resulting in a tremendous deterioration of physical and neurocognitive function as well as affecting psychosocial aspects [1]. Neurological events are observed in 1%–11% of patients undergoing TAVI [2]. The highest risk for embolization of debris into the brain has been shown to be periprocedural during valvuloplasty, valve positioning, and implantation of the new valve and is mainly described as a result of manipulation at highly calcified structures or embolization of intraaortic atheromatous material or thrombi. In addition, emboli can originate from the aortic arch, the left ventricular outflow tract, or even from particles of the equipment used during the procedure [3].

Apart from clinical strokes, subclinical strokes, defined as new ischemic brain lesions detected by diffusion-weighted magnetic resonance imaging (DW-MRI) without any clinical signs, are found in approximately 90% of patients undergoing TAVI. Nonetheless, the clinical significance of these "silent" strokes remains unclear [4].

Since TAVI is expected to further expand into lower-risk patient groups [5] and patients undergoing TAVI want to maintain their ability to independently practice their daily activities instead of simply staying alive [6], special efforts to prevent embolic stroke or other neurological events remain of utmost importance.

One option for protecting brain structures from embolization of debris is using cerebral embolic protection devices (CEPDs). CEPDs are intended to reduce the risk for embolic events by filtering and capturing particles or by deflecting embolic debris downwards into the descending aorta. Even though using CEPDs is steadily increasing and new technologies are constantly arising, the evidence for the widespread use of CEPDs and prevention of stroke is not yet clear [7]. The available literature is mainly based on observational studies

Table 1. Overview of currently available and investigational CEPD

	Sentinel (Boston Scientific, Corp., US)	Emblok (Innovative cardiovascular solutions, Grand Rapids, MI, US)	Emboliner (Emboline Inc., Santa Cruz, CA, US)	TriGuard 3 (Keystone Heart, Caesarea, Israel)	Point-guard (Transverse medical Inc., US)	Protembo (Protembis GmbH, Germany)
Device						
Access	Right radial, 6 F	Femoral, 11 F	Femoral, 9 F	Femoral, 8 F	Femoral, 10 F	Left radial, 6 F
Coverage	2-vessels capture	3-vessel capture	3-vessel and body capture	3-vessel coverage	3-vessel coverage	3-vessel coverage
Pore size	140	125	150	145	105	60
Main trials	MISTRAL-C (2017) SENTINEL (2017) CLEAN-TAVI (2017) PROTECTED-TAVR (ongoing) PROTECT-HF (ongoing)	European study (ongoing)	SafePass trial (planned)	DEFLECT I–III REFLECT I–II (2021)	CENTER-Trial (ongoing)	PROTEMBO SF Trial (ongoing)
Regulatory status	CE mark/FDA approved	Investigational	Investigational	CE mark/investigational	Investigational	Investigational

Abbreviations: CEPD, cerebral embolic protection device; CE, Commiteé Europeenne; FDA, Food and Drug Administration

and small-sized randomized trials, which are not powered to provide clear evidence for the use of CEPDs. Furthermore, most of the studies assessed imaging endpoints instead of major clinical events, which raises further uncertainties.

In the current review, we summarize current knowledge and describe recent advances in CEPDs in patients undergoing TAVI.

TYPES OF EMBOLIC PROTECTION SYSTEMS

Currently available CEPDs

Currently, there are mainly two mechanisms of protecting brain structures from embolic debris during TAVI. There are deflector devices that redirect debris towards the descending aorta, and there are filter devices that retain embolic material and debris (Table 1).

The dual filter device Sentinel CEPD (Boston Scientific, Marlborough, MA, US) is the most studied (Table 2) and the only device that is approved for clinical use in both Europe and the US. The system is advanced through a 6 F sheath through the right radial or brachial artery. The two 140 µm pore polyurethane filters are placed proximally in the brachiocephalic trunk and distally in the left common carotid artery before TAVI. The left vertebral artery remains unprotected so that 9 of 28 brain territories are protected by the filter system. There is only one size available resulting in some anatomical variations where sufficient protection cannot be provided.

The Sentinel device was studied in several observational studies and randomized trials. The largest randomized trial (SENTINEL) [8] was published in 2017 and randomized 363 patients in a 1:1:1 fashion (the safety arm n = 123 [use of CEPD and assessment of clinical events without imaging or neurocognitive testing]; the imaging device arm n = 121; the control arm n = 121). After the procedure, embolic debris was found in 99% of all filters. However, the trial could not show a significant reduction of median total new lesion volume in the protected brain areas (102.8 mm^3 in the device arm vs. 178 mm^3 in the control arm; $P = 0.33$) using DW-MRI 2–7 days after TAVI.

The efficacy of the Sentinel CEPD was also investigated in the single-center randomized CLEAN-TAVI trial [9] which included 100 patients undergoing TAVI. The study performed brain MRI at baseline, two and seven days after TAVI and observed a significant reduction in the number of new lesions in the CEPD group as determined by DW-MRI (4 in the CEPD arm vs. 10 in the control arm; $P < 0.001$) and a significant decrease in the volume of new cerebral lesions after 48 hours (242 mm^3 in the CEPD arm vs. 527 mm^3 in the control arm; $P < 0.001$). Despite these promising results, there was no significant reduction in clinical stroke (n = 5 in the CEPD arm vs. n = 5 in the control arm; $P > 0.05$).

The multicenter randomized MISTRAL-C trial [10] evaluated the Sentinel CEPDs in 65 patients and found debris in 100% of the filters. The trial further showed a significantly lower rate of patients with neurocognitive deterioration when using CEPDs (4% vs. 27%; $P = 0.017$). Even though multiple lesions (>10 lesions on DW-MRI) were only seen in patients without CEPDs (20% vs. 0%; $P = 0.03$), there was only a numerical, non-significant reduction in the number of new brain lesions in DW-MRI (73% vs. 87%; $P = 0.31$).

The TriGuard CEPD (Keystone Heart Ltd., Caesarea, Israel) is the only deflector device, that received CE marking (however, without Food and Drug Administration approval yet). It is inserted through an 8 F sheath in the femoral artery (contralateral to the main access site) and placed within the inner curvature of the aortic arch allowing maximal blood flow to the brain arteries and covering all

Table 2. Randomized controlled trials evaluating CEPD

Trial	Study population (n)	Main objectives	Assessment of the main endpoints	Main results
Sentinel (2017)	363 Multicenter RCT	Efficacy and safety of Sentinel CEPD	Assessment: DW-MRI at 2-7 days NE at baseline, at discharge, 30 days 30-day safety (VARC-2)	• Debris in 99% of all filters • Numerically less strokes at 72h (3% vs. 8.2%; $P = 0.053$) • Numerically less new lesion volume (102.8mm^3 vs. 178 mm^3; $P = 0.33$) • No significant difference in neurocognitive function at 30 days • Numerically lower stroke rate at 30 days (5.6 vs. 9.1; $P = 0.25$) • At 30 days lower lesion volume of protected areas • Correlation between lesion volume and neurocognitive decline ($P = 0.0022$)
Clean TAVI (2016)	100 Single center RCT	Effect of Sentinel CEPD on number of new lesions on DW-MRI	Assessment: DW-MRI at baseline, 2 days and 7 days NE 2 at and 7 days	• Lesions in 98% of patients • Less new lesions (4 vs. 10; $P < 0.001$) • Lower volume of new cerebral lesions after 48 hours (242 mm^3 vs. 527 mm^3; $P < 0.001$) • No difference in clinical stroke (10% vs. 10%; $P = 1.0$) • New neurological symptoms similar (n = 5; $P = 1.0$ in both groups)
Mistral-C (2016)	65 Multicenter RCT	Efficacy and performance of Sentinel CEPD	Assessment: MRI baseline and 5–7 days NE baseline and 5–7 days	• Debris found in 100% of filters • Lesions found in 78% of patients • Numerically less new lesions (73% vs. 87%; $P = 0.31$) • Numerically lower lesion volume (95 mm^3 vs. 197 mm^3; $P = 0.171$) • ≥10 lesions only in control group ($P = 0.03$) • Sign reduction in patients with multiple lesions (20 vs. 0 %; $P = 0.03$) • Neurocognitive deterioration 4% vs. 27% ($P = 0.017$)
Deflect III (2015)	85 Multicenter RCT	Safety, efficacy, and performance of TriGuard HDH	Primary endpoint: in hospital procedural safety (death, stroke, disabling bleeding, acute kidney injury, major vascular complications) Assessment: MRI at 2–6 days NE at baseline, pre-discharge, 30-days	• Primary endpoint numerically lower (21.7% vs. 30.8%; $P = 0.34$) • Full coverage 89% • Per treatment population analysis: • Freedom from new lesions at discharge: 26.9% vs. 11.5%; P = not specified • Freedom from new lesions at 30 days: 11.5% vs. 9.1%; $P = 0.78$) • Numerically lower NIHSS at discharge (3.1 vs. 15.4%; $P = 0.16$)
REFLECT II (2020)	220 Multicenter RCT	Efficacy & safety of TriGuard 3	Assessment: MRI 2–5 days Death or stroke at 30 days NIHSS worsening 2–5 days	• Primary efficacy 45.7% vs. 54.3%; $P = 0.857$ • Full coverage 60% • Technical success 71%, • Numerically lower total lesion volume (215.4 mm^3 vs. 188.1 mm^3; $P = 0.405$) • Sign. more vascular complication in CEPD group, according to author TAVI associated (7% vs. 0%; $P = 0.04$) • Numerically higher event rate in CEPD group (15.9 vs. 7%; $P = 0.11$)

Abbreviations: DW-MRI, diffusion-weighted magnetic resonance imaging; MRI, magnetic resonance imaging; NE, neurological examination, NIHSS, National Institutes of Health Stroke Scale; RCT, randomized controlled trial; TAVI, transcatheter aortic valve implantation; VARC, Valve Academic Research Consortium; other — see Table 1

3 cerebral vessels. It is a single-wire nitinol frame and mesh filter with a pore size of 130 µm. DEFLECT III [11] was the first randomized multicenter trial for the first-generation TriGuard HDH including 85 patients. TriGuard HDH was shown to be safe and achieved full coverage of the brain arteries in 89% but failed to show a significant reduction in new lesions on DW-MRI in the intention-to-treat analysis when compared to the control group. In the per treatment group (subjects with complete brain vessel coverage), there was a trend toward greater freedom from new DW-MRI lesions (26.9% in the CEPD arm vs. 11.5% in the control arm) and an improved cognitive function in patients with CEPDs (65.4% vs. 30.4%; $P = 0.02$), but the explorative study was not powered to detect statistically significant effects on safety and efficacy outcomes. In a pooled analysis, including 142 subjects from DEFLECT I and III and the Neuro-TAVR (transcatheter aortic valve replacement) registry [12], there was a Valve Academic Research Consortium (VARC-2) defined significant reduction of in-hospital stroke (6% vs. 0%; $P = 0.05$), a reduced incidence of stroke as defined by worsening of the National Institutes of Health Stroke Scale (NIHSS) combined with new ischemic lesions on DW-MRI (0 vs. 19%; $P = 0.002$), and lesion volume on DW-MRI (315 + 620 mm^3 vs. 511 + 893 mm^3; $P = 0.04$), as well as an improved cognitive function favoring the protected groups.

TriGuard HDH was subsequently investigated once more within the REFLECT I trial, enrolling 258 patients. It met the safety endpoints but did not meet the predefined hierarchical composite effectiveness endpoint of all-cause mortality or any stroke at 30 days, Montreal Cognitive Assessment worsening at 30 days, or NIHSS worsening at 2–5 days, and total volume of cerebral ischemic lesions detected by DW-MRI at 2–5 days after TAVI compared with unprotected controls. Full coverage of the brain arteries was achieved in only 57%, and the trial was terminated early which led to the development of the next generation TriGuard 3 [13], providing an easier use and a larger, self-stabilizing filtration surface, which was further investigated in the multicenter, randomized REFLECT II trial [14]

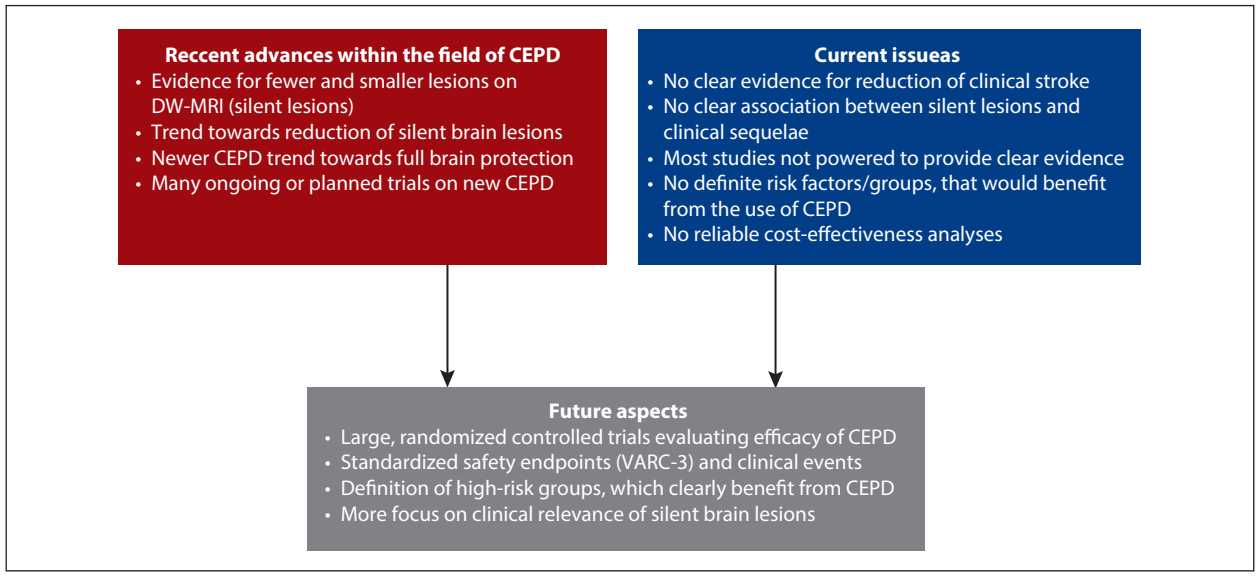

Figure 1. Recent advances and open questions
Abbreviations: see Tables 1 and 2

evaluating performance and safety in 220 TAVI patients. The trial met its safety endpoint (a composite of all-cause mortality, stroke, life-threatening or disabling bleeding, stage 2/3 acute kidney injury, coronary artery obstructions with subsequent intervention, major vascular complication, and valve-related dysfunction requiring intervention), defined by VARC-2, which was compared with a historical performance goal. However, there was a numerically higher number of life-threatening bleedings (5.7% vs. 0%; $P = 0.12$) and a significantly higher number of major vascular complications (7% vs. 0%; $P = 0.04$). Full coverage of the brain arteries was 60% and the primary hierarchical composite efficacy endpoint (including death or stroke at 30 days, National Institutes of Health Stroke Scale score worsening in hospital, and cerebral ischemic lesions on DW-MRI at 2 to 5 days) was not met with TriGuard 3 compared to the control group.

Investigational CEPD

Several CEPDs are being developed. These devices have different mechanisms of action and are in different stages of clinical evaluation.

The deflector device Embrella was studied in the non-randomized PROTAVI-C study including 93 patients [15] and showed a lower volume of new lesions on DW-MRI in the device group compared with the control group ($P = 0.003$). Nevertheless, new brain lesions were observed in 100% of the patients.

Another deflector device is the Embol-X CEPD (Edwards Lifescience, Irvine, CA, US). A randomized trial by Wendt et al. [16] evaluated 30 patients receiving Embol-X CEPD and showed significantly smaller lesion volumes in the supply region of the middle cerebral artery (33 mm^3 vs. 76 mm^3; $P = 0.04$), as well as in the vertebral and basilar artery territory.

PointGuard (Transverse Medical Inc., Denver, CO, US) is a complete cerebral embolic protection deflector system with a dynamic stabilization spring for positioning and minimizing debris migration. It provides full perimeter edge and sidewall conformity while providing maximum blood flow to the brain. The CENTER trial is currently investigating its performance and safety.

ProtEmbo (Protembis GmbH, Aachen, Germany) is another deflector device that is advanced through the left radial artery and, therefore, avoids the way along the carotid arteries, which are commonly heavily calcified in elderly patients. In the same way, it avoids interference with TAVI. The device has a low-profile design and has a very small pore size of 60 µm, hence protecting the brain from small-sized embolizing particles. The PROTEMBO SF trial is evaluating feasibility, safety, and efficacy of the ProtEmbo system for patients undergoing TAVI. First results are expected soon.

Emblok (Innovative Cardiovascular Solutions, LLC., Grand Rapids, MI, US) is an 11 F sheath device containing a 4 F pigtail catheter advanced through femoral access. It is a 125 µm pore-size nitinol filter system that allows the embolic filter and a radiopaque pigtail catheter to be advanced simultaneously through femoral access. It fits in various anatomies of the aorta with a diameter up to 35 mm. Currently, the system is available only for investigational use. The results of the clinical trial evaluating feasibility and safety are expected in the near future.

Further ideas for protecting the brain from embolization tend to include the protection of peripheral arteries and especially the renal arteries (Emboliner and Captis).

Results from initial studies which evaluate feasibility and safety are expected soon.

CURRENT ISSUES AND RECENT ADVANCES

Definition of standardized study endpoints

The incidence of postprocedural neurologic events and stroke is highly dependent on the definition, ranging from predominantly clinical to imaging-based definitions that include new lesions detected on DW-MRI without any neurocognitive alterations (silent strokes). As a result, stroke can be underreported as well as overreported within different trials. Depending on the assessment and on the definition applied, it is reported in around 5% when defining stroke based on clinical symptoms to >90% when focusing on silent lesions detected by DW-MRI [3, 17]. Systematic evaluation by an experienced neurologist can further increase the incidence [18].

Historically, there has been a lack of uniform definition which inhibited comparability. Recently, VARC-3 introduced updated definitions of neurologic events associated with TAVI, which represents a step towards standardization in future studies and provides harmonization with previous Neurologic Academic Research Consortium (NeuroARC) definitions.

According to VARC-3, stroke is classified as overt CNS (central nervous system) injury (NeuroARC type 1) with either ischemic stroke, hemorrhagic stroke, or stroke that is not otherwise specified. Covert CNS injury (NeuroARC type 2) is described by pathological evidence or by imaging. Neurologic dysfunction without CNS injury (NeuroARC type 3) is defined as transient focal neurological signs lasting <24 hours (transient ischemic attack) or delirium without CNS injury. Furthermore, periprocedural events are classified as acute (<24 hours) or subacute (24 hours–30 days) [19].

Assessment of stroke remains complex since neurological tests remain challenging in the elderly and could lead to false-positive or false-negative results. A neurologic assessment is recommended to be performed by an experienced neurologist to detect slight deviations. An assessment by a non-neurologist may still be acceptable in clinical practice. However, for clinical trials on CEPDs, VARC-3 clearly recommends neurologic assessment by an experienced neurologist.

The need for routine performance of MRI or a transcranial doppler examination is not yet clear. MRI usually detects 68%–100% of ischemic brain lesions but is limited to the time span after TAVI [4]. Procedural transcranial doppler ultrasound detects 100% of cerebral embolic signals, which mainly arise during valve deployment [20]. Studies, investigating the optimal method for detecting stroke using imaging are still missing.

Even though there is evidence for a reduction of new brain lesions and volume of new lesions, there is no clear evidence for prevention of clinical sequelae. The clinical impact of embolized debris detected by MRI is controversial, but silent infarction has been described to be associated with premature neurocognitive deterioration and dementia [21, 22]. Studies evaluating these effects should follow soon.

Risk factors for stroke

To date, there is no clear evidence on whether to use CEPDs for all patients, for specific groups at high risk, or for none of the patients undergoing TAVI. In clinical practice, CEPDs are often used in patients thought to be at high risk for cerebral embolism.

Risk factors for developing TAVI-related stroke include patient-related characteristics such as age, prior stroke, and atrial fibrillation, as well as procedure-related factors, such as long procedure time, rapid pacing, or valve repositioning. Whereas procedure-related factors are related to an increase in the risk of early stroke, patient-related risk factors are associated with late stroke (>10 days) [23]. Furthermore, there could be an increased risk for cerebral embolism in the bicuspid valve or valve-in-valve procedures. In addition, there are reports about different stroke rates for different valves [24] and the modulating effect of oral anticoagulation on preventing cerebral embolism during TAVI should be investigated in large studies.

Currently, however, conditions that could increase the risk for cerebral embolic events are still ill-defined. A preprocedural model for risk assessment to identify patient groups that would benefit most from CEPD is missing.

Reasons for stroke despite using CEPDs

Reasons for embolic events despite using embolic protection are multiple. One possible reason could be incomplete sealing due to specific features of the device or individual anatomy. Further reasons include an unprotected left vertebral artery which originates from the left subclavian artery and the fact that there is only one available filter size when focusing on the Sentinel device.

Second, since not only manipulation at the valve but also the placement of protection devices could mobilize different structures, this could be identified as a possible source for emboli or debris causing cerebral embolism [3, 25].

One additional mechanism for cerebral events that has been described is hemodynamic instability and the resulting hypotension during TAVI procedures, where CEPDs would not contribute to increased safety. Hemodynamic instability could arise, for example, in the case of rapid pacing in patients with reduced left ventricular ejection fraction and general anesthesia as a potential factor, increasing the number of neurological events. These mechanisms need to be studied in the future.

Cost-effectiveness

One point that needs to be elucidated in this context is cost-effectiveness, which is of importance since the

number of TAVI procedures is rapidly increasing and the procedure is expected to further expand into younger and lower-risk patient groups. Specifically for those patients, prevention of serious complications such as periprocedural stroke needs specific attention. The market for CEPDs is expected to increase rapidly and several trials on new CEPDs will follow soon. Since more than 50% of patients experiencing stroke are unable to return to work, and most of them end up with serious financial problems, sequelae such as permanent disability and psychosocial issues should be specifically taken into account [18, 26]. The benefit of preventing stroke should be balanced against the costs of the device. Since healthcare expenditures for periprocedural stroke with all its subsequent annual costs and psychosocial consequences could potentially tremendously exceed the costs of CEPDs, there should be evaluations on cost-effectiveness and the number needed to treat (NNT) from large, randomized trials.

Currently, analyses about cost-effectiveness and clear evidence for the benefit of routine use of CEPD are missing.

Future aspects for clinical trials on CEPD

Until now, there is limited evidence on the routine use of CEPDs in all patients, and clear recommendations on which patients might benefit from the use of CEPD are still lacking. The low event rate in most of the trials precludes definite conclusions as to the clinical benefit of CEPDs. Although evidence for efficacy has been provided by registries and pooled analyses [26, 27], no convincing evidence from large randomized controlled trials is currently available, and it seems that at least 3000 patients are needed for an adequately powered randomized controlled trial (RCT).

In addition, the time span for diagnosing TAVI-related stroke differs between the currently available studies and ranges between 24 hours and 30 days. Since not only the TAVI procedure but also new-onset atrial fibrillation or other conditions can lead to stroke, results may be confounded. Kahlert et al. [28] showed that most embolic events occur during valve implantation. Therefore, timing up to 7 or even 30 days could distort the rate of periprocedural stroke due to the impact of atrial fibrillation or the periprocedural management of oral anticoagulation.

Results of the large randomized PROTECTED TAVR (Stroke PROTECTion With Sentinel During Transcatheter Aortic Valve Replacement) trial (NCT04149535) are expected in 2022. The trial randomized 3000 patients to either the use of Sentinel CEPD or no use of CEPD with the primary endpoint of neurologist-assessed in-hospital stroke within the first 72 hours. The BHF PROTECT-TAVI (British Heart Foundation Randomised Trial of Routine Cerebral Embolic Protection in Transcatheter Aortic Valve Implantation, n = 7730, ISRCTN16665769) is set to compare TAVI with filter protection versus unprotected TAVI for the endpoint of any new stroke within 72 hours. These results will provide further important answers.

Besides this, there should be large studies on the effects and clinical sequelae of subclinical or silent strokes. Available data mainly focus on clinical stroke, whereas the clinical significance and long-term sequelae of asymptomatic lesions after TAVI have not been defined.

Third, most of the studies excluded patients with a very high risk for embolic events such as prior stroke, carotid artery disease, porcelain aorta, bicuspid valves, or valve-in-valve procedures. Future trials should include these high-risk groups so that clear evidence for the use of CEPD could be provided at least for specific patient groups.

New CEPDs are in development with a trend toward full-brain and even full-body protection. Access site, sheath size, and mesh pore size differ between these devices. The perfect protection device should protect the entire brain and offer easy delivery and positioning with stability throughout the whole procedure; it should be clinically effective and safe.

CONCLUSIONS

Whether to use CEPDs in all patients, in a selective group of patients, or in none of the patients remains a matter of debate. Although current results indicate a reduction in the number and size of silent lesions, hard evidence of clinical efficacy of CEPD during TAVI is still missing. Results from large RCTs are expected soon, and these will provide information on the effect of CEPDs in terms of clinical stroke after TAVI. The clinical relevance of protection from silent lesions of brain injury requires further studies.

In conclusion, currently available results from RCTs and observational trials show consistent device safety but clear evidence for routine use of CEPD during TAVI is still missing. Furthermore, available studies show substantial limitations and should be interpreted carefully. Large, RCTs will follow soon and will provide the essential information still missing.

Article information

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Biochemical and clinical evaluation of endothelial injury after distal or traditional transradial access in percutaneous interventions

Karol Momot[1], Maciej Zarębiński[2], Krzysztof Flis[2], Katarzyna Czarzasta[1], Liana Puchalska[1], Małgorzata Wojciechowska[1]

[1]Laboratory of Center for Preclinical Research, Department of Experimental and Clinical Physiology, Medical University of Warsaw, Warszawa, Poland
[2]Department of Invasive Cardiology, Lazarski University, John Paul II Independent Public Specialist Western Hospital, Grodzisk Mazowiecki, Poland

Editorials by
Ruzsa et al.,
Brilakis et al.

Correspondence to:
Maciej Zarębiński, MD, PhD,
Department of Invasive Cardiology,
Lazarski University,
John Paul II Independent Public Specialist Western Hospital,
Daleka 11, 05–825 Grodzisk Mazowiecki, Poland,
phone: +48 22 755 92 90,
e-mail: maciej@zarebinski.pl

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ABSTRACT

Background: Distal transradial access (dTRA) has been proposed as an alternative to traditional transradial access (TRA) in cardiac catheterization.

Aims: The study aimed to compare these two transradial approaches: TRA and dTRA in terms of clinical and biochemical aspects.

Methods: Two hundred patients who qualified for the elective coronary procedure were included. The patients were assigned to one of the groups depending on their vascular access. The groups were compared in terms of perceived pain using the Visual Analogue Scale (VAS), time of gaining access, need for conversion, and local complications. Additionally, in forty patients circulating endothelial injury markers: endothelin 1 (ET-1), interleukin 8 (IL-8), and soluble vascular cell adhesion molecule-1 (sVCAM-1) were assessed.

Results: Successful cannulation was obtained in 84 (100%) in the TRA group and in 98 (84%) subjects in the dTRA (P <0.001). dTRA was associated with higher level of pain perceived at the time of gaining vascular approach than TRA; median VAS score (interquartile range [IQR]): 4 (2–5) vs. 2 (2–4) (P = 0.04). The mean time (standard deviation [SD]) needed to cannulate the artery in dTRA was longer than in TRA: 81 (8) seconds vs. 50 (4) seconds (P = 0.04). ET-1 concentration was (SD) 2.08 (0.19) pg/ml [dTRA] vs. 2.00 (0.29) [TRA] pg/ml (P = 0.83); sVCAM-1: 12.71 (3.97) ng/ml vs. 12.86 (4.29) ng/ml (P = 0.98); IL-8: 8.81 (0.42) ng/ml vs. 9.15 (0.52) ng/ml (P = 0.62). Th number of complications after procedures did not differ between these two approaches.

Conclusions: Cannulation of dTRA is associated with a lower success rate and higher pain perceived. dTRA is not inferior to TRA when safety issues and vascular injury are considered.

Key words: percutaneous interventions, coronary angiography, radial access

INTRODUCTION

A vast increase in the number of percutaneous diagnostic and therapeutic procedures performed within the last two decades has led to the need for arterial access associated with decreased complication rates and shorter postoperative care. The advantages of radial artery access over femoral have been well proven. The radial cannulation, which is predominantly used in coronary interventions, may be complicated by occlusion of the artery. The occlusion rate increases with repeating interventions. The distal transradial access (dTRA) (Figure 1) via the anatomical snuffbox decreases this complication rate even more, and it has been proposed as an alternative to

WHAT'S NEW?

This study provides a wider perspective on distal transradial access in percutaneous interventions. This report is the first one that compares transradial approaches in terms of endothelial injury. We list advantages and disadvantages of distal and traditional transradial access. We confirm that new distal transradial access should be widely used in invasive cardiology and radiology.

Figure 1. Distal transradial access

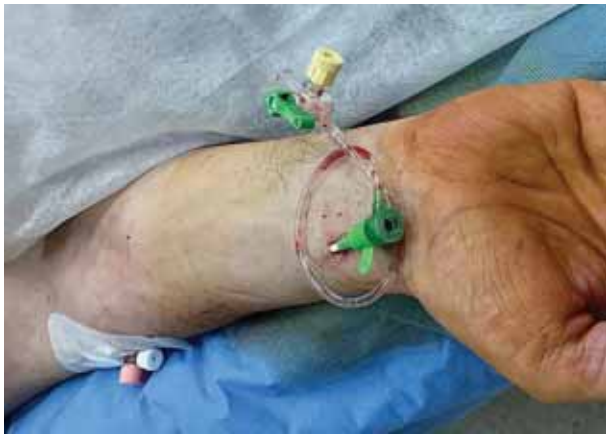

Figure 2. Traditional transradial access

traditional transradial access (TRA) (Figure 2) in percutaneous interventions. The anatomical snuffbox is located on the radial side of the wrist, it is bounded by the tendon of the extensor pollicis longus posteriorly and of the tendons of the extensor pollicis brevis and abductor pollicis longus anteriorly. The radial artery crosses the floor that is formed by the scaphoid and the trapezium bones [1].

First studies pointed out that dTRA was associated with an increased rate of cannulation failure, prolonged duration of cannulation, increased number of attempts and skin punctures compared to the TRA [2]. This was mainly due to the smaller diameter of the vessel, tortuosity of the radial artery in the area of the anatomical snuffbox, and operators' lack of experience. There are no data comparing the two accesses in terms of endothelial damage. During percutaneous intervention and hemostatic compression, mechanical stress on the cannulated vessels occurs. It is caused by the needle puncturing the artery wall, the sheath inserted in the lumen of the artery, and external pressure of the dressing. Studies show that after exposure to stress factors, the endothelium releases numerous substances like cytokines which can be assessed in blood plasma [3–9]. We believe that these substances are also released during percutaneous interventions.

In this study, concentrations of markers of endothelial injury were measured. This is a novel perspective as it is the first comparison of the analyzed percutaneous approaches based on biochemical assessment. The markers: endothelin 1 (ET-1), interleukin 8 (IL-8), and soluble vascular cell adhesion molecule-1 (sVCAM-1) were chosen based on relevant literature.

METHODS

Study patients

Two hundred adult patients, scheduled for elective coronary angiography or angioplasty, were recruited. Procedures were performed between November 2020 and April 2021. Participants signed written informed consent forms. The study was approved by the local Ethics Committee (no. KB/167/2020). Patients with estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2, dialyzed, with coronary artery bypass grafting (CABG), and/or diagnosed with active cancer were not included in this study. Based on research carried out by Koutouzis et al. [2] and our experience with the lack of distal pulse and the need for conversion from distal to traditional access, all qualified patients were allocated, by block randomization at a 3:2 ratio, into two groups of 120 and 80 patients receiving a dTRA and TRA approaches, respectively. Four subjects out of 120 initially assigned to the dTRA approach did not present a palpable pulse in an anatomical snuffbox before the procedure, and they were reassigned to the TRA group without any attempts to cannulate dTRA. Therefore, operators attempted to obtain 116 distal approaches and 84 traditional approaches. After a failed attempt to cannulate dTRA, these subjects were converted to TRA and were included in a third group named conversion (n = 18). Thus, the final dTRA group included 98 subjects. Demographic data of the patients are presented in Table 1. In 40 random patients (20 from the dTRA group and 20 from the TRA group) after the dressing removal, blood from the cephalic vein was collected and plasma concentrations of ET-1, IL-8, sVCAM-1 were determined using the enzyme-linked immunoassays (ELISA).

Table 1. Demographic data

Characteristics	TRA group (n = 84)	dTRA group (n = 98)	Conversion group (n = 18)	*P*-value
Age, years, mean (SD)	67 (10)	65 (10)	63.3 (9)	0.20
Male sex, n (%)	53 (63)	63 (64)	8 (44)	0.31
BMI, kg/m^2, mean (SD)	29.4 (5.7)	29.0 (5.2)	28.6 (6.4)	0.83
Obesity, n (%)	29 (35)	30 (31)	5 (28)	0.65
Current smoking, n (%)	40 (48)	35 (36)	6 (33)	0.21
Lipid disorders, n (%)	38 (45)	44 (45)	6 (33)	0.60
Diabetes or prediabetes, n (%)	30 (36)	27 (28)	4 (22)	0.35
Hypertension, n (%)	58 (69)	73 (74)	12 (66)	0.54
CKD, n (%)	4 (5)	9 (9)	1 (6)	0.36
Medications				
ASA, n (%)	40 (48)	62 (63)	10 (56)	0.13
ADP/P2Y inhibitors, n (%)	13 (15)	23 (23)	3 (17)	0.38
NOAC, n (%)	11 (13)	12 (12)	2 (11)	0.96
Statins, n (%)	38 (45)	44 (45)	6 (33)	0.60

Abbreviations: ADP, adenosine diphosphate; ASA, acetylsalicylic acid; BMI, body mass index; CKD, chronic kidney disease; dTRA, distal transradial access; NOAC, non-vitamin K antagonist oral anticoagulants; TRA, traditional transradial access

Procedure

The procedures of coronary interventions without ultrasound guidance were performed by European Association of Percutaneous Cardiovascular Interventions (EAPCI) certified operators, using radial access in more than 95% of routine procedures. The sheath size used for all the procedures was 6 F. Time needed to gain vascular access was assessed. The amount of injected contrast and the total radial dose were recorded. After the procedure, a pressure dressing was applied to the puncture site. The dressing was removed after 120 minutes. The puncture site was assessed for the presence of hematoma and pulse. After the removal of the dressing, 10 ml of blood from the cephalic vein was collected into tubes with EDTA-K2 anticoagulant and then centrifuged. Samples with obtained plasma were immediately frozen and stored at –20°C until the moment of biochemical assessment. Plasma concentrations of markers were analyzed using ELISA: IL-8 Human ELISA Kit (KHC0081; Thermo Fisher Scientific, Inc., Waltham, MA, US), Human sVCAM-1/CD106 ELISA Kit (MBS2505831; MyBioSource, San Diego, CA, US), and Endothelin-1 Quantikine ELISA Kit (DET100; R&D Systems, Inc., Minneapolis, MN, US). Each ELISA test was carried out in accordance with the instructions provided by the manufacturer.

Statistical analysis

Quantitative variables are presented as medians (interquartile range [IQR]) or means (standard deviation [SD]). The ANOVA test (normal distribution) and the Kruskal–Wallis H test (non-normal distribution) were performed in the comparison of numerical variables between the three groups. Appropriate *post-hoc* tests were then performed (Dunn and Tukey tests, respectively). Student t-test (normal distribution) and the Mann–Whitney U test (non-normal distribution) were used to perform inter-group comparisons. Equality of variances was assessed by Levene test. Categorical variables are expressed as numbers and percentages and compared using the χ^2 test. Statistical data were considered significant with a *P*-value <0.05. All statistical analyses were performed using Statistica 13 software.

RESULTS

The success rate of obtaining a vascular approach in the dTRA group was 84% and 100% in the TRA group (*P* <0.001). In eighteen dTRA subjects (16%) operators failed to gain vascular access. The approach was changed to TRA, and then access was successfully gained. These eighteen subjects were included in the third group named "conversion". Data on the procedure: the mean time required to gain the access, local complications, pain when gaining the vascular approach and during the maintenance of pressure dressing are presented in Table 2. The results of the biochemical evaluation are presented in Figure 3. Regardless of the approach, concentrations of endothelial markers were not correlated with smoking, diabetes, hypertension, kidney disease, or coronary disease. Subjects treated with statins had lower ET-1 concentration (SD) than subjects without statin therapy, irrespective of the access: 1.63 (0.24) pg/ml vs. 2.33 (0.21) pg/ml (*P* = 0.04). Subjects with obesity had higher levels of IL-8 than those without obesity, regardless of the approach (*P* = 0.04) (Figure 4).

DISCUSSION

Markers of endothelial injury

At the moment of publication, several studies have compared these two approaches. However, this research is the first one that provides a closer look at them in terms of endothelial injury. The aim was to evaluate selected markers of vascular injury, dysfunction, and inflammation between patients after distal transradial access and traditional transradial access. It is assumed that during percutaneous interventions endothelial injury, inflammation, and dysfunction are caused by vascular sheath and catheter insertion and hemostatic compression. These factors are closely linked to mechanical stretch, shear stress, and external pressure,

Table 2. Characteristics of procedures

Characteristics	TRA group (n = 84)	dTRA group (n = 98)	Conversion group (n = 18)	*P*-value
Time needed to gain vascular access, seconds, mean (SD)	50 (4)[1]	81 (8)	277 (51)[2, 3]	<0.001
Hematoma after procedure, n (%)	5 (6)	12 (12)	4 (22)	0.09
Radial artery occlusion after procedure, n (%)	2 (2)	3 (3)	1 (6)	0.78
VAS 1 score, median (IQR)	2 (2–4)	4 (2–5)	4 (2–5)	0.04
VAS 2 score, median (IQR)	2 (1–4)	2 (1–4)	2 (2–4)	0.57
Revascularization with stent implantation, n (%)	34 (40)	40 (41)	5 (28)	0.57
Radial dose during procedure, mGy, mean (SD)	958 (115)	888 (79)	630 (161)	0.37
Amount of contrast during procedure, ml, mean (SD)	110 (6.6)	117 (6.8)	101 (12.4)	0.50

[1]TRA vs. dTRA, *P* = 0.04. [2]dTRA vs. Conversion, *P* <0.001. [3]TRA vs. Conversion, *P* <0.001

Abbreviations: VAS, Visual Analogue Scale; VAS 1, pain at the time of gaining vascular approach; VAS 2, pain during the maintenance of pressure dressing; other — see Table 1

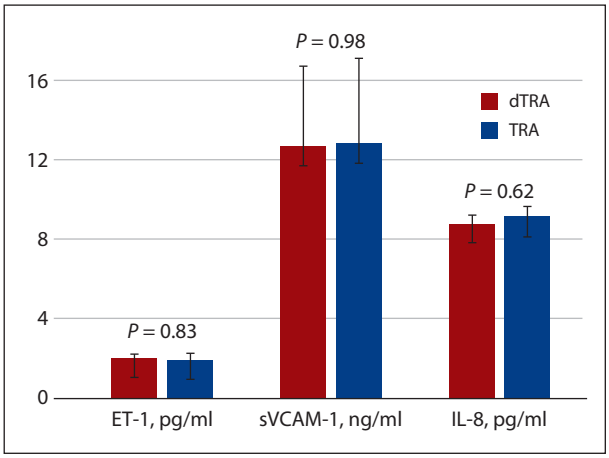

Figure 3. Biochemical evaluation of endothelial markers depending on the approach, 15 minutes after removal of hemostatic compression

Abbreviations: ET-1, endothelin 1; IL-8, interleukin 8; sVCAM-1, soluble vascular cell adhesion molecule-1; other — see Table 1

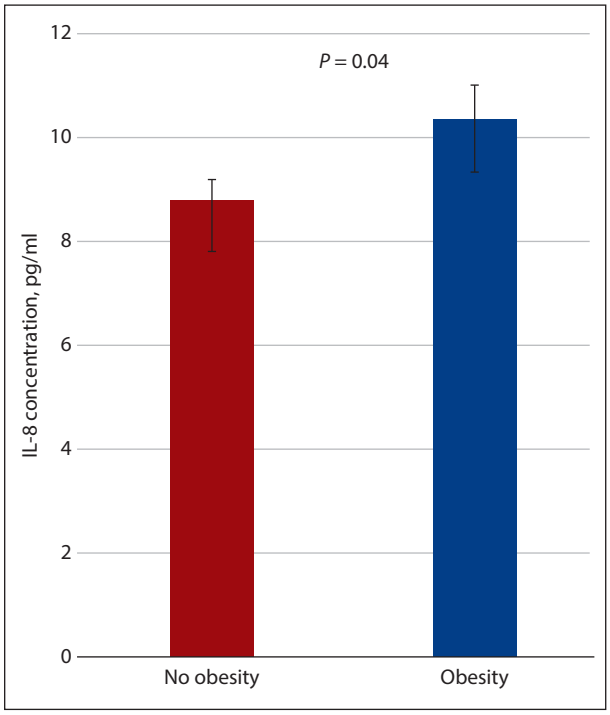

Figure 4. Interleukin-8 concentration regardless of the approach, 15 minutes after removal of hemostatic compression

Abbreviations: see Figure 3

which are factors stimulating release of endothelial injury markers in vitro. The choice of these markers was based on the literature found via PubMed, ScienceDirect, Scopus, or Google Scholar.

Endothelin 1

ET-1 is produced mainly by vascular endothelial cells (ECs), and it is considered the most common ET in humans. This particle is frequently assessed in diagnostics of endothelial dysfunction, injury, or inflammation. At the normal state, ET-1 is mainly secreted abluminally towards the vascular smooth muscles, and its levels in the blood are fairly low. However, in the case of endothelium stimulus, ET-1 is released into the blood from ECs [6, 10]. The mechanical strain of the vessel damages the vascular wall and stimulates secretion of ET-1 from ECs [11, 12]. Previous studies also indicate shear stress as a factor promoting ET-1 production [7, 8].

Soluble vascular cell adhesion molecule-1

sVCAM-1 is a circulating particle derived from damaged or activated ECs [3]. Damaging the endothelial glycocalyx of vessel walls leads to an increase of sVCAM-1 levels [13]. Shear stress is also the factor that stimulates sVCAM-1 from ECs [9]. Elevation of blood pressure activates the expression of adhesion molecules [14]. Prolonged mechanical wall stretch promotes VCAM-1 gene expression in ECs [15]. sVCAM-1 plays an important role in accelerating atherosclerosis by facilitating the attachment of inflammatory cells to the vascular endothelial wall and promoting their subsequent migration through the endothelium [16].

Interleukin 8

IL-8 is a proinflammatory chemokine produced by ECs. IL-8 is stored inside ECs, and ET-1 promotes releasing this chemokine *in vitro* [17]. Elevated levels of IL-8 have been found in the area of the injured endothelium [5]. The IL-8 concentration starts to increase 1 hour after the exposure to the stress factor, and it is caused by IL-8 gene expression [18]. External mechanical pressure on the ECs significantly raises IL-8 secretion from these cells *in vitro* [4]. IL-8 levels are increased as a result of many inflammatory conditions, so careful exclusion criteria for patients are required. Platelet-derived microparticles (PMPs), which are produced in the case of shear stress, induce IL-8 secretion by ECs [19]. IL-8 is a proinflammatory cytokine with atherogenic effects, it accelerates the movement of neutrophils and T lymphocytes under the endothelium and promotes monocyte adhesion to the vascular wall.

