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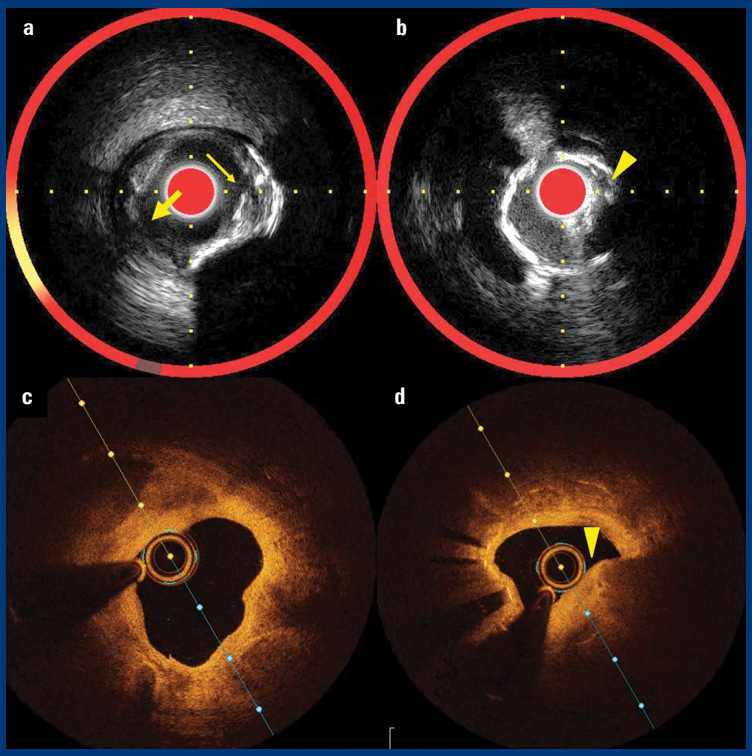

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A systematic review and meta-analysis of effect of vitamin D levels on the incidence of COVID-19

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Abstract

Background: *Coronavirus disease 2019 (COVID-19) is a disease primarily affecting the respiratory tract, however due to the nature of the pathogenesis it is able to affect the whole body. So far, no causative treatment has been found and the main strategy when dealing with COVID-19 relies on widespread vaccination programs and symptomatic treatment. Vitamin D due to its ability to modulate the immunological system has been proposed as a factor playing role in the organism response to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Therefore, we decided to perform this meta-analysis which aimed to establish a connection between vitamin D status and COVID-19 infection.*

Methods: *Study was designed as a systematic review and meta-analysis. PubMed, EMBASE, Web of Science, Cochrane Collaboration Databases and Scopus electronic databases were searched for relevant studies from database inception to May 10th, 2021. Mean differences (MDs) with their 95% confidence intervals (CI) were calculated.*

Results: *Thirteen studies providing data for 14,485 participants met the inclusion criteria. Mean vitamin D levels in SARS-CoV-2 negative patients was 17.7 ± 6.9 ng/mL compared to SARS-CoV-2 positive patients 14.1 ± 8.2 ng/mL (MD = 3.93; 95% CI 2.84–5.02; I^2 = 99%; p < 0.001).*

Conclusions: *Low serum vitamin D levels are statistically significantly associated with the risk of COVID-19 infection. Supplementation of vitamin D especially in the deficiency risk groups is indicated.*
(Cardiol J 2021; 28, 5: 647–654)

Key words: vitamin D, COVID-19, coronavirus disease 2019, SARS-CoV-2, systematic review, meta-analysis

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Introduction

Since the outbreak of the new type of coronavirus disease called novel coronavirus disease 2019 (COVID-19) in Wuhan China in 2019 [1, 2] medical systems all over the world have been under immense pressure, resulting in a rapid increase in the cost of care [3]. The virus infects the host via angiotensin converting enzyme 2 (ACE2) [4]. Due to the fact that ACE2 expression is the highest in the respiratory tract [5] it is the respiratory symptoms that are most prominent in COVID-19, however the ACE2 is expressed in the whole body which explains the multisymptomatic nature of the disease [6]. Due to rapidly spreading nature of the disease and its ability to disorganize the healthcare systems by the increased number of patients requiring intensive care the research was focused on finding a causative treatment. Several drugs have been proposed which include, but are not limited to: hydroxychloroquine [7, 8], janus kinase 2 inhibitor Fedratinib [9] or Remdesmivir [10]. None of which had been able to demonstrate utility in the treatment of COVID-19. Therefore, the efforts were focused on the development of the vaccines and so far, there are several drugs on the market that are able to relieve some of the tension placed on the healthcare system by COVID-19 [11, 12]. However, while vaccination programs are widespread and the number of vaccinated patients grows, the underlying risk factors for the severe course of COVID-19 are still being investigated. So far, several factors were established i.e.: obesity [13], diabetes [14] and smoking [15]. The common denominator for all of these risk factors is the disturbed immunological response which may in fact be the underlying mechanism for the severe course of COVID-19. One of the most common and thoroughly examined causes of immunosuppression is vitamin D deficiency [16]. Vitamin D plays a key role the modulation of the immunological response in both autoimmune and infectious diseases [17], via multiple patterns. Among many others it modulates the maturation of macrophages [18], regulates the T-lymphocyte stimulatory function of antigen-presenting cells [19] and regulates B-lymphocyte proliferation [18]. Therefore, it comes as no surprise that in the era of COVID-19, vitamin D became an object of interest for much research worldwide in terms of preventing the severe course of the disease. We decided to perform this meta-analysis in order to establish a possible link between the levels of vitamin D and COVID-19 infections.

Methods

This trial was prepared following the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [19]. Before commencing the study, analyses methods as well as inclusion and exclusion criteria to be used were agreed upon. Because of the nature of this systematic review and meta-analysis, this study was exempt review by the institutional review board.

Literature search

A systematic review was carried out using PubMed, EMBASE, Web of Science, Cochrane Collaboration Databases and Scopus electronic databases. The most recent search was performed on May 10th, 2021. Titles and abstracts were screened by two authors independently (A.G. and W.G.). All retrieved articles were reviewed by two authors (J.S. and A.G.). Any disagreement was resolved through consensus or, if necessary, by discussion with a third author (L.S.).

The search was performed using the following terms: "25-hydroxyvitamin D" OR "25(OH)D" OR "vitamin D" AND "coronavirus" OR "SARS--CoV-2" OR "COVID-19". A manual search of references listed in reviews and reports was also performed. Only full articles in the English language were considered. All references were saved in an EndNote (End Note, Inc, Philadelphia, PA) library used to identify duplicates.

Inclusion and exclusion criteria

Studies included in this meta-analysis met the following PICOS criteria: (1) PARTICIPANTS; patients > 18 years of age, (2) INTERVENTION; SARS-CoV-2 positive patients, (3) COMPARISON; SARS-CoV-2 negative patients, (4) OUTCOMES; detailed information for vitamin D-3 levels, (5) STUDY DESIGN; randomized controlled trials, quasi-randomized or observational studies comparing cardiac arrest during and before the COVID-19 period for their effects in patients with cardiac arrest. Reviews, simulation trials, animal studies, letters, conference papers and case studies were excluded.

Data extraction

Two reviewers (L.S. and W.G.) independently assessed each article to determine which article met the inclusion criteria. Any disagreements were resolved by consensus with a third reviewer (A.G.). The following information was extracted from each included study: the first author's name,

year of publication, study design, country, sample size, age, gender, vitamin D level in SARS-CoV-2 positive and negative patients.

Quality assessment

Two reviewers (A.G. and H.K.) independently extracted individual study data and evaluated studies for risk of bias. Any disagreements were discussed and resolved in a consensus meeting with the third reviewer (M.M.). The revised tool for risk of bias in randomized trials — RoB 2 tool was used to assess the quality of randomized studies [20]. Moreover, the Robvis application was used to visualize risk of bias assessments [21].

The evaluation consisted of the following domains: confounding, participant selection, classification of interventions, deviation from interventions, missing data, outcome measurement and selection of reported results. Each domain was assessed according to the following scale: serious, moderate and low.

Statistical analysis

All statistical analysis were performed using RevMan v.5.4 (The Cochrane Collaboration, Oxford, Copenhagen, Denmark) and STATA v.16.1. (StataCorp LLC, Texas, USA). All tests were 2-sided and a p value of less than 0.05 was considered as statistically significant. To analyze dichotomous outcomes the Mantel-Haenszel method was used, and results are reported as odds ratios with a 95% confidence interval (CI) and two tailed p values. The inverse variance model with a 95% CI was used to analyze continuous outcome differences and data are reported as the mean difference (MD). Results are presented as risk ratios with 95% CI for dichotomous measures. When the continuous data were reported in the articles as the median and interquartile range, estimated means and standard deviations were calculated using the formula described by Hozo et al. [22].

Data heterogeneity was assessed using the tau-squared and I-squared statistics. Heterogeneity

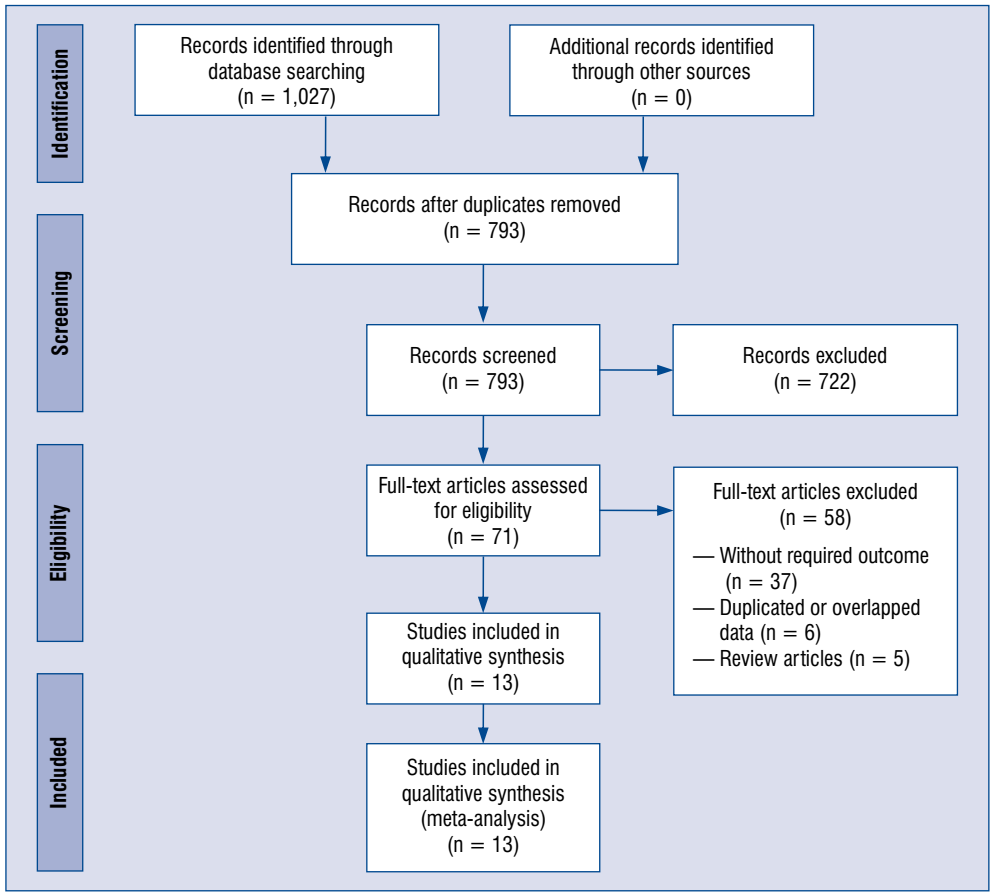

Figure 1. Flow diagram showing stages of the database search and study selection as per Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guideline.

was detected with the chi-squared test with n – 1 degrees of freedom, which was expressed as I^2 [23]. For all analysis a random model was used.

Results

Characteristics of studies included in the meta-analysis

A detailed description of the process of study selection was presented in Figure 1. We found 1,027 potential citations during the search of databases. 234 articles were excluded because they were duplicates, and 722 articles were also excluded because they were unrelated studies. The remaining 71 articles were fully reviewed, and 13 studies providing data for 14,485 participants met the inclusion criteria and were included in the current meta-analysis [24–36]. The details of selected trials are summarized in Table 1. Of those trials, 3 studies were performed in United Kingdom, 2 studies in Iran, 2 in Saudi Arabia, 2 in Italy, and 1 in each of the following countries: Spain, Republic of Korea, Israel and China.

Result of the meta-analysis

Polled analysis of all 13 studies reported vitamin D levels in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) negative versus positive patients is shown in Figure 2. Mean vitamin D levels in SARS-CoV-2 negative patients was 17.7 ± 6.9 ng/mL compared to SARS-CoV-2 positive patients 14.1 ± 8.2 ng/mL (MD = 3.93; 95% CI 2.84–5.02; I^2 = 99%; $p < 0.001$).

The detailed risk of bias abuts the methodological quality of the included studies that are elaborated and summarized in Figures 3 and 4.

Discussion

The number of reports indicating the potential role of vitamin D deficiency in the COVID-19 increases [37]. The potential role in the prevention of a severe course of COVID-19 was further strengthened by the identification of calcitriol (active form of vitamin D) as the regulator of renin-angiotensin system (RAS), of which an overactivation is associated with poor prognosis [38, 39]. Abdollahi et al. [24] found that patients who suffer from vitamin D deficiency are more vulnerable to COVID-19 infection. However, he underlines that the patients suffering from COVID-19 were more likely to be overweight or obese, while obesity is an independent risk factor for a more severe course of the disease [40] it must be noted that patients who are

Table 1. Patient characteristics in included studies.

Study	Country	Study design	SARS-CoV-2 negative group			SARS-CoV-2 positive group		
			Number	Age	Sex, male	Number	Age	Sex, male
Abdollahi et al. 2020	Iran	Case-control study	201	48 ± 16.95	Not specified	201	46.34 ± 13.5	Not specified
Alguwalhes et al. 2021	Saudi Arabia	Retrospective study	72	59.1 ± 16.8	38 (52.8%)	150	55.5 ± 15.8	97 (64.7%)
Al-Daghri et al. 2021	Saudi Arabia	Multi-center case-control study	82	32 ± 13	41 (50.0%)	138	50 ± 13	79 (57.2%)
Baktash et al. 2020	United Kingdom	Prospective cohort study	35	83.4 ± 8.1	15 (42.9%)	70	80.2 ± 8.6	42 (60.0%)
D'Avolio et al. 2020	Italy	Retrospective study	80	72.3 ± 6.1	39 (48.8%)	27	73.5 ± 4.6	19 (70.4%)
Hernández et al. 2020	Spain	Retrospective case-control study	197	61 ± 1.7	123 (62.4%)	216	60.2 ± 4	130 (60.2%)
Im et al. 2020	Republic of Korea	Prospective cohort study	50	52.4 ± 20.2	Not specified	150	52.2 ± 20.7	Not specified
Livingston et al. 2021	United Kingdom	Prospective cohort study	57	68.5 ± 18.1	19 (33.3%)	47	68.6 ± 18.7	20 (42.6%)
Mardani et al. 2020	Iran	Case-control study	60	40.8 ± 15.5	30 (50.0%)	63	43.3 ± 14.5	35 (55.6%)
Merzon et al. 2020	Israel	Population-based study	7,025	47.4 ± 0.2	2,849 (40.6%)	782	35.6 ± 0.4	385 (49.2%)
Raisi-Estabragh et al. 2020	United Kingdom	Prospective cohort study	3,184	68.9 ± 8.7	1,505 (47.3%)	1,326	68.1 ± 9.2	696 (52.5%)
Sulli et al. 2021	Italy	Case-control study	65	76 ± 13	30 (46.2%)	65	76 ± 13	30 (46.2%)
Ye et al. 2020	China	Case-control study	80	41.8 ± 3.5	32 (40.0%)	62	44.3 ± 7.8	23 (37.1%)

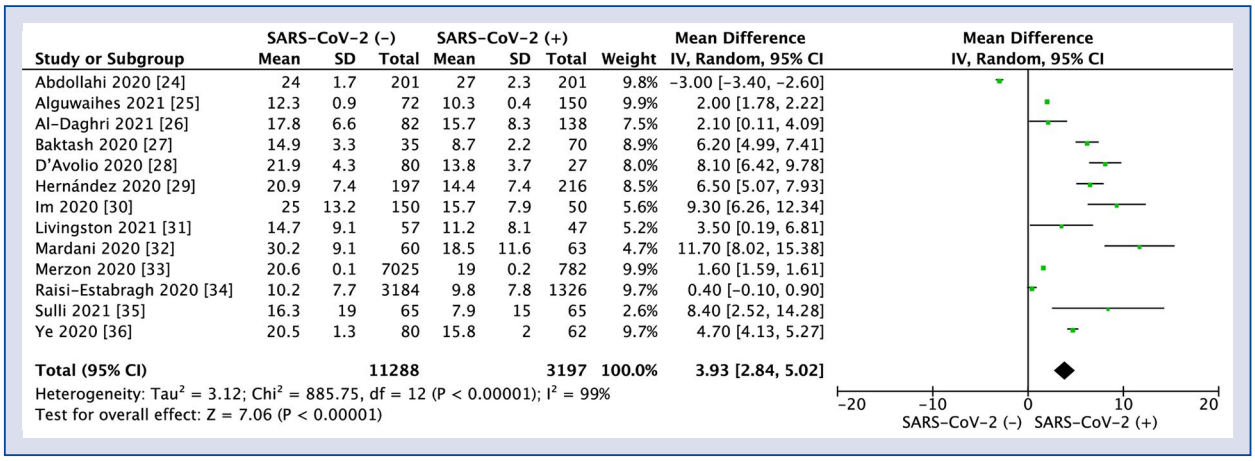

Figure 2. Forest plot of vitamin D levels between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) negative versus positive patients. The center of each square represents the weighted odds ratios for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results; SD — standard deviation.

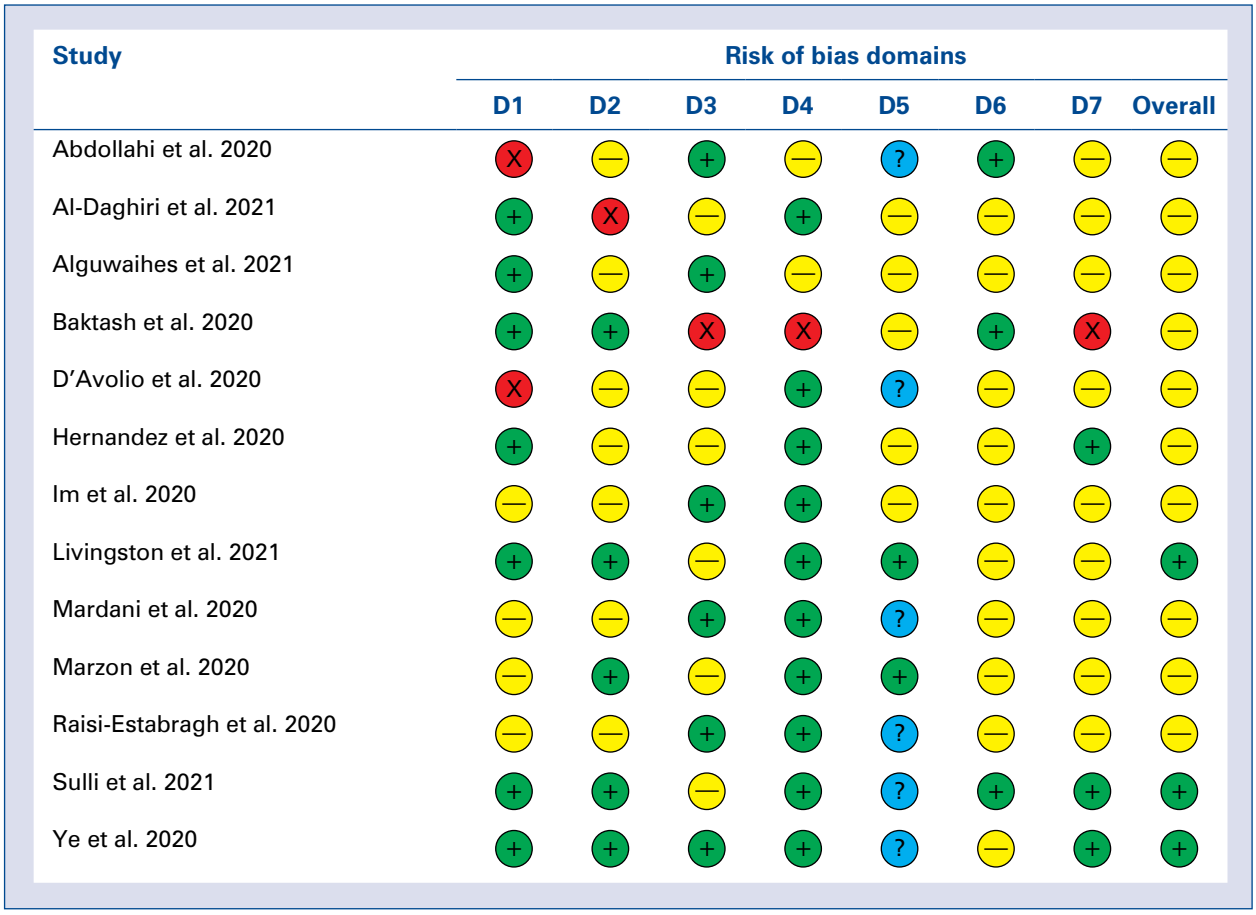

Figure 3. A summary table of review authors' judgements for each risk of bias item for each study. Domains: D1 — bias due to confouding; D2 — bias due to selection of participats; D3 — bias in classification of interventions; D4 — bias due to deviations from intended interventions; D5 — bias due to missing data; D6 — bias in measurement of outcomes; D7 — bias in selection of the reported result. Judgement: X Serious; — Moderate; + Low; ? No information.

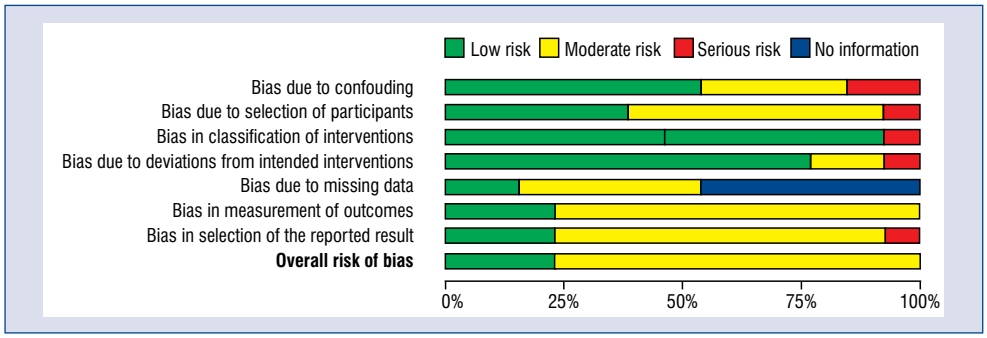

Figure 4. A plot of the distribution of review authors' judgements across studies for each risk of bias item.

obese are also more likely to suffer from vitamin D deficiency [41]. Another group that suffers from the vitamin D deficiency are older patients [42] both due to the worse overall state of health and due to drugs, they take. The study by Baktash et al. [27] found that the patients who are older than 65 years and present with the COVID-19 symptoms are more likely to be vitamin D deficient, have elevated markers of cytokine release syndrome and have an increased risk of respiratory failure. However, no difference was found in terms of mortality between the patients who were deficient and those who had their vitamin D within normal ranges, indicating that in the older group the overall poor prognosis is associated with the general health status and presence of comorbidities. These findings are consistent with those achieved by D'Avolio et al. [28], who also found that vitamin D was lower in the patients positive for COVID-19, while indicating that the supplementation of vitamin D might be useful for prevention of infection.

The strategy of vitamin D supplementation as indicated by Grant et al. [43] suggests the rapid increase of vitamin D serum levels through the high supplementation for a few weeks going as high as 10,000 IU/day in order to achieve the normal range. This strategy has been used for considerable time and has proven to be safe in delaying frailty [44]. In the study by Al-Daghri et al. [26] vitamin D deficiency was only observed in the group of older patients, those with type 2 diabetes and lower density lipoprotein levels. Interestingly the author, contrary to Grant et al. [43] supports the idea of rather moderate vitamin D loading in deficient patients, not exceeding 2000 iu/day, which is supported by Bergman [45]. Alguwaihes et al. [25] provides interesting data regarding vitamin D deficiency and the risk of COVID-19 in a hospital setting. While he did not find any evidence suggesting that the risk of infection increases in deficient patients, they are, in fact, at higher risk of mortality, possibly through an unregulated inflammatory response and cytokine storm [46]. Contrary to these findings Hernandez et al. [29] found no difference in the severity of the disease when accounting for vitamin D deficiency, however he did find a higher prevalence of deficiency among hospitalized COVID-19 patients. When analyzing the nutritional status of patients suffering from COVID-19, Im et al. [30] they found that patients suffering from COVID-19 presented a higher percentage of vitamin D deficiency when compared with a control group, additionally while not statistically significant 30 out of 38 patients who suffered from respiratory distress were deficient in vitamin D. What is worth noting is that the patients who required mechanical ventilation were deficient in at least one nutrient. Therefore, it is advised to monitor and react to the nutritional status of the COVID-19 patients [47]. Mardani et al. [32], in his study, analyzed an association in the level of vitamin D and the severity of COVID-19, along with levels of ACE2 and neutrophil to lymphocyte ratio (NLR). The NLR is a useful tool to assess systemic inflammation [48] also in acute lung injury and acute respiratory distress syndrome [49] which are common findings in the severe course of COVID-19. Having found lower levels of vitamin D in COVID-19 patients, the authors concluded that the deficiency may cause an immunological imbalance, overactivation of the RAS pathway and therefore a hyperinflammation state. Raisi-Estabragh et al. [34] in her study found that vitamin D deficiency was not an independent risk factor for black, Asian and minority ethnicities and that a cascade of factors play a role rather than a single one that can be pinpointed. In a study by Ye et al. [36], he found that vitamin D deficiency increases risk of COVID-19 infection, while the supplementation of it provides protective effects against

a severe course of the disease. These findings are further reinforced by Sulli et al. [35] who found that vitamin D deficiency is associated with more severe lung involvement, longer disease duration, and risk of death in elderly COVID-19 patients. A study by Livingstone et al. [31] among vitamin D deficiency indicates that social deprivation plays role in COVID-19 infection. While studies for the general population showed that social distancing is beneficial for the reduction in COVID-19 incidence rate [50], we must differentiate between social distancing and deprivation since the latter is a well-established risk factor for worsening of health outcomes [51]. Merzon et al. [33] identified vitamin D deficiency as an independent risk factor not only for COVID-19 infection, but also hospitalization, other risk factors included were being male and over the age of 50.

All of the studies measured levels of vitamin D at the moment of acute COVID-19 infection, however as previous studies showed [52], acute respiratory infection does not alter the vitamin D levels, therefore a sample on admission is representative.

Conclusions

Low serum vitamin D levels are statistically and significantly associated with the risk of COVID-19 infection. Supplementation of vitamin D especially in deficiency, risk groups are indicated.

Acknowledgments

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Conflict of interest: None declared

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Transseptal puncture without fluoroscopy using a radiofrequency needle: A case series

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Abstract

Background: *The non-fluoroscopy approach with the use of a three-dimensional (3D) navigation system is increasingly recognized as a future technology in the treatment of arrhythmias. However, there are a limited number of articles published concerning transseptal puncture without the use of fluoroscopy.*

Methods: *Presented in this paper is the first series of patients (n = 10) that have undergone transseptal puncture without the use of fluoroscopy under transesophageal echocardiography control using a radiofrequency transseptal needle and a 3D navigation system.*

Results: *All patients were treated without complications. In 6 patients, re-pulmonary vein isolation was performed. In 5 cases, linear ablation of the left atrium for treatment of left atrial macro re-entry tachycardia was provided. In 2 patients, focal atrial tachycardia was treated, 1 patient underwent cavo tricuspidal isthmus (CTI) ablation and 1 patient, re-CTI ablation. The ablation of complex fragmented atrial electrograms was done in 2 patients. In 1 case, right atrial macro re-entry tachycardia was treated.*

Conclusions: *Transseptal puncture without using fluoroscopy is safe and effective when using a radiofrequency needle, a 3D navigation system and transesophageal echocardiography.* (Cardiol J 2021; 28, 5: 655–662)

Key words: non-fluoroscopic approach, transseptal puncture, radiofrequency needle, three-dimensional mapping system

Introduction

Interest in non-fluoroscopy radiofrequency (RF) ablation (RFA) for the treatment of supraventricular tachycardia (SVT) arising from the right atrium (RA) has increased greatly over the last decade [1]. A new generation of three-dimensional (3D)-navigation systems allow the operator to build a map of the right-sided chambers with no, or minimal use of fluoroscopy. Number of publications in accordance with the safety and efficacy of non-fluoroscopy RFA of SVT have recently been published [2, 3]. Little is known about the safety and efficacy of transseptal puncture (TSP) using the non-fluoroscopy technique. As such, this paper presents a series of TSPs and RFA of the left atrium (LA) using a RF needle, 3D navigation system and transesophageal echocardiography (TEE), without the use of fluoroscopy.

Methods

Thirteen consecutive patients were enrolled in this study. Three patients were excluded because of persistent foramen ovale or interatrial septal (IAS) defect after the first RFA. Nevertheless, they were also successfully ablated using the no-fluoroscopy technique.

In 10 patients (6 female) with a mean age of 70.6 ± 6.5 years, an RF needle was used for TSP. All patients underwent initial ablation therapy for atrial fibrillation (AF). Nine patients had pulmonary

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vein isolation (PVI) using cryoballoon, 1 patient had PVI using an RF catheter and 2 patients had re-PVI using an RF catheter after the first PVI procedure was conducted using a cryoballoon. Two patients had paroxysmal form and 8 patients had a persistent form of AF. Typical atrial flutter was documented in 4 cases. Eight patients had arterial hypertension, 2 patients suffered from apoplexy, 1 patient had diabetes, and 1 patient had chronic obstructive pulmonary disease (COPD). In 2 patients, ischemic heart disease was diagnosed, one was treated with coronary artery bypass grafting and the other with coronary stenting. None of the patients had implanted cardiac devices.

All procedures were done under sedation and uninterrupted anticoagulation. Intravenous infusion of Propofol and Fentanyl injection was used. Intravenous heparin was administered during the procedure to maintain an activated clotting time (ACT) in excess of 300 s.

Vascular access was obtained from the right femoral vein. 4 F and 8 F short sheaths and one 8.5 F long sheath (SL1 with atraumatic tip, SWARTZ, Abbott, USA) was inserted (see details below).

The 3D navigation system (Ensite Precision™ Cardiac Mapping System, Abbott, USA) was used in all cases. Initial anatomical mapping of right-sided heart structures was performed using a 4 F decapolar steerable diagnostic catheter (Inquiry™, Abbott, USA), which then was placed in the coronary sinus (CS). For mapping of the LA and the pulmonary veins, a circular mapping catheter (Advisor™ FL, Sensor Enabled™, Abbott, USA) or a multipolar mapping catheter (Advisor™ HD Grid, Sensor Enabled™, Abbott, USA) was used. Mapping and ablation were performed with an irrigated ablation catheter (Flexability™, Abbott, USA). The TSP was performed with a RF-Needle (NRG® Transseptal Needle, Baylis Medical Company Inc., Canada) in all cases. All TSPs were performed under TEE imaging using a compact cardiovascular ultrasound system (CX50, PHILIPS, Netherland) with a TEE array transducer (X7-2t, PHILIPS, Netherlands).

The TSP with RF needle

The technique was divided into three steps.

1. Right-sided anatomical mapping. The anatomical mapping of right-sided structures using a steerable diagnostic catheter is safe and effective, and does not take a lot of time. First, mapping of the venous system and the inferior vena cava (IVC) was undertaken. Followed by mapping of the RA especially the IAS, superior vena cava (SVC) and the CS. Afterwards, a long transseptal sheath was inserted into the femoral vein over a long wire (10–20 cm) to ensure that the tip of the sheath was in the venous system. After the dilator and wire was withdrawn, the sheath was aspirated and flushed with saline and the ablation catheter was inserted. Once the RF catheter was in the venous system, its trajectory was tracked through the 3D anatomical course of the venous system which was established using a diagnostic catheter. Once the ablation catheter was placed in the SVC, the long sheath was slid carefully over it. It was inserted until an impedance difference occurred (once the tip of the sheath made contact with the catheter electrodes) and the catheter shape was moved out from the 3D anatomical map borders. This confirmed "housing" of the RF catheter in the sheath. Then the catheter was withdrawn and the sheath was aspirated and flushed again with saline (Fig. 1, **Suppl. Video 1**).

2. The blind phase. We called this phase blind because it could not be completely controlled with the 3D navigation system and the TEE. Once the SL1 sheath was placed in the desired position, it was fixed and the dilator was inserted over the wire. To avoid uncontrolled contact of the dilator with the SVC tissue, it was inserted into the sheath until marker "2" on the dilator. After the wire was withdrawn the dilator was aspirated and flushed with saline.

The RF-needle was then inserted into the dilator in consideration of special markers. The RF needle has a short pin directly after the handle part, from this pin the needle arises. The distance from the end of this pin to the dilator orifice should be equal to the length of the pin itself (Fig. 2A). The RF needle was then flushed with saline and connected to the cable and pressure line. Once this position was reached, the RF-needle together with the dilator was fixed and the sheath was slid gently back until a connection (click) with the dilator occurred (Fig. 2B). Afterwards, the sheath and the dilator were sliding together backwards for 2–3 mm, while the RF needle remained fixed. Once the tip of the RF needle left the dilator, a unipolar point appeared on the 3D map (Fig. 2C). The whole assembly of the sheath, dilator and the needle were now slid back until a drop into the fossa ovalis occurred. It should be noted that the needle and the sheath position were similar to the standard TSP technique.

3. Transeptal puncture. Once the RF-needle was pulled back from the SVC and dropped into the fossa ovalis, the TEE image showed the "tenting" of the interatrial septum, ensuring a correct needle

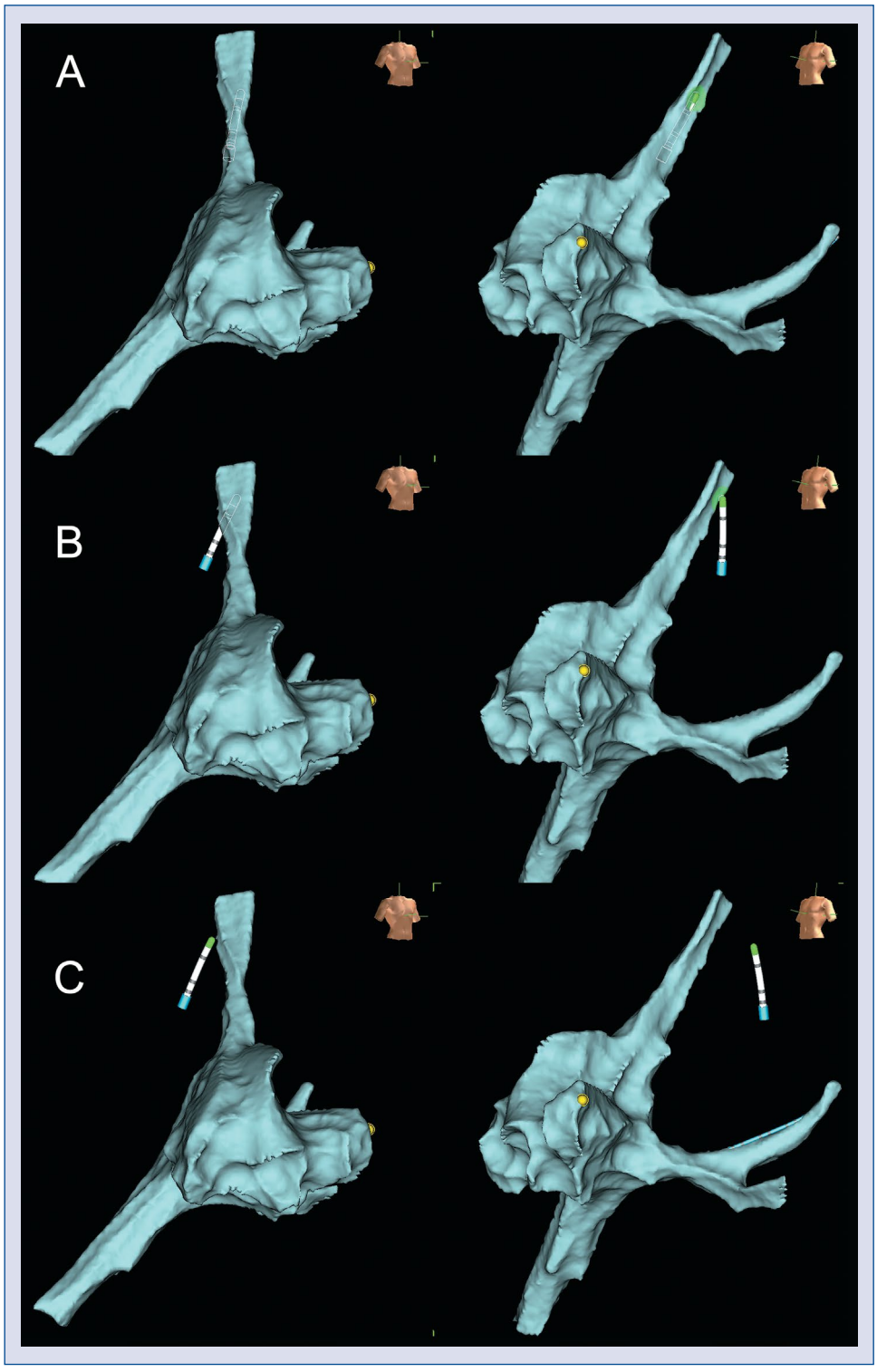

Figure 1. An anatomical map of the right atrium, inferior and superior vena cava and coronary sinus. The bundle of His is marked with a yellow point. The multipolar diagnostic catheter placed in the coronary sinus (blue color). On the left side, the right anterior oblique projection is presented. On the right side, the left anterior oblique projection is presented; **A.** The ablation catheter is placed in the superior vena cava; **B.** The SL1 sheath slides over the catheter (which is stabilized in this position) until its tip comes into contact with the proximal poles of the ablation catheter resulting in an impedance change and shifting the part of the catheter shape out of the map; **C.** Once the sheath slides a bit more distally, the distal poles of the ablation catheter come into contact with the sheath and the whole catheter shape jumps out from the map. This is a sign that the tip of the SL1 sheath is now in the place of the distal part of the catheter (position A).

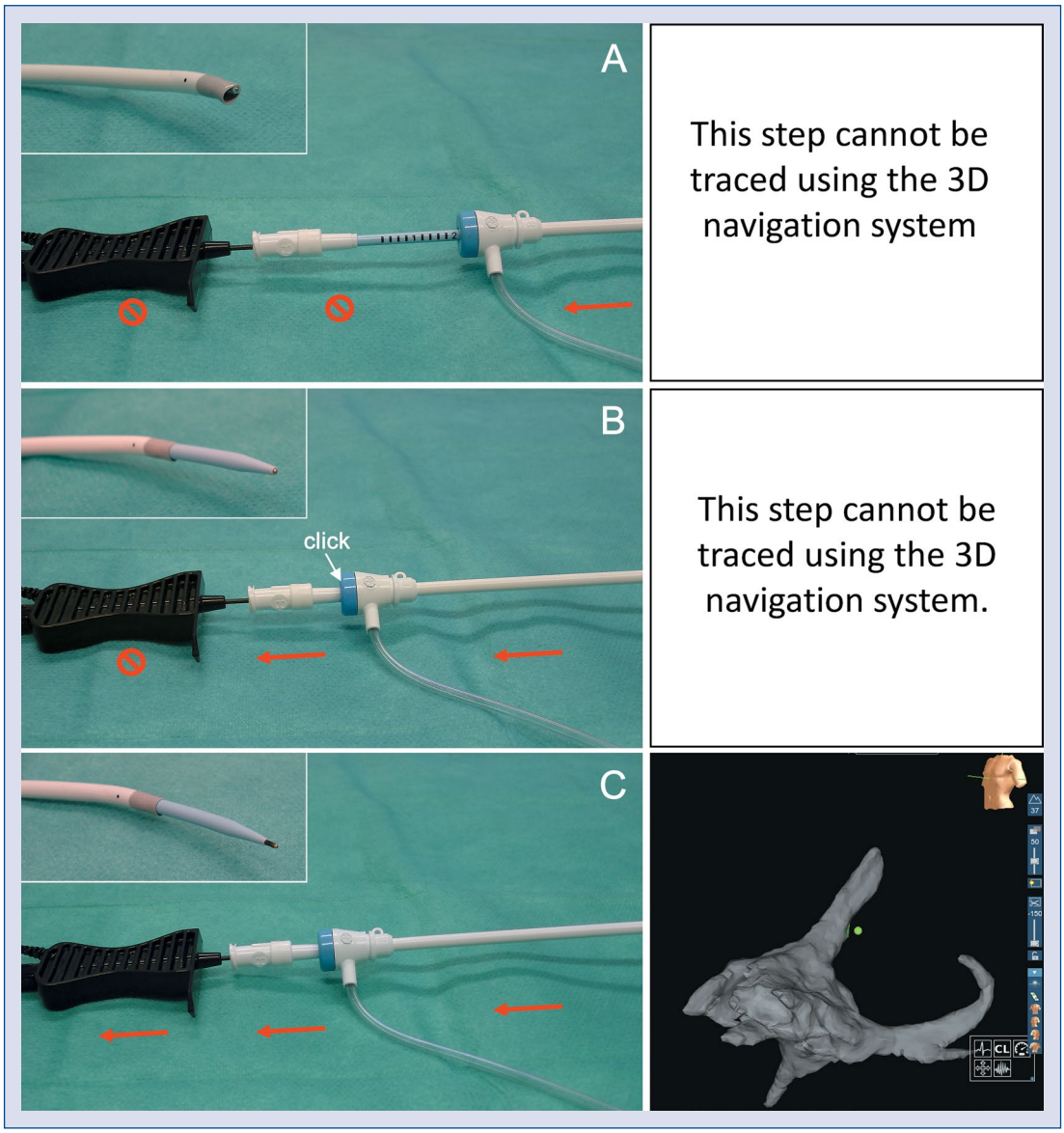

Figure 2. The steps of the "blind phase"; **A.** At the start position, the dilator is inserted into the sheath until the marker "2". The radiofrequency (RF) needle is inserted into the dilator until the distance between the end of the pin on the needle and the dilator orifice is equal to the length of the pin itself. Now the needle and dilator are fixed and the sheath slides back over the dilator; **B.** The connection of the sheath with the dilator (a specific "click") confirms the connection. Now the dilator and the sheath are sliding back and the needle is still fixed; **C.** The final position of the sheath dilator and the needle assembly before pulling back. The first two steps (A and B) cannot be traced using the three--dimensional (3D) navigation system. The right side (C) shows the 3D anatomical map of the right atrium, superior vena cava and coronary sinus in the left anterior oblique projection. The green point depicts the unipolar signal of the RF-needle once it appears out from the dilator. In the left upper corner of each picture, the corresponding picture of the distal part of the sheath is shown. Please note the gummy tip of the SL1 sheath, which offers additional safety.

position. After reaching the correct position, RF energy was delivered. Specific spontaneous echo contrasting occurred during the energy application on the TEE picture. The "tenting" of the IAS disappeared and the needle was inserted into the LA. The needle was aspirated and flushed with saline, and a spontaneous contrasting effect was seen at this moment in the LA, confirming the correct position of the needle (Fig. 3, **Suppl. Videos 2, 3**).

A single TSP was used and the ablation catheter was placed beside the multipolar mapping

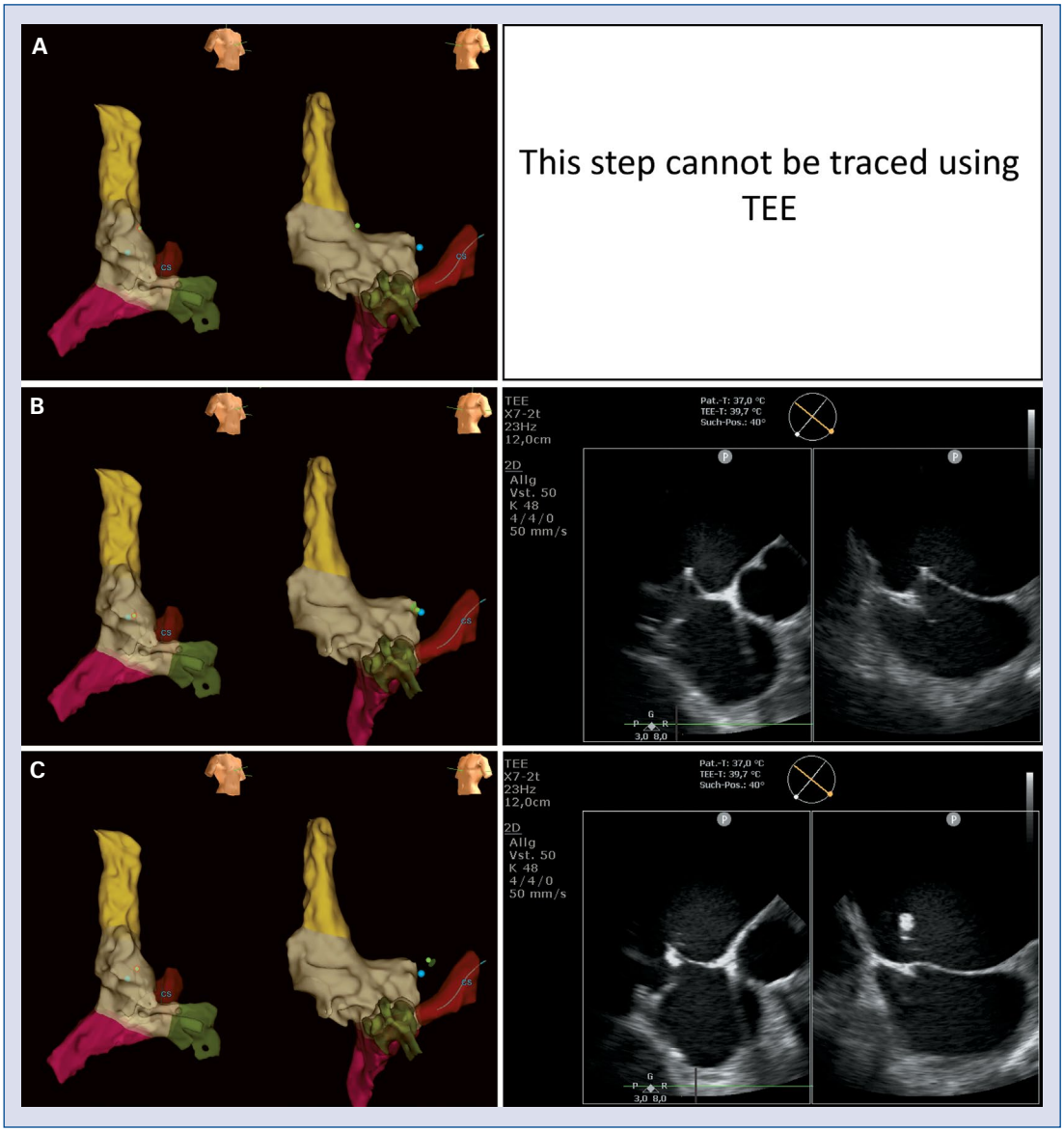

Figure 3. Left side three-dimensional anatomical map of the anatomical structures in the right anterior oblique and left anterior oblique projections; right atrium (grey), superior vena cava (SVC) (yellow), inferior vena cava (purple), coronary sinus (red) and right ventricle (green). The blue point depicts the ideal location for transseptal puncture, which was marked with the radiofrequency (RF)-catheter before. On the right side, transesophageal echocardiography (TEE) pictures of the interatrial septal (IAS) in short and bicaval planes; **A.** The RF-needle (the green point) moves from the SVC towards the IAS. This step cannot be traced using TEE; **B.** The tip of the RF-needle reached the desired place. The TEE picture showing the "tenting" of the IAS confirms a safe position of the needle; **C.** The tip of the needle is in the left atrium, out of the right atrium map. TEE pictures show specific spontaneous echo contrasting during energy application. Note, the "tenting" disappears after RF delivery.

catheter once the SL1 sheath was pulled back into the RA.

The mapping of LA was provided with a multipolar catheter (Advisor™ FL Circular Mapping Catheter, Sensor Enabled™, Abbott, USA, n = 6; Advisor™ HD Grid Mapping Catheter, Sensor Enabled™, Abbott, USA, n = 4).

At first the anatomy of all pulmonary veins were collected (LSPV-LIPV-RSPV-RIPV) followed by a complete geometry of the LA-box. Next the anatomy of the LA-roof was completed. The following step was mapping the left atrial appendage, the anterior wall and atrial septum. Finally, the inferior wall of the LA was mapped.

Table 1. Periprocedural characteristics.

