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Address
II Klinika Kardiologii
Uniwersytet Jagielloński
Collegium Medicum
ul. Kopernika 17
31-501 Kraków, Poland
e-mail: editor.pki@termedia.pl

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e-mail: m.demska@termedia.pl

Marketing and Advertising
Renata Dolata
phone: +48 61 822 77 81 ext. 508
e-mail: r.dolata@termedia.pl

Distribution and Subscriptions
phone: +48 61 656 22 02

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LETTER TO THE EDITOR

Fenestrated total arch thoracic endovascular aortic repair: coming of age

George Joseph

Department of Cardiology, Christian Medical College, Vellore, India

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Total aortic arch replacement is one of the most demanding of cardiovascular surgical procedures despite advances in related surgical technique and anesthesiology. In a recent retrospective study of 3265 patients who underwent open total arch replacement, in-hospital mortality at specialized centers was 10.8%, and permanent neurologic deficit rate was 6.8% [1]. Zone 0 hybrid arch exclusion has similar mortality (10.3% vs 10.2%) and permanent neurological deficit (8.9% vs. 6.2%) as open total aortic arch replacement [2]. Given this situation, the less invasive alternative of thoracic endovascular aortic repair (TEVAR) seems alluring. But total arch TEVAR faces several challenges, the principal ones being preservation of flow into all the aortic arch branches despite covering their ostia with the arch endograft and avoiding intra-procedural cerebral embolization. Several other problems may be encountered during arch TEVAR, which may be anatomic (tortuous arch, type-3 arch, Gothic arch), hemodynamic (due to the force of left ventricular ejection), device-related (inability to conform to arch anatomy and material fatigue) and access-related (lack of suitable large-bore femoral access, iliac disease and aortic tortuosity) [3]. One or more of these factors may conspire to cause device delivery failure, malposition, malapposition and ultimately treatment failure.

Branched TEVAR, using inner branched devices, is one of two main methods of total arch endovascular repair [4]. The double inner branched arch endograft (Cook Medical, Bloomington, IN, USA) has been the most investigated; early results in 38 patients (technical success 84.2%, 30-day mortality 13.2%, cerebrovascular complications 15.8%) were not optimal [5], but later outcomes with this device have been much better [6]. The technique requires a left carotid to left subclavian bypass to preserve flow into the latter, unless a three-branched version of the endograft is used [7]. There are other limitations: the device has to be custom made, does not appose to the aortic wall in the branch-bearing section, has fixed orientation of branches, requires a right carotid or axillary cut-down for delivering the innominate stent, has its proximal sealing zone deep in the ascending aorta (where it may cover ostia of coronary bypass grafts) and the nose cone of the delivery system almost inevitably has to cross the aortic valve [8]. Outcomes obtained with another branched device designed for total arch TEVAR, the Relay double inner branched stent-graft (Terumo Aortic, Glasgow, UK), have been disappointing: initial results in 24 patients revealed 16.7% in-hospital mortality and 25% cerebrovascular event rate [9].

Fenestrated TEVAR is the other major method of total arch TEVAR. The main difficulty of fenestrated arch repair is accurate positioning of fenestrations; given the wide variation seen in aortic arch anatomy, customization to suit individual anatomy is necessary, and off-the-shelf devices are unlikely to work in a large segment of patients. *In situ* fenestration of arch endografts has been one way of dealing with this issue; however, when using this technique in total arch TEVAR, adjunctive procedures to maintain cerebral perfusion are required during the operation [10]. This technique could potentially result in fraying of fenestration edges and cause type-3 endoleak.

Another approach to fenestrated arch TEVAR has been the use of non-sealing fenestrations that are much larger than the target arch branches and allow some flexibility in endograft positioning; these endografts are custom-designed to suit the patient's arch anatomy and may have stent struts going across them. One example is the Najuta semi-custom thoracic fenestrated stent-graft (Kawasumi Laboratories, Tokyo, Japan), which is loaded in a pre-shaped sheath appropriate for the patient's aortic arch anatomy [11]. Another example is the

Corresponding author:
George Joseph MD, DM, Department of Cardiology, Christian Medical College, Vellore 632004, India, phone: +91 9894783163, e-mail: joseph59@gmail.com
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homemade double-fenestrated stent-graft reported by Canaud *et al.* [12]. Deployment of covered stents through the fenestrations in these two devices will not produce local sealing or is not possible because of crossing stent struts; sealing is achieved by apposition of the endograft to the aortic wall, and the technique is thus appropriate only for distal arch or inner curve pathology.

Yet another approach to fenestrated total arch TEVAR is the use of physician-modified endografts with customized small (sealable) fenestrations and partial constraining of the endograft to enable manipulation of the endograft in the arch to align the fenestrations and to create a perigraft working space for cannulation of arch branches through the fenestrations. The technique of constraining endografts using a longitudinal diameter-reducing wire was described by Oderich [13]. Recently Zhu *et al.* [14] reported use of this technique to constrain arch endografts with both small and oversized fenestrations in total arch endovascular repair. Their diameter-reducing wire was located directly opposite (180 degrees away) from the fenestrations on the endograft; with correct endograft deployment, the fenestrations would face the outer curve and the wire would be on the inner curve of the arch; however the splinting effect of this wire could lim-

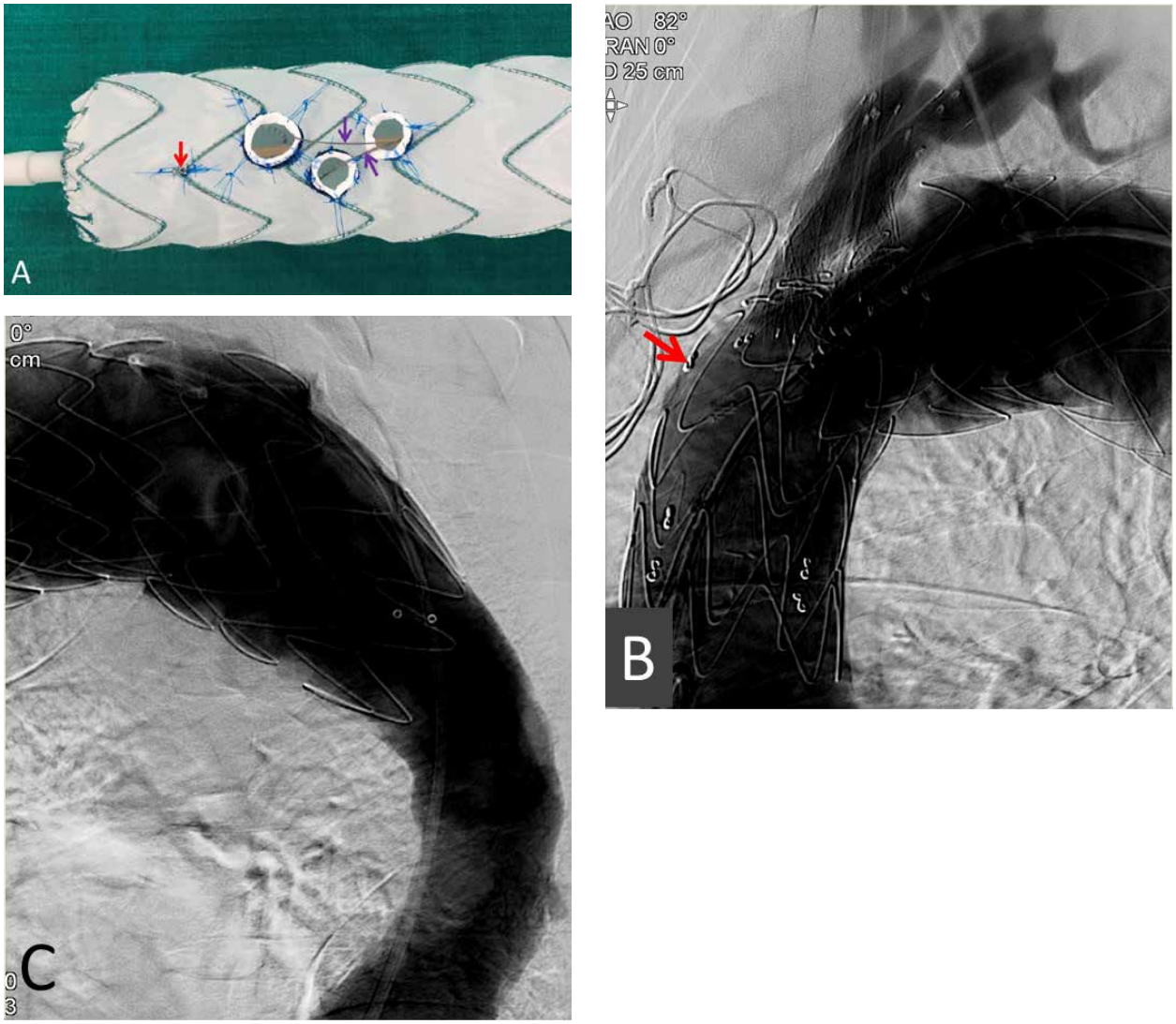

Figure 1. A – Valiant Captivia thoracic endograft with three fenestrations meant for the innominate, left common carotid and left subclavian arteries respectively (from left to right). Short cuffs made of vascular graft are attached to each fenestration to improve sealing. Two pre-cannulating nitinol guidewires (purple arrows) are seen emerging from the left subclavian artery fenestration and returning through the other two. A figure-8 (????????) radio-opaque marker (red arrow) is fixed on to the endograft at 12 o'clock position. **B**, **C** – Completion aortograms obtained after deployment of the above endograft in a patient with distal aortic arch aneurysm. The figure-8 (???????) marker is seen on the outer curve of the endograft. Flow into the arch branches is preserved and there is no endoleak

it the ability of the endograft to flex on the side of the lesser curve and potentially lead to malalignment. Having this wire run along the aspect of the arch endograft facing the outer curve is not appropriate as it would interfere with the fenestrations. In this issue of the "Advances in Interventional Cardiology" Kazimierczak *et al.* describe a novel technique of constraining arch endografts that overcomes the above problem by using dual lateral diameter-reducing wires located 90° away from the fenestrations; besides allowing greater constraining of the endograft, this technique restricts flexion of the endograft to the plane of the arch which may help align the fenestrations better.

Manipulation of constrained endografts to align fenestrations in the aortic arch increases the risk of embolization, and therefore techniques that allow immediate and complete deployment of unconstrained fenestrated arch endografts in one go are preferable; the pre-requisite for this is a system for accurate positioning of fenestrations. Use of externalized guidewires that pre-cannulate fenestrations in unconstrained arch endografts is one approach to total arch TEVAR that enables immediate and complete endograft deployment and ensures easy access through fenestrations into target branches [15]. However, pre-cannulation of more than one fenestration with externalized guidewires is technically complex and limits its widespread use.

At our center we have moved away from externalizing pre-cannulating guidewires and have developed an alternate reliable and simple system for obtaining axial and rotational accuracy of fenestration position [4]. Customized, sealable fenestrations with robust, radiopaque edges are created for all three arch branches, based on computed tomography angiography data, on a Valiant Captivia thoracic endograft (Figure 1 A, Medtronic Vascular, Santa Rosa, CA, USA). A short cuff made of vascular graft is affixed to the fenestration edge to provide better sealing when required, as within an aneurysm zone or adjacent to an intimal tear. Cuffed fenestrations are pre-cannulated, but the wire is not externalized; instead, it loops back through another fenestration – catheters can ride up these wires to cross the respective fenestrations after which a parallel guidewire can be passed through the catheter into the target arch branch. A radiopaque figure-8 marker is fixed at the 12 o'clock position on the endograft and brought up just under the endograft cover during re-sheathing. Correct rotational orientation is obtained by appropriate rotation of the endograft delivery system as it rides up a stiff guidewire from the descending aorta into the arch: the figure-8 marker should be seen on edge at the outer curve of the arch when viewed fluoroscopically, orthogonal to the plane of the arch. Correct axial orientation is obtained by positioning the left carotid artery fenestration just ahead of a taut guidewire passing from the left carotid artery to the left femoral artery (this wire marks the posterior margin of the left carotid artery origin accurately). The endograft is not constrained in any way and once in position, it is fully deployed in one go (achieving maximal wall apposition immediately and trapping aortic debris underneath). Short self-expanding covered stents (Fluency; Bard Peripheral Vascular, Tempe, AZ, USA) are usually deployed within the fenestrations (Figures 1 B, C). The technique is completely percutaneous, using only 4 Fr or 6 Fr arterial accesses other than the large endograft delivery access. The ease and success of the technique have convinced us that total arch TEVAR using fenestrated endografts is ready to replace open and hybrid arch surgery in most situations. Industrial manufacture of such customized fenestrated arch endografts would be the next logical step to enable widespread use of the technique.

Conflict of interest

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Interventional cardiology procedures in Poland in 2018. Summary report of the Association of Cardiovascular Interventions of the Polish Cardiac Society (AISN PTK) and Jagiellonian University Medical College

Dariusz Dudek[1], Zbigniew Siudak[2], Marek Grygier[3], Aleksander Araszkiewicz[3], Maciej Dąbrowski[4], Jacek Kusa[5], Michał Hawranek[6], Zenon Huczek[7], Paweł Kralisz[8], Tomasz Roleder[9], Stanisław Bartuś[10], Wojciech Wojakowski[11]

[1]Institute of Cardiology, Jagiellonian University Medical College, Krakow, Poland
[2]*Collegium Medicum*, Jan Kochanowski University, Kielce, Poland
[3]1st Department of Cardiology, Poznan University of Medical Sciences, Poznan, Poland
[4]Department of Interventional Cardiology and Angiology, Institute of Cardiology, Warsaw, Poland
[5]Pediatric Cardiology Department, Regional Specialist Hospital – Research and Developement Centre, Wroclaw, Poland
[6]3rd Department of Cardiology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland
[7]1st Department of Cardiology, Medical University of Warsaw, Poland
[8]Department of Invasive Cardiology, Medical University of Bialystok, Bialystok, Poland
[9]Regional Specialist Hospital, Research and Development Center, Wroclaw, Poland
[10]2nd Department of Cardiology, Jagiellonian University, Krakow, Poland
[11]Department of Cardiology and Structural Heart Diseases, 3rd Division of Cardiology, Medical University of Silesia, Katowice, Poland

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The ORPKI (*Ogólnopolski Rejestr Procedur Kardiologii Inwazyjnej*) electronic data capture is continuously modified to address the changing landscape of interventional cardiology procedures in Poland, especially the growing number of structural heart disease interventions and changes in practice recommendations such as multivessel percutaneous coronary intervention (PCI) in ST-segment elevation myocardial intervention (STEMI). It is endorsed by Association of Cardiovascular Interventions of the Polish Cardiac Society (*Asocjacja Interwencji Sercowo-Naczyniowych Polskiego Towarzystwa Kardiologicznego* – AISN PTK) and operated by the Jagiellonian University Medical College and includes 163 interventional cardiology centers in Poland (total number the same as in 2017), of which 95 are formally accredited by AISN PTK. Currently there are 613 certified PCI operators in Poland. AISN PTK conducts the PCI and transcatheter aortic valve implantation (TAVI) operators' certification process based on the previously published eligibility criteria. The ORPKI database not only allows the nationwide monitoring of the procedural trends but also documents individual operators' procedural volumes.

According to current analysis of the ORPKI database in comparison to 2017, there was a decrease in the total number of coronary angiographies (CAG) [1]. There were 182 226 CAG (4733 per 1 million inhabitants per year) in 2018, which corresponds to a decrease of 8.1% compared to 2017 (Figure 1). This trend has been observed since 2015, and current numbers correspond to those of the year 2010. In terms of procedural features in 2018 we observed a 2% increase in the use of the radial approach for coronary angiography (86%), also with high, similar to 2017, prevalence among STEMI patients (75%). This trend is reassuring because it adheres to the current recommendations of European Society of Cardiology (ESC) Guidelines and improves patient outcomes. Complications of coronary angiography in 2018 are presented in Table I.

The total number of PCI procedures was 104 283 and was lower by 8.7% (2709 PCIs per 1 million inhabitants per year) than reported to the ORPKI database in 2017 (Figure 1). The majority of the procedures were indicated by the acute coronary syndromes (ACS): 35% acute myo-

Corresponding author:
Zbigniew Siudak MD, PhD, *Collegium Medicum*, Jan Kochanowski University, al. IX Wieków Kielc 19, 25-526 Kielce, Poland, phone: +48 883 992 288, e-mail: zbigniew.siudak@gmail.com
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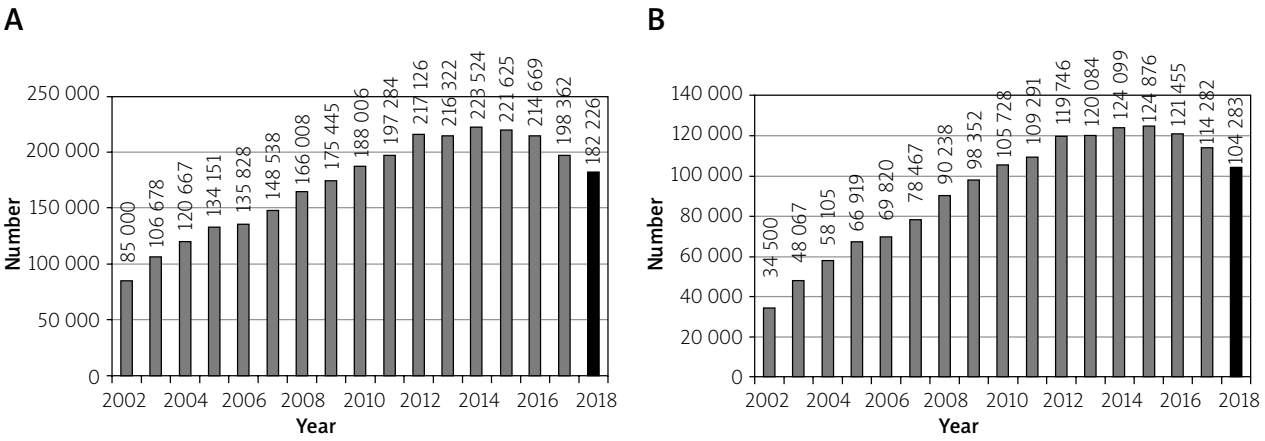

Figure 1. Number of coronary angiography (**A**) and PCI (**B**) procedures in Poland in the years 2002–2018

Table I. Complications of coronary angiography in Poland in 2018

Parameter	Percent	In comparison to 2017
Death	0.04	↓
Stroke	0.01	↔
Major bleeding at access site	0.04	↔
SCA	0.17	↓
Allergic reaction	0.02	↓

SCA – sudden cardiac *arrest.*

Table II. Complications of PCI in Poland in 2018

Parameter	Percent	In comparison to 2017
Death	0.34	↓
Myocardial infarction	0.11	↔
Major bleeding from access site	0.10	↔
SCA	0.42	↓
Allergic reaction	0.10	↔
Artery perforation	0.20	↑
No reflow	0.55	↔

SCA – sudden cardiac *arrest.*

Table III. Additional intracoronary assessment in 2018 during angiography and PCI

Parameter	*N*	Change % from 2017
FFR	9076	↑ 12%
IVUS	3652	↑ 44%
OCT	384	↑ 61%

OCT – optical coherence tomography.

cardial infarction (19% STEMI and 20% non-ST-segment elevation myocardial intervention (NSTEMI)), 26% unstable angina (decrease by 4% from 2017) and the remaining 35% for stable angina. The number of primary PCIs per 1 million inhabitants per year is currently 524. There were 67 070 PCIs for ACS, including 20 219 primary PCIs for STEMI, 20 666 for NSTEMI, and 26 185 for unstable angina.

Current generation drug-eluting stents were used in 99% of cases. Only 102 bioresorbable stents were implanted (0.1% of all PCIs). Aspiration thrombectomy was used in only 2477 cases, which corresponds to a 21% decrease in comparison to 2017. A substantial increase in use of guideline-recommended ticagrelor as an adjunct pharmacotherapy was observed both for STEMI (prehospital: 17%, in-hospital: additional 17%) and NSTEMI (prehospital: 0%, in-hospital: 15%) with the use of prasugrel < 1%. PCI complications during PCI are presented in Table II – the values remain stable throughout the years of observations.

In 2018 there was a significant increase in the use of modern imaging and diagnostic techniques such as intravascular ultrasound (IVUS) and fractional flow reserve (FFR). In our opinion the intravascular imaging and physiological assessment of stenosis severity are still underused, but the trend observed in 2018 is reassuring. There is growing awareness of the utility of intravascular imaging for the optimization of PCI especially in anatomically complex lesions (Table III). Optical coherence tomography is still not reimbursed in Poland.

Concerning structural heart disease and vascular procedures, there were 1261 TAVI in 22 centers, 400 left atrial appendage occlusion (LAAO) and 148 MitraClips in 2018, which corresponds to a moderate increase in comparison to 2017. Given the expanding indications for TAVI and confirmed benefits of mitral valve repair with MitraClip, our conclusion is that these procedures are not available to a substantial number of patients with clear indications. It should be noted that transcatheter vas-

cular interventions are performed by vascular surgeons and interventional radiologists and are not reported to the ORPKI database.

In conclusion, the number of coronary diagnostic and therapeutic procedures reported to ORPKI 2018 is lower than in the previous years. On the other hand, we observed increased adoption of the guideline recommended intravascular imaging and physiology assessment, radial approach, new-generation drug-eluting stent (DES) and use of modern antiplatelet drugs. Also the number of structural heart disease interventions slightly increased, but their availability is still suboptimal. Optimization of cathlab structure and location with efficient reimbursement plays a crucial role in the maintenance of Polish interventional cardiology [2, 3]. Also there is a need for increased reporting of the procedures to the ORPKI database. As highlighted before, we always compare against previous data published by ORPKI bearing in mind that some underreporting takes place and seems constant throughout the duration of the registry sine 2004 [4, 5].

This publication presents an analysis of individual procedural data from 163 interventional cardiology centers in Poland that have voluntarily joined the ORPKI database. To account for possible underreporting observed in 2018 AISN PTK makes every effort to correct for the missing data and provide reliable information on interventional cardiology in Poland.

Conflict of interest

The authors declare no conflict of interest.

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Review paper

Pericardial tamponade as a complication of invasive cardiac procedures: a review of the literature

Maria Adamczyk, Jarosław Wasilewski, Jacek Niedziela, Piotr Rozentryt, Mariusz Gąsior

3rd Department of Cardiology, Medical University of Silesia, Silesian Centre for Heart Diseases, Zabrze, Poland

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Abstract

Cardiac tamponade (CT) is a rare but often life-threatening complication after invasive cardiac procedures. Some procedures favor CT. Furthermore, the incidence depends on patients' comorbidities, sex and age and operators' skills. In this paper we review studies and meta-analyses concerning the rate of iatrogenic CT. We define the risk factors of CT and show concise characteristics for each invasive cardiac procedure separately. According to our analysis CT occurs especially after procedures requiring transseptal puncture or perioperative anticoagulation. The overall rate of CT after such procedures varies among published studies from 0.089% to 4.8%. For this purpose we searched the PubMed database for clinical studies published up to December 2018. We included only those studies in which a defined minimum of procedures were performed (1000 for atrial fibrillation ablation, 6000 for percutaneous coronary intervention, 900 for permanent heart rhythm devices, 90 for left atrial appendage closure, 300 for transcatheter aortic valve implantation and percutaneous mitral valve repair with the Mitra-Clip system). The search was structured around the key words and variants of these terms. In addition, secondary source documents were identified by manual review of reference lists, review articles and guidelines. The search was limited to humans and adults (18+ years).

Key words: percutaneous coronary intervention, electrophysiology, pericardial tamponade, transcatheter aortic valve implantation, left atrial appendage closure, percutaneous mitral valve repair.

Introduction

Nowadays, open heart surgery procedures are being replaced with minimally invasive attempts. This trend has led to a growing number of invasive procedures in cardiology. Pericardial tamponade (PT) is one of the most severe complications after such procedures. In this paper we review studies and meta-analyses concerning the rate of iatrogenic PT and concisely present brief characteristics for each procedure separately.

Pericardial tamponade as a result of catheter-based procedures

PT occurs when the pressure in the pericardial space exceeds the pressure in one or more cardiac chambers. The occurrence of hemodynamic abnormalities and clinical symptoms depends on the rate of fluid accumulation relative to pericardial stretch and the effectiveness of compensatory mechanisms. Thus, abrupt intrapericardial content accumulation (i.e. hemorrhage from cardiac rupture) occurs in the context of a relatively stiff, unyielding pericardium and quickly overwhelms the pericardial capacity to stretch before most compensatory mechanisms can be activated. In those situations, volumes such as 50–100 ml of fluid may result in hemodynamic decompensation [1]. In the cases of slow increase in pericardial fluid volume there is more time for pericardial capacity to stretch and for compensative mechanisms to be activated, so even 2 l or more may accumulate before critical, life-threatening PT occurs [2].

Iatrogenic acute PT is a life-threatening complication that can lead to death. It often involves hemodynamic instability and requires cardiopulmonary resuscitation in 20% and blood transfusion in more than 25% of patients [3].

Within the cardiology lab, PT develops most often rapidly, usually as a result of perforation of the heart structures. The perforation may be caused by a guidewire, balloon dilator, sheath, pacemaker lead, or excessive ablation energy. The presentation depends in part on at least 5 factors: the size of the device responsible for the perforation, the structure that is perforated, such as atrial versus ventricular myocardium, left versus right

Corresponding author:
Maria Adamczyk MD, 3rd Department of Cardiology, Medical University of Silesia, Silesian Centre for Heart Diseases, 9 Skłodowskiej St, 41-800 Zabrze, Poland, e-mail: maria.ester.adamczyk@gmail.com
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chamber, the hemodynamic state during perforation, mechanical properties of the pericardium itself, and the coagulation status. The thicker wall of the left ventricle (LV) (≤ 10 mm) may act to seal small perforations, balancing the higher intra-chamber pressures in contrast to the right ventricle (RV) (≤ 4 mm). Small perforation of the ventricles in a patient without anticoagulation may not be clinically apparent. Perforation of the left atrium (LA) is potentially much more serious, primarily because procedures involving the LA are always associated with anticoagulation, and because LA pressure is typically higher than RA pressure. The pressure within the structure that is perforated is a major determinant of the development and severity of PT. Thus, conditions such as pulmonary hypertension and aortic valve stenosis may significantly affect hemodynamic instability in PT [4].

The risk of iatrogenic PT or pericardial effusion increases with the need for transseptal puncture and intraprocedural anticoagulation [5]. With growing acceptance of retrograde catheterization of the left ventricle, the use of the transseptal technique for diagnostic purposes has declined. However, in recent years, substantial renewed application of the transseptal method has occurred for special diagnostic and therapeutic purposes [6]. The procedures requiring transseptal puncture are the following: patent foramen ovale and ventricular septal defect closure, percutaneous heart valve repair or replacement (for mitral regurgitation and aortic stenosis), LA appendage occlusion and electrophysiological procedures such as pacemakers or cardioverter-defibrillators implantation and ablation procedures within the left heart [6].

Pericardial tamponade as a complication of atrial fibrillation ablation

Mentioning atrial fibrillation (AF) ablation, PT was observed as the most frequent complication leading to death. The incidence of PT is higher than with other procedures that employ transseptal catheterization. PT may be characterized as acute when occurring during or immediately after the procedure, or delayed when detected later than 1 h after completion of the procedure [7].

There is evolution of catheter-based AF-ablation techniques. Radiofrequency catheter ablation (RFCA) and cryo-balloon ablation (CBA) are the two standard ablation systems used for pulmonary vein antrum isolation at present. Anticoagulation strategies posit that anticoagulation therapy should be administered prior to or immediately following transseptal puncture during AF catheter ablation [8]. PT may occur any time during trans-septal puncture, extensive catheter manipulation, application of RF energy or steam pops under an intense anticoagulation regimen [7].

According to the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical AF ablation, the rate of PT after AF ablation ranges from 0.2% to 5% [8]. It was based mostly on a prospective multicenter observational study performed by Cappato *et al.* [9], analyzing 45 115 AF ablations, where the incidence of PT was 2.3%. In this study PT was found as the most frequent fatal complication leading to intraoperative pump failure or post-operative early cardiac arrest. From the reported 32 deaths, 7 occurred due to tamponade (5 as acute and 2 as late PT), in comparison to atrioesophageal fistulas, as the second most frequent fatal complication, counting 5 deaths. In another multicenter prospective study of 6065 Medicare patients, analyzed by Ellis *et al.* [10], the incidence of PT due to AF ablation increased from 1.3% in 2001 to 3.6% in 2006. Patients who died experienced higher rates of perforation/tamponade (12.0% vs. 3.1% in the remainder of the study sample, $p = 0.01$).

In the study by Mujović *et al.* [11], in 2 of 12 cases, tamponade resulted in electromechanical dissociation and cardiorespiratory arrest, while in the remaining ten patients tamponade was associated with significant hypotension. Two patients required surgical treatment. Nine patients received blood transfusions; in seven of them auto-transfusion was carried out. It seems that direct auto-transfusion is simple and requires no additional equipment; it may abolish the need for allogeneic blood transfusion and can "buy" time until surgery [12]. However, direct auto-transfusion may cause systemic inflammation, and therefore the processing of the drained blood via the cell salvage system is recommended prior to its return [13]. Auto-transfusion of a larger volume of blood, i.e., more than 1500 ml, may lead to consumptive coagulopathy [12, 13], which occurred in one patient in this study. The rate of PT, its related mortality and management of PT after AF ablation procedures are summarized in Table I [9–11, 14–21].

Deshmukh *et al.* [22] had identified 93 801 AF patients treated with catheter ablation obtained from the Nationwide Inpatient Sample (NIS) data set from 2000 to 2010. They observed that in patients older than 80 years, the catheter ablation of AF was associated with a significantly higher total complication rate (9.37%, $p < 0.001$). From this group, cardiac complications were the most frequent adverse outcomes (2.54%). Within cardiac complications, CT was included but not defined alone. Also women overall had higher complication rates than men (7.51% vs. 5.49%, $p < 0.001$). A similar conclusion about sex differences was reached by Michowitz *et al.* [15], and Elayi *et al.* [23], who analyzed a group of 85 977 patients undergoing catheter ablation of AF. In this group PT appeared in 0.7% of men vs. 1.3% of women ($p < 0.001$) and the rate of at least one major and overall complications was significantly higher among women than among men, but without a significant difference in mortality between groups.

There are studies [24–26] proving no significant differences in the frequency of pericardial effusions/peri-

Table I. Studies concerning information about rate of pericardial tamponade as a complication of ablation of atrial fibrillation, PT-related mortality, management and outcomes, up to December 2018

Author(s) [ref.]	Type of procedure	Type of study	Time interval	No. of procedures/ patients	*N* (%) PT per all procedures	No. (%) PT-related mortality	*N* (%) PCC/ST
Cappato [9]	Catheter ablation of AF	Multicenter prospective observational	1995–2006	45 115/32 569	2.3	2.11	–
Ellis [10]	RFCA of AF	Multicenter observational retrospective	2001–2006	/6065	3.1	1.59	–
Hamaya [14]	CBA/RFCA of AF	Single center prospective cohort	2002–2016	5 222/3 483	0.98	1.96	86.3/3.9
Michowitz [15]	Catheter ablation of AF	Multicenter prospective cohort	2000–2012	34 942/	0.84	1	99/16
Voskoboinik [16]	RFCA of AF	Single center prospective observational	2004–2017	2 750/	0.18	0	–
Hoyt [17]	Catheter ablation of AF	Single center prospective	2001–2010	/1 190	1.1	0	100/0
Dagres [18]	RFCA of AF	Single center prospective	2005–2008	1 000/	1.3	0	85/15
Mujović [11]	RFCA	Single center prospective	2011–2016	1 500/1 352	0.8	0	100/17
Aldhoon [19]	RFCA of AF	Single center, prospective	2006–2010	1 192/959	0.16	0	100/0
Baman [20]	RFCA of AF	Single center, prospective	2007–2010	/1295	1.2	0	100/0
Mugnai [21]	CBA/RFCA of AF	Single center retrospective cohort	2008–2014	1352/	1.0	0	92/8

AF – atrial fibrillation, CBA – cryoballoon catheter ablation, PT – pericardial tamponade, PCC – pericardiocentesis, RFCA – radiofrequency catheter ablation. ST – surgical treatment.

Table II. Meta-analyses comparing efficacy and safety of RFCA vs. CBA of AF

Author(s) [ref.]	Year of publication	Study range	Group of patients	Percentage of pericardial tamponade as procedure complication/ conclusion
Jiang [27]	2017	1998–2016	2336	CBA 0.4% vs. RFCA 1.5% (OR = 0.32, 95% CI: 0.13–0.78, $p = 0.01$), with no significant heterogeneity ($I^2 = 0\%$, $p = 0.98$)
Ma [28]	2017	Up to Dec 2016	9141	CBA 1.05% vs. RFCA 1.86%, $p = 0.02$
Cardoso [29]	2016	Up to April 2016	8668	CBA 0.3 RFCA 1.4 (OR = 0.31; 95% CI: 0.15–0.64; $p < 0.01$)

RFCA – radiofrequency catheter ablation. CBA – cryoballoon catheter ablation, AF – atrial fibrillation.

cardial tamponade between CBA and RFCA. Meanwhile the recent dedicated meta-analyses have shown higher or considerably higher risk of PT in an RF catheter ablation group (Table II) [27–29].

Pericardial tamponade as a result of percutaneous coronary intervention

Pericardial tamponade is a rare complication of percutaneous coronary intervention (PCI). It is mostly caused by coronary artery perforation (CP) that may occur as the consequence of guide wire advancement, balloon inflation or rupture, and utilization of atherectomy devices [30, 31]. It usually occurs after grade III CP as defined by the Ellis criteria [32]. However, RV perforation due to temporary pacing wires was also found to be an important cause of PT [33, 34].

Pericardial tamponade following a CP is frequently associated with poor outcomes and may increase the risk of death by more than 3 fold (OR = 3.3; 95% CI: 1.01–10.65; $p = 0.047$) compared with patients who sustained CP without PT [35]. The incidence and predictors of CP have been studied in several large PCI series [30,

31, 36–43]. Generally summarizing, the reported risk factors for perforation include elderly patients, female gender, previous coronary artery bypass grafting, and use of rotational and laser atherectomy. Also PCI of chronic total occlusion (CTO) may be associated with higher risk for procedural complications, including coronary perforation. In the summary analysis from 65 studies by Patel *et al.*, 419 perforations of 18 061 patients undergoing CTO PCI were reported. In this series, the reported rate of CP was 2.9% with a tamponade frequency of 0.2% [44].

Most PCI studies are focused on coronary artery perforation as the major complication, mentioning and calculating PT within this group. In a meta-analysis by Shimony *et al.* [45] involving 197 061 PCIs, the pooled incidence of CP was 0.43%. The overall percentage of PT after CP was 19.3 (11.9–28.9). In our review CP leads to PT in 11.5–35% (Table III).

The large, multicenter, prospectively collected and retrospectively analyzed study from the British Cardiovascular Intervention Society Database counting 527 121 cases revealed 470 (0.89%) patients having PT as a complication after PCI, 222 patients in the group with CP (14.18%) and 248 in the group without CP (0.05%) [36]. In the previous studies the percentage of PT was higher, 0.12% and 1.21% [33, 42].

In most PCI studies, PT was diagnosed in the cardiac catheterization laboratory by echocardiography or by fluoroscopy that revealed immobile heart borders or the extravasation of the blood from CP. However, late presentation (up to 24 h; mean time 2–4) has tended to occur. In the study by Fejka *et al.* [42] 14 of 31 PT had late appearance of PT (mean time: 4.4 h) and the most frequent mode of presentation was progressive hypotension culminating in 5 patients in cardiac arrest. In their study PT was associated with very high overall mortality (42%), while 64% of patients presenting PT required intra-aortic balloon pump, ventilatory support and blood transfusion, 61% cardiopulmonary resuscitation and 35% transvenous pacemaker implantation.

The treatment of CP depends on the perforated structure. With coronary perforations, a variety of approaches are possible by prolonged balloon inflation in addition to reversing anticoagulation, covered stents if the artery is large enough to accommodate these devices, or embolization for small vessels [4].

Pericardial tamponade as a result of permanent heart rhythm device implantation

The use of implantation of permanent heart rhythm devices (PHRD), which include permanent pacemakers (PPM) and implantable cardioverter defibrillators (ICD), is increasing due to the expansion of indications and aging

Table III. Studies concerning information about rate of coronary perforation and pericardial tamponade as a complication of percutaneous coronary intervention, PT-related mortality, management and outcomes, up to December 2018

Author(s) [ref.]	Type of procedure	Type of study	Time interval	No. of procedures/ patients	*N* (%) PT per all procedures No. of CP/PT	PT-related mortality (%)	*N* (%) PCC/ST
Kinnaird [36]	PCI	Multicenter prospectively collected database	2006–2013	527 121/	0.089% 1762 CP (from which 14% PT)	–	97/3
Von Sohsten [33]	PCI	Single center prospective	1994–1996	6999/	0.21%	0	73/60
Fejka [42]	PCI	Single center prospective	1993–2000	25 697/	0.12%	42	61/39
Stathopoulos [35]	PCI	Single center prospective	1999–2006	23 399/	0.11% 73 CP (from which 35% PT)	7.7	100/11.5
Shimony [40]	PCI	Single center prospective	2001–2008	/9 568	57 CP (from which 16% PT)	–	–
Kiernan [38]	PCI	Single center retrospective	2000–2008	14 281/	68 CP (from which 17% PT)	–	–
Fasseas [41]	PCI	Single center retrospective	1990–2001	/16 298	95 CP (from which 11.5% PT)	–	–
Danek [43]	CTO PCI	Multicenter prospective	2012–2017	2 097/2 049	85 CP (from which 14% PT)	–	–

CP – coronary artery perforation, CTO – chronic total occlusion, PCI – percutaneous coronary intervention, PT – pericardial tamponade, PCC – pericardiocentesis, ST – surgical treatment.

of the population. Despite the fact that post-implantation pericardial effusion can be a sign of lead perforation (LP), there are other mechanisms leading to pericardial effusion, such as traumatic inflammation of the myocardium and pericardium from the lead screw, or irritation of the visceral pericardium via immune mediated mechanisms [46].

Lead perforation is a rare complication after PHRD implantation and may involve large veins, atrial or ventricular walls or coronary sinus. LP develops most often acutely (i.e., less than 24 h after the procedure), which may potentially result in PT or death. Also it can occur 24 h after the device implantation in a subacute or chronic fashion. Another classification distinguishes between early (symptoms occur up to 1 month after implantation) and delayed perforations [47].

The clinical presentation of LP may be different in the late form, with most patients presenting pacemaker malfunction, stabbing chest pain and shortness of breath. A distinguishing feature of delayed in opposition to acute LP is the decrease or absence of PT or death [48]. Published event rates for LP range from 0.1% to 0.8% for PPM and 0.14–5.2% for ICD leads; in those publications perforations occurred mostly within 1 month after implantation [48–50] (Table IV).

Factors that are thought to contribute to acute LP are similar to those in late LP: patient characteristics, concomitant therapies such as steroids or anticoagulants, implant techniques and the design characteristics of the lead [49]. Patient-related factors in PPM implantations include old age, female sex, low body mass index and for ICD implantations it is additionally worsened heart failure class, left bundle branch block and non-single-chamber ICD implant [50]. Thin heart muscle itself, such as in a patient with myotonic muscular dystrophy and dilated cardiomyopathy, may favor perforation [51]. The use of atrial leads, helical screw ventricular leads, active fixation and temporary stimulation was reported to increase the incidence of perforation [47, 52]. The risk factors concerning defibrillator leads are as follows: double spirals, number of shocks delivered, excessive length or small diameter of the lead, high resistance (small tip surface) and apical position [47, 53].

Ohlow *et al.* [46] prospectively observed 968 consecutive patients undergoing PHRD implantations who had undergone echocardiographic evaluation before and 24 h after the operation. Fourteen of them (1.44%) had had PT requiring pericardiocentesis (n = 12; 86%) or surgical treatment (n = 2, 14%). In 10 of those patients a hemorrhagic effusion suggested cardiac perforation of an implanted lead; acute pericarditis was observed in the remaining four patients.

In the latest study Moazzami *et al.* [54] reported their findings after analyzing the United States National Inpatient Sample (USNIS) database from 922 549 patients implanted with PPM. PT occurred in 2695 (0.28%) patients. The authors found that female sex, implantation of dual-chamber pacemakers, and chronic liver disease predicted greater odds of PT, whereas hypertension and atrial fibrillation were associated with lower odds of tamponade. The association of chronic liver disease with PT may be related to the potential for bleeding due to coagulopathy, systemic tissue characteristics from liver disease, or anatomic consideration from hepatomegaly. The protective association of atrial fibrillation may be related to implantation of fewer atrial leads, enlarged LA or atrial fibrosis, whereas hypertension may be related to hypertrophy of the cardiac chambers [55].

Temporary transvenous pacing (TTP) with electrodes guided to the RV is burdened with the risk of PT as well.

Table IV. Studies concerning information about rate of pericardial tamponade as a complication of selected electrophysiology procedures, PT-related mortality, management and outcomes, up to December 2018

Author(s) [ref.]	Type of procedure	Type of study	Time interval	No. of procedures/ patients	*N* (%) PT or LP per all procedures	PT-related mortality (%)	*N* (%) PCC/ST
Moazzami [54]	PPM	Multicenter retrospective	2008–2012	/922 549	0.28 PT	6.7	–
Ohlow [46]	PHRD PPM ICD	Single center observational	2007–2010	/968	All 1.44 PT PPM 2.6 PT ICD 0.7 PT	14 PPM 0 ICD 14	86/14
Hsu [50]	ICD	Multicenter retrospective	2006–2011	/440 251	0.14 LP	5.6	–
Carlson [49]	PHRD PPM ICD	Multicenter prospective (incidence in OPTIMUM and ACS registry)	2006–2007	/5928	PPM: 0.5 LP ICD: 0.33 LP	–	–
Metkus [56]	TTP	Multicenter retrospective	2004–2014	/360 223	0.6 PT	5	–

CP – cardiac perforation, ICD – implantable cardioverter defibrillator, LP – lead perforation, PT – pericardial tamponade, PCC – pericardiocentesis, PPM-permanent pacemaker, PHRD – permanent heart rhythm devices, ST – surgical treatment, TLP – transvenous lead extraction, TTP – temporary transvenous pacing.

Performing analysis about complications and outcomes of over 360 000 TTPs using the USNIS database, Metkus *et al.* defined the rate of PT as 0.6% [56].

A review of studies concerning the rate of PT and LP after PHRD implantation, management and PT-related death is presented in Table IV.

With the growing number of PHRD implantations in recent years, in parallel, a rise in lead malfunction and recalls has resulted in increased transvenous lead extractions (TLE) [57]. In 2016 the biggest multicentre prospective overview of TLE safety and efficacy conducted by the EHRA, entitled The European Lead Extraction ConTRolled Registry (ELECTRa), was published [57]. The primary endpoint was TLE safety defined by in-hospital procedure-related major complications including death. In 3510 patients 6493 leads including 4917 (75.7%) pacing and 1576 (24.3%) ICD leads were targeted for extraction. The mean dwell time of extracted leads was 6.4 ±5.4 years (median: 5 years, IQR: 2–9). Indications for TLE were infective in 52.8%. Among 58 deaths, 17 were procedure-related. The most common procedure-related complications were cardiovascular complications requiring pericardiocentesis or surgical repair occurring in 49 (1.4%) patients. Apart from thoracic and peripheral vascular lesions, 28 patients had cardiac avulsion and 2 cardiac avulsion with thoracic vascular tears. The clinical manifestations of these complications were PT, haemothorax and hemorrhagic shock. The authors did not report the exact number of PTs, but we may assume that this number may correspond to the number of cases concerning cardiac avulsion [30]. However, the authors provided accurate information about 17 causes of procedure-related deaths. According to their results, PT led to death in 6 cases, undergoing surgical treatment in all of them. This emphasizes what a hazardous complication pericardial tamponade is. Moreover, procedure-related major complications and death were more common in female patients (OR = 2.11, 95% CI: 1.23–3.62, $p = 0.0067$), leads with a dwell time > 10 years (OR = 3.54, RR: 1.6–7.83, $p = 0.0018$), with the use of powered sheaths (OR = 2.4, 95% CI: 1.41–4.09, $p = 0.0013$) and a femoral approach (OR = 3.60, 95% CI: 1.64–7.87).

Pericardial tamponade as a result of left atrium appendage occlusion

Occluding the left atrial appendage (LAA) is an alternative treatment for stroke prevention in high-risk patients with contraindications to oral anticoagulants. The risk of causing PT is due to the fact that the LA appendage itself can be extremely thin-walled.

In addition to surgical technique, percutaneous methods of LAA closure were developed. For clinical use both Watchman and the Amplatzer Cardiac Plug (ACP) devices have been approved. Moreover, in 2013 a second generation of the ACP, the Amplatzer Amulet left atrial appendage occluder, was released [58]. The Watchman device is basically a plug that should be precisely implanted to avoid both its protrusion into the LA as well as the creation of a cul-de-sac where thrombus may form. The ACP consists of two parts joined by a central pin. Being short, the ACP can be implanted in a shallow position in the LAA, as only the proximal 2 cm are needed for its occlusion. The occlusive disc permits the complete closure of the LAA orifice [59]. In a prospective randomized controlled trial by Holmes *et al.* [60], with the intervention group consisting of 463 LAAC implantations, the most frequent primary safety event was severe pericardial effusion (defined as the need for percutaneous or surgical drainage). It occurred in 22 (4.8%) patients; 15 of them were treated with pericardiocentesis and 7 underwent surgical intervention. None of those patients died, although length of hospital stay in these patients was longer than in the control group (244 patients) without severe pericardial effusion (median 4 days longer). Effusion rates declined with investigator experience. In a meta-analysis by Wei *et al.* [61] assessing the efficacy and safety of transcatheter LAA closure in patients with nonvalvular AF, the incidence of pericardial effusion/tamponade was estimated as 0.02 (95% CI: 0.02–0.03). The studies assessing the rate of PT, its management and PT-related mortality after LAA closure are summarized in Table V.

Pericardial tamponade as a result of transcatheter aortic valve implantation (TAVI)

The European Society of Cardiology guidelines advocate the use of TAVI in patients with severe aortic stenosis and high risk for SAVR (surgical aortic valve replacement), favoring TAVI mostly in older patients [62]. In a retrospective cohort study evaluating 16 755 patients diagnosed with AS in the Japanese healthcare setting, in-hospital outcomes between TAVI and SAVR were evaluated. The incidence of pericardial tamponade was significantly higher in the SAVR patients (1.5% in SAVR vs. 0.5% in TAVI; $p = 0.03$) [63]. There are three major pathophysiological situations that may lead to PT during TAVI: first, annular or aortic root rupture during balloon valvuloplasty and valve implantation with subsequent arterial bleeding into the pericardium; second, perforation of the right RV caused by the temporary pacing lead; and third, perforation of the LV by an extra-stiff guidewire during its placement or at later stages of the procedure [64, 65]. In existing literature, PT has been described as occurring in 0.2–4.3% of cases, with a higher probability in retrograde trans-vascular techniques than with trans-apical access [66, 67] (Table V).

Pericardial tamponade as a result of percutaneous mitral valve repair with the Mitra-Clip system

Percutaneous edge-to-edge mitral valve repair using the Mitra-Clip device represents a less invasive

Table V. PT-related mortality, management and outcomes in selected cardiac procedures, up to December 2018

Author(s) [ref.]	Type of procedure	Type of study	Time interval	No. of procedures/ patients	*N* (%) PT per all procedures	PT-related mortality (%)	*N* (%) PCC/ST
Guerios [59]	LAAC	Single center prospective	2009–2011	/96	1.1	–	–
Matsuo [71]	LAAC	Single center prospective	2009–2012	/179	1.1	0	100/0
Berti [72]	LAAC	Single center prospective	2009– 2014	/110	2.7	0	–
Kim [73]	LAAC	Single center prospective	2010–2015	/96	2	50	–
Holmes [60]	LAAC	Multicenter randomized	2005–2008	463/	4.8	0	68/32
Hamm [66]	TV AVI TA AVI	Multicenter prospective	2011	/2695 /1181	1.4 0.2	–	–
Rezq [67]	TAVI	Single center retrospective	2007–2012	/389	4.3	23.5	100/29
Eggebrecht [69]	Mitra–Clip	Multicenter prospective	2010–2013	/828	1.9	–	100/0
Maisano [70]	Mitra–Clip	Multicenter prospective	2011–2012	/567	1.1	–	–

LAAC – left atrial appendage closure, Mitra-Clip – percutaneous mitral valve repair with the Mitra-Clip system, PT – pericardial tamponade, PCC – pericardiocentesis, ST – surgical treatment, TAVI – transcatheter aortic valve implantation, transvascular (TV) or transapical (TA) aortic valve implantation (AVI).

treatment option for patients with symptomatic severe mitral regurgitation [68]. With the need for cardiologic techniques such as trans-septal puncture as well as navigation of catheter devices within the LA and LV, the risk of tamponade may grow. There are two large prospective multicenter studies that have analyzed the risk and outcomes of complications during and after Mitra-Clip based on the German Transcatheter Mitral Valve Interventions register [69] and the European ACCESS-EU registry [70] (Table V [60, 66, 67, 69–73]). The risk of PT was 1.9% and 1.1% respectively, suggesting that transseptal puncture followed by advancement of the 24 Fr guiding sheath is safe [69].

Discussion

Pericardial tamponade is a rare complication of invasive cardiac procedures, mostly associated with poor outcomes. It generally develops acutely, but late forms with atypical presentation may occur. The incidence depends on patients' comorbidities, concomitant pharmacotherapy, sex, age, operators' skills, the size of the device responsible for the perforation, the structure of the heart that is perforated, the hemodynamic state during perforation and mechanical properties of the pericardium itself. Some procedures, especially those requiring transseptal puncture or perioperative anticoagulation, favor CT.

Summarizing our review, the overall rate of iatrogenic PT varies among published studies from 0.089 to 4.8%, with the highest rate after left atrial appendage closure, transcatheter aortic valve implantation, and atrial fibrillation ablation. Concerning electrophysiological procedures, the rate of PT was quite divergent between multicenter and single center studies (Tables I, IV). Generally, the PT-related post-procedural mortality ranged from 0% to 50% (medium 7.3%) and was highest in LAAC and TAVI groups, then PCI, PHRD and the AF ablation procedures respectively. The need for surgical treatment after iatrogenic PT ranged from 0% to 60% (medium 15%). The most frequent group of PTs requiring surgical treatment was the PCI group, the second group consisted of LAAC and TAVI procedures and the last group consisted of AF ablation and PHRD procedures. These conclusions may not be precise. Many of the mentioned studies only determine predictors of iatrogenic PT or the endpoint of those studies was only the rate of PT, and a follow-up was not performed.

Additionally, we have observed that older age and female sex were common risk factors predisposing to PT. Some techniques as well as echocardiographic or fluoroscopic guidance during such procedures may decrease the overall complication rate.

Conclusions

Pericardial tamponade is a rare complication of invasive cardiac procedures with the overall rate of iatrogenic PT varying among published studies from 0.089% to 4.8%, with the highest rate after left atrial appendage closure, transcatheter aortic valve implantation, and atrial fibrillation ablation. Iatrogenic CT was associated with poor outcomes as high incidence of in-hospital death and need for surgical intervention.

Conflict of interest

The authors declare no conflict of interest.

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Original paper

Impact of direct stenting on clinical outcomes for small vessel coronary artery disease in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction

Kahraman Cosansu[1], Cagin Mustafa Ureyen[2], Mehmet Bulent Vatan[1], Mustafa Tarik Agac[1], Harun Kilic[1], Ramazan Akdemir[1]

[1]Department of Cardiology, Sakarya University Education and Research Hospital, Sakarya, Turkey
[2]Department of Cardiology, Antalya Education and Research Hospital, Antalya, Turkey

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Abstract

Introduction: Direct stenting (DS) is associated with improved markers of reperfusion during primary percutaneous coronary intervention (PPCI) for ST-elevation myocardial infarction (STEMI). However, data evaluating its impact in small vessel coronary artery disease (CAD) are lacking.

Aim: To compare DS and conventional stenting (CS) for small vessel CAD on clinical outcomes of patients with STEMI undergoing PPCI.

Material and methods: A cohort of 616 STEMI patients treated with DS (202 patients) or CS (414 patients) in small vessel (≤ 2.75 mm) lesions was retrospectively analyzed. The primary endpoint was to compare the occurrence of major adverse cardiac events (MACE) between groups during 2-year follow-up. The secondary end points included in-hospital target lesion revascularization (TLR) and in-hospital death.

Results: The primary end-point, MACEs, occurred in 9.2% in the DS group and 12.3% in the CS group ($p > 0.05$). The rates of TLR, myocardial infarction (MI) and target vessel revascularization (TVR) were not significantly different between groups ($p > 0.05$). The stent thrombosis (ST) rate was significantly lower in the DS group (1.0% vs. 4.2%, $p = 0.04$) at 2 years. However, DS was not found to be an independent predictor of ST in multivariate analysis. There were no significant differences in in-hospital rates of death and TLR. The DS compared to CS resulted in greater rates of postprocedural TIMI grade 3 flow, and lower risk of edge dissection. The procedure time, radiation exposure and contrast administration were found to be significantly lower in the DS group.

Conclusions: In selected patients with STEMI undergoing PPCI for small vessel CAD, DS is not only safe and feasible but also reduces ST rates, contrast load, and procedural and radiation exposure time.

Key words: direct stenting, ST-elevation myocardial infarction, primary percutaneous coronary intervention, conventional stenting, small vessel coronary artery.

Summary

The impact of direct stenting on small vessel coronary culprit lesions in patients with ST-segment elevation myocardial infarction has not been investigated yet. The present study clearly emphasizes that direct stenting in selected lesions appears to be a safe and successful procedure, providing lower stent thrombosis and procedural complication rates. The procedural and radiation exposure time, and contrast load were also lower in the DS group.

Introduction

The primary therapeutic strategy in patients with acute ST-elevation myocardial infarction (STEMI) is percutaneous coronary intervention (PCI) with stent implantation [1]. The conventional stenting (CS) technique requires routine pre-dilatation with the balloon catheter

Corresponding author:
Kahraman Cosansu MD, Department of Cardiology, Sakarya University Education and Research Hospital, Sakarya, Turkey,
e-mail: kahraman141@gmail.com
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to ensure easy passage of the stent and to increase the full expansion of stent. With the innovation in stent and delivery system design, direct stenting without balloon pre-dilatation has become a feasible strategy in many catheterization laboratories [2]. Direct stenting (DS) without lesion pre-dilatation is employed in 30–40% of PCIs and has been compared to stenting with pre-dilatation in observational studies as well as randomized trials. DS without balloon pre-dilatation is thought to provide beneficial effects by reducing distal embolization and thereby microvascular obstruction [3]. Prospective studies as well as meta-analyses demonstrate 22–50% reductions in restenosis, target lesion revascularization (TLR), myocardial infarction (MI) and death associated with DS compared to CS [4–6]. Pre-dilation may induce intimal dissection necessitating multiple or altogether longer stents, increasing the risk of restenosis [7]. DS also offers significant reductions in procedure time, radiation exposure, contrast administration, and adjunctive material, use and also cost reduction was achieved by direct stenting [8]. However, a number of disadvantages have been suggested for DS, including failure to cross the lesion, incomplete stent deployment, an increase in guide trauma, undersizing the stent, and poor visualization, which may result in errors in stent positioning [9]. It also might increase procedural risks and may lead to suboptimal clinical results.

Aim

There are no previous studies comparing DS with a conventional approach for small vessel coronary artery disease (CAD) for clinical outcomes of patients with ST-elevation myocardial infarction (STEMI). The aim of the study was to assess in-hospital and long-term clinical outcomes of STEMI patients with small vessel CAD treated with direct stenting as compared with those treated with stenting after pre-dilatation.

Material and methods

Study design and population

This was a retrospective, observational, single-center study. The current study included 616 consecutive patients undergoing a primary PCI with stenting for small vessels (≤ 2.75 mm) in Sakarya University Education and Research Hospital, Sakarya, Turkey from January 2013 to January 2017. The patients were divided into two groups, treated with DS (n = 202, 32.8%) or CS (n = 414, 67.2%). Small vessel CAD was considered a need for implantation of stents ≤ 2.75 mm (diameter of the reference vessel and diameter of the implanted stent: ≤ 2.75 mm). All patients > 18 years of age presenting with STEMI within 12 h of symptom onset or between 12 and 24 h if they had persistent symptoms with evidence of ongoing ischemia were included in the study. DS was the primary modality of treatment in all patients wherever possible. All patients where DS was done formed the direct stenting group (DS group), and the rest were included in the CS group. Patients in the CS group underwent balloon pre-dilatation prior to stenting. The exclusion criteria were a concomitant large diameter PCI in the same coronary artery, left main coronary artery lesions, contraindications to inhibit platelet function with aspirin and clopidogrel, cardiogenic shock, a PCI consisting of in-stent restenosis (ISR) for the culprit lesion, life expectancy < 12 months and pregnancy. Lesions that were heavily calcified or associated with excessive proximal tortuosity were also excluded. An additional exclusion criterion was a lack of relevant patient or procedural related data.