General

There were no statistically significant differences between the dTRA and TRA groups in the number of cases of hematoma, lack of the distal pulse after interventions, the mean amount of contrast used, and radial dose. The findings were similar to the results in other studies [2, 20]. Researchers point out that the cannulation time was longer in the dTRA group, which was also in line with our observations [20]. In our research, the level of pain at the time of gaining the vascular approach was significantly higher in the dTRA and conversion groups. The longer time of cannulation and more severe pain during the procedure can be probably explained by less experience of operators in using dTRA. Additionally, in some subjects, inexperienced operators had to make conversions when using dTRA. Probably anatomical characteristics of the radial artery in the snuffbox (tortuosity and small diameter) make the distal approach more complicated and require more experience from operators. In line with the results of other studies, operators should practice gaining a distal approach to obtain the same successful cannulation rate, level of pain, and time needed to gain access as in TRA [21, 22]. The advantage of dTRA postulated in other studies is shorter hemostatic compression after the procedure, but in the presented report it was identical in all patients as we wanted to provide the same conditions for biochemical and pain assessment [20, 23]. dTRA offers two more forearm approaches to evaluate, and this may reduce the need for femoral artery cannulation. If the radial artery occlusion has occurred during TRA, dTRA provides a possibility to recannulate the occluded radial artery [23]. dTRA offers the option to have the patient's left hand close to the right groin, which is more comfortable for the patient and the operator. dTRA is also beneficial for right-handed patients whose dominant upper limb is without immobilization during hemostatic compression [1]. The radial artery gives branches before entering the anatomical snuffbox; therefore, occlusion after dTRA is related to a smaller area of ischemia than after TRA. Since a standard sheath size of 6 F allows most coronary interventions, dTRA may probably serve as a good choice also for complicated high-risk procedures. The safety cannulation with a larger sheath has not been tested in our study, but with the use of thin-walled sheaths, it seems quite possible to apply advanced intravascular techniques, which require a larger lumen. Januszko et al. showed that TRA, as opposed to femoral access, is related to a higher risk of coronary artery perforation in patients treated with rotational atherectomy [24]. As this complication may also refer to using dTRA, future studies should be conducted.

There were no differences between dTRA and TRA in the plasma markers of endothelial injury. This means that in both groups the endothelial damage was similar and that in terms of biochemical assessment, dTRA is at least as safe as TRA. Regardless of the approach, elevated IL-8 levels in obese patients suggest that obesity may be connected with greater damage to the endothelium, but it cannot be excluded that IL-8 is constantly elevated in obese subjects, which would be in agreement with other studies [19]. Furthermore, patients treated with statins have significantly lower levels of ET-1 than patients without this treatment, which confirms that statin therapy reduces vascular inflammation [25].

The main limitations of this study were the lack of biochemical evaluation before percutaneous intervention and small sample size.

CONCLUSIONS

There were no differences between dTRA and TRA in the quotative markers of local endothelial injury. dTRA was more painful for the patient during the cannulation, but the difference should diminish as the operators gain experience. Consequently, the choice of dTRA is as good as that of TRA. Considering dTRA advantages listed in the discussion, it should be widely used in percutaneous interventions in invasive cardiology, neurology, and radiology.

Article information

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Clinical characteristics of Kawasaki disease in Polish children: A retrospective study

Anna Smorczewska-Kiljan[1], Magdalena Marszał[1], Joanna Friedman-Gruszczyńska[2], Anna Wieteska-Klimczak[1], Janusz Książyk[1], Maciej Jaworski[3], Piotr Buda[1]

[1]Department of Pediatrics, Nutrition, and Metabolic Diseases, The Children's Memorial Health Institute, Warszawa, Poland
[2]Department for Pediatric and Congenital Heart Surgery, The Children's Memorial Health Institute, Warszawa, Poland
[3]Department of Biochemistry, Radioimmunology and Experimental Medicine, The Children's Memorial Health Institute, Warszawa, Poland

Correspondence to:
Piotr Buda, MD, PhD,
Department of Pediatrics, Nutrition, and Metabolic Diseases,
The Children's Memorial Health Institute,
Dzieci Polskich 20,
04–736 Warszawa, Poland,
phone: +48 22 815 12 14,
e-mail: p.buda@ipczd.pl

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ABSTRACT

Background: Kawasaki disease (KD), an acute, generalized vasculitis, is associated with an increased risk of coronary heart disease and is the most common cause of acquired heart disease in childhood. The incidence of KD is increasing worldwide.

Aims: Our study aims to analyze KD's clinical course in children and to evaluate risk factors for persistent changes in coronary vessels after 6–8 weeks of treatment.

Methods: The retrospective analysis included patients with KD hospitalized in a single tertiary care hospital. The diagnosis, as well as treatment, were based on the current worldwide treatment standards. The clinical course, selected laboratory parameters, the treatment effect, and following cardiac complications were analyzed in different age groups.

Results: In the years 2006–2019, 140 patients aged from two months to 16 years: 52 girls and 88 boys, were diagnosed with KD. Coronary artery aneurysms (CAA) at weeks 6–8 of disease were found in 16% of patients. Boys and infants were more likely to develop aneurysms at weeks 6–8 of the disease ($P = 0.045$; $P = 0.03$; respectively). The CAA frequency was related to the atypical course ($P = 0.02$), late diagnosis ($P = 0.04$), presence of changes in the coronary arteries at the time of diagnosis ($P < 0.001$), immunoglobulin resistance ($P = 0.002$), a lower hemoglobin concentration ($P < 0.001$), and a higher platelet count ($P = 0.02$). There were 28% of patients resistant to first-line time treatment. In this group, we found CAA in 31% of children.

Conclusions: We found that late diagnosis, low hemoglobin level, high platelet count, CAA presence at diagnosis, atypical course of KD, and resistance to intravenous immunoglobulins are predictors of CAA after 6–8 weeks in KD patients.

Key words: acquired heart disease, coronary artery aneurysm, Kawasaki disease, vasculitis

INTRODUCTION

Kawasaki disease (KD) is an acute, self-limiting, generalized, small to medium-sized vessel vasculitis, most commonly occurring in children under five years of age. It was described for the first time in 1967 by Tomisaku Kawasaki [1, 2]. This disease is presently the most common cause of acquired heart disease in childhood. It is associated with an increased risk of coronary heart disease [3–6]. The etiology of the disease remains unknown. It is suggested that in genetically predisposed persons, there is an incorrect activation of the immune system and oligoclonal immune response to bacterial, viral, or other unidentified environmental factors, which results in damage of vascular endothelial cells and necrotizing vasculitis [4]. The incidence in the Japanese population is 138 cases/100 000 children under the age of five years. In Great Britain, the number of new cases has doubled recently and is now 8.1/100 000 [7]. The disease is most common in young children, with most patients aged between six months and five years old, with a predominance in males (1.5:1) [4, 5, 7].

WHAT'S NEW?

Kawasaki disease (KD), an acute, generalized vasculitis, is the most common cause of acquired heart disease in childhood. Epidemiological data for KD in Poland are still unknown. Only a few single-center studies have been published. To our knowledge, this retrospective single-center study is based on the largest population of children with KD from Poland. Coronary artery aneurysms (CAA) are one of the main complications of KD. Literature data indicate that many predictors of CAA have been previously identified. We found three significant, independent risk factors for CAA after 6–8 weeks in KD patients: late diagnosis, low hemoglobin level, and the presence of CAA at diagnosis.

The diagnosis of KD is based on clinical criteria. The course of the disease is acute, three-phase, and self-limiting [4–6]. Since the inflammatory process affects all vessels, the clinical manifestation can involve many systemic symptoms. According to the American Society of Cardiology (ASC)/American Heart Association (AHA), the typical form of KD is defined as the occurrence of fever and at least four clinical symptoms that are the criteria for diagnosis [3, 4]. The incidence of atypical forms is increasing. Sometimes the only clinical sign may be fever and abnormalities in laboratory tests, which can cause diagnostic errors. The diagnosis of atypical KD can be also confirmed by the presence of changes in echocardiography.

The main complication of the disease is coronary artery lesions. Risk factors for the development of coronary artery aneurysms (CAA) were previously reported in the medical literature. The risk of permanent changes in coronary arteries in untreated cases is up to 25%, and it decreases significantly (4%) if patients are adequately treated [9, 10]. Standard treatment for KD is based on an infusion of 2 g/kg immunoglobulin and orally administered acetylsalicylic acid optimally implemented before day 10 of the disease. Approximately 10%–20% of patients are resistant to this type of treatment (no resolution of fever, no or only slight decrease in inflammation parameters) [3, 4, 11]. In such cases, re-treatment of intravenous immunoglobulins (IVIG) and/or use of immunosuppressive drugs (glucocorticosteroids, cyclosporin, biological treatment) are considered [4–6, 12].

Our study aims to analyze KD's clinical course in patients hospitalized in our department and to evaluate risk factors for persistent changes in coronary vessels after 6–8 weeks of treatment.

METHODS

The retrospective analysis included patients with Kawasaki disease hospitalized in the Department of Pediatrics, Nutrition, and Metabolic Diseases of the Children's Memorial Health Institute in Warsaw from 2006 to 2019. Patients were referred to our hospital due to persistent fever with high parameters in the acute phase. In all patients, the diagnosis of KD was made based on the AHA criteria: classic KD was defined as the presence of fever for at least 5 days, together with at least 4 of the 5 following principal clinical features. The diagnosis of atypical KD was established in children with prolonged unexplained fever, fewer than 4 of the principal clinical findings, and compatible laboratory or echocardiographic findings [4]. At the time of diagnosis, all patients underwent basic laboratory tests, chest X-rays, and echocardiography (ECHO). ECHO included an assessment of cardiac function, measurements of internal diameters, and Z-scores of coronary arteries that were performed according to the methodology described by Lopez et al. [13]. CAA were defined using z-score classifications: coronary artery aneurysms (z-score >2.5), no coronary artery aneurysms (z-score <2.5). Dilatation of coronary aneurysm defined using the AHA criteria (2 <z-score <2.5) was not included in the analysis (detailed characteristic of coronary abnormalities is ongoing).

Differential diagnosis was performed in all children. Children with other causes of systemic inflammation were excluded from the study.

Our patients were divided into age groups (under 12 months of age, 1–5 years, over five years of age) and clinical type (atypical vs. typical).

All patients were treated with empirical antibiotic therapy and an infusion of intravenous immunoglobulins at a dose of 2 g/kg body weight with orally administered acetylsalicylic acid (ASA) at 30–100 mg/kg body weight/day. The lack of effect of the first-line treatment (resistance to IVIG) was defined as the persistence of fever and acute phase parameters elevation 36 hours after the end of IVIG infusion. In some patients with significant risk factors for resistance to IVIG (age less than one year, elevated inflammatory parameters, liver dysfunction, hypoalbuminemia, anemia, heart failure, dilation of the coronary arteries from baseline echocardiography), and in severely ill patients, glucocorticosteroids (GCS) were administered together with the first infusion of IVIG. Because using GCS in children with KD is still controversial and varies depending on individual recommendations [4–6, 12], the decision for treatment with GCS was made in each case based on the most recent recommendations. IVIG was re-transfused with or without GCS in patients with no effect of first-line treatment. Echocardiography at weeks 6–8 of disease was performed in all patients.

The clinical course, selected laboratory parameters, the treatment effect, and following cardiac complications were analyzed in different age groups.

Statistical analysis

Statistica v. 10 (StatSoft Inc., Tulsa, OK, US) was used for statistical calculations. The Shapiro-Wilk test was used for assessing departures of analyzed variables from the Gaussian distribution. Continuous variables were presented as median (interquartile range [IQR]). Categorical variables were presented as the number of patients. The Mann-Whitney test was used for quantitative variables to compare between two studied groups. The χ^2 test was used to examine differences between categorical variables. Univariable and multivariable logistic regression was performed to assess significant predictors of coronary artery aneurysms. Initially, all variables were included in the model. A backward stepwise procedure was carried out for the removal of nonsignificant factors. This model was adopted as the final one. A *P*-value of less than 0.05 was considered significant.

Institutional ethics committee approval was not required as this was a retrospective observational study.

RESULTS

In the years 2006–2019, 140 patients with KD aged from two months to 16 years (median 2.50 years), 52 girls and 88 boys, were hospitalized in our department. In the group of infants (under 12 months), there were 32 children, in the group between 1 and 5 years old — 79 children, over 5 years — 29 children.

The patients were also divided into a group with a typical disease course — 93 (75%), 39 girls, 54 boys, and a group with atypical patients — 47 (25%), 13 girls, 34 boys.

Apart from fever, the most common symptoms found in the whole group were skin lesions and conjunctivitis (85.7%), followed by mucosal lesions (79.3%), swelling of the hands and feet (62.9%), and lymphadenopathy (63.4%).

Tables 1–2 show that selected clinical and laboratory parameters in patients with coronary lesions persist at weeks 6–8 of disease compared to the group with normal echocardiography during this period. Boys and infants were more likely to develop aneurysms at weeks 6–8 of disease ($P = 0.045$; $P = 0.03$, respectively). Their frequency is also related to the atypical course ($P = 0.02$), late diagnosis ($P = 0.04$), presence of changes in the coronary arteries at the time of diagnosis ($P < 0.001$), immunoglobulin resistance ($P = 0.002$), a lower hemoglobin value ($P < 0.001$), and a higher platelet value ($P = 0.02$). Statistically significant differences were presented using box plots (Supplementary material, *Figures S1–S5*). Uni- and multivariable logistic regression analysis are presented in Tables 3 and 4.

In 16 patients with predisposing factors to IVIG resistance (4 girls, 12 boys), glucocorticosteroids were used together with the first infusion of IVIG (Figure 1). There were 39 (28%) patients with resistance to first-line treatment, 35 out of 124 treated with IVIG only (28%), and 4 out of 16 treated with IVIG plus GCS (25%). We found CAA in 12/39 (31%) children. There was no statistically significant relationship between the use of steroids and the occurrence of dilated coronary arteries at weeks 6–8 of disease in the whole group. All IVIG-resistant patients were re-infused with IVIG 2 g/kg, six patients received GCS with a repeated infusion of IVIG. At the time of diagnosis, an aneurysm of the coronary vessels (z-score >2.5) was found in 32 patients (22.9%), the highest rate was in the under-12-month-old group (14/32 — 43.8%). CAA at weeks 6–8 of disease was found in 22/140 (16%) patients. In patients treated only with IVIG infusions, changes in the coronary arteries were found in 18 out of 118 cases (15%). In the group in which GCS was added to the treatment (with the first or second IVIG), changes in the coronary arteries at weeks 6–8 were found in 4 out of 22 cases (18%) (Figure 1).

DISCUSSION

The incidence of KD is increasing worldwide [14–16]. Epidemiological data for KD in Poland are still unknown. Only a few single-center studies have been published [17–22]. Although it is a single-center retrospective study, to our knowledge, it is based on the largest population

Table 1. Comparison of clinical parameters in the group of patients with coronary artery aneurysms (CAA) persisting at 6-8 weeks of disease to the group with no CAA

		No CAA at weeks 6–8 (n = 118)	CAA at weeks 6–8 (n = 22)	*P*-value
Day of diagnosis	Median (IQR)	8.0 (6.0–10.0)	9.5 (8.0–12.0)	0.04
Age, years	Median (IQR)	2.5 (1.5–4.5)	1.3 (0.8–1.8)	0.004
IVIG	Sensitive, n (%)	91 (77)	10 (45)	0.002
	Resistant, n (%)	27 (23)	12 (55)	
GCS	No, n (%)	81 (69)	15 (68)	0.97
	Yes, n (%)	37 (31)	7 (32)	
Sex	Male, n (%)	70 (59)	18 (82)	0.04
	Female, n (%)	48 (41)	4 (18)	
Clinical course	Classical, n (%)	83 (70)	10 (45)	0.02
	Atypical, n (%)	35 (30)	12 (55)	
ECHO at diagnosis	Normal, n (%)	102 (86)	6 (27)	<0.001
	Z-score >2.5, n (%)	16 (14)	16 (73)	

Abbreviations: CAA, coronary artery aneurysms; other — see Figure 1

Table 2. Comparison of laboratory parameters in the group of patients with coronary lesions persisting at 6–8 weeks of disease to the group with no coronary artery aneurysms (CAA)

	No CAA at weeks 6–8	Median (IQR)	CAA at weeks 6–8	Median (IQR)	*P*-value	Median difference
PCT, ng/ml	n = 81	0.79 (0.35–2.29)	n = 18	0.815 (0.200–5.510)	0.55	-0.025
ESR, mm/h	n = 104	68.5 (48–92)	n = 18	70 (48–118)	0.40	–1.5
CRP, mg/dl	n = 117	9.95 (5.61–15.3)	n = 21	13.5 (4.56–19.80)	0.59	–3.56
Leukocytosis, 10^3/µl	n = 118	16.1 (11.2–20.5)	n = 22	16.1 (14.2–20.5)	0.36	0
% of neutrophils	n = 108	59 (48–67)	n = 22	49 (45–64)	0.09	10
Hb, g/dl	n = 118	10.45 (9.6–11)	n = 22	9.3 (8.7–10.2)	<0.001	1.15
PLT, K/µl	n = 118	425 (315–518)	n = 22	528 (356–818)	0.02	–103
Na, mmol/l	n = 113	138.0 (136–140)	n = 22	137 (136–140)	0.56	1
Albumin, g/l	n = 104	34 (30–37)	n = 22	32.3 (29.8–34.8)	0.15	1.7
NT-proBNP, pg/ml	n = 37	1202 (352–3110)	n = 9	2104 (521–4223)	0.78	–902

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; NT-proBNP, N-terminal pro-B natriuretic peptide; PCT, procalcitonin; PLT, platelets; other — see Figure 1 and Table 1

Table 3. Univariable logistic regression analysis

	OR (95% CI)	*P*-value
Age, years	0.736 (0.550–0.986)	0.04
Day of diagnosis	1.115 (1.002–1.241)	0.04
Hemoglobin, g/dl	0.358 (0.203–0.632)	<0.001
Platelets, K/µl	1.003 (1.000–1.005)	0.02
Female sex	0.528 (0.278–1.006)	0.05
cKD, typical	0.557 (0.339–0.915)	0.02
CAA at admission, presence	4.865 (2.640–8.966)	<0.001
IVIG, resistance	1.925 (1.168–3.170)	0.01

Abbreviations: CI, confidence interval; cKD, classical Kawasaki disease; OR, odds ratio; other — see Figure 1

Table 4. Multivariable logistic regression analysis

	OR (95% CI)	*P*-value
Hemoglobin, g/dl	0.386 (0.184–0.808)	0.01
Day of diagnosis, days	1.159 (1.011–1.330)	0.04
CAA at admission, presence	4.280 (2.211–8.285)	<0.001

Abbreviations: see Figure 1 and Table 3

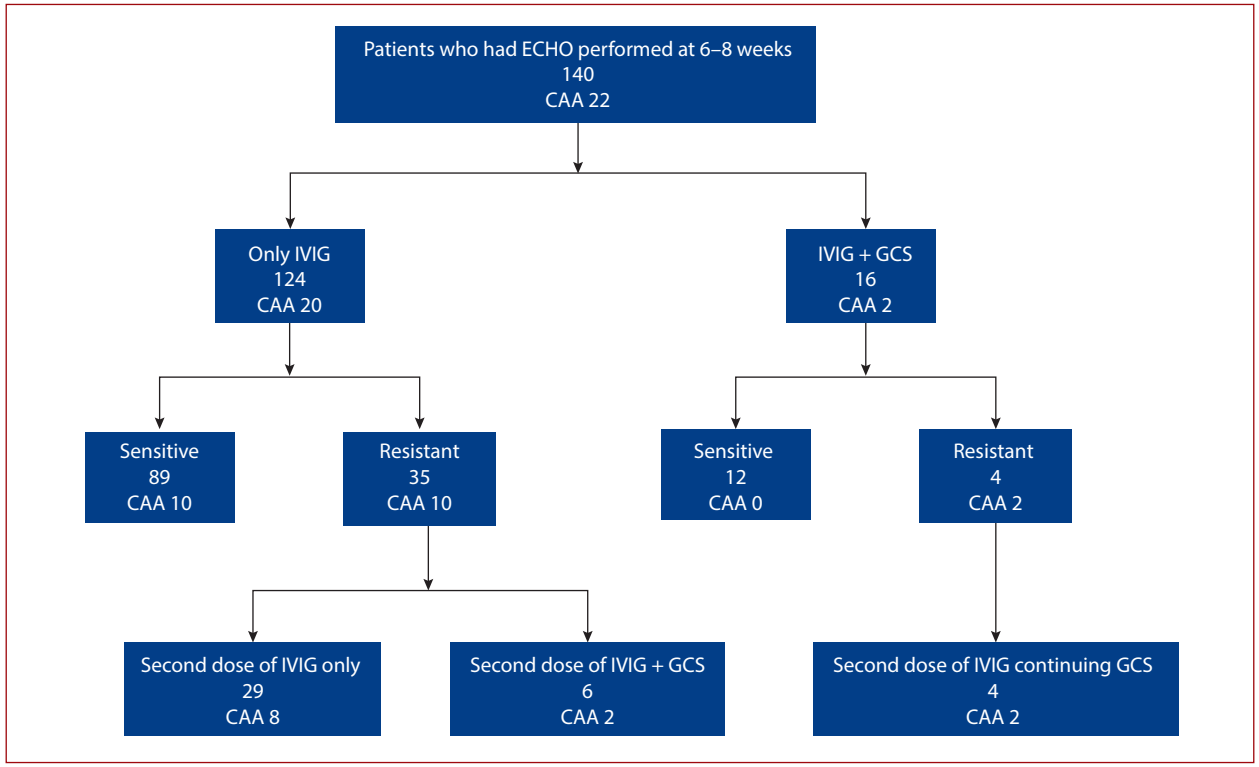

Figure 1. Treatment regimen in patients who underwent echocardiography at weeks 6–8

Abbreviations: CAA, coronary artery aneurysms; ECHO, echocardiography; IVIG, intravenous immunoglobulins; GSC, glucocorticosteroids

of children with KD from Poland. It is worth emphasizing that all patients came from Poland (particularly the Masovian Voivodeship), and there were no ethnic differences (homogeneous Caucasian population). Our genetic studies revealed that polymorphisms of genes *KIF25*, *PTRPJ*, *SPECC1L*, and *RNP2* might be linked with KD incidence in Polish children [23].

Our data confirm a higher incidence in males patients and in children under 5 years of age, which is consistent with literature data. We found that classical KD is more common than atypical in each age group. Atypical KD mainly occurs in infants. Our data suggest that the most common symptoms of KD are fever (99%), skin lesions, conjunctivitis (85.7%), followed by mucosal lesions (79.3%), swelling of the hands and feet (62.9%), and lymphadenopathy (63.4%). In infants, fever could be a sole clinical symptom.

In our study, coronary artery aneurysms were found in nearly 22.9% of KD at the time of diagnosis and in 16% at weeks 6–8 in children treated with IVIG. In other countries, the development of CAA despite IVIG treatment ranges from 19 to 42% [24, 25]. Boys and infants are statistically more likely to develop aneurysms at weeks 6–8 of the disease. This finding is consistent with previous studies.

Literature data indicate that many predictors of CAA have been previously identified. Yan et al. [8] performed a meta-analysis confirming that sex, IVIG resistance, IVIG treatment beyond ten days after the onset of symptoms, and increased C-reactive protein (CRP) levels are significant risk factors for CAA. Zheng X et al. [26] performed the first meta-analysis that revealed the strongest association between the incidence of CAA and IVIG resistance. In our study, we identified seven factors: age, atypical course, late diagnosis, presence of changes in the coronary arteries at the time of diagnosis, IVIG resistance, low hemoglobin level, and high platelet count. Berdej-Szczot et al. [27] found similar independent risk factors in Polish children: prolonged fever, late diagnosis, poorly symptomatic course of the disease, and a high platelet count.

Among seven risk factors found in univariable analysis, multivariable analysis showed only three of them as significant, and independent: low hemoglobin concentration, late diagnosis, and the presence of aneurysms in the first ECHO examination.

In the preliminary analyzes, there was a relationship between sex and the occurrence of CAA (using the χ^2 test), while in the univariable logistic regression model, no such relationship was shown, and the *P*-value was slightly higher than 0.05.

However, Yan et al. [8] in their meta-analysis cannot deny a potential connection between platelet count and CAA development. Further studies are needed to investigate the association between CAA and previously identified factors.

All patients received IVIG together with ASA. In 16 patients, glucocorticosteroids (GCS) were used with the first infusion of IVIG.

In the population under study, 28% of patients were resistant to first-line time treatment, with no differences between groups treated with IVIG infusion only and treated with IVIG plus GCS. This proportion is higher than the 10%–20% reported in previous studies [4].

Recently, many recommendations for the diagnosis and treatment of Kawasaki disease have been published. The most important ones include the scientific statement of the AHA in 2017, the guidelines of the Italian Pediatric Society (2018), and the European rheumatological guidelines (2018) [4–6, 12]. While the diagnosis of KD is consistent in most respects, there are controversies in therapeutic management. The most controversial is the risk scales of IVIG resistance and using GCS. In recent years, the usefulness of the most common IVIG resistance risk scales for European populations has been verified. Researchers from Poland, Germany, and Italy showed that Kobayashi, Sano, and Egami scales are not reliable for identifying patients resistant to IVIG in the European population [27–29]. Because of these findings (and the small size of the patient group), we did not perform such analyses in this study.

Glucocorticosteroids have been used for decades to treat systemic vasculitis but are not yet widely used as an initial treatment for KD. The authors of meta-analyses showed that the frequency of abnormalities in the coronary arteries was significantly lower in children who received GCS with IVIG than only in IVIG therapy [30]. Other researchers suggest that long-term steroid treatment should be considered in all children diagnosed with the disease [31]. Otherwise, Yang et al. [32] showed that GCS treatment, combined with IVIG, reduces the incidence of coronary aneurysms, but only in Japanese patients, which was not observed in other nations' patients. Opposing opinions are also presented. Some believe that conclusions from these studies should not be extrapolated to non-Asian populations due to the possible influence of various environmental, genetic, and economic factors on the effects of therapy [33]. Others state that the use of GCS is an independent risk factor for the development of coronary aneurysms, especially giant aneurysms (child population from China), and may interfere with vessel remodeling (study on a group of 80 patients) [34, 35].

The lack of reliable risk scales for IVIG resistance for the European population may limit using glucocorticosteroids due to doubts about treatment indications and potential side effects.

In our study, we did not find a relationship between the use of GCS and the presence of coronary abnormalities at weeks 6–8 of disease. Further research is required to provide evidence of the effectiveness of GCS and IVIG as first-line treatments.

Interestingly, no CAA was found in patients treated with initial therapy IVIG and GCS with positive effect (without a necessity of second-line treatment) vs children treated only with IVIG not requiring a second-line treatment. Be-

cause of the small sample size, we did not find a statistically significant correlation.

Furthermore, in children treated with GCS and IVIG as initial therapy, CAA developed less often than in a group of children treated with GCS as a second-line treatment (together with the second dose of IVIG). This finding is consistent with the results of the meta-analysis performed by Chen et al. [29]. Still, we cannot confirm it.

In our opinion, treatment with GCS, especially in children with the presence of multi-organ failure resulting from systemic vasculitis (not only medium-sized vessels) should not be avoided. Because of the lack of reliable studies on this topic, GCS treatment decisions should be made individually, based on clinical experience.

Our study ended in 2019, but it is worth mentioning that since 2020 we found an increasing incidence of Kawasaki-like disease after the beginning of the SARS-CoV-2 epidemic. The new entity was proposed so-called pediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2 (PIMS-TS) or multisystem inflammatory syndrome in children (MIS-C; an alternative name proposed in the US and adopted by the World Health Organization (WHO) [36–38]. Whether this is a form of KD triggered by SARS-CoV-2 or a different entity is still a matter of debate. Children with PIMS-TS are usually older, mucocutaneous symptoms are less common, while gastrointestinal and respiratory symptoms are more frequent. Patients are at higher risk of developing myocarditis with acute heart failure and may require longer time in the hospital and admittance to an intensive care unit. Recently, Lam Y et al. [39] proposed an algorithm (KIDMATCH) for screening patients for MIS-C, KD, or other febrile illness. Many treatment protocols recommend using IVIG and aspirin with/without GCS as first-line therapy. Indications for using GCS and dosing depend on the phenotype of the disease and differ in many medical centers. PIMS-TS remains the diagnostic and therapeutic challenge, the effect of immunomodulatory therapy needs further evaluation in both observational and trial settings [40–42].

The main limitation of our study is the small sample of the examined population. A central case reporting system to report and monitor all KD cases in the Polish pediatric population is ongoing, it belongs to the MultiOrgan Inflammatory Syndromes COVID-19 Related Study (MOIS-CoR) that reports patients diagnosed with PIMS-TS and KD. The detailed characteristic of coronary abnormalities in patients included in our study is of interest to our cardiologists and is unfinished. Follow-up of patients is continuing to provide additional data.

CONCLUSIONS

We found six predictors of CAA after 6–8 weeks in KD patients, all of them are consistent with previous studies. The late diagnosis, low hemoglobin level, and the presence of CAA at diagnosis were identified as significant and independent risk factors.

Supplementary material

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

Article information

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Recording an isoelectric interval as an endpoint of left bundle branch pacing with continuous paced intracardiac electrogram monitoring

Hao Wu, Longfu Jiang, Jiabo Shen

Department of Cardiology, HwaMei Hospital, University of Chinese Academy of Sciences, Ningbo, Zhejiang, China

Correspondence to:
Longfu Jiang, MD,
Department of Cardiology,
HwaMei Hospital,
University of Chinese Academy of Sciences,
41 Xibei Street, Ningbo, Zhejiang, 315010, China,
phone: +86 057 483 871 071,
e-mail: longfujianghwamei@163.com

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ABSTRACT

Background: The present study aimed to evaluate the feasibility and safety of the novel left bundle branch pacing (LBBP) procedure that uses isoelectric interval as an endpoint for lead implantation.

Methods: A total of 41 patients with indications for pacing were enrolled. All patients underwent a novel LBBP procedure guided by recording an isoelectric interval as an endpoint for lead implantation. The procedural details and electrophysiological characteristics were then analyzed.

Results: A total of 38/41 (92.7%) cases were confirmed of left bundle branch (LBB) capture. An isoelectric interval was observed in 36/41 cases (87.8%). A total of 36/41 (87.8%) cases with LBB potential were observed. The mean unipolar LBBP threshold at the implant was 0.5 ± 0.2 V. The mean sensed amplitude of the R wave and the pacing impedance at the implant were 12.9 ± 5.0 mV and 723.5 ± 117.1 Ω. During the final threshold testing, a transition from non-selective to selective LBBP (S-LBBP) was demonstrated in 26 patients. A transition from non-selective LBBP (NS-LBBP) to left ventricular septal myocardial capture was observed in 12 patients.

Conclusion: Using an isoelectric interval as an endpoint to guide the LBBP was feasible in a high proportion of captured LBB cases.

Key words: conduction system pacing, isoelectric interval, intracardiac electrogram, John Jiang's connecting cable, left bundle branch pacing

INTRODUCTION

Left bundle branch pacing (LBBP) is a novel physiological pacing modality that is based on the transventricular septal left ventricular (LV) pacing method [1]. This technique has been widely adopted by medical centers in different countries since it was reported in 2017 [2]. Prior research has demonstrated its feasibility and effectiveness [3–6]. Previous studies usually use electrocardiogram (ECG) characteristics, such as paced right bundle branch block (RBBB) pattern, time from stimulus to R-wave peak time (RWPT) in V4–V6, and LBB potential as a guide to performing LBBP [2]. However, these ECG characteristics were not precise enough to tell when to stop screwing the lead. Using a mechanically induced premature ventricular complex (PVC) to guide LBBP, has been reported [7], but PVC cannot exist persistently. The implantation procedure for LBBP is still in the empirical stages and therefore lacks a precise endpoint for lead implantation.

Continuous pacing while lead screwing in LBBP was reported by Jastrzębski et al. [8, 9]. With no doubt, the ability to monitor in real-time the paced QRS morphology is very helpful in LBBP, but it is not easy to achieve by the traditional connecting cable. Our center (Department of Cardiology, HwaMei Hospital, University of Chinese Academy of Sciences) began using John Jiang's connecting cable for LBBP in July 2019. It allows for simultaneous monitoring and recording of ECG and intracardiac electrogram (EGM) during lead deployment. Recently, our group reported

WHAT'S NEW?

This study is the first to report on the novel left bundle branch (LBB) pacing procedure that uses isoelectric interval as an endpoint for lead implantation. The novel procedure was feasible in a high proportion of captured LBB cases (92.7%). LBB has a different capture threshold from the left septal myocardium, and an isoelectric interval can only be recorded when the left septal myocardial threshold is higher than the left bundle branch threshold after decreasing the pacing output to near-threshold. By contrast, when the left bundle branch threshold is higher than the left septal myocardial threshold, the V5 R-wave peak time prolongs abruptly due to the loss of LBB activation during the threshold test. This study showed that the left ventricular septal myocardial threshold and LBB threshold were all lower than 2 V at the final threshold test, which indicates that the selective LBB pacing may only exist in the threshold test.

on a case where John Jiang's connecting cable was used for LBBP and found that a distinct isoelectric interval was recorded in intracardiac EGM during selective LBBP (S-LBBP) [10]. We then developed a novel LBBP lead implantation technique assisted by John Jiang's connecting cable to record an isoelectric interval in the pacing lead as an endpoint for lead implantation with continuous monitoring of paced EGM. Herein, we report on the novel LBBP technique that uses isoelectric interval as an endpoint for lead implantation. The feasibility and safety of the novel procedure were also evaluated.

METHODS

Study design and patient population

This study involved patients referred for permanent pacemaker implantation therapy between April and August 2021 at the HwaMei Hospital, Ningbo. All enrolled patients underwent a novel LBBP procedure. All patients were indicated for pacing therapy according to the current guidelines [11]. The Institutional Review Board approved the study protocol (no. SL-KYSB-NBEY-2021-079-01), and all patients provided written informed consent.

Implantation procedure

Preparation

A 3830 (SelectSecure, 69 cm, Medtronic, Minneapolis, MN, US) pacing lead was delivered using a C315 HIS (Medtronic, Minneapolis, MN, US) sheath *via* left subclavian or left axillary vein access and connected by John Jiang's connecting cable. The modified connecting cable had a special rotating device with an IS-1 connector port, which was connected to the distal pin of the lumenless Medtronic 3830 lead (cathode). The special rotating device was like a double-layer metal ring, and the mechanism of the device was similar to that of bearings, allowing components to move with respect to each other. Twelve-lead ECG along with EGM from the pacing lead were continuously recorded with an EP-Workmate™ recording system (Abbott Laboratories, Chicago, IL, US). The band-pass filter for the pacing lead was set to: "High Pass-200 Hz\Low Pass-500 Hz".

Lead implantation

A C315 HIS sheath in the right anterior oblique (RAO) 30° was advanced into the right ventricle. The sheath was then slowly withdrawn until the tip reached the area just across the tricuspid valve annulus (TVA). About 20 ml of the contrast medium were then injected via the sheath for right ventriculography to visualize the TVA. A TVA image was saved as a reference marker to help locate the target entry site without searching for a HIS potential or the typical paced morphology with an electrocardiographic "W" pattern in lead V1. A previous study has demonstrated that the HIS bundle travels in the membranous part of the atrioventricular septum and penetrates the posterior site of the basal interventricular septum (IVS) just inferior to the tricuspid septal leaflet [12]. The target site for LBBP was identified in the proximal interventricular septum 2.0–2.5 cm below the summit of the tricuspid, along an imaginary line connecting the summit of the tricuspid to the right ventricular apical (RVA) in the RAO 30° fluoroscopic view.

Continuous unipolar pacing at 2 V/0.5 ms was performed during the whole period of lead implantation. At the beginning of implantation, the lead was screwed on rapidly, and the R-wave in the precordial lead R/S transition was elevated while the impedance increased (Figure 1), indicating that the lead had begun to enter the right side of the ventricular septum. The most common precordial lead where R/S transition occurred was V3 or V4.

As the lead reached the left side of the ventricular septum, the R/S transition zone gradually advanced to lead V1 (Figure 1), while the impedance began to decrease gradually. The output was intermittently increased to 5 V/0.5 ms to monitor whether the V5 RWPT shortens abruptly compared to the initial pacing output (2 V/0.5 ms). This means that the lead was closer to the conduction system, slowing down the screwing speed and increasing the measuring impedance frequency.

The V5 RWPT for two adjacent paced beats first shortened abruptly to ≥10 ms with the same output (2 V/0.5 ms), and the lead was screwed in very slowly (Figure 2), gradually decreasing the pacing output. The lead screwing was stopped if an isoelectric interval was directly observed in

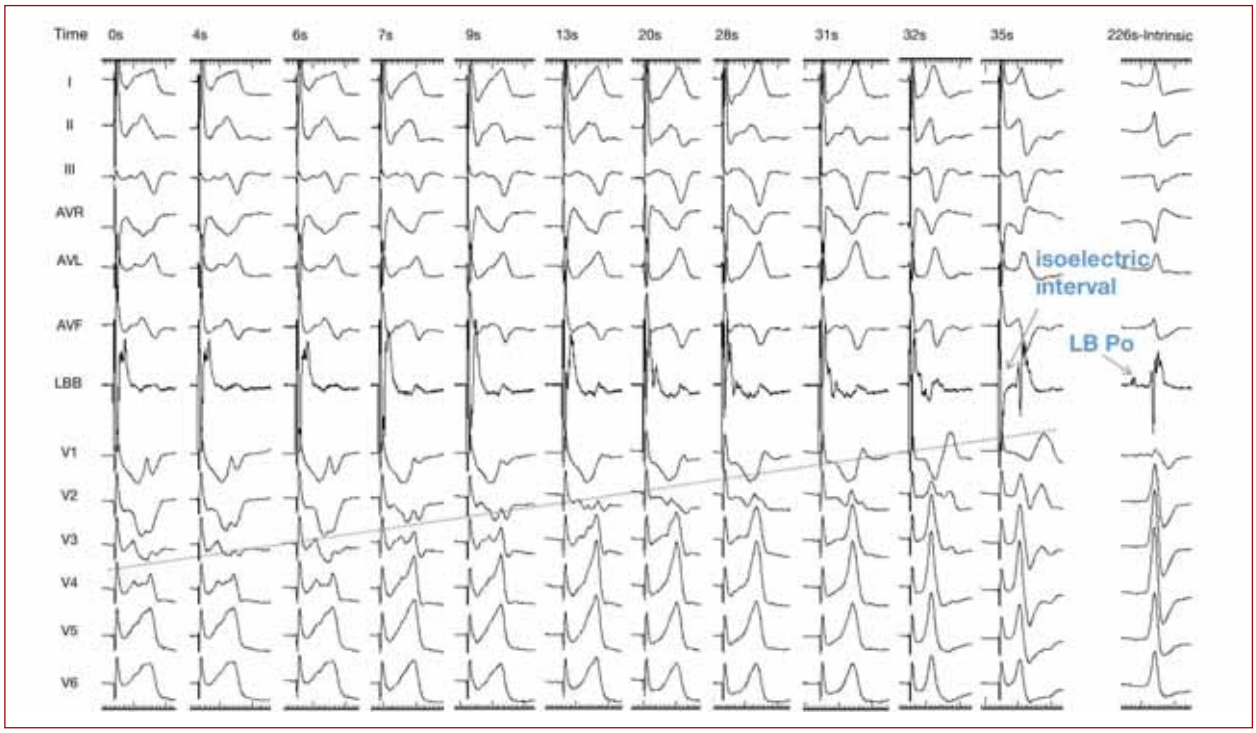

Figure 1. Electrophysiological characteristics during the whole period of lead implantation. The overall total lead screwing procedural time was 35 seconds. The precordial R/S transition zone gradually advanced to lead V1 as the lead traversed from the right to left side of the septum. A distinct isoelectric interval was observed at the end of lead screwing. LBB potential can be recorded in intrinsic rhythm

Abbreviations: LBB, left bundle branch

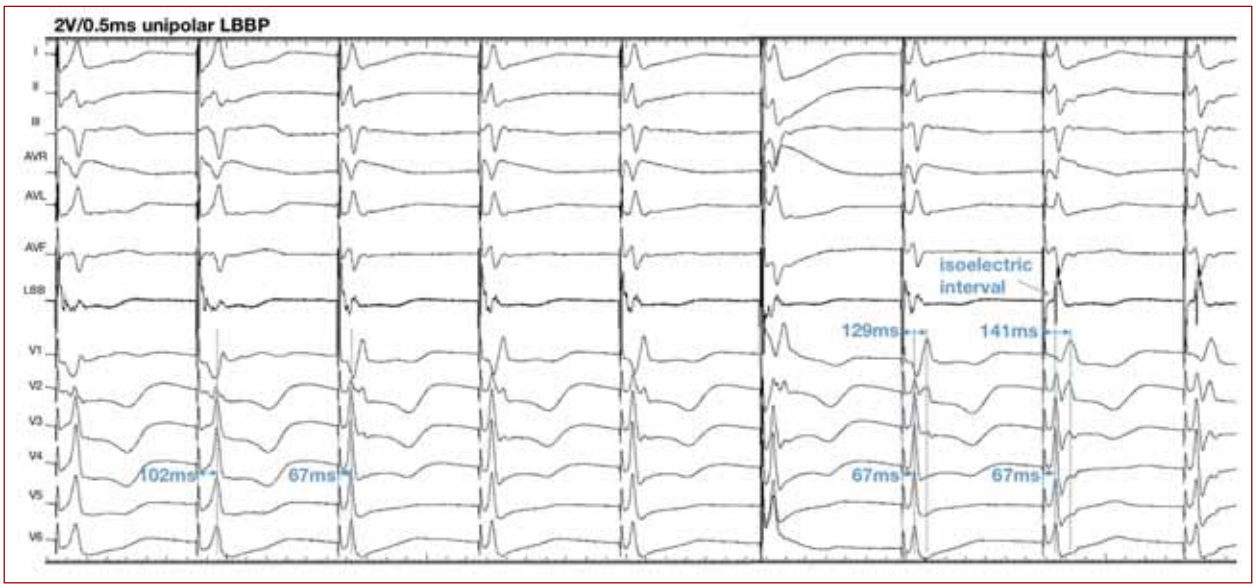

Figure 2. Electrophysiological characteristics at the end of lead implantation. As the lead almost reached to the LBB, the V5 RWPT for two adjacent paced beats was suddenly shortened from 102 ms to 67 ms with the same output (2 V/0.5 ms). And after the lead reach to the LBB, a distinct isoelectric interval was observed in the LBBP lead and V5 RWPT remained the same (67 ms), V1 RWPT increased from 129 ms to 141 ms

Abbreviations: LBBP, left bundle branch pacing; RWPT, R-wave peak time; other — see Figure 1

intracardiac EGM with the initial pacing output (2 V/0.5 ms) or during a decrease in pacing output (Figure 2). If the isoelectric interval still cannot be observed, screw the lead very slowly with near-threshold output until the unipolar impedance decreases to 600 Ω or the amplitude of current of injury (COI) starts to decrease.

Final threshold test and pacemaker implantation

After the lead was in place, the LBB potentials were recorded. In the left anterior oblique 45° fluoroscopy view, about 5 ml of the contrast agent were injected through the sheath to delineate the right ventricular (RV) septal wall and to demonstrate the lead depth in the interventricular septum. Lead tension was adjusted and then the sheath was removed. The pacing lead was fixed, and the final threshold test was performed before connecting the pacemaker. After it was connected, the pacemaker was placed in a prefabricated bag and the skin was sutured.

Strict criteria for confirming LBB capture

LBB capture is confirmed by paced QRS morphology of RBB delay pattern (qR or rSR in lead V1) along with all of the following criteria: (1) demonstration of non-selective left bundle branch (NS-LBB) to selective left bundle branch (S-LBB) capture or NS-LBB to left ventricular septal (LVS) myocardial capture transition during threshold testing; (2) differential pacing at 8V and 2 V produce short and constant RWPT as measured in leads V5 (preferably <70 ms).

Data collection

Baseline patient characteristics and indications for pacing were documented in addition to baseline QRS duration and echocardiographic data. Pacing thresholds (unipolar pacing), R-wave amplitudes, and impedances were recorded. The presence of isoelectric interval and intracardiac isoelectric stimulus-ventricular potential interval (S-V interval) was noted. Abrupt shortening to ≥10 ms in two adjacent paced beats with the same output (2 V/0.5 ms) of the V5 RWPT and shortening duration were also recorded in addition to the presence of LBB potential and its amplitude. The characteristics of different changes in ECG and EGM morphology during the final threshold test and the RWPT (stimulus — the peak of the R wave in surface leads V1, V6) with different outputs (threshold, 2 V, and 8 V) were determined (measured using the electrophysiology recording system at a speed of 600 mm/s). The length of the septum lead from the RV to LV wall along the course of the lead was measured. The lead implantation procedural duration was recorded and was defined as the time from the TVA visualization to the removal of the C315 HIS sheath.

Acute procedure-related complications, such as lead dislodgement, pneumothorax, pericardial effusion, pocket hematoma, and loss of capture were recorded.