Case	AF form	PVI	Re-PVI	LAMRT (linear ablation)	CFAEs	RAMRT	CTI
1	Persistent	CRYO	RSPV, LIPV	–	–	–	–
2	Persistent	CRYO	LSPV, RIPV	–	–	CT	Re-CTI
3	Persistent	CRYO	–	Left isthmus, LA anterior	IAS, LA inferior	–	–
4	Paroxysmal	CRYO	RSPV, RIPV	IAS	–	–	–
5	Persistent	CRYO/RF	–	Left isthmus	–	–	–
6	Persistent	CRYO/RF	RIPV	Left isthmus, IAS	IAS, LA inferior, LA posterior	–	–
7	Persistent	CRYO	–	Left isthmus, LA–Roof, inferior box–line	–	–	–
8	Persistent	RF	All PVs	–	–	–	–
9	Persistent	CRYO	RSPV	–	–	–	–
10	Paroxysmal	CRYO	–	–	–	–	CTI

AF — atrial fibrillation; CFAE — complex fragmented atrial electrograms; CT — crista terminalis; CTI — cavo tricuspidal isthmus; IAS — inter atrial septum; LA — left atrium; LAMRT — left atrial macro re-entry tachycardia; LIPV — left inferior pulmonary vein; LSPV — left superior pulmonary vein; PVs — pulmonary veins; PVI — pulmonary vein isolation; RAMRT — right atrial macro re-entry tachycardia; RF — radiofrequency; RIPV — right inferior pulmonary vein; RSPV — right superior pulmonary vein

A voltage map was collected simultaneously with the anatomical map, which supplies additional information of the LA substrate. Pulmonary vein gaps were marked with tag points during mapping as well. During AF a complex fragmented atrial electrograms (CFAEs) map was also provided.

Results

Intravenous infusion of 49.5 ± 27 mL Propofol 1% and 0.043 ± 0,027 mg Fentanyl injection was needed for stable sedation. No re-map was needed in this study.

After safe TSP was done in all cases, an LA anatomical and voltage map was created. The re-isolation of pulmonary veins was the initial strategy. In 4 cases, all pulmonary veins were isolated. In 6 patients, re-PVI was performed (1 patient — 4 PVs; 3 patients — 2 PVs; 2 patients — 1 PV).

In 5 cases, linear ablation of the LA for treatment of left atrial macro re-entry tachycardia was provided. In 2 patients, focal atrial tachycardia was documented, 1 patient underwent cavo tricuspidal isthmus (CTI) ablation and 1 patient re-CTI ablation. The ablation of CFAEs was done in 2 patients. In 1 case, RA macro re-entry tachycardia was treated. Mean procedural time (the time from groin puncture until hemostasis, including waiting time) was 107.5 ± 37.1 min. No complications occurred during or after the procedure. Mean hospitalization time was 3 ± 0.9 days. All patients remained on anti-arrhythmic therapy for 3 months after ablation. After an 8.9 ± 4-month follow-up period, 2 patients had an arrhythmia recurrence. The periprocedural characteristics are presented in Table 1.

Discussion

Non-fluoroscopy technique for treatment of SVT

As mentioned above, a non-fluoroscopy approach using a 3D navigation system is increasingly recognized as a future technology in arrhythmia treatment. The treatment of right-sided SVT without fluoroscopy is already a well approved method and is a standard technique at many institutions including the one documented [2, 3]. Herein, it is strongly recommended to start with right-sided SVT ablation once it has been decided to implement a non-fluoroscopy technique in your laboratory. Only after a learning curve is completed, consider starting with a non-fluoroscopy TSP [4].

Non-fluoroscopy mapping and ablation of the LA after TSP

To investigate the effectiveness and safety of the reconstruction of LA and PVI without fluoroscopy, Zhang et al. [5] enrolled 342 patients with paroxysmal AF. After X-ray-guided TSP, patients were divided in two groups — reconstruction of LA and PVI with and without the use of fluoroscopy. The X-ray time of LA reconstruction and PVI was

7.6 ± 1.3 min in the group with fluoroscopy and the total X-ray exposure dose was more than 6-fold higher compared to the group without fluoroscopy. Fluoroscopy time before LA reconstruction was similar in both groups (2.8 ± 0.4 and 2.4 ± 0.6 min) [5]. Recently, Raju et al. [6] published the experience using the near zero fluoroscopy ablation technique for complex LA ablations using the electroanatomic mapping system and TEE. The authors showed that the reduction of fluoroscopy time and radiation dose was statistically relevant in the non-fluoroscopy group compared with the control group. Moreover, in the majority of patients with patent foramen ovale (36% in this study), zero fluoroscopy was possible [6].

The right-sided and left-sided atrial reconstruction without fluoroscopy using a 3D-navigation system seems to be an effective and safe method. The next most important question is; if the transseptal punction is also safe and effective when using a non-fluoroscopy technique. By re-PVI, the incidence of the iatrogenic atrial septal defect after 12–36 months after PVI varies 20–37% using cryoballoon and 9–19% using the RFA technique. That means that up to one-third of re-PVI procedures after initial cryoballoon therapy (which have been increasing over the last few years) can be performed without using TSP [7].

TSP without fluoroscopy

Ferguson et al. [8] published a series documenting 21 patients with AF where 19 patients underwent TSP without fluoroscopy, using intracardiac echocardiography (ICE), and an electroanatomic mapping system. For double TSP, the authors used a conventional transseptal needle which was facilitated by electrocautery. This technique showed good results and was deemed safe in all cases [8]. Bulava et al. [9] demonstrated the result of ablation on 80 patients with paroxysmal AF randomized 1:1 ratio to undergo PVI with and without fluoroscopy. TSP in the group without fluoroscopy was performed by ICE guiding and using the CARTO 3 system. The total procedure and ablation time were comparable in both groups. All but 1 patient received zero fluoroscopy treatment in the non-fluoroscopy group. No procedure-related complications occurred in this study [9]. O'Brien et al. [10] demonstrated that after an adequate learning curve fluoroscopy-free TSP and ablation of complex left-sided atrial arrhythmias were safe and feasible in most patients. More recently, Sawhney et al. [11] published a stepwise approach to the non-fluoroscopy TSP technique in 32 patients using an Endrys Coaxial needle, which was visualized on the CARTO system without the use of TEE or ICE. The TSP was performed safely and effectively using the non-fluoroscopic technique in a select group of patients [11].

The RF transseptal needle

Recently, a RF needle was developed. The first data showed that the use of an RF needle for TSP was associated with a lower total procedural time and lower risk of acute cerebral embolism during the catheter ablation of AF [12]. In this study Tokuda et al. [12] enrolled 383 consecutive patients who underwent catheter ablation for AF that required TSP using mechanical or RF transseptal needles. All patients had a cerebral magnetic resonance imaging performed 1 or 2 days after the procedure. Total procedure time was significantly shorter in the RF group than the non-RF group (167 ± 50 vs. 181 ± 52 min, $p = 0.01$). The incidence of acute cerebral embolism was lower in the RF group than the non-RF group (19 vs. 32%, $p = 0.02$). This can be attributed to some advantages of using the RF-needle: It enables crossing the thin aneurismal septum while reducing excessive tenting; can cross the fibrotic septum while reducing mechanical force; can cross the septum at a precise location; and the rounded atraumatic tip reduces the risk of skiving and embolism. As mentioned above, it also reduces transseptal procedure and fluoroscopy time vs. mechanical needle. Is easy to visualize on fluoroscopy (as well as on TEE) because of the radiopaque marker; and is easy to trace the tip of the needle on the 3D mapping system [13–16].

In the present study, the RF needle for TSP was used without the use of fluoroscopy. A single TSP was used and the ablation catheter was placed beside the multipolar mapping catheter. Double TSP can also be performed by repeating the above-described steps.

According to available research, this is the first series of patients where the transseptal punction was performed with RF-needle using the non-fluoroscopy technique. With regard to the advantages described above, based on prior experience, it can be said that the RF needle is well suited for the non-fluoroscopy technique. Using this technique, it is possible to:

— Trace the RF-needle tip in the 3D navigation system before, during and after TSP (minimizing the blind phase);
— To see the highly echogenic tip of the RF--needle in the TEE image;

— To monitor the pressure shift during the TSP;
— To see the spontaneous contrast effect in the LA while injecting the saline in the RF-needle after TSP.

This method is not only effective, but also safe. The safety concern in the present study was based on the following points:

— Always sliding the sheath, introducer and the needle backwards during the blind phase;
— Live TEE imaging during the TSP;
— Adequate sedation of the patient, which allows a stable map; the soft tip of the SL1 sheath provides better safety.

Limitations of the study

The non-fluoroscopy group of patients was not compared with conventional groups. Limited number of patients.

Conclusions

Non-fluoroscopy TSP using an RF needle, traced with the 3D navigation system and TEE is a safe and effective technique. Further investigation of this method is needed.

Conflict of interest: Philipp Sommer — Consultant for Abbott, Boston Scientific, BiosenseWebster and Medtronic.

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The low acute effectiveness of a high-power short duration radiofrequency current application technique in pulmonary vein isolation for atrial fibrillation

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Abstract

Background: *Application of high power radiofrequency (RF) energy for a short duration (HPSD) to isolate pulmonary vein (PV) is an emerging technique. But power and duration settings are very different across different centers. Moreover, despite encouraging preclinical and clinical data, studies measuring acute effectiveness of various HPSD settings are limited.*

Methods: *Twenty-five consecutive patients with symptomatic atrial fibrillation (AF) were treated with pulmonary vein isolation (PVI) using HPSD. PVI was performed with a contact force catheter (Thermocool SF Smart-Touch) and Carto 3 System. The following parameters were used: energy output 50 W, target temperature 43°C, irrigation 15 mL/min, targeted contact force of > 10 g. RF energy was applied for 6–10 s. Required minimal interlesion distance was 4 mm. Twenty minutes after each successful PVI adenosine provocation test (APT) was performed by administrating 18 mg adenosine to unmask dormant PV conduction.*

Results: *All PVs (100 PVs) were successfully isolated. RF lesions needed per patient were 131 ± 41, the average duration for each RF application was 8.1 ± 1.7 s. Procedure time was 138 ± 21 min and average of total RF energy duration was 16.3 ± 5.2 min and average amount of RF energy was 48209 ± ± 12808 W. APT application time after PVI was 31.1 ± 8.3 min for the left sided PVs and 22.2 ± ± 4.6 min (p = 0.005) for the right sided PVs. APT was transiently positive in 18 PVs (18%) in 8 (32%) patients.*

Conclusions: *Pulmonary vein isolation with high power for 6–10 s is feasible and shortens the procedure and ablation duration. However, acute effectiveness of the HPSD seems to be lower than expected. Further studies combining other ablation parameters are needed to improve this promising technique.*
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Key words: ablation, atrial fibrillation, reconnection, adenosine, high power

Introduction

Since the pioneering study of Haissaguerre et al. [1] demonstrating pulmonary vein (PV) as the main source for atrial fibrillation (AF), pulmonary vein isolation (PVI) with either radiofrequency (RF) energy or cryo-balloon is widely used in treatment of AF. Nevertheless, in 30–50% of cases AF recurs despite complete electrical disconnection of the PVs. The major cause of recurrence is recon-

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nection of the initially isolated PVs. Indeed, 80% of the patients with recurrence of AF demonstrate at least one reconnected PV [2, 3]. Thus, successful ablation outcomes require durable lesion formation which depends on the RF current delivered, the duration of RF energy delivered, the contact force applied on the tissue and stability of the ablation catheter. On the other hand, some safety concerns arise regarding collateral tissue damage, like esophageal injury. In recent years, a new technique of applying high power RF energy in short duration (HPSD) had been introduced. Most of the data about HPSD technique is derived from ex vivo and in vivo studies which have consistently shown sufficient lesion formation and fewer complications with the HPSD technique compared to conventional lower power and longer duration techniques (30–40 W for 30 s) [4, 5]. So far, limited non-randomized clinical data have shown promising results regarding arrhythmia-free survival with the HPSD technique [6–9]. Nevertheless, there is no consensus about the power and duration settings for HPSD, whereas energy levels above 40 W are considered as high power and duration of application for 6–10 s as short duration.

The acute effectiveness of a PVI can be evaluated with an adenosine provocation test (APT), which unmasks dormant PV conduction after apparently successful PVI [2]. Two major trials analyzed APT guided PVI to enhance outcome with conflicting results about its utility [10, 11]. Nevertheless, APT is the only method in determining at least the acute effectiveness of an ablation technique during PVI procedure.

Knowing that there is no consensus about the optimal HPSD settings and that there are very limited data which evaluated acute efficiency of any HPSD techniques, this acute study was performed using APT to evaluate the acute efficiency of lesions created with the HPSD settings which are in use at the documented institution.

Methods

Patient population

Consecutive ablation naïve patients with symptomatic paroxysmal or persistent AF were enrolled in this prospective observational registry. The study complied with the Declaration of Helsinki and the protocol was approved by the ethical commission of the University of Regensburg. Informed consent was obtained from all patients.

Inclusion criterion was paroxysmal or persistent symptomatic AF with an indication for PVI according to current AF classification criteria [2].

Ablation procedure

A left atrial thrombus was excluded in all patients before the procedure using computerized tomography. In only 1 patient, a transesophageal echocardiography had been performed to exclude left atrium (LA) thrombus because of inconsistent tomography result. Using the tomography data, the left atrial anatomy was extracted with help of the Carto Merge software (Biosense Webster Inc., Diamond Bar, CA, USA) and defined the PV anatomy of each patient including accessory PVs or left main trunks before the ablation procedure.

The ablation procedure was performed under continued oral anticoagulation, in deep analgosedation or general anesthesia. After venous access, a double transseptal puncture was performed using the Brockenbrough technique. Asteerable sheath was used (DireX, Boston Scientific, Malborough, MA, USA) to guide the ablation catheter. Activated clotting time was kept between 300 and 350 s.

A circumferential mapping catheter (LassoNav) and a 3.5 mm ablation catheter (Navistar Thermocool Smart Touch SF; Biosense Webster Inc., Diamond Bar, CA, USA) were placed in the LA. An electroanatomic map of the LA was created with the Carto 3 System using a fast automated mapping tool (Version 6, Biosense Webster Inc., Diamond Bar, CA, USA). Antral PVI with RF ablations applied only round the PV ostia of the ipsilateral PVs was performed without ablations taken between the ipsilateral PVs. Obtaining a contact force of 10–15 g on the posterior wall and 15–20 g on the anterior wall was tried. The applied RF energy was 50 W at each point with a temperature limit of 43°C and a saline irrigation rate of 15 mL/min. The minimum duration of each application was 6–10 s, depending on the stability and contact force applied as determined by the physician. Keeping the inter-lesion distance by 4–6 mm, as measured by the dedicated tool of the Carto system was tried.

Pulmonary vein isolation was confirmed with demonstration of input into and exit block out of the PV. During ablation around the PV, the PV signals in the Lasso catheter were monitored continuously; after the disappearance of PV signals meaning input block, stimulation from inside the ipsilateral PV was performed with the ablation catheter using maximal output of the cardiac stimulator to confirm exit block from the PV. When local PV capture was not successful with the ablation catheter or if there was no cross-talk between the ipsilateral PVs, then each PV was separately stimulated from all the electrodes of the Lasso catheter sequentially

Adenosine provocation test

For each PV, adenosine provocation test was performed by administering 18 mg adenosine bolus intravenously 20–40 min after successful isolation to unmask the dormant PV conduction. In patients with left main trunks, it was performed for each arm of the distal PV an APT separately. Before APT, spontaneous recovery of the PV was excluded with the lasso catheter by checking for entrance and exit block. After administration of adenosine, intracardiac recordings were continuously monitored. Adenosine effect was recognized when at least one P wave was not conducted due to atrioventricular block. In the case of ineffectiveness of 18 mg adenosine, the test was repeated with doubling of the adenosine dose. PV reconnection was diagnosed when the circular mapping catheter detected PV potentials in a previously isolated PV. A PV reconnection was classified as temporary if the PV signals disappear again when the effect of adenosine diminished or as permanent if the PV signals persisted.

Follow-up

As this is an acute study, the patients were followed-up for only 4 weeks after the PVI to exclude rare complications such as esophageal injury, which may occur 2–4 weeks after PVI. No data about the rhythm state had been collected as the patients were in the blanking period after PVI.

Control group

Results were compared from the current study with a patient collective from a previous study, where conventional RF ablation was compared with visually guided laser balloon ablation [12]. In that study the RF arm, PVI was performed by creating a circumferential ablation with ablation at the carina when needed using conventional settings (30 W at the posterior wall and 40 W at the anterior wall of the PV with a duration of 30 s for each RF application).

Statistical analysis

Values are distributed as means ± standard deviation for normally distributed continuous variables, median and interquartile range (IQR) for skewed distributions (assessed by means of the Kolmogorov-Smirnov one sample test) and counts and percentages for categorical variables. Statistical analysis was conducted using the Student t-test (unpaired) for continuous variables with normal distribution and the Mann-Whitney U test for variables with non-normal distribution. The χ^2 test or the Fisher exact test was used to compare the categorical variables in different groups. Statistical significance was defined as $p < 0.05$. Statistical analysis was performed using SPSS 25 (SPSS Inc., Chicago, IL, USA).

Table 1. Clinical characteristics.

Number of patients	25
Age [years]	62.7 ± 10.6 (range 31–80)
Gender male	16 (64%)
Body mass index	27.1 ± 4.1 (range 21.0–35.9)
Paroxysmal AF	19 (76%)
Persistent AF	6 (24%)
Duration of AF [years]	3.1 ± 1.5 (range 0.5–7.0)
CHA_2DS_2-VASc score	2.5 (0–6)
LA size [mm]	41.7 ± 5.4 (34–58)
LA volume [mL]	35.6 ± 13.2 (19–57)
LVEF [%]	57 ± 10 (range 30–70)
Hypertension	13 (52%)
Diabetes mellitus	3 (12%)
Sleep apnea syndrome	2 (8%)
Coronary artery disease	5 (20%)
Dilated cardiomyopathy	1 (4%)
Prior stroke/TIA	1 (4%)
Previous antiarrhythmic drugs failed	7 (28%)

AF — atrial fibrillation; LA — left atrial; LVEF — left ventricular ejection fraction; TIA — transient ischemic attack

Results

Patient population

A total of 25 consecutive patients were included. The clinical characteristics are summarized in Table 1.

Procedural data

The average procedure time was 138 ± 21 min and fluoroscopy duration and doses were 13.2 ± 6.8 min and 1182 ± 314 cGy, respectively. Only 2 (8%) patients had left main trunk with distally separated PVs. A separate APT in patients with a left main trunk was also performed, two PV were also calculated in these patients. All of the PVs in 25 patients were isolated successfully using 131 ± 41 RF lesions. Average duration of ablation

energy application was 16.3 ± 5.2 min and average amount of applied RF energy was 48209 ± 12808 W. Ablation duration per point was 8.1 ± 1.7 s on average (Table 2).

Mean contact force was 14.25 ± 2.70 g. Lesions created with suboptimal contact force, defined as applied force less than 10 g, were in the minority with 5.2% of all the ablation lesions, as depicted in the Figure 1.

Twenty-four (96%) of the 25 left sided PV pairs and 22 (88%) of the right sided PV pairs had been isolated after completion of the first ablation circle, in the other patients a conduction gap was sought to isolate the PVs.

Entrance and exit block could be demonstrated in all PVs; local capture from the ipsilateral PV was successful in 90 (90%) PVs. In 10 (10%) PVs there was no cross talk; in these PVs exit block could be demonstrated by stimulation with the lasso catheter in each PV.

Table 2. Procedural data.

Total procedure duration [min]	138 ± 21
Total fluoroscopy duration [min]	13.2 ± 6.8
Total radiation dose [cGy]	1182 ± 314
Total ablation count	131 ± 41
Total ablation duration [min]	16.3 ± 5.2
Total ablation energy [W]	48209 ± 12808
Ablation duration per lesion [s]	8.1 ± 1.7
Contact force [g]	14.2 ± 2.7
Pulmonary veins (PVs)	100
Successful isolation [%]	100
Isolation with first circle (left side)	24 (96%)
Isolation with first circle (right side)	22 (88%)
Time to APT (left side) [min]	31.1 ± 8.3
Time to APT (right side) [min]	22.2 ± 4.6
Reconnected PV (left side)	6 (6%)
Reconnected PV (right side)	12 (12%)
Patients with reconnected PVs	8 (32%)

APT — adenosine provocation test

Adenosine provocation test

All isolated PVs underwent an APT. In 3 (12%) patients for the left sided PVs and in 6 (24%) for patients of the right sided PVs, additional RF ablation after the first successful isolation had to be performed because of spontaneous reconnection detected before APT to re-isolate the PVs.

Time to APT was longer for the left sided PVs compared to the right sided PVs (31.1 ± 8.3 min vs. 22.2 ± 4.6 min, p = 0.005).

An APT was positive in 8 (32%) patients. Reconnection was detected in 9 PV pairs (3 left sided and 6 right sided PV). All of the reconnections were transient and disappeared with the cessation of the adenosine effect. Only 1 patient had a transient reconnection in all PVs.

Differences in clinical and procedural parameters in APT positive and negative patients

Clinical characteristics of patients with or without reconnection did not differ (each p = NS). Only a minority of the patients had general anesthesia (4 patients, 16%). None of the patients

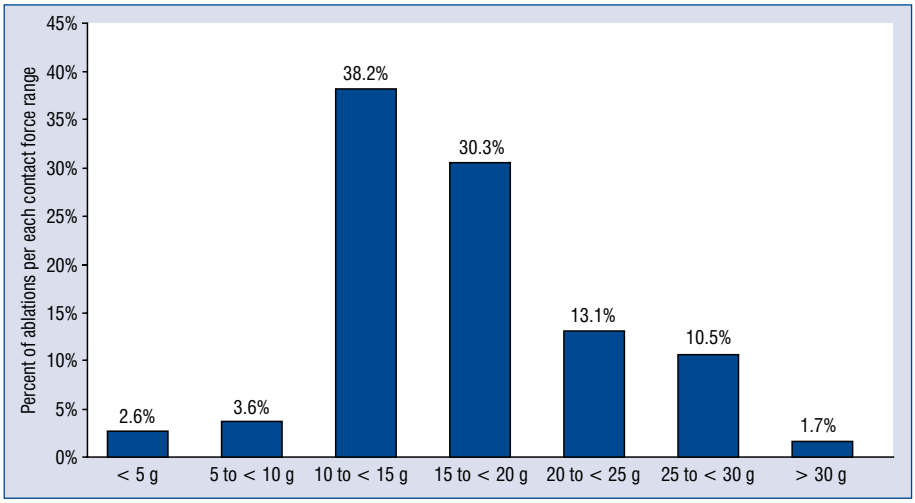

Figure 1. Percentage of the ablation application by average contact force ranges. Contact force < 10 g as suboptimal was defined

Table 3. Comparing ablation data between adenosine provocation test (APT) positive and negative pulmonary vein.

Parameters	APT negative	APT positive	P
Ablation count	59 ± 17	60 ± 21	0.55
Ablation duration [min]	8.1 ± 4.6	7.7 ± 2.3	0.44
Ablation energy [W]	21716 ± 6255	22201 ± 6594	0.77
Contact force [g]	14.5 ± 3.4	14.1 ± 4.9	0.16

with general anesthesia had a reconnection. Also, a spontaneous reconnection detected just before the APT did not negatively influence the final APT result after re-isolation ($p = 0.25$). There were also no differences in the total number of RF applications, applied RF energy, ablation duration as well as in the mean contact force in PVs with reconnection and without reconnection; as shown in the Table 3.

Comparison with a historical control group using conventional ablation settings

The control group consisted of 25 patients (65 ± 11 years) with paroxysmal AF. Ninety-eight percent of the PVs could be isolated successfully (right inferior PV cannot be isolated due to esophagus temperature rise). Procedure time (237 ± 60 min vs. 138 ± 21 min, $p = 0.001$) and ablation duration (60.2 ± 17.2 min vs. 16.3 ± 5.2 min, $p < < 0.001$) were significantly longer and total applied ablation energy (227000 ± 67000 W vs. 48209 ± ± 12808 W, $p < 0.001$) was significantly higher in the former conventional study group in comparison to the current HPSD group. Despite the fact that significantly more ablation energy was applied in the conventional group, the first pass isolation rate was significantly lower than in the current study (48% to 92%, $p < 0.001$). Moreover, in the conventional RF ablation group, significantly more PV showed dormant reconnection than in the current study (29 PVs vs. 18 PVs, 31% vs. 18%, $p = 0.04$).

Complications

There were no acute severe complications after the procedure such as stroke or transient ischemic attack, pericardial tamponade, phrenic nerve paralysis or procedure related death. Two (8%) patients developed light groin hematomas requiring manual compression. In the short follow-up period of 4 weeks, none of the patients developed an atrial esophageal fistula or complaints suggesting esophageal injury.

Discussion

The main finding of the present study is that using RF energy of 50 W for 6–10 s ablations is feasible and effective in successfully isolating the PV, but with an acute reconnection rate in 18% in 32% of the patients. As expected, the total procedure time was shorter (138 ± 21 min) when compared to a recent study which used conventional ablation settings with and without ablation index (AI) data, 192 ± 42 min and 149 ± 33 min, respectively [2]. There were no severe acute and late complications at 4 weeks, which could be attributed to the high-power ablation.

The high power RF energy in short duration technique is being used increasingly worldwide in recent years [6–9]. The proposed main advantage of HPSD technique is its ability to destroy the tissue by using the resistive heating which occurs at the very beginning of the RF application [4, 5, 13]. As shown in in-vivo and ex-vivo studies, keeping the duration of high power ablations very short, around 5 s, limits the conductive heating phase creating lesions at comparable size but which are less deep as compared to lesions created by conventional low power long duration (the 25–30 W for 30 s ablations) technique [4]. As the lesion depth is less, the risk of producing collateral injury on the esophagus or the phrenicus nerve should be unlikely. Bhaskaran et al. [4] showed that 50 W ablations for 5 s produced transmural lesions without overheating of the tissue and thus avoiding stem pops. In their in vivo studies they showed that lesion width with 40 W/30 s ablations were larger than with 50 W/5 s but stem pop rate was also high 10.5%, whereas no stem pop occurred with 50 W/5 s. Borne et al. [5] also showed that HPSD technique produces lesions with similar volumes but with less depth than low power ablations. They elegantly showed that any increase in power settings (doubling of power increases lesion volume by 6.7) is much

more effective than any increase in duration (the doubling of duration increases lesion volume by 2.2) [5].

Despite the benefits shown in ex- and in vivo studies, clinical trials showing the acute effectiveness with the HPSD technique in the left atrium are limited. Moreover, there is also no consensus about the optimum power and duration settings for HPSD ablations. Kanj et al. [6] compared 50 W ablations during PVI with 35 W ablations and found a better 6-month outcome (82% vs. 66%) with 50 W. But they also noticed more stem pops and pericardial effusions in the 50 W group, as they did not shorten the ablation duration with 50 W and ablated as usual for at least 30 s [6]. Bunch et al. [7] described a so-called "painting" technique where they moved the catheter back and forth while ablating with 50 W. They reported 85% freedom from AF at 1-year without adverse effects and complication due to high power [7]. Of note, these two trials are from an era where contact force catheters were not available. The first study with HPSD ablation using contact force comes from Winkle et al. [8]. Using the EnSite™ Velocity™ platform and St. Jude Tacticath™ open irrigated-tip contact force catheter, they delivered 50 W ablations. The duration of ablation (mean 11.2 ± ± 3.7 s) was determined either by pacing loss or by achievement of a target lesion size index of 5.5–6. They reported a freedom from AF 86% and 83% at 1 year, in patients with paroxysmal and persistent AF, respectively [8]. As expected, both procedure (101 ± 19.7 min) and total RF energy time (895 ± ± 258 s) were very short and there were no complications reported. The largest clinical data about HPSD technique comes again from Winkle et al. [9]. They analyzed complication rates in 13,974 patients who underwent PVI with high power in four centers from 2006 till 2017. The ablation settings varied significantly with RF powers 45–50 W and duration ranging from 2 to 10 s. They concluded that 45–50 W ablations for short durations can be performed with very low complication rates [9].

In the documented clinic herein, 50 W had been chosen as the high-power energy level, as this is the safest energy level creating sufficient lesion size according to in-vitro studies [4, 5]. Also, the duration of the application was chosen according to the above-mentioned studies. The minimum duration of ablation in vitro studies was 5 s; thus, to compensate for the delay of the ablation generator in generating the desired power in vivo, we decided to apply ablation energy for a minimum of 6 s at each site [4]. We stopped the energy application at 10 s, according to the data shown by Winkle et al. [9]. Despite the present strict ablation protocol, the acute reconnection rate, which was the main objective of the study, was higher than expected. A 18% reconnection rate in 32% of patients is rather comparable with older studies when reconnection rates were evaluated with APT before the contact force era [14, 15]. Andrade et al. [16] showed several years ago a reconnection rate of 8% in 16% of the patients with PVI using contact force catheters compared to 35% reconnection in 50% the patients ablated with standard RF catheters.

These results are consistent with the data from the present study with conventional ablation settings [12]. Compared with the current study, the reconnection rate was higher, whereas the first pass isolation rate with conventional settings was strikingly lower in the conventional ablation group despite using a much higher amount of ablation energy and longer ablation duration [12]. This means that applying more energy in total but with a lower maximal power and with less catheter stability during the necessarily longer ablation time is less efficient in lesion formation.

The mean contact force in the current study was 14.2 ± 2.7 g and thus apparently sufficient according the EFFICAS I study data, which showed at least 10 g contact force should be applied to improve ablation success [17]. Moreover, ablations with suboptimal contact force defined as < 10 g were at a minimum level (5.2%) in the present study. Interestingly, the ablation duration (8.1 ± 1.7 s) in the present study was lower than in the study by Winkle et al. (11.2 ± 3.7 s) [8]. On the other hand, it cannot be said that the ablation lesions created in the current study were not effective because there was a very high first pass isolation rate (90% for the left and 85% for the right PVs) which is closely comparable with the elegantly designed study by Phlips et al. [18]. In their CLOSE-guided PVI concept, Phlips et al. [18] compared the efficacy and safety of a PVI protocol using the combination of contact force, interlesion distance and AI with the conventional ablation technique using just contact force. The ablation energy was just 35 W. The first pass isolation rate was 58% for the conventional group, and 96% for the CLOSE-guided group, slightly better than in the present study [18]. Importantly, the acute reconnection rate of 3% was very low in their CLOSE-guided group.

In the light of these data it seems that the lesions created with the HPSD strategy are at first effective, but this effect is not long lasting since APT after the PVI was positive in 18% of the PVs.

One explanation could be the very short duration of the RF applications in the current study. Longer applications, even if only just a few seconds more, might be needed even in the HPSD technique creating sufficient lesions. Since AI incorporates various parameters such as contact force, applied power and stability, the duration of application is dependent on these parameters. Using AI data, in combination with HPDS strategy, could create more sufficient lesions, with longer or even shorter ablation duration, dependent on the AI.

At the start of this study a decision was made not to use the AI parameter because at that time, there was no clinical or in vitro about using AI in high power and short duration ablation. Also, there were some safety concerns coming from the developing company (Biosense Webster) because of a lack of data. Recently, two studies showed better outcomes with high power energy applications using AI data. Chen et al. [19] showed promising data with a first-round PVI of 92% using 50 W limited by an AI value of 550 at the anterior and 400 at the posterior wall. Preliminary clinical results were also very promising with 96% freedom of AF. Unfortunately, they did not use the adenosine test to evaluate acute effectiveness of PVI with their ablation settings [19]. Okamatsu et al. [20] compared the acute effectiveness of the HSPD with low and medium power settings in a non-randomized manner. Each group consisted of 20 patients. In the low and medium power groups, the ablation energy was 30 W at the anterior and 20 W at the posterior wall and 40 W and 30 W, respectively. In the high power group, it was 50 W at the anterior and 40 W at the posterior wall. AI was again different in this study; 400 at the anterior, 360 at the posterior and 260 at the esophagus. The high-power group had the best first-pass isolation rate (85%) with no reconnection after APT (0%). Again, in these studies the AI targets and the RF power settings were different, thus a direct comparison could not be performed [20].

According to the present data, it can be concluded that ablation with HPSD using only the duration criteria (6–10 s) alone seems not very effective, at least in an acute phase, and combining the HSPD with AI parameter might improve the efficiency of this technique. There is great need for further studies to determine the most effective and safe settings for this promising technique.

Limitations of the study

This is a small, non-randomized, single-center study with a low number of patients, but with a very impressive end point, which was not expected. No significant differences were found when comparing clinical and procedural data in APT positive and negative groups. The reason for this could be the low number of patients, making statistical tests difficult to perform.

Again, the small number of patients in the present study makes it difficult to make firm conclusions but there are some interesting findings which should be investigated in studies with more patients. Such as that all 4 patients with general anesthesia did not have reconnection under adenosine gives the impression that general anesthesia could be helpful in creating consistent lesions, as shown by Di Biase et al. [21].

Although no complications occurred, such as phrenicus nerve damage or atrial-esophageal fistula which could be attributed to high power ablation, it is difficult to conclude that high power ablation with 50 W is safe due to the small number of patients. Moreover, no esophageal temperature monitoring during or gastroscopy after ablation was performed, thus no real safety data is available from the present study. On the other hand, till now other studies using high power did not report complications due to high power energy [9].

Conclusions

Pulmonary vein isolation using the HPSD technique with energy output of 50 W for 6 to 10 s is feasible but acute effectiveness was lower than expected, thus this promising technique needs to be further optimized using additional ablation parameters such as an ablation index.

Conflict of interest: None declared

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Impact of single versus double transseptal puncture on outcome and complications in pulmonary vein isolation procedures

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Abstract

Background: *The aim of the current study was to analyze the impact of single versus double transseptal puncture (TSP) for atrial fibrillation (AF) ablation.*

Methods: *Consecutive patients undergoing AF ablation were prospectively included in the AF ablation registry and were analyzed according to single versus double TSP.*

Results: *A total of 478 patients (female 35%, persistent AF 67%) undergoing AF ablation between 01/2014 and 09/2014 were included. Single TSP was performed in 202 (42%) patients, double TSP in 276 (58%) patients. Age, gender, body mass index, CHA_2DS_2-VASc score, left ventricular ejection fraction and operator experience (experienced operator defined as ≥ 5 years of experience in invasive electrophysiology) were equally distributed between the two groups. Repeat procedures (re-dos) were more frequently performed using single TSP access ($p < 0.001$). Left atrial (LA) diameter was larger in patients with double TSP ($p = 0.001$). Procedure duration in single TSP was identical to double TSP procedures ($p = 0.823$). Radiation duration was similar between the two groups ($p = 0.217$). There were 49 (10%) patients with complications after catheter ablation. There were no differences between complication rates and TSP type ($p = 0.555$). Similarly, recurrence rates were comparable between both TSP groups ($p = 0.788$).*

Conclusions: *There was no clear benefit of single or double TSP in AF ablation.* (Cardiol J 2021; 28, 5: 671–677)

Key words: atrial fibrillation, catheter ablation, pulmonary vein isolation, transseptal puncture, complications

Introduction

Transseptal puncture (TSP) is one of the most challenging steps in catheter ablation of atrial fibrillation (AF). It is a critical moment because of the potential risk of aortic puncture or puncture of the pericardial space. While single TSP reduces the risk associated with the puncture, double transseptal access simplifies the procedure in terms of immediate visualization of signals in the pulmonary vein, as well as avoidance of multiple changes of ablation and multipolar catheter through the single sheath.

There are three options for transseptal access. First, the single transseptal approach strategy. Second, the single-puncture-double-transseptal approach with one puncture being performed and the second sheath/catheter being advanced in the

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left atrium (LA) beneath the first access site [1]. Thirdly, there is the option of double-puncture--double-transseptal access. Despite the great practical relevance, the impact of this decision by the operator is yet unclear — therefore, the aim of this study was to investigate whether single or double transseptal access is superior in terms of procedure time, radiation time, complication rates and outcome.

Methods

Consecutive patients admitted for ablation of AF were prospectively included in the AF ablation registry. The Leipzig AF Ablation Registry has been approved by the Ethics Authority. Data from patients between January 2014 and September 2014 were analyzed. The patients were ≥ 18 years old. Patients undergoing cryo-ablation and procedures with radiation-saving technology (MediGuide, Abbott, St. Paul, MN, USA) were excluded to allow an unbiased comparison of the datasets.

Baseline characteristics were analyzed, procedural aspects with a focus on procedure and fluoroscopy time, complication rates, and follow-up data are presented herein.

Ablation procedure and TSP

Indication for catheter ablation was based on the current European Society of Cardiology Guidelines [2]. Procedural steps have been described prior [3]. In brief, the patients were deeply sedated (midazolam, propofol) and received analgetics (fentanyl) as described by Kottkamp et al. [4]. Placement of the diagnostic right ventricular apex and coronary sinus catheter was performed via left femoral venous access. Invasive arterial monitoring was performed via left femoral artery. Sheaths for TSP were placed into the right femoral vein. The decision for single versus double TSP was at the operators' discretion.

In cases of a single TSP, the guide wire was advanced into the superior vena cava. The steerable sheath (Agilis, Abbott, St. Paul, MN, USA); the curve [S, M, L] of the sheath was selected on the basis of a previously performed cardiac magnetic resonance imaging [CMR]) was advanced into the superior vena cava, the wire was removed and the TSP needle was inserted. In a left anterior oblique (LAO) view, the steerable sheath was withdrawn until typically 2 "jumps" were observed. The position was confirmed in a right anterior oblique view (RAO). A small amount of contrast dye was injected to prove septal tenting in LAO. Then, the puncture was performed and documented with an X-ray film. As soon as the needle was in the LA, the correct localization was confirmed by contrast dye injection and optionally by recording pressure via the needle tip. Subsequently, the steerable sheath was advanced into the LA, and the needle withdrawn. If a second TSP was planned, the same steps were performed with a non-steerable long sheath (SL 0, Abbott, St. Paul, MN, USA).

An electroanatomical reconstruction of the LA was performed by use of a three-dimensional (3D) mapping system (Carto 3, Biosense Webster, Diamond Bar, CA, USA; Ensite Velocity, Abbott, St. Paul, MN, USA), in a subgroup of these patients a fusion between the reconstructed 3D-CMR model and the electroanatomical reconstruction was done. Isolation of the pulmonary veins was confirmed by bidirectional block around the ipsilateral veins at an antral level. Linear lesions or focal ablations were added according to voltage information that was collected during sinus rhythm in all patients (Figs. 1, 2) [5].

Follow-up

Routine follow-up at the documented center included visits at 3, 6, and 9 months after ablation and then every 12 months thereafter [3]. Early recurrences within 3 months were considered as a blanking period. Atrial arrhythmias (≥ 30 s) were defined as recurrences. Usually, an electrocardiogram (ECG) was performed on each visit. If patients complained about symptoms, intensified resting and 1–7 days Holter-ECG-monitoring was performed. Only patients with at least one Holter-ECG or implantable device (pacemaker or implantable cardioverter-defibrillator [ICD]) and a follow-up of at least 6 months were included into the recurrence analysis.

Complications

Complications were classified into three groups: pericardial effusion (PE), groin complications and cerebrovascular incidents. PE was counted if relevant effusion was detected, puncture or operation was required. Groin complications were counted if a procedure (control, injection, stenting or operation) was required. The third category was cerebrovascular incidents including stroke and transient ischemic attack (TIA).

Statistical analyses

Mean values (and standard deviation [SD]) for normally distributed data, median (and interquartile range [IQR]) for skewed data and for categori-

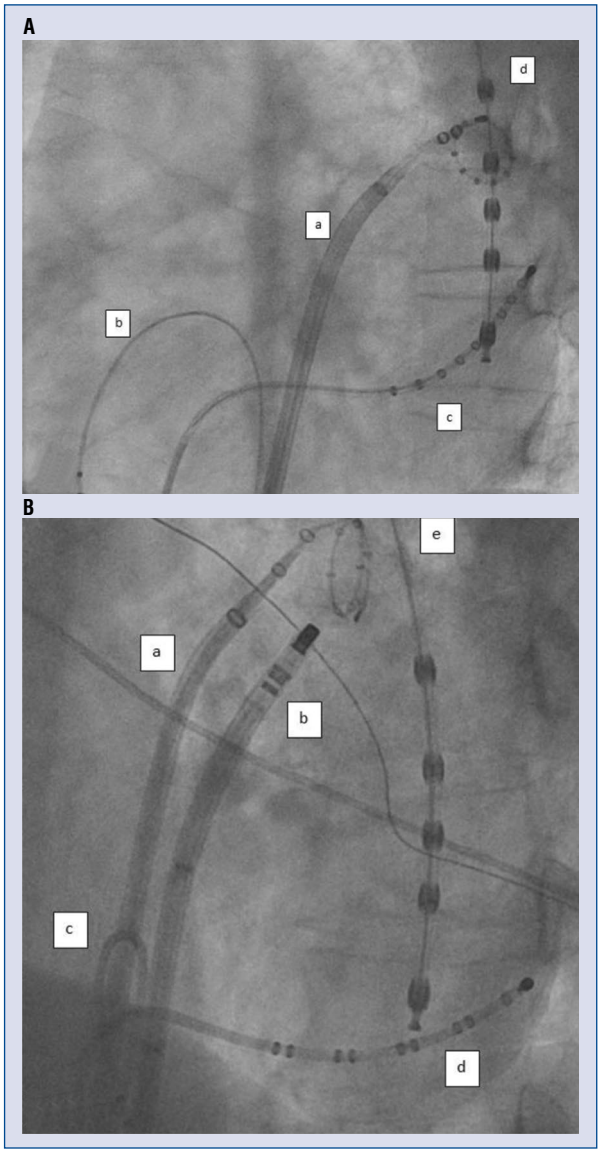

Figure 1. A. Left anterior oblique (LAO) 50° view. Single transseptal puncture; a — Agilis sheath (St. Jude, Abbott, St. Paul, MN, USA) in the left atrium with a 10 polar spiral-catheter in the left superior pulmonary vein; b — diagnostic catheter in the right ventricular apex; c — diagnostic catheter in the coronary sinus; d — temperature probe in esophagus; **B.** LAO 50° view. Double transseptal puncture; a — SL0 Sheath (St. Jude, Abbott, St. Paul, MN, USA) in the left atrium with a 10 polar spiral-catheter in the left superior pulmonary vein; b — Agilis sheath (St. Jude, Abbott, St. Paul, MN, USA) with ablation catheter ostial of the left superior pulmonary vein; c — diagnostic catheter in the right ventricular apex; d — diagnostic catheter in coronary sinus; e — temperature probe in the esophagus.

cal data proportions in percentage were used. The Spearman rank method was used for correlations. The unpaired t-test and the Mann-Whitney test were used for differences in continuous variables and χ^2 test for differences in categorical variables. Multivariable analysis (including variables with a p-value < 0.2 found on univariable analysis) was performed to find predictors for the complications. A p-value < 0.05 was defined as statistically significant. The statistical analyses were done with SPSS statistical software version 23 (SPSS Inc., Chicago, USA).

Results

The study included 478 patients undergoing radiofrequency AF catheter ablation between January and September 2014 at the Heart Center Leipzig (age 62 ± 10 years, 35% females, 67% persistent AF). The median follow-up was 23 months (IQR 4–37).

Single TSP was performed in 202 (42%) patients, double TSP in 276 (58%) patients. Age, gender, body mass index and CHA_2DS_2-VASc score, left ventricular ejection fraction and operator experience (defined as ≥ 5 years of experience in invasive electrophysiology) were equally distributed between the two groups. Repeat procedures (re-dos) were more frequently performed using single TSP access (p < 0.001). LA diameter was larger in patients with double TSP (p = 0.001). Procedure duration did not differ significantly between the two groups (p = 0.823). Radiation duration was similar for the two groups (p = 0.217), but the radiation dose was significantly lower in single TSP procedures (p < 0.001). TSP type did not affect the recurrence rate (p = 0.788) (Table 1, Fig. 3).

Complications

There were 49 (10%) patients with clinically relevant complications. There were 25 (5.2%) patients with pericardial effusion/tamponade, 19 (4.0%) with groin complications, and 5 (1%) patients suffered stroke/TIA. There was no significant difference in total complication rates between single and double TSP (p = 0.555), however, numerically there were less PE (10 vs. 15), less groin complications (n = 9 vs. n = 10) and less strokes (n = 1 vs. n = 4) in the single TSP group (Table 2). Univariable analysis showed no significant association between age, gender of patient, AF type, LA size, CHA_2DS_2-VASc score, re-do procedures or operator experience on the complication rate (Table 3).

Rhythm outcomes

During follow-up, 195 (41%) patients received long-term monitoring with Holter-ECG or had an

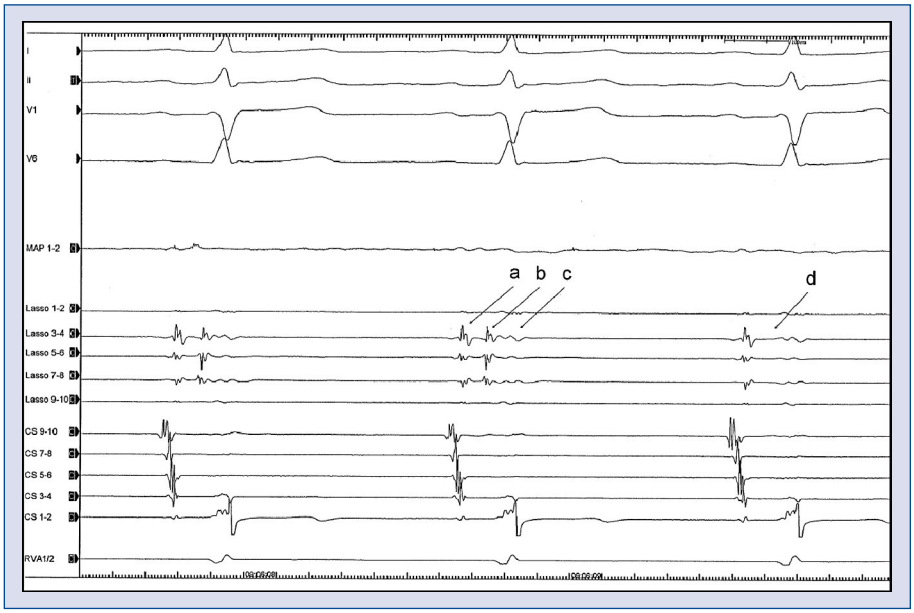

Figure 2. Electrocardiogramm during ablation. I, II, V1, V6 = Surface-electrocardiogram, MAP = ablation catheter, Lasso 1–10 = 10 polar spiral-catheter in the left superior pulmonary vein: a — farfield atrial signal; b — pulmonary vein signal; c — farfield ventricular signal; d — no pulmonary vein signal anymore; CS 1–10 — catheter in the coronary sinus; RVA — catheter in the right ventricular apex. The 10 polar spiral-catheter is placed in the left superior pulmonary vein. During ablation around the left superior pulmonary vein, the pulmonary vein signal on the spiral-catheter disappears (b → d). This means that the vein was isolated, because there was hence, no signal passing the ablation line.

Table 1. Clinical characteristics of the study population.

	Single TSP (n = 202)	Double TSP (n = 276)	P
Age [years]	62 (55–71)	64 (57–71)	0.110
Females,	79 (39%)	89 (32%)	0.131
Persistent AF	138 (68%)	184 (67%)	0.762
Re-ablation	75 (37%)	48 (17%)	< 0.001
BMI [kg/m^2]	28 (25–32)	28 (26–32)	0.119
CHA_2DS_2-VASc score	2 (1–3)	2 (1–3)	0.339
LAd [mm]	43 (39–47)	45 (41–48)	0.001
LVEF [%]	60 (55–64)	60 (51–64)	0.781
Radiation time [min]	18.6 (11.5–25.5)	16.2 (10.1–25.0)	0.217
Radiation dose [cGycm^2]	3782 (1.800–7.200)	6200 (3.038–10.323)	< 0.001
Procedure time [min]	150 (120–180)	145 (120–175)	0.823
Experienced operator	74%	79%	0.208
Recurrences > 6 months*	55 (71%)	79 (69%)	0.788
Complications	20 (10%)	29 (11%)	0.555

*Recurrences > 6 months in patients with available implanted device (pacemaker, ICD, ILR) available in 193 patients (40% of the study population). Data presented as number (%) or median (interquartile range); AF — atrial fibrillation; BMI — body mass index; LAd — left atrial diameter; LVEF — left ventricular ejection fraction; TSP — transseptal puncture

implantable device such as pacemaker/defibrillator allowing continuous monitoring and had a follow-up of 6 months or more. In this subgroup, there were 55 (71%) and 79 (69%) with recurrences for single and double TSP, respectively (p = 0.788) (Table 1, Fig. 3).