This study complied with the Declaration of Helsinki, and it was approved by the independent medical ethics committee of Sakarya University Education and Research Hospital.

Study protocol

During primary PCI, those patients who had thrombolysis in myocardial infarction (TIMI) flow of ≥ 1 at initial injection or after wire placement underwent DS. Stenting was performed after pre-dilatation in patients whose vessel was still completely occluded after insertion of the wire. Coronary stenting was considered angiographically successful if residual stenosis of < 30% and coronary thrombolysis in myocardial infarction grade flow 3 were obtained at the end of the procedure. During the procedure, an intra-arterial bolus of unfractionated heparin was given at a dose of 80 U/kg. After the intervention, all patients received aspirin indefinitely, clopidogrel, prasugrel or ticagrelor for at least 12 months and other cardiac medications according to ACC/AHA guidelines [10]. Angiographic findings such as vessel dimensions, pre- and post-procedural stenoses and lesion length were determined by visual estimation using the guiding catheter as a reference object for calibration. The angiographic characteristics were also further analyzed by an independent interventional cardiologist not involved in the procedure and checked for inter-observer agreement.

Data collection

Baseline demographics, clinical characteristics and procedural data were collected retrospectively. Thrombus burden, calcification status and postprocedural TIMI flow grade were evaluated by two experienced interventional cardiologists. The contrast volume, procedural time and fluoroscopy time data were obtained from the records of the coronary angiography laboratory. The in-hospital and 2-year follow-up information on clinical outcomes (e.g. in- hospital death, recurrent MIs, TLR, target vessel revascularization (TVR) and definite ST) were collected from electronic medical records, a registry database or phone calls, which asked about relevant end-point clini-

cal events. Routine or control angiography during the follow-up without a clinical indication was not undertaken. However, event-driven coronary angiographies after the initial PCI were performed within the 2-year follow-up period.

Study endpoints and definitions

The primary end-point of the study was the composite of major adverse cardiac events (MACEs), which were defined as TLR, TVR, MI or definite ST during the follow-up period. The secondary end-points included in-hospital TLR and in-hospital death. TVR was defined as any clinically driven PCI or bypass grafting of the target vessel. TLR was defined as any clinically driven repeat PCI or bypass grafting of the treated lesion, including the placement of an in-stent or in-segment 5 mm proximal or distal to the initial stent edges. An MI was defined according to current guidelines [11]. Definite ST was defined based on the criteria of the Academic Research Consortium [12]. Total ischemic time was defined as the time from the onset of chest pain to the first balloon inflation during primary PCI. Angiographic thrombus burden was graded using TIMI thrombus classification, and it was classified as low thrombus burden (grades 1, 2 and 3) and high thrombus burden (grades 4 and 5) [13]. In this study, no-reflow and edge dissection were defined as procedural complications.

Statistical analysis

For the statistical analysis, SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL) was used. Continuous data were expressed as mean ± standard deviation, and the categorical data were expressed as percentages. The normal distribution of the data was assessed by the Kolmogorov-Smirnov test. Comparisons between groups were performed using the χ^2 or Fisher's exact test for qualitative variables, as appropriate. The independent *t*-test was used for normally distributed continuous variables, and the Mann-Whitney *U* test was conducted for non-normally distributed continuous variables, as appropriate. The baseline characteristics and clinical outcomes of the patients treated with direct stenting versus those treated with pre-dilatation prior to stenting were compared. Kaplan-Meier analysis was used to calculate the time to the clinical end-point, and the log-rank test was applied to compare between-group differences. To determine the impact of the DS strategy on 2-year ST, multivariate logistic analysis was performed. Clinical, procedural and angiographic criteria were entered into a univariate model with 2-year ST as the dependent variable. Variables reaching significance, or borderline significance, on univariate analysis ($p \leq 0.1$) were subsequently incorporated into a multivariate model. Independent variables are presented as odds ratios with 95% confidence intervals. The Cox model included age, gender, multivessel disease, stent length, stent diameter, target vessel, lesion location, complication, postdilatation, prior PCI, prior MI, prior CABG, diabetes mellitus (DM), hypertension (HT), hyperlipidemia, smoking, renal failure, thrombus burden, left ventricular ejection fraction (LVEF), and DS. For multivariate analysis, the following covariates were considered for entry into the multivariate models (only those with *p*-values < 0.10 were retained via stepwise regression): DS, gender, prior PCI, prior MI, and stent diameter. A *p*-value < 0.05 was considered statistically significant in all tests.

Results

Characteristics of patients

The baseline demographics and baseline clinical characteristics of groups are shown in Table I. The two groups were comparable in terms of demographics and clinical characteristics and all values were similar between the two groups ($p > 0.05$). However, significantly lower baseline LVEF ($p = 0.009$) and higher age ($p = 0.019$) were found in the CS group. The total ischemic time was found similar in both groups.

Characteristics of the lesions, and PCI procedures

The lesional and procedural characteristics are summarized in Table II. There was no difference in terms of culprit artery and lesion location between groups. In both groups, the lesions were located mostly in the middle part of the vessel and the culprit artery was mostly the right coronary artery (RCA). Moreover, the stents were significantly longer ($p = 0.001$) and stent diameter was lower ($p = 0.050$) in the CS group. The incidence of procedural complications were significantly higher in the CS group as compared with the DS group ($p = 0.01$). The DS compared to CS resulted in greater rates of postprocedural TIMI grade 3 flow ($p = 0.048$) and lower risk of edge dissection ($p = 0.038$). However, there was no difference between the two groups with regards to thrombus burden, calcification, or rate of aspiration thrombectomy. DS when compared with the CS technique significantly decreased both procedure time (43.5 ±12.6 min vs. 47.7 ±15.2 min, $p < 0.001$) and fluoroscopy time (9.7 ±4.4 min vs. 11.7 ±5.7 min, $p < 0.001$). Moreover, contrast volume used in the DS group was significantly lower than the CS group (128.8 ±52.6 ml vs. 151.3 ±83.7 ml, $p < 0.001$).

Clinical outcomes

At the 2-year follow-up, 52 (25.7%) patients in the DS group and 98 (23.7%) patients in the CS group needed to undergo angiographic evaluations. The outcomes of the patients during the follow-up period are summarized in Table III. At the 2-year follow-up, the primary composite end-point, MACEs, occurred in 9.2.% of the DS group and

Table I. Baseline demographics and clinical characteristics

Variables	DS (*n* = 202)	CS (*n* = 414)	*P*-value
Male, *n* (%)	142 (70.3)	300 (72.5)	0.505
Age, mean ± SD [years]	63.0 ±11.9	65.4 ±12.1	0.019
Smoker, *n* (%)	102 (50.5)	191 (46.1)	0.309
Ejection fraction, mean ± SD (%)	47.7 ±9.2	45.5 ±10.7	0.009
Diabetes mellitus, *n* (%)	81 (40.1)	168 (40.7)	0.891
Hypertension, *n* (%)	93 (46.0)	188 (45.5)	0.903
Hyperlipidemia, *n* (%)	36 (17.8)	93 (22.5)	0.179
Prior MI, *n* (%)	19 (9.4)	40 (9.7)	0.919
Prior PCI, *n* (%)	20 (9.9)	34 (8.2)	0.487
Prior CABG, *n* (%)	3 (1.5)	12 (2.9)	0.286
Renal insufficiency, *n* (%)	25 (12.4)	64 (15.5)	0.302
TI time, mean ± SD [min]	116.5 ±40.6	113.8 ±38.9	0.435

Data presented as mean ± standard deviation or number (%). DS – direct stenting, CS – conventional stenting, MI – myocardial infarction, PCI – percutaneous coronary intervention, CABG – coronary artery bypass graft, TI time – total ischemic time.

Table II. Lesions and procedural characteristics

Parameter	DS (*n* = 202)	CS (*n* = 414)	*P*-value
Culprit artery:			
Left anterior descending	60 (29.8)	139 (33.5)	0.165
Left circumflex	15 (7.4)	69 (16.7)	
Right coronary	113 (55.9)	158 (38.2)	
Other	14 (6.9)	48 (11.6)	
Procedural complication:	15 (7.5)	61 (14.7)	0.010
Edge dissection	7 (3.0)	27 (6.5)	0.038
No reflow	8 (4.5)	34 (8.2)	0.059
Procedural characteristics:			
Post-dilation	27 (13.4)	48 (11.6)	0.528
Aspiration thrombectomy	12 (5.9)	23 (5.6)	0.847
Stent length, mean ± SD [mm]	18.67 ±5.93	20.85 ±6.17	0.001
Stent diameter, mean ± SD [mm]	2.48 ±0.10	2.46 ±0.14	0.050
Procedure time, mean ± SD [min]	43.5 ±12.6	47.7 ±15.2	< 0.001
Fluoroscopy time, mean ± SD [min]	9.7 ±4.4	11.7 ±5.7	< 0.001
Contrast volume, mean ± SD [ml]	128.8 ±52.6	151.3 ±83.7	< 0.001
Postprocedural TIMI flow III, *n* (%)	190 (94.1)	371 (89.6)	0.048
Lesion location:			
Proximal	63 (31.1)	153 (37.0)	0.586
Mid	111 (55.0)	193 (46.6)	
Distal	28 (13.9)	68 (16.4)	
Additional stent, *n* (%)	42 (20.8)	89 (21.5)	0.841
Multivessel disease, *n* (%)	27 (13.4)	39 (9.4)	0.137
Calcific lesion, *n* (%)	27 (13.4)	65 (15.7)	0.446
Thrombus burden:			
Low thrombus burden	146 (72.3)	302 (72.9)	0.847
High thrombus burden	56 (27.7)	112 (27.1)	

Data are presented as mean ± standard deviation or number (%). DS – direct stenting, CS – conventional stenting, TIMI – thrombolysis in myocardial infarction.

Table III. Clinical outcomes at 2 years and in-hospital

Parameter	DS (*n* = 202)	CS (*n* = 414)	*P*-value
MI	12 (6.2)	38 (10.0)	0.130
TLR	6 (3.1)	25 (6.6)	0.079
TVR	11 (5.7)	30 (7.9)	0.336
ST	2 (1.0)	16 (4.2)	0.040
MACE	18 (9.2)	47 (12.3)	0.265
In-hospital death	9 (4.5)	34 (8.2)	0.086
In-hospital TLR	3 (1.5)	6 (1.4)	0.972

Data are n (%). DS – direct stenting, CS – conventional stenting, MI – myocardial infarction, TLR – target lesion revascularization, TVR – target vessel revascularization, ST – stent thrombosis, MACE – major adverse cardiovascular events.

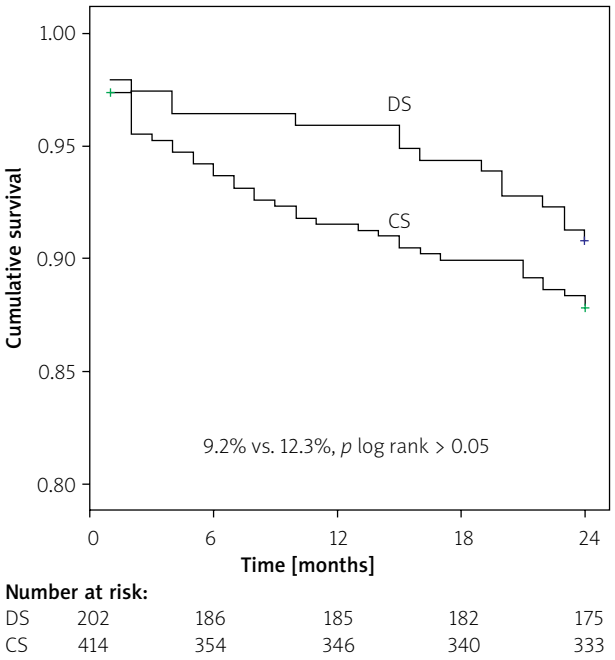

Figure 1. Kaplan-Meier curve estimate of freedom from major adverse cardiac events (MACE) at 24-month follow-up

DS – direct stenting, CS – conventional stenting.

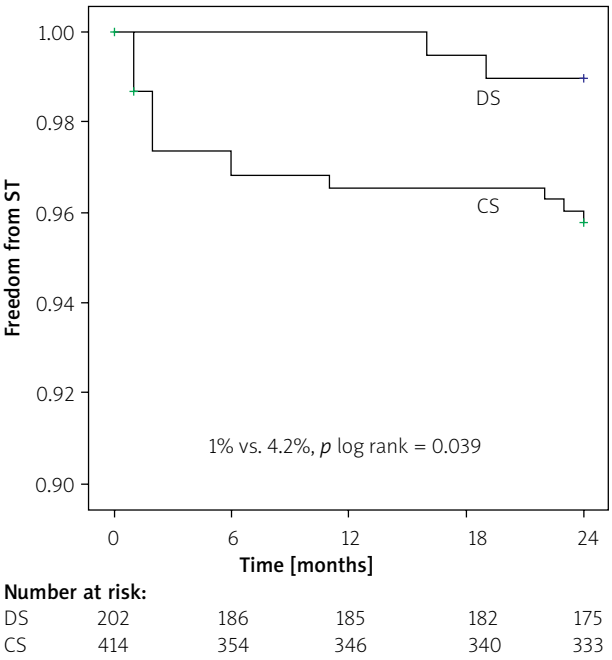

Figure 2. Kaplan-Meier curve estimate of freedom from stent thrombosis (ST) at 24 month follow-up

DS – direct stenting, CS – conventional stenting.

12.3% of the CS group ($p > 0.05$). There was also no significant difference in TVR and MI rates between the two groups after 2 years ($p > 0.05$). Moreover, there was no significant difference between groups in TLR rates during hospitalization ($p > 0.05$). Although TLR and in-hospital death tended to be lower in the DS group, the differences between groups were not significant ($p = 0.07$ and $p = 0.08$, respectively). However, the ST rate was significantly higher in the CS group as compared with the DS group ($p = 0.04$).

Kaplan-Meier survival analysis revealed no difference in event-free MACE ratio between the patients treated with DS and CS (9.2% vs. 12.3%; p log rank > 0.05) (Figure 1). The time-to-event curves reflected a higher incidence of ST in the CS group for small-vessel culprit lesions (4.2% vs. 1.0%; p log rank = 0.039) (Figure 2).

DS was found to be a predictor of ST at 2 years (hazard ratio (HR) = 0.07, 95% confidence interval (CI): 0.01–0.66, $p = 0.021$) in univariate Cox analysis. However, when adjusted for confounding factors, DS was not an independent predictor of ST at 2 years in multivariate Cox analysis (HR = 0.24; 95% CI: 0.05–1.04; $p = 0.058$).

Discussion

This is the first study to include STEMI patients with small vessel coronary artery disease who were treated

with DS or CS and report their long-term outcomes. The main findings of the current study are as follows: First, the rate of MACEs, the primary end-point, was similar in the direct stenting group as compared with that in the patients treated with conventional stenting. Second, there were no statistically significant difference in TLR, TVR, MI, in-hospital death and in-hospital TLR. However, conventional stenting was associated with a significantly higher stent thrombosis rate at 2-year follow-up and also higher procedural complication. DS was not found to be an independent predictor of ST at 2 years in multivariate analysis. Moreover, DS was associated with a shorter procedure and fluoroscopy time, as well as lower contrast volume and postprocedural TIMI III flow.

DS is defined as the technique of coronary stent implantation without predilatation by balloon. To perform direct stenting, it is mandatory to visualize the length of the culprit lesion and the diameter of the vessel. However, in a STEMI patient, TIMI flow is most often ≤ 1 before wire placement [14]. During primary PCI, patients who had TIMI flow of ≥ 2 at initial injection or after wire placement are suitable for direct stenting. The direct stenting technique has a number of theoretical advantages. Prospective studies and meta-analyses have consistently demonstrated significant benefit of DS in terms of safety, procedural outcomes, MACE rate and mortality [15]. Superior clinical outcomes associated with DS may be driven by reduced wall damage and inflammatory response from balloon predilation [16], and fewer intimal dissections [17]. Balloon predilation before stenting is associated with higher risk of distal embolization and microvascular occlusion, which is associated with more reperfusion failure and lower probability of final TIMI 3 flow [3, 18]. In our study, a relatively high incidence of procedural complications and lower TIMI III flow rate were observed in the conventional stent group versus the direct stent group, compatible with previous results. However, underestimation of true vessel size, failure to cross the lesion, non-dilatable lesions, inadequate stent expansion and late stent malapposition were possible limitations of DS [19].

Routine use of manual thrombus aspiration in primary PCI resulted in improved myocardial reperfusion and reduced 1-year cardiac mortality in the TAPAS study [20]. However, the efficacy of routine thrombus aspiration could not be confirmed in either the TASTE [21] or the TOTAL [22] trial, prompting international guidelines to advise its use in selected patients only [23]. In a recent study, Mahmoud *et al.* reported that clinical outcomes and myocardial reperfusion measures did not differ significantly between DS and CS and there was no interaction with thrombus aspiration [24]. In this study, we used thrombus aspiration only in selected patients, and thrombus aspiration was used at a similar rate in both groups.

The results of studies investigating the usefulness of the DS strategy in terms of clinical outcomes are contradictory. In recent years, several meta-analyses comparing DS and CS have been published. However, these studies have not been performed in STEMI patients or in small vessel coronary artery disease. Therefore, the outcome rates in our study are important in terms of being the first data in this patient group. Magalhaes *et al.* reported significantly lower MACE and TLR rates following DS as compared with CS in a meta-analysis of elective procedures [15]. In another meta-analysis, myocardial infarction was significantly reduced with direct stenting compared with conventional stenting, but the target-vessel revascularization rate was similar between groups [6]. Moreover, Alak *et al.* found a significant reduction in the risk of in-hospital cardiovascular death, but no significant differences were observed in myocardial infarction or target lesion revascularization [25]. Different results were found in each of these three metaanalyses, which might have resulted from studies with different methodologies in different patient groups. They included many old treatment elements, including antiplatelet therapy with ticlopidine and implantation of mostly bare metal stents.

In the literature, there are few studies comparing DS and CS in terms of clinical outcomes in STEMI patients. Kalayci *et al.* found that DS in primary PCI was associated with better postprocedural angiographic results and long-term survival; however, the DS group had similar in-hospital and long-term mortality to matched patients in the CS group [26]. In another study, direct stenting compared to conventional stenting was associated with a significantly lower rate of all-cause death and stroke, but there were non-significant differences in target lesion revascularization, myocardial infarction, stent thrombosis and major bleeding at 1-year follow-up [27]. McCormick *et al.* reported that patients receiving DS had reduced mortality at 30-day and 1-year follow-up [28]. In the EUROTRANSFER registry, direct compared with conventional stenting resulted in significantly higher rates of postprocedural TIMI grade 3 flow, lower risk of no-reflow and significant reduction in 1-year mortality [29]. In the present study, the rate of edge dissection was lower and the rate of TIMI III flow was higher in the DS group. However, there was no difference in terms of no-reflow between groups. In-hospital death and TLR at 2 years were also lower in the DS group, but it did not reach significance. The rate of stent thrombosis is higher in patients with small vessel CAD as compared with those with non-small vessel CAD in the literature [30]. In the previous studies ST rates were found to be similar in DS and CS groups in non-small vessel CAD. In the current study, although the stent thrombosis rate was higher in the CS group in STEMI patients with small-vessel CAD, DS was not found to be an independent predictor of ST at 2 years in multivariate analysis. Increased stent throm-

bosis in the CS group may be associated with the use of longer and smaller diameter stents in this group. In addition, the suboptimal procedural result (TIMI flow grade < 3) is a predictor of ST, and in our study the TIMI III flow rate was lower in the CS group.

Limitations

Several limitations of the present study should be acknowledged. First, the present trial was a single centre pilot study representing the experience of only one hospital and the results can only be hypothesis-generating. Second, only about 25% of our patients received follow-up coronary angiography according to clinical indications, and the potential bias related to the incomplete angiographic follow-up might have had a substantial impact on the analytic results. Third, a bias cannot be excluded as to which patients seemed suitable for direct stent implantation.

Conclusions

As in our study, there is no other study comparing DS and CS in terms of clinical outcomes in small-vessel CAD patients with STEMI. Direct stenting without predilation in selected lesions seems to be a safe and successful procedure that provides a lower stent thrombosis and procedural complication rate and potential advantages as savings in procedural time, contrast load, and shortened radiation exposure time. However, larger and randomized studies with longer follow-up are mandatory before routine clinical use is recommended.

Conflict of interest

The authors declare no conflict of interest.

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ST-segment re-elevation following primary angioplasty in acute myocardial infarction with patent infarct-related artery: impact on left ventricular function recovery and remodeling

Krzysztof Krawczyk, Konrad Stepien, Karol Nowak, Jadwiga Nessler, Jaroslaw Zalewski

Department of Coronary Artery Disease and Heart Failure, Jagiellonian University Medical College, John Paul II Hospital, Krakow, Poland

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Abstract

Introduction: Spontaneous recanalization of the infarct-related artery (IRA) in ST-segment elevation myocardial infarction (STEMI) before primary angioplasty (PCI) improves clinical outcomes.

Aim: To investigate the impact of ST-segment re-elevation (reSTE) following PCI in patent IRA on left ventricular (LV) function recovery and remodeling.

Material and methods: Of 155 STEMI patients with patent IRA, 19 (12.3%) patients with TIMI-2 ($T2_{Res}$) and 85 (54.8%) with TIMI-3 ($T3_{Res}$) had further STE resolution following PCI, 20 (12.9%) with TIMI-3 did not require PCI ($T3_{noPCI}$) and 31 (20.0%) with TIMI-2/3 had reSTE of ≥ 1 mm following PCI as compared with pre-PCI recordings ($T23_{reSTE}$). LV ejection fraction (LVEF, %) and LV end-diastolic and end-systolic volume indexes (LVEDVI, LVESVI, ml/m^2) were measured by echocardiography 2 days and 6 months following PCI.

Results: In 6-month observation the improvement of LVEF in $T3_{Res}$ (by 3.9 ±5.1%) and in $T3_{noPCI}$ (by 5.7 ±6.1%) patients was higher as compared with $T23_{reSTE}$ (0.2 ±7.0%, $p < 0.05$ versus both). LVEDVI increased in $T23_{reSTE}$ patients by 6.6 ±12.6 ml/m^2, but decreased in $T3_{Res}$ by 3.8 ±9.7 ml/m^2 and in $T3_{noPCI}$ by 2.4 ±6.2 ml/m^2 (for both $p < 0.05$ vs. $T23_{reSTE}$). LVESVI increased in $T23_{reSTE}$ patients (by 3.8 ±10.8 ml/m^2), did not change in $T2_{Res}$ (by 0.1 ±9.0 ml/m^2), but decreased in $T3_{Res}$ (by 4.2 ±7.2 ml/m^2, $p < 0.05$ vs. $T23_{reSTE}$) and in $T3_{noPCI}$ patients (by 4.7 ±7.7 ml/m^2, $p < 0.05$ vs. $T23_{reSTE}$). ReSTE was an independent predictor of LVEF, LVEDVI and LVESVI changes ($p < 0.001$ for all).

Conclusions: ReSTE following PCI in a patent IRA is associated with a lack of improvement of LV contractility and subsequent LV remodeling.

Key words: acute myocardial infarction, primary percutaneous coronary intervention, ST-segment elevation.

Summary

The current study constitutes one of the infrequent reports regarding the clinical relevance of ST-segment re-elevation (reSTE) following primary percutaneous coronary intervention (PCI) in patients with a spontaneously recanalized infarct-related artery (IRA). We found that reSTE was independently associated with both lack of improvement of global and infarct-related contractility as well as increase of left ventricular (LV) volumes in 6-month observation. Moreover, the procedure accompanied by reSTE was related to worse LV function and structure recovery as compared with patients with subsequent ST-segment resolution following PCI. Our findings provide evidence that myocardial injury reflected by reSTE is associated with the loss of beneficial effects of spontaneous IRA reperfusion on subsequent LV remodeling. Further studies on therapies to prevent reSTE following primary PCI are necessary.

Introduction

Spontaneous reperfusion characterized by a patent epicardial infarct-related artery (IRA) on initial angiography improves the prognosis in patients with myocardial infarction (MI). This phenomenon affects up to 30% of patients with ST-segment elevation myocardial infarction (STEMI) [1]. Based on the results of recent EUROMAX

Corresponding author:
Krzysztof Krawczyk MD, Department of Coronary Artery Disease and Heart Failure, Jagiellonian University Medical College, John Paul II Hospital, 80 Pradnicka St, 31-202 Krakow, Poland, e-mail: krzysztof15.krawczyk@gmail.com
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[2] and HORIZONS-AMI [3] trials, baseline thrombolysis in myocardial infarction (TIMI) 2 or 3 flow derived from spontaneous reperfusion was associated in contemporary practice with a higher rate of final TIMI 3 flow grade, decreased frequency of adverse cardiovascular events and reduced short- and long-term mortality. Similar beneficial effects were found with pharmacological reperfusion prior to percutaneous coronary intervention (PCI) [4]. According to the current guidelines [5] in patients with spontaneously normalized ST-segment elevation, angiography within 24 h is recommended. Moreover, recent studies showed that deferred PCI in spontaneously reperfused STEMI patients was associated with similar infarct size [6] and clinical outcomes [1, 6] as compared with immediate PCI.

The fourth universal definition of MI focused on the issue of myocardial damage associated with revascularization procedures. The procedure-related myocardial injury and MI associated with PCI (type 4a MI) were separated depending on the level of high-sensitivity cardiac troponin and the presence of new ischemic changes in ECG, cardiac imaging or angiographic findings of flow-limiting complications of PCI [7]. Previous studies reported that the incidence of peri-procedural MI varies from 5 to 30% and is associated with an increased risk of death (adjusted hazard ratio (HR) = 1.20, 95% CI: 1.04–1.39) [8]. When PCI is performed in a prothrombotic milieu in MI patients, it is extremely difficult to estimate the magnitude of myocardial injury associated with the procedure, while the extent of infarct-related necrosis is many times greater.

It was found that ST-segment re-elevation (reSTE) following primary PCI observed in one fifth of patients with anterior STEMI with an occluded IRA on initial contrast injection was not associated with increased infarct size, left ventricular (LV) function or clinical outcomes at 1 year [9, 10]. In contrast, lack of ST-segment resolution or reSTE within 24 h following PCI was associated with increased enzymatic injury and reduced LV function [11]. Moreover, in STEMI patients, microvascular obstruction and intramyocardial hemorrhage were more frequently observed in contrast-enhanced cardiac magnetic resonance of patients with reSTE during primary PCI [12]. Previous results also suggested that myocardial expansion of the infarcted portion [13] and pericarditis following MI may contribute to reSTE, but most of the available studies concerned patients with an occluded IRA.

Aim

We hypothesized that reSTE following primary PCI in a patent IRA might be associated with the loss of beneficial effects of spontaneous reperfusion. We sought to investigate the significance of reSTE during PCI in STEMI patients with a spontaneously recanalized IRA on LV function recovery and remodeling.

Material and methods

Of 969 consecutive STEMI patients we studied 155 (16%) patients with a patent IRA treated in one center with primary PCI. The inclusion criteria were chest pain onset within 12 h with concomitant ST-segment elevation of ≥ 1 mm in at least 2 contiguous leads or ≥ 2 mm in at least 2 contiguous precordial leads in qualifying ECG done during the first medical contact as well as initial TIMI 2 or 3 flow in the IRA on initial contrast injection during angiography. The exclusion criteria were cardiogenic shock on admission, previous coronary artery bypass surgery, history of malignancy, venous thromboembolism, liver injury (alanine aminotransferase > 1.5 ULN), serum creatinine > 177 µmol/l and current oral anticoagulation.

At first medical contact all patients received 300 mg of aspirin; 114 (73.5%) of them were loaded with 600 mg of clopidogrel and 88 (56.8%) received an intravenous bolus of 5000 IU of unfractionated heparin (UFH). On admission, hemoglobin, red blood cell count, white blood cell count, platelet count, glucose, creatinine, and high-sensitivity C-reactive protein were determined by routine laboratory techniques. Immediately before PCI, patients received a weight-adjusted bolus of UFH to achieve activated clotting time of 200–250 s. During primary PCI, 12 patients received abciximab as a bailout procedure. The Export Aspiration Catheter (Medtronic Inc., Minneapolis, Minnesota, USA) was used in 35 (22.6%) patients.

The study protocol complying with the Declaration of Helsinki was approved by the Ethics Committee of the Jagiellonian University. All subjects gave informed consent for their participation in the study.

ECG

Standard 12-lead ECGs (25 mm/s) obtained at the first medical contact (qualifying ECG (Q)), before PCI (B) and immediately after the procedure (A) were analyzed. The sum of ST-segment elevations in all leads (ΣST) was measured at the J point by a single investigator blinded to the clinical and angiographic findings. If the sum of STE following PCI was higher by at least 1 mm as compared with pre-PCI recordings, this patient was classified as re-elevated. Resolution of ST-segment elevation between qualifying ECG and ECG performed before (STR_B) and after (STR_A) primary PCI was calculated according to the formulas: $STR_B = 100\%*(\Sigma ST_Q - \Sigma ST_B)/\Sigma ST_Q$ and $STR_A = 100\% \times (\Sigma ST_Q - \Sigma ST_A)/\Sigma ST_Q$.

Angiography analysis

Angiogram analysis was performed off-line for the determination of the IRA, epicardial blood flow, thrombus burden and distal embolization, based on visual inspection. Epicardial blood flow was evaluated by means of the TIMI flow scale [14], myocardial perfusion was scored according to the TIMI myocardial perfusion

grades (TMPG) [15] and thrombus burden was assessed according to the TIMI thrombus grades [16], all before and after primary PCI.

In addition, angiograms were analyzed for the presence of collateral flow to the IRA or the presence of flow-limiting lesions in non-IRA arteries. A detailed evaluation was performed in two contralateral projections. Two experienced investigators reviewed each coronary angiogram in a blinded fashion. In case of a lack of agreement between the two investigators, a third one was sought, and a conclusion was made.

Assessment of cardiac function

Two-dimensional transthoracic echocardiography (TTE) was performed twice, 2 days (2D) and 6 months (6M) after primary PCI, at rest in a left decubitus position, using a Vivid S5 ultrasound machine (GE, Solingen, Germany) equipped with the multi-frequency harmonic transducer 3Sc-RS (1.3–4 MHz). All measurements were carried out according to joint recommendations of the American Society of Echocardiography and European Association of Echocardiography [17] by one observer blinded to clinical and angiographic data. Images were recorded in the parasternal long axis, parasternal short axis, apical four-chamber, apical two-chamber, and apical long axis views of the LV. In apical four-chamber and apical two-chamber views, LV end-diastolic (LVEDV) and end-systolic (LVESV) volumes and ejection fraction (LVEF) were calculated according to the biplane Simpson method. The values of LVEDV and LVESV were subsequently indexed to the body surface area (LVEDVI, LVESVI [ml/m^2]). The wall motion score index was calculated for IRA territory (IRA-WMSI) [18]. Based on the current recommendations [17], a 16-segment model for LV segmentation and classification of territories supplied by each coronary artery were used. Wall motion of each segment was analyzed individually by a trained physician and scored as normal or hyperkinetic – 1, hypokinetic – 2, akinetic – 3 and dyskinetic (or aneurysmatic) – 4. The function of each segment was validated in multiple views and the IRA-WMSI was expressed as the average value from all analyzed segments in the IRA territory.

Clinical outcomes

A 1-year clinical outcome included death, recurrent MI, and recurrent hospitalization due to symptoms of heart failure. Event-free survival after 1-year observation was defined as freedom from death, reinfarction, and repeated cardiovascular hospitalization.

Data were obtained from the hospital records and supplemented by direct and/or telephone interview with the patient. Cardiac function at the end of the study was assessed according to the New York Heart Association functional scale (NYHA). The NYHA functional class was determined by direct contact or telephone interview with patients.

Statistical analysis

Statistical analyses were performed with Statistica 6 (StatSoft, Inc). Continuous variables are expressed as a mean ± standard deviation or median (interquartile range) and categorical variables as a number (percentage). Continuous variables were first checked for normal distribution by the Shapiro-Wilk statistic and compared by ANOVA when normally distributed or by the Kruskal-Wallis test for non-normally distributed variables, both with appropriate post-hoc tests. Categorical variables were analyzed by χ^2 or Fisher's exact test. Pearson's or Spearman's rank correlation coefficients were calculated to test the association between two variables with a normal or non-normal distribution, respectively. Multivariate regression analysis was used to determine independent predictors of changes of LV function and remodeling. A *p*-value of less than 0.05 was considered statistically significant.

Results

Of 155 STEMI patients with a patent IRA at baseline, 19 (12.3%) patients with TIMI-2 flow ($T2_{Res}$) and 85 (54.8%) patients with TIMI-3 flow ($T3_{Res}$) achieved further STE resolution following PCI, 31 (20.0%) patients with TIMI-2 (n = 5) or 3 (n = 26) flow developed reSTE of ≥ 1 mm following PCI as compared with pre-PCI recordings ($T23_{reSTE}$) and the last 20 (12.9%) patients with baseline TIMI-3 did not require PCI because of residual stenosis of less than 50% ($T3_{noPCI}$).

Patients' baseline and procedural characteristics are shown in Tables I and II. The studied groups did not differ in terms of demographic variables, cardiovascular risk factors, time of ischemia, laboratory results, IRA distribution or prehospital pharmacological regimen (Table I). Among the compared groups, there were also no significant differences in the thrombus burden expressed as TIMI thrombus grade (TTG) or distal embolization; however, incomplete TMGP-0/1 perfusion was more frequently observed in $T2_{Res}$ patients before PCI and in $T2_{Res}$ and $T23_{reSTE}$ patients after PCI as compared with remaining subgroups; therefore these patients required abciximab use the most frequently (Table II).

Changes of ST-segment elevation

Among the compared groups, there was no significant difference in the sum of STE in qualifying ECG (p = 0.10); however, there were significant differences of STE in ECGs recorded before (p = 0.005) and after PCI (p < 0.001) (Figure 1 A). Before PCI, STE was significantly higher in $T2_{Res}$ patients as compared with $T3_{Res}$ (mean difference: 4.0 mm, 95% CI: 0.7–7.3 mm) and $T3_{noPCI}$

Table I. Baseline characteristics of studied patients

Parameter	$T3_{Res}$ *n* = 85	$T23_{reSTE}$ *n* = 31	$T2_{Res}$ *n* = 19	$T3_{noPCI}$ *n* = 20	*P*-value
Age [years]	56 (49–64)	57 (49–66)	61 (50–67)	59 (53–69)	0.55
Male gender	64 (75.3)	26 (83.9)	14 (73.7)	14 (70.0)	0.62
Cardiovascular risk factors:					
Hypertension	52 (61.2)	15 (48.4)	14 (73.7)	11 (55.0)	0.33
Diabetes mellitus	18 (21.2)	7 (22.6)	6 (31.6)	4 (20.0)	0.99
Dyslipidemia	47 (55.3)	16 (51.6)	12 (63.2)	12 (60.0)	0.78
Smoking	55 (64.7)	19 (61.3)	13 (68.4)	14 (70.0)	0.81
Family history of coronary artery disease	18 (21.1)	6 (19.4)	4 (21.1)	5 (25.0)	0.91
Prior stroke	1 (1.2)	1 (3.2)	0	1 (5.0)	0.59
Peripheral artery disease	4 (4.7)	2 (6.5)	1 (5.3)	1 (5.0)	0.98
Renal failure	3 (3.5)	1 (3.2)	0	0	0.71
Previous MI	7 (11.8)	3 (9.7)	2 (10.5)	1 (5.0)	0.92
Prior PCI	5 (5.9)	2 (6.5)	0	0	0.49
Killip class on admission:					0.27
1	79 (92.9)	27 (87.0)	14 (73.7)	18 (90.0)	
2	4 (4.7)	2 (6.5)	3 (15.8)	2 (10.0)	
3	2 (2.4)	2 (6.5)	2 (10.5)	0	
Chest pain on admission	9 (10.6)	5 (16.1)	5 (26.3)	2 (10.0)	0.30
Onset of chest pain to balloon inflation, min	270 (212–382)	255 (210–285)	225 (170–280)	242 (201–333)	0.11
Loading dose of clopidogrel to admission, min	70 (50–108)	71 (51–110)	62 (45–101)	67 (50–105)	0.42
White blood cells [×10³/µl]	10.7 (9.0–13.7)	11.2 (9.2–13.8)	10.9 (9.0–13.6)	11.2 (9.2–13.8)	0.35
Hemoglobin [g/dl]	14.5 (13.4–15.2)	14.2 (13.0–14.5)	14.3 (13.2–14.7)	14.4 (13.1–14.8)	0.42
Platelet count [×10³/µl]	218 (190–271)	230 (184–269)	222 (178–255)	240 (193–281)	0.57
Glucose [mmol/l]	8.4 (7.2–10.3)	7.5 (6.6–9.0)	7.7 (6.8–9.2)	7.9 (7.1–9.4)	0.23
Creatinine [µmol/l]	94 (78–105)	88 (77–103)	92 (79–105)	95 (80–107)	0.41
hs C-reactive protein [mg/l]	1.9 (1.0–6.2)	2.9 (1.7–28.6)	2.3 (1.2–8.4)	4.1 (2.7–32.6)	0.16
Hospitalization [days]	5 (3–6)	4 (3–6)	4 (3–6)	4 (3–6.75)	0.76
12-month follow-up:					
Death	0	0	0	0	NA
Recurrent MI	2 (2.4)	0	0	0	0.68
Symptoms of heart failure (NYHA ≥ 2)	10 (11.8)	7 (22.6)	3 (15.8)	1 (5.0)	0.29
Recurrent hospitalization due to heart failure	4 (4.7)	2 (6.5)	2 (10.5)	1 (5.0)	0.80

Data are expressed as number (percentage) or median (interquartile range). MI – myocardial infarction, NYHA – New York Heart Association, PCI – percutaneous coronary intervention, $T2_{Res}$ – TIMI-2 flow with ST-segment resolution following PCI, $T23_{reSTE}$ – TIMI-2/3 flow with ST-segment re-elevation following PCI, $T3_{noPCI}$ – TIMI-3 flow without PCI, $T3_{Res}$ – TIMI-3 flow with ST-segment resolution following PCI.

(5.0 mm, 95% CI: 0.8–0.1 mm). After PCI, residual STE was significantly higher in $T23_{reSTE}$ as compared with $T3_{Res}$ (5.0 mm, 95% CI: 3.4–6.8 mm) and $T2_{Res}$ (2.3 mm, 95% CI: 0.5–5.2 mm). There were also significant differences of STR_B (p = 0.008) and STR_A (p < 0.001) (Figure 1 B). STR_B was significantly lower in $T2_{Res}$ patients as compared with $T3_{noPCI}$ (36.8%, 95% CI: 8.2–65.4%). STR_A was significantly lower in $T23_{reSTE}$ as compared with both $T3_{Res}$ (36.0%, 95% CI: 24.2–47.4%) and $T2_{Res}$ (22.8%, 95% CI: 6.4–39.1%).

Table II. Antithrombotic pharmacotherapy and invasive procedure

Parameter	$T3_{Res}$ *n* = 85	$T23_{reSTE}$ *n* = 31	$T2_{Res}$ *n* = 19	$T3_{noPCI}$ *n* = 20	*P*-value
Aspirin, 300 mg *p.o.*:					1.0
Pre-hospital FMC	85 (100)	31 (100)	19 (100)	20 (100)	
Clopidogrel, 600 mg *p.o.*:					0.65
Pre-hospital FMC	65 (76.5)	22 (71.0)	13 (68.4)	14 (70.0)	
During PCI	30 (23.5)	9 (29.0)	6 (31.6)	6 (30.0)	
Unfractionated heparin					0.98
Pre-hospital FMC, 5000 IU *i.v.*	48 (56.5)	17 (54.8)	11 (57.9)	12 (60.0)	
Abciximab *i.v.*:					0.002
During PCI, as a bail-out procedure	2 (2.6)	6 (19.4)	4 (21.1)	0	
Infarct-related artery:					0.21
Left anterior descending	35 (41.2)	18 (58.0)	12 (63.2)	10 (50.0)	
Left circumflex	9 (10.6)	2 (6.5)	1 (5.3)	2 (10.0)	
Right coronary artery	41 (48.2)	11 (35.5)	6 (31.5)	8 (40.0)	
TIMI at baseline:					NA
2	0	5 (16.1)	19 (100)	0	
3	85 (100)	26 (83.9)	0	20 (100)	
TIMI after PCI:					0.008
2	2 (2.4)	4 (12.9)	4 (21.1)	NA	
3	83 (97.6)	27 (87.1)	15 (78.9)	NA	
TMPG before PCI:					< 0.001
0/1	3 (3.5)	4 (12.9)	8 (42.1)	4 (20.0)	
2/3	82 (96.5)	27 (87.1)	11 (57.9)	16 (80.0)	
TMPG after PCI:					< 0.001
0/1	5 (5.9)	13 (41.9)	6 (31.6)	NA	
2/3	80 (94.1)	18 (58.1)	13 (68.4)	NA	
Distal embolization	5 (5.9)	2 (9.7)	1 (5.3)	0	0.73
TIMI thrombus grade					0.39
0–2	76 (89.4)	26 (83.9)	15 (78.9)	19 (95.0)	
3–4	9 (10.6)	5 (16.1)	4 (21.1)	1 (5.0)	

Data are expressed as number (percentage). FMC – first medical contact, PCI – percutaneous coronary intervention, TIMI – thrombolysis in myocardial infarction, TMPG – TIMI myocardial perfusion grade, $T2_{Res}$ – TIMI-2 flow with ST-segment resolution following PCI, $T23_{reSTE}$ – TIMI-2/3 flow with ST-segment re-elevation following PCI, $T3_{noPCI}$ – TIMI-3 flow without PCI, $T3_{Res}$ – TIMI-3 flow with ST-segment resolution following PCI.

Evolution of LV systolic function

Among the compared groups, there were significant differences of LV ejection fraction 2 days (p = 0.001) and 6 months following PCI (p = 0.005) (Figure 2 A). $LVEF_{2D}$ was significantly lower in $T23_{reSTE}$ patients as compared with $T3_{Res}$ (mean difference: 7.4%, 95% CI: 2.5–12.3%). In 6-month observation, LVEF increase in $T3_{Res}$ (by 3.9 ±5.1%) and in $T3_{noPCI}$ (by 5.7 ±6.1%) patients was higher as compared with that in $T23_{reSTE}$ patients (0.2 ±7.0%, $p < 0.05$ for both) (Figure 2 B). At 6M, LVEF was significantly lower in $T23_{reSTE}$ as compared with $T3_{Res}$ (5.5%, 95% CI: 1.6–16.5%) and $T3_{noPCI}$ (3.3%, 95% CI: 6.4–39.1%). In $T2_{Res}$ patients, LVEF did not change significantly in 6-month observation.

There were also significant differences in wall motion score index values calculated for infarct-related territory (IRA-WMSI) both 2 days (p = 0.03) and 6 months following PCI ($p < 0.001$) (Figure 2 C). The $IRA\text{-}WMSI_{2D}$ was significantly higher in $T23_{reSTE}$ patients as compared with $T3_{Res}$ (mean difference: 0.25, 95% CI: 0.02–0.49). In 6-month observation, IRA-WMSI improvement in $T3_{Res}$ (by 0.33 ±0.25) and in $T3_{noPCI}$ (by 0.24 ±0.29) patients was higher as compared with $T23_{reSTE}$ patients (0.08 ±0.35,

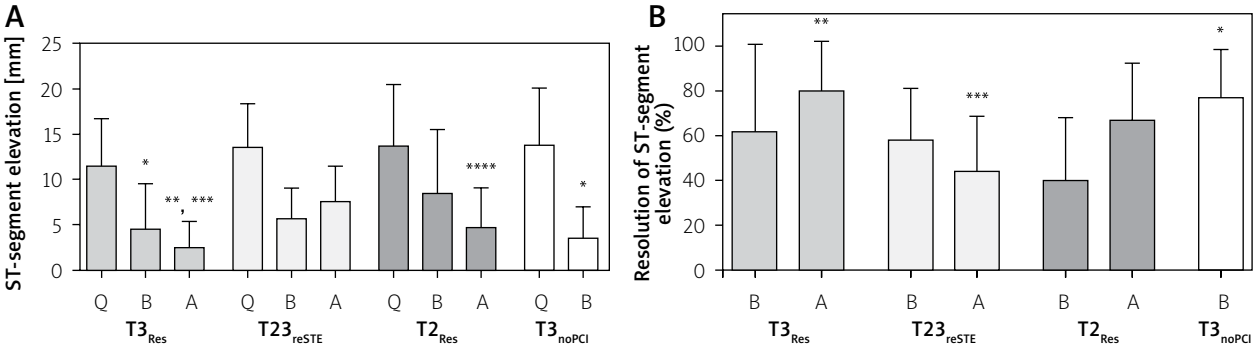

Figure 1. Changes of ST-segment elevation and ST-segment elevation resolution in the studied patients

*Data are shown as mean and standard deviation. Q, B, A – ECG recorded at first medical contact, before and after PCI, respectively. $T2_{Res}$ – TIMI-2 flow with ST-segment resolution following PCI, $T23_{reSTE}$ – TIMI-2/3 flow with ST-segment re-elevation following PCI, $T3_{noPCI}$ – TIMI-3 flow without PCI, $T3_{Res}$ – TIMI-3 flow with ST-segment resolution following PCI. *P < 0.05 vs. B-T2Res, **p < 0.001 vs. A-T23reSTE, ***p < 0.05 vs. A-T2Res, ****p < 0.05 vs. A-T23reSTE.*

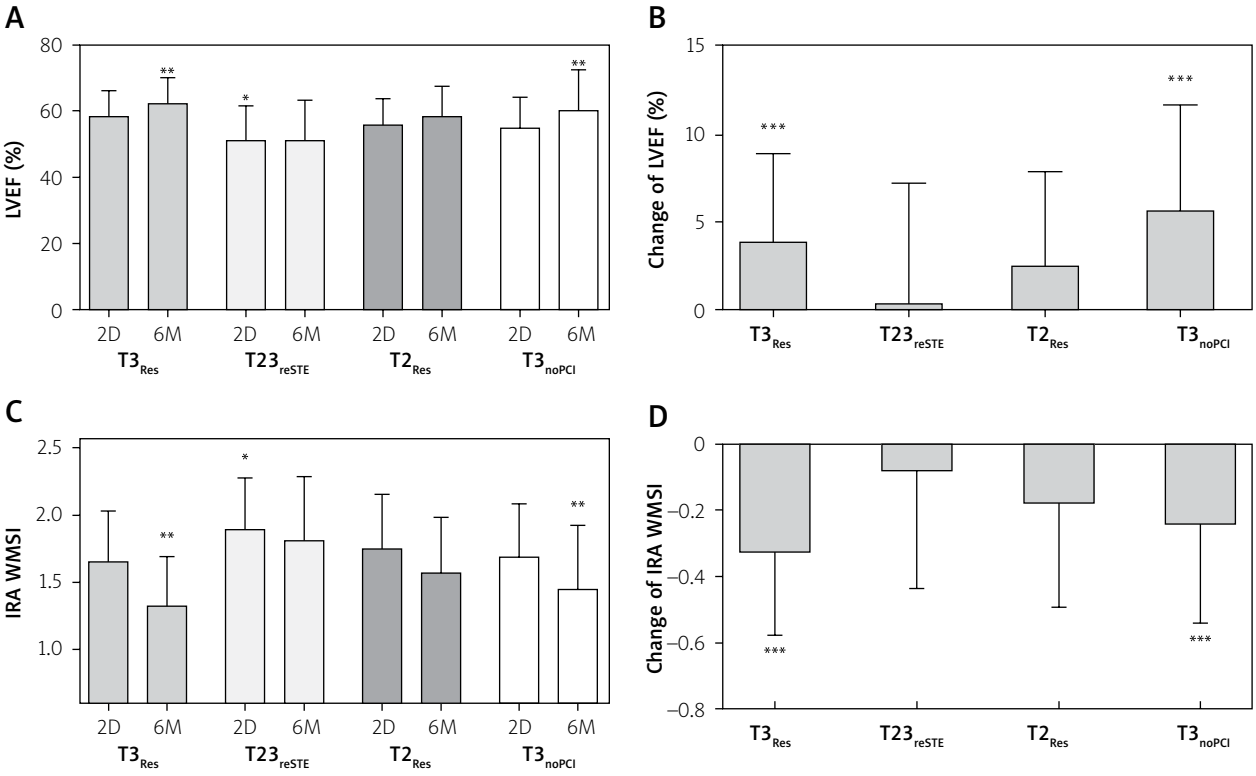

Figure 2. Changes of global and infarct-related contractility of left ventricle

*Data are shown as mean and standard deviation. 2D – measurements performed 2 days after PCI, 6M – measurements performed 6 months after PCI, LVEF – left ventricular ejection fraction, IRA WMSI – wall motion index score for infarct-related territory, $T2_{Res}$ – TIMI-2 flow with ST-segment resolution following PCI, $T23_{reSTE}$ – TIMI-2/3 flow with ST-segment re-elevation following PCI, $T3_{noPCI}$ – TIMI-3 flow without PCI, $T3_{Res}$ – TIMI-3 flow with ST-segment resolution following PCI. *P < 0.001 vs. 2D-$T3_{Res}$, **p < 0.01 vs. 6M-$T23_{reSTE}$, ***p < 0.05 vs. $T23_{reSTE}$.*

$p < 0.05$ for both) (Figure 2 D). In $T2_{Res}$ patients, IRA-WMSI did not change in 6-month observation. At 6 months, differences in IRA-WMSI were more pronounced and IRA-WMSI was significantly higher in $T23_{reSTE}$ as compared with $T3_{Res}$ (0.49, 95% CI: 0.25–0.72) and $T3_{noPCI}$ (0.36, 95% CI: 0.04–0.68).

LV remodeling

There were no differences among the compared groups in terms of baseline LVEDVI ($p = 0.89$) and LVESVI ($p = 0.08$) (Figures 3 A, C). In 6-month follow-up, LVEDVI increased in $T23_{reSTE}$ by 6.6 ±12.6 ml/m^2 and decreased in group $T3_{Res}$ by 3.8 ±9.7 ml/m^2 and $T3_{noPCI}$ by 2.4 ±6.2 ml/m^2 (for both $p < 0.05$ vs. $T23_{reSTE}$) (Figure 3 B). In $T2_{Res}$ patients, LVEDVI did not change significantly in 6-month observation. Therefore, after 6 months, LVEDVI was significantly higher in $T23_{reSTE}$ as compared with $T3_{Res}$ (9.9 ml/m^2, 95% CI: 0.6–19.3 ml/m^2) (Figure 3 A).

In 6-month follow-up, LVESVI increased in $T23_{reSTE}$ (by 3.8 ±10.8 ml/m^2) patients, did not change significantly in

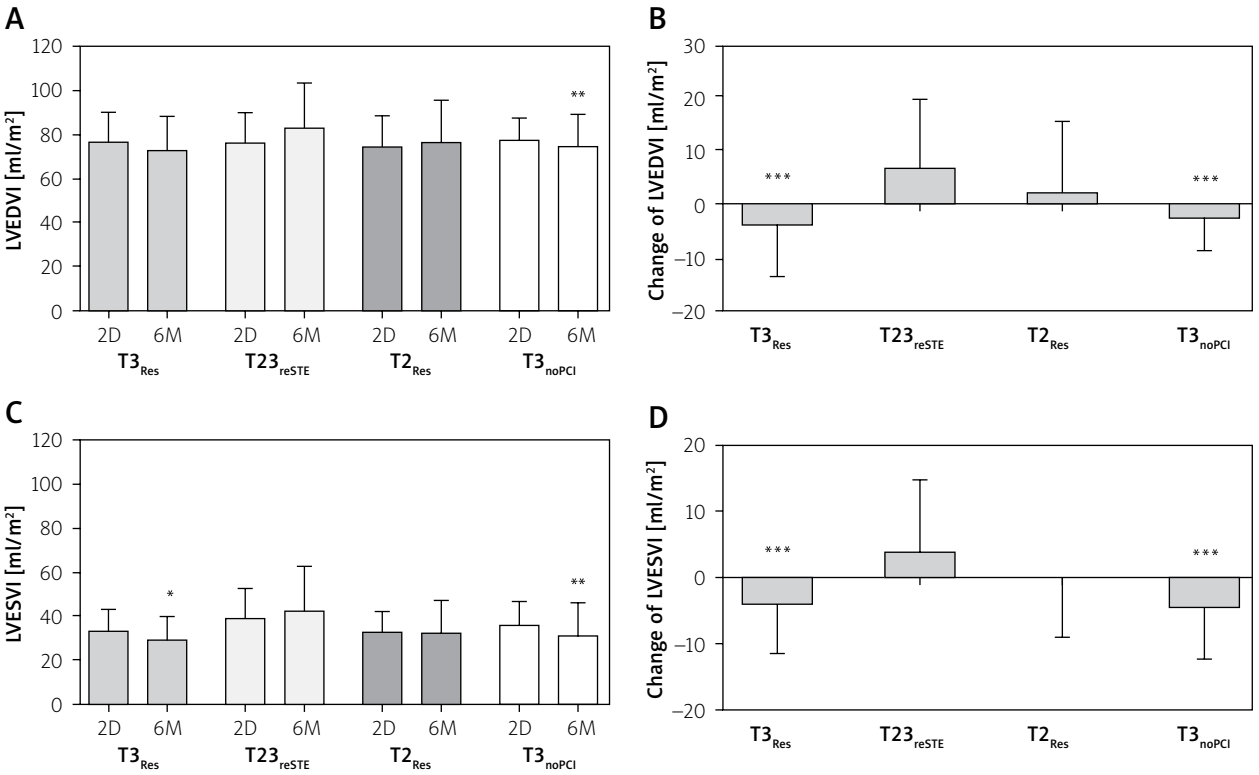

Figure 3. Changes of left ventricular volume indexes

*Data are shown as mean and standard deviation. 2D – measurements performed 2 days after PCI, 6M – measurements performed 6 months after PCI, LVEDVI – left ventricular end-diastolic volume index, LVESVI – left ventricular end-systolic volume index, $T2_{Res}$ – TIMI-2 flow with ST-segment resolution following PCI, $T23_{reSTE}$ – TIMI-2/3 flow with ST-segment re-elevation following PCI, $T3_{noPCI}$ – TIMI-3 flow without PCI, $T3_{Res}$ – TIMI-3 flow with ST-segment resolution following PCI. *P < 0.001 vs. 6M-$T23_{reSTE}$, **p < 0.01 vs. 6M-$T23_{reSTE}$, ***p < 0.05 vs. $T23_{reSTE}$.*

$T2_{PCI}$ (by 0.1 ±9.0 ml/m²) patients, whereas it decreased in $T3_{Res}$ (by 4.2 ±7.2 ml/m²) and in $T3_{noPCI}$ (by 4.7 ±7.7 ml/m²) patients (for both $p < 0.05$ as compared with $T23_{reSTE}$) (Figure 3 D). Finally, after 6 months LVESVI was significantly higher in $T23_{reSTE}$ as compared with $T3_{Res}$ (13.8 ml/m², 95% CI: 5.8–21.9 ml/m²) and with $T3_{noPCI}$ (11.5 ml/m², 95% CI: 0.5–22.4 ml/m²) (Figure 3 C).

Clinical outcomes

The time of hospitalization and the number of patients with symptoms of heart failure in the NYHA scale ≥ 2 after 12 months were similar in all groups (Table I). In 12-month follow-up, there were no deaths, 2 (1.3%) patients had recurrent MI and 9 (5.8%) required hospitalization due to symptoms of heart failure. There were no significant intergroup differences (Table I).

Predictive value of reSTE

The multivariate models for the recovery of LV function and LV remodeling are shown in Table III. Independent variables identified as associated ($p < 0.2$) with dependent variables in the univariate model (Tables I, II) were included in the multivariate regression models. Moreover, significant correlations between independent variables including $LVEF_{2D}$ and infarct territory ($r = 0.31$, $p < 0.001$), $LVEF_{2D}$ and the incidence of reSTE ($r = 0.28$, $p < 0.001$), $LVEDVI_{2D}$ and infarct territory ($r = 0.19$, $p = 0.011$) and $LVESVI_{2D}$ and infarct territory ($r = 0.40$, $p < 0.001$) were found. In final multivariate models, reSTE and baseline LVEF independently affected changes of LVEF with variance of $R^2 = 0.31$ ($p = 0.002$) (Table III), whereas only reSTE independently predicted changes of both LVEDVI and LVESVI with variance of $R^2 = 0.35$ and $R^2 = 0.36$, respectively ($p < 0.001$ for both).

Discussion

To our knowledge, the current study constitutes one of the infrequent reports regarding clinical relevance of reSTE following primary PCI in patients with spontaneously recanalized IRA. We demonstrated that reSTE was independently associated with both lack of improvement of global and infarct-related contractility and increase of LV volume in 6-month observation. Moreover, the procedure accompanied by reSTE was related to worse LV function and structure recovery as compared with patients with subsequent ST-segment resolution following PCI. Our findings provide evidence that myocardial injury reflected by reSTE is associated with the loss of beneficial effects of spontaneous IRA reperfusion on further LV remodeling.