Table 1. Basic study group characteristics (n = 41)

Age, years, mean (SD)	73.7 (9.2)
Male sex, n (%)	25 (60.9)
Pacing indication, n (%)	
Sick sinus syndrome	10 (24.3)
Atrioventricular block	27 (65.9)
Atrial fibrillation with bradycardia	2 (4.9)
Heart failure	2 (4.9)
Comorbidities, n (%)	
Diabetes mellitus	18 (43.9)
Hypertension	23 (56.1)
Atrial fibrillation	13 (31.7)
Cardiomyopathy	3 (7.3)
Coronary heart disease	4 (9.8)
Heart failure	7 (17.1)
Left ventricular ejection fraction, %, mean (SD)	64.6 (7.4)
Left ventricular end-diastolic dimension, mm, mean (SD)	50.4 (6.1)
Native QRS type, n (%)	
Narrow	27 (65.8)
RBBB	9 (22.0)
LBBB	4 (9.8)
NIVCD	1 (2.4)
Native QRS duration, ms, mean (SD)	107.5 (33.2)

Abbreviations: LBBB, left bundle branch block; NIVCD, non-specific intraventricular conduction disturbance; RBBB, right bundle branch block

Statistical analysis

Continuous variables were reported as mean (standard deviation [SD]). Categorical variables were expressed as percentages. Repeated measures ANOVA was used for more than two-group comparisons with an LSD *post hoc* test for two-group comparisons. A *P*-value of <0.05 was considered significant. Statistical analysis was performed using IBM SPSS Statistics for Macintosh (version 26.0, IBM Corp, Armonk, NY, US).

RESULTS

Baseline characteristics

A total of 41 patients with LBBP were screened. The baseline characteristics of the study population are shown in Table 1. The mean age was 73.7 (9.2) years and 60.9% of patients were men. Indications for pacing included atrioventricular block (65.9%), sick sinus syndrome (24.3%), atrial fibrillation with bradycardia (4.9%), and heart failure (4.9%). The main comorbidities were hypertension (56.1%), diabetes mellitus (43.9%), and atrial fibrillation (31.7%). The mean LV ejection fraction was 64.6 (7.4) %. The mean LV end-diastolic dimension was 50.4 (6.1) mm. The mean native QRS duration was 107.5 (33.2) ms. The native QRS type was narrow (65.8%), RBBB (22%), LBBB (9.8%), and non-specific intraventricular conduction disturbance (2.4%).

Procedural characteristics and complications

Among 41 patients who underwent the LBBP procedure, a total of 36 cases (87.8%) reached the endpoint during

Table 2. Pacing and procedure-related characteristics (n = 41)

Abrupt V5 RWPT shortening to ≥10 ms, n (%)	38 (92.7)
Mean duration of shortening, ms, mean (SD)	18.1 (5.2)
Isoelectric interval, n (%)	36 (87.8)
Be observed directly, n (%)	16 (39.0)
Be observed during decreasing the pacing output, n (%)	20 (48.8)
S-V interval, ms, mean (SD)	30.6 (5.7)
LBB potential, n (%)	36 (87.8)
LBB potential amplitude, mV, mean (SD)	0.2 (0.1)
Sensing, mV, mean (SD)	12.9 (5.0)
Threshold, V, mean (SD)	0.5 (0.2)
Impedance, V, mean (SD)	723.5 (117.1)
Lead depth, mm, mean (SD)	13.0 (2.1)
Lead implantation procedural duration, min, mean (SD)	40.2 (23.8)

Abbreviations: S-V interval, intracardiac isoelectric stimulus-ventricular potential interval; other — see Figure 2

the lead implantation procedure, all of which were confirmed as LBB capture during the threshold testing. Two cases did not reach the endpoint but still were confirmed as LBB capture during the threshold testing. The other three cases were considered unsuccessful at capturing LBB due to the failure to screw the lead into the septum in the ideal lead location. The lead was finally placed into the left septum too close to the apex, which was out of the LBB distribution range.

The pacing and procedure-related characteristics of the study are shown in Table 2. Final paced QRS morphology in lead V1 was either a qR or rSR type in all 41 patients. A total of 38 cases (92.7%) exhibited an abrupt V5 RWPT shortening to ≥10 ms in two adjacent beats with the initial pacing output (2 V/0.5 ms) during lead implantation. The isoelectric interval was observed in 36 cases (87.8%) at the end of lead implantation, of which 16 cases (39.0%) were directly observed with an initial pacing output (2 V/0.5 ms) and 20 cases (48.8%) were observed during a decreasing pacing output. A total of 36 (87.8%) cases of LBB potential were observed, whereas the potentials could not be recorded in two patients with LBBB.

No lead-related complications were observed in the present study. There were no lead dislodgements, pneumothorax, pericardial effusion, pocket hematoma, or loss of capture.

Electrophysiological characteristics and different morphological changes in paced QRS and EGM at the final threshold test

Before the pacemaker was implanted, the final threshold test was performed in 41 patients. An isoelectric interval with the initial pacing output (2 V/0.5 ms) could not be recorded in any patient. There were different morphological changes in paced QRS and EGM during the final threshold test. The electrophysiological characteristics are shown in Table 3. Different changes in ECG and EGM during different periods of the LBBP procedure are shown in Figure 3.

During the final threshold testing, a transition from NS-LBB to S-LBB capture was demonstrated in 26 patients (Figure 4A). An isoelectric interval in the LBBP lead was observed, while V1 RWPT was prolonged due to the loss of direct LV septal myocardial activation, which was reported by a previous study [14]. The LV septal myocardial capture threshold was 0.8 (0.3) V, the LBB capture threshold was 0.4 (0.2) V. The V5 RWPT remained short and constant at different pacing outputs (the V5 RWPT with threshold output [LBB capture threshold] vs. that with low output [2 V/0.5 ms] vs. that with high output [8 V/0.5 ms]): (69.1 [7.4] ms vs. 68.7 [7.4] ms vs. 68.3 [7.1] ms). The V1 RWPT with the threshold output (LBB capture threshold) was significantly higher than that with low output (2 V/0.5 ms): (119.2 [15.9] ms vs. 106.6 [10.8] ms; P <0.001). There were no significant differences between the V1 RWPT with high output (8 V/0.5 ms) and that with low output (2 V/0.5 ms): (104.2 [9.6] ms vs. 106.6 [10.8] ms).

In 12 patients, a transition from NS-LBB to LVS capture was observed during the final threshold testing (Figure 4B). This presented as an abrupt V5 RWPT prolongation with near-threshold output due to the loss of LBB activation, and the isoelectric interval could not be observed. Specifically, the LBB capture threshold was 1.1 (0.3) V and the LV septal myocardial capture threshold was 0.4 (0.1) V. The V5 RWPT with threshold output (LV septal myocardial capture threshold) was significantly higher than that with low output (2 V/0.5 ms): (87.1 [10.1] ms vs. 65.9 [6.3] ms; P <0.001). The V5 RWPT remained the same at the output of 8V to 2V. the V5 RWPT with high output (8 V/0.5 ms) vs. that

Table 3. Different changes in near-threshold output and electrophysiological characteristics at the final threshold test

The changes in near-threshold outputs	Patients	V1 RWPT			*P*	V5 RWPT			*P*	LV septal threshold, V, mean (SD)	LBB threshold, V, mean (SD)
		Threshold output, ms, mean (SD)	2V output, ms, mean (SD)	8V output, ms, mean (SD)		Threshold output, ms, mean (SD)	2V output, ms, mean (SD)	8V output, ms, mean (SD)			
NS-LBBP to S-LBBP	(n = 26)	119.2 (15.9)	106.6 (10.8)[a]	104.2 (9.6)[a]	<0.001	69.1 (7.4)	68.7 (7.4)	68.3 (7.1)	0.072	0.8 (0.3)	0.4 (0.2)
NS-LBBP to LV-septal	(n = 12)	112.0 (13.8)	105.0 (13.0)	102.4 (10.8)	0.071	87.1 (10.1)	65.9 (6.3)[b]	64.9 (6.0)[b]	<0.001	0.4 (0.1)	1.1 (0.3)
No changes	(n = 3)	107.0 (32.5)	109.5 (24.7)	98.5 (19.1)	0.082	98.0 (8.0)	93.0 (8.7)	80.3 (12.0)	0.109	NA	NA

[a]P <0.05 vs. V1 RWPT under threshold output. [b]P <0.05 vs. V5 RWPT under threshold output

Abbreviations: NA, not applicable; other — see Figures 2 and 4

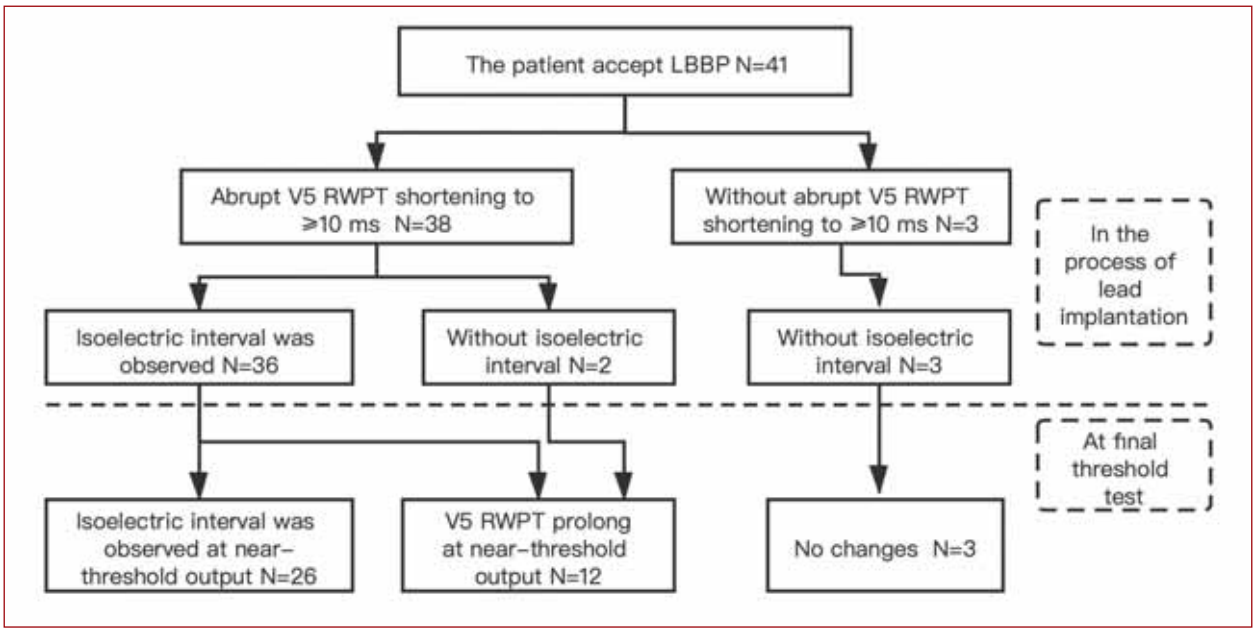

Figure 3. Flowchart for different changes in electrocardiogram and electrogram during different stages of the LBBP procedure
Abbreviations: see Figure 2

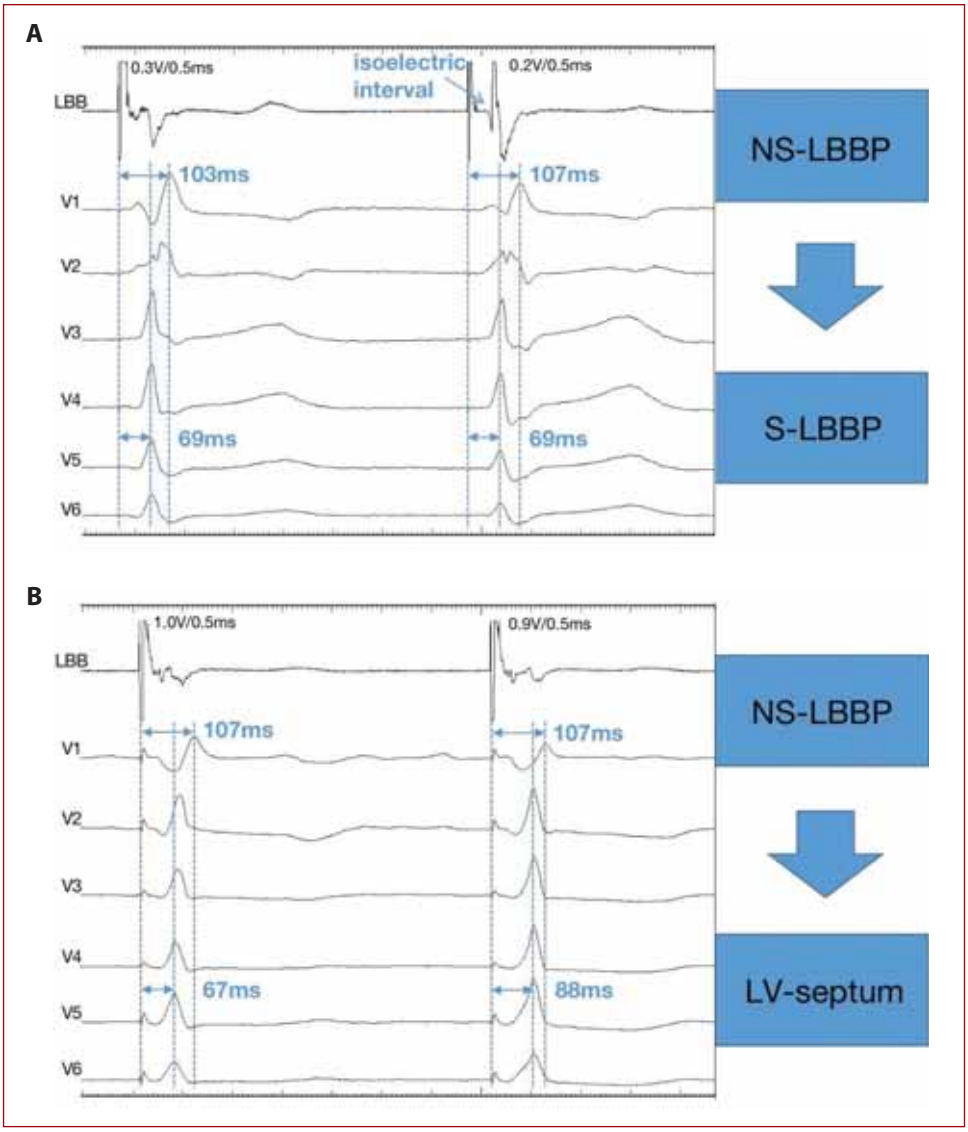

Figure 4. Different changes in electrocardiogram and LBBP lead electrogram morphology during a decrease in pacing output in the final threshold test. **A.** Non-selective LBBP transfer to selective LBBP. Decreasing the output from 0.3 V to 0.2 V changes to selective LBB capture and a distinct isoelectric interval observed in the LBBP lead. V5 RWPT remains the shortest (69 ms), V1 RWPT increases from 103 ms to 107 ms. **B.** Non-selective LBBP transfer to left ventricular septum capture. Decrease in output from 1 V to 0.9 V changes to septal myocardial activation. V5 RWPT increases from 67 ms to 88 ms, while V1 RWPT remains the same (107 ms). Electrogram in LBBP lead shows no discernible change

Abbreviations: LV, left ventricular; NS-LBBP, non-selective LBBP; S-LBBP, selective LBBP; other — see Figure 2

with low output (2 V/0.5 ms): (64.9 [6.0] ms vs. 65.9 [6.3] ms). There were no significant differences between the V1 RWPT with different outputs (V1 RWPT with threshold output [LV septal myocardial capture threshold] vs. that with low output [2 V/0.5 ms] vs. that with high output [8 V/0.5 ms]): (112.0 [13.8] ms vs. 105.0 [13.0] ms vs. 102.4 [10.8] ms).

Three patients showed no discernible change in QRS or local EGM morphology during the final threshold testing. A sizeable shortening in V5 RWPT at high outputs (8 V/0.5 ms) was observed, although it was not statistically significant, likely because the sample size was too small. This suggests that only LV septal myocardial capture was performed.

DISCUSSION

This study first reports a novel LBBP lead implantation technique, which uses the isoelectric interval as an endpoint for lead implantation and was feasible in 87.8% of patients. There were no lead-related complications in this study. This study preliminarily indicates that this novel LBBP lead implantation technique is feasible and safe. The LBB capture rate with strict criteria (demonstration of NS-LBB to S-LBB capture or NS-LBB to LVS capture transition during threshold testing) was reported as 124/468 (26.4%) [14] or 21/51 (41%) [15] in prior studies. In this study, a total of 36 cases (87.8%) reached the endpoint, all of which were confirmed as diagnosis of LBB capture during the threshold testing, which may indicate that this novel LBBP lead implantation technique can increase the LBB capture rate.

The past study has shown that the physiological Purkinje activation was like distal to proximal activation of the ventricular component [16]. An isoelectric interval in the pacing lead can be recorded because direct myocardial capture is absent and therefore ventricular activation over the pacing lead occurs late following initial conduction only over the LBB-Purkinje system. Recording an isoelectric interval was defined as S-LBBP and had a specificity of 100% for confirmation of LBB capture, which was demonstrated by a previous study [17]. That novel endpoint is precise because patients who reach the endpoint were all diagnosed as LBB capture in our study.

Although this novel LBBP lead implantation technique can offer such a precise endpoint, it also has a limitation – not every patient can get the isoelectric interval even if they have LBB capture. In our study, two patients did not reach the endpoint but still were shown as LBB capture during the threshold testing. We think LBB should have a different capture threshold with the left septal myocardium, and that an isoelectric interval can only be recorded when the left septal myocardial threshold is higher than the LBB threshold. By contrast, when the LBB threshold is higher than the left septal myocardial threshold, the isoelectric interval cannot be recorded. That is why these two patients cannot get the isoelectric interval even if they have LBB capture. It reminds us that when applying this novel LBBP lead implantation technique in clinical practice, other electrophysiological characteristics, like impedance and COI, should also be monitored to help to determine the depth of the lead to avoid perforation. Sometimes we need to give up seeking the isoelectric interval to ensure the safety of patients. In addition, the isoelectric interval with near-threshold pacing output during the final threshold test was consistently recorded in only 26/41 (63.4%) patients. We hypothesize that there are two possible reasons. One reason is that the lead would displace proximally during sheath withdrawal or manipulation of the atrial lead, which can result in making the LBB threshold higher than the left septal myocardial threshold. The mean LBB threshold in the patients who had the transition from NS-LB to LVS capture was 1.1 V although it was higher than that in the patients with the transition from NS-LBB to S-LBB capture, but still it had an acceptable value. Another reason is that the left septal myocardial threshold may transiently rise after the lead approaches the LBB area, which was a visible COI on the unipolar electrogram in most of the patients. This causes a higher left septal myocardial in comparison with the LBB capture threshold and results in a transient recording of the isoelectric interval in most of the patients at the end of the lead screwing procedure. With improvement in injury, reduction in the left septal myocardial threshold below the LBB threshold might have resulted in less selective LBB capture later.

In addition, our study showed that the V5 RWPT for two adjacent paced beats shortens abruptly to ≥10 ms with the same output (2 V/0.5 ms) in the process of lead screwing. This was recorded in 38 cases, all of which were confirmed as LBB capture. It may indicate that when the V5 RWPT for two adjacent paced beats shortens abruptly to ≥10 ms with the same output (2 V/0.5 ms), the lead captures the LBB as NS-LBB. It seems the shortening of V5 RWPT on 2V was also a good endpoint for lead screwing. But in some patients, we can see more than one shortening of V5 RWPT, and the shortening was not easy to recognize using the monitor alone, it always needed measuring. It is obvious that the isoelectric interval is a more visible marker than the shortening of V5 RWPT. What is more, the isoelectric interval can guide the lead more closely to LBB than using the shortening of V5 RWPT as an endpoint, and it can achieve a lower LBB threshold.

Study limitations

This study should be interpreted in the context of several limitations. First, this study was performed at a single center with small sample size. Further prospective multi-center randomized controlled clinical trials are needed to validate the novel endpoint for lead implantation. Second, long-term follow-up for the evaluation of clinical outcomes and adverse events is lacking.

CONCLUSION

This study showed that this novel LBBP lead implantation technique, which uses the isoelectric interval as an endpoint for lead implantation, is feasible and safe. As a result, a high proportion of LBB cases with a low LBB capture threshold were revealed. This method can provide a precise endpoint for lead implantation and help facilitate LBBP implantation.

Supplementary material

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

Article information

Conflict of interest: The corresponding author owns the patent for John Jiang's connecting cable, which allows for monitoring and recording of electrocardiograms and intracardiac electrograms during the transseptal placement of the pacing lead. The other author declares no conflict of interest.

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Assessment of clinical characteristics of cardiac amyloidosis as a potential underlying etiology in patients diagnosed with heart failure with preserved ejection fraction

Selda Murat[1], Yuksel Cavusoglu[1], Halit Emre Yalvac[1], Ilknur AK Sivrikoz[2], Sinem Kocagil[3]

[1]Department of Cardiology, Eskisehir Osmangazi University, Eskisehir, Turkey
[2]Department of Nuclear Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey
[3]Department of Medical Genetics, Eskisehir Osmangazi University, Eskisehir, Turkey

Correspondence to:
Selda Murat, MD, PhD, Department of Cardiology, Eskisehir Osmangazi University, 26040 Eskisehir, Turkey, phone: +90 222 239 37 50, e-mail: selda.eraslan@hotmail.com

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ABSTRACT

Background: Heart failure with preserved ejection fraction (HFpEF) is heterogeneous clinical syndrome. Transthyretin cardiac amyloidosis (CA) is an underdiagnosed cause of HFpEF. Red flags are extremely useful for suspecting CA.

Aims: We aimed to evaluate the frequency of cardiac and extracardiac manifestations of CA in HFpEF patients based on red flags.

Methods: Baseline characteristics of 85 patients were recorded during admission. Electrocardiogram and echocardiography were performed. All patients were examined for red flags. Cardiac scintigraphy was performed in 85 patients.

Results: The mean (standard deviation [SD]) age of the study group was 67.9 (9.8) years, and 52 (61.2%) patients were female. At least 1 red flag was observed in 67% of HFpEF patients. Only 4 of the patients had more than 3 red flags. The mean number of red flags in a patient with HFpEF was 1.3. Extracardiac clinical red flags were observed in only 9 (10.5%) patients. Cardiac clinical red flags were extremely rare. An electrocardiographic red flag was detected in 2 out of 10 patients and an echocardiographic red flag in 4 out of 10 patients with HFpEF. Scintigraphy showed that 17.6% of all patients have had a grade 2 or 3 cardiac uptake. The patients with wild-type transthyretin CA had twice as many red flags as those without.

Conclusion: The results of the study showed that patients diagnosed with HFpEF had an average of 1.3 red flags suggestive of CA. In real life, extracardiac red flags are rare, while electrocardiographic and echocardiographic red flags are more common in patients with HFpEF.

Key words: cardiac amyloidosis, diastolic heart failure, heart failure with preserved ejection fraction, red flags, transthyretin

INTRODUCTION

Heart failure (HF) with preserved ejection fraction (HFpEF) is a heterogeneous clinical syndrome with multiple underlying causes with increased prevalence in the elderly population and women. Furthermore, it is more associated with comorbidities such as hypertension (HT), diabetes (DM), obesity, and chronic kidney disease (CKD) [1]. Recently, it has been established that cardiac amyloidosis (CA) is an important cause of HFpEF than previously thought [2, 3]. The disease has two main subtypes: transthyretin CA (ATTR-CA) and immunoglobulin light chain CA (AL-CA). ATTR-CA is further subdivided into wild-type (ATTRwt-CA) and mutant (ATTRm-CA) [4]. Gonzalez-Lopez et al. [5] reported that 13.3% of patients with HFpEF with left ventricular hypertrophy (LVH) showed uptake of 99mTc3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy, which suggested cardiac involvement of ATTRwt-CA. However, diagnosis of CA remains a frequent clinical challenge, especially in the early stages, and

WHAT'S NEW?

Data from the present study showed that at least one red flag for cardiac amyloidosis was observed in almost 70% of the patients with heart failure with preserved ejection fraction (HFpEF). The mean number of red flags in a patient with HFpEF was 1.3. Extracardiac and cardiac clinical red flags were extremely rare in patients. Approximately, an electrocardiographic red flag was detected in 2 out of 10 patients, and an echocardiographic red flag was observed in 4 out of 10 patients with HFpEF. What is more, HFpEF patients with wild-type transthyretin cardiac amyloidosis had twice as many red flags as HFpEF patients without cardiac amyloidosis.

CA is still under-diagnosed [6]. Red flags have been defined as a set of cardiac and extracardiac signs and symptoms, which are extremely useful for suspecting the disease in CA [4, 7]. In this study, we evaluated the frequency of cardiac and extracardiac manifestations of ATTR-CA in patients with HFpEF and aimed to identify red flags that would further alert clinicians to the diagnosis of CA in real-life.

METHODS

We conducted a prospective, observational, single-center study. The study was approved by our institutional ethics committee. All participants provided written informed consent.

Study population

A total of 100 patients diagnosed with HFpEF who were admitted to the Department of Cardiology of Eskisehir Osmangazi University were screened between October 2020 and July 2021. The diagnosis of HFpEF was based on the European Society of Cardiology guidelines [8]. Patients with severe valvular heart disease, previous myocardial infarction, sarcomeric hypertrophic cardiomyopathy, or myocardial storage diseases were excluded. Finally, 85 patients who underwent cardiac scintigraphy with the clinician's suspicion of CA were included in the study.

Study design, data collection, and definition

Demographic characteristics, comorbidities, laboratory findings, and medications were collected during admission. CKD was defined as the presence of an estimated glomerular filtration rate (eGFR) of ≤60 ml/min/1.73 m^2. N-terminal pro-brain natriuretic peptide (NT-proBNP) and the serum or urine monoclonal proteins results were evaluated. Comprehensive transthoracic echocardiography (ECHO) was performed and electrocardiograms (ECG) were recorded. Extracardiac clinical red flags including polyneuropathy, dysautonomia, history of carpal tunnel syndrome (CTS), biceps tendon rupture or lumbar spinal stenosis, positive family history, macroglossia, and cardiac red flags, including hypotension or intolerance to β-blockers/angiotensin-converting enzyme inhibitors, low-voltage or pseudoinfarct pattern or atrioventricular (AV) conduction anomalies on ECG were investigated. Findings including granular sparkling of the myocardium, increased right ventricular (RV) wall thickness, increased valve thickness, pericardial effusion, and reduced longitudinal strain with the apical sparing pattern were investigated as ECHO red flags. 99mTechnetium-pyrophosphate (99mTc-PYP) cardiac scintigraphy was performed in 85 patients. Transthyretin (TTR) gene sequencing was performed in positive patients to identify the mutant type. Also, these patients were evaluated for AL-CA with serum-free light chains and immunofixation electrophoresis.

Echocardiography and electrocardiography

Comprehensive ECHO was performed by a physician using a commercially available system (EPIQ 7C, X5-1 transducer, Philips Medical Systems, Andover, MA, US). Echocardiographic raw data were stored digitally as digital imaging and communications in medicine (DICOM) and transferred for offline analysis to a workstation with the Philips QLAB software. All dimensions were obtained from 2D imaging according to the recommendations of the guidelines [9, 10]. Global longitudinal strain (GLS) was measured in the three apical views. The relative apical sparing index was defined using the equation: average apical LS/(average basal LS + mid-LS) [11]. A standard 12-lead ECG was recorded.

Cardiac scintigraphy

For the primary analysis, which was based on myocardial tracer uptake, two methods were used: (1) semi-quantitative visual scoring of cardiac retention (0–1–2–3) at 3 hours; and (2) quantitative analysis of heart retention was calculated by drawing a region of interest (ROI) over the heart in the standard manner at 1 hour. The fraction of mean counts in the heart ROI-to-contralateral chest ROI was calculated as the heart to contralateral lung (H/CL) ratio [12, 13]. In the absence of monoclonal protein in the serum and urine, grade 2 to 3 myocardial uptake or a H/CL ratio of ≥1.5 were considered positive for ATTR-CA. Grade 2–3 uptake with a H/CL ratio ≥1.5 or grade 0–1 uptake with a H/CL ratio <1.5 were considered concordant results. Grade 2–3 uptake with a semi-quantitative score of 1 or H/CL ratio 1–1.5 were considered equivocal [12, 13].

Statistical analysis

Continuous variables were presented as means (standard deviation [SD]) and compared using t-tests if they were normally distributed and described using medians (interquartile ranges [IQR]) if they were not; the Mann–Whitney

U test was used for comparisons. Poisson regression analysis was used to evaluate the distribution of RF incidences in the ATTR-CA positive/negative groups. We expressed descriptive data as number (%) for categorical variables and compared them *via* the χ^2 test or Fisher exact test. A $P<0.05$ was considered statistically significant. IBM SPSS Statistics 21.0 software (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY, US; IBM Corp.) was used in the analyses.

RESULTS

The mean (SD) age of the study group was 67.9 (9.8) years and 52 (61.2%) were female. Overall, 20 (23.5%) patients were in New York Heart Association (NYHA) class III–IV, and median (IQR) NT-proBNP was 1000 (433.5–2040.5) pg/ml. Other baseline features are summarized in Table 1.

Echocardiographic and electrocardiographic findings

Mean (SD) left ventricular ejection fraction (LVEF) was 59.7 (4) %, mean LV-GLS was –14.3 (2.5)%. The number of patients with left ventricular wall thickness (LVWT) ≥15 mm, 12–14 mm, and ≤11 mm was 27 (31.8%), 29 (34.1%), and 29 (34.1%), respectively. Reduced LV-GLS with the apical sparing pattern was detected in 9 (10.5%) patients and granular sparkling of myocardium in 2 (2.3%) patients. According to the ECG findings, 2 (2.3%) patients had low/decreased QRS voltage to degree of LVWT, 5 (5.8%) patients had pseudoinfarct pattern, and 3 (3.5%) patients had AV conduction disease. Other ECHO and ECG findings are summarized in Table 2.

Scintigraphy results

Scintigraphy showed that 15 (17.6%) patients had a grade 2 or 3 cardiac uptake; the H/CL ratio was ≥1.5, and concordance was positive. In the absence of monoclonal protein in the serum and urine, positive bone scintigraphy is considered diagnostic for ATTR-CA. All patients with a positive scan underwent genetic testing of the TTR gene, and no mutations were found.

Frequency of cardiac and extracardiac amyloidosis red flags in patients with HFpEF

At least 1 red flag was observed in 57 (67%) of the 85 patients with HFpEF. The mean number of red flags in a patient with HFpEF was 1.3. Only 4 (4.7%) patients had more than 3 red flags. Extracardiac clinical red flags were observed in only 9 (10.5%) patients. Among all patients, 31 (36.4%) patients had extracardiac laboratory red flags. Cardiac clinical red flags were extremely rare and were observed in only one of the 85 patients. Approximately, an ECG red flag was detected in 1 out of 10 patients and an ECHO red flag in 4 out of 10 patients with HFpEF. The presence of disproportionately elevated NT-proBNP to degree of HF was present in 8 (9.4%) patients. Patients with ATTR-CA had twice as many red flags as those without (2.46 vs. 1.04). However, ATTR-CA diagnosis was more common in patients with 2 or more red flags (Tables 3 and 4).

Table 1. Baseline clinical characteristics

Variable	TTR-CA negative (n = 70)	TTR-CA positive (n = 15)	*P*-value
Age, years, mean (SD)	66.8 (10.0)	72.1 (8)	0.046
≥65 years, n (%)	39 (55.7)	12 (80)	0.05
Male sex, n (%)	27 (38.6)	6 (40)	0.56
BMI, kg/m^2, mean (SD)	30.4 (5.62)	30.2 (4.0)	0.90
Hypertension, n (%)	55 (78.6)	12 (80)	0.60
Diabetes, n (%)	31 (44.3)	3 (20)	0.07
Coronary artery disease, n (%)	22 (31.4)	6 (40)	0.36
Atrial fibrillation, n (%)	23 (32.9)	8 (53.3)	0.11
Chronic kidney disease, n (%)	30 (42.9)	3 (20)	0.08
NYHA class I, n (%)	1 (1.4)	0	0.61
NYHA class II, n (%)	51 (72.9)	13 (86.7)	
NYHA class III, n (%)	13 (18.6)	2 (13.3)	
NYHA class IV, n (%)	5 (7.1)	0	
SBP, mm Hg, mean (SD)	127.8 (17.7)	123.7 (19.5)	0.42
Heart rate, bpm, mean (SD)	77.5 (18.3)	79.3 (24.4)	0.75
Creatinine, mg/dl, median (IQR)	0.96 (0.77–1.3)	0.89 (0.80–1.10)	0.28
NT-proBNP, pg/ml, median (IQR)	966.5 (425.5–2037.7)	1113.0 (768.0–2385.0)	0.37
β-blocker, n (%)	53 (75.7)	12 (80)	0.51
Calcium channel blockers, n (%)	18 (25.7)	5 (33.3)	0.38
ACEI/ARB, n (%)	37 (52.8)	7 (46.6)	0.41
Furosemide, n (%)	40 (57.1)	10 (66.7)	0.35
MRA, n (%)	16 (22.9)	6 (40)	0.15

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; TTR-CA, transthyretin cardiac amyloidosis

Table 2. Baseline echocardiographic and electrocardiographic features

Variable	TTR-CA negative (n = 70)	TTR-CA positive (n = 15)	*P*-value
LV ejection fraction, %, mean (SD)	60.0 (4.14)	58.6 (3.76)	0.22
LV end-diastolic diameter, mm, mean (SD)	47.6 (3.72)	48.4 (3.65)	0.47
IVSd, mm, median (IQR)	12.8 (11.0–15.0)	13.0 (11.0–16.0)	0.78
Posterior wall thickness, mm, median (IQR)	12.0 (10.0–13.0)	12.0 (11.0–14.0)	0.40
IVS thickness ≥12 mm, n (%)	45 (64.3)	11 (73.3)	0.78
RWT, median (IQR)	0.48 (0.42-0.53.5)	0.47 (0.46-0.60)	0.44
Right ventricular wall thickness, mm, median (IQR)	4.0 (3.0-4.5)	4.0 (3.0-5.0)	0.97
LV mass index, g/m^2, median (IQR)	115.5 (100.0–145.5)	129.0 (104.0–159.0)	0.52
LA diameter, mm, mean (SD)	43.7 (5.85)	45.9 (5.83)	0.20
LA area (cm^2), median (IQR)	19.5 (16.5–24.0)	21.0(20.0–26.0)	0.15
LAVI, ml/m^2, median (IQR)	34.0 (26.0–45.0)	37 (32.0–49.0)	0.24
LAVI >34 ml/m^2, n (%)	34 (48.6)	10 (66.7)	0.16
GLS, %, mean (SD)	–14.7 (2.37)	–12.5 (2.78)	0.003
Apical/(mid + basal) LS ratio, median (IQR)	0.90 (0.84–0.95)	1.08 (0.85–1.49)	0.006
Peak TR velocity> 2.8 m/s, n (%)	28 (40)	5 (33.3)	0.43
sPAP, mm Hg, median (IQR)	35.0 (27.7–50.0)	35.0 (32.0–48.0)	0.78
E-wave, cm/s, mean (SD)	81.8 (21.0)	77.9 (27.2)	0.53
E/e' lat, means (SD)	11.6 (3.01)	12.6 (2.98)	0.22
E/e'≥15 E/e' 9–14	12 (17.1) 47 (67.1)	4 (26.7) 10 (66.7)	0.52
TAPSE, mm, mean (SD)	18.1 (2.78)	16.7 (2.19)	0.08
Right ventricular hypertrophy, n (%)	8 (11.4)	2 (13.3)	0.56
Interatrial septum hypertrophy, n (%)	2 (2.9)	1 (6.7)	0.45
Low QRS, n (%)	—	2 (13.3)	0.03
PR interval, ms, median (IQR)	150.0 (120.0–160.0)	160.0 (160.0–200.0)	0.048
AV block (first degree), n (%)	2 (2.9)	1 (6.7)	0.44
BBB, n (%)	17 (24.3)	2 (13.3)	0.29
Pseudo-infarct pattern, n (%)	2 (2.9)	3 (20)	0.04

Abbreviations: AF, atrial fibrillation; AV, atrioventricular; BBB, bundle branch block; GLS, global longitudinal strain; IVS, interventricular septum; IVSd, interventricular septal dimension; LA, left atrium; LAVI, left atrial volume index; LV, left ventricle; LVH, left ventricular hypertrophy; RWT, relative wall thickness; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; other — see Table 1

Table 3. Details of the presence of red flags in patients with HFpEF

Variables	Total (n = 85)	TTR-CA negative (n = 70)	TTR-CA positive (n = 15)	*P*-value
Extracardiac red flags				
Extracardiac clinical, n (%)	8 (9.4)	5 (7.1)	3 (20)	0.14
Extracardiac laboratory, n (%)	40 (47.1)	34 (48.6)	6 (40)	0.38
Cardiac red flags				
Clinical, n (%)	1(1.2)	0	1 (6.7)	0.18
Electrocardiogram, n (%)	9 (10.5)	5 (7.1)	4 (26.7)	0.048
Laboratory, n (%)	8 (9.4)	3 (4.3)	5 (33.3)	0.004
Echocardiography, n (%)	32 (37.6)	22 (31.4)	10 (66.7)	0.013
Total number of RF	110	73	37	0.013
Patients with 0–1 RF number, n (%)[a]	55 (64.7)	51 (72.9)	4 (26.7)	0.002
Patients with 2–7 RF number, n (%)[a]	30 (35.2)	19 (27.1)	11 (73.3)	0.001
RF number/patients number ratio	1.3	1.04	2.46	<0.001

[a]Patients with 0–1 RF number vs. patients with 2–7 RF number *P*-value: 0.001

Abbreviations: RF, red flag; other — see Tables 1 and 2

DISCUSSION

The results of this prospective study demonstrated that (1) 67% of patients with HFpEF had at least one of the red flags; (2) HFpEF patients with ATTR-CA had twice as many red flags as those without; (3) extracardiac clinical red flags are rarely seen in patients. We concluded that the presence of ECHO red flags and disproportionately elevated NT-proBNP are more common warnings to suspect CA.

ATTRwt-CA has been increasingly recognized as an underdiagnosed cause of HFpEF. It is valuable to recognize clinical findings for the underlying etiology in patients with HFpEF at an early stage. In previous studies, the prevalence of ATTR-CA was reported to be between 13% and 19% in patients with unexplained LVH with HFpEF [5, 14, 15]. Also, in a study conducted on patients with HFpEF without LVH, it was reported that ATTR-CA was detected in 5% of

Table 4. Frequency of cardiac and extracardiac amyloidosis red flags in patients with HFpEF

Variable	TTR-CA negative (n = 70)	TTR-CA positive (n = 15)	*P*-value
Polyneuropathy, n (%)	4 (4.3)	2 (13.3)	0.21
Dysautonomia, n (%)	2 (2.9)	1 (6.7)	0.45
Macroglossia, n (%)	—	—	—
Bilateral carpal tunnel syndrome, n (%)	—	—	—
Ruptured biceps tendon, n (%)	—	—	—
Lumbar spinal stenosis, n (%)	—	—	—
Family history, n (%)	—	—	—
Renal insufficiency (GFR <60 ml/min/1.73 m^2), n (%)	30 (42.8)	3 (20)	0.28
Proteinuria, n (%)	12 (17.1)	3 (20)	0.52
Hypotension or normotensive if previous hypertensive, n (%)	—	1 (6.7)	0.18
Pseudoinfarct pattern, n (%)	2 (2.9)	3 (20)	0.04
Low/decreased QRS voltage to degree of LV thickness, n (%)	0	2 (13.3)	0.03
AV conduction disease, n (%)	2 (2.9)	1 (6.7)	0.44
Disproportionately elevated NT-proBNP, n (%)	3 (4.3)	5 (33.3)	0.004
Granular sparkling of the myocardium, n (%)	0	2 (13.3)	0.03
Increased right ventricular wall thickness, n (%)	8 (11.4)	2 (13.3)	0.56
Increased valve thickness, n (%)	14 (20)	6 (40)	0.09
Pericardial effusion, n (%)	3 (4.3)	3 (20)	0.06
Reduced LS with apical sparing pattern, n (%)	1 (1.5)	8 (57.1)	<0.001

Abbreviations: GFR, glomerular filtration rate; HF, heart failure; LS, longitudinal strain; other — see Tables 1–3

these patients [2]. In our study, 65.9% of patients had LVH, of which approximately one-third was unexplained LVH. Patients with HFpEF were included in our study regardless of age and LVMT. Although it is frequently reported that ATTR-CA is seen in the elderly and men [16], reports show that it also affects wider age ranges and younger and female patients [17]. Our study included a different patient population than the "elderly male" profile usually included in studies about CA. This reflects the HFpEF patient profile that we encounter in daily practice.

Extracardiac and cardiac clinical red flags

Extracardiac and cardiac clinical red flags are less frequent in patients with HFpEF. Orthostatic hypotension (OH) affecting an estimated 40%–60% of patients with ATTRm-CA is a manifestation of autonomic dysfunction [18]. Orthostatic hypotension is diagnosed in 5-11% of middle-aged adults and approximately 20%–30% of people 65 years and older, but the incidence of OH in the HF population is not clear [19, 20]. However, a recent review showed that the incidence of OH in HF varies from 8% to 83% [21]. Also, there is often accompanying neurological involvement such as sensorimotor polyneuropathy in CA, but purely neurological manifestations are rare (4%) [22]. In addition, ATTRwt-CA is known to be associated with CTS, lumbar spinal stenosis, and ruptured biceps tendon [4]. Carpal tunnel syndrome is the most frequent focal peripheral neuropathy in the general population and has been shown to have a prevalence ranging from 0.2% to 4% [23]. In cases of CA, its frequency varies in relation to variables such as amyloid subtypes, duration of the disease, male sex, and age. CTS is present in about 25% of patients and can occur years before diagnosis [24]. Besides, in patients with a history of HT, "spontaneous" resolution of HT over the preceding few months is a valuable history for the diagnosis of CA and has been identified as a cardiac clinical red flag [4, 25]. In the present study, 3% of the patients with HFpEF had autonomic dysfunction findings, and 6% had polyneuropathy. While 2 patients had unilateral CTS, there was no patient with bilateral CTS. The absence of bilateral CTS may be related to the small size of our patient population. "Spontaneous" resolution of HT was observed in only one patient, and this patient was positive on scintigraphy.

Proteinuria and CKD are characterized as extracardiac clinical red flags, these conditions are already common in the HFpEF population. Although the prevalence of proteinuria and CKD varies depending on the age and comorbidities of the patient population included in the studies, it has been reported that 30%–41% of patients with HfpEF have proteinuria [26–28], and 26%–49% have CKD [29]. Similar to previous studies, in our study population, we observed proteinuria in 15 (17.6%) patients (8 with CKD, 7 without CKD) and CKD in 33 (38.8%) patients. Also, there were no patients planned for kidney transplantation. The most common reasons for the increase in the number of red flags were the presence of CKD and/or proteinuria.

ECG, ECHO, and laboratory red flags

Electrocardiographic abnormalities in HF with reduced ejection fraction are widely described and guide medical and device therapy. However, other than a high prevalence of atrial fibrillation, little is known about ECG features associated with HFpEF. ECG variables can help predict the etiology in patients with HFpEF but are very heterogeneous. It has been reported that 10-30% of patients with HFpEF have electrocardiographic LVH. ECG abnormalities reported in patients with HFpEF include atrial fibrillation (prevalence 12%–46%), long PR interval (11%–20%), pathological Q

waves (11%–18%), and left bundle branch block (0%–8) [30]. In our study population, 27% of patients had electrocardiographic LVH, 5 (5.8%) had a pseudo-infarct pattern, and 3 (3.5%) had AV conduction disease. In addition, there were two patients with low voltage on ECG in the limb leads inconsistent with LV wall thickness and these patients were ATTR-CA positive. Analysis of easy-to-assess ECG variables in patients with HFpEF can be of substantial help in the diagnostic workup of ATTRwt-CA.

Besides, ECHO is essential for the initial evaluation of patients with suspected and diagnosed of HFpEF. In addition, it has been reported that cardiac magnetic resonance imaging is a valuable tool in determining the etiology in patients with HFpEF [31]. Diastolic dysfunction, LA enlargement, LVH, RV enlargement, and elevated pulmonary artery systolic pressure were common in patients with HFpEF. Apart from these findings, RV hypertrophy, thickening of cardiac valves and interatrial septum, granular appearance of the myocardium, and pericardial effusion are common in patients with CA. In the present study, the most common finding among ECHO red flags was thickening of cardiac valves, but there was no difference between the two groups (P >0.05). Another "classical" ECHO features of CA were the "granular sparkling and reduced LS with apical sparing pattern", which were significantly higher in the patients with ATTRwt-CA. The results of this study were similar to the results of previous studies for echocardiographic red flags [4].