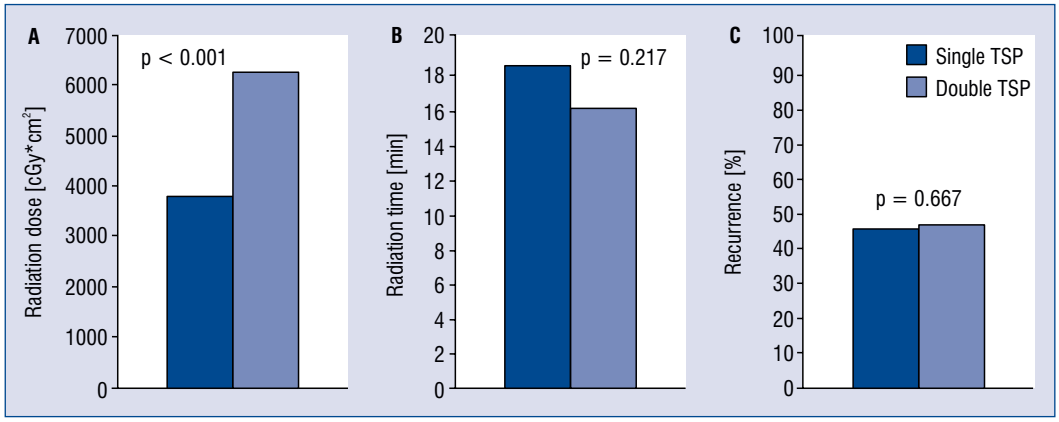

Figure 3. A. Radiation dose in single and double transseptal puncture (TSP); **B.** Radiation time in single and double TSP; **C.** Recurrence in single and double TSP.

Table 2. Complications accordingly to the transseptal puncture (TSP) type; p = 0.555.

	Total (n = 478)	Single TSP (n = 202)	Double TSP (n = 276)
None	429 (89.6%)	182 (89.7%)	247 (89.5%)
Pericardial effusion	25 (5.2%)	10 (4.9%)	15 (5.4%)
Groin complications	19 (4.0%)	9 (4.4%)	10 (3.6%)
Strokes	5 (1.0%)	1 (0.5%)	4 (1.4%)

Table 3. Prediction of complications.

	Univariable analysis	
	Odds ratio (95% CI)	P
Age	1.034 (0.984–1.087)	0.187
Females	2.124 (0.846–5.334)	0.109
Persistent AF	1.059 (0.395–2.840)	0.910
BMI [kg/m^2]	0.957 (0.868–1.055)	0.376
CHA_2DS_2-VASc score	1.240 (0.925–1.662)	0.151
Re ablation of AF	1.035 (0.365–2.935)	0.948
Experienced operator	1.602 (0.458–5.601)	0.461
TSP type	1.623 (0.606–4.345)	0.335
Procedure time [min]	1.006 (0.997–1.016)	0.171
Radiation time [min]	1.013 (0.971–1.057)	0.551
LAd [mm]	1.031 (0.958–1.109)	0.413

CI — confidence interval; AF — atrial fibrillation; BMI — body mass index; TSP — transseptal puncture; LAd — left atrial diameter

Discussion

Transseptal puncture

Despite the large and growing number of AF ablations and the practical relevance to the question whether single or double TSP is better, there is, according to available research, no study comparing single versus double TSP for AF ablation procedures.

The TSP is a crucial moment in the procedure of pulmonary vein isolation. Complications of TSP are puncture of the aorta and puncture of the posterior pericardial space. While in the SAFER Registry 0.9% PEs were described in all procedures [6], Haegeli et al. [7] showed, in double TSP procedures that there were 2.6% of pericardial effusions which required an intervention. Katritsis et al. [8] have shown that TSP in AF ablation procedures are associated with a higher incidence of pericardial tamponade compared to TSP in other cardiac procedures. In the present study population, the overall rate of PE was 5%, but PE requiring an intervention was low with only 0.8%. This is likely due to the large experience at the documented center.

The number of recurrences is high. However, because Holter monitoring was intensified in patients with symptoms and only those with Holter-ECG (or pacemaker/ICD) were included in the analysis, the rate of recurrences is likely estimated too high.

Some findings are interesting and the results need further explanations: for example, the finding that the X-ray time did not differ significantly between the two groups. Possibly, the higher radiation time which is needed for the second TSP in the double TSP group was compensated by the need for fluoroscopic control of the spiral and ablation catheter during the catheter exchange. That for each TSP an X-ray film was recorded, was probably the reason for a higher radiation dose in the double TSP group.

Secondly, the finding that single TSP only was more frequently performed in re-do procedures. This can be explained by the sometimes more challenging TSP because of an induration of the interatrial septum — therefore some operators may have skipped the initially planned second TSP.

And thirdly, there were more double TSP in larger LA diameters. Probably, operators skipped the second TSP in small LA due to anticipation of negative effects of 2 transseptal sheaths in a small LA. Interestingly despite the fact that double TSP needs an additional access in the groin for a second sheath, an only statistically non-significant difference was observed in groin complication rate between the two groups.

Silent cerebral events are more frequent in single transseptal access LA ablations, compared to double tansseptal access, due to the need for exchanging catheters over a single transseptal access as described by Deneke et al. [9]. In the current study, silent cerebral events were not assessed, for instance by use of magnetic resonance imaging after ablation. Although double TSP was associated with more clinical cerebrovascular events compared to single TSP, the difference was not significant. Pathophysiologically, micro air-embolisms are most likely to be caused by catheter exchanges, while macro embolisms are usually caused by thrombi. This may explain the difference in the results.

Overall, both approaches have advantages and disadvantages. The double TSP access has the advantage that one can simultaneously monitor the electrical signals in the pulmonary veins. Thus, the operator can often stop the ablation as soon as the signals in the pulmonary veins have disappeared. Furthermore, in linear lesions it is easier to check the lines by differential pacing. A single TSP requires more experience of the operator to promptly detect the signals in the pulmonary veins. Here, the pace and ablate strategy was frequently used for verification before the ablation catheter is taken out and multipolar catheter (Lasso, Biosense Webster, Diamond Bar, CA, USA or Advisor, Abbott, St. Paul, MN, USA) is inserted. This is an excellent method because pacing to ensure unexcitability along ablation lines has demonstrated to improve outcomes compared with bidirectional block alone [10]. It might be expected that with continuous pulmonary vein potential monitoring in double TSP, it is possible to reduce the duration of the procedure. On the other hand, the second TSP takes time. There was an inablity to show that ultimately, the procedure time tends to be shorter with double TSP.

It should be mentioned that all double TSP were performed by double puncture. Single-puncture double-transseptal access is not performed at the documented center. However, the latter has been shown to be safe in previous studies [11].

Limitations of the study

The main limitation of the study is that the decision on whether to use single or double TSP was at the operators' discretion and not based on randomization. On the other hand, 369 (77%) of the procedures were performed by operators who have ≥ 5 years invasive electrophysiological experience and thus the expertise was high and equally distributed between the two groups, reducing bias. It may be that in smaller LA, single TSP was preferred due to reasons of steerabilty.

Another limitation is the lack of assessment of iatrogenic ASD (iASD) after the procedure. However, Hammerstingl et al. [12] reported that persistent iASD occurred after double access through one puncture in 8 out of 27 (30%) patients. The study of Rillig et al. [13] has shown 1 out of 31 (3%) patients have a persistent iASD 12 months after double TSP. Cryo-balloon PVI also often goes along with a persistent iASD because of the use of a 12 French sheath (FlexCath Advance, Medtronic, Minneapolis, MN, USA) [14]. This sheath is larger than Agilis and SL 0 (8 and 7 French, Abbott, St. Paul, MN, USA). Nevertheless, iatrogenic ASD has not been found to lead to an increased risk of paradoxical embolism or relevant shunting [13, 15].

Complications

In the present study, there was no inverse association of the operator experience and lower complication rates. This might be a result of the fact, that experienced operators performed more complex procedures. Female sex was not associated with higher complication rates as it is described in the literature [16–21]. This could be partly explained by a relatively small ablation

cohort and a low number of complications. Neither was a higher CHA_2DS_2-VASc score associated with higher complication rate. CHA_2DS_2-VASc score and early institutional experience showed a higher complication rate in the literature [19–22]. This was also attributed to the small sample size and low complication rate.

Conclusions

There was no clear benefit of single or double TSP in AF ablation. Recurrence and complication rate did not differ significantly.

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The prognostic value of left atrial and left ventricular strain in patients after ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention

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Abstract

Background: *Global longitudinal strain (GLS) based on two-dimensional speckle-tracking echocardiography (2D-STE) might better reflect left ventricular (LV) contractile performance than conventional parameters. Recently, left atrial (LA) strain has been used as a more accurate alternative to assessing LA performance. The aim in this study was to assess the clinical prognostic value of left ventricular GLS (LV GLS) and peak atrial longitudinal strain (PALS) in patients after ST-segment elevation myocardial infarction (STEMI).*

Methods: *The study enrolled 199 patients who underwent primary percutaneous coronary intervention (pPCI) for first STEMI. Conventional and 2D-STE were performed within 48 h after pPCI. LV GLS and PALS were related to LV remodeling at 6-month follow-up and to adverse events.*

Results: *Diabetes mellitus, GLS and PALS independently predicted LV remodeling. With multivariable Cox proportional hazards, diabetes mellitus, GLS and PALS were predictive of adverse clinical outcomes. However, PALS did not add significant incremental value beyond LV GLS in the prediction of LV remodeling (increase in area under the receiver-operator characteristic curve [AUC]: 0.05, $p = 0.24$) and clinical events (even a decrease in AUC: 0.03, $p = 0.69$).*

Conclusions: *Both GLS and PALS provide independent prognostic value for adverse LV remodeling and clinical outcomes after STEMI. However, the ability of the combination of PALS and GLS to predict LV remodeling and clinical outcomes may not be superior to that of a single indicator.* (Cardiol J 2021; 28, 5: 678–689)

Key words: acute myocardial infarction, atrial strain, global longitudinal strain, echocardiography, remodeling, prognosis

Introduction

It is well known that outcomes of ST-segment elevation myocardial infarction (STEMI) have dramatically improved in recent years because of the introduction of modern thrombolytic drugs and percutaneous coronary intervention (PCI). However, left ventricular (LV) remodeling still occurs in 30–35% of patients [1, 2]. There is a progressive change in myocardial wall and ventricular structure, including expansion in the infarct region, wall thinning, and ventricular dilation in the non-infarcted region [3], which may be followed by adverse cardiovascular events and an increase mortality rate [4]. The introduction of two-dimensional speckle-tracking echocardiography (2D-STE) may

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contribute to quantification of LV global and regional systolic function [5]. Previous studies have shown that global longitudinal strain (GLS) can be used to predict LV remodeling and cardiovascular events after STEMI [6–9]. However, some studies showed that like GLS, global circumferential strain (GCS) and circumferential strain rate are independent predictors of LV remodeling [10].

Left atrial (LA) volumes and LA function have been recognized as significant predictors of adverse events in a range of cardiovascular diseases [11, 12]. Recently, 2D-STE is shown to be feasible for measuring LA deformations, thus allowing analysis of LA reservoir function (peak atrial longitudinal strain [PALS]) during the LV systolic phase [13]. More recently, LA reservoir function measured by PALS has shown good predictive value, even independently of LV GLS and LA volume [14, 15]. However, the additional value of PALS in patients with decreased LV GLS is questionable. A previous study proved that the prognostic value of PALS in patients with acute myocardial infarction (AMI) is dependent on LV GLS and LA size [16].

Accordingly, the purpose of this study was to examine patients with STEMI in: the clinical and prognostic importance of both LV GLS and PALS on LV remodeling and clinical outcome and prognostic information incremental of PALS to clinical data as well as reduced LV GLS.

Methods

Study population

In this prospective study, a total of 216 patients diagnosed with STEMI treated with primary PCI (pPCI) were enrolled from September 2017 to March 2018. The inclusion criteria were as follows: age 18 to 80 years, STEMI with onset of pain < 12 h before pPCI, and admission with STEMI based on present guidelines [17]. The exclusion criteria were: previous myocardial infarction or coronary artery bypass, significant valvular dysfunction, ventricular arrhythmia, atrial fibrillation or paced rhythm, and noncardiac disease with a life expectancy of < 1 year.

All patients were treated according to present cardiology guidelines. Before pPCI, they were given a loading dose of acetylsalicylic acid (ASA), 600 mg of clopidogrel, and 100 IU/kg of heparin (maximum 5,000 IU). This prospective study was approved by the Ethics Committee of the First Hospital of Lanzhou University. All patients signed informed consent forms.

Echocardiography

Echocardiographic data were obtained using the EPIQ 7C (Kininklijke Philips NV, Eindhoven, The Netherlands). Echocardiographic images were obtained by recording three consecutive heart cycles during apnea according to the guidelines of the American Society of Echocardiography [5]. Two experienced observers performed all patient views offline using an echocardiographic analysis system (QLAB Advanced Tissue Motion Quantification, Phillips).

Left ventricular end-systolic volume (LVESV), LV end-diastolic volume (LVEDV) and LV ejection fraction (LVEF) were determined using the biplane Simpson method in 4-, 3-, and 2-chamber views. The LV was divided into 16 segments, and segments were graded (1 = normokinetic, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic) according to subjective assessments of wall motion amplitude and changes in LV thickness at systole. The wall motion score index (WMSI) was defined as the sum of the segment score ratings divided by the number of segments scored. Pulsed-wave Doppler variables were measured by placing at the tip of the mitral valve (MV) leaflets from the apical 4-chamber view during diastole. The peak velocity of early (E) and late (A) diastole and the MV deceleration time were measured, and the E/A ratio was calculated. The measurements of myocardial peak early velocity (e') were performed at the lateral and medial mitral annulus. E/e' were obtained by dividing E by e'.

LV strain analysis

Two-dimensional echocardiographic images were obtained from 4-, 3-, and 2-chamber and midventricular short-axis views with frame rates of 60 to 90 frame/s. 2D-STE was performed using the commercially available software QLAB Advanced Tissue Motion Quantification (Philips) equipped with STE analysis. The LV endocardial and epicardial borders were initially traced at end-diastole, and the software automatically tracked the region of interest of the myocardium. Longitudinal peak systolic strain (LPSS), was obtained for each segment from which the software provided strain curves in all 16 segments. The GLS was calculated as the average of the observed segmental values of LPSS from the apical 4-, 3-, and 2-chamber view (Fig. 1A). For LV circumferential peak systolic strain and radial peak systolic, 2D-STE analyses were performed on the LV short-axis midventricular view. Global circumferential strain and global radial strain were calculated as the mean of values from LV short-axis views.

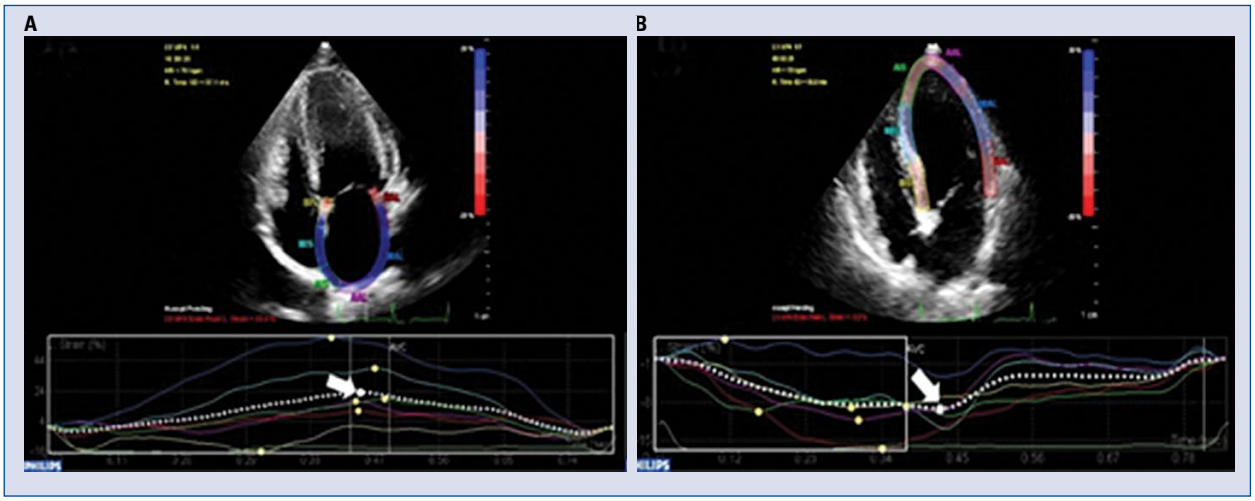

Figure 1. Two-dimensional speckle-tracking of the left ventricle (LV). The resulting strain curves for LV are shown with markings corresponding to peak global longitudinal strain (**A**); the resulting strain curves for left atrium are shown with markings corresponding to peak atrial longitudinal strain (**B**).

LA function analysis

The biplane Simpson method was used to analyze LA function. LA volume at LV end-systole (LAVmax), LA volume at LV end-diastole (LAVmin), and LA volume before atrial active contraction at the onset of the P-wave (LAVpreA) were obtained from apical 4- and 2-chamber views. All LA volumes were indexed to the body surface area [5]. From these volumes, the indexes of LA mechanical function were calculated: (1) total atrial emptying fraction: LA total ejection fraction = ((LAVmax – LAVmin) / LAVmax) × 100; (2) active atrial emptying fraction-an index of LA active contraction: LA active ejection fraction = = ((LAVpreA – LAVmin) / LAVpreA) × 100; (3) passive atrial emptying fraction-an index of LA conduit function: LA passive ejection fraction = ((LAVmax – LAVpreA) / LAVmax) × 100; (4) atrial expansion index of reservoir function: LA expansion index = = (LAVmax – LAVmin) / LAVmin × 100 [18].

For 2D-STE analysis of LA function, 2D gray-scale images were obtained in apical 4- and 2-chamber views, consistent with software and version for analyzing LV strain. To measure PALS (LA reservoir function), the beginning of QRS wave of the electrocardiogram was used as a reference point [13]. After selecting the cardiac cycle, the LA endocardial border was manually traced, automatically creating a region of interest to cover the thickness of LA myocardium from a total of 12 atrial segments (Fig. 1B). PALS values were estimated in each LA segment from two apical views, and the mean of global PALS was calculated. Patients in whom more than two segments with poor images could not be analyzed were excluded [2].

Follow-up and endpoint definition

At least 6 months after STEMI (18.3 ± 5.0 months), conventional echocardiography was performed. LV remodeling assessed by echocardiography was defined as an LVEDV increase of > 20% compared with baseline echocardiographic data [2]. Cardiovascular medical professionals completed follow-up phone calls in all patients each month after discharge from the hospital. Major adverse clinical events were a composite of death from any cause, hospitalization for heart failure and reinfarction, which were determined by both clinical visits and telephone calls. Hospitalization for heart failure occurring because of exacerbation of exertional dyspnea, with typical symptoms of pulmonary congestion and initiation of intravenous diuretics. Reinfarction was defined as a typical sign of chest pain, elevated cardiac enzyme levels, and obvious changes on the electrocardiogram [19].

Statistical analysis

Data for continuous variables are presented as the mean ± standard deviation or median and interquartile range, and categorical variables are presented as frequencies and percentages. Continuous variables are compared using the

independent-samples t test. Categorical variables were compared by the χ^2 test. To examine determinants of LV remodeling as a dependent variable, logistic forward regression analysis was applied. Univariate analysis was performed to choose the independent variables, and those variables with borderline values ($p < 0.10$) were submitted for multivariate analysis. The ability of clinical and echocardiographic parameters to predict adverse events were tested in univariate Cox proportional hazards models. To estimate the independent prognostic value of the above parameters, multivariate Cox proportional hazards analysis was also performed. Receiver operating characteristic (ROC) curve analysis were constructed, and areas under curves (AUC) were measured to determine cutoff values with maximum sensitivity and specificity. All statistical tests were two-sided, and a p value < 0.05 was considered statistically significant.

Results

Subject characteristics

A total of 216 patients with their first acute STEMI treated with pPCI were initially evaluated. Seventeen patients were excluded: before echocardiographic examination, 2 (0.9%) patients died during hospitalization, and 5 (2.3%) patients were not available to undergo echocardiography due to poor cooperation. Another 10 (4.6%) patients did not have sufficient image quality for tracking of the LV and LA walls. No patients were lost to follow-up. Thus, 199 patients were enrolled in the present study. Mean age was 57.4 ± 10.7 years, and 150 were males.

Prediction of LV remodeling at 6 months

At 6-month follow-up, the incidence of adverse LV remodeling was 25%. The baseline characteristics and echocardiographic parameters of both the LV remodeling group and the non-LV remodeling group are summarized in Table 1. Except for diabetes mellitus, the incidence of risk factors associated with cardiovascular disease did not differ significantly between the two groups. Anterior wall STEMI appeared in 106 (52%) patients and was the most common (76%) kind of adverse LV remodeling. After immediate pPCI therapy, a comparison of echocardiographic data showed larger LVEDV, LVESV and LA volume index (LAVI); lower LVEF, LA total ejection fraction, LA active emptying fraction and LA reservoir function and higher WMSI were observed in the LV remodeling group. There were significant reductions in both LV GLS and GCS, as well as in PALS, regardless of myocardial infarction location.

Univariate analysis demonstrated the variables to be correlated to the LV remodeling, namely diabetes mellitus, creatinine kinase-MB, LAVI, LA total ejection fraction, LA active emptying fraction, LA reservoir function, PALS, WMSI, GLS and GCS. Therefore, these parameters were included in a forward stepwise multivariate analysis, and diabetes mellitus, GLS and PALS were demonstrated to independently predict LV remodeling (Table 2).

The AUC for LV GLS and PALS were 0.86 and 0.89, respectively. However, PALS did not add significant incremental value beyond LV GLS (AUC increased from 0.86 to 0.91; $p = 0.24$) in the prediction of LV adverse remodeling. The best cutoff values of LV GLS and PALS for LV remodeling were –11.3% (sensitivity: 71.4%, specificity: 84.0%) and 28.9% (sensitivity: 72.7%, specificity: 87.8%) (Fig 2A–C).

Clinical events during follow-up

During a mean follow-up of 18.3 ± 5.0 months, 23 (11.6%) patients reached one or more composite endpoints: 3 (1.5%) patients died, 9 (4.5%) patients had reinfarction, and 11 (5.5%) patients required hospital admission to control heart failure symptoms, who were in the event group; the other 176 patients were divided into the event-free group. Comparison of clinical and echocardiographic features between patients who achieved the composite endpoint and those who did not are displayed in Table 3.

Diabetes mellitus, LAVI, LA total ejection fraction, LA active emptying fraction, LA reservoir function, PALS, LVEF, LV GLS and GCS were univariable predictors of adverse events. All these parameters were included in a multivariate Cox proportional hazards model, and diabetes mellitus, LV GLS and PALS were independently associated with the composite events (Table 4)

The AUC for LV GLS and PALS were 0.86 and 0.83, respectively. Similarly, PALS did not add significant incremental value beyond LV GLS (AUC decreased from 0.86 to 0.83; $p = 0.69$) in the prediction of the composite event. The best cutoff values of LV GLS and PALS for LV remodeling were –12.3% (sensitivity: 95.7%, specificity: 67.0%) and 28.9% (sensitivity: 88.1%, specificity: 65.2%) (Fig. 3A–C).

Figure 4A, B showed survival curves by the Kaplan-Meier analysis for patients divided by the best value of LV GLS and PALS: patients with LV

Table 1. Baseline characteristics of patients with and without left ventricular remodeling.

Parameter	Non-remodeling (n = 150)	Remodeling (n = 49)	P
Clinical parameters			
Number	150 (75%)	49 (32%)	
Male	73%	75.5%	0.76
Age [years]	57.9 ± 10.5	55.9 ± 11.0	0.26
BMI [kg/m^2]	24.5 ± 3.7	24.7 ± 3.9	0.75
Diabetes	18 (12.0%)	19 (38.8%)	0.001
Hypertension	65 (43.3%)	18 (36.7%)	0.42
Hyperlipidemia	53 (35.3%)	18 (36.7%)	0.86
Smoking	102 (68%)	32 (65.3%)	0.73
Systolic BP [mmHg]	111.2 ± 16.9	110.5 ± 17.3	0.82
Diastolic BP [mmHg]	73.1 ± 14.8	69.1 ± 9.6	0.07
Heart rate [bpm]	74.4 ± 15.3	74.5 ± 7.4	0.95
QRS width [ms]	97.9 ± 16.4	102.2 ± 21.1	0.14
S-TO-B [min]	328.0 ± 174.4	383.9 ± 175.6	0.053
D-TO-B [min]	49.1 ± 19.1	53.2 ± 21.2	0.20
eGFR [mL/min/1.73 m^2]	92.1 ± 27.3	99.0 ± 28.8	0.13
Creatinine [μmol/L]	71.9 ± 26.3	67.6 ± 11.5	0.19
Grace (scores)	95.8 ± 26.7	98.7 ± 22.6	0.49
Crusade (scores)	22.7 ± 13.2	19.9 ± 11.8	0.26
CK-MB [ng/mL]	332.2 ± 143.4	436.2 ± 117.9	0.001
CK-MB peak time after onset [h]	15.5 ± 5.1	19.4 ± 5.2	0.001
Killip class ≥ II	14 (9.3%)	6 (12%)	0.56
Anterior wall MI	66 (44.0%)	37 (75.5%)	0.001
ST max before PCI [mm]	3.8 ± 2.0	4.5 ± 2.4	0.07
Multivessel coronary disease	42 (28%)	20 (41%)	0.09
Medication during hospitalization			
ASA	150 (100%)	49 (100%)	1
Clopidogrel/Ticagrelor	150 (100%)	49 (100%)	1
Beta-blockers	113 (75%)	35 (71%)	0.59
ACEI/ARB	89 (59%)	29 (59%)	0.99
Statins	135 (90%)	45 (92%)	0.70
Initial LV function			
LVESV [mL]	86.9 ± 21.6	104.4 ± 28.7	0.001
LVEDV [mL]	41.3 ± 13.2	56.6 ± 17.6	0.001
LVEF [%]	52.9 ± 4.5	46.3 ± 3.8	0.001
WMSI	1.31 ± 0.1	1.37 ± 0.1	0.001
Deceleration time [ms]	171.3 ± 39.2	159.0 ± 53.4	0.09
E/A ratio	0.9 ± 0.3	0.9 ± 0.5	0.47
E/E′	11.8 ± 3.1	12.5 ± 3.8	0.21
Moderate or severe MR	6 (4%)	4 (8%)	0.06
GLS [%]	–14.7 ± 2.9	–10.6 ± 2.4	0.001
GCS [%]	–14.5 ± 3.5	–12.7 ± 2.9	0.001
GRS [%]	39.1 ± 8.6	38.7 ± 7.8	0.75
LA function			
LAVI [mL/m^2]	26.8 ± 5.0	32.8 ± 7.5	0.001
LA total ejection fraction [%]	54.9 ± 6.0	52.4 ± 5.4	0.01

→

Table 1 (cont.). Baseline characteristics of patients with and without left ventricular remodeling.

Parameter	Non-remodeling (n = 150)	Remodeling (n = 49)	P
LA passive emptying fraction [%]	28.3 ± 8.1	28.2 ± 5.6	0.95
LA active emptying fraction [%]	36.9 ± 6.6	33.7 ± 4.9	0.002
LA reservoir function [%]	125.7 ± 31.2	112.8 ± 25.7	0.01
PALS [%]	32.5 ± 5.9	23.0 ± 4.8	0.001
Follow-up LV function			
LVESV [mL]	88.8 ± 23.1	131.2 ± 35.1	0.001
LVEDV [mL]	39.1 ± 15.3	74.2 ± 23.4	0.001
LVEF [%]	56.5 ± 5.8	43.9 ± 3.9	0.001
Composite endpoint during follow-up			
Total number of complications	9 (6.0%)	14 (29%)	0.001

Data are expressed as mean ± standard deviation or number (%). ACEI — angiotensin-converting enzyme inhibitors; ARB — angiotensin II receptor blocker; ASA — acetylsalicylic acid; BMI — body mass index; BP — blood pressure; CK — creatine kinase; D-TO-B — door-to-balloon time; E/A — mitral inflow peak early velocity/mitral inflow peak late velocity; E/E′ — mitral inflow peak early velocity/mitral annular peak early velocity; eGFR — estimated glomerular filtration rate; GCS — global circumferential strain; GLS — global longitudinal strain; GRS — global radial strain; LA — left atrium; LAVI — left atrium volume index; LV — left ventricular; LVEDV — left ventricular end-diastolic volume; LVEF — left ventricular ejection fraction; LVESV — left ventricular end-systolic volume; MI — myocardial infarction; MR — mitral regurgitation; PALS — peak atrial longitudinal strain; ST max — maximum ST-segment elevation from a single lead; S-TO-B — symptom-to-balloon time; WMSI — wall motion score index

Table 2. Factors predicting adverse left ventricular remodeling after 6-month follow-up in univariate and multivariate analysis.

Parameters	OR	95% CI	P
Univariate analysis			
Diabetes	4.64	2.18–9.90	0.001
CK-MB [ng/mL]	1.01	1.0–1.01	0.001
LA function			
LA max [mL/m^2]	1.18	1.11–1.26	0.001
LA total ejection fraction [%]	0.93	0.88–0.98	0.01
LA active emptying fraction [%]	0.92	0.87–0.97	0.003
LA reservoir function [%]	0.98	0.97–0.99	0.01
PALS [%]	0.71	0.64–0.79	0.001
LV function			
WMSI	10.70	1.95–58.82	0.006
GLS [%]	1.81	1.50–2.18	0.001
GCS [%]	1.21	1.06–1.37	0.004
Multivariate analysis			
Diabetes	4.93	1.63–14.87	0.005
PALS [%]	0.77	0.68–0.87	0.003
GLS [%]	1.36	1.11–1.67	0.001

CI — confidence interval; CK — creatine kinase; GCS — global circumferential strain; GLS — global longitudinal strain; LA — left atrium; LV — left ventricular; OR — odds ratio; PALS — peak atrial longitudinal strain; WMSI — wall motion score index

GLS > –12.3% (log-rank χ^2 = 37.3, p = 0.001) and PALS < 23.8% (log-rank χ^2 = 47.0, p = 0.001), and had composite event rates of 3% and 4%, respectively.

Discussion

The major results of this study showed the prognostic value of LV GLS and PALS measured

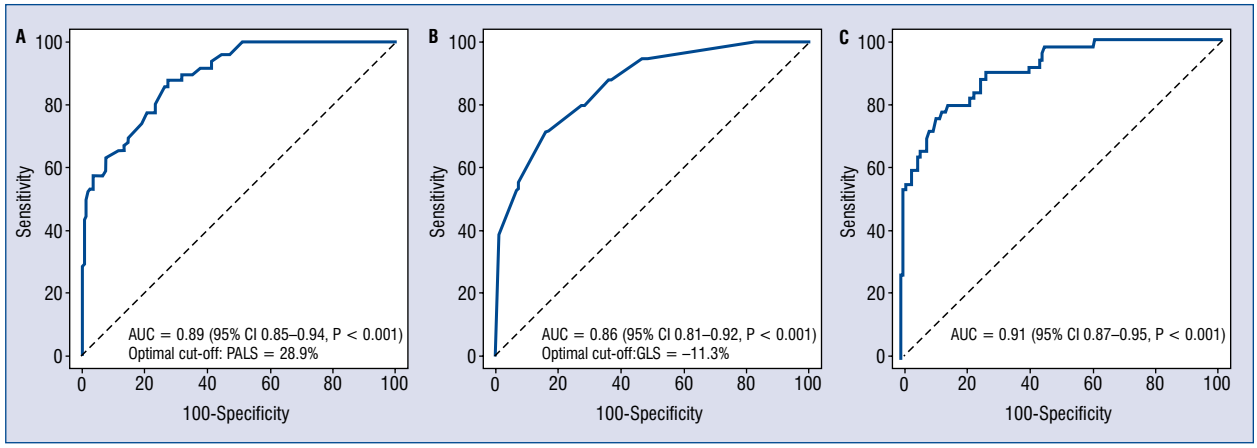

Figure 2. Receiver operating-characteristic curve for prediction of left ventricular remodeling 6 months after acute myocardial infarction using the independent variable peak atrial longitudinal strain (PALS) (**A**), left ventricular global longitudinal strain (LV GLS) (**B**) and PALS combined with GLS (**C**); AUC — area under curve.

Table 3. Baseline characteristics of patients, event and event-free.

Parameter	Event-free	Event	P
Clinical parameters			
Male	72%	87%	0.21
Age [years]	57.4± 10.5	57.7 ± 11.4	0.90
BMI [kg/m^2]	24.4 ± 3.5	25.3 ± 5.0	0.25
Hypertension	74 (42.0%)	9 (39.1%)	0.83
Hyperlipidemia	59 (35.5%)	12 (52.2%)	0.10
Smoking	116 (65.9%)	18 (78.2%)	0.34
Systolic BP [mmHg]	110.4 ± 16.3	115.6 ± 21.3	0.17
Diastolic BP [mmHg]	72.0 ± 13.7	73.1 ± 14.2	0.71
Heart rate [bpm]	74.6 ± 14.1	73.0 ± 11.3	0.61
QRS width [ms]	97.4 ± 15.9	110.9 ± 25.2	0.001
S-TO-B [min]	334.5 ± 176.4	397.2 ± 162.3	0.11
D-TO-B [min]	48.9 ± 19.5	56.1 ± 19.0	0.10
eGFR [mL/min/1.73 m^2]	93.5 ± 26.2	96.2 ± 38.3	0.66
Creatinine [μmol/L]	71.4 ± 24.7	66.6 ± 11.9	0.36
Grace (scores)	96.6 ± 25.4	95.2 ± 28.9	0.79
Crusade (scores)	21.8 ± 12.9	22.7 ± 12.4	0.78
Killip class ≥ II	14 (8.0%)	6 (26.1%)	0.007
Anterior wall MI	83 (47.2%)	20 (87.0%)	0.001
CK-MB [ng/mL]	347.4 ± 146.5	437.2 ± 98.5	0.005
CK-MB peak time after onset [h]	16.2 ± 5.3	18.4 ± 5.1	0.06
ST max before PCI [mm]	4.0 ± 2.1	3.7 ± 1.9	0.59
Multivessel coronary disease	54 (30%)	8 (35%)	0.81
LA function			
LA max [mL/m^2]	27.7 ± 5.8	33.1 ± 7.5	0.001
LA total ejection fraction [%]	54.7 ± 5.9	50.7 ± 5.3	0.002
LA passive emptying fraction [%]	28.6 ± 7.6	25.6 ± 7.9	0.07
LA active emptying fraction [%]	36.4 ± 6.5	33.6 ± 4.4	0.04

→

Table 3 (cont.). Baseline characteristics of patients, event and event-free.

Parameter	Event-free	Event	P
LA reservoir function [%]	124.8 ± 30.6	105.8 ± 22.4	0.003
Moderate or severe MR	8 (5%)	2 (9%)	0.07
PALS [%]	31.1 ± 5.9	22.7 ± 5.7	0.001
Initial LV function			
LVESV [mL]	88.3 ± 21.7	113.5 ± 34.0	0.001
LVEDV [mL]	42.9 ± 13.4	61.5 ± 17.6	0.001
LVEF [%]	51.9 ± 5.1	46.6 ± 4.0	0.002
GLS [%]	–14.1 ± 3.1	–10.2 ± 1.9	0.001
GCS [%]	–14.2±3.3	–12.6 ± 3.5	0.03

Data are expressed as mean ± standard deviation or number (%). BMI — body mass index; BP — blood pressure; CK — creatine kinase; D-TO-B — door-to-balloon time; eGFR — estimated glomerular filtration rate; GCS — global circumferential strain; GLS — global longitudinal strain; LA — left atrium; LV — left ventricular; LVEDV — left ventricular end-diastolic volume; LVEF — left ventricular ejection fraction; LVESV — left ventricular end-systolic volume; MI — myocardial infarction; MR — mitral regurgitation; PALS — peak atrial longitudinal strain; PCI — percutaneous coronary intervention; ST max — maximum ST-segment elevation from a single lead; S-TO-B — symptom-to-balloon time

Table 4. Factors predicting adverse events according to Cox proportional hazards regression model using univariable and multivariate analysis.

Parameters	HR	95% CI	P
Univariate analysis			
Diabetes	4.96	2.18–11.2	0.001
CK-MB [ng/mL]	1.01	1.00–1.01	0.007
LA max [mL/m^2]	1.14	1.08–1.20	0.001
LA total ejection fraction [%]	0.90	0.84–0.96	0.01
LA active emptying fraction [%]	0.93	0.87–0.99	0.04
LA reservoir function [%]	0.97	0.96–0.99	0.01
PALS [%]	0.82	0.76–0.88	0.001
LVEF [%]	0.82	0.76–0.89	0.001
GLS [%]	1.55	1.31–1.83	0.001
GCS (%]	1.08	1.01–1.16	0.02
Multivariate analysis			
PALS [%]	0.88	0.78–0.99	0.04
GLS [%]	1.30	1.01–1.66	0.03
Diabetes	4.61	1.50–14.19	0.008

CI — confidence interval; CK — creatine kinase; GCS — global circumferential strain; GLS — global longitudinal strain; HR — hazard ratio; LA — left atrium; LV — left ventricular ejection fraction; PALS — peak atrial longitudinal strain

by 2D-STE in patients with STEMI after pPCI, as follows: (1) reductions in PALS and LV GLS are both strongly correlated to LV remodeling and the composite event; (2) however, PALS does not add significant incremental prognostic value to LV GLS.

Acute myocardial infarction is characterized by regional myocardial damage that results in systolic and diastolic dysfunction with a risk of adverse LV remodeling. For several decades, previous researchers have focused on the pathophysiology and prognosis of LV systolic dysfunction after AMI and have shown that LV remodeling mostly occurs in cases of transmural infarction and if at least 20% of LV mass is destroyed [3]. Although LVEF and WMSI have traditionally been used to evaluate the degree of myocardium injury and even WMSI is considered an independent predictor of LV remodeling [20, 21], either of them has

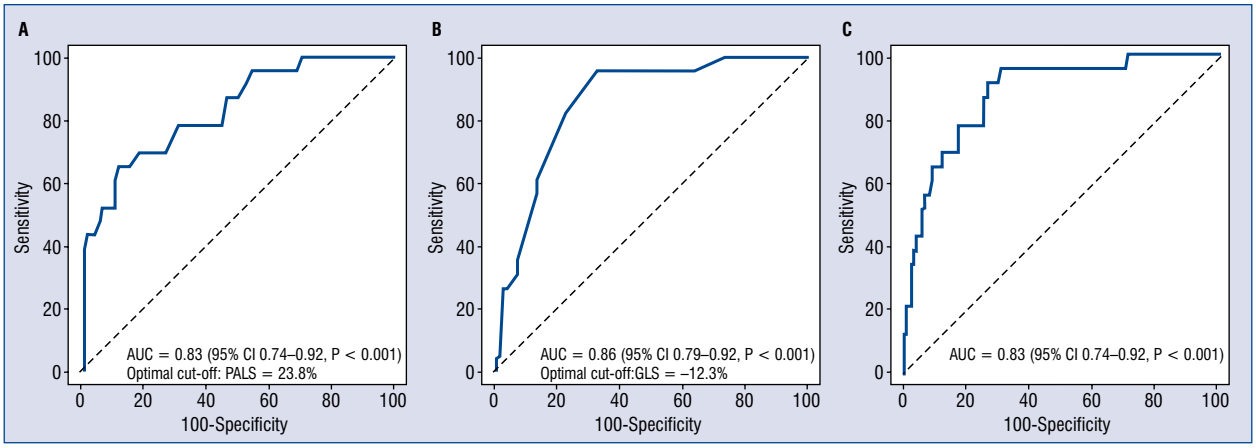

Figure 3. Receiver operating-characteristic curve for prediction of clinical adverse events using the peak atrial longitudinal strain (PALS) (**A**), left ventricular global longitudinal strain (LV GLS) (**B**) and PALS combined with GLS (**C**).

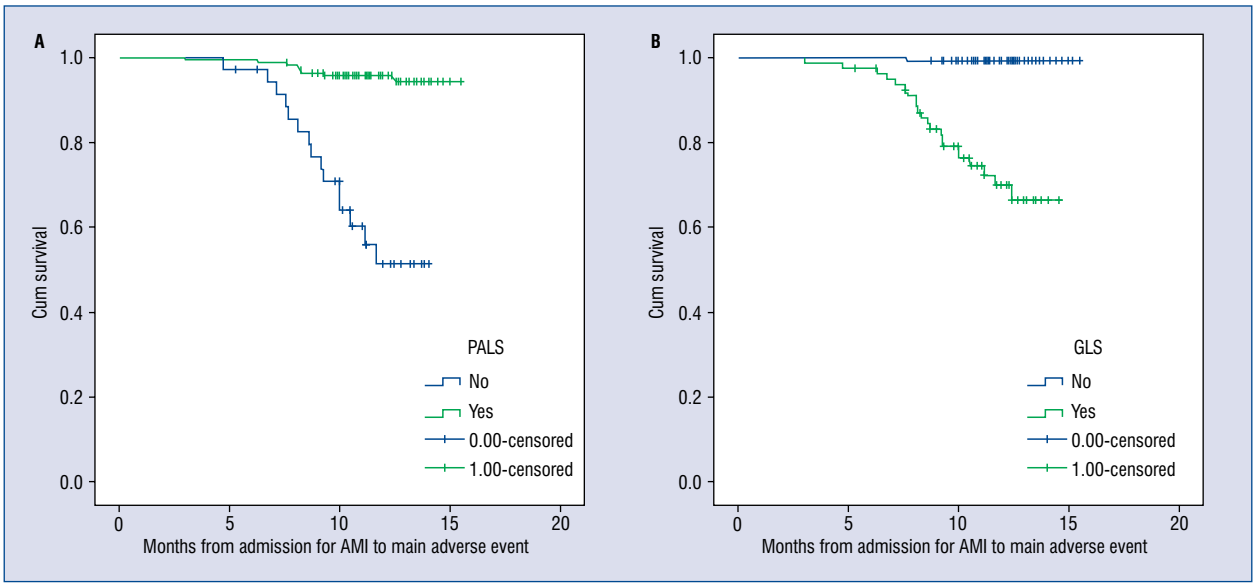

Figure 4. Survival analysis according to peak atrial longitudinal strain (PALS) and global longitudinal strain (GLS) values Kaplan-Meier survival curves for patients according to PALS (the optimal cutoff 23.8%) (**A**) and left ventricular GLS (the optimal cutoff –12.3%) (**B**); AMI — acute myocardial infarction.

limitations for risk stratification after AMI [22]. 2D-STE, as a semiautomatic method, is not only applied to estimate the motion of the myocyte but also can distinguish the passive and active motility of LV segments, suggesting it is a more sensitive measurement of LV function [23]. The present results showed that LV GLS not LVEF and WMSI is an independent predictor of LV remodeling, and the AUC was 0.86, and the best cutoff value was –11.3%, which is similar to the –12.46% reported by Lacalzada et al. [24]. This may be because strain can better distinguish between passive and active motion of each segment of LV, and hence GLS appears to be more useful than LVEF and WMSI in predicting LV remodeling. Hung et al. [10] found that not only GLS but also GCS and circumferential strain rate are independent predictors of LV remodeling at 20 months after adjusting for clinical variables. It seems that circumferential function plays an essential role in maintaining LV structure, so circumferential dysfunction would lead to LV dilatation. In the current study, GCS

was not an independent predictor by multivariate analysis. The reason for the contradictory data in predicting LV remodeling by GCS may be the different follow-up periods after AMI.

Park et al. [7] demonstrated that not only GLS showed good predictive value for LV remodeling in patients with anterior wall AMI but also predicted death or heart failure as composite events, indicating that GLS was also a good predictor of adverse clinical events. A previous study confirmed that LV strain and strain rate were superior to LVEF and WMSI in risk stratification for long-term outcome, and a GLS value > –15.1% was an independent predictor of all-cause mortality [25]. However, the VALIANT Echo study, in a sample of 603 patients with LV dysfunction, heart failure, or both 5 days after myocardial infarction, showed that both longitudinal and circumferential strain and strain rate are the independent prognostic indicators in patients with high-risk myocardial infarction [10]. In the present study, it was shown that GLS is an independent predictor and the optimal GLS cutoffs for predicting composite events is > –12.3%, with a sensitivity and specificity of 95.7% and 67.0%.

Currently, LA function is assessed by LA volume, mechanical function and strain. Previous observation reported that LA volume is significantly related to cardiovascular disease and is independently correlated to death or heart failure [26]. LA mechanical function consists of the reservoir function, conduit and contractile function. LA reservoir function, which reflects LA relaxation, is particularly important during acute ischemia [27]. However, assessing changes in LA volume during different periods of the cardiac cycle is highly time-consuming; in addition, applying a simple geometric model to an asymmetric chamber may affect the estimation of LA volume [28]. Recently, by directly evaluating LA myocardial deformation to assess LA reservoir function post-AMI, clinically relevant information can be provided. PALS, which is evaluated by speckle-tracking derived strain, shows the direct evaluation of the atrial myocardium and may better reflect the properties of LA [29, 30]. Antoni et al. [31] confirmed the value of PALS to predict adverse events in patients after AMI treated with PCI, since only 48 of 320 patients (15%) reached the composite endpoint. This event rate was higher than the rate herein, where 23 of 199 patients (11.6%) experienced these events, perhaps due to a significantly shorter follow-up time. However, Ersboll et al. [16] found that the magnitude of PALS during the reservoir phase depends on the GLS and LA size, and measurement of PALS has no independent prognostic value. In patients with post-AMI, LA relaxation may be damaged by myocyte loss and LV filling pressure may also increase, both of which may be present, possibly limiting atrial expansion independently of LV longitudinal contraction damage, consequently increasing the risk of LV remodeling and adverse events [31, 32]. In the present study, PALS, like LV GLS, was found to be another independent predictor of LV remodeling; and a higher PALS value < 23.8%, with a sensitivity and specificity of 88.1% and 65.2%, was shown to be an independent predictor of a composite event.

In the current study, the independent prognostic value of PALS and LV GLS in patients with STEMI after pPCI was observed. Additionally, PALS did not add significant incremental value beyond LV GLS in the prediction of LV remodeling (AUC: 0.05, $p = 0.24$) and clinical events (even a decrease in AUC: 0.03, $p = 0.69$). The highly predictive values of GLS and PALS are further underscored.

Limitations of the study

A number of limitations of this study should be acknowledged. First, this is a single-center experience. In addition, the enrolled population was limited to patients with their first STEMI treated with pPCI, with low-risk AMI, and patients who died before completing their 6-month echocardiogram were excluded. Therefore, selection bias and potential selection bias should be taken into account when interpreting the findings. Finally, although the longitudinal, circumferential and radial strain of LV was analyzed, the impairment of right ventricular function was not assessed, which needs further study.

Conclusions

In conclusion, in patients with STEMI in any location treated with pPCI, both LV GLS and PALS are both more sensitive to myocardial damage and provide independent prognostic value for adverse LV remodeling and clinical events. However, the ability of the combination of PALS and GLS to predict LV remodeling and clinical outcomes may not be superior to that of a single indicator.

Conflict of interest: None declared

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The role of hemostatic markers as venous stenosis or occlusion predictors following first transvenous cardiac device implantation

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Abstract

Background: *Among patients with an implanted cardiac implantable electronic device (CIED), ipsilateral upper extremity vein stenosis or occlusion (VSO) is observed more frequently than in the general population. However, there are no data available concerning the relationship between hemostatic markers (and their dynamics) and the occurrence of VSO. The aim of this study was to assess the predictive value of beta-thromboglobulin, the von Willebrand factor (vWF), fibrynogen and D-dimer for VSO development among first time CIED recipients.*

Methods: *This is a single-center, prospective study of consecutive first time CIED recipients without upper extremity VSO in baseline ultrasound examination. Biochemical data were collected from all the patients before CIED implantation (first measuring), up to 7 days subsequent (second measuring) and 6 months after the operation (third measuring). Primary endpoint was defined as the presence of upper extremity VSO at the implantation site during the ultrasound examination 6 months after the operation.*

Results: *The study included 71 patients (mean age 73.1 ± 10.5 years; 39 [55%] male). The incidence of VSO within 6-months follow up was 21.1%. Average concentrations of hemostatic markers increased significantly in all patients immediately after CIED implantation. Serial hemostatic marker concentrations were similar in patients who met or did not meet the primary endpoint, apart from vWF. The mean concentration was significantly elevated in the group of 15 patients who reached the primary endpoint ($p = 0.032$).*

Conclusions: *A significant increase in vWF concentration at 6 months post implantation may be a marker for VSO occurrence.* (Cardiol J 2021; 28, 5: 690–696)

Key words: cardiac implanted electronic devices, vein stenosis or occlusion, hemostatic markers

Introduction

Among patients implanted with a cardiac implantable electronic device (CIED), ipsilateral upper extremity vein stenosis or occlusion (VSO) is observed more frequently than in the general population and occurs in 14–64% of patients with CIED [1–3]. Although VSO is usually asymptomatic it can lead to upper extremity edema, paresthesia or pain and limits CIED upgrade.

Currently, several mechanisms of VSO formation are suggested. The most frequently mentioned one is the thromboembolic mechanism [4, 5]. The postulated thromboembolic mechanism of VSO

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formation prompts the search for biochemical indicators of pro-thrombotic activity, which would correlate with the risk of VSO.

