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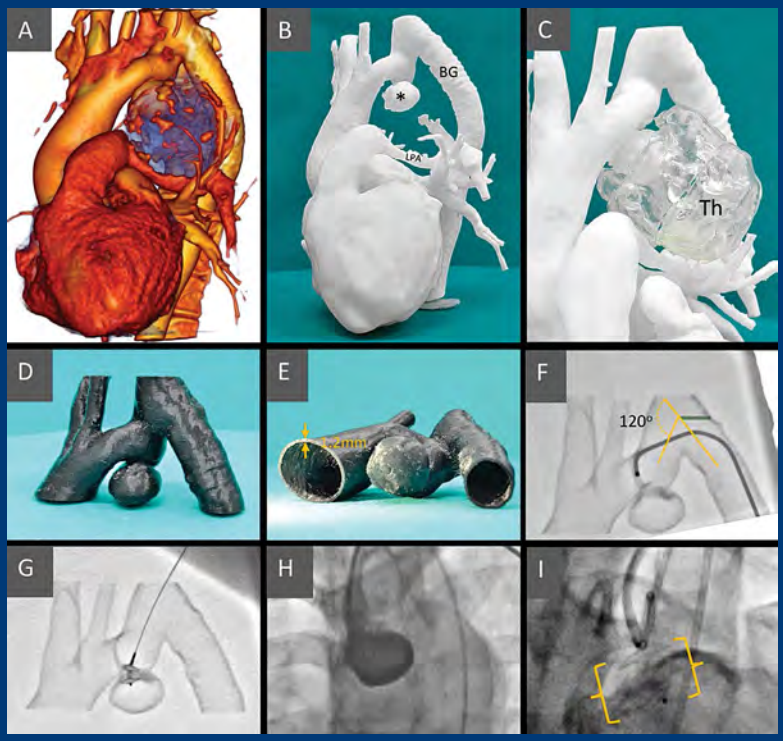

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POSITION PAPER

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Expert opinion on the creating and operating of the regional Pulmonary Embolism Response Teams (PERT). Polish PERT Initiative

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Abstract

Pulmonary Embolism Response Team (PERT) is a multidisciplinary team established to stratify risk and choose optimal treatment in patients with acute pulmonary embolism (PE). Established for the first time at Massachusetts General Hospital in 2013, PERT is based on a concept combining a Rapid Response Team and a Heart Team. The growing role of PERTs in making individual therapeutic decisions is identified, especially in hemodynamically unstable patients with contraindications to thrombolysis or with co-morbidities, as well as in patients with intermediate-high risk in whom a therapeutic decision may be difficult. The purpose of this document is to define the standards of PERT under Polish conditions, based on the experience of teams already operating in Poland, which formed an agreement called the Polish PERT Initiative. The goals of Polish PERT Initiative are: improving the treatment of patients with PE at local, regional and national levels, gathering, assessing and sharing data on the effectiveness of PE treatment (including various types of catheter-directed therapy), education on optimal treatment of PE, creating expert documents and supporting scientific research, as well as cooperation with other communities and scientific societies. (Cardiol J 2019; 26, 6: 623–632)

Key words: pulmonary embolism, pulmonary embolism response team, catheter-directed therapy, embolectomy

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Introduction. PERT definition. Polish PERT Initiative

Acute pulmonary embolism (PE) is one of the most common diseases of the cardiovascular system. It is estimated that PE occurs at a frequency of 39–115/100,000 population/year and causes over 400,000 deaths in Europe every year [1–3]. It is the third most frequent vascular disease, after myocardial infarction and stroke [1, 2]. The clinical presentation of PE is heterogenous: from mild impairment of exercise tolerance (low-risk PE), through severe dyspnoe with symptoms of right ventricular overload (intermediate-risk PE) to hemodynamic collapse, "obstructive" shock and death (high-risk patients) most often related to acute insufficiency of the right ventricle (RV) and respiratory failure [1–3]. Although most patients with PE can be successfully treated with anticoagulants, hemodynamically unstable patients require urgent systemic thrombolysis (ST). Thrombolytic therapy, however, has significant limitations. First of all, it is associated with a significant increase in the risk of major bleeding (13%), including up to 3% of patients treated with ST, who have dangerous intracranial bleeding, mainly cerebral hemorrhagic stroke [4]. In the group of patients of the ZATPOL — Polish national prospective registry, it has been shown that the occurrence of major bleeding in acute PE significantly worsened the prognosis [5]. In high-risk (hemodynamically unstable) patients, the clinical benefit of thrombolysis exceeds the risk of bleeding, but in intermediate-risk patients the potential clinical benefit of ST does not balance the risk of major bleeding and does not reduce mortality [6]. On the other hand, about 5–10% of patients who are initially hemodynamically stable may experience a sudden and unexpected clinical deterioration [7]. According to the guidelines of the European Society of Cardiology, in the case of contraindications to thrombolysis or its failure, surgical embolectomy is recommended [3]. However, a severe preoperative condition and high incidence of comorbidities, as well as limited availability of cardiac surgery result in high mortality in this group. Furthermore, it has been shown that thrombolytic therapy is often not used in high-risk patients, even though there are no contraindications [8]. Moreover, in intermediate-high-risk patients, the decision on thrombolysis or surgical therapy is often taken too late, and hemodynamic deterioration in this group of patients is associated with high mortality [9]. Consequently, new techniques for transcatheter invasive treatment of PE (catheter-directed therapy [CDT]) have been developed, which can remove thrombi from the pulmonary arteries without the additional risks posed by systemic thrombolysis or cardiac surgery. In the last decade, many new devices and techniques have been proposed for transcatheter treatment of PE [10]. There is also a growing number of scientific data from clinical observational studies and registries confirming the clinical effectiveness of interventional treatment with a reduction in the number of patients with significant bleeding. However, only few randomized trials comparing CDT with standard anticoagulant and thrombolytic therapy are available in the literature [11, 12]. Nonetheless, quick and correct diagnosis, proper risk stratification and selection of optimal therapy from a constantly growing pharmacological and intervention armamentarium, seems to be crucial in patients with acute PE.

In 2013, in Massachusetts General Hospital in Boston (United States), the world's first multispecialist team was created for quick consultation and selection of the therapy in patients with PE [13]. This team was named the Pulmonary Embolism Response Team (PERT). The PERT concept was based on a combination of two other proven clinical practice models: The Heart Team and the Rapid Response Team [14, 15]. The growing role of PERTs in making individual therapeutic decisions is pointed out, especially in hemodynamically unstable patients with contraindications to thrombolysis (e.g. with active bleeding shortly after surgery) or with significant co-morbidities (including cancers), as well as in patients with intermediate-high risk patients in whom this treatment may accelerate clinical improvement and improve prognosis [13–15]. Treatment methods should also include various methods of CDT as an alternative to ST and surgical embolectomy. The current guidelines of the European Society of Cardiology recommended set-up (class recommendations IIa/level of evidence C) of in-hospital PERTs adapted to local resources and access to specialists [3].

The purpose of this document is to define the standards of PERT under Polish conditions, based on the experience of teams already operating in Poland, which was formed in April 2019 an agreement called the Polish PERT Initiative (PPI). The goals of PPI are improving the treatment of patients with PE at local, regional and national levels, involving gathering, assessing and sharing of data on the effectiveness of PE treatment (including various types of CDT), disseminating the knowl-

edge about optimal treatment of PE, optimizing financing of procedures in this area, creating expert documents and supporting scientific research, as well as cooperating with other communities and scientific societies.

PERT models, interdisciplinary cooperation, minimal organizational and institutional framework

A clear organization model of PERT has yet to be defined. The world's first PERT from Massachusetts General Hospital involved specialists from various fields, serving for immediate consultation and selection of therapy in patients with PE [16]. The first PERT served as a model for other medical centers and soon these centers combined their experience within the National PERT Consortium [17]. The data presented by the PERT Consortium shows a vast diversity in the organization of teams and the patient population they are dealing with [18, 19]. The essence of PERT's activity is to coordinate the diagnostic and therapeutic process of patients with PE of severe or atypical course by choosing the optimal management strategy based on the expert knowledge of a multidisciplinary team of specialists of whom it is comprised.

The PERT coordinator should be continuously available by phone (24/7) on a dedicated phone number and after accepting the application must be able to organize quick consultations (< 30 min) with relevant specialists. These consultations may be a teleconference, during which all participants have access to a patient's medical data and imaging tests. The PERT should include specialists with practical experience in the treatment of acute PE using various methods, as well as experts to assist in case of complications or the presence of comorbidities that require modification of standard methods of acute PE. Among the physicians directly involved in the process of treating a patient upon PERT care there are usually specialists who have experience in the field of intensive cardiac therapy, echocardiography and interventional cardiology, as well as cardiac surgeons, specialists in emergency medicine, anesthesiologists and radiologists, including interventional radiologists. The second group of specialists whose consultations may be necessary in selected cases should include neurologists, neurosurgeons, oncologists, vascular surgeons, hematologists and specialists in lung disease. It seems that the specialists listed in the first group should constitute a permanent PERT team. However, the final composition of PERT varies between centers and depends on resources and experience. The most important tasks of PERT in the acute phase of PE include choosing optimal pharmacotherapy (including determining indications or contraindications for thrombolysis), interventional treatment (thrombus fragmentation, CDT, venous filter implantation) or cardiac surgery (pulmonary embolectomy). For those reasons, the ideal organizational solution is to create PERT in hospitals with all available treatment options in one location. If PERT is located in a hospital without a cardiac surgery department, it should have the formal cooperation with a cardiac surgery center ensuring the possibility of immediate transfer of patients for further treatment. Optimally, every PERT should have access to treatment with extra corporeal membrane oxygenation (ECMO) device, which is the equipment of cardiac surgery departments in Poland. In addition to the acute phase of PE treatment, the role of PERT may be to support the optimization of management in subsequent months, including determining the method and duration of chronic anticoagulation, possible implantation of the inferior vena cava filter and patient monitoring for the occurrence of chronic thromboembolic pulmonary hypertension (CTEPH).

Risk stratification in PE, qualification to treatment

Hemodynamically unstable patients, i.e. with systemic hypotension, in shock, requiring infusion of catecholamines or cardiopulmonary resuscitation constitute a group of patients with high risk of early death with early mortality exceeding 15% and contain about 5% of patients with PE. Hypotonia is defined as systolic blood pressure < 90 mmHg or a decrease in systolic blood pressure of at least 40 mmHg for > 15 min if it is not associated with new arrhythmias, hypovolemia or sepsis. Confirmation of the diagnosis of high-risk PE is not only the finding of RV dysfunction in echocardiographic or tomographic assessment [3].

Patients with high-risk PE require immediate reperfusion treatment. Systemic thrombolysis in high-risk PE patients is recommended as class I (evidence level B), surgical embolectomy as class I recommendation (evidence level C), and catheter-directed therapy as class IIa recommendation (evidence level C) [3]. Among initially hemodynamically stable patients with the presence of RV overload and positive markers of myocardial overload, 5–10% will develop hemodynamic instability despite anticoagulation [6]. Therefore, patients

Table 1. Bova score — risk stratification scale in medium-risk acute pulmonary embolism.

Parameter	Points
Systolic pressure 90–100 mmHg	2
Elevated troponin concentration (above the cutoff level)	2
Right ventricle dysfunction: Echocardiography: ≥ 1 of the following: RV/LV > 0.9, sPAP > 30 mmHg, RV diameter > 30 mm, or RV hypokinesis; Multidetector computed tomography: RV/LV > 1	2
Tachycardia > 110/min	1
≥ 5 points – 30-day risk: 42% complications (death of PE, decompensation, recurrence of acute PE); 10% mortality in PE	

LV — left ventricle; PE — pulmonary embolism; RV — right ventricle; sPAP — systolic pulmonary artery pressure.

with intermediate-high-risk PE at an early stage of hospitalization require monitoring, preferably in an intensive care unit. In the case of hemodynamic instability, it is advisable to implement thrombolytic treatment (class I recommendation/evidence level B), for which the alternative is surgical embolectomy or CDT (class IIa recommendation/evidence level C) [3]. The Bova scale allows the identification of patients at risk of decompensation and death dependent on PE from among initially stable hemodynamically stable patients (Table 1) [20].

Interventional therapy in PE

At the beginning of transcatheter therapy for a patient with PE, a pulmonary artery angiography from the femoral or internal jugular vein should be performed initially using 5–7 F diameter pigtail catheters [21]. Pulmonary angiography enables visualization of thrombi not only in the main pulmonary, lobar or segmental arteries but even in smaller (subsegmental) vessels. During pulmonary angiography, hemodynamic measurements should be made in the right atrium and right ventricle, and the pulmonary trunk to assess the severity of PE and exclude the overlapping of acute PE on CTEPH. Mechanical reperfusion involves the introduction of a catheter into the pulmonary arteries from the femoral or internal jugular vein to remove thrombi and reduce pulmonary resistance, facilitate the return of RV function, improve the patient's clinical condition and prognosis [22]. Percutaneous embolectomy involves a variety of methods, from mechanical thrombus fragmentation, to thrombus aspiration and a pharmacomechanical approach of mechanical or ultrasound-assisted thrombus fragmentation with local administration of reduced-dose thrombolysis (Table 2). Before the procedure, one should perform echocardiographic examination not only to assess RV function, but also to exclude thrombi in the right heart cavities and exclude thrombosis in the punctured femoral vein. In the published meta-analysis of Bajaj et al. [23], periprocedural success, defined as hemodynamic stabilization, reduction of hypoxia and discharge from hospital, was achieved in 87% of patients treated with endovascular treatment. The first Polish experiences with transcatheter methods (AngioJet system, Indigo Penumbra aspiration thrombectomy, EKOS system and Cleaner system) have recently been published [24–29].

Another interventional technique supporting the treatment of acute PE is the implantation of vascular filters into the inferior vena cava. Venous filters protect the patient's pulmonary arteries from subsequent embolism from deep veins of the lower extremities or the pelvic venous plexus. The results of PREPIC studies indicate that venous filters reduce the incidence of PE, while slightly increasing the incidence of venous thrombosis, without reducing overall mortality [30, 31]. In a recent analysis of the database of an American health fund, which included 16,950 patients with PE and concomitant cancer, a venous filter was used in 19% of patients. A reduction of mortality was demonstrated in a group of patients > 60 years of age in whom the filter was implanted, in relation to the group of conservatively treated patients [32]. Current European Society of Cardiology guidelines recommend the implantation of venous filters in patients with PE and absolute contraindications to anticoagulation or in patients

Table 2. Selected methods of catheter-directed therapy in patients with acute pulmonary embolism.

Transcatheter therapies with local thrombolysis		Transcatheter therapies without thrombolysis	
Method	**Catheter/device**	**Method**	**Catheter/device**
Rheolytic thrombectomy with local thrombolysis	AngioJet PE® catheter 6 F with the local thrombolysis application system Power Pulse™ (Boston Scientific, Minneapolis, MN USA)	Rheolytic thrombectomy	6 F AngioJet PE® catheter (Boston Scientific, Minneapolis, MN, USA)
Ultrasound assisted catheter-directed thrombolysis	EkoSonic® 5.2 F (EKOS, Boston Scientfic, Minneapolis, MN, USA)	Aspiration therombectomy	Aspirex® 8 F, 10 F catheters (Straub Medical, Switzerland): Angiovac cannula — veno-venous bypass (26 F – 16–20 F access) (AngioDynamics, Latham, NY, USA): Continuous aspiration catheter Indigo® (Penumbra, Alameda, CA, USA): 8 F catheter connected to the suction pump Aspiration using vacuum (40–60 mL syringe) with guiding catheter (e.g. 8–9 F multi-purpose catheter)
		Mechanical thrombectomy	Flowtriever® (Inari Medical, Irvine, CA, USA): 20 F catheter and the device made by three self-expanding nitinol disks
Thrombus fragmentation with local thrombolysis	Pigtail catheters (5–6 F) or balloon catheters (5–10 mm)	Thrombus fragmentation	Pigtail catheters (5–6 F) or balloon catheters (5–10 mm)

who have recurrent PE despite adequate treatment (class IIa recommendation/evidence level C) [3]. Currently, the standard is an application of retrievable filters, which can be used in patients with PE or venous thrombosis before extensive surgery requiring temporary cessation of anticoagulation. After stabilization of the patient's condition and resolution of contraindications to anticoagulation, removal of the filter should always be considered. Depending on the type of filter, it can be removed up to 6 months after implantation [33].

Methods of surgical treatment of PE. Application of ECMO

In high-risk PE, surgical pulmonary embolectomy should be used in patients with absolute contraindications to thrombolytic therapy or if it is ineffective and should be considered in selected patients at intermediate risk [3, 34, 35]. A separate group consists of patients with thrombi passing from the right atrium to the left side through the patent foramen ovale.

Pulmonary embolectomy can be performed in any center equipped with an extracorporeal circulation device. Under Polish conditions, mainly cardiac surgery centers with their personnel and equipment are accessible.

An alternative and attractive tool can also be mobile devices that are extracorporeal techniques (ECLS/ECMO), in which, by using quick access through peripheral vessels, it is possible to stabilize the patient in shock or hypotension. The prior mentioned devices for extracorporeal perfusion techniques are more and more often used in areas of modern intensive therapy of critical states.

In the Wielkopolska region, the PERT program was created in parallel with the program of univer-

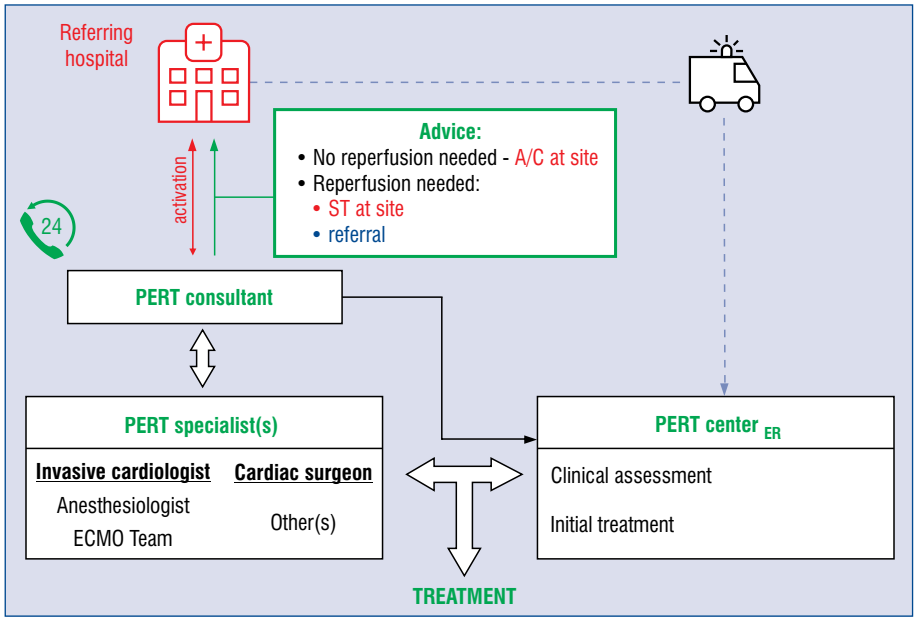

Figure 1. Proposed Pulmonary Embolism Response Team (PERT) operating model. A dedicated PERT consultant is ready 24/7 to respond to an activation call from a regional healthcare provider, collect necessery information on the patient consulted and contact an on-call PERT specialist(s) to determine whether reperfusion therapy is needed, and discuss treatment options. Their conclusion is communicated back to the referring physician as PERT therapeutic advice, which may include: (1) continue anticoagulation at the referring site, in cases where no reperfusion is required; (2) start systemic thrombolysis at the site immediately if shock or cardiac arrest is present; (3) transfer the patient to a PERT center, if reperfusion is required and there are contraindications to systemic thrombolysis, risk of major bleeding is high or the patient needs surgical intervention. ECMO — extracorporeal membrane oxygenation; A/C — anticoagulation; ST — systemic thrombolysis; ER — emergency room.

sal access to extracorporeal techniques, including ECMO, as part of an organizational program "ECMO for Wielkopolska" (ECMO for Greater Poland) [36–38]. Such organizational cooperation gives a real chance to use a wide spectrum of applications in extracorporeal techniques in PE therapy, particularly for high risk associated with cardiogenic shock [38].

Extracorporeal techniques with the use of ECMO in PE therapy with potential use in the treatment of PE are as follows:

1. Veno-arterial (VA) ECMO — as a partial RV bypass in cardiogenic shock with hypotension:
   - As part of extended cardiopulmonary resuscitation when PE is the cause of in-hospital cardiac arrest or out-hospital cardiac arrest;
   - As a bridge to surgical embolectomy or transcatheter therapy;
   - As RV support after surgical embolectomy in extracorporeal circulation;
   - As a support during parenteral heparin anticoagulation.
2. Veno-arteriovenous (VA-V) ECMO — incidentally in the treatment of shock with concomitant RV failure as a RV assist device.
3. Veno-venous (VV) ECMO — incidentally after pulmonary embolism therapy with concomitant refractory respiratory failure with hypoxia and hypercapnia.
4. Partial VV Angiovac system with the possibility of conversion to VA ECMO.

PERT: Proposed operating model

As PERT is modeled on a philosophy of rapid response, it is crucial to constitute a clear and sound operating protocol [13–16]. This protocol should accommodate PERT structure, activation pathways and operating mode. There are two basic elements of any PERT operating model. First of all, the PERT activation should be accessible via a commonly known telephone number. A dedicated on-call PERT consultant should be ready to answer a PERT activation call. The activation call may come from any healthcare provider in the region (district

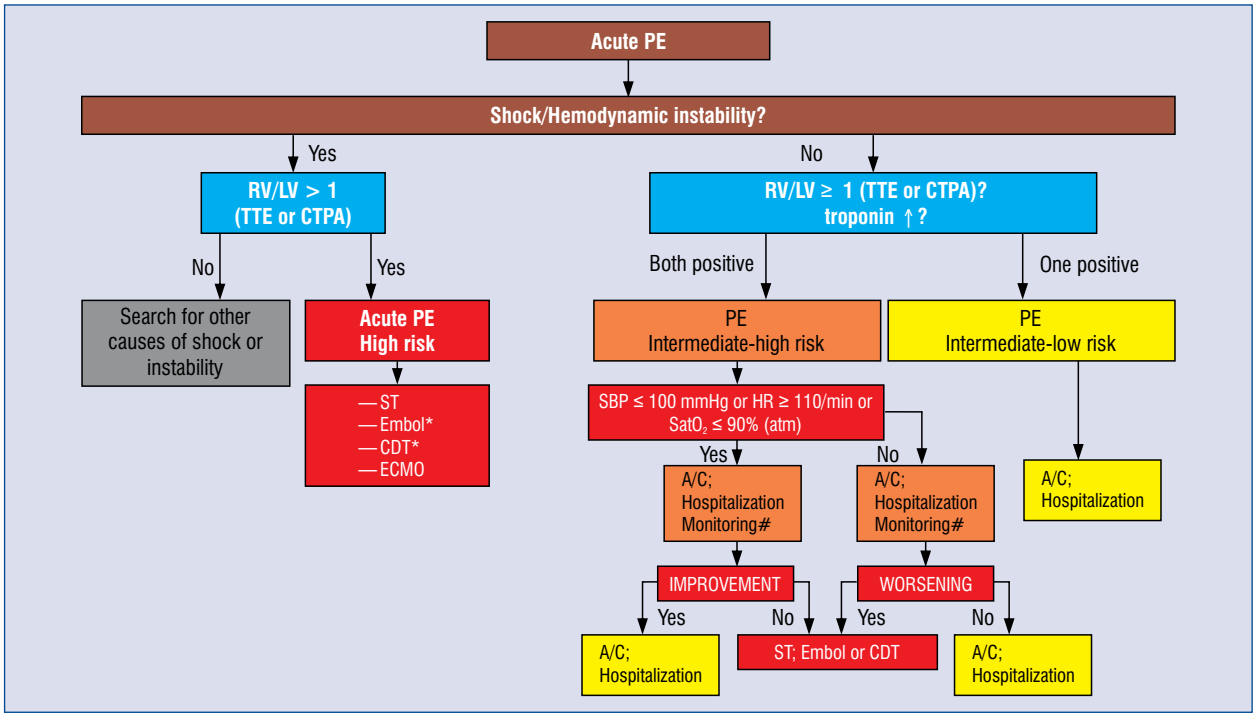

Figure 2. Proposed therapeutic algorithm in acute pulmonary embolism for the use of Pulmonary Embolism Response Teams. A/C — anticoagulation; CDT — catheter-directed therapy; CTPA — computed tomography pulmonary angiography; ECMO — extracorporeal membrane oxygenation; Embol — surgical embolectomy; HR — heart rate; PE — pulmonary embolism; RV/LV — right-to-left ventricular dimeter index; $SatO_2$ — arterial blood oxygen saturation; SBP — systolic blood pressure; ST — systemic thrombolysis; sPESI — simplified Pulmonary Embolism Severity Index; TTE — transthoracic echocardiography; *If ST is contraindicated or has failed; #Monitoring and observing period of the deterioration/improvement of the patient's condition should be individualized depending on clinical conditions and should not exceed 6–12 hours to decide on intensification of treatment.

hospital, outpatient clinic, ambulance) networked with the PERT center in a hub-and-spoke model. The role of the PERT consultant is to collect necessary information on the patient consulted from a referring physician, including: clinical status and duration of symptoms, PE burden and hemodynamic significance, RV function and adverse outcome risk factors, comorbidities, contraindications to specific treatments like thrombolysis, surgical embolectomy or CDT. To facilitate the process of data collection, a standardized form should be in use (see the next paragraph). Depending on the PERT center institutional policies, structure and personnel resources, the PERT consultant may be an intentionally dedicated individual or any other on-call physician, who is capable of executing the PERT operating model upon activation.

The second key element of the PERT operating model is cooperation between PERT specialists. The on-call PERT specialists including, at least, an interventional cardiologist and cardiac surgeon who should be ready to enter cooperation upon a PERT consultant request. There are several modes of PERT specialist mobilization, among which a staged approach seems to be the most resource efficient and practical (Fig. 1). In contrast to activation of all PERT members upfront, in the staged model the PERT consultant initially contacts one on-call PERT specialist to determine whether reperfusion therapy is needed and discuss treatment options. If a decision is not possible, another PERT specialist(s) may be asked for an opinion. After reaching a final conclusion it is communicated back to the referring physician as a PERT therapeutic recommendation. The goal should be to complete this process within 30 min from activation.

If no reperfusion therapy is required at the time of consultation, the patient may continue anticoagulation treatment at the referring hospital. The referring physician should stay in touch with the PERT center in case a patient deteriorates. If, in contrast, reperfusion therapy is indicated at the site, systemic thrombolysis should primarily

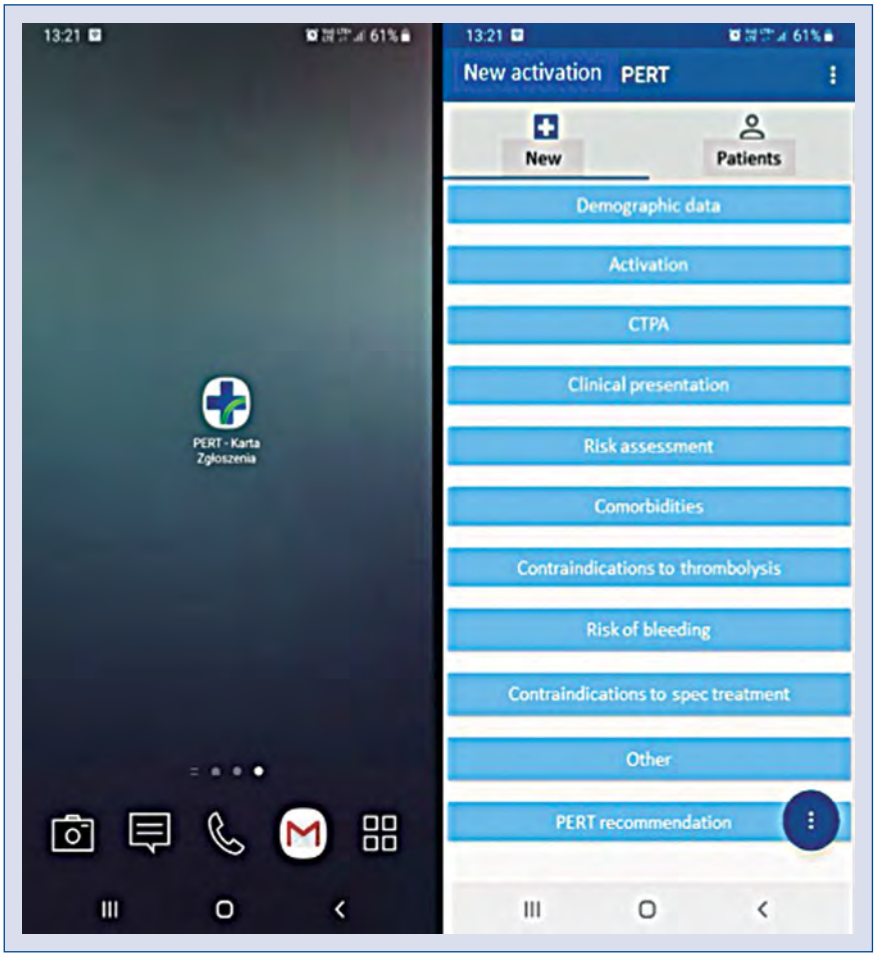

Figure 3. Mobile application developed by the Pulmonary Embolism Response Team (PERT) of the John Paul II Hospital in Krakow, Poland and is used to collect pulmonary embolism patient data and to conduct PERT consultations.

be considered, or if contraindications to ST are present, risk of major bleeding is high or surgical intervention is needed, the patient should be transferred to the PERT center. To support the decision-making process a therapeutic algorithm may be adapted (Fig. 2).

Communication and data collection tools

To promote rapid and efficient course of PERT consultations, it may be useful to formulate PERT activation and decision cards. These documents should i.e. contain referral center contact details, patient demographic data, duration of symptoms, distribution of thrombi in computed tomography, clinical status and risk of death defined by contemporary algorithms (e.g. Bova score), comorbidities, risk factors of venous thromboembolism, contraindications to thrombolysis and anticipated risk of bleeding complications. Said forms may then serve as a background for the PERT decision-making process. With the advent of modern technologies, it has become available to acquire PERT activation documents in the form of mobile applications (Fig. 3). Use of mobile technologies is expected to make the process of data collection easier and more universal and to facilitate sharing information between PERT specialists during consultations.

It is also desirable to record data on activations, operating modes, PERT decisions and patient follow-up in the form of a registry. A regular evaluation of accumulated data should provide insight in general PE quality measures such as mortality and morbidity, but also PERT — specific measures such as: time from activation to decision, time from decision to therapeutic anticoagulation or to reperfusion therapy, methods and effects of reperfusion treatment, PERT structure and activation modes, application of contemporary guidelines, etc. Such data may also help to improve knowledge on the role of PERT in acute PE care.

Conclusions

1. Organization of multidisciplinary PERT in reference centers for management of high- and intermediate-high risk PE is recommended depending on local resources and available expertise.
2. The most important tasks of PERT in the acute phase of PE include choosing optimal pharmacotherapy (including determining indications or contraindications for thrombolysis), interventional treatment (catheter-directed therapy, venous filter implantation) or cardiac surgery (pulmonary embolectomy).
3. It is crucial to constitute a clear and sound operating protocol. Such protocol should accommodate the PERT structure, activation pathways and operating mode.
4. A PERT coordinator should continuously be available by phone (24/7) on a dedicated phone number and after accepting the application must be able to organize a quick consultation (< 30 min) with relevant specialists.
5. Among the physicians directly involved in the process of treating a patient under PERT care there are usually specialists who have experience in the field of intensive cardiac therapy, echocardiography and interventional cardiology, as well as cardiac surgeons, specialists in emergency medicine, anesthesiologists and radiologists including interventional radiologists.
6. The second group of specialists whose consultations may be necessary in selected cases should include neurologists, neurosurgeons, oncologists, vascular surgeons, hematologists and specialists in lung diseases.
7. To promote rapid and efficient course of PERT consultations, it may be useful to formulate PERT activation and decision cards (if possible, in the form of mobile applications).

PERTs operating in Poland

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Conflict of interest: None declared

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Predictors of periprocedural complications in patients undergoing percutaneous coronary interventions within coronary artery bypass grafts

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Abstract

Background: *During the first decade following the coronary bypass grafting, at least ten percent of the patients require percutaneous coronary interventions (PCI) due to graft failure. Saphenous vein grafts (SVG) are innately at a higher risk of periprocedural complications. The present study aimed to investigate predictors of periprocedural complications of PCI within coronary artery bypass grafts.*

Methods: *This study analyzed data gathered in the Polish National Registry (ORPKI) between January 2015 and December 2016. Of the 221,195 patients undergoing PCI, data on 2,616 patients after PCI of SVG and 442 patients after internal mammary artery (IMA) were extracted. The dissimilarities in periprocedural complications between the SVG, IMA and non-IMA/SVG groups and their predictors were investigated.*

Results: *Patients in the SVG group were older ($p < 0.001$), with a higher burden of concomitant disease and differing clinical presentation. The rate of de-novo lesions was lower, while restenosis was higher at baseline in the SVG ($p < 0.001$). The rate of no-reflows ($p < 0.001$), perforations ($p = 0.01$) and all periprocedural complications ($p < 0.01$) was higher in the SVG group, while deaths were lower ($p < 0.001$). Among the predictors of no-reflows, it was found that acute coronary syndromes (ACS), thrombectomy and past cerebral stroke, while the complications included arterial hypertension, Thrombolysis in Myocardial Infarction (TIMI) flow before PCI and thrombectomy.*

Conclusions: *Percutaneous coronary interventions of SVG is associated with increased risk of specific periprocedural complications. The ACS, slower TIMI flow before PCI and thrombectomy significantly increase the periprocedural complication rate in patients undergoing PCI of SVG.* (Cardiol J 2019; 26, 6: 633–644)

Key words: percutaneous coronary interventions, coronary artery by-passes, periprocedural complications, no-reflow, predictors

Introduction

Within 10 years of coronary artery bypass graft surgery (CABG), even half of patients can be observed with graft failure [1]. Failed patency is usually caused by graft failure or a combination of graft failure and progression of coronary atherosclerosis. Neointimal hyperplasia is considered

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to be the main reason for the occlusion of venous grafts [2]. The optimal management of patients presenting with graft failure remains a subject of debate. Surgical reoperation is associated with high complication rates and mortality compared to conventional percutaneous coronary interventions (PCI) [3]. Also, repeat operations are associated with higher morbidity and mortality rates as well as poorer outcomes compared to initial operations [4]. Although endovascular treatment of saphenous vein grafts (SVGs) is connected with better results in comparison to re-CABG, there is still a great gap between PCI performed on native arteries and SVG, which reflects poorer results including higher in-hospital mortality among patients undergoing PCI of SVG [5]. Among several predictors of outcomes, the elevated markers of myocardial injury may translate into increased mortality when compared to patients with native vessel PCI [6]. Other variables which have been associated with increased risk of complications after PCI of SVG lesions include old, diffusely diseased, totally occluded grafts and grafts containing intraluminal thrombus with increased lesion friability and propensity for distal embolization [7].

The aim of the present study was to determine the procedural success, periprocedural complications and predictors of typical complications for SVG PCI in a consecutive series of patients undergoing a non-staged SVG intervention in Poland in 2015 and 2016.

Methods

Study population, design and definitions

Data from all patients who underwent PCI in Poland between January 2015 and December 2016 were analyzed. Prospectively collected data on PCI practice in Poland were obtained from the ORPKI Polish National dataset, which is coordinated nationwide by Jagiellonian University Medical College in cooperation with AISN PTK (Association of Cardiovascular Interventions Polish Cardiac Society). Database characteristics and data collection methods have been previously presented [8, 9]. Patients were categorized according to whether they had undergone PCI of SVG or the right/left internal mammary artery (IMA). PCI of all other coronary arteries, except SVGs and IMAs were included into the non-IMA/SVG group. All indices recorded in the ORPKI database are based on periprocedural data uploaded by the operator after each procedure. Therefore, they do not include all in-hospital complications, mainly those which occurred after the procedure until discharge from the hospital. Also, follow-up data after discharge was not collected due to lack of patient ID details. The decision to perform PCI of SVG or IMA was at the operators' discretion at each center according to current guidelines [10]. All clinical decisions, such as vascular access, thrombectomy, treatment with glycoprotein (GP) IIb/IIIa inhibitors or bivalirudin, were at the operators' discretion. The definition of periprocedural complications including death, perforation, dissection, myocardial infarction (MI), allergic reaction, cerebral stroke, puncture site bleeding, no-reflow or cardiac arrest remained to the operators' personal preferences and knowledge [8].

Statistical analysis

All continuous variables were evaluated with the Kolmogorov-Smirnov test for distribution. Continuous variables are presented as mean ± ± standard deviation and median ± interquartile range. Categorical variables are presented as numeric values and percentages. Continuous variables were compared using the two-tailed Student t-test and the Mann-Whitney U-test, whereas categorical variables used the χ^2 test. Statistical significance was accepted at a 0.05 level of probability. The statistical analyses were performed using Statistica 10.0 software (Dell Software, Inc, Round Rock, TX, USA) and SPSS STATISTICS 24 (IBM, USA).

Multifactorial analysis

Since the periprocedural complication rates in the IMA group of patients did not differ significantly from the non-IMA/SVG group when particular complications were compared, the present analysis concentrated on the comparison of the SVG and the non-IMA/SVG group. To identify predictors of all complications, no-reflows, deaths and perforations, univariate and multivariable analysis was performed. In this analysis, the following variables were tested in the SVG group: age, gender, diabetes, previous cerebral stroke, MI, PCI, CABG, smoking status, concomitant diseases including psoriasis, hypertension, kidney disease, chronic obstructive pulmonary disease, clinical presentation of coronary artery disease (CAD) at baseline (stable angina [SA] vs. acute coronary syndrome [ACS], SA vs. acute MI [AMI], SA vs. unstable angina [UA], UA vs. AMI), pharmacological treatment before PCI and during PCI (acetylsalicylic acid [ASA], unfractionated heparin [UFH], low-molecular weight heparin [LMWH], $P2Y_{12}$ inhibitors,

thrombolysis, GP IIb/IIIa inhibitors, bivalirudin), angiographic presentation of CAD (single-vessel disease [SVD] vs. others, left-main coronary artery [LMCA] involvement vs. others), vascular access (radial vs. femoral), fractional flow reserve (FFR), intravascular ultrasound (IVUS), optical coherent tomography (OCT), thrombectomy, pharmacological treatment, Thrombolysis in Myocardial Infarction (TIMI) flow before PCI (1–2 vs. 2–3), contrast dose and radiation exposition, PCI of chronic total occlusions (CTO) or bifurcation, stent implantation, drug-eluting stent (DES) implantation, number of implanted DES stents (1 vs. 2 or more stents), bare-metal stent (BMS) implantation, number of implanted stents regardless of type (1 vs. 2 or more stents), bioresorbable scaffold (BRS) implantation, PCI with drug-coated balloon (DCB) and PCI with DCB/plain old balloon angioplasty (POBA)/failed. Also performed were univariate and multivariable analysis of potential predictors of all complications, no-reflows, deaths and perforations in the overall group of patients. In this analysis, rotablations (RAs), were additionally included.

Results

General characteristics

The general characteristics of patients examined in the current study including concomitant diseases, past cardiovascular procedures, gender and age in the assessed groups of patients and according to PCI of SVG and IMA are presented in Table 1.

Clinical presentation, coronary angiography and vascular access

The clinical presentations of CAD included SA, UA, non-ST-segment elevation MI (NSTEMI), ST-segment elevation MI (STEMI), AMI or others where such indications like cardiac arrest or valvular diseases were included. Coronary angiography was divided into four groups: SVD, multi-vessel disease (MVD) without LMCA involvement, MVD with LMCA involvement and isolated LMCA involvement. Vascular access was assessed as femoral access, right and left radial access and others. All the above-mentioned indices were compared in three separate groups: non-IMA/SVG group, IMA and SVG group and are presented in Table 1.

Procedural variables

Selected procedural indices were compared which involved procedural contrast dose, radiation exposition, use of FFR, IVUS and OCT, type of lesion undergoing PCI including CTO, bifurcations, type of the procedure with stent type (BMS, DES, BRS, DCB, POBA or failed PCI) and the use of additional devices such as RA or thrombectomy in three separate groups of patients: non-IMA/SVG group, SVG and IMA group. This is presented in Table 2.

Pharmacological treatment

Pharmacological treatment was also compared before and during PCI between three selected groups of patients including non-IMA/SVG group, IMA and SVG group, which was presented in Table 2. Among the assessed pharmaceutics, there were antiplatelet agents, heparins, thrombolysis and bivalirudin. This comparison is presented in Table 3.

Culprit lesion characteristics

Also distinguished and compared were the type and frequency of culprit lesion undergoing PCI in the selected three groups of patients which included de-novo rates, restenosis rates, and in-stent thrombosis rate. The restenosis rate was also divided into BMS, DES, BRS, DCB and POBA restenosis. In general, the frequency of the de-novo lesions was lower in the SVG group as compared to the non-IMA/SVG group ($p < 0.001$), and was also lower when compared to IMA group ($p < 0.001$). Whereas, the rate of restenosis was higher in the IMA ($p = 0.02$) and SVG group ($p < 0.001$) compared to the non-IMA/SVG group. Moreover, the rate of restenosis in the SVG PCI group was significantly higher when compared to IMA group ($p < 0.001$). The rate of in-stent thrombosis did not differ significantly between groups. However, it was highest in the SVG PCI group (0.7%). All indices are presented in Table 4.

Periprocedural complications

The periprocedural complications included those which occurred in the operating room and do not cover all complications which took place during subsequent days of hospitalization. the Death rates, cerebral strokes, MI, dissections, no-reflows, puncture site bleedings, allergic reactions and perforations in the non-IMA/SVG group as well as the IMA and SVG groups were assessed. Overall complication rate per patient and per complication in all above-mentioned groups were also compared. Overall complication rates reached 1.92% when assessed per patient and 2.29% when assessed per complication in the non-IMA/SVG group of patients and was significantly higher in SVG group compared to non-IMA/SVG group for

Table 1. Baseline characteristics.

Variable	PCI non--IMA/SVG (n = 218,137)	PCI IMA (n = 442)	P Non-IMA/ /SVG vs. IMA	PCI SVG (n = 2,616)	P Non-IMA/ /SVG vs. SVG	P SVG vs. IMA
Age [years]	67.0 ± 10.8	68.9 ± 9.7	< 0.001	70.5 ± 8.9	< 0.001	< 0.001
Gender, males	147,749 (67.7%)	339 (76.7%)	< 0.001	2,059 (78.7%)	< 0.001	0.34
Diabetes	51,720 (23.7%)	135 (30.5%)	< 0.001	822 (31.4%)	< 0.001	0.71
Hypertension	154,999 (71.0%)	337 (76.2%)	0.01	2,079 (79.5%)	< 0.001	0.12
COPD	5,512 (2.5%)	11 (2.5%)	0.95	71 (2.7%)	0.54	0.78
Cerebral stroke	7,156 (3.3%)	18 (4.1%)	0.35	116 (4.4%)	0.001	0.73
Myocardial infarction	67,106 (30.8%)	255 (57.7%)	< 0.001	1,596 (61%)	< 0.001	0.18
PCI	80,685 (37.0%)	240 (54.3%)	< 0.001	1,522 (58.2%)	< 0.001	0.12
Smoking	42,251 (19.4%)	45 (10.2%)	< 0.001	278 (10.6%)	< 0.001	0.77
Kidney failure	11,820 (5.4%)	36 (8.1%)	0.01	273 (10.4%)	< 0.001	0.13
Clinical presentation:						
Stable angina	60,356 (27.7%)	114 (25.8%)	0.36	583 (22.3%)	< 0.001	0.1
Unstable angina	64,459 (29.6%)	191 (43.2%)	< 0.001	1,070 (40.9%)	< 0.001	0.36
NSTEMI	40,371 (18.5%)	80 (18.5%)	0.81	667 (25.5%)	< 0.001	< 0.001
STEMI	50,787 (23.3%)	54 (12.2%)	< 0.001	273 (10.4%)	< 0.001	0.26
Others	1,833 (0.8%)	3 (0.67%)	0.94	23 (0.9%)	0.83	0.99
Vascular access:						
AMI	91,158 (41.8%)	134 (29.9%)	< 0.001	940 (35.9%)	< 0.001	0.02
Radial right	125,559 (57.6%)	47 (10.6%)	< 0.001	524 (20.0%)	< 0.001	< 0.001
Radial left	35,974 (16.5%)	149 (33.7%)	< 0.001	661 (25.3%)	< 0.001	< 0.001
Femoral	55,007 (25.2%)	237 (53.6%)	< 0.001	1,394 (53.3%)	< 0.001	0.89
Coronary angiography:						
Other	1,597 (0.7%)	9 (2.0%)	0.001	37 (1.4%)	< 0.001	0.32
SVD	137,080 (69.2%)	235 (58.4%)	< 0.001	1,387 (56.8%)	< 0.001	< 0.001
MVD, LMCA (–)	51,412 (26.0%)	128 (31.8%)	0.007	723 (29.6%)	< 0.001	0.37
MVD, LMCA (+)	7,736 (3.9%)	38 (9.4%)	< 0.001	326 (13.4%)	< 0.001	0.02
Isolated LMCA	1,814 (0.9%)	1 (0.2%)	0.16	4 (0.2%)	< 0.001	0.7

Data given as mean ± standard deviation or number and percentages. P-value by χ^2 test for categorical variables. T-test for continuous variables. AMI — acute myocardial infarction; COPD — chronic obstructive pulmonary disease; LMCA — left-main coronary artery; MVD — multi-vessel disease; NSTEMI — non-ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention; STEMI — ST-segment elevation myocardial infarction; SVD — single-vessel disease

both estimations (2.63% vs. 1.92%, p = 0.008 and 3.09% vs. 2.29%, p = 0.007). It did not differ significantly between PCI IMA and non-IMA/ /SVG groups, while the difference was significant between IMA and SVG group (1.58 vs. 3.09, p = = 0.02) for overall complication rate and was lowest in IMA group. The periprocedural mortality rate was the lowest in IMA group compared to the SVG and non-IMA/SVG group, however it did not reach statistical significance (0.22% vs. 0.34% vs. 0.46%, respectively). No-reflows were more frequent in SVG group compared to non-IMA/SVG group (1.37% vs. 0.51%, p < 0.001) and IMA-group (1.37 vs. 0.44, p = 0.01). Also, perforation rate was significantly higher in SVG subgroup compared to non-IMA/SVG PCI group (0.38% vs. 0.17%, p = = 0.01). There were no perforations noticed in IMA group of patients. No significant differences were noticed in rates of other complications between selected subgroups of patients. The distribution of particular complication rates in selected subgroups is presented in Figure 1A.

Procedural effectiveness

In IMA group, periprocedural effectiveness assessed as TIMI flow 2–3 after the procedure compared to non-IMA/SVG group (96.1% vs. 96.8%, p = 0.46), while in SVG group, it was significantly

Table 2. Procedural variables.

Variable	PCI non--IMA/SVG (n = 218,137)	PCI IMA (n = 442)	P Non-IMA/ /SVG vs. IMA	PCI SVG (n = 2,615)	P Non-IMA/ /SVG vs. SVG	P IMA vs. SVG
Type of PCI:						
BMS	7,209 (3.3%)	6 (1.35%)	0.02	56 (2.14%)	< 0.001	0.27
DES	187,042 (85.7%)	357 (80.7%)	0.002	2,155 (82.4%)	< 0.001	0.4
BRS	2,925 (1.3%)	3 (0.67%)	0.22	5 (0.19%)	< 0.001	0.06
DCB	4,708 (2.1%)	9 (2.0%)	0.86	117 (4.47%)	< 0.001	0.01
POBA/failed	16,253 (7.4%)	67 (15.1%)	< 0.001	282 (10.8%)	< 0.001	0.007
Rotablation	974 (0.4%)	0 (0%)	0.15	1 (0.03%)	0.001	0.68
Thrombectomy	7,001 (3.2%)	10 (2.26%)	0.25	114 (4.35%)	< 0.001	0.03
Bifurcation	11,803 (5.4%)	55 (12.4%)	< 0.001	37 (1.41%)	< 0.001	< 0.001
CTO	9,235 (4.2%)	52 (11.8%)	< 0.001	34 (1.3%)	< 0.001	< 0.001
OCT	392 (0.2%)	0 (0%)	0.37	8 (0.3%)	0.13	0.24
IVUS	1,876 (0.9%)	0 (0%)	0.05	6 (0.22%)	< 0.001	0.31
FFR	3,248 (1.5%)	3 (0.7%)	0.15	7 (0.26%)	< 0.001	0.16
Contrast [mL]	175.6 ± 78.5	224.3 ± 108.0	< 0.001	217.78 ± 93.9	< 0.001	0.19
Radiation [Gy]	1,069.5 ± 963.6	1,204.3 ± 1048.4	0.005	1,216.5 ± 1058.8	< 0.001	0.83

Data given as mean ± standard deviation or number and percentages. P-value by χ^2 test for categorical variables. T-test for continuous variables. BMS — bare-metal stent; BRS — bioresorbable scaffold; CTO — chronic total occlusion; DCB — drug-coated balloon; DES — drug-eluting stent; FFR — fractional flow reserve; IVUS — intravascular ultrasound; OCT — optical coherence tomography; POBA — plain old balloon angioplasty

Table 3. Pharmacological treatment.

Medication	PCI non--IMA/SVG (n = 218,137)	PCI IMA (n = 442)	P Non-IMA/ /SVG vs. IMA	PCI SVG (n = 2,616)	P Non-IMA/ /SVG vs. SVG	P SVG vs. IMA
Pharmacotherapy before PCI						
Acetylsalicylic acid	106,921 (49.0%)	174 (39.4%)	< 0.001	1,281 (49.0%)	0.96	< 0.001
Unfractionated heparin	32,414 (14.8%)	44 (9.9%)	0.003	314 (12.0%)	< 0.001	0.21
LMWH	2,030 (0.9%)	1 (0.2%)	0.12	30 (1.1%)	0.25	0.07
$P2Y_{12}$ inhibitors						
Clopidogrel	120,066 (55.0%)	213 (48.2%)	0.003	1,532 (58.6%)	< 0.001	< 0.001
Ticagrelor	10,988 (5.0%)	24 (5.4%)	0.7	122 (4.7%)	0.38	0.48
Prasugrel	1,157 (0.5%)	2 (0.4%)	0.82	6 (0.2%)	0.03	0.39
GP IIb/IIIa inhibitors	21,066 (11.8%)	42 (11.9%)	< 0.001	395 (17.5%)	< 0.001	0.008
Bivalirudin	17 (0.007%)	0 (0%)	0.85	0 (0%)	0.65	-
Thrombolysis	44 (0.02%)	0 (0%)	0.74	0 (0%)	0.42	-
Pharmacotherapy during PCI						
Acetylsalicylic acid	36,977 (16.9%)	63 (14.2%)	0.13	495 (18.9%)	0.007	0.01
Unfractionated heparin	183,913 (84.3%)	359 (81.2%)	0.07	2,309 (88.3%)	< 0.001	< 0.001
LMWH	8,419 (3.8%)	22 (5.0%)	0.22	65 (2.5%)	< 0.001	0.003
$P2Y_{12}$ inhibitors						
Clopidogrel	91,783 (42.1%)	181 (40.9%)	0.63	1,124 (43.0%)	0.35	0.42
Ticagrelor	10,213 (4.7%)	20 (4.5%)	0.87	126 (4.8%)	0.74	0.79
Prasugrel	990 (0.4%)	2 (0.4%)	0.99	14 (0.5%)	0.53	0.82
GP IIb/IIIa inhibitors	836 (0.4%)	3 (0.7%)	0.31	10 (0.4%)	0.91	0.4
Bivalirudin	566 (0.2%)	0 (0%)	0.28	4 (0.1%)	0.28	0.41
Thrombolysis	344 (0.1%)	2 (0.4%)	0.11	3 (0.1%)	0.58	0.1

Data given as number and percentage. P-value by χ^2 test. GP — glycoprotein; LMWH — low molecular weight heparin

Table 4. Characteristics of culprit lesion.

Variable	PCI non--IMA/SVG (n = 241,234)	PCI IMA (n = 493)	P Non-IMA//SVG vs. IMA	PCI SVG (n = 2,779)	P Non-IMA//SVG vs. SVG	P SVG vs. IMA
Number of patients	218,137 (100%)	442 (0.2%)	–	2,616 (1.2%)	–	–
Overall lesions count	241,234 (100%)	493 (0.2%)	–	2,779 (1.1%)	–	–
De-novo lesions	228,971 (94.9%)	459 (93.1%)	0.06	2,378 (85.6%)	< 0.001	< 0.001
Restenosis (overall)	11,065 (4.6%)	33 (6.7%)	0.02	380 (13.7%)	< 0.001	< 0.001
Drug-eluting stent restenosis	7,447 (3.1%)	25 (5.1%)	0.01	309 (11.1%)	< 0.001	< 0.001
Bare-metal stent restenosis	3,120 (1.3%)	4 (0.8%)	0.34	45 (1.6%)	0.13	0.17
Bioresorbable scaffold restenosis	134 (0.05%)	1 (0.2%)	0.16	8 (0.3%)	< 0.001	0.73
Drug-coated balloon restenosis	107 (0.04%)	1 (0.2%)	0.09	7 (0.2%)	< 0.001	0.83
Plain-old balloon angioplasty restenosis	257 (0.1%)	2 (0.4%)	0.04	11 (0.4%)	< 0.001	0.97
In-stent thrombosis	1,198 (0.5%)	1 (0.2%)	0.35	21 (0.7%)	0.054	0.16

Data given as number and percentage. P-value by χ^2 test.

lower when compared to non-IMA/SVG group (93.8% vs. 96.8%, p < 0.001). The effectiveness of PCI SVG assessed by the TIMI scale was also poorer in PCI SVG group compared to non-IMA//SVG PCI group after PCI and separation into TIMI 0 group (5% vs. 2.25%, p < 0.001) and TIMI 4 group (90.3% vs. 94.1%, p < 0.001). The TIMI flow distributions in selected groups of patients according to TIMI grade before and after PCI are presented in Figure 1B.

Predictors of selected periprocedural complications in non-IMA/SVG group

Among significant independent predictors of increased rate of all complications in non-IMA//SVG group of patients, the following distinctions were made: age, gender, diabetes, past cerebral stroke, past MI, kidney failure, ACSs, PCI of patients with coronary angiography image other than SVD, femoral access, thrombectomy, RA and cardiac arrest, while among predictors of lower rate of periprocedural complications, also found were: past CABG and patent coronary artery before PCI expressed as TIMI flow 2–3 (Fig. 2A).

Independent predictors of the higher rate of no-reflows in non-IMA/SVG group of patients assessed by multivariable analysis included age, past cerebral stroke, past MI, smoking, hypertension, AMI, other angiographic image than SVD, femoral access and thrombectomy, while among predictors of lower rate of no-reflows patent artery before PCI expressed as TIMI flow 2–3 (Fig. 2B) was also found.

In non-IMA/SVG group of patients, it was found that age, diabetes, past cerebral stroke, past MI, kidney failure, ACSs, other angiographic image than SVD, femoral access, thrombectomy, and cardiac arrest to be among the independent predictors of an increased rate of death, while for predictors of decreased risk of periprocedural death the following was confirmed: male gender, past CABG, hypertension and patent artery before PCI expressed as TIMI flow 2–3 (Fig. 3A).

Among independent predictors of increased risk of procedural perforations in non-IMA/SVG group of patients undergoing PCI assessed in multivariable analysis included the following: age, hypertension, other than single vessel CAD in angiography, PCI of coronary arteries other than LMCA, RA and cardiac arrest, while decreased risk predictors included male gender and TIMI flow 2–3 before PCI (Fig. 3B).

Predictors of selected periprocedural complications assigned to the SVG group

Considering all complication rates, the multivariable analysis revealed hypertension (odds ratio [OR]: 4.4, 95% confidence interval [CI]: 1.05–18.5, p = 0.04) and thrombectomy (OR: 3.3, 95% CI: 1.4–7.6, p = 0.005) as predictors of increased rate of all periprocedural complications while among predictors of decreased rate of death, TIMI flow 2–3 before PCI (OR: 0.4, 95% CI: 0.2–0.8, p = = 0.01) in the SVG group was distinguished. Among predictors of increased rate of no-reflows in SVG group assessed by multivariable analysis, these

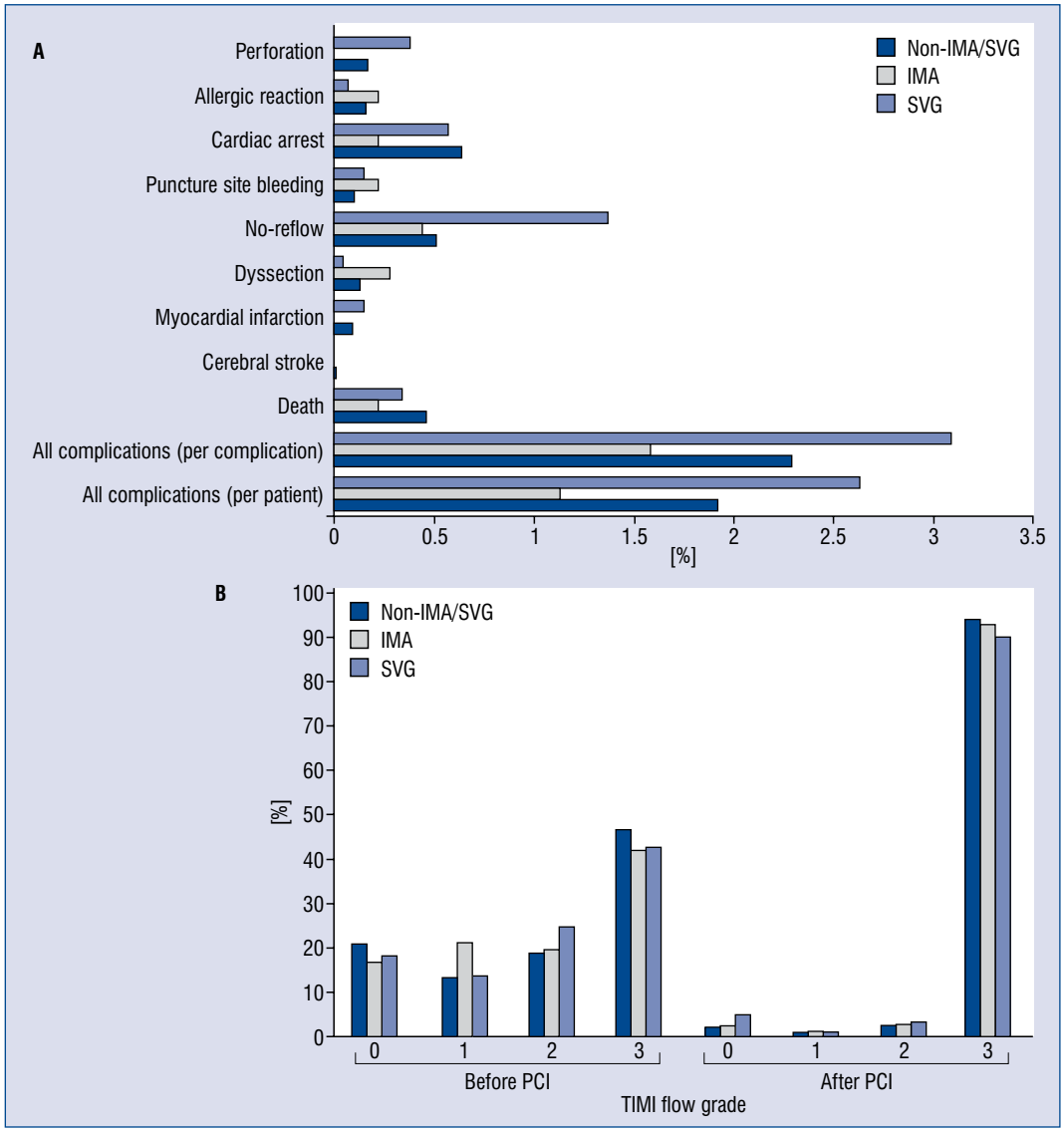

Figure 1. A. The distribution of Thrombolysis in Myocardial Infarction (TIMI) flow grades before and after percutaneous coronary interventions (PCI) expressed as percentages in the non-internal mammary artery (IMA)/saphenous vein grafts (SVG) group, IMA and SVG groups of patients undergoing PCI; **B.** The distribution of periprocedural complications expressed as percentages in the non-IMA/SVG group, IMA and SVG groups of patients undergoing PCI.

were found: past cerebral stroke (OR: 3.3, 95% CI: 1.0–10.4, p = 0.04), ACSs (OR: 5.5, 95% CI: 1.2–23.9, p = 0.02) and thrombectomy (OR: 4.4, 95% CI: 1.7–11.4, p = 0.002). Multivariable analysis did not reveal any significant predictors of death in the group of patients undergoing PCI of SVG. The only significant predictor of perforation in the group of patients undergoing PCI of SVG was male gender (OR: 0.17, 95% CI: 0.04–0.8, p = 0.02).

Discussion

The current study confirmed the significant separateness of PCI performed within SVGs when compared to native arteries in terms of several indices such as coronary angiography image, clinical presentation of CAD, culprit lesion characteristics or concomitant diseases, age and gender. This along with many other factors involved, also determines the different panel of predictors of periprocedural complications and their type. The greatest differences in the incidence of periprocedural complications, because of the similarity of PCIs performed on internal mammary arteries to native coronary arteries, were noticed in patients undergoing PCIs of SVGs, and they included an increased rate of all periprocedural complications, no-reflows and perforations. Furthermore, considering significant

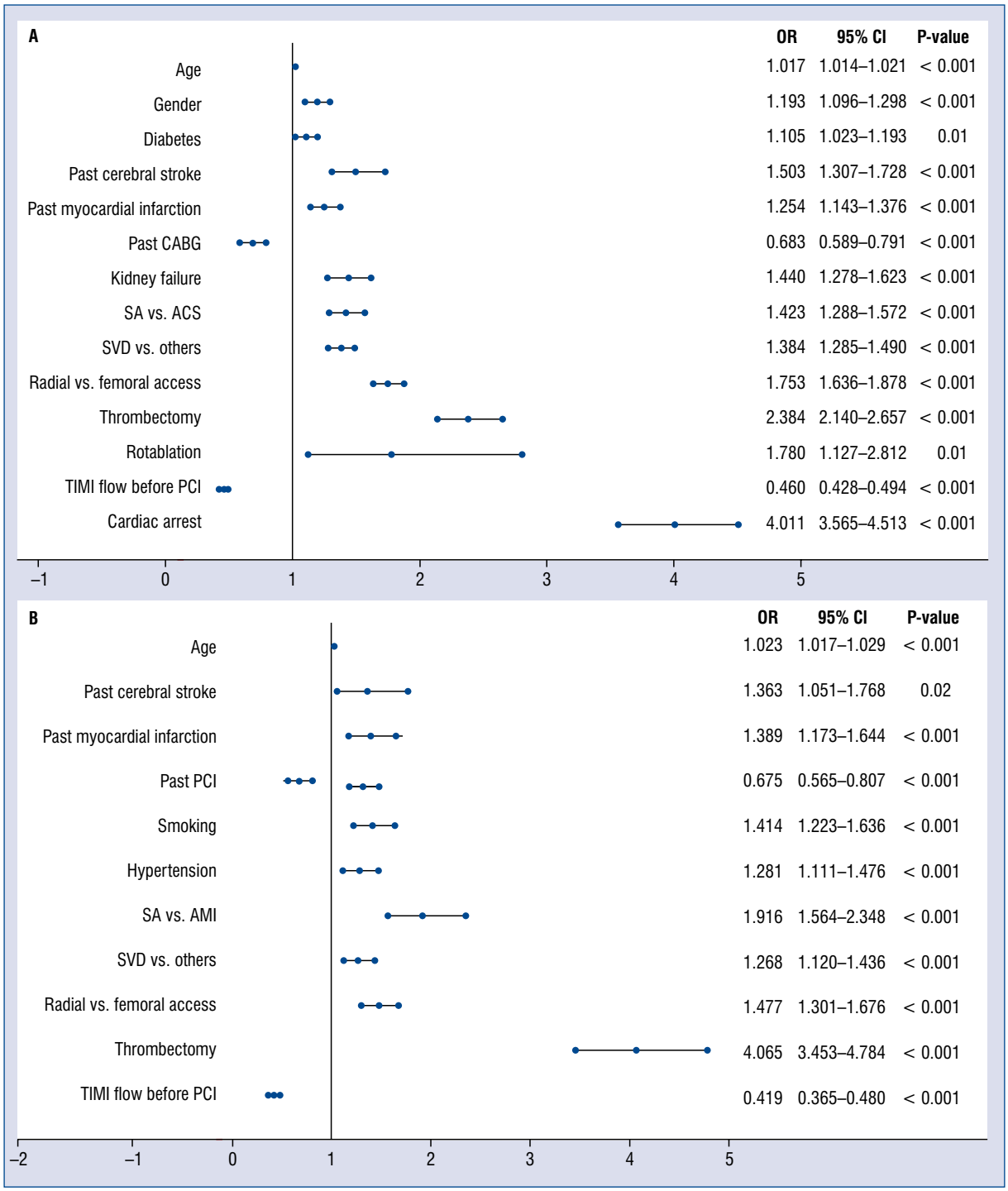

Figure 2. A. Predictors of all periprocedural complications assessed by multivariable analysis in the overall group of patients undergoing percutaneous coronary interventions (PCI); **B.** Predictors of no-reflows assessed by multivariable analysis in the overall group of patients undergoing PCI; ACS — acute coronary syndrome; AMI — acute myocardial infarction; SA — stable angina; CABG — coronary artery bypass grafting; CI — confidence interval; OR — odds ratio; SVG — saphenous vein grafts; TIMI — Thrombolysis in Myocardial Infarction.

predictors of periprocedural complications assessed using multivariable analysis, their number was much smaller and was limited to more specific factors among which, and the most deserving of them, included clinical presentation of CAD, TIMI flow before PCI, use of thrombectomy and gender.

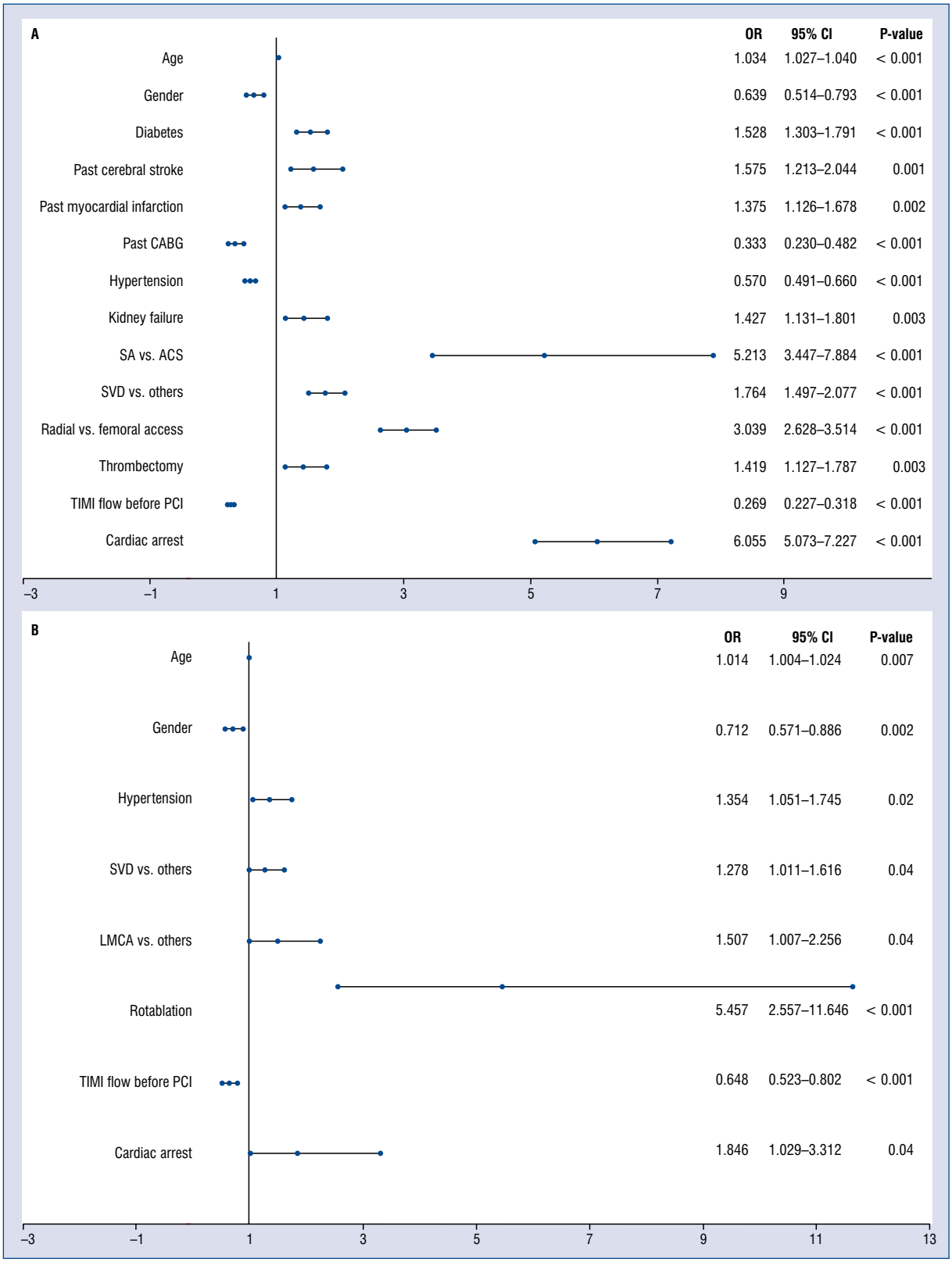

Figure 3. A. Predictors of deaths assessed by multivariable analysis in the overall group of patients undergoing percutaneous coronary interventions (PCI); **B.** Predictors of perforations assessed by multivariable analysis in the overall group of patients undergoing PCI; ACS — acute coronary syndrome; AMI — acute myocardial infarction; SA — stable angina; CABG — coronary artery bypass grafting; CI — confidence interval; LMCA — left-main coronary artery; OR — odds ratio; SVG — saphenous vein grafts; TIMI — Thrombolysis in Myocardial Infarction.

Considering past CABG procedure, patients in the IMA and SVG groups are older, more often males and more frequently burdened with an accompanying disease such as diabetes, kidney failure or hypertension. The higher incidence of atherosclerosis risk factors is associated with more advanced atherosclerosis in this selected group of patients. Interestingly, the incidence of chronic obstructive pulmonary disease was similar when comparing all three groups, while there were less smokers in the group of patients undergoing PCI IMA and SVG compared to the non-IMA/SVG group. This could be explained by the fact that CABG procedure is a motivating factor for smoking cessation. Also, the higher rate of peracted MIs and PCIs in IMA and SVG group compared to non-IMA/SVG group is undoubtedly related to the peracted CABG procedure. A similar relationship may be an explanation for the higher prevalence of MVD in IMA and SVG groups. Similarly, a higher incidence of UA in IMA and SVG groups compared to non-IMA/SVG group, and lower frequency of STEMI and NSTEMI is associated with the presence of a more complicated cardiac vascularization system and associated vascular disorders like the steal syndrome. PCI procedures in patients after CABG are much more frequently performed with femoral access, due to the fact that radial access in many cases prevents even intubation of the culprit vessel.

Among predictors of periprocedural complication specific for PCI of SVGs, studies published to date have revealed increased intraluminal pressure, graft wall ischemia, thrombosis, fibrin deposition or trauma, secondary repair as well as graft age [11]. For example, Cicek et al. [12] published a study which included 48 patients at a mean age of 62 years, 92% were men. Indications for revascularization included SA in 71% of patients, UA in 23% and AMI in 6%. Stent deployment was performed in all patients. The GP IIb/IIIa inhibitor was used in 56% patients. No-reflow, defined as TIMI 1 flow, was observed in 2 patients and slow flow, defined as TIMI 2 flow, was observed in 3 patients. Overall, no reflow/slow flow phenomenon occurred in 10% of patients (n = 4, 2 patients with UA and 2 patients with AMI), which was higher compared to the present group. Angiographic success was achieved in 98% of patients, which was also higher compared to the present group when TIMI flow 2 and 3 was assumed as angiographic success (94%). All patients survived after stent implantation, but 2 patients experienced non Q-wave MI and 1 patient experienced Q wave MI [12]. No relation between no reflow/slow flow and GP IIb/IIIa inhibitor use, hypercholesterolemia or lesion length was found [12]. Another study, which presented procedural results of multiple SVG stenting demonstrated distal embolization in 3.4% of patients in the single SVG group and in 0.9% of patients in the multiple SVG group [13]. Furthermore, a study performed on 51 patients who underwent stenting of the bypass graft demonstrated distal embolization in 13.6% of PCIs [14]. They also reported lower rates of non-Q MIs in patients treated with stent implantation compared to POBA (2% vs. 7%). The procedural success rate after SVG stenting in this study was 97% [15]. Sdringola et al. [16] detected four independent risk factors for the no reflow/slow flow phenomenon as probable thrombus, ACSs, degenerated vein graft and ulcerated plaque. All of this data was not compared, however ACSs were similar predictors of an increased rate of periprocedural no-reflows in patients undergoing PCI of SVG. It was also demonstrated that past cerebral stroke was an independent predictor of increased rate of no-reflows. One possible explanation is that patients after cerebral stroke are usually immobilized to some degree, which decreases hemodynamic response of the cardiovascular system on stress. Consequently, it is related to impaired endothelial response and increased thrombogenicity. The PAMI-2 trial comparing the effectiveness of PCI in patients with grafts and native coronary arteries were revealed among predictors AMI and PCI of native coronary arteries. The procedural success assessed as TIMI flow grade 3 was lower in graft PCI (70%) compared to native arteries (94%). The reason for this difference was explained by authors as due to extensive thrombus, atherosclerosis burden in bypass grafts and increased rate of distal embolization [17]. However, they did not confirm the relationship between distal embolization and GP IIb/IIIa inhibitor use. Other authors have shown that GP IIb/IIIa inhibitors reduce thrombus burden in SVG lesions and may decrease distal embolization during PCI [18]. In the abovementioned studies, the study group was small and GP IIb/IIIa inhibitor use was limited. They were unable to definitively conclude that GP IIb/IIIa inhibitors reduced distal embolization. Based on our data, univariate analysis confirmed the significant relationship between treatment with GP IIb/IIIa inhibitors before and during PCI and the rate of periprocedural deaths, no-reflows and all complication counts in the overall group of patients undergoing PCI ($p < 0.001$ in all comparisons). However, multivariable analysis did not confirm such a re-

lationship. Similar univariate analysis performed in the SVG group revealed only the relationship between no-reflows and overall complication rates for treatment with GP IIb/IIIa inhibitors before PCI, but not after it. Also, multivariable analysis did not confirm those relationships. Large-scale, randomized studies should be performed to clarify this. Another abovementioned study revealed that after stenting of SVG, the lesion length and total cholesterol levels were independent predictors of distal embolization [14]. The present study did not possess this kind of data except for hypercholesterolemia, which was not an independent predictor of periprocedural complications. Kuroda et al. [14] did not observe any no reflow/slow flow during PCI of in-stent restenosis lesions of SVGs. In SVG group from the present study, target lesions were significantly more often restenosis and less frequently de-novo lesions compared to non-IMA/ /SVG group. Univariate analysis did not reveal any relationships between particular periprocedural complications and the presence of restenosis. On the contrary, in-stent thrombosis rate was significantly associated with increased death rate ($p < < 0.001$) and overall complication rate ($p = 0.04$) in univariate analysis. In-stent restenosis lesions are pathologically distinct from de novo lesions. In degenerated SVGs, de novo lesions had friable atherogenic material. Bhargava et al. [13] compared two group of patients undergoing PCI of SVG in SVD and MVD groups. The overall angiographic and procedural success rates were similar in both groups. Similarly, major in-hospital complications including death, Q wave MI and emergent CABG were similar in the single stent SVG and multiple stent SVG groups (2.7% and 2.8%). However, the periprocedural non Q wave MI rate defined as creatinine kinase-MB > 5 times above the norm was significantly higher in SVG group (28% vs. 16%). The frequency of GP IIb/IIIa inhibitor use did not differ significantly between both investigated groups and was higher in the multiple stent group (4% vs. 6.5%) [13]. Porto et al. [19] confirmed that the use of post-dilatation was significantly higher in the group of patients who subsequently developed filter no-reflow (57% vs. 26%, $p = 0.04$). In the presented study it was found, that hypertension was an independent predictor of increased rate of overall complications count in SVG group. At the same time it was observed that in the SVG group, hypertension correlated positively with increased rate of no-reflows ($p = 0.02$, $r = 0.04$) and cardiac arrests ($p = 0.04$, $r = 0.03$). This could, at least in part explain this relationship. It was also noticed that the only independent predictor of coronary artery perforation during PCI of SVG was male gender. This is not in line with previously published results performed on the overall group of patients treated with PCI, where female gender was found to be an independent predictor of increased rate of periprocedural perforations [20]. Additionally, in the current study males in SVG group were significantly younger compared to females, which additionally raises some questions.

Limitations of the study

First of all, this is rather a study based on the nationwide volunteer registry rather than a prospective randomized clinical trial. This tends to decrease and underestimate the detection of periprocedural complication rate and other crucial variables which are dependant on a subjective assessment of the operator, despite a large overall interventional volume included in the present analysis. Furthermore, the current analysis does not include all in-hospital complications which undoubtedly weakens its value. The lack of data evaluating the process of neointimal hyperplasia in the present study, such as intravascular ultrasound or OCT, makes it impossible to assess the relationship between the analyzed risk factors and the type and severity of processes leading to occlusion of evaluated bypasses. Undoubtedly, an advantage of the current study is that the results are closer to real life rather than to randomized clinical trials and shows clinical data depicting the results of SVG PCIs in Central Europe.

Conclusions

The group of patients undergoing PCI of SVG is at increased risk of periprocedural complications. Among the periprocedural complications typical for PCI of SVG, the following was distinguished: death, no-reflow, perforation and overall periprocedural complication count. Also, the panel of independent predictors of periprocedural complications is different in patients undergoing PCI of SVG compared to non-IMA/SVG, and in the current study, for selected factors it included male gender, ACS, thrombectomy, TIMI flow before PCI, past cerebral stroke and hypertension.