NT-proBNP is a marker of neurohormonal activation that is useful in the diagnosis and prognosis of HF. Previous studies comparing NT-proBNP levels in different forms of amyloid cardiomyopathy suggested that NT-proBNP values are lower in ATTR-CA than in AL-CA, besides increased ventricular wall thickness [32]. In addition, NT-proBNP levels that are disproportionate to the degree of HF are suggestive of ATTRwt-CA [33]. It has even been reported that some patients with suspected hypertrophic cardiomyopathy, with LVH and normal NT-proBNP levels, may have undiagnosed ATTR-CA [34]. In this study, there was no significant difference in NT-proBNP levels between HFpEF patients with and without CA. However, "the presence of disproportionately elevated NT-proBNP to degree of HF" was significantly higher in patients with ATTRwt-CA.

Study limitations

The presence of persisting elevated troponin could not be evaluated as a cardiac laboratory red flag. Cardiac magnetic resonance imaging findings that were part of the red flag assessment were not evaluated. Another limitation is that endomyocardial biopsies were not performed in this study. Diagnostic tests were performed for storage diseases and hypertrophic cardiomyopathy in clinically suspected patients, but not routinely in all patients.

CONCLUSION

The results of the study showed that patients diagnosed with HFpEF had an average of 1.3 red flags suggestive of CA. Extracardiac and cardiac clinical red flags were extremely rare in patients. Approximately, an electrocardiographic red flag was detected in 2 out of 10 patients and an echocardiographic red flag in 4 out of 10 patients with HFpEF. Furthermore, red flags were twice as common in HFpEF patients with CA than in HFpEF patients without CA.

Article information

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Quality of life in patients with a subcutaneous vs. transvenous implantable cardioverter-defibrillator

Marta Jagosz[1]*, Ewa Jędrzejczyk-Patej[2]*, Wiktoria Kowalska[1], Michał Mazurek[2], Szymon Warwas[1], Dominika Wiktor[1], Adam Sokal[2], Oskar Kowalski[2, 3], Radosław Lenarczyk[4], Beata Średniawa[4], Zbigniew Kalarus[4]

[1]Student Scientific Society at the Department of Cardiology, Congenital Heart Diseases and Electrotherapy, Medical University of Silesia, Katowice, Division of Medical Sciences in Zabrze, Zabrze, Poland

[2]Department of Cardiology, Congenital Heart Diseases and Electrotherapy, Silesian Center for Heart Diseases, Zabrze, Poland

[3]Department of Dietetics, School of Public Health in Bytom, Medical University of Silesia, Katowice, Poland

[4]Division of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Department of Cardiology, Silesian Center for Heart Diseases, Zabrze, Poland

*Both authors equally contributed to the study

Correspondence to:
Marta Jagosz, MD,
Department of Cardiology,
Congenital Heart Diseases and Electrotherapy,
Silesian Center for Heart Diseases,
M Skłodowskiej-Curie 9, 41–800 Zabrze, Poland,
phone: +48 32 37 33 682,
e-mail: martajagosz96@gmail.com

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ABSTRACT

Background: The implantable cardioverter-defibrillator (ICD) and subcutaneous ICD (S-ICD) are well-accepted life-saving devices for treating potentially lethal ventricular arrhythmia, but little is known about quality of life (QoL) in patients with S-ICD and ICD.

Aims: Our study aimed to compare QoL in patients with S-ICD and ICD.

Methods: All consecutive patients who had S-ICD implanted between October 2015 and September 2021 were included in the study. A cohort of transvenous ICD (TV-ICD) patients was matched to S-ICD subjects by sex, age, indications for the device, and type of prevention. All patients were requested to fulfill two standardized questionnaires to assess QoL: 36-Item Short Form Health Survey (SF-36) and Minnesota Living with Heart Failure Questionnaire (MLHFQ) 6 months after device implantation.

Results: Patients with S-ICD (n = 49) and TV-ICD (n = 49) did not differ regarding baseline characteristics. There were no statistically significant differences between S-ICD and TV-ICD subgroup, both for mental and physical QoL assessed in SF-36 and MLHFQ (all P = NS). The median MLHFQ total score was 24 (9–41) for S-ICD and 28 (14–43) for TV-ICD (P = 0.83). The median total score for the SF-36 questionnaire was 62.5 (29–86) vs. 59 (38–77) for S-ICD and TV-ICD, respectively (P = 0.78).

Conclusions: Quality of life after device implantation does not differ significantly between the groups of patients with subcutaneous and conventional implantable cardioverter-defibrillator.

Key words: quality of life, implantable cardioverter-defibrillator, subcutaneous cardioverter-defibrillator, prognosis

INTRODUCTION

The implantable cardioverter-defibrillator (ICD) is a well-accepted life-saving therapy for lethal ventricular arrhythmias. It has an undeniable advantage over antiarrhythmic drugs for the primary and secondary prevention of sudden cardiac death (SCD) [1]. While clinically effective, ICDs carry short- and long-term complications associated with intracardiac leads, such as lead failure occurring with the upward trend linked to the longer follow-up. Indeed, this complication reaches 20% of 10-year-old leads [2]. To overcome lead-related issues, the subcutaneous ICD (S-ICD) was created. S-ICD is a class IIa indication when pacing therapy for bradycardia, anti-tachycardia, or resynchronization therapy is not required, and a class IIb indication in patients with inadequate vascular access, prone to infections, especially after transvenous ICD (TV-ICD) removal and in young patients [1]. Throughout the last years, the importance of S-ICD has been increasing

WHAT'S NEW?

Physical and mental quality of life (QoL) in patients with subcutaneous implantable cardioverter-defibrillator (S-ICD) and transvenous ICD (TV-ICD) did not differ 6 months after device implantation. The data about QoL in patients with TV-ICD compared to S-ICD are important for clinicians and patients, especially in cases of similar indications for S-ICD and TV-ICD implantation.

in Poland, and the main selection factor is the young age of a patient [3, 4].

Therapy with ICD successfully enabled prolonging patients' life; however, symptoms of anxiety affect around 24%–87% of ICD recipients, and approximately 13%–38% of ICD patients suffer from significant anxiety disorders [5]. Regardless of a decrease in lead-related complications both perioperative and long-term, little is known about S-ICDs' psycho-social impact. Thus, this study aimed to compare the quality of life (QoL) in patients with S-ICD and TV-ICD.

METHODS

Study population

The study population consisted of consecutive patients who had S-ICD implanted between October 2015 and September 2021 in a tertiary cardiology center in Poland. All patients were observed prospectively in a single-center S-ICD registry.

Subjects with S-ICD were matched with TV-ICD recipients by age, sex, indications for the device, and type of prevention in the same time interval.

All patients met the criteria for ICD implantation, in line with the current European Society of Cardiology guidelines [1]. Patients were informed about the procedure and potential complications and signed informed written consent. The study was conducted in compliance with recognized international standards, i.e., the Declaration of Helsinki.

Implantation of S-ICD

Each recipient received the EMBLEM™ MRI S-ICD Device (Boston Scientific, Natick, MA, US). All implantations of S-ICD were performed under general anesthesia using the three-incision technique. Fluoroscopy was used to determine the intended device and lead locations. The first incision was made to accommodate the pulse generator at the mid-axillary line between the 5th and 6th intercostal spaces under the latissimus dorsi muscle. Two other parasternal incisions were made to enable lead tunnelization. A defibrillation threshold test (DFT) was made to test the device's functionality. The optimal localization of the S-ICD was assessed with the post-implant X-rays.

Implantation of TV- ICD

The implantations of TV-ICD were performed under local anesthesia. The subclavian vein was accessed by venesection of a cephalic vein or a puncture of the subclavian vein or axillary vein, depending on favorable anatomical conditions and operators' decisions.

The right ventricular pacing/defibrillation lead was inserted with fluoroscopy. The pulse generator was implanted into a subcutaneous pocket. A prophylactic dose of antibiotic was given pre-procedurally to all the ICD recipients (cefazolin single dose iv; or clindamycin single dose iv in the case of allergy to cephalosporins).

Follow-up

Patients were followed 1 week, 1 month, 6 months post-implantation, and every 6 months subsequently. Clinical assessment was performed during post-implantation hospitalization and the whole follow-up. Data was collected from appointments, hospital files, telemonitoring of the devices, and available sources.

Quality of life

Health-related QoL was evaluated *via* Minnesota Living with Heart Failure Questionnaire (MLHFQ) and Medical Outcomes Study 36-Item Short-form General Health Survey (SF-36), completed by two groups of patients 6 months after implantation. MLHFQ is dedicated to heart failure (HF) patients and is used to screen daily the impact of their condition which cannot be received directly from clinical measurements. The questionnaire consists of 21 questions, each ranked on a six-point Linkert scale. A final score ranges from 0 to 105 and represents general wellbeing. This questionnaire also provides scores for two dimensions: physical (8 items, range 0–40) and emotional (5 items, range 0–25).

To screen for potential variations between groups in an aspect of generic measure for health-related QoL, the SF-36 was evaluated. SF-36 measures eight scales divided into two concepts: the mental dimension, comprising vitality, emotional role, social functioning, mental health; and the physical dimension comprising bodily pain, physical functioning, physical role, and general health. SF-36 total score ranges from 0 to 171 with the mental dimension (0–68) and the physical dimension (0–103).

Statistical analysis

The continuous parameters were expressed as median (interquartile range [IQR]), whereas categorical variables as numbers and percentages. The groups were compared using the χ^2, Student t-test, or Mann–Whitney U tests, as appropriate.

Table 1. Baseline characteristics of the study population

	Whole population (n = 98)	TV-ICD (n = 49)	S-ICD (n = 49)	*P*-value
Age, years	44 (32–55)	48 (37–56)	36 (28–54)	0.06
Male sex, n (%)	63 (64.3)	32 (65.3)	31 (63.3)	0.83
NYHA class III or IV, n (%)	15 (15.3)	7 (14.3)	8 (16.3)	0.78
Primary prevention, n (%)	58 (59.2)	30 (61.2)	28 (57.1)	0.68
Ischemic cardiomyopathy, n (%)	36 (36.7)	22 (44.9)	14 (28.6)	0.09
LVEF, %	33 (25–53)	32 (25–46)	37 (25–55)	0.15
Comorbidities, n (%)				
Stroke/TIA	4 (4.1)	2 (4.1)	2 (4.1)	1.0
HA	41 (41.8)	23 (46.9)	18 (36.7)	0.31
Type 2 DM	15 (15.3)	11 (22.5)	4 (8.2)	0.049
CKD	14 (14.3)	6 (12.4)	8 (16.3)	0.56
Paroxysmal AF	11 (11.2)	8 (16.3)	3 (6.1)	0.11
Permanent AF	10 (10.2)	6 (12.2)	4 (8.2)	0.50
Procedural course				
Procedure time, min	95 (80–132)	80 (60–95)	120 (100–150)	0.40
Radiation dose, mGy	3.9 (0.9–18)	13.3 (4–26)	1.4 (0.5–4)	<0.001
DAP, mGy×cm^2	57.6 (4.8–398)	352 (37–720)	11.3 (1–59)	<0.001
Hospitalization time, days	3 (2–8)	2 (2–3)	4 (2–12)	0.09
Time from implantation to discharge, days	1 (1–2)	1 (1–2)	1 (1–3)	0.42
Medications at discharge, n (%)				
ACEI	59 (60.2)	33 (67.3)	26 (53.1)	0.15
Aldosterone antagonist	59 (60.2)	34 (69.4)	25 (51.0)	0.06
β-blocker	87 (88.8)	46 (93.9)	41 (83.7)	0.11
Diuretics	46 (46.9)	24 (48.9)	22 (44.9)	0.69

Continuous variables are presented as median (IQR). *P* – for comparison of patients with TV-ICD and S-ICD

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; CKD, chronic kidney disease; DAP, dose-area product; DM, diabetes mellitus; HA, hypertension arterial; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack; S-ICD, subcutaneous implantable cardioverter-defibrillator; TV-ICD, transvenous implantable cardioverter-defibrillator

The *P*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the software package Statistica version 12.

RESULTS

Study population

Between October 2015 and September 2021, forty-nine patients had S-ICD implantation. During this period, 636 patients were implanted with TV-ICD. Forty-nine TV-ICD recipients were matched with S-ICD subjects by age, sex, indications for the device, and type of prevention in the same time interval. No statistically significant difference in baseline characteristics was found between S-ICD and matched TV-ICD subjects (Table 1).

S-ICD was implanted for primary prevention of SCD in 57.1% of the cases (n = 28). Thirteen S-ICD recipients (26.5%) had had previous conventional TV-ICD and then explantation for the following reasons: 4 patients had revealed cardiac device-related infective endocarditis (CDRIE), 2 patients had had a pocket infection, and there had been 7 cases of lead failure.

TV-ICD was implanted for primary prevention in 61.2% of the patients (n = 30), and ischemic cardiomyopathy occurred in 22 subjects (44.9%).

There were some periprocedural differences between the study groups resulting from the technique of S-ICD and TV-ICD implantation procedures (Table 1). No perioperative complications were observed in S-ICD and TV-ICD patients. There were no ventricular tachycardia/ventricular fibrillation (VT/VF) episodes in either cohort before discharge from the hospital.

Follow-up

During a median follow-up of 736 days (range 190––2325 days), there were two device-related complications observed in the S-ICD group. Two months post-implantation, one patient needed lead revision due to the risk of device externalization, and 3 years after the S-ICD implantation, sudden exhaustion of the battery of the device was observed. One lead revision and one lead exchange due to dysfunction were observed in the TV-ICD group.

Up to 6 months, post-implantation 1 patient (2.04%) had 1 appropriate S-ICD shock due to VF, and 3 patients (6.12%) experienced inappropriate shocks: one of them had 3 inappropriate S-ICD therapies, and 2 others experienced 1 shock. All of them were caused by atrial fibrillation (AF) with a rapid ventricular response. In the group of conventional ICD up to 6 months post-implantation, 1 patient (2.04%) had 1 inappropriate ICD shock (AF with rapid response), up to 1 year, one patient (2.04%) had 1 VT with anti-tachycardia pacing therapy (ATP).

During long-term follow-up, 1 patient in the TV-ICD group had 3 inappropriate ICD shocks due to AF with rap-

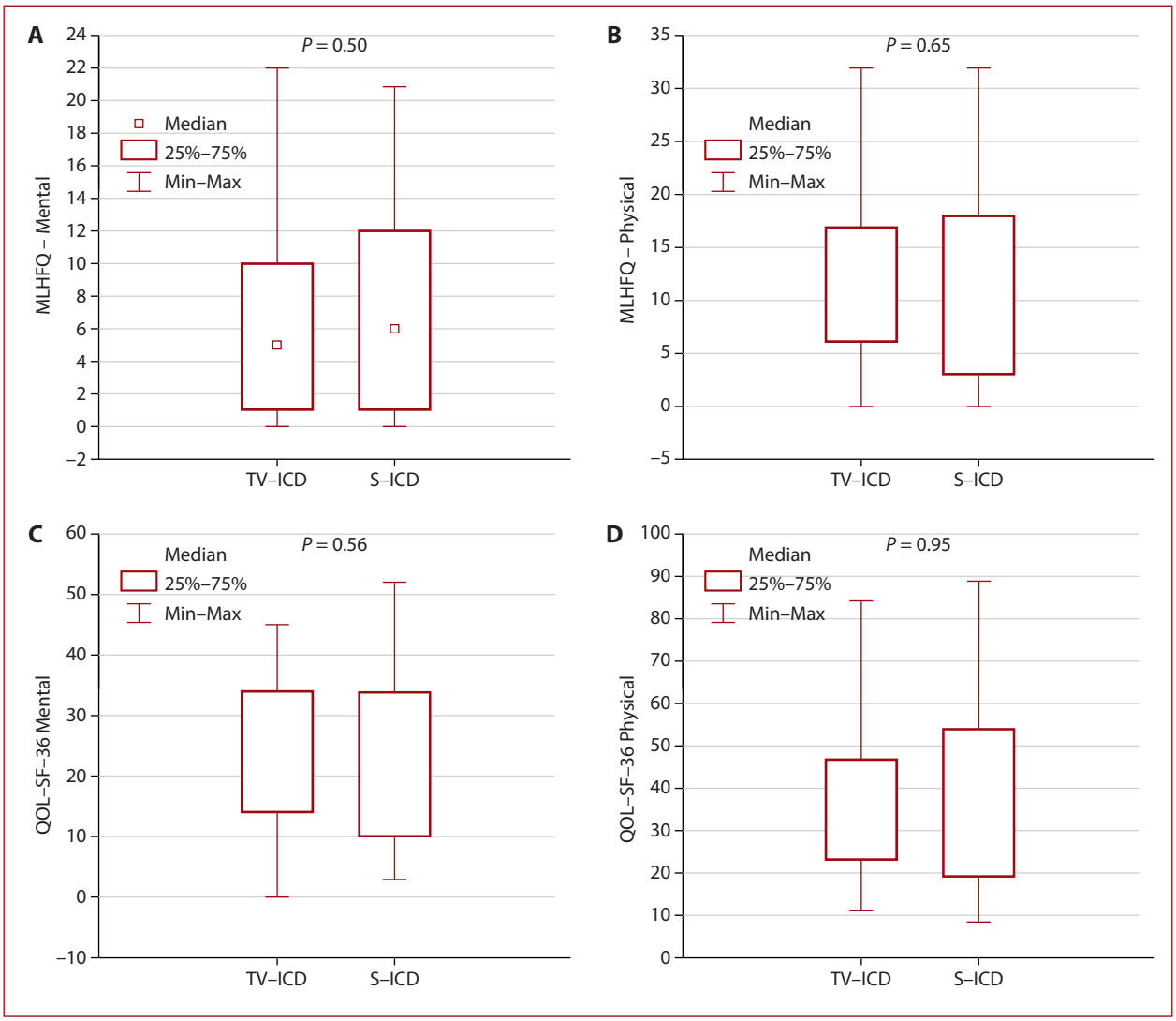

Figure 1. Median scores for MLHFQ and S-36 questionnaires for both cohorts (**A**) MLHFQ mental aspect (**B**) MLHFQ physical aspect (**C**) S-36 mental aspect (**D**) S-36 physical aspect

Abbreviations: MLHFQ, Minnesota Living with Heart Failure Questionnaire; S-36, Medical Outcomes Study 36-Item Short-form General Health Survey; other — see Table 1

id response, and 3 subjects with S-ICD had inappropriate device therapies: one due to sinus tachycardia, one due to AF rapid response, and one due to T-wave oversensing. One patient in the S-ICD group and one with TV-ICD had an electrical storm.

Five patients (10.2%) from the S-ICD group died from non-arrhythmia-related causes and seven (14.3%) from the conventional ICD group during the whole follow-up ($P = 0.54$).

Quality of life

Health-related QoL results did not significantly differ between the two cohorts. The median MLHFQ total score was 24 (9–41) for S-ICD and 28 (14–43) for TV-ICD ($P = 0.83$). For the mental and physical dimensions, the median score was 6 (1–12) and 8.5 (3–18) for S-ICD, respectively, whereas for TV-ICD: 5 (1–10) and 12 (6–17) (S-ICD vs. TV-ICD: $P = 0.50$ and $P = 0.65$).

Patients in the two groups did not vary in terms of the median total score for the SF-36 questionnaire either: it was 62.5 (29–86) vs. 59 (38–77) for S-ICD and TV-ICD, respectively ($P = 0.78$). The median of mental dimension was 21.5 (10–34) for S-ICD and 18.5 (14–34) for TV-ICD ($P = 0.56$), for the physical dimension 41 (19–54) for S-ICD and 36 (23–47) for TV-ICD ($P = 0.95$). A comparison of median scores for MLHFQ and S-36 questionnaires for both cohorts is presented in Figure 1.

DISCUSSION

The main finding of our study is that physical and mental QoL in patients with S-ICD and TV-ICD measured with the use of two kinds of questionaries did not differ 6 months

after device implantation. To the best of our knowledge, only a few studies have compared the quality of life in patients with S-ICD and TV-ICD.

In recent years, apart from hard endpoints such as mortality, the crucial role of QoL in patients with chronic diseases has been emphasized. A high quality of life index indicates that the patient, despite the disease, perceives himself as functioning well physically, mentally, and socially. On the other hand, the low quality of life index shows that the disease limits these functions from the patient's point of view. Patients with ICDs experience limitations in many spheres of activity. Most people are aware of the impact of the disease on life expectancy related to the implanted device, and this knowledge also increases perceived stress. In the case of pacemakers, it has been shown that these devices not only affect prognosis but also improve patients' QoL [6–8]. In the case of the ICD, the issue is a bit more complicated. Numerous randomized trials have shown that these devices extend the life of patients with HF at risk of SCD [9,10]. But how do they affect the QoL?

Pacemakers reduce symptoms associated with atrioventricular block or sick sinus syndrome, so one may expect that they would have a positive effect on QoL [6–8]. ICD does not affect the symptoms of HF, so can QoL in this group of patients improve after device implantation? The improvement of QoL in patients with TV-ICD and S-ICD between baseline and 3 months and between baseline and 6 months was significant, but not between 3 months and 6 months [11].

Our result is consistent with findings of the QoL substudy of the EFFORTLESS S-ICD Registry. [12]. The authors used the 12-Item Short-Form Health Survey (SF-12) at baseline, 3 and 6 months after implantation and applied the Type D Scale (DS14) at baseline to assess the Type D personality in the context of QoL. The result of this study was that both S-ICD and ICD patients were not different in terms of physical and mental QoL. Two other studies showed similar findings — no differences between QoL in patients with S-ICD and TV-ICD were found [11, 13]. Only in one study the physical aspect of QoL was significantly higher in the S-ICD cohort than in the TV-ICD cohort, while the mental aspect of QoL did not differ between the two groups [11].

Data about QoL in patients with TV-ICD compared to S-ICD are important for clinicians and patients, especially in cases of similar indications for S-ICD and TV-ICD implantation. The same QoL in patients with S-ICD and TV-ICD observed in studies indicate that the difference in size and weight between the pulse generator of the S-ICD and the TV-ICD device has a negligible impact on QoL. It seems that other factors, in particular, symptoms of HF and personality, may be more significant determinants of QoL than the type of device itself [14, 15]. It was observed previously that posttraumatic stress disorders occur in almost 15% of ICD patients irrespective of the system [11]. A comparison between TV-ICD and S-ICD showed no statistically significant difference in posttraumatic stress, depression, or anxiety measured by the posttraumatic stress diagnostic scale (PDS) and the Patient Health Questionnaire (PHQ) [11].

One more important aspect is the effect of ICD therapies on QoL. The impact of ICD shocks — both appropriate and inappropriate — on patient wellbeing is widely described in the literature [16, 17]. In the published data, the rates of both appropriate and inappropriate therapies in primary and secondary prevention are nearly equal and steady level during long follow-up [18]. ICD patients represent a high-risk population for the development of panic disorders, and a direct correlation between development of anxiety disorder and frequency of repeated shocks was observed [19]. However, the link between device shocks and patient-centered outcomes is not as unequivocal as described before. The psychological profile and severity of underlying heart disease would be just as significant cause of distress as ICD shocks in this cohort of patients [20]. Some studies in patients with TV-ICD showed that the severity of HF, anxiety, and depression have a more significant impact on QoL than shocks [21, 22]. One study in patients with TV-ICD vs. S-ICD confirmed that personality, HF class, and depression were associated with QoL to a greater extent than the type of device and ICD therapy. [13] What is more, not only do the ICD shocks cause emotional distress but also these negative emotions and stress itself cause malignant arrhythmia that requires ICD therapies. Chronic anxiety may increase vulnerability to arrhythmias by sustained sympathetic stimulation or depressed vagal tone [23]. Therefore, it seems essential to evaluate and control the QoL in those patients to prevent the vicious circle of depression and ICD discharge.

Study limitations

A small number of patients implanted with S-ICD was the basic limitation of this study. Unfortunately, this new technology approved by Food and Drug Administration in 2012 had limited reimbursement by the National Healthcare Fund in Poland before January 2019. The consequent limitation of the study was that we did not evaluate pre-implantation QoL in our patients. The key intention of the present study was to demonstrate the non-inferiority of those two types of devices, and we did not evaluate pre-implantation QoL in our patients thus we have only post-implantation data. The QoL was assessed 6 months after implantation because it was shown that in patients with implanted ICD the QoL improves significantly after the patient gets used to the device, i.e. after about 6 months [24]. We computed the questionnaires using the Polish key that has the opposite calculation from the international data — low scores mean high QoL, while high scores mean impaired QoL.

CONCLUSION

Quality of life 6 months after ICD implantation does not differ significantly between patients with subcutaneous and conventional types of ICD.

Article information

Conflict of interest: EJP, OK, MM, AS, and RL received consultant fees from Medtronic, Biotronik, Abbott, and Boston Scientific. BŚ received consultant fees from Bayer, Boehringer-Ingelheim, Pfizer, Bristol-Myers-Squibb, Medtronic Bakken Research Center (past) and lectures fees from Bayer, Boehringer-Ingelheim, Pfizer, Novartis, MEDICALgorithmics, and ZOLL. ZK received speaker bureaus for Pfizer, Boehringer-Ingelheim, and Abbott.

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Does the presence of physician-staffed emergency medical services improve the prognosis in out-of-hospital cardiac arrest? A propensity score matching analysis

Kamil Bujak[1], Klaudiusz Nadolny[2, 3], Przemysław Trzeciak[1], Robert Gałązkowski[4], Jerzy Robert Ładny[5], Mariusz Gąsior[1]

[1]3rd Department of Cardiology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland
[2]Faculty of Medicine, Katowice School of Technology, Katowice, Poland
[3]Departament of Health Sciences, WSB University, Dąbrowa Górnicza, Poland
[4]Department of Emergency Medical Service, Medical University of Warsaw, Warszawa, Poland
[5]Department of Emergency Medicine, Medical University of Bialystok, Białystok, Poland

Correspondence to:
Kamil Bujak, MD,
3rd Department of Cardiology,
Faculty of Medical Sciences
in Zabrze,
Medical University of Silesia
in Katowice;
Silesian Center for Heart Diseases,
M Skłodowskiej-Curie 9,
41–800 Zabrze, Poland,
phone: +48 32 37 33 860,
e-mail: kamil_bujak@o2.pl;
k.bujak@sccs.pl

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ABSTRACT

Background: Substantial differences in survival after out-of-hospital cardiac arrest (OHCA) have been observed between countries. These might be attributed to the organization of emergency medical service (EMS) systems, including prehospital physician involvement. However, limited data exist on the physician's role in improving survival after OHCA.

Aims: To compare prehospital and in-hospital outcomes of OHCA patients attended by physician-staffed EMS vs. paramedic-staffed EMS units.

Methods: Among all patients enrolled in the regional, prospective registry of OHCA in southern Poland, we excluded those aged <18 years, with unwitnessed or EMS-witnessed cardiac arrest, without attempted cardiopulmonary resuscitation (CPR), attended by more than one EMS, or with traumatic cardiac arrest. The groups were matched 1:1 using propensity scores for baseline characteristic variables that might influence physician-staffed EMS dispatch.

Results: A total of 812 OHCA cases were included in the current analysis. Among them, 351 patients were attended by physician-staffed EMS. There were no differences in baseline characteristics in the propensity-score matched cohort consisting of 351 pairs. The return of spontaneous circulation (ROSC) was more often achieved in the physician-staffed EMS group (42.7% vs. 33.3%; $P = 0.01$). The prehospital survival rate was also higher in this group (34.1% vs. 19.2%; $P < 0.01$). However, there were no significant differences in survival rate to discharge between cases treated by physician-staffed and paramedic-staffed EMS (9.7% vs. 7.0%; $P = 0.22$).

Conclusions: OHCA patients attended by physician-staffed EMS were more likely to have ROSC and survive till hospital admission. However, better prehospital outcomes might not translate into improved in-hospital prognosis in these patients.

Key words: cardiopulmonary resuscitation, emergency medical service, out-of-hospital cardiac arrest, paramedic, physician

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) affecting 55 persons per 100 000 population per year worldwide is a significant public health problem [1]. In Poland, the incidence rate of OHCA has been shown to be even higher (over 25 000 cases yearly; 69 per 100 000 person-years) [2]. Even though within the last few years, improving temporal trends in OHCA outcomes have been observed in some countries [3–5]; globally, the survival to hospital discharge remains low, not exceeding 10% [1]. Substantial variability in OHCA outcomes between countries might be attributed to

WHAT'S NEW?

Data on the role of emergency medical service (EMS) physicians in out-of-hospital cardiac arrest (OHCA) is limited. Notably, there have not been any studies comparing outcomes of OHCA cases attended by physician-staffed EMS and paramedic-staffed EMS units in the context of the Polish EMS system. Using Utstein-style OHCA registry data and propensity-score matching, we have shown for the first time that OHCA patients attended by physician-led EMS are more likely to have the return of spontaneous circulation and have a higher survival rate to hospital admission. However, a higher pre-hospital survival rate in patients treated by physician-staffed EMS does not translate into improved in-hospital prognosis.

social, demographic, economic, and cultural factors, as well as differences in the organization of emergency medical service (EMS) systems, including prehospital physician involvement [6].

Although most of the recent observational studies showed improved outcomes for OHCA patients attended by physician-staffed EMS, compared with paramedic teams, controversies still exist about the physician's role in prehospital scenarios [3, 7–13]. Therefore, we aimed to assess whether the presence of physician-staffed EMS at the scene is associated with improved prehospital and in-hospital outcomes of OHCA compared with EMS teams without physicians, using a regional, prospective, Utstein-style registry of OHCAs in southern Poland.

METHODS

SIL-OHCA registry

The Silesian Registry of Out-of-Hospital Cardiac Arrests (SIL-OHCA; ClinicalTrials.gov Identifier: NCT03654859) was a prospective, population-based registry of OHCAs in Upper-Silesia, Poland (7% of Polish population; 2.7 million people). All EMS-treated OHCA patients between January 1, and December 31, 2018 were enrolled. Prehospital data were collected by EMS providing CPR using paper-based case-report forms conforming to the Utstein guidelines [14]. Subsequently, the prehospital data were digitalized, checked for duplicates and logical errors, and linked with the administrative data from a national insurer (National Health Fund [NHF]). The NHF database includes data on hospital stay duration, procedures performed during the index hospitalization, and in-hospital survival status. Information on medical procedures performed during index hospitalization was based on an International Classification System for Surgical, Diagnostic, and Therapeutic Procedures (ICD-9-CM) codes. Approval for research was waived by the Bioethics Committee of the Medical University of Silesia (no. PCN/CBN/0022/KB/159/21), given the observational nature of the study. The study design of SIL-OHCA and other details on the registry have been presented previously [15–17].

System description

The population served by Voivodeship Rescue Service in Katowice is 2.7 million people (7% of the Polish population), and the annual number of EMS responses is about 250 000. During the study period, the Voivodeship Rescue Service in Katowice was the only public EMS provider in the area covered by the registry (the Upper-Silesia region, which is a highly urbanized part of Poland; 1.2% of the area of Poland) and operated 88 EMS ambulances, including 59 paramedic-manned ambulances, consisting mainly of at least two paramedics (or less often EMS nurses) and 29 physician-manned ambulances (so-called "specialized teams") consisting of at least two paramedics or EMS nurses and one physician (in most cases specialist in anesthesiology and intensive care or emergency medicine, and rarely in internal diseases, general surgery, pediatrics, pediatric surgery or orthopedics, and traumatology). OHCA cases recognized by the dispatcher usually received priority for physician-staffed EMS dispatch if the expected response time for physician-staffed EMS and paramedic-staffed EMS were equal. However, in the case of a lack of available physician-staffed ambulances or an estimated longer response time of those teams, the first available paramedic team was dispatched to avoid delays.

In the case of OHCA, paramedics and EMS nurses in Poland are credentialed to perform procedures recommended by the European Resuscitation Council (ERC) guidelines on advanced life support (ALS), i.e., using a manual defibrillator, securing the airway with either a tracheal tube or supraglottic devices, and administering resuscitation drugs [18, 19]. Moreover, according to Polish law, paramedics and EMS nurses are allowed to withhold or terminate CPR. However, contrary to physicians, they are not credentialed to certify deaths. Furthermore, in Poland, the first-responder system has not been widely implemented, except for the firefighters of the State Fire Service, who are trained for CPR, including the use of an automated external defibrillator (AED), and may be dispatched by the dispatcher to initiate CPR when a long delay to EMS arrival is expected.

Patients

Out of all patients included in SIL-OHCA, we excluded from the current analysis those aged below 18 years, with unwitnessed collapse or cardiac arrest witnessed by EMS, without attempted or continued CPR by EMS, treated by more than one EMS team, those with traumatic cardiac arrest, or with missing data on the type of EMS. Subsequently, the included patients were divided into two groups according to

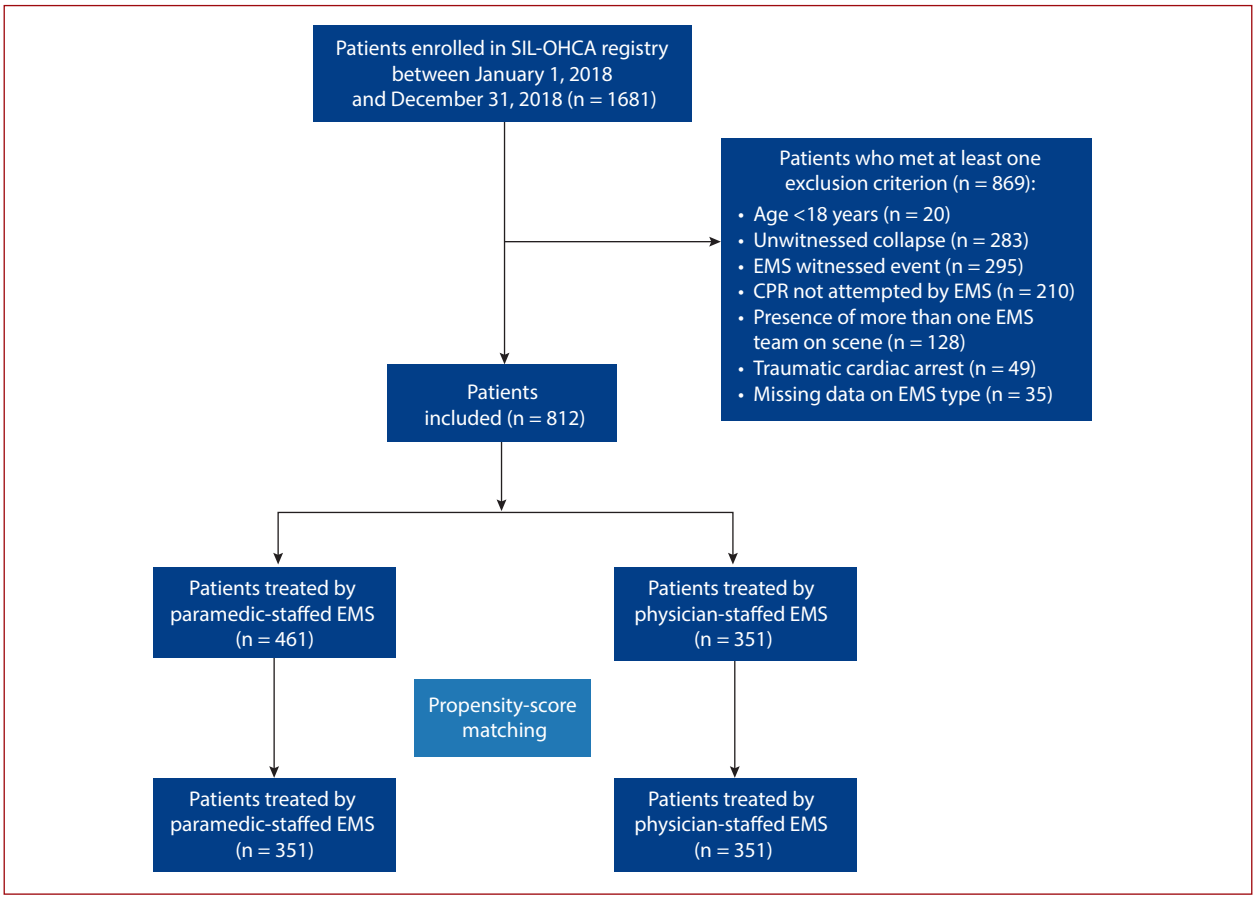

Figure 1. Flowchart of the study population

Abbreviations: SIL-OHCA, Silesian Registry of Out-of-Hospital Cardiac Arrests; other — see Table 1

the physician's presence or absence on board. A flowchart of the study has been shown in Figure 1.

Definitions

Return of spontaneous circulation (ROSC) was defined as the achievement of ROSC at any point during the resuscitation attempt. Survival to hospital admission was interpreted as arrival at the emergency department and transfer of care to the medical staff at the receiving hospital after ROSC. Survival to discharge was considered as discharging the patient from hospital alive. The medical etiology of OHCA refers to all cases without evidence of trauma, drowning, intoxication, electrocution, or asphyxia. Response time and defibrillation time were defined as the period from incoming call to arrival of the ambulance and the first shock delivery. The time to termination of CPR was the period from arrival of the ambulance to cessation of CPR. The above-mentioned and other definitions were based on the 2015 Utstein recommendations [14].

Statistical analysis

Categorical variables are shown as the number of patients and percentage. The normality of continuous data was assessed using the Shapiro–Wilk test, and owing to nonnormal distribution, these variables are shown as median and interquartile ranges. Categorical and continuous variables were compared by the χ^2 test and Mann–Whitney U test, respectively. To manage differences in the baseline characteristics between patients treated by physician-staffed and paramedic-staffed EMS, one-to-one propensity score matching (nearest neighbor algorithm) was used. The groups were matched for baseline characteristics that potentially might influence the decision of physician-staffed EMS dispatch, i.e., sex, age, previous cardiovascular disease, previous stroke, malignancy, chest pain before cardiac arrest, location of OHCA, cause of cardiac arrest, bystander CPR before EMS arrival, response time, and first monitored rhythm. Before matching, missing data on baseline characteristics were imputed using the k-nearest neighbors algorithm. Crude odds ratios (OR) and 95% confidence intervals (CI) were calculated for the association between the presence of physician-staffed EMS and ROSC, survival to hospital admission, and survival to hospital discharge in the propensity-score matched cohort. The level of statistical significance was P <0.05 (two-tailed). Statistica version 13.3 (TIBCO Software, Palo Alto, CA, US) was applied for all computational analyses.

Table 1. Baseline characteristics of OHCA patients attended by physician-staffed EMS vs. paramedic-staffed EMS (before propensity-score matching)

	Paramedic-staffed EMS (n = 461)	Physician-staffed EMS (n = 351)	*P*-value
Male sex, n (%)	327 (70.9)	244 (69.5)	0.66
Age, years, median (IQR)	67 (58–78)	66 (58–77)	0.41
Previous CVD, n (%)	141 (30.6)	98 (27.9)	0.41
Previous stroke, n (%)	41 (8.9)	21 (6.0)	0.12
Malignancy, n (%)	34 (7.4)	30 (8.6)	0.54
Chest pain before OHCA, n (%)	52 (11.3)	31 (8.8)	0.25
Location, n (%)			0.57
Home	347 (75.3)	258 (73.5)	
Other	114 (24.7)	93 (26.5)	
Cause, n (%)			0.08
Medical	423 (91.8)	309 (88.0)	
Other	38 (8.2)	42 (12.0)	
Bystander CPR, n (%)	253 (54.9)	172 (49.0)	0.10
Response time, minutes, median (IQR)	8 (6–10)	9 (6–12)	<0.01
First monitored rhythm			0.75
VF/pulseless VT, n (%)	128 (27.8)	101 (28.8)	
PEA/asystole, n (%)	333 (72.2)	250 (71.2)	

Categorical variables are shown as the number of patients (%). Continuous data are presented as median (IQR)

Abbreviations: CVD, cardiovascular disease; CPR, cardiopulmonary resuscitation; EMS, emergency medical service; OHCA, out-of-hospital cardiac arrest; PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia

Table 2. Prehospital and in-hospital outcomes of OHCA patients attended by physician-staffed vs. paramedic-staffed ambulances (before propensity-score matching)

	Paramedic-staffed EMS (n = 461)	Physician-staffed EMS (n = 351)	*P*-value
ROSC	147 (32.2)	147 (42.7)	<0.01
Survival to hospital admission	75 (18.2)	118 (34.1)	<0.01
Survival to hospital discharge	25 (6.3)	30 (9.7)	0.10

Data are shown as number of patients (%)

Abbreviations: ROSC, return of spontaneous circulation; other — see Table 1

RESULTS

A total of 812 OHCA patients were included in the analysis. Among them, 351 were attended by physician-led EMS and 461 by EMS without a physician. There were no differences in sex, age, comorbidities, presence of chest pain preceding OHCA, location of cardiac arrest, the rate of bystander CPR before EMS arrival, and initial shockable rhythm between groups. However, the response time of paramedic-staffed EMS was significantly shorter. Moreover, there was a trend towards a higher rate of other causes of OHCA than medical in cases treated by physician-staffed EMS teams (Table 1). The presence of a physician on the scene was associated with a higher rate of ROSC and higher survival to admission. However, there were no differences regarding survival status at discharge (Table 2).

After propensity-score analysis, there were no differences in baseline characteristics between 351 matched pairs of patients (Table 3). EMS physicians more frequently performed endotracheal intubation and were less likely to use supraglottic airway devices than paramedic-led EMS teams. Moreover, atropine and amiodarone were more often administered to patients receiving physician-led CPR. On the other hand, there was a trend regarding ECG e-transmission to the nearest invasive cardiology center after ROSC, which was less frequently performed by emergency teams with a physician on board. There were no other significant differences in prehospital and in-hospital treatment between the groups, including administration of other drugs, time to the first defibrillation and the total number of defibrillation shocks, vascular access, and coronary revascularization (Table 4). In patients who did not achieve ROSC, the decision of CPR termination was made earlier, when the physician was present on the scene. The duration of hospital stay was similar in both groups (Table 4).

The data on ROSC, survival to admission, and survival to discharge in propensity-matched cohorts were available for 692 (98.6%), 659 (93.9%), and 610 (86.9%), respectively. CPR provided by physician-staffed units was associated with a higher rate of ROSC and survival to hospital admission. However, there was no significant difference in survival to hospital discharge (Figure 2).