The concentration of D-dimers is a biochemical marker of the thromboembolic process. The precursor of D-dimers is fibrinogen: one of the coagulation system proteins. It seems that among patients after CIED implantation, the concentration of D-dimers and fibrinogen should be higher in patients with VSO [6]. Platelet activation results in secretion of many clotting activators, including beta-thromboglobulin (beta-TG). The von Willebrand factor (vWF), a glycoprotein involved in the hemostasis process, prevents the degradation of factor VIII of the coagulation pathway, promoting the formation of connections between collagen fibers, glycoproteins of the intercellular matrix and endothelial cells and blood platelets.

However, there are no specific data available concerning relationship between concentrations of the aforementioned hemostatic markers (and their dynamic) and the occurrence of VSO after CIED implantation. The aim of this study was to assess the predictive value of beta-TG, vWF, fibrynogen and D-dimer concentrations for VSO occurrence among first-time CIED recipients.

Methods

Study population

A single-center, prospective study was performed of consecutive first-time CIED recipients hospitalized in the documented department.

Patients included were those with:

— qualification for first-time intravenous implantation of the CIED system;
— written, informed consent to participate in the study.

Patients excluded were those with:

— upper extremity, shoulder girdle or jugular vein stenosis confirmed by preoperative imaging;
— venous compression syndromes of the upper extremity (thoracic outlet syndrome, cervical rib, compressive soft tissue tumors);
— thrombophilia;
— previous intervention on venous system at the intended implantation site.

Clinical assessment and follow-up

Each patient underwent an ultrasound examination to assess the condition of the venous system of the upper extremity, shoulder girdle and jugular veins before the planned operation and 6 months after the operation. The assessment of jugular veins and veins of shoulder girdle were performed in the supine position, while radiopaque and axillary veins were additionally assessed in the sitting position. A duplex Doppler mode consisting of a real-time B-mode image with a color-flow Doppler overlay was used for assessing the morphology and venous flow. All ultrasound examinations were carried out by experienced echocardiographers (all certified with the second-degree accreditation in echocardiography of the Echocardiography Working Group of the Polish Cardiac Society) using the Philips EnVisor C (Philips Electronics NV, Netherlands). The tests were examined using a 5–13 Mega-Hertz array transducer in both longitudinal and transverse sections.

All clinical conditions analyzed in the study, like diabetes or prediabetes, chronic heart failure, arterial hypertension, atrial fibrillation or atrial flutter, cancer, previous stroke or transient ischemic attack, were assessed based on subject medical history and in accordance with current guidelines.

The procedure of CIED implantation was performed in a reference cardiology unit by an expected electrophysiologist. For each subject the first-choice procedure to gain vascular access was venesection of cephalic vein. If this was unsuccessful, a subclavian vein puncture under ultrasound imaging was performed. Patient characteristics due to the number of implanted leads and type of vascular access was presented in a previous paper [7].

The concentrations of beta-TG, vWF, fibrynogen and D-dimer were measured before CIED implantation (first measuring), up to 7 days subsequent (second measuring) and 6 months after the operation (third measuring). Manual EIA kits were used to measure beta-TG and vWF (Shanghai Sunred Biological Technology Co, Shanghai, China). Roche Diagnostics laboratory kits were used in order to conduct D-dimer and fibrynogen tests using Cobas 6000 analyzer.

Study endpoints

Primary endpoint was defined as the presence of VSO in the vein system of the upper extremity, shoulder girdle or jugular vein at the implantation site during the ultrasound examination 6 months after the operation. For veins accessible to direct insonation, the criteria of noncompressibility, visualization of echogenic intravascular mass, and the absence of respiratory variation were used (subclavian vein). For veins inaccessible to direct inosonation, the criterion of monophasic flow at the stenosis site with no retrograde wave or no

Table 1. The mean concentrations of biochemical markers measured at 1st, 2nd and 3rd measuring point in the whole study group.

Hemostatic marker	Mean ± SD	Median (IQR)
Fibrynogen [mg/dL]		
1st measuring	351.5 ± 81.8	343 (86–530)
2nd measuring	424.3 ± 95.5	408 (178–627)
3rd measuring	404.2 ± 98	391 (212–619)
D–dimer [mg/dL]		
1st measuring	723.5 ± 664	458 (170–3210)
2nd measuring	1252.1 ± 1068.3	875 (326–6586)
3rd measuring	1021.4 ± 778.5	766 (230–3890)
von Willebrand factor [μg/L]		
1st measuring	13.26 ± 5.55	12.25 (3.78–27.56)
2nd measuring	18.35 ± 9.29	16.64 (5.37–66.55)
3rd measuring	19.56 ± 11.11	17.38 (0.32–56.86)
Beta–thromboglobulin [μg/L]		
1st measuring	14.24 ± 5.77	13.43 (3.42–30.37)
2nd measuring	18.12 ± 6.93	18.18 (2.21–34.18)
3rd measuring	17.86 ± 6.5	10.06 (5.61–32.7)

Continuous and ordinal variables are shown as median (interquartile range [IQR]) and as mean ± standard deviation (SD).

color signal or flow in the vessel lumen was used (middle part of subclavian, brachiocephalic vein) to detect VSO [8, 9].

Statistical analysis

Statistical analysis was performed using Statistica v. 12. Quantitative variables are expressed as mean ± standard deviation and median (interquartile range). Categorical variables are presented as an exact number and percentage of patients. Differences between two groups for continuous variables were tested by the Mann-Whitney U-test. The comparisons of categorical variables were analyzed using the χ^2 independence test. Two-way tables were assessed with the χ^2 test with double-sided Fisher exact test due to a limited number of patients. A p value < 0.05 was defined as statistically significant. The dynamics of biochemical marker changes were assessed using the Friedman test. Post hoc analysis with the Wilcoxon signed ranks test was performed using the Bonferroni correction for multiple comparisons (1 vs. 2, 2 vs. 3, 1 vs. 3 measuring point), resulting in a significance level set at $p < 0.017$.

Results

The study population consisted of 71 patients (mean age 73.1 ± 10.5 years; 39 [55%] male). Detailed patient characteristics were summarized in Supplemental Content (**Suppl. Table S1**). Implanted device systems comprised: cardioverter-defibrillator (n = 26), single-chamber or dual-chamber pacemakers (n = 34) and cardiac resynchronization therapy (n = 11). The incidence of VSO within 6-month follow up was 15 (21.1%) patients.

The mean concentrations of biochemical markers and their dynamics assessed at the 1st, 2nd and 3rd measuring points in the whole study group are presented in Table 1 and Figure 1. The average concentration of each biochemical marker increased significantly between the 1st and the 2nd measuring points.

The average values of biochemical markers at all measuring points were similar among patients who met or did not meet primary endpoint, except for vWF concentrations at the 3rd measuring point. The average concentration of the vWF 6 months after the CIED implantation was significantly greater in the group of patients with VSO than in the other subjects ($p = 0.03$). It was due to an additional increase of vWF concentration between the 2nd and 3rd measuring point observed only among patients with VSO (Fig. 2). The mean concentrations of biochemical markers and their dynamics in subgroups with and without primary endpoint were presented in Table 2 and Figure 2.

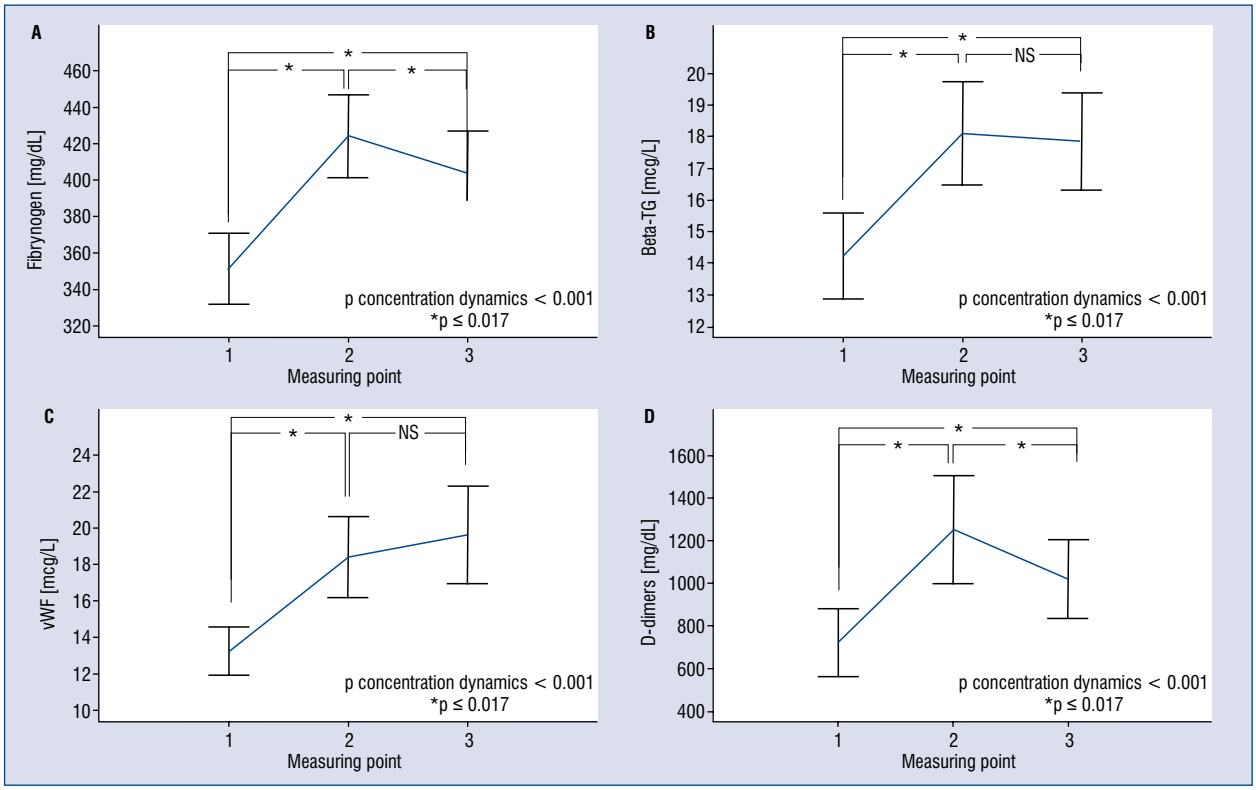

Figure 1. The mean concentrations of biochemical markers measured at 1st, 2nd and 3rd measuring point in the whole study group; beta-TG — beta-thromboglobulin; vWF — the von Willebrand factor; NS — non-significant.

Table 2. The mean concentrations of biochemical markers measured at 1st, 2nd and 3rd measuring point among patients who met or did not meet the primary endpoint.

Hemostatic marker	Endpoint		Non-endpoint		p
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
Fibrynogen [mg/dL]					
1st measuring	347 ± 87.5	313 (244–530)	352.7 ± 81	352 (86–481)	0.61
2nd measuring	410.7 ± 91.3	388 (264–564)	427.9 ± 97	413.5 (178–627)	0.54
3rd measuring	398 ± 100.6	376 (234–591)	405.9 ± 98.2	396.5 (212–619)	0.82
D-dimer [mg/dL]					
1st measuring	762.9 ± 864.6	424 (170–3210)	712.9 ± 608.5	458.5 (170–2908)	0.58
2nd measuring	1247.3 ± 1132.6	825 (357–4506)	1253.4 ± 1061.1	929 (326–6586)	0.71
3rd measuring	1091.1 ± 949.7	736 (400–3890)	1002.8 ± 734.8	766 (230–3148)	0.92
Von Willebrand factor [μg/L]					
1st measuring	14.62 ± 5.77	15.29 (4.9–23.3)	12.89 ± 5.49	11.7 (3.78–27.56)	0.31
2nd measuring	16.54 ± 6.85	15.7 (8.63–30.6	18.83 ± 9.84	16.92 (5.37–66.56)	0.41
3rd measuring	23.71 ± 10.14	18.79 (14.67–42.5)	18.45 ± 11.19	16.47 (0.32–56.86)	0.32
Beta-thromboglobulin [μg/L]					
1st measuring	16.2 ± 8.58	13.42 (3.42–30.37)	13.72 ± 4.72	13.52 (4.09–25.75)	0.64
2nd measuring	18.31 ± 8	19.01 (2.21–34.18)	18.07 ± 6.7	17.59 (3.03–34.14)	0.77
3rd measuring	18.11 ± 6.63	17.07 (7.95–30.63)	17.79 ± 6.53	17.04 (5.61–32.7)	0.91

Continuous variables are shown as median (interquartile range [IQR]) and as mean ± standard deviation (SD). P values are given for differences between the patients with and without primary endpoint.

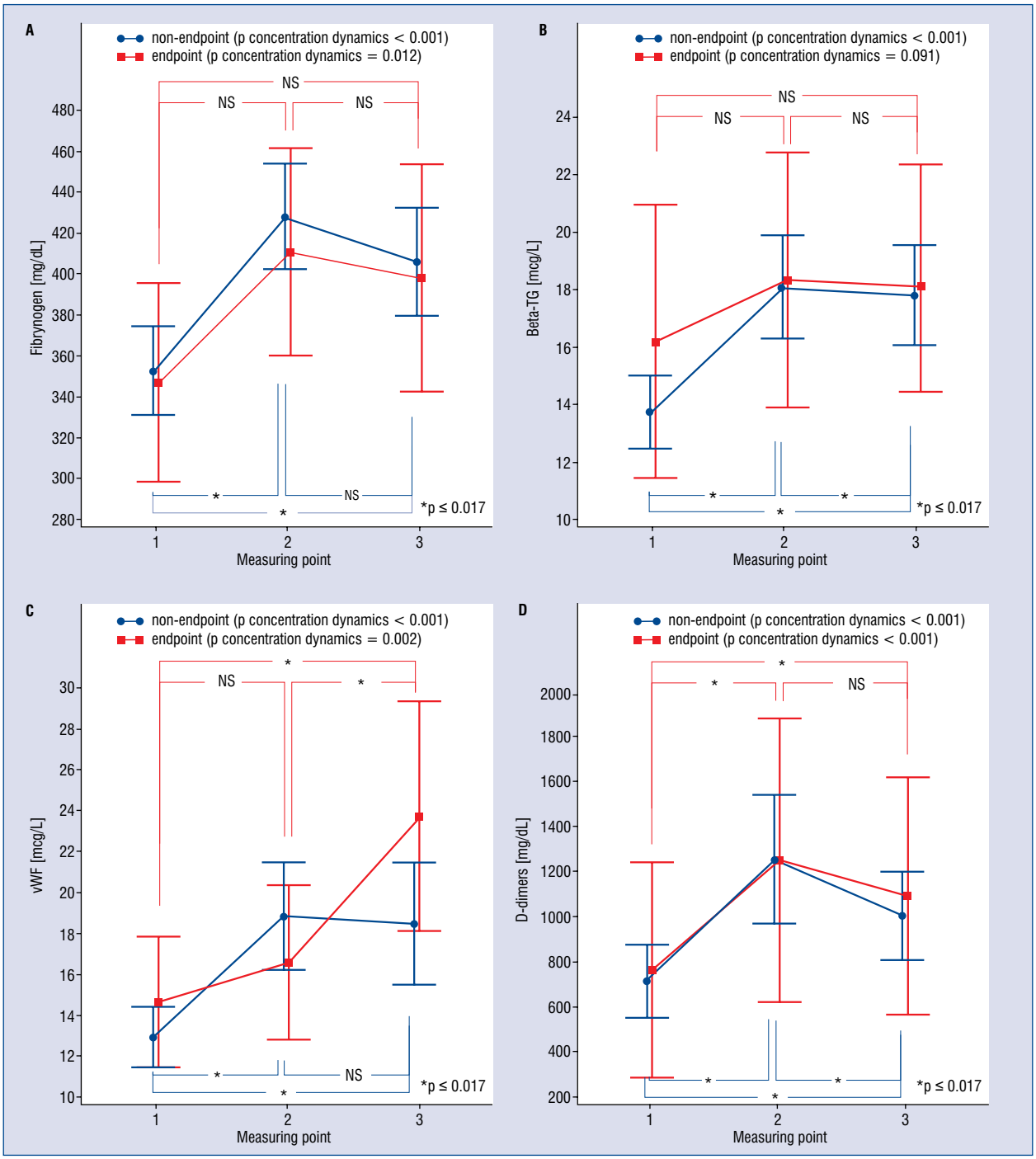

Figure 2. The mean concentrations of biochemical markers measured at the 1st, 2nd and 3rd measuring point among patients who met or did not meet the primary endpoint; beta-TG — beta-thromboglobulin; vWF — the von Willebrand factor; NS — non-significant.

The observation that anticoagulation therapy or presence of cancer was not associated with an increased risk for primary endpoint occurrence as described in a previous publication [7].

Discussion

The present paper was focused on simultaneous analysis of the dynamics of concentrations

of biochemical markers of inflammation (fibrinogen), coagulation activity (D-dimers) and platelet activation (vWF and beta-TG), in the population of first-time CIED recipients. According to available research, this is the first report describing dynamics of hemostatic markers among first-time CIED recipients followed-up by up to 6 months and their relationship with VSO, one of the most common complications of the lead placement into the vascular system. It should be emphasized that this report is important with regard to ensuring a better understanding of the mechanism of VSO occurrence and its prediction after CIED implantation.

Nevertheless, in starting the discussion, readers may be kindly forwarded to a previous paper presenting results of comparisons between subjects with and without study endpoints [6]. As it is a real-life population of first time CIED recipients, patients were included who had clinical conditions like atrial fibrillation, arterial hypertension, chronic heart failure, previous stroke or cancer. Though, during the follow up neither antithrombotic or anticoagulant treatment nor any of these conditions significantly increased the prevalence of VSO. Moreover, the presence of diabetes or prediabetes reduced the risk of VSO supporting the thesis of the inductive influence of inflammation. Reported observations built a multivariable prognostic model for VSO occurrence in the previously mentioned paper [7].

The procedure of CIED implantation, with intervention in the vascular system, initiated a significant increase in the concentration of biochemical markers. This is understandable considering the intervention itself (incision or puncture of a large venous vessel and preparation of the device pocket). However, only the vWF concentration, measured six months after the CIED implantation was significantly increased among patients who reached the primary endpoint. Moreover, the only marker that its concentration increased between the 2nd and 3rd measuring point among patients with VSO was vWF. It is worth mentioning that VSO occurrence is mostly associated with vessel trauma and subsequent inflammation [10]. This is consistent with the literature as vWF is synthesized in endothelium and is realized due to cell injury [11]. Moreover, inflammatory leukocytes release oxidizing agents that can render vWF more stable, with enhanced platelet binding, explaining higher concentrations of vWF among patients with VSO [12].

Results of this study propose possible clinical implantation of serial vWF measurement in a screening for VSO among first-time CIED recipients. Significant increases of vWF concentration between 7th day and 6th month follow-up from CIED implantation may identify patients with VSO. Still, as this is a pilot prospective study, additional observations in this field are required.

The fibrinogen and D-dimer concentrations have significantly decreased between 2nd and 3rd measuring points regardless of the occurrence of VSO. Also, the beta-TG concentration was reduced within 6 months (but not significantly). It is an important finding considering a conviction that promoted hemostasis and thrombosis should result in increase of fibrin-degradation-product concentration.

Finally, it is worth exploring the role of beta-TG. This protein is stored in alpha-granules of platelets and is released in large amounts after platelet activation. It acts as a megakaryocyte maturation factor and helps in regulating platelet production, thus it has been recognized as a marker for activated platelets. Current studies suggest that an increased level of activated platelets, measured by higher plasma levels of beta-TG, is associated with increased risk of incidence of cardiovascular disease [13, 14]. For instance, the Plicner et al. [15] study included 108 consecutive patients undergoing coronary artery bypass grafting, demonstrated that increased platelet activation contributes to the occurrence of perioperative myocardial infarction in an early postoperative period. However, Kubota et al. [16], a study with 746 participants, do not support the hypothesis that higher concentrations of beta-TG reflect an increased risk of cardiovascular endpoints in the general population.

Limitations of the study

The present study is single-centered and nonrandomized. The size of the study population was the result of the test methodology (the study group encompassed only a population of first time CIED recipients) and the cost of biochemical markers and limited funding. Moreover, the study population is homogeneous as all of patients who underwent their first cardiac device implantation and were assessed exactly at 6 months postoperatively. Another limitation of this study is the single image approach to diagnose VSO. However, color Doppler ultrasonography is a non-invasive method with high sensitivity (80%) and a specificity (90–100%) for detecting VSO [17, 18]. Another limitation is the fact that no attempt was made to study the ratio between the caliber of the vein and number of leads inserted.

Conclusions

All biochemical hemostatic marker levels increased significantly in response to transvenous CIED insertion and the presence of electrodes in the venous system. A significant increase in vWF level at 6 months post implantation may be a marker of VSO occurrence.

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Conflict of interest: None declared

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Barriers and facilitators to participating in cardiac rehabilitation and physical activity in a remote and rural population: A cross-sectional survey

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Abstract

Background: *Cardiac disease requires ongoing active management which may include attendance at formal cardiac rehabilitation (CR) and increased physical activity (PA). However, uptake rates are sub-optimal. This study aimed to identify factors associated with attendance at CR and PA in a rural Scottish population.*

Methods: *A cross-sectional postal survey assessing factors potentially associated with attending CR and participating in PA. Data were also collected from hospital electronic medical records. Binary logistic and ordinal regressions were used to identify barriers and facilitators to participation.*

Results: *The cohort consisted of 840 participants referred to the CR department of a regional Scottish hospital. After applying the inclusion/exclusion criteria, 567 patients were sent a questionnaire. The number of returned questionnaires was 295 (52.0%). Responders were predominantly male (75.9%), with a mean age of 68.7 years. At the multivariate level, the only factor associated with CR attendance was a lack of perceived need (odds ratio [OR] 0.02, 95% confidence interval [CI] 0.01–0.06). Analyses of PA associations identified self-efficacy as the only significant facilitator (OR 1.29, 95% CI 1.05–1.59), and a lack of willpower as the only barrier (OR 0.42, 95% CI 0.18–0.97). Other factors were linked to CR attendance and PA at a univariate level only.*

Conclusions: *This study characterised CR and PA participation, and explored demographic, medical, and psychological factors associated with both activities — with the most important being perceived need, self-efficacy and willpower. These findings may be beneficial in clinical practice by targeting these factors to increase CR attendance and PA levels.* (Cardiol J 2021; 28, 5: 697–706)

Key words: cardiac rehabilitation, physical activity, barriers, facilitators, rural

Introduction

Heart disease is a leading cause of mortality worldwide [1]. Cardiac rehabilitation (CR) aims to reduce morbidity and mortality from heart disease by targeting modifiable risk factors, such as obesity, smoking and lack of exercise [2]. The most important element of CR, in terms of reducing cardiovascular mortality, hospital admissions, and increasing health-related quality of life, is exercise (or physical activity [PA]) [3].

It is recommended that all adults should achieve a weekly minimum of 150 min of moderate-intensity PA, or 75 min of vigorous-intensity PA, in bouts of 10 min or more [4]. Despite the proven benefits and endorsement in national guidelines,

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in 2012 it was shown that 47% of adult women and 37% of adult men in Scotland were not achieving these recommendations [5]. In addition, CR uptake remains suboptimal, with only 51% of eligible patients attending in England, Wales and Northern Ireland [6].

Factors associated with poor CR attendance include: age, gender, lack of knowledge, cost, lack of transport, self-efficacy, motivation, and social support [7, 8]. Distance from classes may be particularly important in remote rural populations [9, 10]. Factors associated with lower PA (distinct from CR attendance) include: poor health, lack of time, knowledge or access to facilities, costs, gender, motivation and self-efficacy, to name a few [11]. These factors remain relatively understudied in rural areas and the paucity of evidence in such populations may have particular implications for Scotland, where over 20% of the country is classed as remote or rural [6, 12].

This study aimed to explore factors influencing participation in CR and PA after a cardiac event in a remote and rural Scottish population to identify potential targets for future interventions to improve participation rates.

Methods

Design

The study employed a cross-sectional survey design.

Participants

Consecutive patients referred for standard CR classes at a regional hospital in the North of Scotland from May 2016 to May 2017 were included, the catchment area of this hospital being over 30,000 km^2 and including several CR sites. Patients were referred to CR following an acute coronary syndrome (myocardial infarction or unstable angina), angina, heart failure, post-cardiac surgery (valves, transplantation or coronary artery bypass grafting [CABG]), percutaneous coronary intervention (PCI), cardiac device implantation, adult congenital heart disease, out-of-hospital cardiac arrest, or a step-change in their cardiac condition. Exclusion criteria were: previous referrals of the same patient, not resident in catchment area, aged less than 18, non-cardiac or unclear diagnosis, or if CR, PA or questionnaire completion was deemed inappropriate for the specific patient (e.g. frailty, life-limiting or distressing illness, severe dementia or other severe psychiatric condition). The latest referral of the participant was used if the patient had been invited to CR on more than one occasion.

Instruments

The survey contained 4 sections, which combined several questionnaires, and respectively collected data regarding: demographics; quality of life; CR; and PA. All individual questionnaires have previously been validated and demonstrate adequate psychometric properties.

The demographic section included questions about age, gender, working status and occupation, smoking status, education, home occupants, feelings of loneliness, and transport access.

Quality of life was assessed using the European Quality of Life 5 Dimensions (EQ-5D-5L) instrument and the European Quality of Life Visual Analogue Scale (EQ-VAS), with permission for use being obtained [13, 14]. A single index value of health state (0 being low, to 1 being higher) was generated from the EQ-5D-5L, using the Devlin et al. [14] value set. The EQ-VAS asks participants to rate their overall health out of 100 (0 being "the worst health imaginable", and 100 being "the best").

Cardiac rehabilitation experience was assessed by initially asking 3 questions: were they invited to CR; did they attend all, some or none of the classes; and whether they had ever previously attended CR. Barriers and facilitators to attending CR were assessed using the Cardiac Rehabilitation Barriers Scale (©CRBS, permission for use obtained) [15]. The ©CRBS (©CRBS: [15]) comprises 21 items and uses a 5-point Likert scale instrument (strongly disagree to strongly agree) to assess potential barriers in 4 key areas: perceived need/health care factors (e.g. "I don't need cardiac rehab", "my doctor did not feel it was necessary"); logistical factors (e.g. distance, cost); work/time conflicts, and comorbidities/functional status (e.g. "I am too old", "I don't have the energy") [15].

Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) short version [16]. Participants were grouped into low, moderate or high PA levels based on the IPAQ group scoring guideline [17]. Barriers to PA were assessed by the Barriers to Being Active Quiz, which comprises 21 statements, measuring barriers over 7 areas: social influences, fear of injury, and lack of; skill, energy, willpower, time, and resources [18]. The scoring of this questionnaire produces a binary predictor — barrier present or absent.

Social support was assessed with the Social Support and Exercise Survey [19]. Participants rated how often family and friends participated in certain activities regarding PA, with higher scores indicating more social support for exercise. PA self-

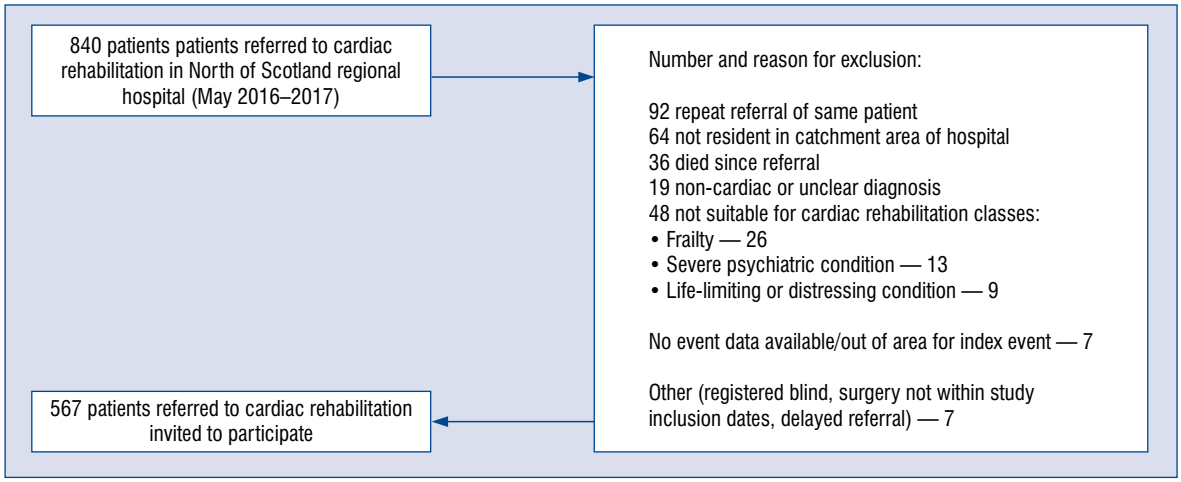

Figure 1. Displaying the process of participant exclusion.

efficacy was measured using a 12-item instrument, asking participants to rate their confidence in their ability to be active in various circumstances [20]. The items were then scored into 3 themes, self-efficacy for: overcoming barriers to being active, completing the activity itself, and scheduling time to be active. A higher score indicates higher PA self-efficacy in that subscale. Motivation for PA was assessed using the intrinsic, extrinsic and amotivation subscales from the Behavioural Regulation in Exercise Questionnaire [21, 22].

Procedures

The cohort was screened using electronic hospital medical records and participants identified who satisfied the inclusion/exclusion criteria. A subject specialist (cardiologist) adjudicated any uncertainties regarding patient inclusion. Identified participants were then sent a study pack containing a personalised cover letter, patient information sheet, consent form, the questionnaire, and a stamped addressed return envelope. A reminder pack was sent after 2–3 weeks to non-responders, with data collection being terminated after 6 weeks. Ethical approval was obtained from the Bromley Research Ethics Committee (study reference number 17/LO/1389, project number 231385).

The diagnosis, management, and co-morbidity data reported at the time of the index event was collected from electronic hospital medical records. Participant postcodes were used to assess rurality and socioeconomic status using the Scottish Government 6-fold Urban Rural Classification 2013/14, and the Scottish Index of Multiple Deprivation (SIMD) 2016 quintiles, respectively [12, 23].

Statistical analysis

All data were anonymised, then entered and analysed using SPSS (version 24, IBM Corp., Armonk, NY, USA). The analysis was conducted in two stages. In step one, each independent variable was examined in a univariate analysis using a variety of descriptive statistics, χ^2, independent *t*-tests, and ANOVA approaches to explore group differences.

In step two, all factors associated with the outcome (CR attendance or PA level) at the 10% significance level were included within a multivariate analysis using binary and ordinal logistic regressions. Binary logistic regression was used to identify factors associated with attending CR (attended all classes vs no classes). Participants who reported attending "some" classes (n = 49, 17.3%) were excluded as it was not possible to distinguish the degree of attendance and therefore their responses could have confounded the results. A similar approach was employed to identify associations with PA, however, ordinal logistic regression was used, due to the presence of three groups.

Results

Study cohort

The initial cohort was composed of 840 individuals referred to CR. After applying inclusion/exclusion criteria, 567 individuals were invited to participate. This process, and participant exclusion rationale, is summarised in Figure 1.

Sample characteristics

Of the 567 patients, 295 (52%) returned a questionnaire. The mean age of responders was

68.7 ± 10.5 years (range 33–90), with 224 (75.9%) men. Compared to non-responders, responders were older (non-responders mean age 65.0 vs. responders 68.7, $p < 0.001$), had a higher proportion of men (75.9% in responders vs. 66.9% non-responders, $p = 0.022$) and tended to be from more affluent areas ($p = 0.001$). There were no significant differences between responders and non-responders in terms of rurality, diagnosis, management, or co-morbid status.

Barriers to attending cardiac rehabilitation

Table 1 compares the characteristics of responders who attended (n = 101) and did not attend (n = 133) CR, and displays the multivariate analysis. Attenders were less likely to be smokers ($p = 0.023$), were from more affluent areas ($p = 0.041$), from less rural areas ($p = 0.026$), and have fewer morbidities on average ($p = 0.031$). Attenders scored lower than non-attenders on all barrier's subscales ($p < 0.001$).

Factors with univariate significance at the 10% level ($p \leq 0.1$) were entered into the final multivariate model. The model was significant ($p < 0.001$; Nagelkerke $R^2 = 0.690$). Lack of perceived need for CR was the only significant factor, and was associated with a 50-fold reduction in attendance (odds ratio [OR] 0.02, 95% confidence interval [CI] 0.01–0.06, $p < 0.001$).

Barriers to physical activity

Table 2 compares the characteristics of participants when grouped by PA levels according to the IPAQ, and shows the multivariate analysis. Compared to low active participants, higher active patients were more likely to be younger ($p = 0.008$), non-smokers ($p = 0.015$), in employment ($p = 0.033$), living with a spouse or partner ($p = 0.03$), less lonely ($p = 0.049$) and had access to a bicycle ($p = 0.006$). They were also more likely to report higher quality of life ($p < 0.001$) and have less co-morbidities on average ($p < 0.001$). Higher active patients also reported higher social support from family and friends, self-efficacy and intrinsic motivation to be active. Conversely, increased co-morbidity, lack of positive social influence, lack of will power, and lack of skill were associated with lower levels of activity. CR attendance for the index event was also associated with higher levels of PA ($p = 0.009$).

Factors with univariate significance at the 10% level were entered into a multivariate model, which was significant ($p = 0.001$, test of parallel lines $p = 0.074$; the Pearson χ^2 statistic goodness-of-fit $p = 0.236$, Nagelkerke $R^2 = 0.316$). Two significant predictors of PA emerged: self-efficacy for overcoming barriers to being active (OR 1.29, 95% CI 1.05–1.59, $p = 0.016$), which was associated with higher activity levels (a facilitator); and lack of willpower (OR 0.42, 95% CI 0.18–0.97, $p = 0.043$), which was associated with lower levels of activity (a barrier).

Discussion

This study demonstrated that perceived need for CR, and self-efficacy for overcoming barriers and willpower for PA were significant predictors of participation. These are important findings, suggesting factors that could be targeted with interventions in clinical practice to address low participation in cardiac patients.

Cardiac rehabilitation

Cardiac rehabilitation participation rate in this population was found to be 53.0%, with a completion rate of 67.3%. This is broadly consistent with United Kingdom (UK) national averages (51% and 77% respectively in 2017 [6]). Within this UK audit [6], differences in attendance were reported by diagnostic and management subgroups, such as increased uptake in PCI and CABG patients, however, no such differences were identified in this study. This may be due to differences in diagnostic and management definitions, sample differences (e.g., the audit sample was much larger), or modes of CR delivery examined (only traditional exercise class CR was investigated in this study).

Perceived need was identified as the single most important factor associated with CR non-attendance. This finding is consistent with previous studies citing perceived need, or the items used to score this subscale, as significant barriers [10, 24, 25]. Perceived need consists of patient and healthcare provider factors. The healthcare factors include: lengthy referral processes, no contact from the department, not knowing about CR, and the perception that their doctor did not think CR was necessary [15]. These healthcare factors provide potential targets for service improvement, and enhancing these aspects of the programme may exert a positive effect on patient understanding of CR necessity, and therefore increase attendance. For example, previous research has suggested that the "strength of referral" (how strongly physicians advocate CR) among other physician-related factors are key in uptake, and may prove a vital intervention target for the service [26, 27]. Personal factors associated with perceived need (e.g. "I don't

Table 1. Characteristics of attenders compared with non-attenders and factors associated with attendance.

	Non-attender (n = 133)	Attender (n = 101)	P	Multivariate+	
				OR (95% CI)	P
Age, range; n = 234	68.9 ± 11.5, 33–90	68.6 ± 9.8, 37–86	0.793	–	–
Men; n = 234	99 (74.4%)	79 (78.2%)	0.605	–	–
Scottish index of multiple deprivation score quintile; n = 232:					
1 or 2 (most deprived)	28 (21.1%)	12 (12.1%)	0.041	1.00	
3	47 (35.3%)	28 (28.3%)		1.51 (0.37–6.09)	0.566
4 or 5 (least deprived)	58 (43.6%)	59 (59.6%)		2.89 (0.82–10.25)	0.100
Scottish urban rural 6-fold classification; n = 230:					
Other urban area	24 (18.3%)	35 (35.4%)	0.026	1.00	
Remote small town	29 (22.1%)	16 (16.2%)		0.72 (0.19–2.75)	0.628
Accessible rural	14 (10.7%)	6 (6.1%)		0.25 (0.05–1.39)	0.113
Remote rural	64 (48.9%)	42 (42.4%)		0.63 (0.20–1.99)	0.428
Working (full or part-time); n = 228	43 (32.8%)	28 (28.9%)	0.622	–	–
Feelings of loneliness (sometimes or often); n = 229	50 (37.9%)	41 (42.3%)	0.593	–	–
Home occupants; n = 230:					
Alone	32 (24.2%)	18 (18.4%)	0.108	–	–
Spouse/partner	91 (68.9%)	78 (79.6%)		–	–
Other (family/friends/pets)	9 (6.8%)	2 (2.0%)		–	–
Smoking; n = 231:					
Never	50 (37.9%)	42 (42.4%)	0.023	^	^
Ex-smoker	62 (47.0%)	53 (53.5%)		^	^
Smoker	20 (15.2%)	4 (4.0%)		^	^
Highest level of education; n = 229:					
School	67 (51.1%)	36 (36.7%)		1.00	
College	37 (28.2%)	35 (35.7%)	0.094	0.80 (0.28–2.32)	0.686
University	27 (20.6%)	27 (27.6%)		1.42 (0.42–4.81)	0.575
Diagnosis; n = 234:					
Non-ST elevation MI	41 (30.8%)	36 (35.6%)	0.714	–	–
ST elevation MI	35 (26.3%)	19 (18.8%)		–	–
Unstable angina	12 (9.0%)	11 (10.9%)		–	–
Stable angina	26 (19.5%)	19 (18.8%)		–	–
Other (HF, arrhythmia or structural cardiac disease)	19 (14.3%)	16 (15.8%)		–	–
Management; n = 234:					
Medical	25 (18.8%)	16 (15.8%)	0.291	–	–
Percutaneous coronary intervention	89 (66.9%)	63 (62.4%)		–	–
Surgical	18 (13.5%)	18 (17.8%)		–	–
Cardiac device	1 (0.8%)	4 (4.0%)		–	–
Co-morbidities; n = 234:					
Number of co-morbidities, range	2.8 ± 2.1, 0–13	2.3 ± 1.6, 0–8	0.031	0.77 (0.57–1.06)	0.106
Previous attendance at CR before index event; n = 232	11 (8.3%)	13 (13.0%)	0.348	–	–
Barriers subscales; n = 204:					
Perceived need/healthcare factors	2.66 ± 0.62	1.49 ± 0.49	< 0.001	**0.02 (0.01–0.06)**	**< 0.001**
Logistic factors	2.36 ± 0.91	1.64 ± 0.77	< 0.001	1.79 (0.80–3.98)	0.155
Work/time conflicts	2.22 ± 0.90	1.75 ± 0.87	< 0.001	1.68 (0.86–3.29)	0.128
Co-morbidities/functional status	2.33 ± 0.99	1.54 ± 0.64	< 0.001	0.74 (0.39–1.39)	0.345
Total ©CRBS barriers; n = 205	2.47 ± 0.58	1.57 ± 0.55	< 0.001	–	–

Chi-square and independent *t*-tests used to analyse categorical and continuous data, respectively; n (percent)/mean ± standard deviation (SD) of complete data detailed for each variable row.
MANOVA of barriers subscales (not including total barriers); attenders (n = 89) compared with non-attenders (n = 115), Wilks' Lambda = 0.472, [F (4,199) = 55.588], p < 0.001
+Multivariate regression analysis based on complete data for 198 responders (113 non-attenders; 85 attenders). Univariate significance taken at 10% level ($p \leq 0.1$), excludes total barriers due to correlation with individual barrier scales. Nagelkerke R^2 of adjusted model = 0.690, p < 0.001.
^ Sample size of current smokers too small to enter into multivariate analysis
©CRBS: Shanmugasegaram S, Gagliese L, Oh P, Stewart DE, Brister SJ, Chan V, Grace SL. Psychometric validation of the cardiac rehabilitation barriers scale. Clin Rehabil. 2012; 26(2): 152–164.
CI — confidence interval; CR — cardiac rehabilitation; MI — myocardial infarction; OR — odds ratio

Table 2. Characteristics of participant activity groups and factors associated with being active.

	Low active (n = 64)	Moderately active (n = 85)	High active (n = 136)	P	Multivariate+	
					OR (95% CI)	P
Age, range; n = 285	72.1 ± 11.2, 41–87	68.3 ± 9.0, 47–85	67.2 ± 10.6, 33–90	0.008	0.98 (0.94–1.02)	0.307
Men; n = 285	44 (68.8%)	66 (77.6%)	109 (80.1%)	0.200	–	–
Scottish index of multiple deprivation score quintile; n = 283:						
1 or 2 (most deprived)	16 (25.0%)	14 (16.5%)	21 (15.7%)	0.133	–	–
3	16 (25.0%)	23 (27.1%)	52 (38.8%)		–	–
4 or 5 (least deprived)	32 (50.0%)	48 (56.5%)	61 (45.5%)		–	–
Scottish urban rural 6-fold classification; n = 281:						
Other urban area	15 (24.2%)	26 (30.6%)	31 (23.1%)	0.179	–	–
Remote small town	18 (29.0%)	15 (17.6%)	21 (15.7%)		–	–
Accessible rural	8 (12.9%)	8 (9.4%)	13 (9.7%)		–	–
Remote rural	21 (33.9%)	36 (42.4%)	69 (51.5%)		–	–
Working (full or part-time); n = 278	15 (23.4%)	24 (29.3%)	54 (40.9%)	0.033	1.20 (0.52–2.76)	0.672
Feelings of loneliness (sometimes or often); n = 279	32 (50.8%)	29 (34.5%)	44 (33.3%)	0.049	2.15 (0.94–4.88)	0.068
Home occupants; n = 281:						
Alone	22 (34.4%)	13 (15.5%)	26 (19.5%)		1.00	
Spouse/partner	38 (59.4%)	69 (82.1%)	102 (76.7%)	0.030	1.66 (0.49–5.66)	0.416
Other (family/friends/pets)	4 (6.3%)	2 (2.4%)	5 (3.8%)		0.53 (0.05–5.55)	0.598
Smoking; n = 282:						
Never	24 (37.5%)	38 (45.2%)	49 (36.6%)		1.00	
Ex-smoker	28 (43.8%)	43 (51.2%)	75 (56.0%)	0.015	1.45 (0.72–2.91)	0.294
Smoker	12 (18.8%)	3 (3.6%)	10 (7.5%)		0.71 (0.16–3.18)	0.657
Highest level of education; n = 280:						
School	34 (54.8%)	36 (42.9%)	56 (41.8%)		–	–
College	14 (22.6%)	28 (33.3%)	48 (35.8%)	0.388		–
University	14 (22.6%)	20 (23.8%)	30 (22.4%)		–	–
Access to transport:						
Car; n = 282	53 (82.8%)	79 (94.0%)	122 (91.0%)	0.067	0.80 (0.16–3.92)	0.779
Convenient public transport; n = 279	46 (74.2%)	66 (79.5%)	90 (67.2%)	0.132	–	–
Bicycle; n = 279	24 (38.7%)	38 (45.2%)	81 (60.9%)	0.006	0.91 (0.43–1.92)	0.801

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Table 2 (cont.). Characteristics of participant activity groups and factors associated with being active.

	Low active (n = 64)	Moderately active (n = 85)	High active (n = 136)	P	Multivariate+	
					OR (95% CI)	P
Diagnosis; n = 285:						
Non-ST elevation MI	22 (34.4%)	29 (34.1%)	42 (30.9%)		–	–
ST elevation MI	16 (25.0%)	15 (17.6%)	26 (19.1%)		–	–
Unstable angina	5 (7.8%)	9 (10.6%)	16 (11.8%)	0.366	–	–
Stable angina	10 (15.6%)	16 (18.8%)	38 (27.9%)		–	–
Other (HF, arrhythmia or structural cardiac disease)	11 (17.2%)	16 (18.8%)	14 (10.3%)		–	–
Management; n = 285:						
Medical	10 (15.6%)	15 (17.6%)	21 (15.4%)		–	–
Percutaneous coronary intervention	44 (68.8%)	52 (61.2%)	93 (68.4%)	0.220	–	–
Surgical	7 (10.9%)	16 (18.8%)	22 (16.2%)		–	–
Cardiac device	3 (4.7%)	2 (2.4%)	0 (0.0%)		–	–
Co-morbidities, range; n = 285	3.6 ± 2.4, 0–13	2.6 ± 1.7, 0–6	2.1 ± 1.5, 0–7	< 0.001	0.81 (0.64–1.02)	0.072
Cardiac rehabilitation attendance; n = 281:						
Previous attendance at cardiac rehabilitation before index event	8 (12.9%)	11 (12.9%)	12 (9.0%)	0.570	–	–
Cardiac rehabilitation attendance (index event); n = 274:						
None	39 (62.9%)	30 (37.5%)	59 (44.7%)	0.009	1.00	
All or some	23 (37.1%)	50 (62.5%)	73 (55.3%)		0.89 (0.42–1.87)	0.749
Quality of life:						
Index value (score range 0–1); n = 281	0.71 ± 0.26	0.86 ± 0.15	0.89 ± 0.15	< 0.001	2.06 (0.13–32.36)	0.606
EQ-VAS (score range 0–100); n = 280	64.28 ± 21.04	77.21 ± 15.37	81.35 ± 14.90	< 0.001	1.02 (0.99–1.05)	0.305
Psychological barriers to physical activity:						
Barriers to being active:						
Lack of time; n = 258	9 (17.3%)	9 (11.8%)	20 (15.4%)	0.662	–	–
Social influence; n = 263	13 (24.1%)	5 (6.3%)	7 (5.4%)	< 0.001	0.23 (0.05–1.18)	0.079
Lack of energy; n = 258	9 (18.0%)	11 (14.1%)	16 (12.3%)	0.614	–	–
Lack of willpower; n = 261	21 (40.4%)	26 (32.9%)	21 (16.2%)	0.001	**0.42 (0.18–0.97)**	**0.043**
Fear of injury; n = 265	10 (18.5%)	9 (11.5%)	9 (6.8%)	0.057	1.53 (0.36–6.44)	0.560
Lack of skill; n = 261	15 (28.3%)	8 (10.3%)	14 (10.8%)	0.004	1.32 (0.37–4.67)	0.670
Lack of resources; n = 265	8 (14.8%)	4 (5.1%)	10 (7.6%)	0.123	–	–

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Table 2 (cont.). Characteristics of participant activity groups and factors associated with being active

	Low active (n = 64)	Moderately active (n = 85)	High active (n = 136)	P	Multivariate+	
					OR (95% CI)	P
^ Social support and exercise survey (score range 10–50); Wilks' Lambda = 0.898, [F (4,470) = 6.496], p < 0.001; n = 239						
Family participation	17.50 ± 9.78	23.54 ± 10.35	25.90 ± 11.67	< 0.001	1.00 (0.97–1.04)	0.972
Friend participation	14.48 ± 6.95	15.78 ± 7.27	19.19 ± 10.20	0.002	1.03 (0.98–1.08)	0.236
^ Physical activity self-efficacy (score range 1–10); Wilks' Lambda = 0.833, [F (6,430) = 6.875], p < 0.001; n = 220						
Self-efficacy to overcome barriers	4.38 ± 2.39	5.22 ± 2.13	6.54 ± 2.14	< 0.001	**1.29 (1.05–1.59)**	**0.016**
Self-efficacy to complete activity	6.38 ± 2.47	7.55 ± 2.08	8.16 ± 1.57	< 0.001	1.10 (0.84–1.43)	0.483
Self-efficacy to schedule activity	4.98 ± 2.75	6.41 ± 2.31	7.00 ± 2.21	< 0.001	0.84 (0.67–1.06)	0.144
^ Physical activity motivation (score range 0–4); Wilks' Lambda = 0.902, [F (6,538) = 4.749], p < 0.001; n = 274						
Amotivation	0.39 ± 0.70	0.33 ± 0.58	0.20 ± 0.54	0.081	0.99 (0.51–1.91)	0.977
External regulation	0.64 ± 1.10	0.75 ± 0.94	0.54 ± 0.82	0.260	–	–
Intrinsic regulation	2.28 ± 1.29	2.62 ± 1.10	3.08 ± 0.92	< 0.001	1.08 (0.69–1.69)	0.724

Chi-square and ANOVA tests used to analyse categorical and continuous data, respectively; n (percent)/mean ± standard deviation (SD) of complete data detailed for each variable row. +Multivariate regression analysis based on complete data for 168 responders (24 low active, 57 moderately active and 87 high active). Univariate significance taken at 10% level ($p \leq 0.1$). Nagelkerke R^2 of adjusted model = 0.316, p = 0.001; ^ Data analysed in 3 separate MANOVA tests
CI — confidence interval; HF — heart failure; MI — myocardial infarction; OR — odds ratio

need rehab") could also be targeted through patient education and advice to improve these perceptions.