Table III. Independent predictors of changes of LVEF, LVEDVI and LVESVI

Dependent variable	Independent variable	Univariate model			Multivariate model		
		Coefficient B	*P*-value	95% CI for coefficient B	Coefficient B	*P*-value	95% CI for coefficient B
Delta LVEF $R^2 = 0.31$, $p < 0.001$	reSTE (Yes/No)	–3.73	0.001	–6.00– –1.47	–4.35	< 0.001	–6.71– –1.99
	$LVEF_{2D}$ (per 1%)	–0.09	0.17	–0.17–0.07	–0.11	0.047	–0.22– –0.01
Delta LVEDVI $R^2 = 0.35$, $p < 0.001$	reSTE (Yes/No)	9.25	< 0.001	5.06–13.44	8.58	< 0.001	4.32–12.84
	LAD as IRA (Yes/No)	4.09	0.023	0.57–7.60	2.70	0.122	–0.73–6.12
Delta LVESVI $R^2 = 0.36$, $p < 0.001$	reSTE (Yes/No)	7.47	< 0.001	4.14–10.81	7.08	< 0.001	3.63–10.54
	LAD as IRA (Yes/No)	2.29	0.112	–0.54–5.11	0.95	0.514	–1.91–3.81
	$LVESVI_{2D}$ (per 1 ml/m^2)	0.09	0.162	–0.04–0.22	0.03	0.660	–0.10–0.16

IRA – infarct-related artery, LAD – left anterior descending artery, LVEF – left ventricular ejection fraction, LVEDVI – left ventricular end-diastolic volume index, LVESVI – left ventricular end-systolic volume index, reSTE – ST-segment re-elevation following PCI, 2D – measurements performed two days after PCI, R^2 – variance.

Our study also provides some evidence regarding the mechanism of reSTE. We have shown that angiographically visible distal embolization occurred in around 10% of patients with reSTE and occurred in a similar proportion in the remaining analyzed groups and other studies [19, 20]. Moreover, we found no significantly different distribution of TIMI thrombus grades in the compared groups, which suggests a lack of unquestionable association between reSTE and angiographically evident residual epicardial thrombus. Simultaneously, the results of our study emphasize the role of impaired microvascular perfusion in patients with reSTE. Incomplete TMPG-0/1 reperfusion after PCI was the most frequent in patients with reSTE. Moreover, in about 30% of patients with reSTE, myocardial perfusion was deteriorated from baseline TMPG-2/3 to 0/1 following PCI. This observation is consistent with our previous findings [21] and reports on microvascular injury assessed with cardiac magnetic resonance in patients with reSTE [12]. It might be speculated that during balloon inflation, the components of ruptured plaque containing connective tissue elements and subendothelial matrix proteins are exposed to the bloodstream and initialize platelet activation, thrombin generation followed by thrombus formation and promote vasospasm. Prothrombotic material protruding through the struts during stent implantation together with the already present intraluminal thrombus may lead to epicardial blood flow deterioration [22] and microvascular plugging [23]. Identification of the key factor involved in myocardial perfusion deterioration in patients with reSTE after spontaneous reperfusion requires further studies with the use of optical coherent tomography. Interestingly, in our study reSTE was associated with a similar systemic inflammatory response as measured by white blood cell count and hsCRP level. In contrast, a previous study reported that CRP concentration in STEMI patients with reSTE was higher, reflecting more intensified reperfusion injury [11].

In our group, unfavorable echocardiographic findings related to reSTE did not affect the duration of hospitalization or 1-year clinical outcomes. Research conducted so far regarding the impact of reSTE following PCI on LV function concerns mainly patients with initially occluded IRA. In a small observational study including 41 STEMI patients, Weaver *et al.* [12] found a significant relationship between reSTE and the extent of myocardial injury assessed by contrast-enhanced cardiac magnetic resonance. In turn, Okuda *et al.* [11] revealed that reSTE in patients who underwent both primary PCI and thrombolysis was associated with larger infarct size and poorer LVEF and LVEDVI at 6 months. A recently published subanalysis of the large randomized CIRCUS trial [9] showed no unfavorable effects of reSTE on LV contractility and remodeling at 1-year follow-up. Patients with and without the reSTE primary endpoint composed of all-cause mortality and heart failure were found with similar proportion (19.2 vs. 19.8%, $p = 0.887$) at 1 year. It should be emphasized that only patients with a large anterior wall infarction were included in this study, which may mask the effects associated with reSTE. Our findings suggest that the incidence of reSTE following PCI in a patent IRA produces the risk of LVEF deterioration on average by 4.4% and the risk of LVEDVI or LVESVI increase by 7 or 8.5 ml/m^2, respectively.

In the context of high prevalence of impaired tissue-level microvascular perfusion in patients with reSTE following PCI in a spontaneously reperfused IRA and its unfavorable long-term LV consequences, implementation of appropriate preventive and therapeutic strategies seems to be a key goal. As was documented in the DEFER-STEMI study [24], deferred PCI in selected STEMI patients reduced no-reflow, distal embolization and other thrombotic complications as compared with immediate stenting. However, other studies provided considerably less optimistic conclusions. In DANAMI 3-DEFER [25], deferred PCI did not reduce the occurrence of death,

heart failure, MI or subsequent revascularization as compared with conventional PCI. Moreover, routine deferred stenting was associated with a higher frequency of target vessel revascularization. A recent meta-analysis summarizing prior randomized trials showed that the deferred-stenting strategy did not reduce the occurrence of no-reflow, death, MI or repeated revascularization despite improved LVEF in long-term observation [26]. Based on these findings, routine deferred stenting is not recommended in the current European Society of Cardiology (ESC) guidelines [27]. Another intensively investigated strategy is thrombus aspiration. The two recent randomized trials TASTE [28] and TOTAL [29] showed no clinical benefit of routine thrombus aspiration in STEMI patients, suggesting possible increased risk of stroke. A meta-analysis of the trials TAPAS [30], TASTE and TOTAL finally confirmed that routine thrombus aspiration in STEMI patients did not improve clinical outcomes [31]. This meta-analysis, however, highlighted the group with high thrombus burden in which use of aspiration thrombectomy was associated with lower cardiovascular mortality (HR = 0.80, 95% CI: 0.65–0.98) but also with increased risk of stroke or transient ischemic attack (OR = 1.56, 95% CI: 1.02–2.42). Based on these data, routine thrombus aspiration is also not recommended in current ESC guidelines but in cases of large residual thrombus burden, after opening of the IRA, thrombus aspiration may be considered [27]. The current guidelines of ESC, however, permit the application of IIb/IIIa inhibitors as bailout therapy in the case of large thrombus, slow- or no-reflow, and other thrombotic complications [27]. Furthermore, a recently published study demonstrated the beneficial effect of early intracoronary administration of nicorandil on microcirculation damage [32]. Other strategies aimed at reduction of reperfusion injury, including cyclosporine, which activates mitochondrial potassium channels, failed to improve clinical outcomes and prevent LV remodeling [33], despite previous experimental studies indicating its beneficial effects on infarct size and microvascular obstruction [34].

Our study has several limitations. First, the sample size and the number of clinical adverse events are not large enough to draw clinical conclusions. Second, left ventricular remodeling was assessed by echocardiography, although cardiac magnetic resonance is a more accurate and objective method. Third, all participants were meticulously studied with serial ECGs only in the periprocedural period. Subsequent ECGs, including 60–90 min after PCI, were not prospectively recorded. Fourth, platelet reactivity [35], fibrin clot properties [36] and intracoronary thrombi [37] were not analyzed. However, these laboratory tests were beyond the main scope of this study.

Conclusions

ReSTE following PCI in patients with spontaneously recanalized IRA is associated with a lack of improvement of LV contractility and subsequent LV remodeling and therefore abolishes the beneficial effects of spontaneous reperfusion. Further studies on therapies to prevent reSTE following primary PCI are necessary.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

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Original paper

Acute coronary syndromes and atherosclerotic plaque burden distribution in coronary arteries among patients with valvular heart disease (BIA-WAD registry)

Łukasz Kuźma[1], Hanna Bachórzewska-Gajewska[1,2], Marcin Kożuch[1], Krzysztof Struniawski[1], Szymon Pogorzelski[1], Tomasz Hirnle[3], Sławomir Dobrzycki[1]

[1]Department of Invasive Cardiology, Medical University of Bialystok, Bialystok, Poland
[2]Department of Clinical Medicine, Medical University of Bialystok, Bialystok, Poland
[3]Department of Cardiac Surgery, Medical University of Bialystok, Bialystok, Poland

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Abstract

Introduction: Valvular heart diseases (VHD) are a significant problem in the Polish population. Coexistence of coronary artery disease (CAD) in patients with VHD increases the risk of death and affects the further therapeutic strategy.

Aim: Analysis of atherosclerotic plaque burden distribution in coronary arteries and long-term prognosis among patients with VHD.

Material and methods: Inclusion criteria were met by 1025 patients with moderate and severe VHD. Mean observation time was 2528 ±1454 days.

Results: Severe aortic valve stenosis (AVS) occurred in 28.2%, severe mitral valve insufficiency (MVI) in 20%. CAD with severe angiographic stenoses was noted in 42.3% (n = 434). Among patients with severe MVI, CAD was noted in 47.1% of cases, and prior acute coronary syndromes (ACS) in 27.1% of patients (n = 58). In severe AVS patients, significant angiographic atherosclerotic changes were observed in 29.6% (n = 86), and prior ACS in 7.6% (n = 22) of patients. During the observation 52.7% of patients died, including 62.9% of patients with severe MVI and 51.6% of those with severe AVS. Age (OR = 1.038; 95% CI: 1.005–1.072; p = 0.022) and coexisting aortic valve insufficiency (AVI) (OR = 2.39, 95% CI: 5.370–11.065, p = 0.035) increased the mortality rate.

Conclusions: Severe AVS is starting to be the most prevalent VHD. CAD is one of the most significant factors deteriorating prognosis of patients with VHD. AVI and age were significant risk factors for mortality. The worst prognosis was observed in severe MVI, which may result from more frequent occurrence of CAD in this group. A lesser burden of CAD and ACS in the group of patients with severe AVS did not affect survival.

Key words: aortic stenosis, mitral insufficiency, coronary artery disease, myocardial infarction.

Summary

Coexistence of coronary artery disease (CAD) in patients with valvular heart diseases (VHD) increases the risk of death and affects the further therapeutic strategy. Patients with mitral valve insufficiency are most burdened with CAD and prior acute coronary syndrome. Coexistence of coronary artery disease in patients with VHD increases the risk of death and has an influence on the choice of therapeutic strategy.

Introduction

Cardiovascular diseases are responsible for 46% of deaths in the Polish population despite the constantly developing progress in medical sciences [1]. The most common cardiovascular disorders are coronary artery disease, including acute coronary syndromes, and valvular heart disease (VHD), the frequency of which has been growing continuously in recent years. The greatest increase in prevelance is observed for aortic stenosis (AVS), whereas the number of mitral stenosis cases (MVS) has dropped significantly [2, 3]. This association was reported

Corresponding author:
Łukasz Kuźma MD, PhD, Department of Invasive Cardiology, Medical University of Bialystok, 24 A Sklodowskiej-Curie St, 15-276 Bialystok, Poland, phone: +48 85 831 84 96, e-mail: kuzma.lukasz@gmail.com
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in both national and global registries. The European Registry of Valvular Heart Diseases contains records of 5001 patients from 92 centers from 25 countries. The analysis includes patients in moderate and severe grading of valvular heart disease. The most frequently occurring disease is aortic stenosis (33.9%) and mitral insufficiency (MVI) (24.8%). In the largest Polish registry, WAD-POL, containing 1663 patients; aortic stenosis was found in 27.5%, and mitral regurgitation in 38.0% of the population [4]. The reason for the prevalence of aortic valve stenosis patients stems from the degenerative etiology of the disease [5]. Demographic analyses considering dynamic aging of the Polish society show that there will be nearly 200,000 more elderly in the third decade of the 21st century [6]. The population's longer survival rate corresponds with an increased percentage of valvular heart diseases of degenerative etiology and worse prognosis of those with coexisting diseases such as coronary artery disease (CAD) or myocardial infarction. Not only does coronary artery disease have similar risk factors as aortic stenosis, but also it is of degenerative and atherosclerotic etiology. Therefore, it is not surprising that advanced coronary artery disease often coexists with valvular heart diseases. Moreover, such patients have a history of acute coronary syndrome (ACS), which has a particular influence on the choice of therapeutic strategy.

Until the beginning of the 21st century, conventional cardiosurgical methods such as valve replacement (VR) were a standard treatment for patients with valvular heart diseases, yet only within the last 10 years have they gradually been substituted by low-invasive techniques. The most widespread procedure is transcatheter aortic valve implantation (TAVI), while a non-surgical approach for mitral regurgitation treatment is also being introduced [7–9]. These methods are particularly indicated in high-risk patients, providing better prognosis.

Taking into consideration insufficient data of patients with coronary artery disease and valvular heart disease, this study provides information of mentioned subjects.

Aim

Analysis of atherosclerotic plaque burden distribution in coronary arteries and long-term prognosis among patients with valvular heart disease.

Material and methods

Medical records of 12 954 patients hospitalized in the Department of Invasive Cardiology of the Medical University of Bialystok in 2006–2010 were analyzed. 1025 patients with moderate and severe valvular heart disease met the inclusion criteria.

Assignment of patients to particular groups was based on the ESC guidelines for the management of valvular heart disease published in 2012 [5]. Prior cardiosurgical valve replacement was the exclusion criterion. The set of variables subjected to interpretation consisted of demographic data, medical history, coronary angiography, percutaneous and surgical treatment. Follow-up study included the analysis of medical documentation of the Cardiosurgery Department and the Invasive Cardiology Department of the Medical University of Bialystok, phone call interview and provided information on the duration and type of procedure performed. There was no follow-up concerning the aforementioned data in 26 (2.5%) cases. All-cause mortality was collected from the Polish Ministry of Digital Affairs on 09.11.2018. The mean follow-up period from the onset to the procedure was 360 ±796 days, and that from the cardiosurgical procedure to death was 2480 ±1445 days. Complete follow-up duration was 2528 ±1454 days.

The study was approved by the Local Bioethics Committee of the Medical University of Bialystok no. R-I-002/20/2013.

Statistical analysis

Distribution of the variables was assessed with the Kolmogorov-Smirnov test. Student's *t*-test was applied for comparative analysis of continuous variables. Evaluation of differences between dichotomic variables was performed using the χ^2 test. The Wald test for logistic regression was used to determine mortality risk factors. $P < 0.05$ was considered statistically significant.

Results

One hundred and twenty-five patients with moderate and severe valvular heart disease were included in the study. The mean age of the study population was 67.1 ±10.3 years, mostly male (56.6%) (Table I). Aortic valve stenosis was the most common defect and occurred in 28.2% of studied subjects (n = 289), while severe mitral regurgitation was found in 210 (20.5%) patients. Severe aortic regurgitation and severe aortic stenosis occurred in a similar percentage and affected 8% of patients. The most prevalent severe, combined valve disease was coexisting aortic valve stenosis and mitral valve insufficiency (n = 13). The remaining severe multivalve disorders were found in single cases (Tables I and II).

Coronary artery disease occurred in 73.4% of the subjects (n = 752), significant angiographic stenoses were noted in 42.3% (n = 434) of patients, including the left anterior descending artery (LAD) 24.9% (n = 256), left circumflex artery (Cx) 23.0% (n = 236) and right coronary artery (RCA) 22.9% (n = 235). Significant atherosclerotic lesions in the left main coronary artery (LM) were observed in 4.1% of patients (n = 42) (Figure 1). In the group with severe MVI, coronary artery disease was found in 47.1% of cases, and prior acute coronary syndrome in 27.1% of patients (n = 58). In the group with severe AVS, significant angiographic atherosclerotic changes were observed in 29.6% (n = 86) and prior ACS in 7.6%

Table I. Valvular heart disease and coronary artery disease in the analyzed population

Parameter	All patients (*N* = 1025)	Patients with aortic stenosis (*N* = 411)	Patients with aortic insufficiency (*N* = 194)	Patients with mitral stenosis (*N* = 74)	Patients with mitral insufficiency (*N* = 531)
Age	67.1 (SD = 10.1)	68.0 (SD = 10.1)	64.1 (SD = 10.4)	64.7 (SD = 9.1)	67.2 (SD = 10.1)
Male	56.7% (*N* = 579)	58.2% (*N* = 239)	64.6% (*N* = 122)	24.3% (*N* = 18)	56.7% (*N* = 301)
Moderate VHD	60.9 % (*N* = 624)	29.7% (*N* = 122)	79.9% (*N* = 155)	55.4% (*N* = 41)	60.5% (*N* = 321)
Severe VHD	53.6% (*N* = 549)	70.3% (*N* = 289)	20.6% (*N* = 39)	44.6% (*N* = 33)	39.5% (*N* = 210)
Isolated severe VHD	42.0% (*N* = 431)	49.4% (*N* = 203)	13.4% (*N* = 26)	21.6% (*N* = 16)	31.6% (*N* = 168)
Multiple VHD	25.8% (*N* = 264)	20.0% (*N* = 82)	35.6% (*N* = 69)	37.8% (*N* = 28)	23.6% (*N* = 125)
CAD without significant stenosis	31.0% (*N* = 318)	31.1% (*N* = 128)	30.7% (*N* = 58)	39.2% (*N* = 29)	21.5% (*N* = 114)
CAD with significant stenosis	42.4% (*N* = 434)	36.5% (*N* = 150)	34.4% (*N* = 65)	17.6% (*N* = 13)	50.1% (*N* = 266)
SVD	14.4% (*N* = 147)	13.9% (*N* = 57)	14.8% (*N* = 28)	9.5% (*N* = 7)	15.3% (*N* = 81)
MVD	28.0% (*N* = 287)	22.6% (*N* = 93)	19.6% (*N* = 37)	8.1% (*N* = 6)	34.8% (*N* = 185)
ACS	21.6% (*N* = 223)	10.7% (*N* = 44)	13.2% (*N* = 25)	5.4% (*N* = 4)	31.6% (*N* = 168)
STEMI	9.4% (*N* = 96)	6.8% (*N* = 28)	8.5% (*N* = 16)	2.7% (*N* = 2)	17.3% (*N* = 92)
NSTEMI	12.4% (*N* = 127)	3.9% (*N* = 16)	4.8% (*N* = 9)	2.7% (*N* = 2)	14.3% (*N* = 76)
Death	52.7% (*N* = 540)	54.0% (*N* = 222)	43.4% (*N* = 82)	43.2% (*N* = 32)	57.4% (*N* = 305)

ACS – acute coronary syndrome, CAD – coronary artery disease, MVD – multi-vessel disease, NSTEMI – non-ST elevation myocardial infarction, SVD – single-vessel disease, STEMI – ST elevation myocardial infarction, VHD – valvular heart disease.

of patients (*n* = 22) (Table II). The percutaneous coronary intervention (PCI) was performed in 22.9% of patients (*n* = 227), with PCI of Cx in 13.2% (*n* = 136), and PCI of LAD in 11.2% (Table III).

Fifty-four percent of patients underwent cardiac valvular surgery (*n* = 539). Thirty percent of these procedures were combined with coronary artery bypass grafting. TAVI was performed in 3.2% of severe aortic stenosis patients. Seventy-four subjects underwent PCI during follow-up (7.4%) (Table IV).

52.7% (*n* = 540) of patients died during follow-up; 62.9% of them (*n* = 132) had severe mitral regurgitation, 78.6% (*n* = 33) significant stenosis of the left main coronary artery and 72.4% (*n* = 92) had a history of non-ST elevation myocardial infarction. 43.6% of patients who underwent cardiac surgery died compared to 68% who did not have surgery. Interestingly, 17 deaths were reported within the first 14 days of inclusion in the study, 6 of which concerned subjects who underwent surgery (Figure 2).

Multivariate regression analysis – the Wald test – determined aortic regurgitation as the most significant risk factor for mortality (Nagelkerke R^2 = 0.759; overall prediction rate = 90.1%). AVI increased the mortality rate 2.4-fold (OR = 2.39; 95% CI: 5.370–11.065; p = 0.035). An increase of age by 1 year raised the risk of mortality by 0.4% (OR = 1.038; 95% CI: 1.005–1.072; p = 0.022). The adjusted hazard ratio for death with follow-up prolongation of 1 year was 2.8 (OR = 2.815; 95% CI: 2.247–3.526; p = 0.001) and coronary artery disease without diagonal stenosis was 0.204 (OR = 0.204; 95% CI: 0.075–0.561; p = 0.002).

Discussion

Distribution of gender in the population of the Podlaskie Voivodeship has been unchanged for years. In 2016, men constituted 48.7% of the Podlaskie Voivodeship's population [10]. In the studied group, the percentage is higher, 56.6% (*n* = 579), which could be attributed to the fact that male sex is an independent risk factor for the development of degenerative valvular heart disease, coronary artery disease and acute coronary syndrome (Table I). The mean age of the study subjects was 67.1 ±10.1 years, which corresponds to the contemporary medical data, according to which, with the declining rheumatoid etiology of the disease the dominant causes of valvular disease are the degenerative processes associated with old age [11]. This is confirmed by comparative analysis of patients with individual valvular diseases; patients with severe aortic stenosis were older than other patients, 68.1 ±10.4 vs. 66.2 ±9.9, $p < 0.001$, while patients with mitral stenosis, the dominant background of which is rheumatoid processes, were significantly younger, 62.0 ±9.4 vs. 67.0 ±10.1, p = 0.01. A significantly lower percentage of men was also present in this group, 36.0% (*n* = 9) vs. 57.6% (*n* = 570), p = 0.006 (Table II).

Changing etiology contributes to a different epidemiology of valvular heart diseases. In the studied group, mi-

Table II. Coronary artery disease in patients with severe valvular heart disease

Parameter	Patients with severe VHD (*N* = 549)	Patients with multiple severe AVS/MVI VHD (*N* = 14)	Other patients with severe VHD (*N* = 260)	*P*-value	Patients with severe AVS (*N* = 289)	Other patients with severe VHD (*N* = 260)	*P*-value	Patients with severe AVI (*N* = 39)	Other patients with severe VHD (*N* = 510)	*P*-value	Patients with severe MVS (*N* = 33)	Other patients with severe VHD (*N* = 516)	*P*-value	Patients with severe MVI (*N* = 210)	Other patients with severe VHD (*N* = 339)	*P*-value
Male	53.5% (*N* = 293)	85.6% (*N* = 12)	52.6% (*N* = 281)	0.005	53.6% (*N* = 155)	53.1% (*N* = 138)	0.5	74.4% (*N* = 29)	53.5% (*N* = 293)	0.004	36.0% (*N* = 9)	55.0% (*N* = 284)	< 0.001	61.2% (*N* = 104)	55.7% (*N* = 189)	0.5
Age	67.0 (SD = 10.2)	71.7 (SD = 10.4)	66.4 (SD = 10.1)	0.034	68.1 (SD = 10.4)	66.2 (SD = 9.9)	< 0.001	58.0 (SD = 9.6)	67.0 (SD = 9.7)	< 0.001	62.0 (SD = 9.4)	67.0 (SD = 10.1)	0.006	67.3 (SD = 9.1)	66.0 (SD = 10,3)	0.4
CAD	30.0% (*N* = 167)	35.8% (*N* = 5)	30.3% (*N* = 162)	0.3	29.6% (*N* = 86)	31.1% (*N* = 81)	0.1	20.0% (*N* = 8)	31.2% (*N* = 159)	0.3	6.1% (*N* = 2)	31.9% (*N* = 165)	0.018	47.1% (*N* = 99)	20.1% (*N* = 68)	< 0.001
SVD	13.1% (*N* = 72)	0.0% (*N* = 0)	13.5% (*N* = 72)	< 0.001	12.4% (*N* = 36)	13.8% (*N* = 36)	1.0	15.6% (*N* = 6)	12.9% (*N* = 66)	0.7	6.1% (*N* = 2)	13,6% (*N* = 70)	0.1	13.8% (*N* = 29)	12.7% (*N* = 43)	0.7
MVD	21.7% (*N* = 119)	21.4% (*N* = 3)	21.7% (*N* = 116)	1.0	17.3% (*N* = 50)	26.5% (*N* = 69)	0.008	8.0% (*N* = 2)	22.9% (*N* = 117)	< 0.001	0.0% (*N* = 0)	23.0% (*N* = 119)	< 0.001	33.4% (*N* = 70)	14.5% (*N* = 49)	< 0.001
ACS	15.1% (*N* = 83)	0.0% (*N* = 0)	15.5% (*N* = 83)	0.1	7.6% (*N* = 22)	23.5% (*N* = 61)	< 0.001	7.7% (*N* = 3)	15.7% (*N* = 80)	0.1	0.0% (*N* = 0)	16.1% (*N* = 83)	< 0.001	27.1% (*N* = 58)	7.4% (*N* = 25)	< 0.001
STEMI	6.6% (*N* = 36)	0.0% (*N* = 0)	6.7% (*N* = 36)	< 0.001	2.4% (*N* = 7)	11.1% (*N* = 29)	< 0.001	5.1% (*N* = 2)	6.7% (*N* = 34)	0.7	0.0% (*N* = 0)	6.9% (*N* = 36)	< 0.001	12.9% (*N* = 27)	2.7% (*N* = 9)	< 0.001
NSTEMI	8.6% (*N* = 47))	0.0% (*N* = 0)	8.8% (*N* = 47)	0.2	5.2% (*N* = 15)	12.3% (*N* = 32)	< 0.001	2.6% (*N* = 1)	9.0% (*N* = 46)	0.027	0.0% (*N* = 0)	9.1% (*N* = 47))	< 0.001	14.7% (*N* = 31)	4.7% (*N* = 16)	< 0.001
Death	53.3% (*N* = 292)	65.3% (*N* = 9)	52.9% (*N* = 281)	0.4	51.6% (*N* = 149)	55.1% (*N* = 142)	0.3	30.7% (*N* = 12)	54.9% (*N* = 280)	0.003	42.4% (*N* = 14)	53.9% (*N* = 278)	0.2	62.9% (*N* = 132)	47.2% (*N* = 160)	< 0.001

AVI – aortic valve insufficiency, AVS – aortic valve stenosis, CAD – coronary artery disease, MVI – mitral valve insufficiency, MVS – mitral valve stenosis, NSTEMI – non-ST elevation myocardial infarction, SVD – single-vessel disease, MVD – multi-vessel disease, STEMI – ST elevation myocardial infarction, VHD – valvular heart disease.

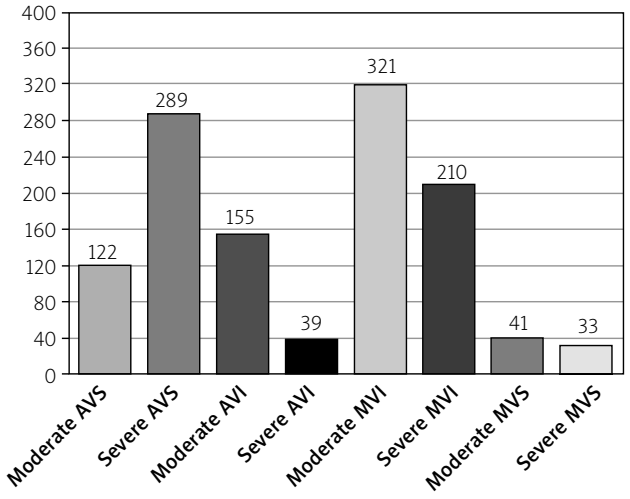

Figure 1. Valvular heart diseases in the study population

tral regurgitation was present in nearly 50% of patients (n = 531). The most prevalent severe valvular disease was aortic stenosis, which occurred in 28.2% of the subjects (n = 289). Similar findings have also been reported in other European studies. In the Euro Heart Survey on Valvular Heart Disease registry, which focused on moderate and severe grades of valvular heart diseases, aortic disease occurred in 44% of patients, with aortic valve stenosis accounting for 34% of cases. Mitral valve regurgitation occurred in 25% of patients, and combined mitral disease in 34% [3]. The WadPol Registry of Heart Diseases, the largest Polish registry of valvular diseases, includes the history of 1663 patients with acquired valvular heart disease in 2007–2008. The most prevalent one was mitral regurgitation, 38% of cases, and aortic valve stenosis was found in 27.5% of patients [4]. The analysis of the valvular diseases etiology revealed the dominance of degenerative over rheumatoid etiology of aortic valve diseases, 50.2% vs. 30.6%. Mitral valve disease presented a similar etiology pattern, with a degenerative background in 41.2% of patients, and rheumatoid etiology in every third patient (30.7%).

In the analyzed group, coronary artery disease occurred in 74.4% (n = 752), whereas significant angiographic stenoses were observed in 42.3% (n = 434) of patients. The lesions were most commonly found in left anterior descending artery (24.9%, n = 256), followed by circumflex artery 23.0% (n = 236) and right coronary artery 22.9% (n = 235). Left main coronary artery was the least affected, 4.1% (n = 42) (Table III). Mentioned findings of the atherosclerotic changes in epicardial coronary arteries are similar to the reports in the current literature. The majority of publications on the topography of coronary artery lesions focus on the greater involvement of the left coronary artery in comparison to the right, which is confirmed by numerous autopsy and angiographic studies. LAD is more often affected by atherosclerotic changes and calcifications than RCA and Cx [12]. Similar data are presented in studies evaluating coronary artery calcium score, confirming the predominance of atherosclerosis in LAD, followed by the RCA, Cx and LM [13]. In a retrospective analysis of over 13 000 coronarographies, an isolated change in RCA was found in 6.5% of cases, while a similar lesion was present over five times more frequently in the left artery (34.7%) [14–17]. Enrico *et al.* in a study of 73,282 deposits in angio-CT scans of coronary arteries presented similar results by showing that nearly half of them were located in the LAD, and every third in RCA and circumflex artery [18–20]. The analysis also showed that patients with severe aortic stenosis were less often diagnosed with coronary artery disease, which concerned both patients with ischemic heart disease with and without significant atherosclerotic lesions, as well as with multi-vessel disease, 17.3% (n = 50) vs. 26.5% (n = 69), $p < 0.001$ (including prior STEMI and NSTEMI), 7.6% (n = 22) vs. 23.5% (n = 61), $p < 0.001$ (Table II). Significant atherosclerotic changes in epicardial coronary arteries were less common in all coronary arteries in comparison to the group with other valve defects, whereas the majority of lesions were found in LAD, 17.6% (n = 51). The lower prevalence of coronary disease is also reflected in the analysis of invasive treatment. 9.4% of patients with severe aortic stenosis underwent PCI in comparison to 18.8% of patients with other valvular diseases ($p < 0.001$) (Table III). The lower number of PCIs in this group stemmed from the need for valvular surgery, which was combined with surgical revascularization. Valvular cardiac surgery was performed in 81.3% of patients with severe aortic stenosis and only in 38.4% of patients with other valvular diseases ($p < 0.001$) (Table IV). These results contradict the hypothesis of a similar pathomechanism and similar risk factors of coronary disease and aortic valve stenosis.

Patients with severe aortic regurgitation had lower prevalence of coronary artery disease with significant atherosclerotic stenoses (20.5% vs. 35.7%, $p < 0.03$), and acute coronary syndrome, 7.7% (n = 3) vs. 15.7% (n = 80), p = 0.1. Small size of the group and low prevalence of coronary artery disease resulted in a low number of percutaneous coronary interventions and combined procedures (Table IV).

Similar observations were made for the group of patients with severe mitral stenosis. A moderate grade of the disease occurred in only 4% of patients (n = 41) (Figure 1). This group was significantly younger in comparison with other patients, and it was also the only group with the majority of women, with the coexistence of coronary artery disease and acute coronary syndrome noted in individual cases.

Patients with mitral valve insufficiency made up 52% of the study population, and the subgroup of patients

Table III. Angiographic characteristics and percutaneous coronary interventions in patients with severe valvular heart disease

Parameter	Patients with severe VHD (*N* = 549)	Patients with multiple severe AVS/MVI VHD (*N* = 14)	Other patients with severe VHD (*N* = 260)	*P*-value	Patients with severe AVS (*N* = 289)	Other patients with severe VHD (*N* = 260)	*P*-value	Patients with severe AVI (*N* =39)	Other patients with severe VHD (*N* = 510)	*P*-value	Patients with severe MVS (*N* = 33)	Other patients with severe VHD (*N* = 516)	*P*-value	Patients with severe MVI (*N* = 210)	Other patients with severe VHD (*N* = 339)	*P*-value
CAD[1]	34.9% (*N* = 191)	21.4% (*N* = 3)	35.2% (*N* = 188)	0.6	29.6% (*N* = 86)	40.4% (*N* = 105)	0.021	20.5% (*N* = 8)	35.7% (*N* = 182)	0.03	6.1% (*N* = 2)	36.6% (*N* = 189)	< 0.001	47.1% (*N* = 99)	27.1% (*N* = 92)	< 0.001
PCI[2]	13.9% (*N* = 76)	0.0% (*N* = 0)	14.2% (*N* = 76)	< 0.001	9.4% (*N* = 27)	18.8% (*N* = 49)	0.006	2.6% (*N* = 1)	14.7% (*N* = 75)	< 0.001	3.0% (*N* = 1)	14.5% (*N* = 75)	< 0.001	22.8% (*N* = 48)	8.3% (*N* = 28)	< 0.001
LM[3]	3.1% (*N* = 17)	0.0% (*N* = 0)	3.2% (*N* = 17)	< 0.001	2.8% (*N* = 8)	3.5% (*N* = 9)	0.8	2.5% (*N* = 1)	3.1% (*N* = 16)	0.8	0.0% (*N* = 0)	2.7% (*N* = 17)	< 0.001	3.8% (*N* = 8)	2.7% (*N* = 9)	0.5
PCI LM[4]	0.3% (*N* = 3)	0.0% (*N* = 0)	0.5% (*N* = 3)	0.1	0.7% (*N* = 2)	0.4% (*N* = 1)	0.6	0.0% (*N* = 0)	0.5% (*N* = 3)	0.1	0.0% (*N* = 0)	0.5% (*N* = 3)	0.1	0.05% (*N* = 1)	0.6% (*N* = 2)	0.9
LAD	19.8% (*N* = 109)	14.3% (*N* = 2)	20.0% (*N* = 107)	0.6	17.6% (*N* = 51)	22.3% (*N* = 58)	0.2	10.0% (*N* = 4)	20.6% (*N* = 105)	0.1	0.0% (*N* = 0)	21.1% (*N* = 109)	< 0.001	26.7% (*N* = 56)	15.6% (*N* = 53)	0.003
PCI LAD	6.6% (*N* = 36)	0.0% (*N* = 0)	6.7% (*N* = 36)	< 0.001	5.9% (*N* = 17)	7.3% (*N* = 19)	0.7	0.0% (*N* = 0)	7.1% (*N* = 36)	< 0.001	0.0% (*N* = 0)	6.9% (*N* = 36)	< 0.001	9.1% (*N* = 19)	5.0% (*N* = 17)	0.1
RCA	17.0% (*N* = 93)	21.4% (*N* = 3)	16.9% (*N* = 90)	0.7	14.8% (*N* = 40)	20.4% (*N* = 53)	0.028	5.0% (*N* = 2)	17.8% (*N* = 91)	0.002	3.0% (*N* = 1)	17.9% (*N* = 92)	< 0.001	25.7% (*N* = 54)	11.5% (*N* = 39)	< 0.001
PCI RCA	4.9% (*N* = 27)	0.0% (*N* = 0)	5.1% (*N* = 27)	< 0.001	3.4% (*N* = 10)	6.5% (*N* = 17)	0.2	0.0% (*N* = 0)	5.3% (*N* = 27)	< 0.001	3.3% (*N* = 1)	5.0% (*N* = 26)	0.5	8.1% (*N* = 17)	2.9% (*N* = 10)	0.017
Cx	18.7% (*N* = 103)	14.3% (*N* = 2)	18.9% (*N* = 101)	0.7	16.6% (*N* = 48)	21.2% (*N* = 55)	0.2	7.7% (*N* = 3)	19.6% (*N* = 100)	0.013	3.0% (*N* = 1)	19.8% (*N* = 102)	< 0.001	25.2% (*N* = 52)	15.0% (*N* = 51)	0.004
PCI Cx	9.3% (*N* = 51)	0.0% (*N* = 0)	9.6% (*N* = 51)	< 0.001	5.2% (*N* = 15)	13.8% (*N* = 36)	0.004	2.6% (*N* = 1)	9.8% (*N* = 50)	0.016	0.0% (*N* = 0)	9.8% (*N* = 51)	<0.001	16.6% (*N* = 35)	4.7% (*N* = 16)	< 0.001
Diag	7.5% (*N* = 41)	0.0% (*N* = 0)	7.7% (*N* = 41)	< 0.001	3.8% (*N* = 11)	11.5% (*N* = 30)	0.002	0.0% (*N* = 0)	8.0% (*N* = 41)	< 0.001	0.0% (*N* = 0)	7.5% (*N* = 41)	< 0.001	14.2% (*N* = 30)	3.2% (*N* = 11)	< 0.001
PCI Diag	1.5% (*N* = 8)	0.0% (*N* = 0)	1.5% (*N* = 8)	0.005	0.03% (*N* = 1)	2.7% (*N* = 7)	0.033	0.0% (*N* = 0)	1.6% (*N* = 8)	< 0.001	0.0% (*N* = 0)	1.6% (*N* = 8)	0.005	3.3% (*N* = 7)	0.3% (*N* = 1)	0.018
OM	7.7% (*N* = 42)	0.0% (*N* = 0)	7.9% (*N* = 42)	< 0.001	6.9% (*N* = 20)	5.7% (*N* = 15)	0.7	0.0% (*N* = 0)	8.1% (*N* = 42)	< 0.001	0.0% (*N* = 0)	7.9% (*N* = 42)	< 0.001	10.4% (*N* = 22)	5.9% (*N* = 20)	0.1
PCI OM	2.9% (*N* = 16)	0.0% (*N* = 0)	2.9% (*N* = 16)	< 0.001	2.0% (*N* = 6)	3.8% (*N* = 10)	0.3	0.0% (*N* = 0)	3.1% (*N* = 16)	< 0.001	0.0% (*N* = 0)	3.1% (*N* = 16)	< 0.001	4.8% (*N* = 10)	1.8% (*N* = 6)	0.1

[1]Number of patients with CAD, [2]number of patients undergoing PCI, [3]number of lesions, [4]number of procedures AVI – aortic valve insufficiency, AVS – aortic valve stenosis, CAD – coronary artery disease, Cx – circumflex artery, Diag – diagonal artery, LAD – left anterior descending, LM – left main artery, MVI – mitral valve insufficiency, MVS – mitral valve stenosis, OM – left marginal artery, RCA – right coronary artery, PCI – percutaneous coronary intervention, VHD – valvular heart disease.

Table IV. Percutaneous coronary interventions and cardiac procedures during follow-up

Parameter	All patients (*N* = 999)	Patients with severe AVS (*N* = 284)	Other patients (*N* = 715)	*P*-value	Patients with severe AVI (*N* = 38)	Other patients (*N* = 961)	*P*-value	Patients with severe MVS (*N* = 31)	Other patients (*N* = 968)	*P*-value	Patients with severe MVI (*N* = 206)	Other patients (*N* = 793)	*P*-value
PCI	7.4% (*N* = 74)	3.9% (*N* = 11)	8.8% (*N* = 63)	0.005	5.3% (*N* = 2)	7.5% (*N* = 72)	0.6	0.0% (*N* = 0)	7.6% (*N* = 74)	0.1	5.8% (*N* = 12)	9.1% (*N* = 72)	0.1
TAVI	0.9% (*N* = 9)	3.2% (*N* = 9)	0.0% (*N* = 0)	< 0.001	0.0% (*N* = 0)	0.9% (*N* = 9)	0.6	0.0% (*N* = 0)	0.9% (*N* = 9)	0.6	0.0% (*N* = 0)	1.1% (*N* = 9)	0.2
Surgery	54.0% (*N* = 539)	81.3% (*N* = 231)	43.1% (*N* = 308)	< 0.001	71.1% (*N* = 27)	53.3% (*N* = 512)	0.026	74.2% (*N* = 23)	53.3% (*N* = 516)	0.018	48.5% (*N* = 100)	55.4% (*N* = 439)	0.2
Percentage distribution of surgeries:													
VR	67.7%	82.3%	63.1%	0.038	92.9%	66.4%	0.6	85.7%	67.7%	0.1	70.5%	67.2%	0.3
VR + CABG	30.0%	18.7%	29.7%	0.4	7.1%	29.0%	0.5	14.3%	28.3%	0.9	26.5%	28.2%	0.6
Isolated CABG	3.3%	0.0%	7.2%	0.2	0.0%	4.6%	0.9	0.0%	4.5%	0.9	2.9%	4.6%	0.2

AVI – aortic valve insufficiency, AVS – aortic valve stenosis, CABG – coronary artery bypass grafting, PCI – percutaneous coronary intervention, RCA – right coronary artery, TAVI – transcatheter aortic valve implantation, VHD – valvular heart disease, VR – valve replacement.

with severe insufficiency accounted for 20.5% (Tables I and II). 61.17% of the group (n = 104) were men with mean age of 67.3 ±9.1 years. In this group coronary artery disease and acute coronary syndromes were significantly more prevalent, 27.1% (n = 58) vs. 7.4% (n = 25), $p < 0.005$, which could suggest more frequent ischemic etiology of mitral regurgitation in this group [21]. Angiographic images revealed that stenosis in LAD (26.7%, n = 56) and RCA (25.7%, n = 54) were the most frequent lesions. Diagonal artery stenosis was significantly more common than in other valvular diseases (14.2% (n = 30) vs. 3.2% (n = 11), $p < 0.001$) (Table III). Percutaneous coronary angioplasty was performed in 22.8% (n = 48) of patients with severe mitral valve insufficiency vs. 21.19% with other valvular diseases (Table III). 38.4% of patients with mitral valve insufficiency underwent cardiac surgery (group with other valvular diseases 49.6%, p = 0.035) with a combined procedure in every fourth patient.

Fifty-four percent of study subjects underwent surgery, with the highest prevalence of aortic stenosis (81.3%), which was significantly higher than in the rest of the group ($p < 0.001$). TAVI was performed in 9 cases; in single cases the procedure was combined with planned PCI (n = 6) (Table IV).

In the National Registry of Cardiac Surgery Procedures, the most common are aortic stenosis procedures and surgical revascularization, often in patients with coexisting mitral regurgitation. Multi-valve operations constituting over 10% of all cardiosurgical procedures [22]. Roques *et al.* reported 67.3% of aortic valve procedures and 41.8% of mitral valve operations. CABG was performed in 20% of cases. In the study of Ghosh two-valve procedures represented 10% of all cases, and 32% patients had a valvular operation combined with CABG [11, 14].

52.7% (n = 540) of patients with valvular heart disease died during the follow-up (n = 1025), regardless of the severity of the defect. The comparison of patients who survived and died found that higher mortality occurred in the group of patients with severe mitral regurgitation, 62.9% (n = 132) vs. 37.1% (n = 78), $p < 0.001$. Patients who died more often had significant stenoses in coronary arteries and acute coronary syndromes. Such interdependence was not observed in case of non-significant coronary artery lesions. The independent mortality risk factors were: age (OR = 1.038; 95% CI: 1.005–1.072; p = 0.022) and aortic regurgitation (OR = 2.39, 95% CI: 5.370–11.065; p = 0.035). In the current literature mortality risk factors in patients with valvular heart disease are: age, type and stage of progression of the valvular defect, low ejection fraction of the left ventricle, coexistence of coronary artery disease, high NYHA class, hypertension, diabetes, chronic kidney disease and pulmonary hypertension. Perioperative risk in patients with valvular heart disease increases with the necessity of additional

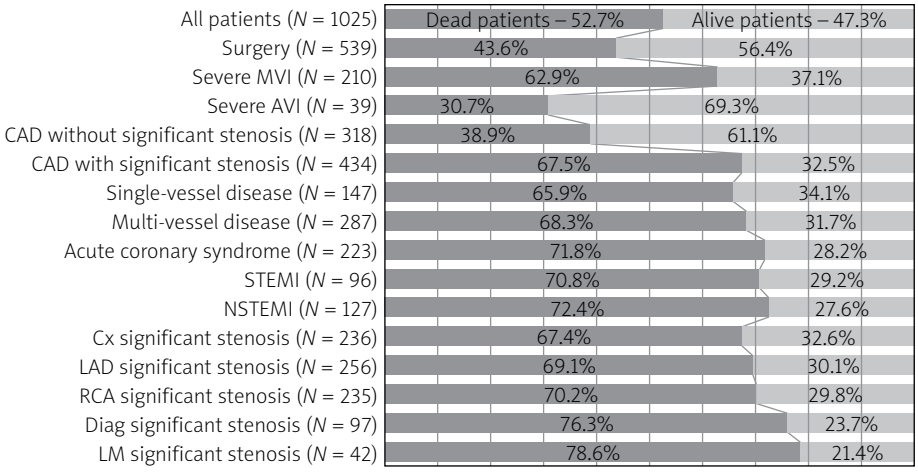

Figure 2. Comparison of dead and alive patients (only significant differences presented, $p < 0.05$)

AVI – aortic valve insufficiency, CAD – coronary artery disease, Cx – circumflex artery, Diag – diagonal artery, LAD – left anterior descending, LM – left main artery, NSTEMI – non-ST elevation myocardial infarction, MVI – mitral valve insufficiency, STEMI – ST elevation myocardial infarction, RCA – right coronary artery.

valve repair and surgical myocardial revascularization. The time of qualification for the procedure, before the development of myocardial dysfunction and pulmonary hypertension, is crucial in the prognosis of these patients [15–17].

During the follow-up 43.6% of patients after cardiac surgery died; 2.46% of subjects died within the first 14 days after the operation. The highest mortality rate affected patients with multiple valve disease, 65.3%. Those results were similar to the data presented in the literature. According to the ESC EuroHeart registry, periprocedural mortality in single valve procedures is 0.9–3.9%, whereas in multivalve procedures it is 6.5%. In the STS registry the mortality rate in multiple valve procedures accounts for 10% of cases and is 2-fold higher compared to a single valve operation [23]. A British registry with data collected between 2004 and 2008 presents periprocedural mortality in aortic valve procedures at the level of 2.8%. Mitral valve repairs resulted in 2% periprocedural mortality vs. 6.1% in mitral valve replacements [24]. In the studies conducted during a similar period, 20-year survival was estimated at 30% in patients after aortic valve replacement, and 20% after mitral valve replacement [25]. Peterseim *et al.* reported 10-year survival in half of cases. Independent mortality risk factors were age, kidney and lung disease, and coronary artery disease [26]. In a study of young adults mean 15-year survival was 80% in the AVR group and 71% in the MVR group of patients [27, 28].

Conclusions

Severe aortic stenosis is becoming more prevalent than severe mitral regurgitation in the Polish population. Severe mitral insufficiency coexists with significant stenoses in coronary arteries and with acute coronary syndromes more frequently than other valvular heart diseases. Coronary artery disease is one of the most significant factors worsening the prognosis of patients with acquired heart diseases. LAD stenosis is the most common lesion in the coronary arteries, while severe stenosis of the diagonal artery occurs more often in mitral insufficiency. Non-significant lesions and marginal branch stenosis had no influence on survival. Acute coronary syndrome is an additional burden in the group of patients with valvular heart diseases. The independent risk factors for death were coexisting aortic valve insufficiency and age. The worst prognosis was in the group of patients with severe MVI, which may result from higher prevalence of coronary artery disease in this group. A lesser burden of coronary artery disease and acute coronary syndrome in the group of patients with severe AVS did not affect survival.

Conflict of interest

The authors declare no conflict of interest.

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Original paper

Determinants of prolonged hospitalization in patients who underwent trans-femoral transcatheter aortic valve implantation

Yousuke Taniguchi[1], Kenichi Sakakura[1], Koichi Yuri[2], Yusuke Imamura[2], Takunori Tsukui[1], Kei Yamamoto[1], Hiroshi Wada[1], Shin-ichi Momomura[1], Atsushi Yamaguchi[2], Hideo Fujita[1]

[1]Division of Cardiovascular Medicine, Saitama Medical Center, Jichi Medical University, Saitama, Japan
[2]Department of Cardiovascular Surgery, Saitama Medical Center, Jichi Medical University, Saitama, Japan

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Abstract

Introduction: Transcatheter aortic valve implantation (TAVI) has grown to be an alternative treatment for severe symptomatic aortic valve stenosis (AS) in elderly patients. Although TAVI is a less invasive surgery than surgical aortic valve replacement, some patients may require prolonged hospitalization.

Aim: To find the determinants of prolonged hospitalization in patients who underwent trans-femoral TAVI.

Material and methods: A total of 94 AS patients who underwent trans-femoral TAVI were included as the final study population, and divided into the conventional hospitalization group (≤ 21 days) (n = 74) and prolonged hospitalization group (> 21 days) (n = 20). We compared clinical characteristics between the two groups, and multivariate logistic regression analysis was performed to find the determinants of prolonged hospitalization.

Results: In multivariate logistic regression analysis, moderate or severe mitral regurgitation (OR = 4.49, 95% CI: 1.16–17.47, p = 0.03), taking statins or angiotensin converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARB) on admission (statins: OR = 0.13, 95% CI: 0.02–0.71, p = 0.02, ACE inhibitors/ARB: OR = 0.25, 95% CI: 0.06–0.96, p = 0.04), estimated glomerular filtration rate (eGFR) (per 15 ml/min/1.73 m^2 incremental) (OR = 0.49, 95% CI: 0.26–0.90, p = 0.02) and current chopsticks user (OR = 0.05, 95% CI: 0.01–0.41, p < 0.01) were significantly associated with prolonged hospitalization.

Conclusions: Moderate or severe mitral regurgitation was significantly associated with prolonged hospitalization, while current chopsticks user, eGFR (per 15 ml/min/1.73 m^2 incremental), taking ACE inhibitors/ARB or statins before the procedure were inversely associated with prolonged hospitalization in patients who underwent trans-femoral TAVI.

Key words: hospitalization periods, chopsticks, aortic valve stenosis.

Summary

Transcatheter aortic valve implantation (TAVI) has grown to be an alternative treatment for severe symptomatic aortic valve stenosis (AS) in elderly patients. Although TAVI is a less invasive procedure, some patients may require prolonged hospitalization. The aim of this study was to find the determinants of prolonged hospitalization in patients who underwent trans-femoral TAVI. We found that moderate or severe mitral regurgitation and decreased estimated glomerular filtration rate were significantly associated with prolonged hospitalization, while current chopsticks user and taking angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers or statins before TAVI were inversely associated. This was confirmed by multivariable logistic regression analysis.

Introduction

Transcatheter aortic valve implantation (TAVI) has grown to be an alternative treatment for severe aortic valve stenosis (AS) in elderly patients irrespective of surgical risk [1, 2]. Since TAVI was a less invasive surgery than surgical aortic valve replacement (SAVR) [1, 3–5], the length of hospitalization was shorter in patients who underwent TAVI than in patients who underwent SAVR

Corresponding author:
Yousuke Taniguchi MD, Division of Cardiovascular Medicine, Saitama Medical Center, Jichi Medical University, 1-847 Amanuma-cho, Omiya-ku, Saitama-city, Saitama, Japan 330-8503, phone: +81 48 647 2111, fax: +81 48 648 5188 252-0375, e-mail: sunnyvalley@omiya.jichi.ac.jp
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[1, 4]. Moreover, trans-femoral TAVI is less invasive than trans-apical TAVI [6]. Prolonged hospitalization should be avoided for elderly patients, because the cognitive function and athletic performance in elderly tend to decline during hospitalization [7–9]. However, some patients who underwent TAVI still require prolonged hospitalization. The reasons for prolonged hospitalization have not been fully investigated in Japanese patients.

Aim

The aim of the present study was to find the pre-procedural factors that have an association with prolonged hospitalization in patients who underwent trans-femoral TAVI.

Material and methods

Patients

We included consecutive patients who underwent TAVI in our medical center from July 2014 to December 2017. Each candidate for TAVI was referred to the heart team in our medical center, and the treatment strategy including TAVI, SAVR, or non-surgical therapy was discussed on a weekly heart team conference. Exclusion criteria were TAVI by the (1) trans-apical approach, (2) trans-iliac approach, (3) trans-subclavian approach, and (4) direct aorta approach.

According to the length of the whole hospitalization period, the study population was divided into the conventional hospitalization group (≤ 21 days) and the prolonged hospitalization group (> 21 days) [10]. Clinical characteristics were compared between the conventional and prolonged hospitalization groups, and multivariate logistic regression analysis was performed to find the determinants of prolonged hospitalization.

Trans-femoral TAVI procedure

In our medical center, trans-femoral TAVI was performed by surgical cut-down approaches. Before induction of anesthesia, we inserted a 5 Fr sheath into a femoral artery and a 5 Fr sheath into a femoral vein, which were kept during the TAVI procedure as rescue lines. A temporary pacemaker was inserted via the internal jugular vein for rapid ventricular pacing. After general anesthesia, we revealed another femoral artery by the cut-down method and inserted an 8 Fr sheath into the femoral artery. We exchanged the 8 Fr sheath for the main sheath (14 to 18 Fr) following insertion of the stiff guide wire. Valve crossing was performed using a straight wire. After successful valve crossing, we exchanged the straight wire for a stiff wire that had a pre-shaped safety curve. According to the agreement of our heart team, we sometimes performed balloon aortic valvuloplasty and/or protection of coronary arteries before implantation of a biological aortic valve. Then, we implanted a biological aortic valve (balloon-expandable type or self-expandable type). During the operation, activated coagulation time was maintained ≥ 250 s.

Definitions

Hypertension was defined as receiving treatment for hypertension before admission. Dyslipidemia was defined as total cholesterol > 220 mg/dl, low-density lipoprotein cholesterol > 140 mg/dl, or medical treatment for dyslipidemia. Diabetes mellitus (DM) was defined as hemoglobin A_{1c} (HbA_{1c}) > 6.5% (national glycol-hemoglobin standardization program (NGSP) value) or medical treatment for DM [11]. Estimated glomerular filtration rate (eGFR) was calculated by the modification of diet in renal disease (MDRD) method adjusted for the Japanese population [12, 13]. Atrioventricular block was defined as PR interval > 200 ms or certain dissociation of atrioventricular conduction [14]. Acute decompensated heart failure (ADHF) was defined as New York Heart Association class ≥ II, evidence of congestion revealed by physiological findings, chest X-ray and/or echocardiogram, or diagnosis by experienced cardiologists [15, 16]. Recent percutaneous coronary intervention (PCI) was defined as a history of PCI within 1 year from TAVI. The number of aortic valve cusps, diameter of annulus, maximum velocity of aortic valve, value of E/A, severity of aortic valve regurgitation and mitral valve regurgitation (MR) were investigated by echocardiography. Left ventricular ejection fraction were measured by the Teichholz method, and aortic valve area was calculated by the continuity equation method. We also performed contrast enhanced computed tomography (CT) to obtain information regarding annulus area, annulus perimeter, diameter of Valsalva sinus, diameter of sino-tubular junction, coronary height, and characteristics of access vessels. Each STS score [17–19] and logistic EuroSCORE [20, 21] were calculated before the procedure using online available calculators. Post-procedural events such as new stroke or conduction disturbance were defined according to the Valve Academic Research Consortium 2 [22]. Furthermore, ability to have meals by using chopsticks was routinely checked at the time of hospital admission by a nurse in the medical ward. Patients who were able to eat meals with chopsticks were defined as current chopsticks users. In general, almost all Japanese are chopsticks users, at least when they are young. Thus, non-current chopsticks users at admission were at least former chopsticks users.

Statistical analysis

Categorical data were presented as number and percentage, and continuous data were presented as mean ± standard deviation (SD). Normally distributed continuous variables were compared using the unpaired Student's *t*-test. Other continuous variables were compared using the Mann-Whitney *U*-test. Categorical data were

compared using the χ^2 test or Fisher's exact test. Multivariate logistic regression analysis was performed to find the determinant of prolonged hospitalization. In this model, the prolonged hospitalization group was used as a dependent variable. In the present study, our goal was to find the predictors from baseline clinical factors. Therefore, in multivariate analysis, we selected independent variables from baseline clinical factors. Furthermore, we used well-known variables such as albumin value and STS score. We also added right bundle branch block (RBBB) because RBBB was a major risk of *de novo* pacemaker implantation. Variables that showed significant differences ($p < 0.05$) between the two groups in univariate comparisons were also used as independent variables. Variables that had missing values were not included in the multivariate analysis. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. A *p*-value < 0.05 was considered statistically significant. All analyses were performed using the statistical software SPSS PASW Statistics 18, release 18.0.0/Windows (IBM Corp.).

Results

We screened the consecutive 129 patients who underwent TAVI in our medical center from July 2014 to December 2017. We excluded 31 trans-apical approached cases, 2 trans-iliac approached cases, 1 trans-subclavian approached case, and 1 direct aorta approached case. A total of 94 AS patients who underwent trans-femoral TAVI were included as the final study population. The study population was divided into the conventional hospitalization group (≤ 21 days) ($n = 74$) and prolonged hospitalization group (> 21 days) ($n = 20$) (Figure 1). The mean length of hospitalization in the conventional hospitalization and prolonged hospitalization groups was 14.9 ±2.9 days and 31.2 ±16.0 days, respectively ($p < 0.001$).