DISCUSSION

Emergency medical service systems' organization differs between countries, which may partially be the reason for

Table 3. Baseline characteristics of OHCA patients attended by physician-staffed EMS vs. paramedic-staffed EMS (after propensity-score matching)

	Paramedic-staffed EMS (n = 351)	Physician-staffed EMS (n = 351)	*P*-value
Male sex, n (%)	239 (68.1)	244 (69.5)	0.68
Age, years, median (IQR)	67 (57–77)	66 (58–77)	0.98
Previous CVD, n (%)	99 (28.1)	98 (27.9)	0.93
Previous stroke, n (%)	21 (6.0)	21 (6.0)	1.0
Malignancy, n (%)	27 (7.7)	30 (8.6)	0.67
Chest pain before OHCA, n (%)	29 (8.3)	31 (8.8)	0.79
Location, n (%)			0.67
Home	253 (72.1)	258 (73.5)	
Other	98 (27.9)	93 (26.5)	
Cause, n (%)			0.55
Medical	314 (89.5)	309 (88.0)	
Other	37 (10.5)	42 (12.0)	
Bystander CPR, n (%)	178 (50.7)	172 (49.0)	0.65
Response time, minutes, median (IQR)	8 (6–11)	9 (6–12)	0.1
First monitored rhythm, n (%)			0.62
VF/pulseless VT	107 (30.5)	101 (28.8)	
PEA/asystole	244 (69.5)	250 (71.2)	

Categorical variables are shown as the number of patients (%). Continuous data are presented as median (IQR)

Abbreviations: see Table 1

Table 4. Prehospital and in-hospital treatment of OHCA according to presence or absence of a physician on the scene (after propensity score matching)

	Paramedic-staffed EMS (n = 351)	Physician-staffed EMS (n = 351)	*P*-value
Prehospital treatment			
Defibrillation time, minutes, median (IQR)	10.5 (8–18)	13.5 (7–26)	0.43
Number of defibrillation shocks, median (IQR)	2 (1–4)	2 (1–4)	0.64
Supraglottic airway, n (%)	140 (42.8)	57 (17.1)	<0.01
Endotracheal intubation, n (%)	195 (59.6)	251 (75.4)	<0.01
Routes of medication administration, n (%)			0.31
Peripheral IV	317 (99.1)	314 (98.1)	
IO	3 (0.9)	6 (1.9)	
Adrenaline, n (%)	310 (97.5)	310 (95.4)	0.15
Amiodarone, n (%)	113 (35.5)	140 (43.1)	0.05
Atropine, n (%)	104 (32.7)	148 (45.5)	<0.01
Lidocaine, n (%)	1 (0.3)	2 (0.6)	0.57
Magnesium sulfate, n (%)	12 (3.8)	6 (1.9)	0.14
UFH, n (%)	11 (3.5)	19 (5.9)	0.15
ECG e-transmission after ROSC, n (%)	43 (42.2)	40 (30.8)	0.07
Transport to hospital without ROSC, n (%)	6 (1.9)	10 (2.9)	0.42
Time to termination of CPR, minutes, median (IQR)	37 (28–49.5)	32 (21–42.5)	<0.01
In-hospital treatment			
Coronary angiography, n (%)	22 (7.3)	32 (10.4)	0.18
Myocardial revascularization, n (%)	16 (6.1)	22 (9.2)	0.19
ICD/CRT-D implantation, n (%)	5 (1.7)	3 (1.0)	0.45
Duration of hospital stay, days, median (IQR)	9 (4–19)	11 (2–30)	0.45

Categorical variables are shown as the number of patients (%). Continuous data are presented as median (IQR)

Abbreviations: CRT-D, cardiac resynchronization therapy defibrillator; ECG, electrocardiogram; IO, intraosseous; IV, intravenous; UFH, unfractionated heparin; other — see Tables 1 and 2

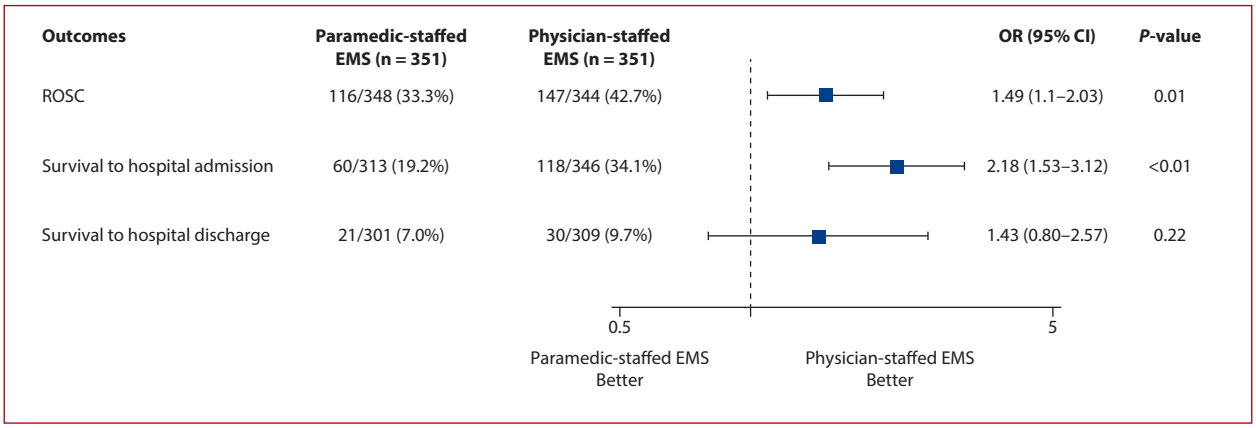

Figure 2. The prehospital and in-hospital outcomes of out-of-hospital cardiac arrest patients attended by physician-manned vs. paramedic-manned ambulances (after propensity-score matching)

Abbreviations: see Table 1 and 2

the variability of OHCA outcomes worldwide [10, 20]. One of these differences refers to the utilization of physician-led EMS or paramedic-led EMS [21]. Both models are being used in developed countries, and limited data support the advantage of one of these options [9, 21]. However, the physician-led EMS model is associated with increased costs [10]. Therefore, the application of physician-staffed EMS should be informed by robust, high-quality scientific data demonstrating improved patient outcomes.

Unfortunately, in the context of OHCA, there are no randomized clinical trials comparing physician- and paramedic-led EMS models, to the best of our knowledge. Moreover, such a randomized clinical trial may be challenging to carry out due to potential costs and logistic issues. Then, the best available evidence on the role of EMS-physician in OHCA so far comes from several observational studies and a meta-analysis pooling their results [3, 9, 13]. Almost all of them showed that the physician's presence in the prehospital setting is associated with improved prehospital outcomes, survival to discharge or 30-day survival, and 1-month neurologically intact survival [3, 8, 9, 13, 22–25]. On the contrary, our study has demonstrated that in the cohort of Polish, non-traumatic OHCA patients, physician-led CPR is associated with improved ROSC and survival-to-admission rates, but this does not translate into higher survival to discharge as compared to CPR provided by paramedics. Notably, there are remarkable differences in our study's design and EMS system in Poland as opposed to previous reports.

First, the presence of physicians on the scene in previous studies was defined in various ways [3, 9, 13]. Physicians are not an integral part of the EMS team in some EMS systems and arrive at the scene independently from EMS. Therefore, it is hard to assess their contribution to the CPR [9]. Moreover, in other studies, only physicians who had happened to be at the scene at the moment of the patient's collapse or who had happened to be in the ambulance for the training of the ambulance crew might have been engaged in prehospital CPR [8]. Contrary to these studies, in Poland, EMS physicians are an integral part of so-called "specialized" emergency medical units; they accounted for one-third of all ambulance teams in the area covered by our registry during the study period.

Second, OHCA cases in Poland usually receive priority for physician-staffed EMS dispatch (if both teams are available when receiving an emergency call and expected response times are the same). However, as we have shown in our study, most of the bystander witnessed, non-traumatic OHCA cases are attended by paramedic-staffed EMS to reduce response time. Thus, the absence of a physician on the scene is mainly driven by the lack of availability of physician-manned ambulances at a given moment, which is random. However, similar to previous studies, we could not exclude that physician-staffed EMS might not have been dispatched if it was futile in the assessment of dispatchers [3, 9]. Therefore, to reduce the selection bias, we excluded patients with initially poor prognosis, i.e., patients with unwitnessed collapse, traumatic cause, and those treated by more than one EMS team (as the dispatch of the second ambulance is usually associated with prolonged CPR and no ROSC); we also matched groups using propensity scores. Notwithstanding, our study still might be biased by unmeasured confounding owing to its observational design.

Third, not in all EMS systems paramedics are allowed the same scope of practice in terms of ALS as the EMS physicians [8–10]. Conversely, in Poland, in the prehospital settings, paramedics are credentialed to perform procedures such as endotracheal intubation, using manual defibrillators, obtaining intravascular access, and administering guideline-recommended medications during CPR. However, in our study, the physician-manned ambulance teams more often performed endotracheal intubation than paramedics. There are at least two possible explanations for this. First, considering that endotracheal intubation in the OHCA setting is challenging, and paramedics, who are

less experienced in this procedure than physicians (mostly anesthesiologists, who obtain these skills also during planned procedures in the operating room), were more likely to choose supraglottic airway (SGA) devices [26]. The second possible explanation is that the crew size of physician-manned ambulances is usually larger (three vs. two medically trained rescuers), which provides an extra pair of hands for endotracheal intubation. Although, it contrasts with previous randomized simulation trials, which have not shown the advantage of three rescuers compared to two rescuers in ALS effectiveness [27, 28].

Nonetheless, it is worth emphasizing that the advantage of endotracheal intubations during OHCA is controversial [26]. The only ALS interventions consistently shown to improve outcomes are high-quality chest compressions and early defibrillation [18, 19]. In this context, it should be noted that the time interval from call to ambulance arrival in the physician-staffed EMS group before propensity-score matching was significantly longer, probably due to the lower availability of these ambulances. Although the response time is one of many factors influencing ROSC and survival after OHCA, it is important to stress that the longer response time of physician-staffed ambulances might reduce the potential benefits of physician-led CPR.

Moreover, our study also has other limitations that should be acknowledged. Based on our data, we could not determine whether there are any differences in post-ROSC care, which may explain improved prehospital survival in patients treated by physician-led EMS. Patients after ROSC are often unstable, so there might be some potential benefits from physicians' experience and skills, but further studies need to evaluate this hypothesis. What is more, since in-hospital data was derived from administrative data, we had no information on neurological outcomes at discharge. Finally, the generalizability of our findings is limited and may not apply to other countries or regions with much different legislation and EMS systems organization.

In summary, our study showed that OHCA patients attended by physician-staffed EMS were more likely to have ROSC and survive till hospital admission. However, better prehospital outcomes might not translate into improved in-hospital prognosis in these patients.

Article information

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Comparison of postoperative complications following cardiac surgery with or without added surgical ablation in patients with coronary and/or valvular heart disease plus atrial fibrillation

Marta Czapka, Łukasz Moskal, Adam Rowiński, Katarzyna Baczyńska, Ireneusz Szwedo, Wojciech Kustrzycki, Romuald Cichoń

Medinet Heart Center, Wrocław, Poland

Correspondence to:
Marta Czapka, MD,
Medinet Heart Center,
Kamieńskiego 73a,
51–124 Wrocław, Poland,
phone: +48 531 736 432,
e-mail:
marta.m.czapka@gmail.com

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INTRODUCTION

Atrial fibrillation (AF) is the most common supraventricular arrhythmia associated with an increased risk of death, stroke, heart failure, and thromboembolic events, which results in an increased number of hospitalizations [1–4]. Moreover, the prevalence of AF increases with age [4, 5]. According to epidemiological data, 1%–2% of the population suffers from this arrhythmia [1]. Patients with atrial fibrillation complain of a significant reduction in the quality of life in comparison to healthy people of the same age and those with similar cardiovascular diseases [6]. Effective treatment of presented arrhythmia, like surgical ablation, appears to be a priority given the impact of atrial fibrillation on the quality of life and life expectancy. Numerous studies show that patients with atrial fibrillation who underwent ablation have a comparable survival rate to those without AF [7]. It has also been demonstrated that the 1-year survival rate after coronary artery bypass grafting (CABG) is greater in patients after additional ablation compared to those without the procedure [8]. Therefore, a combination of elective cardiac surgery and ablation seems to be the appropriate treatment choice for patients with atrial fibrillation. Nevertheless, there is still a great number of patients who do not receive optimal surgical treatment [5, 8].

We assessed the postoperative complications rate in patients who underwent a combined procedure (primary and concomitant surgical ablation of AF) in comparison to patients who received only the primary procedure.

METHODS

We retrospectively reviewed all patients hospitalized in the Medinet Heart Center between the years 2016 and 2018 who met inclusion criteria (presence of paroxysmal AF or different than paroxysmal AF) and exclusion criteria (life-saving surgery, incomplete medical documentation). For baseline characteristics of our patients, the information on sex, age, type of AF (paroxysmal AF and other than paroxysmal AF), presence of arterial hypertension, history of stroke, creatinine level in the blood, and the level of EuroSCORE II was acquired.

Performed cardiac interventions were divided into the CABG, valve surgery, and combined groups.

Data on creatinine levels in the first 3 days after surgery, dialysis, stroke, intestinal ischemia, multiorgan failure (MOF), reoperation because of bleeding, postoperative wound infection, exacerbation of renal failure, pneumonia, and death constituted postoperative complications.

Continuous variables were expressed as mean standard deviation (SD) for normal distributions, while others were presented as median (interquartile range [IQR]). Categorical data are given as frequency (percentages). Normality was tested using the Shapiro-Wilk test.

The Student t-test was used for comparisons between the groups of parametric

Table 1. Comparison of the participants

Parameters		Group A (with ablation) (n = 51)	Group B (without ablation) (n = 62)	*P*-value
Baseline characteristics				
Age, years, mean (SD)		65.7 (8.4)	69.4 (8.6)	0.03
Female gender, n (%)		14 (27.5)	21 (33.9)	0.18
AF, n (%)	Paroxysmal	20 (39.2)	17 (27.4)	0.18
	Other	31 (60.8)	45 (72.6)	
Atrial hypertension, n (%)		30 (58.8)	35 (56.5)	0.80
Stroke, n (%)		3 (5.9)	3 (4.8)	1.00
Creatinine level before surgery, mg/dl, median (IQR)		1.06 (0.87–1.22)	1.08 (0.88–1.29)	0.70
EuroSCORE II, median (IQR)		0.02 (0.01–0.03)	0.02 (0.01–0.04)	0.85
Postoperative complications				
Dialysis, n (%)		2 (3.9)	2 (3.2)	1.00
Stroke, n (%)		1 (2.0)	1 (1.6)	1.00
Intestinal ischemia, n (%)		0 (0)	0 (0.0)	1.00
MOF, n (%)		2 (3.9)	1 (1.6)	0.59
Reoperation due to bleeding, n (%)		10 (19.6)	10 (16.1)	0.63
Postoperative wound infection, n (%)		1 (2.0)	2 (3.2)	1.00
Exacerbation of renal failure, n (%)		5 (9.8)	4 (6.5)	0.73
Pneumonia, n (%)		1 (2.0)	0 (0.0)	0.45
Death, n (%)		3 (5.9)	3 (4.8)	1.00
Creatinine level — first 3 days after surgery, mg/dl, median (IQR)		1.19 (0.83–1.65)	1.46 (1.05– 1.97)	0.15

Abbreviations: AF, atrial fibrillation; MOF, multiorgan failure

variables. For the non-parametric hypothesis, the χ^2 test or the exact Fischer test was applied. The Mann-Whitney U test was used for skewed variables. All statistical tests were evaluated at a significance level of 0.05. The PQStat 1.6.8 software was used during the statistical analysis.

RESULTS AND DISCUSSION

The study group consisted of 113 patients hospitalized in the Medinet Heart Center. They were divided into two groups: one without surgical ablation (group A, n = 51) and one with patients who had combined cardiac surgery and surgical ablation (group B, n = 62). To check the homogeneity of both groups, preoperative demographic risk factors such as gender and age were analyzed. Both groups were comparable with regard to female sex (group A, n = 14 vs. group B, n = 21; *P* = 0.18), but differed in a reference to age (group A, n = 65.7 [8.4] years vs. group B, n = 69.4 [8.6] years; *P* = 0.03).

The prevalence of paroxysmal AF and non-paroxysmal AF (persistent + permanent) was comparable in both groups (*P* = 0.18).

In terms of comorbidities: arterial hypertension (group A, n = 30 vs. group B, n = 35; *P* = 0.80), history of stroke (group A, n = 3 vs. group B, n = 3; *P* = 1.00), and creatinine levels (group A, n = 1.1 mg/dl vs. group B, n = 1.2 mg/dl; *P* = 0.70; 1.06 [0.87–1.22] mg/dl to 1.08 [0.88–1.29] mg/dl (median [IQR]) in the blood, both groups were comparable. No statistically significant difference was observed regarding EuroSCORE II between both groups (Table 1).

Patients included in our research have undergone various procedures, including CABG (group A, n = 3, group B, n = 15), valve surgery (group A, n = 8, group B, n = 10), and a combined procedure (group A, n = 40, group B, n = 37).

Depending on the scope of ablation, the following types were performed: isolation of right and left pulmonary veins, extended ablation (including isolation of pulmonary veins and other additional ablation lines, usually [additionally] isolation of the left atrium posterior wall — box lesion, right atrial ablation, and others), and Maze IV (complete set of ablation lines according to the Maze IV scheme).

As a result, we compared the occurrence of stroke, intestinal ischemia, MOF, exacerbation of kidney failure, pneumonia, death, the incidence of surgical wound infection, and necessity of reoperation due to hemorrhage after surgery. We also compared creatinine levels in the blood on three consecutive days after the operation (Table 1).

Regarding the usage of catecholamines and steroids intraoperatively, the two groups did not differ significantly. No patient required implantation of a permanent pacemaker after surgery. All patients received the same anticoagulant treatment consisting of low-molecular-weight heparin at the beginning and vitamin K antagonists (VKA) afterward.

Effective ablation, regardless of the method, frees most patients from arrhythmia episodes and improves their quality of life [6, 7, 9]. The literature compares the survival of patients undergoing successful ablation to those without atrial fibrillation in history [7]. This is especially important for patients referred to cardiac surgery departments, as a great number of them are diagnosed with atrial fibrillation. Consequently, management of those patients requires close cooperation between cardiac surgeons and electrophysiologists [10].

Our findings in terms of the risk of death and complications are consistent with other studies on this topic [8, 11, 12]. In addition, mortality after cardiac surgery due to

any reason is lower in those patients who have undergone additional ablation [8]. Restoring the sinus rhythm gives patients a chance for a better and longer life.

Even though the efficiency of concomitant surgical ablation and cardiac surgery has been shown, it is still underused. The length of aortic cross-clamp and overall procedure constitute the main reasons among cardiac surgeons to refrain from surgical ablation [13].

Our study has shown that adding ablation to elective cardiac surgery does not increase the risk of death or the incidence of other complications. Prolonging the time of the procedure, increasing the time of cardiac arrest did not affect the mortality or number of complications.

We strongly recommend performing concomitant surgical ablation during cardiac surgery since this is a safe procedure and is of great importance in terms of patients' prognosis for substantially improved quality of life.

Article information

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Effect of sodium-glucose co-transporter-2 inhibitors on right ventricular function in patients with type 2 diabetes mellitus: A pilot study

Dimitrios Patoulias[1], Maria Toumpourleka[2], Alexandra Katsimardou[1], Ioanna Zografou[1], Konstantinos Stavropoulos[1], Konstantinos Imprialos[1], Asterios Karagiannis[1], Michael Doumas[1], Christodoulos Papadopoulos[2]

[1]2nd Propaedeutic Department of Internal Medicine, General Hospital "Hippokration", Aristotle University of Thessaloniki, Thessaloniki, Greece
[2]3rd Department of Cardiology, General Hospital "Hippokration", Aristotle University of Thessaloniki, Thessaloniki, Greece

Correspondence to:
Dimitrios Patoulias, MD, 2nd Propaedeutic Department of Internal Medicine, General Hospital "Hippokration", Aristotle University of Thessaloniki, Konstantinoupoleos 49, 54642 Thessaloniki, Greece, phone: +30 694 690 07 77, e-mail: dipatoulias@gmail.com

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) and cardiovascular disease are interconnected [1]. Subjects with T2DM feature an excess risk for heart failure (HF) development [2] although mechanisms are not fully defined [3].

Right ventricular (RV) function is adversely affected by both prediabetes and T2DM [4, 5]. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have shown outstanding cardiovascular and renal benefits in T2DM. Recently, they have been incorporated into the treatment algorithm of HF with reduced left ventricular ejection fraction (HFrEF), according to the 2021 European Society of Cardiology (ESC) guidelines [6] while national societies have also adopted this evidence [7]. However, there is no evidence of their effect on RV function.

Therefore, we conducted a pilot study, to assess the effect of SGLT2i on RV function in patients with T2DM.

METHODS

This is a single-arm, prospective, observational study, conducted between January 2020 and August 2021. The study protocol was approved by the Ethics Committee of the School of Medicine, Aristotle University of Thessaloniki, and performed in accordance with the Declaration of Helsinki.

Subjects aged 18–75 years old, with an established diagnosis of T2DM (≥12 months), glycated hemoglobin (HbA_{1C}) values 6.5%––10.0%, stable antidiabetic and antihypertensive treatment over the last 6 months, and an indication for the initiation of an SGLT2i, were eligible to participate, after providing written informed consent. Enrolled participants were initiated to dapagliflozin or empagliflozin once daily.

We set as the primary efficacy outcome the change in tricuspid annular plane systolic excursion (TAPSE). We also assessed a number of echocardiographic parameters: basal linear RV end-diastolic diameter (4-chamber view), RV end-systolic (RVES) area, RV end-diastolic (RVED) area, RV s', RV e', RV a', RV e'/a', and RV systolic pressure (RVSP) [8].

We assessed several anthropometric and laboratory markers of interest. Blood samples were drawn after overnight fasting. We also evaluated major safety outcomes.

An echocardiographic study was performed by the same cardiologist, highly trained and blinded to clinical information, according to the current guidelines for the echocardiographic assessment of RV, at baseline and at the end of the prespecified follow-up period [8]. An echocardiographic assessment of left ventricular (LV) function was also performed.

Statistical analysis

Continuous variables are presented as mean (standard deviation [SD]) or median (interquartile range [IQR]), according to the normality of distribution, while categorical variables are presented as relative frequencies and percentages (n [%]). The Shapiro-Wilk

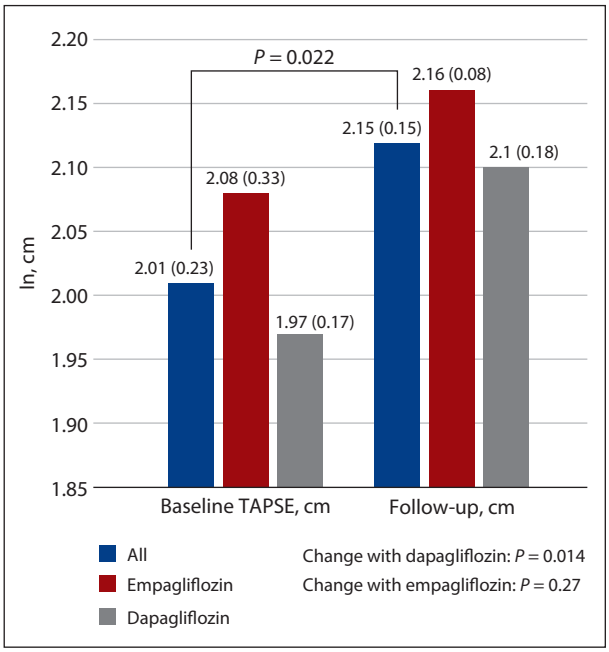

Figure 1. Effect of sodium-glucose cotransporter-2 inhibitor, empagliflozin, and dapagliflozin on right ventricular systolic function as assessed with tricuspid annular plane systolic excursion

Abbreviations: TAPSE, tricuspid annular plane systolic excursion

test was used to test for normality. In the case of normal distributions, we performed hypothesis testing using a one-tailed paired t-test, otherwise we used a one-tailed Wilcoxon signed-rank test. Pearson coefficient correlation test was used to assess the correlation of endpoint of interest (change in TAPSE) with numerical variables of interest. *P*-values <0.05 were considered significant. R-4.1.3 software for Windows (The R Foundation) was utilized for statistical analysis.

RESULTS AND DISCUSSION

Twenty subjects were included. Their mean age was 62.8 (7.87) years, while the median T2DM duration was 9.5 (4.5–12.25) years. Fifteen patients were male. Mean value of HbA_{1c} was 7.43% (1.76%), while mean body mass index (BMI) was 31.31 (5.59) kg/m^2. Main baseline characteristics are summarized in Supplementary material, *Tables S1* and *S2*. A follow-up visit was planned 6 months after the initiation of an SGLT2i. Due to special regulations imposed in the context of the COVID19 pandemic, the mean treatment duration and follow-up period finally lasted 9.35 (3.4) months.

SGLT2i resulted in a significant increase in TAPSE from 2.01 (0.23) to 2.12 (0.15) cm ($P = 0.02$; Figure 1). No difference between the two SGLT2i was documented ($P = 0.7$). Change in TAPSE was significant in subjects with prior cardiovascular disease ($P = 0.024$), while it was non-significant for subjects without such history ($P = 0.26$). No significant effect of SGLT-2i on other indices of RV systolic and diastolic function was demonstrated (Supplementary material, *Table S3*).

We did not document a significant correlation between change in TAPSE and rest echocardiographic, anthropometric, or laboratory parameters during the trial, except for a significant positive correlation between change in TAPSE and change in RV diameter at the mid-cavitary level ($r = 0.46$; $P = 0.042$; Supplementary material, *Figure S1*). Improvement in blood pressure (BP), body weight, and glycemic control with SGLT2i were not significant, possibly due to small sample size. No significant correlation between change in TAPSE and change in BP, body mass index, or HbA_{1c} was demonstrated. No major safety issues were reported.

In this pilot study, treatment with SGLT2i resulted in a significant improvement in TAPSE. In a former trial, empagliflozin did not affect RV mass index (RVMi), RV end-diastolic and end-systolic volume index (RVEDVi, RVESVi), and RV ejection fraction (RVEF), while echocardiographic assessment documented a non-significant decrease in TAPSE [9]. In another trial, 3-month treatment with empagliflozin resulted in a significant decrease in the pulmonary artery (PA) diastolic pressure in patients with HF regardless of left ventricular ejection fraction or presence of T2DM [10]. Results concerning PA systolic pressure and mean PA pressure were consistent [10]. Experimental data have suggested that empagliflozin decreases RV hypertrophy and fibrosis, while it also inhibits PA remodeling in a model of pulmonary hypertension [11].

At present, it seems impossible to determine the mechanisms underlying this beneficial effect on TAPSE. Osmotic diuresis and natriuresis [12], along with inhibition of Na^+/H^+ exchanger (NHE) activity and increase in mitochondrial Ca^{2+} concentration [13], amelioration of cardiac fibrosis and inflammation [14], and improvement in coronary microvascular function [15] might be among those mechanisms. Preload and afterload reduction, mainly by natriuresis, might be the most significant factor that leads to TAPSE increment and improved RV function.

The small sample size and study design represent the main limitations. We should also highlight the specific limitations of 2D echocardiography in clinical practice. cMRI is the modality of choice for accurate anatomic and cardiac tissue characterization although is much more expensive and not widely available. In addition, it would be interesting to assess the impact of SGLT-2i on RV function in patients with HF, in whom the beneficial effect could hypothetically be more pronounced. Unfortunately, only one patient in our cohort had a history of HF.

Finally, our results should be interpreted with caution. Both TAPSE and RV s' velocity assessed by tissue Doppler imaging (TDI) are angle-dependent and reflect only the longitudinal function of the basal segment of the RV, neglecting the contribution of the apical and RV outflow tract components to RV global systolic performance. While usually they exhibit similar changes, TAPSE is more load dependent than TDI S' velocity. Thus, one can

speculate that since SGLT2i may promote natriuresis and reduce preload, TAPSE might show an improved value after SGLT2i therapy, in contrast to RV S', which is less load-dependent and possibly needs more time to show a significant change.

To sum up, this is the first study to assess the effect of SGLT2i on RV function in patients with T2DM. These results should be a motive for further assessment of the effect of SGLT2i on RV function, based on its prognostic role. Larger studies will shed further light on this interesting topic.

Supplementary material

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

Article information

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The relationship between anisocytosis, quantitative and qualitative characteristics of coronary atherosclerosis, and major adverse cardiac events in patients with coronary artery disease: Rationale and study design

Anna Oleksiak[1], Cezary Kępka[2], Mariusz Kruk[2]

[1]Department of Intensive Cardiac Therapy, National Institute of Cardiology, Warszawa, Poland
[2]Department of Coronary and Structural Heart Diseases, National Institute of Cardiology, Warszawa, Poland

Correspondence to:
Anna Oleksiak, MD, PhD,
Department of Intensive Cardiac Therapy,
National Institute of Cardiology,
Alpejska 42, 04–628 Warszawa, Poland
phone: +48 22 343 43 15,
e-mail: aoleksiak@ikard.pl

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INTRODUCTION

Red cell distribution width (RDW) is a quantitative measure of anisocytosis, which is the measured index of erythrocyte dispersion with the average value (Figure 1A). In our previously published original study, we showed that the RDW is an independent and strong predictor of death and myocardial infarction (MI) in secondary prevention in patients with coronary artery disease (CAD), with a cut-off value of 14% [1].

In 2009, Tonelli et al. [2] demonstrated in an analysis involving 4111 patients that increasing RDW is associated with mortality and major adverse cardiovascular events (MACE) in patients after MI. Similar conclusions were presented in recent research including patients with acute coronary syndrome or undergoing percutaneous coronary intervention (PCI) [3–5]. Higher levels of the RDW are associated with a higher incidence of cardiovascular events also in patients with chronic heart failure [6, 7]. In another study, RDW has been identified as an independent predictor of mortality in patients with heart failure due to ischemic etiology, but there was no such relationship for heart failure due to valvular abnormalities [8].

The increasing number of publications confirmed the prognostic value of RDW in patients with CAD; however, the substrate pathophysiology of this relationship is unknown. Some authors suggest that the presence of anisocytosis may reflect chronic subclinical inflammation, inflammatory biomarkers, oxidative stress, and abnormal erythropoiesis [9, 10]. We showed, however, that this relationship does not depend on the level of hemoglobin [1]. In addition, the National Health and Nutrition Examination Survey (NHANES) enrolling 8513 participants showed that the RDW, but not high-sensitivity C-reactive protein (hs-CRP), were associated with cardiovascular mortality independently of traditional risk factors in patients with no previously diagnosed heart disease [11]. None of the studies included potential confounders: the level of hemoglobin, white blood cell count, hs-CRP, levels of iron, vitamin B12, and folic acid.

Other potential mechanisms could include a relationship between the RDW and atherosclerosis or the presence of vulnerable plaques. In an original study published in 2015, Lappegard et al. [12] showed that anisocytosis is associated with the progression of atherosclerosis in carotid arteries in a group of 4677 patients and a 1% increase in the RDW was associated with an increase in the total plaque area of about 0.6 mm^2. For coronary arteries — this problem has not yet been investigated.

The study aims to investigate the relationship between anisocytosis and CAD patients' prognosis and clarify whether there is a link between anisocytosis and quantitative and qualitative parameters of atherosclerotic plaques in coronary arteries.

METHODS

This is a prospective, single-center, observational study (the study flowchart is presented

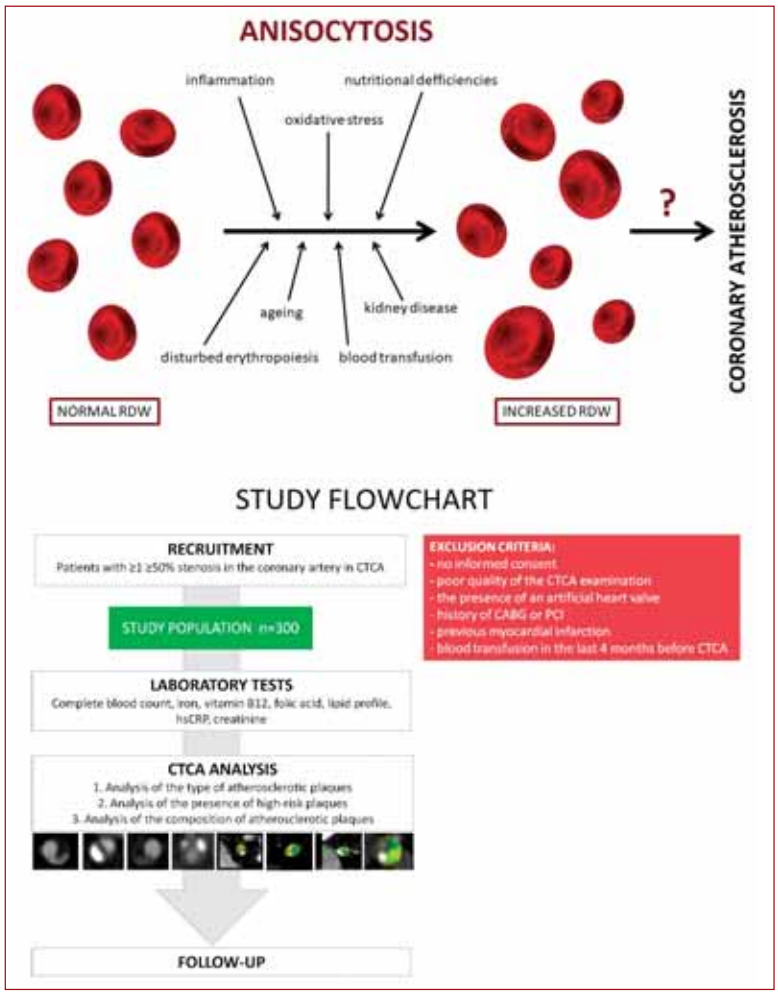

Figure 1. A. The overview of the pathophysiology of anisocytosis. **B.** Study flowchart

Abbreviations: CABG, coronary artery bypass grafting; CT, computed tomography; CTCA, computed tomography coronary angiography; hs-CRP, high sensitivity C-reactive protein; PCI, percutaneous coronary intervention; RDW, red cell distribution width

in Figure 1B). Three hundred consecutive patients were enrolled in the study. The inclusion criteria were signed informed consent; age over 18 years; ≥1 plaque with ≥50% narrowing of the coronary artery lumen with a reference diameter >2.0 mm on computed tomography coronary angiography (CTCA). The exclusion criteria were poor quality of CTCA enabling analysis; the presence of artificial heart valves; previous revascularization; previous myocardial infarction and being a recipient of red blood cell concentrate during the last four months before the CTCA. All patients had their clinical histories and blood tests taken, including lipids, complete blood count (CBC), creatinine, hs-CRP, iron, vitamin B12, and folic acid levels. Anisocytosis was defined as RDW-CV (coefficient of variation) out of the reference ranges which were 11.6%–14.4% for men and 11.7%–14.4% for women. A quantitative and qualitative analysis of CTCA for assessment of atherosclerotic plaques was performed using Syngo CT Coronary (Siemens, Germany), including the presence of high-risk plaque features: low-attenuation plaque (LAP), napkin-ring sign (NRS), positive remodeling (PR), spotty calcium (SC) (Syngo, Siemens), type of plaque (calcified, non-calcified, mixed) (Syngo, Siemens), and their composition (calcified, fibrous, fibro-fatty, necrotic core) (QAngioCT, Medis). The patient management was according to the current European Society of Cardiology (ESC) guidelines. Participation in the study did not influence standard ESC treatment recommendations. The study was approved by the Ethics Committee of the National Institute of Cardiology.

Follow-up and study outcomes

Patient history data were obtained from the patients' interviews and medical documentation. The follow-up data were collected based on outpatient visits or using a standardized telephone questionnaire. The follow-up was planned as at least 24 months from CTCA, therefore, by definition, the shortest observation period was 2 years, and the longest exceeded 5 years (recruitment started in 2016). The follow-up data were regularly collected after the first and second year from CTCA. Additional follow-up checks up were performed for all patients in January 2022. Data about invasive procedures, as well as non-invasive functional tasting after CTCA, were also collected.

The primary study outcome is a composite of death, nonfatal myocardial infarction according to the 4th Universal Definition of Myocardial Infarction, and revascularization due to CAD progression, confirmed by invasive angiography during long-term follow-up. Out of the enrolled patients, 18 had elective coronary artery bypass grafting, and 65 had elective percutaneous coronary intervention as the result of the index angiography after CTCA. Others were managed medically based on the clinical status and functional ischemia testing. Those procedures were not counted as events.

The secondary study outcomes include the presence of high-risk coronary plaque features, plaque composition, and the plaque burden.

Statistical analysis

The size of the group was estimated based on the differences in the mean RDW values. Assuming mean RDW at 13.4% (1.1%), 30 events would allow detection of a 6% difference between events/non-events, with alpha error of 0.05 and power of 80%. Based on the previous literature, we assumed an 11% (30 patients) event rate over the planned follow-up period, translating into 270 enrolled subjects [1]. We recruited about 10% patients more than needed; the final study group included 300 patients.

Continuous data with normal distribution will be presented as means (standard deviation [SD]). Non-normally distributed variables will be presented as medians with interquartile ranges (IQR). Patients with and without anisocytosis will be compared for demographic data, clinical characteristics, and CTCA findings. The predictive value of the variables will be evaluated with Cox univariable and multivariable proportional hazards regression analysis. Kaplan-Meier curves will be presented for primary study outcomes. P <0.05 will be considered statistically significant. All analyses will be performed using MedCalc Software (version 13.2.2, Ostend, Belgium).

RESULTS AND DISCUSSION

The study recruited 300 patients (191 men) at the mean age of 67 (8) years who underwent laboratory tests, advanced coronary plaque assessment, and follow-up. Full study results will be presented in the main paper.

Anemia is quite common and often underestimated clinical problem in CAD patients, which can exacerbate angina symptoms due to insufficient blood oxygenation, and thus — with the coexistence of stenotic coronary arteries — impaired oxygen supply to the myocardial muscle.

The study aims to provide prospectively collected information about the relationship between anisocytosis and CAD patients' prognosis during long-term follow-up and between anisocytosis and the quantitative and qualitative parameters of atherosclerotic plaques, including high-risk plaque features, plaque composition, and plaque burden. The study will provide unique information on the importance of anisocytosis in patients with CAD.

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Intravascular ultrasound-guided primary stenting of spontaneous carotid artery dissection

Galina Zlatancheva[1], Dobrin Vassilev[1], Kiril Karamfilov[1], Julia Petrova[2], Dora Zlatareva[3], Robert J Gil[4]

[1]Cardiology Clinic, "Aleksandrovska" University Hospital, Sofia, Bulgaria
[2]Neurology Clinic, "Aleksandrovska" University Hospital, Sofia, Bulgaria
[3]Head of Department of Diagnostic Imaging, Medical University, Sofia, Bulgaria
[4]Department of Invasive Cardiology, Central Clinical Hospital of the Ministry of the Interior, Warszawa, Poland

Correspondence to:
Galina K Zlatancheva, MD, PhD, Cardiology Clinic, "Aleksandrovska" University Hospital, 1, Georgi Sofiyski St, 1431, Sofia, Bulgaria, phone: +35 929 230 467, e-mail: zlatancheva.gal@gmail.com

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INTRODUCTION

One of the increasingly common causes of ischemic stroke in young and middle-aged patients, with small female dominance, is spontaneous carotid artery dissection (SCAD). The main mechanism for stroke on those occasions, is thromboembolism, while others believe that hemodynamic insufficiency plays a crucial role [3, 4]. The etiology and pathogenesis of SCAD are not yet fully understood [2]. It is thought that SCAD may be caused by external factors (hypertension or trauma), internal factors (primary arterial wall disease), or a combination of both [2]. It can be asymptomatic or symptomatic. Symptoms in most patients with carotid dissection include headache or neck pain. The treatment of SCAD is still controversial, ranging from conservative treatment with antiplatelet drugs only to open surgery or endovascular treatment [1–4].

METHODS

For the last one year in our clinic we treated endovascularly three patients with spontaneous dissection of the internal carotid artery. All cases were performed under intravascular ultrasound guidance to visualize, as much as possible, dissection extension and to guide the right size of devices and verify the outcomes. Patients provided written informed consent to participate.

In all three cases, first we advanced a 6 F guide catheter in the common carotid artery. Then we crossed the dissection through the true lumen with a 0.014-inch glide wire. We confirmed the position by contrast injection under fluoroscopy. After that, we placed a distal protection filter Spider-Fx 5 mm. The distal protection device was required to prevent distal embolization of thrombus fragments formed in the false lumen. We preferred the implantation of the Wallstent and BioFreedom stents. MicroNet-covered stents are a possible alternative, but they have a higher crossing profile [15, 16].

A 31-year-old woman was admitted with a headache and gradually developing weakness in her right limbs, with preserved coordination. On nuclear magnetic resonance of the head, the dissection of the left internal carotid artery (ICA) with a length of about 25 mm was visualized, with a demonstration of acute and early subacute ischemic changes in the left cerebral hemisphere (Figure 1A). The patient was loaded with clopidogrel and aspirin. Carotid angiography was performed. The size and extension of the artery and dissection were unclear from the contrast-enhanced computed tomography (CT) and angiography, and a decision for intravascular ultrasound (IVUS) examination was taken. It was possible to advance an IVUS probe to the level of C3 segment with a good determination of distal vessel size. After placement of the distal protection filter Spider-Fx 5.0 mm, a balloon dilation with a Sprinter balloon 3.0 × 30 mm at 2–3 atm was performed to visualize better distal vasculature. Then, 2 stents were implanted from proximal to distal — Wallstent 7.0/50 mm, BioFreedom 4.0/24 mm. The final IVUS does not show residual dissection (Figure 1B–D). After the procedure, the patient was without headache and nausea, but still with the persistence of right hemiparesis and hypesthesia on the right. A week later, control CT demonstrated well-apposed stents,

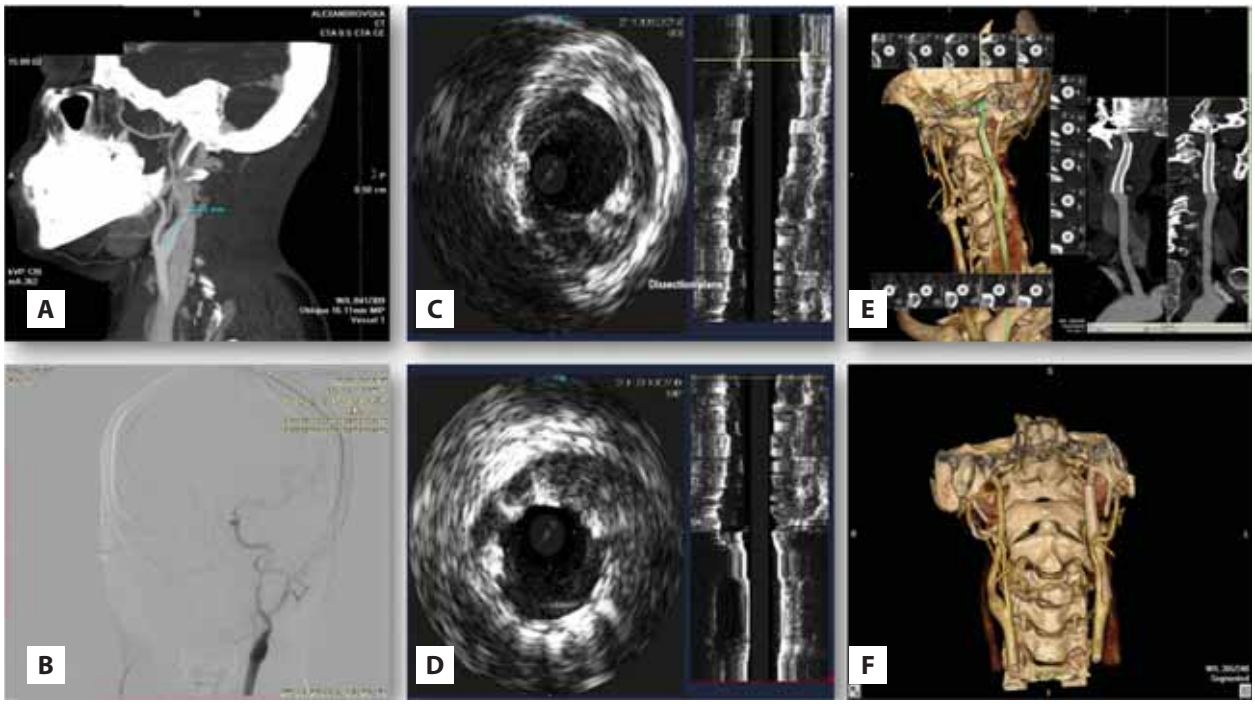

Figure 1. A. Nuclear magnetic resonance of the head, the dissection of the left internal carotid artery. **B.** Conventional digital subtracted angiography visualized the dissection of the left internal carotid artery. **C.** Intravascular ultrasound probe to the level of C3 segment with a good determination of distal vessel size and showing dissection plane. **D.** Final result after stenting. **E** and **F.** Nuclear magnetic resonance of the head at the third month of follow-up — the lumen of the stent area appears well contrasted

with a minimal residual wall hematoma of the left ICA, an ischemic area formed in the area of the precentral curve in the basin of the left middle cerebral artery. On contrast-enhanced CT performed during follow-up, the stents were without restenosis, with resorption of hematoma behind the stent struts and maturation of ischemic changes in the left hemisphere (Figure 1E, F).

A 63-year-old woman was admitted to the hospital after a loss of consciousness, lasting 5 minutes, occurring during a walk. In recent months, she had two similar episodes — one during defecation, the other during a meal. In her history, she had long-lasting arterial hypertension (over 10 years) with no optimal drug control and diabetes diagnosed 7–8 years earlier — patient has diabetes mellitus, she is on drug treatment, without insulin. On 24-hour electrocardiography monitoring, she was without evidence of arrhythmias or conduction abnormalities. The neurological status was normal. Duplex ultrasonography (DUS) of carotid arteries was performed, and dissection of the left carotid artery was observed. During the examination, the patient abruptly lost consciousness. She was immediately transferred to the catheterization laboratory. Clopidogrel and Aspirin loading doses were given. We performed carotid angiography, which demonstrated dissection in the common carotid artery with extension to the ICA. An IVUS examination was performed and dissection up to the level of C2 segment was visualized. An intervention was made with direct stent implantation, Wallstent 7.0/50 mm and SPIDER-FX 5.0 mm distal protection. On control IVUS, there was no evidence of residual dissection. After the procedure, the patient remained hemodynamically stable, with no abnormalities in neurological status. She was followed up at 3 and 6 months after the procedure with DUS (patient refused control CT), and no neurological symptoms were detected (see Supplementary material).