Distance from classes has been identified as an important barrier in rural populations [9, 10]. However, in the current study, neither rurality or the logistics barriers subscale (which includes distance, cost and access to transport) showed significant associations with CR attendance in the fully adjusted model. However, these factors were significant at the univariate level and may merit future research. Study findings may vary due to differences in the geography of Australia and Canada compared to Scotland (degree of rurality), or because there are several CR class sites dispersed across the area considered in this study. This is to ensure the remote rural areas are provided a service, therefore meaning that although the patient's address is considered rural, a CR site may be relatively near to them and distance may not be a barrier to attendance.

Physical activity

Within the current study, 22.5% were classed as low active, 29.8% as moderately active, and 47.7% as high active. The most important factors associated with PA levels were self-efficacy to overcome barriers to being active and lack of willpower. The positive association between self-efficacy and PA has been extensively reported [28–30]. Although not linked to CR attendance in this study, CR does provide a potential opportunity for patients to develop strategies to overcome barriers to being active, which may support this behaviour in the future. For example, a previous randomised controlled trial compared group-mediated cognitive behavioural interventions (which incorporated training on how to identify and overcome barriers to being active to encourage self-regulation), with a traditional exercise-based CR programme [31]. This study found that those in the cognitive behavioural intervention group showed a greater increase in fitness, and better adherence to an active lifestyle in the long-term, compared with traditional CR. The intervention group also had a greater increase in self-efficacy at post-intervention [31].

Therefore, including such targeted behaviour training to increase self-efficacy and assist patients to identify and overcome barriers to being active, may prove invaluable in CR. In addition to this, other techniques have been shown to increase both self-efficacy and PA, including: action planning, reinforcing efforts towards the desired behaviour, and providing instruction, all of which could be im-

plemented within CR [32]. Furthermore, national guidelines recommend that psychoeducation and techniques such as goal setting, action planning, and self-monitoring to improve self-efficacy should be considered in CR to improve adherence to the programme, and long-term maintenance of PA [2].

Willpower has previously been identified as a barrier to behaviour change. Lack of willpower was the most commonly reported reason for not adopting desired habits (such as increasing PA) in a study exploring health behaviours in a sample of obese Canadian participants [33]. A lack of willpower was also a more common barrier to behaviour change than work or family responsibilities [34]. Willpower itself has several synonyms and definitions but can be thought of as one's ability to consciously self-regulate behaviour (or self-control). Previous work has suggested that a key component to behaviour change is "perceived behavioural control", which is defined as "the perceived ease or difficulty of performing the behaviour" relating to beliefs about factors that may impact one's ability to perform the desired behaviour [35]. These factors may be internal (e.g. one's willpower) or external (e.g. money required to use facilities to be active). It has been suggested that self-efficacy may contribute to perceived behavioural control, and so the methods above to target self-efficacy, may also be useful in addressing willpower [35].

An association between CR attendance and future activity levels was not demonstrated in this study. This contrasts with the UK CR audit [6], but is consistent with some other studies [36]. One possible explanation for these contrasting results is that high baseline activity levels before CR may cause some programmes to appear less effective if a higher proportion of patients were active at baseline [6]. Therefore, the benefits may not be apparent at a single site comparison, such as in this study. Furthermore, baseline activity levels in this study are unknown.

This study has several strengths: the respondents were largely representative of the target patient cohort, achieved a 52% response rate, and the study focused on a remote and rural Scottish population — a group which has been broadly neglected in previous research. However, the use of hospital letters to establish co-morbidity may have led to an underestimation of co-morbidity burden, although this was a consistent approach so no bias would result between patient groups. The self-reported information is subject to both reporter and recall bias.

Future research could aim to address these identified barriers and enhance facilitators. This could involve some of the targeted interventions previously mentioned to improve perceived need, willpower and self-efficacy to overcome barriers to being active in cardiac patients. The effect of any interventions on these factors could be monitored over time and the change in numbers of patients participating in CR and PA examined with longer follow-up.

Conclusions

The most important factor identified for CR attendance was lack of perceived need, and for PA the most important factors were self-efficacy to overcome barriers and lack of willpower. The identified factors could potentially be targeted in clinical practice to identify at-risk patients, and strategies implemented to overcome these associations to encourage CR and PA participation in these individuals.

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The "athlete's heart" features in amateur male marathon runners

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Abstract

Background: *Training on a professional level can lead to cardiac structural adaptations called the "athlete's heart". As marathon participation requires intense physical preparation, the question arises whether the features of "athlete's heart" can also develop in recreational runners.*

Methods: *The study included 34 males (mean age 40 ± 8 years) who underwent physical examination, a cardiopulmonary exercise test and echocardiographic examination (ECHO) before a marathon. ECHO results were compared with the sedentary control group, reference values for an adult male population and those for highly-trained athletes. Runners with abnormalities revealed by ECHO were referred for cardiac magnetic resonance imaging (CMR).*

Results: *The mean training distance was 56.5 ± 19.7 km/week, peak oxygen uptake was 53.7 ± 6.9 mL/kg/min and the marathon finishing time was 3.7 ± 0.4 h. Compared to sedentary controls, amateur athletes presented larger atria, increased left ventricular (LV) wall thickness, larger LV mass and basal right ventricular (RV) inflow diameter ($p < 0.05$). When compared with ranges for the general adult population, 56% of participants showed increased left atrial volume, indexed to body surface area (LAVI), 56% right atrial area and interventricular septum thickness, while 47% had enlarged RV proximal outflow tract diameter. In 50% of cases, LAVI exceeded values reported for highly-trained athletes. Due to ECHO abnormalities, CMR was performed in 6 participants, which revealed hypertrophic cardiomyopathy in 1 runner.*

Conclusions: *"Athlete's heart" features occur in amateur marathon runners. In this group, ECHO reference values for highly-trained elite athletes should be considered, rather than those for the general population and even then LAVI can exceed the upper normal value.* (Cardiol J 2021; 28, 5: 707–715)

Key words: echocardiography, cardiac magnetic resonance, athlete's heart, marathon runners, sport cardiology, hypertrophic cardiomyopathy

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Introduction

Regular and moderate physical activity has a positive effect in humans, however the "upper dose" of beneficial endurance exercise has not been determined [1, 2]. Participation in sport events like marathon runs has recently become very popular. The characteristics of marathon runners is evolving, with a growing percentage of non-elite amateur runners who are often middle-aged [3]. Long-term endurance training on a professional level can lead to multiple structural adaptations, called the "athlete's heart" [4]. As marathon participation requires intense physical preparation, the question arises whether the features of "athlete's heart" can be present in recreational runners. And if so, which echocardiographic criteria should be applied in this group: those for the general adult population or those for highly trained elite athletes.

Methods

Study participants and study protocol

Male amateur marathon runners who planned to attend the 2nd PZU Marathon in Gdansk, Poland were recruited by invitation to local running clubs. Volunteers were informed about the purpose and plan of the study and gave written consent. All participants were questioned about medical history and those with chronic diseases, or at age < 20, or > 55 years were not eligible. Two weeks before the marathon run, each of the participants underwent physical examination, treadmill cardiopulmonary exercise test (CPET) and echocardiographic examination (ECHO).

Fifteen sedentary males matched with age, body mass index (BMI) and body surface area (BSA) with marathon runners constituted the control group for ECHO. They were healthy men without any history of practicing endurance exercise. In the next step, data obtained in marathon runners were compared with reference values for cardiac chambers in male adults, provided by the American Society of Echocardiography and European Association of Cardiovascular Imaging [5]. Subsequently, results were also compared with reference values for elite athletes: 1) right chamber's dimensions with Normative Reference Values of Right Heart in Competitive Athletes [6], and 2) left chambers diameters with values reported in studies on populations of elite athletes [4, 6–8], as to our knowledge there is no single paper providing all normative reference values for the left heart in this group.

The study protocol set up that participants with abnormalities revealed by ECHO were referred for cardiac magnetic resonance imaging (CMR). These included: increased interventricular septum diameter (≥ 13 mm), abnormal left ventricular (LV) contractility (ejection fraction [EF] < 52% or abnormal global longitudinal strain > –18.9%), abnormal right ventricular (RV) systolic function (tricuspid annular plane systolic excursion < 17 mm, RV strain of > –20% or spectral tissue Doppler derived tricuspid lateral annulus peak systolic velocity < 9.5 cm/s) [5, 9, 10]. The study protocol was accepted by Independent Bioethics Commission for Research of the Medical University of Gdansk (NKBBN/104/2016).

Cardiopulmonary exercise test

Cardiopulmonary exercise test was performed on the treadmill (H/P/Cosmos Saturn treadmill) using the Bruce protocol. First stage started at 2.7 km/h and at 10% gradient, then the speed and incline were increased in 3 min intervals. Jaeger OxyconPro equipment with Jlab Manager V5.32.0 software was used to measure the oxygen intake (VO_2), carbon dioxide output (VCO_2), minute ventilation (VE), expiratory gas concentrations throughout the respiratory cycle on a breath-by-breath basis. The peak oxygen intake (VO_2peak) was calculated as the highest volume averaged over 10 s at maximal endurance. The anaerobic threshold (AT) was calculated with the V-slope method and was corrected by the ventilator equivalent method.

Echocardiography

Transthoracic ECHO was performed using Vivid E9 (General Electric Medical Health) in marathon runners and sedentary controls. ECHO measurements were carried out according to the recommendations of the American Society of Echocardiography and European Association of Cardiovascular Imaging [5]. Left ventricular measurements: LV end-diastolic dimension (LV ED), LV end-systolic dimension (LV ES), diastolic interventricular septum (IVS) and posterior wall (LV PW) thickness, left atrial (LA) anteroposterior (AP) dimension and proximal RV outflow diameter (RVOT prox) were performed in the parasternal long-axis view. The LV end-diastolic (LV EDV) and LV end-systolic (LV ESV) volumes were measured with the biplane method of discs summation (the modified Simpson's rule) and then LV EF was calculated. The 2-dimensional (2D) speckle-tracking LV global longitudinal peak strain (LV GLS) measurements were obtained from 2-, 3-, and 4-chamber

apical views and were averaged. The LV mass was assessed by the area-length method and was then indexed to BSA. In the end systole, the LA volume was indexed to BSA (LAVI) and was calculated by the area-length technique from apical 2- and 4-chamber views, whereas the right atrial (RA) area was measured in the apical 4-chamber view. The basal RV inflow diameter (RVd) and the 2D speckle-tracking-derived RV strain were obtained in the RV-focused apical 4-chamber view. The RV systolic function was assessed by measuring the tricuspid annular plane systolic excursion (TAPSE) in the M-mode and spectral tissue Doppler-derived tricuspid lateral annulus systolic peak velocity (S'RV). The offline analyses of data were carried out using commercially available software — EchoPack 201 (General Electric).

Cardiac magnetic resonance

Cardiac magnetic resonance examinations were performed with a 1.5 Tesla scanner (Magnetom Aera, Siemens Healthcare) with an 18-channel phased-array receiver coil with repeated breath-holds, according to protocol [11]. Segmented steady-state free-precession sequence was used to acquire cine images of the heart in 2-, 3-, and 4-chamber views, as well as in short-axis views to obtain a stack of contiguous short-axis slices which include the entire LV and RV having a slice thickness of 8 mm with 2 mm gaps. In the majority of cases the parallel acquisition technique with acceleration factor of 2 was used. Late gadolinium enhancement (LGE) was assessed 7–15 min post administration of gadolinium-based contrast agent at a dose of 0.1 mmol/kg body mass, with an inversion recovery spoiled gradient echo sequence (single slice per breath hold). Inversion time was repeatedly optimized to null normal myocardium. A short-axis stack identical to that performed in cine steady-state free precession as well as 2-, 3-, and 4-chamber long axis images (slice thickness of 8 mm with in-plane resolution typically 1.5 × × 1.5 mm) were acquired in each individual. Data was analyzed using commercially available software by an experienced observer.

Statistical analysis

Continuous variables are presented as mean ± standard deviations (SD) or median and range. The Shapiro-Wilk test was used to estimate the distribution. A comparison of the amateur marathon runners and controls was performed by the Student t-test for independent samples or the Mann–Whitney U test where appropriate. A p value < 0.05 was considered statistically significant. The data were analyzed using Statistica 13 software (Statsoft Poland).

Table 1. Characteristics of amateur marathon runners studied (n = 34).

Parameter	Marathon runners
Training distance [km/week]	56.5 ± 19.7
Training time [h/week]	6.5 ± 2.3
Marathon finishing time [h]	3.7 ± 0.4
Cardiopulmonary exercise test:	
VO_2peak [mL/kg/min]	53.7 ± 6.9
$VO_2$60sec [mL/kg/min]	19.9 ± 3.7
VO_2AT [mL/kg/min]	39.7 ± 6.9
Respiratory exchange ratio	1.2 ± 0.1
Time of effort [min:s]	12:46 ± 1:24
HR max [bpm]	178 ± 12
HR in 180 s of recovery [bpm]	111 ± 16

Data are shown as mean ± standard deviation; VO_2peak — peak oxygen intake; $VO_2$60sec — oxygen intake at 60 s of recovery; VO_2AT — oxygen intake at anaerobic threshold; HR — heart rate

Results

Thirty-four amateur marathon runners were included in the study. Results of electrocardiographic examination in these subjects have recently been published [12]. Table 1 shows data on training habits and CPET. Table 2 presents features of marathon runners in comparison with sedentary controls. There were no significant differences in age, weight, height, BSA and BMI between amateur runners and controls ($p > 0.05$). All participants were healthy men of Caucasian race.

Data on ECHO parameters obtained in the amateur marathon runners studied and sedentary controls are presented in Table 2. Compared to controls, amateur athletes had larger atria, increased LV wall thickness, larger LV mass and RVd ($p < 0.05$). There were no differences regarding other ECHO parameters. A comparison of parameters obtained from amateur marathon runners with reference values for the general male adult population and for professional athletes is presented in Table 3. It shows the percentage of amateur athletes exceeding the upper reference value for the adult population (URP) and the upper value range for highly-trained athletes (URA). The IVS population norm of 10 mm was exceeded in 19 (56%) runners and in 3 (9%) participants it was ≥ 13 mm (13 mm,

Table 2. Results of echocardiographic examination performed in amateur marathon runners and subjects from the control group.

Parameter	Marathon runners (n = 34)	Control group (n = 15)	P
Age [years]	41 (24–55)	42 (24–55)	> 0.6709 ^
Weight [kg]	80 (67–97)	80 (64–100)	> 0.3878 ^
Height [cm]	180 (165–188)	177 (169–195)	> 0.7643 ^
BSA [m^2]	2.0 (1.8–2.2)	2.0 (1.7–2.2)	> 0.5206 ^
BMI [kg/m^2]	25 (19–29)	25 (22–31)	> 0.2069 ^
LAVI [mL/m^2]	36 (21–51)	27 (17–35)	**< 0.0001 ^**
RA area [cm^2]	19 (14–25)	16 (11–20)	**< 0.0005 ^**
LV EDV [ml]	122 (78–176)	105 (66–164)	> 0.0732 ^
LV ED [mm]	52 (45–58)	50 (39–59)	> 0.0729 ^
IVS [mm]	11 (7–17)	10 (7–10)	**< 0.0001#**
LV PW [mm]	11 (7–14)	10 (7–11)	**< 0.0206 ^**
LV mass [g/m^2]	97 (61–117)	77 (62–108)	**< 0.00001 ^**
LV EF [%]	66 (51–86)	62 (56–74)	> 0.1896 ^
LV GLS [%]	–20 [–17 – (–25)]	–20 [–17 – (–23)]	> 0.4363 ^
RVOT prox [mm]	30 (21–38)	30 (25–36)	> 0.6764 ^
RVd [mm]	37 (25–47)	30 (27–40)	**< 0.0179 ^**
TAPSE [mm]	24 (19–32)	23 (20–27)	> 0.4550 ^
RV strain [%]	–22 [–27 – (–18)]	–24 [–26 – (–19)]	> 0.2978 ^

Data are shown as median (range); ^ The Student t-test; #The Mann–Whitney U test; BSA — body surface area; BMI — body mass index; LAVI — left atrial volume indexed to body surface area; RA — right atrial; LV — left ventricular; EDV — end-diastolic volume; ED — end-diastolic dimension; IVS — interventricular septum diastolic diameter; PW — posterior wall diameter; EF — ejection fraction; GLS — global longitudinal peak strain; RVOT prox — proximal right ventricular outflow tract diameter; RVd — right ventricular diameter; TAPSE — tricuspid annular plane systolic excursion; RV — right ventricular

Table 3. Results of echocardiographic examination performed in amateur marathon runners (n = 34) in comparison with reference ranges for the general male adult population and with reference ranges for professional athletes.

Parameter	Reference ranges for adults (range)	Runners with values exceeding the URP N (%)	Reference ranges for highly trained athletes (range)	Runners with values exceeding the URA N (%)
LA AP [mm]	30–40[5]	13 (38)	24–48[8]	0 (0)
LAVI [mL/m^2]	16–34[5]	19 (56)	26–36[8]	17 (50)
RA area [cm^2]	10–18[10]	19 (56)	14–23[6]	3 (9)
LV EDV [mL]	62–150[5]	3 (9)	180–340[4]	0 (0)
LV ED [mm]	42–58[5]	0 (0)	44–66[7]	0 (0)
IVS [mm]	6–10[5]	19 (56)	7–16[7]	1 (3)
LV PW [mm]	6–10[5]	14 (41)	7–13[7]	2 (6)
LV mass [g/m^2]	50–102[5]	10 (29)	62–176[7]	0 (0)
RVd [mm]	25–41[5]	5 (15)	38–42[6]	3 (9)
RVOT prox [mm]	20–30[5]	16 (47)	26–33[6]	6 (18)

URP — upper reference value for the adult population; URA — upper reference value for highly trained athletes; LA AP — left atrial antero-posterior dimension. For other abbreviations see Table 2

14.7 mm and 17 mm). The LV PW was ≥ 13 mm in 2 runners (13.6 mm and 14 mm). One subject was diagnosed with hypertrophic cardiomyopathy (HCM). All participants with LV enlargement (as indicated by LV EDV) showed IVS > 10 mm, but only 3 runners with IVS > 10 mm presented with

Table 4. Results of cardiac magnetic resonance imaging (CMR) performed in amateur marathon runners with abnormalities revealed in echocardiographic (ECHO) examination.

No.	Reason for CMR ECHO abnormalities	CMR results
M06	LV GLS Avg –17%, with abnormal LV GLS pattern GLS 2C –16%, GLS 4C –17%, GLS Aplax –17% (n: > –18.9%)[9] RVd 47 mm	Slightly reduced LV EF (53%) and RV EF (44%). Enlarged LV (LV ESV 86 mL) and RV (RV ESV 118 mL)
M29	IVS 14.7 mm E'LAT 8 cm/s (n: > 10 cm/s)[34] RV strain –19% (n: > –20%)[10]	Slightly reduced LV EF (54%) and RV EF (42%), LV hypertrophy (IVS 13 mm), enlarged LV (LV ESV 79 mL) and RV (RV ESV 119 mL)
M38	IVS 17 mm LV EF 51% E'SEPT 6 cm/s (n: > 7 cm/s)[34] LV GLS Avg –18%, abnormal LV GLS pattern GLS 2C –17%, GLS 4C –17% (n: > –18.9%)[9] RVOT prox 31 mm	Hypertrophic cardiomyopathy (IVS 17 mm), LGE present Slightly reduced RV EF (47%) and enlarged RV (RV ESV 97 mL) Increased LA area (30 cm^2)
M39	IVS 12 mm LV GLS Avg –17%, abnormal LV GLS pattern GLS 2C –17%, GLS 4C –16% (n: > –18.9%)[9] RV strain –18% (n: > –20%)[10] LV ED 52 mm	Slightly reduced RV EF (42%) and enlarged RV (RV ESV 112 mL)
M40	IVS 13 mm E'SEPT 7 cm/s (n: > 7 cm/s)[34] S'RV 9 cm/s (n: > 9.5 cm/s)[10] RV strain –19% (n: > –20%)[10] RVOT prox 32 mm LV ED 49 mm	Atrial septal defect Slightly reduced RV EF (48%) and enlarged RV (RV ESV 103 mL)
M41	IVS 12 mm Abnormal LV GLS pattern: GLS Avg –17%, GLS 2C –16% (n: > –18.9%)[9] LV EDV 176 mL	Slightly reduced LV EF (56%) and RV EF (49%). Enlarged LV (LV EDV 245 mL, LV ESV 107 mL) and RV (RV EDV 239 mL, RV ESV 123 mL)

For abbreviations see Table 2, for echocardiographic reference values see Table 3; values outside the range for adults. For cardiac magnetic resonance reference values see Table 5; No. — number of marathon runners; Avg — averaged; 2C — two chamber view; 4C — four chamber view; Aplax — apical long axis view; S'RV — spectral tissue Doppler tricuspid lateral annulus peak systolic velocity; LGE — late gadolinium enhancement; E'— spectral tissue Doppler mitral early diastolic peak velocity (SEPT — measured on IVS; LAT — measured on lateral wall)

an enlarged LV. One runner had mildly abnormal LV EF of 51%. The LV GLS was abnormal in 4 (12%) runners (> –18.9%) whereas the RV strain was altered in 6 (18%) amateurs (> –20%). The median S'RV was 14 cm/s (range 9–19 cm/s). In 1 participant the abnormal S'RV below 9.5 cm/s was found, whereas TAPSE was within normal ranges.

There was a negative correlation between the achieved marathon times and training distance ($r = –0.4$, $p < 0.05$) or oxygen uptake at the anaerobic threshold (VO_2AT) ($r = –0.38$, $p < 0.05$). The training distance [km/week] correlated with LAVI ($r = 0.44$, $p < 0.05$). The RA area correlated with LAVI ($r = 0.46$, $p < 0.05$) and RVd ($r = 0.49$, $p < 0.05$).

The CMR was performed in 6 (18%) amateur marathon runners. The reasons for the CMR referral are presented in Table 4; all showed several abnormalities in ECHO and the most frequent was increased IVS. Results from CMR imaging are presented in Tables 4 and 5. The major abnormality was enlarged volume and depressed RV function. The RV ESV was increased in all runners and RV EDV in 1 individual. All those 6 participants presented reduced RV EF with a median of 46%. The LV was enlarged in 3 subjects (LV ESV was increased in all of them, while LV EDV in 1). In 3 participants LV EF was slightly below the lower reference limit. In 1 participant CMR imaging confirmed HCM with asymmetric hypertrophy (LVH) of LV segments: basal infero-septum and basal antero-septum with maximum wall thickness of 17 mm. In addition, the LGE revealed myocardial fibrosis within hypertrophic ventricular segments. LGE was present only in this participant. In addition, in 1 individual CMR raised suspicion of atrial septum defect of 6 mm in diameter.

Discussion

The study group represented a non-elite runner population. However, the reported finishing

Table 5. Results of cardiac magnetic resonance examination (CMR) in amateur marathon runners.

Parameter	Study participants (n = 6); median (range)	Reference values for men < 60 years [35] (range)
LA area 4C [cm^2]	24 (18–30)	15–29
RA area 4C [cm^2]	22 (20–30)	14–30
LV EDV [mL]	182 (152–245)	119–203
LV ESV [mL]	76 (60–107)	33–77
LV EF [%]	59 (53–62)	57–75
LV mass [g]	165 (155–199)	107–187
RV EDV [mL]	202 (184–239)	119–219
RV ESV [mL]	115 (97–123)	32–92
RV EF [%]	46 (42–49)	50–78

For abbreviations see Table 2; LA — left atrial; RA — right atrial; 4C — four chamber view; RV EF — right ventricular ejection fraction; ESV — end-systolic volume

times vary between studies, the average time of the marathon run among amateur participants oscillates around 3.5 h, similar to the present group [13]. Professional athletes cover this distance within 2.3 h [14]. Regarding training volumes, the weekly distance in highly-trained elite and national-class runners is 145.3 ± 25.6 km [14], whereas in the current group it was 56.5 ± 19.7 km, comparable to other studies on amateurs [15]. The mean VO_2peak was similar to those previously reported among runners with comparable running performance [13]. The more time subjects spent on training the better marathon time they achieved. The VO_2AT appeared to be prognostic for obtained outcome at the finishing-line.

Training-induced changes in cardiac morphology, named the "athlete's heart" are a common finding among professional athletes. Recurrent exercise-induced pressure or volume overload causes cardiac remodeling with increased chamber dimensions, LV mass and LV wall thickness [4, 7]. Physiological in elite athletes, these modifications in the general adult population are considered pathological. Type of exercise, its intensity, duration of training, age, sex, race, BSA and other unrecognized individual factors can influence the occurrence of "athlete's heart" [4, 16]. It can appear even after 8 weeks of intense training and may disappear after sport termination [17, 18]. The question arises, whether the "athlete's heart" features also develop in middle-aged recreational runners. In the present group of amateur marathon runners, the cardiac dimensions assessed by ECHO frequently exceeded those obtained in sedentary controls, as well as reference ranges for the general adult population. Atrial enlargement was one of the most common findings and both atria were significantly larger in comparison to sedentary controls. Due to significant hemodynamic overload and increased atrial pressure during intense exercise, larger LA in professional athletes were expected with volumes on average of 7.0 mL/m^2 greater than those met in the general population [19, 20]. Noteworthy, in the present study was that LAVI in amateur runners exceeded not only upper value ranges for the general population, but in half of them upper ranges were also reported for highly trained athletes. The more time runners spent on training the more their LA was enlarged, which was demonstrated by positive correlation between LAVI and weekly training distance. More than half of the current group had an enlarged RA area and changes in RA correlated with those of LA. Possibly, atria of amateur runners are especially prone to enlargement and this magnification may not happen without consequences — as we know that exercise-induced atrial remodeling increases the risk of atrial fibrillation [21]. The next important finding in the amateur runners studied was the LV thickening, which was significant in comparison with sedentary controls. The measurement of the wall thickness is especially important in differential diagnosis between physiological exercise-induced LVH and HCM. HCM remains one of the most common causes of sudden cardiac death in elite athletes and individuals with this diagnosis are advised to discontinue competitive sport activity [22, 23]. The LV wall of 13–14 mm is the grey zone in differential diagnosis among athletes and HCM patients, whereas ≥ 15 mm or evident asymmetric hypertrophy suggests pathology [16, 23]. The prevalence of LV wall thickness ≥ 13 mm was reported

as 1.7% among athletes, however training-related IVS can (rarely) reach even 16 mm [7]. In the group studied the IVS of ≥ 13 mm was more frequent. Two cases raised suspicion of HCM, and was later confirmed in one individual. The recognition of HCM never relies on a single ECHO parameter and the assessment of diastolic function may also be helpful [16, 23]. The exercise-related LV thickening usually corresponds with LV enlargement, whereas in HCM patients the LV diastolic volume is rather small [16]. In the current study, LV dilation was rarely encountered and IVS thickening was not observed parallel to LV enlargement. What can be used to differentiate "athlete's heart" with cardiomyopathies is the speckle tracking-derived LV GLS assessment, which enables detection of systolic abnormalities much earlier than the LV EF deteriorates [23, 24]. The sedentary population norms of LV GLS vary between studies, according to meta-analysis it should not be > –18.9%. Nevertheless, one should take into account the software that was used — in EchoPAC from GE the lower limit of normal range for LV GLS is –18% [5, 9]. Noteworthy, LV GLS normal values for athletes resemble those for the general population and abnormal LV GLS (especially when > –15%) in athletes should not be regarded as cardiac training adaptation, but rather as pathological and should prompt further diagnostics [24].

As RV remodeling is one of the most characteristic features of "athlete's heart" it is necessary to apply special normative reference values for RV evaluation in elite athletes [6]. In healthy sportsmen, the size of RV is increased but its function is preserved, although according to recent meta-analysis athletes present lower RV EF in CMR than the general population (with mean of 52%) [25]. The RV enlargement is also typical for arrhythmogenic RV cardiomyopathy, which should be ruled out in differential diagnosis [26]. In the present study nearly half of the amateur runners showed enlarged RV (RVOT prox). Standard 2D echocardiographic evaluation of RV remains challenging, because of its complicated structure and lack of a single parameter that would precisely describe RV systolic function [27]. The assessment of RV is very important, as RV, may be "the Achilles heel" of the competing heart. In the current study 6 participants presented with slightly reduced RV systolic function, as indicated by abnormal RV strain and also decreased S'RV in one subject. It has also been shown previously in elite athletes, that adaptation for training means better RV deformation and that there is a correlation between training experience and RV strain; the more years of training — the more negative the RV strain values can be [28].

ECHO remains the main tool in the recognition of the "athlete's heart" and in differential diagnosis with cardiomyopathies. Nevertheless, CMR provides the most accurate estimation of both ventricles including the prevalence of myocardial fibrosis [29]. The presence of LGE in hypertrophic segments may suggest HCM, but it does not always mean a certain diagnosis [23, 30]. Generally, in elite athletes, CMR mainly demonstrates the biventricular enlargement of volumes: EDV and ESV [29, 31]. Usually these changes are symmetrical and those in the RV reflect those in the LV [25, 32]. In the present study nearly half of participants presented enlarged RV but it was not accompanied by an increase in LV diameters or volumes. These observations were previously explained as RV sensitiveness and an expected response to increased overload [25]. Nevertheless, current results concerning the RV and LV systolic function suggest difficulties of RV for amateur marathon runners to adapt to exercise and can support a thesis that RV as an "Achilles heel" of the competing heart. Not only RV but also RA may limit the heart function, as in the present group, both right heart chambers were dilated and the RA area and RVd correlated positively. Probably, the right heart of predisposed individuals, when exposed to repetitive episodes of overload, may be prone to irreversible damage. The recurrent extreme effort can lead to so-called Phidippides cardiomyopathy, in which the focal areas of cardiac fibrosis develop and become the substrate for ventricular arrhythmias and a reason for sudden death [33].

Conclusions

The results of the present study demonstrate that "athlete's heart" features do develop in amateur marathon runners. One of the most important findings was increased LAVI, which exceeded even the upper reference limit for highly-trained athletes in half of the study participants. It may reflect abnormal atrial response to pressure overload in recreational marathon runners not sufficiently adapted to endurance exercise. Another important issue was the high prevalence of IVS thickening among amateur athletes and a confirmed diagnosis of HCM in one participant. Echocardiography should play a pivotal role in the medical assessment of this population. In individuals with the history of marathon attendance ECHO reference values for

highly trained elite athletes may be more helpful than those applied for the general adult population. CMR imaging is indicated when it is difficult to differentiate between physiological "athlete's heart" remodeling and conditions like hypertrophic cardiomyopathy.

Conflict of interest: None declared

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The effect of hidden female smoking on the relationship between smoking and cardiovascular disease

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Abstract

Background: *Smoking is a known risk factor for cardiovascular morbidity and mortality, but several Korean studies have shown differing results on the association of current smoking status and the risk of cardiovascular disease (CVD). The aim of the present study was to investigate the association between smoking status and CVD (myocardial infarction and stroke) using national representative population-based samples. The aim was also to investigate the effects of hidden smokers on the association between CVD and smoking.*

Methods: *Data were acquired from 28,620 participants (12,875 men and 15,745 women), age 19 years or older, who participated in the Korea National Health and Nutrition Examination Survey (KNHANES) conducted from 2008 to 2016.*

Results: *The multivariable logistic regression analysis showed that ex-smoking status was correlated with CVD when self-reported (odds ratio [OR]: 1.62; 95% confidence interval [CI]: 1.20–2.19) and for survey-cotinine verified-smoking status (OR: 1.57; 95% CI: 1.20–2.19). Interestingly, the present study showed current smoking was not significantly associated with CVD. For the effect of sex on smoking and CVD, self-reported and survey-cotinine-verified ex-smoking status were correlated with CVD in males (OR: 1.45; 95% CI: 1.04–2.04 and OR: 1.43; 95% CI: 1.02–2.02) and in females (OR: 2.74; 95% CI: 1.59–4.71 and OR: 2.92; 95% CI: 1.64–5.18). The ratios of cotinine-verified to self-reported smoking rates were 1.95 for women and 1.08 for men.*

Conclusions: *In the current study, while ex-smoking status was significantly associated with CVD, current smoking status was not. Female ex-smoking status had a higher adjusted odds ratio for CVD than males compared to non-smoking status. An effect of hidden female smoking was also found on the association between smoking status and CVD in Korean adults.* (Cardiol J 2021; 28, 5: 716–727)

Key words: smoking, myocardial infarction, stroke, hidden smoker

Introduction

Smoking is a known risk factor of cardiovascular morbidity and mortality [1]. However, while more than 4000 chemical substances contained in a cigarette are known to have adverse effects on various cardiovascular diseases (CVD) [2], the pathophysiological mechanisms underlying the

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association between smoking and CVD have not been fully elucidated.

The CHANCES consortium (Consortium on Health and Ageing: Network of Cohorts in Europe and the United States) study showed a strong relationship between tobacco smoking and CVD [3]. This study used data from 10 cohort studies that showed a cardiovascular mortality hazard ratio of 2.07 (95% confidence interval [CI]: 1.82–2.36) for current smokers and 1.37 (95% CI: 1.25–1.49) for former smokers compared to participants who had never smoked. Another meta-analysis study based on prospective studies showed that the relative risk (RR) of sudden cardiac death due to CVD, including coronary heart disease and stroke, was 3.06 (95% CI: 2.46–3.82) for current smokers and 1.38 (95% CI: 1.20–1.60) for former smokers compared to participants who had never smoked [4].

Moreover, the INTERHEART study showed that current smoking status (odds ratio [OR] 2.87) was significantly associated with myocardial infarction (MI) [5], and a UK biobank study showed that the hazard ratios for MI were 3.46 (95% CI: 3.02–3.98) in female current smokers and 2.23 (2.03–2.44) in male current smokers [6]. One meta-analysis study showed that the pooled relative risk of stroke associated with current smoking status vs. non-smoking status was 1.67 (95% CI: 1.49–1.88) in men and 1.83 (95% CI: 1.58–2.12) in women [7].

However, several Korean studies showed contrasting results on the association between current smoking status and CVD risk in adults [8, 9]. A national study showed that smoking status was significantly associated with stroke (RR: 1.060, 95% CI: 1.022–1.100) but not MI (RR: 1.004, 95% CI: 0.958–1.051) [8]. In addition, another national study showed that, compared to a non-smoking group of Korean adult males, the ORs (95% CI) for physician-diagnosed stroke and MI in a current smoker group were 0.84 (0.74–0.94) and 0.96 (0.82–1.12), respectively, and 1.38 (1.24–1.53) and 1.45 (1.26–1.67), respectively, in a past smoker group [9].

Recently, a report showing that ratios of cotinine-verified to self-reported smoking rates were 2.36 for women and 1.12 for men in Korea [10]. In a previous report, an effect was found of hidden female smoking on the association between smoking and hypertension in Korean adults [11]. It is currently proposed that contradictory results from other countries may be due to hidden female smokers.

Therefore, the first aim of the study was to investigate the association between smoking status and CVD using different nationally representative population-based samples. The second aim was to investigate the effects of hidden female smokers on the association between CVD and smoking in Korean adults.

Methods

Study population

This study was based on data obtained from the 2008–2016 KNHANES study. KNHANES, which was a cross-sectional survey designed to examine the health and nutritional status of the non-institutionalized Korean population.

Of the total 76,909 KNHANES participants, 48,289 participants were excluded due to the following criteria: under 18 years old, no smoking history, no MI information, no stroke information, no urine cotinine test, no history of renal failure information, or serum creatinine ≥ 1.5 mg/dL. The remaining 28,620 participants (12,875 men and 15,745 women) were included in the final analysis.

General characteristics, anthropometry, and laboratory tests

The contents of the questionnaire used in KNHANES included sex, age, marital status, employment status, education level, monthly family income, number of household members, residence area, and body mass index (BMI). The questionnaire also ascertained the presence of or history of hypertension, diabetes, MI, and stroke. The respondents' residential areas were categorized as urban (an administrative division of a city) or rural (not classified as an administrative division of a city). The definition of a city in Korea is a place where more than 50,000 people live. Monthly family income indicates monthly-equalized family income and was calculated by dividing the total family income by the square root of the number of household members. In KNHANES, monthly family income was classified into quartiles in order to determine the monthly household income level (1: low, 2: middle low, 3: middle high, and 4: high). Education level was defined as less than middle school, middle school, high school, and college or more. BMI was calculated as weight (kilograms) divided by height (meters squared) and was categorized into three groups: normal weight (< 23 kg/m^2), overweight (23–25 kg/m^2), and obese (≥ 25 kg/m^2) [12].

Cigarette smoking status was divided into three categories: smoker, ex-smoker, and never smoked. Respondents who reported having consumed ≥ 100 cigarettes in their lifetime or re-

Table 1. Definition of survey-cotinine-verified smoking status.

Self-reported smoking status	Cotinine-verified smoking status	
	Non-smoker (≤ 50 ng/mL)	Smoker (> 50 ng/mL)
Non-smoker	Non-smoker (n = 16,595)	Smoker (n = 813)
Ex-smoker	Ex-smoker (n = 4712)	Smoker (n = 517)
Smoker	Smoker (n = 176)	Smoker (n = 5,807)

sponded "yes" to the question, "Do you smoke cigarettes now?" were regarded as smokers. Participants answering "no" to the same question were classified as ex-smokers. Respondents who consumed < 100 cigarettes in their lifetime were regarded as never having smoked.

Urinary cotinine was measured by tandem mass spectrometry with a tandem mass API 4000 (Applied Biosystems, Carlsbad, CA, USA) and by gas chromatography and mass spectrometry with a Perkin Elmer Clarus 600T (PerkinElmer, Turku, Finland). Respondents with urinary cotinine concentrations ≥ 50 ng/mL were considered cotinine-verified smokers, and those with cotinine levels < 50 ng/mL were cotinine-verified non-smokers [13].

To define MI and stroke, the following survey question was used in this study: "Have you ever been diagnosed with myocardial infarction or stroke by a physician?" For convenience, CVD to MI and stroke were limited. In a similar questionnaire, blood pressure (BP) measurements and medication history were used to define hypertension with the following question: "Have you ever been diagnosed with hypertension by a physician or take a medicine now?" Seated BP was measured using a standardized automated oscillometric device after a 5-min rest period. If BP was abnormally high or low, BP was reassessed with a mercury sphygmomanometer by a trained nurse. Hypertension was defined as having elevated BP (systolic BP [SBP] ≥ 140 mmHg and/or diastolic BP [DBP] ≥ 90 mmHg). Participants currently prescribed anti-hypertensive medication were also considered to be hypertensive. Diabetes was defined as a fasting blood glucose (FBG) of 126 mg/dL. Participants who reported being diagnosed with diabetes by a physician and prescribed diabetes medication including insulin were also considered to be diabetic.

To better understand the link between MI, stroke, and smoking, a new variable was created for defining smoking status (survey-cotinine-verified smoking status [SCS]) (Table 1). It was assumed that smoking in this variable included all smoking types, including light, intermittent, passive, hidden, and active heavy smoking (Table 1).

Statistical analysis

All statistical analyses was conducted using the Statistical Package for the Social Sciences (SPSS) complex sample procedures since KNHANES data were collected through a representative, stratified, and clustered sampling method. Values are presented as number of participants or estimates (95% CI). Data are expressed as the mean ± standard deviation (SD) and as the median for continuous variables and as percentages (%) for categorical variables.

Calculations of crude odd ratios and 95% CI values for CVD in relation to potential risk factors were performed using univariable logistic regression models. Finally, multivariable logistic regression analysis was carried out to identify the relationships between risk factors and CVD to evaluate the relationship of self-reported and cotinine-verified smoking status with CVD. Sex, age, marital status, employment status, education level, monthly family income, number of household members, residence area, smoking status, BMI, presence of hypertension and presence of diabetes were corrected for in the final multivariable logistic regression model.

Statistical analysis was conducted using SPSS version 21.0 (SPSS Inc. Chicago, IL, US). For all analyses, p values were two-tailed, and a p value < 0.05 was considered statistically significant.

Results

Clinical characteristics

A total of 28,620 subjects from the KNHANES were included in this study. Mean age was 49.55 ± ± 16.35 years. Slightly over half (52.3%) were male. The majority of participants were married (75.0%), employed (64.2%), and had an education level of high school or higher (73.9%). Most subjects lived in urban areas (83.1%) (Table 2).

Table 2. Demographic characteristics of subjects.

Characteristics	Sample size	Estimate % (95% CI)
Sex (n = 28,620)		
Male	12,875	52.29 (51.74–52.85)
Female	15,745	47.71 (47.15–48.26)
Age (n = 28,620)		
< 50	14,332	62.00 (61.04–62.97)
50–59	5515	18.89 (18.27–19.51)
60–69	5000	11.30 (10.85–11.77)
≥ 70	3773	7.81 (7.41–8.24)
Marital status (n = 26,740)		
Married	20,644	74.95 (74.03–75.84)
Single (separated or divorced)	3491	10.10 (9.61–10.62)
Never-married	2605	14.95 (14.15–15.80)
Employment status (n = 28,541)		
Employed	17,307	64.19 (63.40–64.97)
Unemployed	11,234	35.81 (35.03–36.60)
Education level (n = 28,541)		
< High school	9918	26.10 (25.18–27.05)
High school	9755	38.94 (38.08–39.80)
> High school	8868	34.96 (33.89–36.04)
Monthly family income (n = 28,310)		
< 25^{th}	5284	14.80 (14.06–15.57)
25–50^{th}	7149	24.85 (23.96–25.76)
50–75^{th}	7851	29.64 (28.68–30.61)
≥ 75^{th}	8026	30.72 (29.40–32.06)
Number of household members (n = 28,608)		
1	2521	7.26 (6.68–7.88)
2	7695	21.58 (20.84–22.33)
3	6968	26.67 (25.82–27.54)
4	7725	30.92 (29.95–31.91)
≥ 5	3699	13.58 (12.80–14.39)
Residence area (n = 28,620)		
Urban	22,156	83.14 (81.04–85.05)
Rural	6104	16.86 (14.95–18.96)
Smoking status		
Self-reported 1 (n = 28,620)		
Non-smoker	17,408	56.41 (55.73–57.09)
Ex-smoker	5229	18.05 (17.55–18.56)
Smoker	5983	25.54 (24.87–26.22)
Cotinine-verified (n = 28,620)		
Non-smoker	21,483	70.33 (69.58–71.07)
Smoker	7137	29.67 (28.93–30.42)
Survey-cotinine verified (n = 28,620)		
Non-smoker	16,595	53.57 (52.85–54.29)
Ex-smoker	4712	15.98 (15.49–16.47)
Smoker	7313	30.45 (29.72–31.20)
Body mass index (n = 28,620)		
< 23	12,318	43.64 (42.90–44.37)
23–25	6812	23.71 (23.13–24.30)
≥ 25	9415	32.66 (31.95–33.37)
Hypertension (n = 28,620)	7917	23.69 (23.04–24.36)
Diabetes (n = 28,620)	3082	8.80 (8.42–9.20)
Myocardial infarct or stroke (n = 28,620)	811	1.98 (1.81–2.16)
Myocardial infarct	236	0.60 (0.51–0.70)
Stroke	599	1.44 (1.30–1.60)

Table 3. Self-reported and cotinine-verified smoking status in male and female participants.

Self-reported smoking status	Total	Cotinine-verified smoking status (estimate % [95% CI])	
		Non-smoker	Smoker
Male (n = 12,875)			
Total		53.4 (52.3–54.4)	46.6 (45.6–47.7)
Non-smoker	26.0 (25.0–26.9)	24.8 (23.9–25.7)	1.2 (1.0–1.4)
Ex-smoker	30.6 (29.6–31.5)	27.4 (26.5–28.3)	3.2 (2.9–3.6)
Smoker	43.5 (42.4–44.5)	1.2 (1.0–1.5)	42.3 (41.2–43.3)
Female (n = 15,745)			
Total		88.9 (88.2–89.6)	11.1 (10.4–11.8)
Non-smoker	89.8 (89.1–90.4)	85.1 (84.3–85.9)	4.7 (4.2–5.2)
Ex-smoker	4.3 (4.0–4.8)	3.5 (3.2–3.9)	0.8 (0.7–1.0)
Smoker	5.9 (5.4–6.4)	0.3 (0.2–0.4)	5.6 (5.1–6.1)

Smoking status

Self-reported smoking prevalence was 25.5%, whereas the prevalence of cotinine-verified smokers in the overall population was 29.7% (Table 2). Cotinine-verified smoking prevalence for men and women was 43.3% (5,578/12,875) and 9.9% (1,559/15,745), respectively (Table 3). The overall prevalence of self-reported ex-smokers and current smokers was 18.1% and 25.5%, the percentages were 30.6% and 43.5% in men and 4.3% and 5.9% in women (Tables 2, 3). Of the 7,137 cotinine-verified male and female smokers, 813 (11.4%) were self-reported non-smokers and 517 (7.2%) were self-reported ex-smokers. Specifically, 2.3% and 7.3% of male cotinine-verified smokers were self-reported non-smokers and ex-smokers, respectively, whereas 43.7% and 7.1% of female cotinine-verified smokers were self-reported non-smokers and ex-smokers, respectively (Table 3). The ratios of cotinine-verified to self-reported smoking rates were 1.95 (1,559/801) for women and 1.08 (5,578/5,182) for men (Table 3).

Relationship between MI or stroke and smoking

In a univariate analysis, subjects with MI or stroke were prone to be male ($p < 0.01$), older ($p < 0.01$), single (separated or divorced) ($p < 0.01$), unemployed ($p < 0.01$), less educated ($p < 0.01$), obese ($p < 0.01$), have a lower monthly family income ($p < 0.01$), have fewer household members ($p < 0.01$), living in a rural setting ($p < 0.01$), have hypertension ($p < 0.01$), and have diabetes ($p < 0.01$) compared to subjects without CVD (Table 4). For self-reported smoking status, ex-smoking status was significantly correlated with CVD ($p < 0.01$), and for SCS, ex-smoking status was also correlated with CVD ($p < 0.01$). However, for all three types of smoking status, current smoking status was not significantly correlated with CVD using univariate statistical analysis ($p > 0.05$) (Table 4).

The multivariate logistic regression analysis showed that for self-reported smoking status, ex-smoking status was correlated with CVD (OR: 1.62; 95% CI: 1.20–2.19). Also, for SCS, ex-smoking status was correlated with CVD (OR: 1.57; 95% CI: 1.20–2.19) (Table 5).

To determine the effects of sex on smoking and CVD, sex differences were analyzed separately. For male participants, self-reported status and survey-cotinine-verified ex-smoking status were correlated with CVD (OR: 1.45; 95% CI: 1.04–2.04, OR: 1.43; 95% CI: 1.02–2.02). Female self-reported status and survey-cotinine-verified ex-smoking status were also correlated with CVD (OR: 2.74; 95% CI: 1.59–4.71, OR: 2.92; 95% CI: 1.64–5.18) (Tables 6, 7). Therefore, the current results indicate that sex affected the incidence of CVD in this study.

Discussion

The main findings of this study showed that, while ex-smoking status was significantly associated with CVDs, current smoking status was not, and female ex-smoking status had higher adjusted OR for CVD than males compared to non-smoking status. In addition, there was an effect of hidden female smoking on the association between smoking status and CVD in Korean adults.

Smoking is an established risk factor for cardiovascular morbidity and mortality [1].

Table 4. Crude odds ratios and 95% confidence intervals (CI) for myocardial infarction and stroke prevalence.