Conflict of interest: None declared

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The potential hazard of a non-slip element balloon causing distal longitudinal stent deformation: The first clinical experience and *in vitro* assessment

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Abstract

Background: *A new complication, longitudinal stent deformation (LSD), is increasingly reported with recent intracoronary stent designs. There have been experiences of unusual cases of distal LSD caused by entrapment of a Lacrosse® non-slip element (NSE) balloon (Goodman Co., Ltd., Nagoya, Japan), which has three flexible nylon elements to prevent slippage. Accordingly, the aim of this study is to report the clinical experience of distal LSD caused by the NSE in the documented center and to investigate the incidence and mechanisms involved.*

Methods: *Coronary intervention cases were retrospectively reviewed using the NSE balloon in hospital between May 2014 and June 2017. In bench testing, distal LSD was reproduced in a silicon tube model to identify its mechanism.*

Results: *A total of 95 patients with 107 lesions underwent coronary interventions with NSE. Of these, 72 lesions (12 de-novo lesions and 60 in-stent restenosis) were treated using in-stent dilatation. Two distal LSD cases occurred, representing an incidence of 2.78% (2/72) among all procedures; 16.7% (2/12) of the de-novo lesions developed LSD. In vitro experimentation allowed indentification of the mechanisms involved and bailout strategies.*

Conclusions: *This is the first study to evaluate NSE balloon catheter entrapment complicated by distal LSD in which reconstruction of the deformed stent and retrieval of the NSE could be achieved successfully. There is a potential hazard for distal LSD during post-dilatation using the NSE balloon due to its structural characteristics. Careful assessment is needed to prevent this complication.* (Cardiol J 2019; 26, 6: 645–652)

Key words: coronary artery disease, balloon angioplasty, complication, drug eluting stent

Introduction

Recent advances in intracoronary drug-eluting stents (DES) have led to the development of the thin strut platform with fewer connectors. This has improved delivery and conformability during percutaneous coronary intervention (PCI). However, several investigations, including bench testing, have increasingly reported a new complication of longitudinal stent deformation (LSD) because these new stent designs have reduced longitudinal strength [1–4]. LSD is defined as the distortion or shortening of intracoronary stents after successful stent deployment. This can occur in three possible patterns: 1) deformation with intra-stent wrinkling and overlapping of the proximal and distal stent fragments within a single stent; 2) deformation with elongation and 3) deformation with shortening [5]. The fundamental cause of LSD is impact from any secondary device through a stent and

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Table 1. The incidence of distal longitudinal stent deformation caused by non-slip element balloon.

	De-novo lesion	In-stent restenosis	Total
No. of lesions	12	60	72
No. of stent deformations	2	0	2
Incidence of stent deformations	16.70%	–	2.78%

contact with a guide catheter in a proximally deployed stent. This is more common in complex lesions such as ostial, bifurcation, left main trunk, and severely calcified lesions, and is also associated with the use of an extra-support guiding catheter and extra guidewires [6, 7]. However, unusual cases of distal LSD were experienced caused by a Lacrosse® non-slip element (NSE) balloon (Goodman Co., Ltd., Nagoya, Japan). The mechanism of this type of LSD is strongly associated with structural features of the NSE balloon itself. The NSE has three flexible nylon elements placed along the outside of the balloon every 120° for scoring effect while dramatically reducing slippage during inflation for in-stent restenosis, calcified, tapered, tortuous, bifurcated, and ostial lesions. Proximal and distal connections attach the elements and balloon catheter. Consequently, spaces exist between the elements and the balloon body [8]. The distal connection carries the potential risk of entrapment in a stent platform during post-dilatation, leading to distal LSD. Herein, is described local clinical experience with distal LSD caused by an NSE balloon, and discussion of the incidences and mechanisms involved.

Methods

This is a case series study on cases of coronary intervention cases collected at the documented hospital. The database was retrospectively examined and PCI cases were reviewed using the NSE balloon between May 2014 and June 2017. All PCI procedures were recorded on a digital computer-based program, and data concerning distal LSD caused by the NSE balloon were identified from this digital archive. The definition of distal LSD is the shortening of the distal portions of intracoronary stents after in-stent dilatation using an NSE balloon. Intravascular imaging devices, such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT), were used during all PCI procedures at three common time points: pre-stenting, post-stenting (in the case of in-stent restenosis, only pre-dilatation), and after post-dilatation using the NSE. The identification of LSD cases were performed manually by screening these angiographic findings and the IVUS or OCT imaging databases, and the incidence was estimated. In addition, a bench test was performed to identify the mechanism underlying this type of LSD using silicon tube models. As an *in vitro* assessment, the distal LSD was reproduced and was caused by the NSE balloon.

Results

During the study period, a total of 95 patients, with 107 lesions, underwent PCI using the NSE balloon for acute coronary syndrome or stable angina. Thirty-five lesions were excluded because the NSE balloon was used only for pre-dilatation; therefore, in-stent dilatation using the NSE balloon was performed for 72 lesions (12 *de-novo* lesions and 60 in-stent restenosis). When all procedures were considered, distal LSD, caused by the NSE balloon occurred in 2 cases. Table 1 shows that the incidence of stent deformation was 2.78% (2/72) among all procedures and 16.7% (2/12) when considering only *de-novo* lesions. The true incidence of this type of LSD remains unknown due to the small study population; however, a high incidence rate was found during procedures for *de-novo* lesions. On the other hand, this complication did not occur in patients being treated for in-stent restenosis. The 60 cases of in-stent restenosis were detected by performing follow-up coronary angiogram 6 to 20 months after stenting. All the previous stents were sealed by neointimal tissue from OCT findings, therefore, it might be impossible that the NSE was entrapped in the distal edge of the stent. Table 2 summarizes the clinical and procedural details of patients with *de-novo* lesions. Both LSD cases were not complex, but simple *de-novo* lesions and stent deformations occurred at the distal edge of the stent when performing post-dilatation with the NSE balloon and pulling it back. The operators detected the stent deformations by fluoroscopy and IVUS or OCT images and could successfully bail-out to perform further dilatation with a non-compliant balloon. There were no adverse events during the procedural clinical course.

Table 2. Clinical and procedural details of patients with *de-novo* lesions.

Case no.	Age	Gender	Diagnosis	PCI	Calci-fication	Target lesion	Stent type	Stent size	NSE balloon	Lesion of post-dilatation	Stent deformation
1	56	Male	EA	Elective	N	Diagonal branch	SYNERGY	2.75/20 mm	2.75/13 mm	Stent proximal-distal	Y
2	79	Male	EA	Elective	N	Mid LAD	SYNERGY	3.0/16 mm	3.0/13 mm	Stent proximal-distal	Y
3	79	Male	EA	Elective	Y	Proximal LAD	Resolute Integrity	3.0/30 mm	3.0/13 mm	Stent proximal-distal	N
4	77	Male	EA	Elective	N	Diagonal branch	Xience Xpedition	2.5/18 mm	2.5/13 mm	Stent mid-distal	N
5	84	Female	STEMI	Emergent	N	LMT-proximal LAD	Ultimaster	2.5/33 mm	2.25/13 mm	Stent distal	N
6	73	Male	EA post CABG	Elective	Y	LMT-proximal LAD	BMX-J	3.5/28 mm	2.25/13 mm	Stent distal	N
7	54	Male	EA	Elective	N	Mid LCX	SYNERGY	2.25/15 mm	2.25/13 mm	Stent proximal-distal	N
8	74	Male	EA	Elective	N	Proximal LAD	Xience Xpedition	3.0/38 mm	2.75/13 mm	Stent proximal-distal	N
9	68	Male	EA	Elective	N	mid RCA	SYNERGY	3.0/38 mm	3.0/13 mm	Stent proximal-distal	N
10	59	Male	EA	Elective	N	Mid LCX	SYNERGY	3.0/38 mm	3.25/13 mm	Stent proximal-distal	N
11	80	Male	STEMI	Emergent	N	Distal RCA	Xience Alpine	2.5/38 mm	2.5/13 mm	Stent distal	N
12	61	Male	OMI	Elective	N	Distal RCA	SYNERGY	3.0/38 mm	3.0/13 mm	Stent proximal	N

PCI — percutaneous coronary intervention; NSE — non-slip element; EA — exertional angina; LAD — left anterior descending artery; LMT — left main trunk; STEMI — ST-segment elevation myocardial infarction; CABG — coronary artery bypass grafting; LCX — left circumflex artery; RCA — right coronary artery; OMI — old myocardial infarction; N – no; Y — yes

The specific details of the 2 cases are described below.

Case 1

A 56-year-old man was admitted with chest pain. He was diagnosed with exertional angina based on diagnostic coronary angiography and underwent PCI of the mid-left anterior descending (LAD) artery and the first diagonal branch, respectively (Fig. 1A). The procedure began with the diagonal branch. First, pre-dilatation was attempted using a 2.75/13 mm NSE balloon, but the device could not be introduced through the target lesion due to tortuosity of the diagonal branch. Pre-dilatation was then performed using a 2.75/15 mm non-compliant balloon, and a 2.75/20 mm SYNERGY stent (Boston Scientific, Natick, MA, USA) was deployed at nominal pressure without protrusion to the LAD artery. IVUS revealed distal stent malapposition (Fig. 1B). Post-dilatation was therefore performed with the same NSE balloon. Delivery to the distal end of the stent was performed without complication and post-dilatation was completed at rated burst pressure (18 atm). However, LSD was detected at the distal end of the stent by fluoroscopy after removal of the NSE (Fig. 1C). It was considered that while the NSE balloon was pulled back, the three elements and the distal connection of the balloon were caught in the stent platform. This led to stent deformation, with the distal edge of the stent shortened. The deformed stent was recovered by additional dilatation with non-compliant balloon, which successfully dilated the stent (Fig. 1D). Finally, treatment proceeded with the LAD artery, and final angiogram showed good blood flow.

Case 2

This patient was a 79-year-old male receiving hemodialysis due to end-stage renal disease. He underwent a diagnostic coronary angiogram for chest pain during hemodialysis, which revealed severe stenosis of mid-LAD artery (Fig. 2A). He was diagnosed with exertional angina and PCI was performed for the mid-LAD artery. After pre-dilatation with a 3.0/13 mm NSE balloon, a 3.0/16 mm SYNERGY stent was deployed at nominal pressure. OCT images revealed malapposition at the distal end of the stent (Fig. 2B), and post-dilatation was performed with the same NSE balloon. Delivery of the device into the stent and inflation of the balloon at rated burst pressure (18 atm) was performed without complications; however, the NSE could not be withdrawn after deflation. Therefore, it was pushed distal to the stent once and pulled back

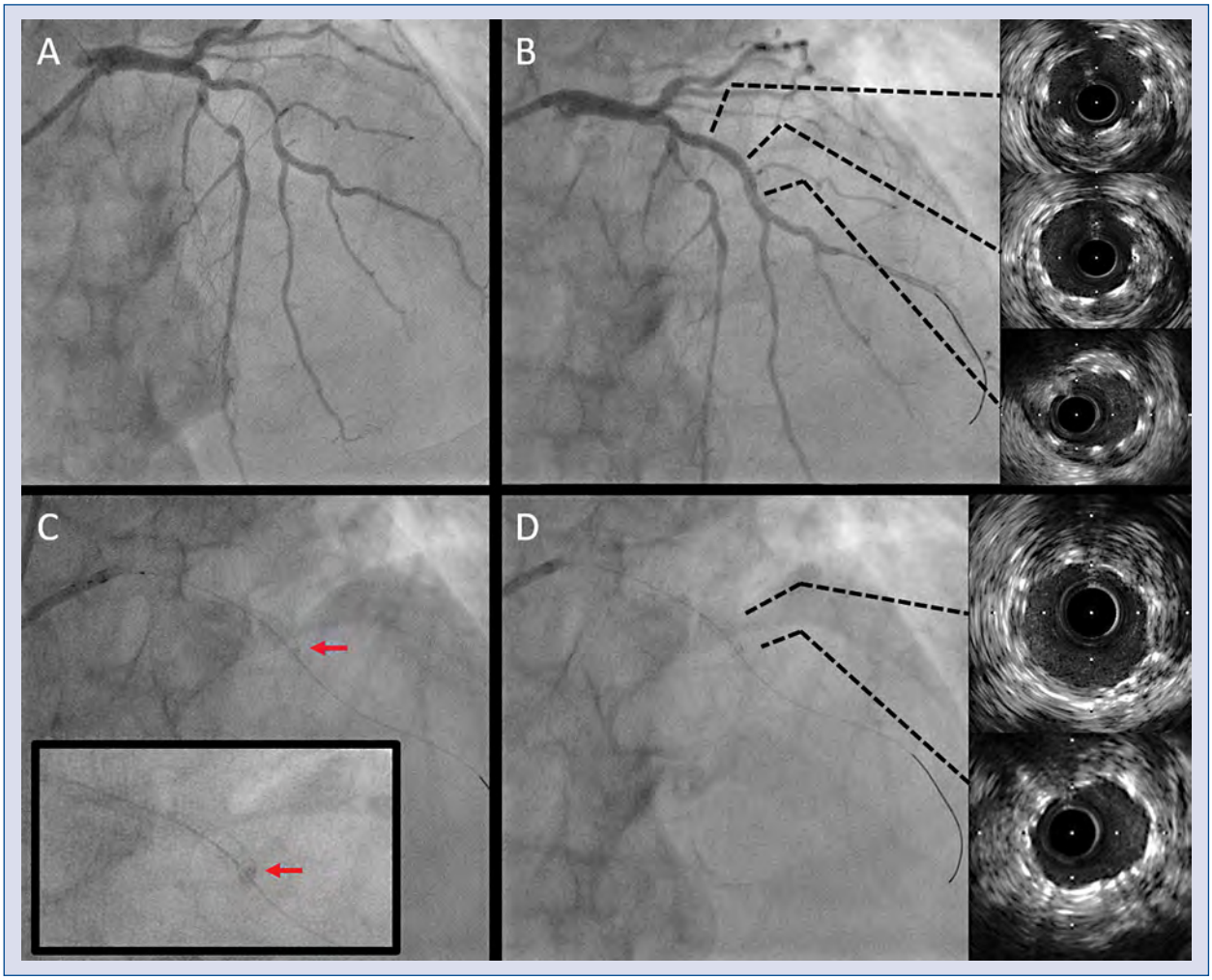

Figure 1. Case 1. **A.** The pre-procedural coronary angiogram revealed severe stenosis at the left anterior descending (LAD) artery and the first diagonal branch. **B.** After deployment of a 2.75/20 mm SYNERGY stent (Boston Scientific, Natick, MA, USA) at the diagonal branch without protrusion to the LAD artery, intravascular ultrasound (IVUS) showed distal stent malapposition. **C.** Post-dilatation using a 2.75/13 mm non-slip element (NSE) balloon was performed. When pulling back the NSE after deflation, slight resistance was encountered. Then longitudinal stent deformation was detected, with shortening of the distal end of the stent, using fluoroscopy after removal of the NSE (red arrow). **D.** Further dilatation, with a 2.75/15 mm non-compliant balloon, was then performed. Fluoroscopy and IVUS subsequently showed that the deformed stent had been successfully dilated.

again slowly and carefully. After successful removal of the NSE, LSD was identified at the distal end of the stent using magnified fluoroscopy (Fig. 2C) and OCT images (Fig. 2D). Therefore, further dilatation was performed with a 3.25/8 mm non-compliant balloon, which successfully dilated the deformed stent (Fig. 2E, F). After the procedure, the distal connection of the NSE was turned up (Fig. 3). This revealed that the NSE balloon was stuck by entrapment to the distal connection and elements in the stent platform. Finally, the entrapment was successfully relieved by pushing the NSE through the distal stent once.

Bench test report

Several silicon tube models were used to successfully reproduce distal LSD caused by NSE balloon. Here, 2 typical cases are presented. In the first case, using a bifurcation model (inner diameter 4.0–3.5–3.5 mm), a Runthrough® NS guide wire (Terumo Corporation, Tokyo, Japan) was positioned and a 3.0/28 mm SYNERGY stent was deployed at nominal pressure (Fig. 4A). Then, we delivered a 3.0/13 mm NSE balloon, which had already been inflated and deflated out of the silicon tube, into the stent. During repeated pushing/pulling, the NSE balloon became entrapped in the distal end of the

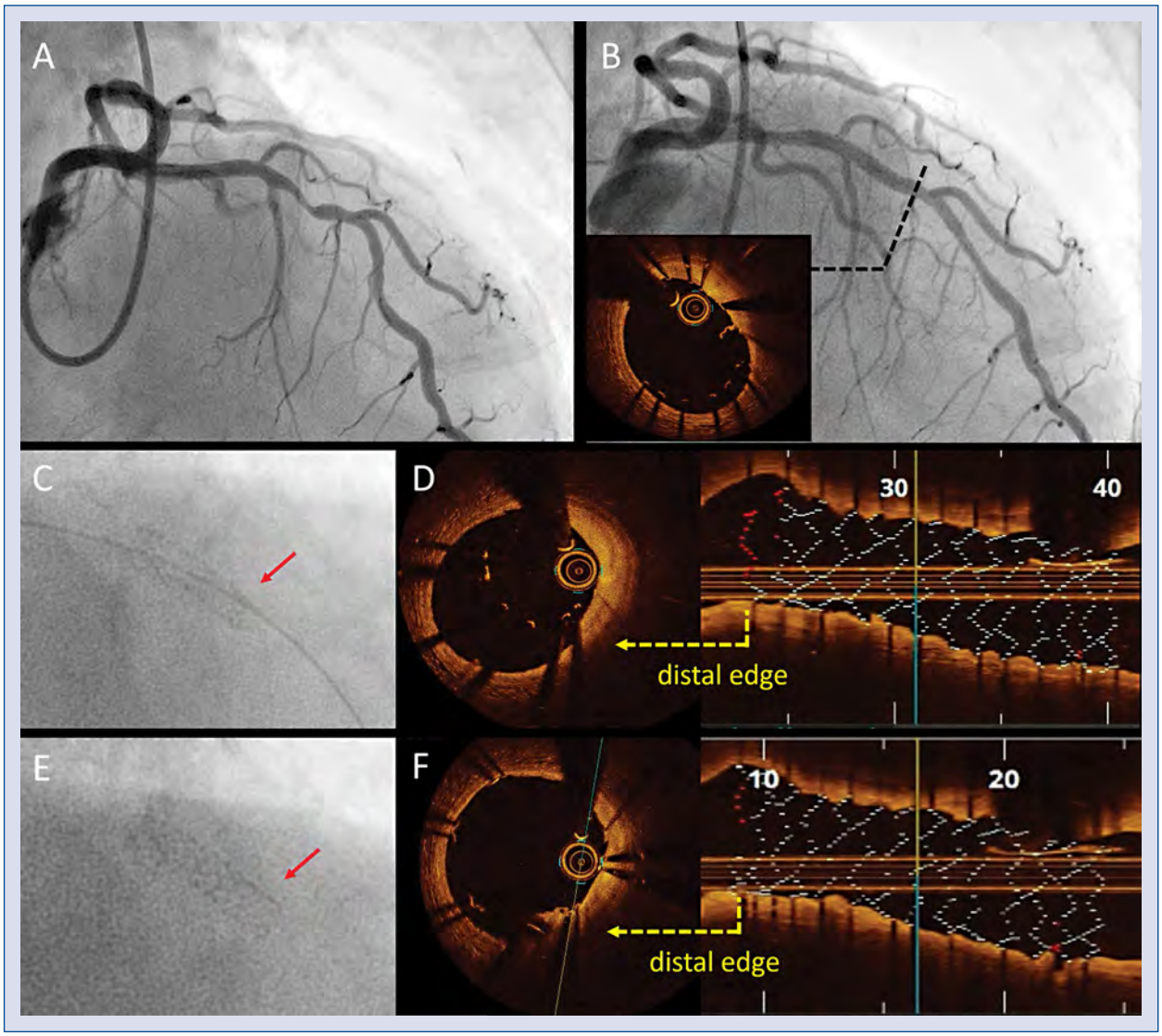

Figure 2. Case 2. **A.** The coronary angiogram showed severe stenosis at the mid-left anterior descending (LAD) artery. **B.** After deployment of a 3.0/16 mm SYNERGY stent at the LAD artery, optical coherence tomography (OCT) images revealed malapposition of the distal end of the stent. **C.** After post-dilatation with a 3.0/13 mm non-slip element balloon, longitudinal stent deformation was identified at the distal end of the stent using magnified fluoroscopy (red arrow). **D.** OCT images revealed shortening of the distal edge of the stent. **E, F.** After further dilatation with a 3.25/8 mm non-compliant balloon, the stent was checked for successful reconstruction using magnified fluoroscopy (red arrow) and OCT images.

stent (Fig. 4B). As the NSE was pulled back, the distal stent was gradually shortened (Fig. 4C, D). There was slight resistance; therefore, it was pushed distal to the stent once and pulled back again carefully. The entrapped NSE was successfully removed and distal LSD occurred (Fig. 4E).

In the second case, using a bifurcation silicon tube (inner diameter 3.5–3.5–2.5 mm), a 2.5/28 mm SYNERGY stent was deployed at nominal pressure (Fig. 5A). Delivery of a 2.5/13 mm NSE balloon through the stent was performed without complication (Fig. 5B). However, while pulling back the NSE, it became entrapped at the distal edge of the stent and LSD occurred (Fig. 5C). Although it was pushed to the distal stent once and pulled back again, as in the first case, the NSE was entrapped each time and could not be removed. Therefore, there was an attempt to inflate the NSE balloon at high pressure at the distal part of the stent, and the deformed stent was dilated (Fig. 5D). Accordingly, the NSE was successfully withdrawn through the stent (Fig. 5E).

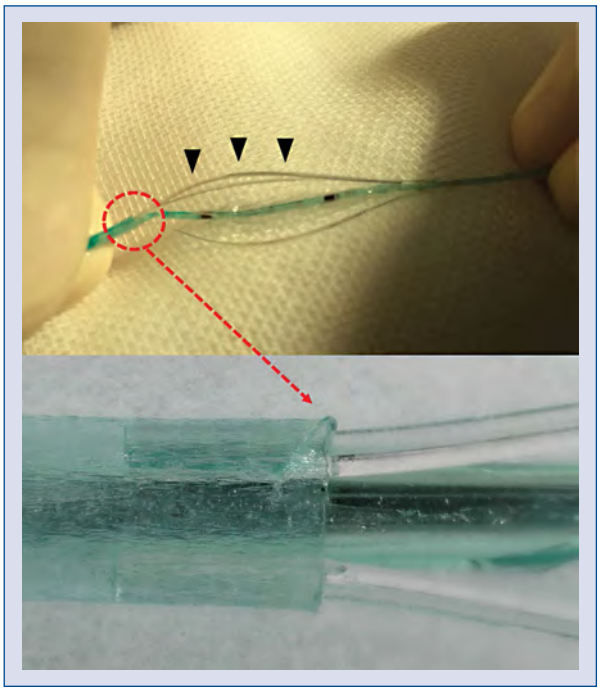

Figure 3. Image of non-slip element (NSE) balloon. After the procedure, the NSE balloon catheter was checked, revealing that the distal connection of the NSE was turned up (red arrow). The black arrowhead shows the structural feature of three elements that are attached only proximally and distally and not bonded to the balloon body.

Discussion

According to available research this is the first report to describe NSE balloon catheter entrapment complicated by distal LSD in which reconstruction of the deformed stent and retrieval of the NSE could be achieved successfully. There was discussion about the high incidence rate and mechanisms associated with this complication using a combination of database screening and bench test analyses.

Initially, the most important factor related to distal LSD was the structural features of NSE balloon, which becomes easily entrapped in the stent platform. The NSE balloon is beneficial for pre-dilatation in de novo lesions or in stent restenosis lesions because it characteristically features three nylon elements. The elements on the balloon are separated from each other by 120°. These are attached proximally and distally; therefore, the balloon body and elements are not bonded. Although it is plausible that any secondary devices through the deployed stent could cause LSD [1–3], these structural features are assumed to lead to easier entrapment at the stent platform compared with other devices.

Secondly, traction between devices and the distal edge of the stent may induce distal stent shortening. Bench tests indicated that wire bias and an under-expanded distal edge may be associated with LSD in the post-dilatation intravascular scenario. The mechanism by which the NSE caused stent crushing was by wire bias leading to contact between the distal connection and the stent edge. In Figure 4, the distal connection was entrapped at the distal edge of the stent due to wire bias, causing contact between the distal connection and stent edge along the inner curve of the bend. In Figure 5, wire bias caused contact along the outer curve of the bend. At this point, the stent edge may not have been fully embedded in the vessel wall. Thus, wire bias and an under-expanded distal edge might be the primary triggers of NSE entrapment. In such intravascular situations, using the NSE balloon post-dilatation carries a potentially high risk for distal LSD.

On the other hand, the main reason that NSE balloon was used for post-dilatation was only to reduce the total number of balloon devices. Sufficient expansion could achieved by NSE at high pressure when stent and NSE balloon sizes were similar. Inflation at rated burst pressure (18 atm) can make the balloon diameter increase to about a quarter size up (0.25 mm). However, post-dilatation with NSE at rated burst pressure could produce strong traction between devices which may be associated with the occurrence of LSD. In addition, the position of post-dilatation can have a strong impact on results. According to the mechanism demonstrated in the bench test, LSD can only occur when post-dilation was performed at the distal part of the stents. In clinical practice, NSE can be safely used for post-dilatation by not advancing it to the distal stents.

Other strategies were also considered to overcome entrapment and to aid in NSE balloon removal. The importance of treating LSD has been demonstrated by previous reports in which LSD was thought to be related to a subsequent adverse event, such as stent thrombosis [2, 6]. A careful assessment is also required to analyze the difficulty in removing the NSE balloon from highly deformed stents. If this occurs, some measures are required to extract the trapped device. First, the balloon catheter must not be pulled the by force when resistance is encountered. Pulling with greater force, will result in more deformation of the stent, and the stent will ultimately be crushed. Therefore, push-

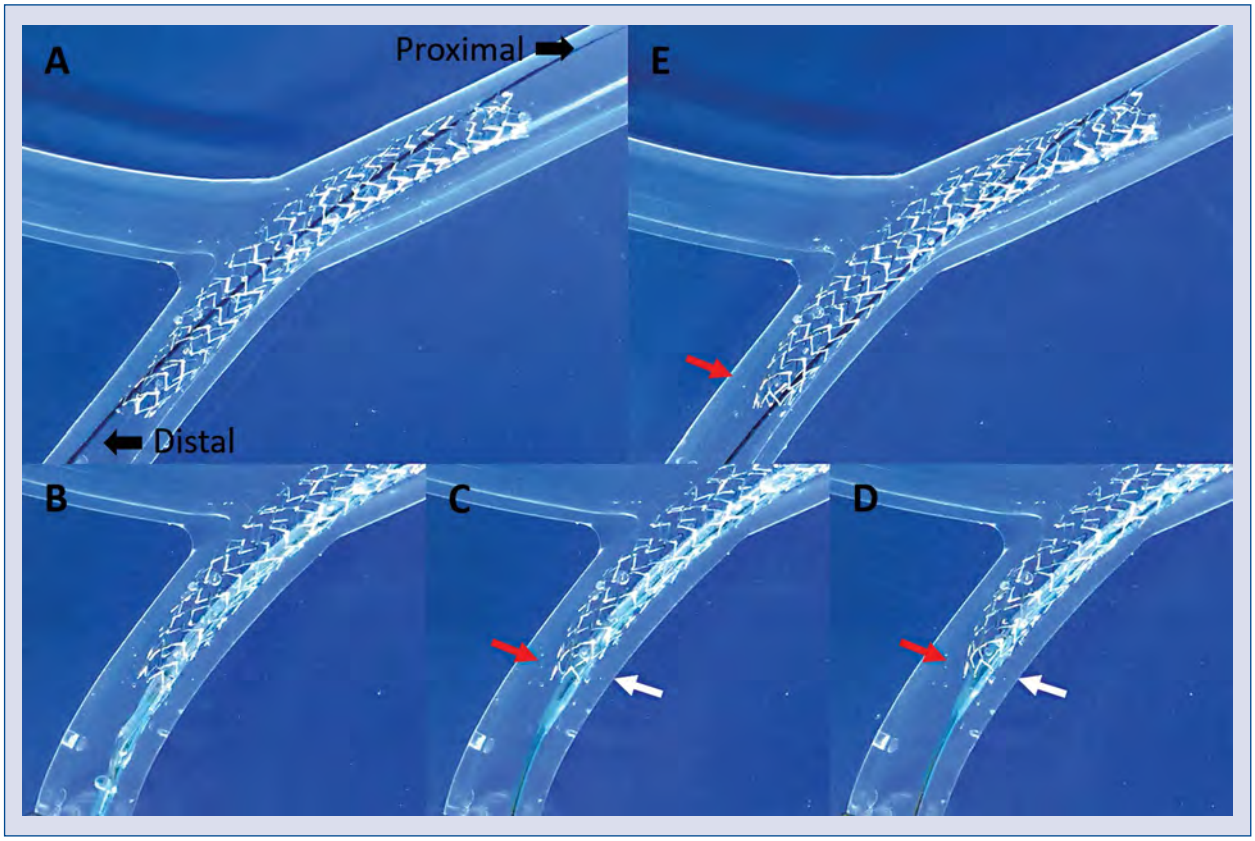

Figure 4. Longitudinal stent deformation (LSD) in case 1 was reproduced in the bench test. **A.** Using a bifurcation model (inner diameter 4.0–3.5–3.5 mm), the Runthrough® NS guide wire (Terumo Corporation, Tokyo, Japan) was positioned and a 3.0/28 mm SYNERGY stent was deployed at nominal pressure. **B.** A 3.0/13 mm non-slip element (NSE) balloon was delivered, which had already been inflated and deflated out of the silicon tube, into the stent. **C, D.** When the NSE was pulled back, the distal connection was entrapped along the inner curve of the bend (white arrow) and the distal stent was gradually shortened (red arrow). **E.** The catheter was pushed into the distal stent once and pulled back carefully. Then, the entrapped NSE was successfully removed and distal LSD occurred (red arrow).

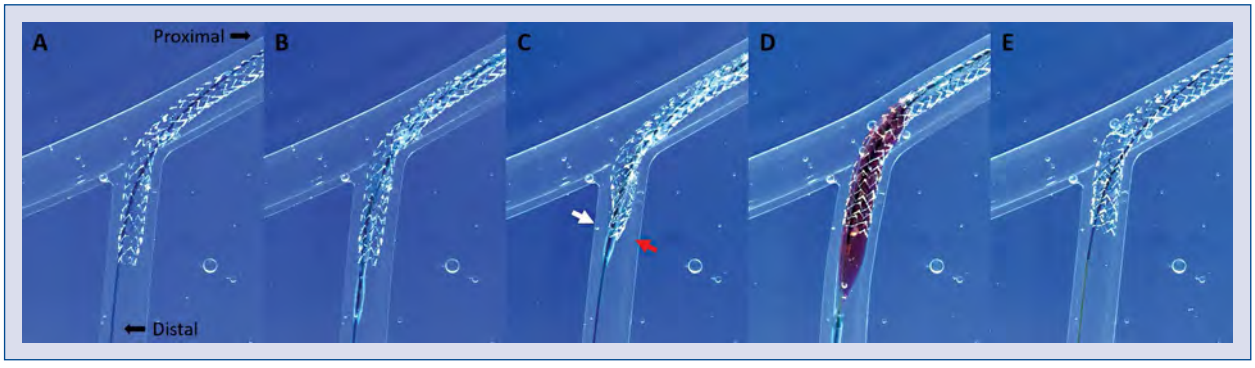

Figure 5. Longitudinal stent deformation (LSD) in case 2 reproduced in the bench test. **A.** Using a bifurcation silicon tube (inner diameter 3.5–3.5–2.5 mm), a 2.5/28 mm SYNERGY stent was deployed at nominal pressure. **B.** Delivery of a 2.5/13 mm non-slip element (NSE) balloon through the stent was performed without complications. **C.** While pulling back the NSE, the distal connection was entrapped in the distal edge of the stent along the outer curve of the bend (white arrow) and distal LSD occurred (red arrow). **D.** The device could not be removed because the deformation had progressed significantly. Therefore, reconstruction of the deformed stent by balloon dilatation at high pressure was performed. **E.** Accordingly, the NSE was successfully withdrawn through the stent.

ing the device distal to the stent once was needed, if possible. Advancing the balloon, may disengage the balloon and stent, and then gentle traction of the entrapped device is a simple and frequently effective technique. Case 2 and Figure 4 show the successful removal of NSE using this method. Second, in cases of severe stent deformation, the device was repeatedly trapped at the stent distal edge every time. Consequently, stent deformation may have progressed significantly. Thus, reconstruction of the deformed stent by balloon dilatation is the primary procedure with which to allow for the safe retrieval of the entrapped device. The NSE will need to be inflated to dilate the deformed stent, which will then permit further attempts at withdrawal. Figure 5 shows successful removal using this method. In the worst case, in which it is impossible to remove the NSE with any method, the patient may require cardiac surgery to extract the trapped device. The clinical outcomes of patients after successful removal of entrapped devices and the reconstruction of deformed stents are relatively good [2].

Limitations of the study

There are some limitations associated with the present study. Firstly, this was a retrospective single-center study that included a small patient population. Thus, selection bias may exist and could have influenced the conclusion. The results need to be confirmed by a larger multicenter study. Secondly, factors concerning different types of DES were not evaluated in the present study. Several bench testing reports have suggested that longitudinal stent compression is associated with stent design; on the other hand, lower resistance does not always correlate with significantly higher crush rates under clinical conditions [9–13]. In the present study, only the SYNERGY stent was used in the bench test. It remains unclear as to whether differences in stent types are related to the mechanism of LSD. Finally, although successfully treated LSD is not usually associated with adverse events at least in the short-term, the long-term clinical outcome remains unknown.

Conclusions

In conclusion, there is a significant potential hazard of distal LSD during post-dilatation when using the NSE balloon due to its characteristic structural features. Considering the aforementioned mechanism and bailout strategies, careful clinical assessment is required to prevent entrapment in the stent platform.

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Conflict of interest: None declared

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Effect of intracoronary adenosine on ergonovine--induced vasoconstricted coronary arteries

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Abstract

Background: *This study aimed to evaluate the effect of adenosine on epicardial coronary artery diameter during ergonovine provocation testing.*

Methods: *A total of 158 patients who underwent an ergonovine provocation test with intracoronary adenosine injection between 2011 and 2014 were selected. Patients were divided into four groups based on the severity of percent diameter stenosis following intracoronary ergonovine administration: Group 1, induced spasm < 50%; Group 2, 50–89%; Group 3, 90–99%; and Group 4, total occlusion.*

Results: *Spasm positivity was observed in 44 (27.8%) cases in the study population (mean age, 57.4 ± ± 10.7 years). Intracoronary adenosine increased the diameter of the ergonovine-induced epicardial artery by 0.51 ± 0.31 mm, 0.73 ± 0.39 mm, 0.44 ± 0.59 mm, and 0.01 ± 0.04 mm in Groups 1, 2, 3, and 4, respectively. Subsequent administration of nitroglycerin further increased vessel diameter by 0.49 ± 0.28 mm, 0.93 ± 0.68 mm, 2.11 ± 1.25 mm, and 2.23 ± 0.69 mm in Groups 1, 2, 3, and 4, respectively. The ratios of adenosine-induced diameter to reference diameter were significantly lower in patients with spasm positive results (0.68 [0.59–0.76] vs. 0.18 [0.00–0.41], $p < 0.001$ in the study population; 0.60 [0.54–0.67] vs. 0.40 [0.27–0.44], $p < 0.001$ in Group 2) with the best cut-off value of 0.505 (sensitivity 0.955, specificity 0.921).*

Conclusions: *Intracoronary administration of adenosine dilated the ergonovine-induced vasoconstricted epicardial coronary artery. The ratio of adenosine-induced diameter to reference diameter was significantly lower in patients with spasm positive results.* (Cardiol J 2019; 26, 6: 653–660)

Key words: ergonovine, adenosine, vasospasm, coronary artery, angina

Introduction

Coronary artery spasm has been recognized as the main pathomechanism for variant angina, as well as acute myocardial infarction and sudden cardiac death in severe cases [1–4]. It has been shown to be correlated with early atherosclerosis and has a higher prevalence in Asian populations than Caucasians [5, 6]. Ergonovine maleate is a weak vasoconstrictor, and induces a vasoconstrictor response in susceptible epicardial coronary arteries. This response is mediated by endothelium-independent smooth muscle hyperconstriction and more pronounced with endothelial dysfunction

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[7, 8]. In patients with confirmed variant angina, ergonovine provocation can induce coronary artery spasm at the same site where spontaneous spasm was observed with high diagnostic sensitivity and specificity [9, 10]. Adenosine is an endogenous neurotransmitter that can be synthesized by de novo purine biosynthesis or produced by degradation of 5'-adenosine triphosphate and 5'-adenosine monophosphate [11, 12]. Its biologic effects include inhibition of platelet aggregation, modulation of the inflammatory response, negative chronotropic and dromotropic effects, and induction of coronary vasodilation, predominantly affecting microvessels < 150 μm in diameter [13]. Due to its potent vasodilator effect in coronary microvessels, it has been the most widely used drug to achieve hyperemia while measuring fractional flow reserve (FFR) in the coronary artery bed. However, the effect of adenosine on the ergonovine-induced vasoconstricted epicardial coronary artery has not been elucidated. The purpose of this study was to investigate the response of ergonovine-induced vasoconstricted epicardial coronary artery to adenosine and to clarify the suitability of FFR measurement using intracoronary adenosine on that vasocontricted epicardial coronary artery.

Methods

Study population

From June 2011 to June 2014, the spasm provocation test with selective intracoronary injection of ergonovine was performed in 464 patients deemed to have variant angina. When a spasm was induced, adenosine administration into the spasm-induced coronary artery has been recommended routinely since 2011. A total of 158 patients who received intracoronary adenosine during the provocation test were identified and analyzed retrospectively. Informed consent for the test using both ergonovine and adenosine was obtained from each patient, and the study was approved by the Institutional Review Board of the hospital.

Ergonovine provocation test

The left coronary artery (LCA) and the right coronary artery (RCA) were provoked to spasm according to a standard manner recommended by the Japanese Circulation Society [14, 15]. Calcium antagonists, long-acting nitrates, and nicorandil were discontinued at least 48 h before the provocation test, except for as needed sublingual nitroglycerin.

Baseline coronary angiography was obtained with a 5-French (Fr) catheter via the femoral or radial artery (57 cases), which have been the default access points since 2012. The provocation test was performed when there was no significant stenosis (> 75% luminal narrowing). Stepwise doses of methylerogometrine maleate (ER) (Daewon Pharm, Seoul, Korea) were selectively administered into the LCA (10, 20, and 20 μg) and RCA (10, 10, and 20 μg) with 3-min intervals between each dose. RCA spasm provocation was initiated after a 5-min washout period following LCA provocation. Coronary angiograms were obtained with each ER administration or when chest pain and/or ST-segment changes occurred. A selective dose of adenosine, 60 μg for the LCA and 40 μg for the RCA corresponding to the standard dose for FFR measurement, was injected into the coronary artery which had the maximum induced spasm and was followed by repeated coronary angiogram [16]. Intracoronary nitroglycerin was then administered until the spasm was entirely relieved and final coronary angiogram was performed.

A positive response was defined as transient greater than 90% diameter stenosis on coronary angiography, regardless of symptoms or sign of ischemia, or greater than 70% diameter stenosis with ischemic electrocardiography (ECG) changes and/or chest pain.

Quantitative angiographic analysis

End-diastolic cineframes in the same projection were selected and analyzed separately by two independent investigators using QCA software (Xcelera, Philips Medical Systems, the Netherlands). The coronary artery luminal diameter was measured in millimeters using a contrast-filled catheter as the calibration source. The most severely narrowed segment was termed the spasm segment and its diameter in response to ER, adenosine, and nitroglycerin were termed $Diameter_{ER}$, $Diameter_{Ade}$, and $Diameter_{Nit}$, respectively. When control angiograms of the LCA were obtained after a full-dose provocation of the RCA, the diameter was noted as $Diameter_{Control}$. Reference diameter ($Diameter_{Ref}$) was defined as the average of the diameter of the nearest normal-looking segments before and after the spasm segment. The degree of induced spasm was calculated as $[1 - (Diameter_{ER} / /Diameter_{Ref})] \times 100$ and noted as %Spasm. The differences in diameter between $Diameter_{ER}$ and $Diameter_{Ade}$, and between $Diameter_{Nit}$ and $Diameter_{Ade}$ were noted as ΔAdenosine and ΔNitroglycerin, respectively. The sum of the change in diameter between $Diameter_{ER}$ and $Diameter_{Nit}$ was calculated as $\Delta Sum = Diameter_{Nit} - Diameter_{ER}$.

Statistical analysis

For the purpose of this study, patients were categorized into four groups according to the %Spasm as follows: Group 1, 0–50%; Group 2, 50–90%; Group 3, 90–99%; Group 4, total occlusion. The normality of continuous data was tested using the Kolmogorov-Smirnov test. Skewed variables were analyzed after logarithmic or power transformation, accordingly. Continuous variables are expressed as the mean ± standard deviation (SD) or median (interquartile range) and assessed with the Student t-test or Mann-Whitney U test. Within-group comparisons were performed with repeated measures analysis of variance (ANOVA) with post hoc analysis using Bonferroni corrections. Comparison of the mean values among groups was made using one-way ANOVA. Trends were assessed using the linear-by-linear association χ^2 test or the linear term in ANOVA. Categorical variables are presented as frequencies and compared using the Fisher exact probability test. The receiver-operating curve was created to draw the best cut-off value of the ratio of $Diameter_{Ade}$ / /$Diameter_{Ref}$ and discriminate the result of the spasm test. Correlations between variables were tested using linear regression analysis. Multivariate linear regression analysis was applied to identify the predictors for the $Diameter_{Ade}$ / $Diameter_{Ref}$ ratio. Statistical significance was defined as $p < < 0.05$. All statistical calculations were performed using the SPSS software version 17.0 (IBM SPSS Inc., Chicago, IL).

Results

Clinical characteristics

A total of 158 patients were included in the study and categorized into the following four groups: Group 1, 50 (32.9%) patients; Group 2, 82 (51.9%) patients; Group 3, 9 (5.7%) patients; and Group 4, 15 (9.5%) patients. The mean age was 57.4 ± 10.7 years without significant differences among groups (Table 1). There was a tendency for increasing male population ($p < 0.001$) and current smoking ($p = 0.037$) from Groups 1–4. No significant difference was seen in the incidence of diabetes mellitus, hypertension, hyperlipidemia and clinical presentations between groups.

Methylerogometrine maleate provocation test was performed via the radial artery in 57 (36.1%) and femoral artery in 101 (63.9%) patients (Table 2). Overall, 44 (27.8%) patients had a positive response. There were no provocation-related adverse events including death, myocardial infarction, stroke, or bleeding that required a procedure or transfusion. There was 1 case of contrast allergy, and 3 cases of self-limiting and transient bradycardia in response to adenosine.

Changes in vessel diameter

The investigated vessels were the left anterior descending artery (LAD) and its branches in 60 (38.0%) patients, left circumflex artery (LCX) and its branches in 12 (7.6%), RCA and its branches in 82 (51.9%), and left main in 4 (2.5%) patients. Two representative cases are depicted in Figure 1. The cumulative dose of injected ER was significantly lower in Groups 3 and 4, compared with the other groups. Although $Diameter_{Ref}$ was similar between groups, $Diameter_{ER}$, $Diameter_{Ade}$, and $Diameter_{Nit}$ progressively decreased from Group 1 to Group 4.

Adenosine was administered into the same coronary artery immediately after the angiogram of the last dose of ER in 114 cases (32 LCA, 82 RCA). In the remaining 44 cases, adenosine was injected into the LCA after a full provocation of the RCA, where control angiograms of the LCA revealed an increase in diameter of the vessel ($Diameter_{ER}$, 1.65 ± 0.75 mm; $Diameter_{Control}$, 1.90 ± 0.75 mm). Adenosine further dilated the vessel ($Diameter_{Ade}$, 2.31 ± 0.76 mm), but lesser than $Diameter_{Nit}$ (2.82 ± 0.82 mm) in those patients. Overall, the increase in diameter with adenosine (ΔAdenosine) progressively decreased from Group 1 to Group 4, but the amount by nitroglycerin (ΔNitroglycerin) did vice versa. Adenosine did not increase the vessel diameter in Group 4 ($Diameter_{ER}$, 0.00 ± 0.00; $Diameter_{Ade}$, 0.01 ± 0.04, paired t-test $p = 0.334$).

Adenosine response based on test results

All patients in Group 3 and 4 had spasm positive results using the angiographic definition, while 20 (24.5%) had spasm positive results in Group 2. There was a significant increase in diameter following adenosine and nitroglycerine injection regardless of the result of the spasm test. Overall, there was a significant interaction between the pattern of diameter increase and the test result ($n = 158$; $F [1.597, 249.1] = 77.271$; $p < 0.001$) (Fig. 2A). There was a greater increase in diameter following adenosine injection (ΔAdenosine) in those with spasm negative results, than in those with spasm positive results (0.64 ± 0.36 vs. 0.41 ± ± 0.50, $p = 0.002$). The increase in diameter following nitroglycerine (ΔNitroglycerin) was significantly greater in those with spasm positive results than those with spasm negative results (1.84 ± 0.98 vs.

Table 1. Demographic and laboratory characteristics.

	Group 1 (n = 50)	Group 2 (n = 82)	Group 3 (n = 9)	Group 4 (n = 15)	Total (n = 158)	P
Age [years]	56.7 ± 11.7	58.1 ± 10.9	60.0 ± 7.0	54.7 ± 7.6	57.4 ± 10.7	0.569
Male	23 (44.2%)	52 (63.4%)	7 (77.8%)	14 (93.3%)	96 (60.8%)	0.002
BMI [kg/m^2]	23.6 (21.5–25.5)	24.5 (23.1–26.5)	25.1 (23.1–28.8)	23.4 (22.4–26.0)	24.1 (22.5–26.3)	0.232
Hypertension	17 (32.7%)	31 (37.8%)	7 (77.8%)	5 (33.3%)	60 (38.0%)	0.090
Diabetes mellitus	5 (9.6%)	12 (14.6%)	2 (22.2%)	4 (26.7%)	23 (14.6%)	0.265
Hyperlipidemia	35 (67.3%)	46 (56.1%)	5 (55.6%)	8 (53.3%)	94 (59.5%)	0.551
Current smoking	9 (17.3%)	28 (34.1%)	6 (66.7%)	5 (33.3%)	48 (30.4%)	0.014*
Chest pain	41 (78.8%)	62 (75.6%)	9 (100.0%)	13 (86.7%)	125 (79.1%)	0.393
CCS grade 3 and 4	25 (48.1%)	41 (50.0%)	4 (44.4%)	10 (66.7%)	80 (50.6%)	0.619
Syncope	4 (7.7%)	11 (13.4%)	0 (0.0%)	0 (0.0%)	15 (9.5%)	0.370
Post CPR	1 (1.9%)	1 (1.2%)	1 (11.1%)	1 (6.7%)	4 (2.5%)	0.142
SBP [mmHg]	127.7 ± 21.0	124.4 ± 17.1	125.3 ± 27.7	122.5 ± 16.3	125.3 ± 19.0	0.718
HR [bpm]	71.7 ± 16.0	73.7 ± 13.2	69.3 ± 16.1	69.5 ± 10.4	72.4 ± 14.1	0.595
TC [mg/dL]	197.3 ± 33.5	181.1 ± 39.0	168.9 ± 30.0	190.7 ± 69.3	186.6 ± 41.2	0.080
Cr [mg/dL]	0.71 (0.65–0.88)	0.82 (0.68–0.97)	0.88 (0.72–1.05)	0.80 (0.67–0.89)	0.80 (0.66–0.94)	0.229
Hb [g/dL]	12.8 ± 2.5	13.7 ± 1.6	15.0 ± 1.6	14.6 ± 1.3	13.6 ± 2.0	0.001
hsCRP [mg/dL]	0.06 (0.03–0.17)	0.08 (0.02–0.25)	0.14 (0.03–0.22)	0.09 (0.03–0.37)	0.08 (0.03–0.22)	0.836

Values are mean ± standard deviation or median (interquartile range) or number (percentage). *P value for trend was < 0.05. BMI — body mass index; CCS — Canadian Cardiovascular Society; CPR — cardiopulmonary resuscitation; SBP — systolic blood pressure; HR — heart rate; TC — total cholesterol; Cr — creatinine; Hb — hemoglobin; hsCRP — high sensitivity C-reactive protein

Table 2. Angiographic characteristics.

	Group 1 (n = 50)	Group 2 (n = 82)	Group 3 (n = 9)	Group 4 (n = 15)	Total (n = 158)	P
Spasm positive	0 (0.0%)	20 (24.4%)	9 (100%)	15 (100%)	44 (27.8%)	< 0.001
Radial approach	15 (28.8%)	27 (32.9%)	6 (66.7%)	9 (60.0%)	57 (36.1%)	0.031*
Investigated vessel						
LAD and subbranches	15 (28.8%)	35 (42.7%)	1 (11.1%)	9 (60.0%)	60 (38.0%)	0.038
LCX and subbranches	3 (5.8%)	5 (6.1%)	2 (22.2%)	2 (13.3%)	12 (7.6%)	0.185
RCA and subbranches	31 (59.6%)	41 (50.0%)	6 (66.7%)	4 (26.7%)	82 (51.9%)	0.121
Left main	3 (5.8%)	1 (1.2%)	0 (0.05)	0 (0.0%)	4 (2.5%)	0.536
Cumulative dose of ergonovine [μg]	90 (90–90)	90 (90–90)	60 (40–90)	30 (10–55)	90 (90–90)	< 0.001
$Diameter_{Ref}$ [mm]	3.46 ± 0.74	3.49 ± 0.78	3.49 ± 0.89	3.14 ± 0.79	3.45 ± 0.77	0.455
$Diameter_{ER}$ [mm]	2.14 ± 0.56	1.12 ± 0.42	0.29 ± 0.09	0.00 ± 0.00	1.30 ± 0.82	< 0.001*
$Diameter_{Ade}$ [mm]	2.66 ± 0.66	1.85 ± 0.57	0.73 ± 0.61	0.01 ± 0.04	1.88 ± 0.97	< 0.001*
$Diameter_{Nit}$ [mm]	3.14 ± 0.76	2.77 ± 0.77	2.84 ± 0.99	2.25 ± 0.67	2.86 ± 0.81	0.001*
$Diameter_{Ade}/Diameter_{Ref}$	0.76 ± 0.09	0.54 ± 0.15	0.22 ± 0.20	0.01 ± 0.02	0.55 ± 0.26	< 0.001*
ΔAdenosine [mm]	0.51 ± 0.31	0.73 ± 0.39	0.44 ± 0.59	0.01 ± 0.04	0.58 ± 0.42	< 0.001*
ΔNitroglycerin [mm]	0.49 ± 0.28	0.93 ± 0.68	2.11 ± 1.25	2.23 ± 0.69	0.97 ± 0.83	< 0.001*
ΔSum [mm]	1.00 ± 0.42	1.66 ± 0.70	2.55 ± 0.96	2.25 ± 0.67	1.54 ± 0.78	< 0.001*

Values are mean ± standard deviation or median (interquartile range) or number (percentage).*P value for trend was < 0.05. LAD — left anterior descending artery; LCX — left circumflex artery; RCA — right coronary artery

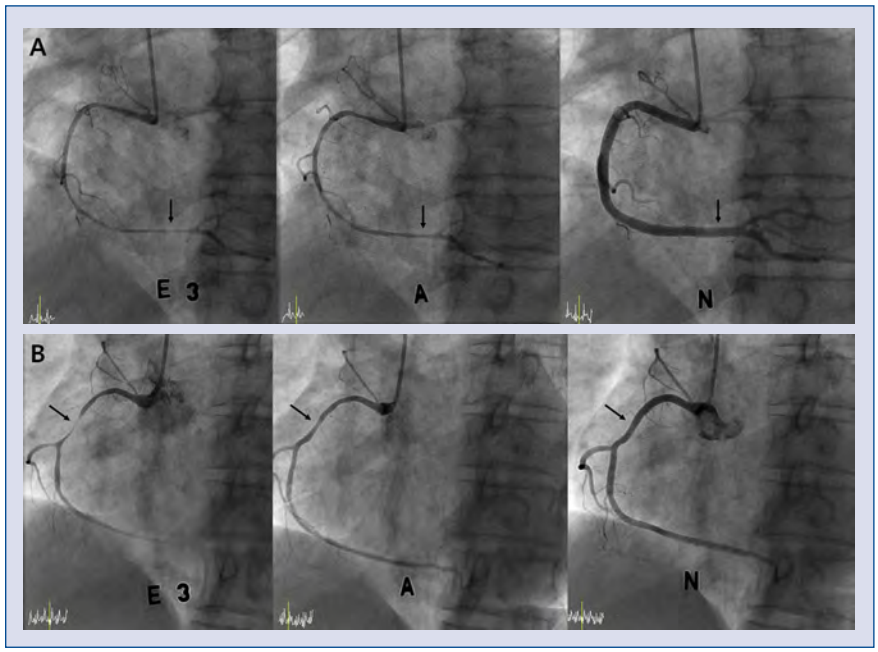

Figure 1. Coronary angiogram of representative cases. **A.** The sequential coronary angiogram of the right coronary artery (RCA) of an 82-year-old male. Intracoronary injection of ergonovine provokes spasm in the distal part of the RCA with a diameter of 0.60 mm (85% stenosis, arrow). Intracoronary administration of adenosine dilates it to a diameter of 0.88 mm. A full vasodilation is achieved by nitroglycerine injection and the calculated reference vessel diameter is 3.92 mm resulting in the ratio of $Diameter_{ade}$ to $Diameter_{ref}$ of 0.23; **B.** The sequential coronary angiogram of the RCA of a 59-year-old female. The induced spasm is noted in the middle segment of the RCA (91% stenosis, arrow). Intracoronary administration of adenosine dilated it to a diameter of 1.84 mm with the ratio of $Diameter_{Ade}$ to $Diameter_{Ref}$ of 0.67.

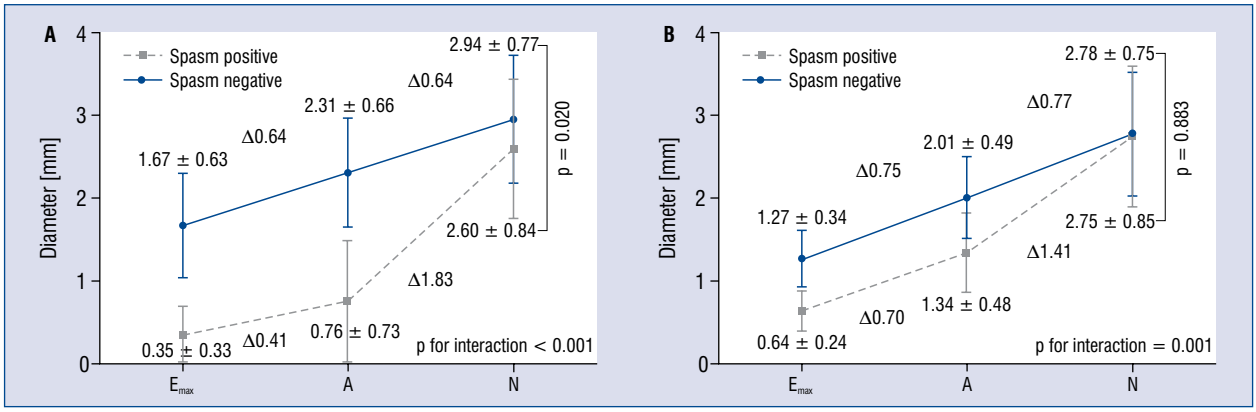

Figure 2. Mean diameter changes after ergonovine, adenosine, and nitroglycerin administration. **A.** Mean diameter changes in response to a maximum dose of ergonovine (E_{max}), adenosine (A), and nitroglycerin (N) according to the result of a spasm test in the overall study population; **B.** Mean diameter changes in response to the agents, respectively, in Group 2 (induced spasm between 50% and 90%); p values for interaction between the groups with negative and positive results.

0.64 ± 0.44, $p < 0.001$). There was also a significant interaction between diameter changes and the test results in Group 2 (F [1.567, 125.323] = 11.877, $p < 0.001$) (Fig. 2B). The ΔAdenosine of those with spasm negative results and with spasm positive results were similar (0.75 ± 0.37 vs. 0.70 ± ± 0.46, $p = 0.648$). However, the ΔNitroglycerin was significantly greater in those with spasm positive results than in those with spasm negative results (0.77 ± 0.51 vs. 1.41 ± 0.89, $p < 0.001$).

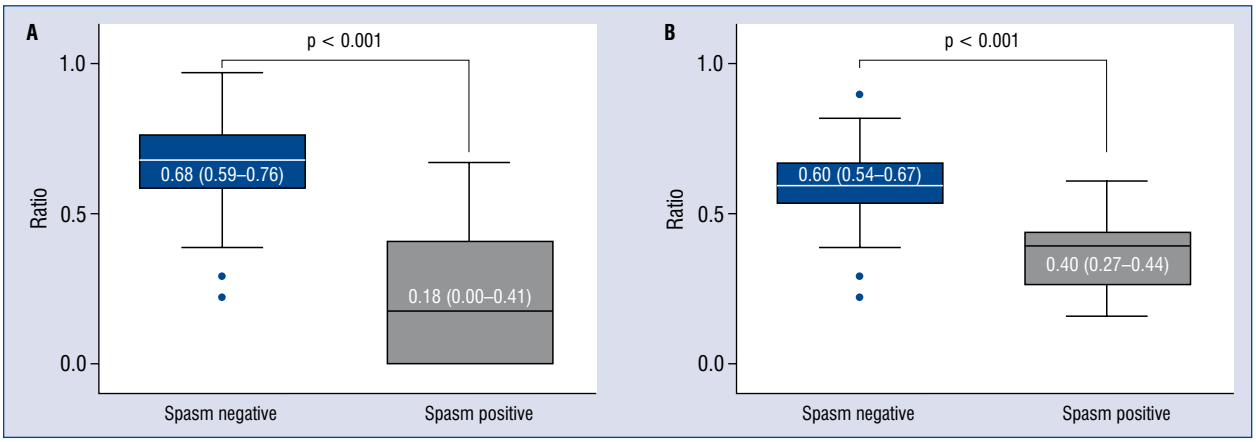

Figure 3. Box plot for the ratio of $Diameter_{Ade}$ to $Diameter_{Ref}$. **A.** Ratio of vessel diameter in response to adenosine injection ($Diameter_{Ade}$) to diameter of the reference vessel ($Diameter_{Ref}$) according to the test result in the overall study population; **B.** Ratio of $Diameter_{Ade}$ to $Diameter_{Ref}$ in Group 2 (induced spasm between 50% and 90%). Values are presented with median (interquartile range); p values are derived by Mann-Whitney U test.

Ratio of $Diameter_{Ade}$ to $Diameter_{Ref}$

Compared with the reference vessel diameter or the ratio of $Diameter_{Ade}$ to $Diameter_{Ref}$, vessel diameter after adenosine injection was significantly smaller in patients with spasm positive results than in those with negative results in the overall study population (median, 0.18 vs. 0.68, $p < 0.001$) (Fig. 3A). A similar trend was seen for the ratio in Group 2 (median, 0.40 vs. 0.60, $p < 0.001$) (Fig. 3B). The best cut-off value for the prediction of a spasm positive result was 0.505, with a sensitivity of 96% and specificity of 92% (Fig. 4). Multivariate linear regression analysis found that current smoking (odds ratio [OR] 0.219; confidence interval [CI] 0.047–0.390) and drinking alcohol (OR 0.095; CI 0.033–0.157) were significantly associated with a $Diameter_{Ade}$ to $Diameter_{Ref}$ ratio less than 0.505, after adjusting for age, sex, investigated vessel, HbA1c, and high sensitivity C-reactive protein.

According to available research, this is the first study investigating the effect of adenosine on ER-induced constricted coronary arteries in humans. It was demonstrated that: 1) intracoronary administration of adenosine dilated the ER-induced constricted coronary artery; 2) this effect was not observed in the completely occluded coronary artery in response to ER; 3) the vessel diameter after adenosine administration and its ratio to the reference vessel diameter were significantly smaller in patients with spasm positive results than in those with spasm negative results; and 4) the ratio cut-off value of 0.505 had a high sensitivity (96%) and high specificity (92%) in the prediction of a spasm positive result.

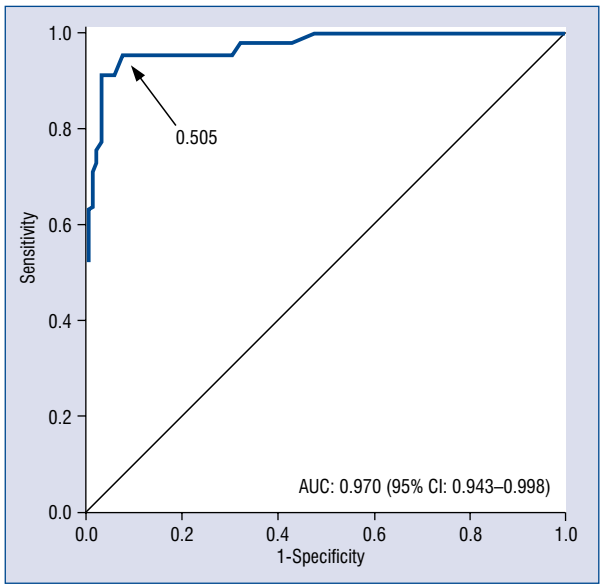

Figure 4. Receiver operating characteristics curve for $Diameter_{Ade}/Diameter_{Ref}$ for the result of spasm positive. A ratio of vessel diameter in response to adenosine injection ($Diameter_{Ade}$) to the diameter of the reference vessel ($Diameter_{Ref}$) of 0.505 best predicts a positive spasm result with a sensitivity of 96% and specificity of 92%; AUC — area under curve; CI — confidence interval.

Discussion

Coronary blood flow is regulated via changes in vessel diameter, and vascular resistance of the coronary arteries adjusts to meet the demands for myocardial oxygen [13, 17]. This intrinsic ability

of the heart is called autoregulation. It occurs over a wide range of coronary perfusion pressures, primarily mediated by metabolic, myogenic, and endothelial mechanisms [18]. Autoregulatory dilation occurs substantially in small coronary arterioles with diameters less than 150 μm, which are the major site of action of adenosine. Adenosine is a purine nucleoside produced naturally in myocardial cells from the breakdown of adenosine triphosphate during myocardial ischemia [13]. This dilation of small coronary arterioles reduces vascular resistance and decreases the pressure of upstream vessels, followed by vasodilation of larger arterioles and small arteries (140–300 μm diameter), resulting in an increase in coronary blood flow [17, 19]. The question is how the large epicardial coronary artery reacts toan increased blood flow. Shiode et al. [20] demonstrated that adenosine infusion (100 μg/min) via a 3-Fr infusion catheter settled in the middle segment of LAD increased coronary blood flow by +399% in 12 patients with angiographically normal coronary arteries. The proximal segment of LAD, where there was no direct contact with infused adenosine, had a larger diameter by 9.2% in response to blood flow augmentation [20]. This phenomenon is explained by flow-dependent coronary dilation. Lupi et al. [21] further validated epicardial coronary artery vasodilation with intracoronary adenosine infusion in 24 patients with angiographically normal coronary arteries. The increase in coronary diameter strongly correlated with peak coronary blood flow velocity in response to adenosine infusion, suggesting that the phenomenon was caused by a flow-mediated mechanism rather than a direct effect of adenosine [21]. A similar result was obtained with dipyridamole, which dilates epicardial coronary arteries indirectly by inhibiting intramyocardial adenosine re-uptake, provided supportive evidence of a flow-mediated mechanism. Drexler et al. [22] observed flow-dependent epicardial coronary artery dilation using papaverine. However, that response was significantly reduced in the coronary arteries with non-flow-limiting atherosclerosis, suggesting that endothelial function was involved [22]. It has been recognized that flow stimulation induces the endothelium to release endogenous vasodilators including nitric oxide, which subsequently dilates coronary arteries [23, 24]. This mechanism was supported by an observation that such flow-mediated dilation was abolished by removing the endothelium [25]. We found that intracoronary-administered adenosine dilated the epicardial coronary artery that had been vasoconstricted by ER. However, adenosine did not dilate a completely occluded epicardial coronary artery in cases where adenosine could not reach the microvessels that it acted upon to induce flow augmentation. This result supports the theory that the dilation of epicardial coronary artery is induced by a flow-dependent and endothelial mechanism rather than a direct local effect of adenosine on the epicardial artery. The response was hampered in patients with spasm positive results. Researchers previously reported that healthy endothelial function render the epicardial coronary artery more resilient to vasospasm by producing nitric oxide [26]. This data may explain the hampered response to adenosine which was observed in the patients studied herein. Furthermore, we may posit that patients with poor adenosine response, based on a $\text{Diameter}_{\text{Ade}}$ to $\text{Diameter}_{\text{Ref}}$ ratio less than 0.50, are be more prone to vasospasm.

According to the Japanese Circulation Society, a positive finding on coronary angiography is defined as a transient, total or sub-total occlusion (> 90% stenosis) of the coronary artery [15]. However, a sizable number of patients have significant transient occlusion (> 50% stenosis), but do not meet this criterion. In this study, 24.4% of patients in Group 2 (50–90% stenosis) had a spasm positive result with definite ischemic ECG change. In a clinical context, a poor response of spasm-induced epicardial coronary artery to intracoronary adenosine would be a marker for vasospasm severity. It may also be an adjunctive marker to discriminate patients with vasospasm angina from those without vasospasm when ergonovine provocation shows intermediate response.

Limitations of the study

Several limitations are acknowledged in the present study. First, coronary blood flow and intracoronary pressure was not measured directly. However, it was reasonable to assume that flow would increase and pressure decrease after adenosine injection, as shown in previous studies. Second, a small number of patients were enrolled from an Asian population at a single center. Therefore, results should be confirmed in larger studies with a more diverse population. Nevertheless, the present findings add to an understanding of coronary dynamics in vasospasm.

Conclusions

The present study found that intracoronary administration of adenosine dilated the ergonovine-induced vasoconstricted epicardial coronary artery.

However, this was not the case in a completely occluded coronary artery with induced vasospasm, suggesting that dilation was endothelial-dependent and flow-mediated. Adenosine by itself does not adequately dilate the epicardial arteries. This is of note especially during FFR manipulation and measurement, where nitroglycerin should not be overlooked.

Conflict of interest: None declared

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Comparative effectiveness of torasemide versus furosemide in symptomatic therapy in heart failure patients: Preliminary results from the randomized TORNADO trial

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Abstract

Background: *Recent reports suggest that torasemide might be more beneficial than furosemide in patients with symptomatic heart failure (HF). The aim was to compare the effects of torasemide and furosemide on clinical outcomes in HF patients.*

Methods: *This study pilot consisted of data from the ongoing multicenter, randomized, unblinded endpoint phase IV TORNADO (NCT01942109) study. HF patients in New York Heart Association (NYHA) II–IV class with a stable dose of furosemide were randomized to treatment with equipotential dose of torasemide (4:1) or continuation of unchanged dose of furosemide. On enrollment and control visit (3 months after enrollment) clinical examination, 6-minute walk test (6MWT) and assessment of fluid retention by ZOE Fluid Status Monitor were performed. The primary endpoint was a composite of improvement of NYHA class, improvement of at least 50 m during 6MWT and decrease in fluid retention of at least 0.5 Ω after 3-months follow-up.*

Results: *The study group included 40 patients (median age 66 years; 77.5% male). During follow-up 7 patients were hospitalized for HF worsening (3 in torasemide and 4 in furosemide-treated patients). The primary endpoint reached 15 (94%) and 14 (58%) patients on torasemide and furosemide, respectively ($p = 0.03$).*

Conclusions: *In HF patients treated with torasemide fluid overload and symptoms improved more than in the furosemide group. This positive effect occurred already within 3-month observation.* (Cardiol J 2019; 26, 6: 661–668)

Key words: heart failure, hospitalization, loop diuretics, prognosis, symptoms

Introduction

Heart failure (HF) is one of the leading cardiovascular problems in Europe, with a prevalence of 1–2% in the adult population in developed countries [1]. Despite an intensive delivery of healthcare and education to affected patients, its incidence continues to increase, resulting in 50% or greater mortality in a 5-year observation [1]. Loop diuretics are cornerstone in the treatment of signs of

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fluid overload and congestion in patients with HF. Despite rapid relief of symptoms in patients with acute decompensated HF, long-term use of these agents has been consistently associated with adverse events, including electrolyte disturbance, activation of the renin–angiotensin–aldosterone and the sympathetic nervous systems (RAAS and SNS), which could accelerate HF progression [2, 3].

Torasemide and furosemide are representatives of loop diuretics with an identical diuretic mechanism, but different pharmacokinetic properties and additional effects. Compared to furosemide, torasemide has greater bioavailability, a higher degree of protein binding, and a longer half-life. These properties make that torasemide works faster, longer and less frequently causes rapid micturition than furosemide. Torasemide after oral administration is well absorbed from the gastrointestinal tract, even in overhydration caused by heart, kidney and liver diseases. Moreover, torasemide potency is 4 times greater than furosemide. Torasemide also has anti-aldosterone activity and inhibits myocardial fibrosis and remodeling [4–8]. According to previous studies, torasemide decreases rates of HF hospitalizations and hospital stay, improves exercise tolerance, quality of life, left ventricular function, cardiac sympathetic nerve activity, myocardial fibrosis, pulmonary congestion, peripheral edema, and blood pressure compared with furosemide [9–12]. These favorable effects of torasemide suggest that this agent would be more beneficial than furosemide in patients with HF.

The main purpose of the present study was comparison of the furosemide with torasemide's effects on HF symptoms, including New York Heart Association (NYHA) class, fluid retention and exercise tolerance in patients with HF.

Methods

Study design

This pilot study consisted of data from the ongoing multicenter, randomized, open, phase IV TORNADO (TORasemide oN hemodynAmic and Neurohormonal Stress, and carDiac remOdeling in Heart Failure) study, registered in ClinicalTrials.gov: NCT01942109. The study was approved by a local ethical review board and an informed consent was obtained from each patient. The detailed methods and description of the study design have been described previously [13]. Briefly, the study included patients who were hospitalized in years 2015–2018 in two cardiology centers in Poland, including academic center and a district hospital. All patients were diagnosed with HF in NYHA II–IV class, irrespective of left ventricular ejection fraction (LVEF) and treated with optimal HF therapy. The diagnosis of HF, according to current guidelines [1], was based on clinical (typical HF signs and symptoms), echocardiographic and biochemical (increased concentrations of N-terminal pro-B-type natriuretic peptide [NT-proBNP] or BNP parameters). All demographic, clinical, etiology of HF, laboratory data, as well as information on medication, were collected.

Heart failure patients on a stable dose of furosemide were randomized to the treatment with torasemide or unchanged treatment with furosemide (randomization 1:1). After randomization, furosemide has been continued in its current fixed-dose or was replaced by equipotential dose of torasemide (4:1, according to the previous studies and manufacturer's data [6]). Figure 1 shows the flow chart of the study design.

Study endpoints

During the baseline hospitalization and on control visit (3 months after enrollment) echocardiographic examination and 6-minute walk test (6MWT) were performed. To assess the level of fluid retention, measurement of thoracic base impedance was made using ZOE Fluid Status Monitor. The device works in line with principle: the less resistance — impedance measured in ohms — the more fluid is in the chest.

In the current analysis the primary endpoint was a composite of improvement of NYHA functional class, improvement of at least 50 m during 6MWT, and decrease of at least 0.5 Ω in fluid retention after 3 months from recruitment. Different composite endpoint compared to the initially registered endpoints (i.e. events associated with HF — deaths, hospitalization) was purposely chosen because of low patient number and one-time functional assessment at 3-month follow up.

Statistical analysis

Continuous and ordinal variables are expressed as a median (interquartile range). Categorical data were presented as a number of patients and percentages. Group comparisons were performed using the Fisher exact test for qualitative variables and t test for quantitative, normally distributed variables, and the Mann-Whitney U test for quantitative, non-normally distributed variables (normality of distribution was checked with the Shapiro-Wilk test). For all analyses, a p value of less than 0.05 was considered statistically significant.

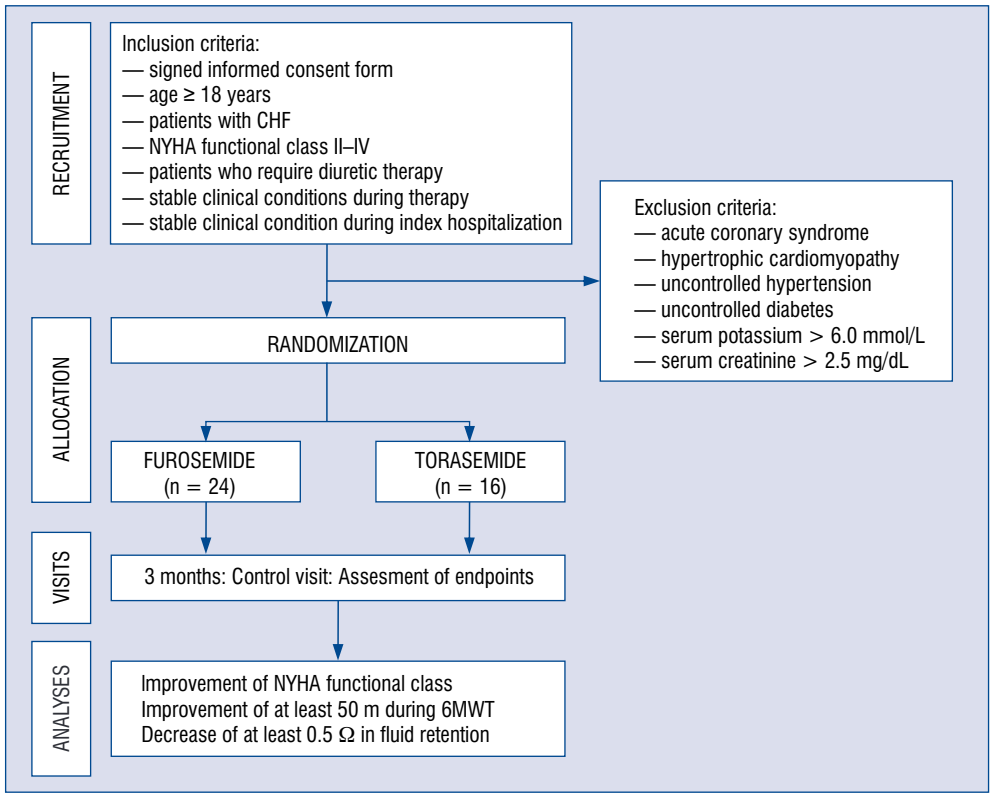

Figure 1. Flow chart of patient enrollment in the study; CHF — congestive heart failure; NYHA — New York Heart Association; 6MWT — six-minute walking test.

Results

Baseline characteristics

The current analysis of the TORNADO study included 40 patients. During hospitalization, 60% of them (n = 24) were randomized to further treatment with furosemide and 40% (n = 16) to treatment with torasemide. Median age of the study group was 66 years and 77.5% were male. Mean diuretic dose (converted in a ratio of 4:1 on furosemide dose) was 100 mg and 70 mg in the furosemide and torasemide groups, respectively (p = 0.16). Most common etiology of HF was ischemic heart disease (50%). Patients in the torasemide and furosemide groups were similar in terms of age, gender, chronic diseases, NYHA class, LVEF, heart rate, systolic blood pressure, laboratory findings (serum concentrations of hemoglobin, creatinine, sodium, potassium, NT-proBNP), HF recommended pharmacotherapy (angiotensin converting enzyme inhibitor, angiotensin receptor blocker, beta-blocker, mineralocorticoid receptor blocker) and implantable devices (pacemaker, cardiac resynchronization therapy, cardioverter defibrillator). Baseline characteristics of both study groups are presented in Table 1.

Follow-up admission

Patients completed 3-months follow-up. During the follow-up 7 patients were hospitalized for HF worsening (3 vs. 4 in torasemide and furosemide groups, respectively). The primary endpoint reached 15 (94%) patients of the torasemide group and 14 (58%) patients of the furosemide group (p = 0.03). The changes in NYHA functional class, 6MWT and ZOE Fluid Status Monitor test from baseline to the end of follow-up are presented in the Table 2 and Figures 2–4. During follow-up period, an equal percentage of patients treated with furosemide and torasemide reached primary endpoint in the NYHA class improvement form. Torasemide-treated patients were more often, but not statistically significant, observed to reach primary endpoint as improvement of at least 50 m during 6MWT (n = 0.09) or decrease of at least 0.5 Ω in fluid retention during 3 months as compared to patients on furosemide (n = 0.51). These results reflect a significant decrease in fluid retention and improvement in 6MWT in the whole torasemide group as compared to whole furosemide group in which increase in fluid retention and deterioration in 6MWT was observed.

Table 1. Comparison of 40 patients with heart failure treated with furosemide or torasemide.

Parameter	All patients (n = 40)	Furosemide (n = 24)	Torasemide (n = 16)	P
Demographics				
Age [years]	66 [51–81]	65 [58–80]	74 [49–85]	0.29
Gender [male]	31 (77.5)	20 (83.3)	11 (68.8)	0.28
Body mass index [kg/m^2]	30 [23–39]	30 [24–39]	30 [20–38]	0.51
Heart failure				
Symptoms of HF at admission	12 (30.0)	6 (25.0)	6 (37.5)	0.40
Previous HF hospitalization	25 (62.5)	16 (67.7)	9 (56.3)	0.51
Heart failure etiology:				
Ischemic	20 (50.0)	12 (50.0)	8 (50.0)	1.00
Hypertensive	5 (12.5)	2 (8.3)	3 (18.8)	0.33
Dilated cardiomyopathy	7 (17.5)	5 (20.8)	2 (12.5)	0.50
Valve disease	2 (5.0)	2 (8.3)	0 (0.0)	0.24
NYHA [class]	2 [2–3]	2 [2–3]	2 [2–3]	0.94
Ejection fraction [%]	37 [27–52]	35 [29–47]	38 [24–54]	0.93
Medical history				
Smoking	20 (50.0)	13 (54.2)	7 (43.8)	0.52
Ischemic heart disease	19 (47.5)	11 (45.8)	8 (50.0)	0.80
Previous CABG/PCI	17 (42.5)	12 (50.0)	5 (31.3)	0.24
Hypertension	23 (57.5)	14 (58.3)	9 (50.0)	0.896
Diabetes	18 (45.0)	12 (50.0)	6 (37.5)	0.44
Dyslipidemia	18 (45.0)	12 (50.0)	6 (37.5)	0.44
Atrial fibrillation	17 (42.5)	9 (37.5)	8 (50.0)	0.58
Cardiac electronic implantable device	17 (42.5)	9 (37.5)	8 (50.0)	0.58
Stroke/TIA	2 (5.0)	2 (8.3)	0 (0.0)	0.27
Peripheral vascular disease	5 (12.5)	3 (12.5)	2 (12.5)	1.00
Chronic kidney disease	14 (35.0)	9 (37.5)	5 (31.3)	0.08
Clinical status				
Heart rate [bpm]	75 [60–100]	75 (18.5)	80 [60–100]	0.95
Systolic BP [mmHg]	135 [110–160]	135 [116–160]	133 [100–150]	0.29
Diastolic BP [mmHg]	78 [64–101]	80 [70–101]	70 [60–80]	0.07
Laboratory findings				
NT-proBNP [pg/mL]	1681 [483–5902]	2106 [656–7032]	1273 [374–5435]	0.30
Sodium concentration [mmol/L]	141 [137–146]	141 [137–146]	141 [138–144]	0.56
Potassium concentration [mmol/L]	4.4 [3.9–4.9]	4.5 [3.9–4.9]	4.4 [3.9–4.9]	0.86
Creatinine concentration [mg/dL]	1.3 [0.9–1.8]	1.3 [1.0–1.9]	1.2 [0.7–1.6]	0.10
Pharmacotherapy				
Beta-blocker	34 (89%) N = 38	22 (96%) N = 23	14 (93%) N = 15	0.76
ACEI	26 (68) N = 38	17 (74) N = 23	9 (60) N = 15	0.37
Angiotensin receptor blocker	7 (18) N = 38	2 (8.7) N = 23	5 (33) N = 15	0.06
Aldosterone antagonist	23 (61) N = 38	15 (65) N = 23	9 (60) N = 15	0.75

Values are showed as median (interquartile range) or number (percentage); ACEI — angiotensin-converting enzyme inhibitor; BP — blood pressure; CABG — coronary artery bypass grafting; HF — heart failure; PCI — percutaneous coronary intervention; TIA — transient ischemic attack

Table 2. Changes in the components of the primary from baseline to the end of 3-month follow-up.