A 37-year-old man arrived in hospital with a 10-day history of numbness and a deviated tongue on the left. He did not report any comorbidities or use any medications. On CT of the brain (without contrast), there was no evidence of stroke. On DUS, a flap was visualized at the ostium of the left ICA, with severely reduced blood flow and thrombosis. Antiplatelet therapy with clopidogrel and aspirin loading doses were given. Magnetic resonance tomography was performed, which showed dissection in the distal part of the left ICA. Carotid angiography confirmed the occurrence and localization of dissection. An IVUS examination was performed with lesion interrogation. After using low-pressure balloon predilation with a coronary balloon 3.0 × 25 mm at 2–3 atmospheres, Wallstent 7.0 × 50 mm was implanted. After the procedure, the patient was without abnormalities in neurological status. The patient was followed up at 3 and 6 months after the intervention. The control CT one year later showed no pathological abnormalities, and the stent was without restenosis (see Supplementary material).

We followed the patients at 12 and 24 months. They are all alive and none of them have neurological symptoms. They continue treatment with only one antiplatelet drug, clopidogrel.

RESULTS AND DISCUSSION

For the first time in the late 1970s, Fisher et al. and Mokri et al. [7, 8] described dissections of carotid and vertebral arteries. The main complication of SCAD is stroke. It can occur in the first 24 hours or up to one month after dissection. The outcomes can be fatal or lead to serious impairments in quality of life. Mechanisms for stroke include thromboembolism, or hemodynamic insufficiency — a decrease in cerebral blood flow from the primary cervical lesion [4, 6, 7]. Using non-invasive and invasive methods, the dissection of the carotid artery can be depicted well enough and a decision about the subsequent treatment can be made.

The main goal in the treatment of SCAD is to prevent ischemic complications that may occur as it progresses. However, there are still controversies about the choice of treatment. It is recommended that the first-line treatment at the beginning of the healing process is the inclusion of antithrombotic drugs. There are no studies to prove their effectiveness [5]. The question is whether to continue only with drug therapy or to switch to surgical or interventional treatment. Of course, in certain circumstances, the choice is clear when we have patients with subarachnoid hemorrhage, recurrent hemorrhagic or ischemic events after initiation of drug treatment, or patients who developed dissecting pseudoaneurysms, also in the case of inability to take antithrombotic drugs [10, 11]. In the last decade, however, carotid stenting has progressed dramatically. Revascularization with stent placement may improve perfusion and limit embolism in patients with embolic or hemodynamic symptoms, just like in our cases. The results show that it can be used safely and effectively even during acute ischemic stroke [12, 13]. Intravascular ultrasound examination has been introduced to improve immediate outcomes after percutaneous transluminal balloon angioplasty and stent placement in carotid stenosis [14]. Here, to the best of our knowledge, we report for the first time the IVUS-guided strategy for the treatment of SCAD. The ultrasound examination has much higher resolution than angiography and CT. This allows for a much more accurate determination of the beginning and end of the dissection region, as well as vessel diameters and lesion length. With the help of IVUS, one can accurately identify stent underexpansion, malapposition, and plaque protrusion. Although further research is needed in this direction, we show that the use of IVUS before and after stenting of acute spontaneous carotid artery dissection can be safe and lead to successful long-term outcomes.

CONCLUSIONS

Endovascular stent placement appears to be a safe and effective option to restore vascular lumen integrity and prevent stroke. Using IVUS as a guide for stent placement and post-stenting confirmation will help ensure proper positioning and improved patency.

Supplementary material

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

Article information

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Papillary fibroelastoma of the aortic valve

Virginija Rudienė[1], Sigita Glaveckaitė[1], Mindaugas Matačiūnas[2], Edvardas Žurauskas[3], Kęstutis Ručinskas[1]

[1]Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania
[2]Department of Radiology, Nuclear Medicine and Medical Physics, Institute of Biomedical Sciences, Vilnius University Faculty of Medicine, Vilnius, Lithuania
[3]National Center of Pathology, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania

Correspondence to:
Virginija Rudienė, MD,
Faculty of Medicine Vilnius University,
M.K. Ciurlionio 21, Vilnius 03101, Lithuania
phone: +37 065 554 952,
e-mail: vr.rudiene@gmail.com

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Cardiac papillary fibroelastomas (CPFs) are benign primary cardiac tumors and are most often found on the downstream side of cardiac valves [1–3]. The most often affected valve is aortic, but these tumors could implicate all valves. The clinical presentation varies from asymptomatic to embolic complications, which can lead to cerebral stroke, myocardial infarction, and sudden cardiac death [1, 2, 4, 5]. In approximately 30% of cases, they are found incidentally, during autopsies, echocardiography, or cardiac surgery [2, 5].

A 34-year-old male was referred to the cardiology department for further evaluation due to dizziness and blinking in the eyes. Neurological examinations (carotid ultrasound imaging, transcranial color-coded duplex ultrasonography, and head computed tomography) were without abnormalities. Transthoracic echocardiography revealed a 0.9 × 1.2 cm oval-shaped mobile mass attached to the left coronary cusp of the tricuspid aortic valve (Figure 1A–B, the arrows). The mass did not cause any outflow tract obstruction or aortic regurgitation. A contrast-enhanced computed tomography scan of the chest confirmed the presence of a hypodense nodular lesion of approximate size of 1.1 × 1.4 × 1.2 cm in the aortic root, adjacent to the origin of the right and left coronary arteries (Figure 1C, the arrow). Based upon the above findings, a differential diagnosis was made which included: papillary fibroelastoma, myxoma, thrombus, and inflammatory mass. A coronary computed tomography angiography was normal. The decision was made to perform an excision of the tumor under cardio-pulmonary bypass. The valve-sparing surgery was done. At the time of surgery, a gel-like tumor of 1.2 × 1.0 × 1.0 cm was found (Figure 1D). The tumor with a pedicle was attached at the base of the commissure between the right and left coronary cusps of the aortic valve.

The pathological analysis confirmed the nature of the mass and revealed multiple, branching fronds of paucicellular, avascular fibroelastic tissue lined by a single layer of the endocardium (Figure 1E–F). The postoperative period was complicated by hemorrhagic anemia and bacterial infection. The patient was discharged after 13 days. There was no recurrence seen on an echocardiogram 6 months after surgery.

The pathogenesis and risk factors of CPFs are unclear. Cardiac papillary fibroelastomas could be diagnosed at any age but most commonly occurs in middle-aged and older adults. Echocardiography is the principal diagnostic examination. Transesophageal echocardiography is more sensitive compared with transthoracic due to typically small sizes of these tumors and their attachment to the endocardial surface. Multimodality imaging (computed tomography and magnetic resonance angiography) could be helpful for differential diagnosis. A biopsy of the tumor is not usually needed. The treatment of CPFs is not clearly defined by guidelines. The surgery is recommended for larger than 1 cm left-sided papillary fibroelastomas, and it reduces the risk of thromboembolic complications [5]. CPFs can be safely excised with preservation of the native valve in experienced surgical centers [4]. Tamin et al. [4] demonstrated that the risk-to-benefit ratio of cardiac surgery is influenced by older age, comorbidities, and perhaps the uncertainty of embolic risk.

Usually, surgical resection is safe and has low perioperative mortality, and it is associated with perfect long-term outcomes [4, 5].

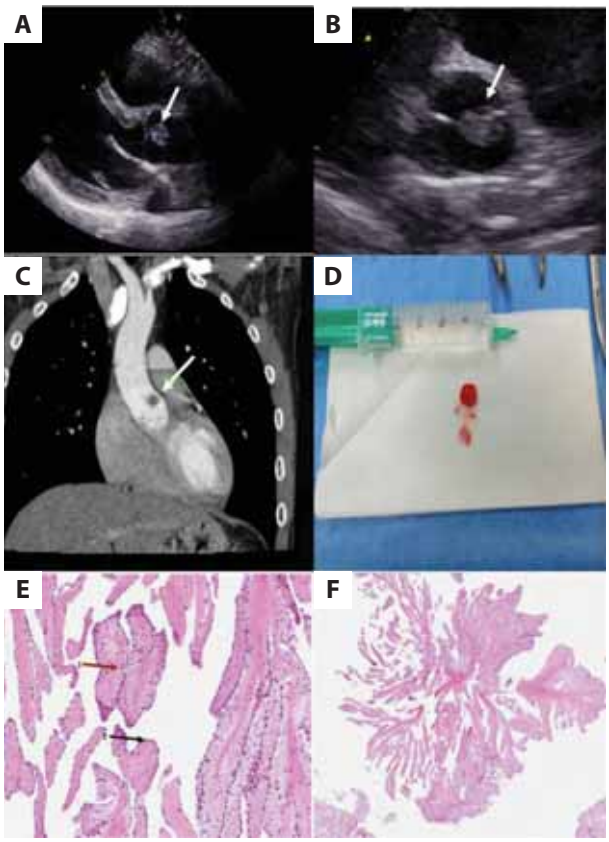

Figure 1. Papillary fibroelastoma of the aortic valve seen on transthoracic echocardiography (**A, B**) and contrast-enhanced computed tomography images (**C**) (the arrows). The microscopic image of the excised mass (**D**) and histo-anatomopathological analysis of the mass (**E–F**, the red — stroma, the black arrow — endocardium)

Article information

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Radiofrequency catheter ablation of an asymptomatic intermittent accessory pathway after heart transplantation

Krzysztof Myrda[1], Alicja Nowowiejska-Wiewióra[1], Michał Zembala[2], Mariusz Gąsior[1,3]

[1]3rd Department of Cardiology, Silesian Center for Heart Diseases, Zabrze, Poland
[2]Department of Cardiac Surgery, Heart and Lung Transplantation and Mechanical Circulatory Support, Silesian Center For Heart Diseases, Zabrze, Poland
[3]3rd Department of Cardiology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland

Correspondence to:
Krzysztof Myrda, MD,
3rd Department of Cardiology,
Silesian Center for Heart Diseases,
M Skłodowskiej-Curie 9,
41–800 Zabrze, Poland,
phone: +48 506 603 277,
e-mail: k_myrda@interia.pl

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Percutaneous ablation is the recommended treatment for patients whose symptoms are related to the presence of an accessory pathway (AP). For asymptomatic patients, the electrophysiological study (EPS) is one of the methods to stratify the risk of sudden cardiac death (class IIa, level of evidence B). An effective refractory period of the AP during isoprenaline stimulation lower than or equal to 250 ms, the finding of multiple pathways, and inducible tachycardia dependent on the presence of the AP indicate the need for ablation [1]. However, this clinical situation and scientific evidence are related to a fully innervated heart, both sympathetically and parasympathetically.

We report the case of a 63-year-old female after orthotopic heart transplantation (OHT) by bicaval anastomosis in June 2020. The reason for referring the patient to our department was intermittent preexcitation syndrome, which occurred in the second year of the follow-up after OHT and was not associated with clinical symptoms. In the report from the Polish transplant coordination center ("Poltransplant"), the death of the donor was due to irreversible central nervous system damage as a result of a gunshot. There were no data on heart rhythm disturbances, including life-threatening arrhythmias in the donor. On the patient's admission, the resting electrocardiogram (ECG) showed the right bundle branch block (RBBB) (Figure 1A) with intermittent preexcitation (Figure 1B). No signs of acute cellular rejection ("0" according to the International Society for Heart and Lung Transplantation [ISHLT] scale) were found on in-hospital histological examination of myocardial biopsy material. After obtaining written informed consent, EPS was performed. During pacing maneuvers, antegrade conduction involved an AP and increased to 380 ms under isoprenaline infusion. On the other hand, retrograde conduction was observed *via* physiological pathways and reached 490 ms. No arrhythmia could be induced using standard pacing maneuvers from either the atrium or ventricle. Next, a single transseptal puncture was performed under fluoroscopy and transesophageal echocardiography. For electroanatomical mapping and ablation, the Thermocool® SmartTouch™ (Biosense Webster, Irvine, CA, US) catheter was selected, and the whole procedure was supported by a 3D electroanatomical system. The radiofrequency applications in the lateral region of the mitral annulus resulted in the complete conduction block through the AP (Figure 1D). The patient was discharged without the in-hospital recurrence of preexcitation on the resting ECG (Figure 1C) and Holter monitoring.

In such a rare case, in the resting ECG, apart from the RBBB, preexcitation syndrome occurred intermittently and was not associated with clinical symptoms. The results of EPS did not clearly indicate the need for ablation. However, data on the patient's management were strongly limited, and the decision on further better treatment was ambiguous [2]. An argument in favor of ablation could be the progressive reinnervation of the donor's heart after OHT accompanied by an increase in the number of adrenergic receptors [3]. This may have an impact on preexcitation manifestation on the resting ECG late after OHT, resulting from changes in the conduction properties of both the atrioventricular node and AP. It may be a factor increasing the risk of sudden cardiac death in such patients.

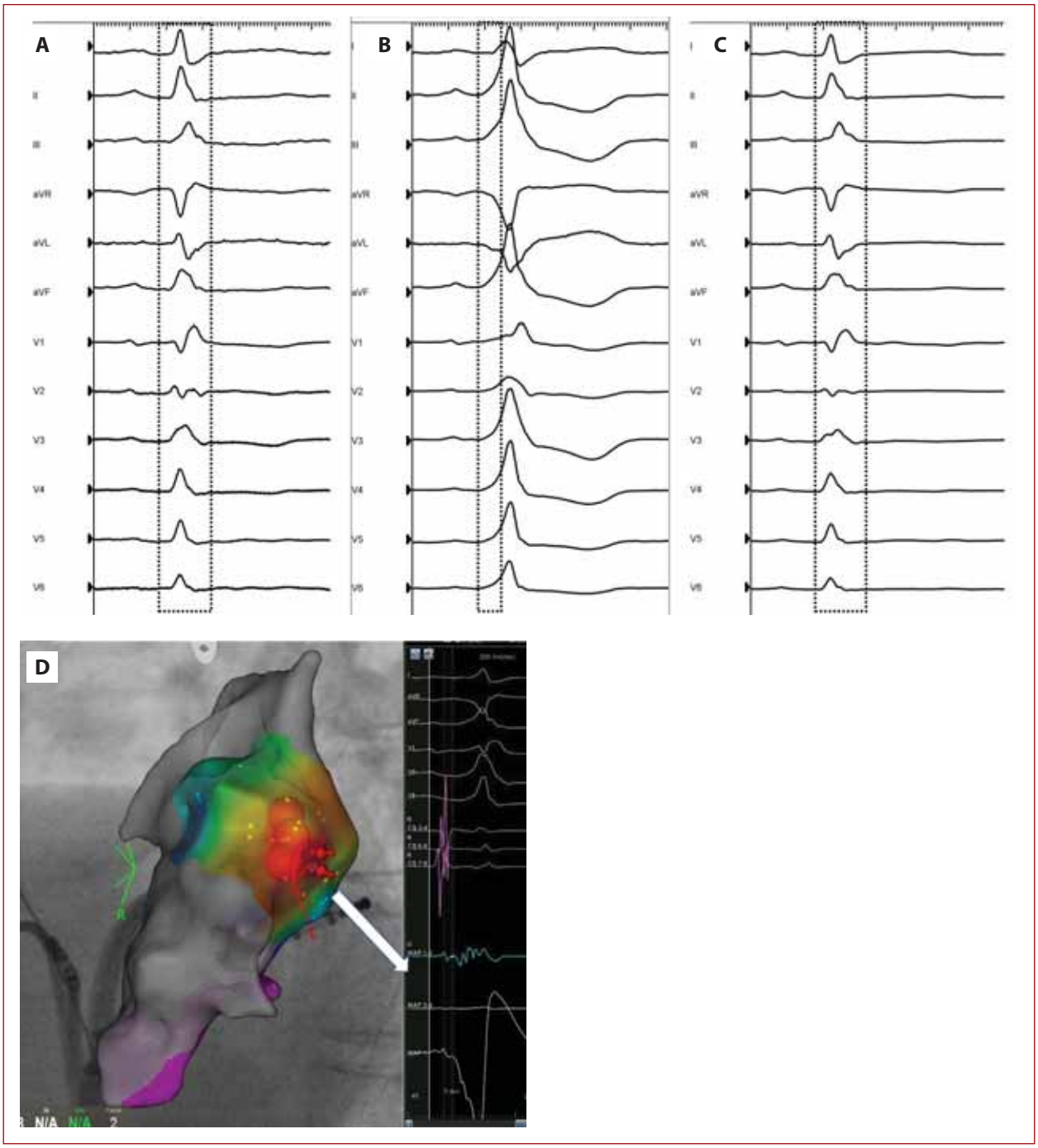

Figure 1. A–B. Resting ECG showing RBBB and the delta wave morphology before ablation; **C.** Resting ECG after ablation with persistent RBBB; **D.** Activation map with application points created using the 3D electroanatomical system — Carto 3 UniVu (Biosense Webster, Diamond Bar, CA, US) — with local bipolar and unipolar signals at ablation sites (the white arrow)

Abbreviations: ECG, electrocardiogram; RBBB, right bundle branch block

Article information

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Permanent cardiac arrest in a patient with a left ventricular assist device support

Katarzyna Ratman[1], Agnieszka Biełka[1], Mariusz E Kalinowski[1], Mirosława M Herdyńska-Wąs[1], Piotr Przybyłowski[2], Michał O Zembala[3, 4]

[1]Department of Cardiac Surgery, Heart Transplantation and Mechanical Circulatory Support, Silesian Center For Heart Diseases, Zabrze, Poland
[2]Department of Cardiac, Vascular and Endovascular Surgery and Transplantology in Zabrze, Medical University of Silesia in Katowice, Silesian Center for Heart Diseases in Zabrze, Poland
[3]Department of Cardiac Surgery, Heart and Lung Transplantation and Mechanical Circulatory Support, Silesian Center For Heart Diseases, Zabrze, Poland
[4]Pomeranian Medical University, Szczecin, Poland

Correspondence to:
Katarzyna Ratman, MD, PhD, Department of Cardiac Surgery, Heart Transplantation and Mechanical Circulatory Support, Silesian Center For Heart Diseases, M Sklodowskiej-Curie 9, 41–800 Zabrze, Poland, phone: +48 323 733 857, e-mail: ratmankatarzyna@gmail.com

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The left ventricular assist device (LVAD) support significantly reduces mortality in end-stage heart failure patients and potentially restores eligibility for heart transplantation in patients with initially significant pulmonary hypertension [1, 2]. Ventricular fibrillation and asystole lead to a decrease in right ventricular output and left ventricular preload, which significantly diminishes efficiency of LVAD support [3–5]. In this clinical vignette, we present a patient with an implanted continuous-flow LVAD (CF-LVAD) who developed permanent asystole as a consequence of an electric storm.

A 38-year-old male patient with an end-stage heart failure due to non-ischemic, post-inflammatory cardiomyopathy, qualified for heart transplantation in February 2018 and then implanted with a CF-LVAD HeartMate 3 (HM3, Abbott Inc, Chicago, IL, US) in May 2018 as a bridge-to-transplant due to recurrent episodes of circulatory decompensations, was referred to our institution in February 2019 with P-wave asystole (Figure 1B). In February 2014, the patient was implanted with a cardiac resynchronization therapy defibrillator (CRT-D) for primary prevention of sudden cardiac death. On admission, the patient was conscious and presented low blood pressure (mean arterial pressure [MAP], 53 mm Hg) and diminished pump flow of 2.4 l/min, which was accompanied by low-flow LVAD alarms. Other pump parameters, such as power consumption, speed, and pulsatility index (PI) were within the normal range (3.7 Watt, 5500 rpm, 3.0 PI, respectively). An echocardiography revealed an image of akinetic myocardium of both ventricles filled with enhanced echogenic blood (four-chamber view measurements: right ventricle 50 mm, left ventricle 60 mm, intraventricular septum in the middle position) with permanently closed aortic valve and constantly opened tricuspid and mitral valve. On CRT-D interrogation we found numerous, adequate high voltage interventions for a ventricular storm (Supplementary material, *Figure S1*) a day before admission and subsequent permanent asystole. Laboratory tests showed features of severe multiorgan failure (Supplementary material, *Table S1*). Intravenous fluid therapy under strict control of the fluid balance allowed for a rapid improvement of pump flow and achievement of satisfactory MAP (70–80 mm Hg) while systemic heparinization with unfractionated heparin prevented pump thrombosis. The patient remained conscious and hemodynamically stable with gradual end-organ function improvement. He was consulted by a psychiatrist due to the results of laboratory tests that revealed the presence of metabolites of psychoactive substances. The consultant emphasized the elevated risk of noncompliance but did not state absolute contraindications to orthotopic heart transplantation (OHT) and after several psychotherapy sessions, the patient declared full commitment to abstinence and further good compliance. Due to the estimated high risk of hemodynamic deterioration, the patient was listed for an urgent OHT, which was performed 11 days later. Pathomorphological examination of the patient's native heart

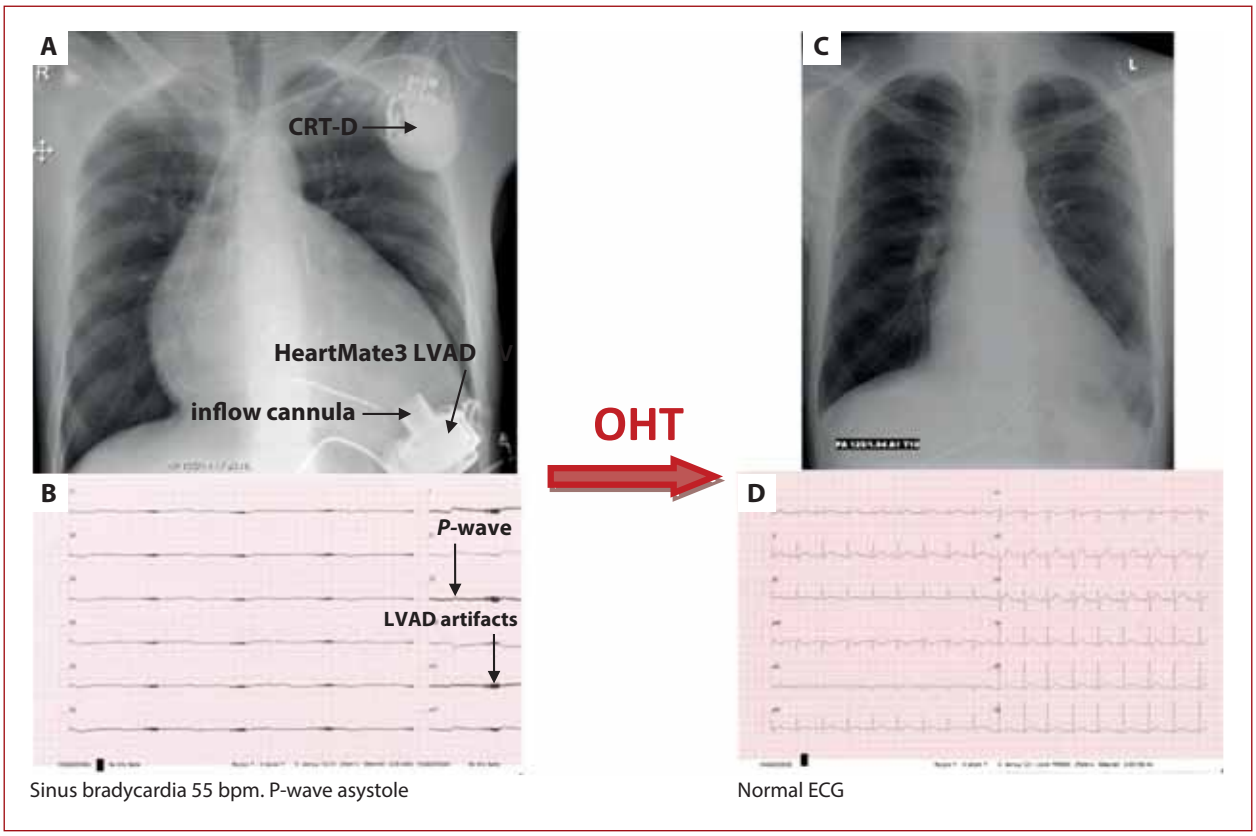

Figure 1. Chest X-ray and ECG before and after OHT

Abbreviations: CRT-D, cardiac resynchronization therapy defibrillator; ECG, electrocardiogram; OHT, orthotopic heart transplantation; LVAD, left ventricular assist device

revealed numerous foci of necrosis. The post-transplantation short- and long-term course was uneventful. The patient was treated according to the routine immunosuppressive protocol and presented stable levels of immunosuppressive drugs. All the follow-up echocardiographic examinations showed normal graft function, and there were no significant cellular and humoral rejections in the consecutive protocol biopsies. A chest X-ray and electrocardiogram before and after OHT are presented in Figure 1. He stayed in good condition and did not present any signs of drug and alcohol abuse at check-up visits. Unfortunately, he died due to a post-traumatic intracerebral hemorrhage 27 months after OHT.

Article information

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A curious case of cardiac fat deposition in a patient with hypereosinophilic syndrome

Katarzyna E Gil, Karolina M Zaręba

Division of Cardiovascular Medicine, The Ohio State University Wexner Medical Center, Columbus, OH, United States

Correspondence to:
Katarzyna E Gil, MD, PhD,
Division of Cardiovascular Medicine,
The Ohio State University Wexner Medical Center,
452 W 10th Ave, Columbus,
43210 OH, United States,
phone: +16 149 075 600,
e-mail:
katarzyna77.gil@gmail.com

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A 60-year-old woman with a history of eosinophilia, asthma, allergic rhinitis, chronic obstructive pulmonary disease, hypertension, coronary artery disease, and embolic stroke, presented with hemorrhagic stroke and persistent hypoxemia. The patient was noted to have eosinophilia and elevated immunoglobulin E (IgE) in peripheral blood with a positive radioallergosorbent test for anti-Aspergillus IgE antibodies. The sputum culture contained Aspergillus, whereas bronchoalveolar lavage was hypocellular with negative polymerase chain reaction for Aspergillus antigen. Computed tomography (CT) of the chest revealed enlarged lymph nodes, as well as patchy upper lobe ground glass opacity with centrilobular nodules throughout the lungs. Based on initial findings, the patient was diagnosed with allergic bronchopulmonary aspergillosis and started on steroid therapy with resolution of eosinophilia and improvement in lung infiltration.

Given elevated troponins on admission, a cardiac workup was simultaneously performed. Transthoracic echocardiography revealed global left ventricular (LV) hypokinesis with ejection fraction (LVEF) of 45%–50%. Single-photon emission CT showed no evidence of ischemia. Cardiovascular magnetic resonance (CMR), after 2 months of steroid therapy, showed thinning and hypokinesis of the inferolateral walls, prominent LV trabeculae, and moderately decreased systolic function (LVEF, 35%). Given the atypical dense appearance of the trabeculated LV myocardium on long-axis cine imaging, additional fat water cine imaging was requested by the supervising physician. Fat water cine imaging demonstrated prominent fatty infiltration of the subendocardium and trabeculae (Figure 1A, B). Late gadolinium enhancement (LGE) imaging demonstrated fibrosis involving the subendocardium and trabeculae in the inferolateral and anterior walls, as well as apical segments (Supplementary material, *Figure S1*). Fat water LGE images were utilized to demonstrate both fatty infiltration and fibrosis in the LV (Figure 1C). In addition, the patient exhibited elevated native T1 signal (1129 ms; site specific normal <1084 ms), and mildly elevated T2 signal (56 ms, site specific normal <52 ms) (Supplementary material, *Figure S1*). Given the clinical scenario, findings were concerning for hypereosinophilic syndrome (HES) with Loeffler's endocarditis (LE). In light of this discovery, the initial hypoxemia and pulmonary parenchymal opacities may have been signs of HES lung involvement.

HES is a group of rare diseases characterized by unexplained peripheral blood hypereosinophilia with evidence of end-organ damage [1, 2]. Cardiac involvement is present in about 20%–60% of cases [1, 2]. LE is defined as inflammation of both myocardium and endocardium with eosinophilic infiltration [1, 2]. LE has heterogeneous clinical manifestations ranging from an asymptomatic form to restrictive cardiomyopathy (RCM) [1]. Patients present with heart failure, intracardiac thrombosis, arrhythmias, myocardial ischemia, and pericarditis [1]. Three stages of the disease may overlap [1]. The necrotic stage with eosinophilic infiltration and myocardial inflammation is followed by a thrombotic stage with common distal embolization, and a fibrotic stage [1, 3].

A comprehensive CMR with tissue characterization can aid in diagnosis and guide response to therapy in HES with LE [4]. CMR often reveals T2 signal elevation in the acute phase and patchy or diffuse subendocardial LGE in a noncoronary distribution in the

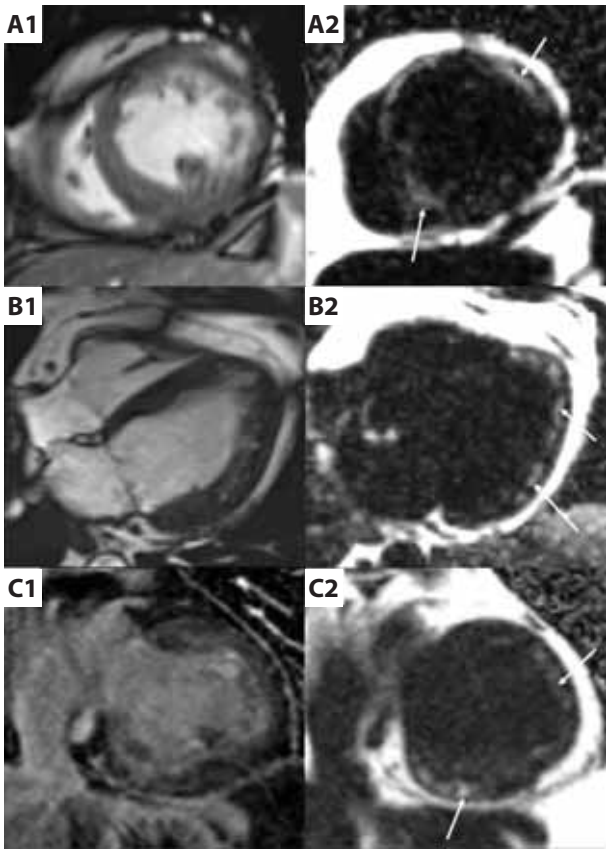

Figure 1. Midmyocardial and subendocardial fatty infiltration (the arrows) in the left ventricle on steady-state free-precession cine and fat water short axis and horizontal long-axis cine images (**A1** and **B1**: SSFP images; **A2** and **B2**: fat images). Fatty infiltration on fat water late gadolinium enhancement images best seen in the outflow tract view (**C**: phase sensitive inversion recovery water image in **C1** and fat image in **C2**)

chronic phase [1]. The case is unique in the presence of myocardial fat deposition, previously described only once, and may represent an atypical feature of the disease [5]. The pathophysiologic mechanism of fat deposition is unknown in HES [5]. The images confirming fatty infiltration are generally not included in standard myocarditis or cardiomyopathy protocols in CMR laboratories. Therefore, fatty infiltration would not have been detected were it not for the alertness of the supervising physician.

Supplementary material

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

Article information

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Aortic dissection four months after SARS-CoV-2 infection in a patient with Fabry disease whose targeted treatment was stopped 2 months earlier

Marcin Kamil Dobrowolski[1], Magdalena Marczak[2], Rafał Dąbrowski[2]

[1]Department of Cardiology, WKK Westküstenkliniken Heide und Brunsbüttel, Heide, Germany
[2]National Institute of Cardiology, Warszawa, Poland

Correspondence to:
Marcin Kamil Dobrowolski, MD, Department of Cardiology, WKK Westküstenkliniken Heide und Brunsbüttel, Esmarchstraße 50, 25746 Heide, Germany,
phone: +49 160 143 34 38,
e-mail: dobmarcin@gmail.com

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Fabry disease is a rare storage disease involving the absence or decreased activity of alpha-galactosidase A enzyme [1]. This leads to the accumulation of glycolipids (globotriaosylceramides [GB3]) with consistent cell damage and fibrosis. It results mostly in renal, cardiac, neurological, and other systems' complications [2].

A 43-year-old male patient with a history of Fabry disease, hypertension, dyslipidemia, and obesity was transported by the ambulance service in a critical condition with suspected acute coronary syndrome to the emergency room of one of German hospitals. The patient was not vaccinated against COVID-19 and suffered from COVID-19 four months earlier. For this reason, he was not hospitalized. The ambulance service was called by the patient's mother after she noticed her son's speech disorders lasting about 2 hours and progressive disturbances of consciousness. For over 4 days, the patient had complained of chest pains radiating to the back, arms, and abdomen, as well as nausea and vomiting. Due to the prevailing COVID-19 pandemic, the patient had not received intravenous therapy (agalsidase alfa) for 2 months.

In the emergency room, the patient was deeply unconscious (Glasgow Coma Scale [GCS], 6–7), with saturation dropping to 60% despite intensive oxygen therapy. Pulse was regular but imperceptible, heart tones muted, pressure on the right arm was 130/80 mm Hg, on the left — 165/80 mm Hg. Significant stasis in the jugular veins has been observed. The electrocardiogram record showed significant ST-segment elevation in the leads from the inferolateral and anterior walls (Figure 1A, B).

Echocardiography was performed urgently due to suspected aortic dissection. A large amount of fluid was observed in the pericardium (Figure 1C).

Contrast-enhanced computed tomography of the thoracic and abdominal aorta was performed (Figure 1D–E). The diagnosis of aortic dissection was confirmed. It was decided to intubate the patient to avoid aspiration and to immediately transport him by air to the university department for further surgical treatment. While waiting for transport, the patient experienced cardiac arrest four times in the asystole mechanism. Despite the continuation of the resuscitation procedure, in the presence of the air ambulance service and the lack of recovery of the electromechanical activity of the heart, a decision was made to discontinue medical activities.

Despite his relatively young age, the patient had several risk factors for cardiovascular diseases: hypertension, dyslipidemia, obesity, and confirmed and treated Fabry disease. Aortic dissection is not a typical symptom of Fabry disease. In this complex clinical situation, it is difficult to unequivocally state, but also to exclude what would have the direct impact on extensive aortic dissection [3].

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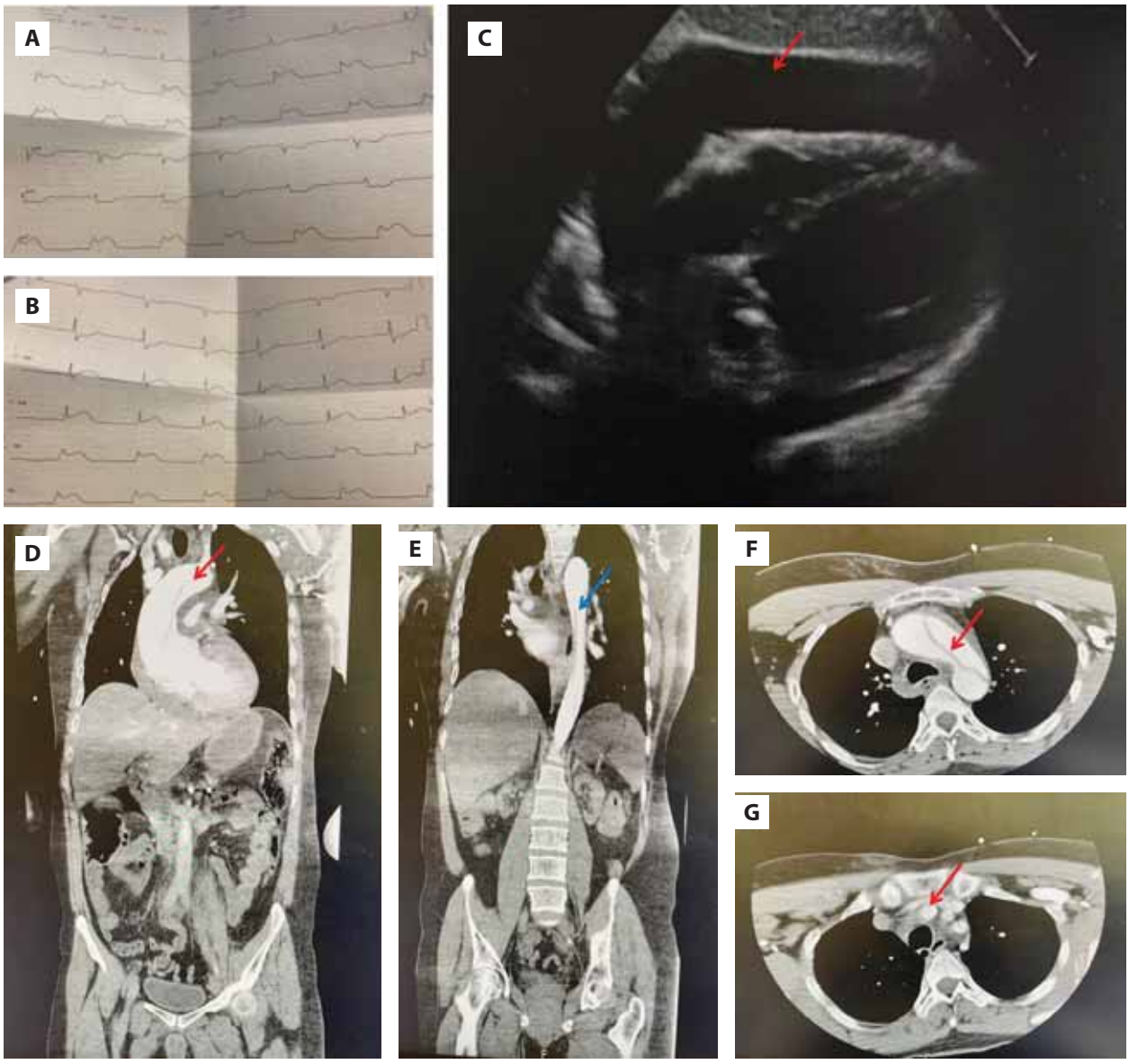

Figure 1. A, B. Electrocardiogram: significant ST-segment elevation in leads II, III, aVF, V3–6. **C.** Echocardiogram: a large amount of fluid in the pericardium (the arrow). **D, E.** Contrast-enhanced computed tomography with coronal plane showing dissection of the ascending aorta and the aortic arch (the red arrow) and the descending thoracic aorta (the blue arrow). **F, G.** Contrast-enhanced computed tomography with transverse plane showing dissection across the aortic arch and initial segment of the brachiocephalic trunk, the left common carotid, and the left subclavian artery (the red arrows)

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Peripartum cardiomyopathy — challenges of diagnosis and management. Stay alert and implement BOARD treatment

Wiktoria Ciepłucha[1], Aleksandra Ciepłucha[2], Thilini Walgamage[1], Mehala Subramaniapillai[1], Malsha Walgamage[1], Aneta Klotzka[2], Agnieszka Katarzyńska-Szymańska[2], Adrian Gwizdała[2], Daria Keller[2], Maciej Lesiak[2]

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

Correspondence to:
Wiktoria Ciepłucha, MD,
1st International Scientific Group on Cardiovascular Medicine at 1st Department of Cardiology Poznan University of Medical Sciences,
Długa 1/2, 61–848 Poznań, Poland,
phone: +48 618 549 146,
e-mail: wiktoria.cieplucha@gmail.com

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A 27-year-old woman at the 27th week of pregnancy presented with preeclampsia (hypertension + proteinuria), which shortly progressed into eclampsia. Antihypertensive medications (labetalol, nifedipine, methyldopa) and intravenous magnesium sulfate were implemented. Four days later, she experienced a hypertensive crisis and loss of consciousness that necessitated an emergency C-section. Due to resistant hypertension and signs of heart failure (HF), she was transferred to the cardiac intensive care unit. Echocardiography showed decreased left ventricular ejection fraction (LVEF, 45%) with impaired global longitudinal strain, pericardial and bilateral pleural effusions (Figure 1). N-terminal pro-B-type natriuretic peptide (NT-proBNP) was increased (8661 pg/ml). Cardiac magnetic resonance (CMR) demonstrated myocardial edema without other signs of myocarditis. Within two days postpartum, the blood pressure and HF symptoms stabilized with β-blockers, furosemide, urapidil, and nitroglycerin. Due to suspected peripartum cardiomyopathy (PPCM), we implemented bromocriptine and anticoagulation along with oral electrolyte supplementation.

Despite the initial improvement, on the 7th day postpartum, the patient experienced cardiac arrest due to ventricular tachycardia (VT) treated with a successful cardiopulmonary resuscitation with defibrillation. Intravenous magnesium supplementation was restarted due to serum magnesium level at the lower limit of the normal range.

Further hospital stay was unremarkable. After one month, CMR revealed no edema or fibrosis, with LVEF of 58% and NT-proBNP of 61 pg/ml. Given all the data and clinical course, the final diagnosis of PPCM was confirmed. A cardioverter-defibrillator was not implanted due to a likely reversible VT cause (electrolyte disturbances and acute phase of cardiomyopathy).

Identifying the etiology of acute HF in a peripartum woman is critical for further management and prenatal counseling. Traditionally, PPCM is a diagnosis of exclusion that meets three criteria: HF towards the end of pregnancy or within months following delivery, LVEF <45%, and the absence of other identifiable causes of HF [1].

In this patient, the hypertensive crisis could have been considered a cause of acute HF, which by definition excludes the diagnosis of PPCM. However, in recent years a link between PPCM and preeclampsia was established. The pathogenesis of PPCM is multifactorial, including genetic predisposition, inflammation, oxidative stress, and hormonal dysregulation. In particular, oxidative stress promotes abnormal cleavage of prolactin into the antiangiogenic subfragment. The damage to the vascular endothelium caused by these prolactin-derived factors can impair cardiomyocyte metabolism and manifest as PPCM [2, 3]. Similarly, preeclampsia is a disease of vascular endothelium with increased levels of antiangiogenic factors produced by the placenta [3]. This preliminary evidence highlights the common etiologies of these two diseases.

According to the European Society of Cardiology EURObservational Research Programme registry, preeclampsia coexisted in

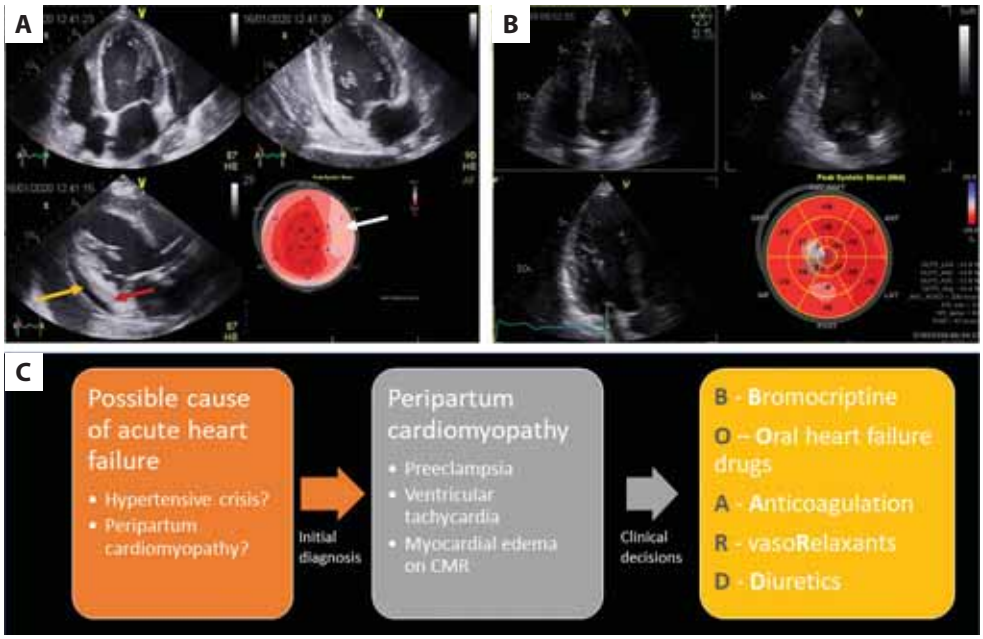

Figure 1. A. Initial echocardiography with impaired regional systolic function and global longitudinal strain of –13.8% (the white arrow — impaired global longitudinal strain of the lateral wall; the yellow arrow — pericardial effusion; the red arrow — the thickened edematous inferolateral wall). **B.** Follow-up echocardiography with improved regional function and global longitudinal strain of –14.4%. **C.** Suggested diagnostic workflow and clinical management of peripartum cardiomyopathy including the BOARD algorithm

Abbreviations: CMR, cardiac magnetic resonance

25% of women with PPCM [4]. Arrhythmias were reported in 19% of women with PPCM, of whom 7% had ventricular tachycardia or a cardiac arrest; the mortality rate reached 6% [5]. Therefore, implementing therapy according to the BOARD algorithm (Bromocriptine, Oral heart failure drugs, Anticoagulation, vasoRelaxants, Diuretics) is highly recommended [2, 4] (Figure 1C).