The comparisons of baseline characteristics are shown in Table I. The prevalence of current chopsticks users was significantly greater in the conventional hospitalization group (97.3%) than in the prolonged hospitalization group (65.0%) ($p < 0.001$). The ADHF at admission was lower in the conventional hospitalization group (54.1%) than in the prolonged hospitalization group (80.0%) ($p = 0.04$). The eGFR was greater in the conventional hospitalization group (57.5 ±23.2 ml/min/1.73 m^2) than in the prolonged hospitalization group (42.7 ±18.4 ml/min/1.73 m^2) ($p = 0.01$). Moderate or severe MR was more frequently observed in the prolonged hospitalization group (40.0%) than in the conventional hospitalization group (13.5%) ($p = 0.01$). STS score was significantly lower in the conventional hospitalization group (6.19 ±5.72) than in the prolonged hospitalization group (9.82 ±11.91) ($p = 0.006$), whereas logistic EuroSCORE was not different between the groups ($p = 0.77$).

Table II shows the comparisons of procedures and complications following TAVI between the two groups. There were no significant differences except complications following TAVI. We also checked the direct reasons why the hospitalization period was prolonged. The most frequent reason was new pacemaker implantation, and the second most frequent reason was peri-operative ADHF (Figure 2).

Table III shows the multivariate logistic regression analysis to identify the determinants of the prolonged hospitalization group. Moderate or severe MR was significantly associated with prolonged hospitalization (OR = 4.49, 95% CI: 1.16–17.47, $p = 0.03$). Current chopsticks user was inversely associated with prolonged hospitalization (OR = 0.05, 95% CI: 0.01–0.41, $p < 0.01$). Furthermore, eGFR value (per 15 ml/min/1.73 m^2 incremental) (OR = 0.49, 95% CI: 0.26–0.90, $p = 0.02$), taking statins (OR = 0.13, 95% CI: 0.02–0.71, $p = 0.02$) or angiotensin converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARB) (OR = 0.25, 95% CI: 0.06–0.96, $p = 0.04$) on admission were also inversely associated with prolonged hospitalization.

Discussion

We included 94 AS patients treated by trans-femoral TAVI, and analyzed the determinants of prolonged hospitalization using multivariate logistic regression analysis. The most frequent cause of prolonged hospitalization

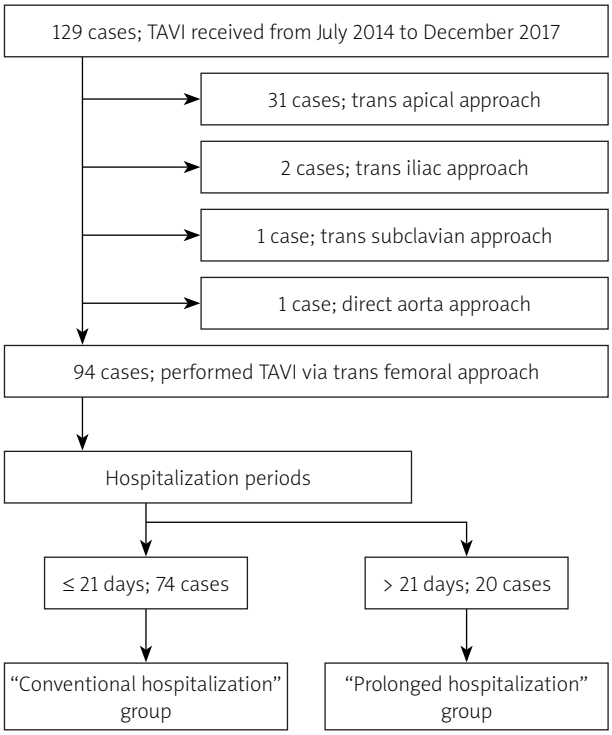

Figure 1. Flowchart of patient inclusion: a flowchart of how to determine the final study population, conventional hospitalization group and prolonged hospitalization group

TAVI – trans-catheter aortic valve implantation.

Table I. Comparison of baseline characteristics

Parameter	Overall (*N* = 94)	Conventional hospitalization (*n* = 74)	Prolonged hospitalization (*n* = 20)	*P*-value
Age [years]	83.7 ±5.1	83.7 ±4.7	83.7 ±6.6	0.97
Female gender, *n* (%)	56 (59.6)	45 (60.8)	11 (55.0)	0.64
Height [cm]	152.4 ±9.4	152.1 ±9.6	153.6 ±8.8	0.53
Weight [kg]	51.7 ±10.8	51.4 ±10.2	53.1 ±13.0	0.75
Body surface area (BSA) [m^2]	1.49 ±0.18	1.49 ±0.18	1.52 ±0.20	0.77
Smoking, *n* (%)	10 (10.6)	7 (9.5)	3 (15.0)	0.36
Chopsticks user, *n* (%)	85 (90.4)	72 (97.3)	13 (65.0)	< 0.001
ADHF, *n* (%)	56 (59.6)	40 (54.1)	16 (80.0)	0.04
Hypertension, *n* (%)	75 (79.8)	62 (83.8)	13 (65.0)	0.07
Dyslipidemia, *n* (%)	34 (36.2)	28 (37.8)	6 (30.0)	0.52
Diabetes mellitus, *n* (%)	21 (22.3)	18 (24.3)	3 (15.0)	0.29
History of atrial fibrillation, *n* (%)	15 (16.0)	9 (12.2)	6 (30.0)	0.06
Old cerebral infarction, *n* (%)	9 (9.6)	7 (9.5)	2 (10.0)	0.61
History of COPD/IP, *n* (%)	9 (9.6)	7 (9.5)	2 (10.0)	0.61
Malignant diseases, *n* (%)	9 (9.6)	6 (8.1)	3 (15.0)	0.29
Recent PCI, *n* (%)	13 (13.8)	11 (14.9)	2 (10.0)	0.44
Laboratory data:				
Albumin [g/dl]	3.9 ±0.4	4.0 ±0.4	3.8 ±0.5	0.02
Creatinine [mg/dl]	1.10 ±0.98	0.98 ±0.62	1.57 ±1.70	0.01
eGFR [ml/min/1.73 m^2]	54.3 ±23.0	57.5 ±23.2	42.7 ±18.4	0.01
Hemoglobin [g/dl]	11.6 ±1.8	11.7 ±1.8	11.1 ±1.8	0.16
Platelet [× 10^5/µl]	21.0 ±18.6	22.0 ±20.6	17.4 ±7.0	0.27
PT-INR	1.11 ±0.41	1.06 ±0.21	1.31 ±0.78	0.06
APTT [s]	34.0 ±7.8	33.0 ±4.8	37.8 ±13.8	0.21
BNP [pg/ml]	571.7 ±1027.2	531.8 ±1084.8	731.3 ±758.5	0.08
Electrocardiogram:				
Atria-ventricular block, *n* (%)	12 (12.8)	7 (9.5)	5 (25.0)	0.08
RBBB, *n* (%)	12 (12.8)	9 (12.2)	3 (15.0)	0.49
LBBB, *n* (%)	6 (6.4)	4 (5.4)	2 (10.0)	0.38
Echocardiogram:				
LVEF (%)	63.0 ±12.8	63.4 ±12.6	61.8 ±13.4	0.74
Left atrial diameter [mm]	46.9 ±7.5	46.4 ±7.4	48.7 ±7.7	0.24
LVD diastole [mm]	47.1 ±6.5	47.0 ±6.4	47.5 ±7.1	0.75
LVD systole [mm]	30.8 ±7.0	30.7 ±6.9	31.1 ±7.3	0.84
E/A	0.81 ±0.50	0.73 ±0.30	1.20 ±0.93	0.003
Aortic valve peak velocity [m/s]	4.74 ±0.69	4.77 ±0.71	4.64 ±0.64	0.57

Table I. Cont.

Parameter	Overall (*N* = 94)	Conventional hospitalization (*n* = 74)	Prolonged hospitalization (*n* = 20)	*P*-value
Aortic valve mean PG [mm Hg]	56.1 ±18.9	56.6 ±19.6	54.6 ±16.7	0.73
Aortic valve area [cm^2]	0.69 ±0.48	0.70 ±0.52	0.62 ±0.20	0.34
Moderate or severe AR, *n* (%)	21 (22.3)	20 (27.0)	1 (5.0)	0.03
Moderate or severe MR, *n* (%)	18 (19.1)	10 (13.5)	8 (40.0)	0.01
Pulmonary hypertension, *n* (%)	35 (37.2)	23 (31.1)	12 (60.0)	0.02
Medications, *n* (%):				
Aspirin	36 (38.3)	32 (43.2)	4 (20.0)	0.06
P2Y12 inhibitors	20 (21.3)	18 (24.3)	2 (10.0)	0.14
Oral anti-coagulants	8 (8.5)	5 (6.8)	3 (15.0)	0.23
Statins	35 (37.2)	32 (43.2)	3 (15.0)	0.02
ACE inhibitors or ARB	47 (50.0)	42 (56.8)	5 (25.0)	0.01
β-blockers	26 (27.7)	17 (23.0)	9 (45.0)	0.05
Diuretics	50 (53.2)	37 (50.0)	13 (65.0)	0.23
Oral hypoglycemic agents	10 (10.6)	9 (12.2)	1 (5.0)	0.32
Insulin user	2 (2.1)	2 (2.7)	0 (0)	0.62
Inotropic agents	2 (2.1)	1 (1.4)	1 (5.0)	0.38
Steroids	6 (6.4)	4 (5.4)	2 (10.0)	0.38
STS score	6.96 ±7.54	6.19 ±5.72	9.82 ±11.91	0.006
Logistic EuroSCORE	9.73 ±7.01	9.47 ±6.52	10.68 ±8.75	0.77

ADHF – acute decompensated heart failure, COPD – chronic obstructive pulmonary disease, IP – interstitial pneumonia, PCI – percutaneous coronary intervention, eGFR – estimated glomerular filtration rate, PT-INR – prothrombin time-international normalized ratio, APTT – activated partial thromboplastin time, BNP – brain natriuretic peptide, RBBB – right bundle branch block, LBBB – left bundle branch block, LVEF – left ventricular ejection fraction, LVD – left ventricular diameter, PG – pressure gradient, AR – aortic valve regurgitation, MR – mitral valve regurgitation, ACEI – angiotensin converting enzyme inhibitors, ARB – angiotensin II receptor blockers, STS – Society of Thoracic Surgeons.

was new pacemaker implantation (30%), followed by peri-operative ADHF (25%) (Figure 2). Multivariate logistic regression analysis revealed that moderate or severe MR was significantly associated with prolonged hospitalization, whereas current chopsticks user was inversely associated with prolonged hospitalization. Furthermore, eGFR value (per 15 ml/min/1.73 m^2 incremental) and taking statins or ACE inhibitors/ARB at admission were also inversely associated with prolonged hospitalization.

We should discuss why moderate or severe MR was significantly associated with prolonged hospitalization. Because patients in the present study were very elderly (83.7 ±5.1 years old), the etiology of MR would be secondary such as volume over caused by heart failure rather than primary such as mitral valve prolapse [23, 24]. As peri-operative ADHF was the second most common reason for prolonged hospitalization, moderate or severe MR might reflect the severity of ADHF before trans-femoral TAVI.

We revealed that current chopsticks user at admission was inversely associated with prolonged hospitalization. Current chopsticks user may reflect the patient's frailty as well as nutritional status. In patients with acute heart failure, nutritional status was associated with prolonged hospitalization [25, 26]. Furthermore, frailty is known to be associated with prolonged hospitalization, re-hospitalization, and death in elderly patients in acute care settings [27]. Therefore, "current chopsticks user" can be a simple predictor reflecting the patient's nutrition status and frailty in patients with AS.

The eGFR was also inversely associated with prolonged hospitalization. This association may be related to acute kidney injury (AKI) after TAVI. AKI after TAVI was reported to be a risk factor for prolonged hospitalization [28]. The chance of AKI after TAVI might be enhanced by decreased eGFR [29].

ACE inhibitors/ARB user at admission was inversely associated with prolonged hospitalization. Since ADHF

Table II. Comparison of procedure and after TAVI

Parameter	Overall (*N* = 94)	Conventional hospitalization (*n* = 74)	Prolonged hospitalization (*n* = 20)	*P*-value
Devices:				0.39
SapienXT	29 (30.9)	23 (31.1)	6 (30.0)	
Sapien3	38 (40.4)	32 (43.2)	6 (30.0)	
Corevalve	13 (13.8)	8 (10.8)	5 (25.0)	
EvoluteR	14 (14.9)	11 (14.9)	3 (15.0)	
Size:				0.21
20 mm	3 (3.2)	2 (2.7)	1 (5.0)	
23 mm	41 (43.6)	36 (48.6)	5 (25.0)	
26 mm	37 (39.4)	27 (36.5)	10 (50.0)	
29 mm	13 (13.8)	9 (12.2)	4 (20.0)	
Operation time [min]	148 ±49	151 ±54	136 ±22	0.55
Exposure time [min]	45 ±16	47 ±16	38 ±14	0.03
Contrast volume [ml]	163 ±69	167 ±72	147 ±55	0.26
Complications, *n* (%):				
Convert to open heart surgery	1 (1.0)	1 (1.3)	0 (0)	0.78
Cerebral infarction	2 (2.1)	0 (0)	2 (10.0)	0.04
New pacemaker implantation	8 (8.5)	2 (2.7)	6 (30.0)	0.001

was the cause of prolonged hospitalization, ACE inhibitors/ARB might improve patient's heart failure [30, 31]. Another reason was that unstable AS patients tended to have less chance to be prescribed ACE inhibitors/ARB, because ACE inhibitors/ARB have been considered not to be safe for symptomatic severe AS [32]. Similarly, statin user at admission was inversely associated with prolonged hospitalization. Unstable AS patients did not have a chance to be prescribed statins.

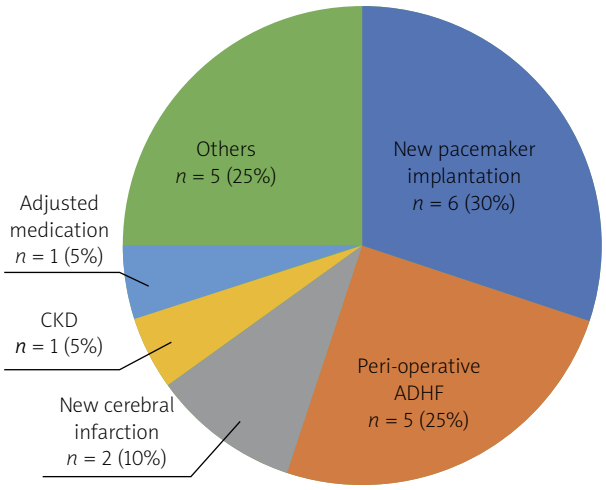

Figure 2. Main causes of prolonged hospitalization periods

ADHF – acute decompensated heart failure, CKD – chronic kidney disease.

Current risk scores such as STS score or EuroSCORE calculate the risk of death associated with surgery, but do not address prolonged hospitalization. Prolonged hospitalization is closely associated with decline of activities of daily living (ADL) in elderly patients [7–9]. It may be important to find a new risk score to address the prolonged hospitalization for patients who undergo TAVI. Although our study would be helpful to find such a risk score, we need more data and future studies to establish a new risk score.

Study limitations

First, since this study was a retrospective study, there was a potential selection bias. The most frequent reason for prolonged hospitalization was new pacemaker implantation. This could be caused by the procedure of TAVI or selection of bioprosthetic valves, while the type and size of bioprosthetic valves were not different between the conventional and prolonged hospitalization groups. Although we proposed current chopsticks user as a simple indicator of prolonged hospitalization, it is

Table III. Multivariate logistic regression analysis

Independent variables: "Prolonged hospitalization"	OR	95% CI	*P*-value
Current chopsticks user at admission	0.05	0.01–0.41	< 0.01
Moderate or severe MR	4.49	1.16–17.47	0.03
Pre eGFR (per 15 ml/min/1.73 m^2 incremental)	0.49	0.26–0.90	0.02
Statins	0.13	0.02–0.71	0.02
ACE inhibitors or ARB	0.25	0.06–0.96	0.04

MR – mitral valve regurgitation, eGFR – estimated glomerular filtration rate, ACE – angiotensin converting enzyme, ARB – angiotensin II receptor blockers. Initial step included current chopsticks user at admission, moderate or severe MR, Pre eGFR, statin, ACE inhibitors/ARB, ADHF, albumin value, right bundle branch block, atrioventricular block and STS score before procedure.

unclear whether current chopsticks user can be an indicator of prolonged hospitalization in patients who undergo trans-apical TAVI. Since minimum thoracotomy is necessary for trans-apical TAVI, the predictors of prolonged hospitalization may be more complex in trans-apical TAVI as compared to trans-femoral TAVI. As the study population was relatively small, the statistical analysis has an inherent risk of β error [33]. We should mention about the length of hospitalization. The length of hospitalization was much longer in our hospital than in US or European countries (Table II). Although the safety of short hospitalization after TAVI have been reported [34, 35], clinical experience of TAVI might not be sufficient yet in Japan as compared to US or European countries, which might have the length of hospitalization longer than in our study. Furthermore, the drive to minimize the length of hospitalization may be weaker in Japan than in other countries, because the cost of additional hospital stay, especially the self-pay burden, is quite low in Japan. TAVI with percutaneous femoral puncture or local anesthesia was less frequently performed in Japan than in US or European countries [36], which might prolong the length of hospitalization in our study. However, in several conditions, the duration of hospitalization is gradually getting shorter in our center. We should also discuss the many ADHF patients at the baseline of the present study. Since it was difficult to distinguish ADHF from advanced chronic heart failure, we might include advanced chronic heart failure as ADHF.

Since our study population consists entirely of Japanese patients who can use or could use chopsticks, whether a patient is a current chopsticks user or not was a meaningful question that reflects frailty. However, current chopsticks user may not reflect frailty in western countries.

Conclusions

In patients who underwent trans-femoral TAVI, moderate or severe MR was significantly associated with prolonged hospitalization. Current chopsticks user, eGFR value, and taking ACE inhibitors/ARB or statins before the procedure were inversely associated with prolonged hospitalization. Current chopsticks user would be a simple indicator reflecting frailty as well as nutritional status for patients with TAVI.

Conflict of interest

The authors declare no conflict of interest.

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Original paper

Comparison of early postoperative results between conventional and transapical mitral valve repair

Aleksejus Zorinas[1], Artūras Lipnevicius[1], Viktorija Bleizgytė[1], Vilius Janušauskas[1], Daina Liekienė[1], Mindaugas Budra[1], Robertas Stasys Samalavičius[2], Agnė Drąsutienė[1], Diana Zakarkaitė[1], Audrius Aidietis[1], Kęstutis Ručinskas[1]

[1]Clinic of Cardiac and Vascular Diseases, Vilnius University, Vilnius, Lithuania

[2]Centre of Anaesthesia, Intensive Care, and Pain Management, Department of Intensive Care, Vilnius University, Vilnius, Lithuania

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Abstract

Introduction: Conventional mitral valve repair (CMVR) is well-established, safe and effective treatment for degenerative mitral regurgitation (MR). Transapical off-pump implantation of artificial chordae (TA) has been introduced into practice and gained interest among surgeons. However, there are no publications comparing the results between TA and CMVR.

Aim: To compare early postoperative outcomes of CMVR with TA in patients with degenerative MR.

Material and methods: This was a retrospective cohort study. A total of 169 patients who underwent mitral valve repair between 2011 and 2018 were included in this analysis. Patients were divided into two groups: the TA group, $n = 78$ and CMVR group, $n = 91$. The groups were compared for early postoperative outcomes.

Results: Patients in the TA group were younger, 54.2 ±11.1 vs. 59.5 ±12.8 years ($p = 0.005$). Patients in the CMVR group had more complicated postoperative course with higher incidence of blood transfusion (42.9% vs. 7.8%, $p = 0.001$), atrial fibrillation (25.3% vs. 11.7%, $p = 0.031$), renal insufficiency (15.4% vs. 2.6%, $p = 0.007$) and stroke (2.1% vs. 0%). In the early postoperative period, one patient died in the TA group, and there were no deaths in the CMVR group ($p = 0.277$). Residual moderate to severe mitral regurgitation was present in nine (11.5%) TA patients, while none of the patients in the CMVR group had moderate or a higher degree of residual regurgitation ($p = 0.001$).

Conclusions: Off-pump transapical MV repair is a feasible and safe procedure with low postoperative morbidity rates. Higher rates of mitral regurgitation reoccurrence would require a careful and thorough selection of the patients suitable for the TA approach.

Key words: minimally invasive surgery, mitral regurgitation, transapical mitral valve repair.

Summary

Degenerative mitral valve disease is a common cause of primary mitral regurgitation. Conventional mitral repair is an established treatment for this pathology. The development of less invasive conventional mitral repair approaches is aimed to minimize surgical trauma, thus enhancing recovery. However, patients are still exposed to risk related to the use of cardiopulmonary bypass and aortic cross-clamp. Recently presented techniques of transapical mitral repair allow the implantation of artificial chordae to the prolapsing or flailing mitral leaflet without exposure to the risk factors mentioned above. Transapical implantation of artificial chordae results in immediate physiological restoration of the mitral valve anatomy intraoperatively while respecting the dynamic shape of the mitral apparatus. Although single centers have published their experience of this treatment modality, there have been no trials comparing outcomes of conventional and transapical mitral repair. Taking into the account early results of our retrospective analysis, we believe that transapical mitral repair is a feasible and safe procedure. Transapical mitral repair demonstrated good early postoperative results with low postoperative blood loss and a low rate of blood product transfusion. However, compared to the conventional mitral repair, it has a greater recurrence rate of moderate or severe mitral regurgitation. Therefore, careful selection of eligible patients for transapical mitral repair by a highly experienced team is imperative.

Corresponding author:
Aleksejus Zorinas PhD, Clinic of Cardiac and Vascular Diseases, Vilnius University, 2 Santariskiu St, 04816 Vilnius, Lithuania, phone: +37 069829079, e-mail: aleksejus.zorinas@santa.lt

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Introduction

Degenerative mitral valve (MV) disease is a common cause of primary mitral regurgitation (MR) in developed countries [1]. Reconstructive MV surgery has become an established gold standard treatment for this condition. Development of less invasive surgical approaches is aimed at minimizing surgical trauma and enhancing recovery; however, the patients still remain exposed to risks of cardiopulmonary bypass (CPB) and aortic cross-clamp.

Recently developed techniques of transapical MV repair allow the implantation of artificial expanded polytetrafluoroethylene (ePTFE) chordae to the prolapsing or flailing mitral leaflet without CPB. These techniques are truly minimally invasive as only a small incision of the chest at the apex of the left ventricle (LV) is required to access the MV.

Transapical MV repair results in immediate physiological restoration of the MV anatomy intraoperatively while respecting the dynamic shape of the MV [2, 3].

Although individual centers have published their experience of transapical mitral repair, there have been no trials where early outcomes of conventional and transapical MV repair are compared.

This is a retrospective non-randomized study with a patient cohort at a single center.

Aim

The aim of the study was to compare early postoperative results following conventional MV repair (CMVR) and transapical off-pump mitral repair (TA) using the NeoChord DS1000 device (NeoChord Inc., Minneapolis, MN, USA).

Material and methods

The study involved 169 patients who underwent MV repair for severe degenerative MV disease between 2011 and 2018. Transthoracic echocardiography and 2D/3D transesophageal echocardiography were used for selection of the patients in both treatment groups. All candidates had indications for surgical MV repair according to the current ACC/AHA and ESC/EACTS guidelines [4, 5]. This study was approved by the local Regional Bioethics Committee.

MV pathology included single or bi-leaflet MV prolapse or flail, with or without chordal rupture. Patients with a restrictive mechanism of regurgitation (rheumatic disease, cardiomyopathy), ischemic mitral regurgitation, MV infectious lesions and patients with a central regurgitation jet were excluded from the study. All patients with degenerative MV disease were discussed by the Heart Team for eligibility to perform either CMVR surgery or a TA procedure. Patients with a favorable MV anatomy who agreed to undergo a transapical procedure were selected for the TA.

Patients were divided into two groups according to the type of surgery: the TA group and the CMVR group.

Seventy-eight patients underwent a TA procedure. Flailing leaflet with rupture of one or more chordae was revealed in 60 (77%) patients. The rest of the patients had MR due to a prolapsing leaflet with intact native chordae. Patients in the TA group were stratified into 4 categories as per anatomical type of mitral pathology (2): type A (15 patients), isolated P2 prolapse; type B (43 patients), disease of the P2 and adjacent segments; type C (16 patients), single or bi-leaflet prolapse with peri-commissural segments involved; type D (4 patients), isolated A2 prolapse.

The CMVR group included 91 patients who underwent on-pump conventional MV repair. The patients were also stratified according to the type of mitral pathology: type A, 11 patients; type B, 18 patients; type C, 60 patients; type D, 2 patients.

Patients in both groups underwent MV repair during the same time frame. Type B patients mostly underwent transapical mitral repair, while type C patients were mostly treated with a conventional surgical procedure.

Statistical analysis

Statistical analysis was performed using the data acquisition and analysis software package SPSS 21.0 (IBM Corp., Armonk, NY, USA). The quantitative normality of continuous data was evaluated using the criteria of histograms, rectangular diagrams, and the Shapiro-Wilk test ($p > 0.05$). Quantitative data with a normal distribution are presented as a mean value ± standard deviation. Student's *t* test for independent samples was used to compare the mean values. The quantitative continuous data outside the normal distribution are presented as median and quartile intervals. The Mann-Whitney-Wilcoxon test was used to compare such data. The categorical data are expressed as a percentage. Their variables were compared using the χ^2 or Fisher criterion. A *p*-value less than 0.05 was regarded as statistically significant.

Results

Demographics and comorbidities

Patients in the TA group were older, 59.5 ±12.8 vs. 54.2 ±11.1 years ($p = 0.005$). Male gender was dominant in both groups (Table I).

STS and EuroSCORE II risk scores did not differ between the groups: 0.47% and 0.83% in the TA group vs. 0.43% and 0.84% in the CMVR group, respectively.

Patients in the CMVR group were of higher NYHA functional class: 74.7% presented with NYHA III class vs. 35.9% in the TA group. The patients in the CMVR group had a higher incidence of both paroxysmal (22% vs. 6.4%) and permanent (17.6% vs. 0%) atrial fibrillation preoperatively.

Table I. Demographics and comorbidities

Variables	CMVR group	TA group	*P*-value
Patients, *n*	91	78	
Male patients, *n* (%)	52 (57.1)	53 (67.9)	0.099
Age, mean ± SD [years]	54.2 ±11.1	59.5 ±12.8	0.005
BMI, mean ± SD [kg/m^2]	26.4 ±6.1	26.8 ±4.6	0.634
STS score (%), median (IQR)	0.43 (0.31–0.70)	0.47 (0.24–0.74)	0.142
EuroSCORE II (%), median (IQR)	0.84 (0.67–1.13)	0.83 (0.67–1.35)	0.689
NYHA I, *n* (%)	1 (1.1)	4 (5.1)	0.123
NYHA II, *n* (%)	21 (23.1)	45 (57.7)	0.001
NYHA III, *n* (%)	68 (74.7)	28 (35.9)	0.001
NYHA IV, *n* (%)	1 (1.1)	1 (1.3)	0.912
Creatinine, median (IQR) [µmol/l]	78 (68–93)	74 (64–92)	0.220
Creatinine clearance, mean ± SD [ml/min]	100 ±31.9	99.6 ±34.6	0.987
Creatinine clearance less than 85 ml/min, *n* (%)	24 (26.37)	24 (31.2)	0.525
CAD, *n* (%)	5 (5.5)	6 (7.7)	0.394
Diabetes, *n* (%)	5 (5.5)	2 (2.6)	0.290
COPD, *n* (%)	1 (1.1)	3 (3.8)	0.11
Preoperative stroke, *n* (%)	2 (2.2)	3 (3.8)	0.427
Pulmonary hypertension (> 55 mm Hg), *n* (%)	13 (14.29)	10 (12.8)	0.208
Paroxysmal AF, *n* (%)	20 (22)	5 (6.4)	0.004
Permanent AF, *n* (%)	16 (17.6)	0	0.000
Pacemaker, *n* (%)	1 (1.1)	0	0.538
Hypertension, *n* (%)	36 (39.6)	42 (53.8)	0.044

AF – atrial fibrillation, BMI – body mass index, CAD – coronary artery disease, CMVR – conventional mitral valve repair, COPD – chronic obstructive pulmonary disease, EuroSCORE – European System for Cardiac Operative Risk Evaluation, IQR – interquartile range, NYHA – New York Heart Association, SD – standard deviation, STS – Society of Thoracic Surgeons, TA – transapical.

Preoperative echocardiographic data

There was no significant difference in left ventricular systolic function between the groups (Table II). Echocardiography revealed a slightly increased left atrial volume and mitral annular dimensions in the CMVR group.

All patients in both groups underwent surgery for severe mitral regurgitation. There was a higher incidence of significant tricuspid regurgitation (TR) in the CMVR group: 35.2% of CMVR patients had moderate TR vs. 14.1% in the TA group (p = 0.002).

Intraoperative data and early postoperative results

In the CMVR group, 75 (82.4%) procedures were performed using artificial ePTFE chordae; an annuloplasty ring was used in 89 (97.8%) cases, and concomitant TV procedures were performed in 79 (86.8%) patients (TV Kay bicuspidalization in 74 cases and ring annuloplasty in 5 cases).

The median duration of surgery among CMVR patients was longer as compared to the TA procedure – 312 min vs. 120 min (Table III).

There was one conversion to conventional repair in the TA group, mitral repair failed as a result of iatrogenic injury to the posterior MV leaflet caused by the artificial chord delivery device.

The average number of implanted ePTFE chordae in the TA group was 3.5 per patient (range: 1–7 per patient). Three or four chordae were implanted in 52 (68%) patients. The most common site for the implantation was the P2 segment (92% patients). A good intraoperative result with no residual MR was achieved in 43 (56%) and mild MR in 28 (36%) patients. There were 4 (5%) patients with residual moderate MR and 2 (3%) patients with failed repair and residual severe MR. They did not

Table II. Preoperative echocardiographic data

Parameter	CMVR group	TA group	*P*-value
LVEF (%), mean ± SD	56 ±6	57 ±5	0.401
LVEDD, mean ± SD [mm]	59.8 ±7	59.1 ±6.2	0.540
LVESD, mean ± SD [mm]	36.5 ±7.5	35.6 ±6.3	0.429
LA volume index, mean ± SD [ml/m^2]	75 ±24	73 ±26	0.596
MV annulus AP diameter, mean ± SD [mm]	38.2 ±6.6	36.2 ±5.6	0.064
MV annulus ML diameter, mean ± SD [mm]	46.6 ±6.5	44.7 ±6.5	0.100
MR severe, *n* (%)	91 (100)	78 (100)	0.330
TR none/trivial, *n* (%)	27 (29.6)	34 (43.6)	0.060
TR mild, *n* (%)	32 (35.2)	33 (42.3)	0.341
TR moderate, *n* (%)	32 (35.2)	11 (14.1)	0.002

AP – antero-posterior, CMVR – conventional mitral valve repair, LA – left atrium, LVEDD – left ventricular end-diastolic diameter, LVEF – left ventricular ejection fraction, LVESD – left ventricular end-systolic diameter, ML – medio-lateral, MR – mitral regurgitation, MV – mitral valve, SD – standard deviation, TA – transapical, TR – tricuspid regurgitation.

Table III. Intraoperative data and early postoperative results

Variables	CMVR group	TA group	*P*-value
Intraoperative variables:			
Duration of surgery, median (IQR) [min]	312 (280–361)	120 (110–146)	< 0.001
CPB, median (IQR) [min]	178 (149–206)	NA	
Aortic cross-clamp time, median (IQR) [min]	123 (96–149)	NA	
TV repair	79 (86.8)	NA	
Conversion to full sternotomy, *n* (%)	NA	1 (1.3)	
Residual MR none/trivial, *n* (%)	75 (82.4)	43 (55.8)	< 0.001
Residual MR mild, *n* (%)	16 (17.6)	28 (36.4)	0.007
Residual MR moderate, *n* (%)	0	4 (5.2)	0.03
Residual MR severe, *n* (%)	0	2 (2.6)	0.12
Blood products:			
Transfusion of RBC, *n* (%)	39 (42.9)	6 (7.8)	< 0.001
Transfusion of platelets, *n* (%)	9 (9.9)	2 (2.6)	0.057
Transfusion of FFP, *n* (%)	17 (18.7)	3 (3.9)	0.03
Blood products (total), *n* (%)	43 (47.3)	6 (7.8)	< 0.001
Postoperative variables:			
Chest tube drainage, median (IQR) [ml]	300 (200–550)	200 (150–300)	0.001
New atrial fibrillation, *n* (%)	23 (25.3)	9 (11.7)	0.031
New PPM within 30 days postoperatively, *n* (%)	11 (12.1)	2 (2.6)	0.003
Re-exploration, *n* (%)	3 (3.3)	3 (3.9)	0.577
Duration of postoperative CMV, median (IQR) [h]	7 (514)	4 (2.5–5)	< 0.001
Length of ICU stay, median (IQR) [h]	67.5 (44–113)	22 (20–24)	< 0.001
Myocardial infarction, *n* (%)	0	0	
Stroke, *n* (%)	2 (2.2)	0	0.191
Wound infection, *n* (%)	1 (1.1)	0	0.354
Renal failure (creatinine elevation by 150%), *n* (%)	14 (15.4)	2 (2.6)	0.007
Hemofiltration, *n* (%)	3 (3.3)	0	0.106
Hospital stay, median (IQR) [days]	16 (14–21)	8 (7–9)	< 0.001
Mortality, *n* (%)	0	1 (1.3)	0.277
MR severe at 30 days	0	9 (11.7)	0.001

CMV – controlled mechanical ventilation, CMVR – conventional mitral valve repair, CPB – cardiopulmonary bypass, FFP – fresh frozen plasma, ICU – intensive care unit, IQR – interquartile range, MR – mitral regurgitation, PPM – permanent pacemaker, RBC – red blood cells, TA – transapical, TV – tricuspid valve.

undergo any further procedure as they were reluctant to undergo conventional repair at the time of consent.

In the CMVR group, the median number of implanted PTFE chordae was 2 per patient (IQR: 2–3). No residual MR was achieved in 75 (82.4%) patients and mild MR in 16 (17.6%). A second pump run due to an unacceptable result of the repair was necessary in 3 (3.3%) patients.

At 30 days, none of the patients in the CMVR group had severe MR, while in the TA group, 9 (11.7%, $p = 0.001$) patients had moderate or severe MR (2 (2.6%) patients had moderate and 7 (9.1%) severe).

Postoperative blood loss in the TA group was significantly lower compared to the CMVR group, 200 ml vs. 300 ml, $p = 0.001$. It determined a significantly lower rate of blood product transfusion in the TA group of patients (7.8% vs. 42.9% for RBC, $p < 0.005$; 7.8% vs. 47.3% for all blood products, $p < 0.001$). There was no difference in re-exploration rate between the groups.

One patient died in the TA group on the 2nd postoperative day. Death occurred due to bleeding-related cardiac tamponade. Following evacuation of the pericardial tamponade, the patient immediately developed ventricular fibrillation. Direct cardiac compressions led to rupture of the right ventricle with a subsequent lethal outcome.

Early postoperative mortality was 1.3% in the TA group and 0% in the CMVR group.

Patients in the CMVR group had a higher rate of postoperative atrial fibrillation (11.7% vs. 25.3%, $p < 0.05$) and PPM insertion (2.6% vs. 12.1%, $p < 0.05$). After the TA procedure, a permanent pacemaker was implanted in two patients; those were patients with preoperatively known sick sinus node syndrome.

Median time to weaning from ventilation was significantly shorter in the TA group: 4 h vs. 7 h ($p < 0.005$). There was a substantial difference in the ICU length of stay between the TA and CMVR groups (22 h vs. 67.5 h, $p < 0.005$) as well as postoperative in-hospital stay (8 days vs. 16 days, $p < 0.005$).

The rate of postoperative stroke was 2.2% in CMVR patients, and there was one patient with postoperative wound infection (1.1%). None of these complications were recorded in the TA group.

Postoperative renal failure (elevation of creatinine level > 150% above baseline) was more common in the CMVR group (15.4% vs. 2.6%). Three (3.3%) patients in the CMVR group and none in the TA group required hemofiltration or hemodialysis.

Discussion

The ePTFE chord has become a standard material in modern MV surgery, and recent studies have shown reliable long-term results of mitral repair using ePTFE chordae [6, 7]. Castillo *et al*. reported the absence of moderate or severe MR to be 90.3 ±3.7% at 7 years [6]. The David group published 25-year results showing freedom from reoperation of 90.2% and freedom from recurrent severe MR of 91.0% after 18 years [7].

The recent concept of transapical delivery of ePTFE chords was developed in order to reduce the invasiveness of the surgery and the rate of complications related to the use of cardiopulmonary bypass. This type of repair also enhances postoperative recovery of the patient and reduces duration of ICU and in-hospital stay [8].

Since the introduction of the technology, more than 1000 patients in Europe and the USA have successfully undergone the NeoChord procedure [9]. This system allows minimally invasive off-pump delivery of the ePTFE chordae to the prolapsing or flail MV leaflet and enables the adjustment of the length of the chordae under direct echocardiographic control while the valve is fully functioning under physiologic conditions of the beating heart. This TEE guided procedure is currently standardized and is described in detail in recent publications of Colli *et al.* [5, 9] and Samalavicius *et al.* [10].

Another novel technology for transapical mitral repair is the Harpoon Mitral Valve Repair System (H-MVRS; Harpoon Medical Inc., Baltimore, Maryland, USA). It uses a similar approach to the NeoChord system; however, the mechanism of ePTFE chordae anchoring is different: the device perforates the leaflet and anchors the artificial chord by a self-tying suture knot [1, 11]. According to 2019 data, there were 65 patients who underwent this procedure, and it was successful in 62 (95.4%) patients. There was no early mortality or major adverse events. The reported rate of AF was 18%. However, 14% of the patients had reoperation and another 2% had severe residual MR at 12 months [12].

Multiple reports have demonstrated the safety and feasibility of transapical MV repair using the NeoChord DS1000 device with an effective reduction of MR achieved during the procedure [8, 13]. Colli *et al.* recently published procedural outcomes and 12-month follow-up data of the largest series at a single institution [14], followed by a manuscript presenting multicenter European experience [8]. Reported intraoperative results are quite similar to those presented in this study: two thirds of the patients received three or four artificial chordae, rates of conversion to conventional surgery and mortality were 1.4–1.9% vs. 1.3% in this series. Procedural success was slightly lower in our series – MR reduction to mild or less was achieved in 71 (91%) patients compared to 96.7–98.6% reported by Colli *et al.* The fact that there were more patients with no residual MR in the CMVR group could be explained by a wider choice of components in the conventional repair such as annuloplasty ring, closure of clefts and others. Furthermore, patients who had higher than mild residual MR, which could not be repaired any further, underwent MV replacement and were not included in this study.

Our experience shows that the NeoChord procedure is beneficial only for patients with a non-complicated

lesion of the mitral valve (mostly isolated P2 prolapse or flail, type A and B) at the early stages of the disease when the valve can be repaired by isolated implantation of the artificial chordae. Other patients with more complex mitral pathology, multiple prolapsing segments, annular dilatation, poor predicted coaptation and paracommissural disease (type C) should undergo conventional surgery. Conventional surgery can offer more options for a better result, and also chances of unsuccessful repair and necessity for replacement of the valve in these patients are higher. The subgroup of patients with a more complex MR anatomy (type C) was larger in the CMVR group, due to selection bias of the investigators, meaning that patients with more favorable anatomy (i.e. types A and B) were selected for the TA repair.

Modern direct or indirect transcatheter annuloplasty devices allow transapical repair to be used in more complex patients. Six recently reported cases of transapical mitral repair and concomitant annuloplasty using annuloplasty transcatheter devices (COMBO approach) showed one of the potential directions for further development of transapical technology [15]. Addition of an annuloplasty option to transapical repair would improve the results of transapical repair, particularly in complex mitral pathology with annular dilatation.

Although the conventional approach can often be beneficial for patients with complex mitral pathology, our study shows a lower rate of postoperative adverse events in the TA group compared with the CMVR group. Transapical repair is a much less invasive procedure; therefore, both postoperative bleeding and rates of blood products are much lower. Red blood cell transfusion was required in 6 (7.8%) patients and this is very close to the 8% rate reported by Colli *et al*. in the multicenter European study. Meanwhile the most commonly reported incidence is about 50% after conventional and about 40% after minimally invasive mitral surgery [16]. Even though transfusions were rare in the TA group, the incidence of re-exploration was similar in both groups (3.3% vs. 3.9%) and higher in comparison to European experience (1.4%).

Postoperative atrial fibrillation affects up to a third of patients after conventional surgery and 15–20% of patients following minimally invasive mitral surgery [16–18]. Our study shows significant reduction in AF rate after a transapical procedure (11.7% vs. 25.3%), although multicenter NeoChord data report the incidence to be 22.5% [8].

Postoperative neurologic complications are often related to CPB and cross-clamping of the aorta with a reported range of 0.7–2.8% [18, 19]. Both our study and European experience show that the transapical approach helps to avoid this complication [8].

Significantly shorter postoperative recovery in comparison to conventional surgery, including shorter mechanical ventilation, ICU stay, and postoperative in-hospital stay, is often emphasized in the publications reporting outcomes of transapical repair. In this study the duration of ventilation and in-hospital stay in the CMVR group was almost double compared to the TA group.

Our study has demonstrated safety and feasibility of the TA procedure with a lower rate of postoperative adverse events in the TA group in comparison to conventional surgery. Nevertheless, the TA procedure is associated with a higher rate of early postoperative failures: no patients in the CMVR group developed severe MR at 30 days; meanwhile, severe residual MR was present in 2 (2.6%) patients immediately after the procedure and in 7 (9.1%) patients at 30-day follow-up.

Both patients with severe intraprocedural residual MR and 5 out of 7 patients with severe MR at 30-day follow-up were type C as per anatomical changes preoperatively. Therefore, we conclude that type C patients should not be considered as candidates for a transapical procedure due to high recurrence of MR.

Study strengths and limitations

This is a retrospective non-randomized analysis with a limited number of patients. The Heart Team biased the patient selection for the procedure, according to MV anatomy. The patients in the TA and CMVR groups were not equal; there were more patients with complex MV pathology (group C) in the CMVR group. The groups were too small to perform propensity matching.

Conclusions

Transapical MV repair using the NeoChord DS1000 device is a feasible and relatively safe procedure. The procedure time is relatively short and MV repair is performed without exposing the patient to CPB-related risks. Mitral repair using the NeoChord device demonstrated good early postoperative results with low postoperative blood loss and a low rate of blood product transfusion. However, transapical MV repair using the NeoChord DS1000 device, as compared to conventional repair, has a greater recurrence rate of severe MR. Therefore, careful selection of eligible patients by a highly experienced team is imperative.

Conflict of interest

Dr. A. Drąsutiene, D. Zakarkaitė and A. Aidietis have worked as consultants for NeoChord Inc. The others authors declare no conflict of interest.

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Original paper

Comparison of transesophageal and intracardiac echocardiography in guiding percutaneous left atrial appendage closure with an Amplatzer Amulet device

Witold Streb, Katarzyna Mitręga, Tomasz Podolecki, Stanisław Morawski, Mariola Szulik, Ewa Jędrzejczyk-Patej, Tomasz Kukulski, Zbigniew Kalarus

1st Department of Cardiology, Congenital Heart Diseases and Electrotherapy, Silesian Center for Heart Diseases in Zabrze, Medical University of Silesia in Katowice, Poland

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Abstract

Introduction: Percutaneous occlusion of the left atrial appendage (LAAO) is becoming an extensively used method of stroke prevention in individuals with contraindications to oral anticoagulants. Transesophageal echocardiography (TOE) is the gold standard for LAAO guiding, but intracardiac echocardiography (ICE) appears to be a potential alternative.

Aim: To compare the LAAO procedure guided by TOE or ICE with respect to procedural success and safety.

Material and methods: TOE-guided LAAO was performed in 12 patients and ICE-guided LAAO in 11 patients. ICE was performed using an 8F AcuNav probe and the ACUSON SC2000 system. For LAAO the Amplatzer Amulet was used. After 1 month TOE was performed.

Results: Procedural success was achieved in all patients in TOE and ICE groups. There was 1 complication (groin hematoma). The procedure time was significantly longer in the TOE group (43 to 80 min; median: 54 min) compared to the ICE group (28 to 67 min; median: 45 min), (p = 0.02) The time needed to puncture the interatrial septum and time needed to remove the sheath did not differ between groups. Fluoroscopic time was insignificantly longer in the ICE group (9.91 ±4.01s) compared to the TOE group (7.69 ±3.21s), and a significantly larger contrast media volume was used in the ICE group (30.00 ±6.67 ml vs. 40.45 ±23.18 ml, p = 0.03). There were no statistically significant differences in the results between TOE and ICE groups in follow-up assessments.

Conclusions: LAAO using the Amplatzer Amulet may be successfully and safely guided by ICE. ICE offered shorter procedure time and similar results irrespectively of left atrial appendage anatomy compared to TOE guidance.

Key words: transesophageal echocardiography, left atrial appendage occlusion, intracardiac echocardiography.

Summary

The current study aimed to compare the course and results of the left atrial appendage (LAAO) procedure guided by transesophageal echocardiography (TOE) or intracardiac echocardiography (ICE) particularly with respect to procedural success and safety, but also with regard to the optimal effect of the implantation. We found that the procedure time was significantly longer in the TOE group. However, the fluoroscopic time and contrast media used were insignificantly longer in the ICE group compared to the TOE group. The optimal implantation effect was obtained regardless of whether TOE or ICE was used.

Introduction

During the last years percutaneous occlusion of the left atrial appendage (LAAO) has become an extensively used method of stroke prevention in individuals with contraindications to oral anticoagulants. The proper visualization of the left atrium is crucial for both procedure planning and guiding. However, imaging of the left atrial appendage remains challenging with respect to assessment of left atrial anatomy as well as for guiding of the LAAO procedure. In the preliminary assessment of the left atrium the most commonly used imaging modality

Corresponding author:
Witold Streb MD, 1st Department of Cardiology, Congenital Heart Diseases and Electrotherapy, Silesian Center for Heart Diseases, Medical University of Silesia, 2 Szpitalna St, 41-800 Zabrze, Poland, phone: +48 531 000 414, e-mail: streb@wp.pl
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is transesophageal echocardiography (TOE), particularly when using 3-dimensional echocardiography [1]. Also TOE remains the gold standard for exclusion of thromboembolic material within the left atrium and in its appendage [2, 3]. Nevertheless, some authors emphasize the advantages of computed tomography or cardiac magnetic resonance for exploration of the anatomy of the left atrial appendage and for the precise measurement of its dimensions [4, 5]. Thus the debate on the optimal imaging strategy for the pre-procedural visualization of the left atrium is still open.

Less attention was paid for the comparison of imaging techniques which are potentially useful in monitoring the LAAO procedures. The fundamental one is fluoroscopy. However, it has many disadvantages. First of all it allows one to obtain only mono-plane images. Secondly, soft tissue is not visible, hence the visualization of the left atrial appendage requires an injection of contrast agents. Therefore most centers reach for support from transesophageal echocardiography. This semi-invasive technique overcomes the limitations of fluoroscopy and is safe. It delivers valuable data regarding the dimensions of the left atrial appendage and allows the post-deployment assessment including the interference of the occluder with adjacent structures or the registration of residual flow within the lobe of the appendage. Based on fluoroscopy and transesophageal echocardiography some newer techniques have been developed, such as fusion imaging, facilitating further the navigation of the LAAO as well as improving the results of occluder implantation [6].

Nevertheless, the navigation of the LAAO with transesophageal echocardiography requires anesthesia or sedation of the patient. Taking into account that patients referred for LAAO are suffering from multiple disorders, both sedation and anesthesia raise the higher risk of complications for them compared to the general population. Among them there are also patients with absolute contraindications to TOE (e.g., esophagectomy) or those with relative contraindications, e.g. hepatic illnesses and esophageal varices.

Intracardiac echocardiography (ICE) similar to TOE may be potentially useful for the navigation of the LAAO procedure. However, evidence that ICE guidance can be equally effective is still lacking.

Aim

The current study aimed to compare the course of the LAAO procedure guided by TOE or ICE particularly with respect to procedural success and safety.

Material and methods

Among patients diagnosed with atrial fibrillation and referred for LAAO, the echocardiographic eligibility criteria for LAAO were assessed by TOE. After this preliminary selection, 23 patients agreed to participate in the study. All of these patients had both an increased risk of stroke (CHADSVASc score ≥ 2), and contraindications for oral anticoagulation. Informed consent was obtained from each individual for performing the procedure of percutaneous left atrial appendage occlusion as a method of stroke prophylaxis. The patients were informed about the advantages of LAAO and potential risk of the procedure. It was also explained that LAAO would be guided by either transesophageal echocardiography or intracardiac echocardiography. The imaging modality used for guidance of LAAO was chosen based on the order of patients enrolled in the study. Thus each second patient enrolled in the study had LAAO guided by ICE, and the remaining ones by TOE.

Procedure

For LAAO the Amplatzer Amulet occluder was used. The size of occluder chosen for LAAO was based on the results of measurements performed during the TOE prior to the procedure and compared with the fluoroscopic measurements made during LAAO. The occluder used was 2–4 mm larger than the landing zone diameter according to the suggestions in the occluder sizing charts distributed by the producer.

The vascular access was obtained by the puncture of the right femoral vein. Later the Brockenbrough needle passed through the interatrial septum in its lower, posterior portion. The site of puncture was guided either by TOE or ICE. Later the sheath was changed for that dedicated for the delivery of the Amplatzer Amulet – 12 F or 14 F sheath – depending on the occluder size.

The device was positioned in the neck of the left atrium appendage under echocardiographic (TOE or ICE) and fluoroscopic guidance. The criteria of proper implantation included:

– 2/3 of the occluder lobe placed below the landing zone,
– the axis of the occluder parallel to the axis of the left atrial appendage neck,
– compression of the lobe of the occlude,
– lack of protrusion of the disk above the orifice of the left atrial appendage,
– separation between the lobe and disk of the device,
– lack or a trace of leak in the left atrial appendage after implantation.

After removal of the catheter from the vein, the hemostatic suture was applied, followed by the compression bandage left for 3 h.

Transesophageal echocardiography

The electrocardiographic (ECG)-gated TOE was performed using Vivid E9 (6 VT-D probe; 5 MHz). 3-dimensional TOE zoom images were obtained from one ECG cycle in two-chamber view. Then gain was turned to optimize the images with particular care not to allow

for a drop-out effect. The landing zone area was reconstructed by the alignment of three perpendicular planes at the level of the circumflex artery using the multi-plane technique. The measurements were taken during the left atrial appendage filling period. The largest diameter of the left atrial appendage landing zone was used as a reference for the selection of occluder size. During the procedure the X-plane views were used for the navigation of the transseptal puncture and for monitoring of device deployment in the left appendage neck. After that the sealing effect was confirmed by the lack of flow within the appendage by color using Doppler with the scale reduced < 30 cm/s.

Intracardiac echocardiography

ICE imaging was performed using a single-use, 8F AcuNav Diagnostic Ultrasound Catheter (Siemens Medical Solutions, USA) and ACUSON SC2000 ultrasound system (Siemens Medical Solutions USA, Inc.). An AcuNav catheter was inserted by the puncture of the left femoral vein. The ICE probe was linked to the ultrasound system by a reusable SwiftLink connector. The catheter handle and the SwiftLink were placed in a sterile cover. The AcuNav handle allows one to change the position of a tip of a catheter in four directions (anterior, posterior, left and right). It was introduced to the heart chambers via the puncture of the left femoral vein.

With the tip of the ICE probe placed in the right atrium the probe was turned clock-wise and banded posterior to obtain a view of the septum. After the transseptal puncture the sheath for transseptal puncture was exchanged with the sheath and dilator designed for the introduction of Amplatzer Amulet. With a wire placed in the left upper pulmonary vein the Amplatzer sheath was placed in the left atrium and then withdrawn. Crossing the interatrial septum with a sheath and its dilator was repeated 2–3 times. This maneuver facilitated the passage of the ICE probe via the interatrial septum. Crossing of the ICE probe through the interatrial septum required the adjustment of its position in the right atrium by manipulation of its handle and alignment with the wire put in the left upper pulmonary vein under fluoroscopy in a different view. When advanced in the left atrium the ICE probe was maneuvered to achieve the best left atrial appendage view (Figure 1). Typically it was obtained with an ultrasound catheter deflected in the posterior direction and with clockwise rotation. Following the expansion of the occluder, its position was assessed and lack of flow within the appendage was confirmed by using color Doppler with the scale reduced < 30 cm/s.

Patient preparation

Prior to the procedure all patients received a loading dose of aspirin and clopidogrel if not already on treatment. A prophylactic cefazolin dose and 0.9% saline infusion was given to all subjects prior to LAAO. General anesthesia was used in the group of patients who had LAAO under the guidance with TOE. In patients in whom the procedure was guided by ICE only local anesthesia without sedation was used.

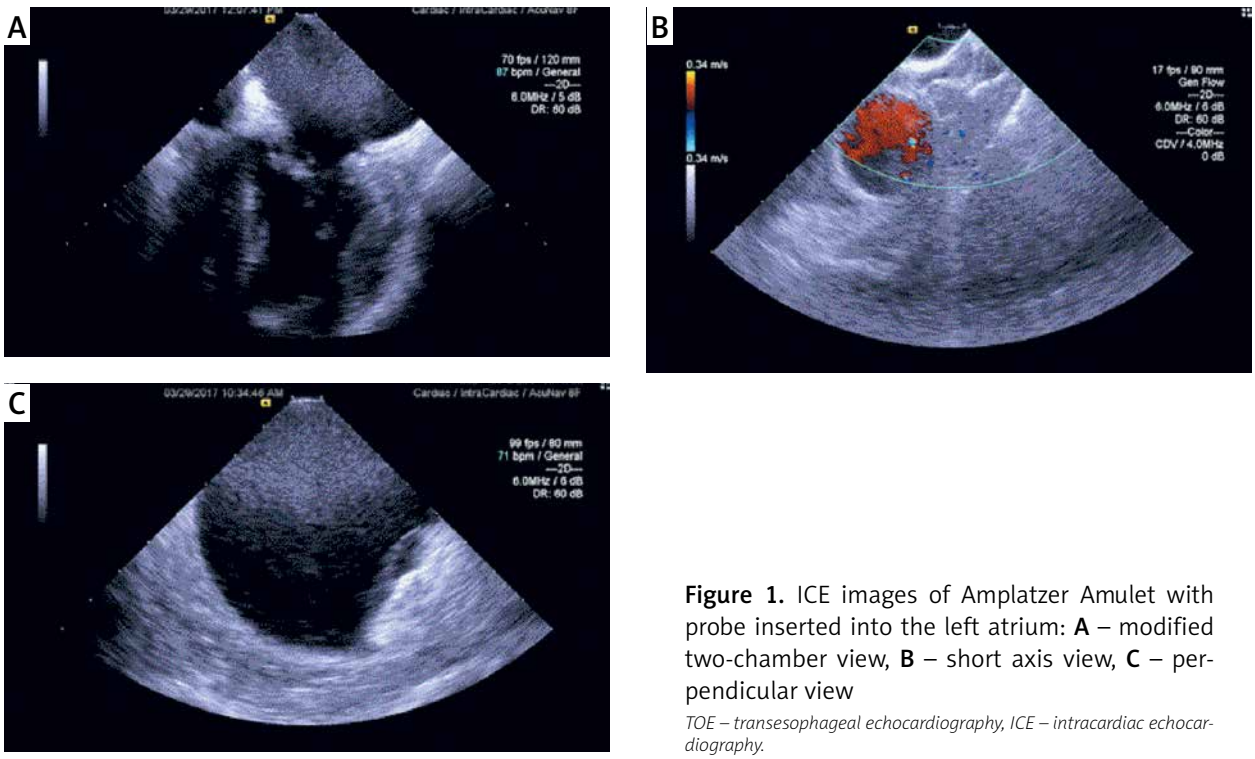

Figure 1. ICE images of Amplatzer Amulet with probe inserted into the left atrium: **A** – modified two-chamber view, **B** – short axis view, **C** – perpendicular view

TOE – transesophageal echocardiography, ICE – intracardiac echocardiography.

Follow-up

The follow-up was planned 30 days after implantation. The information regarding the outcome events (stroke, hemorrhage, late vascular complications) was gathered. All of the participating patients had a follow-up TOE to assess the result of implantation and to exclude thrombus in the left atrium before termination of the dual antiplatelet therapy.

Statistical analysis

Statistical analysis was performed using the Statistica ver. 12 (StatSoft Inc.) software. The quantitative data are presented as median and interquartile ranges, and the categorical data are reported as percentages. For the comparison the χ^2 or Mann-Whitney *U*-test was used. Values of $p < 0.05$ were considered statistically significant.