Variable	Furosemide			Torasemide		
	On admission	3-month follow up	P	On admission	3-month follow up	P
ZOE® Fluid Status Monitor [Ohm]	17 (15–24)	18 (15–23)	0.68	18 (15–24)	17 (15–19)	0.05
NYHA class	3 (2–3)	2 (1–3)	0.37	3 (2–4)	2 (2–3)	0.18
6MWT [m]	309 (172–450)	320 (120–454)	0.10	243 (120–432)	340 (100–500)	0.29

Values are showed as median (interquartile range); NYHA — New York Heart Association; 6MWT — six-minute walk test

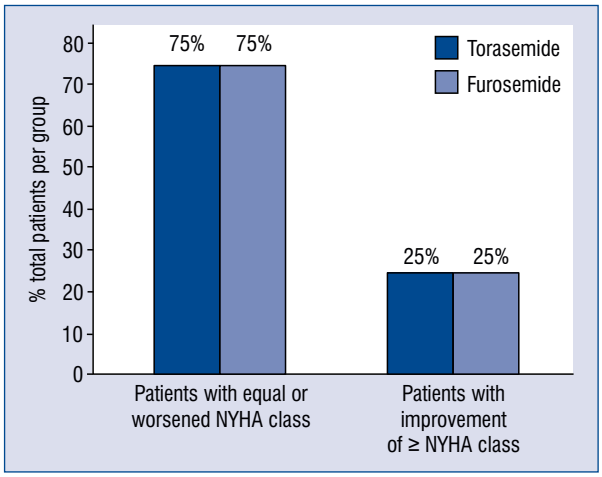

Figure 2. Changes in New York Heart Association (NYHA) functional class from baseline to the end of follow-up. The proportion of patients with/without NYHA class improvement (≥ 1 NYHA class) from baseline to the end of 3-month follow-up in torasemide-treated patients (p = 0.77 compared to furosemide-treated patients).

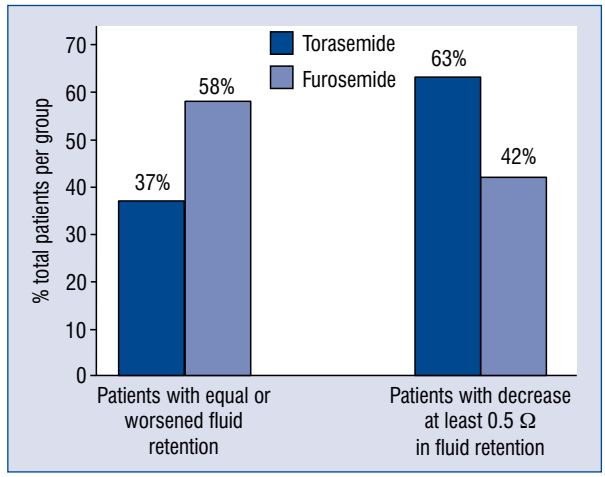

Figure 4. Changes in fluid retention from baseline to the end of follow-up. The proportion of patients with/without decrease (≥ 0.5 Ω) in fluid retention from baseline to the end of 3-month follow-up in torasemide-treated patients (p = 0.51 compared to furosemide-treated patients).

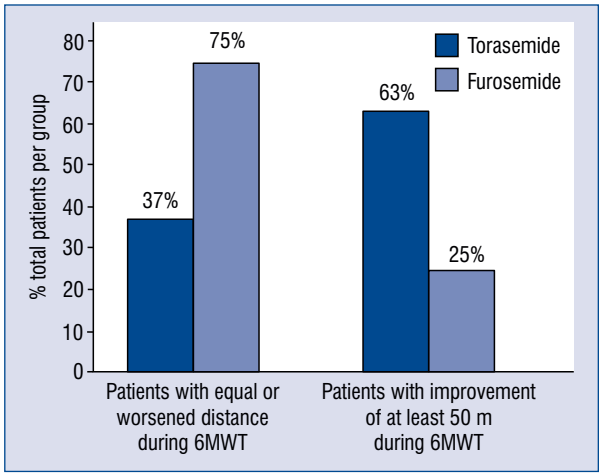

Figure 3. Changes in six-minute walk test (6MWT) from baseline to the end of follow-up. The proportion of patients with/without improvement in walking distance (≥ 50 m) during 6MWT from baseline to the end of 3-month follow-up in torasemide-treated patients (p = 0.09 compared to furosemide-treated patients).

Discussion

The results of this study showed that patients randomized to torasemide had a higher likelihood of reaching the primary composite endpoint of improvement of NYHA functional class, decreased fluid retention, elongated walking distance compared to patients randomized to furosemide. This may indicate that diuretic effect of torsemide compared to furosemide can cause the higher loss of body water leading to greater weight loss that can facilitate walking. Significant, but not statistically, improvement in walking distance and decreased fluid retention among torasemide-treated patients may be also explained by phenomenon of "regression to the mean" — which describes the tendency of extreme measurement on a first occasion to become less extreme when checked again. In this study, it was easier for a patient on torasemide to have a larger improvement in 6MWT and decrease

in fluid retention if the initial walking distance was too low and fluid retention was too high.

Recently published data from the QUALIFY (QUAlity of adherence to guideline recommendations for Life-saving treatment in HF) survey, reported 70% adherence to the guideline-recommended drugs what reflects fairly satisfactory HF therapy [14]. The current HF guidelines recommended the use of loop diuretics as a class I indication to improve symptoms in HF patients with both reduced and preserved LVEF [1]. There is no clear answer which of the loop diuretics should be preferred. The favourable use of furosemide in HF might be explained by its early market introduction in 1960s, whereas torasemide was approved by Food and Drug Administration in 1990s and became generic at the beginning of the twenty-first century. However, some studies suggest that torasemide outperform furosemide's clinical and economic properties by reducing hospital admissions and in-hospital stay [15–17].

Furosemide, the most commonly used loop diuretic in clinical practice, is known to activate the RAAS and the SNS, which could accelerate HF progression. In contrast to furosemide, torasemide was shown to have favorable effect on RAAS inhibition, through blockade of the aldosterone receptor [4, 5]. Our analysis revealed that torasemide-treated patients tended to gain more benefits in symptomatic HF therapy than furosemide what emphasized the importance of obtaining prospective data comparing these two loop diuretics.

There are no previous studies showing direct comparison of torasemide and furosemide on fluid retention. Our study showed more pronounced decrease in fluid retention with torasemide than furosemide treatment. This probably translated into improved NYHA class and elongated walking distance in the torasemide group. Recent analysis from the Heart Failure Registries of the European Society of Cardiology revealed that use of torasemide was associated with significantly lower NYHA class comparing to furosemide treatment ($p = = 0.04$). During follow-up torasemide use was associated with a lower risk (12.9% vs. 20.0%; $p = 0.03$) of worsening ≥ 1 NYHA functional class (12.9% vs. 20.0%; $p = 0.03$) [18]. TORIC (TORasemide In Congestive HF) study that revealed significantly higher efficiency of torasemide than furosemide and other diuretics in functional improving of at least 1 grade in NYHA class (45.8% vs. 37.2%; $p = 0.00017$) [19]. It is in line with the metanalysis of Kido et al. [20] that showed that torasemide is associated with statistically significant improvement in NYHA functional class for patients with HF compared with furosemide ($p = 0.0004$). However, torasemide did not provide significant benefits in reducing mortality or rehospitalization rates for HF ($p = 0.15$) or cardiovascular disease ($p = 0.22$) compared with furosemide. Moreover, there was no significant difference in mortality between torsemide and furosemide ($p = 0.99$).

According to large international ASCEND-HF trial, clinicians tend to use torasemide in the setting of patients with features of more severe disease including refractory volume overload [21]. The preferential use of torsemide in these circumstances may be related to torasemide's smaller inter- and intraindividual variation in bioavailability, longer action increased bioavailability, longer half-life and maintained absorption in the setting of intestinal edema [6, 21, 22]. Moreover, diuretic therapy with torasemide instead of furosemide optimizes the quality of daily life of patients with HF by reducing number of mictions at 3, 6 and 12 h after diuretic intake, and urgency to urinate [6, 13, 22]. Other studies have also demonstrated improvement in sympathetic nerve activity as well as decreased left ventricle volumes and levels of BNP with torsemide compared to furosemide therapy [23, 24]. Additional benefits with torsemide over furosemide include less urinary potassium loss resulted in reduced arrhythmia burden [25]. In DiNicolantonio et al. [7] meta-analysis of randomized controlled trials in 471 patients with systolic HF, compared with furosemide, torasemide caused a 14% reduction in all-cause mortality. It is in line with the TOrasemide In Congestive Heart Failure (TORIC) study results that reported significantly lower mortality in the torasemide ($n = 17$, 2.2%) than in furosemide/other diuretics groups ($n = 27$, 4.5%; $p < 0.05$) [19]. Analysis of the Polish parts of Heart Failure Registries of the European Society of Cardiology, Pilot and Long-Term, revealed that use of torasemide was associated with a significant 24% risk reduction of the composite endpoint of all-cause death and hospitalization for worsening HF (26.4% vs. 34.7%; $p = 0.04$). These benefits may be due to the additional advantages of torasemide such as anti-aldosterone effect [18].

Patients discharged after hospitalization for HF remain at high risk of death and hospital readmission due to recurrence of the symptoms of HF. Therefore, every effort should be made to develop an optimal treatment strategy in this group of patients. It is worth mentioning a recently-started ToRsemide compArisioN With furoSemide FOR-Management of Heart Failure (TRANSFORM-HF)

study that aim is to compare the effects of furosemide versus torsemide on clinical outcomes over 12 months in approximately 6000 patients previously hospitalized for HF [26].

Limitations of the study

The main limitation of the study is the small sample size of the assessed population. The small number of participants did not enable assessment of the impact of torasemide and furosemide in different clinically relevant subgroups i.e. elderly, patients with chronic kidney disease, dilated cardiomyopathy. Noteworthy, the number of patients was sufficient to observe differences between the effects of torasemide and furosemide on clinical outcomes in HF patients. Moreover, the size of studied population made it possible to follow all subjects closely for the duration of the study and gathering considerably detailed information on each study participant.

Conclusions

Based on our study, patients randomized to torasemide had a higher likelihood of improvement of NYHA functional class, decreased fluid retention, elongated walking distance during 6MWT compared to patients randomized to furosemide entire follow-up period. This may indicate that diuretic effect of torsemide compared to furosemide can cause the higher loss of body water leading to greater weight loss that can facilitate walking. The above results and the impact of both drugs on the designed endpoint will confirm final results of TORNADO trial with the intention of being published by the end of 2020. However, further large-scale randomized trials comparing loop diuretic strategies would provide an opportunity to improve HF outcomes and reduce health care expenditures with currently available therapies.

Conflict of interest: None declared

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Long-term lipoprotein apheresis in the treatment of severe familial hypercholesterolemia refractory to high intensity statin therapy: Three year experience at a lipoprotein apheresis center

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Abstract

Background: *Severe familial hypercholesterolemia (FH) individuals, refractory to conventional lipid-lowering medications are at exceptionally high risk of cardiovascular events. The established therapeutic option of last choice is lipoprotein apheresis (LA). Herein, it was sought to investigate the clinical usefulness of LA in a highly selected group of severe heterozygous FH (HeFH), as recently described by the International Atherosclerosis Society (IAS), for their efficacy in lipid reduction and safety.*

Methods: *Efficacy and safety of LA were investigated in 318 sessions of 7 severe HeFH females with cardiovascular disease, over a mean period of 26.9 ± 6.5 months. Relative reduction of low density lipoprotein cholesterol (LDL-C) ≥ 60%, clinical complications and vascular access problems were evaluated and compared between the direct adsorption of lipoproteins (DALI) and lipoprotein filtration (Membrane Filtration Optimized Novel Extracorporeal Treatment [MONET]). Additionally, lipoprotein (a) [Lp(a)], total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), triglycerides (TG) and fibrinogen concentrations were investigated.*

Results: *The relative reduction of LDL-C, TC, TG and Lp(a) were 69.4 ± 12.9%, 59.7 ± 9.1, 51.5 ± ± 14.2% and 71.3 ± 14.4%, respectively. A similar efficacy was found in both systems in LDL-C removal. DALI system led to larger depletions of Lp(a) (80.0 [76–83]% vs. 73.0 [64.7–78.8]%; $p < 0.001$). The frequency of clinical side effects and vascular access problems were low (8.5%).*

Conclusions: *Long-term LA in severe HeFH individuals is safe and efficiently reduces LDL-C and Lp(a). Higher efficacy of the DALI system than MONET in Lp(a) removal may indicate the need for individualized application of the LA system in severe HeFH individuals.* (Cardiol J 2019; 26, 6: 669–679)

Key words: lipoprotein apheresis, severe familial hypercholesterolemia, lipoprotein (a)

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Introduction

Severe familial hypercholesterolemia (FH) patients are at exceptionally high risk of cardiovascular disease (CVD) [1]. Although some authors have suggested that individuals with heterozygous FH (HeFH) and untreated low-density lipoprotein cholesterol (LDL-C) greater than 309 mg/dL suffer from severe HeFH, the definition of severe phenotype of FH was not clear [2]. Recently, the International Atherosclerosis Society (IAS) considered not only initial LDL-C values, but also the presence of risk conditions, as well as clinical or advanced subclinical atherosclerotic CVD [2–7]. These high-risk conditions proposed by IAS include diabetes, arterial hypertension, smoking history, chronic kidney disease, positive family history of early CVD in first-degree relative, low high-density lipoprotein cholesterol (HDL-C) and elevated lipoprotein (a) [Lp(a)]. Among high risk features special attention should be directed to increased Lp(a) with its strong atherogenic and thrombogenic effect, and resistance to conventional lipid-lowering medications [5, 8]. Individuals with severe phenotype of FH often do not adequately respond to high-intensity lipid-lowering medications and do not achieve treatment goals [9]. The recommended target level for severe FH individuals for secondary prevention is LDL-C below 70 mg/dL [9]. Thus, more aggressive forms of therapy might be beneficial in severe FH to arrest the progression of atherosclerosis and reduce cardiovascular event rate [10–12]. The treatment option in severe FH widely used since the 80s has been long-term lipoprotein apheresis (LA) [13, 14]. LA is an extracorporeal technique of selective removal of lipoproteins. Various lipoprotein apheresis systems are routine in clinical use currently. Whole blood adsorption of lipoproteins includes direct adsorption of lipoproteins with polyacrylamide (DALI) and dextran sulfate cellulose adsorption. Atherogenic lipoproteins may also be eliminated in following primary plasma separation methods: lipoprotein filtration (MONET), heparin-induced extracorporeal LDL-C precipitation (HELP), silicate gel adsorption, immunoadsorption (IMA) and dextran sulfate cellulose [15]. LA procedures need to be repeated every 1–2 weeks due to LDL-C and Lp(a) level rebound effect. All LA techniques have been shown to effectively reduce LDL-C along with Lp(a) concentrations by more than 60%, while being well tolerated in long-term application. LDL-apheresis treatment also exerts a pleiotropic effect, improving rheological properties of the blood and reducing inflammatory markers [16, 17]. Regular apheresis sessions have been proved to slow the progression of atherosclerosis and reduce the incidence of cardiovascular events [12, 18–20]. The main goal of LA treatment in HeFH is to achieve an LDL-C reduction ≥ 60% at each therapeutic session [21]. Additionally, time-averaged LDL-C less than 100 mg/dL might be considered as a goal [21].

Although data confirming the effectiveness and safety of lipoprotein apheresis have been published, the studies often aggregated patients with undefined hypercholesterolemia, homozygous FH, HeFH and isolated increased Lp(a), treated with various apheresis systems and differing lipid-lowering medication regimens [22, 23]. This lack of stratification by type of dyslipidemia resulted in misleading findings. Therefore, the main purpose of the current research was to investigate the clinical usefulness of lipoprotein apheresis in a highly selected group of severe HeFH, according to the IAS definition, for their efficacy in lipid reduction and safety. Additionally, the safety and effectiveness of DALI and MONET systems were compared in the current study group.

Methods

The study was carried out prospectively in a large Polish lipoprotein apheresis center, established at the First Department of Cardiology, Medical University of Gdansk, following the Good Clinical Practice guidelines. Researchers obtained written informed consent before patient inclusion, in accordance with the Declaration of Helsinki. All treatment protocols and medical records for each patient undergoing LA were reviewed, except for initial sessions in the first month of treatment.

Patients

The primary indication to LA treatment was HeFH with symptomatic CVD and LDL-C concentration of more than 160 mg/dL despite maximally tolerated intensive lipid-lowering medications [14]. Seven female patients with definite FH according to the modified Dutch Lipid Network Criteria and confirmed a mutation in *LDLR* or *APOB* gene, fulfilling the criteria of severe FH by the IAS, were enrolled into the study [4, 24]. At the initiation of LA treatment, all patients had a history of a documented CVD and at least three additional high risk-features for severe FH. All individuals were treated with rosuvastatin in a dose of 40 mg daily with or without ezetimibe 10 mg daily by more than 12 months before starting LA and continued such

treatment on apheresis. The mean age of patients at the start of LA therapy was 54.5 ± 5.5 years. Detailed clinical and biochemical characteristics of investigated patients are presented in Table 1.

Lipoprotein apheresis

Lipoprotein apheresis sessions (n = 318) were performed in weekly or biweekly intervals using two techniques, according to patient characteristics over a period of 37 months. Concomitant angiotensin converting enzyme inhibitors (ACEI) therapy was a contraindication to DALI treatment. LA therapy was started 6.0 ± 1.5 years after the clinical diagnosis of FH. 162 DALI sessions with large adsorber configurations (DALI 1000, DALI 1250) and 156 MONET procedures were performed over a mean period of 26.9 ± 6.5 months [25]. To provide adequate effectiveness, at least 1.5 of blood volume was processed during DALI therapeutic sessions, and at least 45 mL of plasma volume/kg was treated during MONET sessions [26]. Both acid citrate dextrose (ACD-A) and heparin in the priming solution were used as an anticoagulant. Arteriovenous (AV) fistula was established as access in all patients due to the insufficiency of peripheral venous access. Initial sessions in the first months and procedures interrupted before expected blood/plasma volume purification were excluded from the final analysis of biochemical parameters.

Biochemical parameters

All biochemical parameters were measured in one laboratory at scheduled intervals. LDL-C levels were subsequently calculated using the Friedewald formula unless triglycerides (TG) were above 400 mg/dL. Acute reduction in total cholesterol (TC), LDL-C, HDL-C, TG, Lp(a) and fibrinogen were calculated from pre- and post-apheresis results. The time-averaged mean LDL-C level was calculated according to the formula devised by Kroon, where C_{MAX} and C_{MIN} are defined as the immediate pre- and post-treatment values: $C_{AVG} = C_{MIN} + 0.73 \times C_{MAX} - C_{MIN}$ [27]. The effectiveness of LA was expressed as an achievement of acute post-apheresis LDL-C reduction by more than 60%. Alternatively, the time-averaged LDL-C below 100 mg/dL was a goal of treatment. Additionally, HDL-C, TC, TG, Lp(a) and fibrinogen reductions were investigated.

Side-effects

Clinical complications and vascular access problems were investigated at each therapeutic apheresis session. Clinical complications were

Table 1. Clinical and biochemical characteristics at lipoprotein apheresis initiation.

	1	2	3	4	5	6	7
Age [years]	58	47	61	65	58	56	54
FH-causing gene mutation	*LDLR*	*LDLR*	*APOB*	*LDLR*	*LDLR*	*LDLR*	*LDLR*
Body mass index [kg/m^2]	24	24	35	29	26	31	34
Waist circumference [cm]	90	80	98	95	95	103	117
Hip circumference [cm]	100	97	104	105	103	116	124
High risk features for severe FH							
Diabetes	–	+	+	IFG	–	+	–
Hypertension	+	+	+	+	+	+	+
Smoking history	+	+	+	+	–	–	+
Family history of early CVD in first-degree relative	+	+	+	+	+	+	+
Lp(a) max [g/L]	1.37	0.8	0.54	0.2	1.18	0.22	0.6
CKD (GFR < 60 mL/min/m^2)	–	–	–	–	–	–	–
HDL-C < 40 mg/dL	–	–	–	–	–	–	+

Table 1 (cont.). Clinical and biochemical characteristics at lipoprotein apheresis initiation.

	1	2	3	4	5	6	7
Cardiovascular history							
Coronary artery disease	+	+	+	+	+	+	+
ACS	0	6	0	1	1	0	1
ACS, age of first	NA	41	49	57	51	NA	42
PCI	5	2	10	0	6	3	3
PCI, age of first	46	41	49	NA	51	49	42
CABG	–	–	–	1	–	1	1
CABG, age	NA	NA	NA	57	NA	45	42
TIA	–	–	+	+	–	–	–
Stroke	–	2	–	–	–	–	–
Stroke, age of first	NA	45	NA	63	NA	NA	NA
Carotid artery stenosis	–	–	+	+	+	–	–
Peripheral artery disease	–	–	+	–	–	+	–
Revascularization of carotid or peripheral artery	–	–	+	+	–	–	–
Heart failure	–	+	–	–	–	–	+
LVEF [%]	60	20	50	60	50–55	55	40
Biochemical parameters							
TC max [mg/dL]	538	536	392	797	500	431	562
LDL-C max [mg/dL]	453	440	318	759	422	352	475
HDL-C max [mg/dL]	63	61	45	55	39	48	35
TG max [mg/dL]	111	182	145	195	196	146	258
Apo A1 [mg/dL]	1.91	1.91	1.07	1.5	1.87	1.38	1.46
ApoB [mg/dL]	0.86	1.37	1.17	1.21	1.85	2	1.22
Hypolipidemic treatment							
Statin, age of implementation	46	35	49	45	40	34	38
Intensive lipid-lowering treatment [years]	12	12	10	8	18	7	16
Statin, type and dose	rosuvastatin 40 mg	rosuvastatin 40 mg	rosuvastatin 40 mg	rosuvastatin 40 mg	rosuvastatin 40 mg	rosuvastatin 40 mg	rosuvastatin 40 mg
Ezetimibe 10 mg daily	–	+	+	+	+	+	+
Other lipid-lowering medications	–	–	–	–	–	–	–
Age at apheresis initiation [years]	55	44	59	63	55	54	52
Apheresis technique	MONET	MONET	MONET	MONET	DALI	DALI	DALI

Conversion factors to SI units are as follows: glucose, 0.05551; cholesterol, 0.02586 and triglycerides 0.0114. TC-max, LDL-C-max, HDL-C max, TG max are the highest values before statin initiation.
ACS — acute coronary syndrome; Apo — apolipoprotein; *APOB* — apolipoprotein B gene; CABG — coronary artery bypass graft; CKD — chronic kidney disease; CVD — cardiovascular disease; DALI — direct adsorption of lipoproteins; FH — familial hypercholesterolemia; GFR — glomerular filtration rate; HDL-C— high density lipoprotein cholesterol; IFG — impaired glucose tolerance; *LDLR* — low density lipoprotein receptor gene; LDL-C — low density lipoprotein cholesterol; Lp(a) — lipoprotein (a); LVEF — left ventricular ejection fraction; MONET — Membrane Filtration Optimised Novel Extracorporeal Treatment; NA — not applicable; PCI — percutaneous coronary intervention; TC — total cholesterol; TG — triglicerydes; TIA — transient ischemic attack

Table 2. Lipoprotein apheresis — biochemical parameters.

	Mean ± SD	Median	Minimum	Maximum
TC pre-apheresis [mg/dL]	308.9 ± 94.1	294.0	153.0	569.0
TC post-apheresis [mg/dL]	121.6± 39.3	114.0	62.0	354.0
TC [% reduction]	59.7 ± 9.1	61.5	32.4	78.9
LDL-C pre-apheresis [mg/dL]	222.8 ± 89.5	207.5	54.0	490.0
LDL-C post-apheresis [mg/dL]	68.8 ± 37.6	66.0	1.0	177.0
LDL-C [% reduction]	69.4 ± 12.9	71.8	17.3	98.3
Interval LDL-C [mg/dL]	181.4 ± 72.8	154.9	40.0	395.8
HDL-C pre-apheresis [mg/dL]	42.5 ± 10.1	41.0	15.0	75.0
HDL-C post-apheresis [mg/dL]	32.4 ± 6.8	32.0	11.0	53.0
HDL-C [% reduction]	22.7 ± 10.9	21.7	0.0	62.16
TG pre-apheresis [mg/dL]	220.8 ± 162.7	157.0	46.0	1121.0
TG post-apheresis [mg/dL]	103.8 ± 84.8	72.0	23.0	616.0
TG [% reduction]	51.5 ± 14.2	53.2	10.8	83.6
Lp(a) pre-apheresis [g/L]	0.5 ± 0.4	0.39	0.08	1.37
Lp(a) post-apheresis [g/L]	0.12 ± 0.09	0.09	0.01	0.57
Lp(a) [% reduction]	71.3 ± 14.4	76.1	21.4	94.1
Fibrinogen pre-apheresis [mg/dL]	3.25 ± 0.63	3.25	2.2	6.47
Fibrinogen post-apheresis [mg/dL]	1.96 ± 0.77	2.02	0.63	3.96
Fibrinogen [% reduction]	39.7 ± 21.2	45.6	2.8	76.0

Data are presented as mean ± standard deviation (SD) and median with minimum and maximum. Abbreviations — see Table 1.

specified as follows: hypotension with systolic blood pressure < 90 mmHg and accompanying symptoms (paleness, nausea), hypocalcemia, oedema, severe bleeding, anemia, and thrombocytopenia. Vascular complications included puncture problems, hematoma, bleeding and stenosis of AV fistula.

Statistical analysis

Continuous data were presented as a mean value and standard deviation (SD) or as a median and interquartile range (IQR) or as a median and minimum and maximum value. Categorical data were presented as percentages. Normal distribution was verified by the Kolmogorov-Smirnov test. Continuous data were compared by the Student t-test or U-Mann Whitney test depending on the distribution. Categorical data were compared by the χ^2 test and Fisher exact test. P value less than 0.05 was considered statistically significant. Data were analyzed using SPSS software v.21 (IBM, Chicago, Illinois, USA).

Results

Lipoprotein apheresis

The mean duration time of the procedure was 140.0 (60–240) min. ACD-A was used in a mean volume of 329.8 ± 134.9 mL, with the ratio of citrate: blood ranging from 1:20 to 1:40 in both DALI and MONET. DALI sessions were significantly shorter than MONET (130.0 [120–140] vs. 170.0 [158.0–183.7]; p < 0.001) with less ACD-A consumption (244.0 [215–302] vs. 431.0 (374.5–486.5); p < 0.001). Average blood volume processed during DALI sessions was 8540 ± 155 mL. During MONET sessions average plasma volume 2903.5 ± 867.1 mL was achieved.

Cholesterol, lipoprotein (a) and fibrinogen

Laboratory parameters before and during chronic LA treatments are summarized in Table 2. Mean pre-apheresis values of TC and LDL-C were high (308.9 ± 94.1 and 222.8 ± 89.5 mg/dL, respectively). Apheresis reduced both lipids acutely to 121.6 ± 39.3 mg/dL and 68.8 ± 37.6 mg/dL, respectively. Mean pre-apheresis values of HDL-C were below the normal range for females (42.5 ± 10.1 mg/dL). Apheresis reduced HDL-C to a lesser extent than other lipids (22.7 ± 10.9%). Apheresis sessions removed TG by 51.5 ± 14.2% in the mean, starting from 220.8 ± 162.7 mg/dL. Apheresis session led to acute depletion of Lp(a) from pre-apheresis concentration of 0.5 ± 0.4 g/L to 0.12 ± 0.09 g/L. Fibrinogen was reduced by

Table 3. Biochemical parameters in DALI versus MONET system.

	DALI	MONET	P
TC pre-apheresis [mg/dL]	238.0 (207–295)	372.0 (254.5–409.5)	< 0.001
TC post-apheresis [mg/dL]	100.0 (83–121)	114.0 (101.5–134.5)	0.003
TC [% reduction]	58.8 (54.8–64.5)	65.6 (61.2–69.7)	< 0.001
LDL-C pre-apheresis [mg/dL]	141.0 (122–170)	286.0 (191.5–326.5)	< 0.001
LDL-C post-apheresis [mg/dL]	37.5 (26–57)	69.0 (49.5–88.0)	< 0.001
LDL-C [% reduction]	72.6 (66.5–83.5)	74.1 (69.9–77.9)	0.8
Interval LDL-C [mg/dL]	113.4 (96.9–137.5)	228.5 (155.6–260.3)	< 0.001
HDL-C pre-apheresis [mg/dL]	36.0 (34–39)	50.0 (42.5–58.0)	< 0.001
HDL-C post-apheresis [mg/dL]	31.0 (28.2–34.0)	36.0 (30.0–40.0)	< 0.001
HDL-C [% reduction]	14.3 (9.5–20.6)	30.3 (25.7–34.2)	< 0.001
TG pre-apheresis [mg/dL]	285.0 (184–383)	132.0 (104.0–185.0)	< 0.001
TG post-apheresis [mg/dL]	126.50 (73–198)	63.0 (49.5–81.5)	< 0.001
TG [% reduction]	51.81 (45.2–62.2)	54.4 (44.3–62.6)	0.9
Lp(a) pre-apheresis [g/L]	0.43 (0.22–0.72)	0.77 (0.35–1.09)	0.001
Lp(a) post-apheresis [g/L]	0.08 (0.04–0.13)	0.17 (0.12–0.24)	< 0.001
Lp(a) [% reduction]	80.0 (76–83)	73.0 (64.7–78.8)	< 0.001

Data are presented as median (interquartile range [IQR]). Abbreviations — see Table 1.

39.7 ± 21.2% starting from the pre-apheresis level of 3.25 ± 0.63 mg/dL (Table 2).

DALI vs. MONET

Higher pre- and post-apheresis TC, LDL-C, HDL-C and Lp(a) concentrations in MONET sessions vs. DALI (Table 3) were observed. In contrast, the pre- and post-apheresis TG levels were higher in patients treated by DALI system, compared to MONET (Table 3). MONET system led to higher TC and HDL-C reductions, compared to DALI (Fig. 1).

The pre-apheresis concentrations of fibrinogen were similar in DALI and MONET groups. In comparison to MONET, DALI treatment led to a lower removal of fibrinogen (62.5 [52.1–68.0]% vs. 19.8 [13.9–25.2]%; p < 0.001) (Fig. 1). Post-apheresis fibrinogen concentration in MONET sessions was below normal range (1.15 [1.00–1.52] mg/dL).

Analyzing all LA therapeutic sessions, the relative reduction of LDL-C up to 69.4 ± 12.9% (71.8 [17.3–98.3]%) was achieved. Comparing both systems, their similar efficacy was found (72.6 [66.5–83.5]% vs. 74.1 [69.9–77.9]%; p = 0.809) (Fig. 2). A large number of LA sessions resulted in at least a 60% reduction of LDL-C (82% of DALI treatments and 78% of MONET treatments).

Calculated time-averaged LDL-C was 181.4 ± ± 72.8 (154.9 [40–395.8]) mg/dL. The DALI system resulted in the achievement of a lower time-averaged LDL-C, than MONET (113.4 vs. 228.5 mg/dL; p < 0.001).

The acute reduction of Lp(a) of 71.3 ± 14.4% (76.1 [21.4–94.1]%) was achieved. It was observed that DALI system was more efficient in relative removal of Lp(a) than MONET (80.0 [76–83]% vs. 73.0 [64.7–78.8]%; p < 0.001) (Fig. 2).

Additional analysis revealed that 54% of all sessions resulted in a post-apheresis LDL-C of less than 70 mg/dL. A higher percent of DALI vs. MONET sessions resulted in decreasing LDL-C below 70 mg/dL (88% vs. 32%).

Side effects

The total incidence of clinical side effects was low (8.5%). Major complications were observed in 2 cases of DALI treatment. One episode of bradykinin syndrome (hypotension, flush, bradycardia and dyspnea) with Quincke odema and lumbar pain was observed. The patient was switched to MONET system. Heparin-induced thrombocytopenia (HIT) with thrombosis in extracorporeal system appeared in another individual. Heparin was replaced by fondaparinux and DALI treatment was continued.

The total incidence of hypotension, vascular problems, and hypocalcemia was low (7.5%, 6.12%, 1.7%, respectively). However, the frequency of complications related to vascular access was higher in MONET sessions vs. DALI (10.5% vs. 1.4%,

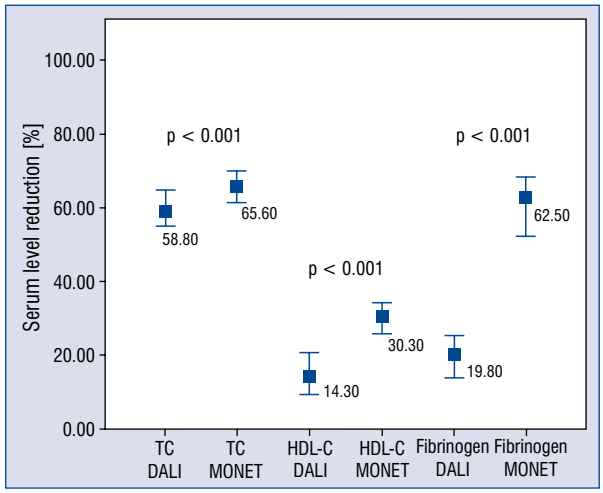

Figure 1. Reduction of total cholesterol (TC), high density lipoprotein cholesterol (HDL-C) and fibrinogen in DALI vs. MONET. Data are presented as median and interquartile range.

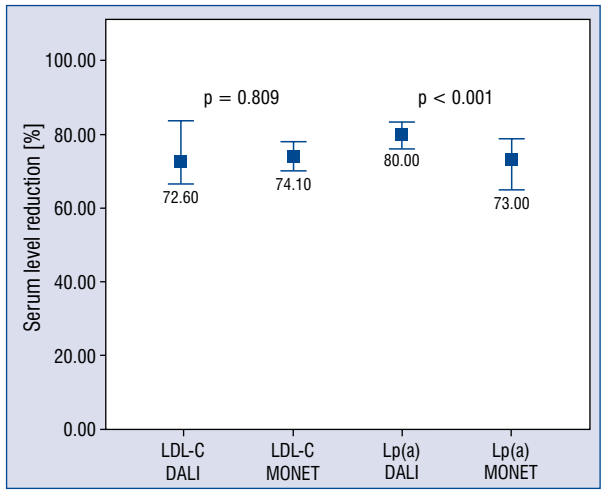

Figure 2. Reduction of low density lipoprotein cholesterol (LDL-C) and lipoprotein (a) [Lp(a)] in DALI vs. MONET. Data are presented as a median and interquartile range.

p = 0.001). Mild, transient hypotension occurred with similar frequency in DALI and MONET (4.9% vs. 9.9%, p = 0.12). Administration of crystalloid infusion before and during apheresis substantially reduced the frequency of symptomatic hypotension. Blood flow at the start and the end of procedures was not related with the incidence of hypotension (Table 4). Hypocalcemia incidence rate was similar during MONET sessions (3.3% vs. 0%, p = 0.06). Anemia occurred in one individual undergoing DALI and one treated by MONET system. Angina episodes were not recorded, as well as abdominal pain.

Discussion

The study was undertaken to assess the efficacy and safety of lipoprotein apheresis in a highly selected group of severe FH individuals, by IAS definition. Investigated patients presented a pattern of severe HeFH with an advanced CVD, high LDL-C at initial presentation (> 310 mg/dL) and at least three additional high-risk features. Increased Lp(a) level greater than 50 mg/dL was present in more than half of them (4/7) [28]. Administration of high-intensity oral lipid-lowering agents failed to reduce LDL-C below 160 mg/dL. Although cardiovascular risk in HeFH is largely driven by chronic exposure to elevated LDL-C, cardiovascular risk factors in HeFH are additive, indicating very high CVD risk in the present cohort. Therefore, treatment strategy should be aggressive, targeting an ideal goal of LDL-C below 70 mg/dL. In the current study, LDL-C was acutely reduced from 223 mg/dL to 69 mg/dL, which corresponded to a relative reduction of 69%. Relative decreases of LDL-C greater than 60% was reached in a large number of treatments (close to 80%) indicating a good quality of treatment. In LDL-Apheresis Atherosclerosis Regression Study (LAARS) the achieved acute 63% reduction in LDL-C led to the angiographic

Table 4. Influence of crystalloid infusion on hypotension during lipoprotein apheresis (LA) treatment.

	Symptomatic hypotension during apheresis (n = 22)	Apheresis session without hypotension (n = 272)	P
Crystalloid infusion	14 (63.63%)	54 (19.85%)	< 0.001
Crystalloid infusion before procedure	8 (36.36%)	39 (14.34%)	0.01
Crystalloid infusion during procedure	9 (40.91%)	20 (7.35%)	< 0.001
Blood flow at start of LA [mL/min]	52.86 ± 9.16	50.81 ± 8.71	0.3
Blood flow 2 at the end of LA [mL/min]	96.00 ± 29.00	101.17 ± 20.25	0.4

Data for blood flow are presented as mean ± standard deviation.

arrest of the progression of coronary artery disease in a majority of patients treated with simvastatin and biweekly LA [29]. Other studies carried out in HeFH, on various systems of apheresis reported 55–70% mean LDL-C reduction [21, 30, 31]. Nevertheless, it was found that post-apheresis LDL-C values were below 70 mg/dL only in 54% of LA sessions. When DALI and MONET systems were compared, single DALI sessions achieved LDL below 70 mg/dL more often when compared to MONET (88% vs. 32%). These results may be easily explained by higher pre-apheresis LDL-C observed in patients treated with MONET as compared to DALI. Premature discontinuation of MONET sessions due to adverse events decreased the percent of efficacious LA sessions, compared to other reports [31]. Last but not least, the staff and site experience are a known factor influencing the course of LA sessions [32].

Considering the achievement of a time-averaged LDL-C below 100 mg/dL as a goal of LA therapy, it was out of range in the present study (181 mg/dL). However, it agrees with previous studies. In a large study of 118 patients treated by LA in Dresden, the time-averaged LDL-C was 119.8 mg/dL, similar to the present DALI patients. It may be explained by lower pre-apheresis LDL-C in the Dresden group, than the cohort herein (148.8 mg/dL vs. 223 mg/dL) [33].

The mean reduction of Lp(a) observed in this study was close to 70%. DALI treatment led to larger depletion of Lp(a) than MONET. Ramlow et al. [31] showed equal Lp(a) removal and slightly better efficacy of LDL-C removal for DALI treatment than MONET. It is suspected that a more efficient removal of Lp(a) in the present DALI system might be an effect of an application of larger adsorbers (DALI 1000 and 1250) or higher blood volume processed. However, there are other factors determining the acute lipoprotein reduction in DALI-apheresis such as weight, height, pre-apheresis lipid levels, as well as blood flow rate through the adsorber.

The present findings also confirmed that direct adsorption and lipoprotein filtration varied in selectivity. MONET substantially reduced fibrinogen concentration, which may improve blood viscosity and its rheological properties. Bleeding complications were not reported, even though 2 patients were administrated with oral anticoagulants. MONET system led to slightly higher HDL-C reduction compared to DALI. However, the reduction was lower, than other lipids. Thus, results agree with previous reports [31].

A mean rate of side effects of 8.5% was observed, which is in the line with data from a large study by Dittrich-Riediger et al. [33]. Serious AE were incidental as in previous reports [34]. Despite ACEI cessation before DALI initiation, bradykinin syndrome was reported in the present study. Another patient treated by DALI was affected by HIT. DALI system is known to cause bradykinin release with peaks at 1000–2000 mL of treated blood volume and ACEI block bradykinin degradation into inactive metabolites. Thus, they are contraindicated in patients treated by DALI system. Angiotensin receptor blockers may be administrated, as in the present case. HIT is an extremely rare complication of LA. However, some authors reported thrombocytopenia previously. The most frequently observed complications of lipoprotein apheresis in the present study were vascular access problems and hypotension, as previously reported by other authors [33, 35]. A higher incidence of vascular access problems was found compared to other studies [23]. In a large multicenter, prospective study of German patients undergoing DALI and MONET apheresis, Kozik-Jaromin et al. [35] reported 27 puncture problems in 3451 sessions [35]. However, hematoma and bleeding as problems with vascular access were also reported herein. Otherwise, some data indicate an increased rate of venous puncture problems were found in female vs. male patients [33]. All investigated individuals in the present cohort were females. Secondly, the type of the vascular access determined issues with its maintenance. Accessing peripheral veins might be the best option for lipoprotein apheresis treatment [36]. In the United Kingdom analysis of peripheral vein cannulation represented even 79% of initial vascular access strategies with AV fistula use accounting for 15%, with a trend to AV cannulation [37]. Unfortunately, due to unavailability of large veins for repeated puncture, arteriovenous fistulas were established in all patients of the present study. Detailed analysis showed that 1 patient undergoing MONET suffered from recurrent stenosis and thrombosis of arteriovenous fistula. Kozik-Jaromin et al. [35] excluded the first 3 months of treatment from analysis, not only the first month of treatment as in the present study. Increased rate of AE during all 12 months of treatment was observed in previous reports.

Mild, transient hypotension, mainly caused by initial "blood donation" into the extracorporeal circuit, occurred with 7.5% frequency. The German Registry of Lipoprotein Apheresis (GLAR) showed a lower rate of hypotension of 1.09–1.28% [21]. However, as demonstrated herein, hypoten-

sion may be avoided by crystalloid infusion to the contralateral vein before and during an apheresis session. Some authors have described routine intravenous administration of saline or HAES at apheresis session initiation, and this may have been the reason for this difference. Symptomatic hypocalcemia caused by citrate infusion was rare in the present study. Oral supplementation of calcium prior to a DALI session was introduced in susceptible patients, as well as routine optimization of ACD-A.

Long-term LA with efficient LDL-C and Lp(a) removal was a consequence to improvement of the CVD course in the patients studied. The incidence of major adverse cardiac events (MACE; defined as cardiovascular death, non-fatal acute coronary syndrome and repeat coronary revascularization) decreased after LA initiation. MACE rate was reduced from 41 events before LA inception to 8 during the period of LA treatment. The positive impact of LDL apheresis on cardiovascular morbidity in individuals with hypercholesterolemia has been previously confirmed in several observational trials [38]. Sampietro et al. [39] reported a significant reduction of adverse cardiac or vascular events in 30 individuals with FH or familial combined hypercholesterolemia and CVD. Adverse cardiac or vascular events incidences occurred prior and after LA treatment inception, which were 86 and 15 events, respectively [39].

According to available research, this is the first report focused on the most severe phenotype of HeFH refractory to an equal regimen of statin (rosuvastatin 40 mg daily) at particularly high cardiovascular risk. All patients were female. Thus, gender influence on cardiovascular risk can be omitted. LA in the present study was carried out and documented by one physician at a specialized apheresis center. The treatment and observation period were long.

Study results highlight the importance of more aggressive forms of treatment such as LA in severe HeFH individuals with advanced CVD, additional high-risk features, and LDL-C greater than 160 mg/dL, despite high-intensity statin therapy. The present findings also point to the fact that despite LA there was a substantial unmet need for novel schedules of treatment to control LDL-C in those individuals [4]. In further studies on cardiovascular outcome in real-world practice, it might be interesting to clarify if severe HeFH individuals with CVD and increased Lp(a) concentration benefit from DALI treatment with large adsorbers (1000 or 1250) in combination with novel drugs [40].

Limitations of the study

The present study is small in size, which was caused by a low number of HeFH patients treated by lipoprotein apheresis in Poland. Despite an increase in the proportion of patients treated with strong statins in recent years, treatment goals in hypercholesterolemia are not being achieved [41]. Based on the prevalence of severe FH eligible to LA of 2.4% and approximately 1000 FH individuals with molecular confirmation in Poland (unpublished data), it is estimated that there are 24 severe HeFH, of which 7 are currently being treated with LA [42].

Conclusions

Long-term LA in severe HeFH individuals is safe and efficiently reduces LDL-C and Lp(a). Higher efficacy of DALI system vs. MONET in Lp(a) removal may indicate a need for individualized application of LA system in severe HeFH individuals.

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Conflict of interest: None declared

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Mast cell derived carboxypeptidase A3 is decreased among patients with advanced coronary artery disease

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Abstract

Background: *Coronary artery disease (CAD) affects milions of people and can result in myocardial infarction (MI). Previously, mast cells (MC) have been extensively investigated in the context of hypersensitivity, however as regulators of the local inflammatory response they can potentially contribute to CAD and/or its progression. The aim of the study was to assess if serum concentration of MC proteases: carboxypeptidase A3, cathepsin G and chymase 1 is associated with the extension of CAD and MI.*

Methods: *The 44 patients with angiographically confirmed CAD (23 subjects with non-ST-segment elevation MI [NSTEMI] and 21 with stable CAD) were analyzed. Clinical data were obtained as well serum concentrations of carboxypeptidase A3, cathepsin G and chymase 1 were also measured.*

Results: *Patients with single vessel CAD had higher serum concentration of carboxypeptidase than those with more advanced CAD (3838.6 ± 1083.1 pg/mL vs. 2715.6 ± 442.5 pg/mL; p = 0.02). There were no significant differences in levels of any protease between patients with stable CAD and those with NSTEMI. Patients with hypertension had ≈2-fold lower serum levels of cathepsin G than normotensive individuals (4.6 ± 0.9 pg/mL vs. 9.4 ± 5.8 pg/mL; p = 0.001). Cathepsin G levels were also decreased in sera of the current smokers as compared with non-smokers (3.1 ± 1.2 ng/mL vs. 5.8 ± 1.2 ng/mL, p = 0.02).*

Conclusions: *Decreased serum level of carboxypeptidase is a hallmark of more advanced CAD. Lower serum levels of carboxypeptidase A3 and catepsin G are associated with risk factors of blood vessel damage suggesting a protective role of these enzymes in CAD.* (Cardiol J 2019; 26, 6: 680–686)

Key words: mast cells, carboxypeptidase A3, cathepsin G, chymase 1, coronary artery disease

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Introduction

Chronic inflammation plays an important role in the pathogenesis of coronary artery disease (CAD) and acute myocardial infarction (AMI).The link between mast cell (MC) proteases and a local inflammation process is an attractive research area. After activation, MC releases a wide range of proteases that have a potential pro or anti-inflammatory effect [1–3]. The major MC proteases include tryptase, chymase 1, carboxypeptidase A3 and cathepsin G.

In previously published work, it was shown that tryptase and endothelin-1 released from activated MC are elevated in patients with an AMI [4]. Therefore, in the current study theaim was to analyze if other MC proteases chymase 1, carboxypeptidase A3 and cathepsin G play also have a role in CAD and AMI.

Chymase 1 is a serine protease stored in MC. It is released after stimulation during an inflammatory or ischemic injury that is known to be a hallmark of AMI. The protein release is associated with activation of matrix metalloproteinase-9, which was shown to increase infarct size in an experimental model [5]. Oyamada et al. [6] have shown, that chymase 1 inhibition results in myocardial protection and attenuates fibrosis after AMI. In addition, chymase plays a crucial role in transformation of angiotensin I to angiotensin II independent from angiotensin converting enzyme [7].

Cathepsin G is a serine protease also synthesized and stored in MC. However, MC are not the only source of the enzyme, it is also released from activated neutrophils and macrophages [8–10]. Despite that cathepsin G may promote early atherogenesis as it is an elastase [11] and collagenase activator [12], Wang et al. [13] suggested that cathepsin G promotes early atherogenesis through its elastinolytic activity, but at the same time suppresses late progression of atherosclerosis. In their study, patients with atherosclerosis had significantly reduced plasma levels of cathepsin G that were in negative correlation with total cholesterol and low density lipoprotein (LDL), but not high density lipoprotein (HDL) or triglycerides, suggesting a role of cathepsin G in degradation of LDL without affecting HDL or triglycerides [13].

A carboxypeptidase A3 (CPA3) is a zinc metalloprotease that is released from MCs and basophils as well. This enzyme degrades proteins and peptides, including the apolipoprotein B; a component of LDL particles [14]. Upon MC activation and degranulation, CPA3 with the chymases and tryptases interacts with heparin proteoglycans [15]. It was shown to play a role in the inactivation of endothelin [16, 17] and degradation of angiotensin II [18], which suggests its antihypertensive activity.

The aim of the study was to check if a concentration of MC derived proteases is elevated in sera of patients with different extensions of CAD, and thus to assess the role of MC in its pathogenesis.

Methods

This was a prospective and single-center study. The study was conducted according to the Declaration of Helsinki and the protocol was reviewed and approved by the local ethics committee. All patients gave written informed consent.

Patients

Between November 2012 and May 2013, 44 consecutive patients were prospectively screened who underwent diagnostic coronary angiography because of non-ST-segment elevation myocardial infarction (NSTEMI) or stable angina with a positive stress test. All the procedures were performed at the Department of Invasive Cardiology, Pomeranian Cardiology Centers, Wejherowo, Poland. Patients with renal failure, malignancy, and acute or chronic inflammatory disease were excluded from the study. Finally, 44 patients (23 NSTEMI and 21 with stable angina) were included. Complete demographic and clinical data were obtained. Accordingly to the extension of CAD, patients were divided into two groups: subjects with one vessel CAD and those with two or three vessel CAD.

Blood sampling and laboratory tests

The blood samples were obtained after puncture of a radial or a femoral artery and they were drawn from the vascular sheath during a coronary angiography.

Then, blood samples were centrifuged at 1000 × g for 15 min to obtain serum. Subsequently, standard clinical parameters were measured and the remaining serum was apportioned into 0.5 mL aliquots, and stored at –80°C until analysis of CPA3, cathepsin G and chymase 1.

Measurement of CPA3, cathepsin G and chymase 1

Carboxypeptidase A3, cathepsin G and chymase 1 concentrations were measured with ELISA (Cloud-Clone Corp., Houston, TX, USA) according to manufacturer instructions. The lower limit of

Table 1. Demographic and biochemical data of 44 patients with significant coronary artery disease (CAD) according to the extension of CAD.

	1 vessel CAD (n = 11)	2–3 vessel CAD (n = 33)	P
Age [years]	68.3 ± 7.1	67.5 ± 2.6	0.7
Male/female	5/6	19/14	0.5
Body mass index [kg/m^2]	30.7 ± 3.7	29.9 ± 1.5	0.6
Total cholesterol [mg/dL]	220.1 ± 48.1	171.3 ± 17	0.01
LDL cholesterol [mg/dL]	158.6 ± 46.8	98.4 ± 16	0.002
HDL cholesterol [mg/dL]	45.7 ± 9.3	44.6 ± 4.2	0.8
Serum creatinine [mg/dL]	1.7 ± 1.3	1.2 ± 0.1	0.1
eGFR	45.9 ± 11.4	53.5 ± 4.4	0.1
LVEF [%]	48.2 ± 5.5	47.6 ± 4.3	0.9
Arterial hypertension	11	13	0.2
Diabetes	4	15	0.6
History of previous MI	2	24	0.005
History of stroke/TIA	3	7	0.7
Current smoker	4	18	0.7

eGFR — estimated glomerular filtration rate; HDL — high density lipoprotein; LDL — low density lipoprotein; LVEF — left ventricular ejection fraction; MI — myocardial infarction; TIA — transient ischemic attack

Table 2. Demographic, biochemical and clinical data of 23 patients with non-ST-elevation myocardial infarction (NSTEMI) and 21 patients with stable coronary artery disease (CAD).

	NSTEMI (n = 23)	Stable CAD (n = 21)	P
Age [years]	68.5 ± 3.8	66.8 ± 3.3	0.5
Body mass index [kg/m^2]	30 ± 1.7	30.3 ± 2.3	0.8
Total cholesterol [mg/dL]	198.1 ± 28	167.5 ± 20.9	0.08
LDL cholesterol [mg/dL]	124.9 ± 27.3	100.9 ± 22.5	0.2
HDL cholesterol [mg/dL]	44.3 ± 5.3	45.6 ± 5.6	0.7
Serum creatinine [mg/dL]	1.5 ± 0.6	1.1 ± 0.1	0.2
eGFR	47.3 ± 6.6	56.4 ± 4.8	0.03
CRP	33.2 ± 25.6	5.3 ± 2.8	0.03
Arterial hypertension	21	18	0.5
Diabetes	9	10	0.6
History of previous MI	7	17	0.001
History of stroke/TIA	3	0	0.09
Current smoker	6	4	0.6
3 vessel CAD/1–2 vessel CAD	3/20	9/12	0.03
LVEF [%]	45.9 ± 4.2	49.7 ± 5.8	0.3

eGFR — estimated glomerular filtration rate; CRP — C-reactive protein; HDL — high density lipoprotein; LDL — low density lipoprotein; LVEF — left ventricular ejection fraction; MI — myocardial infarction; TIA — transient ischemic attack

detection of CPA3, cathepsin G and chymase 1 was < 3.0 pg/mL, < 0.065 ng/mL and < 13.5 pg/mL, respectively. Protein concentration was measured spectrophotometrically (Perkin Elmer VICTOR X4) at a wavelength of 450 ± 10 nm and was determined by comparing the O.D. of samples to a standard curve.

Statistical analysis

The results are expressed as mean ± standard deviation. Comparisons between groups were performed using the t-Student test for continuous variables and χ^2 test for categorical variables. Wizard Statistics 1.8.16 software was used for analysis, p-value < 0.05 was considered statistically significant.

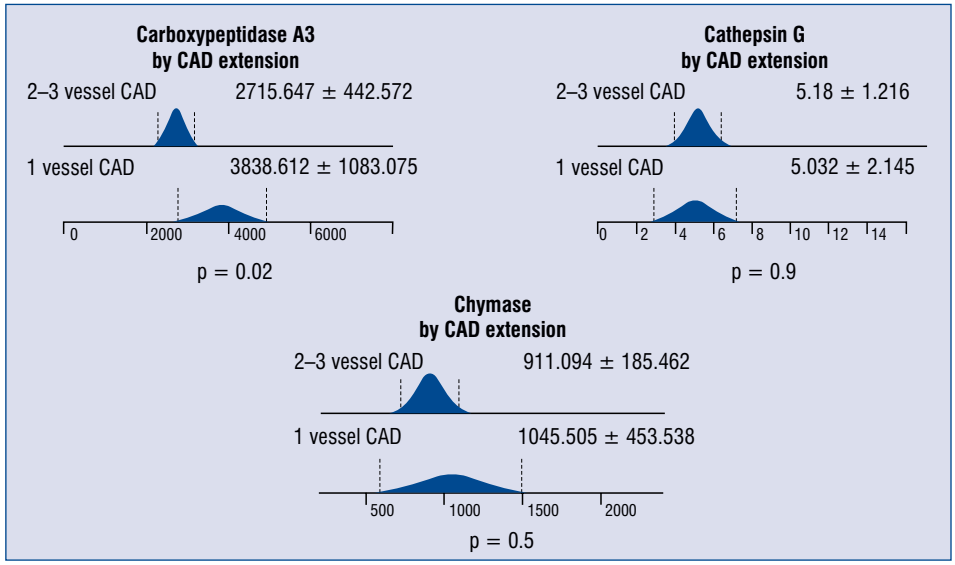

Figure 1. The differences in serum concentrations of carboxypeptidase A3 (pg/mL), chymase 1 (pg/mL) and cathepsin G (ng/mL) in patients with single vessel coronary artery disease (CAD) and 2 or3 vessel CAD.

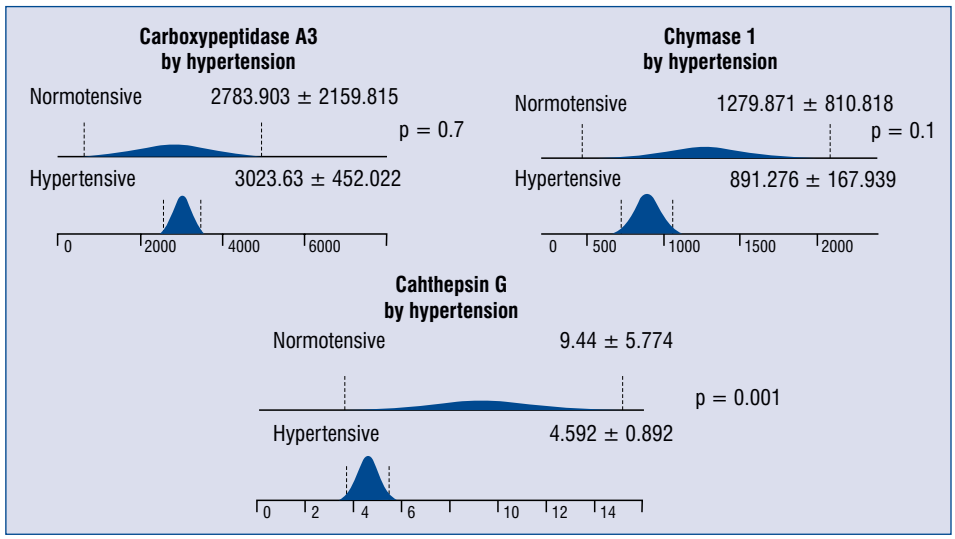

Figure 2. The differences in serum concentrations of carboxypeptidase A3 (pg/mL), chymase 1 (pg/mL) and cathepsin G (ng/ml) among patients with or without hypertension.

Results

The demographic and biochemical data of 44 patients with significant CAD are presented in Table 1. Patients with more advanced CAD had more often had a history of previous myocardial infarction (MI).

The major clinical and biochemical data of 23 NSTEMI patients were compared to subjects with stable CAD are listed in Table 2. Patients with stable CAD had more often had a history of MI in the past and presented more often with three vessel CAD compared to NSTEMI patients. On the other hand, subjects with NSTEMI had significantly higher levels of C-reactive protein and lower glomerular filtration rate.

Patients with one vessel CAD presented a significantly higher level of carboxypeptidase than those with more advanced CAD. Neither the cathepsin G nor chymase differed between the two groups (Fig. 1).

Significantly lower levels of cathepsin G were observed among patients with CAD and hyperten-

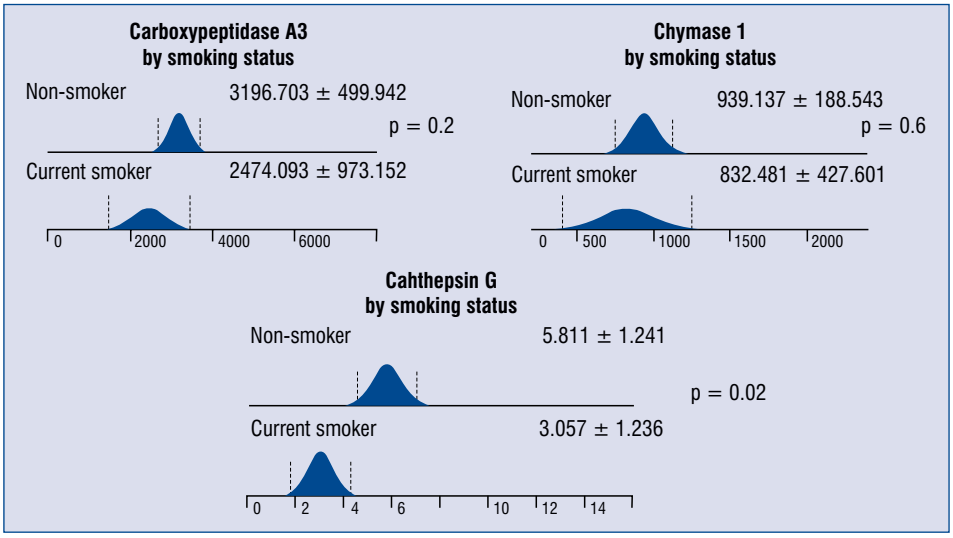

Figure 3. The differences in serum concentrations of carboxypeptidase A3 (pg/mL), chymase 1 (pg/mL) and cathepsin G (ng/ml) among patients with coronary artery disease (CAD) according to their smoking status.

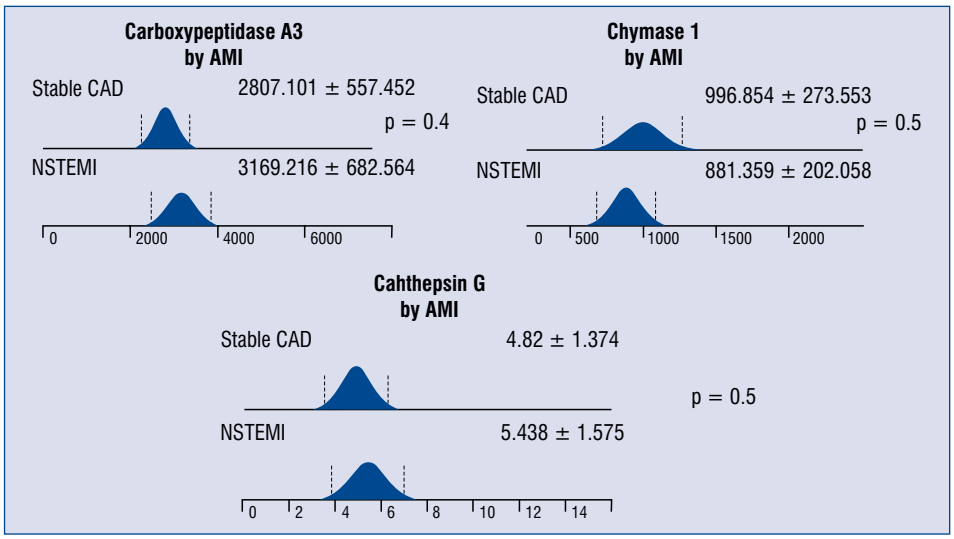

Figure 4. The differences in serum concentrations of carboxypeptidase A3 (pg/mL), chymase 1 (pg/mL) and cathepsin G (ng/ml) in patients with stable coronary artery disease (CAD) and non-ST-segment elevation myocardial infarction (NSTEMI); AMI — acute myocardial infarction.

sion as compared with normotensive CAD subjects (Fig. 2). Lower serum concentrations of cathepsin G in individuals with CAD were also associated with smoking (Fig. 3).

There were no statistically significant differences in levels of any protease between patients with stable CAD and those with NSTEMI (Fig. 4).

Discussion

Mast cells have been extensively investigated in the context of hypersensitivity [19] and little is known about their influence on the human body apart from allergic inflammation. However, in the present study it was shown that serum concentration of MC derived enzyme CPA3 was decreased in patients with more advanced CAD. In addition, higher levels of cathepsin G were found in normotensive CAD patients and in those who were non-smokers. This data has shed new light on MC and the role of their activation in cardiovascular diseases.

Previously, Xiang et al. [20] reported increased chymase concentration in patients with MI. How-

ever, there is no data concerning a possible association of carboxypeptidase and presence of CAD. In the current study, significantly higher levels of CPA3 were observed in patients with angiographically confirmed single vessel CAD as compared with subjects with advanced two or three vessel disease.

Carboxypeptidase A3 and chymase 1 play a key role in the formation as well as degradation of angiotensin II [18]. Whereas chymase is the main tissue converter of angiotensin I to angiotensin II, CPA3 creates peptides Ang-(1–9) and Ang-(1–7) that antagonize angiotensin II [18]. The peptide angiotensin II is not only a strong vasoconstrictor, but it also can promote atherosclerosis via several biologic activities such as: an increased expression of adhesion molecules on endothelial cells, activation of macrophages and upregulation of matrix metalloproteinases and proinflammatory cytokines [21, 22]. Therefore, as an indirect antagonist of angiotensin II, CPA3 exerts a protective effect in CAD. CPA3 was also found to degrade another vasoconstrictor — endothelin-1 and was found to play a cardioprotective effect during ischemia-reperfusion injury [23]. In addition, the present study revealed that lower serum concentration of the peptide was characteristic for patients with more advanced CAD and also for those who were active smokers. As smoking is one of the most widely known risk factors of cardiovascular diseases [24], this data suggests that one of the mechanisms of the deleterious impact of smoking on blood vessels might be an inhibitor of CPA3 production. Thus, all these data together confirms a protective effect of this enzyme in CAD.

When NSTEMI patients were compared with those having stable CAD, nosignificant differences were found in the levels of any of the proteases studied. Previously Xiang et al. [20] reported that serum chymase levels were higher in patients with AMI compared to subjects with stable CAD, however this difference was not statistically significant [20]. The lack of significant differences in serum levels of chymase between patients with MI and stable CAD in the cited study and chymase and carboxypeptidase of the present research may reflect the fact that an underlying mechanism of angiotensin II regulation influences chronic atherosclerosis rather than a formation of unstable coronary plaque and consequently AMI.

The concentration of cathepsin G was significantly lower in current smokers and hypertensive patients than in non-smokers and normotensive individuals, respectively. Wang et al. [13] has shown, that cathepsin G promoted early atherogenesis through its elastinolytic activity, but on the other hand it suppressed late progression of atherosclerosis by degrading LDL. In their study patients with CAD were characterized with significantly lower levels of cathepsin G and higher levels of LDL, than individuals without CAD [13]. In the present study, decreased serum concentration of cathepsin G in CAD patients was associated with tabacco smoking or hypertension. Cathepsin G was found to exert an anti-inflammatory effect by reducing biological activity of inflammatory cytokines [25]. As both hypertension and smoking are associated with inflammation and increased production of pro-inflammatory cytokines [26], lower levels of protease in these patients may reflect an exhaustion of its production in chronic inflammation.

Conclusions

1. Decreased serum concentration of CPA3 is a hallmark of more advanced CAD.
2. Lower serum levels of CPA3 and catepsin G are associated with risk factors of blood vessel damage suggesting a protective role of these enzymes in CAD.

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Conflict of interest: None declared

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Two-dimensional versus three-dimensional transesophageal echocardiography in percutaneous left atrial appendage occlusion

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Abstract

Background: *Real-time three-dimensional transesophageal echocardiography (RT3D TEE) enables better visualization of the left atrial appendage (LAA) and may be superior to real-time two-dimensional transesophageal echocardiography (RT2D TEE) for LAA occlusion (LAAO). The aim of this study was to assess inter- and intra-observer variability of RT2D TEE and RT3D TEE measurements of LAA, and to assess the accordance of RT2D TEE and RT3D TEE with appropriate occluder selection.*

Methods: *Transesophageal echocardiography was performed in 40 patients during LAAO. RT2D TEE and RT3D TEE measurements of the ostium and landing zone were performed independently by two echocardiographers. The appropriate choice of occluder was confirmed with fluoroscopic criteria. After the procedures, RT2D TEE and RT3D TEE evaluation were repeated separately by the same echocardiographers.*

Results: *The mean ostium diameters by RT2D TEE obtained by the two observers were 23.6 ± 4.2 vs. 24.8 ± 5.2 ($p = 0.04$), and the mean landing zone diameters were 17.7 ± 4.4 vs. 19.4 ± 3.9 ($p < 0.01$). In the case of RT3D TEE, the ostium diameters were 29.6 ± 5.3 vs. 29.4 ± 6.4 (p = not significant [NS]) and the landing zone diameters were 21.4 ± 3.8 vs. 21.6 ± 3.9 (p = NS). Intra-observer differences were absent in the case of RT3D TEE. The comparison of RT2D TEE vs. RT3D TEE analyses performed by the same echocardiographer revealed significant differences in the ostium and landing zone measurements (both $p < 0.01$). Agreement between the suggested device size was better for RT3D TEE (weighted kappa was 0.62 vs. 0.28, respectively).*

Conclusions: *The results obtained with RT3D TEE showed significantly larger dimensions of the ostium and the landing zone. RT3D TEE showed lesser inter- and intra-observer variability and better agreement with the implanted device.* (Cardiol J 2019; 26, 6: 687–695)

Key words: left atrial appendage occlusion, real-time two- and three-dimensional transesophageal echocardiography, Amplatzer Occluder

Introduction

Atrial fibrillation (AF) is the most common arrhythmia worldwide and its prevalence is estimated to increase further because of population ageing [1]. The most dangerous complication of AF is ischemic cerebral stroke (ICS). Although oral anticoagulants (OAC) have proven to be effective in preventing ICS [2–4], its risk still remains high in AF patients [5]. In many patients, treatment with OAC may be contraindicated or risky because of conditions such as recurrent bleeding, low compliance, or drug

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intolerance. Left atrial appendage (LAA) occlusion (LAAO) may be considered as an alternative method for ICS prevention [6–8]. According to the guidelines of the European Society of Cardiology, LAAO may be considered in AF patients with high risk of ischemic stroke and contraindications for long-term oral anticoagulation [9].

The technical and clinical success of LAAO depends on correct assessment of the ostium and the landing zone dimensions [10]. Selection of the optimal occluder size remains a challenge as each of the available imaging modalities have some limitations. The main methods of LAA imaging are: conventional cardiac angiography (CCA), transesophageal echocardiography (TEE), and cardiac computed tomography (CCT) angiography [11]. Recent data shows that CCT facilitates a more adequate occluder selection than real-time two-dimensional transesophageal echocardiography (RT2D TEE), and reduces the risk of high-flow leaks and device malposition because of under sizing [12]. However, it is costly, requires injection of a contrast medium, and is not useful for guiding the procedure. Some analyses performed for aortic valve evaluation showed that real-time three-dimensional transesophageal echocardiography (RT3D TEE) may provide more accurate assessment and its results are better correlated with CCT than RT2D TEE [13]. Till date no inter- or intra-observer studies comparing RT2D TEE and RT3D TEE in LAAO procedures have been conducted.

Thus, the aim of this study was to compare RT2D TEE and RT3D TEE in LAAO performed by two independent echocardiographers to determine which method gives more reproducible results and facilitates the selection of the optimal occluder size.

Methods

Left atrial appendage occlusion was performed in 40 consecutive patients with both paroxysmal or persistent/permanent AF (mean age 70 ± 8 years; male 57%) of which 14 were in sinus rhythm during the procedure. In line with the current recommendations, all patients had indications for ICS prevention based on the CHA_2DS_2-VASc score (mean 4.2 ± 1.5). Selection of patients was based on the EHRA/EAPCI expert consensus statement, which included: the presence of contraindications to OAC (e.g. thrombocytopenia, cancer), irreversibly high risk of bleeding according to the HAS-BLED score, and the presence of ICS despite OAC treatment [14]. The mean HAS-BLED score was 3.3 ± 0.9.

Table 1. Group characteristics.

Age [years]	70 ± 8
Male [n]	57% [23]
HAS-BLED score	3.3 ± 0.9
CHA_2DS_2-VASc score	4.2 ± 1.5
Hypertension [n]	82% [33]
Diabetes [n]	37% [37]
Coronary heart disease [n]	75% [30]
Paroxysmal atrial fibrillation [n]	47% [19]

Patients with a LAA thrombus, LAA dimension being too small or too large for LAAO, LAA depth < 10 mm, or an elongated shape of the ostium did not qualify for the procedure. Clinical characteristics of the study population are presented in Table 1.

LAAO procedure

The LAAO procedure was performed under general anesthesia. Access to the right atrium was obtained via the femoral vein. A transseptal puncture was performed to reach the left atrium. Heparin was subsequently administered to obtain activated clotting time above 250 s. After the introduction of a pig-tail catheter to the LAA, CCA of the LAA was performed. The LAA was visualized from different views to find the largest diameter of the LAA neck. The procedures were guided by both fluoroscopy and transesophageal echocardiography.

Transesophageal echocardiography

Electrocardiographic (ECG) gated transesophageal echocardiography was performed using Vivid E9 (6 VT-D probe; 5 MHz). On the day before LAAO, a pre-procedural TEE screening was performed to assess the LAA morphology, exclude an LAA thrombus, and verify the compatibility of the LAA neck dimension with the occluder size.

The ostium, neck, and body of the LAA were visualized in different views. In case of RT2D TEE images, views obtained at ~45°, 90°, and 135° were analyzed. The left circumflex artery was visualized in each case as a reference point for detection of the landing zone. Three measurements were obtained: dimension of the ostium (the line between the left lateral ridge and the ridge separating the LAA from the mitral valve), dimension of the landing zone (starting approximately 10 mm from the left lateral ridge inside the LAA to a point located approximately 5 mm below the circumflex artery), and the depth of the LAA neck (an orthogonal line from the middle of the orifice into the back wall of the LAA).

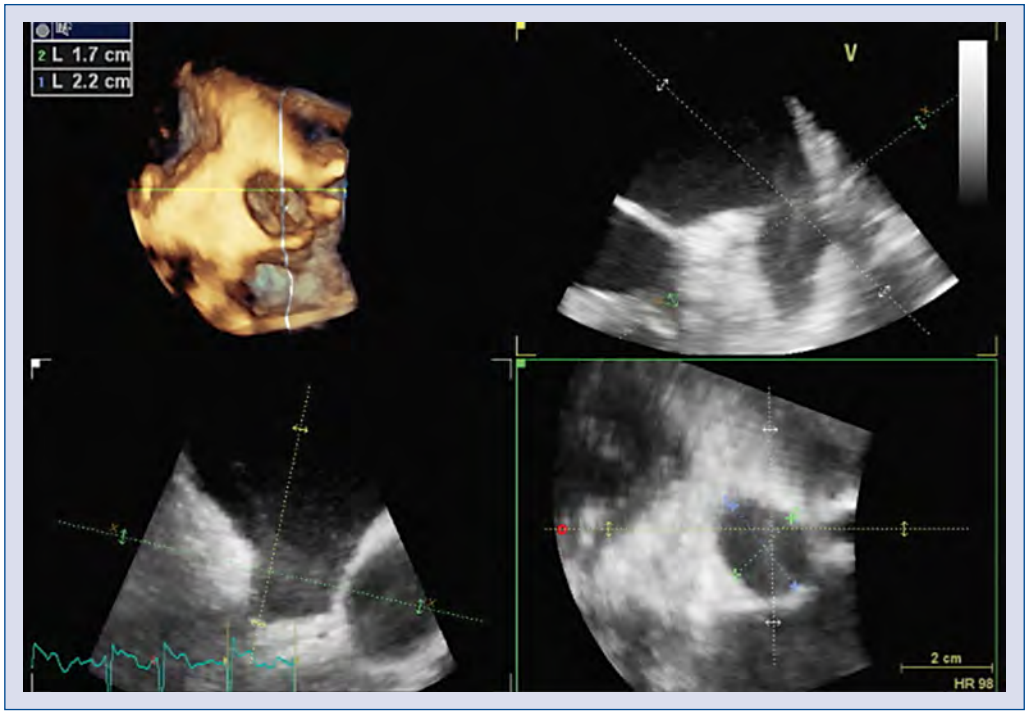

Figure 1. An example of flexi-slice real-time three-dimensional transesophageal echocardiography left atrial appendage image analysis for the measurement of the landing zone dimension.

RT3D TEE zoom images were obtained from one ECG cycle. Gain was adjusted to eliminate artefacts but not to allow for drop-out effect. The ostium and landing zone dimensions were measured in three perpendicular planes using the flexi-slice technique. The ostium level was measured between the pulmonary ridge and the tissue located between the mitral valve and circumflex artery. The landing zone level was assessed approximately 10 mm below the ostium. The largest diameter of LAA ostium was used as a reference for the selection of the occluder size (Fig. 1).

All images were stored on a disk and after the procedure, two independent echocardiographers evaluated the RT2D TEE and RT3D TEE images for ostium and landing zone measurements. The dimensions of LAA ostium and landing zone were assessed twice by each echocardiographer on two different occasions to determine the method with more reproducible results. Based on the two results of LAA landing zone dimensions and the manufacturer sizing chart, retrospectively the best occluder size was selected. The obtained results were then compared with the actual size of the implanted devices.

Occluder sizing

The Amplatzer Cardiac Plug or Amplatzer AMULET (St. Jude Medical, Minneapolis, MN, USA) were used for LAA closure. CCA was used as a referential method for occluder sizing under the condition that the difference with intraprocedural RT2D TEE or RT3D TEE measurement could not be more than 2 mm. If the difference was above 2 mm then measurements were repeated. The size of the device was selected depending on the landing zone dimension, according to the manufacturer sizing chart.

The post-procedural results were assessed with fluoroscopy and transesophageal echocardiography. The criteria for optimal implantation were: separation between the device lobe and the disc, "tire-shaped" lobe, concave-shaped disc, axis of the device lobe parallel to the LAA neck axis, and > 2/3 of the lobe past the circumflex artery.

Statistical analysis

The quantitative data was presented as mean ± standard deviation (SD). Inter- and intra-observer variability was analyzed with Student's t-test for dependent samples. The Bland-Altman plot with multiple measurements per subject was used to assess whether RT2D TEE and RT3D TEE may be used interchangeably. The agreement of RT2D TEE and RT3D TEE with the implanted device was calculated with weighted kappa statistics.

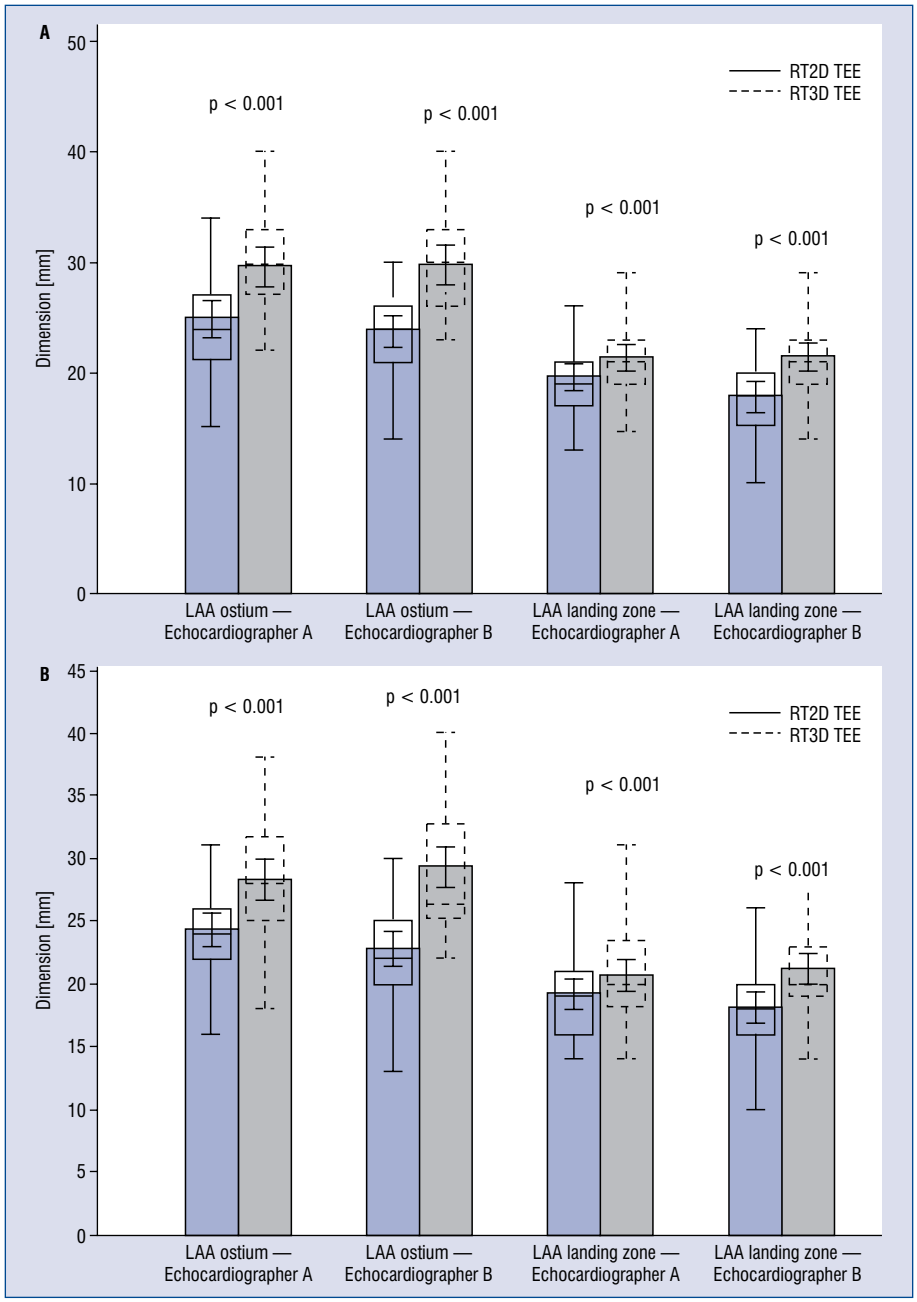

Figure 2. Comparison of real-time two-dimensional transesophageal echocardiography (RT2D TEE) versus real-time three-dimensional transesophageal echocardiography (RT3D TEE) results of left atrial appendage (LAA) ostium and LAA landing zone measurement; **A.** Primary analysis; **B.** Reaanalysis.