Preeclampsia and eclampsia (inevitably associated with arterial hypertension) are the conditions that support, rather than exclude, the diagnosis of PPCM. Careful monitoring and implementation of BOARD algorithm treatment are crucial to avoid life-threatening complications.

Article information

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Harnessing drug-coated balloons for management of left main coronary disease: A promising strategy?

Kenan Yalta[1], Ertan Yetkın[2], Tulin Yalta[3]

[1]Department of Cardiology, Trakya University, Edirne, Turkey
[2]Department of Cardiology, Türkiye Hastanesi, Istanbul, Turkey
[3]Department of Pathology, Trakya University, Edirne, Turkey

Correspondence to:
Kenan Yalta, MD,
Department of Cardiology, Trakya University,
Balkan Yerleşkesi, 22030, Edirne, Turkey,
phone: +90 505 657 98 56,
e-mail: kyalta@gmail.com

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In clinical practice, management of unprotected left main stem (LMS) stenoses with percutaneous coronary intervention (PCI) has been quite challenging, particularly in the presence of bifurcation or aorto-ostial stenoses [1–3]. In this context, certain stent-based PCI techniques have been described as having variable safety and efficacy [1]. In their recently published article, Kovacevic M, et al. [1] have reviewed a variety of issues associated with unprotected LMS stenting. We fully agree with the suggested challenges and their management strategies [1]. However, we also would like to underscore the potential clinical value of drug-coated balloons (DCBs) in management of LMS disease.

It is well known that drug-eluting stents (DESs) have been increasingly used in the setting of LMS stenoses [1] despite a high mortality risk in the case of stent-related complications including stent thrombosis, etc. In particular, these stent-related complications appear to be substantially higher in aorto-ostial and bifurcation points largely due to a variety of adverse rheological, anatomical, and histopathological factors that might potentially be associated with geographic miss along with stent malapposition and/or delayed endothelization [3, 4]. Moreover, "carina shift" might arise as a significant procedural complication frequently encountered in management of bifurcation stenoses (including distal LMS), particularly with the use of certain techniques including cross-over stenting and ostial stenting [1–3].

Consequently, the use of alternative tools and techniques potentially with better safety outcomes might arise as a viable option in management of LMS stenoses, particularly involving aorto-ostial or distal bifurcation points [2, 3]. In this context, harnessing DCBs has been suggested as a safe and effective option for management of de-novo atherosclerosis involving small and large coronary arteries, even in the setting of stenoses with precarious anatomical features (including stenoses at bifurcation points) [2]. In a recent study, management with DCBs alone (with the guidance of optic coherence tomography [OCT]) was demonstrated to work well in most patients with stenosis involving the distal LMS (Medina types 0,1,0 or 0,0,1) [2]. Importantly, none of the patients in the study population had any adverse clinical events at 7.7 ± 6.0 months following PCI with DCBs [2]. However, the clinical value of DCBs remains to be established in more complex types of LMS disease (including Medina 1,1,1, etc.) [3]. Accordingly, we wonder about the opinion and experience of the authors [1] regarding management of unprotected LMS stenoses with DCBs alone (with provisional DES implantation where necessary) [1].

In conclusion, the use of DCBs might obviate stent-related complications (including carina shift, late thrombosis, etc.), and might serve as a reasonable option for management of unprotected LMS stenoses [2, 3]. However, further studies are still needed before labeling them as alternatives to DES, particularly in the setting of LMS stenoses with high-risk anatomical features.

Article information

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Percutaneous coronary intervention to treat unprotected left main: Unmet needs

Marin Pavlov

Department of Cardiology, Dubrava University Hospital, Zagreb, Croatia

Correspondence to:
Marin Pavlov, MD, PhD, Department of Cardiology, Dubrava University Hospital, Avenija Gojka Šuška 6, 10000 Zagreb, Croatia, phone: +38 599 236 02 86, e-mail: marin.pavlov@gmail.com

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We read with much interest the article by Kovacevic et al. [1] about modern dilemmas in interventional treatment of the left main (LM) disease. The authors described clearly and provided solutions for imaging and functional assessment modalities, procedural issues, and options for overcoming hemodynamic instabilities during the procedure. However, some aspects of LM percutaneous coronary interventions (PCI) were left understated.

As reported by the authors, intravascular ultrasound (IVUS), in addition to the assessment of the intermediate stenosis significance, provides a morphological plaque evaluation. However, IVUS is poorly utilized (16.7% in our last cohort [2]), especially in predominantly acute PCI centers with a high percentage of *ad hoc* interventions (63.7% of the patients presented with acute coronary syndrome; 70.0% of the interventions were *ad hoc* in the same cohort). Yet, the data obtained by IVUS are crucial in foreseeing difficult procedures leading to suboptimal outcomes. Avoiding routine pre-interventional IVUS could elicit worse outcomes. Insight into calcium burden, eccentricity, and particularly nodularity often leads to a change in revascularization strategy. Interventional society is very much aware of the results of the two major LM studies [3, 4] with suboptimal results in PCI arms. The usage of IVUS in these studies was 77% and 72%. In the Nordic-Baltic-British Left Main Revascularization (NOBLE) trial substudy analysis, the usage of IVUS was associated with lower LM target lesion revascularization, although the differences in hard outcomes remained non-significant (5.1% vs. 11.6%; $P = 0.01$ [5]; in both studies IVUS was not used for determining the eligibility for PCI strategy, but for post-stenting optimization purposes). Thus, maximizing imaging usage in, preferably, all LM patients with chronic coronary syndrome, and in the majority of acute coronary syndrome patients, or at least in those without acute thrombotic lesions, should be our first goal. I would like the authors to share with readers their current practice and reflections on whether IVUS should be used in all LM PCI procedures.

Recent advances in the PCI strategy (wrist access, potent antiplatelet therapy, debulking devices, latest stent generations, insights into optimal bifurcation technics, options for hemodynamic support) vastly outnumber the advances in surgical strategy. Yet, the PCI strategy is still considered only in the case of patients with a low Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score or those refusing surgery. This "low SYNTAX" score often translates to "low-risk" patients, commonly signifying normal systolic function and an absence of significant comorbidity. Yet those at "high risk" or frail and elderly patients, as Kovacevic et al. [1] stated, could benefit from PCI supported by decongestive strategies such as Impella (Abiomed, Danvers, MA, USA) or iVAC 2L (PulseCath, Amsterdam, The Netherlands), by simply avoiding surgery. How many patients with successful surgery and unfavorable postoperative course have we seen? Should we look up to our older patients with severe aortic stenosis that we now regularly treat percutaneously? Is it fair time for new *noble* studies in *excel*ling field of interventional LM revascularisation? I wonder about the opinion and current practice of the authors in the field of LM PCI for high-risk patients with intermediate and high SYNTAX scores; how do the authors translate current recommendations into everyday workflow?

Article information

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Intravascular imaging and drug-coated balloons for unprotected left main percutaneous coronary interventions: Questions with a predictable or unpredictable answer? Author's reply

Mila Kovacevic[1, 2], Francesco Burzotta[3, 4], Ilija Srdanovic[1, 2], Milovan Petrovic[1, 2], Carlo Trani[3, 4]

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

Correspondence to:
Francesco Burzotta, MD, PhD, Institute of Cardiology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, A. Gemelli 1, 00168 Rome, Italy, phone: +39 06 301 54 187, e-mail: francesco.burzotta@unicatt.it

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We thank the authors [1, 2] for their interest in our publication [3], and we acknowledge their comments regarding the role of intravascular ultrasound (IVUS) and drug-coated balloons (DCB) in the left main bifurcation (LMB) treatment.

In our article, we cited IVUS and DCB as technologies with the potential to improve the outcomes of percutaneous coronary interventions (PCI) in LMB patients. We now take the opportunity to provide some more detailed comments on these important options.

So far, there has been no single strategy available and recommended for treating all types of distal LMB lesions. The decision to use one stent strategy, in preference to another, is mainly based on the distribution of the disease, as well as on the presence and the distribution of calcium and unfavorable bifurcation angles. IVUS is a valuable tool to assess LM disease significance, guide appropriate PCI techniques, and optimize outcomes. Although using IVUS is strongly associated with improved PCI outcomes and is currently highlighted as a class IIa recommendation [4], its use is still not widespread. According to the largest real-world outcome analysis from the British Cardiovascular Intervention Society database including 11 264 patients with unprotected LM, intracoronary imaging guidance significantly increased from 30% in 2007 to 50% in 2014 [5]. Such figures are still far from those collected in countries where full reimbursement is available, like Japan (intravascular imaging is adopted in >85% of all PCI procedures). Thus, the variability in imaging use is probably influenced by economics. To change this status, large clinical trials assessing the true clinical impact of systematic intravascular imaging studies are awaited. Notably, not only IVUS but also optical coherence tomography can be considered, and one large trial [6] has been designed to include complex LMB bifurcations as targets. The results of this kind of trials are also expected to clarify which optimization protocols are effective beyond any doubt in achieving better LMB PCI outcomes when using intravascular imaging.

While waiting for solid clinical data and the consequent economic adjustment, intravascular imaging use is reasonably regarded as a piece of "must-have" equipment in a catheterization laboratory performing PCI on LMB. For instance, if not adopted since PCI start, intravascular imaging should be applied at any time during LMB PCI when a lack of optimal result achievement is suspected [7].

Moving from procedure planning/optimization to PCI device selections, DCBs are regarded as promising adjunctive devices to manage specific LMB anatomic subsets. Based on the results of the previous IVUS studies, we are aware that both isolated distal left main (LM) and isolated side branch (SB) disease are rarely seen [8]. Although considered

a "non-true" LMB, and apparently "simpler" to treat, ostial left anterior descending (LAD) or left circumflex (LCX) disease is one of the most challenging issues in LMB PCI. Current evidence supports either cross-over stenting or precise ostial stenting, depending on the bifurcation angle and discrepancy between main and side branch sizes. Although there are different techniques to facilitate precise ostial stenting, struts hanging in front of the SB ostium (at the polygon of confluence) are frequently seen, as well as carina shifting, influencing adverse events, mainly restenosis. Consequently, cross-over stenting is the treatment of choice, followed by kissing balloon inflation (KBI) for carina recentering (to avoid carina shifting). Whether DCBs may have a part in the ostial lesion treatment is still disputable. A recent small, prospective, and non-randomized study showed that DCB can be a valuable option to treat de novo Medina 0.1.0 and 0.0.1 lesions with the optical coherence tomography guidance [9]. For sure, we should be aware of possible early vessel recoil, complications including flow-limiting dissections, carina shifting if balloons are oversized, and more importantly, we should be ready for a bailout stenting strategy. These aspects are particularly relevant when dealing with isolated ostial LAD, where, due to the substantial amount of jeopardized myocardium, ostial LAD should be treated according to the current recommendation, by DES. For instance, a possible role for DCB is its combination with DES. A recent experience on combining DES for the MB with DCB for the SB in true LMB was reported to be associated with promising 1-year freedom from major adverse cardiac events [10].

In summary, clinical evidence supporting DCB use in LMB is not sufficient to give final recommendations.

As a final remark, we would like to add that no single technical improvement is expected to solve the dilemma of the best treatment for more complex patients with LMB. By itself, the simple SYNTAX score cannot be regarded as the only way to define LMB PCI complexity and risk. Accordingly, a comprehensive multidisciplinary team approach should be adopted to offer individual patients the best decision regarding the modality (surgical or percutaneous) and the planning (support and PCI adjunctive devices) of myocardial revascularization.

Article information

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An expert opinion of the Polish Cardiac Society Working Group on Pulmonary Circulation on screening for chronic thromboembolic pulmonary hypertension patients after acute pulmonary embolism: Update

Michał Ciurzyński[1], Marcin Kurzyna[2], Grzegorz Kopeć[3, 4], Piotr Błaszczak[5], Łukasz Chrzanowski[6], Karol Kamiński[7, 8], Katarzyna Mizia-Stec[9, 10], Tatiana Mularek-Kubzdela[11], Andrzej Biederman[12], Dariusz Zieliński[12], Piotr Pruszczyk[1], Adam Torbicki[2], Ewa Mroczek[13]

[1]Department of Internal Medicine and Cardiology with the Center for Diagnosis and Treatment of Venous Thromboembolism, Medical University of Warsaw, Warszawa, Poland
[2]Department of Pulmonary Circulation, Thromboembolic Diseases, and Cardiology, Center of Postgraduate Medical Education, European Health Center, Otwock, Poland
[3]Pulmonary Circulation Center, Department of Cardiac and Vascular Diseases, Jagiellonian University Medical College, Kraków, Poland
[4]Department of Cardiovascular Diseases with Cardiac Intensive Care Unit, John Paul II Hospital, Kraków, Poland
[5]Department of Cardiology and Intensive Cardiac Care, Stefan Cardinal Wyszynski Provincial Specialist Hospital, Lublin, Poland
[6]Department of Cardiology, Medical University of Lodz, Łódź, Poland
[7]Department of Population Medicine and Lifestyle Diseases Prevention, Medical University of Bialystok, Białystok, Poland
[8]Department of Cardiology, University Hospital in Bialystok, Białystok, Poland
[9]1st Department of Cardiology, School of Medicine in Katowice, Medical University of Silesia, Katowice, Poland
[10]European Reference Network for Rare, Low Prevalence, or Complex Diseases of the Heart (ERN GUARD Heart)
[11]Department of Cardiology, Karol Marcinkowski Medical University, Poznań, Poland
[12]Department of Cardiac Surgery, Medicover Hospital, Warszawa, Poland
[13]Department of Cardiology, University Clinical Hospital, Institute of Heart Diseases, Wrocław, Poland

Correspondence to:
Prof. Michał Ciurzyński, MD, PhD, Department of Internal Medicine and Cardiology with the Center for Diagnosis and Treatment of Venous Thromboembolism, Medical University of Warsaw, Lindleya 4, 02–005 Warszawa, Poland,
phone: +48 22 502 11 44,
e-mail: michal.ciurzynski@wum.edu.pl

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ABSTRACT

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare complication of acute pulmonary embolism (APE). Both pharmacological and invasive treatments for CTEPH are available in Poland, and awareness of the disease among physicians is growing. It has been suggested that the COVID-19 pandemic may increase the incidence of CTEPH and facilitate disease detection during more advanced stages of the illness. Thus, the Polish Cardiac Society's Working Group on Pulmonary Circulation, in cooperation with independent experts in this field, launched the updated statement on the algorithm to guide a CTEPH diagnosis in patients with previous APE. CTEPH should be suspected in individuals after APE with dyspnea, despite at least 3 months of effective anticoagulation, particularly when specific risk factors are present. Echocardiography is the main screening tool for CTEPH. A diagnostic workup of patients with significant clinical suspicion of CTEPH and right ventricular overload evident on echocardiography should be performed in reference centers. Pulmonary scintigraphy is a safe and highly sensitive screening test for CTEPH. Computed tomography pulmonary angiography with precise detection of thromboembolic residues in the pulmonary circulation is important for the planning of a pulmonary thromboendarterectomy. Right heart catheterization definitively confirms the presence of pulmonary hypertension and direct pulmonary angiography allows for the identification of lesions suitable for thromboendarterectomy or balloon pulmonary angioplasty. In this document, we propose a diagnostic algorithm for patients with suspected CTEPH. With an individualized and sequential diagnostic strategy, each patient can be provided with suitable and tailored therapy provided by a dedicated CTEPH Heart Team.

Key words: chronic thromboembolic pulmonary hypertension, acute pulmonary embolism, echocardiography, diagnostic algorithm, computed tomography pulmonary angiography

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) has been an area of particular interest to researchers and specialists in pulmonary circulation disorders in recent years. One important problem is the need for the early diagnosis of CTEPH, both in patients with and without a history of acute pulmonary thromboembolism (APE).

Indeed, the pathogenic mechanism of CTEPH is not limited to mechanical occlusion of a portion of the pulmonary arterial bed by unrecognized organized thromboembolic lesions. Redistribution of blood flow to the obstructed portion of the pulmonary artery bed, as well as feeding it from high-pressure systemic arterioles (especially bronchial arterioles), further leads to progressive, adverse, and irreversible remodeling of pulmonary arterioles and small pulmonary veins, which progressively increases right ventricular overload.

An early diagnosis of CTEPH would allow for the implementation of therapy before the development of these changes in the pulmonary microcirculation, improving the effectiveness of treatment and the long-term prognosis for patients.

The purpose of this article, developed by a team of experts from the Polish Cardiac Society Working Group on Pulmonary Circulation, is to give an update on clinical strategies aimed at promoting an early diagnosis of CTEPH in patients with a history of APE. This is a challenging task for a number of reasons. Although many patients report impaired exercise tolerance after an episode of APE, in the vast majority of cases, this is not associated with resting pulmonary hypertension (PH). It also does not occur in many individuals despite the presence of residual intravascular lesions after APE. On the one hand, exertional dyspnea persisting after APE and even echocardiographic features of right ventricular overload result more often from chronic obstructive pulmonary disease (COPD) or left ventricular dysfunction than from possible residual post-embolic effects. On the other hand, the absence of spontaneously reported symptoms after APE does not rule out CTEPH, especially if the patient restricts their activity believing that they should do so after a severe, life-threatening disease, as they were informed at the time of the diagnosis of APE.

The current 2019 European Society of Cardiology (ESC) guidelines on APE, as well as the document developed by the experts from the European Respiratory Society (ERS), which relate to chronic thromboembolic pulmonary disease (CTEPD), provide guidelines for the early detection, but also exclusion, of sequelae relating to APE which require specific treatment [1, 2].

We consider it particularly important to organize and present this guidance for national use during a period of a rapid increase in pulmonary thromboembolic complications associated with the COVID-19 pandemic. It cannot be ruled out that the health impact of COVID-19 will include an increase in the frequency of CTEPD as well as CTEPH in the months and years to come.

CTEPH EVALUATION IN PATIENTS WITH A HISTORY OF APE: CLINICAL CONSIDERATIONS

More than 70% of patients with confirmed CTEPH have previously experienced at least one episode of APE. In the Polish registry, 83% of patients developed CTEPH after the initial thromboembolic event [1, 3]. There is a growing body of data indicating that, despite complete anticoagulation treatment for at least 3 months, approximately 50% of patients with a history of APE report a persistent decline in physical performance compared to the pre-disease state [4–6]. Recently, the term "post-APE syndrome" has been introduced to include CTEPH, CTEPD, deconditioning, and psychological problems caused by APE [4–6]. Although persistent dyspnea may be caused by other chronic pulmonary and cardiac conditions, the main diagnostic goal of post-APE syndrome is to exclude CTEPH since diagnostic delays significantly worsen patient prognosis and outcomes [7].

In early CTEPH, clinical symptoms are very uncharacteristic, with exertional dyspnea being the most common. Symptoms of right heart failure only appear in advanced forms of the disease. The uncharacteristic clinical picture makes the average time from the onset of CTEPH symptoms to diagnosis >1 year, confirming the low awareness of this disease among healthcare providers [1, 8, 9].

The absence of a history of APE does not exclude a diagnosis of CTEPH. However, patients who had an APE are at a higher risk of developing CTEPH. It is noteworthy that some patients already have features of CTEPH at the time of diagnosis, e.g., an elevated tricuspid regurgitant peak gradient >50 mm Hg on echocardiography [10].

A tricuspid regurgitant peak gradient >50–60 mm Hg and/or other features of significant right ventricular overload are indicative of a chronic thromboembolic process or other concurrent chronic pulmonary or cardiac diseases. Analysis of computed tomography pulmonary angiography (CTPA) images from the acute period of APE is also important. Table 1 shows the radiological features indicative of the chronic component of the disease [1].

In the evaluation of CTPA scans obtained from 341 patients with APE, 22% showed at least one of the following features suggestive of chronic disease: pulmonary trunk dilatation, pulmonary artery stenosis, presence of linear filling defects in the vessel lumen, bronchial artery dilatation, features of right ventricular wall hypertrophy, or flattening of the interventricular septum. At 2-year follow-up, nine (2.6%) patients developed CTEPH. Importantly, the presence of at least one of these characteristics increased the likelihood of developing CTEPH almost 8-fold [9].

The current ESC guidelines for the management of APE do not recommend routine testing for CTEPH in all patients after an episode of disease. However, CTEPH should be suspected in patients with the post-APE syndrome who, despite at least 3 months of effective anticoagulation treatment, have persistent exertional dyspnea or reduced

Table 1. Abnormalities found on CTPA suggestive of CTEPH in patients with APE

Abnormalities indicative of pre-existing thromboembolic pulmonary hypertension as detected by CTPA. Based on the ESC 2019 guidelines [1]
Direct vascular signs
Eccentric wall-adherent filling defect(s), which may calcify
Abrupt tapering and truncation
Complete occlusion and pouch defects
Intimal irregularity
Linear intraluminal filling defects (intravascular webs and bands)
Stenosis and post-stenotic dilatation
Vascular tortuosity
Indirect vascular symptoms
Significant right ventricular hypertrophy, right atrial dilatation
Pericardial effusion
Pulmonary artery dilatation (>29 mm in men and >27 mm in women) and/or pulmonary artery calcification
Systemic collateral arterial supply (bronchial arterial collaterals towards pulmonary post-obstructive vessels)
Pulmonary parenchymal lesions
Mosaic attenuation of the lung parenchyma resulting in geographical variation in perfusion

Abbreviations: APE, acute pulmonary embolism; CTPA, computed tomography pulmonary angiography; CTEPH, chronic thromboembolic pulmonary hypertension; ESC, European Society of Cardiology

Table 2. Factors that increase the risk of CTEPH after APE

Factors that increase the risk of CTEPH after APE
Symptoms of APE lasting more than 2 weeks before diagnosis
Large number of thrombi in the pulmonary arteries during APE
Previous episodes of PE or DVT
Echocardiographic signs of PH/RV dysfunction; RV/LV>1 (echocardiography or CTPA)
Significantly elevated tricuspid regurgitant peak gradient > 50 mm Hg in acute PE
Predisposing conditions: chronic inflammatory diseases (chronic osteoarthritis and chronic inflammatory bowel disease), status post-splenectomy, ventriculoperitoneal valve for hydrocephalus treatment, infected chronic i.v. lines or pacemakers, "non-0" blood type, substitution-treated hypothyroidism, thrombophilia (especially antiphospholipid syndrome and increased factor VIII activity), active cancer

Abbreviations: DVT, deep venous thrombosis; LV, left ventricle; PE, pulmonary embolism; PH, pulmonary hypertension; RV, right ventricle, other — see Table 1

physical capacity compared to the period before the acute episode of disease. Factors that increase the likelihood of developing CTEPH have been identified among individuals with a history of APE [1], as summarized in Table 2. Testing for CTEPH may be considered in patients with at least one of these risk factors.

We suggest that suspicion of CTEPH should be considered and diagnostic echocardiography should be initiated in all patients with persistent dyspnea or limitation of physical function of unclear cause despite 3 months of anticoagulation after an episode of APE, especially in the presence of the coexisting risk factors listed in Table 2 or the presence of changes on CTPA scan indicating a chronic character of the disease.

In addition, if a tricuspid regurgitant peak gradient >50–60 mm Hg is found in patients with APE, a follow-up echocardiogram after at least 3 months of anticoagulant therapy is indicated, regardless of the persistence of clinical symptoms.

NON-INVASIVE ASSESSMENT OF THE PULMONARY CIRCULATION IN PATIENTS WITH A HISTORY OF APE

Transthoracic echocardiography

Despite the dynamic development of imaging modalities, transthoracic echocardiography (TTE) is still the preferred screening test for CTEPH. TTE should be performed in any patient with dyspnea of unclear cause after a history of APE and at least 3 months of optimal antithrombotic therapy. TTE may also be considered in patients 3–6 months after an APE when CTEPH risk factors are present or when abnormalities on CTPA performed during the acute phase of the disease suggest pre-existing chronic thromboembolic changes (Table 1). When the tricuspid regurgitation maximum velocity on transesophageal echocardiography (TEE) is >2.8 m/s, or when the velocity is ≤2.8 m/s, but with other echocardiographic features suggestive of PH, the patient should be referred for a reference healthcare center consultation or pulmonary scintigraphy. Echocardiography should also be performed to assess the morphology and function of the left atrium and left ventricle, as well as the mitral and aortic valves, bearing in mind that the most common cause of PH is left heart pathology. Echocardiographic parameters suggestive of PH proposed in the ESC recommendations for the diagnosis and treatment of PH [1] are shown in Table 3.

Lung scintigraphy

In cases where there is clinical suspicion of CTEPH and echocardiographic features suggestive of PH are present, ventilation-perfusion lung scintigraphy is indicated. A normal scintigraphy result allows for the definitive exclusion of CTEPH. The typical ventilation-perfusion scintigraphy findings in patients with CTEPH are segmental or lobar perfusion defects. Scintigraphy allows for the differentiation between CTEPH and pulmonary arterial hypertension (PAH): the latter is typically associated with normal findings although subsegmental perfusion abnormalities may be present. Performing ventilation scans is intended to increase the specificity of the test, but it is acceptable to compare the perfusion scintigraphy result with a chest radiograph or computed tomography (CT) scan. Patients with CTEPH show normal ventilation or normal pulmonary parenchyma in areas of hypoperfusion.

Lung scintigraphy remains an important test when CTEPH is suspected, with a sensitivity and specificity of 96%–97% and 90%–95%, respectively, for the diagnosis of CTEPH [11]. If the test result is inconclusive, further diagnostic tests should be performed. The sensitivity of the scintigraphic examination has been greatly increased by the introduction of single-photon emission computed tomography (SPECT) imaging; now, with the use

Table 3. Echocardiographic indices suggestive of pulmonary hypertension used to assess the likelihood of PH, assessed in conjunction with tricuspid regurgitation velocity measurement[a]

Ventricles	Pulmonary artery	Inferior vena cava / right atrium
Right ventricular/left ventricular basal diameter ratio >1.0	Right ventricular acceleration time <105 msec and/or midsystolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration)
Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/ /or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/s	Right atrial area (end-systolic) >18 cm^2
	Pulmonary artery diameter >25 mm	

[a]At least two echocardiographic parameters in two different categories

of hybrid techniques, its specificity has also improved. SPECT primarily provides scintigraphic images with much better resolution, while the introduction of CT enables absorption correction and simultaneous imaging of the lung parenchyma, improving the specificity of the study. Indeed, ventilation/perfusion SPECT is fast becoming the preferred scintigraphic method for suspected CTEPH [2]. A list of laboratories performing scintigraphy can be found in the Supplementary material.

CT scan of the lungs

CTPA imaging of the pulmonary arteries combined with high-resolution imaging for the diagnosis of parenchymal lesions is an essential component of the diagnostic workup for CTEPH. However, it should be strongly emphasized that a normal CTPA result does not exclude CTEPH; thus, in the traditional diagnostic algorithm, this test is placed after lung scintigraphy. CTPA has a 94%–95% sensitivity and specificity for the diagnosis of CTEPH [12]. The location and morphology of thrombi visualized by CTPA provide important information used to plan the surgical treatment of CTEPH. In addition, CT scanning illustrates lung parenchymal disease that may account for symptoms suggestive of CTEPH [1].

We have an increasing amount of data on the utility of dual-source CT in the diagnosis of CTEPH. This method allows for better visualization of the subsegmental pulmonary arteries. Research is also underway aimed at examining the feasibility of using magnetic resonance imaging to diagnose patients with CTEPH.

INVASIVE ASSESSMENT OF THE PULMONARY CIRCULATION IN PATIENTS WITH A HISTORY OF APE

Right heart catheterization

Confirmation of PH requires invasive direct measurement of pulmonary artery pressure. The current ESC guidelines set the cut-off point for the diagnosis of PH at 20 mm Hg for mean pulmonary arterial pressure [13]. The definition of CTEPH also includes the condition of documenting a normal pulmonary artery wedge pressure ≤15 mm Hg. The ESC guidelines indicate that right heart catheterization should be performed in patients with suspected CTEPH based on symptoms, risk factors, and non-invasive tests, including echocardiography [1]. Additional indications for right heart catheterization (RHC) include eligibility for pulmonary endarterectomy (PEA) or balloon pulmonary angioplasty (BPA) and the inclusion of specific therapy targeting pulmonary arteries [14]. RHC is a relatively safe procedure; however, even in experienced centers, the risk of fatal complications is anticipated at about 0.05% [15]. Exercise RHC should be considered when CTEPD is suspected, which is characterized by normal resting pulmonary pressure and pulmonary resistance values, and their abnormal increase during exercise. An exercise-induced increase in the slope of the mean pulmonary arterial pressure to cardiac output (mPAP/CO curve >3 mm Hg/l/min) due to persistent embolic material in the pulmonary bed is considered abnormal.

Pulmonary arterial angiography

Pulmonary arterial angiography is still considered the "gold standard" for the diagnosis of CTEPD and CTEPH. It is a basic diagnostic tool used during the qualification of the patient for an appropriate method of surgical treatment. Pulmonary angiography should be performed via the selective injection of contrast medium into the pulmonary arteries. The vasculature of each lung should be imaged during stopped breathing in at least two images e.g., posterior-anterior and lateral. The use of digital subtractive angiography, biplane cameras, and 3D rotational angiography allows clinicians to reduce the volume of the contrast agent used and to better visualize the subsegmental arteries. The technical principles of performing pulmonary arteriography have been described in detail elsewhere [14]. Analysis of angiographic images requires experience and knowledge of the anatomy of the pulmonary circulation. We evaluate the location, extent, and morphology of chronic thromboembolic lesions, which are different from the thrombi found in APE. The assessment of peripheral pulmonary parenchymal perfusion is important.

Coronary angiography should be considered in patients older than 55 years who are eligible for surgical treatment of CTEPH. Currently, routine implantation of venous filters before PEA is not recommended.

DIAGNOSTIC STRATEGY IN SUSPECTED CTEPH AND DIAGNOSTIC ALGORITHM

TTE is recommended if CTEPH is clinically suspected (i.e., dyspnea, worsening of exercise tolerance compared to the period before the episode of APE, etc.) in a patient with a history of APE and at least 3 months of effective antithrombotic therapy. TTE may also be considered in patients 3–6 months post-APE who have risk factors for CTEPH or have lesions suggestive of CTEPH in acute phase CTPA. In special cases involving patients with symptoms of severe right ventricular failure and severe PH who do not improve after initial treatment of APE, eligibility for invasive treatment may be considered earlier than 3 months. However, when a patient with a history of APE reports shortness of breath many months earlier, the first step should be to exclude another episode of APE and consider other causes of dyspnea. If CTEPH is likely, a TTE should be performed to confirm suspected features of right ventricular overload.

If an intermediate or high probability of PH is found on TTE, pulmonary scintigraphy should be performed, or if the test is difficult to access, the patient should be referred to a reference center. If this test is negative, CTEPH can be ruled out as the cause of the clinical and echocardiographic symptoms, and another cause should be sought. When perfusion impairment of at least one segment is found without associated parenchymal or ventilatory abnormalities, a diagnosis of CTEPH is likely. When the scintigraphy image is equivocal, the diagnosis of CTEPH is uncertain. In both of these situations, further diagnostic testing should be performed. CTPA is an imaging study of embolic changes in the pulmonary bed and should be performed when the diagnosis of CTEPH on pulmonary scintigraphy is uncertain or probable. Definitive confirmation of CTEPH is obtained by performing RHC, followed by pulmonary arteriography. If the patient had a CTPA at the time of the diagnosis of APE, a repeat test may be considered after a period of at least 3 months of anticoagulant treatment. The finding of post-thrombotic lesions strongly supports the diagnosis of CTEPH. In this situation, lung scintigraphy may be abandoned, and the patient should be referred for invasive diagnostics to confirm PH. However, normal CTPA does not exclude CTEPH and requires a further differential diagnosis of the cause of PH by pulmonary scintigraphy or arteriography. A proposed diagnostic algorithm for suspected CTEPH is shown in Figure 1.

Patients with suspected CTEPH based on clinical signs and echocardiographic features of right ventricular overload found after 3 months of optimal antithrombotic therapy should be referred to Reference Centers for the diagnosis and treatment of PH, or they should have ventilation-perfusion lung scintigraphy performed and be referred to reference centers if perfusion defects are found in areas of normal ventilation. A list of such centers is included at the end of the article.

PRINCIPLES OF TREATMENT OF CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

The following methods are used to treat CTEPH [1]:

Procedural treatment

A. PEA is the treatment of choice for patients with surgical CTEPH. It involves separating the fibrous thrombus from the vessel wall and removing it. The plane of dissection usually runs at the level of the muscular layer of the artery. The procedure is performed in deep hypothermia, with temporary cardiac arrest. It should only be performed in experienced centers that specialize in this technique. In Poland, 30%–32% of patients with CTEPH are qualified for PEA [3, 16, 17] similar to Japan (23.5%) and in contrast to Western European countries (72.1%) and the US (87.2%) [18, 19]. The incidence of persistent CTEPH after PEA is about 50% in international registers, and 46% in Poland [2, 3]. In an international registry, among patients undergoing PEA, the mortality associated with PH was 3.5% at 32-month follow-up [18]. In contrast, the annual all-cause mortality rate in the US registry was 5.6% [19], while in a single-center study by Polish authors, peri-operative mortality was 9.1% [20].

B. BPA of the pulmonary arteries is a percutaneous procedure that involves unclogging and/or dilating the pulmonary arteries in areas occupied by organized thrombus using a balloon catheter. In an international registry, among patients undergoing BPA, the mortality associated with PH was 1.8% at 32-month follow-up [18]. In the Polish BNP-PL registry, the 3-year survival rate was 92.4%; perioperative complications, such as lung damage, were reported in 6.4% of sessions [21]. Multiple treatment sessions per patient are usually required to achieve clinical and hemodynamic improvement. The procedure should be performed in expert centers for PH.

Pharmacotherapy

A. Anticoagulant treatment is recommended indefinitely in all patients with CTEPH, including after PEA or BPA. Given the long experience, vitamin K antagonist (VKA) with a target international normalized ratio (INR) of 2.0–3.0 is standardly recommended. However, register studies indicate an increasingly common use of oral non-VKA anticoagulants in patients with CTEPH; in Poland, 50% use this group of anticoagulants, and 30.8% use VKA [2, 3]. Observational studies [22, 23] have found no differences in the efficacy and safety of these two groups of drugs. The exception is patients with antiphospholipid syndrome, in whom VKA is recommended [2].

B. Pulmonary artery-targeted treatment with riociguat, a soluble guanylyl cyclase stimulator, and the prostacyclin analog treprostinil in a subcutaneous form, have been registered for the treatment of inoperable CTEPH

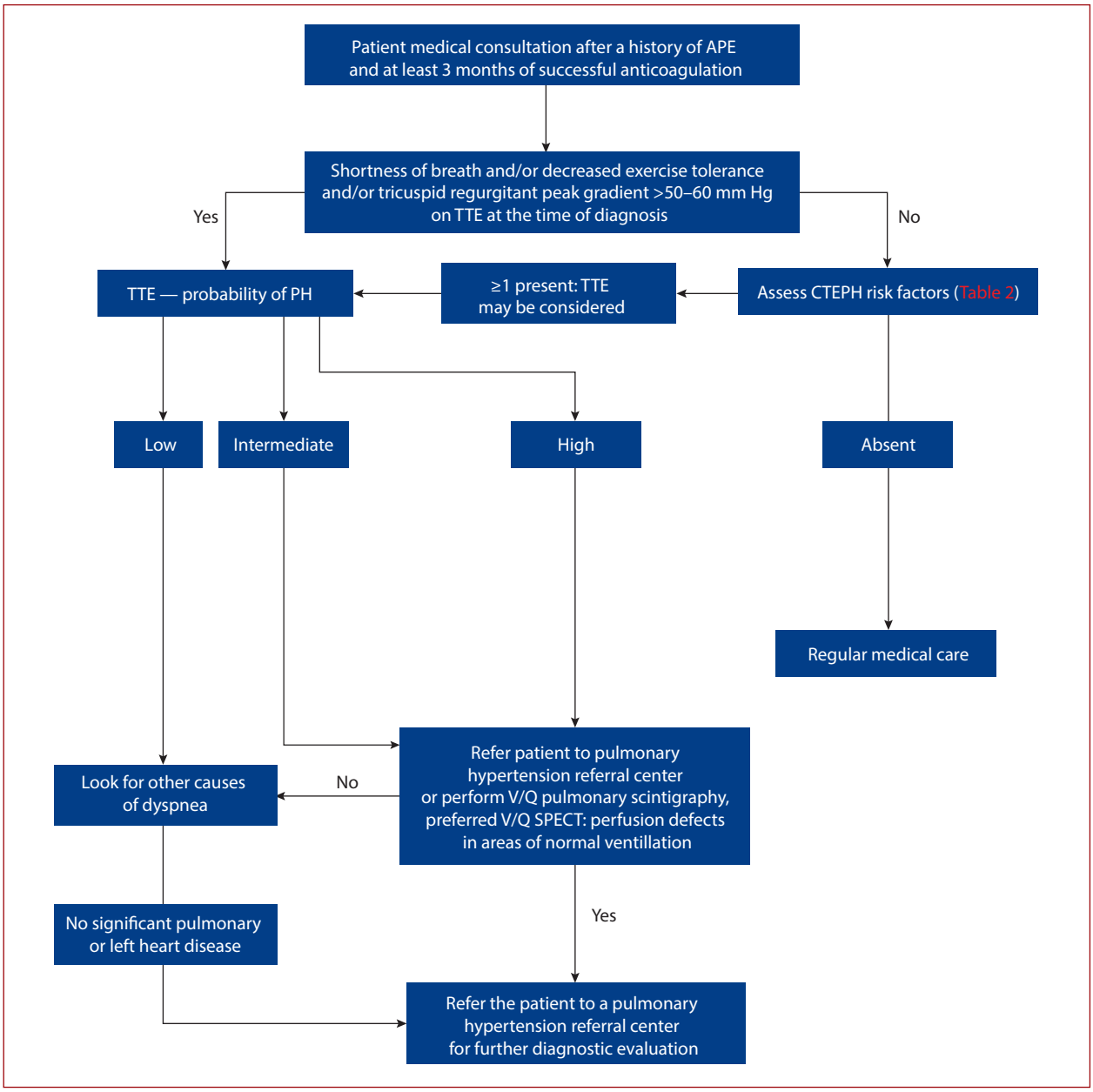

Figure 1. A proposed diagnostic algorithm for suspected CTEPH

Abbreviations: SPECT, single-photon emission computed tomography; TTE, transthoracic echocardiography; V/Q scintigraphy, ventilation-perfusion scintigraphy; other — see Table 1

or CTEPH persistent after PEA because of positive results from multicenter randomized trials [24, 25]. Riociguat is recommended for patients in World Health Organization (WHO) functional class II–III and treprostinil in functional class III–IV. Currently, only riociguat is reimbursed in Poland under the National Health Fund CTEPH Treatment Program, whereas treprostinil may be used only under the procedure of emergency access to drug therapies. Treatment should be provided at reference centers for PH.

C. Oxygen therapy for hypoxemia (PO_2 <60 mm Hg, arterial blood oxygen saturation <91%) [1].

D. Diuretics for fluid retention [1].

Treatment should be individualized for each patient by an interdisciplinary CTEPH team consisting of a surgeon experienced in PEA (in Poland the procedures are performed in cardiac surgery centers), an interventional cardiologist experienced in BPA procedures, and a cardiologist experienced in treating PH. The choice of treatment method is based on the evaluation of the location and extent of thromboembolic lesions (the surgical aspect of surgery), the stage of the disease, hemodynamic parameters, additional conditions, and the benefit-risk ratio (the medical aspect of surgery). In surgical patients, PEA is the method of choice, given its long usage and proven good long-term outcomes. In symptomatic non-operative patients, as well as in symptomatic patients with persistent or recurrent PH after PEA, treatment with riociguat is indicated, i.e., patients in WHO functional class II–III. Combination therapy with

treprostinil should also be considered in patients with WHO class III–IV CTEPH. BPA should be considered in symptomatic patients with inoperable, persistent, or recurrent PH after PEA. This procedure should only be performed at experienced centers.

COVID-19 RELATED TO CTEPH

SARS-CoV-2, the causative agent for COVID-19, led to a global health crisis in 2020 [26]. In addition to pneumonia, clinical characteristics of COVID-19 include multidirectional and often serious consequences, also involving the cardiovascular system. The development of thrombi in the pulmonary circulation is important in this context. The potential mechanism is determined by the local coagulative effect and inflammatory changes triggered by viral infection, with the coexistence of endothelial cell dysfunction in the microvascular segment of the pulmonary circulation. However, the classical profile of venous thromboembolism is also determined by predisposing factors such as immobilization, venous catheters, hypoxemia, and chronic heart failure. From a general perspective, an assessment of the frequency of thromboembolic lesions associated with SARS-CoV-2 co-infection remains considerably difficult; observations were mostly retrospective, study groups were selected based on heterogeneous criteria, and varied diagnostic strategies were used. A systematic review and meta-analysis of 23 studies with a population size of 7178 found a prevalence of 1.6%–65.0% for patients with APE who were hospitalized in general wards (pooled incidence value) 14.7%, and 4.2%–75% in intensive care units (pooled incidence value, 23.4%) [27]. Lesions were more frequently found at the level of segmental and subsegmental arteries. In contrast, a Cochrane review of 16 studies including 7700 hospitalized patients found a weighted mean incidence of 7.4% for venous thromboembolism and 4.3% for APE [28]. An opposed methodology was used in a study from Spain, where the analysis was conducted among 74 814 patients with COVID-19, who presented in 62 hospital emergency departments, which accounts for about 20% of all units in the country. APE was found in 4.92% of patients, and the standardized rate was 9-fold higher than the corresponding diagnosis in the population without coexisting COVID-19 lesions [29].

It is even more complicated to determine the effect of SARS-CoV-2 mass infections on CTEPH. The authors of a brief report from the United Kingdom observed a 32% reduction in the number of patients presenting to a central coordinating center for CTEPH confirmation, compared to the 3 years prior to the onset of the COVID-19 pandemic in 2020 [30]. There are several potential causes for this:

- different hypothesized pathogenic mechanisms;
- a lower risk of CTEPH associated with the more distal location of thrombi and their structural distinctiveness in the event of infectious complications;
- hypothesized higher efficacy of anticoagulant treatment;
- the need for a longer follow-up;
- reduced prevalence of classical predisposing factors for thromboembolism, i.e., elective surgery or air travel; and
- severe overburdening of the health care system worsening the diagnostic process of CTEPH [28].

COVID-19-conditioned mortality rates should also be considered. A brief survey of patients with PH from 47 centers across 28 countries worldwide has been published [31]. Unfortunately, the data correspond to the early stage of demographic observations (April 17, 2020 to May 10, 2020) and suffer from an obvious lack of complete representativeness. SARS-CoV-2 infections affected 70 patients at 19 centers. The overall mortality rate was 19%. It was 14% in patients with CTEPH and 20% in patients with PAH. Thus, the analysis showed a significantly worse prognosis and higher risk in the PH patient population compared to the general SARS-CoV-2 infected population. Patients with CTEPH in the era of the COVID-19 pandemic experience significantly increased levels of anxiety and depression, which may result in reduced frequency of personal visits to treatment centers [32].

Analyzing the literature data and pathophysiological changes caused by SARS-CoV-2 infection, one cannot exclude the possibility of a higher incidence of CTEPH in the future. In addition, the delay in diagnosis caused by the pandemic may result in significant disease progression at the time of CTEPH diagnosis and thus a poorer prognosis for patients.