Results

The group in which LAAO was guided by TOE did not differ significantly from the ICE group regarding the demographic characteristics. The median age was respectively 73.00; IQR = 15.00 vs. 77.00; IQR = 7.00 ($p = 0.69$), and the percentage of males was 33.33% vs. 45.45% ($p = 0.55$).

45.45% of patients in the ICE group and 66.66% in the TOE group had a paroxysmal atrial fibrillation ($p = 0.31$). The majority of the patients referred for LAAO had a history of major bleeding as the main indication for the procedure. Only 4 of 23 patients (2 in each group) had other indications for LAAO than serious bleeding. When comparing the risk of bleeding based on HASBLED score it was higher in the ICE group (3.00; IQR = 1.00) than in the TOE group (2.00; IQR = 0.50), $p = 0.01$. No significant differences between the groups were found with respect to the risk of stroke estimated based on the CHA_2DS_2VASc score. Mean CHA_2DS_2VASc score was 5.00; IQR = 2.00 in the ICE group and 5.00; IQR = 1.50 in the TOE group, $p = 0.45$. Details regarding co-morbidities are shown in Table I.

The comparison of transthoracic echocardiography showed that both groups were similar according to dimensions and function of the left ventricle. LAAO guided by neither TOE nor ICE could be influenced by the morphology of the left atrial appendage. The details regarding left atrial appendage morphology, sizes and its relation to adjacent structures within the left atrium are given in Table II. The only significant difference was found for the area of the left atrial ostium, which was larger in the ICE group.

Time of the entire LAAO procedure ranged from 43 to 80 min in the TOE group with median procedure time 54 min, whereas in the ICE group the time from obtaining the first venous access to leaving the cathlab ranged from 28 to 67 min (median: 45 min). The procedure time was significantly longer in the TOE group ($p = 0.02$). The time needed to puncture the interatrial septum starting from the first femoral access was insignificantly shorter in the ICE group ($p = 0.09$). The comparison of time that elapsed from gaining the first access to the femoral vein to withdrawal of the last sheath from the groin did not reveal statistically significant differences between the groups ($p = 0.97$). The results are illustrated in Figure 2.

During LAAO the proper position of the occluder was hardly ever achieved after the first deployment. It took place only in 2 (16.67%) cases in the TOE group, and in none of the patients in the ICE group. In 2 cases (1 in the TOE group and 1 in the ICE group) it was necessary to change the occluder for another size. Finally successful occlusion of the left atrial appendage was achieved in all patients in TOE and ICE groups. The groups did not differ with regard to the size of occluder which was implanted (median: 28.00; IQR = 3.00 mm vs. 25.00; IQR = 1.50 mm; $p = 0.16$).

Crossing the intra-atrial septum required manipulation with the ICE probe and alignment of its position under fluoroscopy. It could explain the longer fluoroscopic time in the ICE group (10.00; IQR = 8.00s) compared to the TOE group (7.00; IQR = 1.50s), but it was not statistically significant ($p = 0.16$). Also the lack of multi-plane

Table I. Characteristics of study population

Parameter	ICE group	TOE group	*P*-value
Coronary artery disease	5 (45.45%)	7 (58.33%)	0.56
Diabetes mellitus	3 (27.27%)	3 (25.00%)	0.96
History of ischemic stroke	4 (36.36%)	3 (25.00%)	0.58
History of hemorrhagic stroke	1 (9.09%)	0 (0.00%)	0.33
Heart failure	2 (20.0%)	4 (33.33%)	0.52
Hypertension	9 (81.82%)	11 91.67%)	0.53
Uncontrolled hypertension	2 (18.18%)	0 (0.00%)	0.14
Chronic kidney disease	3 (27.27%)	1 (8.33%)	0.26
Fragility syndrome	0 (0.00%)	1 (8.33%)	0.38

Table II. Results of transthoracic and esophageal echocardiography performed prior to the procedure

Parameter	TOE group	ICE group	*P*-value
Minimal diameter of ostium [mm]*	21.0 (4.00)	23.0 (2.00)	0.07
Maximal diameter of ostium [mm]*	27.5 (5.00)	31.0 (7.00)	0.08
Minimal diameter of landing zone [mm]*	17.0 (3.00)	17.0 (3.00)	0.59
Maximal diameter of landing zone [mm]*	20.0 (2.50)	22.0 (7.00)	0.24
LAA ostium area [cm^2]*	4.7 (1.16)	5.5 (1.30)	0.04
LAA depth [mm]*	21.5 (7.50)	24.0 (10.0)	0.62
Morphology of LAA:			
Chicken wing	5 (41.67%)	2 (18.18%)	0.21
Windsock	6 (50.00%)	8 (72.73%)	0.26
Cauliflower	1 (8.33%)	0 (0.00%)	0.33
Cactus	0 (0.00%)	1 (9.09%)	0.29
LLR:			
Sharp and tall	11 (91.67%)	11 (100%)	0.31
Location of LAA ostium in relation to left pulmonary veins:			
High	2 (16.67%)	3 (27.27%)	0.56
Intermediate	8 (67.67%)	5 (45.45%)	0.27
Low	2 (16.67%)	3 (27.27%)	0.56
End diastolic dimension of left ventricle [mm]*	47.50 (9.00)	47.0 (11.00)	0.62
End systolic dimension of left ventricle [mm]*	35.0 (4.00)	32.0 (12.00)	0.44
Left ventricular ejection fraction [%]*	53.5 (16.50)	55.0 (14.00)	0.54
Left atrial diameter [mm]*	43.5 (8.50)	40.0 (7.00)	0.19
Left atrial area [mm]*	24.85 (3.35)	24.0 (8.40)	0.65

**Median with interquartile range (IQR).*

imaging with the ICE probe could result in more attempts to better visualize the left atrial appendage on fluoroscopy resulting in both prolonged fluoroscopic time and significantly higher contrast media volume used in the ICE group (30.00; IQR = 25.00 ml vs. 20.00; IQR = 4.50 ml, $p = 0.03$) (Figure 3).

Complications of the procedure in the studied population were very uncommon. No cardiac tamponade, pericardial effusion, device embolization, or periprocedural stroke was observed. Also very infrequent were vascular complications at the site of access. There was observed only 1 case of hematoma in the groin, which did not require additional treatment. No arterio-venous fistula or pseudoaneurysm was found after the procedure. Lack of complications allowed early mobilization and discharge from hospital. In the studied population the TOE group and ICE group did not differ regarding the time of hospitalization (3.00; IQR = 1.000 day vs. 3.00; IQR = 1.00 day; $p = 0.71$) or the time of immobilization (6.00; IQR = 6.00 h vs. 8.0; IQR = 4.00 h; $p = 0.74$).

After 1 month follow-up no stroke, bleeding or new vascular complications were reported. The follow-up analysis of TOE included the assessment of occluder position, the alignment of the device disk to the tissue of the appendage orifice, the presence of peridevice leak or thrombus on the surface of the occluder. We also categorized the effect of implantation as optimal if no left lateral ridge was left above the disk of the occluder or as suboptimal if part of the left lateral ridge was present above the disk. The detailed results of a follow-up TOE are shown in Table III. There were no statistically significant differences in the results of occluder implantation between TOE and ICE groups with respect to TOE follow-up assessments.

Discussion

According to recent studies, percutaneous obliteration of the left atrial appendage might help to reduce the risk of thromboembolism in non-valvular atrial fibrillation

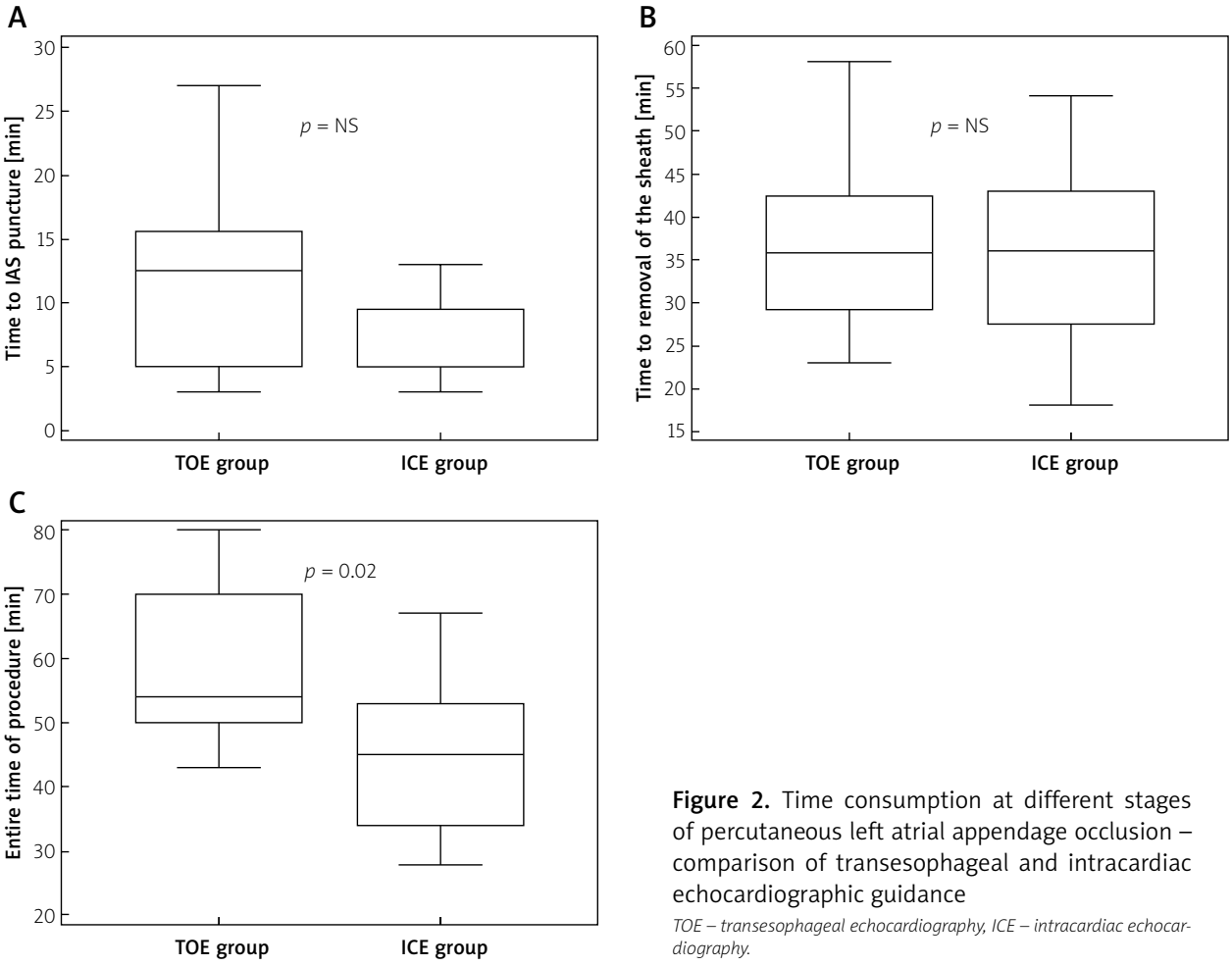

Figure 2. Time consumption at different stages of percutaneous left atrial appendage occlusion – comparison of transesophageal and intracardiac echocardiographic guidance

TOE – transesophageal echocardiography, ICE – intracardiac echocardiography.

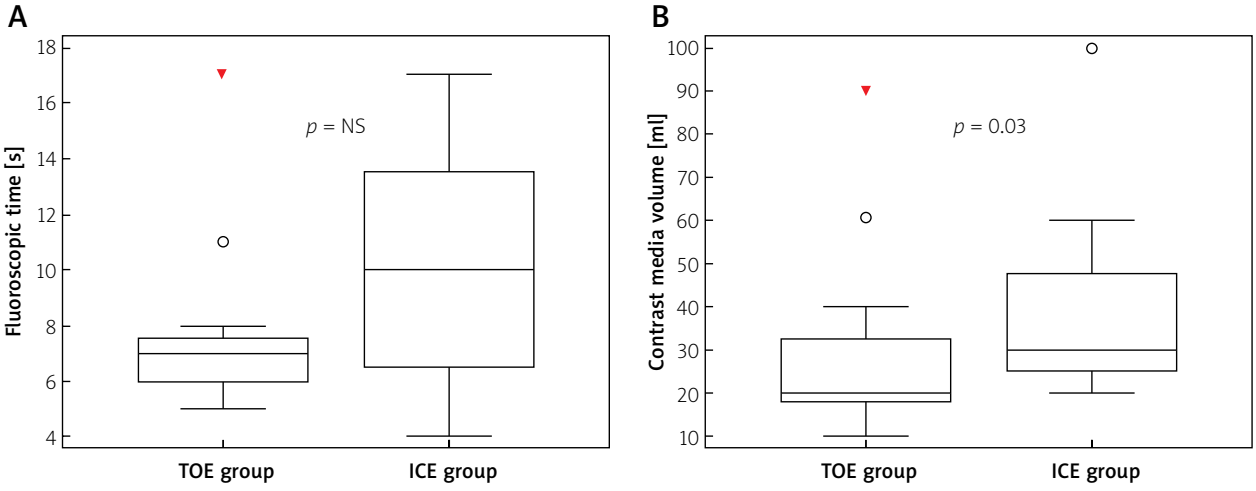

Figure 3. Fluoroscopic time and contrast media volume used for percutaneous left atrial appendage occlusion guided by transesophageal and intracardiac echocardiography

TOE – transesophageal echocardiography, ICE – intracardiac echocardiography.

Table III. Results of follow-up transesophageal assessment

Parameter	TOE group	ICE group	*P*-value
Optimal position of occluder	8 (66.67%)	6 (54.54%)	0.55
Occluder disk protruding to LAA	0 (0.00%)	0 (0.00%)	1.00
Peridevice leak:			
Large	0 (0.00%)	0 (0.00%)	1.00
Small	2 (16.67%)	1 (9.09%)	0.59
Thrombus on device	2 (16.67%)	1 (9.09%)	0.59

[7, 8]. Promising results have been obtained with occluders offered by various manufacturers and nowadays it may be considered by the guidelines as a valuable alternative for patients with a high risk of stroke and contraindications for long-term oral anticoagulation [9–12].

Independently from the type of occluder used, the procedure of LAAO requires an adequate imaging modality for both procedure planning and guiding. Often the usage of fluoroscopy alone to guide LAAO is insufficient, particularly in cases of complex LAA. Thus TOE has become a gold standard technique for management of LAAO, but also this modality has some disadvantages [13]. TOE necessitates the use of general anesthesia or deep sedation, and an experienced TOE echocardiographer and anesthetic team. Thus newer imaging modalities, such as ICE, appear to be a good alternative [14].

Usefulness of ICE was confirmed in periprocedural guiding of such procedures as left heart ablation, closure of interatrial communications, the placement of percutaneous left ventricular assist device cannulas, the performance of percutaneous balloon mitral valvuloplasty, transcatheter aortic valve implantation, and some others [15–17]. Recently there has also been growing interest in application of ICE in guiding of LAAO procedures. It has also been demonstrated that ICE may serve as an alternative to the TOE imaging modality for detecting left atrial appendage thrombus prior to procedures within the left atrium [18, 19].

Compared to TOE, ICE can visualize the left atrial appendage more clearly as a result of higher image resolution. The ICE probe can remain in place within the right or left heart safely for the entire procedure with excellent patient tolerance. Modern ICE probes provide easy applicability, and real-time structural and hemodynamic information, which allow not only the assessment of anatomy but also detection of residual flow after the deployment of the left atrial appendage occluder.

There are a few studies showing that ICE guiding for percutaneous closure of interatrial communications reduces the fluoroscopy time, interventional procedure time, and catheterization laboratory time compared with TOE [20, 21]. In the present study a precise analysis of procedure timing was performed. Similarly to mentioned pediatric procedures in our series the entire time of the procedure in the ICE group, counted starting at the venous puncture and ending when the patient left the cathlab, was significantly lower compared to the TOE group. Data regarding the procedure time during LAAO guided by ICE were published by Frangieh *et al.* [22]. In this study the reported time from femoral venous puncture to transseptal puncture and to closure was longer in the ICE group. In this study, of the TOE-guided LAAO, 17 were combined with TAVI, and 6 procedures in the ICE group were combined with percutaneous coronary interventions. Thus the results are not comparable to our series. Similarly, Berti *et al.* showed that TEE implied lower procedural and fluoroscopy time when compared with ICE [23]. In our study the time from venous puncture to transseptal puncture was not significantly different between groups, and the reduction of the entire procedure time in the ICE group was mainly achieved by the lack of need for the patient's awareness recovery from anesthesia in the ICE group. More consistent data were analyzed recently by Korsholm *et al.*, who similarly showed that LAAO guided by ICE was associated with shorter duration of the procedure [24]. However, different time intervals of the LAAO procedure were used; thus no direct comparison with our results can be performed.

Similarly to TOE, ICE also allows direct monitoring of acute procedure-related complications (e.g., thrombus formation, pericardial effusion). On the other hand, ICE carries some potential disadvantages. The most important possible complications are those associated with right heart catheterization such as pulmonary embolism, pericardial tamponade, but also bleeding from the puncture site, and vascular complications. Moreover, the mono-plane images may limit the usefulness of ICE in left atrial appendage occluder sizing [4].

Matsuo *et al.* demonstrated that ICE is an effective and safe method of guiding the LAAO procedure. In a series of 27 patients who underwent LAAO, the Watchman device was successfully implanted in all cases and no major complications were reported [25]. Minor complications, which occurred in 4 (14.8%) patients, were mainly hematoma of the groin (3 cases, 11.1%). However, implantation of the Amplatzer Amulet requires a different

assessment during the procedure. Unlike the Watchman device, which can be implanted deep in the appendage, the Amplatzer Amulet disk should cover the left atrial appendage ostium. Thus the mono-plane imaging by ICE, and restricted ability to rotate the probe, may limit the usefulness of ICE for guiding the Amplatzer Amulet implantation. Masson *et al.* published data on the safety and efficacy of a prototype of the Amplatzer Amulet – the Amplatzer Cardiac Plug, which was implanted under the guidance by ICE from the left atrium [26]. Procedural success was achieved in 36 of 37 patients (97%). The authors reported 3 major complications (tamponade, myocardial stroke and major bleeding), which is similar to that of published registries for the same devices but under TOE guidance [27, 28]. The impact of the learning curve was also observed in the analyzed series. Frangieh *et al.* [22] compared percutaneous occlusion of the left atrium with the Watchman device that was deployed either under ICE (32 patients, 42%) or under TOE (44 patients, 58%). The device implantation success rate was 100% in both groups. Total contrast media injected during LAAO as well as fluoroscopy time were comparable between both groups. In contrast, in the present study the fluoroscopic time was insignificantly longer in the ICE group, which may be explained by the need of fluoroscopic assessment of ICE probe position. Also the amount contrast medium used during LAAO was larger in the ICE group, and the difference reached statistical significance. It can be explained by lack of experience with ICE, which resulted in an increase of views performed under fluoroscopy to assess the left atrial appendage.

Berti *et al.* [29] showed that ICE was able to perform the tasks typically provided by TEE during implantation of the Amplatzer Cardiac Plug device for left atrial appendage occlusion, such as assessment of its dimension for device sizing, guidance of transseptal puncture, verification of the delivery sheath position, confirmation of location and stability of the device. But contrary to previous studies the procedural success was lower, and it was achieved in 113 of 121 patients (93.4%). The procedural success rate was lower compared to the present data in the ICE group, but a different approach for ICE was used. Instead of insertion of the ICE probe to the left atrium the ICE probe was positioned in the right atrium or in the coronary sinus. Such a position of the probe may result in poorer quality of images; thus the post-deployment assessment was more difficult.

Study limitations

The main study limitation is the small number of patients included in the study. The results might also be influenced by the fact that the operators had long experience in LAAO procedures as well as in TOE guidance of LAAO, whereas the experience with ICE was very limited.

Conclusions

LAAO using the Amplatzer Amulet may be successfully and safely guided by ICE. Despite the lack of anesthesia or sedation, ICE offered a shorter procedure time compared to TOE guidance. Suboptimal implantation of the occluder, as well as presence of leak or thrombus, was seen with the same incidence in both groups.

Acknowledgments

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Conflict of interest

W. Streb, K. Mitręga and Z. Kalarus are proctors of Abott Medical Sp. z o.o.

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Original paper

Long-term observation of adults after successful repair of aortic coarctation

Beata Róg[1], Magdalena Okólska[1], Piotr Weryński[2], Piotr Wilkołek[3], Tomasz Pawelec[4], Jacek Pająk[5], Piotr Podolec[3], Lidia Tomkiewicz-Pająk[3]

[1]Cardiological Outpatient Clinic, Department of Cardiovascular Diseases, John Paul II Hospital, Krakow, Poland
[2]Department of Pediatric Cardiology, Jagiellonian University Medical College, Krakow, Poland
[3]Department of Cardiac and Vascular Diseases, Institute of Cardiology, Jagiellonian University Medical College, John Paul II Hospital, Krakow, Poland
[4]Department of Interventional Cardiology, Jagiellonian University Medical College and John Paul II Hospital, Krakow, Poland
[5]Pediatric Heart Surgery Department and General Pediatric Surgery Department, Medical University of Warsaw, Warsaw, Poland

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Abstract

Introduction: Despite successful repair of aortic coarctation, cardiovascular complications occur.

Aim: To analyse type and frequency of late complications and their impact on exercise capacity in adults after aortic coarctation repair.

Material and methods: Fifty-eight adults after aortic coarctation repair, 36 male, median age 27.46 ±10.57, were compared to 30 healthy volunteers. Physical examination, transthoracic echocardiography, carotid intima-media thickness measurement, cardiopulmonary exercise test and 24-hour ambulatory blood pressure monitoring were performed.

Results: The main complications were: arterial hypertension 48.3%, myocardial hypertrophy in echocardiography 29.34%, recoarctation 25.86%, aortic dilation 13.79% and coronary artery disease 6.89%. Exercise tolerance was reduced in the cardiopulmonary exercise test. The VO_2/kg peak was lower, 29.01 ±8.79 vs. 49.16 ±7.38 ml/kg/min, $p < 0.001$, VE/VCO_2 peak higher 28.18 ±4.69 vs. 26.78 ±3.13, $p = 0.017$. The peak heart rate was reduced, 157.28 ±22.22 vs. 177.93 ±23.08 bpm, $p < 0.001$, peak systolic blood pressure was higher, 174.79 ±17.62 vs. 153.33 ±4.79 mm Hg, $p < 0.001$. Systolic blood pressure in 24-hour ambulatory monitoring correlated with left ventricle mass index, $r = 0.29$, $p = 0.025$, wall thickness, $r = 0.31$, $p = 0.039$. Age at operation was related to left ventricle wall thickness, $r = 0.27$, $p = 0.041$, and carotid intima-media thickness, $r = 0.26$, $p = 0.046$. There was no association of any cardio-pulmonary parameters with time from surgery, type of operation or echocardiography results.

Conclusions: Adults after aortic coarctation repair suffer from arterial hypertension, recurrent aortic stenosis, aortic aneurysms, and coronary artery disease. Reduced exercise capacity in cardio-pulmonary exercise test is related to hypertensive reaction and chronotropic incompetence.

Key words: atherosclerosis risk factors, coarctation of aorta, exercise capacity, cardio-pulmonary exercise test, long-term complications in coarctation of the aorta.

Summary

Despite successful repair of aortic coarctation, cardiovascular complications occur. The aim of this study was to analyse type and frequency of late complications and their impact on exercise capacity in adults after aortic coarctation repair. Adults after aortic coarctation repair suffer from arterial hypertension, recurrent aortic stenosis, aortic aneurysms, and coronary artery disease. Reduced exercise capacity in the cardio-pulmonary exercise test is related to hypertensive reaction and chronotropic incompetence.

Introduction

Coarctation of the aorta (CoA) is a congenital narrowing of the descending aorta at the level of the subclavian artery [1]. It is the fifth most common congenital heart disorder with a prevalence from 5% to 9% of all congenital heart diseases [2] and 2 : 1 predominance in males [3].

Corresponding author:
Lidia Tomkiewicz-Pająk MD, PhD, Department of Cardiac and Vascular Diseases, Institute of Cardiology, John Paul II Hospital, 80 Prądnicka St, 31-202 Krakow, Poland, e-mail: ltom@wp.pl
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Aortic coarctation may occur as a discrete stenosis; it can also be related to long segment narrowing, hypoplasia of the aortic arch, and stenosis of the abdominal aorta, and may have collateral vessels [4]. Unrepaired CoA is associated with congestive heart failure, aortic rupture, infectious endocarditis and intracranial haemorrhage [2] and mortality of more than 80% by the age 50 years [3]. Currently, several treatment options are available, including surgical and transcatheter interventions by balloon angioplasty and stenting, with procedure mortality < 1% [1]. Despite improving short-term results, survival after aortic coarctation repair is decreased, with a survival rate of 74% at 30 years of follow-up [1], due to increased arterial stiffness, arterial hypertension, ischaemic heart disease, atherosclerosis, chronic heart failure, aortic root aneurysms and cerebral vascular accidents [5–10]. Despite a successful repair of aortic coarctation, which improves prognosis and prolongs life, cardiovascular complications occur in most convalescents: arterial hypertension in 32.5% of CoA patients [11], recoarctation of the aorta in 3–26% [5], ischaemic heart disease in 4.9% [12], aortic aneurysms in 26% [5].

Aim

The aim of this study was to describe and analyze the type and frequency of late complications in adult patients after coarctation of the aorta repair, and to assess their impact on exercise capacity.

Material and methods

Fifty-eight adult patients after coarctation of aorta repair being under control of the Cardiology Institute in Krakow, Poland were included in the study. They were compared to 30 healthy, age- and sex-matched volunteers. All the participants underwent physical examination, ambulatory blood pressure measurement, transthoracic echocardiography, carotid intima-media thickness estimation and cardio-pulmonary exercise test. The clinical analysis included: age, body mass index (BMI), body surface area (BSA), arm and leg blood pressure measurement. Data about age at surgery, type of operation, occurrence of recoarctation, vascular complications (e.g. arterial hypertension, coronary artery disease, stroke) and therapy were collected. The patients were included in the study if they were aged ≥ 18 years old and clinically stable for at least 3 months before examination. The exclusion criteria were: acute vascular or inflammatory illness, pregnancy, neoplastic disease, physical disability making cardiopulmonary exercise test unfeasible (one person was excluded due to paraplegia caused by spinal cord damage after operation) and mental disorder making it impossible to obtain informed consent. Patients with coexisting severe congenital heart diseases (e.g. single ventricle heart, transposition of the great arteries) were excluded to avoid their influence on exercise capacity in the cardiopulmonary test. All participants presented in the echocardiography preserved systolic function of the left ventricle (ejection fraction above 50% by Simpson estimation). None of the study group presented an arm-leg pressure gradient above 20 mm Hg. In the case of restenosis in medical history, patients underwent cardiac catheterization before this research and were treated with percutaneous angioplasty or stent implantation with a successful result in hemodynamic measurement.

All the participants signed informed consent before enrolling in the study. The study protocol followed the Helsinki Declaration and was approved by the local ethical committee (license no. 122.6120.27.2016).

24-hour ambulatory blood pressure measurement (ABPM)

Twenty-four hour analysis of the arterial blood pressure was conducted using an automatic sphygmomanometer (automatic sphygmomanometr (Spacelabs Healthcare)). The measurement was taken at the right arm every 15 min during the day and every 30 min during the night (daytime 7 a.m. to 10 p.m., night-time 10 p.m. to 7 a.m.). The average values of the systolic and diastolic pressure were calculated from all scores; the recordings were considered when they included more than 80% valid measurements. The anti hypertensive therapy (if indicated previously) was continued during the examination. Values higher than 135/85 mm Hg during the daytime and above 120/70 mm Hg at night-time were considered indicative of arterial hypertension [13].

Transthoracic echocardiography (TTE)

All subjects underwent comprehensive transthoracic echocardiography using the Vivid 7 system, General Electric Medical Systems, USA with a 2.5 MHz probe in 2D, M and Doppler modes. The left ventricle systolic (Biplane Simpson method) and diastolic function (Tissue Doppler Imaging) were estimated as well as the left ventricle wall thickness and mass, which was indexed for body surface area. The concomitant valvular heart diseases were acquired. The aortic root diameter and a peak systolic transisthmic gradient were obtained from the suprasternal window. According to ESC guidelines [13] left ventricular hypertrophy was diagnosed if left ventricular mass index (LVMI) was higher than 115 g/m^2 for men and 95 g/m^2 for women, while impaired systolic left ventricle function was diagnosed when ejection fraction measured by the Simpson method extended below 50%.

Carotid intima-media thickness (CIMT)

The measurements were obtained from the arterial wall segments of the right and left common carotid arteries, carotid bulbs and internal carotid arteries. The mean CIMT was defined as the mean CIMT of the

near and far walls from both the left and right carotid arteries from three measurements [14]. The Vivid 7 system, General Electric Medical Systems, USA with 7.5 to 10 MHz linear probe was used. The examinations were conducted by one experienced physician, with no blinded results.

Cardiopulmonary exercise test (CPET)

The cardiopulmonary exercise test was performed to evaluate the exercise tolerance in the symptom limited modified Bruce protocol. Oxygen uptake (VO_2), carbon dioxide production (VCO_2) and minute ventilation (VE) were measured at rest and peak exercise with a computerized analyser. The peak oxygen uptake VO_2/kg peak (ml/kg/min) determined by the highest value of workload, peak heart rate and percentage of maximal heart rate were assessed. The ventilatory anaerobic threshold was calculated by means of the V-slope method. The ventilatory equivalent for carbon dioxide (VE/VCO_2) was calculated as the amount of ventilation needed for the elimination of a given amount of carbon dioxide. The respiratory exchange ratio (RER) was assessed by dividing VCO_2 by VO_2 [15, 16]. The cardiopulmonary exercise test was considered as maximal if the respiratory quotient (carbon dioxide production divided by oxygen consumption) was higher than 1.1, maximal heart rate higher than 85% of the age predicted maximal heart rate or maximal exertion of the patient occurred. Exercise capacity was quantified as metabolic equivalents (METs); one metabolic equivalent is the amount of oxygen consumed at rest and is equivalent to 3.5 ml O_2/kg body × min. The blood pressure was measured at rest, every stage during the exercise, at peak workload and at recovery. All the anti-hypertensive therapy (including β-blockers) was suspended 48 h before the exercise test.

Statistical analysis

The continuous data were presented by means of the average value with the standard deviation or by median with the lower and upper quartile in the case of non-normal distribution of the data. To compare the averages between three different populations one-way ANOVA was performed if all assumptions were met, otherwise the Kruskal-Wallis test or Welch test was used. In the case of significant results of one of those analyses, a post-hoc test was applied. Normality was verified by means of the Shapiro-Wilk test, and the Levene test was applied to investigate heterogeneity of variance. Correlation between two continuous variables was assessed based on the Pearson or Spearman coefficient. Results with a *p*-value lower than the significance level $\alpha = 0.05$ were considered as statistically significant. The calculations were performed using the R statistical package version 3.3.1 (www.r-project.org).

Results

Fifty-eight adult patients after coarctation of aorta repair were included in the study, 36 male, 22 female, median age 27.46 ±10.57 years. They were compared to 30 healthy, age- and sex-matched volunteers**.** The median age at coarctation operation time was 8.68 ±8.64 years, the median follow-up time was 20.39 ±9.8 years. The most common type of operation was Dacron/Gore-tex patch repair in 25 (43.1%) patients, 18 (31.03%) were operated on by Waldhausen subclavian flap angioplasty, 7 (12.06%) by end-to-end anastomosis and 8 (13.8%) underwent percutaneous angioplasty with stent implantation in adolescent or adult age. Fifteen (25.86%) were operated on due to concomitant ventricle septal defect (VSD), 6 (12.07%) due to persistent ductus arteriosus (PDA), 10 (17.24%) because of hypoplastic aortic arch, 1 (1.72%) person underwent aortic valve replacement (AVR) and 4 (6.89%) Bentall de Bono operation due to aortic valve dysfunction and aortic aneurysm. In the CoA group, there were 36 (62.06%) people with bicuspid aortic valve. Patients with recoarctation (15, 25.86%) in medical history were treated at median age 15.5 ±8.17 years. None of the observed patients had a blood pressure (BP) difference > 20 mm Hg between upper and lower limbs (Table I).

Transthoracic echocardiography and carotid intima-media thickness

We revealed that CoA patients in comparison to healthy controls have higher echocardiographic parameters: left ventricular mass index (LVMI) 118.09 ±33.28 vs. 96.41 ±19.99 g/m^2, $p < 0.001$, left ventricle diastolic wall thickness: interventricular septum diameter (IVSD) 10.5 ±1.95 vs. 8.9 ±1.06 mm and posterior wall diameter (PWD) 9.81±1.58 vs. 8.80 ±0.96 mm, $p < 0.001$ respectively, ascending aorta diameter 31.50 ±6.16 vs. 28.03 ±1.79 mm, $p < 0.001$ and impaired diastolic function of the left ventricle: E′ velocity 10.05 ±2.66 vs. 11.33 ±2.61 cm/s, $p = 0.034$, E/E' 10.22 ±5.25 vs. 8.01 ±1.76, $p = 0.028$ and mitral annular plane systolic excursion (MAPSE) 15.03 ±1.65 vs. 15.90 ±1.03 mm, $p = 0.011$. Intima-media thickness of the carotid arteries was higher in the CoA group, 0.69 ±0.18 vs. 0.57 ±0.08 mm, $p < 0.001$ (Table II).

We found no statistically significant differences of the left ventricle dimensions and systolic function between CoA patients and healthy controls.

When comparing echocardiographic parameters of the CoA cohort with arterial hypertension (28/58) to normotensive CoA subjects (30/58) then in hypertensive CoA patients these parameters were higher: LVMI 129.84 ±36.79 vs. 107.13 ±25.68 g/m^2, $p = 0.008$, IVSD 11.46 ±1.99 vs. 9.60 ±1.45 mm, $p < 0.001$, PWD 10.42 ±1.79 vs. 9.23 ±1.10 mm, $p = 0.003$, CIMT 0.77 ±0.18 vs. 0.61 ±0.14 mm, $p < 0.001$ and the left ventricle diastolic function was impaired in the hypertensive group, E′ mean 9.32 ±3.09 vs. 10.73 ±2.01 cm/s, $p = 0.042$, E/E′ 11.53 ±6.91 vs. 8.99

Table I. Baseline characteristics of study group

Parameter	CoA (*n* = 58) 22 F/36 M	CG (*n* = 30) 12 F/18 M	*P*-value
Age [years]	27.46 ±10.57	27.50 ±8.60	0.930
Height [cm]	172.05 ±10.81	174.07 ±8.91	0.383
Weight [kg]	73.21 ±15.06	73.30 ±14.14	0.978
BMI [kg/m^2]	23.63 ±12.81	24.49 ±9.90	0.972
BSA [m^2]	1.84 ±0.24	1.87 ±0.21	0.562
Age at operation [years]	8.68 ±8.64	N/D	N/D
Follow-up [years]	20.39 ±9.8	N/D	N/D
Moderate MR (%)	6.89	0	N/D
Severe AS or AR (%)	0	0	N/D
Moderate AS (%)	12.06	0	N/D
Moderate AR (%)	24.14	0	N/D
Bicuspid aortic valve (%)	62.06	0	N/D
Aortic valve replacement (%)	1.72	0	N/D
Aortic aneurysm (%)	0	0	N/D
Aortic dilatation (%)	13.79	0	N/D
Bentall de Bono surgery (%)	6.89	0	N/D
Hypoplastic aortic arch (%)	17.24	0	N/D
Recoarctation (%)	25.86	0	N/D
Arterial hypertension (%)	48.31	0	N/D
Coronary artery intervention (%)	6.89	0	N/D
Cerebral vascular insult (%)	0	0	N/D
β-blocker therapy (%)	53.4	0	N/D
ACE inhibitor therapy (%)	36.2	0	N/D
AT1 blockers (%)	6.9	0	N/D
Ca blockers (%)	17.2	0	N/D
Diuretics therapy (%)	22.4	0	N/D
Statin therapy (%)	34.2	0	N/D
ASA (%)	6.9	0	N/D

AR – aortic valve, regurgitation, AS – aortic valve stenosis, ASA – acetylsalicylic acid, BMI – body mass index, BSA – body surface area, MR – mitral valve regurgitation. Data are presented as means with standard deviation (mean ± SD) or as percentage (%) of total number; p-value ≤ 0.05 is considered as statistically significant.

±2.57, $p = 0.065$, MAPSE 15.00 ±2.03 vs. 15.06 ±1.23 mm, $p = 0.879$.

No statistically significant differences in the echocardiography were observed between CoA subjects who underwent treatment of re-stenosis (15/58) and the cohort without residual coarctation (43/58): LVMI 110.72 ±33.41 vs. 120.67 ±33.24 g/m^2, $p = 0.323$, IVSD 10.66 ±2.44 vs. 10.44 ±1.79 mm, $p = 0.705$, PWD 9.73 ±1.10 vs. 9.83 ±1.73, $p = 0.829$, E′ mean 11.13 ±2.29 vs. 9.67 ±2.70 cm/s, $p = 0.067$, E/E′ 8.53 ±2.95 vs. 10.80 ±5.76, $p = 0.152$, CIMT 0.71 ±0.16 vs. 0.68 ±0.19 mm, $p = 0.561$.

Cardiopulmonary exercise test

The results of the cardiopulmonary exercise tests of CoA patients in comparison with control group revealed statistically significant differences ($p < 0.001$): VO_2/kg AT and VO_2/kg peak were significantly lower 20.09 ±6.0 vs. 36.31 ±10.68 and 29.01 ±8.79 vs. 49.16 ±7.38 ml/kg/min, $p < 0.001$ respectively and VE/VCO_2 peak was higher, 28.18 ±4.69 vs. 26.78 ±3.13, $p = 0.017$, in CoA patients than in the control group. The peak heart rate (HR) and the percentage of maximal heart rate were significantly reduced in the study group. The peak systolic blood pres-

Table II. Echocardiographic parameters: comparison between coarctation of aorta patients and controls

Parameter	Study group (n = 58)	Controls (n = 30)	P-value
LVD [m]	50.41 ±6.19	48.66 ±4.75	0.180
LVS [mm]	31.26 ±5.17	30.13 ±4.18	0.306
LV EF (%)	66.46 ±6.42	67.16 ±4.76	0.599
LVMI [g/m^2]	118.09 ±33.28	96.41 ±19.99	0.0015
IVSD [mm]	10.50 ±1.96	8.90 ±1.06	< 0.001
PWD [mm]	9.81 ±1.58	8.80 ±0.96	0.0019
Ascending aorta [mm]	31.50 ±6.16	28.03 ±1.79	0.003
Maximal gradient at coarctation [mm Hg]	25.86 ±12.96	6.65 ±1.56	< 0.001
E′ mean [cm/s]	10.05 ±2.66	11.33 ±2.61	0.034
E/E′	10.21 ±5.25	8.01 ±1.76	0.028
MAPSE [mm]	15.03 ±1.65	15.90 ±1.03	0.011
CIMT [mm]	0.69 ±0.18	0.57 ±0.08	< 0.001

CIMT – carotid intima-media thickness, IVSD – interventricular septum diameter in diastole, LV EF – left ventricle ejection fraction, LVD – left ventricle diastolic dimension, LVMI – left ventricle mass index, LVS – left ventricle systolic dimension, MAPSE – mitral annular plane systolic excursion, PWD – posterior wall diameter in diastole. Data are presented as means with standard deviation (mean ± SD) or as percentage (%) of total number; pvalue ≤ 0.05 is considered as statistically significant.

sure was higher in the CoA cohort when exercise capacity as metabolic equivalents (METs) and duration of exercise were lower. Significant correlations between VE/VCO_2 and duration of CPET the test (r = 0.35, p = 0.007), HR peak (r = 0.29, p = 0.022), peak workload (r = 0.51, p < 0.001) and peak blood pressure were found (r = 0.29, p = 0.023). In the whole CoA group there were no significant correlations between CPET parameters and age, BMI or time from surgery (Table III).

In comparison between hypertensive CoA patients (28/58) and normotensive CoA patients (30/58), heart rate peak was lower, 149.75 ±20.77 vs. 164.30 ±21.52 bpm, p = 0.011, and systolic blood pressure peak higher in the hypertensive population, 182.93 ±14.70 vs. 167.20

Table III. Cardiopulmonary exercise test: comparison of coarctation of aorta patients to control group

Parameter	Study group (n = 58)	Controls (n = 30)	P-value
SBP resting [mm Hg]	136.55 ±16.27	123.47 ±10.34	< 0.001
DBP resting [mm Hg]	74.95 ±12.29	74.83 ±6.91	0.955
% AT predicted	65.07 ±18.34	94.57 ±2.79	< 0.001
Time peak [min]	15.28 ±3.21	16.82 ±2.78	0.027
HR peak [bpm]	157.28 ±22.22	177.93 ±23.08	< 0.001
% HR max	78.81 ±14.72	95.17 ±2.96	< 0.001
VO_2/kg peak [ml/kg/min]	29.01 ±8.79	49.16 ±7.38	< 0.001
% VO_2/kg predicted	81.91 ±20.81	95.97 ±3.92	< 0.001
RER peak	1.11 ±0.08	1.12 ±0.09	0.415
VE/VCO_2peak	28.18 ±4.69	26.78 ±3.13	0.017
BR peak	45.73 ±23.11	41.76 ±16.95	0.414
MET peak	11.03 ±2.72	12.49 ±0.71	0.005
SBP peak [mm Hg]	174.79 ±17.62	153.33 ±4.79	< 0.001
DBP peak [mm Hg]	77.00 ±14.91	80.00 ±0.21	0.275

BR peak – peak breathing reserve, DBP – diastolic blood pressure, HR peak – heart rate peak, % HR max – percentage of maximal heart rate, SBP – systolic blood pressure, RER peak – peak respiratory exchange ratio, VCO_2 peak – peak carbon dioxide production, VCO_2 rest – carbon dioxide production at rest, VE/VCO_2peak – peak ventilatory equivalent for CO_2, VO2/kg AT – oxygen uptake per kg at anaerobic threshold, VO_2/kg peak – peak oxygen uptake per kg, VO_2/kg rest – oxygen uptake per kg at rest, VO_2 peak – peak oxygen uptake, VO_2 rest – oxygen uptake at rest. Data are presented as means with standard deviation (mean ± SD) or as percentage (%) of total number; p-value ≤ 0.05 is considered as statistically significant.

±16.89 mm Hg, $p < 0.001$. The VO_2/kg peak and the percentage of predicted value for age were similar in these groups: 29.27 ±9.90 vs. 28.76 ±7.77 ml/kg/min, $p = 0.828$, 83.86 ±22.19 vs. 80.10 ±19.64%, $p = 0.497$ respectively. There was no statistically significant difference between the groups in VE/VCO_2 peak: 24.50 ±3.17 vs. 26.08 ±4.36 ml/kg/min, $p = 0.120$, duration of the test: 15.24 ±2.99 vs. 15.30 ±3.44 min, $p = 0.948$ and maximal workload: 11.24 ±2.49 vs. 10.83 ±2.94 MET, $p = 0.562$ (Table IV).

No statistically significant differences in the cardiopulmonary results were observed between CoA subjects who underwent treatment of re-stenosis (15/58) and the cohort without residual coarctation (43/58): VO_2/kg peak 28.13 ±8.77 vs. 29.31 ±8.87 ml/kg/min, $p = 0.656$, VE/VCO_2 peak 24.31 ±3.20 vs. 25.67 ±4.07 ml/kg/min, $p = 0.243$, maximal workload 11.16 ±2.55 vs. 10.98 ±2.80 MET, $p = 0.822$, SBP peak 180.33 ±16.95 vs. 172.86 ±17.62 mm Hg, $p = 0.159$, DBP peak 81.33 ±15.52 vs. 75.49 ±14.57 mm Hg, $p = 0.194$ (Table V).

24-hour ambulatory blood pressure measurement

The results of the 24-hour ABPM of CoA patients in comparison with the control group revealed statistically significant differences: daytime systolic blood pressure (SBP) and diastolic blood pressure (DBP) were higher, 128.13 ±12.47 vs. 106.43 ±6.23 mm Hg and 74.62 ±9.60 vs. 69.83 ±5.29 mm Hg, $p < 0.001$ and $p = 0.013$ respectively; the night values of SBP and DBP were also significantly raised in the CoA cohort (112.08 ±13.63 vs. 97.36 ±10.41 mm Hg and 62.91 ±9.17 vs. 59.03 ±8.28 mm Hg, $p < 0.001$ and $p = 0.026$ respectively.

When analysing ABPM results in the hypertensive CoA cohort in comparison to the normotensive CoA cohort, the SBP during the day and the night time were higher in the first group, 134.46 ±10.36 vs. 122.23 ±11.45 mm Hg and 118.60 ±12.28 vs. 106.03 ±12.06 mm Hg, $p < 0.001$; no other statistically significant differences between these groups were exposed in ABPM.

In comparison of ABPM measurements in CoA subjects who underwent treatment of re-stenosis (15/58) and the cohort without residual coarctation (43/58) there were no statistically significant differences in SBP and DBP values during the day and night time between the groups.

In the whole CoA group, we revealed a statistically significant correlation of systolic blood pressure in ABPM with: left ventricle mass index ($r = 0.29$, $p = 0.025$) and

Table IV. Comparison of hypertensive to normotensive coarctation of aorta patients

Parameter	H CoA (n = 28)	N CG (n = 30)	*P*-value
Age [years]	33.50 ±12.23	25.73 ±7.12	0.004
Age at operation [years]	10.57 ±14.89	6.76 ±9.34	0.245
Follow-up [years]	22.07 ±11.56	18.96 ±7.78	0.232
Hypoplastic aortic arch (%)	28.57	6.66	0.027
Recoarctation (%)	39.28	13.33	0.024
HR peak [bpm]	149.75 ±20.77	164.30 ±21.52	0.011
% HR max	75.21 ±13.50	82.17 ±15.22	0.071
VO_2/kg peak [ml/kg/min]	29.27 ±9.90	28.76 ±7.77	0.828
% VO_2/kg peak predicted	83.86 ±22.19	80.10 ±19.64	0.497
VE/VCO_2peak	24.50 ±3.17	26.08 ±4.36	0.120
SBP peak [mm Hg]	182.93 ±14.70	167.20 ±16.89	< 0.001
DBP peak [mm Hg]	80.82 ±15.19	73.43 ±13.96	0.058
LVMI [g/m^2]	129.84 ±36.79	107.13 ±25.68	0.008
IVSD [mm]	11.46 ±1.99	9.60 ±1.45	< 0.001
PWD [mm]	10.42 ±1.79	9.23 ±1.10	0.003
E′ mean [cm/s]	9.32 ±3.09	10.73 ±2.01	0.042
E/E′	11.53 ±6.91	8.99 ±2.57	0.065
CIMT [mm]	0.77 ±0.18	0.61 ±0.14	< 0.001

CIMT – carotid intima-media thickness, DBP – diastolic blood pressure, HR peak – heart rate peak, % HR max – percentage of maximal heart rate, IVSD – interventricular septum diameter in diastole, LVMI – left ventricle mass index, PWD – posterior wall diameter in diastole, SBP – systolic blood pressure, VE/VCO_2peak – peak ventilatory equivalent for CO2, VO_2/kg peak – peak oxygen uptake per kg, VO_2/kg rest – oxygen uptake per kg at rest, VO_2 peak – peak oxygen uptake. Data are presented as means with standard deviation (mean +SD) or as percentage (%) of total number; p-value ≤ 0.05 is considered as statistically significant.

Table V. Comparison of recoarctation to no-recoarctation of aorta patients

Parameter	Re CoA (n = 15)	NoRe CoA (n = 43)	P-value
Age [years]	26.26 ±6.34	29.93 ±11.12	0.233
Age at operation [years]	5.80 ±5.87	9.58 ±13.87	0.312
Follow-up [years]	20.73 ±9.41	20.37 ±10.07	0.903
Hypoplastic aortic arch (%)	46.66	6.97	< 0.001
Arterial hypertension (%)	73.33	39.53	< 0.001
HR peak [bpm]	62.93 ±15.25	65.81 ±19.40	0.604
% HR max	71.93 ±14.51	81.21 ±14.17	0.034
VO_2/kg peak [ml/kg/min]	28.13 ±8.77	29.31 ±8.87	0.656
% VO_2/kg peak predicted	77.47 ±19.85	83.46 ±21.14	0.341
VE/VCO_2peak	24.31 ±3.20	25.67 ±4.07	0.243
SBP peak [mm Hg]	180.33 ±16.95	172.86 ±17.62	0.159
DBP peak [mm Hg]	81.33 ±15.52	75.49 ±14.57	0.194
LVMI [g/m^2]	110.72 ±33.41	120.67 ±33.24	0.323
IVSD [mm]	10.66 ±2.44	10.44 ±1.79	0.705
PWD [mm]	9.73 ±1.10	9.83 ±1.73	0.829
E′ mean [cm/s]	11.13 ±2.29	9.67 ±2.70	0.067
E/E′	8.53 ±2.95	10.80 ±5.76	0.152
CIMT [mm]	0.71 ±0.16	0.68 ±0.19	0.561

CIMT – carotid intima-media thickness, DBP – diastolic blood pressure, HR peak – heart rate peak, % HR max – percentage of maximal heart rate, IVSD – interventricular septum diameter in diastole, LVMI – left ventricle mass index, PWD – posterior wall diameter in diastole, SBP – systolic blood pressure, VE/VCO_2peak – peak ventilatory equivalent for CO2, VO_2/kg peak – peak oxygen uptake per kg, VO_2/kg rest – oxygen uptake per kg at rest, VO_2 peak – peak oxygen uptake. Data are presented as means with standard deviation (mean ± SD) or as percentage (%) of total number; p-value ≤ 0.05 is considered as statistically significant.

wall thickness (r = 0.31, p = 0.039). Older age at operation was related to left ventricle walls thickness (r = 0.27, p = 0.041) and carotid intima-media thickness (r = 0.26, p = 0.046). Statistical analysis showed no association of any cardio-pulmonary parameters with time from surgery, type of operation or echocardiography results.

Discussion

The principal finding in the present study is that in patients after aortic coarctation repair despite successful short-term outcomes late cardiovascular complications occur.

The main comorbidity after successful repair of aortic coarctation is arterial hypertension, present in 48.3% of subjects in our study, which is compatible with literature data, 32.5% (range: 25–68%) [11]. Hypertensive patients in our study were older. Many of them were treated due to recoarctation and suffered from hypoplastic aortic arch. Patients with arterial hypertension presented higher mass of the left ventricle, greater wall thickness and greater carotid intima-media thickness. They had impaired left ventricle diastolic function. These changes are common in patients with arterial hypertension and widely described in the literature [17–20]. Causes of arterial hypertension in coarctation of aorta patients are multifactorial. The aorta wall, in the section before the narrowing, has a different structure, contains more collagen and less elastin fibre, and lacks smooth muscle cells. The aortic wall stiffness is increased [9], sensitivity reduced and the aorta mechanoreceptors activated. The pathophysiological processes are initiated with an advantage of the sympathetic system, changes in the endocrine system, endothelial dysfunction and remodelling of the vessels, which leads to increase of the peripheral vascular resistance and increase in blood pressure [20]. Data from the literature [21] indicate that among congenital heart diseases arterial hypertension is the most frequent in coarctation of the aorta. The discussion about conditions of coarctation repair (time of intervention and type of operation) to avoid arterial hypertension is still open. In our study patients with arterial hypertension were older and operated on at older age than normotensive subjects. The observations from other studies [22] reveal that younger age at operation is related to lower arterial pressure at follow-up; it is the best if treatment is applied before 9–10 years old. We did not observe the

influence of type of surgery on development of arterial hypertension. The opposite conclusion was presented by Giordano *et al.* [23] – patients after subclavian flap surgery in comparison to end-to-end anastomosis showed a higher incidence of hypertension. The authors explain that fact by greater resection of the abnormal aortic tissue in the second method and lower aortic stiffness as a consequence. Our observations from cardiopulmonary exercise tests revealed that raised initial arterial pressure in the exercise test is a marker of hypertensive disease in CoA subjects. All hypertensive patients presented higher values of the resting arterial pressure in CPET than normotensive ones. On the other hand, only 5 out of 58 patients (8.62%) reached values above 200/110 mm Hg at peak workload, which was considered as a hypertensive reaction to exercise test. All of them were treated due to arterial hypertension before. Many authors [24–30] have analysed arterial pressure reaction on effort during the exercise tests. The main conclusions are that elevated arterial pressure at the beginning of the test and hypertensive reaction at peak exercise are the symptoms of arterial hypertension in longer follow-up.

In the present research, the cardiopulmonary exercise tests of CoA patients in comparison to controls revealed lower values of: VO_2/kg peak, heart rate peak, % max HR, exercise capacity as metabolic equivalents and duration of an exercise. The reason for these results is still uncertain. There may be some influence of chronotropic incompetence, which occurred in 27.58% of subjects if described as maximal heart rate percent below 80% at peak workload. β-blocker therapy was suspended 48 hours before to avoid its impact on heart rate. Data from the literature [31, 32] indicate that chronotropic incompetence in adults after a congenital heart disease operation was related to lower VO_2/kg peak and higher risk of cardiac insufficiency in future. We revealed significant correlations between VE/VCO_2 and duration of CPET, HR peak, peak workload (METs) and peak blood pressure. No other associations were found.

In our study all patients with restenosis (25.86%) underwent cardiac catheterization before this research and were treated with percutaneous angioplasty or stent implantation with a successful result in hemodynamic measurement. Most of them, despite the effective intervention, suffered from arterial hypertension. Data from the literature [33–40] demonstrate a decrease of arterial pressure after percutaneous intervention, although still higher values than in the healthy population. In our observation, patients with aortic recoarctation had more often concomitant hypoplastic aortic arch. Age at operation and length of follow-up had no impact on aortic restenosis occurrence. We did not observe statistically significant differences between any of the echocardiography or cardiopulmonary test results between patients with recoarctation and the no-recoarctation ones. In case of recurrent significant coarctation of the aorta, invasive treatment is recommended as soon as possible, with modification of hypotensive therapy if needed [41].

A significant comorbidity among CoA patients is aortic aneurysm formation. This process is related to disorders of thoracic aorta wall structure and impaired mechanical function of aortic tissue. Arterial hypertension, which is common in this population, additionally has a positive impact on rise in tension of the aortic walls. More frequent aortic aneurysm development is observed in patients with coexisting bicuspid aortic valve, which can be explained by a general vascular disorder of the thoracic aorta in both groups. In our research we did not observe aortic aneurysm of any patients, but 6.89% of our CoA patients had undergone a Bentall de Bono operation. Furthermore, ascending aorta diameter was higher in the CoA group than in controls and 13.79% of CoA subjects had ascending aorta dilatation. All the cases were related to presence of bicuspid aortic valve. We did not reveal any association between ascending aorta diameter and type of aortic coarctation surgery. Data from the literature [42–44] show that aneurysms are more common after patch aortoplasty technique and transcatheter interventions, particularly balloon angioplasty without stent implantation.

A significant comorbidity after successful aortic coarctation repair is premature atherosclerosis. In our observations 6.89% of patients had confirmed coronary artery disease in angiography. These patients were older than the others from the CoA group, were operated on due to CoA in older age (after 18 years old) and suffered from concomitant cardio-vascular risk factors (e.g. hyperlipidemia, obesity and diabetes mellitus). Other authors have reported [7, 45] that coarctation of aorta does not increase risk of coronary artery disease itself, but due to concomitant arterial hypertension and endothelial dysfunction. Strict control of conventional atherosclerosis risk factors after coarctation repair reduces long-tem vascular risk.

Study limitations

Several limitations of the study should be acknowledged. First, the number of patients in the study was small. It is representative for a patient population in real-life clinical practice, but a larger study group is expected. Second, the hypertensive patients in our study were under treatment such as ACE inhibitors and β-blockers, drugs that have an influence on cardio-pulmonary test results. The therapy was suspended 48 h before the examination to reduce its impact on measurement results. Certainly, longer follow-up is required; some comorbidities may occur at a later time.

Conclusions

Despite successful aortic coarctation repair and positive short-term outcomes, adult patients in longer fol-

low-up are exposed to arterial hypertension, vascular complications such as recurrent aortic stenosis, aneurysms formation and premature atherosclerosis. They have reduced exercise capacity, which is related to hypertensive reaction, increased arterial stiffness and chronotropic incompetence. Exercise intolerance occurs as a result of lowered oxygen uptake and increased ventilatory response. These patients require regular follow-up to reduce long-term morbidity and mortality after coarctation repair.

Conflict of interest

The authors declare no conflict of interest.