Results

The mean ostium diameters by RT2D TEE measurements obtained by the two observers were 23.6 ± 4.2 vs. 24.8 ± 5.2 ($p = 0.04$), and the mean landing zone diameters were 17.7 ± 4.4 vs. 19.4 ± 3.9 ($p < 0.01$). In the case of RT3D TEE, the mean ostium diameters were 29.6 ± 5.3 vs. 29.4 ± 6.4 (p = not significant [NS]) and the landing zone diameters were 21.4 ± 3.8 vs. 21.6 ± 3.9 (p = NS). Both the first and repeated measurements of the LAA landing zone and ostium obtained with RT2D TEE were lower than those obtained with RT3D TEE (Fig. 2A, B). The differences were statistically significant.

Analysis of the RT2D TEE data obtained by the two echocardiographers showed significant differences, both with regard to the LAA ostium and the LAA landing zone assessment (both smaller when measured by echocardiographer A). Similar results

Table 2. Inter-observer variability for RT2D TEE and RT3D TEE.

Diameter	Echocardiographer A	Echocardiographer B	P
Primary analysis			
Ostium (RT2D TEE) [mm]	24.8 ± 5.2	23.6 ± 4.2	0.04
Landing zone (RT2D TEE) [mm]	19.4 ± 3.9	17.7 ± 4.4	< 0.01
Ostium (RT3D TEE) [mm]	29.4 ± 6.4	29.6 ± 5.3	NS
Landing zone (RT3D TEE) [mm]	21.6 ± 3.9	21.4 ± 3.8	NS
Repeated analysis			
Ostium (RT2D TEE) [mm]	22.8 ± 4.2	24.3 ± 4.3	< 0.01
Landing zone (RT2D TEE) [mm]	18,1 ± 3.7	19.2 ± 3.6	< 0.01
Ostium (RT3D TEE) [mm]	28.6 ± 5.2	29.3 ± 5.0	NS
Landing zone (RT3D TEE) [mm]	21.2 ± 3.7	20.7 ± 3.8	NS

RT2D TEE — real time two-dimensional transesophageal echocardiography; RT3D TEE — real time three-dimensional transesophageal echocardiography

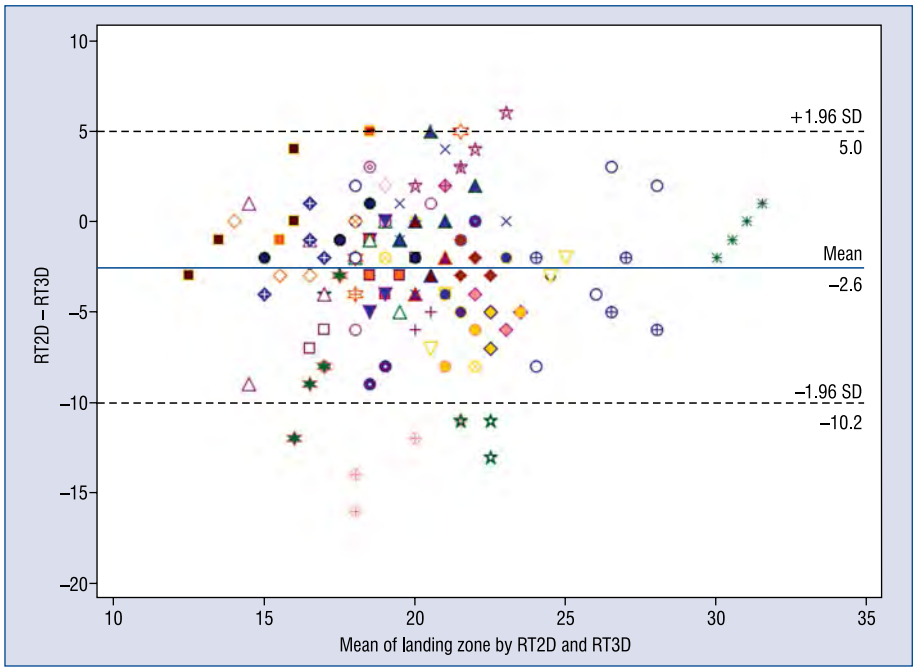

Figure 3. Bland-Altman plot with multiple measurements per subject for landing zone assessed with real-time two-dimensional transesophageal echocardiography (RT2D TEE) and real-time three-dimensional transesophageal echocardiography (RT3D TEE).

were found in repeated analysis of RT2D TEE images. No such differences were seen in the RT3D TEE measurements. The inter-observer variability for RT2D TEE and RT3D TEE data is presented in Table 2 (primary analysis and reanalysis).

The Bland-Altman plot with multiple measurements per subject including repeated measurements of the landing zone performed by both echocardiographers showed that the arithmetic mean difference between RT2D TEE and RT3D TEE dimension was 2.6 mm, and the lower and upper limits of difference were –10.2 mm and 5.0 mm, respectively (Fig. 3). Such differences may have an effect on the selection of occluders.

Intra-observer variability was performed for both echocardiographers. The analysis of ostium and landing zone measurements obtained with RT2D TEE differed significantly for both echo-

Table 3. Summary of intra-observer variability assessment for echocardiographer A and B (p value for T-test for dependent samples).

	P value	
	Echocardiographer A	Echocardiographer B
RT2D TEE Ostium	0.03	< 0.01
RT3D TEE Ostium	NS	NS
RT2D TEE Landing zone	0.03	0.01
RT3D TEE Landing zone	NS	NS

RT2D TEE — real-time two-dimensional transesophageal echocardiography; RT3D TEE — real-time three-dimensional transesophageal echocardiography; NS — not significant

cardiographers. No such differences were seen in RT3D TEE analysis (Table 3).

Based on the dimension of the landing zone obtained with RT2D TEE and the sizing charts provided by the manufacturer, the suggested device size was assigned for each subject. The same was performed for the data obtained with RT3D TEE. The inter-rater agreement (kappa) between the size of the implanted device and that selected with RT3D TEE was good (weighted kappa = 0.68), whereas that selected with RT2D TEE was only fair (weighted kappa = 0.28) (Table 4A, B).

Discussion

Appropriate occluder sizing is crucial for the safety and efficacy of LAAO. A TEE follow-up of patients randomized for LAAO with the Watchman device in the PROTECT-AF study revealed that up to 32% of implanted patients had at least some degree of peri-device flow at 1 month [15]. Although presence of peri-device leak was not associated with an increased risk of thromboembolism in that study, leaks over 5 mm in width indicate insufficient protection against ICS. Underestimation of the landing zone dimension increases the risk of peri-device leak and is a risk factor for early device embolization [16], whereas excessive oversizing may increase the risk of left LAA wall tear or compression of the adjacent structures.

Different imaging modalities, such as CCT, TEE, magnetic resonance imaging and fluoroscopy are used to determine LAA anatomy [17]. Although CCT and fluoroscopy have been shown to facilitate better assessment of LAA than TEE, the latter still remains the standard tool for guidance of LAAO procedures.

Clemente et al. [12] performed a pre-operative evaluation of LAA with TEE, CCT, intracardiac echocardiography, and CCA in 66 consecutive patients who underwent LAAO with the Amplatzer Cardiac Plug [12]. LAA diameters measured with CCT correlated with the diameters obtained with CCA and intracardiac echocardiography, but were slightly larger. TEE had a lower correlation with other imaging methods and a tendency to underestimate the LAA diameter. The authors concluded that CCT reduced device malposition because of under sizing. Similar findings were also reported by Vaitkus et al. [18] who found that CCT enables better visualization of LAA geometry and appropriate occluder selection. However, comparison between CCT and TEE for LAA evaluation was based on 2D imaging modality. Moreover, Budge et al. [19] compared the results of RT2D TEE with those obtained with planar CCT, and 3D segmented computed tomography reconstructions. They concluded that LAA orifice measurements were not interchangeable using these imaging modalities. The mean LAA orifice diameter in segmented CCT was larger (28.5 ± 4.5 mm) than planar CCT and TEE (26.3 ± 4.1 mm and 26.1 ± 6.4 mm, respectively).

The feasibility and accuracy of RT3D TEE in LAA morphology assessment was performed by Shah et al. [20]. The feasibility of RT3D TEE for LAA geometry was studied in the first 37 patients, whereas RT2D TEE and RT3D TEE quantification of the LAA were compared in the subsequent 29 patients. In 8 patients the data also correlated with CCT results. The LAA orifice area on CCT correlated well with RT3D TEE data (r = 0.98) but not with RT2D TEE data (r = 0.13). The Bland-Altman analysis demonstrated that, compared with RT3D TEE, RT2D TEE systematically underestimated the LAA orifice area.

Recently Yosefey et al. [21] showed that RT3D TEE (24.5 ± 4.7 mm) vs. CCT (24.6 ± 5, p = NS) was more accurate in measuring the maximal LAA diameter compared to RT2D TEE (23.5 ± 3.9 mm)

Table 4A. Inter-rater agreement (kappa) for devices selected with real time two-dimensional transesophageal echocardiography (RT2D TEE) and the implanted devices. Weighted kappa 0.28.

Implanted device	Device by RT2D TEE											
	16	18	20	22	24	25	26	28	30	31	34	
16	0	0	0	0	0	0	0	0	0	0	0	0 (0.0%)
18	1	1	0	1	0	0	0	0	0	0	0	3 (7.5%)
20	0	0	1	0	0	1	0	0	0	0	0	2 (5.0%)
22	1	0	6	1	0	0	0	3	0	1	0	12 (30.0%)
24	0	1	0	0	0	1	0	2	0	0	0	4 (10.0%)
25	0	0	0	1	0	2	0	1	0	0	0	4 (10.0%)
26	0	0	0	1	0	1	0	2	0	1	0	5 (12.5%)
28	0	0	0	2	0	2	0	2	0	0	0	6 (15.0%)
30	0	0	0	0	0	0	0	0	0	1	0	1 (2.5%)
31	0	0	1	0	0	0	0	0	0	0	0	1 (2.5%)
34	0	0	0	0	0	1	0	0	0	1	0	2 (5.0%)
	2 (5.0%)	2 (5.0%)	8 (20.0%)	6 (15.0%)	0 (0.0%)	8 (20.0%)	0 (0.0%)	10 (25.0%)	0 (0.0%)	4 (10.0%)	0 (0.0%)	40

Table 4B. Inter-rater agreement (kappa) for devices selected with real time three-dimensional transesophageal echocardiography (RT3D TEE) and the implanted devices. Wighted kappa 0.62.

Implanted device	Device by RT3D TEE										
	18	20	22	24	25	26	28	30	31	34	
18	1	1	1	0	0	0	0	0	0	0	3 (7.5%)
20	0	1	1	0	0	0	0	0	0	0	2 (5.0%)
22	0	2	6	0	3	0	1	0	0	0	12 (30.0%)
24	0	0	0	3	0	0	0	1	0	0	4 (10.0%)
25	0	0	0	0	2	0	0	0	2	0	4 (10.0%)
26	0	0	0	0	1	2	2	0	0	0	5 (12.5%)
28	0	0	1	0	1	0	3	0	0	1	6 (15.0%)
30	0	0	0	0	0	0	1	0	0	0	1 (2.5%)
31	0	0	0	0	0	0	0	0	1	0	1 (2.5%)
34	0	0	0	0	0	0	0	0	1	1	2 (5.0%)
	1 (2.5%)	4 (10.0%)	9 (22.5%)	3 (7.5%)	7 (17.5%)	2 (5.0%)	7 (17.5%)	1 (2.5%)	4 (10.0%)	2 (5.0%)	40

vs. CTA ($p < 0.01$). However, the measurements were performed for the orifice, not the landing zone, which is the reference for occluder sizing. Moreover Nucifora et al. [22] showed higher correlation of CCT with RT3D TEE for assessment of the LAA orifice area compared to RT2D TEE ($r = 0.92$, 95% CI 0.85–0.95 and $r = 0.72$, 95% CI 0.55–0.83, respectively).

In accordance with the cited literature, results of the present study confirmed that the diameter of LAA ostium and LAA landing zone are considerably larger when assessed with RT3D TEE as compared with RT2D TEE. However, previous studies lacked a comparison between the results obtained with CCT or RT3D TEE and the actual fit of occluders used for LAAO. Neither the comparison of images after implantation nor the frequency of peri-device leak was analyzed for RT3D TEE or CCT. Despite previous recommendations for the use of RT2D TEE in occluder selection for LAAO, according to available research, the presented analysis shows the superiority of RT3D TEE over RT2D TEE for

the first time. Moreover, RT3D TEE enables better imaging of the structures surrounding the LAA, thus reducing the probability of malposition. Use of RT3D TEE instead of RT2D TEE also generates practical advantages, such as avoiding potential complications, reducing radiation exposure, and/or shortening procedural times [23]. A possible limitation of RT3D TEE may be the lack of standards for obtaining RT3D TEE images. Nevertheless, it is becoming an elementary navigation method for percutaneous procedures e.g. percutaneous mitral valve repair [24].

Although the accuracy of LAA assessment is similar for both RT3D TEE and CCT, the first does not require contrast agents. It is especially important in patients with renal failure qualified for LAAO. Other advantages include cost effectiveness, lack of radiation, and lesser time consumption.

Conclusions

There are significant differences between RT2D TEE and RT3D TEE in the assessment of the LAA ostium and landing zone diameters. The results showed significantly larger dimensions of both the ostium and the landing zone obtained with RT3D TEE. RT2D TEE measurement of the ostium and landing zone dimensions were associated with significant inter- and intra-observer variability; no such differences were found for RT3D TEE results. RT3D TEE has a better agreement with the implanted occluders than RT2D TEE.

Conflict of interest: W. Streb, K. Mitręga and Z. Kalarus are proctors of St. Jude Medical.

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The impact of renal function on the prognostic value of N-terminal pro–B-type natriuretic peptide in patients with coronary artery disease

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Abstract

Background: *The impact of renal function on the prognostic value of N-terminal pro–B-type natriuretic peptide (NT-proBNP) remains unclear in coronary artery disease (CAD). This study sought to investigate the value of using NT-proBNP level to predict prognoses of CAD patients with different estimated glomerular filtration rates (eGFRs).*

Methods: *A retrospective analysis was conducted from a single registered database. 2087 consecutive patients with CAD confirmed by coronary angiography were enrolled. The primary endpoint was all-cause mortality.*

Results: *The mean follow-up time was 26.4 ± 11.9 months and death events occurred in 197 cases. The NT-proBNP levels increased with the deterioration of renal function, as well as the optimal cut-off values based on eGFR stratification to predict endpoint outcome (179.4 pg/mL, 1443.0 pg/mL, 3478.0 pg/mL, for eGFR ≥ 90, 60–90 and < 60 mL/min/1.73 m^2, respectively). Compared with the routine cut-off value or overall optimal one, stratified optimal ones had superior predictive ability for endpoint in each eGFR group (all with the highest Youden's J statistics). And the prognostic value became weaker as eGFR level decreased (eGFR ≥ 90 vs. 60–90 vs. < 60 mL/min/1.73 m^2, odds ratio [OR] 7.7; 95% confidence interval [CI] 1.7–33.9 vs. OR 4.8; 95% CI 2.7–8.5 vs. OR 3.0; 95% CI 1.5–6.2).*

Conclusions: *This study demonstrated that NT-proBNP exhibits different predictive values for prognosis for CAD patients with different levels of renal function. Among the assessed values, the NT-proBNP cut-off value determined using renal function improve the accuracy of the prognosis prediction of CAD. Moreover, lower eGFR is associated with a higher NT-proBNP cut-off value for prognostic prediction.* (Cardiol J 2019; 26, 6: 696–703)

Key words: coronary artery disease, renal function, N-terminal pro–B-type natriuretic peptide, prognosis

Introduction

N-terminal pro–B-type natriuretic peptide (NT-proBNP) level [1, 2] and estimated glomerular filtration rate (eGFR) [3, 4] are important predictors of clinical prognosis in patients with coronary artery disease (CAD). Prior studies have shown that for such patients, NT-proBNP level is significantly correlated with eGFR; in particular, NT-proBNP level increases as eGFR decreases

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[5, 6]. Moreover, investigations have also revealed that the combined use of NT-proBNP level and eGFR can improve the identification of patients at high risk of acute myocardial infarction and heart failure (HF) [7–9]. Similarly, NT-proBNP levels are influenced by age [10]. Research has indicated that greater age is associated with a higher NT-proBNP cut-off value for diagnosing HF [11]. However, the predictive value of NT-proBNP measurements remains unclear for patients with different eGFRs.

This study sought to investigate the predictive value of using NT-proBNP level to predict prognoses of CAD patients with different eGFRs by analysing 2087 consecutive cases of patients with CAD.

Methods

Study population

The data source for this investigation was the West China Hospital CAD database. This single center database prospectively includes all patients undergoing coronary angiography with known or highly suspected CAD in West China Hospital affiliated to Sichuan University. For this analysis, consecutive patients with CAD were enrolled from July 2008 to January 2012. Patients with CAD were eligible for inclusion if they were restricted to participants with angiographic evidence of ≥ 50% stenosis in ≥ 1 coronary vessels. The exclusion criteria included malignancies, pregnancy, end stage renal disease with hemodialysis or renal transplant and severe liver or hematological diseases. The above criteria were met by 3375 consecutive patients. After further removing those with loss of follow-up (n = 312) or incomplete follow-up data (n = 61), and patients without presence of NT-proBNP data at admission (n = 915), 2087 patients were included in this data analysis. The study protocol was approved by the local institutional review boards in accordance with the Declaration of Helsinki. All subjects provided written informed consent when they were included in the database.

Baseline characteristics

Demographic data, medical history, cardiovascular risk factor, vital signs at admission, medication at discharge, and final diagnosis were obtained from the patient electronic medical records and were reviewed by a trained study coordinator. Blood samples were collected before angiography, and blood biomarkers measured including NT-proBNP (measured with an electrochemiluminescence immunoassay kit. Roche Diagnostics, Grenzach Wyhlen, Germany), liver and kidney function (including the admission serum creatinine levels), blood glucose, serum lipid, and other measurements were analyzed in the Department of Laboratory Medicine, West China Hospital, accredited by the College of American Pathologists. Hypertension was defined as those with systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or those receiving antihypertensive medications. Diabetes mellitus was diagnosed in patients who had previously undergone dietary treatment for diabetes, had received additional oral antidiabetic or insulin medication or had a current fasting blood glucose level of ≥ 7.0 mmol/L or random blood glucose level ≥ 11.1 mmol/L. Patients received care according to usual practice; treatment was not affected by participation in this study.

Renal function assessment

Serum creatinine was finished before the angiography within first 24 h after admission and assessed by a nonkinetic alkaline picrate (Jaffe) method. The Modification of Diet in Renal Disease (MDRD) equation was used to eGFR rate in milliliters per minute per 1.73 m^2 [12]. Patients were divided into three eGFR groups: eGFR ≥ 90 mL/min/1.73 m^2 (normal renal function corresponding to strata used to define chronic kidney disease stages [13]), 60 ≤ eGFR < 90 mL/min/1.73 m^2 (mildly impaired renal function), and eGFR < 60 mL/min/1.73 m^2 (moderately or severely impaired renal function).

Follow-up and endpoint

The follow-up period ended on January 2013. Follow-up information was collected through contact with patients' physicians, patients or their family. All data were corroborated with hospital records. The primary endpoint in this study were all-cause mortality, as documented in the database. Cardiovascular mortality was not used as an endpoint outcome to perform analysis after preliminarily calculating statistics power, which was insufficient for further analysis due to low mortality in the limited follow-up time.

Statistical analysis

Post-hoc analysis was conducted on a retrospective basis. Baseline characteristics were compared among patients categorized by admission eGFR levels. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were reported as counts (percentages).

Analysis of t tests and Pearson χ^2 tests were used to compare the difference for baseline variables among eGFR groups, respectively. Kruskal-Wallis tests were applied to analyze the difference of NT-proBNP levels in patients across renal function status, as well as that between patients with and without endpoint in the same eGFR group. Trend χ^2 tests were used to evaluate tendency changes in all-cause mortality according to eGFR levels and NT-proBNP quartiles. For the investigation of overall optimal NT-proBNP cut-off value in the total population and stratified optimal ones in corresponding eGFR groups to predict the endpoint, receiving operating characteristic (ROC) analysis were conducted. And the following parameters: sensitivity, specificity, as well as Youden's J statistic, an index to measure the performance for these cut-off values to discriminate between low and high risk individuals in an objective manner [14], were calculated for overall and stratified optimal ones, and the non-optimal one (300 pg/mL, as proposed in the literature [15]) in each eGFR groups. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated based on Binary Logistic Regression models, which were used to investigate the risk effect of NT-proBNP levels (as categorical variables, under and above the optimal cut-off values or the non-optimal ones) on the outcome events in different eGFR groups. Two-sided p values of less than 0.05 indicated statistical significance. All analyses were performed with SPSS software (version 24.0).

Results

A total of 2087 patients with CAD were included in this study. Their mean age was 65.0 ± ± 10.7 years, 21.8% of the patients were female, and patients with eGFR ≥ 90 mL/min/1.73 m^2 or < 60 mL/min/1.73 m^2 accounted for 29.6% and 19.1% of total population, respectively. Patients baseline characteristics varied as renal function deteriorated; in particular, compared with patients in a higher eGFR group, participants in the lower eGFR group tended to be older and had a higher proportion of female, smoke exposure, hypertension, diabetes, cardiac dysfunction, and complex coronary lesions at admission, and had a lower percentage of prescription of antiplatelet drugs and statins at discharge (Table 1).

Over a mean follow-up period of 26.4 ± 11.9 months, 197 endpoint outcomes occurred (all-cause mortality rate 9.4%), 107 of that were attributed to cardiovascular deaths (cardiac mortality rate 5.1%). There was a strong association between renal function and all-cause or cardiovascular mortality, and a similar relationship was also observed between NT-proBNP quartiles and all-cause or cardiovascular mortality (all p values for trend < 0.01) (Fig. 1).

Meanwhile, there was a significant correlation between NT-proBNP levels and renal function. The NT-proBNP levels increased with the deterioration of renal function, median value ranging from 341.0 pg/mL at eGFR ≥ 90 mL/min/1.73 m^2 to 1205.0 pg/mL at eGFR < 60 mL/min/1.73 m^2 in patients without all-cause death (p for trend < 0.01), and ranging from 900.0 pg/mL to 6086.5 pg/mL in patients with all-cause death (p for trend < 0.01), meanwhile, the NT-proBNP level of the dead was higher than that of survivors in each eGFR group (all p < 0.01) (Fig. 2, Table 2).

The overall optimal NT-proBNP cut-off value for all patients and the stratified optimal ones for patients with corresponding renal function status to predict all-cause death determined by ROC analysis were as follow: 1440.5 pg/mL for all patients, 179.4 pg/mL for eGFR ≥ 90 mL/min/1.73 m^2, 1443.0 pg/ /mL for eGFR ranging 60–90 mL/min/1.73 m^2, and 3478.0 pg/mL for eGFR < 60 mL/min/1.73 m^2. Compared with non-optimal cut-off value (300 pg/mL) and overall optimal one, the stratified optimal one has a superior ability to discriminate the risk and predict all-cause mortality in each eGFR group (all the three with the highest Youden's J statistics) (Table 3).

After adjustment for potential confounders by multivariate logistic regression analysis, stratified optimal NT-proBNP cut-off value, not overall optimal one or non-optimal one, which increased with the deterioration of renal function status, was the first-rank one to predict endpoint in each eGFR group, and the prognostic values became weaker as eGFR level decreased (eGFR ≥ 90 vs. 60–90 vs. < 60 mL/min/1.73 m^2, OR 7.7; 95% CI 1.7–33.9 vs. OR 4.8; 95% CI 2.7–8.5 vs. OR 3.0; 95% CI 1.5–6.2) (Table 4).

Discussion

This study has demonstrated that 1) NT--proBNP level is negatively correlated with eGFR in CAD patients; 2) the value of NT-proBNP level for predicting prognosis varies for CAD patients with different eGFRs: A lower eGFR level is indicative of decreased diagnostic value of NT-proBNP and a larger optimal NT-proBNP cut-off value for predicting prognosis.

The value of NT-proBNP level for predicting clinical prognosis in patients with cardiovascular

Table 1. Baseline characteristics of the study population.

Characteristics	eGFR [mL/min/1.73 m^2]				P
	Total	≥ 90	60–90	< 60	
No. of patients	2087	618	1071	398	
Age [years]	65.0 ± 10.7	59.1 ± 11.4	66.4 ± 9.6	70.7 ± 7.9	< 0.01
Gender, female	454 (21.8%)	101 (16.3%)	218 (20.4%)	135 (33.9%)	< 0.01
Medical history					
Current smoking	676 (34.1%)	227 (38.1%)	351 (35.0%)	98 (25.7%)	< 0.01
Pre-hypertension	1136 (54.6%)	268 (43.4%)	595 (55.8%)	273 (68.9%)	< 0.01
Pre-diabetes mellitus	472 (22.7%)	112 (18.2%)	228 (21.4%)	132 (33.3%)	< 0.01
At admission					
Systolic blood pressure [mmHg]	130.8 ± 23.6	128.8 ± 24.7	131.4 ± 22.4	132.4 ± 25.1	0.03
Diastolic blood pressure [mmHg]	76.3 ± 13.0	76.7 ± 12.9	76.7 ± 12.6	74.5 ± 14.3	0.01
Heart rate [bpm]	74.8 ± 14.7	74.0 ± 14.0	74.5 ± 14.1	76.9 ± 16.8	0.01
Killip classification ≥ II	268 (12.8%)	69 (11.2%)	123 (11.5%)	76 (19.1%)	< 0.01
Left ventricular ejection fraction [%]	59.4	59.7	60.2	56.7	< 0.01
Laboratory values					
eGFR [mL/min/1.73 m^2]	79.0 ± 24.1	106.3 ± 15.9	75.8 ± 8.3	45.4 ± 12.3	< 0.01
Blood glucose [mmol/L]	7.3 ± 3.5	6.9 ± 2.9	7.1 ± 3.1	8.2 ± 5.0	< 0.01
Diagnosis					
ACS	1552 (74.4%)	446 (72.2%)	803 (75.0%)	303 (76.1%)	0.30
STEMI	308 (14.8%)	98 (15.9%)	143 (13.4%)	67 (16.8%)	0.16
Severity of CAD					
Left main artery	215 (10.3%)	56 (9.1%)	114 (10.6%)	45 (11.3%)	0.50
Three vessel diseases	569 (27.3%)	143 (23.1%)	285 (26.6%)	141 (35.4%)	< 0.01
Discharge medication					
Acetylsalicylic acid	1931 (93.5%)	581 (94.8%)	1008 (95.1%)	342 (87.0%)	< 0.01
Clopidogrel	1886 (91.3%)	574 (93.6%)	974 (91.9%)	338 (86.0%)	< 0.01
Statin	1886 (91.3%)	562 (91.8%)	987 (93.1%)	337 (85.8%)	< 0.01
Beta-receptor blockers	1361 (65.9%)	398 (64.9%)	729 (68.8%)	234 (59.5%)	< 0.01
ACEI or ARBs	1200 (58.1%)	330 (53.8%)	642 (60.7%)	228 (58.0%)	0.02

Data are expressed as means ± standard deviation or counts and percentages, as appropriate. ACEI — angiotensin converting enzyme inhibitors; ACS — acute coronary syndrome; ARB — angiotensin receptor blockers; eGFR — estimated glomerular filtration rate; CAD — coronary artery disease; STEMI — ST-segment elevation myocardial infarction

diseases (CVD) has been proven. The use of NT-proBNP level in diagnosis has been recommended by guidelines for managing HF and acute coronary syndrome (ACS) in clinical practice [16, 17]. However, several studies have found that blood NT-proBNP levels may be significantly affected by renal function [6]. This study found that NT-proBNP level is negatively correlated with eGFR in CAD patients, and the level is significantly elevated in patients with eGFRs of less than 60 mL/min/1.73 m^2 compared with patients with eGFRs of at least 90 mL/min/1.73 m^2. This result is consistent with the findings of previous studies. Potential mechanisms to explain the relationship may be complex. NT-proBNP is mainly excreted by the kidneys, decreases in eGFR lower the body's ability to clear NT-proBNP, resulting in NT-proBNP accumulation [18]; moreover, sodium and water retention in patients with renal dysfunction can cause an increase in ventricular wall tension, leading to increased secretion of NT-proBNP [19], and the underlying pathophysiology of concomitant CVD also make contribution to the elevation of NT-proBNP [20]. Additional renal-cardiac interactions can further complicate the relationship between NT-proBNP level and eGFR. Therefore, NT-proBNP levels in patients with renal insufficiency may not accurately reflect actual cardiac function and prognostic risk;

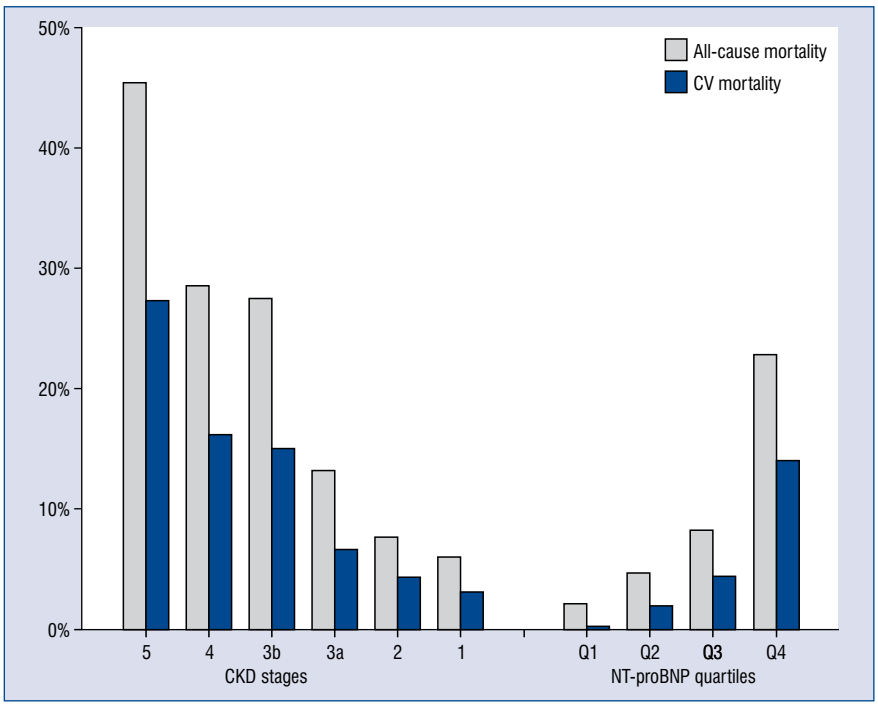

Figure 1. All-cause and cardiovascular (CV) mortality associated with renal function status and N-terminal pro–B-type natriuretic peptide (NT-proBNP) quartiles; eGFR — estimated glomerular filtration rate; CKD stages — chronic kidney disease stages: CKD 1 — eGFR ≥ 90 mL/min/1.73 m^2; CKD 2 — 90 > eGFR ≥ 60 mL/min/1.73 m^2; CKD 3a — 60 > eGFR ≥ 45 mL/min/1.73 m^2; CKD 3b — 45 > eGFR ≥ 30 mL/min/1.73 m^2; CKD 4 — 30 > eGFR ≥ 15 mL/min/1.73 m^2; CKD 5 — 15 mL/min/1.73 m^2 > eGFR.

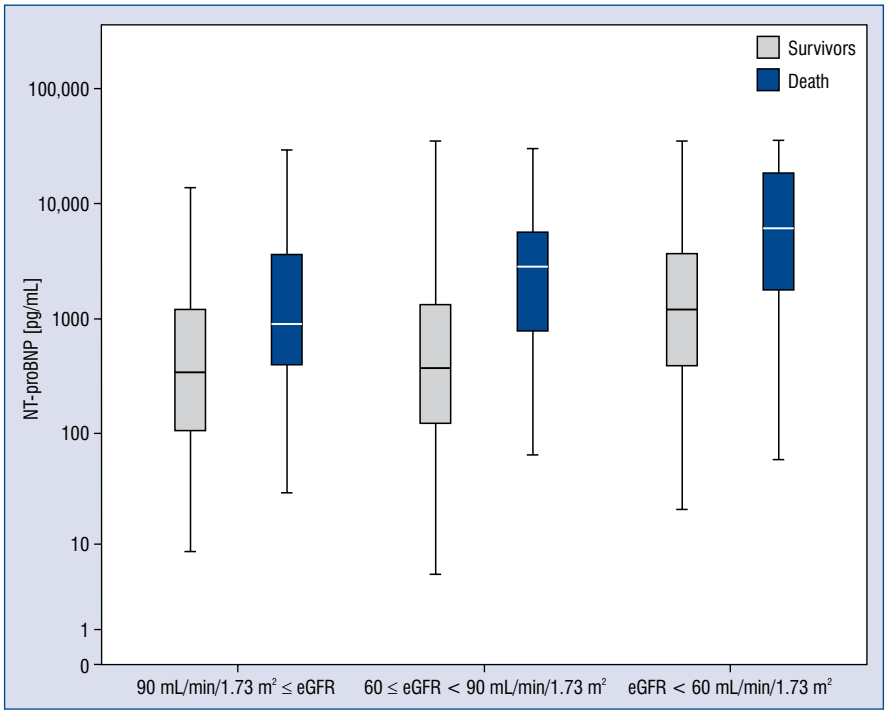

Figure 2. Distribution of N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels according to renal function in patients with or without all-cause death. The boxplots show the median, the lower and upper quartiles, and the range of data; eGFR — estimated glomerular filtration rate.

Table 2. N-terminal pro–B-type natriuretic peptide (NT-proBNP) concentrations in patients with or without all-cause death across estimated glomerular filtration rate (eGFR) groups.

NT-proBNP [pg/mL]	eGFR [mL/min/1.73 m^2]		
	90 ≤ eGFR	60 ≤ eGFR < 90	eGFR ≤ 60
Survivors	341.0 (106.0–1223.0)	371 (123–1330.0)	1205.0 (393.8–3720.0)
Deaths	900.0 (352.0–3753.5)	2875.0 (775.5–5735.8)	6086.5 (1752.5–18722.8)

Data are expressed as median (interquartile).

Table 3. The comparison among non-optimal, overall optimal and stratified optimal and predictive cut--off values of plasma N-terminal pro–B-type natriuretic peptide (NT-proBNP) to predict all-cause mortality.

eGFR [mL/min/1.73 m^2]	NT-proBNP [pg/mL]	Sensitivity	Specificity	Youden's J statistic
Non-optimal predictive cut-off value of NT-proBNP [pg/mL]				
< 60	300.0	0.95	0.21	0.15
60–90	300.0	0.89	0.45	0.34
≥ 90	300.0	0.78	0.48	0.27
Overall optimal predictive cut-off value of NT-proBNP [pg/mL]				
< 60	1440.5	0.77	0.55	0.32
60–90	1440.5	0.67	0.76	0.43
≥ 90	1440.5	0.43	0.80	0.23
Stratified optimal predictive cut-off value of NT-proBNP [pg/mL]				
< 60	3478.0	0.65	0.75	0.40
60–90	1443.0	0.67	0.76	0.43
≥ 90	179.4	0.95	0.37	0.31

eGFR — estimated glomerular filtration rate

Table 4. Adjusted odds ratios for N-terminal pro-B-type natriuretic peptide (NT-proBNP) and the incidence of all-cause mortality.

eGFR [mL/min/1.73m^2]	Strata based on non-optimal cut-off value of NT-proBNP†			Strata based on overall optimal cut-off value of NT-proBNP			Strata based on stratified optimal cut-off value of NT-proBNP†		
	OR*	95% CI	P	OR*	95% CI	P	OR*	95% CI	P
< 60	1.9	0.6–5.8	0.28	2.4	1.1–4.9	0.02	3.0	1.5–6.2	< 0.01
60–90	4.0	1.8–8.8	< 0.01	4.8	2.7–8.5	< 0.01	4.8	2.7–8.5	< 0.01
≥ 90	2.5	1.1–6.0	0.04	1.8	0.8–4.1	0.19	7.7	1.7–33.9	< 0.01

†Non-optimal cut-off value of NT-proBNP = 300.0 pg/mL for all patients; overall optimal cut-off value of NT-proBNP = 1440.5 pg/mL for overall patients; stratified optimal cut-off value of NT-proBNP = 3478.0 pg/mL for patients with eGFR < 60 mL/min/1.73 m^2, 1443.0 pg/mL for patients with eGFR 60–90 mL/min/1.73 m^2, and 179.4 pg/mL for patients with eGFR ≥ 90 mL/min/1.73 m^2.
*Adjusted for age, sex, medical history (pre-hypertension and pre-diabetes mellitus), admission examination (systolic blood pressure, heart rate and Killip class), renal function (eGFR), diagnosis of acute coronary syndrome, and discharge medication (statin, angiotensin converting enzyme inhibitors or angiotensin receptor blockers and beta-receptor blockers)
CI — confidence interval; eGFR — estimated glomerular filtration rate; OR — odds ratio

in particular, "over elevation of NT-proBNP" may be observed.

Over elevated NT-proBNP levels in patients with renal dysfunction may affect the predictive value of NT-proBNP for prognosis. This study showed that in patients with different renal function status, the optimal cut-off value of NT-proBNP determined via eGFR stratification had superior

predictive ability for clinical prognosis than the routine cut-off value (NT-proBNP = 300 pg/mL) or the overall optimal cut-off value for the entire population of CAD patients, simultaneously, a lower eGFR level is indicative of a larger optimal NT-proBNP cut-off value for predicting prognosis. Similarly, various NT-proBNP cut-off values determined for patients of different ages [7, 21, 22]. The underlying mechanism to explain this finding is that the increase of NT-proBNP level reflected not only impaired renal clearance but also the pathophysiological mechanisms of cardio-renal diseases [20], and this biomarker is still a useful indictor for clinical outcome even in patients with moderate or severe renal insufficiency although the prognostic value decreases as the deterioration of renal function. Accordingly, it is necessary to refer to appropriate NT-proBNP cut-off values to assess the prognoses of CAD patients with varying degrees of renal function. Unfortunately, there is a lack of sufficient evidence to determine which cut-off values are appropriate for CAD patients with renal insufficiency. Thus, NT-proBNP has limited utility for predicting prognosis in patients with renal insufficiency. Currently, the guidelines of management for ACS recommend using NT-proBNP level to stratify risk for patients with ACS. However, the Global Registry of Acute Coronary Events (GRACE) score and the Thrombolysis in Myocardial Infarction (TIMI) score, which are the stratification tools recommended by these guidelines, do not include NT-proBNP level as a parameter [16]. European Society of Cardiology (ESC) guidelines for managing HF issue a statement in 2016 that elevated NT-proBNP level is an important indicator of prognosis for patients with HF but does not recommend a definite NT-proBNP cut-off value for use as a reference. Moreover, these guidelines note that NT-proBNP level is affected by many factors, including age, renal function, atrial fibrillation and other complicating diseases. Therefore, patient clinical characteristics should be thoroughly considered when NT-proBNP levels are used to predict prognoses [17].

The strengths of this study: In clinical practice, NT-proBNP is an important indicator in the diagnosis, treatment and prognostic prediction of cardiac function for patients with CVD. The clinical significance of renal function and NT-proBNP measurement for prognosis for patients with CVD has been investigated by many prior studies; however, the findings of these studies only reflect the predictive value of NT-proBNP level and renal function for clinical prognosis [4, 9, 23, 24]. In contrast, this study focused on evaluating different effects and optimal NT-proBNP cut-off values for prognostic prediction in CAD patients with various eGFRs. Thus, relative to prior findings, the results of this study are more practical with respect to clinical applicability. This study showed that the cut-off value of NT-proBNP significantly increases as eGFR decreases. The NT-proBNP cut-off value is nearly 20-fold higher in patients with moderate or severe renal failure than in patients with normal renal function. A similar result was obtained in a previous study of patients undergoing non-cardiac surgery [25].

Limitations of the study

This study was a single-centre observational study and had a few limitations. First, the registry made it difficult to completely avoid selection bias and confounding factors. Second, as the inherent limitation of the real-world study, the bias from the only one-time test of admission serum creatinine could not be ruled out completely. Third, objective echocardiography parameters for systolic and diastolic function were not completely collected in all participants, and the influence of cardiac function on NT-proBNP were not well adjusted, only when Killip was used as a functional classification in statistical analysis. Fourth, the samples in this single-center study weresubject to geographical restrictions, which affected their representativeness and generalization. In summary, caution must be taken when analysing the results of this study. Moreover, NT-proBNP level is affected by many factors, including age, gender and other complicating diseases which make it hard to find out the optimal cut-off value for prognosis prediction. High-quality research reports are needed to provide more clinical evidence on this issue.

Conclusions

This study demonstrated that NT-proBNP exhibits different predictive values for prognosis for CAD patients with different levels of renal function. Among the assessed values, the NT-proBNP cut-off value determined using renal function improve the accuracy of the prognosis prediction of CAD. Moreover, lower eGFR is associated with a higher NT-proBNP cut-off value for prognostic prediction. These results indicate that in clinical practice, renal function must be adequately considered when using NT-proBNP level to assess clinical prognosis for patients with CAD.

Acknowledgements

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Conflict of interest: None declared

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Monotherapy of acetylsalicylic acid or warfarin for prevention of ischemic stroke in low-risk atrial fibrillation: A Easter Asian population-based study

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Abstract

Background: *This study aimed to investigate the effectiveness of monotherapy acetylsalicylic acid (ASA) and warfarin for stroke prevention in low-risk atrial fibrillation (AF) by using a population-based cohort study in Taiwan.*

Methods: *A newly diagnosed low-risk AF patient cohort were identified by using National Health Insurance Research Database (NHIRD) in Taiwan in 2008. The study cohort was observed with a follow-up of 2 years to examine the onset of ischemic stroke (IS) (to 2010). The longitudinal data were analyzed by using generalized estimation equations (GEE).*

Results: *A total of 8,065 newly-diagnosed low-risk AF patients were identified in 2008. 7.4% were prescribed with ASA and 4.6% were prescribed with warfarin. The GEE results showed that low-risk AF patients with hypertension who received warfarin were associated with a statistically significant 58.4% reduction of IS risk (OR = 0.416, p = 0.024, 95% CI 0.194–0.891). Additionally, low-risk AF patients with hyperlipidemia who received warfarin were associated with a 69.3% reduction of IS risk (OR = 0.307, p = 0.044, 95% CI 0.097–0.969).*

Conclusions: *Warfarin is suggested to be prescribed in preventing IS for low-stroke-risk AF patients with hypertension and hyperlipidemia.* (Cardiol J 2019; 26, 6: 704–710)

Key words: atrial fibrillation, acetylsalicylic acid, warfarin, ischemic stroke, hypertension, diabetes mellitus, hyperlipidemia

Introduction

The prevalence of atrial fibrillation (AF) is increasing in United States, European and Asian countries [1–3]. The incidence of AF was about 1.5 per 1000 person-years in Taiwan [4]. In recent years, although many novel oral anticoagulants (NOACs) were proposed and have been demonstrated significantly effective in stroke prevention, especially in high stroke-risk AF patients, for example, rivaroxaban [5], dabigatran [6] and apixaban [7], but the NOACs were relatively more expensive compared to the two widely-used drugs: warfarin or acetylsalicylic acid (ASA). Consequently, warfarin or ASA were considered to be prescribed for low-stroke-risk AF patients [8]. Although most

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published studies aimed mainly to investigate the effectiveness of ASA or warfarin in preventing stroke events for moderate and high-stroke-risk AF patients [9], there remain relatively few studies investigating the effectiveness of preventing stroke events for low-stroke-risk AF patients. One large scale study conducted in the United States found that, among AF patients with high-stroke-risk ($CHADS_2$ score ≥ 2), 38.2% were treated with ASA alone, 61.8% were treated with warfarin or non-vitamin K antagonist oral anticoagulation [9], which indicated that prescribing ASA or warfarin is still very common for high-stroke-risk AF patients. However, prescribing warfarin or ASA to low-stroke-risk AF patients for prevention of stroke is still debatable among clinicians and cardiovascular physicians [10–12], especially for those with metabolic syndromes (including hypertension, diabetes mellitus [DM] and hyperlipidemia) [13]. However, prescribing ASA or warfarin, or combining uses of both drugs to AF patients may be of concern for increasing the risk of unexpected bleeding [14–16], although the incidences of ischemic stroke (IS) is obviously lower for low-risk AF patients. Therefore, investigating the effectiveness of preventing IS of monotherapy of ASA or warfarin in low-stroke-risk AF patients by using a large population-based database is needed [17]. Based on the above mentioned reasons, this study aimed to investigate the effectiveness in preventing IS of monotherapy of ASA or warfarin in low-risk AF patients by using a population-based database, the National Health Insurance Research Database (NHIRD), in Taiwan.

Methods

Study database

This study used claims data from Taiwan's National Health Insurance (NHI) program, which was launched by the Taiwan government in March, 1995 and provided comprehensive health care for 99.5% of its residents in 2010 [18]. The NHIRD contains nationwide information including outpatient, inpatient, dentistry services, prescription drugs, and traditional Chinese medicine services. The diagnostic and procedure codes are based on the International Classification of Diseases, Ninth revision, Clinical Modification (ICD-9-CM) and Procedure Coding System (ICD-9-PCS).

Ethics statement

The Institutional Review Board of School of Nursing, National Taipei University of Nursing and Health Sciences approved this study (CN-IRB-2011-064). The National Health Research Institutes encrypt the personal information to protect individual information of patients. The National Health Insurance Administration guarantees the confidentiality of the personal and health information of patients.

Study population

An incidence-based patient cohort of newly diagnosed AF patients (ICD-9-CM code 427.31) who had at least two outpatient visits with primary disease of AF and whose CHA_2DS_2-VASc scores were < 2 (= 0 or 1) without a history of stroke events (including IS, hemorrhagic stroke [HS], and transient ischemic attack [TIA]) were identified and retrieved from NHIRD in 2008. This study cohort was followed up for up to 2 years (2010) to observe if they had an IS onset which was also defined by using ICD-9-CM code 430-438 [19]. In order to identify real low-risk AF patients, AF patients with severe baseline diseases were also excluded: cancers, coronary artery disease (CAD, including congenital heart defect [CHD], myocardial infarction [MI], and heart failure [HF]), kidney failure (including chronic kidney failure [CKD]), abnormal renal and liver function as well as peripheral artery disease (PAD). Apart from that, based on one recently published study [11] which showed that combining the use of ASA and warfarin may result in unexpected vascular diseases and some cardiovascular disorders, therefore, patients who used concomitant drugs of both ASA and warfarin were also excluded. The enrollment scheme of study patients is shown in Figure 1.

Covariate assessment

The covariate variables including sex, age, baseline hypertension status, DM status and hyperlipidemia status were also taken into account. Additionally, to identify the low-stroke-risk AF patients, CHA_2DS_2-VASc score was adopted and was defined as: congestive HF, hypertension, age (> 65 = 1 point, > 75 = 2 points), DM, previous stroke or TIA (2 points), vascular disease (including PAD, previous MI, aortic atheroma), and sex (female gender). In this study, the study cohort were all with CHA_2DS_2-VASc score < 2 (0 or 1), which was considered suitable for defining "low-risk" for East Asian AF patients [20, 21]. Besides, the HAS-BLED [22] score was also calculated based on ICD-9-CM code. The HAS-BLED scoring system mainly calculates the risk of major bleeding, which was defined as intracranial bleeding, bleeding requiring hospitalization, a hemoglobin decrease

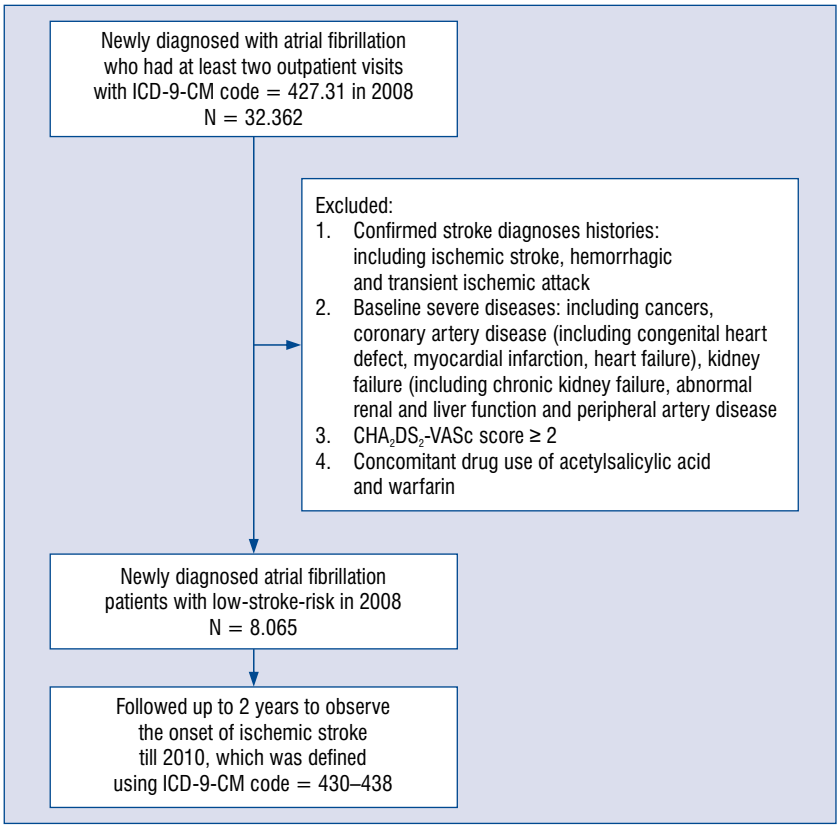

Figure 1. Enrollment scheme of this study.

of more than 2 g/dL, or the need for transfusion secondary to bleeding.

Statistical analysis

The longitudinal data were analyzed by using generalized estimation equations (GEE). GEE is a comprehensive extension of generalized linear models (GLZM) in that they allow for adjusting correlation structure between observations for each subject. The strength of GEE is that they do not require precise specification of multivariate distribution but only of the structure of means or logits for each repeated measurement [23]. In this study, the GEE for longitudinal binary outcome was used (with/without IS) [24]. The modeling was as below:

Define the marginal mean and variances of y_{ij} as $\mu_{ij} = E(\mu_{ij}|X_{ij})$ and $Var(y_{ij}) = \mu_{ij}(1-\mu_{ij})$. Then the marginal logit link function was used:

$$\text{logit}(\mu_{ij}) = \log(\frac{\mu_{ij}}{1-\mu_{ij}}) = \beta' X_{ij}$$

where β is the GEE coefficient vector to be estimated. The GEE estimator $\hat{\beta}$ of β is obtained through estimating the following GEE model:

$$\sum_{i=1}^{n} D'_i V_i^{-1}(y_i - \mu_i) = 0$$

where $\mu_i = (\mu_{i1}, ..., \mu_{ni})'$, $D'_i = \delta\mu_i/\delta\beta$ and V_i is the working covariance matrix of y_i, which can be expressed as $V_i = A_i^{1/2} R_{wi}(\gamma) A_i^{1/2}$, where $R_{wi}(\gamma)$ is a working correlation matrix with parameter γ, which can be estimated from empirical data. In this study, a compound symmetry (or called exchangeable) form of working correlation matrix was used as follows:

$$R_w = \begin{bmatrix} 1 & \rho & \cdots & \rho \\ \rho & 1 & \rho & \rho \\ \vdots & \rho & \ddots & \rho \\ \rho & \cdots & \rho & 1 \end{bmatrix}$$

where ρ was estimated from the data. The odds ratio (OR) of IS of AF patients with and without taking ASA and warfarin were calculated. The results were expressed using ORs with 95% confidence intervals (CIs). My Structured Query Language (MySQL) was used for extraction, linkage, and processing of data. All statistical analyses were performed using IBM SPSS statistical software Version 20 (IBM Corp.,

New York, NY, USA). A two-tailed $p < 0.05$ was considered statistically significant.

Results

This study recruited 8,065 low risk AF patients aged ≥ 20 years old, who had at least two outpatient visits with a primary diagnosis of AF, whose CHA_2DS_2-VASc score < 2 (= 0 or 1), without a history of baseline events of stroke (including HS, IS, and TIA) and without severe baseline diseases which include: cancers, CAD (including CHD, MI, and HF), kidney failure (including CKD) and PAD in 2008. The mean age was 55.95 years old (standard deviation [SD] = 11.60), 78.7% were male and 21.3% were female. Among the study cohort, 4.9% of patients had hypertension, 1.9% with DM, and 2.4% with hyperlipidemia. Additionally, 57.7% of patients were with CHA_2DS_2-VASc score = 0 and 42.3% were with CHA_2DS_2-VASc score = 1. Among the study cohort, 7.4% took ASA and 4.6% took warfarin in 2008 (Table 1).

The distribution of HAS-BLED score was: 89.1% were with 0, 9.5% with 1, and 1.4% with 2. Regarding major bleeding events, according to the database used in this study, there were no major bleeding events found in this study database (Table 1). The incidences of subsequent IS of this study cohort were 2.1% in 2009 and 2.4% in 2010. The results of the GEE model showed that low-risk AF patients who were with hypertension and received warfarin were associated with a statistically significant 58.4% reduction of IS risk (OR = 0.416, p = 0.024, 95% CI 0.194–0.891). Additionally, low-risk AF patients with hyperlipidemia and received warfarin were associated with a statistically significant 69.3% reduction in IS risk (OR = 0.307, p = 0.044, 95% CI 0.097–0.969) (Table 2).

Table 1. Demographic information of study cohort in 2008 (n = 8,065).

	N	%
Age (mean ± SD)	55.95 ± 11.60	
Sex:		
Female	1,719	21.3
Male	6,346	78.7
Hypertension:		
With	396	4.9
Without	7.669	95.1
Diabetes mellitus:		
With	155	1.9
Without	7,910	98.1
Hyperlipidemia:		
With	193	2.4
Without	7,872	97.6
Acetylsalicylic acid:		
Taking	599	7.4
Not taking	7,466	92.6
Warfarin:		
Taking	372	4.6
Not taking	7,693	95.4
CHA_2DS_2-VASc score		
0	4,653	57.7
1	3,412	42.3
HAS-BLED score		
0	7,187	89.1
1	763	9.5
2	115	1.4

SD — standard deviation

Discussion

This study used the Taiwan NHIRD, which is a large-scale population-based database to investigate the effectiveness of preventing IS with a monotherapy of ASA or warfarin among low-stroke-risk AF patients. The results of this study showed that warfarin can help in preventing IS for low-risk AF patients with hypertension and hyperlipidemia. This study agreed with related published studies which defined low-risk solely used CHA_2DS_2-VASc score [25, 26]. Regarding rates of receiving ASA or warfarin, one published study, also using Taiwan NHIRD between 2001 to 2008 showed that the rates of general AF patients (including low-, medium- and high-risk), who received warfarin, ASA, or no treatment in Taiwan was 16%, 62%, and 22% [27]. In comparison with the results of the present study, for low-risk AF patients, 7.4% had a monotherapy of ASA and 4.6% had a monotherapy of warfarin, which were lower than the previously mentioned study [27]. In addition, one published result of a large scale study conducted in the United States [9] in a high-risk group showed that 38.2% of AF patients receiving ASA, and 61.8% receiving warfarin or non-vitamin K antagonist oral anticoagulants.

Regarding the use of ASA for low-risk AF patients, the results of this study did not show a statistically significant effectiveness, which agreed with published studies demonstrating that ASA had limited or non-significant effectiveness for preventing IS in recent years [28, 29]. A randomized clinical trial conducted in Japan showed

Table 2. The results of generalized estimation equations.

Parameter	OR	95% CI for OR		
		Lower	Upper	P
Main effects:				
(Intercept)	0.003	0.002	0.005	< 0.001***
Sex (male vs. female)	0.972	0.687	1.378	0.875
Age	1.010	0.998	1.023	0.106
Year	2.697	2.403	3.027	< 0.001***
ASA	2.377	1.427	3.961	0.001**
WARFARIN	7.345	4.419	12.208	< 0.001***
Hypertension	2.200	1.409	3.436	0.001**
DM	1.760	0.694	4.464	0.234
Hyperlipidemia	3.929	1.516	10.182	0.005**
Interaction effects:				
ASA × Hypertension	1.540	0.737	3.218	0.251
ASA × DM	1.983	0.406	9.693	0.398
ASA × Hyperlipidemia	1.382	0.550	3.469	0.491
WARFARIN × Hypertension	**0.416**	**0.194**	**0.891**	**0.024***
WARFARIN × DM	0.711	0.119	4.238	0.708
WARFARIN × Hyperlipidemia	**0.307**	**0.097**	**0.969**	**0.044***

ASA — acetylsalicylic acid; CI — confidence interval; DM — diabetes mellitus; OR — odds ratio; *p < 0.05; **p < 0.01; ***p < 0.001

that low-dose ASA cannot provide significant effectiveness for stroke prevention among low-risk AF patients [29]. In 2016, the Taiwan Heart Rhythm Society and the Taiwan Society of Cardiology issued Guidelines for the management of AF in Taiwan, which stated that ASA did not benefit in stroke prevention in patients with nonvalvular AF, dual antiplatelet therapy (DAPT) of ASA and clopidogrel did not benefit in the prevention of stroke in patients with nonvalvular AF, unless under other therapeutic indications, such as in patients with acute coronary syndrome and receiving stenting therapy [30]. The results of the present study may support the management guideline. Additionally, one expert opinion proposed that ASA may be over-prescribed among AF patients [31], probably due to the low price of ASA compared with warfarin [32]. Therefore, although ASA was widely prescribed, the results of this study showed that ASA did not benefit in preventing IS for low-risk AF patients.

In addition, it is worth noting that low-risk newly diagnosed AF patients still may have a risk of IS onset in the following 2 years (2.1~2.4% as shown in the present study), which was similar with one large scale study conducted in European countries which showed that IS incidence rates were 2.1, 3.0, and 4.2% for paroxysmal, persistent, and permanent AF, respectively [33]. In summary, results of this study can provide some clinical implications: first, intensive monitoring of stroke events (including HS, IS and TIA), which is strongly suggested and some associated symptoms, for example, FAST [34]: face drooping, arm weakness, speech difficulty and time to call emergency help (ex. 911) and low-risk AF patients should be carefully reminded of this. Second, warfarin can help in preventing IS for low-risk AF patients with hypertension and hyperlipidemia.

Limitations of the study

This study had some limitations. First, the NHIRD did not provide information of potential confounders including smoking, alcohol drinking, life style, diet and other factors, which are associated with the risk of IS. Second, AF patients can buy over-the-counter ASA in drug stores, which were not recorded in NHIRD, so that some AF patients may use warfarin concurrently with ASA, which will result in an underestimate for the number of patients using ASA. One published study proposed that combining the use of ASA and warfarin was inappropriate [11], it is believed that a number of AF patients may concurrently use both

ASA and warfarin, which could not be identified in NHIRD. Third, due to the nature of the study database, it was an outpatient claims database which provided only drug prescriptions without dosage information, therefore the dose effect could not be analyzed and was regarded as another study limitation. Fourth, published studies have shown that poor adherence to anticoagulation guidelines in patients with AF [35–37]. Although we may code one AF patient with the prescription of ASA or warfarin from the claims database, it could not be verified that the information of drug compliance of the recruited AF patients in this study was carried out. Lastly, although there were no major bleeding events found in this study database, there were probably minor bleeding events which were not recorded in NHIRD, which was also regarded as a study limitation.

Conclusions

The present study used a large scale population-based database which showed that monotherapy of warfarin was suggested in prescribing for the prevention of IS in low-stroke-risk AF patients, especially for low-risk AF patients with hypertension and hyperlipidemia.

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Conflict of interest: None declared

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Predictors for early mortality and arrhythmic events in patients with cardiac resynchronization therapy with defibrillator: A two center cohort study

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Abstract

Background: *Guidelines of heart failure therapy include cardiac resynchronization as standard of care in patients with severely depressed left ventricular function and wide QRS complex. It has been shown that patients benefit regarding mortality and morbidity. However, early mortality precludes long-term benefits from the device. The aim of the study was to identify predictors for early occurrence of both death and first-ever implantable cardioverter-defibrillator (ICD) therapy using a large combined database of patients with cardiac resynchronization therapy with defibrillator (CRT-D).*

Methods: *From two registries (tertiary care centers) 904 patients were identified, no single patient was excluded. Early death was defined as death occurring within the 3 years after implantation whereas early ICD therapy as such occurring within the first year. 33 baseline parameters were compared using uni- and multivariate analysis with the Cox model and binary logistic regression.*

Results: *The population was predominantly male (77%), with mean age of 63 ± 11 years and primary prevention indication in 80%. Mean follow-up was 55 ± 38 months. 256 (28%) patients had ICD therapies whereof the first-ever event occurred early in 52%. 270 (30%) patients died after 41 ± ± 31 months, mostly from advancing heart failure (41%), 141 (52%) patients of them early. Independent predictors for early ICD therapy were secondary prevention and renal failure. Independent predictors for early mortality were a history of percutaneous coronary intervention and of peripheral vascular disease.*

Conclusions: *Predictors for early mortality after CRT-D implantation were a history of percutaneous coronary intervention and peripheral vascular disease, present in only a minority of patients, thus limiting their use in clinical practice.* (Cardiol J 2019; 26, 6: 711–716)

Key words: cardiac resynchronization therapy, implantable cardioverter-defibrillator, mortality, predictive model, decision making

Introduction

Implantation of a cardiac resynchronization therapy (CRT) device is standard of care in the therapy of heart failure patients with severely depressed left ventricular function and a wide QRS complex. Several randomized controlled trials have shown remarkable benefits of CRT regarding mortality and morbidity in combination with an implantable cardioverter-defibrillator (ICD) but also with a stand-alone pacemaker [1, 2]. Many patients present with left ventricular ejection fraction (LVEF) below 35%, and thus are implanted with a CRT defibrillator (CRT-D). However, no strong evidence suggests that CRT-D must be used in all patients that are CRT candidates [3]. A relevant number of patients have severe comorbidities and die early after implant. Therefore, they might not

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be in need of the ICD component of a CRT-D [4, 5]. Identification of such patients is considered important, as death as the competing event obviously precludes potential long-term benefit from the ICD component of CRT. Data regarding first-ever ICD therapy are conflicting; studies have shown both linear and asymptotic event curves [6–8]. The aim of this study was to determine independent predictors for early occurrence of both death and first-ever ICD therapy. If meaningful and/or highly prevalent predictors were identified, they could help in decision making for CRT-D or for CRT--pacemaker (CRT-P).

Methods

The study population consisted of all consecutive patients in whom a CRT-D was implanted at the Erasmus Medical Center, Rotterdam, the Netherlands or at the University of Basel Hospital, Switzerland. At the sites, patients are entered into separate registries that were started in Rotterdam in November 1999 (n = 608 patients) and in Basel in February 2000 (n = 296 patients). Last access to the database was July 2015 for Rotterdam patients and May 2015 for Basel patients. Data merging was performed in August 2015. No patients were excluded, leading to a total amount of 904 patients.

Deaths were classified as being due to progressive heart failure, clearly non-cardiac causes, sudden (i.e. a sudden death without post mortem analysis of the CRT-D and/or necropsy) or arrhythmic (i.e. the device could be interrogated showing either ventricular fibrillation that could not have been terminated by all shocks or sinus rhythm after successful shocks with subsequent electromechanical dissociation).

Patient and device characteristics are recorded prospectively at baseline, including 33 parameters such as demographic and cardiovascular items, comorbidities, drugs and laboratory values. Missing values of LVEF of 66 patients from Rotterdam were imputed as well as 5 missing values of blood urea nitrogen levels, and 2 values of QRS width and sodium, respectively, using the median of each parameter [9]. Renal failure was defined as glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2. Appropriate ICD therapy are considered in the ventricular tachycardia (VT) zone of the ICD (tachycardia of 180–220/min, primarily terminated by antitachycardia pacing [ATP] or cardioversion shock if ATP failed) and in the ventricular fibrillation (VF) zone (tachycardias > 220/min terminated by ATP during charging or by cardioversion shock). True ventricular fibrillation terminated by defibrillation was studied separately. In cases where ATP accelerated the VT into the VF zone, the initial VT was considered as the event of interest. The first-ever ICD therapy was defined as early when occurring within 12 months after implantation (median time of first-ever ICD therapy). Death was defined as early when occurring within 3 years after implantation (median time of death). All 33 baseline parameters were compared in univariate analysis for both events.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median with interquartile range and categorical variables as numbers and percentages. To determine the prognostic impact of significant variables, univariate Cox regression and binary logistic regression were used to compute hazard ratios (respectively odds ratios [ORs]) and 95% confidence intervals (CIs). All variables predicting death or ICD therapies significantly with a p value of ≤ 0.1 in the univariate model were entered in a multivariate model using the forward stepwise method. Statistical analyses were performed with the use of IBM SPSS Statistics for Windows, version 23.0 (SPSS Inc. Chicago, IL).

The study is a retrospective merged analysis of data collected prospectively in both centers.

Results

Baseline characteristics and follow-up

A merged population of 904 patients was predominantly male (77%), had a mean age of 63 ± 11 years at implant and a primary prevention indication in 80%. Mean follow-up was 55 ± 38 months. Table 1 depicts all relevant baseline characteristics in detail. Figure 1 shows a flow chart of patients included in the study, mortality rate and mode of death, the arrhythmias treated by the ICD, and their separation into early or non-early events.

ICD therapies

During follow-up, 256 (28%) patients had ICD therapies. The first-ever event occurred early in 134 (52%) patients. In 2/3 ICD, therapy was delivered in the VT zone (82% of them occurring early), in 1/3, in the VF zone of the ICD (77% of them occurring early). Independent predictors for early ICD therapy were secondary prevention (OR 3.21, 1.84–5.56, 0.01) and renal failure (OR 2.08, 1.24–3.50, 0.01). More detailed data is presented in Tables 2 and 3.

Table 1. Baseline characteristics of the 904 patients.

Male gender	700 (77%)
Age at implant [years]	63 ± 11
Weight [kg]	82 ± 16
Body mass index	27 ± 5
Systolic BP [mmHg]	112 ± 19
Ejection fraction [%]	25 ± 7
QRS width [ms]	163 ± 29
Primary prevention	720 (80%)
Sinus rhythm	793 (88%)
NYHA I class	8 (1%)
NYHA II class	297 (33%)
NYHA III class	571 (63%)
Ambulatory NYHA IV class	28 (3%)
Clearance [mL/min/1.73 m^2]	64 ± 25
Renal failure (GFR < 60 mL/min/1.73 m^2)	434 (48%)
Ischemic cardiomyopathy	451 (50%)
Myocardial infarction	371 (41%)
PCI	218 (24%)
CABG	191 (21%)
Diabetes mellitus	224 (25%)
Stroke	112 (12%)
COPD	107 (12%)
Cancer	70 (8%)
PVD	62 (7%)
Drug therapy:	
Diuretics	758 (84%)
ACE-inhibitors	751 (83%)
Beta-blockers	736 (81%)
Statins	508 (56%)
Aldosterone antagonists	416 (46%)
Angiotensin receptor blockers	216 (24%)
Amiodarone	202 (22%)
Digoxin	189 (21%)
Allopurinol	71 (8%)
Sodium [mmol/L]	139 ± 4
Hemoglobin [g/L]	134 ± 18
Blood urea nitrogen [mmol/L]	10 ± 6

ACE — angiotensin converting enzyme; BP — blood pressure; CABG — coronary artery bypass grafting; COPD — chronic obstructive pulmonary disease; GFR — glomerular filtration rate; NYHA — New York Heart Association; PCI — percutaneous coronary intervention; PVD — peripheral vascular disease

Independent predictors for VT as compared to fast VT/VF were beta-blocker therapy (OR 1.77, 1.09–2.86, 0.02) and increasing hemoglobin level (hazard ratio per 1 g/L 1.02, 1.01–1.04, 0.01).

Mortality

Overall, 270 (30%) patients died after a mean 41 ± 31 months, mostly from advancing heart failure (41%) or non-cardiac causes (18%). Of note, the cause of death (not the time of death) was not recorded in the dataset in 33%. 141 (52%) patients had died within the first 3 years and thus early. Independent predictors for early mortality were a history of percutaneous coronary intervention (PCI) (OR 2.01, 1.10–3.66, 0.02) and peripheral vascular disease (PVD) (OR 2.91, 1.08–7.87, 0.04). However, only 24% of patients had a history of PCI and 7% of PVD. A more detailed overview is shown in Table 4.

Discussion

During a mean follow-up of more than 5.5 years, only 28% of these CRT-D patients had appropriate ICD therapies. The first-ever event occurred early in 52%. A third of them were delivered for potentially life-threatening arrhythmias. This rate is slightly lower than the mortality of these severely sick patients (50% renal failure, 66% in the New York Heart Association [NYHA] class III or ambulatory class IV). With the inclusion of 33 parameters to study early ICD therapy and early mortality, it was determined that secondary prevention and renal failure were predictors for early ICD therapy and history of PCI and PVD for early mortality.

It would be both scientifically intriguing and clinically helpful to identify those patients who either die early after ICD implantation (and in whom CRT-D implantation can be questioned and CRT-P offered) or those who never experience ICD therapies. It is thus not surprising that several studies have been undertaken with the focus of early mortality [4, 6, 10, 11]. In the present study only history of PCI and PVD were identified as predictors for early mortality, i.e. at 3 years. However, the clinical application of them has to be questioned, as they were present in only 24% and 7% of patients, respectively. In addition, a sub-analysis from MADIT-CRT showed that a history of PCI, independent of frequency or timing before enrolment, did not influence mortality [12]. Finally, there is no intuitive explanation for these two identified predictors and, due to the low number of patients with these comorbidities, a type I error especially for PVD cannot be excluded. In summary, this study failed to fulfil the particular aim of predicting early mortality in a clinically applicable way.

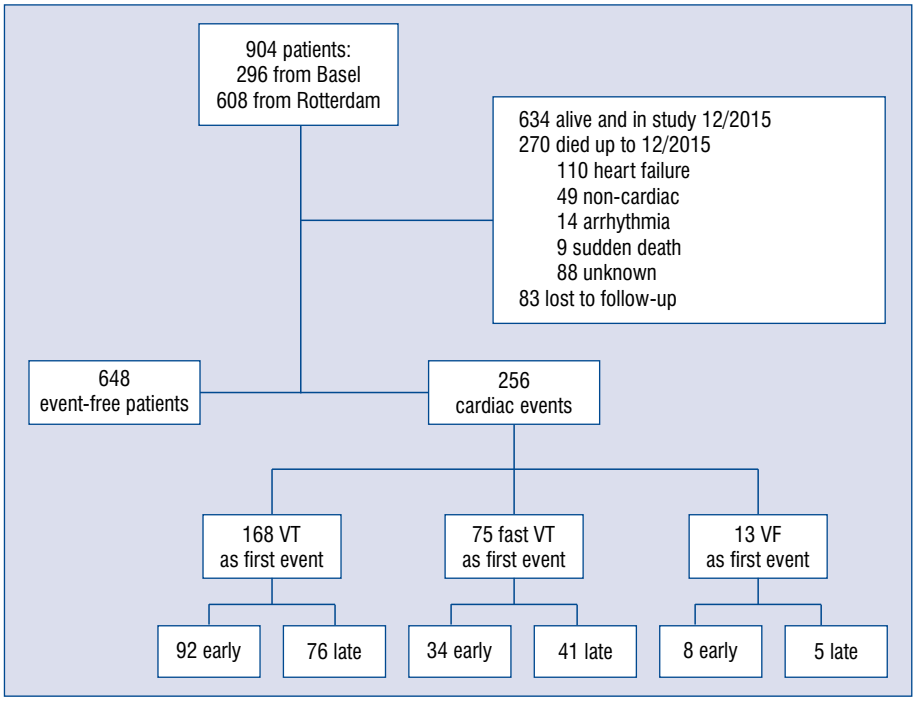

Figure 1. Flow chart of patients and cardiac events; VT — ventricular tachycardia (> 180/min); fast VT — fast ventricular tachycardia (> 220/min); VF — true ventricular fibrillation.

Table 2. Univariable and multivariable analysis for occurrence of first-ever implantable cardioverter-defibrillator therapy without temporal discrimination (only significant parameters are shown, hazard ratio < 1 = no cardiac event, hazard ratio > 1 = cardiac event).

	Univariable analysis			Multivariable analysis		
	HR	95% CI	P	HR	95% CI	P
Secondary prevention	1.596	1.232–2.068	0.000	1.534	1.183–1.990	0.001
Renal failure	1.468	1.142–1.888	0.003	1.408	1.093–1.814	0.008
Amiodarone therapy	1.423	1.075–1.883	0.014	–		
Clearance [mL/min/1.73 m^2]	0.993	0.987–0.999	0.014	–		
Age at implant [year]	1.015	1.005–1.026	0.004	–		
Blood urea nitrogen [mmol/L]	1.022	0.998–1.046	0.074	–		

CI — confidence interval; HR — hazard ratio

In CRT-D patients, no similar data are available to date. In a large ICD only cohort study with a validation cohort (total patient number 2700, 75% primary prevention) [10], four factors predicted mortality at 1 year. They were PVD, age > 70 years, LVEF < 20% and creatinine > 176 mmol/L. Patients with only one factor had a mortality of 4% as compared to 18% in those with four factors. Results were confirmed in a population of 800 patients (100% primary prevention, 28% CRT-D) [4]. Age (here: > 75 years), impaired renal function (here: GFR < 30 mL/min/1.73 m^2), QRS width > 120 ms, and atrial fibrillation were the four predictors. Mortality at 1 year was 2.5% in patients with 0 or 1 risk factors, but 46% in those with all four factors present. However, both papers do not discuss the fact that only 2% of patients were labelled as very high-risk patients, which renders the usefulness of these impressive results less applicable in daily life.

In a study of 225 octogenarians, LVEF < 20% and lack of beta-blocker therapy were the only two

Table 3. Uni- and multivariable analyses for occurrence of first-ever implantable cardioverter-defibrillator therapy with discrimination between early and late events (only significant parameters are shown, odds ratio < 1 = early [≤ 12 months], odds ratio > 1 = late [> 12 months]).

	Univariable analysis			Multivariable analysis		
	OR	95% CI	P	OR	95% CI	P
Secondary prevention	0.302	0.175–0.521	0.000	0.312	0.180–0.543	0.000
Renal failure	0.457	0.277–0.754	0.002	0.480	0.286–0.807	0.006
Amiodarone therapy	0.623	0.355–1.092	0.098			–
ARB therapy	1.671	0.935–2.987	0.083			–
Age at implant [year]	0.969	0.948–0.990	0.005			–
Weight [kg]	1.018	1.001–1.034	0.036			–
Blood urea nitrogen [mmol/L]	0.951	0.906–0.998	0.040		–	
Clearance [mL/min/1.73 m^2]	1.016	1.005–1.027	0.006		–	
Hemoglobin [g/L]	1.015	1.002–1.029	0.029			–

ARB — angiotensin receptor blocker; CI — confidence interval; OR — odds ratio

Table 4. Uni- and multivariable analyses for occurrence of early death (only significant parameters are shown, odds ratio < 1 = early [≤ 36 months], odds ratio > 1 = late [> 36 months]).

	Univariable analysis			Multivariable analysis		
	OR	95% CI	P	OR	95% CI	P
Ischemic cardiomyopathy	0.651	0.396-1.071	0.091	–		
PCI	0.556	0.318-0.973	0.040	0.498	0.273-0.908	0.023
Diabetes mellitus	0.639	0.376–1.086	0.098	–		
PVD	0.313	0.121–0.811	0.017	0.344	0.127–0.930	0.035
Renal failure	0.440	0.265–0.729	0.001	–		
Digoxin therapy	0.600	0.354–1.018	0.058	–		
Weight [kg]	1.019	1.003–1.035	0.019	–		
Body mass index [Unit]	1.051	1.000–1.104	0.050	–		
Systolic BP [mmHg]	1.012	0.999–1.024	0.073	1.015	1.002–1.029	0.025
Blood urea nitrogen [mmol/L]	0.963	0.926–1.000	0.050	–		
Clearance [mL/min/1.73 m^2]	1.018	1.007–1.029	0.001	1.020	1.009–1.031	0.001
Hemoglobin [g/L]	1.013	0.999–1.026	0.060	–		

BP — blood pressure; CI — confidence interval; OR — odds ratio; PCI — percutaneous coronary intervention; PVD — peripheral vascular disease

predictors of mortality at 1 year. Mortality of patients with LVEF < 20% was threefold compared to those with LVEF > 20%, but the patient number at risk are not mentioned, thus severely limiting this statement. Finally, the Italian IRIDE registry [6] reported their results on 600 patients with primary prevention (43% CRT-D). They showed a linear increase of mortality to 24% at 4 years, which is similar to the present results. This is surprising, given the much higher disease burden in the current study (48% renal failure and 71% NYHA class III/IV vs. 11% and 38%, respectively). In addition, even though ICD programing is comparable, the rate of ICD therapies was as high as 50% after 5 years, as opposed to 28% in the study herein.

Other factors are also not especially analyzed in this paper, as e.g. metabolic syndrome with or without obesity, were not shown to influence mortality [13].

To identify predictors of ICD therapy, early or rather late after implantation, is less useful in daily life. This is because a) there are data [7] showing that a substantial proportion of patients have

their first ICD therapy after 5 years and b) especially in secondary prevention guidelines regarding continuation of ICD treatment even in patients without ICD therapy for many years are clear-cut. Nevertheless, this issue has been investigated herein. In the present CRT-D population, only two predictors could be identified (after analysing 33 parameters) for early ICD therapy, secondary prevention (which is commonly known) and renal failure. A Dutch cohort study [8] did not find a predictor using eight parameters. Identifying predictors that somehow "protect" patients from early or late ICD therapy seems alluring at first glance, as one could argue that such a patient might not be in need of the ICD part of CRT. Further studies especially in patients with dilated cardiomyopathy are needed that include parameters not used in the present dataset such as a true left bundle branch block as compared to other forms of QRS widening or late gadolinium enhancement as seen on magnetic resonance imaging.