Characteristics	Odds ratio (95% CI)		
	Total	Male	Female
Sex			
Male	1.40 (1.19–1.65)	–	–
Female	Reference	–	–
Age			
< 50	Reference	Reference	Reference
50–59	8.10 (5.48–11.96)	7.65 (4.78–12.24)	11.07 (5.45–22.47)
60–69	21.90 (15.38–31.19)	21.03 (13.81–32.02)	31.48 (16.18–61.26)
≥ 70	33.92 (24.05–47.85)	28.01 (18.40–42.64)	63.78 (33.44–121.65)
Marital status			
Married	Reference	Reference	Reference
Single (separated or divorced)	2.28 (1.87–2.80)	1.94 (1.30–2.87)	3.48 (2.70–4.49)
Never-married	0.15 (0.08–0.29)	0.15 (0.07–0.31)	0.10 (0.02–0.40)
Employment status			
Employed	Reference	Reference	Reference
Unemployed	2.98 (2.50–3.55)	3.74 (2.99–4.68)	3.44 (2.61–4.55)
Education			
< High school	8.62 (6.45–11.50)	7.44 (5.33–10.39)	20.45 (10.76–38.86)
High school	1.90 (1.37–2.63)	1.83 (1.27–2.64)	2.62 (1.31–5.24)
> High school	Reference	Reference	Reference
Monthly family income			
< 25th	6.30 (4.78–8.30)	5.70 (4.04–8.04)	9.06 (5.89–13.92)
25–50th	2.13 (1.58–2.87)	1.80 (1.24–2.61)	3.17 (2.01–5.00)
50–75th	1.44 (1.06–1.96)	1.24 (0.85–1.82)	2.01 (1.23–3.26)
≥ 75th	Reference	Reference	Reference
Number of household members			
1	2.25 (1.60–3.18)	1.29 (0.74–2.18)	3.91 (2.36–6.47)
2	2.40 (1.79–3.22)	2.34 (1.62–3.40)	2.50 (1.56–3.99)
3	0.93 (0.67–1.30)	0.91 (0.60–1.38)	0.92 (0.55–1.54)
4	0.56 (0.39–0.80)	0.56 (0.36–0.89)	0.50 (0.27–0.91)
≥ 5	Reference	Reference	Reference
Residence area			
Urban	Reference	Reference	Reference
Rural	1.53 (1.25–1.87)	1.39 (1.07–1.81)	1.74 (1.33–2.29)
Smoking status			
Self-reported			
Non-smoker	Reference	Reference	Reference
Ex-smoker	2.69 (2.24–3.24)	3.30 (2.43–4.49)	2.00 (1.26–3.16)
Smoker	0.99 (0.79–1.24)	1.23 (0.87–1.72)	0.61 (0.35–1.08)
Cotinine-verified			
Non–smoker	Reference	Reference	Reference
Smoker	0.67 (0.55–0.83)	0.56 (0.43–0.71)	0.50 (0.32–0.79)
Survey-cotinine verified			
Non-smoker	Reference	Reference	Reference
Ex-smoker	2.79 (2.30–3.38)	3.37 (2.46–4.60)	2.25 (1.39–3.63)
Smoker	0.92 (0.74–1.15)	1.19 (0.85–1.67)	0.53 (0.34–0.84)
Body mass index			
< 23	Reference	Reference	Reference
23–25	1.49 (1.19–1.87)	1.13 (0.84–1.51)	1.98 (1.42–2.77)
≥ 25	1.88 (1.55–2.29)	1.35 (1.03–1.77)	2.70 (2.02–3.59)
Hypertension			
No	Reference	Reference	Reference
Yes	5.60 (4.71–6.67)	4.24 (3.34–5.38)	8.18 (6.24–10.74)
Diabetes			
No	Reference	Reference	Reference
Yes	5.36 (4.47–6.42)	5.89 (4.62–7.50)	4.41 (3.36–5.78)

Table 5. Adjusted odds ratios and 95% confidence intervals for myocardial infarction and stroke prevalence.

Characteristics	Self-reported	Cotinine-verified	Survey-cotinine verified
Sex			
Male	1.70 (1.26–2.27)	2.39 (1.93–2.94)	1.78 (1.35–2.35)
Female	Reference	Reference	Reference
Age			
< 50	Reference	Reference	Reference
50–59	4.88 (3.12–7.65)	4.89 (3.11–7.69	4.84 (3.09–7.59)
60–69	8.52 (5.41–13.44)	8.52 (5.38–13.48)	8.42 (5.33–13.30)
≥ 70	9.81 (6.05–15.92)	9.78 (6.01–15.92)	9.64 (5.93–15.67)
Marital status			
Married	Reference	Reference	Reference
Single (separated or divorced)	0.97 (0.73–1.28)	0.99 (0.75–1.30)	0.97 (0.74–1.28)
Never-married	0.75 (0.36–1.54)	0.69 (0.34–1.43)	0.74 (0.36–1.52)
Employment status			
Employed	Reference	Reference	Reference
Unemployed	1.90 (1.55–2.33)	1.93 (0.57–2.38)	1.90 (1.55–2.34)
Education			
< High school	1.78 (1.29–2.45)	1.80 (1.30–2.48)	1.79 (1.30–2.47)
High school	1.36 (0.96–1.93)	1.38 (0.98–1.94)	1.37 (0.97–1.93)
> High school	Reference	Reference	Reference
Monthly family income			
< 25th	1.69 (1.24–2.30)	1.70 (1.25–2.32)	1.70 (1.25–2.32)
25–50th	1.25 (0.91–1.72)	1.25 (0.91–1.72)	1.25 (0.91–1.72)
50–75th	1.27 (0.92–1.76)	1.28 (0.93–1.77)	1.27 (0.92–1.76)
≥ 75th	Reference	Reference	Reference
Number of household members			
1	0.94 (0.65–1.37)	0.95 (0.65–1.38)	0.94 (0.65–1.38)
2	0.95 (0.68–1.32)	0.96 (0.69–1.34)	0.95 (0.68–1.33)
3	0.82 (0.58–1.17)	0.82 (0.58–1.18)	0.82 (0.58–1.18)
4	0.82 (0.56–1.20)	0.82 (0.56–1.20)	0.82 (0.56–1.21)
≥ 5	Reference	Reference	Reference
Residence area			
Urban	Reference	Reference	Reference
Rural	1.13 (0.91–1.40)	1.12 (0.90–1.39)	1.13 (0.91–1.40)
Smoking status			
Self-reported			
Non-smoker	Reference	–	–
Ex-smoker	1.62 (1.20–2.19)	–	–
Smoker	1.25 (0.92–1.70)	–	–
Cotinine-verified			
Non-smoker	–	Reference	–
Smoker	–	0.88 (0.69–1.11)	–
Survey-cotinine verified			
Non-smoker	–	–	Reference
Ex-smoker	–	–	1.57 (1.16–2.12)
Smoker	–	–	1.15 (0.87–1.53)
Body mass index			
< 23	Reference	Reference	Reference
23–25	1.10 (1.20–2.19)	1.10 (0.87–1.40)	1.10 (0.86–1.40)
≥ 25	1.25 (0.92–1.70)	1.24 (0.99–1.56)	1.24 (0.99–1.56)
Hypertension			
No	Reference	Reference	Reference
Yes	2.06 (1.69–2.50)	2.05 (1.69–2.50)	2.05 (1.69–2.49)
Diabetes			
No	Reference	Reference	Reference
Yes	1.85 (1.52–2.25)	1.86 (1.53–2.27)	1.85 (1.52–2.26)

Adjusted for sex, age, marital status, employment status, education level, monthly family income, number of household members, residence area, smoking status, body mass index, hypertension and diabetes.

Table 6. Adjusted odds ratios and 95% confidence intervals for myocardial infarction and stroke prevalence in male participants.

Characteristics	Self-reported	Cotinine-verified	Survey-cotinine verified
Age			
< 50	Reference	Reference	Reference
50–59	4.63 (2.66–8.06)	4.70 (2.70–8.20)	4.60 (2.64–8.01)
60–69	8.65 (4.93–15.18)	8.80 (5.01–15.45)	8.57 (4.87–15.07)
≥ 70	8.09 (4.33–15.10)	8.17 (4.37–15.27)	7.97 (4.25–14.94)
Marital status			
Married	Reference	Reference	Reference
Single (separated or divorced)	1.01 (0.62–1.65)	1.02 (0.63–1.67)	1.01 (0.62–1.65)
Never-married	0.72 (0.30–1.74)	0.67 (0.28–1.61)	0.72 (0.30–1.72)
Employment status			
Employed	Reference	Reference	Reference
Unemployed	1.92 (1.44–2.56)	1.96 (1.47–2.61)	1.93 (1.45–2.57)
Education			
< High school	1.74 (1.20–2.52)	1.76 (1.22–2.55)	1.75 (1.21–2.53)
High school	1.39 (0.93–2.07)	1.40 (0.94–2.09)	1.39 (0.93–2.08)
> High school	Reference	Reference	Reference
Monthly family income			
< 25th	1.71 (1.14–2.57)	1.71 (1.14–2.57)	1.72 (1.15–2.58)
25–50th	1.11 (0.75–1.65)	1.11 (0.74–1.65)	1.11 (0.75–1.66)
50–75th	1.15 (0.77–1.72)	1.15 (0.77–1.73)	1.15 (0.76–1.72)
≥ 75th	Reference	Reference	Reference
Number of household members			
1	0.77 (0.41–1.45)	0.78 (0.41–1.46)	0.77 (0.41–1.45)
2	0.90 (0.59–1.38)	0.92 (0.60–1.40)	0.91 (0.59–1.39)
3	0.78 (0.50–1.22)	0.78 (0.50–1.23)	0.78 (0.50–1.23)
4	0.84 (0.52–1.36)	0.85 (0.52–1.37)	0.85 (0.52–1.37)
≥ 5	Reference	Reference	Reference
Residence area			
Urban	Reference	Reference	Reference
Rural	1.07 (0.80–1.42)	1.06 (0.80–1.41)	1.07 (0.80–1.42)
Smoking status			
Self-reported			
Non-smoker	Reference	–	–
Ex-smoker	1.45 (1.04–2.04)	–	–
Smoker	1.17 (0.81–1.67)	–	–
Cotinine-verified			
Non-smoker	–	Reference	–
Smoker	–	0.87 (0.65–1.15)	–
Survey-cotinine verified			
Non-smoker	–	–	Reference
Ex-smoker	–	–	1.43 (1.02–2.02)
Smoker	–	–	1.12 (0.78–1.60)
Body mass index			
< 23	Reference	Reference	Reference
23–25	1.11 (0.80–1.53)	1.11 (0.80–1.54)	1.10 (0.80–1.53)
≥ 25	1.37 (0.99–1.89)	1.37 (0.99–1.89)	1.36 (0.98–1.89)
Hypertension			
No	Reference	Reference	Reference
Yes	1.84 (1.41–2.40)	1.85 (1.41–2.41)	1.84 (1.41–2.39)
Diabetes			
No	Reference	Reference	Reference
Yes	2.26 (1.72–2.97)	2.29 (1.74–3.01)	2.26 (1.72–2.98)

Adjusted for age, marital status, employment status, education level, monthly family income, number of household members, residence area, smoking status, body mass index, hypertension and diabetes.

Table 7. Adjusted odds ratios and 95% confidence intervals for myocardial infarction and stroke prevalence in female participants.

Characteristics	Self-reported	Cotinine-verified	Survey-cotinine verified
Age			
< 50	Reference	Reference	Reference
50–59	5.46 (2.32–12.87)	4.98 (2.11–11.77)	5.35 (2.27–12.57)
60–69	8.80 (3.58–21.64)	7.87 (3.18–19.49)	8.56 (3.49–20.99)
≥ 70	13.25 (5.28–33.30)	11.91 (4.71–30.12)	12.83 (5.13–32.11)
Marital status			
Married	Reference	Reference	Reference
Single (separated or divorced)	0.86 (0.60–1.23)	0.91 (0.65–1.29)	0.87 (0.61–1.24)
Never-married	0.74 (0.17–3.25)	0.75 (0.16–3.45)	0.74 (0.17–3.20)
Employment status			
Employed	Reference	Reference	Reference
Unemployed	2.00 (1.46–2.74)	2.04 (1.49–2.80)	2.01 (1.47–2.76)
Education			
< High school	2.06 (0.99–4.29)	2.09 (1.01–4.35)	2.08 (1.01–4.33)
High school	143 (0.71–2.88)	1.44 (0.72–2.90)	1.45 (0.72–2.92)
> High school	Reference	Reference	Reference
Monthly family income			
< 25th	1.79 (1.09–2.91)	1.84 (1.13–3.00)	1.80 (1.10–2.94)
25–50th	1.62 (0.98–2.67)	1.61 (0.98–2.66)	1.63 (0.99–2.68)
50–75th	1.59 (0.95–2.67)	1.61 (0.96–2.69)	1.60 (0.95–2.67)
≥ 75th	Reference	Reference	Reference
Number of household members			
1	1.12 (0.63–1.98)	1.11 (0.63–1.94)	1.12 (0.63–1.98)
2	1.06 (0.61–1.85)	1.06 (0.61–1.84)	1.07 (0.61–1.86)
3	0.91 (0.51–1.64)	0.90 (0.50–1.61)	0.92 (0.51–1.65)
4	0.77 (0.40–1.49)	0.76 (0.40–1.46)	0.78 (0.40–1.49)
≥ 5	Reference	Reference	Reference
Residence area			
Urban	Reference	Reference	Reference
Rural	1.21 (0.90–1.63)	1.19 (0.88–1.59)	1.21 (0.90–1.63)
Smoking status			
Self-reported			
Non-smoker	Reference	–	–
Ex-smoker	2.74 (1.59–4.71)	–	–
Smoker	0.96 (0.53–1.72)	–	–
Cotinine-verified			
Non-smoker	–	Reference	–
Smoker	–	1.19 (0.88–1.59)	–
Survey-cotinine verified			
Non-smoker	–	–	Reference
Ex-smoker	–	–	2.92 (1.64–5.18)
Smoker	–	–	0.90 (0.56–1.44)
Body mass index			
< 23	Reference	Reference	Reference
23–25	1.09 (0.77–1.56)	1.08 (0.76–1.54)	1.08 (0.76–1.54)
≥ 25	1.05 (0.77–1.44)	1.06 (0.78–1.44)	1.05 (0.77–1.43)
Hypertension			
No	Reference	Reference	Reference
Yes	2.43 (1.80–3.28)	2.41 (1.78–3.25)	2.43 (1.80–3.28)
Diabetes			
No	Reference	Reference	Reference
Yes	1.29 (0.97–1.74)	1.31 (0.98–1.75)	1.29 (0.96–1.73)

Adjusted for age, marital status, employment status, education level, monthly family income, number of household members, residence area, smoking status, body mass index, hypertension and diabetes.

Cigarette smoke contains over 4000 compounds, many of which are extremely reactive and affect the physiology of several systems in the body. These compounds include nicotine, tar, carbon monoxide, and nitrogen oxide [14].

Nicotine can elevate BP via various biological mechanisms: sympathomimetic action, modulation of the renin–angiotensin system, and acute vasopressor effects. All of these mechanisms are associated with increases in inflammatory markers through the upregulation of arginine vasopressin and endothelin-1 [15]. Nicotine can also increase low-density lipoprotein and decrease high-density lipoprotein, thereby accelerating the progression of atherosclerosis [2].

Carbon monoxide and hemoglobin combine to produce carboxy-hemoglobin, which induces hypoxia, increases in the number of red blood cells, and increases in blood viscosity, thereby, inducing thrombosis and atherosclerosis [16]. Through these mechanisms, structural damage to the arterial walls from smoking is believed to cause MI and induce stroke.

Previous studies have shown that current smoking status is significantly associated with MI [5, 6] and stroke [7, 17], but the present study has not shown a significant association. Proposed herein, is that the differing results may be due to differences in study design. The study design of the previous studies were case-control and population--based prospective cohorts; the present study design was cross-sectional. Other Korean and Polish studies that used cross-sectional designs showed similar results to the current study [8, 9, 18]. A Korean study using the 2009 Community Health Survey data gathered by the Korea Centers for Disease Control and Prevention showed current smoking was not associated with physician-diagnosed MI (OR: 0.96; 95% CI: 0.82–1.12) and stroke (OR: 0.84; 95% CI: 0.74–0.94), but ex-smoking was associated with physician-diagnosed MI (OR: 1.45; 95% CI: 1.26–1.67) and stroke (OR: 1.38; 95% CI: 1.24–1.53) [9]. In the Polish study, the researchers showed a significant association between former smokers and CVD (OR: 1.33; 95% CI: 1.05–1.68), but not between current smokers and CVD (OR: 1.06; 95% CI: 0.77–1.47) [18]. In addition, after cardiovascular events, patients were advised to quit smoking by physicians [19]. Therefore, the idea that cross-sectional studies, including the present study, might show no association between current smoking and CVD, but a significant association between ex-smoking and CVD.

For stroke, previous Korean studies showed different results. One study showed that ex-smoking status was associated with stroke in Korean male adults, but current smoking was not [9]. Another study showed that current smoking status was associated with stroke (OR: 1.060; 95% CI: 1.022–1.100) [8]. Because the prevalence of stroke increases with age, it was assumed these differing results may be due to differences in participant age. One study included male subjects 30 years or older [9], while another study included subjects 50 years or older [8]. In the current study, participants 19 years or older were included and showed that ex-smoking status, but not current smoking status, was associated with stroke.

In the present study, female ex-smoking status had higher odds ratio for CVD than males, compared to non-smoking status. Two hypotheses are herein proposed. First, the use of oral contraceptives and postmenopausal hormone replacement therapy in female smokers might increase CVD incidence, and the association between ex-smoker and CVD might be higher in female smokers due to smoking cessation after a CVD attack. The use of oral contraceptives and postmenopausal hormonal replacement therapy in smokers was known to increase the risk of MI and stroke [20–22]. Although the use of oral contraceptives did not increase the risk of MI in non-smokers, the use of oral contraceptives significantly increased the risk of MI in smokers [23]. The use of oral contraceptives also showed a higher prevalence of stroke in smokers compared to non-smokers [20], and the use of postmenopausal hormonal replacement therapy showed the same results for MI and stroke [21, 22]. Second, it was assumed these effects might be due to more female hidden smokers than males. In the case of self-reported ex-smokers, the probability of being identified as cotinine-verified smokers was 10.46% for men and 18.6% for women.

In the present study, the ratios of cotinine-verified to self-reported smoking rates were 1.95 for women and 1.08 for men. These rates were similar to the findings of a previous Korean study [10]. That study reported that ratios of cotinine--verified to self-reported smoking rates were 2.36 for women and 1.12 for men [10], but studies in other countries reported no sex differences in underreporting the rate of smoking history [24, 25].

In a study from the United States, the rates of agreement between self-reported and cotinine--verified smokers were 91.6% for women and 89.7% for men [24]. Additionally, a study from

Finland documented that 2.5% of men and 2.7% of women who self-reported as non-smokers had positive serum cotinine levels [25].

This result means there were more hidden female smokers than hidden male smokers in the current study. It was assumed that self-reported smoking in Korean women underestimates the true prevalence as a result of Confucianism. The adoption of Confucianism can result in a patriarchal culture in which female smoking is stigmatized [26]. The discrepancy in the underreporting rates between the sexes could lead to statistical inconsistencies.

To better understand the association between CVD and smoking, a new variable was created; SCS, in order to consider the effects of hidden smoking and other types of smoking. This new variable showed similar results compared to self--reported smoking status. Therefore, it isplausable to suggest that passive and light smoking may affect CVD development and are similar to affects of active smoking.

Light and social smokers often are not detected; many of these individuals have the perception of being non-smokers [27, 28]. However, a recent study reported that social smokers had significantly higher risks of CVD than non-smokers. Moreover, no significant differences in the development of hypertension have been reported between social smokers and current smokers [29]. Another report showed that light smoking was associated with a significantly higher risk of dying from ischemic heart disease [30]. With respect to the relationship between CVD and social and light smoking, a stable pattern of chronic low-level consumption may be assumed to have similar effects on CVD as constant, current active smoking.

Limitations of the study

There are several limitations to this study. First, because this study was based on a survey, there may be selection and recall biases. Second, because this study was cross-sectional in design, a causal relationship between smoking and CVD could not be confirmed. Third, although CVD was defined as MI and stroke in this study, CVD also includes other coronary heart diseases such as angina and peripheral arterial diseases; this was considered to be a limitation in the present study. Finally, potential confounding factors, including amount and duration of smoking, diet patterns, and genetic or sex variations affecting nicotine metabolism, still exist. Further prospective and collaborative worldwide studies are needed to clarify the effect of hidden female smoking on CVD. However, the strength of this study is its use of nationally and widely sampled data to assess sex-specific relationships between smoking status and CVD through the creation of a new variable, SCS. This new variable was used to evaluate the effect of hidden smoking on CVD.

Statement of ethics

This study was approved by the Institutional Review Board (IRB) of Samsung Changwon Hospital (IRB No: SCMC2019-04-005). Informed consent was waived by the board.

Conclusions

This large observational study found that ex-smoking status was associated with CVD and female ex-smoking status had a higher adjusted odds ratio for CVD than males compared to non-smoking status. In addition, there was an effect of hidden female smoking on the association between smoking status and CVD in Korean adults.

Conflict of interest: None declared

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Long-term follow-up after cardiac resynchronization therapy-optimization in a real-world setting: A single-center cohort study

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Abstract

Background: *Suboptimal device programming is among the reasons for reduced response to cardiac resynchronization therapy (CRT). However, whether systematic optimization is beneficial remains unclear, particularly late after CRT implantation. The aim of this single-center cohort study was to assess the effect of systematic atrioventricular delay (AVD) optimization on echocardiographic and device parameters.*

Methods: *Patients undergoing CRT optimization at the University Hospital Zurich between March 2011 and January 2013, for whom a follow-up was available, were included. AVD optimization was based on 12-lead electrocardiography (ECG) and echocardiographic left ventricular inflow characteristics. Parameters were assessed at the time of CRT optimization and follow-up, and were compared between patients with AVD optimization (intervention group) and those for whom no AVD optimization was deemed necessary (control group).*

Results: *Eighty-one patients with a mean age of 64 ± 11 years were included in the analysis. In 73% of patients, AVD was deemed suboptimal and was changed accordingly. After a median follow-up time of 10.4 (IQR 6.2 to 13.2) months, the proportion of patients with sufficient biventricular pacing (> 97% pacing) was greater in the intervention group (78%) compared to controls (50%). Furthermore, AVD adaptation was associated with an improvement in interventricular mechanical delay (decrease of 6.6 ± ± 26.2 ms vs. increase of 4.3 ± 17.7 ms, p = 0.034) and intraventricular septal-to-lateral delay (decrease of 0.9 ± 48.1 ms vs. increase of 15.9 ± 15.7 ms, p = 0.038), as assessed by tissue Doppler imaging. Accordingly, a reduction was observed in mitral regurgitation along with a trend towards reduced left ventricular volumes.*

Conclusions: *In this "real-world" setting systematic AVD optimization was associated with beneficial effects regarding biventricular pacing and left ventricular remodeling. These data show that AVD optimization may be advantageous in selected CRT patients.* (Cardiol J 2021; 28, 5: 728–737)

Key words: cardiac resynchronization therapy, atrioventricular delay, biventricular pacing, left ventricular remodeling

Introduction

Cardiac resynchronization therapy (CRT) is a life-saving treatment in selected patients with symptomatic heart failure and reduced ejection fraction (HFrEF) [1–3]. In patients with persistent symptoms (New York Heart Association [NYHA] II to ambulatory IV) on optimal medical therapy,

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a left ventricular ejection fraction (LVEF) of 35% or less, and a wide QRS complex (> 130 ms), CRT has been shown to prolong life and reduce the risk for recurrent heart failure (HF) hospitalizations [4–8]. However, about one third of patients remain unresponsive to biventricular pacing and do not exhibit improvement in clinical or hemodynamic parameters [5, 6]. Several factors may account for this unsatisfactory therapeutic response in this relevant proportion of patients. Apart from ineffective synchronization secondary to suboptimal left ventricular (LV) lead placement or extensive scar tissue, indeliberate patient selection remains a major source of error [7, 9]. However, even after correct LV lead placement and in the absence of extensive scar tissue, response to CRT may not be evident. Such therapy failure may be attributed to suboptimal device programming, specifically with regard to the atrioventricular delay (AVD) and interventricular (VV) interval [10, 11]. Yet, whether systematic AVD optimization is of prognostic benefit, remains unclear. To date, a number of studies suggest an improvement of clinical, echocardiographic and hemodynamic parameters after AVD optimization. However, the number of patients is very low and follow-up times are short [12–15].

At the documented institution, a standard protocol of echocardiography- and 12-lead electrocardiography (ECG)-guided device optimization after CRT implantation was implemented. It was previously demonstrated that a majority of patients undergoing CRT optimization after implantation presented with suboptimal device settings, particularly regarding AVD [16]. The aim of this study was to evaluate the clinical course after AVD optimization and to study whether patients, in whom the AVD was changed, fared better than those in whom the AVD was left unchanged in this real-world setting.

Methods

All patients with a CRT-device who underwent CRT optimization at the documented device clinic between March 2011 and January 2013 and in whom at least one follow-up including echocardiography was available were included. CRT devices were implanted according to standard protocols at the University Heart Center Zurich. Patients for CRT implantation were selected based on current guideline recommendations [17]. After implantation, a baseline CRT-optimization was performed on a routine basis, patients referred for CRT implantation from elsewhere underwent baseline optimization in cases of explicit referral. Baseline optimization included a comprehensive device optimization protocol with a complete clinical assessment by a HF specialist, a device interrogation, 12-lead ECGs of intrinsic and paced (BiV, RV, LV) rhythms, and a complete echocardiograph exam with optimization of AVD, if deemed necessary [16]. After baseline optimization, follow-up CRT-optimization was performed in cases of non-response or signs of disease progression, i.e. patients were referred for follow-up CRT optimization if there was a decrease or insufficient increase of LVEF after unexplained HF decompensation or in cases of unexplained progressive decline in exercise capacity.

The need for optimization of AVD was based on the degree of QRS fusion on 12-lead ECG and the presence of LV inflow truncation or fusion as assessed by pulsed wave Doppler echocardiography. For detection of electrical fusion, QRS morphology was assessed on 12-lead ECG during intrinsic rhythm, in biventricular stimulated VVI mode (representing "true" biventricular pacing), during right/left ventricular pacing only, and during CRT pacing under current settings. AVD was then programmed for as long as possible without signs of fusion with intrinsic conduction. Optimal LV filling was subsequently determined according to the iterative method [18, 19], i.e., AVD was shortened in steps of 20 ms under parallel assessment of QRS morphology on a 12-lead ECG and mitral inflow on pulsed wave Doppler echocardiography until truncation of the A-wave indicated impairment of LV filling. In a third step, AVD was increased in steps of 10 ms until an optimal separation of E and A wave occurred. This was considered an optimal atrioventricular coupling.

For the current study, clinical, echocardiographic and device parameters at the time of echocardiography and 12-lead ECG-guided CRT optimization (baseline visit) and at the time of the follow-up visit were analyzed. Parameters were compared between patients, in whom the AVD was changed at baseline ("intervention group") and those, in whom no adaptation of the AVD was made ("control group") (Fig. 1, **Suppl. Fig. 1**). Reasons for not changing the AVD were either an interval that was deemed optimal as assessed by the method described above, or if a change in AVD would lead to new QRS fusion or truncation of the A wave.

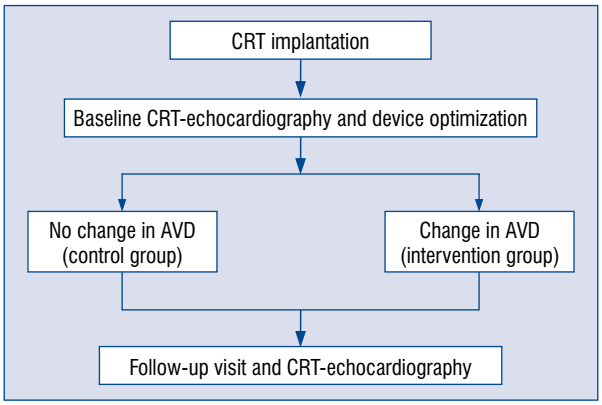

Figure 1. Follow-up flow chart; AVD — atrioventricular delay; CRT — cardiac resynchronization therapy.

Statistical analysis

Continuous variables are expressed as mean and standard deviation; categorical variables are expressed as proportions. Within-group comparisons (baseline vs. follow-up) were performed using the paired Student t-test for continuous variables and the paired Wilcoxon signed-rank tests for categorical variables. Between-group comparisons (intervention group vs. control group) were done using the unpaired Student t-test and the Mann-Whitney-U-test, where applicable. Distribution of data was assessed by the Shapiro-Wilk test and quantile-quantile (Q-Q) plots. Both data at baseline optimization and at follow-up as well as differences in parameters over time were assessed for normal distribution. Proportions were compared using χ^2 tests. Statistical significance was accepted for $p < 0.05$. All p-values are two-sided. Statistical analyses were performed using SPSS version 22.

Results

Eighty-one patients undergoing baseline CRT optimization between March 2011 and January 2013 and in whom a consecutive follow-up was available were included in the analysis. Baseline characteristics are summarized in Table 1. With the exemption of atrial fibrillation (AF), which was absent in the intervention group, and complete atrioventricular block, which was more frequent in the control group, no significant differences were present (Table 1). Median time between CRT implantation and baseline CRT-optimization was 1.7 (IQR 0.4 to 4.2) years. Median follow-up time between baseline optimization and follow-up was 10.4 (IQR 6.2 to 13.2) months. Out of 81 patients, 3 patients were hospitalized for HF during follow-up (2 in the intervention group, 1 in the control group). At baseline, 59 (73%) patients presented with AVD, which was deemed suboptimal either secondary to the presence of QRS fusion on a 12-lead ECG or due to unfavorable LV-filling patterns as assessed by echocardiography [16]. In these patients, AVD was reprogrammed according to the method described above; in the majority of these patients (n = 42, 52%) AVD was decreased, secondary to QRS fusion and/or LV inflow fusion. In 17 (21%) patients AVD was prolonged secondary to LV inflow truncation. Accordingly, the average AVD was significantly shorter at follow-up compared to baseline (120 ± 20 ms at baseline and 100 ± 29 ms at follow-up, p = 0.001). 12 (15%) patients were in AF.

In the overall population, clinical parameters did not change significantly between baseline and the follow-up visit. The proportion of patients with NYHA class II or higher was 79% (n = 58/73) at baseline and 76% (n = 57/75) at follow-up (p = 0.109).

Interestingly, biventricular pacing increased in patients after AVD adjustment over time. While there was no difference in biventricular pacing at baseline, the proportion of patients with a biventricular pacing rate of > 97% increased significantly by the time of follow-up (78% in the intervention group vs. 50% in the control group, p = 0.021; Fig. 2). As proof of concept, reassessment of biventricular pacing at follow-up was performed after exclusion of 6 patients with AF and intact atrioventricular conduction. Biventricular pacing proportions remained significantly higher in the intervention compared to the control group (mean biventricular pacing rate: 94.5 ± 6.8% in the control group, 97.5 ± 4.0% in the intervention group, p = 0.022; percentage of patients with > 97% biventricular pacing: 44% in the control group, 78% in the intervention group, p = 0.031; **Suppl. Table 1**).

Moreover, both interventricular mechanical delay (IVMD) and septal to lateral delay (SLD), as assessed by tissue Doppler imaging, decreased in the intervention group (AVD changed) compared to the control group (AVD unchanged), in which both IVMD and SLD increased from baseline to follow-up (Fig. 3). Although LVEF was not different between the intervention and the control group at follow-up (Fig. 4A), a trend was observed towards reduced end-diastolic LV volumes (Fig. 4B) in the intervention group. Along this line, the proportion of patients with mitral regurgitation, which did not differ between

Table 1. Parameters at baseline during cardiac resynchronization therapy-optimization.

Parameters	Overall population (n = 81)	Control group (n = 22)	Intervention group (n = 59)	P
Age at implantation (years)	64 ± 11	63 ± 16	64 ± 9	0.725
Men (n/total)	63/81 (78%)	17/22 (77%)	46/59 (78%)	0.947
Co-morbidities				
Diabetes mellitus	20/80 (25%)	7/22 (31.8%)	13/58 (22.4%)	0.386
Hypertension	44/81 (54.3%)	13/22 (59.1%)	31/59 (52.5%)	0.87
Dyslipidemia	45/81 (55.6%)	13/22 (59.1%)	32/59 (54.2%)	0.875
Coronary artery disease	32/81 (39.5%)	8/22 (36.4%)	24/59 (40.7%)	0.724
Atrial fibrillation	12/81 (15%)	12/22 (55%)	0/59 (0%)	< 0.001*
Medication				
ACEI/ARBs	79/80 (98.8%)	21/22 (96%)	58/58 (100%)	0.102
Beta-blockers	77/80 (96.3%)	21/22 (96%)	56/58 (96.6%)	0.818
Calcium channel blockers	6/80 (7.5%)	0/22 (0%)	6/58 (10%)	0.117
Spironolactone	47/80 (58.8%)	12/22 (55%)	35/58 (60%)	0.638
Diuretics	69/80 (86.3%)	21/22 (96%)	48/58 (83%)	0.141
Digitalis	10/80 (12.5%)	4/22 (18.2%)	6/58 (10.3%)	0.344
Amiodarone	12/80 (15%)	4/22 (18.2%)	8/58 (13.8%)	0.624
Clinical parameters				
NYHA class:				0.946
NYHA I	15/73 (20%)	5/21 (24%)	10/52 (19%)	
NYHA II	40/73 (55%)	10/21 (48%)	30/52 (58%)	
NYHA III	18/73 (25%)	6/21 (28%)	12/52 (23%)	
NYHA IV	0/73 (0%)	0/21 (0%)	0/52 (0%)	
Weight [kg]	81 ± 19	85 ± 21	80 ± 18	0.32
Systolic BP [mmHg]	118 ± 18	118 ± 18	118 ± 18	0.955
NT-proBNP [pg/mL]	1462 ± 1964	2015 ± 2186	1256 ± 1856	0.152
Echocardiographic parameters				
LVEF [%]	38 ± 10	38 ± 11	37 ± 9	0.78
EDVI [mL/m^2]	88 ± 38	85 ± 39	89 ± 37	0.697
IVMD [ms]	17.3 ± 28.0	12.9 ± 20.6	18.8 ± 30.0	0.41
TDI septal to lateral [ms]	41.7 ± 44.7	15.5 ± 51.2	48.3 ± 40.8	0.013*
TDI anteroseptal to inferolateral [ms]	38.2 ± 48.4	18.8 ± 48.8	42.8 ± 47.7	0.108
ECG and device parameters				
Biventricular pacing [%]	95.6 ± 9.6	93.8 ± 13.0	96.3 ± 8.0	0.304
Bundle branch block*				0.070
LBBB	54/65 (83%)	7/11 (64%)	47/54 (87%)	
RBBB	5/65 (8%)	1/11 (9%)	4/54 (7%)	
IVCD	6/65 (9%)	3/11 (27%)	3/54 (6%)	
Complete AVB	15/80 (19%)	11/22 (50%)	4/58 (7%)	< 0.001*
QRS width [ms]	150 ± 28	142 ± 25	152 ± 28	0.264
PQ interval [ms]**	184 ± 28	172 ± 40	185 ± 27	0.38
Sensed AV interval [ms]	112 ± 20	122 ± 22	110 ± 19	0.156
Paced AV interval [ms]	136 ± 23	146 ± 31	135 ± 22	0.223
VV [ms]	10 ±17	11 ± 21	9 ± 16	0.78
VV changed	16/81 (20%)	2/22 (9%)	14/59 (24%)	0.141

Continuous variables are presented as mean ± standard deviation; categorical variables are presented as proportions.
*Complete AVB excluded. **Patients with complete AVB and patients with atrial fibrillation excluded
ACEI/ARB — angiotensin-converting-enzyme inhibitor/angiotensin receptor blocker; AV — atrioventricular; AVB — atrioventricular block; BP — blood pressure; CRT — cardiac resynchronization therapy; ECG — electrocardiogram; EDVI — end-diastolic volume index; IVCD — intraventricular conduction delay; IVMD — interventricular mechanical delay; LBBB — left bundle branch block; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; NT-proBNP — N-terminal pro-B-type natriuretic peptide; RBBB — right bundle branch block; TDI — tissue Doppler imaging; VV — interventricular delay

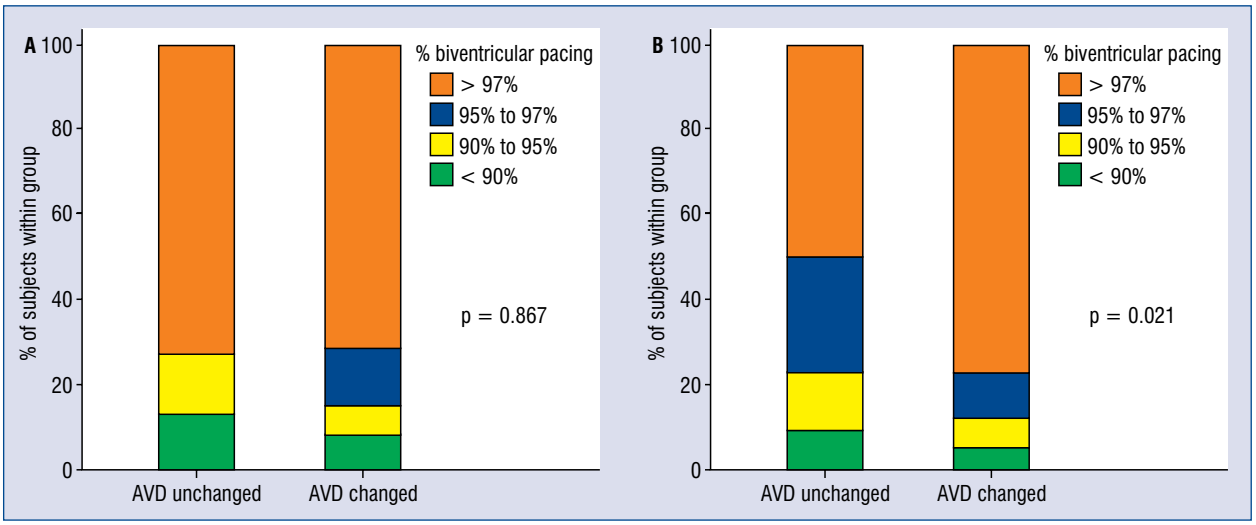

Figure 2. Distribution of biventricular pacing proportions before and after atrioventricular delay (AVD) optimization. Comparison of the intervention (AVD changed) and control (AVD unchanged) group; **A.** Assessment at baseline; **B.** Assessment at follow-up. Mann-Whitney U tests.

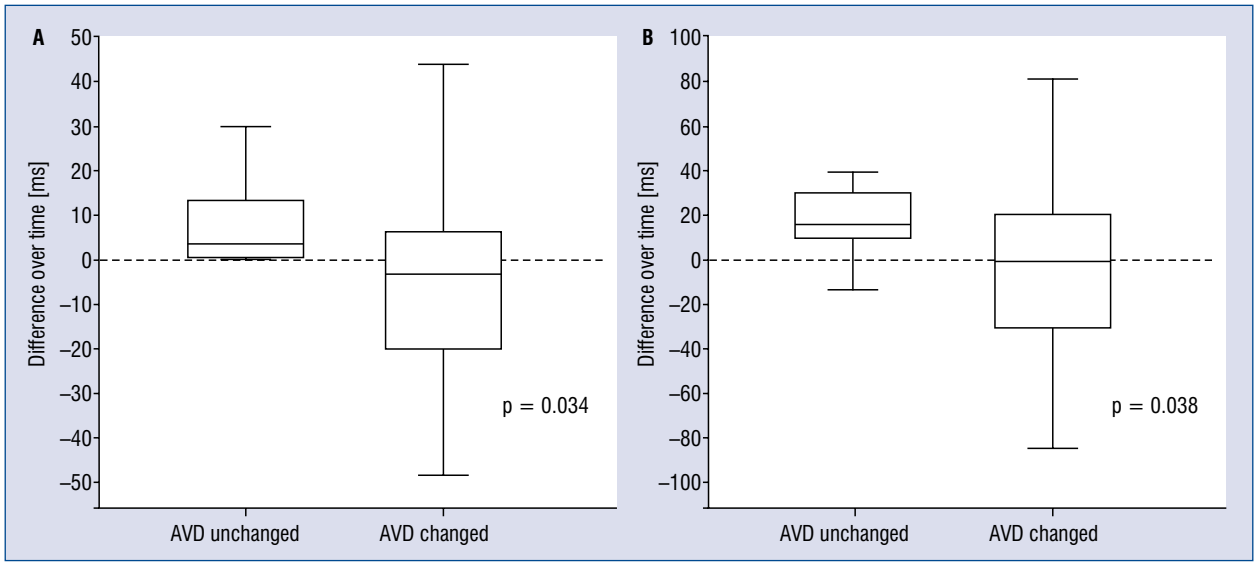

Figure 3. Interventricular mechanical and septal-to-lateral delay in the intervention (atrioventricular delay [AVD] changed) and control (AVD unchanged) group; **A.** Interventricular mechanical delay; **B.** Septal to lateral delay. Box plots indicate interquartile ranges, whiskers indicate minima and maxima. Mann-Whitney U tests.

both groups at baseline (Fig. 4C), decreased in the intervention group while it increased in the control group resulting in a significant difference at follow-up (Fig. 4D).

Discussion

This retrospective is a single-center cohort study in a real-world setting. AVD optimization was associated with an improvement of biventricular pacing, inter- and intraventricular synchronicity, as well as a reduction in mitral regurgitation along with a trend towards reduced end-diastolic LV volumes.

These results corroborate previous findings from several smaller studies with shorter follow-up [12–14]. However, the role of regular evaluation and adjustment of the atrioventricular interval in

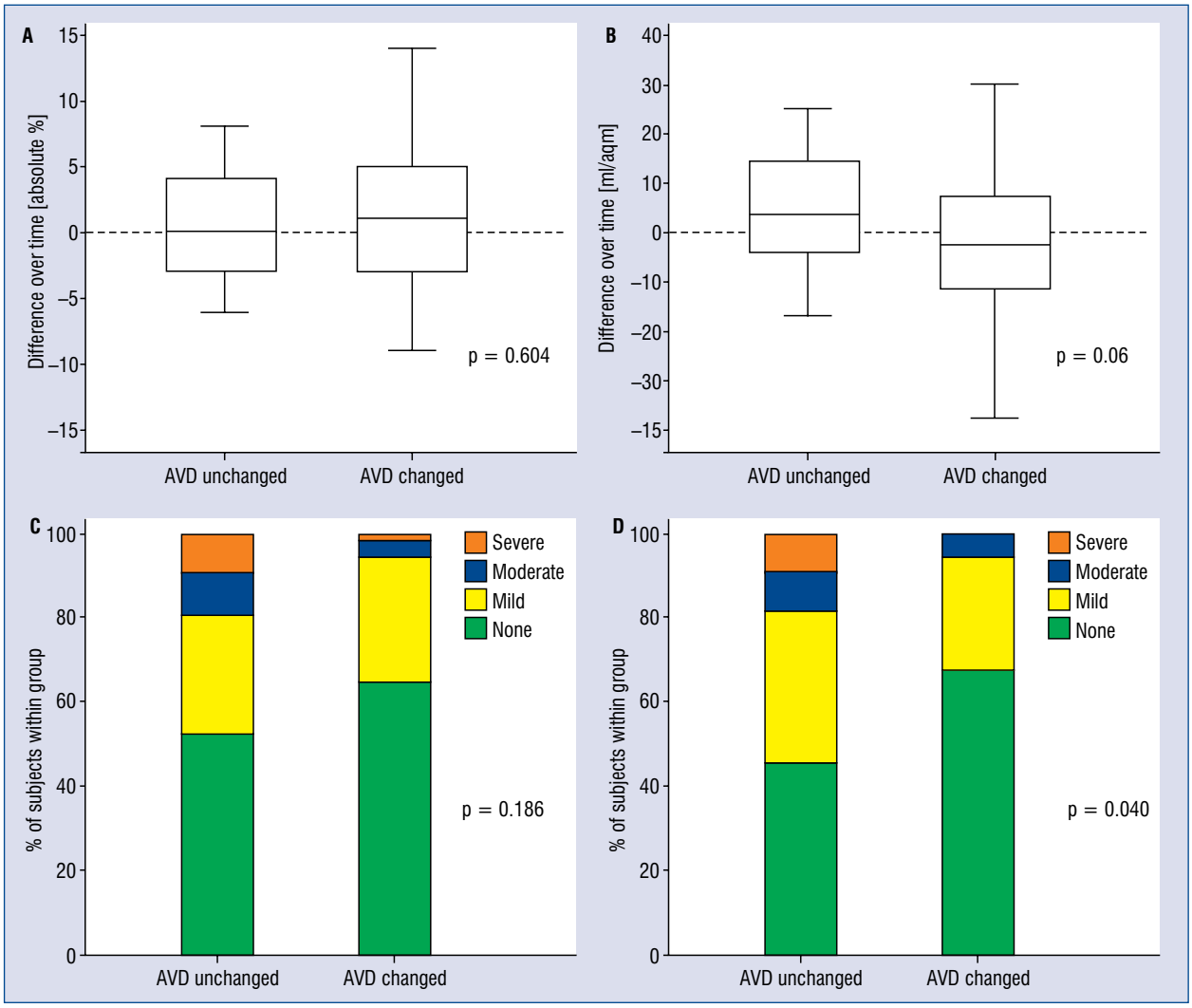

Figure 4. Reverse remodeling upon adapting atrioventricular delays (AVD); **A, B.** Change in left ventricular ejection fraction (**A**) and left ventricular end-diastolic volume index (**B**), respectively, in the intervention (AVD changed) and control group (AVD unchanged) over time. Box plots indicate interquartile ranges, whiskers indicate minima and maxima; **C.** Mitral regurgitation at baseline; **D.** Mitral regurgitation at follow-up. Mann-Whitney U tests.

patients with CRT and the method of AVD optimization remain a matter of debate [20]. In contrast to other studies, the prospective, randomized, controlled SMART-AV trial showed no benefit of general AVD optimization as opposed to a fixed AVD of 120 ms with regard to the primary outcome of LV end-systolic volume at 6 months [21]. It was concluded that regular AVD assessment and optimization was not necessary and a fixed interval of 120 ms would suffice. However, these results may not apply to selected individuals, especially those with a suboptimal response to CRT in combination with suboptimal diastolic ventricular filling. Indeed, Mullens et al. [11] observed suboptimal AVD settings in 45% of those patients who suffered from persistent advanced HF symptoms and/or adverse remodeling after CRT implantation. Furthermore, a sub-analysis of MADIT-CRT, one of the guideline-defining, large randomized, controlled trials, demonstrated that patients programmed to a short AVD (< 120 ms) had a reduced risk of HF or death over the 3 years following CRT implantation compared to those patients with an AVD > 120 ms, further indicating a role of AVD settings on long-term outcome in selected CRT patients [22]. Finally, a post-hoc analysis of the CLEAR study demonstrated an improved outcome for the composite endpoint of all-cause mortality, HF hospitalization, NYHA class and quality of life with regular, systematic AVD optimization as opposed

Table 2. Parameters in patients with changed atrioventricular delay and patients with unchanged atrioventricular delay at follow-up visit.

	Control group (n = 22)	Intervention group (n = 59)	P
Clinical parameters			
NYHA class:			0.745
NYHA I	7/21 (33%)	11/54 (20%)	
NYHA II	9/21 (43%)	34/54 (63%)	
NYHA III	4/21 (19%)	9/54 (17%)	
NYHA IV	1/21 (5%)	0/54 (0%)	
Weight [kg]	83 ± 24	81 ± 19	0.603
Systolic BP [mmHg]	115 ± 17	120 ± 16	0.331
NT-proBNP [pg/mL]	1674 ± 1446	1092 ± 1602	0.169
Echocardiographic parameters			
LVEF [%]	39 ± 12	39 ± 10	0.903
EDVI [mL/m^2]	90 ± 43	87 ± 38	0.794
IVMD [ms]	16.0 ± 20.6	12.8 ± 22.3	0.553
TDI septal to lateral [ms]	31.9 ± 44.5	47.6 ± 46.2	0.184
TDI anteroseptal to inferolateral [ms]	36.2 +/- 52.3	44.1 ± 42.5	0.515
Electrocardiography and device parameters			
Biventricular pacing [%]	95.3 ± 6.0	97.5 ± 4.0	0.034*
Bundle branch block*			
LBBB	7/11 (64%)	46/54 (85%)	0.075
RBBB	1/11 (9%)	5/54 (9%)	
IVCD	3/11 (27%)	3/54 (6%)	
Complete AVB	11/22 (50%)	4/58 (7%)	< 0.001*
QRS width [ms]	141 ± 31	147 ± 23	0.47
PQ interval [ms]**	189 ± 40	195 ± 41	0.92
Sensed AV interval [ms]	121.8 ± 20.4	96.4 ± 28.2	0.006*
Paced AV interval [ms]	144.6 ± 29.8	130.7 ± 30.5	0.17
VV [ms]	7.6 ± 15.4	15.7 ± 22.1	0.144

Continuous variables are presented as mean ± standard deviation; categorical variables are presented as proportions.
*Complete AVB excluded. **Patients with complete AVB and patients with atrial fibrillation excluded
AV — atrioventricular; AVB — atrioventricular block; BP — blood pressure; CRT — cardiac resynchronization therapy; EDVI — end-diastolic volume index; IVCD — intraventricular conduction delay; IVMD — interventricular mechanical delay; LBBB — left bundle branch block; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; NT-proBNP — N-terminal pro-B-type natriuretic peptide; RBBB — right bundle branch block; TDI — tissue Doppler imaging; VV — interventricular delay

to "non-systematic" optimization, irrespective of the optimization method applied [23].

Although an assessment of the effect of CRT optimization on morbidity and mortality was beyond the scope of this real-world study, the data support a potential role for CRT optimization with regard to long-term outcome. The present results further underline the importance of the evaluation and adjustment of device settings, given that a substantial part of CRT patients presented with inadequate atrioventricular intervals at baseline.

A high percentage of biventricular pacing is associated with an improved outcome in CRT patients [24]. Koplan et al. [25] demonstrated that the greatest benefit in reduction of HF hospitalization and all-cause mortality was achieved with a biventricular pacing above 92%. The rationale for an even higher proportion of biventricular pacing was provided by Hayes et al. [26] in a cohort of over 30,000 patients, where mortality was found to be inversely related with the percentage of biventricular pacing. Since a reduced percentage of biventricular pacing is among the main reasons for suboptimal response to CRT [11], these data imply that regular assessments and efforts to increase biventricular pacing are central. However, there

are no data assessing this hypothesis prospectively, and whether certain interventions to improve biventricular pacing such as antiarrhythmic therapy in patients with AF truly impact hard clinical outcomes remains elusive.