CONCLUSION

CTEPH is a rare but very dangerous sequela of APE that can occasionally occur in patients without a history of an APE. The incidence of CTEPH after a history of APE is approximately 1%–4%. In Poland, hundreds of patients develop the disease each year; if epidemiological data for developed countries (e.g., the US, the United Kingdom) are applied to the Polish population, the incidence should be assumed at the level of about 250 patients/year. The COVID-19 pandemic can be expected to result in a higher incidence of CTEPH, and delayed diagnosis is anticipated to result in the development of the more advanced stages of the disease. The prognosis for people with CTEPH depends on proper diagnosis. The lack of a diagnosis and appropriate treatment significantly reduces the quality of life and inevitably leads to death in patients with CTEPH. It is important to identify patients who present with symptoms suggestive of CTEPH after an incident of APE. Therefore, every patient should visit their doctor after 3 months of anticoagulation treatment following diagnostic confirmation of an APE. Initial suspicion of CTEPH should be made by physicians caring for patients in out-patient clinics. When features of right ventricular overload are identified on TTE performed after at least 3 months of optimal anticoagulation therapy, these patients should be referred to reference centers for the diagnosis and

treatment of CTEPH. There are now effective surgical and pharmacological treatments for CTEPH, improving the quality of life and prognosis of patients. All forms of CTEPH therapy are available in Poland.

THE MANAGEMENT OF APE: INFORMATION FOR THE PRIMARY CARE PHYSICIAN

We emphasize the following points concerning the clinical management of APE, with a focus on points of care for the physician.

- First, the patient requires periodic medical follow-up after an incident of APE.
- Each patient should have a follow-up medical visit 3–6 months after an incident of APE. During the visit, determine whether anticoagulation treatment should be continued and suggest a follow-up schedule. TTE should be performed in patients with dyspnea.

Clinicians should suspect CTEPH and refer the patient for further diagnosis under the following circumstances: (1) exertional dyspnea or signs of right heart failure in a patient with a history of APE; or (2) persistent exertional dyspnea in a patient after at least 3 months of antithrombotic therapy, especially when there are signs suggestive of PH on a follow-up TTE.

Patients should be referred for assessment 3 months after an incident of APE in the cardiology or internal medicine outpatient clinic preferably in the center where the patient was treated. A patient with suspected CTEPH should be referred to a CTEPH referral center (see the list of centers attached to this document).

LIST OF POLISH CENTERS THAT DIAGNOSE PATIENTS WITH SUSPECTED CTEPH

- Białystok: Prof. Bozena Sobkowicz, MD, Prof. Karol Kaminski, MD, University Clinical Hospital, Department of Cardiology with Cardiac Intensive Care Unit, M Sklodowskiej-Curie 24A, 15–276 Białystok, phone: +48 85 831 86 56;
- Bydgoszcz: Michal Ziolkowski, MD, Department of Cardiology, Jan Biziel, MD, University Hospital No. 2, Ujejskiego 75, 85–168 Bydgoszcz, phone: +48 52 365 56 16;
- Gdańsk: Prof. Ewa Lewicka, MD, Bozena Zieba, MD, University Clinical Center, Clinical Cardiology Center, Dębinki 7, 80–952 Gdańsk, phone: +48 58 349 39 10,
- Katowice: Prof. Zbigniew Gasior, MD, Department of Cardiology, Faculty of Medicine; Prof. Katarzyna Mizia-Stec, MD, PhD, 1st Chair and Department of Cardiology, WNMK, Medical University of Silesia in Katowice, Prof. L. Giec Upper Silesian Medical Center, Ziolowa 47, 40–635 Katowice, phone: +48 32 252 74 07;
- Kraków: Prof. Grzegorz Kopec, MD, Pulmonary Circulation Center, Department of Cardiac and Vascular Diseases, Jagiellonian University Medical College, Kraków, Poland, Department of Cardiovascular Diseases with Cardiac Intensive Care Unit, John Paul II Hospital, Pradnicka 80, 31–202 Kraków, phone: +48 12 614 22 87;
- Lubin: Andrzej Korda, MD, Regional Cardiology Center, Cardiology Department, Miedziowe Medical Center, M Sklodowskiej-Curie 66, 59–301 Lubin, phone: +48 76 846 04 00;
- Lublin: Piotr Blaszczak, MD, Stefan Cardinal Wyszynski Voivodship Specialist Hospital, Department of Cardiology and Cardiac Intensive Care, Krasnicka 100, 20–718 Lublin, phone: +48 81 537 47 40,
- Lublin: Prof. Michal Tomaszewski, MD, Department of Cardiology, Medical University, Independent Public Clinical Hospital No. 4, Jaczewskiego 8, 20–954 Lublin, phone: +48 81 724 41 51,
- Łódź: Prof. Łukasz Chrzanowski, MD, Department of Cardiology, Medical University of Lodz, Pomorska 251, 92–213 Łódź, phone: +48 42 251 62 16,
- Otwock: Prof. Marcin Kurzyna, MD, Szymon Darocha, MD, Department of Pulmonary Circulation, Thromboembolic Diseases and Cardiology Center of Postgraduate Medical Education, European Health Center Otwock, F Chopin Hospital, Borowa 14/18, 05–400 Otwock, phone: +48 22 710 30 52;
- Poznań: Prof. Tatiana Mularek, MD, Department of Cardiology, Karol Marcinkowski Medical University, Poznań, Poland, Dluga 1/2, 61–848 Poznań, phone: +48 61 854 91 46;
- Warszawa: Prof. Agnieszka Pawlak, MD, Department of Invasive Cardiology, Heart Failure Subdivision, Central Clinical Hospital of the Polish Interior, Woloska 137, 02–507 Warszawa, phone: +48 22 508 11 00;
- Warszawa: Prof. Piotr Pruszczyk, MD, Prof. Michal Ciurzynski, MD, Marek Roik, MD, Olga Dzikowska-Diduch, MD, Department of Internal Medicine and Cardiology, Medical University of Warsaw, Infant Jesus Clinical Hospital, Lindleya 4, 02–005 Warszawa, phone: +48 22 502 11 44;
- Warszawa: Katarzyna Betkier, MD, PhD, Piotr Łyżwa, MD, PhD, Department of Cardiology and Internal Medicine, Ministry of Defense Central Clinical Hospital, Military Medical Institute, Szaserow 128, 04–141 Warszawa, phone: +48 22 261 816 389,
- Wrocław: Ewa Mroczek, MD, University Clinical Hospitals, Heart Institute, Department of Cardiology, Borowska 213, 50–556 Wrocław, phone: +48 71 736 4230;
- Szczecin: Małgorzata Peregud-Pogorzelska, MD, Department of Cardiology with Intensive Cardiac Care, Independent Public Clinical Hospital No. 2 of Pomeranian Medical University, Powstancow Wielkopolskich 72, 70–111 Szczecin, phone: +48 91 466 13 78,
- Zabrze: Ilona Skoczylas, MD, 3rd Department of Cardiology, Medical University of Silesia, Silesian Center for Heart Diseases, M Sklodowskiej-Curie 9, 41–800 Zabrze, phone: +48 32 373 37 88,
- Zabrze: Wojciech Jachec, MD, Clinical Department of Cardiology, Specialized Hospital, M Curie-Sklodowskiej 10, 41–800 Zabrze, phone: +48 32 271 10 10,

LIST OF LABORATORIES PERFORMING LUNG SCINTIGRAPHY

The list of laboratories performing pulmonary scintigraphy can be found in Supplementary files and on the website of the Pulmonary Circulation Section of the Polish Cardiac Society at: http://www.ptkardio.pl/Lista_pracowni_wykonujacych_scyntygrafie_pluc-2718.

Supplementary material

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

Article information

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Sekcji Farmakoterapii Sercowo-Naczyniowej
Polskiego Towarzystwa Kardiologicznego

GDYNIA,
9-10 WRZEŚNIA 2022 ROKU

Przewodniczący Komitetu Naukowego:

prof. dr hab. n. med. Krzysztof J. Filipiak, FESC
dr hab. n. med. Iwona Gorczyca-Głowacka

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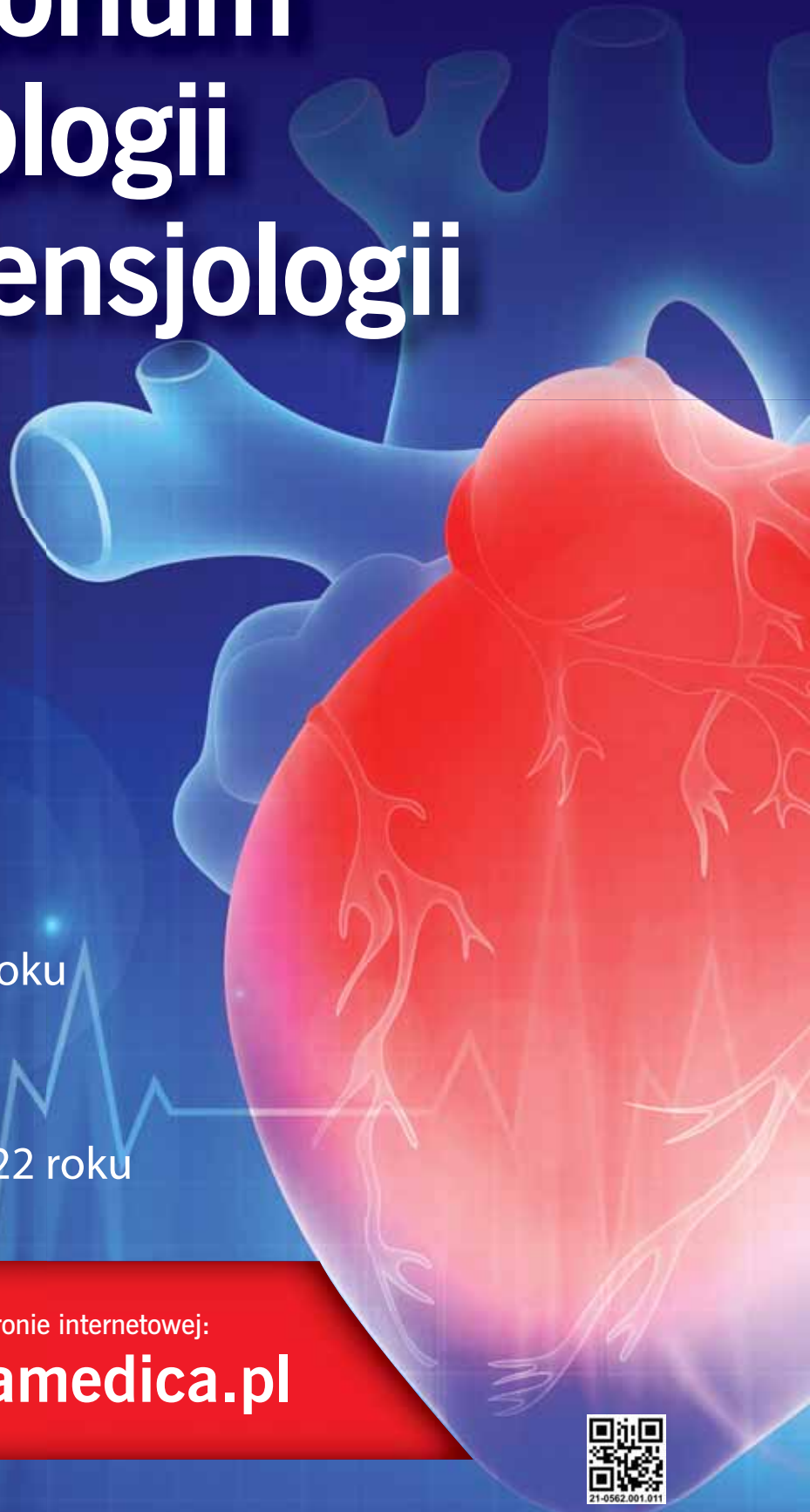
Repetytorium z Kardiologii i Hipertensjologii 2022



WIOSENNE

VIRTUAL MEETING

5 marca 2022 roku

LETNIE

Trójmiasto

4–5 czerwca 2022 roku

JESIENNE

Warszawa

15 października 2022 roku

Więcej informacji i rejestracja na stronie internetowej:

www.kardio.viamedica.pl

21-0562.001.011

Cykl konferencji jest skierowany do wszystkich osób zainteresowanych tematyką. Sesje satelitarne firm farmaceutycznych, sesje firm farmaceutycznych oraz wystawy firm farmaceutycznych są skierowane tylko do osób uprawnionych do wystawiania recept lub osób prowadzących obrót produktami leczniczymi — podstawa prawna: Ustawa z dnia 6 września 2001 r. Prawo farmaceutyczne (Dz. U. z 2017 r. poz. 2211. z późn. zm.).

ORGANIZATOR

VIA MEDICA

HFpEF – niewydolność serca z zachowaną frakcją wyrzutową; **HFrEF** – niewydolność serca z obniżoną frakcją wyrzutową

***** W badaniu EMPEROR-Reduced – randomizowanym, prowadzonym metodą podwójnie ślepej próby w grupach równoległych, kontrolowanym za pomocą placebo badaniu z udziałem 3730 pacjentów z HFrEF – oceniano skuteczność i bezpieczeństwo stosowania produktu JARDIANCE® 10 mg (n = 1863) w porównaniu z placebo (n = 1867). Pierwszorzędowym złożonym punktem końcowym w badaniu EMPEROR-Reduced był zgon z przyczyn SN lub HHF, analizowane jako czas do pierwszego zdarzenia. U pacjentów leczonych produktem JARDIANCE® odnotowano 25% RRR tego punktu końcowego (HR = 0,75; 95% CI: 0,65-0,86; p < 0,001)[2]. **†** W badaniu EMPEROR-Preserved – randomizowanym, prowadzonym metodą podwójnie ślepej próby w grupach równoległych, kontrolowanym za pomocą placebo badaniu z udziałem 5988 pacjentów z HFpEF – oceniano skuteczność i bezpieczeństwo stosowania produktu JARDIANCE® 10 mg (n = 2997) w porównaniu z placebo (n = 2991). Pierwszorzędowym złożonym punktem końcowym w badaniu EMPEROR-Preserved był zgon z przyczyn SN lub HHF, analizowane jako czas do pierwszego zdarzenia. U pacjentów leczonych produktem JARDIANCE® odnotowano 21% RRR tego punktu końcowego (HR = 0,79; 95% CI: 0,69-0,90; p < 0,001)[3].

1. JARDIANCE® Charakterystyka Produktu Leczniczego, 03.03.2022 r. **2.** Packer M., Anker S., Butler J. i wsp. EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020; 383 (15): 1413-1424. (Wyniki badania EMPEROR-Reduced oraz dodatek uzupełniający do publikacji.) **3.** Anker S., Butler J., Filippatos G. i wsp. EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021; 385 (16): 1451-1461. (Wyniki badania EMPEROR-Preserved oraz dodatek uzupełniający do publikacji.)

Skrócona informacja o leku JARDIANCE®

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

Wskazanie	eGFR [ml/min/1,73 m^2] lub CrCL [ml/min]	Całkowita dawka dobowa
Cukrzyca typu 2	≥60	Rozpoczęć od dawki 10 mg empagliflozyny. U pacjentów tolerujących dawkę 10 mg empagliflozyny i wymagających dodatkowej kontroli glikemii dawkę można zwiększyć do 25 mg empagliflozyny.
	45 do <60	Rozpoczęć od dawki 10 mg empagliflozyny.[b] Kontynuować stosowanie dawki 10 mg empagliflozyny u pacjentów, którzy już przyjmują produkt leczniczy Jardiance®.
	30 do <45[b]	Rozpoczęć od dawki 10 mg empagliflozyny. Kontynuować stosowanie dawki 10 mg empagliflozyny u pacjentów, którzy już przyjmują produkt leczniczy Jardiance®.
	<30	Nie zaleca się stosowania empagliflozyny.
Niewydolność serca (z cukrzycą typu 2 lub bez cukrzycy typu 2)	≥20	Zalecana dawka dobowa to 10 mg empagliflozyny.
	<20	Nie zaleca się stosowania empagliflozyny.

[a] Patrz punkty Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania, Działania niepożądane [b] Pacjenci z cukrzycą typu 2 i z potwierdzoną chorobą sercowo-naczyniową

W przypadku leczenia niewydolności serca u pacjentów z cukrzycą typu 2 lub bez cukrzycy typu 2 stosowanie dawki 10 mg empagliflozyny można rozpocząć lub kontynuować leczenie do wartości eGFR równej 20 ml/min/1,73 m^2 lub wartości CrCl równej 20 ml/min. Nie należy stosować empagliflozyny u pacjentów ze schyłkową niewydolnością nerek (SNN), ani u pacjentów dializowanych. Nie ma wystarczających danych, aby uzasadnić stosowanie w tej grupie pacjentów. *Upośledzenie czynności wątroby* Nie ma konieczności dostosowania dawki u pacjentów z upośledzeniem czynności wątroby. U pacjentów z ciężkim upośledzeniem czynności wątroby ekspozycja na empagliflozynę jest zwiększona. Doświadczenie w leczeniu pacjentów z ciężkim upośledzeniem czynności wątroby jest ograniczone, w związku z czym nie zaleca się stosowania empagliflozyny w tej populacji pacjentów. *Pacjenci w podeszłym wieku* Nie ma konieczności dostosowania dawki w zależności od wieku pacjenta. U pacjentów w wieku 75 lat i starszych należy wziąć pod uwagę zwiększone ryzyko zmniejszenia objętości płynów. *Dzieci i młodzież* Nie określono dotychczas bezpieczeństwa stosowania ani skuteczności empagliflozyny u dzieci i młodzieży. Dane nie są dostępne. Sposób podawania Tabletki mogą być przyjmowane jednocześnie z posiłkiem lub niezależnie od niego. Tabletki należy połykać w całości popijając wodą. **Przeciwwskazania:** Nadwrażliwość na substancję czynną lub na którąkolwiek substancję pomocniczą wymienioną w punkcie Wykaz substancji pomocniczych ChPL. **Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania:** Kwasica ketonowa U pacjentów z cukrzycą leczonych inhibitorami SGLT2, w tym empagliflozyną, zgłaszano rzadkie przypadki kwasicy ketonowej, w tym przypadki zagrażające życiu i zakończone zgonem. W niektórych przypadkach obraz kliniczny był nietypowy, tylko z umiarkowanym zwiększeniem stężenia glukozy we krwi, poniżej 14 mmol/l (250 mg/dl). Nie wiadomo, czy zastosowanie większych dawek empagliflozyny zwiększa ryzyko kwasicy ketonowej. Należy uwzględnić ryzyko kwasicy ketonowej w razie wystąpienia niespecyficznych objawów, takich jak: nudności, wymioty, jadłowstręt, ból brzucha, silne pragnienie, zaburzenia oddychania, splątanie, niezwykłe zmęczenie lub senność. W razie wystąpienia takich objawów należy niezwłocznie zbadać pacjentów, czy nie występuje u nich kwasica ketonowa, niezależnie od stężenia glukozy we krwi. Należy natychmiast przerwać leczenie empagliflozyną u pacjentów z podejrzeniem lub rozpoznaniem kwasicy ketonowej. Należy przerwać leczenie u pacjentów hospitalizowanych z powodu dużych zabiegów chirurgicznych lub ostrych ciężkich chorób. U tych pacjentów zaleca się monitorowanie stężeń ciał ketonowych. Preferowane jest oznaczanie stężenia ciał ketonowych we krwi, a nie moczu. Leczenie empagliflozyną można wznowić, gdy stężenie ciał ketonowych będzie prawidłowe, a stan pacjenta ustabilizuje się. Przed rozpoczęciem leczenia empagliflozyną należy rozważyć czynniki w wywiadzie predysponujące pacjenta do kwasicy ketonowej. Do pacjentów ze zwiększonym ryzykiem kwasicy ketonowej zalicza się osoby z małą rezerwą czynnościową komórek beta (np. pacjenci z cukrzycą typu 2 i małym stężeniem peptydu C lub późno ujawniającą się cukrzycą autoimmunologiczną dorosłych – ang. latent autoimmune diabetes in adults – LADA lub pacjenci z zapaleniem trzustki w wywiadzie), pacjentów ze stanami prowadzącymi do ograniczenia przyjmowania pożywienia lub z ciężkim odwodnieniem pacjentów, którym zmniejszono dawkę insuliny oraz pacjentów ze zwiększonym zapotrzebowaniem na insulinę z powodu ostrej choroby, zabiegu chirurgicznego lub nadużywania alkoholu. U tych pacjentów należy ostrożnie stosować inhibitory SGLT2. Nie zaleca się wznawiania leczenia inhibitorem SGLT2 u pacjentów, u których wcześniej wystąpiła kwasica ketonowa podczas stosowania inhibitora SGLT2, chyba że zidentyfikowano i usunięto inną wyraźną przyczynę. Produktu leczniczego Jardiance® nie należy stosować w leczeniu pacjentów z cukrzycą typu 1. Dane z programu badań klinicznych u pacjentów z cukrzycą typu 1 wykazały zwiększone, częste występowanie kwasicy ketonowej u pacjentów leczonych empagliflozyną w dawce 10 mg i 25 mg jako uzupełnienie insuliny w porównaniu z placebo. Niewydolność nerek We wskazaniu cukrzyca typu 2 u pacjentów z wartością eGFR poniżej 60 ml/min/1,73 m^2 lub CrCl <60 ml/min dawka dobowa empagliflozyny jest ograniczona do 10 mg. Nie zaleca się stosowania empagliflozyny w przypadku wartości eGFR poniżej 30 ml/min/1,73 m^2 lub CrCl poniżej 30 ml/min. We wskazaniu niewydolność serca nie zaleca się stosowania produktu leczniczego Jardiance® u pacjentów z wartością eGFR <20 ml/min/1,73 m^2. Nie należy stosować empagliflozyny u pacjentów ze schyłkową niewydolnością nerek (SNN) ani u pacjentów dializowanych. Nie ma wystarczających danych, aby uzasadnić stosowanie w tej grupie pacjentów. Monitorowanie czynności nerek Zaleca się ocenę czynności nerek w następujący sposób: przed rozpoczęciem leczenia empagliflozyną i okresowo podczas leczenia, tzn. co najmniej raz na rok; przed rozpoczęciem leczenia jakimkolwiek innym jednocześnie stosowanym produktem leczniczym, który może mieć niekorzystny wpływ na czynność nerek. Ryzyko zmniejszenia objętości płynów Z uwagi na mechanizm działania inhibitorów SGLT2, diureza osmotyczna towarzysząca glukozurii może spowodować nieznaczne zmniejszenie ciśnienia krwi. W związku z tym należy zachować ostrożność u pacjentów, dla których taki spadek ciśnienia krwi spowodowany przez empagliflozynę mógłby stanowić zagrożenie, takich jak pacjenci z rozpoznaną chorobą układu krążenia, pacjenci stosujący leczenie przeciwnadciśnieniowe z epizodami niedociśnienia w wywiadzie lub pacjenci w wieku 75 i więcej lat. W przypadku stanów, które mogą prowadzić do utraty płynów przez organizm (np. choroba przewodu pokarmowego) zaleca się dokładne monitorowanie stanu nawodnienia (np. badanie przedmiotowe, pomiar ciśnienia krwi, testy laboratoryjne włącznie z oznaczeniem hematokrytu) i stężenia elektrolitów u pacjentów przyjmujących empagliflozynę. Należy rozważyć tymczasowe wstrzymanie leczenia empagliflozyną do czasu wyrównania utraty płynów. Pacjenci w podeszłym wieku Wpływ empagliflozyny na wydalanie glukozy z moczem związany jest z diurezą osmotyczną, co może mieć wpływ na stan nawodnienia. Pacjenci w wieku 75 i więcej lat mogą być w większym stopniu zagrożeni wystąpieniem zmniejszenia objętości płynów. Większa liczba takich pacjentów leczonych empagliflozyną miała działania niepożądane związane ze zmniejszeniem objętości płynów w porównaniu z pacjentami otrzymującymi placebo. W związku z tym należy zwracać szczególną uwagę na przyjmowaną objętość płynów w razie jednoczesnego podawania z produktami leczniczymi mogącymi prowadzić do zmniejszenia objętości płynów (np. leki moczopędne, inhibitory ACE). Powikłane zakażenia dróg moczowych U pacjentów otrzymujących empagliflozynę zgłaszano przypadki powikłanych zakażeń dróg moczowych, w tym odmiednicz̨kowe zapalenie nerek i posocznicę moczopochodną. Należy rozważyć tymczasowe wstrzymanie leczenia empagliflozyną u pacjentów z powikłanym zakażeniem dróg moczowych. Martwicze zapalenie powięzi krocza (zgorzel Fourniera) Zgłaszano przypadki martwiczego zapalenia powięzi krocza (znanego także jako zgorzel Fourniera) u pacjentów płci żeńskiej i męskiej z cukrzycą przyjmujących inhibitory SGLT2. Jest to rzadkie, ale ciężkie i mogące zagrażać życiu zdarzenie, które wymaga pilnej interwencji chirurgicznej i antybiotykoterapii. Pacjentom należy zalecić, aby zgłosili się do lekarza, jeśli wystąpi u nich zespół objawów, takich jak ból, wrażliwość na dotyk, rumień lub obrzęk w okolicy zewnętrznych narządów płciowych lub krocza, z jednoczesną gorączką lub uczuciem rozbicia. Należy pamiętać o tym, że martwicze zapalenie powięzi może być poprzedzone zakażeniem narządów układu moczowo-płciowego lub ropniem krocza. Jeśli podejrzewa się wystąpienie zgorzeli Fourniera, należy przerwać stosowanie produktu Jardiance® i niezwłocznie rozpocząć leczenie (w tym antybiotykoterapię oraz chirurgiczne opracowanie zmian chorobowych). Amputacje w obrębie kończyn dolnych W długoterminowych badaniach klinicznych innego inhibitora SGLT2 zaobserwowano zwiększoną częstość przypadków amputacji w obrębie kończyn dolnych (szczególnie palucha). Nie wiadomo, czy jest to „efekt klasy leków". Podobnie jak w przypadku wszystkich chorych na cukrzycę, ważna jest edukacja pacjentów dotycząca profilaktycznej pielęgnacji stóp. Uszkodzenie wątroby W badaniach klinicznych obejmujących empagliflozynę zgłaszano przypadki uszkodzenia wątroby. Nie ustalono związku przyczynowo-skutkowego pomiędzy empagliflozyną a uszkodzeniem wątroby. Zwiększenie wartości hematokrytu Obserwowano zwiększenie wartości hematokrytu podczas leczenia empagliflozyną. Przewlekła choroba nerek Istnieje doświadczenie dotyczące stosowania empagliflozyny w leczeniu cukrzycy u pacjentów z przewlekłą chorobą nerek (eGFR ≥30 ml/min/1,73 m^2) z albuminurią i bez albuminurii. Leczenie empagliflozyną może być bardziej skuteczne u pacjentów z albuminurią. Choroba naciekowa lub kardiomiopatia takotsubo Nie prowadzono specyficznych badań u pacjentów z chorobą naciekową lub kardiomiopatią takotsubo. Z tego powodu nie określono skuteczności u tych pacjentów. Laboratoryjna analiza moczu Z uwagi na mechanizm działania produktu Jardiance®, pacjenci przyjmujący go będą mieć dodatni wynik testu na zawartość glukozy w moczu. Wpływ na badanie stężenia 1,5-anhydroglucitolu (1,5-AG) Nie zaleca się monitorowania kontroli glikemii za pośrednictwem badania stężenia 1,5-AG, ponieważ oznaczanie stężenia 1,5-AG nie jest miarodajne w ocenie kontroli glikemii u pacjentów przyjmujących inhibitory SGLT2. Zaleca się stosowanie innych metod monitorowania kontroli glikemii. Laktoza Tabletki produktu leczniczego zawierają laktozę. Produkt leczniczy nie powinien być stosowany u pacjentów z rzadko występującą dziedziczną nietolerancją galaktozy, brakiem laktazy lub zespołem złego wchłaniania glukozy-galaktozy. Sód Każda tabletka zawiera mniej niż 1 mmol (23 mg) sodu, to znaczy lek uznaje się za „wolny od sodu". **Działania niepożądane:** Podsumowanie profilu bezpieczeństwa *Cukrzyca typu 2* Łącznie 15 582 pacjentów z cukrzycą typu 2 wzięło udział w badaniach klinicznych oceniających bezpieczeństwo stosowania empagliflozyny, z czego 10 004 pacjentów otrzymywało empagliflozynę w monoterapii lub w skojarzeniu z metforminą, pochodną sulfonylomocznika, pioglitazonem, inhibitorami DPP-4 lub insuliną. W 6 badaniach przeprowadzonych z kontrolą placebo trwających od 18 do 24 tygodni wzięło udział 3 534 pacjentów, z których 1 183 otrzymywało placebo, a 2 351 – empagliflozynę. Ogólna częstość występowania zdarzeń niepożądanych u pacjentów leczonych empagliflozyną była podobna do częstości w grupie otrzymującej placebo. Najczęściej obserwowanym działaniem niepożądanym była hipoglikemia przy stosowaniu w skojarzeniu z pochodną sulfonylomocznika lub insuliną. *Niewydolność serca* Do badań EMPEROR włączono pacjentów z niewydolnością serca i zredukowaną frakcją wyrzutową (N=3 726) lub zachowaną frakcją wyrzutową (N=5 985), którzy otrzymywali leczenie 10 mg empagliflozyny lub placebo. U około połowy pacjentów występowała cukrzyca typu 2. Najczęściej zgłaszanym działaniem niepożądanym łącznie w badaniach EMPEROR-Reduced i EMPEROR-Preserved było zmniejszenie objętości płynów (10 mg empagliflozyny: 11,4%; placebo: 9,7%). Ogólny profil bezpieczeństwa stosowania empagliflozyny był zasadniczo spójny w badanych wskazaniach. Wykaz działań niepożądanych w postaci tabeli W poniższej tabeli przedstawiono działania niepożądane – sklasyfikowane według grup układowo-narządowych oraz według preferowanych terminów MedDRA – zgłaszane u pacjentów, którzy otrzymali empagliflozynę w badaniach prowadzonych z kontrolą placebo (Tabela 2). Działania niepożądane są wymienione według bezwzględnej częstości występowania. Częstość występowania zdefiniowana jest następująco: bardzo często (≥ 1/10); często (≥ 1/100 do < 1/10); niezbyt często (≥ 1/1 000 do < 1/100); rzadko (≥ 1/10 000 do < 1/1 000), bardzo rzadko (< 1/10 000), nieznana (częstość nie może być określona na podstawie dostępnych danych). Tabela 2: Wykaz działań niepożądanych (MedDRA) obserwowanych w badaniach prowadzonych z kontrolą placebo i zgłoszonych po wprowadzeniu produktu do obrotu, w postaci tabeli

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

[a] patrz dodatkowe informacje podane poniżej * patrz punkt Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania

Opis wybranych działań niepożądanych *Hipoglikemia* Częstość występowania hipoglikemii zależała od leczenia podstawowego stosowanego w poszczególnych badaniach i była podobna jak po zastosowaniu placebo u pacjentów stosujących empagliflozynę w monoterapii, jako leczenie skojarzone z metforminą, jako leczenie skojarzone z pioglitazonem w skojarzeniu z metforminą lub bez niej, jako leczenie skojarzone z linagliptyną i metforminą, jako leczenie dodane do terapii standardowej oraz w razie stosowania skojarzenia empagliflozyny z metforminą u nieleczonych uprzednio pacjentów w porównaniu z pacjentami leczonymi osobnymi lekami empagliflozyną i metforminą. Zwiększoną częstość zaobserwowano w przypadku stosowania jako leczenie skojarzone z metforminą i pochodnymi sulfonylomocznika (10 mg empagliflozyny: 16,1%; 25 mg empagliflozyny: 11,5%; placebo: 8,4%), jako leczenie skojarzone z insuliną podstawową w skojarzeniu z metforminą lub bez niej oraz w skojarzeniu z pochodną sulfonylomocznika lub bez niego (10 mg empagliflozyny: 19,5%; 25 mg empagliflozyny: 28,4%; placebo: 20,6% w ciągu pierwszych 18 tygodni leczenia, gdy nie można było dostosowywać dawki insuliny; 10 mg i 25 mg empagliflozyny: 36,1%; placebo: 35,3% w ciągu 78 tygodni badania) i jako leczenie skojarzone z insuliną MDI w skojarzeniu z metforminą lub bez niej (empagliflozyna 10 mg: 39,8%, empagliflozyna 25 mg: 41,3%, placebo: 37,2% podczas pierwszych 18 tygodni leczenia, gdy nie można było dostosować dawki insuliny; empagliflozyna 10 mg: 51,1%, empagliflozyna 25 mg: 57,7%, placebo: 58% w ciągu 52 tygodni badania). W badaniach niewydolności serca EMPEROR obserwowano podobną częstość występowania hipoglikemii podczas stosowania w skojarzeniu z sulfonylomocznikiem lub insuliną (10 mg empagliflozyny: 6,5%; placebo: 6,7%). *Ciężka hipoglikemia (zdarzenia wymagające interwencji)* Nie zaobserwowano zwiększenia częstości występowania ciężkiej hipoglikemii przy stosowaniu empagliflozyny w porównaniu do placebo, w monoterapii, w leczeniu skojarzonym z metforminą, w leczeniu skojarzonym z metforminą i pochodną sulfonylomocznika, w leczeniu skojarzonym z pioglitazonem w skojarzeniu z metforminą lub bez niej, w leczeniu skojarzonym z linagliptyną i metforminą, jako leczenie dodane do terapii standardowej oraz w razie stosowania skojarzenia empagliflozyny z metforminą u nieleczonych uprzednio pacjentów w porównaniu z pacjentami leczonymi osobnymi lekami empagliflozyną i metforminą. Zwiększoną częstość zaobserwowano w przypadku stosowania jako leczenie skojarzone z insuliną podstawową w skojarzeniu z metforminą lub bez niej oraz w skojarzeniu z pochodną sulfonylomocznika lub bez niego (10 mg empagliflozyny: 0%; 25 mg empagliflozyny: 1,3%; placebo: 0% w ciągu pierwszych 18 tygodni leczenia, gdy nie można było dostosowywać dawki insuliny; 10 mg empagliflozyny: 0%; 25 mg empagliflozyny: 1,3%; placebo: 0% w ciągu 78 tygodni badania) i jako leczenie skojarzone z insuliną MDI w skojarzeniu z metforminą lub bez niej (empagliflozyna 10 mg: 0,5%, empagliflozyna 25 mg: 0,5%, placebo: 0,5% podczas pierwszych 18 tygodni leczenia, gdy nie można było dostosować dawki insuliny; empagliflozyna 10 mg: 1,6%, empagliflozyna 25 mg: 0,5%, placebo: 1,6% w ciągu 52 tygodni badania). W badaniach dotyczących niewydolności serca EMPEROR ciężką hipoglikemię obserwowano z podobną częstością występowania u pacjentów z cukrzycą podczas leczenia empagliflozyną i placebo w skojarzeniu z sulfonylomocznikiem lub insuliną (10 mg empagliflozyny: 2,2%, placebo: 1,9%). *Kandydoza pochwy, zapalenie pochwy i sromu, zapalenie żołędzi i inne zakażenia narządów płciowych* Kandydoza pochwy, zapalenie pochwy i sromu, zapalenie żołędzi i inne zakażenia narządów płciowych były obserwowane częściej u pacjentów leczonych empagliflozyną (10 mg empagliflozyny: 4,0%; 25 mg empagliflozyny: 3,9%) w porównaniu z pacjentami otrzymującymi placebo (1,0%). Zakażenia takie obserwowano częściej u kobiet leczonych empagliflozyną w porównaniu z placebo. Różnica ta była mniej wyraźna w przypadku mężczyzn. Zakażenia narządów płciowych miały nasilenie łagodne lub umiarkowane. W badaniach dotyczących niewydolności serca EMPEROR częstość występowania tego typu zakażeń była większa u pacjentów z cukrzycą (10 mg empagliflozyny: 2,3%; placebo: 0,8%) niż u pacjentów bez cukrzycy (10 mg empagliflozyny: 1,7%; placebo: 0,7%) w trakcie leczenia empagliflozyną w porównaniu z placebo. *Zwiększone oddawanie moczu* Zwiększone oddawanie moczu (obejmujące określone wcześniej takie terminy jak częstomocz, wielomocz i oddawanie moczu w nocy) były obserwowane częściej u pacjentów leczonych empagliflozyną (10 mg empagliflozyny: 3,5%; 25 mg empagliflozyny: 3,3%) w porównaniu z pacjentami otrzymującymi placebo (1,4%). Zwiększone oddawanie moczu miało przeważnie nasilenie łagodne lub umiarkowane. Obserwowana częstość oddawania moczu w nocy była podobna dla empagliflozyny i dla placebo (< 1%). W badaniach niewydolności serca EMPEROR zwiększone oddawanie moczu obserwowano z podobną częstością występowania u pacjentów leczonych empagliflozyną i placebo (10 mg empagliflozyny: 0,9%, placebo 0,5%). *Zakażenie dróg moczowych* Ogólna częstość występowania zakażeń dróg moczowych zgłaszanych jako zdarzenie niepożądane była podobna u pacjentów otrzymujących 25 mg empagliflozyny i placebo (7,0% i 7,2%), i wyższa u pacjentów otrzymujących 10 mg empagliflozyny (8,8%). Podobnie jak w przypadku placebo, zakażenia dróg moczowych były zgłaszane częściej u pacjentów leczonych empagliflozyną z przewlekłymi lub nawracającymi zakażeniami dróg moczowych w wywiadzie. Nasilenie (łagodne, umiarkowane, ciężkie) zakażenia dróg moczowych było podobne u pacjentów otrzymujących empagliflozynę i placebo. Zakażenia dróg moczowych były zgłaszane częściej u kobiet leczonych empagliflozyną w porównaniu z placebo; nie było takiej różnicy w przypadku mężczyzn. *Zmniejszenie objętości płynów* Ogólna częstość występowania zmniejszenia objętości płynów (obejmującego określone wcześniej takie terminy jak spadek ciśnienia krwi (określony ambulatoryjnie), spadek skurczowego ciśnienia krwi, odwodnienie, niedociśnienie, hipowolemia, hipotonia ortostatyczna oraz omdlenie) była podobna u pacjentów otrzymujących empagliflozynę (10 mg empagliflozyny: 0,6%; 25 mg empagliflozyny: 0,4%) i placebo (0,3%). Częstość występowania zmniejszenia objętości płynów była zwiększona u pacjentów w wieku 75 lat i starszych leczonych empagliflozyną (10 mg empagliflozyny: 2,3%; 25 mg empagliflozyny: 4,3%) w porównaniu z pacjentami otrzymującymi placebo (2,1%). *Zwiększenie stężenia kreatyniny we krwi i (lub) obniżenie współczynnika filtracji kłębuszkowej* Ogólna częstość występowania przypadków zwiększenia stężenia kreatyniny we krwi i obniżenie współczynnika filtracji kłębuszkowej była podobna u pacjentów otrzymujących empagliflozynę i placebo (zwiększenie stężenia kreatyniny: empagliflozyna 10 mg 0,6%, empagliflozyna 25 mg 0,1%, placebo 0,5%; zmniejszenie szybkości filtracji kłębuszkowej: empagliflozyna 10 mg 0,1%, empagliflozyna 25 mg 0%, placebo 0,3%). Występujące początkowo zwiększenie stężenia kreatyniny we krwi i (lub) obniżenie współczynnika filtracji kłębuszkowej u pacjentów leczonych empagliflozyną jako terapią uzupełniającą leczenie metforminą zwykle ustępowało w trakcie ciągłego leczenia lub było odwracalne po zakończeniu leczenia tym lekiem. Konsekwentnie w badaniu EMPA-REG OUTCOME u pacjentów leczonych empagliflozyną obserwowano występujący początkowo spadek eGFR (średnia: 3 ml/min/1,73 m^2). Następnie wartość eGFR utrzymywała się w czasie trwania leczenia. Średnia wartość eGFR powracała do wartości początkowej po zakończeniu leczenia, co sugeruje, że w patogenezie tych zmian czynnościowych nerek mogą odgrywać rolę ostre zmiany hemodynamiczne. *Zwiększenie stężenia lipidów w surowicy* Średnie zwiększenie procentowe od punktu początkowego dla 10 mg i 25 mg empagliflozyny w porównaniu z placebo wynosiło odpowiednio dla cholesterolu całkowitego 4,9% i 5,7% w porównaniu z 3,5%; dla cholesterolu HDL 3,3% i 3,6% w porównaniu z 0,4 %; dla cholesterolu LDL 9,5% i 10,0% w porównaniu z 7,5%; dla trójglicerydów 9,2% i 9,9% w porównaniu z 10,5%. *Zwiększenie wartości hematokrytu* Średnia zmiana wartości hematokrytu od punktu początkowego wynosiła odpowiednio 3,4% i 3,6% dla 10 mg i 25 mg empagliflozyny w porównaniu z 0,1% dla placebo. W badaniu EMPA-REG Outcome wartości hematokrytu powróciły do wartości wyjściowych po 30-dniowym okresie kontroli po zakończeniu leczenia. Zgłaszanie podejrzewanych działań niepożądanych Po dopuszczeniu produktu leczniczego do obrotu istotne jest zgłaszanie podejrzewanych działań niepożądanych. Umożliwia to nieprzerwane monitorowanie stosunku korzyści do ryzyka stosowania produktu leczniczego. Osoby należące do fachowego personelu medycznego powinny zgłaszać wszelkie podejrzewane działania niepożądane za pośrednictwem Departamentu Monitorowania Niepożądanych Działań Produktów Leczniczych Urzędu Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych: Al. Jerozolimskie 181C, 02-222 Warszawa, tel.: +48 22 49-21-301, faks: +48 22 49-21-309, strona internetowa: https://smz.ezdrowie.gov.pl. Działania niepożądane można zgłaszać również podmiotowi odpowiedzialnemu. **Podmiot odpowiedzialny:** Boehringer Ingelheim International GmbH, Binger Str. 173, 55216 Ingelheim am Rhein, Niemcy. **Numery pozwoleń na dopuszczenie do obrotu:** Jardiance® 10 mg tabletki powlekane: EU/1/14/930/013 (28 tabletek), Jardiance® 10 mg tabletki powlekane: EU/1/14/930/014 (30 tabletek) wydane przez Komisję Wspólnot Europejskich. **Data zatwierdzenia lub częściowej zmiany tekstu ChPL:** 03 marca 2022 **Kategoria dostępności:** Produkt leczniczy wydawany na receptę – Rp. **Cena urzędowa detaliczna:** Jardiance® 10 mg x 28 tabl. – 170,38 zł. Wysokość dopłaty pacjenta: 54,00 zł we wskazaniu: Cukrzyca typu 2, u pacjentów przed włączeniem insuliny, leczonych co najmniej dwoma doustnymi lekami hipoglikemizującymi od co najmniej 6 miesięcy, z HbA1c ≥ 8 % oraz bardzo wysokim ryzykiem sercowo-naczyniowym rozumianym jako: 1) potwierdzona choroba sercowo-naczyniowa, lub 2) uszkodzenie innych narządów objawiające się poprzez: białkomocz lub przerost lewej komory lub retinopatię, lub 3) obecność 3 lub więcej głównych czynników ryzyka spośród wymienionych poniżej: – wiek ≥ 55 lat dla mężczyzn, ≥ 60 lat dla kobiet, – dyslipidemia, – nadciśnienie tętnicze, – palenie tytoniu, – otyłość – na podstawie obwieszczenia Ministra Zdrowia z dnia 21 lutego 2022 r. w sprawie wykazu refundowanych leków, środków spożywczych specjalnego przeznaczenia żywieniowego oraz wyrobów medycznych na 1 marca 2022 r. (DZ. URZ. Min. Zdr. 2022.18).

Boehringer Ingelheim Sp. z o.o.
ul. Franciszka Klimczaka 1, 02-797 Warszawa, tel.: (22) 699 0 699, fax: (22) 699 0 698
www.boehringer-ingelheim.pl • info.waw@boehringer-ingelheim.com

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18. Zjazd Polskiego Towarzystwa Nadciśnienia Tętniczego

Nadciśnienie tętnicze, otyłość, styl życia i zaburzenia nastroju – problemy pacjentów w dobie pandemii i powrót do skutecznej terapii

Gdańsk, 20–22 października 2022 roku

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Konferencja jest skierowana tylko do osób uprawnionych do wystawiania recept lub osób prowadzących obrót produktami leczniczymi — podstawa prawna: Ustawa z dnia 6 września 2001 r. Prawo farmaceutyczne (t. j. Dz.U. z 2019 r. poz. 499).

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Produkt leczniczy **Jardiance®** (empagliflozyna)

jest wskazany do stosowania u dorosłych w leczeniu objawowej przewlekłej niewydolności serca[1].

JARDIANCE® to **pierwszy i jedyny lek o udowodnionej skuteczności** w zakresie redukcji ryzyka zgonu z przyczyn sercowo-naczyniowych lub hospitalizacji z powodu niewydolności serca, zarówno w **HFrEF**, jak i **HFpEF***,†,1-3

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