Limitations of the study

This study has all the limitations of a retrospective database study. There was no "control group" with patients with only CRT-P, who might have had other predictors for early death other than CRT-D patients. Some data had to be imputed. Finally, about 10% were lost to follow-up, and in about the same percentage, the mode of death was unknown. This does, however, not influence prediction of early mortality, as the analysis was performed regarding all-cause mortality.

Conclusions

Predictors for early mortality after CRT-D implantation were a history of PCI and PVD, however present in only a minority of patients. A survey of the available literature suggests that it is difficult to predict early mortality, albeit this would impact on those patients with a high chance of dying and have no benefit from the ICD part of CRT.

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Association of selected factors with long-term prognosis and mortality after dual-chamber pacemaker implant

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Abstract

Background: *Dual-chamber (DDD) pacing is the most widely utilised pacing modality in many parts of the world. The present study aimed to evaluate life expectancy of DDD pacemaker patients in comparison to the age- and sex-matched general population, assess changes in baseline characteristics over three decades of the inclusion period and determine the association between selected variables and patient survival.*

Methods: *This longitudinal study of consecutive de novo DDD pacemaker implantations performed between 1984 and 2014, with all-cause mortality until 2016 as the endpoint, was conducted at a single-center university hospital.*

Results: *Under assessment were 3928 patients with a total of 30,087 patient-years of survival time. Compared to the general population, the observed survival was significantly inferior until 12 years post DDD pacemaker implant (HR = 1.499, $p < 0.001$), whereas after 12 years of follow-up the observed survival was significantly superior (HR = 0.555, $p < 0.001$). A comparison of patient baseline characteristics over three decades revealed the following significant changes: more elderly patients, more female patients, less patients with atrioventricular block, more patients with atrial fibrillation/atrial flutter (AF/AFL) and fewer patients with an apical right ventricular (RV) lead position in the later decades. In multivariate analysis male sex and higher age were the only variables significantly associated with shorter survival time. Indication for pacing, history of pre-implant AF/AFL, RV lead position and device infection were not associated with survival.*

Conclusions: *In the very-long-term follow-up of DDD pacemaker patients, the parameters associated with survival were sex and baseline age at first implantation.* (Cardiol J 2019; 26, 6: 717–726)

Key words: mortality, survival, risk factors, cardiac pacing, atrial fibrillation

Introduction

Population-based observational studies and randomized controlled trials have assessed long-term survival and a variety of factors for their prognostic importance after pacemaker (PM) implant. Evaluated risk factors included baseline factors such as patient gender, age at implantation, decade of implantation, type of bradyarrhythmia, presence of atrial fibrillation (AF), cardiovascular diseases, non-cardiac comorbidities and periprocedural factors such as type of pacing mode, urgency of the procedure, position of the right ventricular (RV) lead and necessity of temporary pacing

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[1–6]. Results have varied depending on population sample size, baseline characteristics, enrolment criteria, length of follow-up and the choice of evaluated factors. Currently, dual-chamber (DDD) pacing is by far the most widely utilized pacing modality in clinical practice in many parts of the world, and its use is exhibiting an increasing trend [7–9]. According to the 2013 European Society of Cardiology (ESC) guidelines, DDD pacing mode is the first choice in patients with sick sinus syndrome (SSS) and atrioventricular block (AVB) [10]. Despite its widespread use, the very-long-term survival of patients with DDD PMs has not been addressed separately from other pacing modalities in an analysis of an unselected, real-world cohort. Therefore, the present aim was to examine prognostic impact of selected variables on survival time and overall mortality of the DDD PM population compared to an age- and sex-matched population. Moreover, patient profiles and long-term survival outcomes were compared after DDD PM implantation across three successive decades at a single center.

Methods

The study cohort consisted of all consecutive patients who underwent de novo DDD PM implantation between 4 October 1984 (first DDD PM implantation) and 31 December 2014 at a high-volume, third-level reference university implantation center. Each patient was followed up after PM implantation up to 31 August 2016 or the time of death before 1 September 2016. The data of patient survival status and deceased patient date of death were collected from the national death registration system. Information on death dates was available up until the end of August 2016. The endpoint was all-cause mortality. The data used in the analysis included (1) patient demographic baseline characteristics: date of birth, age at implantation and sex; (2) index arrhythmia (anti-bradycardia pacing indication): AVB defined as third-degree AVB, second-degree AVB and intraventricular conduction abnormalities (bundle branch block and/or fascicular block) with syncope or symptomatic SSS; (3) history of atrial fibrillation/atrial flutter (AF/AFL) prior to DDD PM implantation; (4) position of the RV lead: apical or non-apical at discharge from the department; (5) time of device-related infection onset and (6) date of death declared in the death certificate. This information was retrospectively gathered from paper and electronic medical records of hospitalizations when DDD PM implantation was performed, operative reports and outpatient pacemaker clinic records. If the patients had various coexisting types of bradyarrhythmia, the following priority ranking was applied for assigning the main indication for anti-bradycardia pacing: third-degree AVB, second-degree AVB, SSS and finally intraventricular conduction abnormality (bundle branch block and/or fascicular block) with syncope in case there was no other cause of syncope. SSS was represented by sinoatrial block, sinus node arrest, tachycardia–bradycardia syndrome and chronotropic incompetence. The term 'history of AF/AFL' was defined as AF and/or AFL documented on electrocardiogram prior to DDD PM implantation and included paroxysmal and persistent AF and/or AFL provided that the restoration of sinus rhythm was planned after DDD PM implantation. Patients with permanent AF/AFL were referred for VVI PMs throughout the study period. Device-related infection included local device infection and cardiac device-related infective endocarditis. The position of the RV lead was determined from operative reports and postprocedure, posteroanterior and left lateral chest radiographs.

Regarding the RV lead implantation technique, on a year-over-year basis, we specified the periods when RV apical lead fixation prevailed and when non-apical localizations were utilized more frequently. The implantation period 1984–2014 was divided into three successive time intervals referred to as decades: the first decade was from 1 October 1984 to 31 December 1994, the second was from 1 January 1995 to 31 December 2004 and the third was from 1 January 2005 to 31 December 2014. On a decade-over-decade basis, the number of patients, their baseline characteristics at the time of implantation and the type of RV lead position were compared.

Regarding survival data, the total duration between the first DDD PM implantation and either the date of death or end of the follow-up period (31 August 2016) was calculated for the whole cohort and referred to as patient-years of survival time. Additionally, life expectancy tables provided by Central Statistical Office for Poland for years 1990–2014 to match each person in the cohort with the age- and sex-matched life expectancy predicted at the year of DDD PM implantation were used [11]. Patients who underwent implantation between 1984 and 1989 were matched with the life expectancy predicted in 1990. The end date of follow-up which is 31 August 2016 was used to censor expected survival.

Table 1. Comparison of the patient baseline characteristics across three successive decades of DDD pacemaker implantations.

	Total population	1st decade X 1984 – XII 1994	2nd decade I 1995 – XII 2004	3rd decade I 2005 – XII 2014	P
Number of patients	3928 (100%)	210 (5.3%)	1144 (29.1%)	2574 (65.5%)	
Age [years]:					**< 0.001**
0–50	290 (7.4%)	41 (19.5%)	135 (11.8%)	114 (4.4%)	
51–70	1537 (39.1%)	127 (60.5%)	531 (46.4%)	879 (34.1%)	
71–80	1498 (38.1%)	33 (16.7%)	400 (35.0%)	1065 (41.4%)	
81–90	576 (14.7%)	8 (3.8%)	76 (6.6%)	492 (19.1%)	
> 90	27 (0.7%)	1 (0.5%)	2 (0.2%)	24 (0.9%)	
Mean age at implantation [years]	69.8 ± 12.1	61.0 ± 13.5	66.5 ± 12.0	72.0 ± 11.3	**< 0.001**
Female sex	1817 (46.3%)	88 (41.9%)	502 (43.9%)	1227 (47.7%)	**0.045**
Atrioventricular block	1318 (33.6%)	113 (53.8%)	296 (25.9%)	909 (35.3%)	**< 0.001**
Sick sinus syndrome	2610 (66.4%)	97 (46.2%)	848 (74.1%)	1665 (64.7%)	
History of atrial fibrillation/ /atrial flutter	1318 (33.6%)	22 (10.5%)	299 (26.1%)	997 (38.7%)	**< 0.001**
Right ventricular lead apical position	1693 (43.1%)	210 (100%)	1107 (96.8%)	376 (14.6%)	**< 0.001**

Statistical analysis

The data were evaluated using IBM SPSS Statistics for Windows, Version 25 (IBM Corp., Armonk, NY, USA). Normality was tested using Shapiro-Wilk test for samples less than or equal to 2000 and Kolmogorov-Smirnov test for samples greater than 2000. Continuous variables are expressed as mean, standard deviation and additionally as median and interquartile range (IQR) for variables with non-normal distribution. Groups were compared using the χ^2 test for discrete variables and the Mann-Whitney U test for continuous variables with non-normal distribution. Event-free rates were calculated using the Kaplan-Meier analysis method and compared using the log-rank test. The associations between patient survival and the selected variables were assessed using a Cox proportional hazards model and presented as hazard ratio (HR) with 95% confidence interval (CI). The associations between patient survival and variables with time-varying effect (strength of a factor was not constant over time) and time-varying covariates (value of the factor was not constant over time) were tested using Cox model with time-dependent covariate. A p value of < 0.05 was considered statistically significant.

Results

A total of 3932 consecutive patients underwent primary DDD PM implantation during the study period. The data of patient survival status on the last day of follow-up were available for 3928 (99.9%) patients. Four (0.1%) patients were excluded from the analysis due to unverified survival status because of unavailability of an identification number. Notably, for all baseline variables considered in the study population (3928 patients), there was no missing data.

The patient baseline clinical characteristics and a comparison of data from successive decades of DDD PM implantation are presented in Table 1. The mean age at the time of implantation was 69.8 ± 12.1, median (IQR) 71.9 (14.2), range 15.3–96.6 years; 53.7% of patients were male; 2610 (66.4%) patients had SSS; 1318 (33.6%) patients had AVB defined as third-degree AVB (552 patients), second-degree AVB (737 patients) and bundle branch block with syncope (28 patients). AF/AFL before implantation was observed in 1318 (33.6%) patients. Women were older than men at the time of implantation: 70.5 ± 11.7, median (IQR) 72.6 (13.1) vs. 69.2 ± 12.4, median (IQR) 71.2 (14.8) years ($p < 0.001$); patients with SSS were older than those with AVB: 70.4 ± 11.2, median (IQR) 72.2 (13.2) vs. 68.6 ± 13.7, median (IQR) 71.3 (16.1) years ($p = 0.004$); and patients with a history of AF/AFL were older than AF/AFL-free patients: 71.9 ± 10.1, median (IQR) 73.0 (12.0) vs. 68.7 ± 12.9, median (IQR) 71.2 (15.2) years ($p < 0.001$). AVB was present in 25.6% of women

and 44.4% of men ($p < 0.001$). The prevalence of AF/AFL before implantation reached 40.9% in women and 27.2% in men ($p < 0.001$). From 1984 to 2005, the majority of RV leads were placed at the RV apex, and from 2006, the majority of RV leads were placed in a non-apical position. A comparison of baseline characteristics among the three successive decades revealed a significant rise in number of procedures, average age at implantation, number of women referred for DDD PM, prevalence of SSS and prevalence of AF/AFL prior to implantation (Table 1). Furthermore, stratification of patients by age group disclosed a significant decreasing trend in the proportion of patients before or in the seventh decade of life and an increasing trend in the proportion of patients in eighth, ninth and tenth decades of life ($p < 0.001$).

A total of 30,087 patient-years of survival time was calculated for 3928 patients. The mean observation time was 7.7 ± 5.3, median (IQR) 6.4 (6.7) years. During the follow-up period 1435 (36.5%) patients died. The mean age of the deceased patients was 79.9 ± 9.7, median (IQR) 81.6 (11.3) years. The Kaplan-Meier estimates for survival probability after DDD PM implantation at 1, 2, 5, 10, 15 and 20 years after the procedure amounted to 96%, 92%, 82%, 62%, 46% and 32%, respectively. With regard to age- and sex-matched survival data, the predicted number of deaths amounted to 1262 (32.1%) and predicted mean observation time was 8.4 ± 4.6, median (IQR) 7.4 (5.8) years. The expected survival curve had a reverse sigmoidal shape and crossed the observed survival at 12 years after implantation. Until 12 years of follow-up the observed risk of death was higher than expected (HR = 1.499, 95% CI 1.376–1.633, $p < 0.001$), whereas after 12 years observed mortality was lower than expected (HR = 0.555, 95% CI 0.468–0.658, $p < 0.001$) (Fig. 1). The Kaplan-Meier curves revealed no significant difference in survival with regard to index arrhythmia (AVB vs. SSS; $p = 0.92$) (Fig. 2A) and a history of AF/AFL before implantation ($p = 0.503$) (Fig. 2B). Male sex was associated with unfavourable survival ($p < 0.001$) (Fig. 2C). Patients with apical RV lead position compared to patients with non-apical lead position had a significantly better survival during the first 10 years after implantation ($p = 0.002$) (Fig. 3A). With regard to the time of implantation, the later the decade of implantation the worse survival was observed with statistically significant linear trend for factor levels ($p < 0.001$) (Fig. 4A). However, after survival adjustment for sex and age at implantation the difference in survival between

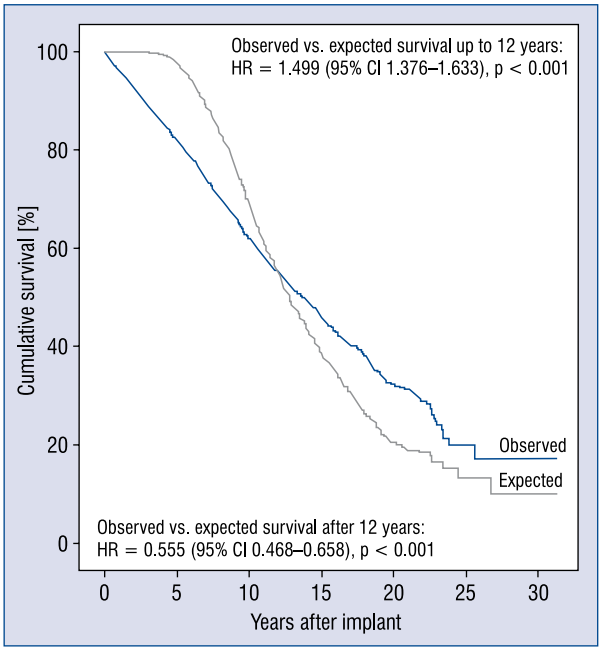

Figure 1. Survival of patients with DDD pacemaker relative to the age- and sex-matched general population. HR — hazard ratio; CI — confidence interval.

apical and non-apical RV lead position group was attenuated ($p = 0.196$) (Fig. 3B). Furthermore, survival during 10 years after implantation after adjustment to sex and age was superior in patients with implantation in third decade compared to patients with implantation in second decade ($p = = 0.017$). Comparing sex- and age-adjusted survival curves for first vs. second decade and first vs. third decade there were no statistically significant differences (Fig. 4B).

The Cox proportional hazard regression model demonstrated that older age at implantation and male sex were significantly associated with higher mortality. By contrast, pacing indication and a history of AF/AFL were not associated with survival (Fig. 5).

During follow-up 43 (1.1%) patients, 20 females, developed device-related infection after a mean follow-up of 7.3 ± 5.3, median (IQR) 7.2 (8.7) years. Twenty-six (60.4%) patients with local infections were observed and 17 (39.5%) patients with cardiac-device related infective endocarditis. Within 1 year from implantation 6 (14%) patients developed device-related infections. Death occurred in 14 (32.6%) patients, 5 females, after a mean period of 9.2 ± 6.0, median (IQR) 8.4 (6.8) years from infection diagnosis. Device-related infection was not associated with an increased risk of death (HR = 0.693, 95% CI 0.097–4.93, $p = 0.714$).

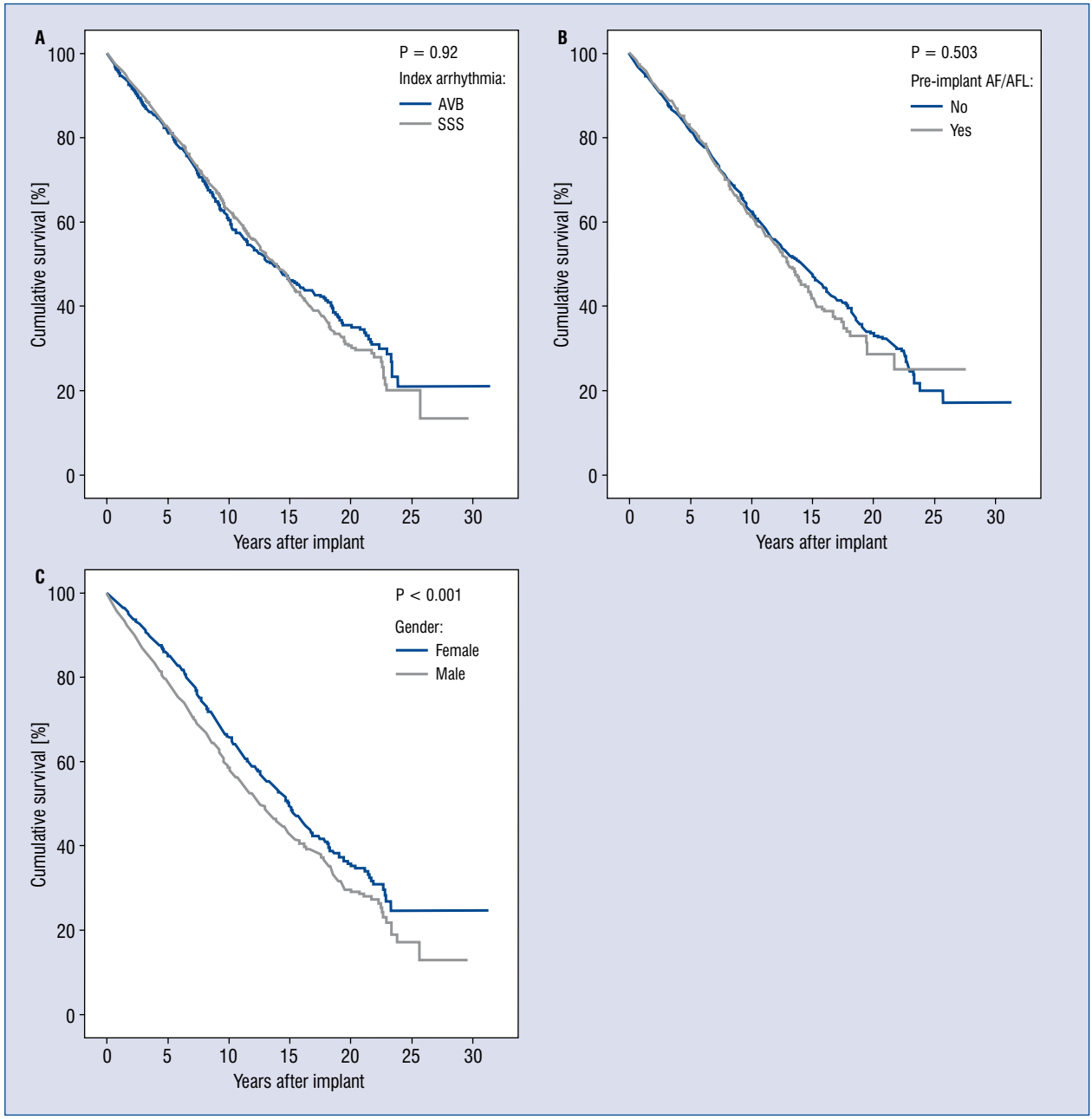

Figure 2. Survival of patients with atrioventricular block (AVB) relative to patients with sick sinus syndrome (SSS) (**A**), survival of patients with a history of atrial fibrillation/atrial flutter (AF/AFL) relative to patients without pre-implant AF/AFL (**B**), survival of women relative to men (**C**).

Discussion

The long-term survival of PM patients has been assessed in several population-based studies of general PM populations that included from 1.5% to 73.3% patients with DDD PM [1, 2, 4, 5, 12–14]. Importantly, no study has analysed mortality in very-long-term DDD PM patients only, or identified independent risk factors for mortality in this population. Therefore, the present study, which had an excellent (99.9%) rate of complete data on overall survival, was designed to allow comparisons in a large group of consecutive patients enrolled without exclusion criteria who received a DDD PM at a single center and were free from permanent AF/AFL at the moment of implantation. With 3928 patients, 30,087 patient-years of survival time and an observation time of three decades, this is one of

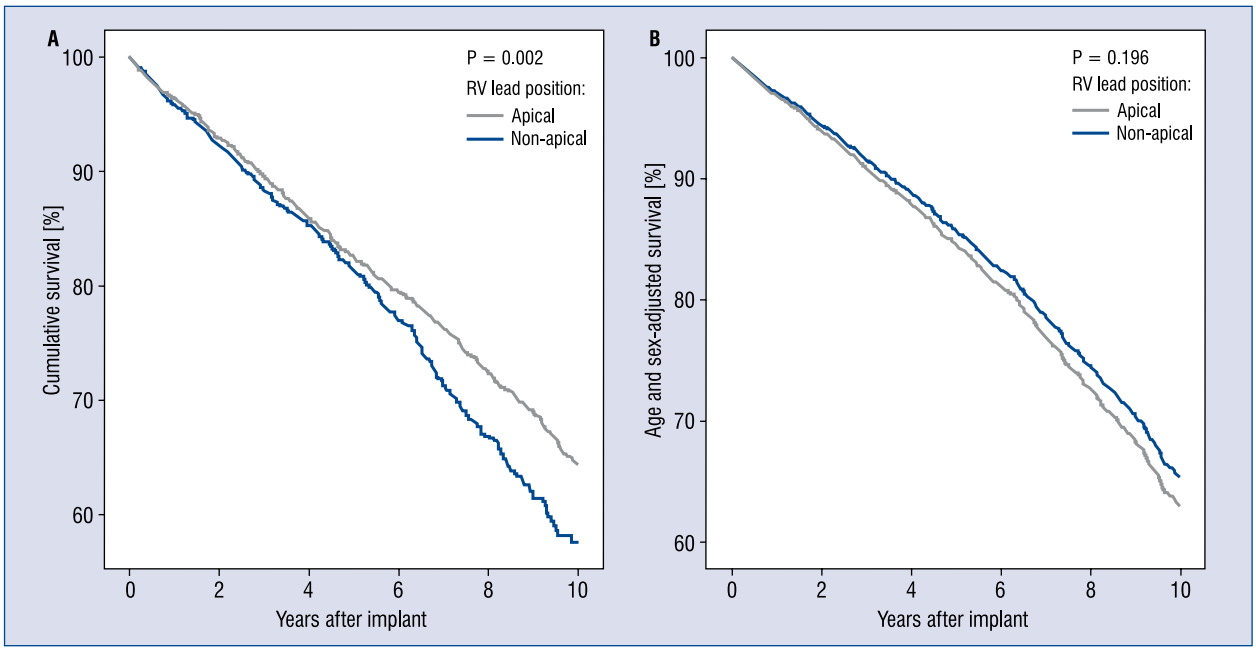

Figure 3. Survival during 10 years after implantation in patients with right ventricular (RV) lead in apical position relative to patients with RV lead in non-apical position (**A**), survival after adjustment for age and sex (**B**).

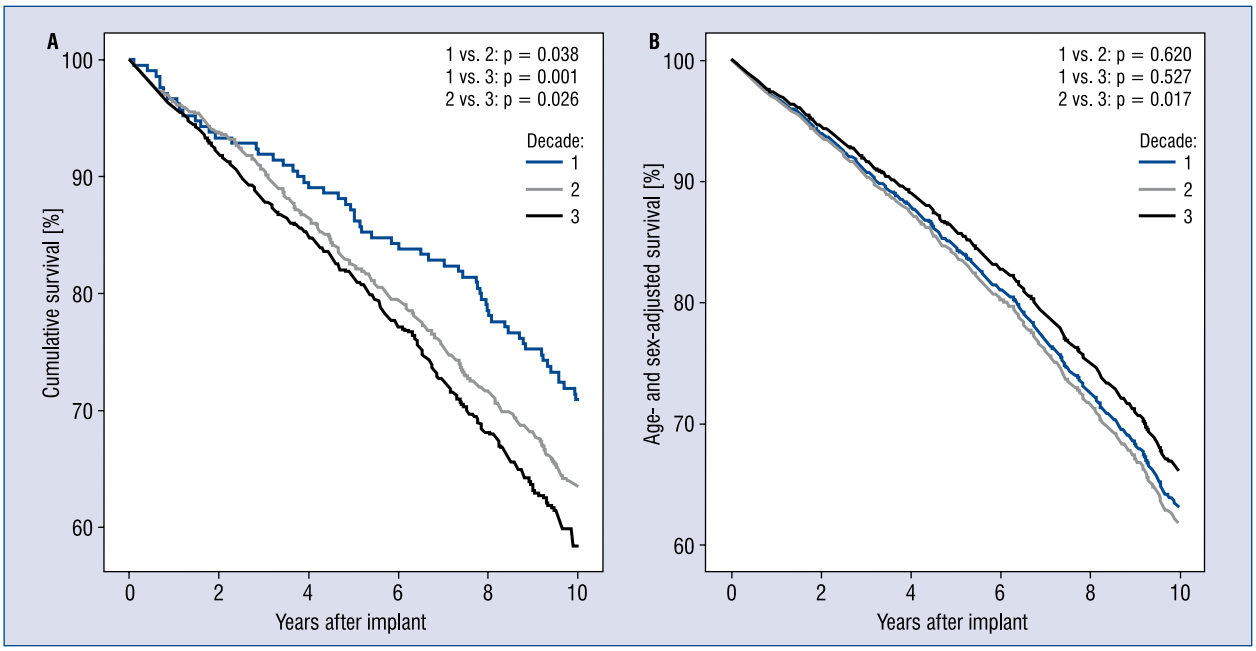

Figure 4. Survival during 10 years after implantation according to the decade of implantation (**A**), survival after adjustment for age and sex (**B**).

the largest studies to reliably examine very-long--term survival in patients referred for primary DDD PM implantation.

In reports on survival of a PM population, authors have concluded that prognosis of PM recipients without significant comorbidities at baseline approached that of the general population [1, 5, 13, 14]. Among the factors contributing most to increased mortality in the PM group relative to the control population were significant non-cardiac

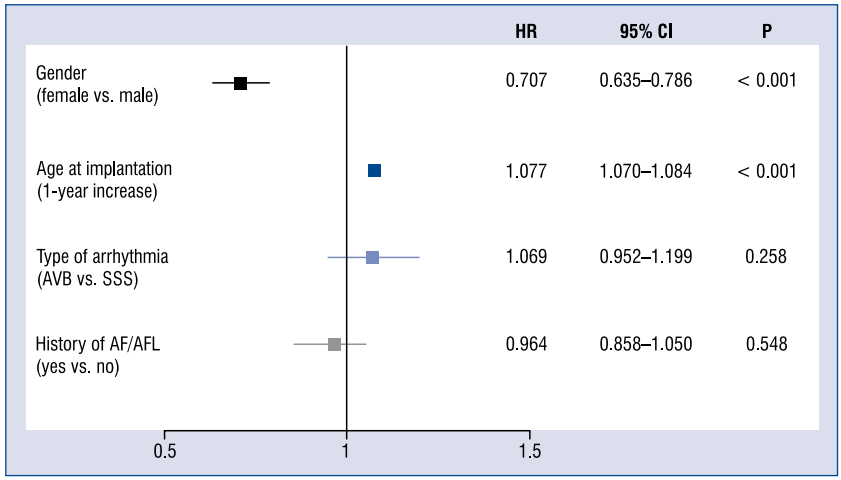

Figure 5. Factors associated with survival in multivariable Cox regression model; AVB — atrioventricular block; SSS — sick sinus syndrome; AF/AFL — atrial fibrillation/atrial flutter; HR — hazard ratio; CI — confidence interval.

comorbidities and structural heart disease [1, 5, 13, 14]. Pyatt et al. [4] have reported significantly higher overall mortality in PM cohort compared to expected mortality during a period of 8 years after implantation. The present data, showing significantly worse overall survival in DDD cohort relative to the expected survival until 12 years after implantation are in agreement with the results of Pyatt et al. [4]. On the other hand, after 12 years post-implant survival among DDD recipients significantly exceeded survival of general population. Presumably, long-term benefit from DDD PM beyond 12 years of follow-up might have applied predominantly to a population without significant comorbidities and were relatively young at baseline. Reasons for improved survival after 12 years, post-implant in DDD PM patients, might have included prevention against sudden bradyarrhythmic death and regular follow-up with cardiologist which might have allowed early recognition and treatment of cardiovascular diseases.

The 1-year survival rate of the present DDD cohort was 96%. These data appear to accord with 1-year overall survival rates from 90.5% to 96% as provided in reports of DDD populations [4, 12, 15, 16] and rates from 91% to 94% as provided in reports of general PM populations [1, 5, 13, 14]. At 5-year follow-up, cumulative survival rate was 82%. Reported 5-year survival rate of DDD cohorts was significantly lower and accounted for 58% to 64.7% [4, 12, 17], whereas in general PM cohorts, this value reached 58.2% to 69% [2, 5, 18]. Long-term estimated survival probability at 10-year follow-up after implantation was 62%, which is broadly consistent with other reports of general PM populations: from 44.8% to 75.4% [2, 13]. The 20-year survival probability was estimated at 32% in the present study compared with 21.4% observed by Brunner et al. [2]. Importantly, in the study Brunner et al. [2], a significant number of patients (38.6%) were lost to follow-up and censored as alive on the day of their last visit, which renders their information on estimated survival rates less accurate.

Regarding baseline characteristics, a higher prevalence of men across the study period was observed, which is in accordance with the majority of studies in DDD PM populations [15–17, 19] and general PM populations [1, 2, 5, 9, 12, 13, 18] except for Scandinavian populations, in which the prevalence of women receiving first DDD PM was reported to be higher than that of men [20, 21]. In the present study, the prevalence of men exhibited a statistically significant decreasing trend from 58% in the first decade to 52% in the third decade, which is opposed to observations of a stable proportion of men in successive eras of PM implantation [1, 2]. The age of patients at first PM implantation increased with each decade, similar to a trend observed in western countries [2, 7, 18]. Furthermore, the present study identified a significant increase in PM utilization among older patients (> 70 years). In countries with advanced health systems, the percentage of PM recipients older than 80 years was > 30% and exhibited a significantly increasing trend [1, 8, 9, 18]. Female patients were older than men at the time of implantation, as it has been observed in a majority of countries [1, 2, 8, 22], and were more likely to present with SSS [1, 2, 22]. There has

been a shift in the main indications, with AVB being more prevalent in 1984–1994 and the domination of SSS in 1995–2014. Unlike the results herein, a higher incidence of high-grade AVB than of SSS throughout the study period has been frequently reported in general PM populations [1, 2, 4, 5, 9, 12–14, 18]. Importantly, in the present study, the prevalence of pre-implant AF/AFL soared across the study period, reaching 39% in the third decade, a trend that can probably be attributed to enhanced detection of AF/AFL, increasing age of patients [23] and shift of indications towards SSS [20, 24].

The significant association between male sex and older age at baseline and worse survival has been noted previously [1, 2, 4, 5, 13] and corresponds to the fact that women generally have a longer life expectancy. As expected, the present study demonstrated that in the Cox regression model, age and male sex were independently associated with mortality after primary DDD implantation. For each additional year of age at implantation, a 7.8% increase in mean risk of death was observed; in the general PM population, this value has been reported as 5% to 9% [2, 4, 5, 12]. By contrast, no significant difference in survival with regard to either index arrhythmia or a history of AF/AFL was detected in the present study. The literature on the influence of index arrhythmia on survival comprises conflicting results. In a multivariate analysis of the study population, Brunner et al. [2] observed that SSS was associated with better survival than was AVB; however, on considering patients with first implantation during the last decade (1991–2000), this effect was no longer significant. Furthermore, Jahangir et al. [12] and Pyatt et al. [4] have identified that AVB is a risk factor for increased mortality compared with SSS [4, 12]. Conversely, Udo et al. [5], Mayosi et al. [14] and Jelić et al. [13] have demonstrated that survival of SSS and AVB patients is comparable.

In the FOLLOWPACE study, a history of atrial tachyarrhythmia was not an independent predictor of survival [5]. Conversely, Bradshaw et al. [1] demonstrated that a history of AF was significantly associated with reduced 1-year and 5-year survival. Of note, with increasing patient age at implantation across the second and third decades, age- and sex-adjusted survival of patients displayed an improving trend. The available data indicate that either the later the first implantation occurs in the study period, the better the prognosis of the PM recipient [2] or that there is no association between the era of implantation and mortality [1]. Regarding the RV lead position, after adjustment for sex and age at implantation there was no significant association with mortality. Witt et al. [6] assessed 3450 unselected patients who underwent DDD PM implantation between 2004 and 2014, among whom the RV lead was positioned at the RV apex in the majority of patients (71.9%) and less commonly at the septum (6.9%) or other RV regions (21.2%). Authors reported that an apical RV lead position was associated with increased mortality compared with a septal position group (31% vs. 24%, $p = 0.02$). Patients with very high levels of pacing, greater than 90%, had a significantly lower mortality rate in the septal pacing group (16% vs. 31%, $p = 0.03$), whereas patients with very low levels of pacing, less than 10%, did not have a significant difference in mortality (13% vs. 23%, $p = 0.10$) [6]. Due to the retrospective design of the present study and the findings of Witt et al. [6], none of the aforementioned results can be taken as a definitive answer to the long-debated question of whether an apical position of the RV pacing lead is worse than a non-apical position.

In the present study, an infection rate of 1.1% per patient was observed, which is in line with previous reports from literature. Hercé et al. [25] in a study based on a registry which included 2496 patients observed 35 (1.4%) cases with device-related infections. Greenspon et al. [26] reported that the rate of device-associated infections in the United States rose from 1.53% in 2004 to 2.41% in 2008, likely due to an increase of patients with multiple comorbidities. Earlier reports on DDD PM population with implantation between 1984 and 2002 showed the rate of device-related infection was less than or equal to 1.2% [27, 28]. The present study shows that device-related infection was not a risk factor for increased mortality during follow-up and patients diagnosed with pacing system infection had relatively good long-term survival. Results herein, are in keeping with the findings of a prospective matched cohort-study of Deharo et al. [29] who observed no significant excess in all-cause long-term mortality in infection cohort compared with controls without device-related infection.

Limitations of the study

The main limitation is the retrospective nature of this study, with all its inherent limitations. First, data regarding other baseline factors that possibly influenced survival, such as a history of concomitant diseases, medications, functional status (New York Heart Association class) and urgency of the procedure (elective/emergency), were not com-

plete for the whole population and were therefore not included in the analysis. Similarly, the percentage of RV pacing was not available for all patients, therefore the association between RV lead position and mortality could not be further analyzed in subgroups with different requirements of RV pacing. Second, the prevalence of pre-implant AF/AFL in the first two decades may have been underrated due to lower awareness and surveillance. Third, selection bias of presumably 'sicker' patients with AVB referred for single-chamber ventricular pacing could not be excluded and presumably 'healthier' patients with SSS to single-chamber atrial pacing because evidence supporting the use of DDD systems as a first-choice pacing mode for both indications was unavailable at the time.

Conclusions

With an increasing number of DDD PM implantations over time, a significant change in patient baseline characteristics was observed: average age at implantation continued to rise, more women were referred for implantation and the prevalence of AF/AFL prior to implantation grew rapidly. During 12 years after implantation, survival of the DDD cohort was significantly worse than in an age- and sex-matched general population, however, after 12 years the survival of DDD recipients were significantly better than expected. Male sex and age were the only clinical variables associated with a shortened survival time and an increased probability of death. Indication for pacing, history of pre-implant AF/AFL, RV lead position and device-related infection were not associated with survival.

Conflict of interest: None declared

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VIA MEDICA

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The effect of acetylsalicylic acid dosed at bedtime on the anti-aggregation effect in patients with coronary heart disease and arterial hypertension: A randomized, controlled trial

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Abstract

Background: *Acetylsalicylic acid (ASA) is one of the basic drugs used in the secondary prevention of coronary artery disease (CAD), and in most cases it is taken in the morning in one daily dose. It is suggested that the morning peak of platelet aggregation is responsible for the occurrence of myocardial infarctions and strokes. Hence, the aim of the study was to observe the effect of ASA (morning vs. evening) dosing on the anti-aggregative effect of platelets in patients with CAD and arterial hypertension (AH).*

Methods: *The study involved 175 patients with CAD and AH. Patients were randomly assigned to one of two study groups, taking ASA in the morning or in the evening. The patients had two visits, one baseline and another after 3 months from changing the time of ASA dosage. The platelet aggregation was determined using the VerifyNow analyzer.*

Results: *In the ASA evening group, a significant reduction in platelet aggregation was obtained. In the ASA morning group, a significant difference in response to ASA was observed, depending on sex. In men, the reactivity of platelets decreased, but in women it increased.*

Conclusions: *In the group of patients with CAD and AH, bedtime ASA dosing is associated with a significant reduction in platelet aggregation. The response to ASA may differ between sexes. The benefit gained by changing the drug administration from the morning to the evening is greater in women.*
(Cardiol J 2019; 26, 6: 727–735)

Key words: acetylsalicylic acid, platelet aggregation, bedtime administration, chronotherapy, circadian rhythm, gender-dependence, randomized controlled trial

Introduction

The functioning of the human body is subjected to cyclical variability in the form of oscillation of physiological phenomena called biological rhythms [1]. These include circadian rhythms that can significantly affect the function of the cardiovascular system [2]. It is suggested that changes in circadian rhythms in the coagulation system are one of the causes of sudden deaths, myocardial

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infarctions (MI), and ischemic strokes that occur more often when switching from the sleep phase to the awakening [2]. It has been shown that during the morning there is an increase in blood pressure, episodes of sudden cardiac death, unstable angina, and rupture of the aortic dissecting aneurysm are more frequent [3–6]. In the Framingham, ISAM, and TIMI II studies the incidence of MI was 3-fold higher in the morning than in the late evening [7–9]. A registry of 45,000 patients showed a higher incidence of ST-segment elevation MI heart attacks in the morning (41%) compared to the afternoon and night hours (respectively, 32% and 26%, $p << 0.001$) [10]. The mechanisms of these phenomena are not fully understood; it is suggested that one of the reasons may be a morning increase in blood viscosity due to platelet hyperaggregation and decreased fibrinolytic activity, leading to an increased risk of thromboembolic events [11–14]. Therefore, it would be useful to use the chronotherapy principles in acetylsalicylic acid (ASA) therapy to reduce the incidence of acute cardiovascular events that occur in the morning. Chronotherapy involves adjusting the concentration and potency of the drug over time in accordance with biological circadian rhythms [15, 16]. To date, few papers about the influence of taking ASA on the morning peak of platelet activity have been published. ASA belongs to the basic drugs used in the secondary prevention of coronary artery disease (CAD), and in most cases it is taken in one daily dose in the morning hours [17, 18]. The epidemiological data and clinical observations described above prompted interest in changing the dose of ASA from a morning dose to bedtime. The aim of the present study was to observe the effect of ASA (morning vs. evening) dosing on the antiaggregative effect of platelets in a high-risk group of cardiovascular patients.

Methods

The study included 200 patients, aged 59.8 years, with diagnosed CAD and arterial hypertension (AH), who were taking ASA 75 mg/day in a single antiplatelet therapy, and who were admitted to the Department of Hypertension. Eventually the inclusion criteria were met by 175 patients (59 women and 116 men). The recruitment period was 21 months (from May 2015 to January 2017). Patients with CAD and AH were randomly assigned to one of two study groups taking ASA in the morning (58 patients) or in the evening (56 patients). The third group, which was the control, included 61 patients with AH, without CAD, and not taking any antiplatelet drugs (Table 1). The study was approved by the Bioethics Committee of Karol Marcinkowski University of Medical Sciences in Poznan (Resolution No. 373/15). Each participant signed informed consent to participate in the study, which was a form approved by the Bioethical Committee. Exclusion criteria for the study were as follows: secondary hypertension, MI and stroke within 6 months prior to the study, chronic heart failure — New York Heart Association (NYHA) III and IV, chronic kidney disease (glomerular filtration rate < 30 mL/min), addiction to alcohol or psychotropic substances, and active cancer. Additional exclusion criteria for the study group were: confirmed hypersensitivity to ASA, history of bleeding due to ASA, taking clopidogrel or other antiplatelet agents, hemorrhagic diathesis, active gastric and/or duodenal ulcer disease, and hypersensitivity to an active substance: ASA, other salicylates or any component of the drug, using non-steroidal anti-inflammatory drugs (NSAID). The exclusion criterion for the control group was the use of ASA preparations in the preceding 30 days. There were no changes in the concomitant treatment (lipid-lowering, antihypertensive, and antidiabetic), and no NSAID were taken during the study.

Scheme of the study

Patients enrolled in the study had two visits in accordance with a prescribed treatment schedule (Fig. 1). On the first qualifying visit (Visit 1), the patients were admitted to the ward where laboratory and imaging examinations with the assessment of the severity of platelet aggregation using the VerifyNow Aspirin Test and randomization regarding the inclusion of ASA morning or evening took place. After 3 months of ASA therapy, Visit 2 was administered, during which the examinations from the initial visit were repeated.

VerifyNow Aspirin Test

During a single whole blood sample collection, 2.2 mL vacuum collection tubes with 3.2% sodium citrate were used, together with 21-gauge needles as recommended by the manufacturer.

VerifyNow Aspirin assay contains lyophilised fibrinogen-coated beads and a platelet agonist — arachidonic acid. It is designed to measure platelet function based on the ability of activated platelets to bind fibrinogen. Fibrinogen-coated microparticles aggregate in whole blood in proportion to the number of unblocked platelet glycoprotein (GP) IIb/IIIa receptors. Light transmittance increases

Table 1. Patient demographic characteristics

	Acetylsalicylic acid		Control group (n = 61)	P
	Morning (n = 58)	Evening (n = 56)		
Female/male	19/39	19/37	21/40	> 0.05*
Smokers/non-smokers	14/44	17/39	17/44	> 0.05*
Age [years]	59.8 ± 7.6	60.3 ± 7.1	59.9 ± 7.1	> 0.05**
Weight [kg]	84.4 ± 9.7	84.9 ± 12.9	84.1 ± 10.1	> 0.05**
Height [m]	1.69 ± 0.1	1.69 ± 0.1	1.69 ± 0.1	> 0.05**
BMI [kg/m^2]	29.52 ± 3.95	29.50 ± 4.4	29.52 ± 4.1	> 0.05**
Waist [cm]	93.1 ± 11.1	92.5 ± 11.4	93.7 ± 11.6	> 0.05**
Hip [cm]	105.2 ± 10.2	105.3 ± 12.3	105.2 ± 10.6	> 0.05**
Waist to hip ratio	0.88 ± 0.05	0.87 ± 0.06	0.89 ± 0.08	> 0.05**
Systolic BP [mmHg]	145.5 ± 5.0	145.2 ± 6.7	145.1 ± 5.2	> 0.05**
Diastolic BP [mmHg]	88.8 ± 4.0	88.8 ± 5.3	89.0 ± 5.5	> 0.05**

Data are shown as number or mean ± standard deviation. Statistics: *Chi-square; **Kruskal-Wallis ANOVA; BMI — body mass index; BP — blood pressure

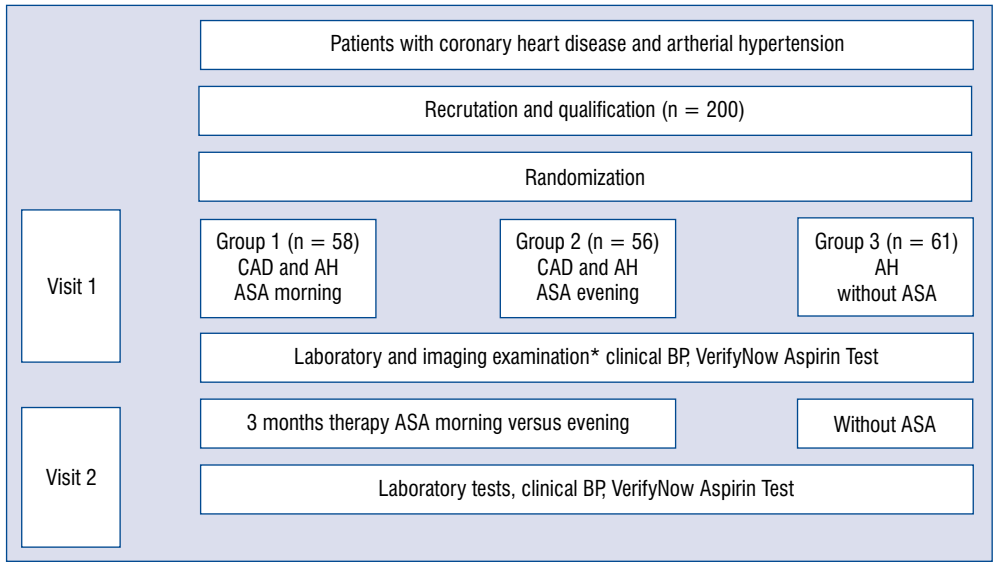

Figure 1. Scheme of the study. *In each group: Laboratory tests, abdominal ultrasound examination, abdominal computed tomography scan, Doppler ultrasound of renal arteries, clinical blood pressure (3×/24 h), electrocardiography, echocardiography, weight, and body mass index assessment; AH — arterial hypertension; ASA — acetylsalicylic acid; BP — blood pressure; CAD — coronary artery disease

as activated platelets bind and aggregate fibrinogen-coated beads. The instrument measures this change in the optical signal caused by aggregation. Assay results are reported as Aspirin Reaction Units (ARU), which are calculated as a function of the rate of aggregation. ARU values < 550 indicate an effective result of ASA, while ARU values > 550 indicate no effect of the drug.

Statistical analysis

Statistical analyses were performed with Statistica, version 12.5 (StatSoft, USA). Since the tested data had not met the assumption of Gaussian distribution (evaluated with Shapiro-Wilk method), non-parametric methods were applied. The Kruskal-Wallis ANOVA test was used for evaluation of the differences in parameters between the three

Table 2. Patient clinical data of the groups.

	Acetylsalicylic acid		Control group
	Morning	Evening	
Coronary heart disease	58	56	0
Arterial hypertension	58	56	61
Diabetes mellitus	15	17	14
Metabolic syndrome	21	20	22
History of myocardial infarction	12	13	0
Previous ischemic stroke or transient cerebral ischemia	5	6	0
History of coronary artery bypass surgery	8	9	0
History of coronary angioplasty	38	37	0
Hyperlipidemia	58	56	61
Atherosclerosis of the lower limbs	7	6	5
Chronic obstructive pulmonary disease	6	7	5
Thyroid disease	4	5	6

Table 3. Drugs used in groups studied.

	Acetylsalicylic acid		Control group
	Morning	Evening	
Acetylsalicylic acid	58[a]	56[a]	0[b]
Anti-hypertensive drugs	2.58[a]	2.66[a]	2.57[a]
β-blockers	58[a]	56[a]	53[a]
Angiotensin-converting enzyme inhibitors	40[a]	34[a]	40[a]
Angiotensin II receptor antagonists	18[a]	22[a]	21[a]
Calcium antagonists	22[a]	25	25
Diuretics/aldosterone antagonists	13[a]	12	16[a]
Concomitant lipid-lowering therapy	58[a]	56[a]	58[a]
Concomitant antidiabetic therapy (metformin)	15[a]	17[a]	14[a]
Proton pump inhibitors	47[a]	45[a]	42[a]

[a, b]Different letters given in the upper index indicate the occurrence of statistical differences in the values of a given parameter between the three groups (Kruskal-Wallis ANOVA, $p < 0.05$)

groups. Changes in parameters in the individual groups during the first and second visit were analyzed using the Wilcoxon signed-rank test — the parametric equivalent of the T-test for related variables. Frequencies, expressed on a nominal scale, were analyzed based on the Pearson χ^2 test. A p-value < 0.05 was considered significant.

Results

Table 1 presents the basic clinical and demographic data of the group of patients studied. Selected parameters: body mass index (BMI), weight, waist, hips did not change significantly in any of the studied groups or in the control group, between groups and between Visits 1 and 2 ($p > 0.05$, Wilcoxon signed-rank test). Table 2 presents the data from the interviewed population, including concomitant diseases. Table 3 summarizes the most important drugs (antihypertensive, hypolipemic and antidiabetic) taken by the patients. What is important, is that there was no significant difference between the groups in the amount of the drugs administered during the therapy and there was no change of drugs during the study. In all patients, a qualitative measurement of platelet aggregation was also performed using the VerifyNow Aspirin Test. Figure 2 presents the results of the examination of inhibition of platelet aggregation in individual groups during the first and second visit.

The result of the Aspirin VerifyNow Test was given as the severity of platelet aggregation in ARU. At the baseline visit, the inhibition of aggregation in ARUs did not differ between the groups and was 489.01 ± 73.0 in the morning ASA group and 488.16 ± 83.0 in the evening ASA group. In the control group, which did not take ASA, the result was 638.31 ± 15.9 ARU. Only in the ASA evening group, a significant reduction in platelet aggregation of 28 ARUs was obtained compared to the morning ASA group (460.10 ± 82.3 h vs. 487.62 ± 77.4 h in the morning; $p < 0.05$).

Figure 3 shows changes in ARU on Visit 2, depending on sex (p-value applies to Mann-Whitney U test), compared to Visit 1. In the group that took ASA in the morning, a significant difference in response to ASA was observed, depending on sex. In men, the reactivity of platelets decreased by 9.5 ± 44.3 ARU, and in women, conversely, it increased by 13.9 ± 48.2 ARU. The size of this decline in the ASA group in the morning in men was lower than in the ASA group in the evening. There was no correlation between age, BMI waist to hip ratio of the patients, and change in

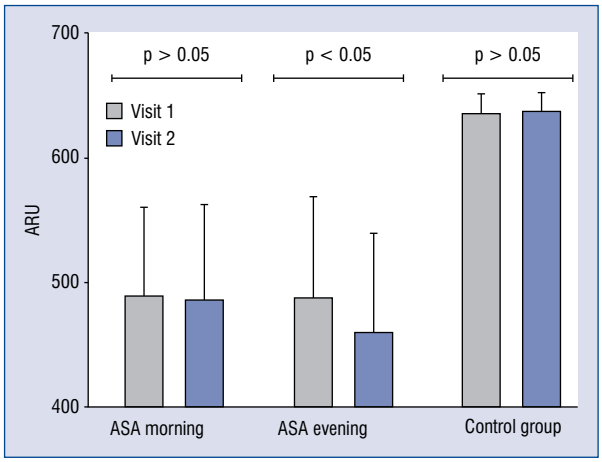

Figure 2. Change in Aspirin Reaction Units (ARU) between Visit 1 and 2 in groups studied (p-value refers to Wilcoxon-signed rank test); ASA — acetylsalicylic acid.

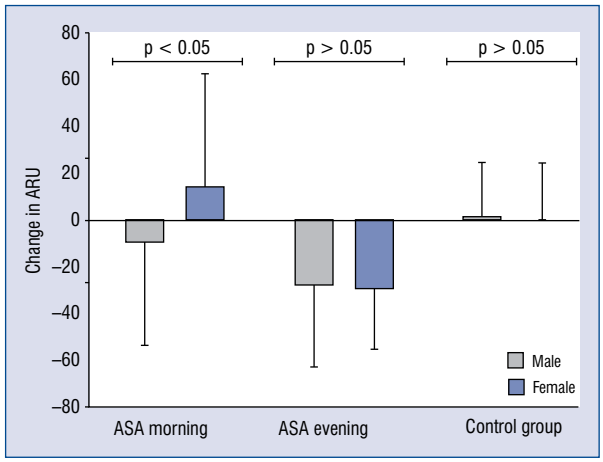

Figure 3. Change in Aspirin Reaction Units (ARU) at Visit 2 in relation to Visit 1 in the groups studied in relation to patient sex (p-value refers to Mann-Whitney U test); ASA — acetylsalicylic acid.

platelet aggregation after the change of dosage to bedtime. The changes in laboratory tests were also noted. Only in the ASA evening group was there a decrease in the number of platelets and an increase in uric acid concentration. There were no changes in other laboratory parameters between groups (Table 4).

Discussion

On the basis of data from epidemiological studies, it has been shown that circadian rhythms can affect both the physiology and pathology in the cardiovascular system [19, 20]. In the early morning hours, a higher incidence of MIs, sudden cardiac death, ventricular malignant arrhythmia, stroke, and acute aortic dissection is observed [21–24]. MIs, which occur between 6 a.m. and 12 noon, cause 21% more damage to the myocardium, which is a factor that worsens prognosis [19, 25]. Aggregation of platelets and the level of aggregation markers have their circadian rhythm peaking between 6 a.m. and 12 noon [26, 27]. The severity of platelet aggregation in the morning may be associated with an increase in the number of acute coronary syndromes [28]. It seems that it is important to look for new ways to properly inhibit platelet aggregation in the morning. One of these methods could be an evening administration of ASA. The aim of the study was to compare the effect of ASA on platelet aggregation, depending on the time of drug administration in the morning versus in the evening, in patients with CAD and first- and second-degree AH, according to European Society of Hypertension (ESH)/European Society of Cardiology (ESC) 2013 [29–31].

In the current observation, in the evening ASA group, a significant reduction in platelet aggregation of 28 ARU was obtained compared to the morning ASA group (460.10 ± 82.3 h vs. 487.62 ± ± 77.4 h in the morning; $p < 0.05$). At the baseline visit, the results of inhibition of aggregation in ARUs did not differ between the groups and were 489.01 ± 73.0 in the morning ASA group and 488.16 ± 83.0 in the evening ASA group. This is in line with the results obtained by Bonten et al. [32]. In their study of 290 patients with normal blood pressure or mild AH, they showed that ASA given in the evening reduced platelet reactivity by an average of 22 ARU compared to the morning ASA group [32]. In another study, in a small group of healthy volunteers, the same researchers marked cyclooxygenase-1 (COX-1)-dependent platelet activity (using the VerifyNow Aspirin Test) and the level of thromboxane B2 (STxB2). They showed reduced platelet activity of 23 ARU platelet in VerifyNow Aspirin Test and a reduction in TXB2 by 1.7 ng/mL in those who took ASA at bedtime compared to those who took ASA in the morning. This confirms the effect of a low-dose ASA taken at bedtime on the reduction of COX-1-dependent platelet activity in healthy people [25, 33].

Acetylsalicylic acid is rapidly and almost completely absorbed in the stomach and duodenum by passive diffusion. Due to the short half-life, which is 2–3 h, ASA inhibits about 90% of platelets that are present in the plasma when the drug is taken.

Table 4. Laboratory tests of the groups studied at Visit 1 and Visit 2.

		Acetylsalicylic acid		Control group
		Morning	Evening	
Hemoglobin [mmol/L]	Visit 1	8.8 ± 0.74[a]	8.7 ± 0.58[a]	8.9 ± 0.73[a]
	Visit 2	8.8 ± 0.7[a]	8.6 ± 0.7[a]	8.9 ± 0.7[a]
	P (Wilcoxon)	> 0.05	> 0.05	> 0.05
Platelets [10^{-9}/L]	Visit 1	225.7 ± 54.3[a]	227.6 ± 56.9[a]	224.5 ± 61.1[a]
	Visit 2	226.9 ± 36.8[a]	197.9 ± 41.5[b]	226.0 ± 60.2[a]
	P (Wilcoxon)	> 0.05	< 0.05	> 0.05
Na [mmol/L]	Visit 1	141.2 ± 2.5[a]	141.1 ± 2.2[a]	141.7 ± 2.1[a]
	Visit 2	141.0 ± 2.1[a]	140.9 ± 2.2[a]	141.9 ± 2.3[a]
	P (Wilcoxon)	> 0.05	> 0.05	> 0.05
K [mmol/L]	Visit 1	4.3 ± 0.45[a]	4.3 ± 0.4[a]	4.2 ± 0.4[a]
	Visit 2	4.3 ± 0.3[a]	4.3 ± 0.4[a, b]	4.2 ± 0.3[b]
	P (Wilcoxon)	> 0.05	> 0.05	> 0.05
Total cholesterol [mmol/L]	Visit 1	4.8 ± 1.1[a]	4.7 ± 1.0[a]	4.7 ± 0.9[a]
	Visit 2	4.7 ± 0.9[a]	4.8 ± 1.1[a]	4.4 ± 0.9[a]
	P (Wilcoxon)	> 0.05	> 0.05	> 0.05
LDL-C [mmol/L]	Visit 1	1.3 ± 0.4[a]	1.4 ± 0.5[a]	1.4 ± 0.5[a]
	Visit 2	1.5 ± 0.5[a]	1.5 ± 0.6[a]	1.7 ± 0.6[a]
	P (Wilcoxon)	> 0.05	> 0.05	> 0.05
HDL-C [mmol/L]	Visit 1	2.6 ± 1.0[a]	2.5 ± 0.9[a]	2.5 ± 0.7[a]
	Visit 2	2.5 ± 0.8[a]	2.4 ± 0.8[a]	2.5 ± 0.7[a]
	P (Wilcoxon)	> 0.05	> 0.05	> 0.05
Triglicerydes [mmol/L]	Visit 1	1.6 ± 0.5[a]	1.6 ± 0.4[a]	1.5 ± 0.8[a]
	Visit 2	1.6 ± 0.4[a]	1.5 ± 0.5[a]	1.7 ± 0.8[a]
	P (Wilcoxon)	> 0.05	> 0.05	> 0.05
GFR [mL/min/1.73 m^2]	Visit 1	80.4 ± 9.7[a]	79.3 ± 12.6[a]	78.8 ± 11.7[a]
	Visit 2	80.6 ± 9.0[a]	82.9 ± 8.9[a]	79.7 ± 9.9[a]
	P (Wilcoxon)	> 0.05	> 0.05	> 0.05
Serum creatinine [μmol/L]	Visit 1	82.2 ± 5.1[a]	82.2 ± 5.1[a]	81.6 ± 5.2[a]
	Visit 2	79.4 ± 15.4[a]	82.9 ± 12.0[a]	82.3 ± 10.9[a]
	P (Wilcoxon)	> 0.05	> 0.05	> 0.05
Glucose [mmol/L]	Visit 1	5.2 ± 0.9[a]	5.2 ± 0.7[a]	5.2 ± 0.6[a]
	Visit 2	5.1 ± 0.7[a]	5.3 ± 0.7[a]	5.1 ± 0.5[a]
	P (Wilcoxon)	> 0.05	> 0.05	> 0.05
Urid acid [umol/l]	Visit 1	331.9 ± 101[a]	334.3 ± 99[a]	330.7 ± 97[a]
	Visit 2	332.7 ± 105[a]	379.1 ± 71[b]	328.9 ± 99[a]
	P (Wilcoxon)	> 0.05	< 0.05	> 0.05
CRP [mg/L]	Visit 1	2.0 ± 1.8[a]	1.9 ± 0.9[a]	1.9 ± 0.8[a]
	Visit 2	2.1 ± 1.6[a]	2.1 ± 1.0[a]	1.8 ± 0.8[a]
	P (Wilcoxon)	> 0.05	> 0.05	> 0.05

[a, b]Different letters given in the upper index indicate the occurrence of statistical differences in the values of a given parameter between the three groups (Kruskal-Wallis ANOVA, $p < 0.05$); CRP — C-reactive protein; GFR — glomerular filtration rate; HDL-C — high density lipoprotein cholesterol; LDL-C — low density lipoprotein cholesterol

It should be remembered that physiologically, at all the times, new and uninhibited plates are released into the blood, which constitute about 10% of the total number. The release of new platelets may be greater in people with vascular disease [34–36]. It has been shown that in up to 25% of patients, inhibition of platelets by ASA decreases gradually within 24 h after its administration [18, 37]. In his work, Kirszbacher et al. [38] confirmed that the time of taking ASA can affect the incidence of cardiovascular events and can change the effectiveness of prophylaxis. If the drug is given in the morning, it was obvious that the highest plasma drug levels occurred after the morning peak of the incidence of a thromboembolic event. Moreover, the method of morning ASA administration has a lower protective value for the prevention of cardiovascular events at night and early in the morning, when the lack of physical activity further promotes platelet aggregation and ischemia. In contrast, the highest plasma concentration of ASA administered late in the evening reaches its maximum before the peak of thromboembolic events [38–40]. Henry et al. [41] evaluated the biological effect of low-dose ASA in 150 patients with CAD. Platelet aggregation increased gradually after taking the drug in the second hour after only 4.7% and after 12 h in 11% of patients, respectively. These results correlated with elevated levels of inflammatory markers, smoking, and diabetes. The authors suggested that administration of ASA once per 24 h (regardless of dose, 75 mg or > 100 mg) does not provide stable 24-h antiplatelet protection in a significant proportion of patients with CAD [41]. Studies by other authors have clearly demonstrated that the antiplatelet effect of ASA decreases within 24 h after a single administration of the drug. The observation referred to 100 patients with diabetes and 73 non-diabetic patients. In both groups, the production of thromboxane (TXA2) was significantly inhibited after 12 h and was followed by a slow recovery of platelet activity. Greater body weight was the only independent predictor of faster return of COX-1 activity, but only in non-diabetic subjects. It has been shown that dosing ASA once a day may cause COX-1 activity to return more rapidly and may result in incomplete TAX2 inhibition. In contrast, 100 mg ASA taken twice a day caused complete TAX2 blocking in both groups. The authors concluded that insufficient inhibition of TAX2 can be easily corrected by changing the diagram from once a day to twice a day [37]. This mechanism, due to limitations and assumptions of this paper, has not been analyzed.

The findings of the present study are in line with previously conducted trials by Bonten et al. [32, 33], and they confirm that bedtime ASA intake has a better effect on decreasing the platelet reactivity than an intake on awakening. However, the present study also demonstrated the significant gender-dependence difference in response to ASA administrated in the morning. In men, the reactivity of platelets decreased by 9.5 ± 44.3 ARU, whereas in women it increased by 13.9 ± ± 48.2 ARU. In men, the size of this decline in the ASA morning group was lower than in the ASA evening group. It is known that the antiplatelet effect of ASA gradually decreases within 24 h after administration [41]. In this study, platelet activity during Visit 2 was measured in the morning, which is 12 h and 24 h after taking ASA, in the group receiving the drug in the evening and in the morning, respectively. The striking difference between men and women in the latter group is probably due to the overall higher platelet reactivity in women [42]. Therefore COX-1 dependent platelet inhibition may be shorter than in men. Therefore, morning intake of ASA in women is not only ineffective in response to platelets, but it can also cause an adverse response, which is particularly important in patients with a high risk of cardiovascular disease. This fact could be an additional argument to dose ASA in the evening because its activity is then independent of sex. However, this requires further observation.

Conclusions

1. In the group of patients with ischemic heart disease and hypertension, dosing ASA at bedtime compared to dosing the morning is associated with a significant reduction in platelet aggregation, which is determined using the VerifyNow analyzer.
2. The response to ASA in patients with ischemic heart disease and hypertension may differ from one sex to another. The research suggests that the benefit gained by changing the drug administration from the morning to the evening is greater in women.

Conflict of interest: None declared

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Right atrial pathology in arrhythmogenic right ventricular dysplasia

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Abstract

Background: *Atrial fibrillation (AF) is the most common atrial arrhythmia in arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVD). Considering the histologic changes known in the right ventricular (RV) in ARVD, the aim of the present study was to examine right atrial (RA) pathology in patients with ARVD.*

Methods: *Histology of RA and RV was assessed from autopsy material in 3 patients with ARVD without persistent atrial arrhythmia. RA histology in 3 patients with permanent AF without ARVD and 5 patients without cardiovascular disease was also studied. Staining with hematoxylin phloxine saffron was performed for the ARVD patients to identify fibrosis, and hematoxylin-eosin for identification of lymphocytes. Masson's trichrome staining was performed for control groups taken from a collection of standard glass slides.*

Results: *In all 3 ARVD cases, RA anomalies were observed that revealed a reduction of cardiomyocytes, the presence of adipocytes, some of them inside the mediomural atrial layer and interstitial fibrosis. In 2 ARVD cases, interstitial fibrosis was also associated with a focus of replacement fibrosis, which was also observed in patients with permanent AF without ARVD. The histologic specimen of the RA and RV from the control group without cardiovascular disease did not display any evidence of fat or fibrosis with a preserved cardiomyocyte architecture.*

Conclusions: *A similar histopathological substrate, as can be observed in the RV of patients with ARVD can also be seen in the RA of these patients. This may explain the high prevalence of atrial arrhythmias, particularly AF, in patients with ARVD.* (Cardiol J 2019; 26, 6: 736–743)

Key words: arrhythmogenic right ventricular dysplasia, atrial arrhythmias, pathological substrate, atrium

Introduction

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVD), first recognized in 1977, is an inherited cardiomyopathy mostly due to mutations in both desmosomal and non-desmosomal genes [1]. ARVD is considered as one of the leading causes of sudden cardiac death in the young and among athletes [2, 3]. In patients with ARVD, a right ventricle (RV) covered by fat has been an impressive pattern observed after opening the pericardium before antiarrhythmic surgery (Fig. 1A). Histopathology of the RV in ARVD is studied at low magnification in order to display the full thickness

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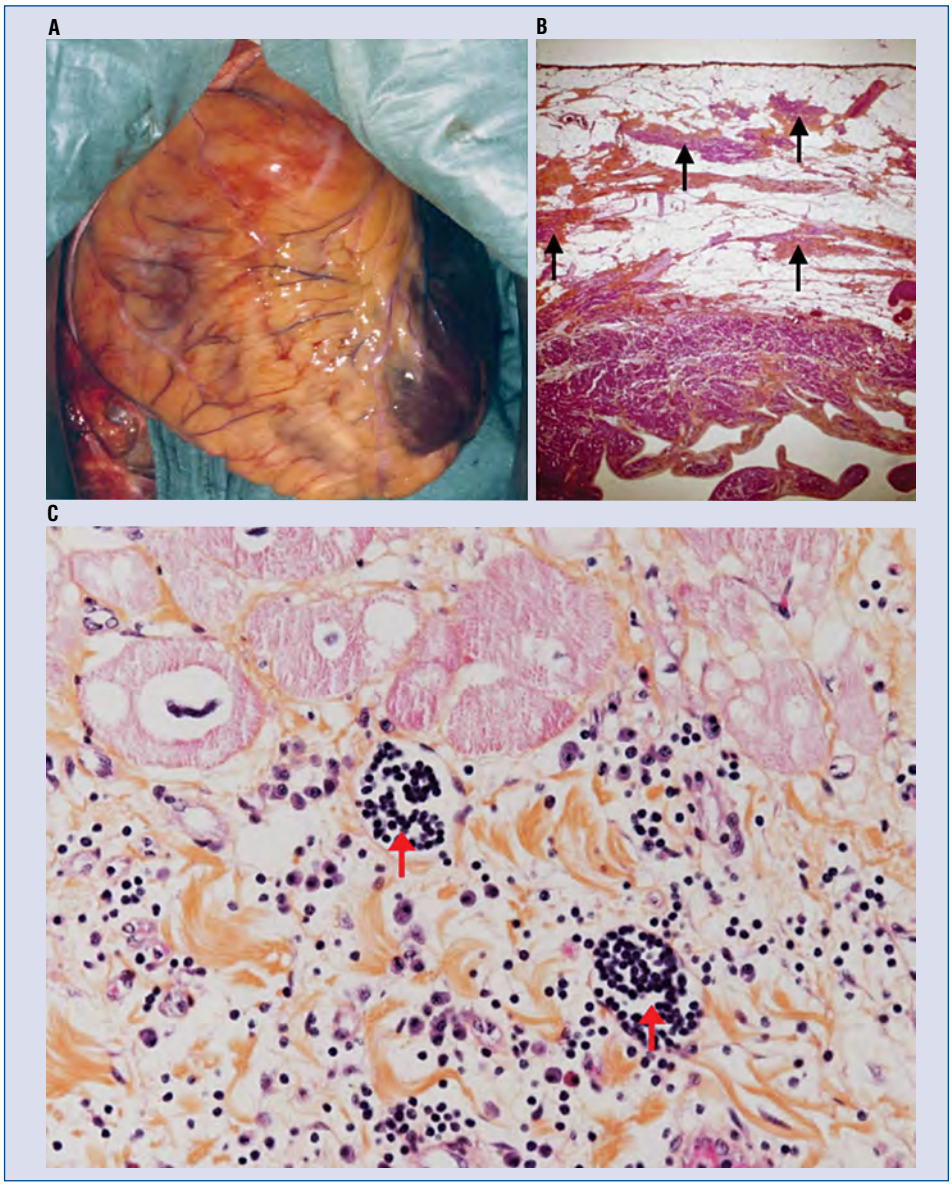

Figure 1. A. Surgical view of a typical right ventricular dysplasia (ARVD) beating heart. The right ventricle (RV) is dilated and totally covered by fat with extension over the left ventricle (LV) apex (dark red). Two aneurysms are visible on the infundibulum and the sub tricuspid area; **B.** Full thickness of the RV in a typical ARVD patient. Note the predominance of adipocytes in subepicardial layers and the presence of strands of cardiomyocytes (solid arrows) bordered by fibrosis within the fat, which is a marker of ARVD (HPS, 20×); **C.** Two foci (red solid arrows) of lymphocytes in zones of interstitial fibrosis in the RV. Also note the presence of eosinophils, monocytes and polymorphonuclears. This histologic specimen was obtained from a patient with ARVD, who was referred for heart transplantation due to a rapid deterioration of global cardiac function (HPS, 400×) (image was provided by Guy H. Fontaine).

of the free wall (Fig. 1B). This shows a particular topographic pattern in which a reduced amount of myocardium and a presence of fat and fibrosis are predominant features on epicardial layers. However, inside this fibro-fatty tissue, it is possible to observe strands of cardiomyocytes, which appear as a pathognomonic histological feature of this disease (Fig. 1B). It is also obvious that the preserved RV myocardium remains mostly apparent in the subendocardial layers frequently dissociated by excessive interstitial fibrosis (Fig. 1B). This can explain why trouble in conduction is mostly observed on epicardial layers, leading to identification of the Epsilon wave of postexcitation. However, fibrosis in the RV is twofold: 1) Interstitial fibrosis made of small layers of

fibrous tissue bordering or embedded cardiomyocytes, and 2) Replacement fibrosis made of large amounts of hyaline fibrosis sometimes interspersed by a variable number of lymphocytes. These lymphocytes were later interpreted as a hallmark of superimposed myocarditis. This can be explained by the increased susceptibility of this abnormal myocardium in attracting inflammatory phenomena such as cardiotropic viruses, which can be a trigger of arrhythmias [4–6].

After the group around Guy Fontaine in Paris, which was the first to demonstrate a high prevalence of supraventricular arrhythmias in ARVD patients [7], this concept was further confirmed on a larger series of patients [8, 9]. Of all atrial arrhythmias in ARVD, atrial fibrillation (AF) is the most common. A recent study of boxer dogs with histopathologically confirmed ARVD identified fibro-fatty infiltration and histopathologically altered intercalated disc and gap junction proteins in atrial myocardium, representing a substrate for atrial arrhythmias associated with ARVD [10]. This supports atrial involvement as part of this disorder. Therefore, this study examines the right atrial (RA) pathology of humans with ARVD in comparison to patients with persistent AF without ARVD and controls without cardiovascular disease (CVD), and considers typical histologic changes of the RV known in ARVD.

Methods

Right atrial histology was assessed in autopsy material from 3 patients with ARVD with atrial arrhythmias, but without a history of persistent AF. This was done in order to minimize the effects of atrial arrhythmia itself on atrial remodeling ("AF begets AF"). The diagnosis of ARVD was confirmed by clinical presentation and characteristic pathological and histopathological changes of the RV at autopsy. A regular technique of tissue processing for glass slides for light microscopic examination, with numeric image processing was performed. Staining with hematoxylin phloxine saffron (HPS) was performed for tissue obtained from the patients with ARVD to have a better identification of fibrosis, and hematoxylin-eosin (HE) for better identification of lymphocytes. Masson's trichrome staining was performed for two control groups taken from a collection of standard glass slides. Examination of all slides was made at low (20×) and high magnification (400×) with special respect to adipocytes, interstitial or replacement fibrosis as well as high magnification for detection of clusters of lymphocytes isolated in myocardium or embedded in fibrosis, which represent a chronic-active form of myocarditis. The RA samples from patients with permanent AF without ARVD were obtained from the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China. RA autopsy samples from individuals without CVD were obtained from the Forensic Medical College of Xi'an Jiaotong, University Health Science Center, China. This was approved by the ethical committee of Xi'an Jiaotong University Health Science Center, China (approval number: 2018007). Informed consent was obtained from all patients or their relatives. Autopsy samples of patients with ARVD from Hôpital de la Salpêtrière, Paris, France, were taken before 1975. Three patients with ARVD did not refuse research associated with their disease, and at that time there was no ethics committee, but Chief of the Department of Cardiology, Hôpital de la Salpêtrière, Paris, France approved the investigation to learn about the etiology of arrhythmias in these patients.

Results

ARVD group

To improve clarity, magnification and staining are indicated in each picture. The reference histologic document of a typical RV free wall, changes in a characteristic patient with ARVD (case 1) is presented in Figure 1B. Note the value of low magnification to display the full thickness of the RV free wall (Fig. 1B) and the value of high magnification in assessing lymphocytes (Fig. 1C).

In summary, reference histological material of the RV shows:

— reduction of cardiomyocytes;
— continuous adipose tissue on the epicardium;
— strands of cardiomyocytes within adipose tissue in the subepicardial layers;
— strands of fibrous tissue all over the free wall, being more severe on endocardial layers;
— paucity or absence of cardiomyocytes in medio-mural layers.

Case 1

The patient was a 28-year-old Caucasian male, 54 kg, born in the Veneto region, Italy. His familial history was not available. Transthoracic echocardiography had shown a left ventricular ejection fraction (LVEF) of 25% and RV fractional area change of 20% after 10 years follow-up for paroxyxmal ventricular tachycardia (VT). The patient experienced almost incessant VT of four different morphologies and then was referred to the present group in Paris for antiarrhythmic surgery.

Ablation by 17 shock of 100 joules delivered by direct current was performed to prevent relapses of VT due to a very high risk for open heart surgery. However, this patient died one week later of a long-standing pulmonary infection prior to the ablation procedure. Autopsy was performed the same day. Gross pathology studied before preservation in formalin confirmed the diagnosis of ARVD, the whole RV was covered by fat. A major increase of trabeculations was observed after opening the RV free wall, which was paper-thin and showed a significant reduction of myocardial tissue (Fig. 2A). The RA histological sample from this patient is also impressive by the major evidence of interstitial fibrosis and small islands of adipocytes embedded or bordered by residual cardiomyocytes, which were considerably reduced in amount (Fig. 2B). Also note an increased thickness of the media layer of the distal coronary vessel, which is well in line with the concept of the presence of cardiac microvascular disease in ARVD [11] and may be responsible for one of the mechanisms for chest pain in ARVD patients [2, 12].

Case 2

The patient was a 48-year-old male of African descent, born in La Martinique, 90 kg, LVEF 25%. He had a history of paroxysmal AF and was referred for VT ablation after several episodes of tolerated sustained VT. However, this patient died due to cardiac tamponade after insertion of the RV endocardial catheters before ablation. The pathology of the RV was typical in ARVD. The histological study of the RA (Fig. 2C) showed evidence of interstitial fibrosis bordering or embedding a reduced number of cardiomyocytes, but was less severe than in the previous case. Presence of some clusters of adipocytes inside the myocardium was also noted. A focus of replacement fibrosis on the epicardial layer with strands of fibrosis towards the endocardial layer was present. This pattern suggests sequelae of healed — epicardial towards endocardial — myocarditis. An absence of lymphocytes is noticeable.

Case 3

This patient was a Caucasian woman in the her late 30s, who had died in hospital of intractable VT leading to an autopsy and subsequent typical histologic diagnosis of ARVD. Histology of the RA showed zones of major fibrosis and others with excessive fat containing residual strands of cardiomyocytes, which were considerably reduced in amount (Fig. 3A, B). Histology of the RV revealed typical characteristics of ARVD (Fig. 3C).

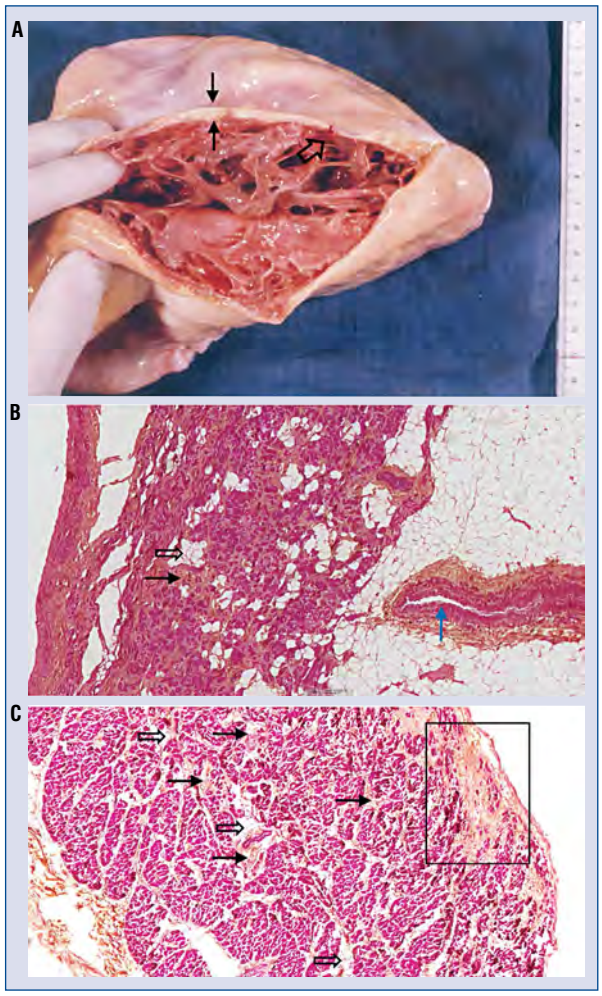

Figure 2. A. The heart is cut from apex to base along the acute margin of the right ventricle (RV) free wall. Note that all the epicardium is covered by fat (black solid arrows). Myocardium remains only on a thin endocardial layer. Also note an increased number of trabeculations (black open arrows). The heart was obtained immediately after the patient's death, before preservation in formalin to maintain the native color of the tissue. Ventricular tachycardia was ablated after 17 shocks of 100 joules delivered in the RV, however, this document shows that no scar was visible on the endocardium (Courtesy of Pr Piccolo, Venice, Italy); **B.** Sample of the right atrial free wall of the same right ventricular dysplasia (ARVD) patient presented on panel A. This sample is impressive showing major evidence of interstitial fibrosis (black solid arrows) and clusters of adipocytes (black open arrows) bordering cardiomyocytes. Also note an increased thickness of the media layer of a distal coronary vessel (blue solid arrows, micro-vascular disease concept, see text); **C.** Evidence of interstitial fibrosis (black solid arrows) bordering or embedding cardiomyocytes, which is less severe than in the previous case. The presence of some clusters of adipocytes (black open arrows) inside myocardium is visible. The presence of fibrosis (black square) on the epicardial layer with strands of fibrosis towards endocardial layers was observed. This pattern suggests sequel of healed epicardial towards endocardial myocarditis. An absence of lymphocytes is noticeable (image was provided by Guy H. Fontaine).