Loss of biventricular pacing can occur as a result of a long AVD due to intrinsic atrioventricular conduction. In such patients, shortening of AVD may increase the degree of biventricular pacing [24–26]. In the present study, patients in whom the AVD was changed (mostly shortened) during CRT optimization had a higher percentage of biventricular pacing at follow-up. The favorable development of hemodynamic parameters in the intervention group may well be a consequence of the higher biventricular pacing proportion in these patients. As adaptation of AVD in order to prevent intrinsic conduction can be performed on the basis of QRS morphology on 12-lead ECG, this raises the question, if echocardiographic assessment during AVD optimization is necessary. It is however important to note that ensuring constant biventricular pacing based on 12-lead ECG alone may lead to programming excessively short AVDs in order to prevent QRS fusion. In this context, echocardiographic monitoring of mitral inflow is crucial in order to avoid impaired left ventricular filling. Herein, echocardiography was therefore regarded as an essential component in the process of AVD optimization.

Taken together, the present findings support the role of systematic AVD optimization to achieve the highest possible percentage of biventricular stimulation and improve hemodynamic parameters. The absolute effect of this improvement, however, was small and it remains to be determined whether this will translate into a reduction in morbidity and mortality.

Limitations of the study

This study has to be interpreted in light of several limitations, most of which are inherent to any "real-world" registry study. All patients analyzed were recruited at a single center, which may introduce a selection and/or referral bias, and may therefore not reflect the situation in other healthcare facilities.

Furthermore, the control group included 12 patients with AF. In CRT-patients AF can lead to loss of biventricular pacing secondary to high ventricular rates. Importantly, several studies have shown similar benefit of CRT in patients with AF and those in sinus rhythm [27–30]. However, more recent evidence points to a worse prognosis of CRT in the context of AF [31, 32]. This is primarily due to high ventricular rates and consecutive electrical fusion or loss of biventricular pacing, highlighting the importance of adequate rate control [33]. This was evident in the CERTIFY registry by Gasparini et al. [34], in which CRT-patients in sinus rhythm were compared to CRT-patients with AF either after atrioventricular junction ablation (AVJA) or without AVJA [34]. After a median follow-up of 37 months, mortality was similar between AF patients after AVJA and patients in sinus rhythm, while AF patients on medical rate control alone had a worse outcome compared to both patients in sinus rhythm and patients with AF and AJVA. This implies that patients with AF and complete atrioventricular block derive equivalent benefit from CRT as do patients in sinus rhythm [33]. Out of the 12 patients with AF in the present cohort, 6 patients had intact intrinsic conduction. Upon exploratory exclusion of these patients, the difference in biventricular pacing between the intervention group and the control group remained significantly different. It can therefore be assumed that the difference in biventricular pacing proportions at follow-up were not driven by patients in AF.

Since this study ought to reflect real-world data, not all variables are distributed evenly between groups. Importantly, there was a higher proportion of patients with complete atrioventricular block in the control group (50% vs. 7%), an effect due to the fact that in these patients AV optimization is oftentimes not necessary as no fusion with intrinsic conduction can occur. Few data exist on the direct comparison between CRT--patients with left bundle branch block and those with complete atrioventricular block. However, in patients with atrioventricular block and reduced LVEF biventricular pacing has been shown to reduce the risk of mortality and morbidity and lead to better clinical outcomes [35]. In the absence of intrinsic conduction, complete atrioventricular block is associated with higher biventricular pacing proportions. Therefore, if present, confounding, may lead to an underestimation of the difference in biventricular pacing proportions in the context of this study. However, as this study was intended to reflect a real-world setting, the current study refrained from excluding patients from the analyses wherever possible. Of note, QRS-width, which is the primary determinant of response in CRT [7], was evenly distributed among the groups in this real-world cohort.

Finally, and as with every registry study, residual confounding between groups may have contributed to the findings; as such, only asso-

ciations and no causality may be inferred [36]. This notwithstanding, the data herein does reflect a "real-world" setting of CRT patients, which may contribute important insight into evolving therapy concepts such as CRT optimization in daily practice.

Conclusions

The present study results imply that AVD optimization may result in an increased biventricular pacing percentage, which has been shown to be associated with better hemodynamic parameters and reduced mortality. Whether these hypotheses hold true, remains to be determined in a well-controlled randomized setting.

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Comparative effect of angiotensin converting enzyme inhibitor versus angiotensin II type I receptor blocker in acute myocardial infarction with non-obstructive coronary arteries; from the Korea Acute Myocardial Infarction Registry — National Institute of Health

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Abstract

Background: *Selecting angiotensin converting enzyme inhibitor (ACEI) or angiotensin II type I receptor blocker (ARB) in patients diagnosed as acute myocardial infarction (AMI) with non-obstructive coronary arteries (MINOCA) is not established. The purpose of this study is to compare the clinical effect of ACEI vs. ARB in MINOCA patients.*

Methods and results: *A total of 273 patients between November 2011 to June 2015, diagnosed with MINOCA who were registered in the Korea Acute Myocardial Infarction Registry — National Institute of Health were enrolled. Patients were divided into ACEI (n = 112) and ARB groups (n = 161). The primary endpoint was cumulative incidence of major adverse cardiac events (MACE) defined as cardiac death, recurrent MI, any new revascularization during 2 years clinical follow-up. Secondary endpoint was heart failure requiring re-hospitalization. Propensity score matching analysis was done. The incidence of primary endpoint was similar (10.4% vs. 15.6%, HR: 0.65; 95% CI: 0.29–1.47; p = 0.301) among both groups. However, the incidence of recurrent MI was significantly lower in ACEI group compared to ARB group (2.1% vs. 10.4%, HR: 0.18, 95% CI: 0.04–0.86; p = 0.031).*

Conclusions: *In the present study, the risk and incidence of MACE was similar between ACEI and ARB therapy in MINOCA patients. However, ACEI significantly reduced the risk of recurrent MI. Further larger scale multi-center randomized clinical trials are needed to clarify the proper use of renin––angiotensin–aldosterone system blocker in these patients.* (Cardiol J 2021; 28, 5: 738–745)

Key words: non-obstructive coronary arteries, angiotensin converting enzyme inhibitor/ /angiotensin II type I receptor blocker, prognosis

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Introduction

Over the past decades, a remarkable evolution has occurred in the field of interventional and pharmacological modalities in acute myocardial infarction (AMI) [1]. Numerous coronary angiographic findings revealed that nearly 95% of AMI patients had obstructive coronary disease [2]. However, the remaining 5% and as many as 10% of AMI patients had no significant stenosis in their luminal coronary angiogram and these patients were coined as AMI with non-obstructive coronary arteries (MINOCA) [3]. Previous clinical studies demonstrated that MINOCA patients were younger and showed a higher portion of female patients compared to conventional patients with obstructive coronary artery disease (CAD) [4, 5]. The prognosis of MINOCA patients were known to be favorable over those with conventional obstructive CAD, however several recent reports demonstrated that the actual prognosis was not benign [6–8]. And yet, accurate evidence based therapeutic guidelines for these specific groups of patients is lacking [9]. Current guidelines strongly recommend (class I, level of evidence A) angiotensin converting enzyme inhibitor (ACEI) for MI patients with left ventricular ejection fraction (LVEF) of less than 40% or with symptoms of heart failure (HF) unless contraindicated [1, 10]. Moreover, ACEI was encouraged for all ST-segment elevation MI patients without contraindications to their use (class IIa, level of evidence A). Guidelines also mentioned that the use of another renin–angiotensin–aldosterone (RAA) system blocker, angiotensin II type I receptor blocker (ARB) should be spared to patients who were intolerant to ACEI (class I, level of evidence B). ARB is considered as an alternative choice. The main principle in MINOCA treatment is treating the underlying mechanism. However as previously mentioned, there are no evidence based therapeutic guidelines in treatment for MINOCA patients [11].

The purpose of the present study is to compare the clinical effect of ACEI and ARB in patients diagnosed as MINOCA in Korean AMI patients.

Methods

Among the 13,650 patients enrolled in Korea Acute Myocardial Infarction — National Institute of Health (KAMIR-NIH) between November 2011 to June 2015, 704 patients that showed insignificant stenosis (< 50%) in their initial coronary angiogram were selected. The KAMIR-NIH is a prospective, open, multi-center, web-based cohort study to investigate the real-world outcome of Korean patients with AMI from 15 centers in Korea and has been supported by a grant of Korea Centers for Disease Control and Prevention since November 2011. Data were collected by trained study coordinators based on standardized protocol. Study protocol was approved by ethics committee at each participating institution. From these 704 individuals, the following patients were excluded sequentially: 87 patients with definite diagnosis such as stress induced cardiomyopathy or myocarditis, 309 patients who have not received either ACEI nor ARB or both, 35 patients who lacked outpatient follow-up data. A total of 273 patients were included in the present study. Patients were further divided into ACEI (n = 112) and ARB group (n = 161) (Fig. 1). The current study was conducted according to the Declaration of Helsinki. The institutional review board of all participating centers approved the study protocol. The approval number was CNUH2011-172 of Chonnam National University Hospital. Written informed consent was obtained from all participating patients.

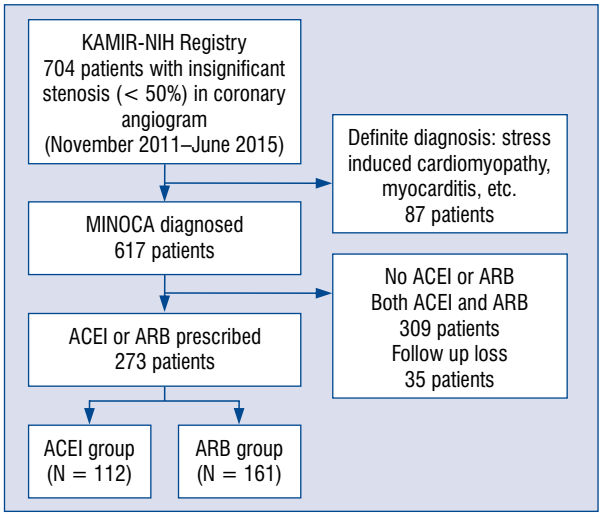

Figure 1. Study flow chart; ACEI — angiotensin converting enzyme inhibitor; ARB — angiotensin receptor blocker; MINOCA — myocardial infarction with non-obstructive coronary artery disease.

Blood samples for baseline laboratory tests were collected in the emergency room before diagnostic coronary angiography was carried out. Coronary angiography was performed by a standard technique through either radial or femoral artery. All patients received 300 mg loading dose of acetylsalicylic acid (ASA) and 300–600 mg loading dose of

clopidogrel before the coronary angiography unless contraindicated. During the hospital period, other medications including beta-blocker, statin, and calcium channel blocker (CCB) were also prescribed. Two-dimensional echocardiography was performed in all patients during the initial hospitalization period and LVEF was evaluated.

Diagnosis was AMI was made according to the clinical presentation, 12-lead electrocardiogram findings and change in cardiac biomarkers. Patients were categorized as MINOCA if the diagnosis of AMI was made and the coronary angiographic findings during initial hospitalization period showed no significant obstructive CAD (stenosis < 50%) [9]. In the present study, the primary end point was the cumulative incidence of major adverse cardiac events (MACE) during 2 years clinical follow up. MACE was composite of cardiac death, recurrent MI, and any new revascularization. The secondary end point was HF requiring re-hospitalization. All deaths were considered cardiac deaths if non-cardiac deaths were excluded. Recurrent MI was defined as recurrent symptoms with new ST-segment elevation in electrocardiogram or re-elevation of cardiac markers to at least twice the upper limit of normal [12]. Any new revascularization was defined as interventional or surgical revascularization method including percutaneous coronary intervention or coronary artery bypass graft surgery.

Statistical analysis

The baseline clinical characteristics of both treatment group were analyzed. Continuous variables were presented as means ± standard deviations and were compared by using unpaired the Student t-test or Mann-Whitney U test. Discrete variables were expressed as percentages and frequencies and were compared using chi-square statistics or the Fisher exact test. To minimize the selection bias in direct comparison between ACEI and ARB, propensity score analysis using multivariable logistic regression was done. Variables included were age, sex, atypical chest pain on admission, Killip class on admission, cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidemia, smoking status), previous angina, previous MI, previous cerebrovascular disease, laboratory findings (serum glucose, renal function test, cardiac enzymes, lipid profiles), LVEF and prescribed medications (ASA, clopidogrel, beta-blocker, statin, and CCB). Patients receiving ARB were matched 1 on 1 to the patients receiving ACEI with the nearest neighbor matching method (caliper width of 0.2 of the standard deviation). In the propensity score matched populations, the baseline characteristics were also analyzed. The risk of each clinical end point in both matched groups were compared by using the Cox proportional hazard regression model with covariables that showed statistical significance ($p < 0.1$) in univariable analysis or were considered clinically important in the multivariate model. Hazard ratio (HR) with 95% confidence interval (CI) were calculated.

All analyses were performed by using SPSS for Windows, version 25.0 (Armonk, NY). All statistical tests were 2-tailed with statistical significance defined as a p value ≤ 0.05.

Results

In the crude population, mean age of the both groups were 66.5 ± 13.3 years (ACEI group) and 68.0 ± 10.9 years (ARB group). ACEI group patients had a higher percentage of smokers (57.1% vs. 34.8%; $p \leq 0.001$) and tended to have a wider history of previous angina (23.2% vs. 13.7%; $p = 0.041$). On the other hand, the ARB patient group had a higher portion of female patients (37.5% vs. 54.7%; $p = 0.005$) and had more medical history of hypertension (50.0% vs. 64.0%; $p = 0.021$). Estimated LVEF was significantly lower in the ACEI group compared to the ARB group (49.9 ± 13.4 vs. 55.5 ± 12.4; $p \leq 0.001$). After propensity score matching, 96 matched pairs of patients were selected and there was no difference in baseline clinical characteristics in both the ACEI and ARB groups (Table 1).

During the 2 year clinical follow-up period, cumulative incidence of primary end point MACE was similar between the ACEI and ARB groups in the crude population (10.4% vs. 15.6%; $p = 0.449$). Also, no difference was observed in the incidence of cardiac death (7.1% vs. 4.3%; $p = 0.561$), recurrent MI (1.8% vs. 6.8%; $p = 0.054$), any new revascularizations (0.9% vs. 5.0%; $p = 0.064$) and HF requiring re-hospitalization (5.2% vs. 7.3%, HR: 0.42, 95% CI: 0.11–1.68, $p = 0.220$). After propensity score matching analysis, the incidence and risk of recurrent MI was significantly lower in the ACEI group compared to the ARB group (2.1% vs. 10.4%, HR: 0.18, 95% CI: 0.04–0.86, $p = 0.031$) (Table 2). Other independent clinical factors for 2 years MACE were female sex (HR: 3.15, 95% CI: 1.06–8.36; $p = 0.039$) and estimated glomerular filtration rate < 60 mL/min/1.73 m^2 (HR: 3.85, 95% CI: 1.36–9.89; $p = 0.011$) (Table 3). Kaplan-Meier curves for clinical outcomes are displayed in Figure 2.

Table 1. Baseline clinical characteristics in crude and propensity score matched populations.

	ACEI group (n = 112)	ARB group (n = 161)	P	ACEI group (n = 96)	ARB group (n = 96)	P
Age [year]	66.5 ± 13.3	68.0 ± 10.9	0.327	66.3 ± 12.9	66.6 ± 11.7	0.860
Female	42 (37.5%)	88 (54.7%)	0.005	39 (40.6%)	39 (40.6%)	1.000
Atypical angina	31 (27.7%)	48 (29.8%)	0.702	27 (28.1%)	22 (22.9%)	0.408
Killip class III, IV	15 (13.4%)	11 (6.8%)	0.069	8 (8.3%)	9 (9.4%)	0.799
Risk factors:						
Hypertension	56 (50.0%)	103 (64.0%)	0.021	50 (52.1%)	54 (56.3%)	0.562
Diabetes mellitus	30 (26.8%)	57 (35.4%)	0.133	28 (29.2%)	35 (36.5%)	0.282
Dyslipidemia	10 (8.9%)	14 (8.7%)	0.947	9 (9.4%)	12 (12.5%)	0.488
Previous angina	26 (23.2%)	22 (13.7%)	0.041	22 (22.9%)	18 (18.8%)	0.477
Previous MI	28 (25.0%)	30 (18.6%)	0.206	23 (24.0%)	23 (24.0%)	1.000
Previous CVA	7 (6.3%)	12 (7.5%)	0.701	7 (7.3%)	6 (6.3%)	0.774
Smoking	64 (57.1%)	56 (34.8%)	< 0.001	50 (52.1%)	47 (49.0%)	0.665
Laboratory findings:						
Serum glucose [mg/dL]	151.9 ± 74.9	155.5 ± 67.9	0.686	153.0 ± 75.4	159.2 ± 75.4	0.569
eGFR [mL/min/1.7 m^2]	79.8 ± 29.4	82.5 ± 44.3	0.573	81.9 ± 28.9	80.9 ± 48.2	0.864
CK-MB [mg/dL]	35.7 ± 98.5	24.7 ± 41.9	0.265	27.4 ± 63.6	29.8 ± 50.8	0.768
Troponin I [mg/dL]	18.3 ± 74.4	7.8 ± 17.2	0.146	17.5 ± 79.2	9.7 ± 19.4	0.345
Total cholesterol [mg/dL]	163.2 ± 45.2	164.4 ± 43.9	0.821	161.5 ± 43.8	168.3 ± 50.8	0.317
Triglyceride [mg/dL]	114.5 ± 115.0	118.9 ± 85.1	0.713	126.4 ± 121.1	131.9 ± 99.7	0.333
HDL cholesterol [mg/dL]	50.3 ± 29.7	45.5 ± 14.2	0.074	47.7 ± 14.5	47.5 ± 15.9	0.937
LDL cholesterol [mg/dL]	94.6 ± 35.0	99.9 ± 31.9	0.189	92.4 ± 33.8	95.1 ± 36.1	0.486
LVEF [%]	49.9 ± 13.4	55.5 ± 12.4	0.001	52.1 ± 11.9	52.3 ± 12.5	0.993
Medications:						
ASA	111 (99.1%)	158 (98.1%)	0.512	95 (99.0%)	94 (97.9%)	0.561
Clopidogrel	102 (91.1%)	141 (87.6%)	0.364	87 (90.6%)	86 (89.6%)	0.809
Beta-blocker	81 (72.3%)	108 (67.1%)	0.356	74 (77.1%)	68 (70.8%)	0.324
Calcium channel blocker	33 (29.5%)	47 (29.2%)	0.961	28 (29.2%)	29 (30.2%)	0.874
Statin	94 (83.9%)	141 (87.6%)	0.392	81 (84.4%)	86 (89.6%)	0.284

Values are presented as the number (%) of patients or mean standard deviation. ACEI — angiotensin converting enzyme inhibitor; ARB — angiotensin receptor blocker; ASA — acetylsalicylic acid; CK-MB — creatine kinase-myocardial band isoenzyme; CVA — cerebrovascular accident; eGFR — estimated glomerular filtration rate; HDL — high density lipoprotein; LDL — low density lipoprotein; LVEF — left ventricular ejection fraction; MI — myocardial infarction

Table 2. Clinical outcomes in crude and propensity matched populations.

	ACEI group (n = 112)	ARB group (n = 161)	P	ACEI group (n = 96)	ARB group (n = 96)	Adjusted HR (95% CI)	P
MACE*:	10 (8.9%)	19 (11.8%)	0.449	10 (10.4%)	15 (15.6%)	0.65 (0.29–1.47%)	0.301
Cardiac death	8 (7.1%)	7 (4.3%)	0.319	8 (8.3%)	6 (6.2%)	1.38 (0.46–4.12%)	0.561
Recurrent MI	2 (1.8%)	11 (6.8%)	0.054	2 (2.1%)	10 (10.4%)	0.18 (0.04–0.86%)	0.031
Any new revascularization	1 (0.9%)	8 (5.0%)	0.064	1 (1.0%)	5 (5.2%)	0.11 (0.01–1.38%)	0.085
HF re-hospitalization	7 (6.3%)	9 (5.6%)	0.819	5 (5.2%)	7 (7.3%)	0.42 (0.29–1.47%)	0.220

*Composite of cardiac death, recurrent MI, and any new revascularization. Values are presented as n (%) of patients or mean ± standard deviation. CI — confidence interval; HF — heart failure; HR — hazard ratio; MACE — major adverse cardiac event; other abbreviations as in Table 1.

Table 3. Clinical predictors of major adverse cardiac event.

	Adjusted HR (95% CI)	P
Female	3.15 (1.06–8.36)	0.039
ACEI	0.79 (0.32–1.97)	0.613
eGFR < 60 mL/min/1.73 m^2	3.85 (1.36–9.89)	0.011

Abbreviations as in Tables 1 and 2.

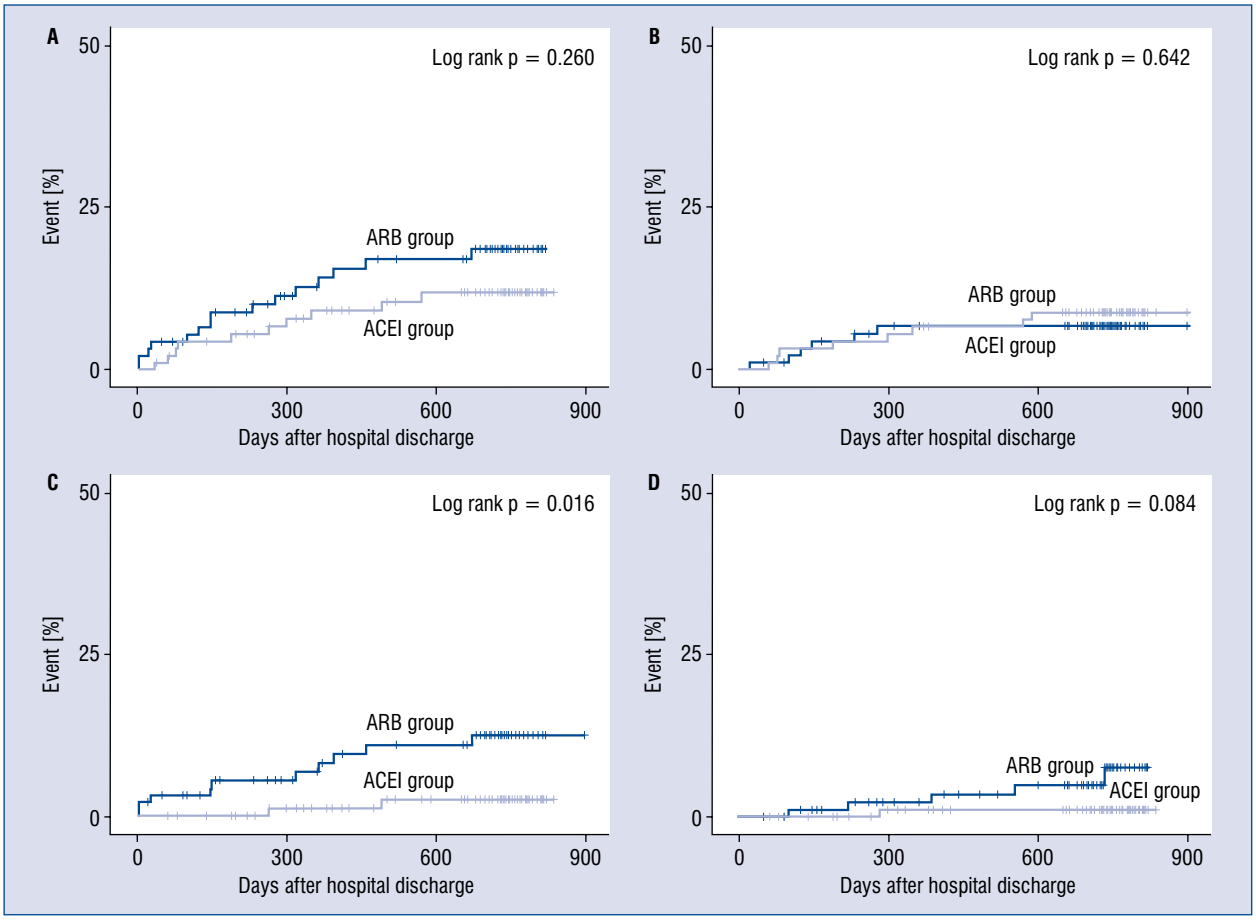

Figure 2. Kaplan-Meier curves for major adverse cardiac event (MACE) (**A**), cardiac death (**B**), recurrent myocardial infarction (MI) (**C**), any new revascularization (**D**); ACEI — angiotensin converting enzyme inhibitor; ARB — angiotensin receptor blocker.

Discussion

Results of the present study indicate that risk of MACE was similar in MINOCA patients treated with either ACEI or ARB. However, after propensity score matching analysis, it was revealed that ACEI therapy significantly lowered the risk of recurrent MI compared to the ARB therapy in MINOCA patients.

Early angiographic studies carried out by DeWood et al. [2] demonstrated that more than 90% of AMI patients show obstructive CAD (≥ 50% stenosis) in their luminal coronary angiogram. Since then, there were emerging interests in the remaining 5–10% of the population group. Clinicians and interventional cardiologists defined this group of patients as MINOCA [9]. The proportion of MINOCA patients in the present study was 4.5%,

which was similar with the other previous reports. The following conditions should be included for a diagnostic approach to MINOCA: (i) Diagnostic criteria of AMI; (ii) No evidence of obstructive CAD (≥ 50% stenosis) in the initial coronary angiography; (iii) The overt cause of a specific diagnosis at the time of initial clinical presentation must be absent [3, 13].

MINOCA patients are known to be younger and showed a higher percentage of female patients compared to patients with conventional obstructive CAD [4, 5]. A recent meta-analysis reported that mean age of MINOCA patients was 58.8 years and the mean age of obstructive CAD patients was 61.2 years. 40% of MINOCA patients were women while only 24% were women in patients with obstructive CAD [5]. The proportion of female patients were 47% in the crude population and 40.6% in the propensity matched population in the present study, which was similar to meta-analysis data. However, our patient's mean age was older in both treatment groups (ACEI group: 66.5 ± 13.3 years, ARB group: 68.0 ± 10.9 years) compared to the meta-analysis data. Early studies revealed that MINOCA patients had better clinical outcomes compared to those with conventional obstructive CAD [4, 6]. But, Kang et al. [14] showed that the incidence of 12 month MACE including all-cause death, MI and ischemic target vessel revascularization was 7.8% which was nearly the same as one vessel or two vessel obstructive CAD. The incidence of 2 years MACE in the present study was 13%. This result could be considered to be higher than other results reported by Rossini et al. (9.1%) [15]. The higher proportion of conventional cardiovascular risk factors such as smoking status and diabetes mellitus could have been the main contributing factor.

The clinical importance of MINOCA should not be underestimated because the proportion of MINOCA patients is not small and this group of patients are younger than conventional groups of patients with obstructive CAD. Nevertheless, the current clinical treatment guideline of MINOCA treatment is lacking. As previously mentioned, the mainstay of MINOCA therapy is based on treating the underlying pathophysiologic mechanism. The exact pathophysiologic mechanism of MINOCA needs further research but there are potential etiologic factors including plaque rupture or erosion, coronary artery spasm, coronary artery embolism or thrombus, microvascular dysfunction, etc. [11, 16, 17].

The benefit of long-term medical treatment in MINOCA patients was shown in several studies. An observational study of MINOCA patients in the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapy (SWEDEHEART) registry presented evidence of clinical benefit in long-term medical therapy for secondary prevention in MINOCA patients. During the mean follow up period of 4.1 years, there was an 18% risk reduction of primary outcomes in patients receiving RAA system blockers including ACEI or ARB [18]. However, there were no studies that directly compared the clinical effect of ACEI and ARB in MINOCA patients. According to available research, the current study is the first to directly compare the clinical effect between ACEI and ARB in MINOCA patients. The results showed that the incidence and risk of MACE in MINOCA patients were similar in the ACEI group and ARB group. The hard endpoint of cardiac death was similar in both treatment groups and this result was consistent with previous randomized clinical trials comparing ACEI and ARB [19, 20]. However, our results indicate that ACEI therapy lowered the risk of recurrent MI compared to the ARB therapy. These results could be inferred as a distinctive drug effect of ACEI by suppression of angiotensin II and bradykinin preservation and eventually resulted in restrained endothelial dysfunction [21, 22]. Another potential cause might be the deleterious effect by overstimulation of angiotensin type II receptor by ARB which also could lead to an increase in angiotensin II levels [23]. Based on these factors, we considered that ACEI should be the first line treatment in MINOCA patients. Herein, we cautiously suggest that ACEI might be a preferable option in MINOCA patients because ACEI reduced the risk of recurrent MI compared to ARB.

Limitations of the study

The present study has several limitations. First, the study was not a randomized controlled clinical trial but a retrospective analysis based on a small sample sized population and selection bias might have existed. Although propensity score matching analysis was done and most potential confounders were adjusted for and analyzed, other variables that were associated with the clinical outcomes might not have been included in the present study. Second, the heterogeneity of MINOCA was not considered and the registry data lacks other diagnostic modalities that clarifies the accurate underlying cause of MINOCA including cardiac magnetic resonance (CMR) imaging or intravascular ultrasound, optical coherence tomography

[11, 16]. This was also the main shortcoming in the SWEDEHEART registry data and the they also stated that ideally the CMR proven myocarditis should have been excluded because one third of patients diagnosed as MI were actually discovered to have combined myocarditis in their CMR findings [18, 24]. An effort was made to select true MINOCA patients by excluding 87 patients diagnosed as stress induced cardiomyopathy or myocarditis however, a more precise and detailed study is needed because the future treatment guideline would be focused on MINOCA patients with unidentified cause. Third, accurate data reflecting the 2 year drug compliance of patients and specific categorization of ACEI and ARB and its prescribed dosage is lacking in the present study.

Further larger scale multi-center randomized clinical trials comparing the clinical effect of ACEI or ARB in MINOCA patients are needed for a proper RAA system blocking agent treatment in these groups of patients and to establish new treatment guidelines in MINOCA.

Conclusions

In the present study, the risk and incidence of MACE was similar between ACEI and ARB therapy in MINOCA patients. However, ACEI significantly reduced the risk of recurrent MI. Further larger scale multi-center randomized clinical trials are needed to clarify the proper use of RAA system blocker in these patients.

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Conflict of interest: None declared

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Predisposing factors for late mortality in heart transplant patients

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Abstract

Background: *Because of the growing prevalence of terminal heart failure on the one hand and organ shortage on the other hand, an optimal care of heart transplant recipients based on the knowledge of potential risk factors not only early, but also in a long-term course after heart transplantation is of great importance. Therefore, the aim of the present study was to identify predisposing factors for late mortality in this patient collective.*

Methods: *Data from long-term heart transplant patients collected during follow-up visits in the current center were retrospectively analyzed. Clinical, laboratory, including immune monitoring and apparative examination results were studied with regard to all-cause mortality.*

Results: *One hundred and seventy-two patients after heart transplantation (mean: 13.2 ± 6.4 years) were divided into two groups: survivors (n = 133) and non-survivors (n = 39). In comparison with survivors, non-survivors were characterized by significantly more pronounced renal insufficiency with more frequent dialysis, anemia and worse functional status. Additionally, non-survivors obtained hearts from relevantly more obese donors. In a multivariate Cox regression analysis the following parameters were shown to be independent risk factors for increased mortality: CD4 percentage < 42%, C-reactive protein ≥ 0.5 mg/dL, presence of rejections requiring therapies in the past, onset of cardiac allograft vasculopathy < 5 years following heart transplantation and no use of beta-blockers.*

Conclusions: *Low CD4+ cell percentages, sustained inflammation, relevant organ rejections, early onset of transplant vasculopathy and no use of beta-blockers are risk factors for higher mortality in a long-term follow-up after heart transplantation.* (Cardiol J 2021; 28, 5: 746–757)

Key words: heart transplantation, immune monitoring, inflammation, organ rejection, transplant vasculopathy, beta-blocker therapy

Introduction

Heart failure is an increasing health disorder worldwide [1]. As ultima ratio therapy, heart transplantation (HTx) has been proven to be an effective method of treatment in selected groups of patients with terminal heart failure refractory to other treatments [2]. However, declining number of heart donors is a growing problem [3] which demands optimized management of the pre-, peri- and post-transplantation stages in order to effectively prolong organ function and reduce mortality. In contrast to numerous investigations on risk factors, potential complications and therapy options in the early phase following HTx [4, 5], there are relevantly few studies examining factors influencing survival many years after HTx [6–8]. Furthermore, the results of these studies cannot be extrapolated to a long-term survival as various factors and/or to a different extent may be associated with short- and long-term survival [6, 7, 9, 10]. Some determinants such as malignancy, infection [6, 7, 11], chronic rejection [7, 11], chronic allograft vasculopathy [11], idiopathic dilated cardiomyopa-

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thy and younger recipient age [8] were associated with late mortality following HTx. However, factors predicting mortality in long-term heart transplant survivors are still unknown in many cases.

Therefore, the aim of the present study was to define determinants favoring prolonged survival in heart transplant patients. Beyond clinical, standard laboratory and apparative findings, the focus was placed on results from immune monitoring which reflects present immune/inflammatory status of patients.

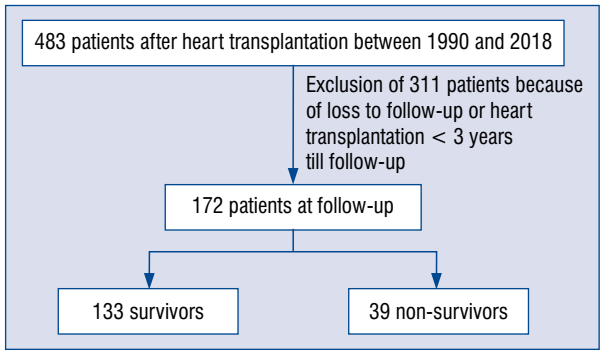

Figure 1. Flowchart of the study.

Methods

Data collection

The current retrospectively analyzed data were collected during the last control visits of heart transplant patients in the out-patient Department of Cardiology I at the University of Muenster. Of 483 patients who underwent HTx in the Department of Cardiothoracic Surgery at the University of Muenster between 1990 and 2018, 311 were excluded from the present study because of loss to follow-up (n = 309) or HTx less than 3 years till follow-up (n = 2) (Fig. 1). During follow-up visits routine examinations including patient history, current complaints and medication, physical examination, assessment of functional capacity, arterial pressure, electrocardiogram, echocardiography and laboratory blood tests were conducted.

Standard laboratory blood tests consisted of measurements of electrolyte concentrations, renal and hepatic function, blood count, clotting parameters, inflammatory factors, N-terminal-pro-B-type natriuretic peptide and levels of immunosuppressive drugs such as cyclosporine A (CsA), everolimus, tacrolimus, mycophenolate mofetil (MMF) and prednisolone depending on the current immunosuppressive medication. Additionally, immune monitoring encompassing total lymphocyte number, numbers and percentages of CD4+, CD8+, CD19+ and natural killer cells was performed. Further, in order to exclude current relevant viral or fungal infections respective molecular and serological examinations were conducted.

Inclusion criteria were HTx at least 3 years till follow-up and age > 18 years at follow-up. Additionally, only patients in whom all the above mentioned parameters were determined within one visit at latest 1 year before the current assessment of the alive status or the date of death were enrolled in the study. All instable patients defined as patients presenting status demanding relevant changes in their current medication and/or hospitalization were excluded from the study. Heart retransplantation was an additional exclusion criterion.

The study was performed according to the Declaration of Helsinki and the study protocol was approved by the local Ethics Committee of the University of Muenster.

Statistical analysis

Statistical analysis was conducted with IBM SPSS Statistics, version 25. Parametric values were expressed as means ± standard deviation (SD). Differences between the means of two groups were assessed by the Student t-test. Comparisons between categorical variables were performed using the χ^2 test. Two-tailed bivariate correlations were determined by the Pearson coefficient.

Potential risk factors for death were examined by the use of univariable and multivariable Cox proportional hazard function analyses. Variables showing a $p < 0.05$ in the univariate Cox analysis were introduced in a multivariable Cox model and a stepwise selection process was used to select the final independent predictors of mortality. Survival in groups depending on the risk factors identified in the multivariable Cox analysis was compared with the log-rank test and was illustrated using the Kaplan-Meier curves. $P < 0.05$ was defined as statistically significant.

Results

Patient characteristics

One hundred and seventy-two patients at least 3 years after HTx (mean: 13.2 ± 6.4 years) were divided into two groups according to survival (survivors, n = 133; non-survivors, n = 39). There were no significant differences in demographics, including age, sex and body mass index,

the presence of cardiovascular risk factors and extent of vasculopathy in coronary, carotid and peripheral arteries and left ventricular ejection fraction (LVEF) between the groups at follow-up. Parameters connected to HTx such as age at the time of HTx, time on the HTx list, urgency of the procedure and the frequency of the ventricular assist device use prior HTx did not relevantly differ between both groups. Non-survivors were characterized by significantly worse functional status according to the New York Heart Association (NYHA) Classification, earlier onset of transplant vasculopathy, more reduced right ventricular systolic function expressed as tricuspid annular plane systolic excursion, less frequent use of beta-blockers (BB) and more frequent use of platelet aggregation inhibitors and they were significantly more often on dialysis. Moreover, patients from the non-survivor group presented a tendency toward a higher average heart frequency and more frequent development of precarcinoma/ /carcinoma. The analysis of donor-associated factors demonstrated relevantly higher body weight in the non-survivor group. Most patients from both groups prior HTx suffered from heart failure as a result of dilated cardiomyopathy, followed by ischemic heart disease and congenital cardiomyopathy. In the group of non-survivors, the majority of patients died of malignancy and infections. The most frequent causes of death of donors comprised traumatic brain injury as well as subarachnoidal and intracerebral hemorrhage, without any relevant differences between the groups (Table 1).

Of note, when comparing patients with early onset of transplant vasculopathy to those with the late one, independently of survival status, patients with early onset of transplant vasculopathy were significantly older prior HTx (55.3 ± 8.3 vs. 44.6 ± ± 15.1 years, p = 0.016, respectively) and donors presented with tendentially higher weight (82.3 ± ± 13.3 vs. 72.4 ± 17.3 kg, p = 0.068, respectively). Additionally, a comparison between patients with and without transplant vasculopathy irrespectively of the time of its onset and the survival status demonstrated some significant differences in clinical and laboratory parameters presented in Table 2.

Immunosuppression and rejection

The most frequent immunosuppressive therapy in both patient groups was a CsA-based one, followed by the everolimus- and tacrolimus-based therapies (Fig. 2A). The overwhelming number of survivors and non-survivors were on an additional therapy with low-dose prednisolone (n = 104, 78.2% vs. n = 34, 87.2%, p = 0.215) without differences in daily doses (3.7 ± 2.4 mg vs. 4.3 ± 2.2 mg, p = 0.198) between both groups.

The analysis of distinct subgroups of patients according to three main immunosuppressants: CsA, everolimus and tacrolimus, each combined with MMF showed in contrast to everolimus and tacrolimus significantly higher blood concentrations of CsA in the non-survivor versus survivor group (Fig. 2B–D).

Mycophenolate mofetil blood levels were similar both in survivors and non-survivors in the above mentioned three subgroups (Fig. 2B–D) and when comparing all survivors and non-survivors taking MMF, independently of the immunosuppressive co-medication (2.2 ± 1.8 ng/mL vs. 2.2 ± 1.6 ng/mL, p = 0.962, respectively).

Cellular-mediated rejections were classified into three grades according to the International Society of Heart and Lung Transplantation (ISHLT) grading system [12].

Total rejection number from HTx till the last follow-up was similar in both groups. There was a tendency toward higher frequency of therapy requiring rejections in the non-survivor group. Of note, the vast majority of therapy requiring rejections occurred within 2 years after HTx in both groups (Table 3).

Immunological status and inflammation

Immunological monitoring revealed significantly lower percentage of CD4+ cells among all lymphocytes in the blood in non-survivors versus survivors. Conversely, CD8+ cell portion was relevantly higher in this patient group. As a consequence, the CD4/CD8 ratio tended to be lower in non-survivors. In contrast, there were no significant differences in the levels of other lymphocyte populations, such as CD19+ cells and natural killer cells between the groups.

Inflammatory response expressed as elevated leukocyte numbers, C-reactive protein (CRP) and interleukin (IL)-6 levels was significantly more pronounced in non-survivors (Table 3).

Chronic kidney disease, heart failure and anemia

Non-survivors were characterized by worse renal function expressed as a lower glomerular filtration rate and higher urea concentrations in the blood. Moreover, the diagnosis of anemia, defined according to the World Health Organization classification as hemoglobin < 13 g/dL for men and hemoglobin < 12 g/dL for women [13],

Table 1. Clinical characteristics of patients at follow-up.

Parameters	Survivors (group 1) N = 133	Non-survivors (group 2) N = 39	P
Age [years]	59.2 ± 15.4	58.5 ± 16.7	0.821
Male sex	96 (72.2%)	32 (82.1%)	0.214
Body mass index [kg/m²]	26.2 ± 5.4	25.1 ± 5.6	0.265
Age at HTx [years]	44.7 ± 15.0	47.6 ± 14.9	0.273
Time on HTx transplant list [months]	288.3 ± 326.1	286.7 ± 350.3	0.980
High urgency	51 (38.3%)	14 (35.9%)	0.782
VAD prior HTx	47 (35.3%)	12 (30.8%)	0.597
Follow-up after HTx [years]	14.0 ± 6.5	10.4 ± 5.2	0.002*
Clinical examination			
NYHA > 1	55 (41.4%)	26 (66.7%)	0.005*
Systolic BP [mmHg]	126 ± 20	121 ± 15	0.158
Diastolic BP [mmHg]	79 ± 11	76 ± 9	0.088
Heart frequency	82 ± 13	86 ± 13	0.099
Echocardiography			
LVEF [%]	55.7 ± 7.3	55.9 ± 11.5	0.917
TAPSE [mm]	16.6 ± 4.2	14.8 ± 4.4	0.019*
Cardiovascular risk factors			
Arterial hypertension	107 (80.5%)	31 (79.5%)	0.894
Diabetes mellitus	33 (24.8%)	13 (33.3%)	0.290
Hypercholesterolemia	117 (88.0%)	35 (89.7%)	0.761
Nicotine abuse:			0.532
Never smoker	117 (88.0%)	32 (82.1%)	
Current smoker	5 (3.8%)	3 (7.7%)	
Former smoker	11 (8.3%)	4 (10.3%)	
Transplant vasculopathy	53 (39.8%)	14 (35.9%)	0.656
Transplant vasculopathy requiring invasive therapy	27 (20.3%)	11 (28.2%)	0.295
Onset of transplant vasculopathy < 5 years after HTx	5 (3.8%)	7 (17.9%)	0.002*
CAD/PAD	18 (13.5%)	8 (20.5%)	0.285
Dialysis	19 (14.3%)	12 (30.8%)	0.019*
Precarcinoma/carcinoma	35 (26.3%)	15 (38.5%)	0.142
Obstructive or restrictive lung diseases	21 (15.8%)	11 (28.2%)	0.080
Cardiovascular medication			
Beta-blocker	78 (58.6%)	15 (38.5%)	0.026*
Calcium channel inhibitor:			0.754
Diltiazem	44 (33.1%)	11 (28.2%)	
Dihydropyridine	33 (24.8%)	9 (23.1%)	
Ivabradine	6 (4.5%)	2 (5.1%)	0.872
ACE inhibitor/AT1R antagonist	83 (62.4%)	18 (46.2%)	0.070
Statin	109 (82.0%)	31 (79.5%)	0.728
Pravastatin equivalent dose	43.2 ± 47.9	37.4 ± 40.6	0.493
Diuretics:			0.258
Thiazide	2 (1.5%)	1 (2.6%)	
Loop diuretics	69 (51.9%)	16 (41.0%)	
Aldosterone antagonists	2 (1.5%)	1 (2.6%)	
Combined diuretics	11 (8.3%)	8 (20.5%)	
Platelet aggregation inhibitors:			0.048*
ASS	33 (24.8%)	12 (30.8%)	
Clopidogrel	24 (18.0%)	2 (5.1%)	
Combined ASS and clopidogrel	7 (5.3%)	6 (15.4%)	
Oral anticoagulation	19 (14.3%)	7 (17.9%)	0.320

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Table 1. Clinical characteristics of patients at follow-up.

Parameters	Survivors (group 1) N = 133	Non-survivors (group 2) N = 39	P
Etiology of heart failure prior HTx			0.312
Dilated cardiomyopathy	63 (47.4%)	14 (35.9%)	
Ischemic cardiomyopathy	46 (34.6%)	19 (48.7%)	
Congenital cardiomyopathy	10 (7.5%)	2 (5.1%)	
Arrhythmogenic right ventricular dysplasia	3 (2.3%)	0 (0.0%)	
Postpartum cardiomyopathy	1 (0.8%)	0 (0.0%)	
Non-compaction cardiomyopathy	2 (1.5%)	0 (0.0%)	
Hypertrophic cardiomyopathy	3 (2.3%)	1 (2.6%)	
Myocarditis-related cardiomyopathy	2 (1.5%)	2 (5.1%)	
Valvular cardiomyopathy	3 (2.3%)	0 (0.0%)	
Toxic cardiomyopathy	0 (0.0%)	1 (2.6%)	
Causes of death			
Malignant tumor		8 (20.5%)	
Sepsis		6 (15.4%)	
Pneumonia		4 (10.3%)	
Sudden cardiac death		4 (10.3%)	
Cardiogenic shock		3 (7.7%)	
Renal failure		2 (5.1%)	
Chronic transplant vasculopathy		2 (5.1%)	
Vascular dementia		1 (2.6%)	
Ascending aortic aneurysm		1 (2.6%)	
Hemorrhagic esophagitis		1 (2.6%)	
Unknown		7 (17.9%)	
Donor parameters			
Age [years]	31.0 ± 13.4	31.1 ± 13.9	0.949
Body weight [kg]	71.6 ± 17.0	78.2 ± 17.2	0.048*
Body height [cm]	172.8 ± 16.8	174.5 ± 22.8	0.615
Sex (male)	71 (53.4%)	22 (56.4%)	0.859
Causes of death:			0.148
Traumatic brain injury	47 (35.3%)	11 (28.2%)	
Subarachnoidal hemorrhage	28 (21.1%)	4 (10.3%)	
Intracerebral hemorrhage	16 (12.0%)	7 (17.9%)	
Meningitis	4 (3.0%)	0 (0.0%)	
Cerebral ischemia	3 (2.3%)	5 (12.8%)	
Intracranial aneurysm	2 (1.5%)	1 (2.6%)	
Cerebral edema	2 (1.5%)	0 (0.0%)	
Hypoxic brain injury	2 (1.5%)	1 (2.6%)	
Polytrauma	2 (1.5%)	2 (5.1%)	
Gun shot skull injury	2 (1.5%)	2 (5.1%)	
Cardiovascular arrest	1 (0.8%)	0 (0.0%)	
Status epilepticus	1 (0.8%)	0 (0.0%)	
Strangulation	1 (0.8%)	1 (2.6%)	
Subdural hematoma	1 (0.8%)	0 (0.0%)	
Intoxication	1 (0.8%)	0 (0.0%)	
Fetal death	0 (0.0%)	1 (2.6%)	
Unknown	20 (15.0%)	4 (10.3%)	
Donor recipient sex match/mismatch			0.470
No data	23 (17.3%)	5 (12.8%)	
Match	84 (63.2%)	25 (64.1%)	
Male → female	17 (12.8%)	8 (20.5%)	
Female → male	9 (6.8%)	1 (2.6%)	

Data are presented as a mean ± standard deviation or number (percentage); *p < 0.05 (significant); ACE — angiotensin-converting-enzyme; ASS — acetylsalicylic acid; AT1R — angiotensin II type 1 receptor; BP — blood pressure; CAD — cerebral artery disease; HTx — heart transplantation; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; PAD — peripheral artery disease; TAPSE — tricuspid annular plane systolic excursion; VAD — ventricular assist device

Table 2. Differences in clinical and laboratory parameters between patients with and without transplant vasculopathy at follow-up.