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Original paper

Severe, recurrent in-stent carotid restenosis: endovascular approach, risk factors. Results from a prospective academic registry of 2637 consecutive carotid artery stenting procedures (TARGET-CAS)

Łukasz Tekieli[1], Piotr Musiałek[2], Anna Kabłak-Ziembicka[1], Mariusz Trystuła[3], Tadeusz Przewłocki[1], Jacek Legutko[1], Karolina Dzierwa[1], Damian Maciejewski[1], Michał Michalski[4], Piotr Pieniążek[1]

[1]Department of Interventional Cardiology, Institute of Cardiology, Jagiellonian University Medical College, John Paul II Hospital, Krakow, Poland

[2]Department of Cardiac and Vascular Diseases, Institute of Cardiology, Jagiellonian University Medical College, John Paul II Hospital, Krakow, Poland

[3]Department of Vascular Surgery and Endovascular Interventions, John Paul II Hospital, Krakow, Poland

[4]Department of Neurology with Stroke Division, John Paul II Hospital, Krakow, Poland

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Abstract

Introduction: Optimal management of severe carotid in-stent restenosis remains unknown. Prevalence and risk factors of first and recurrent carotid in-stent restenosis in the multi-stent approach have not been established yet.

Aim: To evaluate the safety of different methods of endovascular treatment of carotid in-stent restenosis/recurrent restenosis and to establish its rate and risk factors.

Material and methods: Between January 2001 and June 2016, 2637 neuroprotected carotid artery stenting (CAS) procedures were performed in 2443 patients (men: 67.0%; mean age: 67.9 ±8.8 years, symptomatic: 45.5%). Doppler ultrasound (DUS) evaluation was performed at discharge, after 3–6 months, 12 months, and then annually. Peak systolic velocity of 2–3 and > 3.0 m/s as well as end diastolic velocity of 0.5–0.9 and > 0.9 m/s were DUS criteria for 50–69% and ≥ 70% carotid in-stent restenosis (ISR) respectively. For angiographically confirmed ≥ 70% stenosis balloon re-angioplasty was first line treatment.

Results: Out of 95 DUS detected > 50% ISR (95/2637; 3.6%), 53 were confirmed in angiography as ≥ 70% (53/2637; 2.0%, one total occlusion). All patients were treated with bare balloon (n = 19), drug-eluting balloon (n = 27) or stent-supported (n = 6) angioplasty. One procedure was complicated with stroke (1.9%). Angiographic diameter stenosis (DS) was reduced from 83 ±8.3% to 13 ±7.6% (p < 0.001). There were 13 cases of ≥ 70% recurrent ISR. Bilateral and high-grade stenosis were independent risk factors of restenosis. Initial Carotid Wallstent implantation was a risk factor of first and recurrent in-stent restenosis.

Conclusions: Endovascular treatment of carotid in-stent restenosis is safe. Bilateral and high-grade carotid artery stenosis may increase the risk of restenosis. Initial Carotid Wallstent implantation may increase the risk of first and recurrent restenosis.

Key words: risk factors, carotid artery, carotid artery stenting, in-stent restenosis, carotid Wallstent.

Summary

Long-term durability of carotid artery stenting in terms of incidence of recurrent restenosis is a poorly examined issue. Our results suggest that the risk of restenosis is strongly associated with bilateral and high-grade carotid artery stenosis as well as with initial Carotid Wallstent implantation. These findings may influence the procedure strategy in patients with carotid artery stenosis.

Corresponding author:
Łukasz Tekieli MD, PhD, Department of Interventional Cardiology, Institute of Cardiology, Jagiellonian University Medical College, John Paul II Hospital, 80 Prądnicka St, 31-202 Krakow, Poland, phone: +48 607 414 446, e-mail: ltekieli@szpitaljp2.krakow.pl
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Introduction

Carotid artery stenting (CAS) has emerged as a strong alternative to carotid endarterectomy (CEA) in patients with carotid artery stenosis. Fast development of endovascular techniques and increasing operators' experience have resulted in significant reduction of the periprocedural complication rate during CAS [1]. On the other hand, the growing number of CAS procedures performed around the world entails enlarging population of patients with in-stent restenosis (ISR) defined as reoccurrence of stenosis within stent. The prevalence of ISR after CAS ranges from 4.6% to 6.3%, with half of cases occurring within the first 6 months [2]. There are many ISR risk factors established; they include history of prior ipsilateral neck surgery or irradiation ('hostile-neck' lesions), diabetes, female sex, and dyslipidemia [3–5]. Interestingly, the brand of stent has not yet been investigated as a potential risk factor. Although ISR accompanies endovascular carotid stenosis treatment from the very beginning, there are no well-defined guidelines on how to deal with this issue. Both conservative and interventional approaches have their supporters. Although ISR is usually asymptomatic, Donas *et al.* showed that ISR may be associated with thrombus formation and increased risk of thrombovascular events [6].

Moreover, 2-year follow-up in CREST revealed that patients who had restenosis within 2 years were at greater risk for ipsilateral stroke after the periprocedural period than were those who did not have restenosis [7].

The endovascular approach to ISR includes balloon angioplasty alone, cutting-balloon angioplasty, drug-eluting balloon angioplasty, bare-metal and drug-eluting stent angioplasty [8–11]. Long-term durability of carotid artery stenting in terms of incidence of recurrent restenosis is an even less examined issue. The therapeutic approach to first restenosis may influence both the immediate result and further restenosis reoccurrence.

Table I. Characteristics of 2443 patients undergoing 2637 tailored CAS procedures

Parameter	Value
Age, mean ± SD (range) [years]:	67.9 ±8.8 (33–90)
> 75	261 (16.8%)
Men	1685 (67.0%)
Smoking – current or past	1108 (44.1%)
Symptomatic ICA/CCA stenosis	1145 (45.5%)
Ipsilateral stroke*	982 (39.1%)
TIA*	512 (20.4%)
Peripheral artery disease	464 (18.4%)
Diabetes mellitus	783 (31.1%)
Insulin therapy (% of diabetics)	281 (35.9%)
Arterial hypertension	2339 (93.0%)
Hyperlipidemia	1681 (66.8%)
Significant bilateral ICA disease	817 (32.5%)
Contralateral ICA occlusion	334 (13.3%)
CAD by angiography‡	1678 (66.7%)
ICA % stenosis by angiography, mean ± SD (range)	83.7 ±10 (52–99)

*Continuous data are presented as means ± standard deviation; categorical data are given as counts (percentages). CAS – carotid artery stenting, ICA – internal carotid artery, CCA – common carotid artery, TIA – transient ischemic attack, CEA – carotid endarterectomy, CAD – coronary artery disease. *Within 6 months prior to CAS. ‡Coronary artery lesion(s) ≥ 50% by quantitative angiography.*

Aim

The aim of the study was to evaluate the safety of different methods of endovascular treatment of carotid in-stent first/recurrent restenosis and to establish its rate and risk factors.

Material and methods

Study population

Between January 2001 and June 2016, 2637 neuroprotected carotid artery stenting procedures were performed in 2443 patients (men: 67.0%; mean age: 67.9 ±8.8 years, range: 33–90, symptomatic: 45.5%), according to the 'tailored-CAS' algorithm [12]. Patient characteristics are shown in Table I.

Ultrasound evaluation

Neurological and Doppler ultrasound evaluation (DUS) were performed at discharge, 3–6, 12 months after the procedure, and then annually. All DUS examinations were performed in a certified laboratory using a linear 7–10 MHz probe to evaluate the degree of ISR and they were evaluated according to international standards. Restenosis was defined as ≥ 50% diameter reducing stenosis (or occlusion). The peak systolic velocity (PSV) criteria used to evaluate the degree of ISR were 170–299 cm/s for 50–69% stenosis and > 300 cm/s for ≥ 70% ISR. PSV was measured within, distally and proximally to the stent. The highest PSV values were included in the analysis [13, 14]. The minimal time of observation was 12 months.

Endovascular approach

Balloon (non-covered until 2012, drug covered afterwards) angioplasty alone was performed in patients with angiographically confirmed ≥ 70% ISR. The balloon diameter corresponded to the distal internal carotid artery (ICA) reference. For diffused restenosis, extending outside the stent, implantation of another stent was considered. Subsequent, recurrent ≥ 70% ISR was treated with

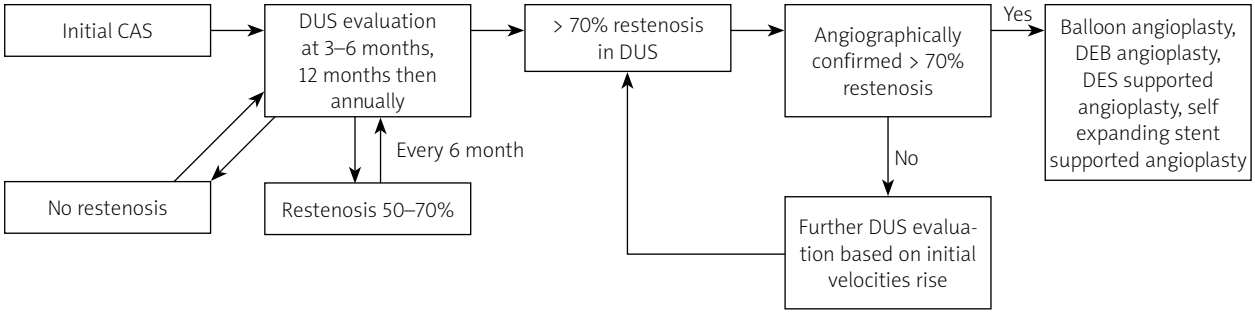

Figure 1. Study flowchart: detection and treatment of carotid in-stent restenosis

drug-eluting balloon (DEB), coronary drug-eluting stent (DES) implantation or self-expanding paclitaxel covered coronary stent supported angioplasty. The study flow chart is shown in Figure 1.

Definitions

- Closed-cell design stent – characterized by interconnected stent struts with small free cell areas (< 5 mm^2),
- Distal neuroprotection – filter system used for capturing embolic material during carotid artery stenting with maintained ICA antegrade blood flow,
- Intolerance – cerebral ischemia symptoms occurring as a result of ICA flow blockage during neuroprotection/angioplasty balloon inflation,
- Neuroprotected carotid artery stenting – stent-supported carotid artery angioplasty using distal or proximal neuroprotection system,
- Proximal neuroprotection – system providing ICA blood flow cessation/reversal by common carotid and external carotid balloon occlusion during CAS,
- Restenosis – ≥ 50% diameter reducing in-stent stenosis (or occlusion) evaluated in ultrasound examination,
- Symptomatic patient – with history of ischemic stroke/transient ischemic attack (TIA), within preceding 6 months,
- 'Tailored-CAS' – patient and lesion adjusted selection of neuroprotection system and stent type; preferential use of proximal neuroprotection and close-cell stent for high-risk lesions (> 95% stenosis, thrombus-containing lesions, 'soft' lesions, i.e. with computed tomography density of < 60 HU) and in symptomatic patients.

Ethics

This study was approved by the Committee on Research Ethics at our hospital, in compliance with the ethical guidelines of the Declaration of Helsinki. All participants gave written informed consent prior to study entry.

Statistical analysis

Continuous data were presented as means ± standard deviation; categorical data were given as counts (percentages). Normality of distribution was assessed by Kolmogorov-Smirnov test. The χ^2 test was used for comparison of categorical data. Potential risk factors included sex, age, smoking status, hypertension, hypercholesterolemia, prior stroke/TIA, prior ipsilateral CEA, contralateral stenosis/occlusion, stenosis grade, peripheral artery disease, stent type (open- vs. closed-cell design), stent brand and stent underexpansion defined as post-CAS stenosis of > 30%. In the case of repeated angioplasty due to restenosis, follow-up procedures were then conducted the same way as after initial angioplasty.

Univariate and multivariate Cox proportional hazard regression models were used to determine risk factors for the development of the first and recurrent restenosis. For each potential risk factor, the hazard ratio and associated 95% confidence interval from univariate analysis was examined. Multivariate analysis was then conducted with a logistic regression model. A p-value of < 0.05 was considered as statistically significant. All analyses were evaluated in Statistica 9.0 (StatSoft Inc).

Results

Demographic and clinical data

Out of 2637 stented arteries, in 95 cases (95/2637; 3.6%) > 50% ISR restenosis was detected in DUS. Of those, 53 (53/2637; 2.0%) patients had ≥ 70% restenosis confirmed in angiography, including one case of asymptomatic total occlusion. No stent fracture was detected. Mean PSV was 221 ±41 cm/s and 427 ±87 cm/s for 50–69% and ≥ 70% restenosis respectively (p < 0.001). All 52 patients (age: 49–77 years, 37 men, 19 patients symptomatic before initial CAS, time from initial CAS to first restenosis mean 22 ±27 months, 56% cases within first year, 22% within second year) were treated successfully by the endovascular approach.

Angiographic data

ISR treatment included bare (n = 19), DEB (n = 27) or DES supported (n = 6, all for diffused restenosis) angioplasty. In 7 cases cutting-balloon use was necessary, as the standard balloon was slipping out of the stent. In the DEB group there were 11 (11/27; 41%) cases of intolerance (cerebral ischemia) requiring shortening of inflation to < 40 s. The success rate was 100%; however, in 2 patients we were not able to cross a stent with distal embolic protection device (EPD) while proximal EPD was not

used due to the risk of system intolerance. Angioplasty in those two cases was then non-protected. One (1.9%) procedure performed with distal EPD was complicated with ipsilateral ischemic stroke that occurred just after procedure completion. Angiographic diameter stenosis (DS) was reduced from 83 ±8.3% to 13 ±7.6% ($p < 0.001$). Characteristics of stents used for initial angioplasty and the restenosis rate in each stent group are shown in Table II. The treatment strategies for recurrent restenosis are shown in Table III.

Follow-up

There were 13 cases (13/52 – 25%; age 52–77 years, 8 men) of ≥ 70% recurrent ISR; all were neurologically asymptomatic. The mean time to second in-stent restenosis was 26 months in the bare balloon group and 23 months in the DEB group (p = NS). The prevalence of recurrent restenosis in the non-covered balloon group was 32% (6/19) vs. 23% (6/26) in the DEB group (p = NS).

Excluding 2 cases of balloon-mounted DES collapse (implanted in the way that they extended from the initial stent due to edge restenosis), there were no further restenoses in the DES group in 20-month follow-up. Further cases of edge restenosis were treated with self-expanding coronary stent. Three patients (3/52 – 5.8%) required a third intervention, and 1 patient with Takayasu arteritis required five interventions.

Bilateral and high-grade stenosis were independent risk factors of restenosis (OR = 2.95, 95% CI: 1.87–4.64, $p < 0.001$ and OR = 1.9, 95% CI: 1.0–3.63, $p = 0.049$ respectively). Initial Carotid Wallstent implantation was a risk factor of first and recurrent in-stent restenosis (vs.

Table II. Numbers and percentages of stents used for initial angioplasty and restenosis rate in each stent group

Stent brand	Initial CAS, *N* = 2637 *n*, % of the group	First > 50% restenosis, *N* = 95 *n*, % of the initial brand group	Second > 70% restenosis, *N* = 13 *n*, % of the initial brand group
Carotid Wallstent	968, 36.7	57, 5.89	8, 0.83
Cristallo Ideale	546, 20.7	11, 2.01	1, 0.18
Xact	381, 14.4	8, 2.10	1, 0.26
Precise	322, 12.2	10, 3.10	1, 0.31
Cguard	145, 5.5	3, 2.1	0
Acculink	97, 3.7	3, 3.09	2, 1.38
Roadsaver	58, 2.2	2, 3.45	0
Vascuflex	50, 1.9	1, 2.00	0
NexStent	21, 0.8	0	
Omni Link	13, 0.5	0	
Exponent RX	8, 0.3	0	
Palmaz	7, 0.3	0	
Mer	5, 0.2	0	
Smart	3, 0.1	0	
Herculink	2, 0.1	0	
Others	10, 0.4	0	

Table III. Technical details of in-stent restenosis (ISR) endovascular treatment

Treated with	First ISR	Second ISR	Third ISR
Uncovered balloon angioplasty	19/52* (36.5%)		
DEB angioplasty	27/52 (50.9%)	4/13 (30.8%)	2/3 (66.7%)
Self-expanding carotid stent	6/52 (11.5%)		
Balloon mounted coronary DES		8/13 (61.5%)	
Self-expanding coronary DES		1/13 (7.7%)	1/3 (23.3%)

**52 cases of first ISR, one case of total occlusion is not included. DEB – drug-eluting balloon, DES – drug-eluting stent.*

combined group including all other stents, OR = 2.71, $p < 0.001$ and OR = 3.11, $p = 0.032$ respectively). Combining the three risk factors together (i.e. bilateral stenosis, high-grade stenosis and Carotid Wallstent implantation) significantly increases the odds ratios of a restenosis to 6.19 (95% CI: 2.90–13.20, $p < 000.1$). Stent underexpansion ($n = 13$) did not increase the risk of restenosis.

Discussion

Despite the limitations of DUS, associated with different biomechanical characteristics of native and stented artery, it is the best tool for in-stent restenosis detection. There are at least several different cut-off criteria proposed, based on PSV, end-diastolic velocity and PSV ratio. We decided to adopt the criteria of Lal *et al.* [13], as they showed a good correlation with angiological findings in detecting severe restenosis in our institution. Only 2 of 53 arteries with suspected ≥ 70% DUS-detected restenosis revealed borderline (40–70%) lumen narrowing in angiography.

Before the era of DEB, the carotid ISR was treated mainly with non-covered balloons with good immediate and long-term results. Our small sample of recurrent restenosis suggests that use of DEB does not significantly prolong the time for the next intervention as compared with non-covered balloons.

There are data showing that restenosis may be symptomatic and that it may be associated with significant risk of distal embolization during angioplasty for in-stent restenosis [6, 9, 10, 15]. This was a reason for the interventional approach to restenosis in our institution. Our results show that endovascular treatment of in-stent restenosis using neuroprotection is effective and safe, which also relates to patients treated for recurrent stenosis. The only case of periprocedural stroke was probably associated with mobilization of plaque fragments during catheter maneuvering and balloon inflation.

To date, there are no well-defined guidelines that establish the most effective approach for ISR treatment. While different endovascular strategies have been reported, mainly with uncovered and covered balloons, none of them may be applied in each patient.

The main disadvantage of DEB use is the necessity of prolonged inflation for optimal drug delivery. Transient, balloon-related flow stoppage in the treated artery may provoke cerebral ischemia, especially in patients with coexisting contralateral occlusion. In our DEB group there was a high (40.7%) percentage of neurological ischemic symptoms occurrence requiring shortening of the time of inflation to < 40 s. However, similar risk of, and time to, subsequent restenosis reoccurrence between uncovered balloon and DEB groups may only be an accidental finding as there are no robust data comparing results of short vs. long inflation of DEB in restenosis treatment in the carotid territory.

As we have shown, recurrent restenosis may be treated safely with secondary balloon angioplasty, or, in some selected cases, with balloon-mounted DES implantation. In 6 out of 8 cases of balloon-mounted DES implantation there was no further restenosis. In 2 cases, edge DES implantation resulted in further stent deformation and artery occlusion in one, as described previously [11]. This is due to the fact that the coronary DES is prone to deformation in the segment of the artery that bends and kinks. This observation prompted us to introduce self-expanding drug-eluting coronary stent for patients with recurrent edge-stent restenosis. Mechanical properties of this stent are similar to self-expanding carotid stents in terms of radial force and resistance to deformation. Edge stent restenosis may be provoked by mechanical repeating wall injury at the border between the stent edge and native vessel wall. The compliance mismatch of the stented segment and native artery wall provokes unnatural artery kinking at the end of stent while neck movement leads in consequence to repeated local intimal irritation and inflammatory response. This phenomenon may be more pronounced with closed-cell design stents (CC). In fact, the comparison of CC and open-cell design stents (OC) indicates significantly increased stiffness in the former group [16]. We hypothesized that the CC stent may have higher rate of restenosis. In fact, this correlation was not found for the whole groups of stents (CC vs. OC); it was only demonstrated for the Carotid Wallstent. This phenomenon is difficult to explain, but there might be several mechanisms responsible for it:

Carotid Wallstent bending stiffness is similar to the majority of stents in our group, but its length change during implantation is definitely the greatest (–22% vs. –5.9% for Precise, –2.4% for Xact and +0.5% for Cristallo Ideale) [16]. Furthermore, stent shortening during follow-up, as described in several case reports, may lead to partial plaque uncovering and accelerate restenosis. Gaudry *et al.* report 3 out of 12 restenoses associated with Carotid Wallstent shortening. Interestingly, lack of stent coverage of the common carotid artery was an independent restenosis risk factor [17]. Moreover, the Carotid Wallstent has the lowest radial force [16], reducing the chance of further stent expansion, and it was shown that at higher radial force, the stent has better chances of making the artery conform to its original shape [18]. Non-circular stent cross section may provoke flow disturbances, increase in shear stress and in consequence stimulate neointima proliferation.

Another interesting finding is that the Carotid Wallstent is the only one made of unique cobalt-chromium-iron-nickel-molybdenum alloy containing an enhanced radiopaque tantalum core, whereas all other stents from our group are made of Nitinol (nickel-titanium alloy). There are data suggesting that in some cases

in-stent restenosis may be influenced by metal allergy [19], including hypersensitivity to molybdenum [20]. The Carotid Wallstent also has the smallest free cell area in the CC group, 1.1 mm^2; while for Xact it is 2.7 mm^2 and ≥ 4 mm^2 for other stents. The higher density of metal mesh, with possible hypersensitivity to metal, may play a role in restenosis development.

The type of stent has not yet been investigated as a potential risk factor of restenosis. In most cases, this is because of a small sample of CAS and/or a single brand of stent used. The present study showed that Carotid Wallstent use strongly correlates with higher risk of restenosis. Although the Carotid Wallstent has not been shown as an in-stent restenosis risk factor so far, our findings are not isolated. Montelione *et al.* report 10 out of 12 symptomatic in-stent restenosis as occurred in the Carotid Wallstent [21].

It should be kept in mind that the difference in stent-dependent segmental elasticity may increase DUS velocities for CC as compared to OC stents and that may influence the restenosis rate overestimation in the former group. This was not the case in our study, as we confirmed all critical restenosis in angiography. Interestingly, in both Acculink stents that developed critical restenosis that was treated with POBA, recurrent restenosis occurred. The small size of the group did not allow for a statistical confirmation of this observation.

Severe ICA stenosis was recognized in our group of patients as a restenosis risk factor, which is consistent with observations from the study of Gaudry *et al.* [17]. It has been found to be associated with higher plaque burden [22]. Bilateral ICA stenosis reflects considerable atherosclerosis progression and higher disease activity. This may explain the strong influence of bilateral ICA stenosis on further in-stent restenosis. Veselka *et al.* found a significantly higher rate of restenosis in the group with bilateral carotid stenosis (vs. unilateral stenosis). This group was also characterized by a higher rate of follow-up death [23]. Another study showed contralateral carotid artery occlusion as a strong independent predictor of in-stent restenosis [24].

On the other hand, ISR was treated successfully with DEB angioplasty with no third reoccurrence except for the patient with Takayasu disease.

Limitations

A limitation of the study is that it is a one-center, non-randomized registry and our findings might not apply to other populations of patients. Another limitation is possible stent selection bias as the use of stent type and brand was operator-dependent. Thus, some groups of stents are represented in small numbers and may not be able to provide sufficiently strong statistical data.

Conclusions

Our findings suggest that balloon angioplasty may not be optimal for edge-stent restenosis as this procedure does not eliminate the source of the problem that is local inflammation caused by repeating edge-stent mechanical injury. We believe that implantation of a self-expanding DES may be considered in this specific clinical situation.

Conflict of interest

The authors declare no conflict of interest.

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Original paper

Five-year outcomes after revascularization of superficial femoral artery occlusion using Ocelot catheter

Przemysław Nowakowski[1,2], Piotr Buszman[3,4], Adam Janas[4], Stefan Kiesz[5], Pawel Buszman[4]

[1]Department of Vascular Surgery, American Heart of Poland, Chrzanow, Poland
[2]Katowice University of Technology, Katowice, Poland
[3]Andrzej Frycz Modrzewski Krakow University, Krakow, Poland
[4]Center for Cardiovascular Research and Development, Katowice, Poland
[5]San Antonio Endovascular and Heart Institute, San Antonio, USA

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Abstract

Introduction: The population of patients with lower limb atherosclerosis includes a considerable proportion of individuals with long superficial femoral artery (SFA) lesions. Chronic total occlusions (CTOs) represent the "last frontier" of percutaneous interventions. While open strategies are considered earlier as standard management for these lesions, the results of a number of trials indicate that endovascular management might become an effective alternative to surgery.

Material and methods: This paper presents 5-year outcomes of a first-in-man (FIM) study (before CE mark) and the registry of OCT Guided Ocelot Catheter (Avinger) for chronic total occlusions of the superficial femoral artery. The study group comprised 10 patients with Rutherford 3 lower limb ischemia including nine men and one woman.

Results: The efficacy of the primary intervention was 90%. Angiography performed at 6 months of the procedure, according to the study protocol, revealed 3 and 1 cases of restenosis and reocclusion, respectively, repaired using PTA and open common and deep femoral artery patch plasty. Doppler ultrasound performed at 1, 2 and 5 years after the primary intervention did not reveal significant target vessel restenosis. The primary and primary-assisted patency was 89%. During a 5-year follow-up, four peripheral percutaneous interventions and one femoropopliteal bypass surgery were performed in non-target limbs. There were no cardiovascular deaths, myocardial infarction or stroke and no amputation was required.

Conclusions: This is a first-in-man study reporting long-term follow-up after SFA CTO revascularization using the Ocelot catheter. The catheter proved to have a satisfactory safety profile and a high proportion of CTO crossings. A 5-year follow-up revealed high primary and primary-assisted patency rates.

Key words: revascularization, superficial femoral artery occlusion, optical coherence tomography.

Summary

The limitations of this FIM study are its non-randomized nature and small sample size. A distinct advantage was that follow-up tools included not only Doppler ultrasound but also angiography, which was in accordance with the study protocol. In conclusion, this is a first-in-man study reporting long-term follow-up after superficial femoral artery (SFA) chronic total occlusion (CTO) revascularization using the Ocelot catheter. The catheter proved to have a satisfactory safety profile and a high proportion of CTO crossings. A 5-year follow-up revealed high primary and primary-assisted patency rates.

Introduction

Chronic total occlusions (CTO) of the superficial femoral artery (SFA) are historically recommended by TASC II as a subgroup where surgical intervention is preferred over endovascular revascularization [1]; according to literature reports approximately 40% of patients with symptomatic peripheral arterial disease have CTO of SFA [1]. Therefore, long SFA occlusion is frequently referred to as an "Achilles heel" and represents the "last frontier" of lower extremity percutaneous revascularizations [2–4].

Corresponding author:
Przemysław Nowakowski MD PhD, Department of Vascular Surgery, American Heart of Poland, Chrzanów, Poland, phone: +48 32 625 81 20, e-mail: nowakowski.mcsn@gmail.com
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Nowadays, the market offers many devices dedicated for revascularization of SFA CTO – non-imaging-guides catheters such as Crosser, TruePath, Frontrunner, but only one of these has built-in optical coherence tomography (OCT) – the Ocelot catheter [5–7]. The OCT provides spatial resolution that is ten times greater compared to intravascular ultrasound (IVUS) currently applied in atherectomy devices [8]. Real time high-resolution visualization may facilitate navigation through long occlusions allowing recanalization in the true lumen, thus avoiding subintimal recanalization, and intraluminal crossing may have the benefit of reducing inflammatory reaction. The OCT give a 3-dimensional rendering of the artery wall and the operator is able to use this information for stent apposition, vulnerable plaque location and target vessel for endovascular treatment. Thanks to intraluminal recanalization physicians may have a wide array of endovascular strategies, including angioplasty, stenting and atherectomy.

Aim

Due to an increasing number of older, cardiologically high-risk patients as a result of comorbidities and the patients' demand for less invasive procedures and faster recuperation we sought to evaluate early and long-term follow-up after first-in-man (FIM) revascularization of long SFA occlusion with the OCT Guided Ocelot Catheter.

Material and methods

The paper concerns a prospective single-center non-randomized first-in-man registry of patients with CTO SFA and severe claudication treated with the Ocelot Catheter (before receiving the CE mark). The purpose of this study was to evaluate short- and long-term outcomes after CTO SFA revascularization using the Ocelot catheter. The periprocedural outcomes as well as vessel patency at 6 months and 5 years of the intervention were evaluated using angiography and Doppler ultrasound (according to study protocol – AVI-OCT-10003 v.0; PB/WKWM/21/2010), respectively.

Patient eligibility and study requirements

Patients were considered eligible for the study if they were diagnosed with chronic limb ischemia graded as Rutherford 3; target vessel diameter > 5 mm and target lesion total occlusion. The exclusion criterion was target limb necrosis, i.e., stage 6 according to the Rutherford classification. All patients were maintained on aspirin (75–150 mg), clopidogrel (75 mg) and statin 2 days prior the intervention. Other medications were prescribed at the physician's discretion. An intra-arterial bolus of 5000 IU heparin was administered during the interventional procedure.

Definitions

The CTO was defined as complete occlusion of the artery. Vessel patency was defined as diameter stenosis ≤ 50%. Inability to cross the lesion, perforation, no reflow and bailout stenting were evaluated as periprocedural outcomes. Serious adverse events comprised cardiovascular death, myocardial infarction, stroke, non-target lower limb vessel revascularization and amputation.

Description of Atherectomy System

Ocelot is a unique CTO-dedicated atherectomy system with built-in OCT for intravascular imaging. This catheter utilizes spiral-fluted wedges to corkscrew the CTO cap while real time OCT provides visualizations to facilitate intravascular navigation. OCT is located at the

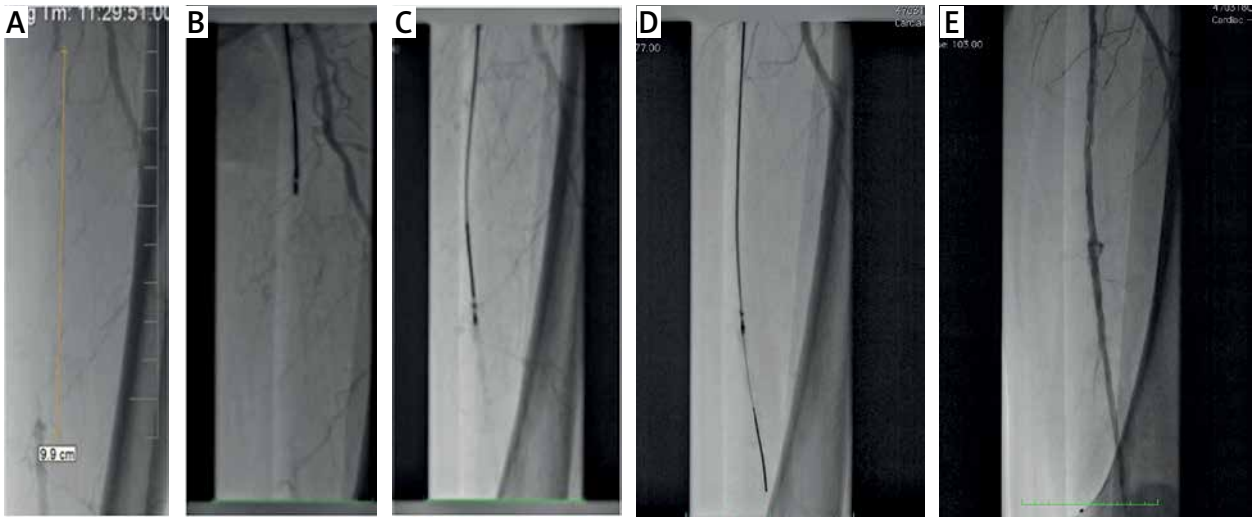

Figure 1. A – SFA CTO, **B** – OCELOT catheter in working position, **C** – OCELOT catheter in working position. Crossing medium SFA the lesion. **D** – Inserting 0.35 guidewire to distal part SFA. **E** – Final effect after balloon angioplasty (5 mm of diameter)

Table I. Baseline demographics, comorbidities and lesion characteristics

Parameter	Value
Male: female, *n* (%)	9 : 1 (90)
Age [years]:	
50–60	1
60–70	7
70–80	2
Comorbidities, *n* (%):	
Diabetes	5 (50)
Hypertension	9 (90)
Hyperlipidemia	6 (60)
Coronary artery disease	7 (70)
Post-PCI CAD	4 (40)
Lesion characteristics (*n* = 10)	
Location: SFA	10
Length [cm]	7.45 ±3.25
Total occlusion	10
Reference diameter [mm]	5.3
Lesion: *de novo*/restenosis	10/0
Calcification: none/moderate/severe	0/9/1

tip of the catheter allowing high-precision navigation without contrast use. Ocelot has a length of 110 cm and a crossing profile of 2 mm, and is compatible with 6 Fr sheaths and 0.014-inch guidewires (Figure 1 A). The second part of the Ocelot system is a Lightbox console, which transmits a laser to the catheter through an optical fiber. The Lightbox creates an image, which can be presented in 2 modes: 1 – sector, 2 – waterfall view.

Statistical analysis

Data are reported as means ± SD for continuous variables and percent and absolute number for categorical variables.

Results

Patient characteristics and procedure

Baseline demographic and clinical characteristics of 10 patients are shown in Table I. The cardiovascular risk factors were prevalent. One patient had a history of myocardial infarction. A history of stroke was present in one patient with minor disability. Mean SFA occlusion (measured in QVA) length was 74.5 ±32.5 mm.

Contralateral access was used in 50% of the patients due to iliac and common femoral artery anatomy. The success rate was 90%. In one patient the catheter could not cross the CTO due to massive calcification. Balloon angioplasty was performed in all cases; bailout stenting for vessel dissection was performed in 4 out of 9 patients (Figures 1 B–E). In all cases Astron Pulsar stents were used. No protection devices were used. Artery perforation and no-reflow syndrome did not occur. No patients developed access-site complications. The mean duration of the procedure and contrast agent volume were 100 ±48 min and 433 ±139 ml, respectively. In the authors' opinion this fact is strongly connected with the type of this study, i.e. first in man, and is not representative for current Ocelot procedures. During the hospital stay, particular attention was paid to hydration of patients before and after the procedure. In the group of patients, no nephropathy requiring dialysis was observed during both 30-day and 5-year follow-up.

Outcomes and follow-up

30-day outcomes

All 9 patients after successful procedure were claudication-free, i.e., asymptomatic (Rutherford 0). In all patients color duplex scan was performed, without symptoms of restenosis in examinations. The patient after a failed procedure was put on medical treatment (ASA, cilostazol, statin); the claudication distance was approximately 100 m. All 9 patients were maintained on medical treatment – ASA 75 mg, clopidogrel 75 mg, statin 40 mg.

6-month angiography follow-up

Angiographic follow-up (according to the study protocol) performed at 6 months of the procedure revealed 89% patency of the target vessel in 8 out of 9 patients. Follow-up angiography revealed significant although non-occlusive restenosis and re-CTO of the target lesion in SFA in three and one patient, respectively. In all patients with restenotic lesions the primary treatment included CTO crossing and balloon angioplasty without stent placement. At 6 months, claudication distance decreased below 100 m and repeat balloon angioplasty was therefore performed. Percutaneous revascularization was also attempted in the re-CTO case but proved unsuccessful. Consequently, common and deep femoral artery endarterectomy with patch plasty was performed.

5-year Doppler ultrasound follow-up

Doppler ultrasound performed at 1, 2 and 5 years of the primary intervention did not reveal important target vessel restenosis above 50% and peak systolic velocity (PSV) > 1.5 m/s. The primary and primary-assisted patency was 89%. During a 5-year follow-up, four peripheral percutaneous interventions and one femoro-popliteal by-

pass surgery were performed in non-target limbs. There were no cardiovascular deaths, myocardial infarction or stroke and no amputation was required. Throughout the follow-up all patients were maintained on medical treatment – ASA 75 mg, clopidogrel 75 mg, statin 40 mg. The long-term double antiplatelet treatment in the H_2 blocker cover was conducted in accordance with the authors' belief that the prevention of cardiovascular events was more effective.

The target limb of eight patients remained asymptomatic (Rutherford 0) from month 6 and throughout year 5 of the primary intervention. Claudication distance in the patient after patch plasty repair remained unchanged (i.e., approximately 100 m).

The patient in whom CTO crossing failed due to massive calcification underwent femoro-popliteal bypass surgery 2 years after the primary intervention due to shortening of claudication distance below 50 m.

Discussion

The CTO SFA recanalizations are mostly performed using the subintimal approach which undoubtedly results from lesion type and operator experience. New tools specially designed for intraluminal interventions allow efficient and safe treatment of long and heavily calcified CTOs that would previously be qualified (TASC II) for surgical repair.

The current study is a direct observational first-in-man registry of patients with CTO revascularized with an optical coherence tomography (OCT) Guided Ocelot Catheter (Avinger). According to available research, the registry for the first time describes very long-term follow-up after OCT guided CTO of SFA revascularization. Moreover, this study was designed to obtain the CE (Conformité Européenne) mark for the OCT Guided Ocelot Catheter (Avinger). All subjects included in the study were high cardiovascular risk, symptomatic patients with long SFA CTO. Those factors determined that they were high-risk for open bypass surgery. Nonetheless, long SFA CTO was actually classified as TASC D, which should be treated with the open surgical procedure rather than endovascular [9]. The OCT Guided Ocelot Catheter is designed for chronic total SFA occlusion revascularization and 10 μm image resolution allows differentiation between various healthy arterial structures including media and adventitia, and diseased arterial walls including atherosclerotic plaque [10]. The high resolution visual guidance would minimize media injury which could yield better long-term outcomes and patency [11].

The first large trial designed to assess safety of the Ocelot Catheter was the single arm prospective multicenter CONNECT study which included 84 patients with femoropopliteal CTO. Efficiency defined as successful CTO crossing with the device was achieved in 89% of included patients. Perforations were reported in 5% of cases, resolved with prolonged balloon occlusion. The clinically significant perforations were not observed [12]. In the CONNECT II study outcomes were very similar with 72% successful crossing with Ocelot alone, whereas 97% were successful when combined with assist or re-entry devices [13]. In the prospective, single-arm, multicenter Vision study of the Ocelot Catheter combined with adjunctive therapy such as stent implantation or used alone outcomes were encouraging. One hundred fifty-eight patients were enrolled, and 198 lesions were treated. The safety profile was satisfactory with no clinically significant perforations, 0.5% dissections and 2% embolic events. The clinically driven repeat target lesion revascularization was 6.4% in the 6-month follow-up [14]. Stavroulakis *et al.* published long-term outcomes of endovascular revascularization with the Ocelot Catheter combined with local antimitotic drug delivery by drug-eluting balloons (DEB). The results are encouraging; in the 33 patients and 37 lesions only 5% had TLR in 12 months and low periprocedural complications [15]. Moreover, OCT Guided Ocelot Catheter is suitable even for very long, calcified CTOs involving the whole SFA [16].

Those studies confirm our observations on safety and feasibility outcomes. Moreover, the long-term follow-ups are also encouraging and comparable to our study. When comparing re-entry devices, the safety and feasibility are similar if they are used in short CTO SFA. When performed in longer CTO the efficiency ratio is more encouraging when orbital atherectomy with OCT is used [17].

Nowadays, when local drug delivery is more and more efficient this technology may by combined with orbital atherectomy in PAD revascularization. Early reports on the combination of plaque modification with atherectomy and subsequent drug-eluting balloons (DEB) seem to be promising [18, 19]. Novel technologies, including local drug delivery nano-technology, may soon become available for the follow-up treatment of plaque modifications after atherectomy.

Study limitations

The main drawbacks of this analysis are those inherent to any single-center observational study [20]. The first-in-man nature of this study could have a significant influence on long-term outcomes due to the learning curve. This is a hypothesis-generating study rather than conclusive.

Conclusions

This first-in-man study with long-term follow-up showed that the OCT Guided Ocelot Catheter has a high success rate of CTO recanalization and very promising long-term outcomes. Nevertheless, the long-term outcomes should be evaluated in comparison with re-entry

devices and drug technology in a prospective randomized trial.

Conflict of interest

The authors declare no conflict of interest.

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Original paper

Cardiac resynchronization in Poland – comparable procedural routines? Insights from CRT Survey II

Mateusz Tajstra[1], Damian Łasocha[2], Elżbieta Gadula-Gacek[1], Mateusz Ostręga[1], Lidia Michalak[3], Dariusz Wojciechowski[4], Marek Zieliński[5], Maciej Kempa[6], Zbigniew Orski[7], Anna Polewczyk[8], Jerzy Ozga[9], Camilla Normand[10], Kenneth Dickstein[10], Cecilia Linde[11], Jarosław Kaźmierczak[12], Łukasz Szumowski[2], Mariusz Gąsior[1], Maciej Sterliński[2]

[1]3rd Department of Cardiology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Poland
[2]Department of Arrhythmia, Institute of Cardiology, Warsaw, Poland
[3]1st Department of Cardiology, Poznan University of Medical Sciences, Poznan, Poland
[4]Department of Cardiology, Wolski Hospital, Warsaw, Poland
[5]Department of Cardiology, Ludwik Perzyna Provincial Polyclinical Hospital, Kalisz, Poland
[6]Department of Cardiology and Electrotherapy, Medical University of Gdansk, Poland
[7]Department of Cardiology and Internal Diseases, Military Institute of Medicine, Warsaw, Poland
[8]Department of Cardiology, Swietokrzyskie Cardiology Center, Kielce, Poland
[9]Cardiology Department II and Intensive Care Unit, Independent Public Complex Hospital, Stalowa Wola, Poland
[10]Cardiology Division, Stavanger University Hospital, Stavanger, Norway
[11]Heart and Vessels Theme, Karolinska University Hospital, Stockholm, and Karolinska Institute, Stockholm, Sweden
[12]Department of Cardiology, Pomeranian Medical University, Szczecin, Poland

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Abstract

Introduction: CRT Survey II was initiated by the European Heart Rhythm Association and the Heart Failure Association, to explore everyday implantation practice of cardiac resynchronization therapy (CRT) devices in a broad spectrum of hospitals in European Society of Cardiology (ESC) member countries.

Aim: To compare Polish and European procedural practice.

Material and methods: Procedural details of Polish patients collected in 37 Polish centres (n = 1241 – Poland group) were compared to the patients enrolled throughout Europe (n = 9847 – CRT II Survey group).

Results: There were significant differences in: successful implantation (96.1% vs. 97.4%), type of device implanted (for CRT-D: 87% vs. 67.6%), implanting physician subspecialty (for electrophysiologist: 69.2% vs. 79.8%), type of location of procedure (for operating room: 19.4% vs. 8.9%), duration of procedure (117.8 ±44 vs. 97.5 ±46.1 min), left ventricle lead type (for multipolar lead: 50% vs. 57.9%), coronary sinus venogram with occlusion rate (41.4% vs. 47.9%) and peri-procedural complication rate (7.5% vs. 5.3%) between Poland and CRT II Survey groups, respectively.

Conclusions: This study provides important information describing current differences in Polish procedural routines in relation to ESC member countries. Heterogeneous CRT implantation practices across European countries still exist. However, it may be related to different clinical profile of patients qualified for CRT implantation in Poland as well as organization of care.

Key words: cardiac resynchronisation therapy, chronic heart failure, survey.

Summary

Details related to the implantation procedure of the cardiac resynchronization therapy (CRT) may be one of the most important factors that could potentially have a significant impact on response to resynchronization therapy. The clinical implications from this investigation can be summarized as follows: first, the percentage of successful attempts of CRT implantation in the entire cohort was high (about 97%); second, CRT implantation practices may vary across European countries; third, in Poland CRT-P is generally less frequently implanted; finally, the periprocedural complication rate was higher in Poland in comparison to the rest of Europe, although this fact could be related to clinical profile and more frequently used combined antithrombotic therapy.

Corresponding author:
Dr Mateusz Tajstra, 3rd Department of Cardiology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, 2 Szpitalna St, 41-800 Zabrze, Poland, phone: +48 32 373 36 19, e-mail: mateusztajstra@wp.pl
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Introduction

Benefits of cardiac resynchronization therapy (CRT) have been clinically proven in randomized clinical trials (RCTs) [1–7]. Therefore, in current practice guidelines CRT is an unambiguously and strongly advocated treatment option in patients with heart failure (HF) [8, 9]. However, in clinical practice patients are often very much older and with more comorbidities than in RCTs.

Details related to the implantation procedure of the CRT may be one of the most important factors that could potentially have a significant impact on response to resynchronization therapy. However, the majority of the currently available data regarding CRT implantation routines and peri-procedural complications have been obtained from RCTs performed mostly in relatively high volume centres by experienced implanters. Therefore, widespread recommendations regarding CRT implementation, including clinical status, ECG findings and optimal implantation techniques, are based explicitly on data from RCTs. However, the first CRT survey demonstrated that a large number of CRT implantation procedures were not performed in line with the guidelines [10] and some details of procedural techniques also varied between participating centres [11].

Moreover, evidence from surveys and registry-based analyses that encompass everyday clinical practice, meaning all eligible, consecutive and high risk patients, may add to RCTs in creation of evidence-based medicine [12].

Aim

Bearing in mind all the facts mentioned above and having at our disposal a large group of patients with CRT implantation details coming from the CRT II Survey – a joint project between the European Heart Rhythm Association (EHRA) and the Heart Failure Association (HFA) – we aimed to compare Polish and European procedural practice associated with CRT implantations in patients enrolled in the CRT II Survey.

Material and methods

Survey infrastructure

The survey was designed as a joint initiative between EHRA and the HFA. The design and rationale of CRT Survey II, along with the detailed contents of the eCRFs, have been published previously [13]. Briefly, the 47 European Society of Cardiology (ESC) member states detailed in the 2014 EHRA White Book were invited to participate [14]. Finally, 42 ESC member countries participated in the survey. The survey gathered data on patients' characteristics, investigations, indications for CRT, implant procedures and short-term outcome including adverse events. Each implanting centre was asked to provide information regarding facility type, size, and operator speciality. Information on operator experience was not collected.

Survey population

Any patient in the 42 participating countries was eligible for inclusion if they were selected and implanted with either a CRT with pacemaker function (CRT-P) or a CRT with an incorporated defibrillator (CRT-D). This included both successful and unsuccessful implantations as well as both *de-novo* CRT devices and upgrades from a previous permanent pacemaker (PPM) or implanted cardiac defibrillator (ICD). Generator replacements or revisions of previously implanted CRT devices were excluded as the survey was designed to cover only de novo CRT implantations or upgrades from a previous PM or ICD. Specific data regarding an implantation procedure included inter alia: location of procedure, duration and fluoroscopy time, left ventricular (LV) lead type placement and its position X-ray evaluation, percentage of coronary venogram performance, and periprocedural complications. Information on lead insertion (venesection or puncture) was not collected.

Study population

A total of 288 centres from 42 European countries enrolled data of a total of 11 088 patients implanted with a CRT device with or without a cardioverter-defibrillator between October 2015 and December 2016. In this cohort of patients 1241 (11.2%) patients recruited in 37 Polish centres – university, regional, and private (Poland group) – are presented in comparison to the total 9847 (88.8%) patients enrolled throughout Europe (CRT II Survey group).

Statistical analysis

Absolute numbers and percentages were shown for categorical variables to describe the patient population, and means (with standard deviations) or medians (with interquartile range) were used for continuous variables. Categorical variables were compared between subgroups by the χ^2 test and continuous variables (numerical values) by the Mann-Whitney-Wilcoxon test. A significance level of $p < 0.05$ was assumed for the statistical tests. All statistical analyses were performed using SAS statistical software (version 9.3, Cary, NC, USA).

Results

The principal clinical implications from this investigation can be summarized as follows: first, the percentage of successful attempts of CRT implantation in the entire cohort was high (about 97%); second, CRT implantation practices may vary across European countries; third, in Poland CRT-P is generally less frequently implanted; finally, the periprocedural complication rate was higher in Poland in comparison to the rest of Europe.

Poland was the greatest participant in the CRT Survey with more than 12% of the total patient material. Polish patients were younger with more ischemic heart disease,

more often received an CRT-D and more often were upgraded from a previous PM or ICD.

We found important differences in Polish procedural routines in relation to the rest of participating European countries, indicating that heterogeneous CRT implantation practices across European countries may still exist.

The baseline clinical characteristics of the study groups are presented in Table I. On the whole, despite younger age, patients treated in Poland had a more severe clinical profile with, among other things, higher rates of: ischemic cardiomyopathy (58.5% vs. 42.7%, $p < 0.001$), previous myocardial infarction (48.4% vs. 34.7%, $p < 0.001$), previous coronary revascularization (51.2% vs. 37.3%, $p < 0.001$), atrial fibrillation (43.8% vs. 40.5%, $p = 0.03$) and lower mean left ventricle ejection fraction (26.4% vs. 28.7%, $p < 0.001$).

General outcome data are presented in Table II. There were 1250 implants attempts in Poland and 9960 in the CRT II Survey group, and 1191 (96.1%) successful in the Poland group vs. 9606 (97.4%) in the CRT II Survey group. Procedural details of the study groups are presented in Table III and Figures 1–3. Among others, significant differences were observed in: previous device implantation (30.7% vs. 27.5%, $p = 0.02$), type of device implanted (for

Table I. Baseline clinical characteristics of study groups

Variable	Poland	CRT II Survey	*P*-value
	n = 1241 (11.2%)	*n* = 9847 (88.8%)	
Age, mean ± SD [years]	67.7 ±9.7	68.6 ±10.9	< 0.001
Males	81.3%	75%	< 0.001
Ischemic cardiomyopathy	58.5%	42.7%	< 0.001
Hypertension	68.4%	63.3%	< 0.001
Diabetes	37.2%	30.7%	< 0.001
Prior myocardial infarction	48.4%	34.7%	< 0.001
Prior coronary revascularization	51.2%	37.3%	< 0.001
Valvular heart disease	32.2%	26.5%	< 0.001
Chronic kidney disease (class ≤ 3)	36%	30.5%	< 0.001
Mean LV-EF, mean ± SD (%)	26.4 ±8	28.7 ±8.1	< 0.001
Atrial fibrillation	43.8%	40.5%	0.03

CRT-D – cardiac resynchronization therapy-defibrillator, LV-EF – left ventricle ejection fraction, SD – standard deviation.

Table II. Baseline clinical characteristics of study groups

Variable	Poland	CRT II Survey	*P*-value
	n = 1241 (11.2%)	*n* = 9847 (88.8%)	
Age, mean ± SD [years]	67.7 ±9.7	68.6 ±10.9	< 0.001
Males	81.3%	75%	< 0.001
Ischemic cardiomyopathy	58.5%	42.7%	< 0.001
Hypertension	68.4%	63.3%	< 0.001
Diabetes	37.2%	30.7%	< 0.001
Prior myocardial infarction	48.4%	34.7%	< 0.001
Prior coronary revascularization	51.2%	37.3%	< 0.001
Valvular heart disease	32.2%	26.5%	< 0.001
Chronic kidney disease (class ≤ 3)	36%	30.5%	< 0.001
Mean LV-EF, mean ± SD (%)	26.4 ±8	28.7 ±8.1	< 0.001
Atrial fibrillation	43.8%	40.5%	0.03

CRT-D – cardiac resynchronization therapy-defibrillator, LV-EF – left ventricle ejection fraction, SD – standard deviation.

Table III. Procedural details of the study groups

Variable	Poland	CRT II Survey	*P*-value
	n = 1241 (11.2%)	*n* = 9847 (88.8%)	
Admission to implantation, mean ± SD [days]	3.4 ± 5.2	3.9 ± 9.8	< 0.001
Previous device implantation	30.7%	27.5%	0.02
Successful implantation attempt	96.1%	97.4%	0.008
Unsuccessful attempt	3.9%	2.6%	
LV lead placement unsuccessful*	87.2%	88.8%	
Type of device:			< 0.001
CRT-D implantation	87%	67.6%	
CRT-P implantation	13%	32.4%	
Operator:			< 0.001
Electrophysiologist	69.2%	79.8%	
HF physician	2.6%	5.3%	
Invasive cardiologist	24.3%	10.9%	
Surgeon	0%	4.8%	
Other	3.9%	1.0%	
Location of procedure:			< 0.001
Cathlab	23.7%	25.5%	
Dedicated electrophysiological lab	16.6%	32.4%	
Device implantation lab	40.2%	32.6%	
Operating room	19.4%	8.9%	
Other	0.1%	0.6%	
Duration of procedure, mean ± SD [min]	117.8 ± 44.1	97.5 ± 46.1	< 0.001
Fluoroscopy time, mean ± SD [min]	20.4 ± 15.6	17.4 ± 17.3	< 0.001
Prophylactic antibiotics	99.2%	98.6%	0.06
Test shock	8.4%	4.3%	< 0.001
Which lead was implanted first:			NS
RV	82.9%	83.6%	
LV	17.1%	16.4%	
LV lead type:			< 0.001
Unipolar	1.5%	0.6%	
Bipolar	48.5%	41.4%	
Multipolar	50.0%	57.9%	
Coronary sinus venogram performed	92.6%	91.4%	NS
Venogram performed with occlusion	41.4%	47.9%	< 0.001
Dilatation of coronary vein performed	2.4%	2.4%	NS
Phrenic nerve stimulation tested	86.5%	90.9%	< 0.001
LV lead position optimization	20.1%	35.6%	< 0.001

**Percentage of non-successful attempts. CRT-D – cardiac resynchronization therapy-defibrillator, CRT-P – cardiac resynchronization therapy-pacemaker, LV – left ventricle, RV – right ventricle, NS – not significant, SD – standard deviation.*

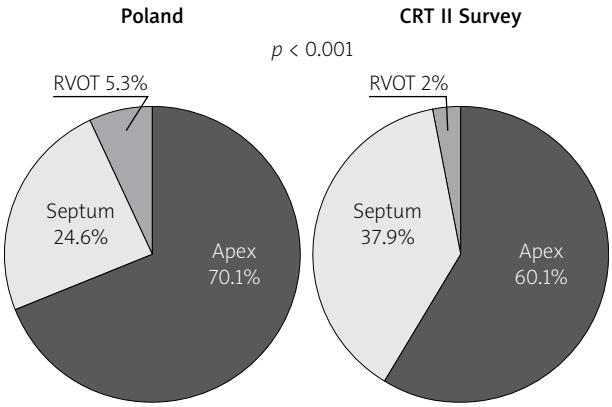

Figure 1. Right ventricle lead placement

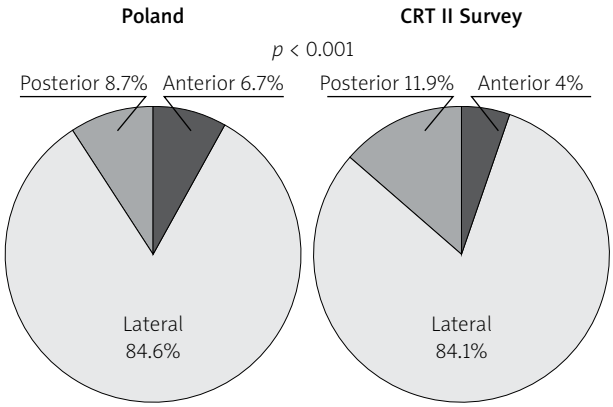

Figure 2. Left ventricle lead position. Left anterior oblique site evaluation

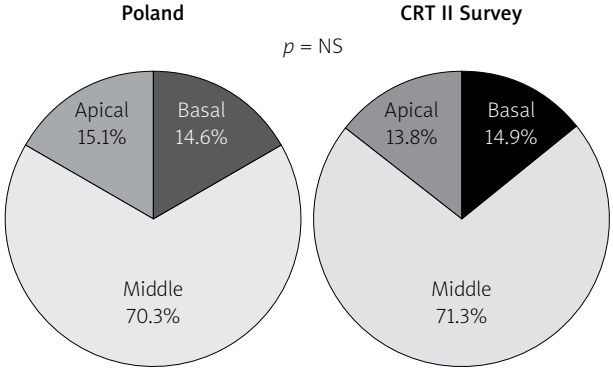

Figure 3. Left ventricle lead position. Right anterior oblique site evaluation

CRT-D: 87% vs. 67.6%, $p < 0.001$), type of operator (for electrophysiologist: 69.2% vs. 79.8%, $p < 0.001$), type of location of procedure (for operating room: 19.4% vs. 8.9%, $p < 0.001$), procedure duration (117.8 ±44 vs. 97.5 ±46.1 min, $p < 0.001$), left ventricle lead type (for multipolar lead: 50% vs. 57.9%, $p < 0.001$), and coronary sinus venogram with occlusion rate (41.4% vs. 47.9%, $p < 0.001$) between Poland and CRT II Survey groups.

Additionally, the periprocedural complication rate was higher in the Polish group than in the CRT Survey group (7.5% vs. 5.3%, $p = 0.001$) (Table IV). In particular pneumothorax and coronary sinus dissection were more common in Poland. This might be associated either with lead insertion technique and operator experience or with higher percentage of Polish patients with dual antiplatelet (13.9% vs. 8.7%, $p < 0.001$) and triple anticoagulation therapy (2.9% vs. 1.9%, $p = 0.02$) (Table V).