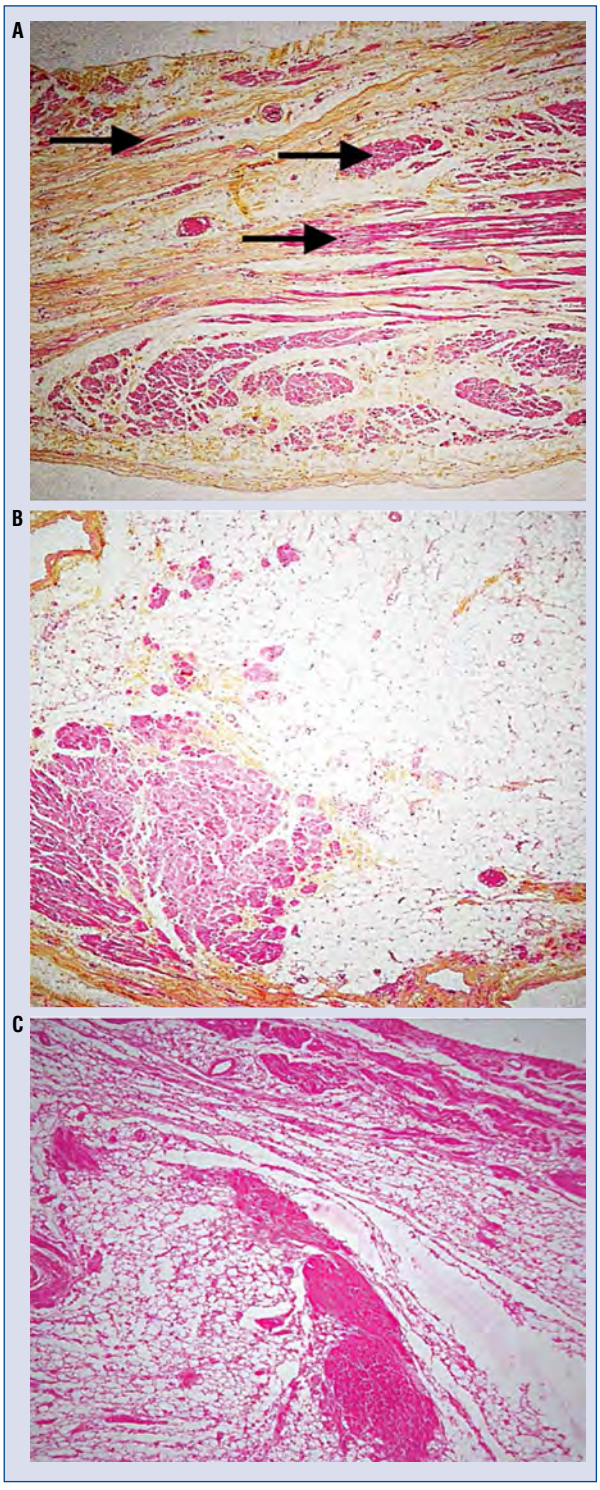

Figure 3. Third patient showing right ventricular dysplasia (ARVD). **A.** Major dissociation of strands of cardiomyocytes (black solid arrows) by fibrosis in the right atrial free wall; **B.** Presence of an excessive amount of epicardial adipocytes occupied by strands of cardiomyocytes in right atrial tissue; **C.** Histology of the right ventricle in this third patient shows a major predominance of adipocytes and fibrosis, a typical characteristic of ARVD (image was provided by Guy H. Fontaine).

Control groups

Three patients with permanent AF without ARVD were chosen as a positive control group (Fig. 4A). They were > 50 years; two were males. Their RA histology (Fig. 4B) shows a major predominance of adipocytes and fibrosis. Five individuals without known CVD, had died of a non-cardiac cause served as negative controls, three were males. They showed a pattern of a homogenous myocardial structure exempt of fat, fibrosis or inflammation (Fig. 4C, 4D).

Discussion

In this autopsy study of RA tissue from patients with ARVD without a history of persistent atrial arrhythmias demonstrated similar histopathological changes when compared to typical RV changes of fibro-fatty infiltration known in ARVD. According to available research, this is the first human study investigating RA histology of patients with ARVD as compared to patients with permanent AF without ARVD and in patients without any CVD. The atrial histopathological changes observed in the ARVD cohort were absent in controls without CVD who had died of a non-cardiac cause, but a similar pattern of RA fibro-fatty infiltration was observed in patients with permanent AF without ARVD.

The pathologic changes observed in the RA are similar to those known in the right (or possibly left ventricle) ARVD. The first case of this series displays a typical picture of what is considered "atrial dysplasia". This term was first reported by the present group in a patient with myotonic dystrophy where the dysplastic phenomenon was localised in a focal zone [13]. The second case shows evidence of diffuse interstitial fibrosis with small clusters of adipocytes inside the atrial myocardium. Another very important anomaly was the patchy distribution of zones of epicardial hyaline fibrosis in agreement with a pattern of healed myocarditis, probably superimposed on the genetically produced dysplastic phenomenon. This pattern suggests sequelae of healed epicardial towards endocardial myocarditis. An increased thickness of the media layer in a distal coronary vessel is in line with the presence of a microvascular disease in ARVD [11], which can explain atypical chest pain in some of these patients [2, 14].

Fibrofatty atrial infiltration has already been described in patients with persistent AF [15]. In the present study, the atrial myocardium in patients with ARVD and those with permanent AF was not made of compact myocardium such as the

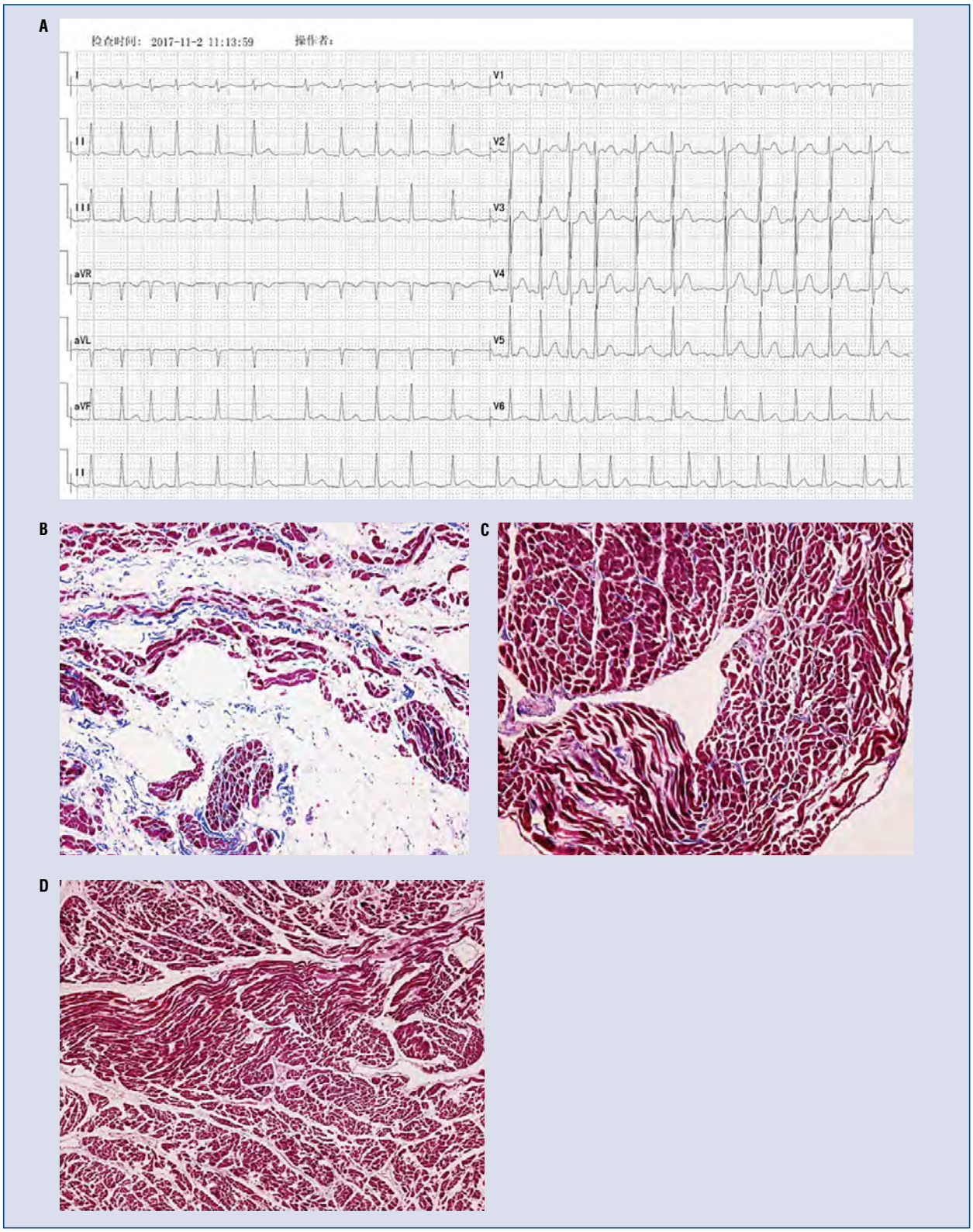

Figure 4. A 46-year-old female patient was diagnosed with permanent atrial fibrillation, without right ventricular cardiomyopathy/dysplasia (ARVD) (**A**). Histology of the right atrium (**B**) in this patient shows a major predominance of adipocytes and fibrosis, similar to that observed in patients with ARVD (Masson's trichrome, 10×). Right atrial (**C**) and right ventricular (**D**) histology of a 21-year-old male without known cardiovascular disease, who died of a non-cardiac cause, shows a homogenous myocardial structure exempt of fat, fibrosis or inflammation (Masson's trichrome, 20×) (image was provided by Guy H. Fontaine).

homogenous structure observed in the normal left ventricle, but showed a spectrum of anomalies known in the RV of patients with ARVD. Of importance, atrial dysplasia in patients with ARVD was present in the absence of a history of persistent atrial arrhythmias. Therefore, it can be hypothesized that atrial dysplasia is not directly related to the presence of atrial arrhythmias in these patients, but should follow a different pathophysiologic mechanism. As expected, these anomalies were absent in patients without CVD.

Concepts herein are clear and simple because they are based on obvious structural heart disease. However, this understanding requires basic knowledge in the field of histology of the myocardium under normal and pathologic conditions. This pathological substrate most likely creates the basis for AF, similar to ventricular arrhythmias well known in patients with ARVD [2, 6, 16]. Yet, the specific mechanisms leading to atrial dysplasia in ARVD remain unclear and require further investigation in future studies. A primary disease of the atria, as suggested in studies of ARVD boxer dogs is possible [10]. However, it is also possible that right and left ventricle dysfunction and adverse ventricular remodeling secondarily leads to increased loading conditions in the atria, which produces atrial dysplasia, similar to patients with persistent AF without ARVD [9, 17].

In short, histologic anomalies in the human ventricular myocardium may lead to ventricular arrhythmias, and in more severe cases, to ventricular fibrillation and sudden death. The same situation, which also seems to be common in the atria, can lead to atrial arrhythmias including AF.

Limitations of the study

This preliminary report was performed with small series of patients with ARVD since it is challenging to obtain atrial tissue for histologic examination from these patients. Moreover, genotyping was not available when these samples were collected. However, the clinical investigation, gross pathology and histopathology were well in line with a diagnosis of ARVD in these 3 patients. From the present descriptive study, it cannot be inferred as to whether the structural changes in the RA of patients with ARVD are secondary due to RV failure, or are primarily due to genetic mutations or epigenetic factors that affect the intercalated disc of atrial tissue. Atrial tissue was only available from the RA. Therefore, histological findings from the left atrium cannot report on, which is important for triggering and maintaining AF in patients without ARVD.

Conclusions

This histologic study of RA tissue in 3 patients with ARVD without a history of persistent atrial arrhythmias demonstrates structural changes similar to those of the RV known in ARVD. The present findings help to explain the underlying substrate and high prevalence of AF in this cardiomyopathy.

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We dedicate this work to our great mentor and teacher Guy H. Fontaine who is deeply missed.

Conflict of interest: None declared

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The effect of beta-blockers on mortality in patients with heart failure and atrial fibrillation: A meta-analysis of observational cohort and randomized controlled studies

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Abstract

Background: *Beta-blockers (BB) are the cornerstone of therapy for heart failure (HF); however, the effects of these drugs on the prognosis of patients with concomitant atrial fibrillation (AF) remain controversial. The objective of this meta-analysis was to evaluate the efficacy of BB on mortality in HF coexisting with AF.*

Methods: *A systematic search of PubMed, Embase and the Cochrane Library databases was conducted. Observational cohort studies and randomized controlled trials reporting outcomes of mortality or HF hospitalizations for patients with HF and AF, being assigned to BB treatment. A non-BB group was also included.*

Results: *A total of 8 clinical studies (5 randomized controlled trials and 3 observational cohort studies) involving 34197 patients were included in the analysis. The pooled analysis demonstrated that BB treatment was associated with a 22% reduction in relative risk of all-cause mortality in patients with HF and AF (RR: 0.78; 95% CI 0.71–0.86; $p < 0.00001$; $I^2 = 27\%$). The pooled analysis of 5 studies reported the outcome of HF hospitalization (2774 patients) which showed that BB therapy was not associated with a reduction of HF hospitalizations (RR: 0.94; 95% CI 0.79–1.11; $p = 0.46$; $I^2 = 38\%$).*

Conclusions: *Meta-analysis suggests the potential mortality benefit of BB in patients with HF and AF. It was concluded herein that it is premature to deny patients with AF and HF to receive BB therapy considering current evidence.* (Cardiol J 2019; 26, 6: 744–752)

Key words: beta-blocker, atrial fibrillation, heart failure, mortality

Introduction

Heart failure (HF) and atrial fibrillation (AF) are two burdensome cardiovascular epidemics of the 21st century [1–3]. Patients with concomitant AF and HF have even higher mortality and hospital admission rates [1–5]. Thus, the importance of concomitant AF and HF cannot be overstated.

Among the many therapies available for HF and AF, beta-blockers (BB) are a cornerstone of management [5–8]. Based on several large randomized clinical trials, BB are strongly recommended (IA) for heart failure with reduced ejection fraction (HFrEF) by both American and European guidelines [5–8]. However, no randomized trials have been performed specifically to investigate the

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efficacy of BB in HF patients with AF. Post-hoc analyses of randomized trials designed to assess BB in HF suggest no benefit of BB in HF patients with AF [9–13]. Furthermore, two recent meta-analyses have failed to show clearly the mortality and morbidity benefit of BB in patients with HF and concomitant AF [14, 15]. Of note, the AF group comprised only 17–21% of the whole patient cohort, and the obtained meta-analyzed results might reflect an under-powered analysis; in addition, the randomized controlled trials (RCTs) included in the previous meta-analyses were published more than 10 years ago, which was different from the current real world. Recently, several large well-designed observational cohort studies examining the prognostic effect of BB in HF and AF has been published after these meta-analyses were performed [16–18].

Given the limited evidence and uncertain effects of BB in HF with coexisting AF, the aim was to conduct an updated meta-analysis of RCTs and observational cohort studies (OCSs) on the effect of BB on outcome in HF and AF.

Methods

Search strategy

Electronic searches were conducted in the PubMed, Embase and the Cochrane Library databases. Search terms included "beta-blocker", "heart failure", "atrial fibrillation", and their variations. There was no language restriction placed on the searches. Each database was searched from inception to June 2017. Additionally, reference lists in the articles chosen for inclusion, and the reference lists of previous reviews were screened to identify other potentially eligible trials.

Inclusion criteria

Trials with the following characteristics were included:

- Population: Adult patients diagnosed as AF and HF (including both heart failure with reduced ejection fraction [HFrEF] and heart failure with preserved ejection fraction [HFpEF]).
- Intervention: The intervention group included patients who received BB treatment.
- Control: The control group included patients who did not receive BB treatment.
- Outcomes: The all-cause mortality or HF hospitalizations had to be the outcome reported, and the duration of follow-up was at least 6 months.
- Types of study: The studies had to be RCTs or OCSs.

Study selection and data extraction

Two authors independently screened titles and abstracts. They obtained full articles that met the inclusion and exclusion criteria and after an independent review.

Information about the study and patient characteristics, methodological quality, intervention strategies, and clinical outcomes was systematically extracted separately by two reviewers. Disagreements were resolved by consensus.

Quality assessment

The quality of random control trial included was assessed by the Jadad quality scale [19]. The quality of the observational study was evaluated by the Newcastle-Ottawa Scale tool (available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

Statistical analysis

The relative risks (RRs) and 95% confidence intervals (95% CI) were used as the common measure across the studies. The hazard ratios (HRs) were considered equivalent to RRs [20, 21]. If the effect estimates were not available in the studies included, RRs were calculated by using the following formula: RR = Probability of events given treatment/Probability of events given no-treatment. If the studies provided the adjusted estimations, they were directly used in the meta-analysis. Statistical heterogeneity across studies was assessed by using the Q statistic with its p value and I^2 statistic. The I^2 statistic is used to quantify the proportion of total variation in the effect estimation that is due to between study variations. An I^2 value greater than 50% indicates significant heterogeneity [22]. Clinical heterogeneity could not be excluded, so the pooled RR was calculated with the random-effects model [23].

Results

Search and selection of studies

The initial search yielded 680 unique titles and abstracts from PubMed, Embase and the Cochrane Library, and approximately potentially relevant articles identified. Of these articles, 5 RCTs [9–13] and 3 OCSs [16–18] fulfilled the eligibility criteria and were included in the present meta-analysis. The details of study selection flow diagram were described in Figure 1.

Characteristics and quality of study included

The characteristics of the studies included are presented in Table 1. In all 8 studies included,

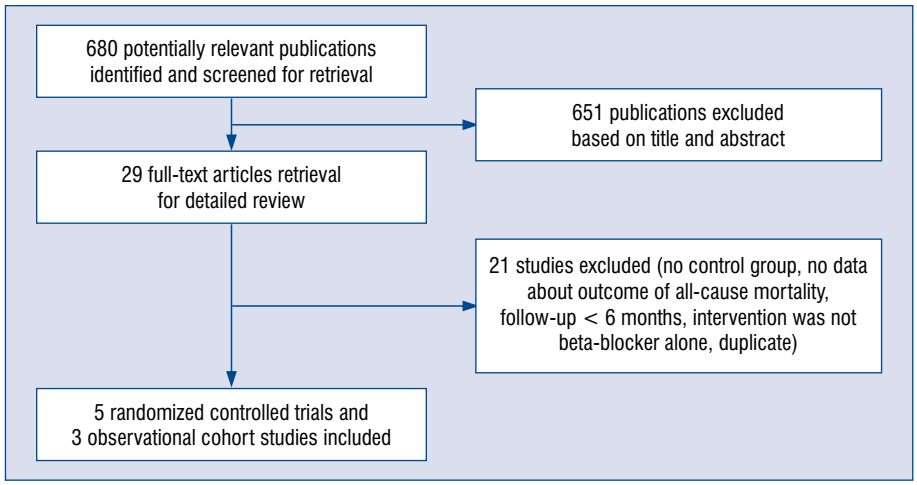

Figure 1. Selection process for articles included in meta-analysis.

5 studies were randomized controlled design and 3 studies were observational cohort design. All the 5 RCTs were specific AF sub-studies of the large HF randomized trials that compared the effect of BB with those of placebo. Among the 3 OCSs, propensity score (PS) analysis was performed with PS matching in 2 studies (AF--CHF study and Danish nationwide registry), and multivariable-adjusted Cox regression analysis was performed in 1 study (Swedish HF Registry). Of the 8 studies, patients with HFrEF were included in the 6 studies (US-Carvedilol, CIBIS-II, MERIT-HF, BEST, Swedish HF Registry and AF-CHF); patients with both HFrEF and HFpEF were included in 2 studies (SENIORS and Danish nationwide registry). A total of 34197 patients were enrolled, including 20235 patients treated with BB and 13962 without BB. The mean follow-up duration ranged from 6 months to 3.1 years. For the 5 RCTs, study quality was scored as "good" for all but one (the US-Carveilol study), which was scored as "fair" by using the Jadad quality scale. For the 3 OCSs, study quality was scored as good (7–9 scores) by using Newcastle-Ottawa Scale tool.

Patient characteristics

Patient characteristics of the studies included are presented in Table 2. Included patients were a mean age of 70 years, 76% were men, mean left ventricular ejection fraction was 27.5%, 35% had New York Heart Association (NYHA) functional class for I/II and 65% had NYHA III/IV. Coronary artery disease was common and ranged from 21% to 56%, respectively; hypertension and diabetes were also common and ranged from 8% to 56% and from 13% to 27%, respectively. Baseline medication included angiotensin converting enzyme inhibitor/angiotensin receptor blocker in 84.8% of the patients, digoxin in 70%, diuretics in 90% and oral anticoagulant in 60%. Baseline heart rate of patients was similar among included studies, ranging from 79 bpm to 88 bpm. 5 RCTs reported the heart rate change at the end of follow-up with a mean heart rate reduction of 10.9 bpm.

Effect of beta-blockers on all-cause mortality

All 8 studies reported the outcome of all-cause mortality. The effect estimations of HRs were provided in 5 studies and RRs in 3 studies. The effect of BB on all-cause mortality in HF and AF was shown in Figure 2. In the pooled analysis of 5 RCTs, BB use was associated with non-significant reduced risk for mortality (RR 0.97; 95% CI 0.79–1.19, $p = 0.79$; heterogeneity, $p = 0.55$, $I^2 = 0$). In the pooled analysis of 3 OCSs, BB use was associated with improved survival (RR 0.74; 95% CI 0.71–0.78, $p < 0.00001$; heterogeneity, $p = 0.22$, $I^2 = 0$). Overall, use of BB reduced risk for mortality by 22% (RR 0.78; 95% CI 0.71–0.86, $p < 0.00001$; heterogeneity, $p = 0.26$, $I^2 = 27\%$).

Effect of BB on HF hospitalization

Five studies reported the outcome of HF hospitalization (CIBIS-II, MERIT-HF, SENIORS, BEST and AF-CHF), including 2774 patients. The pooled analysis showed that BB therapy was not associated with a reduction of HF hospitalizations (RR 0.94; 95% CI 0.79–1.11, $p = 0.46$; heterogeneity, $p = 0.17$, $I^2 = 38\%$ (Fig. 3).

Table 1. Characteristics of included studies.

Study	Year	Study design	Method for analysis	Sample size	BB group (n)	No BB group (n)	Definition of HF	Mean follow-up [years]	Endpoints	Estimate effect	Study quality
US-Carvedilol	2001	RCT	–	136	84	52	LVEF ≤ 35%; NYHA II–IV	0.5	All-cause mortality	RR	Fair
CIBIS-II	2001	RCT	–	521	257	264	LVEF ≤ 35%; NYHA III–IV	1.3	All-cause mortality; HF hospitalizations	RR	Good
MERIT-HF	2006	RCT	–	556	274	282	LVEF < 40%; NYHA II–IV	1.0	All-cause mortality; HF hospitalizations	RR	Good
SENIORS	2012	RCT	–	738	361	377	HF admission < 1 year or LVEF ≤ 35%	1.8	All-cause mortality; HF hospitalizations	HR	Good
BEST	2013	RCT	–	303	146	157	LVEF ≤ 35%; NYHA III–IV	2.0	All-cause mortality; HF hospitalizations	HR	Good
Swedish HF Registry	2015	Prospective OCS	Multivariable--adjusted Cox regression analysis	7392	6739	439	LVEF < 40%	2.4	All-cause mortality	HR	Good
Danish AF Registry	2016	Prospective OCS	Propensity score analysis	23896	11948	11948	A previous hospital diagnosis of HF	3.1	All-cause mortality	HR	Good
AF-CHF	2017	Retrospective OCS	Propensity score analysis	655	426	229	LVEF ≤ 35% with HF symptom or LVEF ≤ 25% without HF symptom	3.1	All-cause mortality; HF hospitalizations	HR	Good

BB — beat-blocker; HF — heart failure; HR — hazard ratios; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; OCS — observational cohort study; RCT — randomized controlled trials; RR — relative risk

Table 2. Patient characteristics.

Study	Mean age [years]	Male [%]	Baseline heart rate [bpm]	Heart rate reduction BB [bpm]	LVEF [%]	NYHA [%]		Types of BB	Combined disease [%]			Medication [%]			
						I/II	III/IV		HTN	DM	CAD	Digoxin	ACEI or ARB	OAC	Diuretics
US-Carvedilol	65	90	87	–13.0	24	42	58	Carvediol	NA	NA	51	99	96	NA	98
CIBIS-II	62	83	88	–8.8	27	0	100	Bisoprolol	17	13	25	85	96	49	98
MERIT-HF	66	86	84	–14.8	28	34	66	Metoprolol	41	24	53	90	91	74	95
SENIORS	77	63	84	–11.0	28	49	51	Nebivolol	56	25	35	70	83	41	92
BEST	65	90	79	–6.9	24	0	100	Bucindolol	54	27	56	95	98	84	NA
Swedish HF Registry	76	73	80	NA	30	48	52	NA	45	22	41	36	71	69	84
Danish AF Registry	78	45	NA	NA	NA	NA	NA	NA	44	17	21	20	47	25	NA
AF-CHF	70	81	79	NA	28	69	31	NA	8	NA	50	64	96	82	74

ACEI — angiotensin converting enzyme inhibitor; ARB — angiotensin receptor blocker; BB — beat-blockers; CAD — coronary artery disease; DM — diabetes mellitus; HTN — history of hypertension; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; NA — not available; OAC — oral anticoagulant

Sensitivity analysis

Leave-one-out sensitivity analysis on all-cause mortality was performed by omitting one study at a time, and found that none of the individual studies significantly influenced the pooled estimate of all-cause mortality. Subgroup analyses showed that when the pooled analysis of all-cause mortality was performed using fixed-effect model, a similar result was observed.

Discussion

Main findings

Meta-analysis of 8 studies involving 34197 patients revealed that BB were associated with a 22% reduction in all-cause mortality. Although the finding was limited to observational studies and trends favored BB for HF hospitalization did not reach statistical significance. Overall, results supported current evidence-based recommendations to pursue BB in all HF patients with or without AF.

Comparison with other studies

The present observed mortality benefit of BB in HF and AF diverged from two earlier meta-analyses [14, 15]. The latest systematic review conducted by Kotecha et al. [15] was more recent and comprehensive, which was an individual patient-level meta-analysis. However, in the 2 earlier meta-analyses, only RCTs were included and the AF group comprised only 17–21% of the whole patient cohort. Therefore, the obtained meta-analyzed results might reflect an under-powered analysis. In meta-analysis, the number of patients in the included 5 RCTs was 2254 with 407 death-events, which is still low for survival analysis, and the possibility that a lack of power may have played a role could not be excluded. Additionally, it is important to recognize that the included 5 RCTs were not specifically designed to assess the effect of BB in patients with AF and HF. Above all, the benefits of BB for all-cause mortality or HF hospitalizations were not observed in the pooled analysis of 5 RCTs, consistent with the earlier meta-analyses.

Our meta-analysis included recently published 3 observational studies with a low heterogeneity. The 3 observational studies from large registries included were well designed by using PS analysis and multivariable-adjusted Cox regression analysis to reduce the effects of confounders (including age, sex, underlying disease, medications, and NYHA functional class). The mortality benefit associated with BB in this analysis was largely driven by the results of Danish AF Registry [15]. However, the

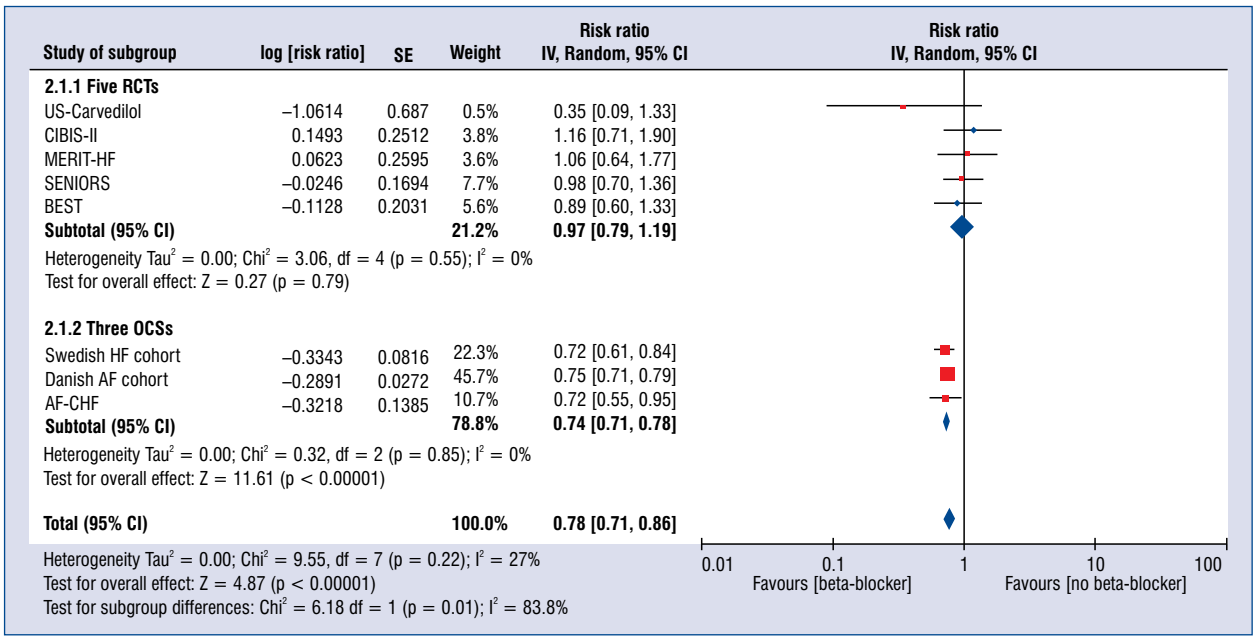

Figure 2. Effect of beta-blockers on all-cause mortality; CI — confidence interval; OCSs — observational cohort study; RCTs — randomized controlled trials.

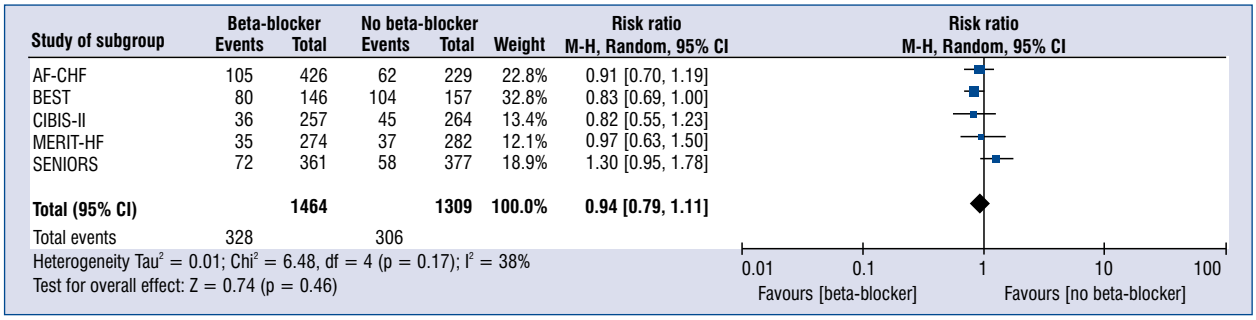

Figure 3. Effect of beta-blockers on heart failure hospitalization.

protective effect still remained after removing this study using the sensitivity analysis. Furthermore, both fixed and random effect models in the pooled analysis shows the significantly similar benefit of BB treatment. Accordingly, the conclusion that the treatment of BB reduces all-cause mortality in patients with HF and AF is fairly reliable.

It must be noted the difference between outcomes in included 5 RCTs and 3 OCSs. The present finding that BB therapy decreased mortality in patients with HF and AF was limited to the 3 observational studies. The controversial results may be partly explained by differences in methodology, patient demographics, HF severity, concomitant medication or follow-up duration. First, baseline characteristics of patients differed in these studies. In 5 RCTs, almost all patients included were symptomatic HF with NYHA II–IV, while in observational studies asymptomatic HF with NYHA I were also included. It seems that patients included in OCSs were at lower risk and had better BB tolerance, which all factors associated with lower mortality. Second, combined treatment was also an important confounder. In 5 RCTs, patients with HF and AF were more commonly treated with digoxin (88%), while in 3 OCSs, only 40% of patients were treated with digoxin. Digoxin had been reported to be associated with increased mortality in AF patients. The potential synthetic adverse effect of digoxin cannot be completely eliminated. Another possible reason as mentioned before was that the small number of patients in the included 5 RCTs was 2254 with 407 death-events which might reflect an under-powered analysis. It was admitted

that a well-designed randomized trial would be of great value according to the highest standards of evidence-based medicine. In RCTs the BB were well defined, with determined type and dose of BB and also heart rate reduction during therapy. While observational studies had inherent limitations including nonuniformly defined variables across studies. The use of BB differed between studies with a different type, dose and course. Based on observational studies, whether the doses and types of BB affect the effects of BB in patients with HF and AF could not be assessed. Until more solid evidence is available, it is premature to deny patients with AF and HF BB therapy considering current evidence.

Possible mechanisms for findings

The optimal heart rate target in AF patients is unclear. Moreover, there is limited evidence for lenient rate control for AF patients with HF. Previous studies have mainly examined sinus rhythm, and whether a higher heart rate is associated with worse outcomes in HF with concomitant AF has not been adequately studied. The lack of a relationship between heart rate and outcomes in patients with HFrEF and concomitant AF has previously been described [24–27]. In Rate Control Efficacy in Permanent Atrial Fibrillation: A Comparison between Lenient versus Strict Rate Control II (RACE II) trial, lenient rate control (< 110 bpm) did not yield worse outcomes than strict rate control (< 80 bpm) overall or in the subgroup of patients with HF [28, 29]. Potential mortality benefit of BB in HF coexisting with AF has been observed in the present meta-analysis. However, this meta-analysis does not provide the possible mechanisms for the survival benefit of BB in those patients without specific initial data on heart rate and heart rate change during BB treatment. The Swedish HF Registry [18] included in the present meta-analysis is the only study to assess an association of heart rate strata and BB use with all-cause mortality in patients with HF in AF. The study showed that higher resting heart rate was associated with increased mortality in AF, which was true only if heart rate > 100 bpm. Furthermore, BB use was associated with reduced mortality in patients with AF, and a lower heart rate was associated with reduced mortality in AF only for those with heart rate ≤ 100 bpm. In our meta-analysis, baseline heart rate of patients were similar among included studies, ranging from 79 bpm to 88 bpm (< 100 bpm); only 5 RCTs had reported the heart rate change for BB treatment at the end of follow-up, with a mean heart rate reduction of 10.9 bpm. However, in the pooled analysis of 5 RCTs, BB use was associated with non-significant reduced risk for mortality. Except for small sample size of an under-powered analysis, another possible explanation is that patients included in the trials benefit less from BB use with a baseline heart rate < 100 bpm. Patients with a higher heart rate may possibly benefit from BB treatment according to the results of Swedish HF Registry.

Implications for clinical practice

Considering the current controversies and challenges, more studies on BB in patients with HF and AF are still needed. Randomized controlled trials on BB for HF with concomitant AF may not be feasible because of ethical reasons. Thus, well designed and analyzed cohort studies from large registry will be more expected, which can give us more information from the real world. Future investigation should also help determine which patients with AF and HF will derive the greatest benefit from BB therapy, including those with HFrEF or HFpEF, older or younger, baseline heart rate. Additionally, the potential benefit of BB and their potential mechanisms beyond HR reduction in HF coexisted with AF also require further study.

Limitations of the study

The present analysis has several limitations that must be taken into consideration when interpreting the results. First, observational studies were included in the analysis and the mortality benefit was largely driven by those OCSs. Because of the observational nature of the cohort study and lack of randomization, the effect of unmeasured or residual confounding could not be ruled out. Although 3 observational studies from large registries were well designed by using PS analysis and multivariate regression analysis to reduce the effects of confounders, it would be specially mentioned that not all the studies adjusted for all covariates, so combined results should be interpreted with caution. Even though a very low heterogeneity was showed in the present analysis, clinical heterogeneity could not be underestimated. Therefore, a random-effect model was used in the meta-analysis and sensitivity analysis was also used to explore possible study characteristics that might have influenced the pooled estimates. Inherent limitations of pooled analysis of studies include the limited availability of confounding variables, including the type and dose of BB, the course of

treatment. Also, in the present analysis, the effects of different BB therapies were pooled and thereby assumed a class effect. However, specific differences in pharmacologic profiles may have added to the heterogeneity of the cohort and thereby the results. Finally, this analysis pooled study group estimates and did not assess individual patient data, which limits the possibility of adjustment for individual patient characteristics.

Conclusions

In summary, the present meta-analysis suggested the potential mortality benefit of BB in HF coexisting with AF, and supported current evidence-based recommendations to pursue BB for those patients. It was concluded that it is premature to deny patients with AF and HF beta-blocker therapy considering current evidence.

Conflict of interest: None declared

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Is downstream cardiac testing required in patients with reduced functional capacity and otherwise negative exercise stress test? A single center observational study

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Abstract

Background: *Exercise stress testing (EST) in patients with poor functional capacity measured by time on treadmill is typically deemed inconclusive and usually leads to further downstream testing. The aim of this study was firstly to evaluate the maximum rate pressure product (MRPP) during initial EST to assessthe need for follow-up testing; and secondly to investigate if MRPP is better than age predicted maximum heart rate (APMHR) for diagnostic outcome based on follow up cardiovascular (CV) events in patients with inconclusive EST due to poor functional capacity.*

Methods: *From a total of 2761 tests performed, 236 tests were considered inconclusive due to poor functional capacity which were available for analysis. From receiver operating characteristic (ROC) analysis, a cut-off value for MRPP of 25000 was chosen using CV events as the outcome measure (sensitivity 97%, specificity 45%). Cases were then categorised into those with an MRPP > 25000 and < 25000.*

Results: *Regardless of treadmill time, any patient attaining an MRPP > 25000 had no abnormal downstream testing or CV events at 2 years follow-up. On ROC analysis MRPP outperformed APMHR for sensitivity and specificity (area under curve 0.76 vs. 0.59, respectively).*

Conclusions: *The results suggest that regardless of functional capacity, individuals whose EST is terminated at maximal fatigue, with no electrocardiogram evidence or symptoms of myocardial ischemia and yields an MRPP > 25000, do not require further downstream testing. Furthermore, this group of patients, while not immune to future CV events, have significantly better outcomes than those not attaining a MRPP > 25000.* (Cardiol J 2019; 26, 6: 753–760)

Key words: rate pressure product, exercise stress testing, myocardial ischemia, double product, myocardial index

Introduction

Exercise stress testing (EST) in patients with poor functional capacity measured solely by time on treadmill is typically deemed inconclusive and usually leads to further investigation such as exercise stress echo or dobutamine stress echo, myocardial perfusion imaging, computed tomography coronary angiography or conventional coronary angiography (CA). There is inherent risk involved to the patient with some of these tests along with the expense of performing such procedures. A more direct as-

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sessment of cardiac workload achieved during EST would enable better discrimination between tests where cardiac stress was inadequate and those with adequate cardiac stress but poor functional capacity. A well validated index of cardiac stress, rate pressure product (RPP), although easily available, is not routinely used in clinical practice to evaluate this important aspect of the test. Normal values for RPP have been proposed for clinical and non-clinical populations at rest and at maximal exercise [1–3]. During EST, RPP has been extensively investigated as a prognostic variable [4–7]. In a retrospective cohort study of 1759 men, rate pressure product reserve (RPPR) (the difference between RPP at rest and maximal exercise) was the strongest predictor of 7-year cardiovascular (CV) status, even after adjustment for age, beta-blocker use and Duke Treadmill Score [4]. In the same study, RPPR was shown to have greater prognostic power than maximum metabolic equivalents (METS), itself a key independent predictor of all-cause and CV mortality [8, 9]. In addition, RPP has been shown to increase the predictive value of EST when screening for coronary artery disease (CAD) [6, 7]. However, no previous study has used RPP as a marker of significant cardiac stress in patients with reduced functional capacity and otherwise negative EST results. The aim of this study was firstly to retrospectively evaluate the MRPP during EST to determine the necessity of downstream testing in patients with reduced functional capacity (> 15% below age and gender predicted functional capacity) with an otherwise negative test for myocardial ischemia; and secondly assess if MRPP outperforms age predicted maximum heart rate (APMHR) for diagnostic outcome based on CV events occuring during the follow-up period.

Methods

The study sample was drawn from the Logan Hospital, a medium-sized public hospital in south-east Queensland, Australia, and was approved by the Metro South Health Service District Human Research Ethics Committee, and conforms to the declaration of Helsinki. Retrospective data were retrieved from all ESTs performed within a 5-year window (July 2007 to June 2012). Presentation with chest pain suspected to be caused by CAD was the main reason for performing EST. All ESTs were administered by the same core group of staff on a computer-controlled treadmill system (Marquette Case; Milwaukee, WI) using the standard Bruce protocol [10]. Manual blood pressure measurements were taken by an experienced operator at least once every stage, at peak exercise, and a minimum of twice during recovery. RPP was calculated by multiplying heart rate (HR) by systolic blood pressure (SBP) at each stage and maximal rate pressure product (MRPP) was identified. Maximum HR and maximum SBP achieved during the test were also recorded. Patients received a thorough evaluation to assess suitability and to rule out clinical evidence of heart failure prior to testing.

The total number of tests performed during the collection period was 2761. Any stress test deemed negative (2019), positive or equivocal (401) (based on electrocardiography changes or symptoms of myocardial ischemia), or indeterminate (69) (due to non-cardiorespiratory limitation) was excluded from the study, leaving a total of 272 inconclusive tests. From the 272 tests a further 36 with known CAD were removed from analysis as different clinical management strategies would be indicated compared to those without known CAD (Fig. 1). The remaining 236 tests were selected for analysis based on a functional capacity < 85% of age and gender predicted totals performed during the initial EST. This chosen cut-off value for functional capacity was selected in order to standardise "poor functional capacity" among our cohort and has been previously demonstrated to infer a 2-fold absolute risk in CV mortality [9, 11, 12]. The decision to perform further testing in this group was determined by the treating physician based on a patient's intermediate or moderate pre-test risk for CAD (minimum of 10% risk in 5 years as per Australian Vascular Disease Prevention Alliance) [13] and poor functional capacity. Tests were typically performed within 4 weeks from the initial test. Mean follow-up was 5 ± 2.4 years (range 2–9 years) by referencing medical records or through contact with the patients' general practitioner. Complete follow-up was possible in all patients up to 2 years and potential cost savings of further downstream testing generated during this period was established.

A receiver operating characteristic (ROC) curve (Fig. 2) was created to establish the MRPP cut-point using CV events at mean follow-up (5 years) as the outcome. The cut-point chosen was the longest vertical deviation from the diagonal line and corresponded to a MRPP of 25000 (sensitivity 97%, specificity 45%, area under curve [AUC] 0.76). Two groups were then established for analysis: inconclusive EST with MRPP > 25000 (MRPP > 25), and inconclusive EST with MRPP < 25000 (MRPP < 25). ROC analysis was also

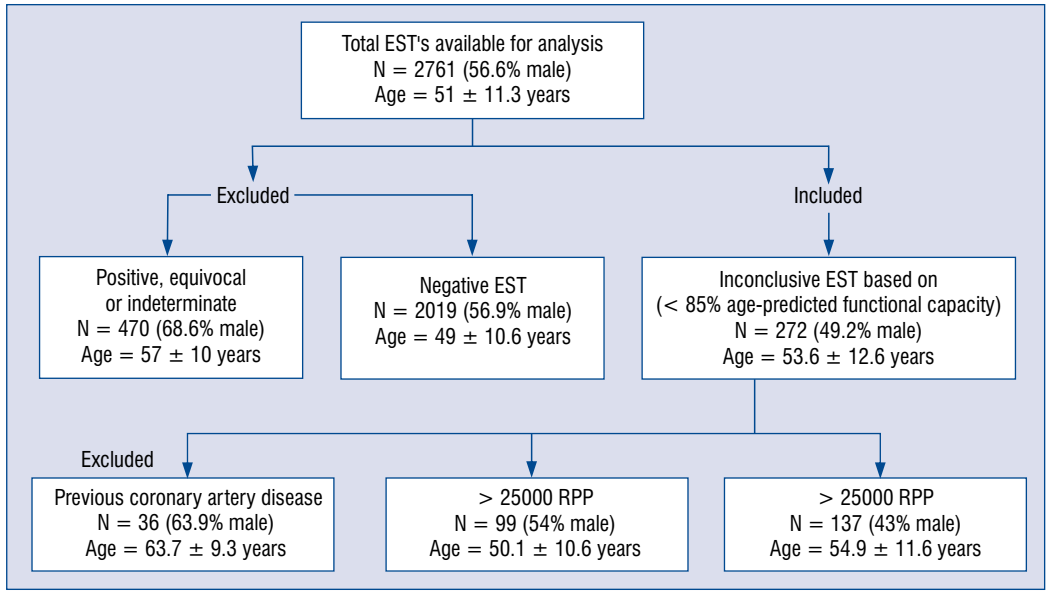

Figure 1. Study sampling frame; EST — exercise stress testing; RPP — rate pressure product.

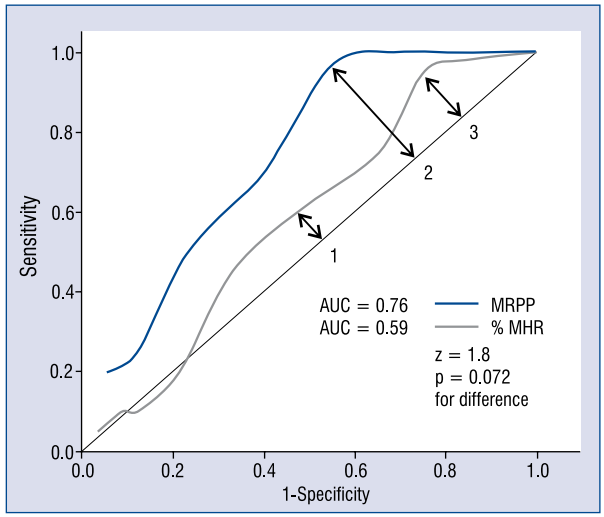

Figure 2. The receiver operating characteristic curve for maximum rate pressure product (MRPP) and age-predicted maximal heart rate (APMHR); 1 — the point corresponding to ≥ 85% APMHR; 2 — the longest vertical duration for MRPP; 3 — the longest vertical duration for APMHR; AUC — area under curve.

performed for APMHR (AUC 0.59) based on the equation 220 minus age, in order to compare the sensitivity and specificity of this commonly used measure of sufficient cardiac stress against MRPP.

Statistical analysis

Quantitative data were summarized as mean ± standard deviation and t tests for independent samples were used to compare variables between the two groups. Kaplan-Meier curves were created to evaluate all-cause mortality, CV mortality (myocardial infarction, heart failure or undifferentiated sudden cardiac death) and CV events (CV mortality, non fatal myocardial infarction, percutaneous coronary intervention [PCI]/balloon angioplasty or coronary artery bypass grafting), and the log rank test was used to assess statistical significance. Cox proportional hazard models were used to establish variables significant for all-cause mortality, CV mortality and CV events. Catagorical data were compared using the Fisher exact test. Data analysis was performed using XLSTAT 2017.6 (Addinsoft, New York) with a 2-tailed p value < 0.05 considered statistically significant.

Results

Table 1 presents the physical characteristics of patients together with their EST measures. There was no significant difference in sex distribution between the two groups ($p = 0.107$), however the MRPP > 25 group were younger ($p < 0.001$). Resting measures of HR and SBP were significantly lower in the MRPP < 25 group ($p < 0.001$ and $p = 0.002$, respectively). There were significant differences in maximum HR, maximum SBP, RPPR, APMHR ($p < 0.001$) treadmill time ($p = 0.009$) and METS ($p = 0.003$) between the groups. There were more patients with obesity in the MRPP > 25 group compared to the MRPP < 25 group ($p = 0.04$).

Table 1. Physical characteristics, exercise stress test measures, cardiovascular disease risk factors and medications at time of stress test by rate pressure product (RPP) group.

	Maximum RPP > 25000	Maximum RPP < 25000	p
Total	99	137	
Age [years]	50.1 ± 10.6*	54.9 ± 11.6	< 0.001
Male	53 (54%)	59 (43%)	0.1
CVD risk factors	2.3 ± 1.4	2.0 ± 1.3	0.1
Resting HR [bpm]	77 ± 15*	71 ± 13	< 0.001
Resting SBP [mmHg]	130 ± 15*	123 ± 17	0.002
Treadmill time [min:s]	5:32 ± 2:28*	4:42 ± 2:28	0.009
Metabolic equivalents	7.2 ± 2.4*	6.5 ± 2.4	0.003
Maximum SBP [mmHg]	188 ± 21*	155 ± 19	< 0.001
Maximum HR [bpm]	162 ± 19*	130 ± 20	< 0.001
RPPR	20177 ± 4243*	11351 ± 3251	< 0.001
APMHR [%]	95.3 ± 9.4*	78.7 ± 11.4	< 0.001
APMHR < 85%	12 (12.1%)*	96 (70.1%)	< 0.001
No risk factors	8 (8.0%)	17 (12.4%)	0.4
Family history	33 (33.3%)	26 (19.0%)	0.06
Diabetes mellitus	30 (30.3%)	24 (17.5%)	0.09
Smoking	32 (32.3%)	59 (43.1%)	0.3
Hypertension	41 (41.4%)	63 (46.0%)	0.7
Dyslipidemia	39 (39.4%)	58 (42.3%)	0.8
Obesity	45 (45.5%)*	36 (26.3%)	0.04
No medications	51 (51.5%)	60 (43.8%)	0.5
Beta-blockers	12 (12.1%)	25 (18.2%)	0.3
Ca2 + blockers	7 (7.0%)	18 (13.1%)	0.2
ACE inhibitors	14 (14.1%)	26 (19.0%)	0.5
ARB's	13 (13.1%)	13 (9.5%)	0.5
Nitrates	1 (1.0%)	7 (5.1%)	0.1
Statins	26 (26.3%)	50 (36.5%)	0.3

*Significant $p < 0.05$. Values show number of cases (n), mean ± standard deviation or percentage (%) of the group. ACE — angiotensin converting enzyme; APMHR — age predicted maximum heart rate; APMHR < 85% — age predicted maximum heart rate less than 85%; ARB — angiotensin receptor blocker; CVD — cardiovascular disease; HR — heart rate; RPPR — rate pressure product reserve; SBP — systolic blood pressure

There were no significant differences between the groups with respect to any other measures (Table 1). Cox proportional hazard analysis failed to demonstrate any significant variable with respect to all-cause mortality or CV mortality. Age was the only significant predictor for CV events (χ^2 5.4, p = = 0.02, hazard ratio 1.07, 95% CI 1.011–1.132). For APMHR, the longest vertical deviation from the diagonal on ROC analysis (Fig. 2) corresponded to 95% (sensitivity 95%, specificity 25%). At 85% APMHR the sensitivity and specificity was 60% and 53%, respectively. While a statistical trend was noted between assessments of ROC curves for MRPP and APMHR, overall this failed to reach significance ($z = 1.8$, $p = 0.072$; Fig. 2).

All-cause mortality between the two groups is shown in Figure 3, with a survival trend towards the MRPP > 25 group ($p = 0.08$). Both CV mortality and events are also displayed in Figure 2. During the 9 year follow-up, 6 patients in the

MRPP < 25 group passed away due to CV cause (5 heart failure, 1 ventricular fibrillation arrest), with no fatalities in the MRPP > 25 group; reaching statistical significance at 6 years ($p < 0.05$). The difference in incidence of CV events (MRPP > 25 = 3 PCI, MRPP < 25 = 3 balloon angioplasty, 5 PCI, 4 NSTEMI, 2 STEMI) between the groups reached statistical significance ($p < 0.05$) from 2 year follow up, with the MRPP > 25 group displaying superior outcomes.

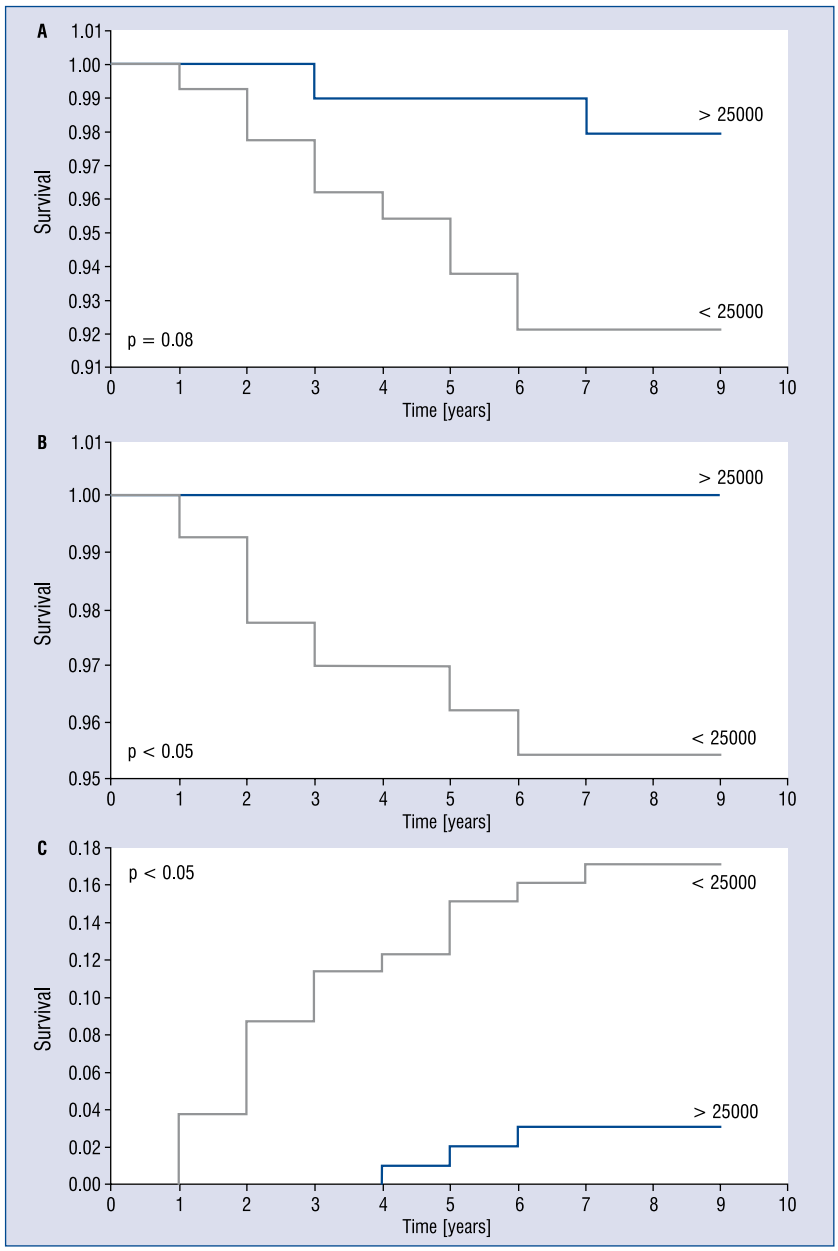

Figure 3. A. All-cause mortality for rate pressure product groups; **B.** Cardiovascular mortality for rate pressure product groups; **C.** Cumulative cardiovascular events for rate pressure product groups.

Table 2 displays the number, type and result of downstream testing in both groups performed during the initial 2 year follow-up period. A total of 81 downstream tests were generated in the MRPP > 25 group and 143 in the MRPP < 25 group. These totals include subsequent testing by CA which was performed on all occasions when the initial downstream test was positive. None of the 17 patients receiving a CA in the MRPP > 25 group had a positive result, conversely there were 11 positive tests discovered from 35 CAs performed in the MRPP < 25 group (Table 2). Table 3 shows the breakdown and costing of further testing in the MRPP > 25 group.

Discussion

The results of the present study suggests that in patients with no known CAD, regardless of functional capacity (treadmill exercise duration), any EST that is terminated at volitional fatigue, with no ECG evidence or symptoms of myocardial ischemia, and yields an MRPP > 25000 provides reassurance that there was no clinically significant

Table 2. Results of further testing for maximum rate pressure product (RPP) groups (as defined in text).

	Maximum RPP > 25000			Maximum RPP < 25000		
Further testing	**Total**	**Outcome**	**Angiogram**	**Total**	**Outcome**	**Angiogram**
Exercise stress test	0			1	(0)	
Resting echocardiogram	1	(0)		2	(0)	
Dobutamine stress echocardiogram	10	(0)		23	5 (+)	4 (+)
		1 re-presented	1 (0)		3 re-presented	3 (0)
Exercise stress echocardiogram	7	(0)		2	(0)	
Myocardial perfusion scan	36	8 (+)	8 (0)	71	12 (+)	2 (+)
					10 re-presented	2 (+)
CTCA	10	(0)		1	(0)	
Coronary angiogram	5	(0)		11	3 (+)	
DNA	30	3 re-presented	3 (0)	26	2 re-presented	2 (0)

All values show number of cases. (+) indicates positive, (0) indicates negative; CTCA — computed tomography coronary angiography; DNA — did not attend follow-up appointment

Table 3. The breakdown of costing from additional testing procedures in the maximum rate pressure product > 25 group*. Angiogram figures and computed tomography coronary angiography (CTCA) are based on the average cost of tests performed.

Test	Total No.	Cost ($AUS)	Total cost ($AUS)
Resting echocardiogram	1	230.65	230.65
Dobutamine stress echocardiogram	10	413.80	4130.80
Exercise stress echocardiogram	7	413.80	2896.60
Myocardial perfusion scan	36	834.90	30056.40
CTCA	10	700.00	7000.00
Angiogram	17	855.50	14543.50
All tests	81		58857.95

*MBS Online Medicare Benefits Schedule, Australian Government, Department of Health, viewed 27 July 2016, http://www.health.gov.au/internet/mbsonline/publishing.nsf/Content/a-z.

CAD for up to 2 years follow-up, potentially alleviating the need for further downstream testing.

In the current study MRPP outperformed an APMHR of ≥ 85% for sensitivity (97% vs. 60%) with a nominal difference in specificity (45% vs. 53%) for the occurrence of CV events during the mean follow up (5 years). The sensitivity of 97% displayed for MRPP in the current study provides great incremental value to an EST performed at reduced functional capacity, as very few of these patients had CV events during mean follow up (5 years). The specificity although modest at 45%, is a reflection of the negative downstream testing that would otherwise not have been performed in the MRPP > 25 group. This could therefore be considered extraneous, as clinical advantage has already been established due to the high sensitivity and warranty periods on EST are not clearly established [14, 15].

While the difference between the ROC curves failed to reach significance ($z = 1.8$, $p = 0.072$), the AUC for MRPP (0.76) over MHR (0.59) clearly demonstrates a superior predictive model. Achieving 85% of APMHR has been demonstrated to be a poor diagnostic and functional endpoint [16]. Traditionally, the inability of HR to reach this figure has been seen as a marker of chronotropic incompetence and a predictor of adverse CV outcome [17–19]. Many of these studies however did not report the corresponding SBP with HR and therefore the MRPP was achieved [17, 18]. A study by Elhendy et al. [19] although not discussed in their findings, clearly demonstrated a significantly reduced MRPP in the group that failed to reach 85% of APMHR. Therefore it may be seen that the SBP response to exercise should be just as important as the corresponding HR response. Bouzas-Mosquera et al. [20] demonstrated

that a substantial increase in SBP alone during exercise testing was associated with a significantly lower risk of mortality and CV events. Individuals achieving greater increases in RPP during exercise have also been shown to have less CV events over time in both those with, and without significant CAD [4, 5, 21]. The current study confirms this finding, where a significant difference in CV-related events was observed between the two groups from 2 years follow up ($p < 0.05$; Fig. 3). A similar significant difference between the groups was observed for RPPR ($p < 0.01$), and although all-cause mortality did not reach statistical significance in the current study, previous studies have demonstrated a similar prognostic advantage when a higher RPPR is achieved [4, 5]. Sadrzadeh Rafie et al. [4] showed that RPPR possessed a greater prognostic power than functional capacity (METS) when comparing individuals with similar functional capacities (> 5 METS). Functional capacity (METS) has been shown to be an important prognostic measure for future CV events and mortality [21–23], and likewise the current findings demonstrated a significant difference between the groups for this measure. Allowing that RPP reflects myocardial oxygen consumption [24, 25], it would therefore seem reasonable that the ability to significantly increase RPP in the absence of any substantial pathology, be reflective of a normal functioning left ventricle.

Age was the only variable that was statistically significant ($p = 0.02$) for the prediction of CV events. This in itself would normally predict a better prognosis and may have also contributed to the older groups (MRPP < 25) poorer treadmill time and inability to produce a MRPP > 25000. Nevertheless the average age of both groups was over 50 years (Table 1) MRPP > 25 = 50.1 ± 10.6 and MRPP < 25 = 54.9 ± 11.6 and Lloyd-Jones et al. [26] demonstrated that having ≥ 2 major CV risk factors at the age of 50 years substantially increased lifetime CV risk and mortality. In the current study, there was no difference between groups in regard to the number of CV risk factors ($p = 0.1$) with both groups possessing greater than 2 (Table 1). It would therefore be reasonable to accept that patients in the current study although exhibiting a difference in age, in general still carried a similar increased risk for future CV events.

There were no patients in the current study achieving a MRPP > 25000 during their EST with a positive downstream test during the initial 2 year follow-up. Thus, there is potential for significant cost savings by avoiding further testing without compromising safety. The total number of additional tests performed in patients with a MRPP > 25000 was 81. Of concern are the additional 8 angiograms that were required when the follow-up cardiac stress testing (myocardial perfusion imaging) yielded false positive results. The 81 tests would not have been required under the proposed model, and would have provided a total cost savings for the documented facility of approximately AUS $59,000 with identical patient outcomes in the mean follow-up period (Table 3) [27].

While inducible myocardial ischemia typically occurs at a similar RPP for an individual [2, 28], a set ischemic threshold is not established between individuals as this can occur at varying RPP, depending on the extent of the ischemia, vessels involved and compensatory mechanisms present [29, 30]. Furthermore, patients that achieve certain parameters that are interpreted as eliciting sufficient cardiac stress, such as > 85% target heart rate or > 10 METS, are not necessarily immune from significant CAD causing myocardial ischemia [13, 31]. It is for this reason that it should be recommended that an MRPP of 25000 not be used as an arbitrary termination point but rather as reassurance once maximal fatigue has been reached and the test is otherwise negative for myocardial ischemia.

Limitations of the study

The present study is a single center cohort study and, therefore, may be subject to selection bias. While the outcome data demonstrates statistical significance for CV events and mortality, the AUC for MRPP (0.76) indicates a moderate predictive model and further studies with greater numbers would be beneficial in order to confirm these observations. Although there was no clinical evidence of HF prior to EST, echocardiography to assess for signs of left ventricular dysfunction prior to testing would have been an advantage. Finally, the use of MRPP as an index of adequate cardiac stress should not replace the clinical decision to use downstream testing in those individuals deemed to have sufficient risk and high suspicion of CAD.

Conclusions

The data herein, suggests that in patients with an intermediate pre-test risk and no previous CAD, any EST that is terminated at maximal fatigue with patients attaining a MRPP > 25000 and no electrocardiogram evidence or symptoms of myocardial ischemia, do not require further

downstream testing. Furthermore, this group of patients, while not immune to future CV events, have significantly better outcomes than those not attaining a MRPP > 25000.

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Conflict of interest: None declared

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Comparison of two infant chest compression techniques during simulated newborn cardiopulmonary resuscitation performed by a single rescuer: A randomized, crossover multicenter trial

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Abstract

Background: *In newborns, ventilation is a key resuscitation element but optimal chest compression (CC) improves resuscitation quality. The study compared two infant CC techniques during simulated newborn resuscitation performed by nurses.*

Methods: *The randomized crossover manikin, multicenter trial involved 52 nurses. They underwent training with two CC techniques: standard two-finger technique (TFT) and novel two-thumb technique (NTTT; two thumbs at 90° to the chest, fingers in a fist). One week later, the participants performed resuscitation with the two techniques. A Tory® S2210 Tetherless and Wireless Full-term Neonatal Simulator was applied, with a 3:1 compression to ventilation ratio. CC quality in accordance with the 2015 American Heart Association guidelines was assessed during the 2-min resuscitation.*

Results: *Median CC depth was 30 mm for TFT and 37 mm for NTTT ($p = 0.002$). Correct hand placement reached 98% in both techniques; full chest relaxation was obtained in 97% vs. 94% for TFT and NTTT, respectively. CC fraction was slightly better for NTTT (74% vs. 70% for TFT; $p = 0.044$), the ventilation volume was comparable for both techniques. On a 100-degree scale (1 — no fatigue; 100 — extreme fatigue), the participant tiredness achieved 72 points (IQR 61–77) for TFT vs. 47 points (IQR 40–63) for NTTT ($p = 0.034$). For real resuscitation, 86.5% would choose NTTT and 13.5% TFT.*

Conclusions: *The NTTT technique proved superior to TFT. Evidence suggests that NTTT offers better CC depth in various medical personnel groups. One-rescuer TFT quality is not consistent with resuscitation guidelines.* (Cardiol J 2019; 26, 6: 761–768)

Key words: newborn, cardiopulmonary resuscitation, chest compression, quality, medical simulation

Introduction

Sudden cardiac arrest in pediatric patients is uncommon [1, 2]. In newborns, correct ventilation is a key element in cardiopulmonary resuscitation and support of transition at birth but correct chest compression (CC) improves resuscitation quality and thus affects vital organ perfusion, the return of spontaneous circulation, and survival rate [3–6]. The quality of CC is often suboptimal owing to incorrect CC technique, fatigue, and the rescuer position or experience [4, 7]. Some diagnostic feedback devices have been tested in order to improve neonatal and newborn cardiopulmonary resuscita-

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tion [8–10] but their role in clinical settings have not yet been established.

The four main quality measurements of cardiopulmonary resuscitation are CC rate, CC depth, release force, and compression duty cycles [3, 4]. The resuscitation guidelines emphasize the reduction of hands-off time in cardiopulmonary resuscitation, optimal CC frequency, depth, and full chest relaxation [4, 11]. The knowledge of the newborn CC technique is important for all medical personnel, including physicians, nurses, midwifes, and paramedics [12].

There are two standard CC techniques in neonatal and newborn resuscitation: the two-finger technique (TFT) and the two-thumb encircling hands technique (TTHT) [3]. For single rescuer resuscitation, TFT is recommended by the American Heart Association (AHA) [3]. However, TFT is often suboptimal in terms of CC depth, correct hand position, full chest relaxation, and coronary perfusion pressure [13–17].

The novel two-thumb technique (NTTT) developed by Smereka et al. [18] consists in using two thumbs directed at the angle of 90° to the chest while closing the fingers of both hands in a fist. The alignment of thumbs with the arms allows body strength to be directed downward to the sternum, in contrast to TFT, which mainly relies on finger and hand strength [18, 19].

The novel technique has been investigated in several studies in different age groups and study participants as well as in different settings, with the consideration of the resuscitation technique, CC and ventilation ratio, and the time of resuscitation efforts [18, 20–22]. The results suggest that NTTT provides several advantages as compared with standard newborn resuscitation techniques, e.g. allowing to overcome problems with the rescuer hand size in TTHT. The initial results of NTTT applied by different medical personnel in different settings and manikins prove that NTTT offers superior hemodynamic parameters than TTHT, as well as better median CC depth and degree of full chest recoil in 2- and 10-min neonatal and infant resuscitation [23, 24].

There are studies suggesting that ventilation influences sternal displacement during simulated pediatric cardiopulmonary resuscitation regardless of the compression method used, and the compression forces are significantly lower during synchronous ventilation with TFT [25].

In the current study, we checked the CC quality during constant ventilation with the standard neonatal 3:1 compression-to-ventilation ratio with mouth-to-mouth and nose ventilation. The aim was to compare the newborn TFT with the authors' NTTT during simulated newborn 2-min one-rescuer cardiopulmonary resuscitation performed by nurses.

Methods

Study design and selection of participants

The study was designed as a prospective, randomized, crossover observational study. The protocol was approved by the Institutional Review Board of the Polish Society of Disaster Medicine (approval No. 23.03.2017.IRB). The participants were recruited from among nurses taking part in emergency medicine training in Warsaw and Wroclaw (Poland).

The study is a continuation of the research conducted by the authors on improving the quality of CCs during pediatric resuscitation [18, 20–24] in various study groups and settings.

The inclusion criteria were the following: practice as a nurse and voluntary participation in the study. The exclusion criteria comprised pain in the wrist or upper limb and back pain. Voluntary written informed consent was obtained from all participants. The study involved 52 nurses.

All participants declared that during their studies they had undergone training in cardiopulmonary resuscitation for adults and children.

Scenario simulation

Prior to the study, all subjects took part in a newborn cardiopulmonary resuscitation training, which referred to the causes of cardiac arrest in this age group, as well as resuscitation rules based on the current AHA guidelines [3]. After the theoretical training, the instructor demonstrated the correct CCs with the studied methods. Two techniques of newborn CCs were applied:

— TFT, previously the standard method for infant CC. When using this method, the rescuer compresses the sternum with the tips of two fingers;
— the NTTT method of CCs in an infant, which consists in using two thumbs directed at the angle of 90° to the chest while closing the fingers of both hands in a fist (Fig. 1).

Then, the participants performed 2-min resuscitation cycles with the tested methods using a SimBaby Classic simulator (Laerdal, Stavanger, Norway).

One week after the training completion, the nurses took part in the final study, during which they were tasked with performing a 2-min car-

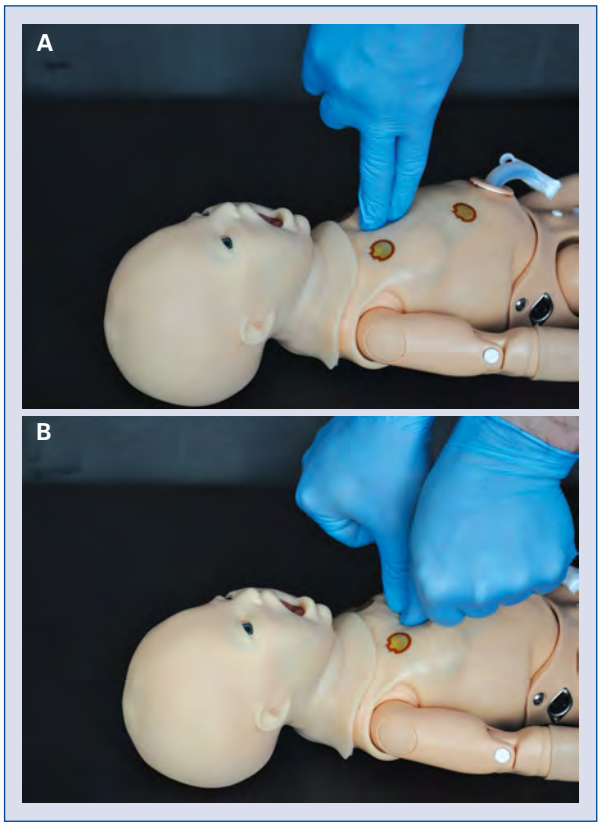

Figure 1. Chest compressions techniques: **A.** Standard two finger technique; **B.** Novel two thumb technique.

diopulmonary resuscitation cycle with the tested techniques. The standard newborn 3:1 compression-to-ventilation ratio with a mouth-to-mouth and nose ventilation rescue breath was applied, with the aim of achieving 90 CCs and 30 rescue breaths per minute [4]. In order to simulate a newborn requiring cardiopulmonary resuscitation, a Tory® S2210 Tetherless and Wireless Full-term Neonatal Simulator (Gaumard Scientific, Miami, FL, USA) was used. The simulator was placed on a hard table, each time set to the height of 2/3 of the participant's thigh for the purpose of standardization.

The order of both the participants and the research methods was random. For this purpose, the Research Randomizer program (randomizer.org) was used and the study participants were divided into two groups. The first group performed resuscitation with the TFT and the other applied the NTTT. After a 2-min resuscitation cycle, the participants had a 1-h rest and then performed resuscitation using the other technique. A detailed randomization procedure is shown in Figure 2.

Measurements

During the whole study, the parameters of CCs were recorded by the software controlling the simulator (Fig. 3), and the whole test was

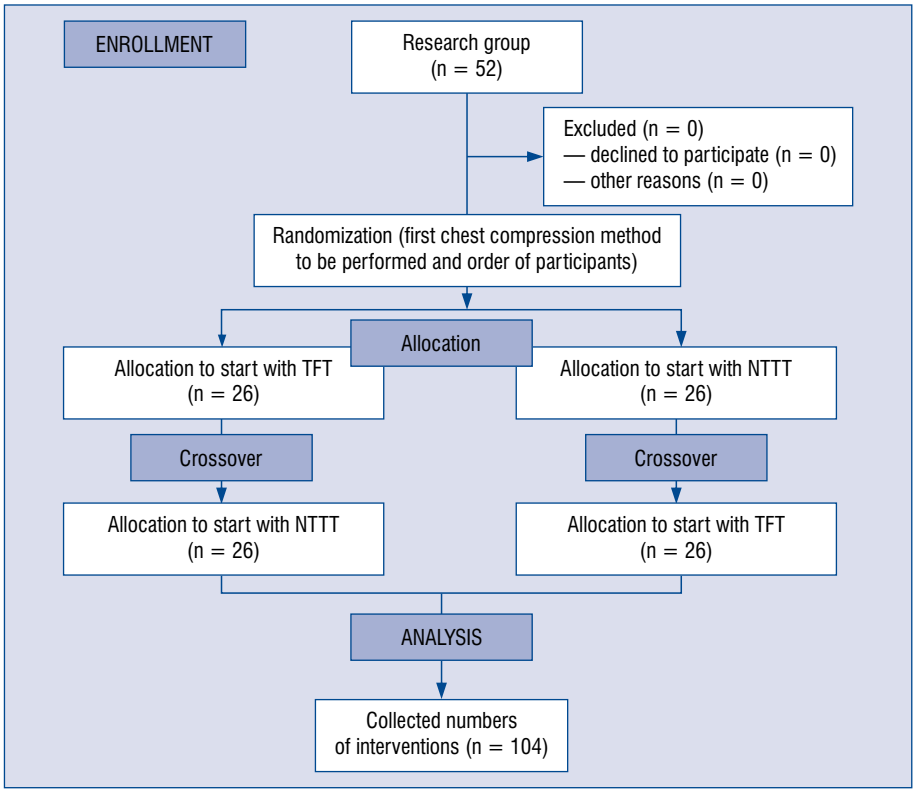

Figure 2. Randomization flow chart; NTTT — novel two-thumb technique; TFT — two-finger technique.

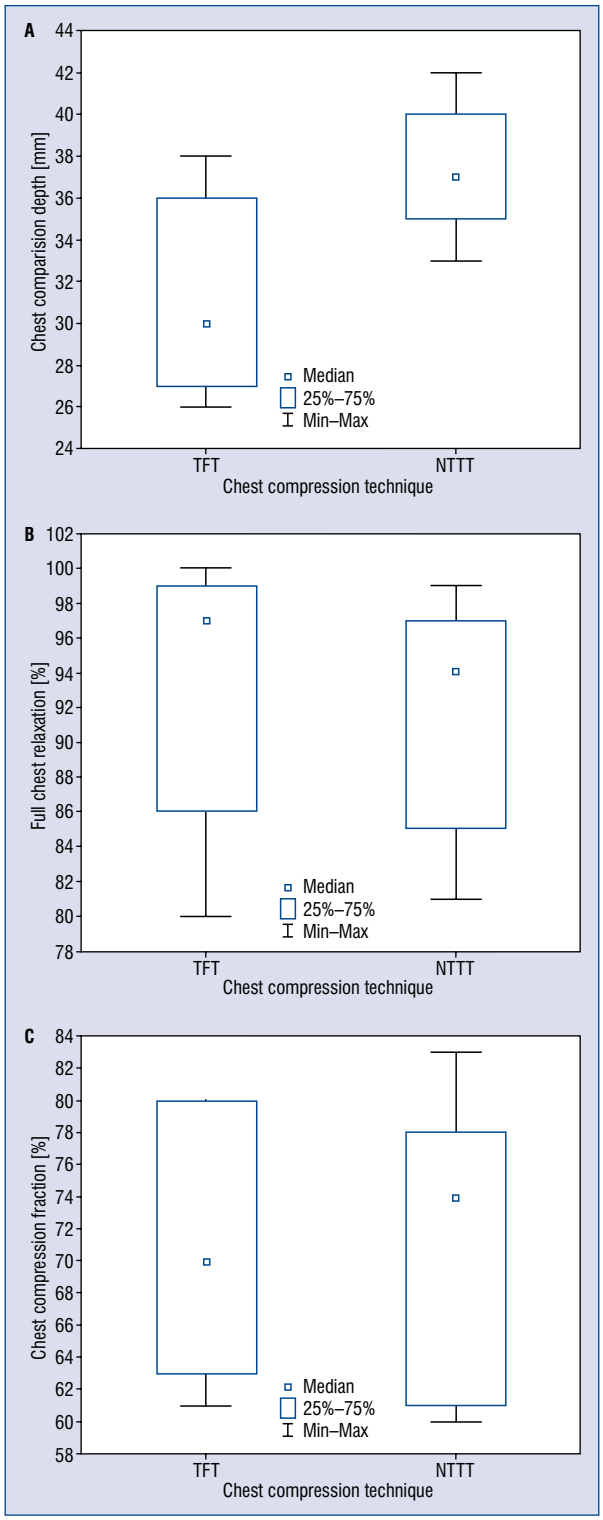

Figure 3. Chest compression quality: **A.** Chest compression depth; **B.** Full chest relaxation; **C.** Chest compression fraction; NTTT — novel two-thumb technique; TFT — two-finger technique.

documented with a GoPro HERO5 Black 4K Ultra HD camera (GoPro, Inc., San Mateo, CA, USA) in order to reconstruct its course over time. The following parameters of CCs quality were analyzed: frequency, depth, degree of full chest relaxation, correctness of hand position on the chest, and CC fraction, which was measured as the total time when the chest was compressed during the 2-min resuscitation. The volume of ventilation during rescue breaths was also measured. In addition, at the end of the study, the participants were asked to determine the level of fatigue on a 100-degree scale (1 — no fatigue; 100 — extreme fatigue) for both procedures. Also, their preferences regarding the technique to be used during real cardiopulmonary resuscitation were evaluated.

Statistical analysis

Continuous and original data are presented as median and interquartile range (IQR), and the categorical data are presented as raw numbers and frequencies. Non-parametric tests were used because the data distribution was not normal, as implied by the Shapiro-Wilk and Kolmogorov-Smirnov tests. The data were analyzed with the Statistica 13.3 statistical package (TIBCO Software Inc., Tulsa, OK, USA). Values of $p < 0.05$ were considered significant.

Results

The study involved 52 nurses (45 females; 86.3%) with median age of 25.5 (IQR 24.5–26) years. Their median work experience was 9.4 (IQR 6–14) years.

Chest compression quality

The median CC depth was 30 mm for TFT and 37 mm for NTTT ($p = 0.002$). Correct hand placement reached 98% in both techniques, and full chest relaxation was obtained in 97% vs. 94% for TFT and NTTT, respectively. CC fraction was slightly better for NTTT (74% vs. 70% for TFT; $p = 0.044$) and the ventilation volume turned out to be comparable for both techniques. CC quality results are shown in Table 1.

Participants' self-assessment

The degree of the participant tiredness that resulted from performing CCs with the two tested techniques was varied, assessed as 72 points (IQR 61–77) for TFT and 47 points (IQR 40–63) for NTTT ($p = 0.034$). During real resuscitation, 86.5% of the study participants would choose NTTT and 13.5% — the currently recommended technique of compression, TFT.

Table 1. Cardiopulmonary resuscitation quality variables.

Parameter	TFT	NTTT	P
Chest compression depth [mm]	30 [27–36]	37 [35–40]	**0.002**
Full chest relaxation [%]	97 [86–99]	94 [85–97]	0.845
Correct hand placement [%]	98 [92–99]	98 [93–100]	0.677
Chest compression fraction [%]	70 [63–80]	74 [61–78]	**0.044**
Ventilation volume [mL]	71 [63–81]	69 [60–83]	**0.012**

TFT — two-finger technique; NTTT — novel two-thumb technique

Discussion

American Heart Association recommends five components of high-quality pediatric cardiopulmonary resuscitation: ensuring CCs of adequate rate and depth, allowing full chest recoil between compressions, minimizing interruptions in CCs, and avoiding excessive ventilation [3, 26]. The suboptimal quality of CCs with TFT was emphasized by several studies indicating that the only main advantage of TFT as compared with TTHT was optimal full chest relaxation [27]. Incomplete chest release can decrease the return of venous blood to the heart and consequently reduce the perfusion pressure [28].

Several modifications for neonatal and infant resuscitation have been proposed, including the "vertical two-thumb technique" [29] and "knocking-fingers" CC technique [30]. A method of "high-impulse cardiopulmonary resuscitation" was also suggested as the alternative for neonatal CC [31]; moreover, changing fingers during TFT was investigated [32, 33]. Currently, only two standard neonatal CC techniques (TTHT and TFT) are recommended by AHA and the European Resuscitation Council (ERC).

The NTTT has been tested in various medical personnel groups. However, in this study we checked the quality of one-rescuer, 2-min newborn resuscitation performed by nurses without the use of a metronome, with the 3:1 compression-to-ventilation ratio with a mouth-to-mouth and nose ventilation rescue breath; the aim was to achieve 90 CCs and 30 rescue breaths per minute [4].

American Heart Association and ERC recommend at least 40 mm or 1/3 of the anterior-posterior diameter as the CC depth [1]. In the present study, median CC depth for standard TFT achieved 30 mm compared with 37 mm for NTTT. Several other studies suggest that CC depth with TFT turns out far below the current resuscitation guidelines [14, 34]. In a study by Smereka et al. [18], in a 3-month-old infant manikin model resuscitation, novice physicians obtained the median CC depth of 26 mm with TFT and 39 mm with NTTT.

Another study of 2-min cardiopulmonary resuscitation using a Newborn Tory® S2210 manikin (Gaumard® Scientific, Miami, FL, USA) to compare TFT chest compressions in different resuscitation positions of the rescuer revealed that in no tested manikin position were TFT nurses able to reach the recommended CC depth (14–25 mm, the best result for the rescuers; forearm position) [35]. When resuscitation was performed on a table with the top adjusted to the height of 2/3 of the rescuer's thigh, the median CC depth for TFT achieved 14 mm only [22]. The second standard CC technique, TTHT, offers better CC depth compared with TFT [21].

Full chest relaxation is another important parameter affecting CC depth, blood flow and pressure. In both analyzed CC techniques, full chest relaxation was obtained in a very high percentage of CCs (97% for TFT and 94% for NTTT; the difference was not statistically significant). In other studies it was emphasized that one of the main advantages of TFT was a high percentage of full chest relaxation, which turned out significantly better with the use of TTHT [20].

Correct hand placement during CCs was observed nearly in 100% for both analyzed techniques. The same results were obtained in a study by Smereka et al. [18] in a 3-month-old infant manikin model resuscitation performed by novice physicians. In the same study, correct hand position for TFT and NTTT reached 100%. The correct hand position was 98.5% vs. 100% for TFT and NTTT, respectively, in a study investigating 120 paramedics for 2-min 3-month-old manikin resuscitation [22].

The CC fraction was better for NTTT comparing with TFT (70% vs. 74%, respectively; the difference was statistically significant). The so-called hands-off time is defined as the time without CC and it should be minimized [10]. Another study by

Smereka et al. [23] revealed that paramedics using NTTT achieved significantly better systolic, diastolic, and mean blood pressure during 10-min resuscitation with TFT.

The fatigue during newborn resuscitation with different CC to ventilation ratio methods is a well-known problem [36–38], resulting in a decreasing quality of CCs over time. It can even appear during a relatively short-lasting neonatal resuscitation (below 10 min) and is associated with lack of aerobic activity and body mass index ≥ 25 [39, 40]. In the standard CC techniques (TFT, TTHT), finger and thumb pain is common [23]. This study revealed that the NTTT technique was less tiring for nurses performing CCs as compared with TFT. For real resuscitation, 86.5% of the study participants would choose NTTT and 13.5% — currently recommended TFT technique. Similar results were obtained in other studies on NTTT, suggesting less hand fatigue and exhaustion among the paramedics and physicians performing resuscitation [23].

Previous studies have proven advantages of NTTT in infant, neonatal, and newborn resuscitation in various simulation settings, including 2-min vs. 10-min CCs, different manikin models, and diverse study methodology [20–24]. In contrast to previous research in newborn simulation settings [21, 35], in this study the standard CC was used: the 3:1 ventilation ratio for newborn resuscitation [4], allowing to achieve approximately 90 CCs per minute. In pediatric patients, the standard recommended CC rate equals 100–120 per minute [3]. CC alone or with epinephrine in a delivery room is associated with poor prognosis [41]. However, there are some studies suggesting that different CC to ventilation ratios (2:1, 3:1, 4:1) result in similar return of spontaneous circulation and similar mortality during resuscitation in a porcine model of neonatal asphyxia [42].

Limitations and strengths

The presented paper has several limitations. Firstly, the use of a newborn manikin cannot fully replicate the properties of human anatomy and physiology, and the study was not a clinical trial. As randomized crossover resuscitation trials are unethical, a decision was made to use a Newborn Tory® S2210 manikin simulator, the most advanced neonatal simulator available. Simulation studies allow achievement of statistical power via a crossover design of the trial. Another limitation is that the study was conducted only among nursing personnel, and only two CC techniques were analyzed. The strength of the study consists in its crossover design.

Conclusions

The novel CC technique for newborn one-rescuer resuscitation performed by nurses turned out better than the standard TFT technique. There is consistently growing evidence that NTTT offers superior CC depth as compared with TFT for newborn resuscitation in various medical personnel groups. The quality of one-rescuer TFT is constantly suboptimal and not consistent with international resuscitation guidelines. Further animal studies are necessary to validate results in terms of clinical usefulness.

Ethical approval: Approval was granted by the Institutional Review Board of the Polish Society of Disaster Medicine (approval no.: 23.03.2017.IRB).

Informed consent: Informed consent was obtained from all individual participants included in the study.

Conflict of interest: None declared

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The effect of chest compression frequency on the quality of resuscitation by lifeguards. A prospective randomized crossover multicenter simulation trial

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Abstract

Background: *The ability to perform high-quality cardiopulmonary resuscitation is one of the basic skills for lifeguards. The aim of the study was to assess the influence of chest compression frequency on the quality of the parameters of chest compressions performed by lifeguards.*

Methods: *This prospective observational, randomized, crossover simulation study was performed with 40 lifeguards working in Warsaw, Wroclaw, and Poznan, Poland. The subjects then participated in a target study, in which they were asked to perform 2-min cycles of metronome-guided chest compressions at different rates: 80, 90, 100, 110, 120, 130, 140, and 150 compressions per minute (CPM).*

Results: *The study involved 40 lifeguards. Optimal chest compression score calculated by manikin software was achieved for 110–120 CPM. Chest compression depth achieved 53 (interquartile range [IQR] 52–54) mm, 56 (IQR 54–57) mm, 52.5 (IQR 50–54) mm, 53 (IQR 52–53) mm, 50 (IQR 49–51) mm, 47 (IQR 44–51) mm, 41 (IQR 40–42) mm, 38 (IQR 38–43) mm for 80, 90, 100, 110, 120, 130, 140 and 150 CPM, respectively. The percentage of chest compressions with the correct depth was lower for rates exceeding 120 CPM.*

Conclusions: *The rate of 100–120 CPM, as recommended by international guidelines, is the optimal chest compression rate for cardiopulmonary resuscitation performed by lifeguards. A rate above 120 CPM was associated with a dramatic decrease in chest compression depth and overall chest compression quality. The role of full chest recoil should be emphasized in basic life support training.* (Cardiol J 2019; 26, 6: 769–776)

Key words: chest compression, cardiopulmonary resuscitation, quality, lifeguard, medical simulation

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Introduction

An ability to perform cardiopulmonary resuscitation is one of the basic skills that lifeguards should possess [1, 2]. According to numerous studies, high-quality chest compression has a direct impact on the effectiveness for the return of spontaneous circulation [3, 4]. Current cardiopulmonary resuscitation guidelines of both the European Resuscitation Council (ERC) and the American Heart Association (AHA) emphasize the need to minimize interruptions in chest compressions and to perform high-quality chest compressions as determined by the correct rate and depth of compressions, full chest recoil, and appropriate positioning of hands on the chest [5–7]. All these factors have a significant impact on the effectiveness of cardiopulmonary resuscitation. The ERC and AHA guidelines recommend that chest compressions should be performed at a rate of 100–120 compressions per minute (CPM). However, there is no clear consensus that would indicate an optimal chest compression frequency for adults and children [8].

The aim of the study was to assess the influence of chest compression frequency on the quality of parameters of chest compressions performed by lifeguards.

Methods

Setting and participants

The study was designed as a prospective observational, randomized, crossover simulation study. The study protocol was approved by the institutional review board of the Polish Society of Disaster Medicine (approval No., 19.02.2018.IRB). The survey was conducted among lifeguards working in Warsaw, Wroclaw, and Poznan, Poland. Being an active lifeguard and a voluntary participant in the survey constituted criteria for inclusion. Among exclusion criteria were: failure to meet the inclusion criteria, as well as back pain or upper limb pain or injury that would prevent performing chest compressions. Written voluntary informed consent was obtained from each participant.

Material and methods

In order to simulate a patient requiring cardiopulmonary resuscitation, an adult simulator, the Resusci Anne Simulator (Laerdal, Stavanger, Norway) was utilized and placed on a flat surface in a brightly lit room [9, 10]. The simulator was equipped with a SimPad PLUS device (Laerdal, Stavanger, Norway), which allowed for control of the simulator and record parameters related to the resuscitation procedure.

Before entering the study, all subjects participated in a course on basic life support (BLS) conducted by AHA instructors. The training was based on the AHA 2015 guidelines [5].

The lifeguards then participated in the targeted study in which they were asked to perform 2-min cycles of chest compressions at different rates: 80, 90, 100, 110, 120, 130, 140, and 150 CPM.

For this purpose, a metronome was used, which was set at the appropriate frequency. After each 2-min cycle of compressions at a certain rate, the participants had a 20-min break after which they performed compressions at a different rate. The order of both the participants and the frequency of chest compressions was random. The Research Randomizer software (www.randomizer.org) was used for this purpose.

Data collection and analysis

The parameters recorded by the SimPad PLUS software were analyzed. The frequency of chest compressions, chest compression fraction, mean time of breaks in chest compressions, correct hand position, chest compression depth, full chest recoil, and proportion of compressions with appropriate depth were studied. Chest compression fraction was defined as the percentage of time during which chest compressions were performed. Chest compression score (0–100%) was calculated by manikin software on the basis of the following parameters: compression depth, compression rate, share of incomplete chest recoil, number of compressions per cycle, and correct hand position on the manikin's chest. According to resuscitation guidelines, the depth of chest compressions should equal 50–60 mm.

Additionally, background information was recorded about the participants, including their age, sex, and work experience.

Statistical analysis

All statistical analysis was performed with Statistica 13.1EN for Windows statistical package (TIBCO Software Inc, Tulsa, OK, USA). Data were described as percentages or medians and interquartile ranges (IQR). Non-parametric tests were applied when data distribution was not normal, as implied by the Shapiro-Wilk and Kolmogorov-Smirnov tests. Values of $p < 0.05$ were considered significant.

Results

The study included 40 lifeguards (14 females, 35%), whose median age was 25.6 (IQR 23–32) years, and median work experience equaled 6.5 (IQR 2–10) years.

The chest compression parameters, including chest compression score, chest compression fraction, no flow time, correct hand position, chest compression depth, full chest recoil, and the proportion of compressions with correct depth for different chest compression rates are shown in Table 1.

The overall chest compression score (Fig. 1) achieved 62 (IQR 58–65), 84 (IQR 82–88), 92 (IQR 87–93), 93.5 (IQR 91.5–97), 73 (IQR 71.5–80), 67 (IQR 64–69), 34 (IQR 29–39.5), 19 (IQR 18–21) for 80, 90, 100, 110, 120, 130, 140 and 150 CPM, respectively.

Median chest compression fraction (Fig. 2) was 99% for 80 CPM and 100% all 90–150 CPM and no flow time was 0 s was for all studied chest compression rates. The percentage of chest compressions with correct hand position achieved 100 (IQR 100–100), 100 (IQR 99–100), 100 (IQR 99–100), 99 (IQR 98–100), 100 (IQR 99–100), 99 (IQR 98–100), 97 (IQR 96–99.5), 98 (IQR 96–100) for 80, 90, 100, 110, 120, 130, 140 and 150 CPM, respectively.

Chest compression depth (Fig. 3) was 53 (IQR 52–54) mm, 56 (IQR 54–57) mm, 52.5 (IQR 50–54) mm, 53 (IQR 52–53) mm, 50 (IQR 49–51) mm, 47 (IQR 44–51) mm, 41 (IQR 40–42) mm, 38 (IQR 38–43) mm for 80, 90, 100, 110, 120, 130, 140 and 150 CPM, respectively.

The percentage of compression with full chest recoil (Fig. 4) achieved 71 (IQR 49–76), 28 (IQR 14–41.5), 39 (IQR 18–44), 34.5 (31–40.5), 11 (IQR 9–21), 16 (IQR 7–15), 17.5 (IQR 16–20), 13 (IQR 11–16) for 80, 90, 100, 110, 120, 130, 140 and 150 CPM, respectively.

Discussion

Lifeguards fulfil their duties at swimming pools and on beaches, and can also perform cardiopulmonary resuscitation as bystanders in emergency situations [11–13]. They are obliged to participate in courses on BLS and automated external defibrillators (AED) on a regular basis [14]. There are several factors influencing high-quality adult chest compression, including trunk and arm muscle mass, basal metabolic rate, mean fat-free mass, and other individual parameters [15–18]. Lifeguards

Table 1. Chest compression quality parameters with different chest compression rates.

Parameter	Chest compression rate								P
	80/min	90/min	100/min	110/min	120/min	130/min	140/min	150/min	
Chest compression score [%]	62 (58–65)	84 (82–88)	92 (87–93)	93.5 (91.5–97)	73 (71.5–80)	67 (64–69)	34 (29–39.5)	19 (18–21)	**< 0.0001**
Chest compression fraction [%]	99 (98–100)	100 (99–100)	100 (100–100)	100 (100–100)	100 (98–100)	100 (98–100)	100 (100–100)	100 (100–100)	NS
No flow time [s]	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–1)	0 (0–0)	**0.0003**
Correct hand position [%]	100 (100–100)	100 (99–100)	100 (99–100)	99 (98–100)	100 (99–100)	99 (98–100)	97 (96–99.5)	98 (96–100)	NS
Chest compression depth [mm]	53 (52–54)	56 (54–57)	52.5 (50–54)	53 (52–53)	50 (49–51)	47 (44–51)	41 (40–42)	38 (38–43)	**< 0.0001**
Full chest recoil [%]	71 (49–76)	28 (14–41.5)	39 (18–44)	34.5 (31–40.5)	11 (9–21)	16 (7–15)	17.5 (16–20)	13 (11–16)	**< 0.0001**
Compressions with correct depth [%]	91 (84–93)	86 (84–89)	89 (87–93)	81 (79–89)	69 (64–72)	58 (56–63)	20 (17–31)	14 (12–16)	< 0.0001

NS — not statistically significant

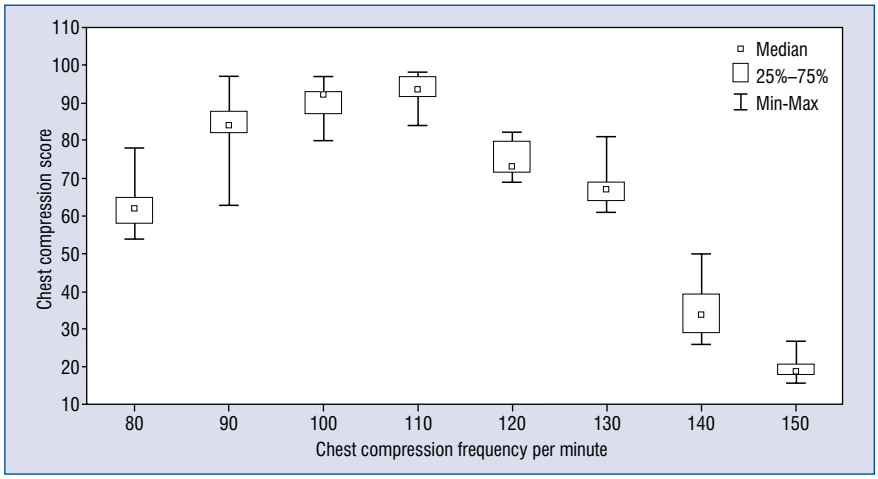

Figure 1. Chest compressions score.

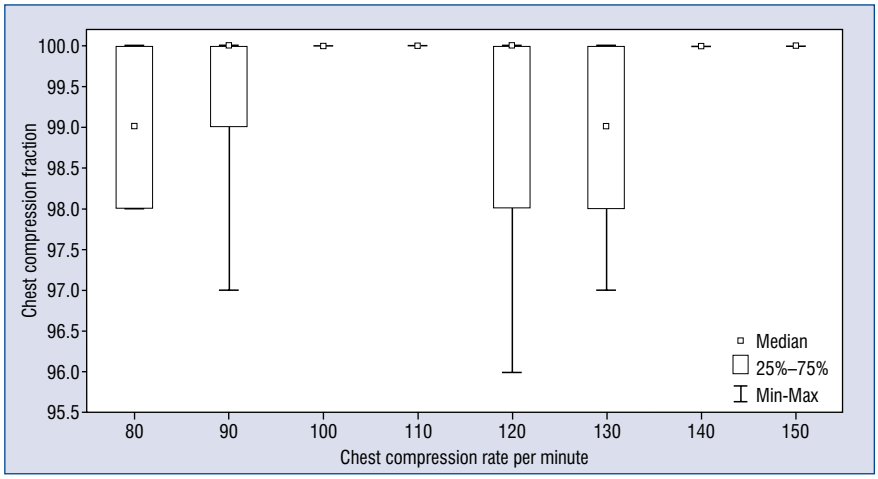

Figure 2. Chest compression fraction.

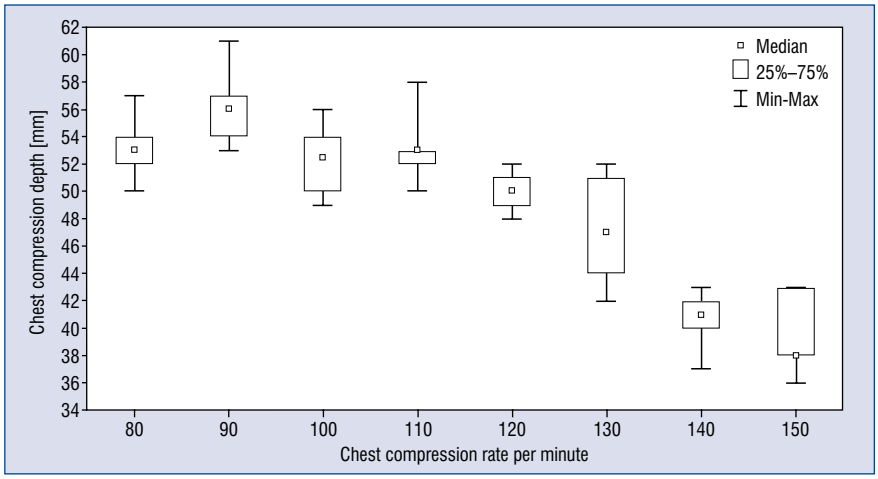

Figure 3. Chest compression depth.

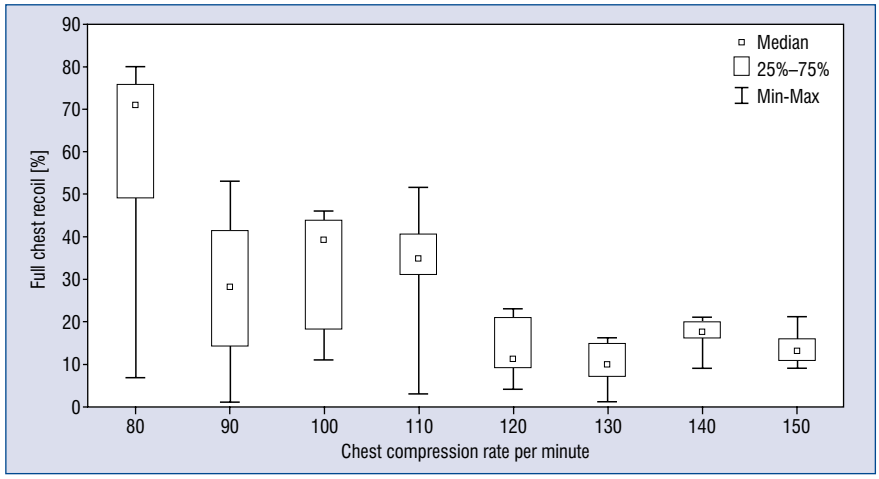

Figure 4. Percentage of full chest recoil.

often meet optimal criteria for body mass index and mean fat-free mass, therefore it can be expected that resuscitation performed by this professional group should be of a high-quality; however, water rescue actions are exhausting and can impede the quality of resuscitation. The quality of chest compression worsens after a water rescue action by 26–28%, so it has been emphasized that the use of additional equipment (fins and rescue tubes) provides benefit in emergency situations [19]. Some publications suggest that lifesavers clear out blood lactate more efficiently when performing an active recovery protocol [20]. The quality of cardiopulmonary resuscitation performed by lifeguards using a CPRmeter monitor improved significantly in the feedback group, compared with the non-feedback group [2]. Chest compressions on inflatable rescue boats (IRBs) were analyzed by Barcala-Furelos et al. [21] and it was suggested that surf-lifeguards could deliver good-quality resuscitation even on a moving IRB, although their performance is worse than onshore.

Cardiopulmonary resuscitation in a lifeguard's daily practice does not occur often, but the quality of chest compressions performed in victims can impede their neurological outcome. In the analysis of interventions undertaken by lifeguards in Brazil, Szpilman et al. [22] revealed that resuscitation was performed rarely and took place for only 1 in every 112,000 lifeguarding actions (0.0009%).

In the present study, it was observed that chest compression rate impeded chest compression quality parameters, including chest compression depth and complete chest recoil, as well as the number of compressions per cycle. The optimal chest compression score was achieved for the rate of 100–110 CPM. Chest compression depth was within the resuscitation guidelines for the rate of chest compressions not exceeding 120 CPM. The percentage of full chest recoil was low for all chest compression rates, excluding the lowest one at 80 CPM, and especially for rates above 110 CPM which were associated with very low full chest recoil percentage (< 18%). Accurate chest compression depth assessment is difficult for healthcare professionals during cardiopulmonary resuscitation. When performing chest compressions, it is possible to precisely differentiate 0.5-cm differences in the compression depth but not possible to accurately determine overall target depth [23].

In a prospective observational study at a single academic medical center carried out by Kilgannon et al. [24], it was suggested that chest compression rates of 121–140 CPM were bound with the highest odds ratio of return of spontaneous circulation (ROSC), and the rates exceeding the currently recommended 100–120 CPM might improve the chances for ROSC among in-hospital cardiac arrest patients. This study was based on resuscitation preformed in a near-ideal in-hospital setting in intubated patients, and several factors could have influenced the results.

Lee et al. [25] analyzed chest compression parameters in 322 students participating in a cardiopulmonary resuscitation contest. The authors noticed that chest compression depth was proportional to chest compression rate, though with significantly more incomplete chest recoils at a rate of more than 120 CPM.

Zou et al. [26] dealt with 2-min chest compression-only resuscitation with guiding sounds at three rates (100, 120, and 140 CPM) in a random

sequence. They noticed that the complete chest compression release and fractions of chest compressions with sufficient depth were deteriorated at a rate of 140 CPM.

The impact of chest compression rate on survival outcome has been analyzed in several publications. Sutton et al. [27] studied the influence of compliance with guidelines referring to chest compression rate during pediatric in-hospital resuscitation on survival outcomes. The chest compression rate within the recommended range was associated with a slightly better outcome. Fernando et al. [28] analyzed out-of-hospital cardiac arrest cases and the quality of cardiopulmonary resuscitation performed by bystanders using AED on the basis of data stored by the defibrillator. They concluded that bystanders performed high-quality resuscitation, compliant with the international guidelines, especially during the first 5 min (but not in the first minute).

Chest compression depth is affected by chest compression rate even during metronome-guided simulated manikin resuscitation [29]. In a simulation study concerning adult cardiopulmonary resuscitation performed with the use of a metronome at different frequencies (80, 100, 120, and 140 ticks/min), the average compression depth increased when the metronome rate increased, and with the metronome rates of 80 and 100 ticks/min it was significantly lower than in procedures without metronome guidance [30].

The achievement of the target chest compression depth and rate, within the international guidelines recommendation, is difficult for many laypersons; however, the use of feedback/prompt devices significantly improves the quality of hands-only resuscitation [31, 32].

Maier et al. [33], in an article published in 1986 in "Circulation", based on animal studies, suggested that the optimal chest compression rate for systemic and coronary perfusion was 120 CPM.

In a study published in 2016, Lee et al. [34] analyzed metronome-guided adult continuous chest compressions with the metronome set to 100, 120, 140, and 160 bpm, in a random order. They revealed that the share of incomplete chest recoils was lower at the rates of 100 and 120 CPM as compared with 160 CPM. Most importantly, the share of chest compressions fulfilling the criteria for high-quality resuscitation at the rate of 120 CPM was significantly higher than at 100 CPM.

Idris et al. [35] suggested in an article published in 2012 in "Circulation" that the chest compression rate was associated with ROSC but not with survival to hospital discharge in out-of-hospital cardiac arrest patients. In 2015, Idris et al. [36] analyzed data abstracted from monitor-defibrillator recordings for the first 5 min of emergency medical service in adult cardiopulmonary resuscitation. They concluded that after adjustment for chest compression fraction and depth, compression rates of 100–120 CPM were associated with greatest survival to hospital discharge.

A meta-analysis by Taliowska et al. [37] concerning the impact of cardiopulmonary resuscitation quality parameters, including chest compression depth and rate, on patient survival from cardiac arrest revealed that chest compression depth and rate were associated with survival outcomes.

Field et al. [38] published a study comparing chest compression rates of 80, 100, 120, 140, and 160 CPM during simulated cardiopulmonary resuscitation in adults. Higher chest compression rates were associated with reduced chest compression depth (39.5 mm at 80 CPM vs. 34.5 mm at 160 CPM, $p < 0.001$). The final conclusion was that rates above 120 CPM were bound with the greatest reduction of chest compression quality.

Monsieurs et al. [39] analyzed chest compression rate and depth recorded with an accelerometer in out-of-hospital cardiac arrest patients. Of all compressions, 36% were performed at a rate exceeding 120 CPM, and only 19% reached the depth of more than 5 cm. In 58% of patients, a statistically significantly lower depth was observed for chest compression rates above 120 CPM compared with 80–120 CPM. The study has concluded that higher compression rates were associated with lower compression depths.

Limitations of the study

There are several limitations in the present study. The study was performed using manikin models with all the limitations for this type of research, however in resuscitation trials, the use of simulators is standard procedure and enables equal and repetitive conditions for all participants [40–43]. The second limitation is the study group. This study analyzed only lifeguards and results may not be similar in other professions, medical personnel or laypersons. However, lifeguards have generally very good health status and are in first line during out-of-hospital cardiac arrest resuscitations. The next limitation is chest compression time. In the present study, a 2-min resuscitation cycle was evaluated, but different values could be obtained during longer resuscitations, such as over a 10-min period. However, it should be noted that

the ERC recommends changing rescuer after about 2 min of chest compression, hence a 2-min cycle herein seems to be justified.

Conclusions

The chest compression rate of 100–120 CPM, recommended by international guidelines, is optimal for cardiopulmonary resuscitation performed by lifeguards. Rates above 120 CPM are associated with a dramatic decrease in chest compression depth and overall chest compression quality. The role of full chest recoil should be emphasized in BLS training.

Conflict of interest: None declared

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Postoperative high-sensitivity troponin T as a predictor of sudden cardiac arrest in patients undergoing cardiac surgery

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Abstract

Background: *The usefulness of high-sensitivity troponin T (hs-TnT) as a predictor of sudden cardiac arrest (SCA) in patients undergoing valve surgery is currently unknown.*

Methods: *A prospective study was conducted on a group of 815 consecutive patients with significant valvular heart disease that underwent elective valve surgery. The primary end-point was postoperative SCA.*

Results: *The postoperative SCA occurred in 26 patients. At multivariate analysis of hs-TnT measured immediately after surgery (hs-TnT I) and age remained independent predictors of the primary end-point.*

Conclusions: *Elevated postoperative hs-TnT was associated with a higher risk of postoperative SCA.*
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Key words: sudden cardiac arrest, high-sensitivity troponin T, valve surgery

Introduction

Postoperative sudden cardiac arrest (SCA) is a complication which significantly increases the risk of hospital death as well as the length of hospital stay. The diagnosis of SCA can be made if the cardiac arrest occurs within an hour of the onset of acute symptoms and has been reversed or not been reversed by ongoing resuscitation. Sudden cardiac arrest usually occurs in the course of cardiac arrhythmias such as ventricular fibrillation, ventricular tachycardia, pulseless electrical activity or asystole. The reasons for sudden arrest are different in younger people than in older people. Young people are dominated by canalopathies and cardiomyopathies. Chronic degenerative diseases such as coronary heart disease, valvular heart disease and heart failure are prevalent in older populations [1–5]. Predictors of SCA include left ventricular ejection fraction (LVEF), programmed ventricular stimulation, QT interval dispersion, late potentials, heart rate variability, microvolt T-wave alternans, baroreflex sensitivity and heart rate turbulence [6, 7]. Among emerging variables that look promising for predicting sudden cardiac death are biochemical indicators such as the B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide, which have shown encouraging results in preliminary investigations [1].

Troponin T (TnT) is a polypeptide that is part of the striated contractile muscle apparatus. A very important aspect from a diagnostic point of view is the fact that the sequence of troponins of cardiac origin differs from the sequence of skeletal troponins. Thanks to this, after obtaining specific monoclonal antibodies, it became possible to use them in the diagnosis of ischemia and hypoxia of cardiomyocytes [8]. In the available literature, numerous articles describe high sensitivity troponin T (hs-TnT) as a biomarker of predictive importance in various diseases of the cardiovascular system, such as heart failure, coronary artery disease (CAD) and aortic stenosis [9–13]. The usefulness of the hs-TnT as a predictor of perioperative SCA in patients with valve disease undergoing valve surgery is currently unknown.

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Methods

The current prospective study was performed on consecutive patients with hemodynamically significant valve defects (aortic stenosis, aortic regurgitation, mitral stenosis and mitral regurgitation) who underwent elective replacement or repair of the valve. The exclusion criteria were: patients under 18 years of age, a lack of consent to participate in the study, autoimmune diseases, chronic inflammatory bowel, active neoplastic diseases and active infective endocarditis.

Complete blood count was performed with K2-EDTA samples, using a Cobas 6000 electronic counter (Roche, Mannheim, Germany). The day before surgery, immediately after patient arrival at the intensive care clinic after surgery and one day after operation, a blood sample for hs-TnT was collected from each patient. The plasma levels of cardiac TnT (cTnT) concentrations were measured by the troponin T hs-STAT (Roche).

All procedures were performed through a midline sternotomy incision under general anesthesia in a normothermia. All patients were given cold blood cardioplegia at the initial dose of 15–20 mL/kg followed by booster doses of 5–10 mL/kg every 20 min. The primary end-point at intra-hospital follow-up was postoperative SCA defined as cardiac arrest within an hour of the onset of acute symptoms and has been reversed or not reversed by ongoing resuscitation. Patients were followed up for 30 days or until death. The follow-up of discharged patients was conducted through direct observation during hospitalization and clinic visits 30 days after surgery. The study was conducted at the Institute of Cardiology, Warsaw, between 1 January 2014 and 20 September 2018. The protocol was approved by the Institutional Ethics Committee.

Statistical analysis

A statistical analysis was performed using the SAS version 9.2. Data are presented as the mean ± standard deviation and the frequency (%). Intergroup comparisons were made using the Mann-Whitney U test, the Pearson χ^2 test or Student t-test. The Shapiro-Wilk test of normality was used to test the sample distribution. Logistic regression was used to assess relationships between variables. The following covariates: age, aortic cross-clamp time, cardiopulmonary bypass time, atrial fibrillation, body mass index, chronic obstructive airway disease, CAD, coronary artery bypass grafting (CABG) procedure, creatinine, hs-TnT, hemoglobin, hypertension, left ventricular end-diastolic and end-systolic diameters, LVEF, New York Heart Association classes, peripheral atherosclerosis, pulmonary blood pressure, tricuspid annulus plane systolic excursion, high-sensitivity troponin T measured immediately after surgery (hs-TnT I) and high-sensitivity troponin T measured 1 day after operation (hs-TnT II) were investigated for association with endpoints in univariate analysis. Significant determinants ($p < 0.05$) identified from univariate analysis were subsequently entered into multivariate models. The Spearman rank correlation coefficient was used to search for associations between the postoperative serum hs-TnT level and cardiopulmonary bypass time, aortic cross-clamp time. Predictive value of hs-TnT I was assessed by a comparison of the areas under the receiver operator characteristics of the respective curve. On the basis of the Youden index, a cut-off point was determined that met with the criterion of maximum sensitivity and specificity for perioperative SCA.

Results

The study included 815 patients who underwent heart valve surgery with or without concomitant procedures. The mean age in the study group was 64 ± 13. Sixty-three (7.7%) patients had significantly impaired left ventricular systolic function (LVEF ≤ 35%). The mean preoperative hs-TnT level was 35 ± 29 ng/L, hs-TnT I level was 925 ± 802 ng/L and hs-TnT II level was 1321 ± 1103 ng/L. Table 1 shows the characteristics of the patients studied. A postoperative SCA occurred in 26 patients (ventricular fibrillation 11 patients, ventricular tachycardia 6 patients, pulseless electrical activity 3 patients and asystole 6 patients). In all patients with SCA resuscitation was initiated, which resulted in the restoration of hemodynamically stable cardiac rhythm in 18 patients. In 8 (1%) patients, cardiopulmonary resuscitation was ineffective. During further follow-up, in another 8 patients after SCA, death occurred due to gradually increasing multi-organ failure. The statistically significant predictors of postoperative SCA at univariate analysis are presented in Table 2. At multivariate analysis hs-TnT I (odds ratio [OR] 1.304, 95% confidence interval [CI] 1.201–1.409; $p = 0.004$), and age (OR 1.059; 95% CI 1.013–1.108; $p = 0.01$) remained independent predictors of the primary end-point. The area under receiver operator characteristic curve for postoperative SCA for hs-TnT I is 0.776 (95% CI 0.702–0.850; Fig. 1). The total mortality in the 30-day follow-up was 4.4%. The main cause of death

Table 1. Baseline characteristics of the study population (n = 815).

Parameters	Values
Preoperative characteristics of patients	
Age [year]	64 ± 13
Atrial fibrillation	350 (42%)
Body mass index [kg/m^2]	27 ± 9
Coronary artery disease	115 (14%)
Chronic kidney disease (GFR < 60 mL/min/1.73 m^2)	250 (31%)
COAD	53 (7%)
Creatinine [mg/dL]	0.9 ± 0.5
Hemoglobin [g/dL]	13.6 ± 1.5
LVEF [%]	57 ± 12
Male: men	470 (57%)
NYHA classes	2.5 ± 0.5
Peripheral atherosclerosis	135 (16%)
Hs-TnT [ng/L]	35 ± 29
Intraoperative characteristics of patients	
Aortic cross-clamp time [min]	95 ± 39
Cardiopulmonary bypass time [min]	123 ± 52
Lactates [mmol/L]	1.6 ± 0.5
Ph	7.4 ± 0.1
Postoperative characteristics of patients	
Hs-TnT I [ng/L]	925 ± 802
Hs-TnT II [ng/L]	1321 ± 1103
Creatinine II [mg/dL]	1.4 ± 0.4
Hemoglobin II [g/dL]	10.2 ± 1.5
The day of SCA [days]	2 ± 1.5
Main procedures	
AVR	411 (50%)
AVR + MVR	61 (7.4%)
AVP	30 (3.6%)
MVR	162 (30%)
MVP	151 (18.5%)
Concomitant procedures	
Aortic surgery	166 (20%)
CABG	111 (14%)
TVP	179 (22%)

Values are represented by the mean and a measure of the variation of the internal standard deviation. AVP — aortic valve plasty; AVR — aortic valve replacement; CABG — coronary artery bypass grafting; COAD — chronic obstructive airways disease; Creatinine II — creatinine measured one day after operation; GFR — glomerular filtration rate; Hemoglobin II — hemoglobin measured one day after operation; Hemoglobin — hemoglobin measured one day before operation; Hs-TnT I — high-sensitivity troponin T measured immediately after surgery; Hs-TnT II — high-sensitivity troponin T measured one day after operation; LVEF — left ventricular ejection fraction; MVP — mitral valve plasty; MVR — mitral valve replacement; NYHA — New York Heart Association; SCA — sudden cardiac arrest; TVP — tricuspid valve plasty

Table 2. Analysis of predictive factors for the occurrence of postoperative sudden cardiac arrest.

Variable	Odds ratio	95% CI	P
Age [years]	1.050	1.008–1.095	0.01
LVEF [%]	0.971	0.944–0.998	0.04
NYHA [classes]	2.377	1.173–4.815	0.01
Hs-TnT I [ng/L]	1.211	1.106–1.326	0.001

CI — confidence interval; Hs-TnT I — high-sensitivity troponin T measured immediately after surgery; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association

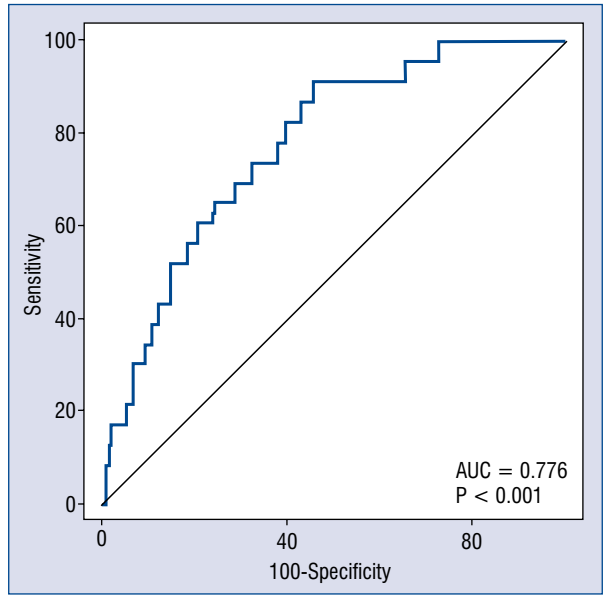

Figure 1. Area under receiver operating characteristic curve of high-sensitivity troponin T measured immediately after surgery for a sudden cardiac arrest following valve replacement/repair surgery.

in the post-operative period was gradually increasing multiple organ dysfunction syndrome. In the subgroup of 115 patients with concomitant CAD, an additional CABG procedure was performed in 111 patients, while in the postoperative period 4 patients experienced SCA. At univariate analysis CAD (p = 0.21) and the additional CABG procedure (p = 0.2) were not predictors of SCA in the early postoperative period. Patients with concomitant CAD did not have significantly higher hs-TnT I levels (p = 0.35) compared with patients without CAD. In the postoperative period 63 patients experienced acute kidney injury (AKI). Patients with postoperative AKI did not have significantly higher hs-TnT I levels (p = 0.36) compared with patients

without AKI, but patients with postoperative AKI had significantly higher hs-TnT II levels (p = 0.02) compared to patients without AKI. A positive correlation was found between the level of hs-TnT II and aortic cross-clamp time (r = 0.35; p = 0.005) as well as between the level of hs-TnT II and cardiopulmonary bypass time (r = 0.47; p = 0.0001), but wasn't found between the level of hs-TnT I and aortic cross-clamp time (p = 0.1) or cardiopulmonary bypass time (p = 0.12). At univariate analysis hs-TnT II (p = 0.09), aortic cross-clamp time (p = 0.13) and cardiopulmonary bypass time (p = 0.11) were not predictors of postoperative SCA. The mean preoperative value of LVEF in the group of patients with SCA was 44% ± 15% and was significantly lower compared to patients with no SCA 58% ± 10% (p = 0.01).

Discussion

Postoperative SCA is a serious complication in patients undergoing heart valve surgery and is associated with very high mortality. The present paper demonstrated the prognostic significance of hs-TnT I in predicting SCA in the early postoperative period in patients undergoing heart valve surgery.

Currently, it is believed that cTnT is the best laboratory parameter in the diagnosis of myocardial injury. Considering the fact that the cytoplasm of cardiomyocytes contains a small amount of free TnT, even small damage to the cell membrane causes their release and the possibility of detection in the blood sample under investigation. Therefore, TnT detected in plasma is a highly specific marker of myocardial injury [14–16]. To date, numerous publications have demonstrated a significant relationship between higher troponin values and worse prognosis in patients with acute myocardial infarction, heart failure or severe aortic valve disease [9–13]. It has also been described that TnT is a predictor of cardiac death in patients with CAD, atrial fibrillation or impaired left ventricular function [17–21]. However, Rahimi et al. [22] did not show a significant correlation between postmortem TnT level and sudden death.

Significant heart valve defects are often result in a volume or pressure overload of the heart cavities. It is worth noting that, a long-lasting additional burden on the myocardium causes progressive degenerative changes of the myocardium, which are accompanied by slow processes of necrosis and fibrosis [23–25]. According to some researchers, increased values of postoperative troponin level are associated with increased permeability of the cell membrane after myocardial reperfusion [26]. However, Opfermann et al. [27] did not find a linear correlation between maximum values of the postoperative TnT and ejection fraction, left ventricular hypertrophy, operating time, cardiopulmonary bypass time, time of cardiac arrest, lowest body temperature, perfusion pressure, cardioplegia volume, reperfusion time, or ventilation time [27]. In the present study, on a group of 815 patients undergoing heart valve surgery only hs-TnT I was an independent predictor postoperative SCA. The presented study did not show a significant correlation between the value of hs-TnT I and the length of aortic clamping time as well as extracorporeal circulation time. Moreover, patients with postoperative SCA were shown to have significantly lower preoperative LVEF compared with patients without SCA. This may suggest that higher values of TnT in the very early postoperative period are associated with the severity of preoperative damage to the myocardium resulting from cardiac valvular disease and increased permeability of hs-TnT across the cell membrane after myocardial reperfusion. Moreover, the higher values of hs-TnT I may indicate a seriously damaged myocardium which is susceptible to the occurrence of life-threatening heart rhythm disturbances that may lead to SCA. It is worth noting that of the 26 patients who experienced SCA, up to 16 patients had a maximum 30-day period before death.

Conclusions

Sudden cardiac arrest occurs in the course of cardiac arrhythmias. Troponin T is a polypeptide that is part of the striated contractile muscle apparatus, moreover it is the best laboratory parameter in the diagnosis of myocardial injury. The results of this study indicate that troponin T measured immediately after surgery is a predictor of SCA in the early postoperative period in patients undergoing heart valve surgery. Further study is needed to clarify the pathomechanisms linking an increased risk of SCA in patients with a higher hs-TnT in the early postoperative period. Enlargement of the number of participants may allow for confirmation of results obtained. The results of this research may be helpful in perioperative strategy for patients undergoing heart valve surgery.

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P2Y12 antagonist ticagrelor inhibits the release of procoagulant extracellular vesicles from activated platelets

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Abstract

Background: *Activated platelets release platelet extracellular vesicles (PEVs). Adenosine diphosphate (ADP) receptors P2Y1 and P2Y12 both play a role in platelet activation, The present hypothesis herein is that the inhibition of these receptors may affect the release of PEVs.*

Methods: *Platelet-rich plasma from 10 healthy subjects was incubated with saline, P2Y1 antagonist MRS2179 (100 μM), P2Y12 antagonist ticagrelor (1 μM), and a combination of both antagonists. Platelets were activated by ADP (10 μM) under stirring conditions at 37°C. Platelet reactivity was assessed by impedance aggregometry. Concentrations of PEVs– (positive for CD61 but negative for P-selectin and phosphatidylserine) and PEVs+ (positive for all) were determined by a state-of-the-art flow cytometer. Procoagulant activity of PEVs was measured by a fibrin generation test.*

Results: *ADP-induced aggregation (57 ± 13 area under curve {AUC] units) was inhibited 73% by the P2Y1 antagonist, 86% by the P2Y12 antagonist, and 95% when combined ($p < 0.001$ for all). The release of PEVs– (2.9 E ± 0.8 × 10^8/mL) was inhibited 48% in the presence of both antagonists ($p = 0.015$), whereas antagonists alone were ineffective. The release of PEVs+ (2.4 ± 1.6 × 10^7/mL) was unaffected by the P2Y1 antagonist, but was 62% inhibited by the P2Y12 antagonist ($p = 0.035$), and 72% by both antagonists ($p = 0.022$). PEVs promoted coagulation in presence of tissue factor.*

Conclusions: *Inhibition of P2Y1 and P2Y12 receptors reduces platelet aggregation and affects the release of distinct subpopulations of PEVs. Ticagrelor decreases the release of procoagulant PEVs from activated platelets, which may contribute to the observed clinical benefits in patients treated with ticagrelor.* (Cardiol J 2019; 26, 6: 782–789)

Key words: extracellular vesicles, platelets, ADP receptors, P2Y12 antagonists, ticagrelor

Introduction

Platelet activation and aggregation in response to atherosclerotic plaque rupture is a key event in the pathogenesis of acute coronary syndrome (ACS) [1]. Platelet P2Y1 and P2Y12 receptors for adenosine diphosphate (ADP) contribute to ACS by initiating and amplifying platelet activation, respectively [2]. Whereas antagonists against the P2Y1 receptor are under development [3], antagonists against the P2Y12 receptor are clinically established to prevent recurrent cardiovascular events in patients with ACS [4].

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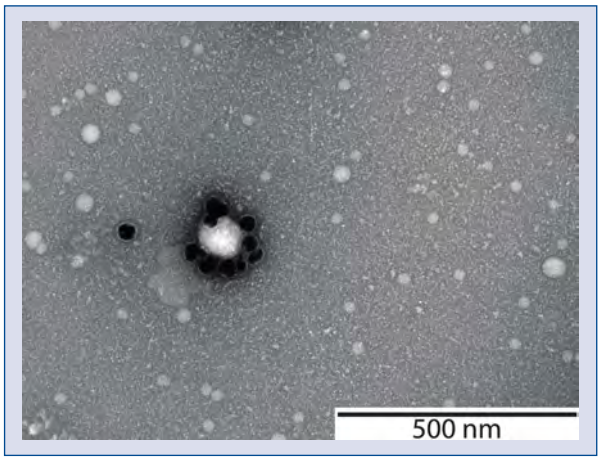

Figure 1. A transmission electron microscope image of platelet extracellular vesicles from human plasma. The vesicles were labelled with gold nanoparticles conjugated to CD61 antibodies. Image courtesy of Chi M. Hau, Vesicle Observation Center, Academic Medical Center, University of Amsterdam, the Netherlands.

In the course of ACS, activated platelets release fragments of their outer cell membrane to the bloodstream, called platelet-derived extracellular vesicles (PEVs) [5]. A transmission electron microscope image of PEVs from human plasma is shown in Figure 1. PEVs are nanoparticles surrounded by a phospholipid membrane which encloses cytoplasmic components such as proteins, lipids, metabolites and nucleic acids, they also contain platelet-derived proteins [5]. The exposure of glycoprotein (GP) IIb/IIIa, a receptor for fibrinogen (CD41/CD61) enables identification of PEVs released from platelets or megakaryocytes among other extracellular vesicles (EVs) present in blood. In turn, the exposure of GP IIb/IIIa along with P-selectin (CD62P) and phosphatidylserine (PS), which enables identification of PEVs released from activated platelets [6]. PEVs exposing P-selectin and PS are likely involved in inflammation and thrombosis [7–10]. P-selectin initiates binding of platelets and PEVs to monocytes via P-selectin glycoprotein ligand-1 (PSGL-1), leading to monocyte activation, cytokine release and exposure of tissue factor (TF) on monocytes [9]. PS along with other negatively charged phospholipids bind clotting factors in the presence of calcium ions, thereby propagating thrombin generation [10]. Hence, PEVs exposing P-selectin and PS may potentially contribute to the development and progression of atherosclerosis [11–13].

Although the potential applications of PEVs as biomarkers [14], risk predictors [15] and therapeutic targets [16] in cardiovascular disease are recognised, the mechanisms underlying the release of PEVs are unclear [17]. Because both P2Y1 and P2Y12 receptors regulate platelet activation, it was hypothesized that inhibition of these receptors may affect the release of PEVs.

Methods

The design of the experiments is shown in Figure 2.

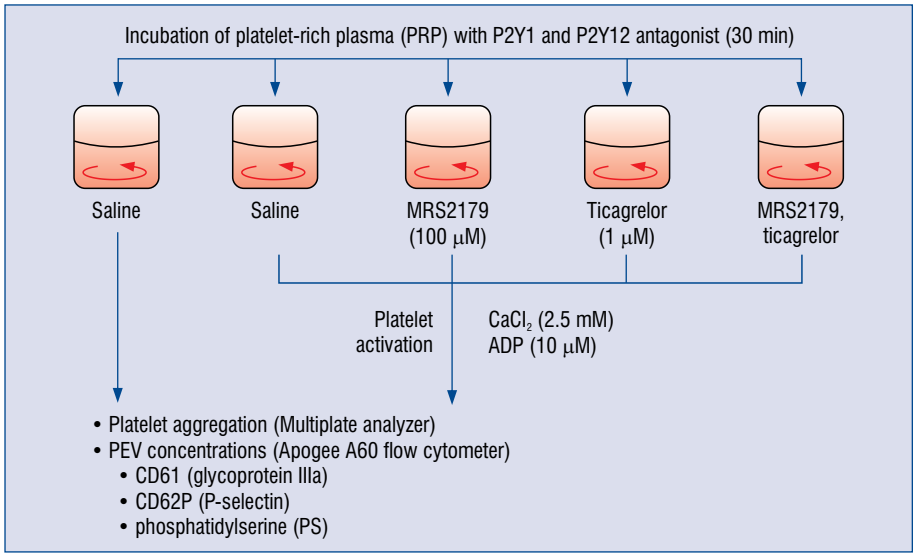

Figure 2. The design of the experiments on the role of the P2Y1 and P2Y12 receptors in the release of platelet extracellular vesicles. $CaCl_2$ — calcium chloride; ADP — adenosine diphosphate; CD — cluster of differentiation; PEVs — platelet extracellular vesicles.

Materials

Trisodium citrate blood collection tubes were obtained from Sarstedt (Germany). Needles were obtained from Vygon (Belgium). The P2Y1 antagonist MRS2179 was obtained from Tocris Biosciences (United Kingdom [UK]). The P2Y12 antagonist ticagrelor was obtained from Cayman Chemical (USA), ADP was from Bio/Data Corporation (USA), and acid citrate dextrose (ACD), phosphate-buffered saline (PBS), sodium citrate and calcium chloride ($CaCl_2$) were obtained from Sigma Aldrich (USA). The Multiplate analyser and reagents were from Roche Diagnostics (Germany), lactadherin-FITC from Hematologic Technologies (USA), CD61-APC from Dako (Denmark), and CD62P-violet and isotype controls from Becton Dickinson (USA). The membrane (0.05 nm) to filtrate the buffers was obtained from Merck Millipore (Germany). The Rosetta Calibration beads were obtained from Exometry (The Netherlands). Innovin (recombinant human TF) was obtained from Siemens (Germany) and anti-factor VIIa from Sanquin (The Netherlands).

Blood collection and handling

Blood samples were obtained from 10 healthy, drug-free donors after overnight fasting and giving informed consent, according to the recent guidelines [18]. Blood was collected using a 19 gauge needle and a plastic tube containing citrate (final concentration 0.109 mol/L). The tourniquet was removed promptly after the venepuncture. The first 2.5 mL of blood collected was discarded to avoid pre-activation of platelets. The tubes were kept in a vertical position for 15 min. Platelet rich plasma (PRP) was prepared by centrifugation of blood for 180 g at 15 min. Centrifugation was performed using Rotina 380 R centrifuge equipped with a swing-out rotor and a radius of 155 mm (Hettich Zentrifugen, Germany) at room temperature with acceleration speed 1, without brake.

Aggregometry

288 μL of citrated PRP was added to 288 μL saline and incubated for 30 min at 37°C with (i) saline, (ii) P2Y1 receptor antagonist MRS2179 (final concentration 100 μM), (iii) P2Y12 receptor antagonist ticagrelor (final concentration 1 μM), and (iv) a combination of both antagonists. Subsequently, the diluted PRP was re-calcified (final concentration 2.5 mM $CaCl_2$) before addition of ADP (10 μM). Platelet aggregation was recorded for 6 min while stirring using Multiplate analyser (Roche Diagnostics, Germany).

Flow cytometry

Platelet-free supernatant was prepared by centrifugation of 600 μL PRP with 120 μL ACD at 800 g for 20 min. PEVs were measured in this platelet-free supernatant collected 30 min after the addition of ADP. Prior to labelling of the supernatant, antibodies were diluted in PBS and centrifuged at 18,890 g for 5 min to remove protein aggregates. To stain, 20 μL of the supernatant was incubated with 2.5 μL CD61-APC, 2.5 μL CD62P-violet, 2.5 μL lactadherin-FITC or isotype controls in the dark for 2 h at room temperature. The reaction was stopped by adding 200 μL citrated PBS solution, adjusted to pH 7.4 and filtered with a 0.05 μm membrane prior to use [18]. PEVs released from platelets (positive for CD61 but negative for P-selectin and PS) are further referred to as PEVs–. PEVs released from activated platelets (positive for all) are referred to as PEVs+ [6]. PEV concentrations were determined by A60 Micro flow cytometer (Apogee Flow Systems, UK) for 60 s at a flow rate of 3.01 μL/min. Prior to measurement, the samples were diluted with PBS to 5,000 events per second to avoid swarm [19]. The applied voltages were 375 V, 520 V, 510 V, and 500 V for the side scatter detector, FITC detector, APC detector, and violet detector, respectively. The gains were 1. The trigger threshold was set on side scatter channel 10. Rosetta Calibration was used to relate side scatter to the diameter of PEVs, assuming a PEV refractive index of 1.4 [20].

The fluorescent gates were based on the isotype controls. To analyse the concentrations of PEVs–, in the first step all PEVs exposing CD62P and PS were gated out, and PEVs exposing CD61 only were detected in the red channel (638-D Red). To analyse the concentrations of PEVs+, in the first step all plasma EVs exposing PS (binding to lactadherin) were detected in the green channel (488-Green). Out of all PEVs exposing PS, PEVs exposing additionally CD61 and CD62P were detected in the red channel (638-D Red) and blue channel (405-Blue). At the time of the experiment, no suitable beads to calibrate molecules of equivalent soluble fluorophores (MESF) were available for the APC and violet channel. Therefore, gates were set in arbitrary units (AU) with the following values: 4,153 AU for CD61-APC; 6,185 AU for CD62P-violet and 2,661 AU for lactadherin-FITC.

Fibrin generation test

The ability of PEVs to generate fibrin was measured in platelet-free plasma in the absence or presence of human recombinant TF (coagulation

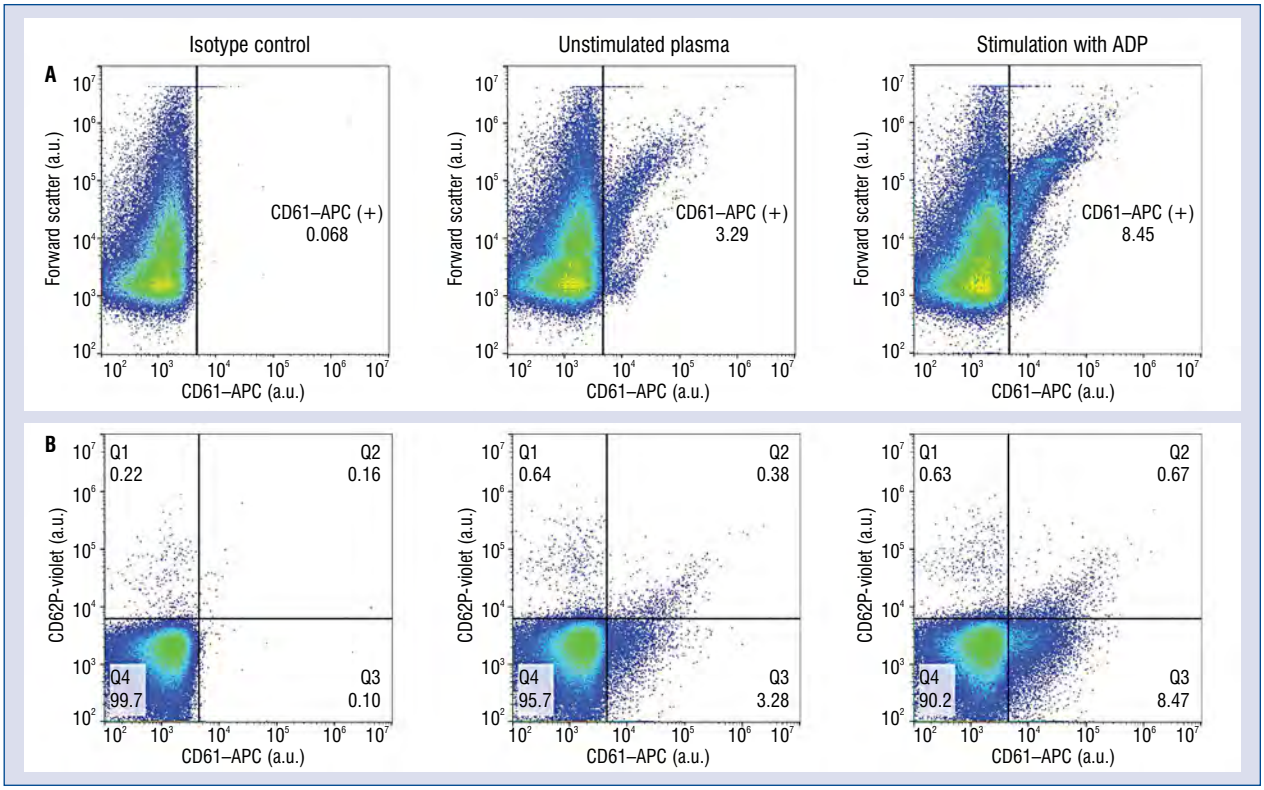

Figure 3. Representative images of platelet extracellular vesicles (PEVs) from adenosine diphosphate-activated platelets in plasma of a healthy donor measured by flow cytometry (A60-Micro, Apogee Flow Systems, Hertfordshire, UK); **A.** PEVs exposing CD61 but not CD62P and phosphatidylserine (PS) and labelled with anti-CD61-APC; **B.** PEVs exposing CD61, CD62P and PS and labelled with anti-CD61-APC, anti-CD62P-Violet and lactadherin-FITC, respectively. In the first step all plasma extracellular vesicles exposing PS (binding to lactadherin) were recorded (data not shown). Out of all PEVs exposing PS, PEVs exposing CD61 and CD62P were recorded (Q2); a.u. — arbitraty units.

factor VII), antibody against factor VIIa (anti-factor VIIa) and excess of lactadherin [21]. After pre-incubation for 5 min at 37°C, clotting was initiated by addition of $CaCl_2$. Fibrin formation over 1 h was determined by measuring the optical density (λ = 405 nm) in duplicate on a spectrophotometer (SPECTRAmax microplate reader, Molecular Devices, USA) at 37°C.

Statistical analysis

Kolmogorov-Smirnov test was used to test for Gaussian distribution. Data were analysed by paired Student's t-test. A Spearman rank correlation test was used to assess the correlation between aggregation results and concentration of PEVs. Statistical analysis was performed with the STATISTICA 12.0 (StatSoft, USA) and Prism 7.0 (GraphPad, USA) software. Flow cytometry data was analysed with FlowJo 9.2 (FlowJo, USA). Data are presented as mean ± standard deviation. All p-values are given as two-sided values, with a p-value < 0.05 considered significant.

Results

Size distribution of PEVs

Activation of platelets with ADP triggered platelet aggregation and the release of PEVs, compared to unstimulated platelets. The release of PEVs– and PEVs+ in response to ADP is shown in Figure 3. Scatter-based size distribution of the total population of PEVs ($CD61^+$) confirmed that PEVs ranged from 150 nm to 1,000 nm in diameter, with the majority of PEVs being below 200 nm. Size distribution of the total population of PEVs is shown in **Supplementary Figure 1.** Please note, that plasma contains (platelet) EVs down to 30 nm, which are below the lower detection limit of flow cytometry [22].

The effects of ADP receptor antagonists on platelet aggregation and release of PEVs

Adenosine diphosphate-induced aggregation (57 ± 13 area under curve [AUC] units) was 73% inhibited by the P2Y1 antagonist alone, 86% by

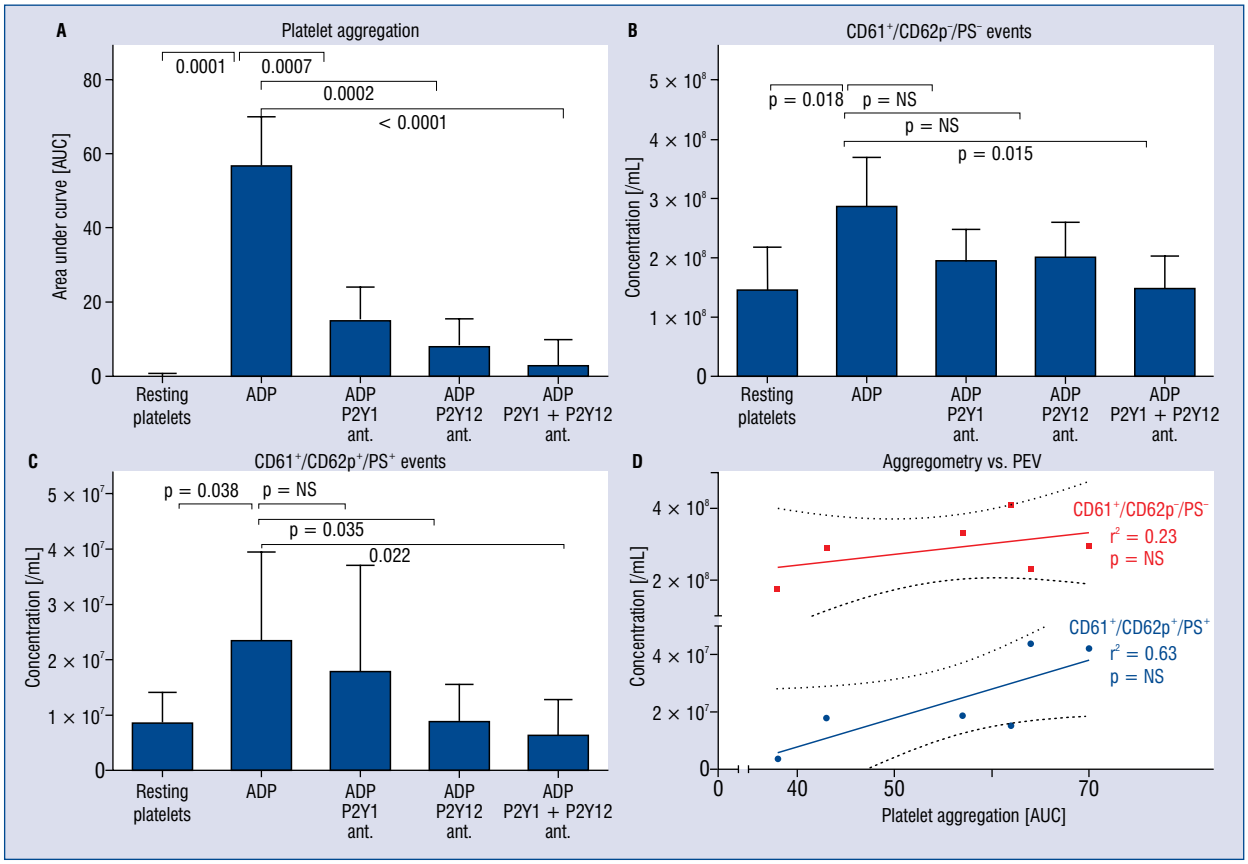

Figure 4. The effect of platelet pre-incubation with a P2Y1 antagonist, a P2Y12 antagonist and a combination of both antagonists on platelet aggregation (**A**) and the release of platelet extracellular vesicles (PEVs) exposing CD61 but not CD62p and phosphatidylserine (PS) (**B**) and PEVs exposing CD61, CD62p and PS (**C**) in response to adenosine diphosphate (ADP). Whereas platelet aggregation correlated weakly with the concentration of $CD61^+/CD62P^-/PS^-$ PEVs, platelet aggregation correlated strongly with the concentration of $CD61^+/CD62P^+/PS^+$ PEVs (**D**).

the P2Y12 antagonist alone, and 95% when both antagonists were combined ($p < 0.001$ for all; Fig. 4A). The release of PEVs– ($2.9 \pm 0.8 \times 10^8$ events/mL) was unaffected by pre-incubation with the P2Y1 antagonist or by the P2Y12 antagonist alone, but decreased by 50% in presence of both antagonists ($p = 0.015$; Fig. 4B). In contrast, the release of PEVs+ ($2.4 \pm 1.6 \times 10^7$ events/mL) was unaffected by the P2Y1 antagonist alone, but was decreased 62% by the P2Y12 antagonist alone ($p = 0.035$), and 72% in the presence of both antagonists ($p = 0.022$; Fig. 4C). Whereas the extent of platelet aggregation weakly correlated with the concentration of PEVs– ($r^2 = 0.2$), the extent of platelet aggregation strongly correlated with the release of PEVs+ ($r^2 = 0.7$, Fig. 4D).

Procoagulant activity of PEVs

Platelet-free plasma containing PS-exposing EVs from ADP-activated platelets did not clot up to 1 h after re-calcification. When human recombinant TF was added, clotting was initiated. The magnitude of clotting was not affected by the presence or absence of P2Y1 and P2Y12 antagonists (data not shown). Clotting was abolished both by covering the PS by an excess of lactadherin and by inhibiting TF activity with anti-factor VIIa. The proposed procoagulant activity of PEVs measured with fibrin generation test is shown in Figure 5.

Discussion

P2Y1 and P2Y12 receptors differentially regulate platelet aggregation and the release of PEVs. Inhibition of either P2Y1 or P2Y12 receptor is sufficient to inhibit ADP-induced platelet aggregation [23], which is consistent with the clinical observation that P2Y12 antagonists reduce the incidence of thrombosis in patients after ACS [4]. Further, inhibition of the P2Y1 and P2Y12 receptors affects

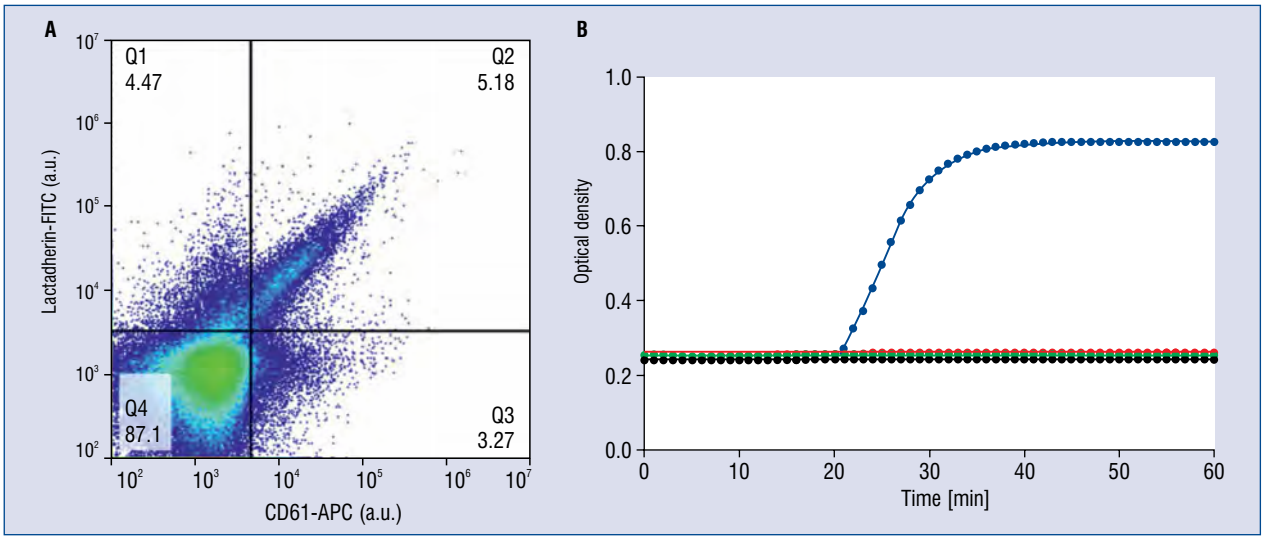

Figure 5. Proposed procoagulant activity of platelet extracellular vesicles (PEVs) in plasma. Fibrin generation test was performed in platelet-depleted, but PEVs-containing plasma stimulated with adenosine diphosphate (ADP). A part of PEVs expose phosphatidylserine ($CD61^+/PS^+$) (**A**). When the plasma clots, the optical density increases (**B**). ADP-stimulated plasma containing phosphatidylserine (PS)-exposing extracellular vesicles (EVs) did not clot (red). Upon the addition of recombinant human tissue factor (TF) to this plasma, clotting was triggered as measured by fibrin generation (blue). The extent of clotting was not affected by the presence of the P2Y1 and P2Y12 receptor antagonists (data not shown). Covering PS-exposing EVs with an excess of lactadherin, or inhibiting the TF-initiated extrinsic coagulation with an anti-factor VIIa antibody, both inhibited plasma clotting (black and green, respectively). Hence, both PS-containing EVs and TF are indispensable for propagation of coagulation.

the release of distinct subpopulations of PEVs upon activation by ADP. The P2Y12 antagonist ticagrelor alone does not inhibit the release of PEVs–, suggesting that PEVs– may circulate in patients treated with ticagrelor and contribute to platelet homeostasis, for example by waste management [24]. On the contrary, ticagrelor decreases the release of PEVs+, that is PEVs exposing the proinflammatory P-selectin and procoagulant PS, suggesting that this subpopulation of PEVs may be decreased in patients treated with ticagrelor. In accordance, other P2Y12 receptor antagonists (clopidogrel, prasugrel and cangrelor) were shown to decrease the release of EVs from activated platelets as well [25–27], although the phenotype of the analysed PEVs was different than in the present study. Clopidogrel decreased the release of PEVs ($CD42a^+$, PS^+) in response to thrombin receptor-activating peptide (TRAP) in a group of 12 patients with ACS [25]. Similarly, both prasugrel active metabolite and cangrelor decreases the collagen- and TRAP-induced release of PEV ($CD42a^+$, PS^+) in a concentration-dependent manner in experimental conditions [26, 27].

Inhibition of P-selectin- and PS-exposing PEVs may. at least partly, explain the combined anti-thrombotic and anti-inflammatory benefits of the P2Y12 receptor antagonists. The potential proinflammatory and procoagulant effects of PEVs are presented in Figure 6. Although PS-exposing EVs, such as those present in the plasma of healthy individuals, do not initiate coagulation in the absence of TF, PS-exposing EVs promote coagulation by providing a procoagulant surface. This procoagulant surface may be crucial in the ACS setting, where TF is exposed on a ruptured atherosclerotic plaque [28], and where PS-exposing EVs together with TF likely contribute to coronary thrombus formation. PEVs+ may contribute to coagulation also indirectly by activating monocytes interaction of PEVs P-selectin with monocyte PSGL-1, leading to cytokine release and production of TF [9]. Thus, by decreasing the concentration of PEV+, ticagrelor likely decreases the proinflammatory/procoagulant surface for interaction between PEVs and monocytes/clotting factors, respectively.

Regarding the recently proved inflammatory hypothesis of atherosclerosis [29] and the lack of consensus regarding the optimal duration of antiplatelet therapy with P2Y12 antagonists [4], determining the effect of P2Y12 antagonists on the release of PEVs helps to explain the mechanisms underlying decreases in inflammation/thrombosis for patients treated with P2Y12 antagonists. To determine the

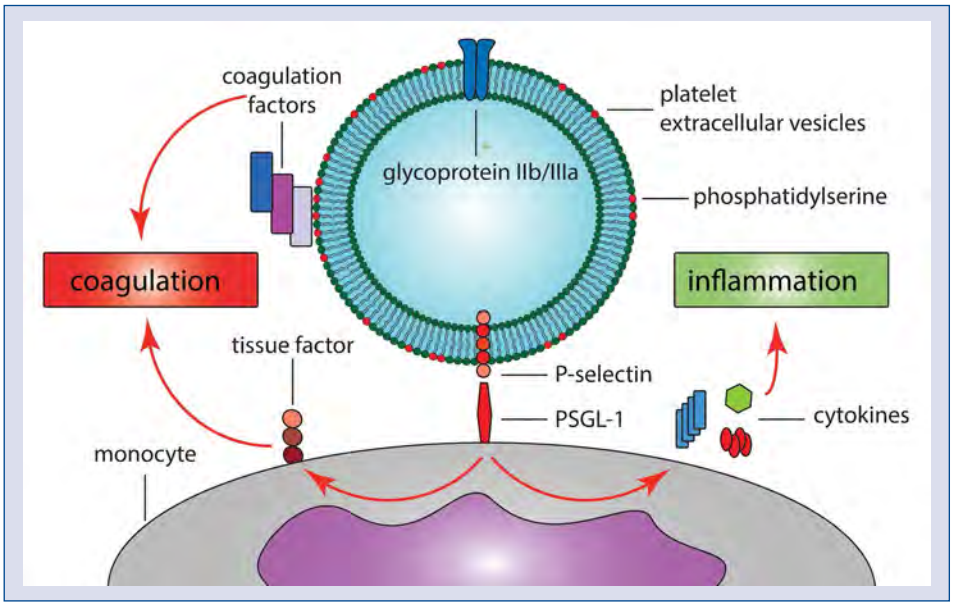

Figure 6. The potential proinflammatory and procoagulant effects of platelet extracellular vesicles (PEVs). PEVs contribute to coagulation both directly by providing procoagulant surface (phosphatidylserine) for the assembly of coagulation factors, and indirectly by binding of P-selectin to P-selectin glycoprotein ligand-1 (PSGL-1) on monocytes, leading to an exposure of tissue factor on monocytes. In addition, interaction between P-selectin and PSGL-1 contributes to inflammation by stimulating the release of pro-inflammatory cytokines from monocytes.

effects of the P2Y12 antagonists on the release of PEVs in a clinical setting, the AFFECT EV (Antiplatelet therapy effect on platelet extracellular vesicles, NCT02931045) study was launched [30]. AFFECT EV compares the effects of clopidogrel and ticagrelor on the release of PEVs in patients with ACS, with the hypothesis that more potent platelet inhibition is associated with larger decrease of PEV release.

Limitations of the study

First, the study was limited by the relatively small size of the study population, and therefore the presented results and conclusions should be considered as hypothesis-generating. Second, the decrease in the release of proinflammatory/procoagulant PEVs by ticagrelor was observed under experimental conditions only, and requires confirmation in a clinical setting. Third, the study identifies only one potential mechanism of the combined anti-thrombotic and anti-inflammatory benefits of the P2Y12 receptor antagonists — decrease of the release of PEVs. Since activated platelets release other proinflammatory/procoagulant molecules along with PEVs, it is likely that other mechanisms contribute to clinical benefits of the P2Y12 receptor antagonists as well.

Conclusions

Despite extensive research into the role and clinical applications of PEVs, the mechanisms regulating the release of PEVs as well as the effects of widely used drugs on the release of PEVs remain to be defined. The present results demonstrate that ADP-activated platelets released two distinct subpopulations of PEVs, which differ in their sensitivity to inhibition of P2Y1 and P2Y12 receptors. The release of (likely) proinflammatory and procoagulant PEVs is decreased by the P2Y12 antagonist ticagrelor, identifying a potential mechanism underlying attenuated inflammation and thrombosis in patients treated with P2Y12 antagonists. Further research is warranted to confirm this mechanism *in vitro* as well as *in vivo*.

Acknowledgements

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Conflict of interest: None declared

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TECHNOLOGY NOTE

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Feasibility of in-house rapid prototyping of cardiovascular three-dimensional models for planning and training non-standard interventional procedures

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Introduction

Interventional treatment has become the golden standard for many congenital heart diseases and pathologies that were just recently considered unsuitable for an interventional approach are now being successfully treated by those who are most experienced. Still, being on the cutting-edge is a source of uncertainty and risk. New technologies, like rapid prototyping also know as three-dimensional (3D) printing may help to reduce this uncertainty. It has been demonstrated that 3D printed models are helpful in planning surgical and interventional treatment of various congenital heart diseases of unusual anatomy [1, 2]. Less is known of application 3D printing for planning and rehearsing management of rare complications of previous treatments.

The problem

A 39-year-old female was treated for coarctation of the aorta with bypass-grafting from the left-subclavian to the distal descending aorta 25 years ago. Recent follow-up echocardiography revealed pressure gradient 30 mmHg in the distal aortic arch. A computed tomography has revealed a torturous course of the aortic arch – subclavian – bypass-graft route but there was no discrete narrowing. There was no continuity via the isthmic aortic segment. Additionally, there was a 5.0 × 6.0 cm aortic aneurism caudally from the distal arch, most of which was filled with thrombotic masses. The active lumen was 2.5 × 3.0 cm with a bottleneck-like inlet 6 × 8 mm (Fig. 1A). The aneurismal mass was compressing the left pulmonary artery, significantly restricting its lumen. The pulmonary perfusion scan (SPECT-CT) has revealed no perfusion of the apical-posterior lobe, residual perfusion of the anterior lobe and diminished perfusion of the remaining left lung resulting in a total left-to-right perfusion ratio of 24%/76%.

Consequently, the patient was admitted to the University Clinical Center in Gdansk, GUCH Unit for treatment. The extent and approach to the treatment were considered including total resection of the aneurismal mass and reconstruction of the left pulmonary artery, but considering the asymptomatic condition of the patient a more conservative approach was preferred — interventional closure of the aneurism. Several problems needed to be addressed. Firstly, the device type and size, considering a risk of narrowing the aortic arch lumen at the site of implantation. Secondly, the route of introducing the device — the curvature of the arch and its branches, as well as the orientation of the inlet to the aneurism had to be considered. The imagery gave background on the anatomy, but the non-standard nature of the procedure made it difficult to plan the procedure with satisfying certainty.