Discussion

Within the last decade cardiac resynchronisation therapy (CRT) has been proven to be a highly effective therapy to reduce morbidity and mortality in chronic HF patients [1–7]. Therefore, current practice guidelines strongly support CRT implantation in optimally pharmacologically treated patients. It is estimated that about 400 patients per million per year might be suitable for

Table IV. Periprocedural complications

Variable	Poland	CRT II Survey	*P*-value
	n = 1241 (11.2%)	*n* = 9847 (88.8%)	
Periprocedural complication:	7.5%	5.3%	0.001
Death*	1.1%	1.3%	NS
Bleeding*:	18.1%	17.4%	NS
Requiring intervention*	41.2%	31.9%	
Pocket haematoma*	88.2%	76.9%	
Pneumothorax*	17%	18.5%	NS
Haemothorax*	2.1%	1.3%	NS
Coronary sinus dissection*	38.3%	38.6%	NS
Pericardial tamponade*	6.4%	3.8%	NS
Other*	22.3%	27.6%	NS

**Percentage of periprocedural complications. CRT – cardiac resynchronization therapy, NS – not significant.*

Table V. Drug therapy at discharge

Variable	Poland	CRT II Survey	*P*-value
	n = 1241 (11.2%)	*n* = 9847 (88.8%)	
β-blocker	96.4%	88%	< 0.001
ACEI/ARB	90.1%	85.9%	< 0.001
MRA	78.7%	61.2%	< 0.001
Loop diuretic	88.9%	80%	< 0.001
Ivabradine	7.9%	5.3%	< 0.001
Digoxin	11.3%	10.3%	0.29
Amiodarone	13.7%	17.8%	< 0.001
Anti-platelet agent	53.3%	42.5%	< 0.001
DAPT	13.9%	8.7%	< 0.001
Oral anticoagulation and P2Y12 inhibitor	5.1%	4.0%	0.06
Triple therapy	2.9%	1.9%	0.02

ACE-I – angiotensin enzyme converting inhibitor, ARB – angiotensin receptor blocker, DAPT – dual antiplatelet therapy, MRA – mineralocorticoid receptor antagonist.

CRT, or up to 400 000 patients per year in ESC countries [8]. Accordingly, we are deeply convinced that the knowledge about everyday clinical practice, including procedural aspects and periprocedural complications related to CRT implantation procedures, will allow us to responsibly improve current standards. Such data, encompassing details about consecutive, real-life, non-selected procedures, can be delivered by surveys and registries.

Cardiac Resynchronization Therapy Survey II provided precious information regarding CRT implantation routines in nearly three hundred centres from 42 European countries. One of the main goals of the survey was to make representative benchmarking both nationally and internationally accessible. Thus, in this substudy we compared Polish and European CRT routines. Polish centres participating have included the largest number of patients. We focused on the technical issues related to CRT implantation procedures – one of the most important factors in the potential response to resynchronization therapy.

Safe and effective CRT device implantation requires the appropriate environment, trained personnel, equipment and optimally located left ventricle (LV) lead. These aspects may affect the frequency, especially of early but also long-term complications.

Considering the above-mentioned "appropriate environment and trained personnel", as far as we are concerned, the link between operator type or location of procedure and type of CRT used has not been studied previously. We found that invasive cardiologists were more likely to implant CRT among eligible patients in Poland in comparison to other participating countries. The underlying reasons for this association and its potential impact on the procedural and especially long-term outcome remain unknown. In our opinion, further research to compare CRT implantations according to clinician training, type of the operator specialty, operator experience and place of the procedure may provide insights into strategies to further optimize CRT use.

Although CRT Survey II did not provide information regarding complications due to a venous access and operator experience, it was previously proved that the blind puncture approach of the subclavian or axillary vein is associated with a higher risk of pneumothorax [15]. There are no direct studies concerning operator experience and complication rate in patients with CRT. However, the risk of CRT implantation infection was significantly higher in patients who had their CRT implanted by an inexperienced operator [16].

Regarding "equipment", this study shows that the multipolar LV lead was a frequent option in the entire cohort. LV lead selection may not only result in more frequent challenges posed during implantation of the CRT system, but also allows to facilitate the optimal outcome in terms of obtaining an adequate capture threshold and avoidance of phrenic nerve stimulation. Multipolar leads offer various pacing configurations to minimize phrenic nerve capture and may permit reprogramming to alternate stimulation vectors to ameliorate this problem without re-intervention [17–19]. The use of a multipolar lead may also be a promising option for patients with ischemic HF and the presence of a scar around the LV lead placement is potentially an important factor of decrease of CRT response. However, the application of multisite pacing using a multipolar lead to increase CRT effectiveness has been investigated with conflicting results [20, 21].

Another issue regards differences between de novo CRT implantations and upgrades from previous devices.

The latest studies demonstrated that implantation procedures in upgraded patients were equally successful and complications similar to *de novo* implantations [22].

Following "optimally located LV lead" mainly (above 80%) and similarly in both groups lateral LV lead position as assessed in the left anterior oblique site was recorded. However, in the Poland group anterior LV lead position was more frequent. Right anterior oblique evaluation, primarily middle placement (about 70%), was observed equally in compared groups. In spite of the fact that there is increasing evidence proving that selection of specific LV sites for pacing may improve CRT outcomes, no data are available from any large RCT and therefore no clear recommendations have been introduced; however, LV lead placement in anterior veins should be avoided. Sub-analysis reports of two major randomized clinical trials support lateral and deny apical placement. The REVERSE study has suggested that lateral position of the LV lead is associated with better outcome in terms of reverse remodelling and results collected from the MADIT-CRT trial have revealed that apical placement of the LV lead is associated with a less favourable outcome [23, 24].

Although there is increasing evidence of the benefit of optimizing the LV positions if the anatomy allows for choices, attempts to optimize LV lead position during implantation overall were not intense and were made less frequently in the Polish group (20.1% vs. 35.6%). The preferred LV lead placement should be over the region of the latest mechanical activation. This approach is supported by the results of the TARGET (Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy) trial, which showed that positioning of the LV lead at the latest activated region resulted in a better echocardiographic and clinical response and less HF hospitalization [25]. Likewise, the position of the LV lead in the region of the latest electrical activation often applied using QLV has been linked to a greater response to CRT [26]. A possible explanation for the reluctance to perform systematic optimisation of the LV lead position is that such an approach might lack a routine to use QLV or other electrical dyssynchrony criteria during the procedure or imaging techniques considered as more demanding for the implanting cardiologists and its advantages are yet to be proved in large randomized clinical trials.

Discussing the results in Polish and the whole CRT Survey groups, there are some major differences (i.e. percentage of complications, optimal LV lead placement and fluoroscopy time). In our opinion, Poland should focus on training so that more experienced operators can perform safe and effective procedures.

Limitations

Several limitations to the current study should be stressed. Surveys have their own limitations which need to be acknowledged and considered during interpretation of findings. Differences in practice between countries can skew the results [27]. Centre participation was voluntary and we estimate that about 11% of patients implanted with CRT in participating countries were enrolled in the survey. Although consecutive inclusion was strongly encouraged, we cannot confirm that all patients were included consecutively. The accuracy of the data has not been audited and there may be a potential selection bias. However, the investigators conducted a 'front-end' data check and post database lock quality control analyses designed to prevent incorrect data being analysed.

Conclusions

This study provides important information describing current Polish differences in procedural routines in relation to the rest of participating European countries. Heterogeneous CRT implantation practices across European countries may still exist. However, it may be related to a different clinical profile of patients qualified for CRT implantation in Poland.

Acknowledgments

Mateusz Tajstra and Damian Łasocha equally contributed to the study.

Conflict of interest

The authors declare no conflict of interest.

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Utility of dual longitudinal diameter-reducing ties in aortic arch thoracic endovascular aortic repair

Arkadiusz Kazimierczak[1], Paweł Rynio[1], Tomasz Jędrzejczak[2], Maciej Lewandowski[3], Piotr Gutowski[1]

[1]Vascular Surgery Department, Pomeranian Medical University, Szczecin, Poland
[2]Cardiac Surgery Department, Pomeranian Medical University, Szczecin, Poland
[3]Cardiology Department, Pomeranian Medical University, Szczecin, Poland

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Introduction

A 69-year-old man underwent open surgical ascending aortic replacement for type-A aortic dissection. Six months after this operation, he became symptomatic. There was persistent chest pain even though anti-hypertensive treatment was effective. Computed tomography angiography showed a widening false lumen (FL) in the aortic arch and in the thoracic aorta (Figure 1). The patient was not suitable for open aortic arch replacement due to high risk (logistic EuroSCORE 34.47%). Standard thoracic endovascular aortic repair (TEVAR) or branched endovascular repair (e.g. COOK) [1] was not considered due to insufficient landing zone distal to a right coronary artery venous bypass graft arising from the ascending aortic graft.

Case report

Stent-graft modification

The patient was selected for endovascular treatment with a physician-modified endograft (PMEG). Due to the presence of vein coronary bypass (VCB), an endograft with four fenestrations to the innominate artery (IA), left subclavian artery (LSA), left common carotid artery (LCCA) and VCB was planned. The PMEG was prepared on the basis of 3D printing [2, 3]. Fenestrations for the IA, LCCA, LSA and VCB were marked, burnt and their edges reinforced. The LSA was pre-cannulated. The VCB fenestration, located in the proximal endograft landing zone, was extra-large and "non-sealing" in nature (Figure 1).

Due to the sharply angled aortic arch it was not possible to insert the rigid delivery system using conventional femoral access and stiff guidewire in the ascending aorta. The delivery system was more rigid because it contained a PMEG with pre-cannulation guidewire (0.36 mm/0.014-inch Terumo Soft, Europe, Interleuvenlaan 40 3001 Leuven, Belgium) for the LSA, four fenestrations for arch vessels and VCB all marked and having reinforced edges and finally double guidewires (V-18 Control, Boston Scientific, USA) to constrain the endograft.

Therefore, externalized transapical guidewire technique (ETAG) was planned.

A Valiant Captivia thoracic endograft (Medtronic, Santa Rosa, CA, USA) of diameter 40 mm and length 200 mm was deployed in a sterile aortic arch model and after optimal positioning of the metal frame the VCB, IA, LCCA and LSA departure points were marked. Then the fenestrations were burned. Their edges were lined with the loop cut out from a snare (Indy OTW Vascular Retriever 8.0-35-55-40) for marking and strengthening the fenestration edge. The endograft was constrained on two (opposite) sides using dual longitudinal diameter-reducing ties (DLT) – each Z-stent along the endograft was constrained using a stainless steel wire (V18 Control) for support and two non-locking Prolene loops [4] (Figure 1). The LSA fenestrations were pre-cannulated using a 0.36 mm/0.014-inch soft Terumo guidewire fed through the delivery system, inserted from the bottom of the endograft and led out through the LSA fenestration [5]. The endograft was re-sheathed avoiding twisting within the delivery system using a transcatheter aortic valve implantation packaging device.

Vascular access

Access to the cardiac apex was obtained using a mini-thoracotomy in the 4 intercostal left space. Access to the right common femoral artery for endograft delivery system insertion was obtained by cut-down. The left

Corresponding author:
Arkadiusz Kazimierczak PhD, Vascular Surgery Department, Pomeranian Medical University, 72 Powstańców Wielkopolskich St, 70-111 Szczecin, Poland, phone: +48 91 466 11 56, e-mail: biker2000@icloud.com
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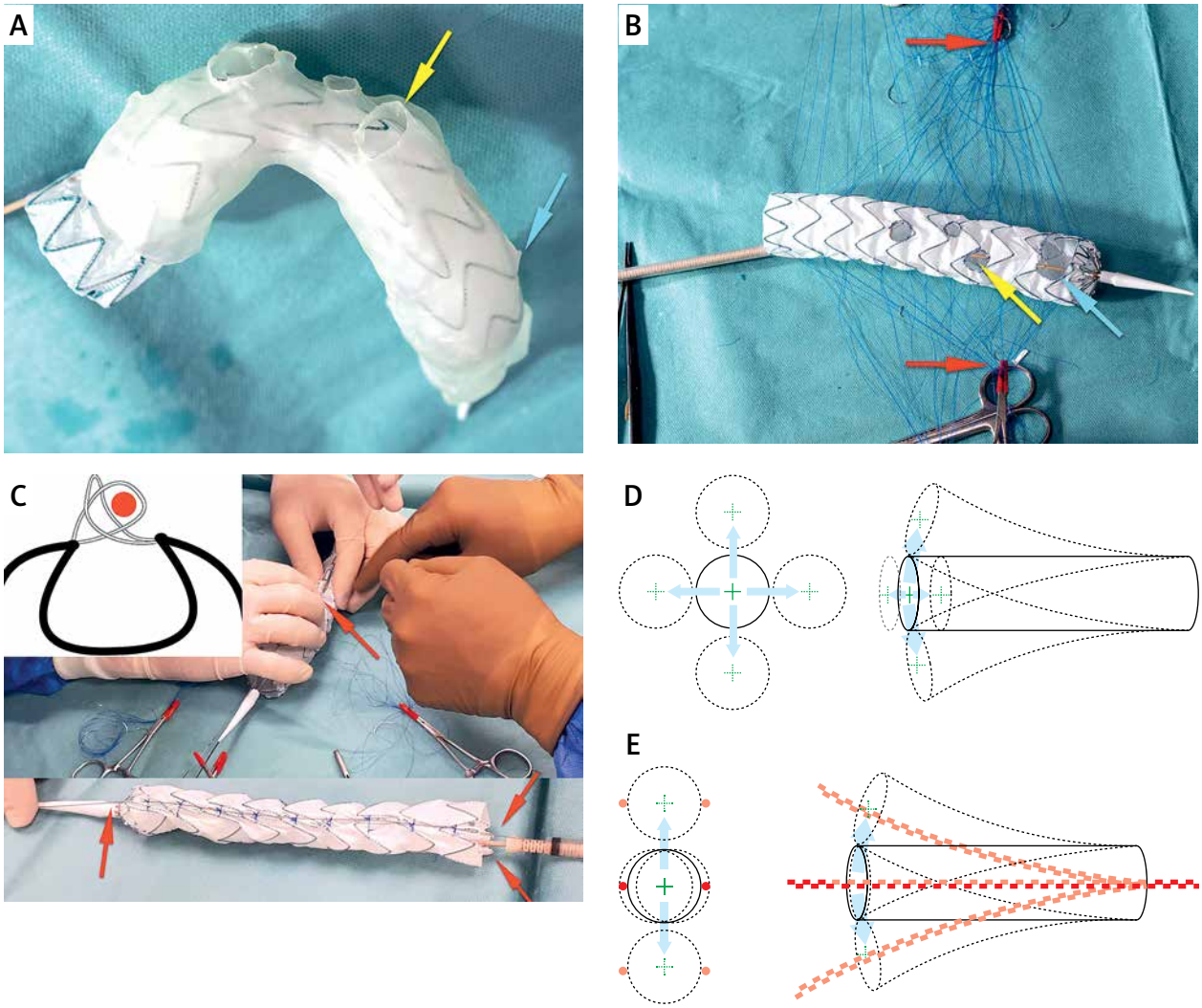

Figure. 1. Principle of graft modification. **A** – 3D printing as a template for PMEG. **B** – Fenestration edge lined with the wire. PMEG ready for completing dual longitudinal diameter-reducing ties. **C** – Dual longitudinal diameter-reducing ties made with two non-locking Prolene loops one of which goes around a V18 Control wire (DLT wire shown in red). **D** – Delivery system without double lateral reducing ties can bend in any direction. **E** – Double lateral reducing ties limit the bending of the delivery system to only one plane. Red arrows indicate the Prolene suture needed to knot non-locking Prolene loops for dual longitudinal diameter-reducing ties. Yellow arrow indicates innominate artery. Blue arrow indicates the coronary bypass outflow

femoral artery was punctured percutaneously to introduce a 7 Fr sheath (this access was used for LCCA stenting and inserting a pigtail diagnostic catheter into the arch). The right subclavian artery was exposed by cut-down for cannulation and stenting of the IA fenestration. Left axillary artery access was obtained by cut-down for stenting the LSA fenestration. The guidewire that passed through the LSA fenestration was exteriorized from the left axillary access prior to insertion of the arch endograft delivery system into the right femoral artery.

Endograft deployment

First, a guiding catheter passed from the left axillary artery to the right femoral artery was used to pass the LSA pre-cannulation wire in the opposite direction. The endograft was then introduced through the same right femoral arterial access into the ascending aorta and arch using ETAG on a 0.36 mm/0.014-inch soft Terumo guidewire introduced from the apex to the right femoral artery under transesophageal echocardiographic and fluoroscopic monitoring.

Prior to endograft deployment, the position of all arch branches was ascertained by arteriography using a pigtail catheter inserted from left femoral arterial access. The endograft was then deployed, but it remained partially constrained because of the DLTs. Partial constraint of the endograft and traction towards the inner aortic curvature (using ETAG) were necessary to leave space for

the cannulation of fenestrations from the side of the outer aortic arch curvature. The IA and LCCA fenestrations were cannulated (the LSA had been pre-cannulated) and covered stents positioned within all three and kept ready for deployment: BeGraft 14 × 38 mm (Bentley InnoMed GmbH, Lotzenäcker 25, 72379 Hechingen, Germany) via 12 Fr/45 cm guiding sheath (Flexor Ansel, COOK Medical, Bloomington, IN 47402-4195 USA) in the IA, Advanta 12 × 29 mm (Getinge, 40 Continental Blvd, Merrimack, NH 03054, USA) via 9 Fr/45 cm guiding sheath (Flexor Ansel, COOK Medical) in the LSA and BeGraft 7 × 38 mm via 7 Fr/90 cm guiding sheath (Flexor Shuttle, COOK Medical) in the LCCA. Then both lateral ties were released and another endograft was implanted into the descending aorta (Medtronic Vailant Captiva, VAMC4238C150TE) distal to the LSA fenestration. This was done to provide a landing zone for endovascular procedures in the thoracic and abdominal aorta in the future. A tri-lobe balloon (Gore, Flagstaff, Arizona, 86003-2400 USA) was used to expand the aortic endografts and their overlap over their entire length except for the last segment of the distal endograft to avoid the phenomenon of stent-induced new entry. Afterwards the ETAG guidewire was removed from the heart. Covered stents in the fenestrations were deployed and their intra-aortic portions (5–8 mm protrusion into the aortic endograft) were flared using balloons 2 mm wider than the nominal stent diameters. Control arteriography confirmed the patency of the arch branch fenestrations and VCB and the lack of endoleak into the false lumen. The remaining indwelling endovascular equipment was removed and the access vessels repaired.

The course after the procedure was not complicated. The patient was discharged 10 days after the second procedure. Computed angiography tomography after 2 months showed good graft function, no endoleak, thrombosed false lumen in the arch, no stent-induced new entry below the thoracic endograft and patent VCB (Figure 2).

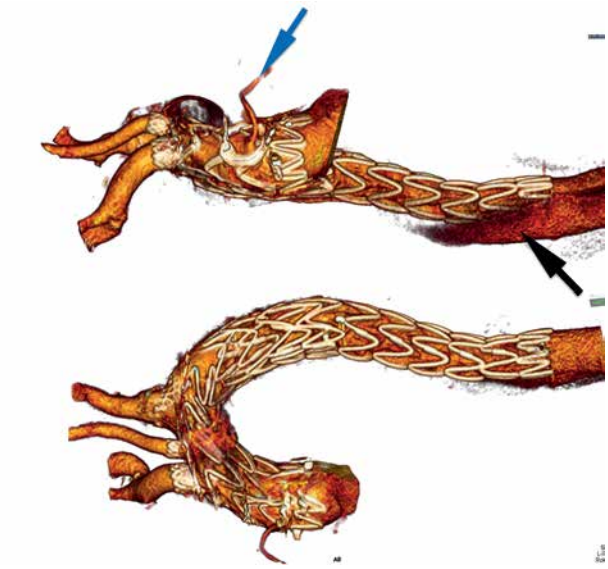

Figure. 2. Good graft function. Black arrow indicates persistent flow in false lumen below the thoracic stent graft. Blue arrow indicates satisfactory positioning of the fenestration on the coronary bypass

Discussion

Since it is not possible to rotate the endograft delivery system once it is in the aortic arch, it is necessary to enter the arch with optimal orientation. This means that the fenestrations must be directed towards the outer curvature of the aortic arch. Endograft segments have a tendency to move into each other at sharp curves, a property gainfully utilized by some endografts for better alignment to the aortic curvature (e.g. GORE TAG) [6]. The presence of rigid linear reinforcement connecting consecutive stent segments makes it impossible for the endograft to bend and concertina towards the side where the reinforcement is located and restricts bending to the opposite direction. An example is the Ankura (Lifetech, Shenzhen, China) endograft: a longitudinal supporting strut orientated to the greater curvature forces the endograft to self-orient and bend towards the side of the lesser arch curvature naturally during insertion into the arch.

We have made use of this mechanism while making arch PMEGs. However, a single lateral tie on the outer curvature would make it impossible to cannulate fenestrations located here. Hence we used DLTs located on opposite sides of the endograft to restrict its bending to one plane only (Figure 1 B). Consequently, when entering the arch, the endograft fenestrations will never orient sideways (laterally). Moreover, it allows adequate constraining of the endograft so as not to restrict blood flow in the aorta and provide sufficient space for the cannulation of fenestrations. It is expected that one diameter reducing tie will reduce the endograft diameter by about 20–30% [4]. Attempts to increase the reduction further with a single tie can lead to endograft infolding and endoleak [7]. In our experience with the use of PMEGs in the aortic arch, as long as we used one diameter reducing tie, we seldom managed to find a suitable place for making fenestrations appropriate for the anatomy of the arch vessels. Only after using DLTs can we appropriately position fenestrations in the endograft. This technical modification has the potential to be used in all arch devices in the future.

It should be borne in mind that any manipulation of partially constrained endografts and fenestration cannulating hardware in the aortic arch (before full aortic endograft wall apposition) increases the risk of embolic stroke. Some authors prefer to use unconstrained arch endografts that appose the aortic wall completely immediately after deployment and trap arch debris underneath [8]. All this is true when the maneuvers are done with-

out keeping the graft close to the inner arch curvature by ETAG. With ETAG the endograft is not in contact with the outer curvature of the aortic arch and the risk of stroke is lower. Moreover, all procedures in the arch are done with complete suppression of the coagulation system (ACT > 300 s). Precise deployment of the fenestration in the arch in a one-step procedure (unconstrained endograft) is not always possible due to tortuous arch anatomy especially with two or more angulations in the arch. Therefore, having an option to cannulate misplaced fenestration (with the help of DLT and ETAG), instead of ending up with the cut-off blood flow to the brain, is a great relief. Therefore, both techniques, DLT and ETAG, could be considered simultaneously. ETAG and DLT make space available on the outer arch curvature and increase the margin for possible misplacement errors. Finally, they reduce the need for rapid cardiac pacing and facilitate passage of the endograft delivery system through sharply angled aortic arches.

It could be suggested the ETAG negates many of the advantages that percutaneous arch repair could offer. However, it is still much less invasive compared to open arch repair (no sternotomy, extra-corporal circulation and hypothermia). In the future ETAG might be even less invasive when percutaneous transapical access becomes widely available [9, 10].

Limitations

This is one of the first three such cases and only proves that it is possible to carry out such a procedure effectively. We do not know whether 100% repeatability of this technique is possible in all anatomical conditions. Therefore, we will collect data from subsequent treatments of this type. These are technically difficult procedures, especially in patients who have degenerating aortic arch dissection after an initially successful Bentall procedure.

Conclusions

Use of dual longitudinal diameter-reducing ties enables proper orientation of the endograft delivery system in the aortic arch. It provides enough space to manipulate the guidewires and catheters during cannulation of the fenestrations and does not restrict the blood flow inside the aorta.

Conflict of interest

The authors declare no conflict of interest.

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Aspiration thrombectomy and histopathologic examination of thrombus for early identification of embolic myocardial infarction

Maciej T. Wybraniec[1], Edyta Reichman-Warmusz[2], Michał Lelek[1], Tomasz Bochenek[1], Romuald J. Wojnicz[2], Katarzyna Mizia-Stec[1]

[1]First Department of Cardiology, School of Medicine in Katowice, Medical University of Silesia, Poland
[2]Department of Histology, School of Medicine with the Division of Dentistry in Zabrze, Medical University of Silesia in Katowice, Poland

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The clinical differentiation between thrombophilia-related coronary embolization and classic atheroma-related acute myocardial infarction (AMI) remains challenging as laboratory tests may be unreliable in the acute setting [1]. Since angiographic and intravascular imaging is often inconclusive, we propose the use of pathological examination of the aspirated thrombus for selection of patients requiring chronic anticoagulation in addition to antiplatelet therapy. This concept has recently been adopted in a 37-year-old patient presenting with 2-hour retrosternal chest pain at rest in the course of inferior wall ST-segment elevation AMI. Pre-procedural transthoracic echocardiography (TTE) showed mildly depressed left ventricular (LV) systolic function with hypokinesis of the inferior wall and presence of a well-organized thrombus attached to apical segments of LV (28 × 21 mm) (Figure 1 A). The coronary angiography performed via a right radial approach showed acute occlusion of the right coronary artery and non-significant, parietal lesions within the left coronary artery. The occlusion was crossed with a Balance Middleweight guide wire (Figure 1 B) and the thrombus was aspirated using an Export thrombectomy catheter (Figure 1 C). The aspirated thrombus (Figure 1 D) was then stored in neutral buffered formalin and Poly-Transport buffer. Subsequently, a 3.5 × 16 mm Promus Element stent was implanted in the lesion and post-dilated with a 4.0 × 15 mm non-compliant balloon, leading to complete restoration of the patency of the vessel with a small distal residual thrombus (Figure 1 E). Prolonged ECG monitoring showed no proof of atrial fibrillation. The histopathologic examination, which comprised standard hematoxylin and eosin staining, showed a complex structure, characterized by hypocellular retracted fibrin conglomerate, partially infiltrated with neutrophils (Figures 1 F and G). The image was consistent with a well-organized, relatively old thrombus, which did not correspond with in situ clot formation due to rupture of the atheromatous plaque. In addition to aspirin and ticagrelor and intra-procedural bolus of unfractionated heparin, the patient received transient 18-hour infusion of eptifibatide, followed by intravenous infusion of unfractionated heparin overlapping with initiation of oral anticoagulation. At post-procedural day 3, the patient was switched from ticagrelor to clopidogrel. The patient was discharged home at post-procedural day 6 with clopidogrel, aspirin and warfarin. The extended laboratory tests at 6 weeks confirmed the presence of a prothrombin heterozygous G20210A mutation responsible for the hypercoagulable state. The follow-up TTE confirmed only partial resolution of the thrombus. At 6-month follow-up aspirin was withdrawn, while clopidogrel was recommended up to 12 months, followed by life-long treatment with a vitamin K antagonist.

Despite unfavourable results of recent randomized controlled trials [2], the use of aspiration thrombectomy might potentially facilitate early diagnosis of thromboembolic AMI by means of early histopathologic examination of the aspirated thrombus, advocating in favour of initiation of chronic anticoagulation therapy during index hospitalization [3]. This approach, however, is limited by the absence of intracoronary imaging in the form of optimal coherence tomography (OCT), which could delineate the absence of intimal rupture, while the older age of the thrombus might also be related to episodes of prior subclinical non-occlusive coronary thrombosis [4]. Still, the presence of LV thrombus and the intracoronary thrombus

Corresponding author:
Maciej T. Wybraniec, First Department of Cardiology, School of Medicine, Medical University of Silesia, 47 Ziołowa St, 40-635 Katowice, Poland, phone: +48 32 359 88 90, e-mail: maciejwybraniec@gmail.com
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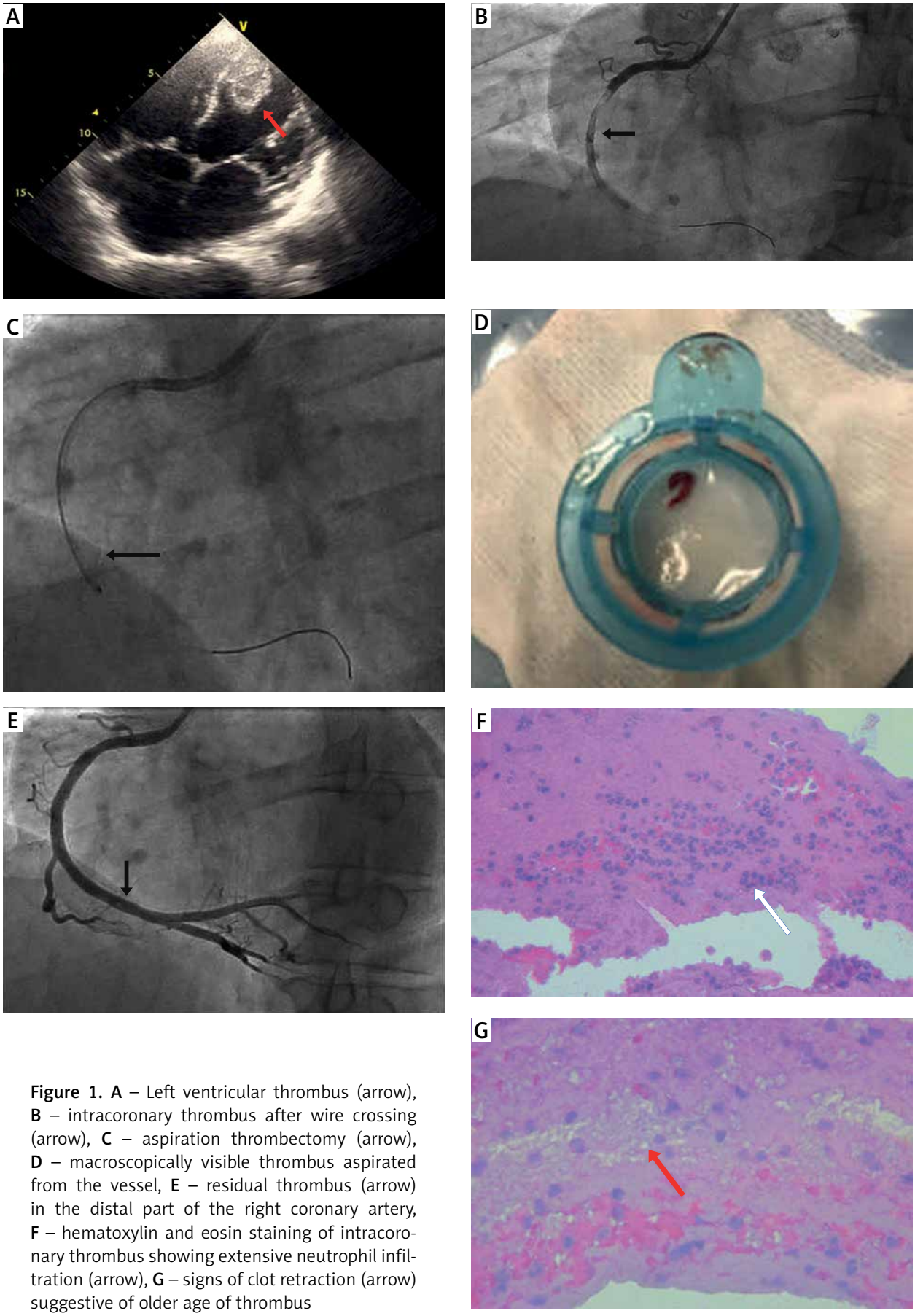

Figure 1. A – Left ventricular thrombus (arrow), **B** – intracoronary thrombus after wire crossing (arrow), **C** – aspiration thrombectomy (arrow), **D** – macroscopically visible thrombus aspirated from the vessel, **E** – residual thrombus (arrow) in the distal part of the right coronary artery, **F** – hematoxylin and eosin staining of intracoronary thrombus showing extensive neutrophil infiltration (arrow), **G** – signs of clot retraction (arrow) suggestive of older age of thrombus

composition should advocate in favour of embolic aetiology of AMI and guide appropriate treatment.

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Conflict of interest

The authors declare no conflict of interest.

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Giant aneurysm of an aortocoronary venous bypass graft treated by an endovascular approach

Michał Sojka[1], Anna Drelich-Zbroja[1], Maryla Kuczyńska[1], Elżbieta Czekajska-Chehab[2], Andrzej Tomaszewski[3], Tomasz Jargiełło[1]

[1]Department of Interventional Radiology and Neuroradiology, Medical University of Lublin, Lublin, Poland
[2]I Department of Medical Radiology, Medical University of Lublin, Lublin, Poland
[3]Department of Cardiology, Medical University of Lublin, Lublin, Poland

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Aneurysmal transformation of a venous coronary bypass graft is a rare (incidence of 0.07%), yet potentially fatal complication of coronary artery bypass grafting. It is postulated > 5 years following coronary artery bypass graft (CABG) multiple factors contribute to the development of graft aneurysm, including atherosclerosis, endothelial dysfunction, changes in smooth muscle orientation in the proximity of valves [1] and trauma during surgical handling of the vein [2]. Establishing the final diagnosis is hampered by unspecific clinical presentation (chest pain, dyspnea), with nearly 1/3 of cases being diagnosed incidentally [1]. In consequence, patients undergo extensive and time-consuming cardiological workup prior to treatment. Despite cardiac surgery remaining the mainstay of treatment for coronary bypass graft aneurysms, minimally invasive endovascular procedures constitute an accepted and effective alternative for patients with multiple comorbidities without mechanical complications [1–3].

We hereby present a unique case of a 71-year-old patient with a giant aneurysmal transformation of an SVG-OM graft resulting in worsening dyspnea due to pulmonary trunk compression, successfully treated by endovascular embolization.

A patient with an implantable cardioverter-defibrillator and a past history of multiple coronary arterial bypass grafting (Ao-DIAG-LAD, Ao-RCA, SVG-OM, LITA-LAD) and angioplasty of the Ao-DIAG-LAD graft was admitted due to worsening dyspnea. Coronary computed tomography (CT) angiography revealed the presence of a partially thrombosed SVG-OM bypass graft aneurysm, measuring 73 × 66 × 61 mm and causing pulmonary trunk narrowing to 11 mm in the anteroposterior (AP) view (Figure 1 A); another fully thrombosed, smaller aneurysm was visible at the occluded distal segment of the graft. A third aneurysm was detected at the proximal Ao-DIAG-LAD graft; full patency of the previously stented graft with no filling of the aneurysm was observed. Although patients with mechanical complications of coronary graft aneurysms, e.g. compression of adjacent vascular structures, are routinely treated by classic cardiac surgery [1], it was decided to refer our patient for less invasive endovascular exclusion of the partially filling SVG-OM graft aneurysm due to extensive post-operative retrosternal fibrosis and signs of cardiac insufficiency (ejection fraction (EF) = 28%). Based on distal graft impatency and severe compression symptoms, occlusion of the afferent graft segment was chosen as the best treatment option in order to promote aneurysm shrinkage. Deployment of a vascular plug seemed to be the method of choice due to a short (< 15 mm) landing zone, rapid, single-device vessel occlusion and no additional mass to be left within the aneurysm sac. Amplatzer Vascular Plug 4 (AVP4 – St. Jude Medical, MN, USA) 6 × 11 mm was selected as the most appropriate device. Consecutive stages of the embolization procedure performed under local anesthesia are presented in Figures 1 B and C. Control angiography confirmed proper positioning of the occluder and lack of contrast filling in the bypass graft and aneurysm sac.

Coronary CT angiograms obtained at 3 and 12 months (Figure 1 D) follow-up confirmed effective occlusion of the bypass graft with complete thrombosis of the aneurysm sac. Aneurysm sac shrinkage to 67 × 63 × 58 mm and 60 × 62 × 51 mm was observed at 3 and 12 months follow-up, respectively. This was accompanied by pulmo-

Corresponding author:
Dr. Maryla Kuczyńska, Department of Interventional Radiology and Neuroradiology, Medical University of Lublin, 8 Jaczewskiego St, 20-954 Lublin, Poland, phone: +48 607 141 921, e-mail: maryla.kuczynska@gmail.com
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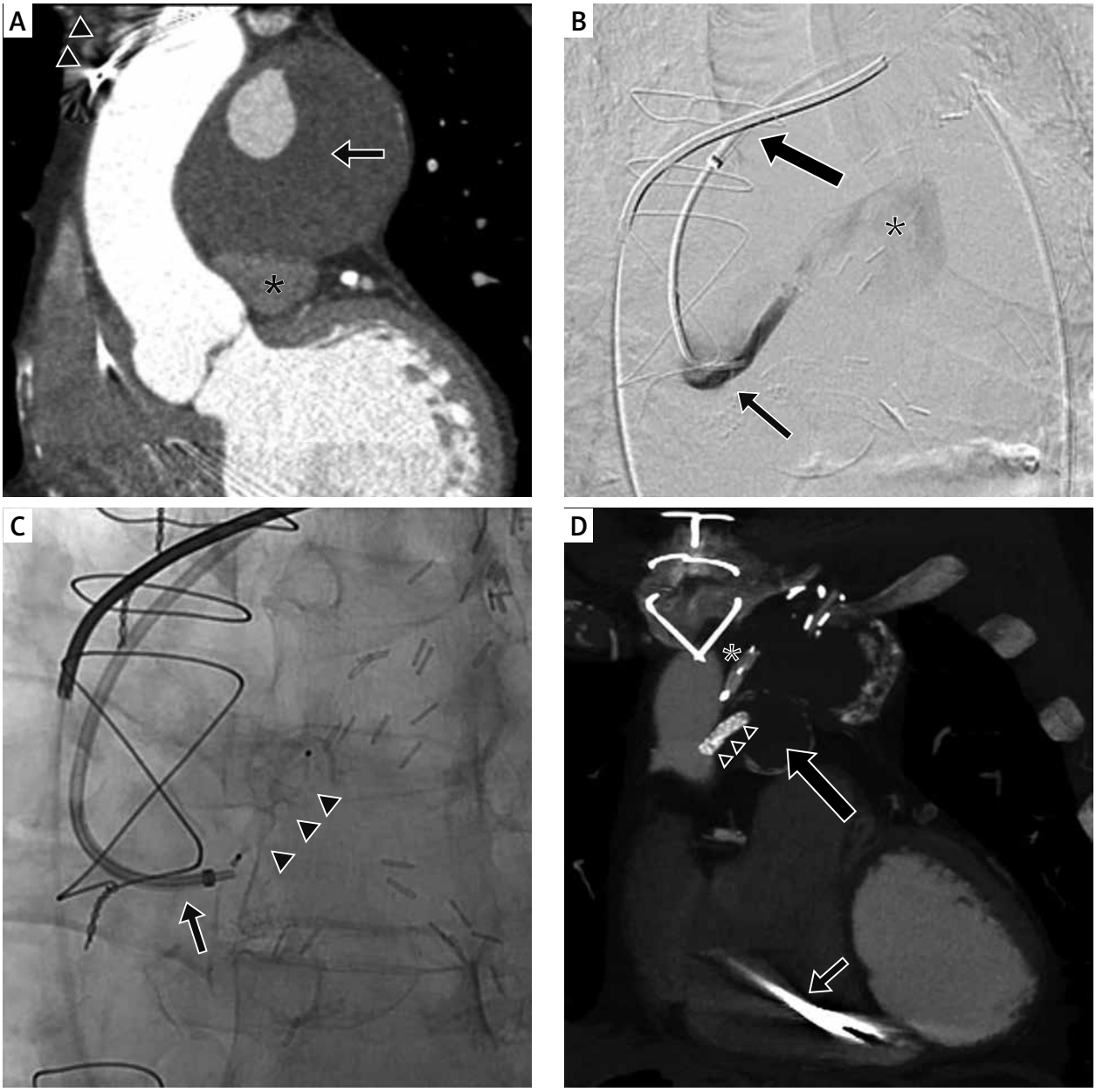

Figure 1. Giant aneurysm of the saphenous vein graft-obtuse marginal branch (SVG-OM) venous bypass graft. **A** – Coronal reconstruction of the coronary angio-computed tomography (angio-CT) depicting giant, partially thrombosed aneurysm of the SVG-OM bypass graft (arrow) compressing the pulmonary trunk (asterisk). Electrode of the implantable cardioverter-defibrillator directing to the right ventricle visible as well (arrowheads). **B** – Pre-procedural angiogram of the SVG-OM bypass graft depicting aneurysm filling with contrast medium (asterisk); a 6 Fr 90 cm-long vascular sheath (Flexor, Cook Medical, IN, USA) was placed at the level of the ascending aorta (thick arrow) through a right femoral access, followed by coaxial, selective positioning of the 5 Fr MPA (Cook Medical, IN, USA) diagnostic catheter in the proximal SVG-OM bypass (arrow). **C** – Preceded by administration of 3000 IU heparin *i.v.*, a 6 mm Amplatzer Vascular Plug (AVP) 4 (arrowheads) was then deployed with a slight oversizing into the 5 mm target graft resulting in complete aneurysm exclusion from the circulation; just before AVP deployment the 6 Fr vascular sheath was advanced to the proximal SVG-OM bypass to provide system stability (arrow). The arterial puncture site was closed by StarClose (Abbott Vascular, IL, USA). The patient received low molecular weight heparin (LMWH) *s.c.* daily for routine postoperative thrombosis prophylaxis, and after discharge was prescribed with optimal medical treatment (acetylsalicylic acid (ASA) 75 mg, statin, angiotensin-converting-enzyme inhibitor (ACEI) and angiotensin II receptor blocker (ARB)) as standard of care, not to impede the effects of AVP with additional antithrombotic agents. **D** – Control coronary angio-CT at 12 months depicts AVP 4 (asterisk) successfully implanted to the proximal SVG-OM bypass graft, with no residual flow through the aneurysm sac. Fully thrombosed aneurysm of the aorta-diagonal branch-left anterior descending artery (Ao-DIAG-LAD) bypass (thick arrow) with stent deployed within patent graft vessel (arrowheads) is visible as well. Electrode of the implantable cardioverter-defibrillator directing to the right ventricle visible as previously (arrow). Pulmonary trunk decompression is also visible

nary trunk decompression to 19 mm in the AP dimension at the 12-month follow-up, and symptom resolution.

Conflict of interest

The authors declare no conflict of interest.

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Treatment of severe tricuspid regurgitation with placement of percutaneous edge-to-edge posteroseptal and anteroseptal leaflet clips

Adam Rdzanek, Arkadiusz Pietrasik, Janusz Kochman, Piotr Scisło

1st Department of Cardiology, Medical University of Warsaw, Warsaw, Poland

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The presence of secondary tricuspid regurgitation (TR) is considered to be an independent risk factor of an unfavorable clinical outcome in patients undergoing left heart valve disease interventions. In recent years, the MitraClip (Abbott, USA) system, originally developed for mitral regurgitation (MR) treatment, has proved to be effective in severe TR reduction in a selected population of patients. However, several anatomic features can hamper MitraClip utilization in this clinical setting. First of all, the presence of a pacemaker lead, causing reduced leaflet mobility, might prevent successful leaflet grasping. Secondly, the regurgitation jet location in the posteroseptal or anteroposterior coaptation line, partially due to the limited echocardiographic visualization of this area, is known to be a predictor of procedural failure during percutaneous edge-to-edge TR treatment. The present case exemplifies a successful solution of this technically demanding anatomic problem.

An 83-year-old woman with severe symptomatic secondary MR (ERO = 0.43 cm^2; MR vol. 48 ml) was scheduled for MitraClip therapy. The preprocedural echocardiographic examination also showed the presence of severe TR (VC-2D 8 mm; VCA-3D 1.1 cm^2) which was exacerbated due to the presence of a pacemaker lead causing partial posterior leaflet immobilization. The TR jet originated from both the posteroseptal and the anteroseptal coaptation line (Figure 1 A).

Mitral valve repair was carried out according to the standard procedure. The implantation of two MitraClip devices led to a significant reduction of MR jets (MR-ERO 0.14 cm^2). After the retrieval of a steerable sheath to the right atrium, tricuspid valve edge-to-edge repair was attempted. Under three-dimensional transesophageal echocardiographic (TEE-3D) guidance, the first clip was placed above the posteroseptal coaptation and orientated perpendicularly to the coaptation line. The pacemaker lead was pushed from the posterior leaflet toward the posteroseptal commissure. Once the clip was advanced to the right ventricle, an X-plane view based on TEE-3D, showing the precise device and leaflet orientation, allowed proper leaflet grasping and pacemaker lead entrapment between the clip and commissure. The second clip, implanted in a similar way between the anterior and septal leaflet close to the center of the valve, caused a further reduction of the regurgitation jet. The final TR parameters were as follows: VC-2D 4 mm; VCA-3D 0.4 cm^2, mean gradient 3 mm Hg (Figure 1 B). Transthoracic echocardiography carried out on the second day following the procedure showed a very good result of placement of both mitral and tricuspid clips (Figure 1 D) with only mild MR and mild to moderate TR presence.

The presented case describes, to the best of our knowledge, the first successful simultaneous posteroseptal and anteroseptal clip placement during complete percutaneous edge-to-edge tricuspid valve repair carried out in Poland.

Corresponding author:
Adam Rdzanek PhD, 1st Department of Cardiology, Medical University of Warsaw, 1 a Banacha St, 02-097 Warsaw, Poland, phone: +48 22 599 19 51, e-mail: ardzanek@poczta.wp.pl
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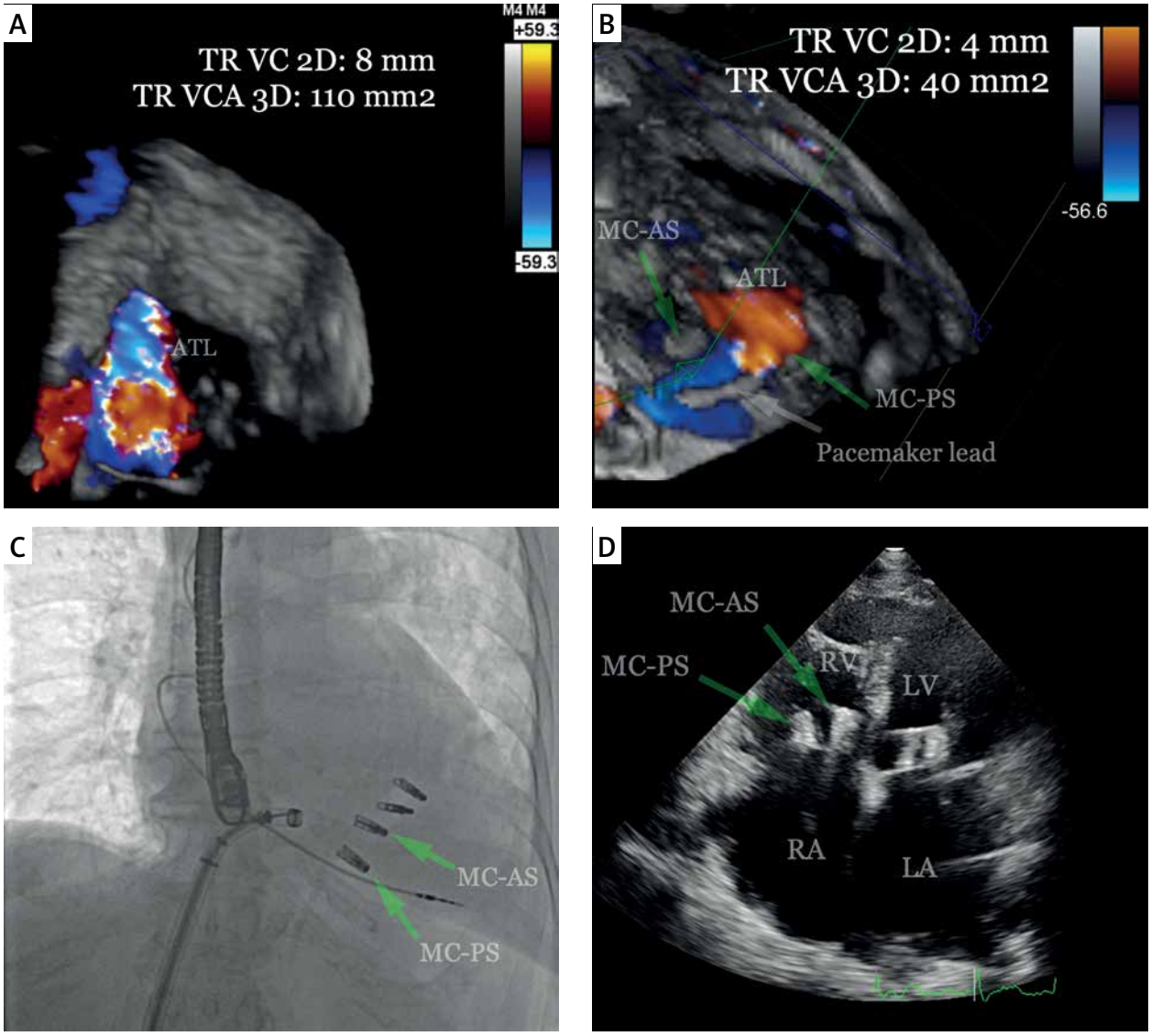

Figure 1. A – Baseline tricuspid regurgitation assessment. TEE-3D, mid-esophageal tricuspid valve planar view showing severe tricuspid regurgitation. **B** – Tricuspid regurgitation after implantation of two MitraClips (arrows) between posteroseptal (MC-PS) and anteroseptal (MC-AS). TEE-3D, mid-esophageal tricuspid valve planar view shows significant reduction of tricuspid regurgitation. **C** – Fluoroscopy showing position of mitral and tricuspid clips and position of pacemaker lead. **D** – Follow-up TEE-2D AP4C. Position of mitral and tricuspid clips

Rapid clinical and haemodynamic improvement in a patient with intermediate-high risk pulmonary embolism treated with transcatheter aspiration thrombectomy

Aleksander Araszkiewicz, Stanisław Jankiewicz, Sylwia Sławek-Szmyt, Aneta Klotzka, Marek Grygier, Tatiana Mularek-Kubzdela, Maciej Lesiak

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

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A 59-year-old man with a history of colon cancer treated surgically three weeks ago was admitted with sudden dyspnoea and chest pain. Three days earlier he developed deep vein thrombosis of the left lower extremity and was treated with full dose low-molecular weight heparin. Physical examination revealed blood pressure 125/70 mm Hg, heart rate 125/min, respiratory rate 28/min. In laboratory tests NT-proBNP was 1961 pg/ml, troponin I 0.4 mg/dl (r.v. < 0.01 mg/dl), arterial oxygen saturation (SaO_2) 88%. Echocardiography revealed signs of right ventricular (RV) enlargement (RV/LV index = 1.9) and hypokinesis of the free RV wall. In computed tomography bilateral massive thrombi affecting lobar pulmonary arteries were observed. Based on these results the patient was diagnosed with intermediate-high risk pulmonary embolism (PE). Calculated PESI score was 139 points (class V – very high risk). Due to relative contraindications to systemic thrombolysis our local Pulmonary Embolism Response Team (PERT) decided to treat this patient with catheter-directed thrombectomy (CDT). Pulmonary angiography was made from right femoral vein access and revealed massive PE especially in the left pulmonary artery (Figure 1 A) [1]. Pulmonary artery pressure was 45/22/32 mm Hg. An intravenous bolus of 7000 IU of unfractionated heparin was administered at the beginning of the procedure. Continuous mechanical aspiration thrombectomy was subsequently performed with a 115 cm 8 Fr Indigo CAT8 TORQ catheter (Penumbra, Almeda, Ca, USA). A separator wire was repeatedly passed through the thrombus to break it down and allow it to be suctioned through the catheter. The thrombus was fragmented and partially removed (Figure 1 B) but distal embolization in the intermediate branch and lower segmental branches appeared (A4-5, A10). For this reason we continued aspiration and entered selectively segmental branches using the support of 6 Fr Judkins Right diagnostic coronary catheter and 0.014'' coronary guidewire to restore and improve the pulmonary flow (Figure 1 B). The decision to terminate the procedure was taken after evaluation of haemodynamic parameters (pulmonary artery pressure decreased to 28/11/16 mm Hg and SaO_2 to 93%) and also the total amount of aspirated blood (350 ml). After the procedure the clinical status of the patient rapidly improved. Anticoagulation was continued with body weight-adjusted low-molecular-weight heparin. On the second day after the procedure normalisation of ECG (Figure 1 D) and echocardiography were obtained and SaO_2 increased to 96% (without oxygen supplementation). On discharge (day 4) NT-proBNP levels dropped to 162 pg/ml and troponin I to 0.013 ng/ml. The patient was discharged home in good clinical condition on full-dose enoxaparin *s.c.* due to neoplastic disease.

Interestingly, the improvement in clinical, haemodynamic and respiratory status was rapidly obtained without achieving complete thrombus removal. Even partial improvement of pulmonary flow can restore sufficient cardiac output and reverse heart overload [2]. Distal embolization during mechanical thrombectomy might however limit the flow to the segmental branches and increase pulmonary arterial resistance even despite continuous aspiration. One should take care of the axial position of the catheter and continue the procedure in distal arteries until the flow is restored. The role of CDT in intermediate-high risk PE patients is still not well established and randomised trials remain rare [3]. However, fast development of the technique and new devices made aspiration CDT easy and safely applicable. It may lead to fast improvement of haemodynamic and clinical

Corresponding author:
Aleksander Araszkiewicz MD, 1st Department od Cardiology, Poznan University of Medical Sciences, 1/2 Długa St, 61-848 Poznan, Poland, phone: +48 608 574 375, e-mail: aaraszkiewicz@interia.pl
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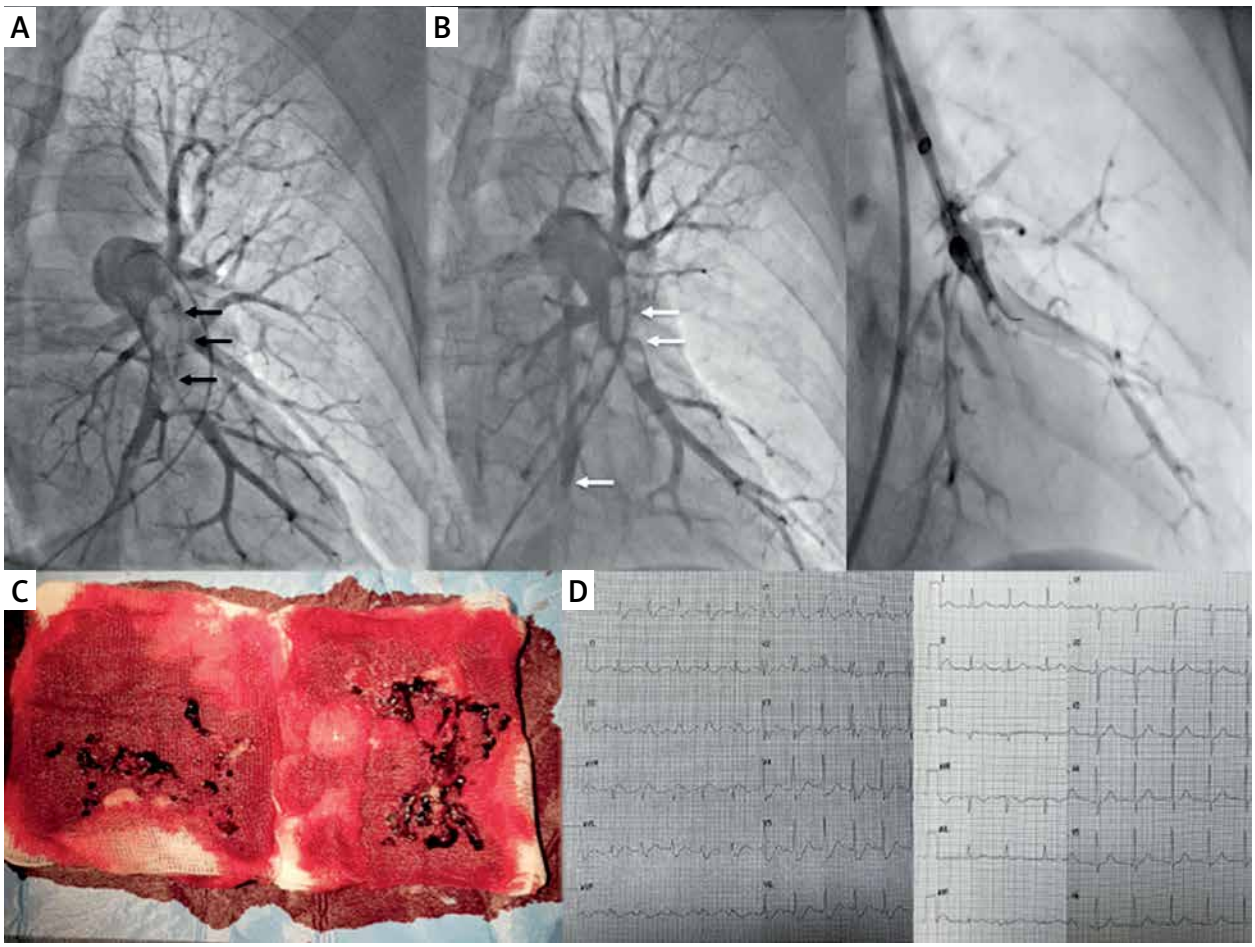

Figure 1. A – Angiogram of the left pulmonary artery before the procedure. Right anterior oblique 30° projection was used to determine the segmental arteries accurately [1]. The massive thrombus affecting lower lobar arteries is visible. **B** – Angiogram after continuous aspiration thrombectomy with Indigo 8 Fr catheter. The thrombus was fragmented and mostly removed, but distal embolization of segmental branches of the intermediate lobe and lower lobe (white arrows) prompted us to continue aspiration. 6 Fr Judkins Right coronary catheter and coronary guidewire were used to selectively intubate segmental arteries and to restore the flow. **C** – Aspirated thrombi from the pulmonary artery. **D** – ECG before the procedure. Sinus rhythm of 115/min with right bundle branch block and signs of right ventricular overload. ECG on next day after the procedure revealed sinus rhythm of 88/min. RBBB completely subsided

status and seems to be a reasonable alternative for intermediate-high risk PE especially in patients with contraindications to systemic thrombolysis or high bleeding risk [3, 4].