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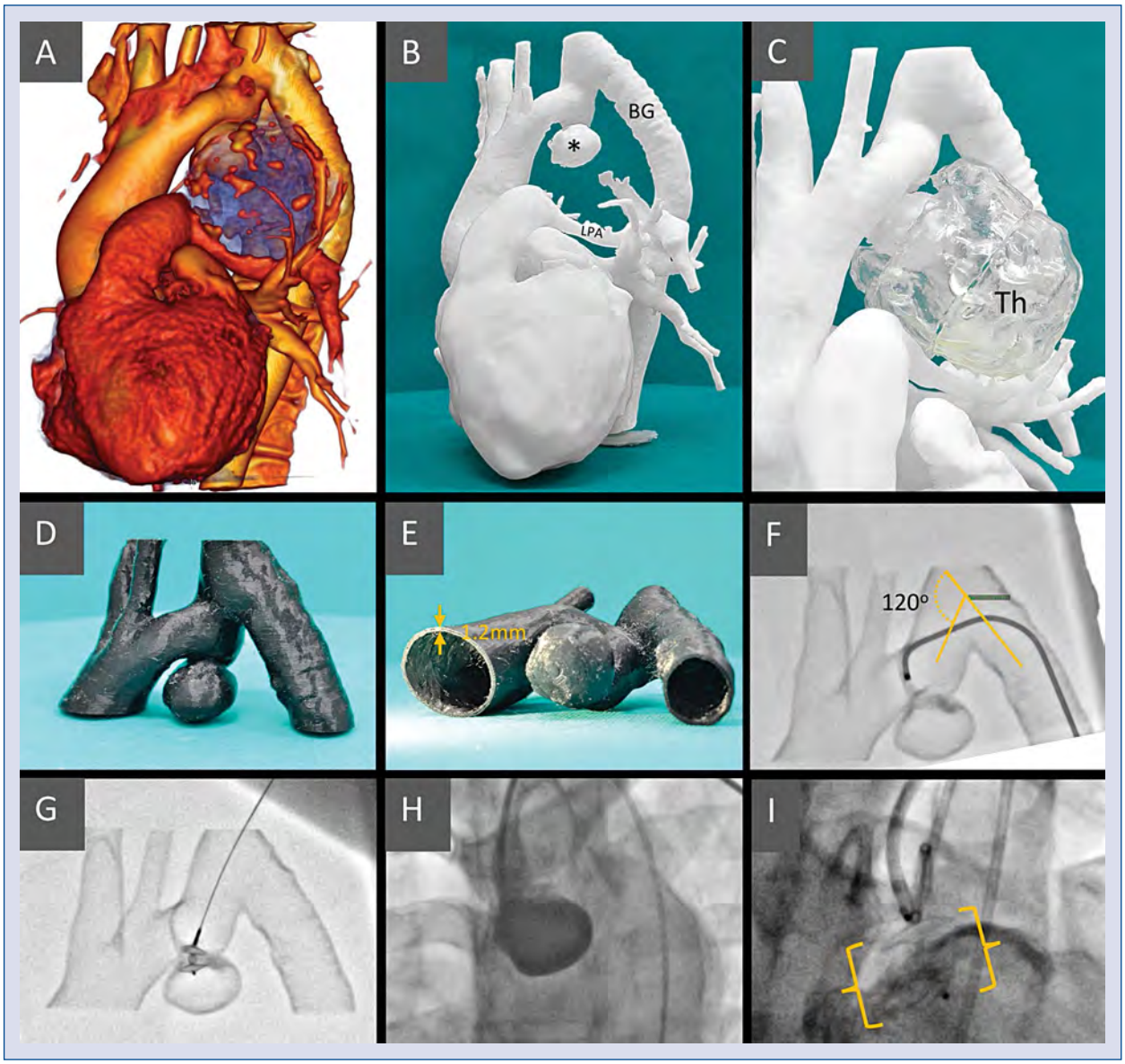

Figure 1. A. Volume rendering of the computed tomography left antero-lateral aspect; the blue area represents the thrombotic mass with numerous calcifications on the surface; **B.** Model I, active aneurism (*), bypass-graft (BG) and the compressed left pulmonary artery (LPA) are clearly visible; **C.** Model I including the thrombotic part of the aneurismal mass (Th) made separately of translucent material; **D, E.** Model II — region of interest, hollow vessels for simulation and training made of semi-flexible material with 1.2 mm wall thickness to ensure model printability and durability; **F.** The simulated procedure from the femoral access, it was difficult to pass through the 120 degree angle to reach the implantation site; **G.** The simulated procedure from the left radial access, a straight route to the aneurism, the device is introduced to the implantation site; **H.** The treatment procedure — the sheath introduced from left radial site, secondary access from femoral to inject contrast medium. ADO II at the implantation site; **I.** The treatment procedure — the sheath introduced from left radial site, secondary access from femoral to inject contrast medium. ADO II at the implantation site.

The solution

Two 3D printed models were made, both 1:1 scale. Model I was a whole-heart and vessels "solidified contrast" type (Fig. 1B, C). Its purpose was to depict the anatomy and spatial relations of the vessels and the aneurism. Model II, limited to the region of interest, i.e. the aneurism and the adjacent vessels, was an empty-inside (hollow) training model (Fig. 1D, E). Representing

Table 1. Time and resources necessary to complete the models. This should be considered an example — the processing times vary, and depend on user experience and software, while the print times depend on the printer and print settings. The transparent part was done separately and was not considered crucial for the model and is not included in the cost analysis.

Step	Time/resource	Model I (anatomy)	Model II (simulation)
1.	DICOM to STL conversion	0 h 45 min	
2.	Digital model	2 h 50 min	
3.	Digital model (hollow)	n/a	0 h 40 min
4.	Print file	0 h 20 min	0 h 20 min
5.	Printing	2 days 13 h 34 min	16 h 42 min
6.	Post-processing	1 h 15 min	0 h 25 min (3 h 20 min)
7.	Printer	Zortrax M200 Plus	Zortrax Inveture
8.	Material type	Ultrat	Semi-Flex + Support Plus
9.	Material usage	236 g	18 g + 16 g

n/a — not applicable

the vessels lumen, its purpose was to allow for a simulated procedure.

The source DICOM imagery was pre-processed in OsiriX MD software and further processed in Meshmixer to repair mesh errors and remove artefacts. At this point, preparations of the two models branched. Model I was passed on to the printer software (Z-Suite) and after applying print parameters, a printable file was generated. Model II was further processed in Meshmixer — a region of interest was separated, and the model was hollowed before a printable file was generated. Both models were checked for quality and precision using a measuring tool to compare the diameters with the source imagery. The processing and print details are presented in Table 1.

Based on the imagery and the digital model, a device type and size were preliminarily selected — ADO II 6 mm. The Model II was used to simulate the procedure. It has been confirmed that the right radial and femoral (Fig. 1F) approaches are suboptimal because of the angles on the way of the catheter and the preferred site was left radial artery (Fig. 1G). The preselected implant was possible to be implanted and had a stable position at the implantation site. Moreover, the aortic lumen did not seem to be significantly obstructed after the implantation. The procedure simulation from the preferred site was repeated 5 times. The first attempt took 3 min 20 s, the last one 1 min 40 s. It was clear that the time to complete was reduced owing to the learning curve of the operator.

The patient treatment was carried out ably and uneventfully, with no complications (Fig. 1H–I). According to the operator (RS), both models were accurate representations of the anatomy and the training model faithfully simulated the actual procedure. Consequently, both models contributed significantly to the success of the treatment.

Conclusions

It is possible to rapidly prototype high quality 3D printed models in-house, at a limited cost provided experienced staff and facilities are present. The main advantages of in-house printing are speed, and the possibility to directly oversee the process at every step to ensure the highest precision possible. Training simulators such as the one depicted above facilitate a more individualized approach to the patient — a trend currently going by the name personalized medicine.

Conflict of interest: None declared

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BRIEF COMMUNICATION

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Is quantitative flow ratio enough to accurately assess intermediate coronary stenosis? A comparison study with fractional flow reserve

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Fractional flow reserve (FFR) is a recommended tool to assess the hemodynamic relevance of borderline stenosis of epicardial coronary arteries but requires costly pressure wires and administration of a hyperemic agent [1]. A novel approach enabling rapid computation of FFR pullbacks from three-dimensional quantitative coronary angiography (3D QCA) has recently been developed [2, 3]. The computational FFR, known as quantitative flow ratio (QFR), may be obtained from 3D QCA using an advanced computer algorithms [2]. However, so far, data on the clinical performance of QFR are rather limited. Thus, the aim herein, was to assess the accuracy of QFR and correlation between QFR and FFR in the assessment of borderline coronary artery stenoses.

Consecutive patients with stable angina, who were scheduled for FFR, were prospectively enrolled. Ethics approval was granted by the institutional ethics review process. Details of FFR procedure were previously described [4, 5]. Computation of QFR was performed offline, using a software package (Medis Suite 2.1.12.2, Medis Medical Imaging System, Leiden, the Netherlands) by two independent corelab analyzers who were blinded to FFR results. The analysis was conducted twice by each analyzer and the mean value (from four calculations) was used for further analysis. The software computed QFR pullback was performed with frame count analysis separately on two diagnostic angiographic projections without pharmacologically induced hyperemia, and empiric hyperemic flow velocities were derived from software computed with two new QFR pullbacks. The QFR pullbacks were chosen based on the best image quality (most well-defined contrast flow) in the frame count analysis as the QFR pullback to compare with the pressure wire-based FFR. The QFR value at the position that matched the location of the pressure transducer on the pressure wire was used for comparison with the FFR value measured by the pressure wire. The flow velocity was derived by dividing the arterial segment length from 3D QCA and the corresponding dye flow time from the frame count analysis. The software allowed for selection of a subsegment of the reconstructed artery with good visualization of the dye flow for calculation of flow velocity. Using the guide catheter for calibration and an edge detection system (CAAS 5.7 QCA system, Pie Medical), the reference vessel diameter and minimum lumen diameter were measured, and the percent diameter stenosis (DS%) was calculated.

A total of 50 patients with 123 borderline coronary artery stenoses were enrolled. Overall, mean age was 66.0 ± 9.3 years, and 72% of patients were male. The left anterior descending artery was the most commonly assessed vessel (39%). Mean angiographic DS% was 44.2 ± 11.7%.

The mean FFR assessed with the femoral vein adenosine infusion at 140 μg/kg/min was 0.82 ± ± 0.10 and 49 (39.8%) vessels had FFR ≤ 0.80, 24 (19.5%) vessels — FFR ≤ 0.75. Figure 1A shows the distribution of the FFR values. Mean QFR value was 0.82 ± 0.09. Forty-seven (38.2%) vessels had QFR value ≤ 0.80 and 30 (24.4%) vessels had QFR ≤ 0.75. A limited intra- and interobserver variability for measuring the QFR was confirmed by intraclass correlation coefficient of 0.991 (95% confidence interval [CI] 0.988–0.993) and 0.990 (95% CI 0.987–0.992), respectively. More importantly, an excellent agreement between FFR and

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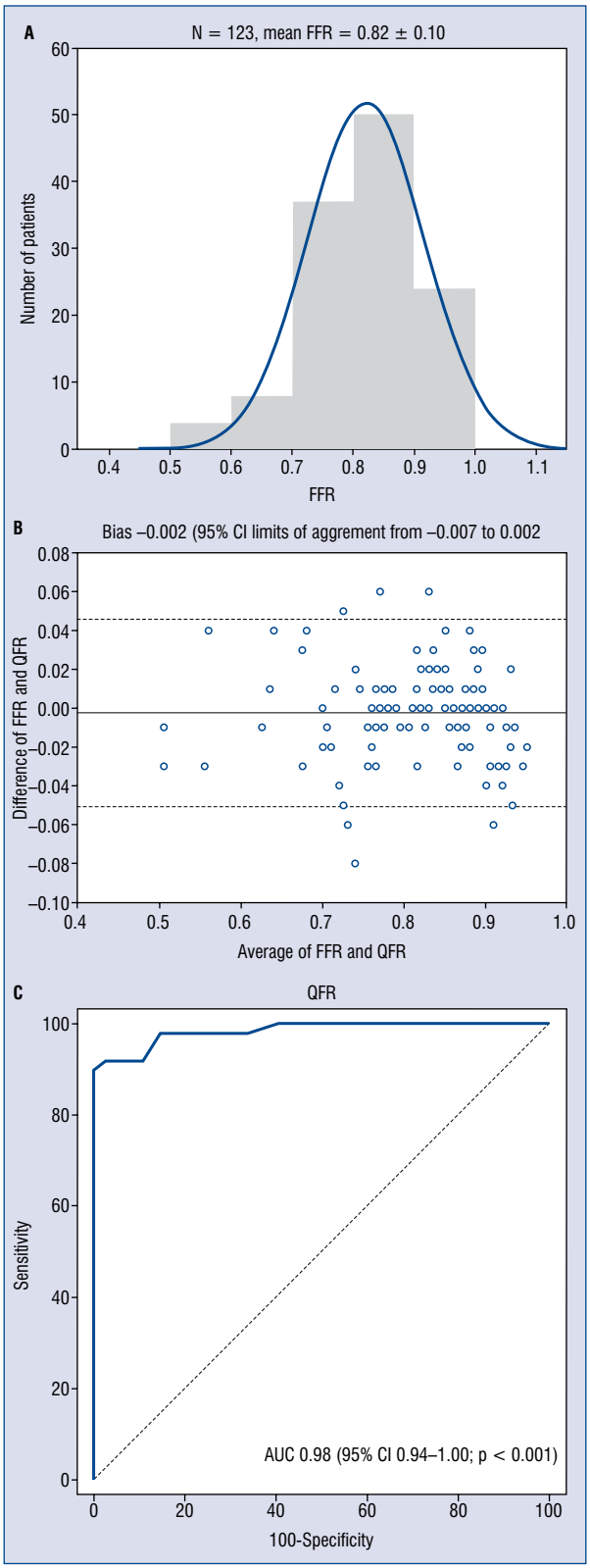

Figure 1. A. Distribution of the fractional flow reserve (FFR) values in the study population; **B.** Overall diagnostic accuracy (AUC in ROC analysis) of quantitative flow ratio (QFR) in detecting FFR ≤ 0.80; **C.** Bland-Altman plot analysis for FFR and QFR.

QFR measurements was confirmed with a mean difference of –0.002 (95% CI –0.007 to 0.002) and ICC 0.965 (95% CI 0.951–0.976) (Fig. 1B). The overall diagnostic accuracy (AUC in ROC analysis) of QFR in detecting FFR ≤ 0.80 was 0.98 (95% CI 0.94–1.00; $p < 0.001$). The optimal cutoff value for QFR was 0.80 with sensitivity, specificity, and accuracy of 91.8%, 97.3% and 95.1%, respectively. 100.0% sensitivity of QFR was noted for a cutoff value of 0.86, but with relatively low specificity (59.5%) (Fig. 1C). Therefore, QFR values between 0.8 and 0.85 remained in the gray zone and should be verified with conventional invasive FFR measurement.

The results of the current study support the diagnostic value of QFR in assessing the hemodynamic severity of borderline coronary stenosis and yield a promising alternative for non-invasive, drug-free assessment of coronary physiology. QFR was presented by Tu et al. [2] as a novel method for fast computation of FFR from coronary angiography. The major attractiveness of QFR is the avoidance of wiring of the coronary artery and administration of vasodilator drugs, which both are mandatory for FFR assessment. QFR empowered by reliable quantification of vessel dimensions, offers a novel and accurate tool for fast computation of FFR. The processing time is expected to be < 2 min for complete longitudinal FFR computation of each coronary vessel and its major side branches; in other words, FFR of the entire coronary tree would be obtained in < 10 min at the time of angiography [6]. Based on the reported validation against invasive FFR, the high diagnostic accuracy of QFR (88%) relative to the traditional anatomic angiographic measures of minimal lumen area (64%) and DS% (68%) offers better discrimination of the clinical significance of intermediate lesions [2]. The diagnostic accuracy of QFR reported by Tu et al. [6] is very good (88%), with AUC of 0.93, a negative predictive value of 91%, and a positive predictive value of 82% as compared to FFR. In the present study, as well as in the FAVOR studies [7], QFR had similar or even better accuracy in confirmation of hemodynamic significance of borderline coronary stenoses. The QFR assessment may be limited by more obstructive, multivessel or even tandem lesions, and microvascular disease. Another factor contributing to QFR accuracy is its reproducibility when analyzed by different core laboratories. Chang et al. [8] compared QFR results obtained by two independent corelabs interrogating vessels in the FAVOR II study. The mean differ-

ence in contrast-flow QFR between the two core laboratories was 0.004 ± 0.03 (p = 0.040). The mean differences of QFR with respect to FFR were comparable between the two core laboratories. In the current study averaged values of QFR were used obtained by two analysts to reduce the risk of miscalculation.

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BRIEF COMMUNICATION

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Imaging-guided percutaneous coronary intervention with ultra-low contrast angiographic control for patients at extreme risk of contrast induced nephropathy

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The occurrence of contrast induced nephropathy (CIN) remains one of the gravest complications of percutaneous coronary intervention (PCI) and is related to increased morbidity and mortality [1, 2]. In select cases renal replacement therapy is required, increasing the rate of major adverse events [3]. Minimizing contrast administration and optimal fluid management are effective in prevention [4], but in select patients a minimal quantity of contrast may lead to CIN. Since indicated the first feasibility reports [5–7], the concept of intravascular ultrasound (IVUS) guided PCI has become appealing for patients at risk of CIN. Presented herein, is a series of IVUS-guided PCI cases with ultra-low contrast volume angiographic control.

The procedure protocol is as follows. Hydrophobic guidewires are placed in main vessel and major sidebranches. Intraluminal position is IVUS-verified. "Dry-cine" positioning of IVUS and ultrasound imaging are co-registered to select optimal strategy. The effect of main vessel stenting is assessed with control IVUS pullbacks. Should a side branch compromise be suspected, the vessel is re-wired and physiological assessment is performed. In order to achieve optimal imaging quality, HD-IVUS is the preferred imaging modality. Post-procedural transthoracic echocardiography is performed to exclude pericardial effusion. Bail-out contrast administration is acceptable yet remains the last resort. Thus, this protocol admits the administration of a minimal quantity of contrast media mixed 1:1 with saline for post-procedural ultra-low contrast angiographic verification only, at the operator's discretion. The acceptable quantity of contrast is calculated from MDRD estimated glomerular filtration rate (eGFR) as follows: x mL of contrast = eGFR/2. The maximum quantity actually administered per patient in the following case series was 4 mL.

Patient 1. A 72-year-old male with chronic kidney disease (CKD) stage 4 was admitted with non-ST-segment elevation myocardial infarction (NSTEMI). Echocardiography showed moderate left ventricular systolic dysfunction (left ventricular ejection fraction [LVEF] 42%), eGFR was 20.9 mL/min/1.73 m^2). Coronary angiography showed multivessel disease (MVD), with diffuse lesions in left anterior descending artery (LAD), obtuse marginal branches (OM1, OM2) and significant aorto-ostial in right coronary artery (RCA) (Fig. 1A, B). Within 24 h CIN had developed, with oliguria and an eGFR drop to 16 mL/min/1.73 m^2. This was treated with hydration. The patient was qualified for coronary artery bypass grafting (CABG). Due to scarce venous material the RCA was not grafted and qualified for "zero contrast" PCI. The artery was wired with a hydrophobic wire. IVUS confirmed diffuse significant stenosis originating in the ostium (Fig. 1C, D). Dry cine of the IVUS sensor was acquired at plaque origin. Direct stenting with a 3.5 × 29 sirolimus eluting stent was performed with post-dilation of the ostium. Control IVUS pullback confirmed proper deployment and apposition of the stent. One control contrast injection was performed (4 mL saline and 4 mL of contrast) to confirm the findings of IVUS (Fig. 1E, G). Further in-hospital stay was uneventful. The patient was discharged on the second day post-PCI with no signs of CIN.

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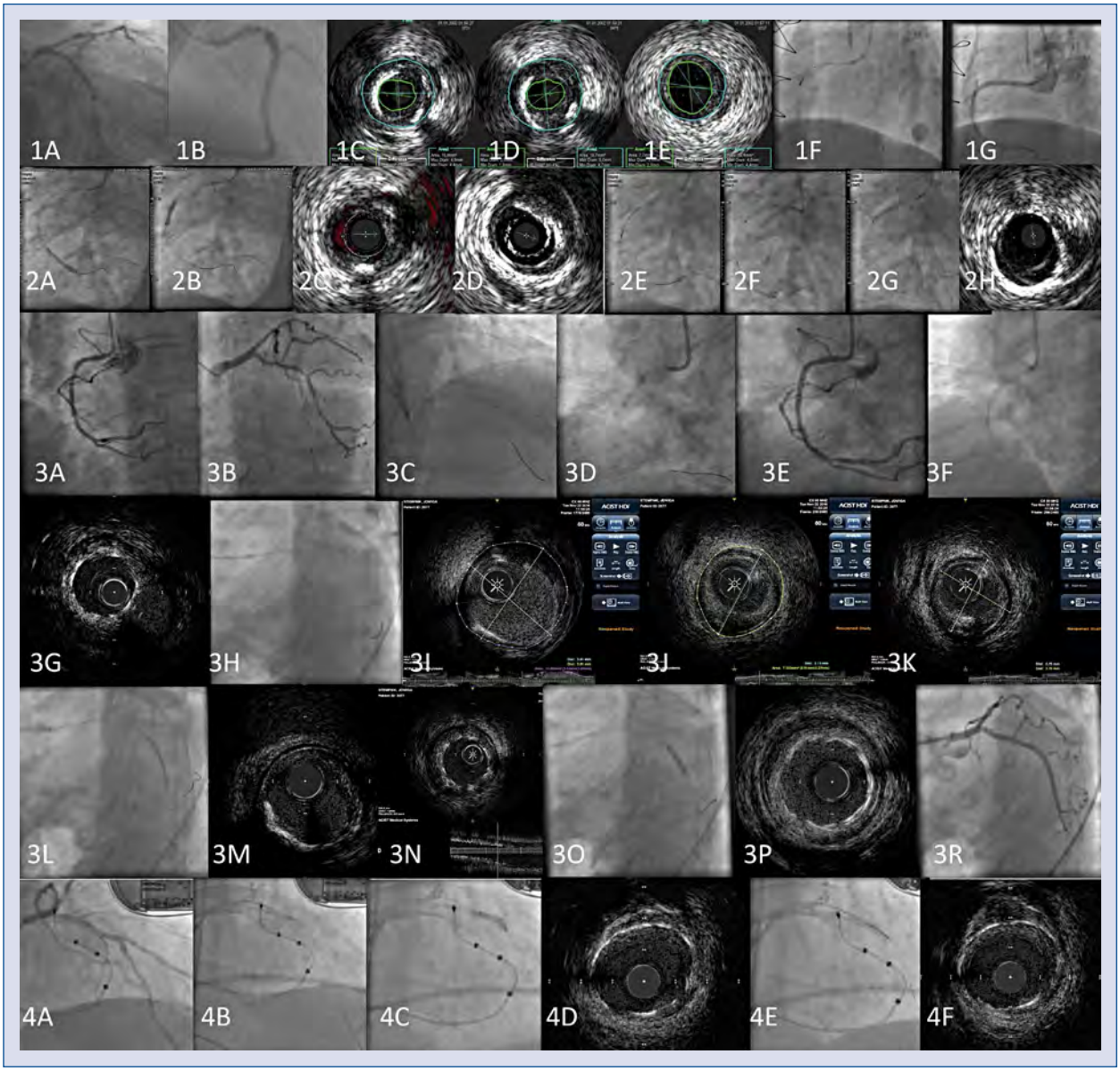

Figure 1. Intravascular ultrasound-guided percutaneous coronary intervention. **1A–G.** Case 1; **2A–H.** Case 2; **3A–R.** Case 3; **4A–F.** Case 4.

Patient 2. A 74-year-old female, with numerous comorbidities (diabetes, stage IV CKD — eGFR on admission 26 mL/min/1.73 m^2, Leriche syndrome), was admitted after an NSTEMI complicated with pulmonary edema. Echocardiography revealed an LVEF of 48% with no valvular disease. The patient was initially qualified for CABG, however after re-assessment (dubious ostial left main lesion, diffuse critical stenoses of the RCA) the patient was qualified for IVUS-guided PCI. The significance of ostial left main lesion was excluded (minimal lumen area [MLA] 8.8 mm^2). As IVUS catheter introduction to the RCA was impossible, numerous predilations were performed (Fig. 2A, B). IVUS pullback revealed diffuse, calcified lesions with a dissection in mid-RCA (Fig. 2C, D). A "mother and child" catheter was introduced to the distal part of the vessel and 3 everolimus eluting stents (EES) were implanted (3.5 × 38; 3.5 × 33; 4.0 × 28; Fig. 2E, F). Control IVUS pullback showed stent underexpansion in the mid and distal RCA. Post-dilation with 3.0 and 4.0 non-compliant balloon resulted in an optimal IVUS result (Fig. 2G, H). However, the patient presented with chest pain. Control echo showed good contractility and no pericardial effusion. A single contrast injection was performed (4 mL of contrast mixed with 4 mL of saline), confirming optimal PCI result, identifying 2 small

(< 1 mm) occluded side branches of the RCA. Further in-hospital stay was uneventful and the patient was released 4 days after the procedure.

Patient 3. A 75-year-old male with hypertension and diabetes was admitted with Canadian Cardiovascular Society (CCS) III angina. Echocardiography showed very good LVEF with no valvular disease. Coronary angiography revealed MVD with critical RCA lesions, significant circumflex artery (Cx) lesions and diffuse LAD lesions (LAD FFR 0.89). Ad hoc RCA PCI with 1 EES was performed (Fig. 3A–E). After the procedure (130 mL of contrast media) CIN was diagnosed and treated with i.v. fluids (creatinine levels 113 → 147 → 117 μmol/L). The patient qualified for a second stage procedure. On readmission (after 3 months) deterioration of renal function was observed (eGFR 28 mL/min/1.73 m^2) with no improvement after 6 days of hydration. The patient qualified for IVUS--HD assessment of the RCA and IVUS-HD guided zero contrast Cx PCI. IVUS-HD of RCA showed optimal effect of prior PCI (Fig. 3F, G). Cx was wired with a hydrophobic wire. IVUS showed diffuse obstructive CAD (Fig. 3H–K). OM1 was wired. Balloon angioplasty with a 2.5 × 30 mm catheter was performed (Fig. 3L). IVUS pullback showed good dilation of the vessel with no significant dissection. Two EES were implanted (2.5 × 23, 3.0 × 30) and, due to some malposition in IVUS (Fig. 3M, N), post dilated with a 3.0 non-compliant balloon (Fig. 3O). IVUS-HD control showed optimal effect (Fig. 3P). Injection of 3.5 mL of contrast showed optimal effect of PCI (Fig. 3R). The patient was discharged after 2 days.

Patient 4. An 80-year-old male with ischemic systolic heart failure and CKD (eGFR 20 mL/ /min/1.73 m^2), after numerous PCIs, after CRT-D implantation, was readmitted due to acute heart failure and electrical storm. Myocardial infarction was excluded. Echocardiographic assessment revealed an LVEF of 20% and a significantly dilated left ventricle (LVEDD 78 mm). The patient was treated medically, requiring bilateral thoracentesis. After stabilization, due to recurrent ventricular tachycardia (VT), the patient was scheduled for coronary angiography. Significant LAD restenosis was observed (Fig. 4A). After the procedure, further deterioration of renal function occurred (creatinine level 202 → 287 μmol/L) — treated with i.v. fluids. The patient was discussed by the Heart Team and qualified for zero contrast PCI. LAD was wired with a hydrophobic wire. As this was restenosis, an additional side branch wiring was not necessary. IVUS confirmed the presence of significant restenosis with MLA of 2.2 mm^2 (Fig. 4B). High-pressure dilation of the restenosis with a non-compliant 3.0 balloon was performed, followed by 3.0 paclitaxel eluting balloon inflations (Fig. 4C). Control IVUS revealed proper stent apposition and lumen dilation (postprocedural MLA of 4.5 mm^2, Fig. 4D–F). No recurrence of VT was observed. The creatinine titers returned to prior levels (207 μmol/L).

The patients were observed for a follow-up period of 12 months. Patients no. 1–3 had uncomplicated follow-up, not requiring further revascularization and/or renal replacement therapy. Patient no. 4 had recurrent episodes of acute heart failure and subsequently died after 3 months and 9 days from index procedure, also with no need for further revascularization or renal replacement therapy.

This primary experience shows, that significant experience in both PCI and IVUS can result in safe and effective IVUS-guided PCI procedures. The acceptance of ultra-low contrast quantity of contrast for final assessment may facilitate the introduction of these procedures in centers aiming to implement a similar protocol for patients at extreme risk of contrast induced nephropathy.

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Surgical correction of aortic regurgitation using a HAART 300™ rigid aortic ring: A novel method to standardize aortic valve repair

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Due to the lack of reproducible surgical repair techniques which yield good long-term results, tricuspid aortic valve regurgitation, until recently, has been managed primarily with replacement of the valve with mechanical or biological prostheses [1]. Therefore, cardiac surgeons have been searching for repair techniques which enable the preservation of native valve for many years [2, 3]. Long-term research showed that a key factor facilitating permanent repair of the aortic valve, similar to mitral or tricuspid valves, was stabilization of the annulus. Stabilization prevents the recurrence of aortic regurgitation due to subsequent dilatation of the aortic root [4, 5]. The recently designed HAART 300™ (BioStable Science and Engineering, Austin, TX) rigid ring implanted under aortic valve cusps (Fig. 1A, B) could be a significant achievement in the area of aortic valve stabilization. The first four cases of HAART 300™ aortic ring implantation in Poland have recently been published [6].

In the present study, early results of tricuspid aortic valve repair with the use of HAART 300™ aortic ring were reviewed in a cohort of 15 patients.

Patients with moderate and severe aortic valve regurgitation were referred for aortic valve repair with the use of HAART 300™ aortic ring, according to European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines on valvular heart disease, published in 2012 and 2017 [7, 8].

The following criteria precluded HAART 300™ aortic ring implantation: bicuspid aortic valve, infective endocarditis and significant cusp fenestrations or calcifications.

Patients with coexisting diseases requiring complex surgical procedures or reparable leaflet defects were not excluded.

Prior to surgery transthoracic echocardiography (TTE) was performed. The left ventricular end diastolic volume, left ventricular end systolic volume and left ventricular ejection fraction were calculated. The dimensions of left ventricular outflow tract, aortic root and ascending aorta were measured. The mitral and tricuspid valves were assessed. Computed tomography angiography of thoracic aorta was performed in patients with aortic dilatation to extend diagnostics and plan the scope of the operation.

When referring patients for repair surgery, El-Khoury classification [2] was used to define the type of aortic regurgitation.

With the use of intra-operative transesophageal echocardiography (TEE), long and short axis views were acquired for measurements and assessment of the aortic valve. Measurements included: aortic annulus (aorto-ventricular junction), aortic root, sinotubular junction, and the diameter of ascending aorta.

Aortic regurgitation grade was established according to a four-point scale: 0 — none or trivial,

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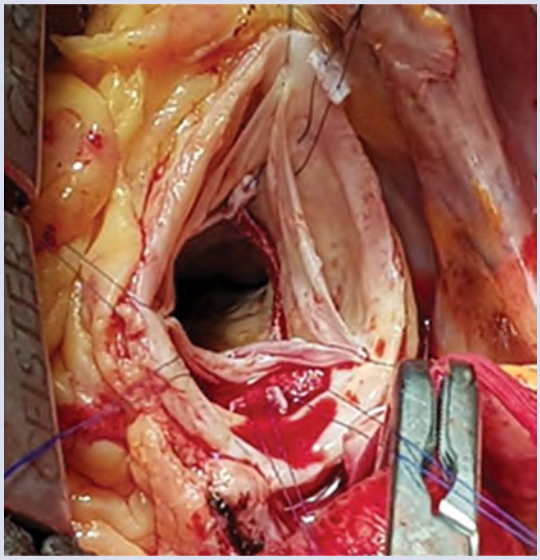
A

B



C

Parameter	Pre-operative TTE	Intra-operative TEE	7 days TTE	Follow up TTE
IA grade [number of patients]:				
0	0	9	8	8
I	0	6	6	5
II	0	0	1	1
III	5	0	0	0
IV	10	0	0	1
LVOT [mm]	23 ± 3	23 ± 3	22.6 ± 2.5	23.3 ± 3.1
Annulus [mm]	25.5 ± 2.2	23 ± 2	23 ± 2	23 ± 2
Aortic root [mm]	46 ± 8.5	36.4 ± 4.4	37 ± 4.4	39.1 ± 5.09
Ascending aorta [mm]	46 ± 10	32.4 ± 3.9	33.2 ± 3.9	34.9 ± 4.2
Ejection fraction [%]	48.3 ± 9	47.3 ± 9.6	47.4 ± 12.4	49.3 ± 7.6
LV EDV [mL]	167 ± 10	–	–	162.1 ± 12
LV ESV [mL]	85.6 ± 8.5	–	–	96.8 ± 10

Figure 1. A. Rigid ring HAART 300™ (BioStable Science and Engineering, Austin, TX); **B.** The ring HAART 300™ underneath the cusp attachment; **C.** Echocardiographic data; IA — aortic regurgitation; LVOT — left ventricular outflow tract; LV EDV — left ventricular end diastolic volume; ESV — left ventricular end systolic volume; TEE — transesophageal echocardiography; TTE — transthoracic echocardiography.

I — mild, II — moderate, III — moderately severe, IV — severe [9].

For correction and stabilization of the aortic valve, a HAART 300™ (BioStable Science and Engineering, Austin, TX) was used [10]. The ring is made of a titanium stent covered with a dacron material, having an elliptic shape and three 10-degree outwardly flaring posts. The ring is available in four different sizes: 19, 21, 23, and 25 mm. The result of aortic valve repair was assessed intra-operatively by measuring the effective coaptation height with Schaffers callipers, aiming at a minimum of 9 mm. The quality of repair was also assessed by echocardiography, which was performed intra-operatively (TEE), on the 7th postoperative day (TTE), and subsequently at 6 month intervals. Effective valve repair was defined as no, trivial or mild central regurgitation.

Fifteen patients aged between 53 and 73 (mean 65.6 ± 5.8) years, including 13 (86.6%) males underwent aortic valve repair with the use of HAART 300™ aortic ring during a period from September 2016 to January 2019. Eleven (73.3%) patients required cusp plication, 9 (60%) patients — replacement of the aorta (including 4 [26.6%] with co-existing aortic root aneurysm in whom

aortic root remodeling was performed), 2 (13.3%) patients required mitral valve repair, 4 (26.6%) patients recieved simultaneous coronary artery bypass grafts.

Intra-operative TEE assessment revealed a perfectly competent aortic valve after repair in 9 (60%) patients, mild central regurgitation in 5 (33.3%) patients, and mild non-central regurgitation in 1 (6.7%) patient (Fig. 1C). In 1 case moderate central aortic regurgitation was revealed in TEE which was related to excessive leaflet plication. During the additional period of aortic cross clamping, the single plication stitch was removed from every cusp resulting in trivial aortic regurgitation.

One patient required reoperation for bleeding. No neurological or thromboembolic complications were noted. On day 7 after surgery, 1 patient required laparotomy due to gastric ulcer perforation. Mean Intensive Care Unit stay was 3.2 ± 1.5 days. The patients were discharged on day 8.1 ± 3.2 post-op.

The TTE performed on day 7 after surgery revealed no aortic regurgitation in 8 (53%) patients, 6 (40%) patients presented with mild, central aortic regurgitation, and 1 (6.7%) patient progressed from mild to moderate non-central regurgitation (Fig. 1C).

Complete follow-up was available in all patients, ranging from 2 months to 30 months after surgery (mean 257 ± 194 days). No deaths were noted during the follow-up period. Competent aortic valve was revealed in 8 (53%) patients and 5 (33%) patients presented with mild, central aortic regurgitation. In 1 (6.7%) patient moderate aortic regurgitation was noted on echocardiography performed 18 months after surgery (Fig. 1C). This was associated with the increase of aortic root diameter from 42 mm on discharge to 52 mm and apparent non-coronary cusp restriction. Finally, in 1 patient moderate aortic regurgitation on discharge progressed to severe within half a year and this patient underwent a redo aortic valve replacement with bioprosthesis.

Implantation of the HAART 300™ ring is a simple and reproducible aortic annuloplasty and annular stabilization technique. This method markedly simplifies the aortic valve repair procedure, and in the early experience of the documented operators, is associated with good short-term results. It provides durable protection for patients preventing recurrent aortic valve regurgitation. It does not preclude simultaneous employment of repair techniques on aortic valve cusps nor the aortic valve sparing procedure in case of coexisting root aneurysm. Moreover, this technique does not increase intra-operative mortality, nor the rate of cardiovascular complications. It seems that the presented method of repair can be used in patients with tricuspid aortic valve regurgitation caused by one or more of the following conditions: aortic annulus dilatation, leaflet prolapse, root and/or ascending aorta aneurysm.

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Conflict of interest: J. Scott Rankin is the creator of the HAART 300™ ring and a consultant in the company BioStable Science and Engineering, Austin, TX.

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BRIEF COMMUNICATION

Computed tomographic quantification of periaortic adipose tissue volume as a correlate of cardiovascular disease

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The accumulation of adipose tissue has long been thought of as a risk factor for cardiovascular disease (CVD) [1]. However, the dynamic effects in metabolic homeostasis and pathology are still being discovered [2]. The complexity of factors associated with obesity including adipokines associated with various adipose tissue depots is frequently overlooked [3]. Intuitively, one of these depots, perivascular adipose tissue (PVAT), is likely contributing to the development and/or progression of CVD given its proximity to arterial vasculature. A subset of PVAT that surrounds the coronary arteries, epicardial fat, has been well studied in the development of coronary artery disease [4]. Another subset of PVAT, periaortic adipose tissue has also been implicated in CVD, however, previous studies have limited their investigation to a specific population, unique depots, or a single CVD [5–7]. Herein, the current study describes the quantification of periaortic adipose tissue volume in both the thoracic and abdominal regions in a unique population and correlates this value to specific measures of CVD.

Once the study protocol and procedures were approved by the University of Cincinnati Institutional Review Board (IRB#2013-8286), An electronic medical record was queried for patients who obtained non-contrasted computed tomography (CT) scans of their chest and/or abdomen over a 2-year period. These deidentified records were reviewed to verify subjects met inclusion/exclusion criteria which were broad, allowing for a diverse patient population. Inclusion criteria included 18 years of age or older and non-contrasted CT scan of chest and/or abdomen. Exclusion criteria where limited to variables that would compromise the measurement of the periaortic tissue volume including previous aortic surgery, gross anatomical anomalies (including trauma) or the use of contrast as the increased attenuation within the lumen would alter the radiodensity of the surrounding tissue.

After appropriate subjects were identified, abdominal and thoracic periaortic adipose tissue volume was quantified in a similar manner as previously conducted [5]. The segment of thoracic aorta that was measured started at the level of the pulmonary artery bifurcation and extended 70 mm inferiorly. The abdominal aortic segment was measured starting at the level of the aortic bifurcation and extended superiorly 40 mm. Adipose tissue was selectively gated using a window width of –195 to –45 Hounsfield units (HU) with a center of –120 HU [5]. The region of interest was encircled with a diameter being 10 mm larger than the anteroposterior aortic diameter and then adipose tissue was selectively gated [6]. The degree of aortic calcification was determined by the volume of hyperattenuation with a minimum of three connected pixels with attenuation over 130 HU [5].

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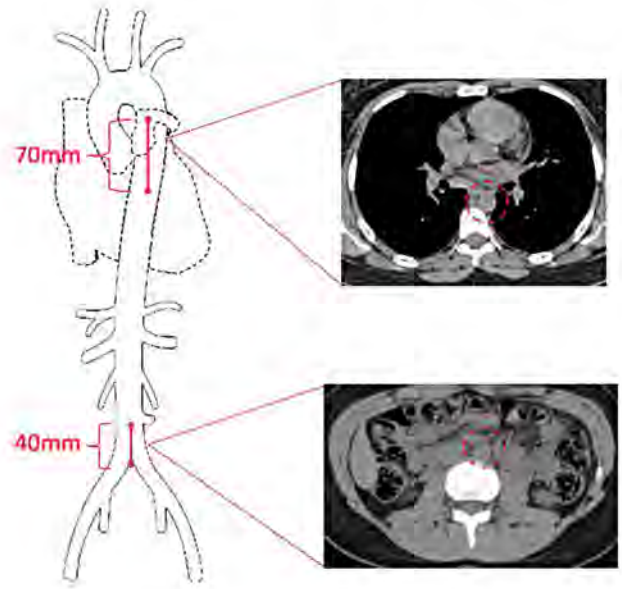
		Total (n=200)	
Age - mean (SD)		52	(15)
Race			
	Caucasian	106	53.0%
	African American	87	43.5%
	Hispanic	4	2.0%
	Other	2	1.0%
	Asian	1	0.5%
Male		128	64.0%
Past Medical History and Medications			
	Diabetes mellitus	47	23.5%
	Hypertension	89	44.5%
	Hyperlipidemia	38	19.0%
	Coronary Artery Disease	28	14.0%
	Congestive Heart Failure	32	16.0%
	Renal Failure	31	15.5%
	Anti-hypertensive Medication	90	45.0%
	Lipid Lowering Agents	42	21.0%
	Aspirin	46	23.0%
	Plavix	6	3.0%
	Anticoagulants	18	9.0%
	Insulin	16	8.0%
	Tobacco Use	100	50.0%
	Alcohol Use	51	25.5%
	Cocaine Use	8	4.0%



		Thoracic Periaortic Adipose Volume	Thoracic Aortic Dimension	Thoracic Aortic Calcification	Abdominal Periaortic Adipose Volume	Abdominal Aortic Dimension	Abdominal Aortic Calcification
Total							
Thoracic Periaortic Adipose Volume	Pearson Correlation	1	0.480	0.117	0.683	0.348	0.097
	Sig. (2-tailed)		0.000	0.114	0.000	0.009	0.478
	N	184	184	184	56	56	56
Thoracic Aortic Dimension	Pearson Correlation	0.480	1	0.156	0.501	0.693	0.123
	Sig. (2-tailed)	0.000		0.034	0.000	0.000	0.366
	N	184	184	184	56	56	56
Thoracic Aortic Calcification	Pearson Correlation	0.117	0.156	1	0.000	0.021	0.489
	Sig. (2-tailed)	0.114	0.034		0.999	0.875	0.000
	N	184	184	184	56	56	56
Abdominal Periaortic Adipose Volume	Pearson Correlation	0.683	0.501	0.000	1	0.581	-0.028
	Sig. (2-tailed)	0.000	0.000	0.999		0.000	0.817
	N	56	56	56	72	72	72
Abdominal Aortic Dimension	Pearson Correlation	0.348	0.693	0.021	0.581	1	0.103
	Sig. (2-tailed)	0.009	0.000	0.875	0.000		0.392
	N	56	56	56	72	72	72
Abdominal Aortic Calcification	Pearson Correlation	0.097	0.123	0.489	-0.028	0.103	1
	Sig. (2-tailed)	0.478	0.366	0.000	0.817	0.392	
	N	56	56	56	72	72	72

Figure 1. Summary of patient demographics, methods and results. **Top left**: Demographic information of the study population; **Top right**: Representative diagram of computed tomographic methods and periaortic adipose tissue volume quantification; **Bottom**: Summary of the Pearson correlations and significance of periaortic adipose tissue volume in the thoracic and abdominal regions to aortic dimension and aortic calcification in the same regions.

The aortic dimension was calculated as the mean of the anteroposterior and transverse diameter of the aorta from the outer edge to the outer edge at the level of the right pulmonary artery for the thoracic aorta and 5 cm above the aortoiliac bifurcation for the mid-abdominal aorta. A representation of the regions can be seen in Figure 1 (top right). All scans were performed on a Siemens SOMATOM scanner. Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools [8]. All statistical analyses were conducted using SPSS 24.0 (IBM Corporation, Armonk, NY). Data is as the median with minimum and maximum reported. Pearson correlation was calculated between periaortic adipose tissue volume in the thoracic and abdominal regions with aortic dimension and calcification in the same regions.

Two hundred cases were reviewed, 184 non-contrast chest CTs and 72 non-contrast abdominal CTs. A detailed list of this demographic information is shown in Figure 1 (top left). Thoracic perivascular adipose tissue volume (PVAT) correlated the best with abdominal PVAT with an r statistic of 0.683 ($p < 0.000$). Thoracic PVAT also correlated well with thoracic aortic dimension ($r = 0.480$; $p < 0.000$). Similarly, abdominal PVAT also correlated with thoracic and abdominal aortic dimension ($r = 0.501$; $p < 0.000$ and $r = 0.581$; $p < 0.000$, respectively). A summary of the data can be seen in the table at the bottom of Figure 1.

In the current study, two distinct regions of the aorta, thoracic and abdominal, were analyzed to quantify PVAT volume via selective gating for adipose tissue. These values were correlated with surrogates of CVD including aortic dimension and aortic calcification. It was found that PVAT volume correlated well with the aortic dimension in both thoracic and abdominal regions. This data is congruent with previously publish studies investigating similar endpoints including CVD risk factors and abdominal aortic aneurysms [5–7].

In conclusion, periaortic adipose tissue volume was higher in individuals with CVD in both the thoracic and abdominal regions, albeit more so around the thoracic aorta. While this association is significant, the direct clinical relevance of these specific depot volumes is still to be determined; therefore, further work needs to be conducted to investigate the association of periaortic adipose volume with cardiovascular outcomes.

Conflict of interest: None declared

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Transvenous extraction of His bundle pacing lead: New challenge in the field of lead extraction

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A 66-year-old male with ischemic heart disease, hypertrophic cardiomyopathy, left ventricular systolic dysfunction with ejection fraction of 40%, chronic heart failure with frequent exacerbations and permanent atrial fibrillation was considered for implantation of implantable cardioverter-defibrillator with His bundle pacing (ICD-DR + HBP). The procedure was undertaken 11 months ago and following failed His bundle pacing implantation a dual-site right ventricular pacing was undertaken. The aim of the index hospital admission was to remove the present pacing system and establish His bundle pacing with biventricular pacing and defibrillator (CRT-D + HBP). Present ICD-DR system consisted of defibrillator lead and lumenless lead designed for His bundle pacing fixed in the intraventricular septum (Fig. 1A). During transvenous lead extraction, contrast venography of the ipsilateral arm venous confluence revealed complete occlusion of the left subclavian vein. In order to overcome this obstruction and regain venous access it was decided to target the removal of the lumenless lead. Given the relatively short lead dwell time, its position was secured by gripping the lead in the right atrium with a Needle Eye Snare, introduced via the femoral approach (Fig. 1B). Then, the lead was successfully and safely extracted via the access site with Byrd dilators (COOK MEDICAL LLC Bloomington, USA). Finally, the ICD lead was extracted and a new CRT-D + HBP system was implanted (Fig. 1C). The procedure was uneventful.

According to available literature, the present case is the first reported description for extraction of a lumenless lead dedicated for His bundle pacing facilitated by stabilization from the femoral approach to overcome complete venous occlusion.

Conflict of interest: None declared

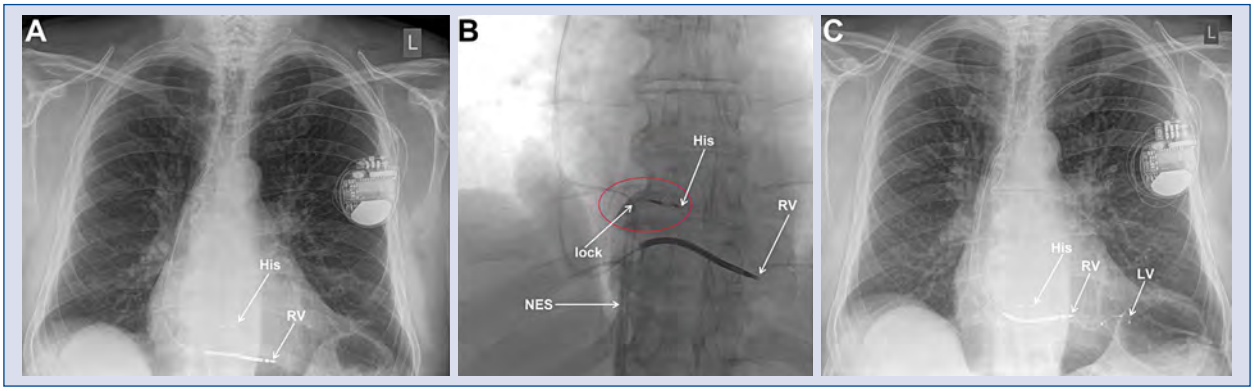

Figure 1. A. Initial ICD-DR system consisted of defibrillator lead Medtronic Sprint 6935M62 (RV) and Medtronic 3830-74cm lumenless lead designed for His bundle pacing (His) connected to atrial channel and fixed in intraventricular septum; **B.** Medtronic 3830-74cm lumenless lead (His) grasped (lock) in the right atrium with Needle Eye Snare (NES), (COOK MEDICAL LLC Bloomington, USA) introduced via femoral approach; **C.** The new CRT-D + HBP system at discharge; LV — left ventricular lead.

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Acute limb ischemia due to intracardiac myxoma in a patient with atrial fibrillation

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An 82-year-old female with a history of paroxysmal atrial fibrillation was hospitalized due to exertional dyspnea which had lasted for 2 weeks, with no peripheral edemas. The transthoracic echocardiography (TTE) revealed a mass in the left atrium (1.6 × 2.2 cm) with connective tissue peduncle attached in the area of fossa ovalis in the intraarterial septum (Fig. 1A, B). The transesophageal echocardiography (TEE) confirmed mobile mass in the left atrium suggesting atrial myxoma (Fig. 1C). Cardiac myxoma removal was offered to the patient, but the patient did not agree to the procedure and was discharged.

Twenty hours after the discharge, the patient presented again in the Emergency Room due to pulmonary edema in the course of rapid atrial fibrillation and symptoms of acute left limb ischemia (no femoral arterial pulse, coldness, cyanosis, and paralysis). TTE showed no myxoma mass in the left atrium. Only connective tissue peduncle remained in the area of fossa ovalis in the intraarterial septum (Fig. 1D, E). Vascular ultrasonography was performed and demonstrated complete occlusion of the left femoral artery. The mass was recovered via percutaneous intervention and examination confirmed it to be myxoma. Revascularization was provided immediately and ensured no vascular or neurological defects. Subsequent TEE revealed a small residue of connective tissue peduncle in the area of fossa ovalis (Fig. 1F). The patient was discharged without complications.

Myxomas can manifest in miscellaneous ways. This might include a fever of unknown origin, acute myocardial infarction, stroke, paraneoplastic effects (including vasculitis, hematological changes, constitutional symptoms). While ischemic symptoms are relatively frequent, they are more often associated with a blood clot mobilization. Tumor embolization in peripheral limb circulation is extremely rare. Nevertheless, myxomas must be kept in mind as one of the probable causes of thromboembolic complications in various vascular sites.

Conflict of interest: None declared

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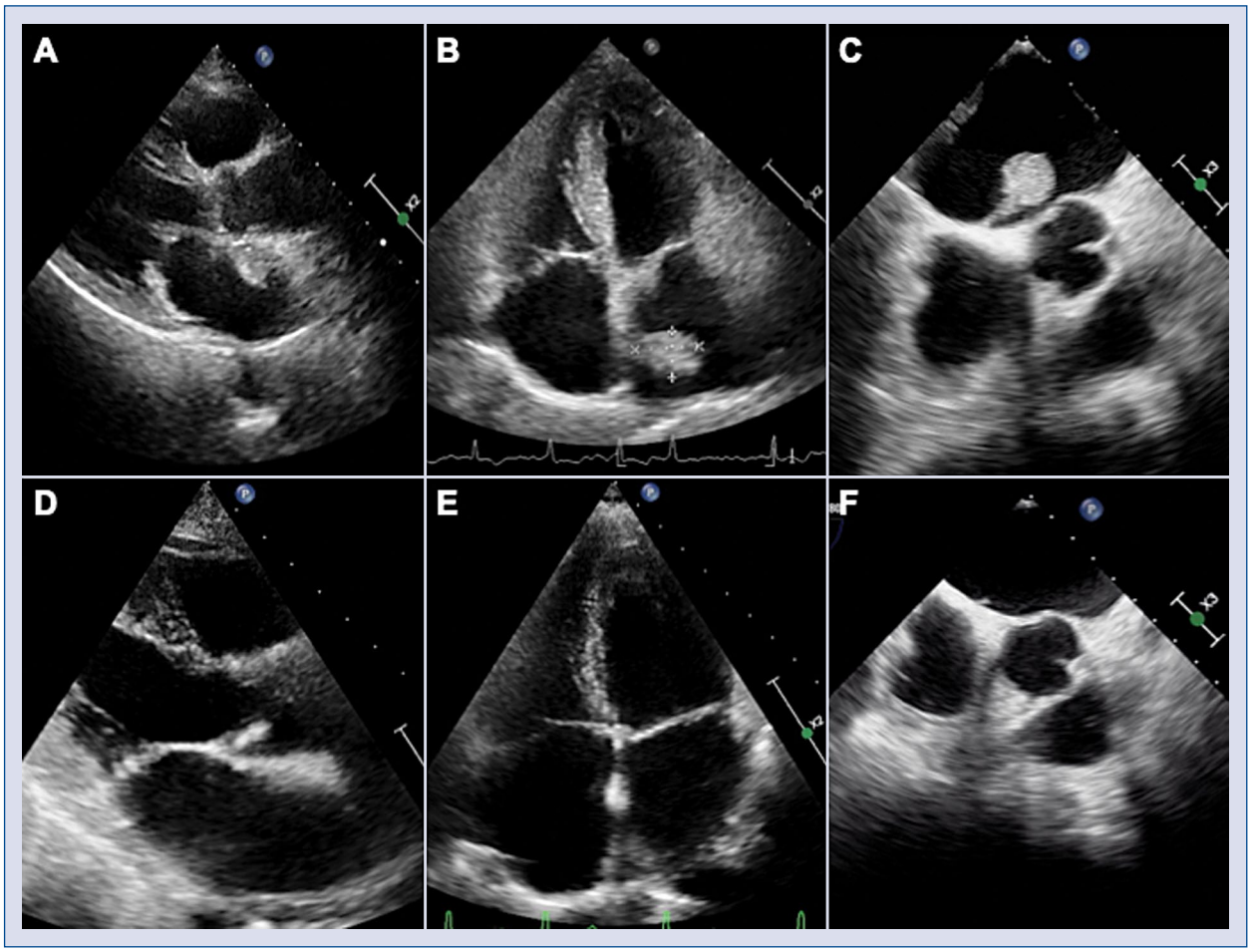

Figure 1. The echocardiography studies; **A.** Transthoracic echocardiography (TTE) on admission — parasternal long axis view; **B.** Transesophageal echocardiography (TEE) on admission — 4-chamber apical view; **C.** TEE on admission; **D.** TTE after vascular intervention — parasternal long axis view; **E.** TTE after vascular intervention — 4-chamber apical view; **F.** TEE after vascular intervention.

VIA MEDICA

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Combined bilateral giant coronary aneurysm and coronary fistula to coronary sinus

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The prevalence of giant coronary aneurysm and fistula in coronary angiogram is 0.02–0.2% and 0.2–2%, respectively. Consequently, combined giant coronary aneurysm and fistula are extremely rare abnormalities of the heart.

A 65-year-old male was coincidentally demonstrated to have abnormalities surrounding the heart by chest computed tomography. The patient had continued medical follow-up because he was asymptomatic, but ejection fraction and left ventricle size had gradually worsened over the years. Transthoracic echocardiography showed multiple abnormal cavities in both the right and left atria (Fig. 1A). Color Doppler in transesophageal echocardiography showed continuous color signal and flow in the abnormal cavity (Fig. 1B, C). In addition, coronary computed tomography revealed a giant bilateral coronary aneurysm (Fig. 1D). Coronary angiography confirmed a huge aneurysm at the left circumflex and right coronary artery with a fistula communicating with the coronary sinus (Fig. 1E, F). The pulmonary blood flow to systemic blood flow (Qp/Qs) ratio measured using right heart catheterization was 1.63. The left to right shunt ratio was 39%. Hence, radical surgery was performed by closure of the arterio-venous fistula and ligation of the bilateral abnormal arteries without a coronary artery bypass graft operation.

Coronary aneurysm and fistula are associated with increased risk of cardiac events, such as cardiac rupture, coronary ischemia, arrhythmia, and thromboembolism. Therefore, it is necessary to establish an immediate diagnosis using multimodality imaging and initiate treatment. If the patient is previously asymptomatic, regular follow-up to check cardiac function and cardiac load is crucial in determining the timing of surgical intervention.

Conflict of interest: None declared

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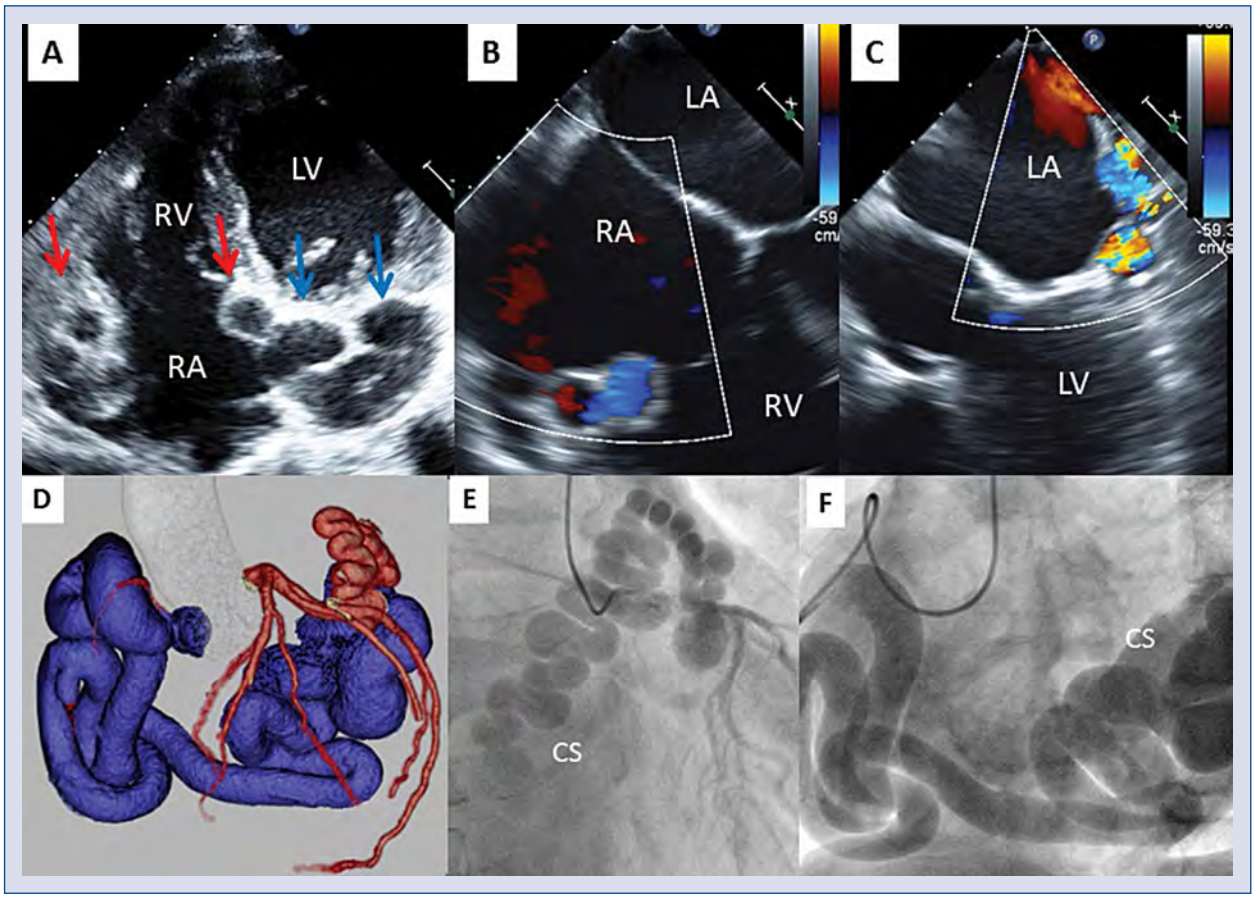

Figure 1. A. Transthoracic echocardiography showed multiple abnormal cavities at both the right atrium (RA; red arrow) and left atrium (LA; blue arrow); **B, C.** Transesophageal echocardiography with color Doppler revealed abnormal flow in cavities around the RA and LA; **D.** Three-dimensional reconstruction of coronary computed tomography showed a bilateral giant coronary aneurysm; **E, F.** Coronary angiography revealed a combined giant coronary artery aneurysm with fistula communication to the coronary sinus (CS); LV — left ventricle; RV — right ventricle.

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Contrast-enhanced echocardiography to rule-out active intrapericardial bleeding following coronary artery perforation

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A 66-year-old man underwent percutaneous coronary intervention on a stenosis of the ramus intermedius for worsening dyspnea and positive exercise testing (Fig. 1A). Weight-adjusted heparin (a total of 8000 IU) was administered as per standard practice. Two drug-eluting stents were implanted at the ostial and proximal segments of the vessel. Final angiography demonstrated a flow-limiting dissection, which was covered with a stent. Upon subsequent contrast injection, an Ellis type 3 coronary artery perforation (CAP) was observed (Fig. 1B). A balloon was inflated proximal to the CAP. Severe hypotension arose, and transthoracic echocardiogram (TTE) showed cardiac tamponade. Pericardiocentesis was performed, with complete resolution of the effusion. A right femoral artery access was secured, and a second guide catheter engaged the left coronary artery (ping-pong technique) (Fig. 1C). Three 3-mm MicroNester 18 (Cook Medical, Bloomington, Indiana) coils were delivered to seal the perforation through the second guide catheter (Fig. 1D, E). The patient was transferred to the intensive care unit. No anticoagulation reversal with protamine was deemed necessary since CAP sealing with coils was considered adequate. Two hours later, de novo formation of pericardial effusion was documented, and additional 150 mL of blood were extracted from the pericardial drainage. Suspecting active intrapericardial bleeding, a new coronary angiogram was performed, which did not identify bleeding from the CAP (Fig. 1F). Contrast-enhanced TTE was performed after intravenous injection of 10 mL of sodium hexafluoride-based ultrasound contrast (SonoVue, Bracco Imaging, San Donato Milanese, Italy). Echocardiographic contrast is strictly intravascular, and is visualized as hyperechoic spots using dedicated imaging protocols. The identification of contrast in the pericardial space implies active extravasation. No evidence of contrast in the pericardial space was detected in our patient, ruling out active bleeding (Fig. 1G, H). The patient remained subsequently stable until hospital discharge. The **Supplementary Movie 1** presents the key passages of this case, including CAP management and contrast-enhanced echocardiography.

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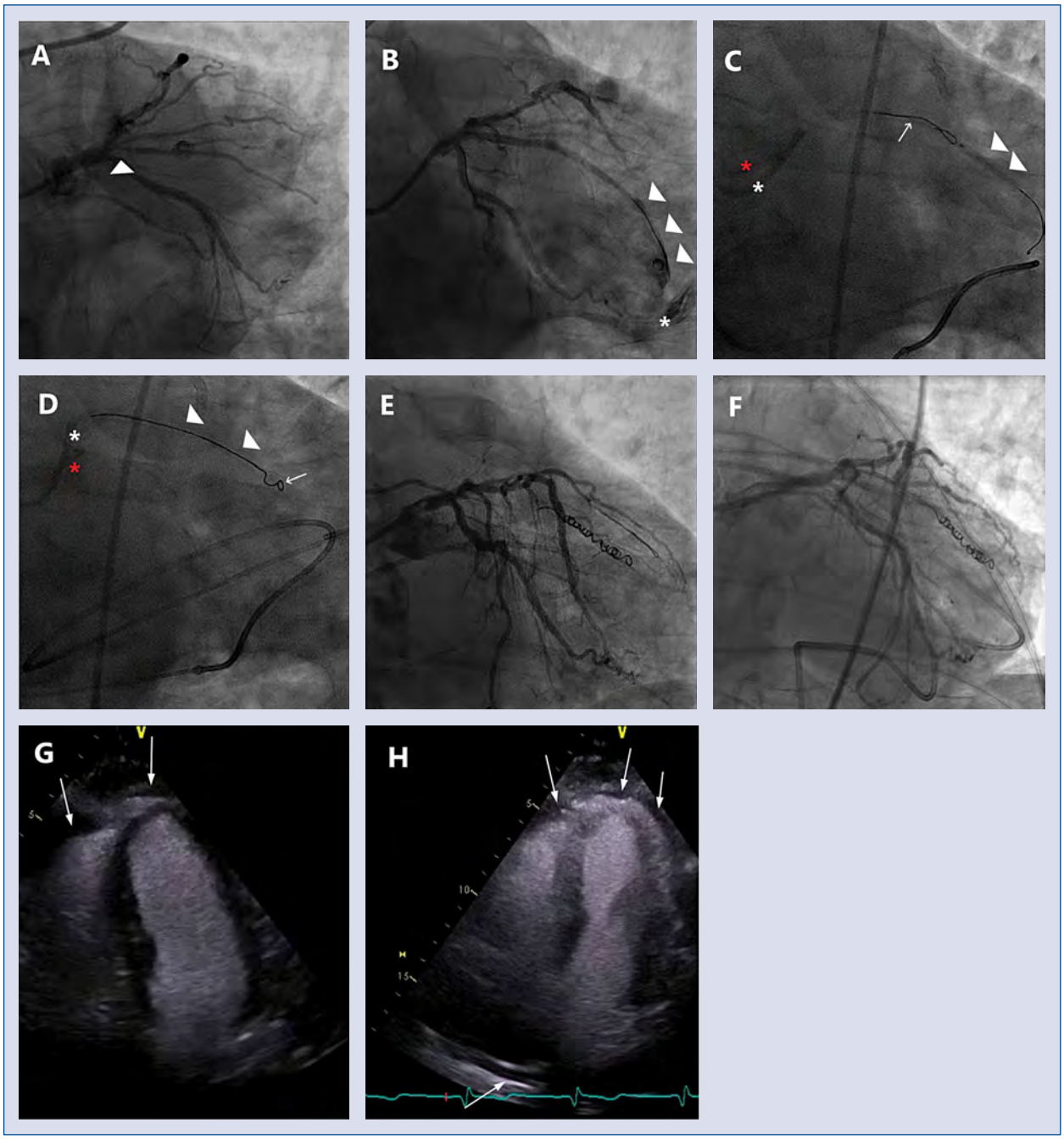

Figure 1. Contrast-enhanced echocardiography to rule-out active intrapericardial bleeding following coronary artery perforation. **A.** Critical stenosis of the ramus intermedius. The arrowhead points at the site of the stenosis; **B.** Ellis type 3 coronary artery perforation (CAP). The arrowheads point at the site of the perforation, while the asterisk marks contrast extravasation into the pericardial space; **C.** Ping-pong technique to achieve balloon occlusion and subsequent CAP embolization. The arrowhead points at the balloon inflated proximally to the CAP through the first guiding catheter. The arrow points at the microcatheter and guidewire through the second guiding catheter. Red asterisk: guiding catheter via the left radial access; white asterisk: guiding catheter via the right femoral access; **D.** Coil deployment in the ramus intermedius. Arrowheads: microcatheter. Arrow: coil; **E.** Complete deployment of the coils and complete sealing of the CAP; **F.** Second-look coronary angiography, showing no active bleeding from the CAP; **G.** Transthoracic contrast-enhanced echocardiogram (4-chamber view), showing no contrast in the pericardial space (arrows); **H.** Transthoracic contrast-enhanced echocardiogram (right ventricle-focused 4-chamber view), showing no contrast in the pericardial space (arrows).

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Congenital right subclavian artery-superior vena cava fistula recognized by transthoracic echocardiography

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A 16-year-old girl presenting with dyspnea and chest pain was admitted to the documented institution. On physical examination, a grade 3/6 continuous murmur was audible on the right sternal border at the 2nd and 3rd intercostal spaces. Standard transthoracic echocardiography (TTE) images via conventional acoustic windows revealed mildly dilated right atrium and right ventricle, mild tricuspid regurgitation and mild pulmonary hypertension. This could not explain the murmur. However, imaging in unconventional right parasternal windows, which was close to the site of the murmur, revealed a dilated right subclavian artery (RSA) with a 7-mm fistula to the superior vena cava (SVC) (Fig. 1A–C; **Suppl. Video 1**). Continuous-wave Doppler showed flow signals measuring 3.5 m/s continuously moving from the RSA into the SVC throughout the cardiac cycle, consistent with the fistula (Fig. 1D). Subsequent computed tomographic angiography confirmed a congenital arteriovenous fistula (AVF) between the RSA and the SVC (Fig. 1E, F). The patient was referred for transcatheter occlusion of the fistula. The arterial angiography showed contrast material leaking from the RSA into the SVC (Fig. 1G). The fistula was successfully closed using a 10/12 mm Amplatzer Ductal Occluder (Fig. 1H). The post-procedure TTE revealed no residual shunt (Fig. 1I). The patient dramatically improved clinical symptoms and made an uneventful recovery after occlusion.

Congenital AVFs are very rare and are usually diagnosed by angiography. Presented herein, an adolescent patient with a congenital RSA-SVC fistula was first recognized by TTE. The present case highlights the need for clinical suspicion of congenital AVFs in unusual locations when evaluating a patient with unexplained cardiac murmur.

Conflict of interest: None declared

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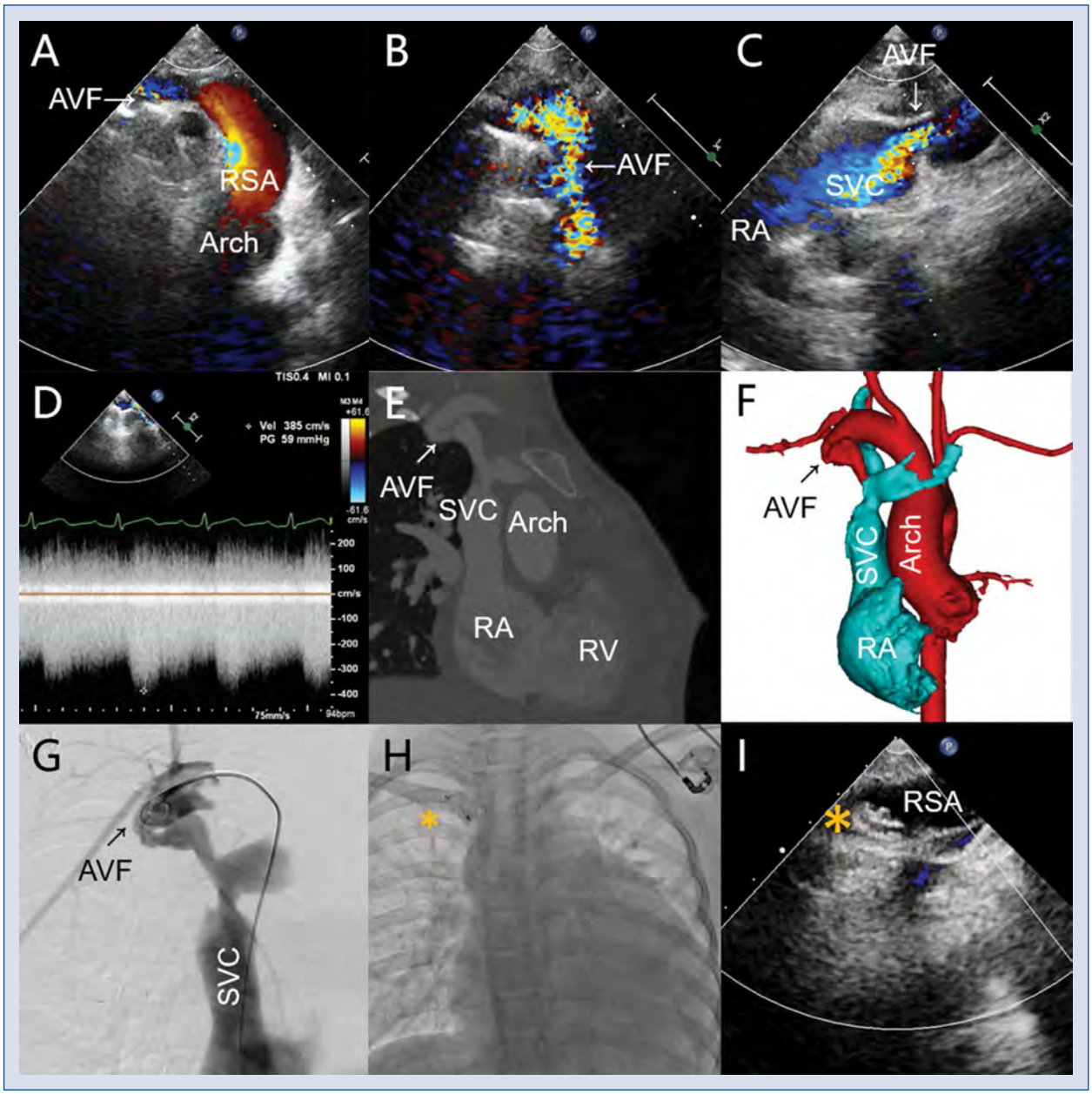

Figure 1. A–C. Transthoracic echocardiography shows the arteriovenous fistula (AVF, arrow) between the right subclavian artery (RSA) and the superior vena cava (SVC); **D.** Color Doppler guided continuous-wave Doppler interrogation of the fistula shows high velocity flow signals moving from the RSA into the SVC throughout the cardiac cycle; **E**, **F.** Computed tomographic angiography and three-dimensional reconstruction shows AVF (arrow); **G.** Arterial angiography indicates contrast material leaking into the SVC through the AVF (arrow); **H.** The fistula is successfully closed using a 10/12 mm Amplatzer Ductal Occluder (asterisk); **I.** Transthoracic echocardiography shows no residual shunt; RA — right atrium; RV — right ventricle.

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An unusual intracardiac foreign body

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A 26-year-old patient, known for HIV and Heroine toxicomania consulted his general practitioner complaining of pain in the right groin since his last IV injection. Groin ultrasound examination demonstrated acute femoral vein thrombosis and a foreign body in the surrounding tissue that an abdominal X-ray identified as a broken needle in projection of the right acetabulum (Fig. 1A). The patient received anticoagulation therapy and it was decided to postpone the needle retrieval. Ten days later, the patient was admitted to the hospital for fever. Enhanced abdominal computed tomography showed bilateral femoral septic thromboses (Fig. 1B) and migration of the needle previously visualized on the abdominal X-ray from the groin region to the right ventricular apex (Fig. 1C). Multiplanar and three-dimensional reconstructions (Fig. 1D) showed that the needle fragment was not free in the ventricular cavity, which was confirmed by unsuccessful percutaneous transcatheter maneuvers to retrieve it. Considering the high risk of cardiac surgery in this patient and the low risk of further distal embolization, a conservative approach was decided for and the patient had an uneventful clinical evolution under antibiotherapy.

Conflict of interest: None declared

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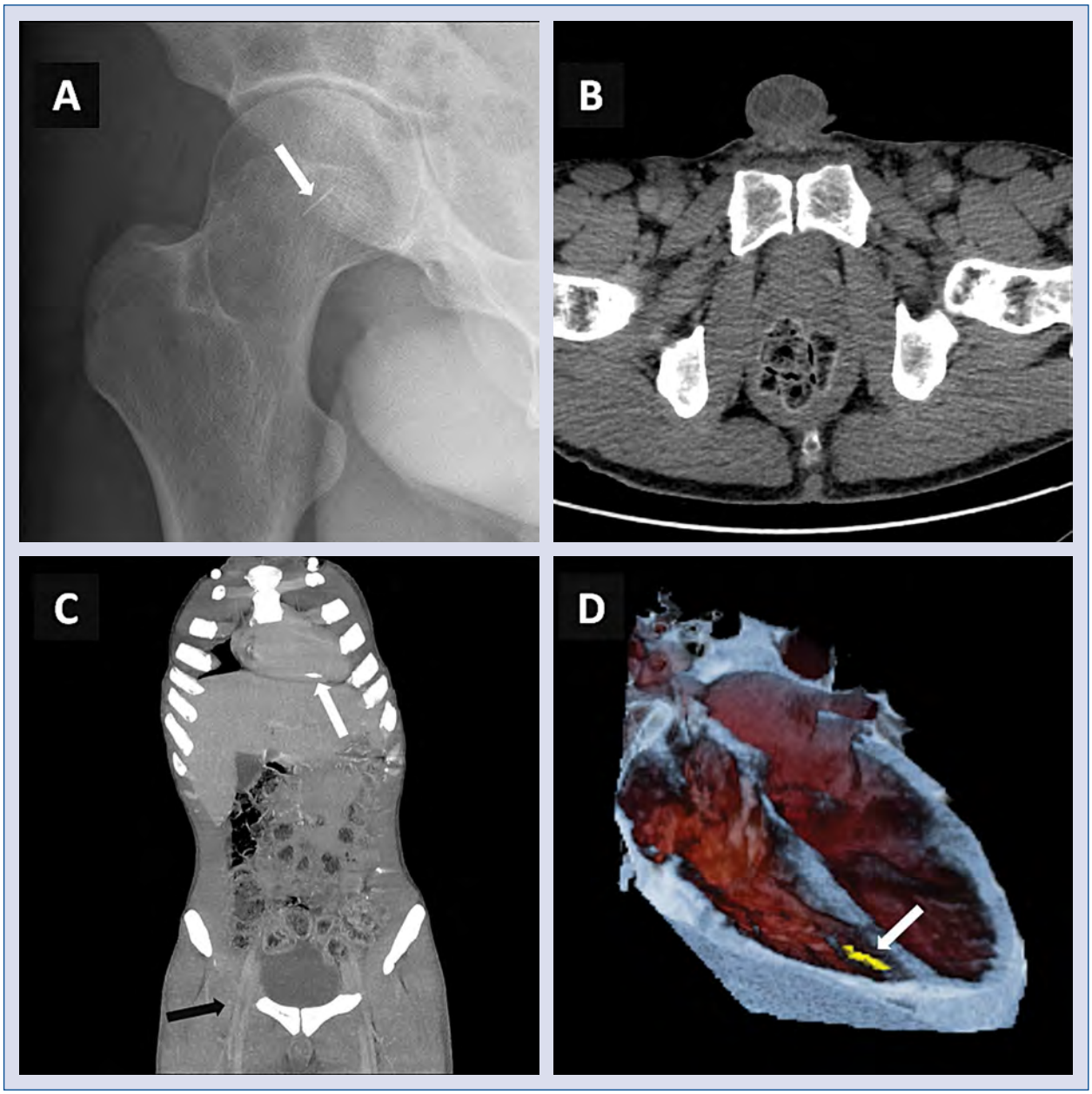

Figure 1. A. Abdominal X-ray demonstrated a broken needle in projection of the right acetabulum; **B.** Enhanced abdominal computed tomography showed bilateral femoral septic thromboses as well as absence of the broken needle previously visualized on abdominal X-ray; **C.** Computed tomography showed presence of the needle in the right ventricular apex; **D.** Multiplanar and three-dimensional reconstructions showed that the needle fragment was not free in the ventricular cavity.