Conflict of interest

The authors declare no conflict of interest.

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Sequential wire shifting technique might be in some cases indispensable to acquire adequate pulmonary wedge pressure during right heart catheterization

Grzegorz M. Kubiak[1], Michał Zakliczyński[1], Michał Hawranek[2], Michał O. Zembala[1], Piotr Przybyłowski[1], Mariusz Gąsior[2]

[1]Department of Cardiac Surgery and Transplantology, SMDZ in Zabrze, Medical University of Silesia in Katowice, Silesian Centre for Heart Disease, Zabrze, Poland

[2]3rd Department of Cardiology, SMDZ in Zabrze, Medical University of Silesia in Katowice, Silesian Center for Heart Diseases, Zabrze, Poland

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Right heart catheterization (RHC), according to current guidelines presented in the Joint Statement of the Polish Cardiac Society's Working Group on Pulmonary Circulation and Association of Cardiovascular Interventions [1], is essential to diagnose pulmonary hypertension (PH), which is a serious limitation in case of heart transplant (HTx) listing. A pulmonary vascular resistance (PVR) value exceeding 3.0 Wood units is associated with raised post-operational mortality [2].

A 60-year old man with ischemic cardiomyopathy had RHC prior to HTx listing. Initial examination 6 months earlier failed to assess pulmonary capillary wedge pressure (PCWP). Moreover, it provoked acute decompensation with the need of urgent treatment. Several issues may have contributed as the patient presented a severe clinical condition with New York Heart Association class IV, INTERMACS class III. Secondly, heart failure (HF) emerged gradually, which resulted in major dilatation of the ventricles. Thirdly, the patient presented with combined pre- and post-capillary hypertension; hence he would fall within the scope previously described as "out-of-proportion" PH. Likewise, in this clinical state, raised PVR may lead to a progressive dilatation of the pulmonary arteries. The heavily remodelled anatomy of the pulmonary vascular bed may present a challenge that needs a real breakthrough unless the procedure remains incomplete; hence the sequential wire shifting (SWS) technique was introduced. Noticeably, the unequivocal result of PCWP merits the simultaneous assessment of left ventricular end-diastolic pressure during left heart catheterization as the gold standard, especially given that it may lead to misclassification of PH with all consequences [3].

A 7-F Balton, Poland sheath is inserted by the use of Seldinger's technique. A Swan-Ganz (SG) catheter (Edward Lifesciences, USA) is introduced into the right ventricle in order to perform single beat calibration of the catheter and pressure transducer based on the routine, previously described manner [4]. Subsequently, the catheter and the pressure transducer are disconnected. Latterly the diagnostic EMERALD, Cordis, USA, guidewire 0.035 × 150 cm, 3 mm J tip wire is inserted into the left pulmonary artery. A multi-purpose (MPA), Cordis diagnostic catheter is introduced with the subsequent removal of the diagnostic wire. A 300 cm J-tip Whisper ES, Abbott, USA, angioplasty wire is placed via the MPA catheter with subsequent removal of the latter. The clinched angioplasty wire is used as a rail for the introduction of the SG catheter. Notably, the use of a peripheral guidewire might be dangerous due to the risk of distal perforation. The acquired value of PCWP is reliable; moreover, re-evaluation of RV pressure represents excellent concordance with the initial values, and last but not least it enables further calculations of PVR. To access the step-by-step description of SWS please refer to Figure 1 and Table I with further commentaries.

In conclusion, SWS is a safe technique to acquire PCWP in a demanding group of patients with HF coinciding with major dilatation of pulmonary arteries in the course of PH. Theoretically, it might be either initially (in the case of presumably raised RV systolic pressure in echocardiography) or provisionally (in the case of impaired intraoperational manoeuvrability) implemented in almost all cases. However, its potential contribution to clinical practice requires further evaluation.

Corresponding author:
Grzegorz M. Kubiak MD, PhD, Department of Cardiac Surgery and Transplantology, SMDZ in Zabrze, Medical University of Silesia in Katowice, Silesian Centre for Heart Disease, 9 Curie-Skłodowska St, 41-800 Zabrze, Poland, phone: +48 32 373 38 57, e-mail: gkubiak@sccs.pl
Received: 17.06.2019, **accepted:** 13.07.2019.

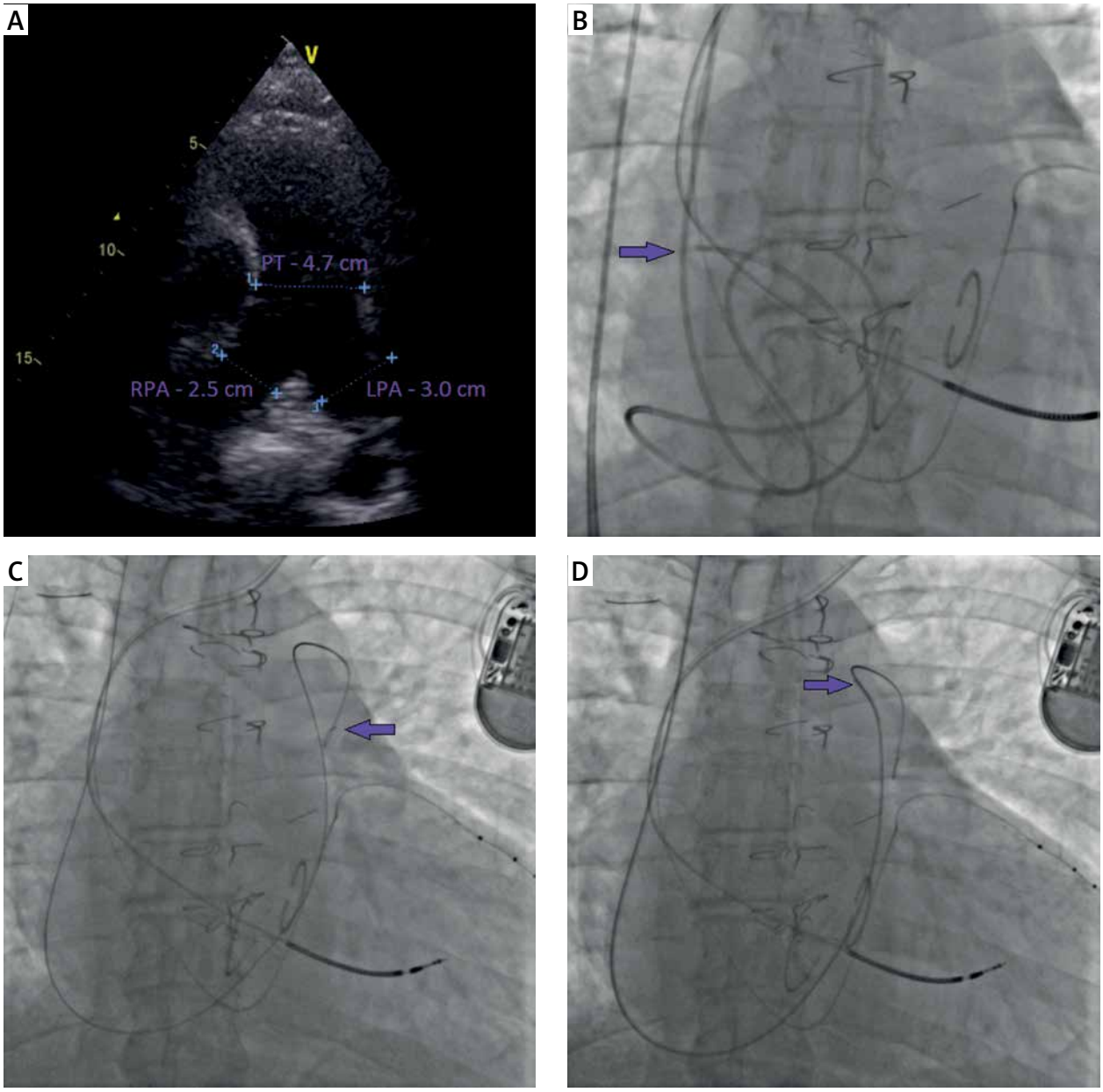

Figure 1. Stages of sequential wire shifting (SWS) technique. **A** – heavily dilated pulmonary vascular bed, **B** – distortion of Edward Lifesciences Swan-Ganz (S-G) catheter, irritation of right atrium (velvet arrow) caused atrial flutter with subsequent clinical decompensation, **C** – diagnostic EMERALD, Cordis, USA, guidewire 0.035 × 150 cm, 3 mm J tip wire is inserted into the left pulmonary artery (velvet arrow), **D** – multi-purpose (MPA), Cordis diagnostic catheter (velvet arrow) is introduced with the subsequent removal of the diagnostic wire

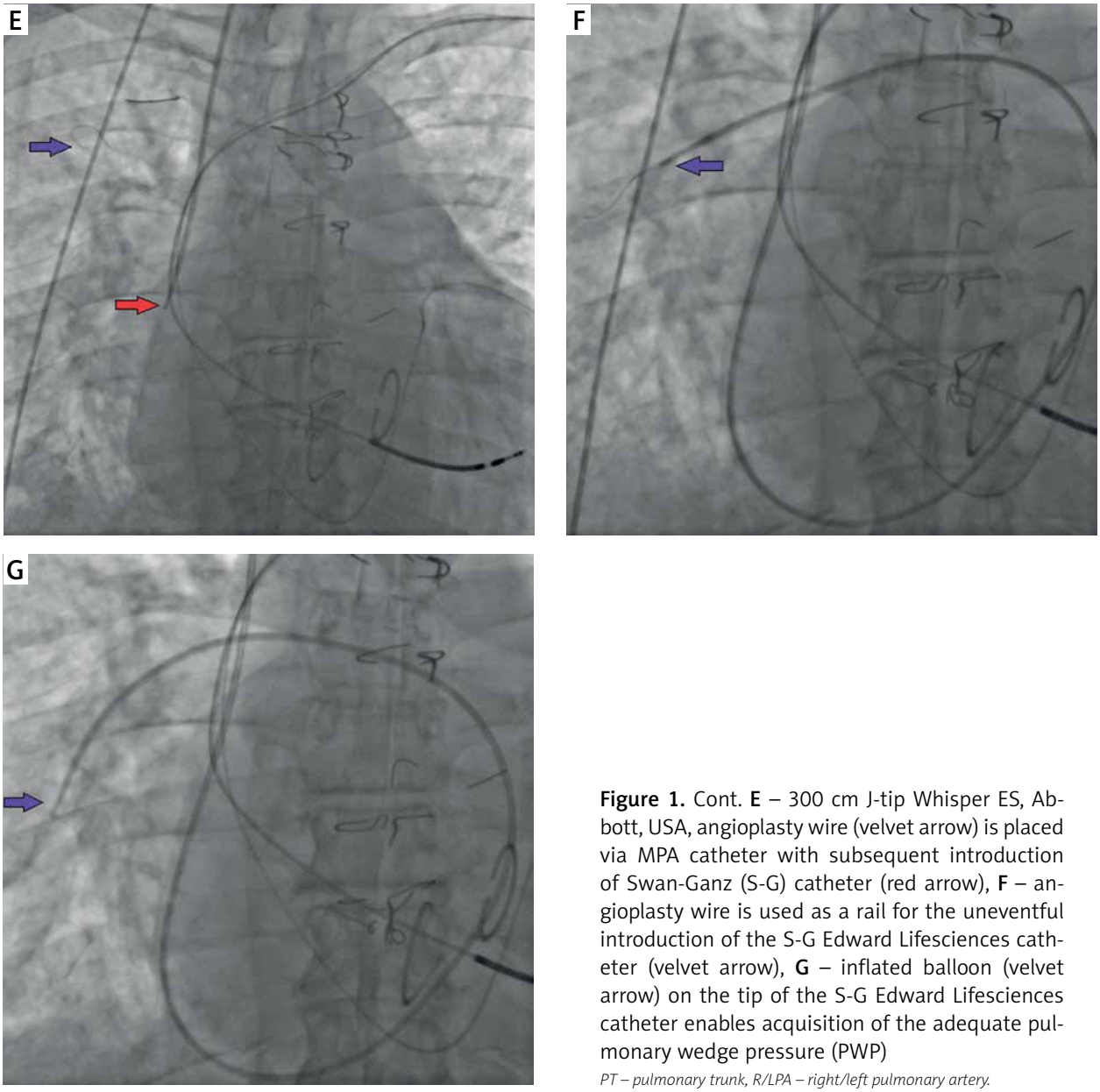

Figure 1. Cont. **E** – 300 cm J-tip Whisper ES, Abbott, USA, angioplasty wire (velvet arrow) is placed via MPA catheter with subsequent introduction of Swan-Ganz (S-G) catheter (red arrow), **F** – angioplasty wire is used as a rail for the uneventful introduction of the S-G Edward Lifesciences catheter (velvet arrow), **G** – inflated balloon (velvet arrow) on the tip of the S-G Edward Lifesciences catheter enables acquisition of the adequate pulmonary wedge pressure (PWP)

PT – pulmonary trunk, R/LPA – right/left pulmonary artery.

Table I. Hemodynamic parameters obtained during RHC

Parameter	Abbreviation	Initial RHC (6.02.2018)	SWS RHC (7.08.2018)
Systemic blood pressure	SBP	105/70 mm Hg	112/82 mm Hg
Mean right atrial pressure	mRAP	10 mm Hg	10 mm Hg
Right ventricular systolic pressure	RVSP	59 mm Hg	67 mm Hg
Mean pulmonary artery pressure	mPAP	41 mm Hg	43 mm Hg
Pulmonary capillary wedge pressure	PCWP	NA	34 mm Hg
Transpulmonary gradient	TPG	NA	9 mm Hg
Cardiac output	CO	4.4 l/min	4.9 l/min
Cardiac index	CI	2.14 l/min/m^2	2.41 l/min/m^2
Pulmonary vascular resistance	PVR	NA	1.83 Wood units

RHC – right heart catheterization, NA – not applicable.

Conflict of interest

The authors declare no conflict of interest.

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The molecular basis for the neutral effect of renal denervation in patients with chronic heart failure not responding to cardiac resynchronisation therapy – a perspective

Márcio Galindo Kiuchi[1], Revathy Carnagarin[1], Vance Bruce Matthews[1], Markus P. Schlaich[1,2,3]

[1]Dobney Hypertension Centre, School of Medicine – Royal Perth Hospital Unit/Medical Research Foundation, University of Western Australia, Perth, Australia

[2]Departments of Cardiology and Nephrology, Royal Perth Hospital, Perth, Australia

[3]Neurovascular Hypertension and Kidney Disease Laboratory, Baker Heart and Diabetes Institute, Melbourne, Australia

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In their elegant study, Drożdż *et al.* reported that renal denervation (RDN) in patients with chronic heart failure (HF) not responding to cardiac resynchronisation therapy (CRT) did not provoke any adverse effects and did not change exercise capacity and hemodynamic parameters [1]. Myocardial systolic functional impairment is related to compensatory neurohumoral overactivity to preserve cardiac output when heart function is deteriorating, a scenario characterised by increased cardiac sympathetic drive. Increased cardiac sympathetic nervous system (SNS) activity as a consequence of excitatory inputs has been described including alterations in peripheral baro- and chemo-receptor reflex responses, higher secretion of the neurotransmitters epinephrine (E) and norepinephrine (NE), as well as renin-angiotensin-aldosterone system (RAAS) activation.

SNS overactivity is characterised by augmented plasma NE and E levels, raised sympathetic discharge of the central nervous system, and enhanced NE spillover, which is increased by 50-fold in HF patients compared to healthy individuals with vigorous exercise. Patients suffering from end-stage systolic HF have reduced postsynaptic β-adrenoreceptor (AR) density, because of the exhaustion of cardiac SNS neuronal NE stores and decreased NE presynaptic reuptake secondary to NE-transporter down-regulation. After release in the heart around 70–90% of the NE released into the synaptic cleft re-enters the presynaptic nerve ending through the NE reuptake transporter (NET or uptake-1) in an energy-consuming process. However, the excess of NE in the synaptic cleft leads to toxic effects and cardiomyocyte apoptosis, as observed in the final stages of HF [2].

The SNS positron-emission-tomography (PET) imaging ^{11}C-meta-hydroxyephedrine (^{11}C-HED) in the clinical and experimental setting principally targets postsynaptic adrenergic receptor density and presynaptic neural activity (e.g., uptake-1 and metabolism). Thus far, (^{11}C-HED) has been the most significant PET radiotracer used as an NE analogue. It has a high affinity for uptake-1 without being metabolised by monoamine oxidases or catechol-O-methyl-transferase. Reduced (^{11}C-HED) uptake has been associated with autonomic dysfunction and low cardiac output in patients with HF, and it has been suggested to be a negative prognostic marker in this cohort [3].

CRT has demonstrated significant modulation of sympathovagal balance, reduced circulating NE and brain natriuretic peptide levels, and RAAS inhibition. Martignani *et al.* revealed a higher level of left ventricular (^{11}C-HED) uptake assessed by PET scans both at baseline and after resynchronisation in the CRT responders compared to non-responders, indicative of the improvement of the cardiac sympathetic nerve activity in the responders [4].

In HF patients who are non-responders to CRT, cardiac sympathetic activation is substantially deranged, thereby potentially compromising the beneficial effects of RDN mediated via afferent sensory signalling.

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Corresponding author:
Márcio Galindo Kiuchi MD, MSc, PhD, FESC, FEHRA, FHFA, Dobney Hypertension Centre, School of Medicine – Royal Perth Hospital Unit, The University of Western Australia, Level 3, MRF Building, Rear 50 Murray St, Perth WA 6000, Australia, phone: +61 8 9224 0242, fax: +61 8 9224 0374, e-mail: marcio.galindokiuchi@uwa.edu.au; marciokiuchi@gmail.com
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Abstracts of original contributions

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The communications presented at the Workshop are printed without alterations from the manuscripts submitted by the authors, who bear the full responsibility for their form and content.

1-P

Assessment of percutaneous coronary interventions among seniors

Ignacy Dobrzycki[1], Hanna Bachórzewska-Gajewska[2,3], Łukasz Kuźma[2], Krzysztof Struniawski[2], Małgorzata Zalewska-Adamiec[2], Marcin Kożuch[2], Sławomir Dobrzycki[1]

[1]Hospital Emergency Department with Intensive Care Unit, Medical University of Bialystok, Medical University of Bialystok Clinical Hospital, Bialystok, Poland
[2]Department of Invasive Cardiology, Medical University of Bialystok, Medical University of Bialystok Clinical Hospital, Bialystok, Poland
[3]Department of Clinical Medicine, Medical University of Bialystok, Bialystok, Poland

Background: In recent years, the percentage of elderly patients has been increased, which means that this group of patients requires individualized treatment.

Aim: To assess the effectiveness of percutaneous coronary interventions (PCI) among seniors.

Methods: 3188 of invasive procedures performed among patients over 75 years old in 2008–2013 met inclusion criteria. Demographical data, comorbidities, type and method of procedure were analyzed. Total mortality was estimated on 20.03.2018.

Results: In the study group 79.5% of procedures were performed in stable coronary artery disease (CAD), 30.5% in acute coronary syndrome (ACS). Post-PCI stroke occurred in 0.9% of the subjects. Local complications were more frequent among women (4.3% vs. 1.6%, $p < 0.001$) and ACS group (4.4% vs. 1.8%, $p < 0.001$). In-hospital mortality rate was 5.4%. Risk factors increasing in-hospital mortality were: cardiac shock RR 0.95 (95% CI: 0.94–0.97), post-PCI creatinine level elevation RR 1.36 (95% CI: 1.03–1.77), and elevated INR RR – 1.57 (95% CI: 1.05–2.36). 10-year survival prognosis for post-PCI patients was 33.9%. Factors resulting in decreased long-term survival were: age RR = 1.07 (95% CI: 1.05–1.08), gender RR = 1.38 (95% CI: 1.23–1.57), prior ACS RR = 1.13 (95% CI: 1.01–1.29), kidney failure RR = 1.15 (95% CI: 1.03–1.28).

Conclusions: Prognosis of seniors, who underwent PCI is good. After considering contraindications, invasive procedures in this group of patients should be performed both in stable CAD and ACS.

2-P

The hybrid algorithm in coronary chronic total occlusions treatment – MSWiA Lublin CTO 5-year registry

Jakub Drozd, Marcin Kowalski, Tomasz Wołyniak, Monika Zaręba-Giezek

Ministry of Internal Affairs and Administration Hospital in Lublin, Lublin, Poland

Background: Treatment of chronic total occlusions (CTO) despite improvement in techniques and results over the last years still seems to be limited to the small number of centers and operators. Application of the hybrid strategy in procedure planning may support further spread of the percutaneous CTO treatment in community.

Aim: Our single center registry aims to provide details and results of recanalizations of coronary CTO performed according to the hybrid algorithm in consecutive patients.

Methods: Between January 2015 and September 2019 clinical and procedural data of consecutive CTO procedures on unselected patients were collected. Lesion complexity was assessed according to Multicenter CTO Registry of Japan (J-CTO) score: 0 – easy, 1 – intermediate, 2 – difficult, ≥ 3 – very difficult. Strategies applied were classified as: anterior wire escalation (AWE), anterior dissection and reentry (ADR), reverse wire escalation (RWE) and RDR (reverse wire escalation, mainly rCART). Angiographic success was defined as < 30% residual stenosis wit TIMI grade 3. Angiographic and clinical complications were reported.

Results: 266 patients were included and 285 procedures were performed in total. Success rate was 92.5% (calculated per patient) and 87.7% (calculated per procedure). Four patients underwent successful staged double CTO recanalization. Fifteen patients out of 31 primary failures underwent second attempt with 73% success rate (11/15). 52 patients (18.2%) were referred for second attempt from other institutions. Mean J-CTO score was 2.6 (0 – n = 13, 1 – n = 41, 2 – n = 80, ≥ 3 – n = 151) and success rate was accordingly: 91.7%, 92.7%, 91.3% and 84.1%). Higher complexity of occlusion required higher number of applied strategies including retrograde access in over a quarter of cases (Table I). Complete revascularizations were obtained in 215 cases (75.4%). One patient died due to acute renal failure complications. Among complications we report 10 (3.5%) myocardial infarctions (1 STEMI due to side branch occlusion), 7 perforations (2.4%) all treated conservatively and 10 cases (3.5%) of acute kidney injury (one dialysis).

Conclusions: Application of the hybrid algorithm in unselected population of patients with CTO is a success-

Table I

J-CTO	Number of strategies applied			Successful strategy			
	1	2	3	AWE	ADR	RWE	RDR
0	13 (100%)	0	0	12 (100%)			
1	36 (87.8%)	4 (9.8%)	1 (2.4%)	34 (89.5%)	1 (2.6%)	3 (7.9%)	
2	49 (61.2%)	19 (23.8%)	12 (15%)	51 (69.9%)	1 (1.3%)	7 (9.6%)	14 (19.2%)
≥ 3	80 (53%)	47 (31.1%)	24 (15.9%)	59 (46.5%)	21 (16.5%)	11 (8.7%)	36 (28.3%)
All	178 (62.5%)	70 (24.6%)	37 (12.9%)	156 (62.4%)	23 (9.2%)	21 (8.4%)	50 (20%)

ful strategy with low rate of complications. Higher complexity of CTO requires more procedural strategies with significantly low success rate in very difficult cases.

3-P

Importance of the hyperemic and non-hyperemic pressure gradients in complex physiological evaluation of coronary vessels

Áron Üveges[1,2], Balázs Tar[2], Csaba Jenei[1], Zoltán Papp[1], Zoltán Csanádi[1], Zsolt Kőszegi[1,2]

[1]University of Debrecen, Department of Cardiology, Debrecen, Hungary
[2]Szabolcs-Szatmár-Bereg County Hospitals, III Department of Internal Medicine, Nyíregyháza, Hungary

Background: FFR is considered as an appropriate tool for the selection of intermediate epicardial coronary lesions for stenting, while coronary flow reserve (CFR) was proposed as the true indicator of myocardial ischemia. Recently, non-hyperemic pressure ratios (RPR: resting pressure ratios and iFR: instantaneous flow reserve) challenged the need for vasodilatation for clinical decision making. We aimed to calculate CFR on the basis of fluid dynamic equations using 3D coronary angiography parameters and measured pressure gradients. We also aimed to compare FFR and RPR values with regard to calculated CFR ones.

Methods: FFR measurements were performed on 32 coronary arteries. The lumen of the interrogated vessel segments was reconstructed in 3D. The components of the pressure gradients due to laminar and "turbulent" flow were modelled by classic fluid dynamic equations, CFR was defined as the ratio between hyperaemic and resting flows.

Results: A good correlation was found between FFR and RPR values ($r = 0.91$, $p < 0.001$), however 8/32 cases demonstrated discordant results. There were significant correlations between FFR and CFR values as well as between RPR and CFR parameters, but the latter demonstrated stronger relation ($r = 0.33$, $p = 0.066$ and $r = 0.52$, $p = 0.002$, respectively). The CFR was calculated to be higher in the discordant 5 cases with RPR > 0.90 and FFR < 0.80 than that in the 3 cases with RPR < 0.90 and FFR > 0.80 (2.50 ±0.71 vs. 1.30 ±0.07, $p = 0.05$).

Conclusions: Our results support the importance of the evaluation of the RPR being in close relation with the CFR. Supplementing FFR with RPR can help the appropriate classification of the functional state of coronary vessel.

4-P

Safety and efficacy of embolic protection devices in saphenous vein graft interventions: a propensity score analysis – multicenter SVG PCI PROTECTA study

Wojciech Wańha[1], Maksymilian Mielczarek[2], Natasza Gilis-Malinowska[2], Tomasz Roleder[3], Szymon Ładziński[1], Marek Milewski[1], Dariusz Ciećwierz[2], Tomasz Figatowski[2], Paweł Gąsior[1], Rafał Januszek[4], Adam Kowalówka[5], Michalina Kolodziejczak[6,7], Stanisław Bartuś[4], Marcin Gruchała[2], Grzegorz Smolka[1], Eliano Pio Navarese[7,8,9,10], Dariusz Dudek[4], Andrzej Ochała[1], Elvin Kedhi[1,11], Miłosz Jaguszewski[2], Wojciech Wojakowski[1]

[1]Department of Cardiology and Structural Heart Diseases, Medical University of Silesia, Katowice, Poland
[2]First Department of Cardiology, Medical University of Gdansk, Gdansk, Poland
[3]Regional Specialist Hospital, Research, and Development Center, Wroclaw, Poland
[4]Second Department of Cardiology, Jagiellonian University Medical College, Krakow, Poland
[5]Department of Cardiac Surgery, Medical University of Silesia, Katowice, Poland
[6]Department of Anaesthesiology and Intensive Care, Antoni Jurasz University Hospital No. 1 in Bydgoszcz, Poland
[7]SIRIO MEDICINE research network

[8]Cardiovascular Institute, Nicolaus Copernicus University, Bydgoszcz, Poland
[9]Interventional Cardiology and Cardiovascular Medicine Research, Mater Dei Hospital, Bari, Italy
[10]Department of Cardiovascular Medicine, University of Alberta, Edmonton, Canada
[11]AZ Sint Jan Brugge, Belgium

Background: Data regarding the efficacy of the embolic protection devices (EPD) in saphenous vein graft (SVG) PCI is controversial.

Aim: The primary objective of the study was to compare 1-year clinical outcomes of SVG PCI with and without EPD in the all-comer population.

Methods: A multi-center registry comparing PCI with and without EPD in consecutive patients undergoing PCI of SVG. The group consisted of 792 patients including 266 (33.6%) patients with MI. The primary composite endpoint was MACCE defined as death, myocardial infarction (MI), target lesion revascularization, and stroke assessed at 1 year.

Results: In an unmatched cohort of patients, there were no significant differences in MACCE (20.5% vs. 26.4%; HR = 0.75, 95% CI: 0.53–1.06, p = 0.105) between EPDs and non-EPD. A trend towards lower risk of death in EPD group (4.2% vs. 7.8%; HR = 0.53, 95% CI: 0.25–1.12, p = 0.094) was present at 1-year, but after propensity score matching no significant differences were observed. No difference in MACCE between PCI SVG with and without EPDs was also found in MI subgroup. In a subanalysis comparing PCI with Spider-EPDs showed a trend towards lower risk of death in the device group vs. no-EPDs (2.1% vs. 7.8%, HR = 0.26, 95% CI: 0.06–1.07, p = 0.062). Also in the MI subgroup, there was a trend towards lower MACCE in patients treated with the support of Spider-EPDs as compared with no EPD (18.7% vs. 34.6%, HR = 0.50, 95% CI: 0.22–1.14, p = 0.099).

Conclusions: SVG PCI using EPDs showed favourable clinical outcomes at 1-year follow-up. There was no statistically significant clinical benefit of routine use of EPD in this all-comer population.

5-P

Prevalence, characteristics and long-term mortality of patients with valvular heart disease in Podlaskie Voivodeship (BIA-WAD2 Registry)

Krzysztof Struniawski[1], Łukasz Kuźma[1], Hanna Bachórzewska-Gajewska[1,2], Paweł Kralisz[1], Marcin Kożuch[1], Szymon Pogorzelski[1], Sławomir Dobrzycki[1]

[1]Department of Invasive Cardiology, Medical University of Bialystok, Bialystok, Poland
[2]Department of Clinical Medicine, Medical University of Bialystok, Bialystok, Poland

Background: Population of patients with valvular heart disease (VHD) has changed in recent years along with diagnostic and treatment management.

Aim: To evaluate prevalence, characteristics and long-term prognosis of patients with VHD.

Methods: Medical records of 36941 patients treated in the Department of Invasive Cardiology of the Medical University of Bialystok in 2006–2016 were retrospectively analyzed. Assessed variables included: angiography characteristics, echocardiography imaging and medical history. Type of treatment and total mortality on 16.05.2019 were estimated. Mean observation time was 1865 days (SD = 1249).

Results: 2661 patients met inclusion criteria with mean age 69.55 (SD = 10.71), men 56.63% (n = 1507). The most frequent VHD were: moderate mitral valve insufficiency (MVI, n = 1082) and severe aortic valve stenosis (AVS, n = 728). Comorbidities with the highest prevalence were: coronary artery disease (CAD) 81.17% (single-vessel 17.25%, multi-vessel 21.8%) and arterial hypertension (70.31%, n = 1871). During follow-up PCI was performed in 28.49% (n = 758), TAVI in 3.58%

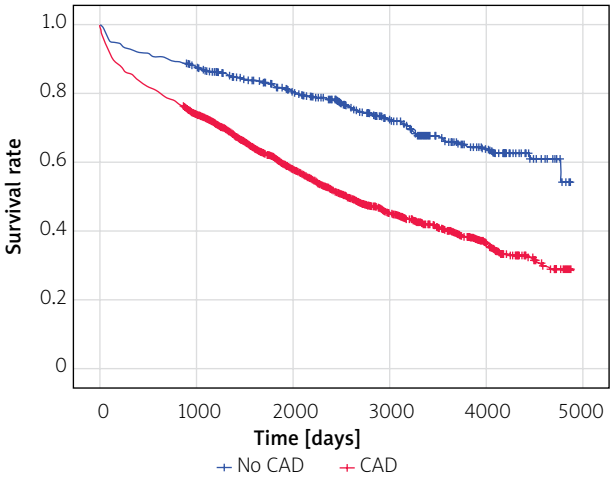

Figure 1. Kaplan-Meier survival curve for patients with VHD depending on CAD

(n = 93), 44.3% (n = 1170) of subjects underwent cardiac surgery. During 14 years observation time 44.08% (n = 1173) of subjects died, with the worst prognosis in moderate AVS group (52.31%, n = 147). In patients with CAD mortality rate was 47.87% (n = 1034) vs. 27.74% (n = 139), $p < 0.001$. The most significant death risk factors were: AVS (severe RR = 2.825, 95% CI: 1.922–4.153, moderate RR = 2.486, 95% CI: 1.681–3.677), chronic pulmonary obstructive disease (RR = 2.512, 95% CI: 1.595–3.956) and CAD (RR = 1.611, 95% CI: 1.142–2.271) (Figure 1).

Conclusions: The most frequent VHD was moderate MVI. Patients with moderate AVS were related with the worst long-term prognosis. CAD is one of the most significant factors worsening the prognosis of patients with VHD.

6-P

Evaluation of the air pollution effect on frequency of admissions for acute coronary syndromes and cardiovascular diseases mortality

Łukasz Kuźma[1], Krzysztof Struniawski[1], Szymon Pogorzelski[1], Paweł Kralisz[1], Konrad Nowak[1], Hanna Bachórzewska-Gajewska[1,2], Sławomir Dobrzycki[1]

[1]Department of Invasive Cardiology, Medical University of Bialystok, Bialystok, Poland
[2]Department of Clinical Medicine, Medical University of Bialystok, Bialystok, Poland

Background: Cardiovascular diseases (CVD) are the biggest threat and the most common cause of death in Poland. Air quality is a well-known risk factor in the development of these diseases.

Aim: Evaluation of the air pollution effect on frequency of admissions for acute coronary syndromes (ACS) and CVD mortality.

Methods: Inhabitants of Bialystok treated for ACS in 2008–2017 met inclusion criteria. Mortality statistics were achieved from Statistical Office for the same time. Concentrations of SO_2, NO_2, PM2.5, PM10 and weather conditions were analyzed. Multivariate Poisson regression test was used for statistical analysis ($p < 0.05$).

Results: In analyzed period of time 2645 patients with ACS and 16370 CVD deaths among inhabitants of Bialystok were reported. After excluding seasonal changes in NSTEMI group there was a greater number of hospitalizations related with increased NO_2 (RR = 1.19, 95% CI: 1.01–1.41, p = 0.04) and PM2.5 concentration (RR = 1.10, 95% CI: 1.01–1.21; p = 0.04). Increased SO_2 concertation by 10 µg/m^3 was connected with higher mortality for cardiovascular reasons (RR = 1.05, 95% CI: 1.01–1.09; p = 0.02). Temperature drop by 10°°C resulted in 11% increase in number of admissions for STEMI (RR = 1.11, 95% CI: 1.01–1.21; p = 0.01) and increased cardiac mortality by 5% (RR = 1.05, 95% CI: 1.02–1.09; $p < 0.001$).

Conclusions: An elevation of PM2.5 concentration increases the risk of NSTEMI. The main air pollutant affecting cardiovascular mortality is SO_2. Temperature drop is related to increased mortality and admissions for STEMI.

7-P

Safety and feasibility of early one-day-discharge after intracoronary imaging

Adam Janas, Aleksander Żurakowski, Piotr Buszman, Stefan Kiesz, Paweł Buszman, Krzysztof Milewski

Center of Cardiovascualr Reaserch and Development, X Ward of Invasive Cardiology Tychy, Ward of Invasive Cardiology in Chrzanów, American Heart of Poland, Poland

Background: Intracoronary imaging in recent years become mandatory tool in the diagnostics of coronary and stent pathology. Nevertheless, the intracoronary imaging could lead to serious consequences like plaque or wall injury, dissections, acute artery occlusions and myocardial infarction or perforation.

Aim: To assess the safety and feasibility of one day discharge after intracoronary imaging.

Methods: This study was a prospective multicenter single arm clinical trial conducted in 2 sites of American Heart of Poland. We included patients with stable angina who underwent planned angiography with intracoronary imaging. Optical coherence tomography (OCT DragonFly®, Abbot) and intravascular ultrasound both mechanical and electronical (IVUS, Volcano- Revolution® and Eagel Eye® catheters, IVUS-NIRS, TVC Imaging System) and planned to be discharged same day after procedure.

Results: Forty patients were included. Mean age was 65.53 ±9.53 years and 24 (60%) were male. The diabetes melitus and hypertension were present, in 14% (6) and 53% (21) patients, respectively. Left radial was chosen more frequent than right one (40% (16) vs. 60% (24), p = 0.11) OCT was used in 40% (16), IVUS Revolution 10% (4) and Eagle Eye 22.5% (9). Whereas TVC IVUS-NIRS system was used in 27.5% (11). Thirty-five (87.5%) subjects were discharged home during same day after procedure. The mean time to discharge after procedure was 3.7 ±0.8 h. There were no any adverse events before discharge and in 24 h phone follow up. Two patients were left overnight due to stent implantation and 3 due to unsuccessful radial access.

Conclusion: One day discharge after intracoronary imaging is safe and feasible.

8-P

Short-term healing response after implantation of thin strut, fast releasing sirolimus-eluting biodegradable polymer-coated stent: preliminary results of an optical coherence tomography study.

Paweł Gasior, Magdalena Dobrolinska, Tomasz Roleder, Magdalena Roleder, Grzegorz Smolka, Andrzej Ochala, Wojciech Wojakowski

Department of Cardiology and Structural Heart Diseases, Medical University of Silesia, Katowice, Poland

Background: Bioresorbable polymer drug eluting stent (DES) technologies promise to enhance vascular healing by reducing polymer exposure to the vessel wall potentially allowing the earlier discontinuation of dual anti-platelet therapy. Experimental data suggest that the early phases of strut healing determines the long-term healing response of DES.

Aim: The present study assessed vessel healing response after implantation of a thin strut (71 µm), fast releasing sirolimus-eluting biodegradable polymer-coated stent (BP-SES, Alex, Balton, Poland) at 30-day follow-up by optical coherence tomography (OCT) imaging.

Methods: Up to date nine patients underwent OCT guided percutaneous coronary intervention (PCI) in *de novo* coronary lesions with implantation of 9 BP-SES (we plan to include total of n = 15 patients). All patients underwent follow-up OCT imaging at 4-weeks following implantation.

Results: A total of 209 cross sections and 1984 struts were included in the final analysis. Mean patient age was 72 ±7 years (67% males). The clinical presentation consisted of acute coronary syndromes (22%) and stable coronary disease (78%). Almost half of the patients (~45%) had a history of previous PCI. All patients received dual anti-platelet therapy during the entire duration of the study. The mean stent diameter and length were 3.25 ±0.46 mm and 20.5 ±3.21 mm respectively. Reference vessel area evaluated by OCT was 8.59 ±3.45 mm^2. Mean minimal lumen area and percent of area stenosis before stent implantation was respectively 1.66 ±0.51 mm^2 and 75.23 ±14.09%. Average lesion length was 24.5 ±5.28 mm. At 4-weeks following stent implantation almost all analyzed struts (89.8%) had evidence of tissue coverage. The percentage of fully embedded struts was 69.92% and protruding covered struts was 19.89%. The percentage area stenosis based on reference was 8.84 ±16.69% at follow-up and no stents had > 30% area stenosis.

Conclusions: The preliminary results of this ongoing study demonstrated favorable vessel healing at 4-weeks OCT follow-up after implantation of a thin strut, fast releasing sirolimus-eluting biodegradable polymer-coated stent. However, results from a larger group of patients are required to consider shorter dual-antiplateled regimens for the studied device.

9-P

In vitro mechanical behavior and in vivo healing response of a new generation biodegradable-polymer coated thin strut sirolimus eluting stent

Paweł Gasior, Łukasz Pyka, Michał Hawranek, Marcin Garbacz, Mariusz Gasior, Wojciech Wojakowski, Andrzej Lekston

[1]Department of Cardiology and Structural Heart Diseases, Medical University of Silesia, Katowice, Poland
[2]Department of Cardiology and Structural Heart Diseases, Medical University of Silesia, Katowice, Poland

Background: Recent advancements in drug-eluting stents (DES) technologies reduced the rate of repeat revascularization. However, treatment complex lesions still remain challenging.

Aim: To evaluate the biomechanical behavior and vascular healing profile of a new generation biodegradable-polymer coated thin strut sirolimus-eluting stent (Alex NG, Balton, Poland).

Methods: *In vitro* biomechanical testing was performed under static conditions. We compared Alex NG with the commercially available previous generation platform (Alex Plus, Balton, Poland) and the leading DES (Orsiro, Biotronik, Germany). We investigated the difference in stent designs and the results obtained after post-expansion with larger balloon sizes. A total of 6 domestic swines were implanted with Alex NG (n = 12) and Alex Plus (n = 6) for healing evaluation at 30 days

Results: With overexpansion 1mm above nominal diameter no fractures or significant deformations were observed in the light microscopy in all studied groups. Furthermore, postdilatation 1.5 mm above the nominal diameter revealed no fractures in Alex NG and Orsiro. Also, the largest cell opening diameter was observed in the Alex NG both at the nominal and upsized diameters. Optical coherence tomography analysis demonstrated comparable neoinitimal thickness at 30 days in Alex NG when compared to Alex Plus (respectively: 0.14 ±0.03 vs. 0.14 ±0.05, p = 0.887). Histology evaluation is pending, and the results will be presented at the meeting.

Conclusions: The new-generation Alex NG demonstrated improved biomechanical behavior to the previous generation platform (Alex Plus) with the results similar

to the Orsiro stent. Furthermore, Alex NG demonstrated favorable healing profile in the imaging in vivo study.

10-P

Transradial and transfemoral approach in patients with prior coronary artery bypass grafting and treated with percutaneous coronary interventions

Rafał Januszek[1,2], Zbigniew Siudak[3], Krzysztof P. Malinowski[4], Wojciech Wańha[5], Wojciech Wojakowski[5], Mariusz Gąsior[6], Stanisław Bartuś[2,7], Dariusz Dudek[2,8]

[1]Department of Clinical Rehabilitation, University of Physical Education, Krakow, Poland
[2]Second Department of Cardiology and Cardiovascular Interventions, University Hospital, Krakow, Poland
[3]Faculty of Medicine and Health Sciences, Jan Kochanowski University, Kielce, Poland
[4]Institute of Public Health, Faculty of Health Sciences, Jagiellonian University Medical College, Krakow, Poland
[5]Department of Cardiology and Structural Heart Diseases, Medical University of Silesia, Katowice, Poland
[6]Third Department of Cardiology, Silesian Centre for Heart Diseases in Zabrze, School of Medicine with the Division of Dentistry in Zabrze, Medical University of Silesia in Katowice, Zabrze, Poland
[7]Second Department of Cardiology, Jagiellonian University Medical College, Krakow, Poland
[8]Department of Interventional Cardiology, Jagiellonian University Medical College, Krakow, Poland

Background: The relationship between periprocedural complications and the type of vascular access in patients with prior history of coronary artery bypass grafting (CABG) and treated with percutaneous coronary intervention (PCI) is less investigated than in the overall group of patients treated with PCI.

Aim*:* To assess the relationship between type of vascular access and selected periprocedural complications in the group of patients with prior history of CABG treated with PCIs.

Methods: Based on the nationwide registry (ORPKI) we analysed 536,826 patients treated with PCI between 2014 and 2018. We extracted 32,225 with prior history of CABG. Then we compared patients with femoral and radial access as well as with right and left radial access. The comparison was proceeded by propensity score matching (PSM).

Results: After PSM, the multifactorial analysis revealed that patients treated with PCI from femoral access were significantly more often related to periprocedural deaths (odds ratio (OR) = 1.79; 95% confidence interval (CI): 1.1–3.0, p = 0.02) and cardiac arrests (OR = 1.98; 95% CI: 1.38–2.87, p < 0.001). Following adjusting for Killip class grade and the occurrence of cardiac arrests before PCI the significance remained for procedural related cardiac arrests (OR = 1.59; 95% CI: 1.09–2.35, p = 0.01). While the comparison of right and left radial access showed no significant differences between procedural related complications.

Conclusions: Femoral access in comparison to the radial is related to higher rate of periprocedural cardiac arrests in patients with prior history of CABG treated with PCI.

11-P

Prognostic model for paravalvular leakage prediction after transcatheter aortic valve replacement based on non-standard computed tomography analysis

Agata Wiktorowicz[1], Adrian Wit[2], Krzysztof P. Malinowski[3], Artur Dziewierz[1], Lukasz Rzeszutko[1], Dariusz Dudek[1], Pawel Kleczynski[1]

[1]Second Department of Cardiology, Jagiellonian University Medical College, Krakow, Poland
[2]Faculty of Physics and Applied Computer Science, University of Science and Technology, Krakow, Poland
[3]Institute of Public Health, Faculty of Health Sciences, Jagiellonian University Medical College, Krakow, Poland

Background: Paravalvular leakage (PVL) is one of the most common complications of transcatheter aortic valve replacement (TAVR), affecting short- and long-term outcomes.

Aim: To identify imaging biomarkers to predict complications of TAVR, with emphasis on the PVL occurrence.

Methods: We analyzed CT scans of 45 TAVR patients with our newly developed software and defined a list of unique quantitative parameters that describe aortic valve calcifications (AVC) in two ways: as a whole stenotic mass and as a local AVC amount in each of three section of stenotic aortic valve (radial presentation). We confronted these parameters with data of baseline characteristic, procedural and long-term outcomes after TAVR.

Results: We found a correlation between the volume of the largest calcium block, calcium perimeter and calcium Feret's diameter in analyzing AVC mass and PVL occurrence after TAVR (p = 0.012, p = 0.001 and p = 0.045, respectively). Local AVC analysis in radial presentation showed that AVC amount is an independent predictor of PVL. Moreover, a 100 mm increase in local AVC amount in each section was associated with 16.1% (95% CI: 4.5–29.1; p < 0.01) increase in the risk of PVL in the corresponding area. Bootstrap validation with 1000 simu-

lations was performed on the multivariable model with C-statistics as a measure of goodness of fit. ROC analysis revealed the cut-off point of 909.187 mm of AVC amount considered in radial presentation. Kaplan-Meier curves showed (p = 0.003; log-rank) worst PVL-free survival in patients with more than 909.187 mm of calcium.

Conclusions: Quantitative AVC assessment for PVL prediction may play an important role in TAVR patients' selection.

12-P

Automatic arrhythmia detection form two-channel ambulatory ECG recordings using Shannon Information Theory-based algorithms

Agnieszka Pregowska[1], Klaudia Proniewska[2], Peter van Dam[3], Dariusz Dudek[4], Janusz Szczepanski[1]

[1]Institute of Fundamental Technological Research, Polish Academy of Sciences, Warsaw, Poland
[2]Department of Bioinformatics and Telemedicine, Jagiellonian University Medical College, Krakow, Poland
[3]PEACS BV Nieuwerbrug, The Netherlands
[4]Institute of Cardiology, University Hospital, Jagiellonian University Medical College, Krakow, Poland

Background: Cardiovascular disease (CVD) accounts for about 45% of deaths in Europe. Development of effective tools for automatic arrhythmia detection from electrocardiogram (ECG) is important, especially in early prevention and diagnosis.

Aim: Designing and implementation of new classification algorithms based on Information Theory concepts for quantifying the irregularity of physiological time series. Entropy, Mutual Information, and complexity are the essence of the approach proposed. The advantage of these indicators is that they take into account inner structures in the sequences of symbols (digitalized signals).

Methods: In this study, we considered a group of subjects healthy individuals (MIT-BIH Normal Sinus Rhythm Database, 18 individuals) and patients with arrhythmias (MIT-BIH Arrhythmia Database, 47 subjects). Before applying the Information Theory-based tools, bio-signals have to be digitalized. Here, the binary sequence conversion was proposed, using the encoding fluctuation addressing method, which strongly exploits the variability of bio-signals by taking into account oscillations of consecutive ECG values around the signal average.

Results: It turned out that normalized Lempel-Ziv complexity (LZC) values were significantly lower for patients with arrhythmias aginst control group (AVR_{ar} = 0.38 vs. AVR_{contr} = 0.86). This means, due to the essence of LZC, that healthy individuals signals exhibit much more patterns than subjects with arrhythmias. Consequently, arrhythmias group signals have LZC much lower (Figure 1). The proposed classifier provided arrhythmias diagnostics with a sensitivity of 90.00 and specificity of 92.00%.

Conclusions: Results obtained support the hypothesis that Information Theory tools can be successfully applied to classified biomedical signals addressing biological systems physiological states and can improve diagnostic speed, accuracy, and reliability.

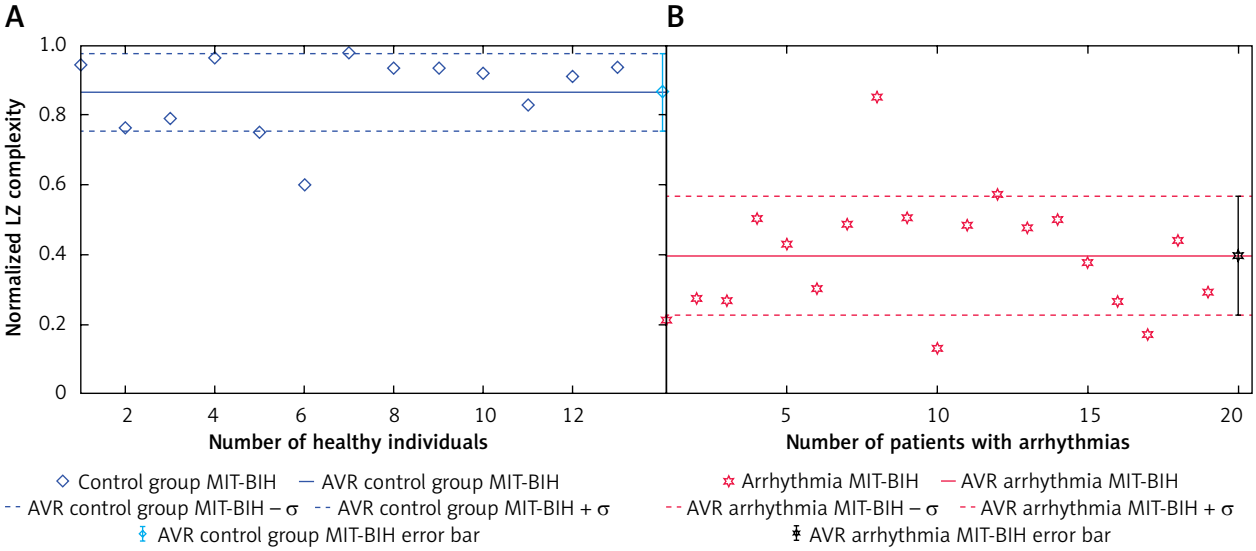

Figure 1. Normalized Lempel-Ziv complexity of ECG, for MIT-BIT control group (blue) (**A**), and for MIT-BIT arrhythmias patients (red) (**B**). The average values and standard deviations within groups are also shown. An important observation is that the intervals with the spread σ around averages do not completely overlap what was illustrated in the middle vertical axis

13-P

Augmented reality as a doctor support to meet the General Data Protection Regulation in Europe

Klaudia Proniewska[1], Damian Dołęga-Dolegowski[1], Agnieszka Pregowska[2], Dariusz Dudek[2]

[1]Department of Bioinformatics and Telemedicine, Jagiellonian University Medical College, Krakow, Poland
[2]Institute of Fundamental Technological Research, Polish Academy of Sciences, Warsaw, Poland
[3]Institute of Cardiology, University Hospital, Jagiellonian University Medical College, Krakow, Poland

Background: General Data Protection Regulation (GSPR) created by the European Nation aims to harmonize data protection rules and everyone in Europe is obligated to follow it. Unfortunately, one can still find, doctors who have on their desk subjects documentation from the current and sometimes even the previous day. On the other hand, display data using PC/Laptops are limited to a few rigorous conditions like the location of the power socket, free space on table/desk, and the display angle.

Aim: This paper aims to develop an Augmented Reality (AR) based application using an advanced technology device – Microsoft's Azure Kinect DK camera and HoloLens glasses.

Methods and results: The scheme of the proposed support systems is presented in Figure 1. Rooms where doctors work, such as a doctor's office, an exam room, an operating room, and a treatment room will be transferred to the digital form in real-time. The proposed solution will give new possibilities and enable additional support in the clinical diagnosis process, during medical procedures and the preview of the procedure from a different non-standard location without spatial restrictions related to the perspective of the Operator. A remote person could mark on his screen or AR device place, on which he/she wants to show, mark or point. The same information can be displayed on surgery glasses as a hint, it does not disturb his/her activities performed. Moreover, the proposed doctors' support tool allows also greater flexibility to learn and interact inside the worldwide medical community.

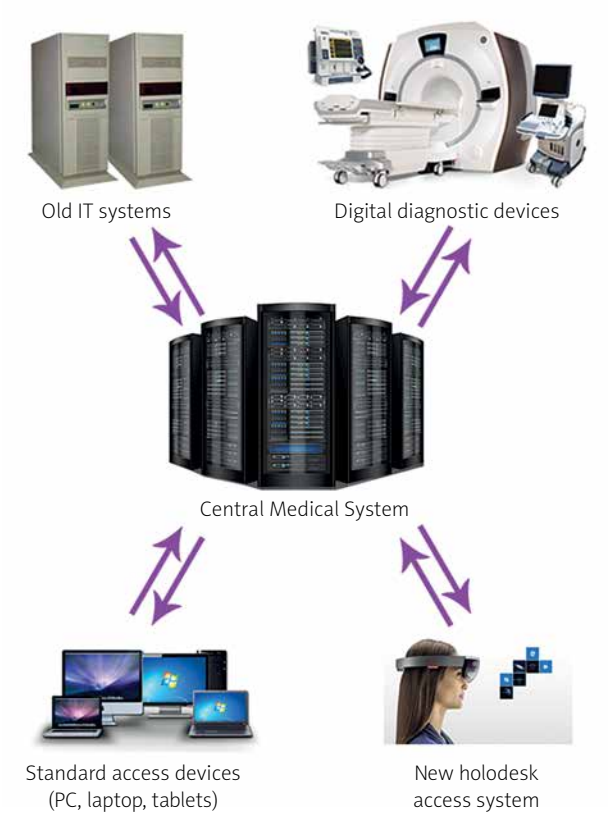

Figure 1. The scheme of the holographic system of the doctors supports

Instructions for Authors

AIM/SCOPE

The journal publishes papers related to research and practice in the broad field of interventional cardiology (coronary, structural, congenital, peripheral, cerebrovascular and experimental), including original research articles, as well as descriptions of novel techniques or findings. Meta-analyses, clinical trials and advances in applied (translational) research will also be considered. In general, full-text case reports will not be considered for publication.

As a forum for Polish interventional cardiologists, the journal also publishes papers discussing issues related to interventional cardiology in Poland including statements and reports on new initiatives within the community. Letters to the Editor with comments on previously published papers will also be considered for publication. Papers are published exclusively in English. All original submissions are subject to peer review.

ARTICLE CATEGORIES

Advances in Interventional Cardiology/Postępy w Kardiologii Interwencyjnej accepts the following categories of articles:

Editorial comments

Editorials contain commentaries on current important clinical studies or scientific issues. They are written on invitation, but unsolicited topical commentaries will also be welcomed for consideration. The manuscript should not exceed 1500 words (not including tables and references). The text should be accompanied by a maximum of 15 references and 2 figures and/or tables. The number of authors should be limited to 4. An abstract and keywords are not required.

Original papers

Original (full length) papers should not exceed 4000 words not including tables and references. Each article should contain a structured abstract (200–250 words). Authors are asked to provide a summary (3-4 sentences) of their paper covering current knowledge on the subject / a gap in the evidence, the major finding, and possible impact on daily practice / further research (the reason for the study - the major finding - the implication). The manuscript should be arranged as follows: Structured Abstract, Summary, Introduction, Aim, Material and Methods, Results, Discussion, Conclusions, Acknowledgments/Conflict of interests statements (if applicable), and References. Figures and tables should be limited to those necessary to highlight key data (a maximum combination of 6 figures and/or tables is allowed). No more than 40 references are accepted. Please limit the number of authors to 10; exceptions are made for multi-center trials and can be requested for other situations, provided that all authors meet the listed requirements.

Short communications

Short communications contain a brief report or preliminary results of original studies that deserve rapid publication. They can also be used to describe a novel treatment technique, or to present a step-by-step approach in the field of cardiovascular interventions. Short communications should be no more than 1500 words not including tables and references. There should be no more than 15 references, with a maximum combination of 2 figures and/or tables, and no more than 6 authors. An abstract and keywords are not required.

Review papers

Review papers should be submitted only after consultation with the Editors. The manuscript should not exceed 5000 words (not including tables and references) and up to 70 references. An unstructured abstract (200–250 words) and 3–6 key words are required for submission. A maximum combination of 6 figures and/or tables, and no more than 6 authors are accepted. Reasonable exceptions can be requested.

Images in intervention

Case reports are not accepted any longer. Interesting clinical or basic science images, illustrating novel findings or unusual clinical presentations in the field of cardiovascular interventions may be submitted as "Images in intervention". Importantly, this category should not be considered as a simplified case report presentation. Thus, authors are asked to focus on the uniqueness of their findings and imaging results. One, high-quality figure should be accompanied by text (no more than 500 words not including references), up to 4 references and a detailed figure legend. The figure can be divided into a maximum of 4 panels. Authors are strongly encouraged to clearly mark structures of interest with markers (arrows, asterisks, lines, etc.). No more than 6 authors are accepted. An abstract and keywords are not required.

Letters to the Editor

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Manuscript type	Abstract	Key words	Word limit (main body of the manuscript)	References	Tables/ figures	No. of authors
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