Parameters	Transplant vasculopathy (n = 105)	No transplant vasculopathy (n = 67)	P
Recipient BMI [kg/m²]	27.1 ± 5.9	25.3 ± 5.0	0.032*
Donor weight [kg]	77.0 ± 15.3	70.8 ± 18.0	0.032*
Donor age [years]	35.4 ± 12.3	28.2 ± 13.5	0.001*
Urea [mg/dL]	37.1 ± 21.0	30.5 ± 17.4	0.028*
Follow-up after HTx [years]	15.6 ± 5.7	11.7 ± 6.3	< 0.001*
Diabetes mellitus	24 (35.8%)	22 (21.0%)	0.032*
Osteoporosis	11 (16.4%)	5 (4.8%)	0.010*
Platelet aggregation inhibitors	46 (68.7%)	38 (36.2%)	< 0.001*
Oral anticoagulation	15 (22.4%)	11 (10.5%)	0.032*
Diuretics	49 (73.1%)	61 (58.1%)	0.045*

Data are presented as a mean ± standard deviation or number (percentage); *p < 0.05 (significant); BMI — body mass index; HTx — heart transplantation

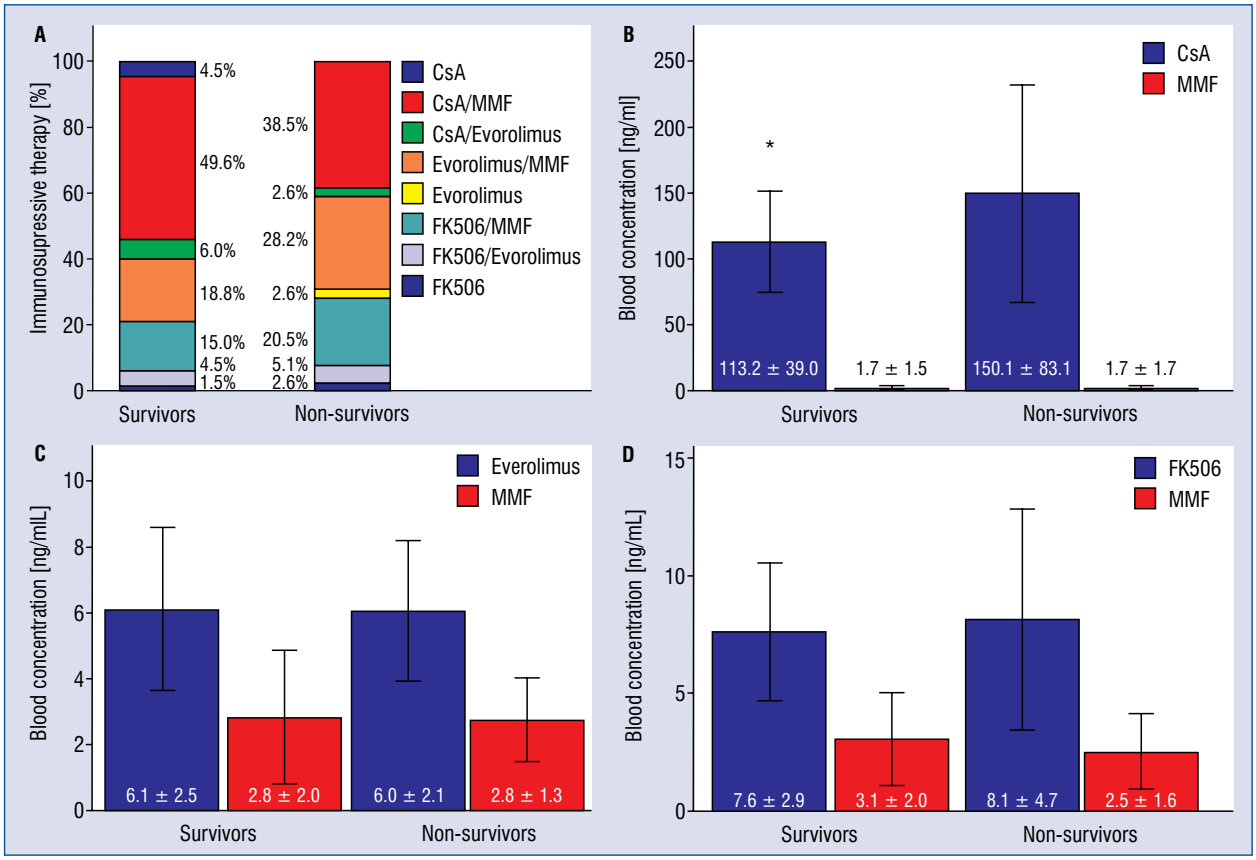

Figure 2. A–D. Immunosuppressive therapy in survivors and non-survivors; CsA — cyclosporine A; MMF — mycophenolate mofetil; FK506 — tacrolimus; *p < 0.05 (significant).

was significantly more frequent in non-survivors. The morphological and biochemical analysis of erythrocytes showed macrocytic and hypochromic anemia.

N-terminal-pro-B-type natriuretic peptide values were significantly higher in non-survivors, although echocardiographically estimated LVEF did not differ between the groups (Table 4).

Table 3. Number and severity of rejections since heart transplantation till the last follow-up as well as immunological and inflammatory factors at follow-up in survivors and non-survivors.

	Survivors (group 1) N = 133	Non-survivors (group 2) N = 39	P
Rejections	73 (54.9%)	24 (61.5%)	0.461
Rejection stage:			0.299
1	31 (23.3%)	7 (17.9%)	
2	39 (29.3%)	14 (35.9%)	
3	3 (2.3%)	3 (7.7%)	
Rejections requiring therapy	45 (33.8%)	18 (46.2%)	0.160
Rejections requiring therapy under 24 months after heart transplantation	40 (88.9%)	13 (72.2%)	0.102
Leukocytes (G/L)	7.3 ± 2.5	8.2 ± 2.7	0.048*
Lymphocytes [cells/μL]	1542.6 ± 687.3	1519.1 ± 960.0	0.865
CD3 [cells/μL]	1217.7 ± 634.6	1212.8 ± 894.2	0.969
CD3 [%]	77.3 ± 11.3	78.0 ± 11.3	0.731
CD4 [cells/μL]	700.1 ± 325.2	616.4 ± 400.0	0.183
CD4 [%]	46.2 ± 10.9	42.0 ± 11.8	0.042*
CD8 [cells/μL]	480.7 ± 427.7	569.4 ± 545.4	0.287
CD8 [%]	28.7 ± 13.5	34.2 ± 16.3	0.035*
CD4/CD8	2.3 ± 2.0	1.7 ± 1.2	0.087
CD19 [cells/μL]	89.7 ± 79.6	73.1 ± 86.3	0.262
CD19 [%]	6.0 ± 5.0	4.5 ± 3.5	0.080
Natural killers [cells/μL]	224.9 ± 151.1	214.1 ± 156.4	0.696
Natural killers [%]	16.0 ± 10.2	15.8 ± 10.3	0.939
Interleukin-6 [pg/mL]	9.5±9.8	14.2±20.3	0.047*
C-reactive protein [mg/dL]	0.8±0.9	1.7±2.6	0.001*

All percentages are expressed as the number of distinct lymphocyte subsets divided by the number of all lymphocytes multiplied by 100%. Data are presented as a mean ± standard deviation or number (percentage); *p < 0.05 (significant)

Table 4. Laboratory parameters connected to the heart and renal function as well as red blood cell parameters in survivors and non-survivors.

	Survivors (group 1) N = 133	Non-survivors (group 2) N = 39	P
NT-proBNP [pg/mL]	3068.0 ± 6172.2	8397.6 ± 11303.3	< 0.001*
GFR [mL/min/1.73 m^2]	46.4 ± 24.1	34.8 ± 22.0	0.008*
Urea [mg/dL]	31.1 ± 17.4	39.9 ± 23.0	0.011*
Erythrocytes [T/L]	4.5 ± 0.7	4.2 ± 0.7	0.039*
Hemoglobin [g/dL]	12.7 ± 1.8	12.0 ± 1.8	0.041*
Hematocrit [%]	39.2 ± 5.2	37.7 ± 5.3	0.116
Mean corpuscular volume [fL]	88.1 ± 5.7	90.1 ± 7.5	0.077
Mean corpuscular hemoglobin [pg]	28.6 ± 2.1	28.8 ± 2.7	0.670
Mean corpuscular hemoglobin concentration [g/dL]	32.4 ± 1.2	31.9 ± 1.3	0.022*

Data are presented as a mean ± standard deviation; *p < 0.05 (significant); GFR — glomerular filtration rate; NT-proBNP — N-terminal-pro-B--type natriuretic peptide

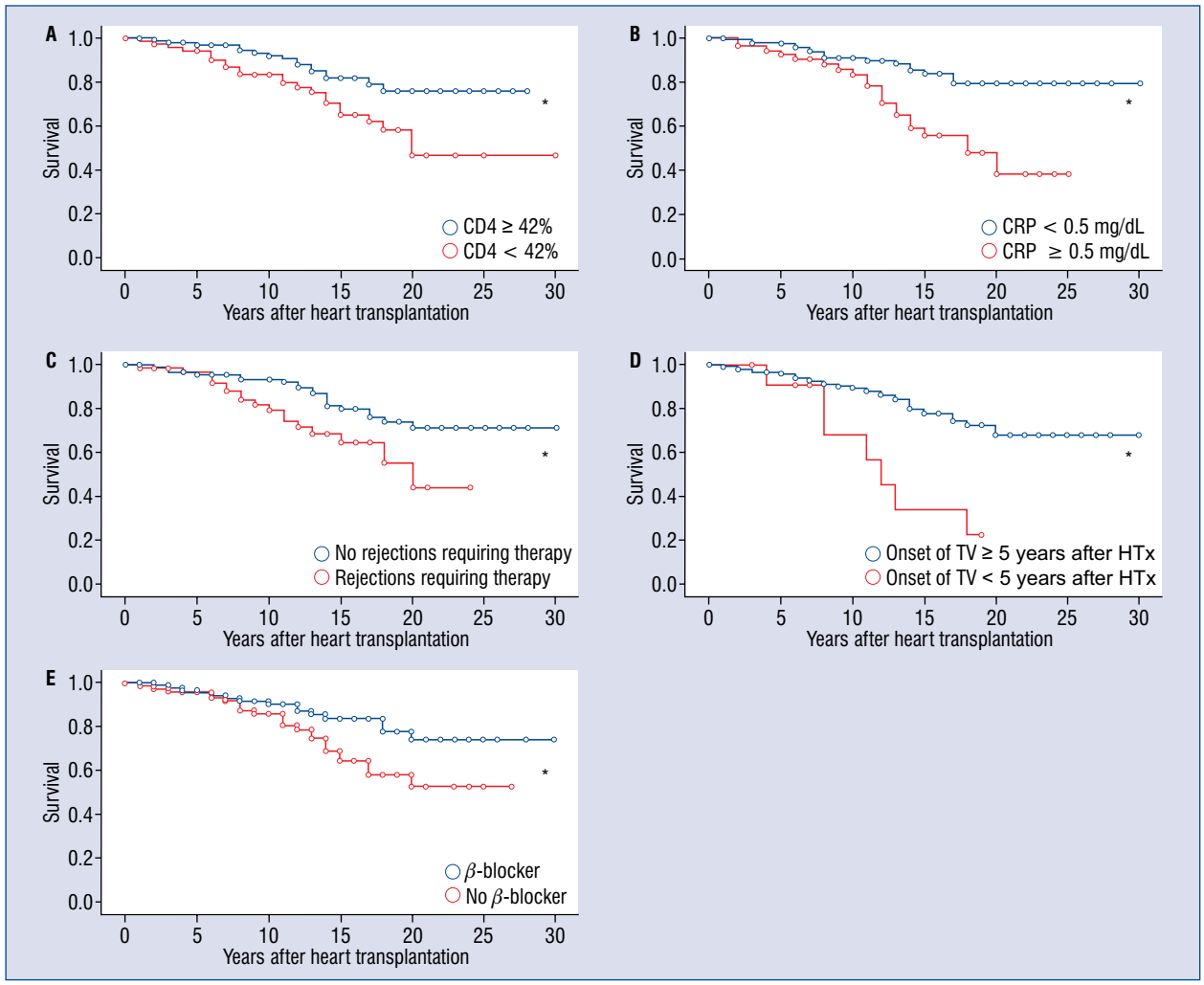

Figure 3. Kaplan-Meier curves show differences in survival of patients after heart transplantation (HTx). Factors positively influencing survival in patients after HTx; **A.** CD4 percentage equal or above 42%; **B.** C-reactive protein (CRP) blood concentrations under 0.5 mg/dL; **C.** No rejections requiring therapy; **D.** Late onset of transplant vasculopathy (TV) 5 years or more following HTx; **E.** The use of beta-blockers; *p < 0.05 (significant).

Univariate and multivariate Cox analyses

In the multivariate Cox analysis only five determinants among other potential risk factors tested in the univariate Cox analysis such as NYHA stages II and III vs. I (p = 0.033) and dialysis (p = 0.108) showed a clear, statistically significant negative influence on the survival of heart transplant patients. These were: percentage of CD4+ cells < 42% (hazard ratio [HR]: 1.984, confidence interval [CI]: 1.020–3.859, p = 0.044), CRP ≥ 0.5 mg/dL (HR: 3.422, CI: 1.767–6.626, p < 0.001), rejections requiring therapies (HR: 2.236, CI: 1.157–4.319, p = 0.017), early onset of transplant vasculopathy < 5 years following HTx (HR: 2.741, CI: 1.145–6.558, p = 0.024) and no use of BB (HR: 2.358, CI: 1.194–4.656, p = 0.013; Fig. 3).

Correlations

The above mentioned five factors influencing survival in the multivariate analysis were correlated with other measures. Significant correlations are depicted in Table 5.

Discussion

The present study has shown that the main factors influencing survival in the long-term follow-up after HTx were connected to immunomodulation/ /inflammation, severe organ rejections, early onset of transplant vasculopathy and drug therapy.

Specifically, higher percentages of CD4+ cells were associated with significantly longer survival. CD4+ cells are central cells in the rejection pro-

Table 5. Statistically significant correlations between factors influencing survival in the multivariate analysis and other measures.

Correlations	P
CD4%	
Negative correlations:	
CD8%, R = –0.635	< 0.001*
Lymphocyte number, R = –0.173	0.023*
Natural killer cells, R = –0.226	0.003*
C-reactive protein, R = –0.153	0.045*
CRP	
Negative correlations:	
CD4%, R = –0.153	0.045*
CD19, R = –0.154	0.044*
Erythrocytes, R = –0.276	< 0.001*
Hemoglobin, R = –0.281	< 0.001*
Hematocrit, R = –0.241	0.002*
MCHC, R = –0.250	0.001*
GFR, R = –0.277	< 0.001*
Positive correlations:	
CD8%, R = 0.187	0.014*
Prednisolone, R = 0.267	< 0.001*
Dialysis, R = 0.312	< 0.001*
CAD/PAD, R = 0.219	0.004*
NT-proBNP, R = 0.450	< 0.001*
Interleukin-6, R = 0.373	< 0.001*
MCV, R = 0.176	0.021*
Diuretics, R = 0.166	0.030*
Rejections requiring therapy	
Positive correlations:	
Rejection grade, R = 0.882	< 0.001*
Transplant vasculopathy under 5 years after HTx	
Positive correlations:	
Age at HTx, R = 0.184	0.016*
Beta-blocker	
Negative correlations:	
Heart frequency, R = –0.274	< 0.001*
Diastolic blood pressure, R = –0.165	0.030*

*p < 0.05 (significant); CAD — cerebral artery disease; GFR — glomerular filtration rate; HTx — heart transplantation; MCV — mean corpuscular volume; MCHC — mean corpuscular hemoglobin concentration, NT-proBNP — N-terminal-pro-B-type natriuretic peptide; PAD — peripheral artery disease

cess [14]. In the early stage after HTx these cells may mediate rejection responses against donor tissue causing cardiovascular damage with subsequent organ failure. Therefore, the consequent immunosuppressive therapy is mandatory to preserve normal structure and function of the transplanted heart. In contrast, aggressive immunosuppression in a long-term course is not needed because of a slowly developing immune tolerance. The present findings indicate that lower percentages of CD4+ cells may be associated with enhanced mortality many years after HTx. It may be related to two main reasons. On the one hand, reduced CD4 levels result mostly from higher blood concentrations of immunosuppressive drugs [15]. In the current study, subgroup analysis according to the immunosuppressive medication demonstrated that non-survivors treated with CsA-based immunosuppressive therapy had relevantly higher CsA blood concentrations compared to the corresponding survivor subgroup. As CsA therapy is connected to many side-effects, e.g. renal insufficiency [16] which indeed was more pronounced in the non-survivor group, relatively low CD4+ cell percentages could be seen as an indicator of an overly intensive drug therapy. However, in the subgroup of patients with tacrolimus-based immunosuppressive treatment, there were no significant differences in tacrolimus blood concentrations in spite of significantly higher CD4+ cell levels in survivors. In the subgroup with everolimus as a main immunosuppressant there were no relevant differences in everolimus or CD4 concentrations between survivors and non-survivors. No significant correlations were found between the percentage of CD4+ cells and the levels of the immunosuppressive medication used. Moreover, although it is known that low blood levels of CD4+ cells may lead to the renal failure [17] and vice versa reduced CD4+ cell percentage may be the result of an impaired renal function [18], no relevant correlations were demonstrated for CD4 percentage and renal function. This emphasizes the high complexity of an immune answer indicating individual response of the body to immunosuppressive therapy, renal function and/or additional mechanisms influencing CD4+ cell levels in the blood. This result shows that monitoring of drug concentrations and/or of renal function in the blood may be not sufficient to assess current immunological status and thus its impact on the body [19]. The other explanation of low CD4+ cell-associated mortality in the current collective of patients could be the creation of a prolonged subclinical immunosuppressive state with susceptibility to the development of sustained inflammation, infections and tumor diseases. Indeed, increased leukocyte numbers were found to be significant, as well as CRP and IL-6 levels in non-survivors. Additionally, CRP correlated negatively with CD4+ cell percentages. Furthermore, CRP was another

factor that predicted higher mortality in a multivariate analysis. Chronic inflammation, indicated by increased CRP levels is a known independent factor for cardiovascular and all-cause mortality [20]. Prolonged immunosuppressive state may have also influenced a tendency toward increased prevalence of precarcinoma/tumor diseases [21]. This could have also emerged from the side-effects of immunosuppressive drugs [21]. In the present study patients were free of infections based on anamnesis, physical examination, laboratory and microbiological tests at follow-up. However, occult infections, not routinely tested in the current laboratory, could not be excluded. The results from the mortality data support the above hypothesis as the main causes of death in our patient population were malignant tumors and infections.

Furthermore, it has been shown that CD4 cell lymphopenia may accelerate the development of cardiovascular atherosclerotic complications in renal transplant recipients [22], which augments mortality risk. In the current study there were no significant differences in the occurrence and severity of transplant vasculopathy between survivors and non-survivors despite relevantly different levels of CD4+ cells. However, data concerning CD4+ cell blood concentrations in the past as atherosclerotic lesions were detected and invasively treated are missing, so that this issue cannot be covered by the present study.

The next parameter which was shown to be relevant in the context of survival was the presence of rejections requiring therapies in the past. In contrast, weaker rejections without the need for drug therapy were not of relevance regarding mortality. As gross of rejections requiring therapies occurred early after HTx, this points to a dual role of CD4+ cells in the outcome depending on the time course after HTx. Whereas an intense suppression of immunological response involving activation of CD4+ cells prevents rejections and thus organ failure early after HTx, the continuation of a strong elimination of CD4+ cells years following HTx may contribute to a higher mortality. Therefore, continuous adjustments of immunosuppressive therapy strategies as well as close monitoring of immunological status in the blood are important actions at every time stage after HTx.

Immunological status, together with the side-effects of drug therapy, cardiovascular risk factors and donor and recipient demographics at the time point of HTx procedure influence the onset of transplant vasculopathy [23]. Interestingly, the present study showed that there were no significant differences in the prevalence of transplant vasculopathy between survivors and non-survivors at the time point of the last follow-up. The presence of transplant vasculopathy was also not a factor influencing mortality in the Cox analysis. Patients with transplant vasculopathy were characterized by elevated cardiovascular risk factors such as diabetes mellitus, renal insufficiency, they were more obese, had longer heart transplant from older and more obese donors and differed from non-transplant vasculopathy patients in cardiovascular medication. Since survivors presented significantly less frequent transplant vasculopathy less than 5 years after HTx compared with non-survivors in this study, this finding suggests that, not just the presence of transplant vasculopathy is critical for survival, but much more the time point of its development. It is known that the immune mechanisms and the influence of immunomodulating drug therapy prevail in the development of transplant vasculopathy at early stages, whereas classical cardiovascular risk factors may play a greater role later in the time course [23]. In the present patient population typical cardiovascular risk factors at follow-up were equally distributed across both groups. Patients with early onset of transplant vasculopathy were significantly older at the HTx and the hearts were derived from tendentially more obese donors. This suggests that the early occurrence of transplant vasculopathy and thus higher risk of longer duration of transplant vasculopathy and the pathomechanisms determining its onset, including donor- and recipient-associated factors may influence long-term outcome following HTx.

The last factor presented to influence survival of long-term heart transplant patients was the therapy with BB in this study. Survivors obtained significantly more frequent BB treatment than non-survivors. As a consequence, the average heart frequency tended to be lower in these patients. Beta-blocker is a known drug reducing mortality in patients with systolic heart failure and in selected populations of patients with myocardial infarction without systolic heart failure [1, 24]. Its beneficial effects on cardiovascular system encompass blockade of beta-adrenoreceptor, reduction in sympathetic activity, antioxidant and anti-arrhythmic properties, positive actions on myocardial metabolism and protection of endothelium [25]. Patients did not show systolic heart failure with on average preserved LVEF in both groups. Some patients were on diltiazem instead of BB therapy. In contrast to BB which application has been associated with better long-term outcomes after HTx, the

use of diltiazem did not show any advantage with regard to survival despite a similar reduction of heart frequencies as under BB [26]. Although it is known that diltiazem enhances CsA and tacrolimus concentrations in the blood and thus reduces the need of higher CsA and tacrolimus doses [27] and has positive effects on transplant vasculopathy [23] and cardiopulmonary performance [28], giving preference to BB therapy in a selected group of patients could be advantageous considering results from this study.

Limitations of the study

The present study has some limitations. The most important one is connected to its retrospective character and thus descriptive results. Additionally, the number of patients enrolled was relatively low. On the other hand, this statement relativizes itself when taking into consideration the monocentric design of the study. Furthermore, no differentiation into CD4 subtypes such as regulatory and effector T cells [29] was performed. However, the aim of this work was to search for simple predictors of mortality which can be determined easily and inexpensively in routine diagnostics. Finally, the findings from immune monitoring were completely available only at the last follow-up visit, so we cannot answer the question about the blood levels of immune cells as transplant vasculopathy was initially diagnosed or as respective organ rejections were detected and treated.

Conclusions

Taken together, the present study showed that lower CD4+ blood levels, systemic inflammation, organ rejections requiring therapies, early diagnosis of transplant vasculopathy and no use of BB therapy were associated with increased mortality in a long-term time course after HTx.

Conflict of interest: None declared

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Pharmacotherapy of atrial fibrillation in COVID-19 patients

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Abstract

The coronavirus pandemic disease 2019 (COVID-19) has changed the face of contemporary medicine. However, each and every medical practitioner must be aware of potential early and late complications of COVID-19, its impact on chronic diseases — especially ones as common as atrial fibrillation (AF) — and the possible interactions between patients' chronic medications and pharmacotherapy of COVID-19. Patients with AF due to comorbidities and, often, elderly age are assumed to be at a higher risk of a severe course of COVID-19. This expert consensus summarizes the current knowledge regarding the pharmacotherapy of AF patients in the setting of the COVID-19 pandemic. In general, anticoagulation principles in quarantined or asymptomatic individuals remain unchanged. Nevertheless, it is advisable to switch from vitamin K antagonists to non-vitamin K antagonist oral anticoagulants (NOACs) whenever possible due to their consistent benefits and safety with fixed dosing and no monitoring. Additionally, in AF patients hospitalized due to mild or moderate COVID-19 pneumonia, we recommend continuing NOAC treatment or to switching to low-molecular-weight heparin (LMWH). On the other hand, in severely ill patients hospitalized in intensive care units, intravenous or subcutaneous dosing is preferable to oral, which is why the treatment of choice is either LMWH or unfractionated heparin. Finally, particularly in critical scenarios, the treatment strategy in COVID-19 patients with AF should be individualized based on possible interactions between anticoagulants, antiarrhythmics, antivirals, and antibiotics. In this consensus, we also discuss how to safely perform COVID-19 vaccination in anticoagulated AF patients. (Cardiol J 2021; 28, 5: 758–766)

Key words: atrial fibrillation, coronavirus, infection, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), coronavirus disease 2019 (COVID-19), non-vitamin K antagonist oral anticoagulants (NOACs), direct oral anticoagulants (DOACs)

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Introduction

The coronavirus pandemic disease (COVID-19) has changed the face of contemporary medicine. After the initial turmoil in hospitals and paralysis of the ambulatory healthcare system in Poland, relevant (although not always sufficient) strategies, including telemedicine and eHealth solutions in ambulatory care, and — in non-specialty hospitals — procedures to ensure adequate management of medical emergencies and urgencies have been implemented. Still, access to both outpatient and inpatient care remains markedly restricted and aggravated by fear of infection, further discouraging patients from seeking medical assistance. This situation needs to be remedied as soon as possible to enable appropriate medical care of "chronic" patients, preventing them from developing acute disease exacerbations, long-term complications, or adverse effects from unsupervised treatment. Nevertheless, there is a need to be vigilant about the possibility of COVID-19 infection in patients and acknowledge that this disease will stay with us for the next few months or — more probably — years. Thus, each and every medical practitioner — irrespective of specialty or place of practice (ambulatory care, a specialty hospital, non-specialty hospital) — must be aware of potential early and late complications of COVID-19, its impact on chronic diseases, and possible interactions between patients' chronic medications and pharmacotherapy of COVID-19.

Older age and cardiovascular diseases are known predictors of a severe course of COVID-19 [1, 2]. Atrial fibrillation (AF) itself has not been identified as an independent risk factor; however, AF patients are largely elderly individuals burdened with concomitant diseases, including hypertension, diabetes, heart failure, and/or coronary artery disease, which are demonstrably related to higher morbidity and mortality in the course of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection [1, 2]. These patients more often require hospitalization for COVID-19 and antiviral treatment. Furthermore, up to 10% of patients with acute respiratory distress syndrome develop new-onset AF [3]. Data in SARS-CoV-2 cases are still scarce, but so far AF was reported in 1 in 5 patients hospitalized for COVID-19, with higher rates in severe cases [4–6]. Thus, a high proportion of patients treated for COVID-19 might be receiving medications for AF, which carries a high potential for drug interactions.

This expert consensus aims to summarize the current knowledge regarding the pharmacotherapy of AF patients in the setting of the COVID-19 pandemic. Of particular focus herein, on optimal anticoagulation in AF patients during the COVID-19 pandemic; drug-drug interactions involving anticoagulants, antiarrhythmics, and antivirals for COVID-19 therapy; and COVID-19 vaccination in anticoagulated AF patients.

Search strategy and expert consensus development

A systematic investigation of all published literature was conducted to minimize the risk of bias. A detailed search of databases (PubMed, CENTRAL, Google Scholar and UpToDate) and internet resources (websites of the American College of Cardiology [https://www.acc.org], American Heart Association [https://www.heart.org], European Society of Cardiology [https://www.escardio.org], Centers for Disease Control and Prevention [https://www.cdc.gov], World Health Organization [https://www.covid19.who.int], European Center for Disease Prevention and Control [https://www.ecdc.eu], National Institutes of Health [https://www.covid19guidelines.nih.gov], Infectious Diseases Society of America [https://www.idsociety.org], Polish Association of Epidemiologists and Infectiologists [https://www.pteilchz.org.pl], Agency for Health Technology and Tariff System [https://www.aotm.gov.pl], Medscape [https://www.medscape.com], and browser Google [https://www.google.com]), covering the period up to 1st May 2021 was conducted by four independent investigators (A.T.K., M.K., J.D.K., and A.K.C.). Particular attention was paid to clinical guidelines, other expert consensus documents, narrative or systematic reviews, and to studies on drug-drug interactions. The following keywords were applied: 'atrial fibrillation', 'coronavirus', 'SARS-CoV-2', 'anticoagulant', 'anticoagulation', 'NOAC', 'DOAC', 'warfarin', 'drug-drug interaction', 'antiarrhythmic', 'antiviral', and 'vaccine'. References of retrieved resources were searched manually for additional relevant publications.

Recommendations were made after extensive discussion of available scientific evidence by all authors. The manuscript was drafted by the first three listed authors (A.T.K., M.K., and J.D.K.) and the last one (A.K.C.). All authors critically revised, corrected, and accepted the manuscript.

Table 1. Recommendations regarding anticoagulation in atrial fibrillation (AF) patients during the coronavirus disease 2019 (COVID-19) pandemic.

1. In non-infected patients, it is advisable to switch from VKAs to NOACs whenever possible due to their consistent benefits and safety with fixed dosing and no monitoring.
2. Anticoagulation principles in quarantined or asymptomatic individuals remain unchanged and NOACs are the preferred anticoagulants in the vast majority of AF patients.
3. We recommend continuing NOAC therapy in mildly symptomatic COVID-19-infected AF patients who do not require hospitalization.
4. We recommend continuing NOAC treatment or switching to therapeutic dosing of LMWH in AF patients hospitalized due to mild or moderate COVID-19 pneumonia. When deciding about anticoagulation, potential interactions of NOACs with anti-COVID-19 medications and co-morbidities (e.g., impaired renal function) should be considered.
5. We recommend anticoagulation with either LMWH or UFH in critically ill COVID-19 patients with AF hospitalized in intensive care units.
6. In AF patients treated with VKA and admitted to the hospital due to COVID-19 infection, including those with prosthetic heart valves or moderate/severe mitral stenosis, we suggest switching anticoagulation to LMWH or UFH.
7. The anticoagulation treatment strategy in COVID-19 patients with AF, particularly in critical scenarios, should be individualized based on possible drug-drug interactions.

LMWH — low-molecular-weight heparin; NOAC — non-vitamin K antagonist oral anticoagulant; UFH — unfractionated heparin; VKA — vitamin K antagonist

Problems with blood test assessment during the COVID-19 pandemic in anticoagulated patients

The current pandemic and deliberate home isolation restrict mobility and reduce access to medical care professionals (both general practitioners and hospitals), as well as services (pharmacies, laboratories, and nursing care). During the COVID-19 pandemic, a substantial number of AF patients treated with vitamin K antagonists (VKAs) did not have their international normalized ratio (INR) assessed to avoid unnecessary contact with other people. Based on 2 years of monitoring, a 12-week INR follow-up interval (using a detailed protocol with titration) extension appears feasible for a subset of patients [7]. Therefore, if it is not possible to switch to non-vitamin K antagonist oral anticoagulant (NOAC) treatment, we suggest measuring INR every 6–12 weeks due to logistic problems in such patients. Patients with heart failure may not be suitable for this intervention [7].

Are there any interactions between the SARS-CoV-2 virus and NOACs?

If an AF patient treated with NOACs is infected with SARS-CoV-2, a healthcare provider should consider both the patient's individual symptoms and medical history and then decide whether and how the therapy needs to be modified. Until such a decision is made, the previous NOAC treatment should be continued.

Anticoagulation in non-COVID-19 patients and in quarantined, asymptomatic, or mildly symptomatic non-hospitalized individuals

It is advisable to switch away from VKAs to NOACs in non-COVID-19 patients with AF whenever possible due to their consistent benefits and safety with fixed dosing and no monitoring [8]. In general, anticoagulation principles in quarantined or asymptomatic individuals remain unchanged and NOACs are the preferred anticoagulants in the vast majority of AF patients (Table 1). Moreover, we recommend continuing NOAC therapy in mildly symptomatic COVID-19-infected AF patients who do not require hospitalization.

Regular kidney function assessments are essential for the safety of NOAC therapy. It is recommended to use the Cockroft-Gault equation for estimation of creatinine clearance (CrCl). In NOAC-treated patients without any history of kidney dysfunction, CrCl should be evaluated at least annually. In case of a clinically relevant decline in CrCl, an adjustment of NOAC dose should be considered. In patients with CrCl ≤ 60 mL/min, a more frequent assessment of renal function is advised. The minimum period between successive kidney function assessments in months may be calculated by dividing CrCl by 10. In patients with co-existing risk factors (e.g., older age, frailty, and multiple comorbidities), more frequent monitoring is suggested [8–10].

Optimal anticoagulation in hospitalized COVID-19 patients with AF

We recommend continuing NOAC treatment or switching to therapeutic dosing of low-molecular-weight heparin (LMWH) in AF patients hospitalized due to mild or moderate COVID-19 pneumonia. The choice of anticoagulant should be individualized. Potential interactions of NOACs with anti-COVID-19 medications and co-morbidities (e.g., impaired renal function) should be considered. This recommendation is in line with opinions of other experts [11].

On the other hand, in severely ill patients hospitalized in intensive care units who are frequently intubated and ventilated, intravenous or subcutaneous dosing is preferable to oral, which is why the treatment of choice is either LMWH or unfractionated heparin (UFH) [12–14].

In AF patients treated with VKA and admitted to the hospital due to COVID-19 pneumonia, including those with prosthetic heart valves or moderate/severe mitral stenosis, we suggest switching anticoagulation to LMWH or UFH. This recommendation is primarily based on frequent interactions between VKAs and drugs used to treat COVID-19 infection (Central illustration).

Importantly, acute kidney injury frequently occurs in patients hospitalized due to COVID-19 infection. Its prevalence ranges from 9% to 35% of patients, depending on disease severity [15]. It should be emphasized that in patients with impaired renal function, doses of both NOACs and LMWHs should be adjusted or even therapy should be stopped, depending on the value of CrCl. On the other hand, although intravenous therapy with UFH requires activated partial thromboplastin time monitoring, it may be safely used regardless of kidney function and — in case of bleeding — its action may be quickly reversed with protamine sulfate. Notably, specific reversal agents for NOACs have been developed, i.e., the more widely available idarucizumab for factor IIa inhibitor (dabigatran) and the less readily available andexanet alfa for the factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) [16].

According to dabigatran labels, the capsules should not be opened — whereas apixaban tablets can be crushed and given *via* gastric tube. However, intensive care unit patients may have poor or fluctuating renal function; dabigatran is contraindicated in patients with renal function < 30 mL/min, while apixaban and rivaroxaban are contraindicated if CrCl is < 15 mL/min [8].

COVID-19 patients frequently present with markedly elevated concentration of D-dimer. In this setting, D-dimer is regarded as a biomarker of disease severity and mortality [17, 18]. Optimal management strategies in COVID-19 patients with high concentrations of D-dimer remain unclear, particularly in those with AF and on therapeutic anticoagulation.

Current therapy of COVID-19 pneumonia

Treatment of COVID-19 infection has substantially evolved over time. Numerous experimental anti-COVID-19 therapies (azithromycin, chloroquine, convalescent plasma, hydroxychloroquine, interferon beta, lopinavir/ritonavir) have been demonstrated to be ineffective. Some of them had considerable potential for interactions with anticoagulants and antiarrhythmics and were used in AF patients.

Contemporary management of mildly symptomatic COVID-19 patients includes rehydration, antipyretic and antitussive drugs, and inhaled budesonide [19]. Primary medications recommended for moderate or severe COVID-19 pneumonia are remdesivir, tocilizumab, dexamethasone, or methylprednisolone. Additionally, the large majority of hospitalized patients require respiratory support (i.e., oxygen supplementation through a nasal cannula, face mask or venturi mask, high-flow oxygen therapy, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation). Antibiotics should be restricted to COVID-19 patients with confirmed or suspected bacterial co-infection.

Are there any interactions between NOACs and antivirals or antibiotics used in COVID-19 patients?

Both LMWHs and UFH are free of interactions with drugs used in COVID-19 therapy (Central illustration). However, they require parenteral administration and may cause heparin induced thrombocytopenia. On the other hand, multiple drug-drugs interactions of VKAs are well known. Although numerous potential interactions between NOACs and medications used for COVID-19 therapy were suggested, no detailed information has been available so far. Unfortunately, dedicated drug-drug interaction studies are lacking. Therefore, we relied on the low-quality evidence summarized on the website of The Liverpool Drug Interaction Group [20].

	acenokumarol	apixaban	acetylsalicylic acid	clopidogrel	dabigatran	dalteparin	edoxaban	enoxaparin	fondaparinux	phenprocoumon	prasugrel	rivaroxaban	streptokinase	ticagrerol	unfractionated heparin	warfarin
acetaminophen																
amoxicillin*	↑									↑						↑
amoxicillin/clavulanic acid*	↑									↑						↑
azithromycin*	↑	↑			↑		↑			↑		↑				↑
cefuroxime*	↑									↑						↑
ceftriaxone*	↑									↑						↑
dexamethasone	↑	↓	↑		↓		↓			↑		↓				↑
levofloxacin*	↑									↑						↑
meropenem*	↑									↑						↑
methylprednisolone	↑	↓	↑		↓		↓			↑		↓				↑
piperacillin/tazobactam*	↑									↑						↑
remdesivir																
tocilizumab	↓	↓		↓						↓	↓	↓		↓		↓

Central illustration. Interactions between anticoagulants, antiplatelets, fibrinolytics and drugs used to treat coronavirus disease 2019 (COVID-19) patients. Notably, the overall quality of this evidence is very low. This table is based on the COVID-19 Drug Interaction website of the University of Liverpool (www.covid19-druginteractions.org). Gray color: No information found on the website, but interaction seems unlikely according to the summary of product characteristics. Green color: no clinically significant interaction is expected, or potential interaction is likely to be of weak intensity, not requiring additional action/monitoring or dose adjustment. Yellow color: Potential weak interaction which may require additional monitoring (e.g., more frequent international normalized ratio monitoring if on vitamin K antagonist). Orange color: Potential interaction which may require dose adjustment. Red color: The drugs should not be co-administered. ↑Potential increased exposure to the anticoagulant, antiplatelet, or fibrinolytic drugs. ↓Potential decreased exposure to the anticoagulant, antiplatelet, or fibrinolytic drugs. *Antibiotics are only indicated in COVID-19 patients if bacterial co-infection is present.

P-glycoprotein (P-gp) inhibitors are likely to increase dabigatran concentration and their use may expose a patient treated with a standard dabigatran dose to the elevated risk of bleeding. Therefore, in such patients we recommend careful clinical surveillance (aimed at early detection of signs and symptoms of bleeding) and/or consideration of dabigatran dose reduction. On the other hand, P-gp inducers may reduce dabigatran blood concentration. As a consequence, potent P-gp inducers should not be co-administered with dabigatran.

Importantly, dabigatran is unlikely to exert any drug-drug interaction related to the cytochrome P450.

No relevant literary citations were identified in either MEDLINE or in EMBASE with keywords indicating NOACs and antiviral agents used for COVID-19 therapy.

No relevant literary citations were identified in MEDLINE and EMBASE with terms indicating NOACs and antivirals. Particularly, remdesivir has no clinically significant drug interactions documented, likely due to its rapid clearance.

Are there any interactions between NOACs and tocilizumab?

The tocilizumab's summary of product characteristics indicates that tocilizumab interacts with cytochrome P450, but any information on drug--drug interaction involving P-gp transport is lacking [21]. Importantly, neither NOACs nor tocilizumab

manufacturers have conducted dedicated studies on interactions between the drugs. The dabigatran's label seems to indicate that there is no interaction of dabigatran related to the cytochrome P450. According to tocilizumab's summary of product characteristics, tocilizumab interacts with cytochrome P450; no information on drug-drug interaction related to P-gp transport was available. According to dabigatran's label, dabigatran is not expected to have any cytochrome P450 related drug-drug interactions. Tocilizumab may increase warfarin metabolism.

Interactions between azithromycin and antiarrhythmic drugs

Although the initial enthusiasm towards azithromycin as an experimental COVID-19 therapy has been tempered by neutral results in randomized clinical trials [22–24], its use may still be considered in patients with concomitant bacterial co-infection. Prolonged cardiac repolarization and prolonged QT intervals pose a risk of developing cardiac arrhythmia and torsades de pointes. Azithromycin — as with other macrolides — may lead to an increased risk of ventricular arrhythmias, including torsade de pointes, and hence to cardiac arrest. Azithromycin is not contraindicated but should be used with caution in patients with ongoing proarrhythmic conditions — especially elderly patients and women: (1) receiving treatment with other drugs known to prolong QT intervals, such as antiarrhythmics of class IA (quinidine and procainamide) and class III (dofetilide, amiodarone, and sotalol); (2) with electrolyte disturbances, particularly in patients with hypokalemia or hypomagnesemia; (3) with significant bradycardia, cardiac arrhythmia or severe heart failure. Several observational studies have shown a rare short-term risk of arrhythmia, myocardial infarction, and mortality of cardiovascular causes associated with azithromycin. These findings should be taken into account and balanced against the clinical benefits when administering azithromycin.

Antiarrhythmic drugs used in the rhythm control strategy

An integral part of AF treatment is restoring sinus rhythm. Rhythm control therapy is often necessary to improve symptoms in AF patients who are symptomatic on rate control therapy. Importantly, the underlying hypoxemia, inflammation, and dyselectrolytemia (i.e., hypokalemia, hypomagnesemia, and acidosis) may be triggers for AF in patients with COVID-19 infection [11]. They should be corrected if possible and then if AF persists, therapy with antiarrhythmics may be considered. In the setting of COVID-19 infection, chemical cardioversion is preferred over its electrical counterpart as the first choice AF management in hemodynamically stable patients [31]. Amiodarone is a known substrate for both CYP3A4 and CYP2C8. The concomitant use of drugs inhibiting these isoenzymes may inhibit amiodarone metabolism and increase its concentration and exposure [25–28]. The document of product characteristics recommends to avoid or to pay extreme caution with the concomitant use of amiodarone with CYP3A4 inhibitors. Interactions between amiodarone and inhibitors of CYP3A4 may be observed for several months after discontinuation of such treatment due to the long half-life of amiodarone.

Propafenone is known to be metabolized by CYP2D6, CYP3A4, and CYP1A2 enzymes. The concomitant use of drugs inhibiting these isoenzymes leads to increased plasma levels of propafenone [28, 29]. Patients should be carefully monitored and the dose adjusted accordingly when propafenone is used with inhibitors of these enzymes. The summary of product characteristics warns against the simultaneous use of propafenone with CYP2D6 and CYP3A4 inhibitors. Moreover, co-administration of CYP3A4 inhibitors may increase exposure to propafenone and the risk of QRS complex prolongation on electrocardiography, dangerous complex ventricular arrhythmias, and blockage of beta-blockers. Adequate caution is necessary if these drugs are used together. Low-doses of propafenone may be considered in selected patients diagnosed with COVID-19 if the electrocardiography is carefully monitored for the early recognition of acquired QTc prolongation, torsade de pointes, and other dangerous ventricular arrhythmias.

In summary, antiarrhythmics have mild interactions with tocilizumab, moderate interactions with steroids, and moderate or severe interactions with antibiotics (Fig. 1). On the other hand, no interactions between antiarrhythmics and remdesivir were reported.

Antiarrhythmic drugs used in the rate control strategy

Both verapamil and diltiazem have been shown to be inhibitors of CYP3A4 enzymes and P-gp.

	amiodaron	digoxin	lidocaine	propafenone	quinidine
acetaminophen					
amoxicillin*		↑			
amoxicillin/clavulanic acid*		↑			
azithromycin*	!	↑			!
cefuroxime*					
ceftriaxone*					
dexamethasone	↓ #	^	#	#	#
levofloxacin*	!	↑			
meropenem*		↑			
methylprednisolone	#	^	#	#	#
piperacillin/tazobactam*					
remdesivir					
tocilizumab	↓		↓		

Figure 1. Interactions between antiarrhythmics and drugs used to treat coronavirus disease 2019 (COVID-19) patients. Notably, the overall quality of this evidence is very low. This table is based on the COVID-19 Drug Interaction website of the University of Liverpool (www.covid19-druginteractions.org). Gray color: No information was found on the website, but interaction seems unlikely according to the summary of product characteristics. Green color: no clinically significant interaction is expected, or potential interaction is likely to be of weak intensity, not requiring additional action/monitoring or dose adjustment. Yellow color: Potential weak interaction which may require additional monitoring. Orange color: Potential interaction which may require dose adjustment. Red color: The drugs should not be co-administered. ↑Potential increased exposure to the antiarrhythmic drug. ↓Potential decreased exposure to the antiarrhythmic drug. *Antibiotics are only indicated in COVID-19 patients if bacterial co-infection is present. ! Both drugs (when co-administered) may lead to marked QT interval prolongation and increase the risk of torsades de pointes. #Steroids may cause hypokalemia, which increases the risk of torsades de pointes with antiarrhythmics. ^ Steroids may cause hypokalemia, which increases the risk of digoxin toxicity.

Simultaneous use of CYP3A4 inhibitors leads to elevations of their plasma levels. Doses of verapamil and diltiazem should potentially be decreased. Beta-blockers such as metoprolol, carvedilol, and propranolol are substrates for the cytochrome CYP2D6 enzyme [30]. Metoprolol is highly dependent on the CYP2D6 enzyme, with about 70–80% of its metabolism being through this pathway. The other beta-blockers are much less reliant on CYP2D6 than metoprolol. The metabolism of digoxin is not dependent on cytochrome P450; its elimination is mainly through the kidneys and involves P-gp [31]. It is also advisable to reduce the dose of digoxin and to continue monitoring. No dosage reduction is indicated in the case of concomitant administration of tocilizumab used in patients with COVID-19 [28].

Based on previous clinical experience and the risk of drug-drug interactions, beta-blockers are recommended as a first-line therapy for rate control strategy [32].

COVID-19 vaccination in patients receiving anticoagulants

Public Health England's Immunization Against Infectious Disease states that the vaccine may be given intramuscular to patients treated with warfarin whose latest INR is lower than the upper limit of the therapeutic range [32].

For the vaccination a thin needle should be used and then firm pressure applied to the site of injection for at least 2 min. The information of possible hematoma from the injection should be conveyed to the patient. If the level of anticoagulation is unknown, the general practitioner or doctor in charge responsible for anticoagulant treatment should be contacted.

COVID-19 vaccine may be also given to patients who are treated with NOACs. The 2021 Update of European Heart Rhythm Association Consensus on NOACs recommends: (1) to skip the morning dose of the NOAC before intramuscular

injection, (2) in NOACs taken twice daily, to take the morning dose 3 h after the vaccination especially in high risk of ischemic stroke, and (3) in NOACs taken twice a day, start NOAC with the next regular dose [8]. The rules concerning reduction the risks of hematoma after vaccination are the same as described for warfarin above.

Summary

Patients with AF due to comorbidities and elderly age are assumed to be at a higher risk of a severe course of COVID-19. In general, anticoagulation principles in quarantined or asymptomatic individuals remain unchanged. It is advisable to switch from VKAs to NOACs whenever possible due to their consistent benefits and safety with fixed dosing and no monitoring. Additionally, in AF patients hospitalized due to mild or moderate COVID-19 pneumonia, we recommend continuing NOAC treatment or switching to LMWH. On the other hand, in severely ill patients hospitalized in intensive care units, intravenous or subcutaneous dosing is preferable to oral, which is why the treatment of choice is either LMWH or UFH. Finally, particularly in critical scenarios, the treatment strategy in COVID-19 patients with AF should be individualized based on possible interactions between anticoagulants, antiarrhythmics, antivirals, and antibiotics. COVID-19 vaccination may be safely performed in anticoagulated AF patients.

Conflict of interest: None declared

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Small vessel coronary artery disease: How small can we go with myocardial revascularization?

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Abstract

The issue of small coronary artery atherosclerosis represents an intriguing aspect of coronary artery disease, which is related with higher rates of peri- and post-procedural complications and impaired long-term outcome. This problem is further complicated by the unclear definition of small coronary vessel. Recent randomized controlled trials have provided new data on possible novel interventional treatment of small coronary vessels with drug-coated balloons instead of traditional new-generation drug-eluting stent implantation. Also, the conservative management represents a therapeutic option in light of the results of the recent ISCHEMIA trial. The current article provides an overview of the most appropriate definition, interventional management, and prognosis of small coronary artery atherosclerosis. (Cardiol J 2021; 28, 5: 767–778)

Key words: small coronary artery disease, small coronary vessel, small vessel disease, drug-coated balloons, drug-eluting stents

Introduction

The first successful percutaneous coronary intervention (PCI) was performed in 1977. Since this time interventional cardiology has made huge progress owing to rapid improvement of technology. However, treatment of stenoses in small coronary arteries remains an uncharted clinical territory in terms of decision-making and optimal technique of intervention. Depending on the applied definition, the prevalence of small vessel disease (SVD) reaches roughly 1/3 of patients with symptomatic coronary artery disease (CAD) [1, 2], especially patients with chronic kidney disease (CKD) [3], diabetes mellitus [4], and active smokers [5–7].

The clinical significance of small vessel atherosclerosis is related to its frequently diffuse nature [8, 9]. Although some patients may present with isolated one-vessel significant stenosis in a small coronary artery (Fig. 1), a considerable group of patients have diffuse atherosclerosis not amenable to endovascular and surgical revascularization (Fig. 2). In this clinical scenario, only optimal medical therapy represents a therapeutic option, and SVD should be regarded as an end-stage phase of CAD [10]. Also, it is important to distinguish SVD from coronary microvascular spasm, which represents a different clinical entity not amenable to percutaneous intervention but tailored for a pharmacological approach [11].

This article, however, primarily discusses clinical scenarios, in which revascularization is a therapeutic option, alongside the best medical therapy (Fig. 1). In this case, one should take into consideration the possible clinical benefits and complications of PCI performed in such clinical circumstance. On the one hand, even a small ischemic territory can cause debilitating angina,

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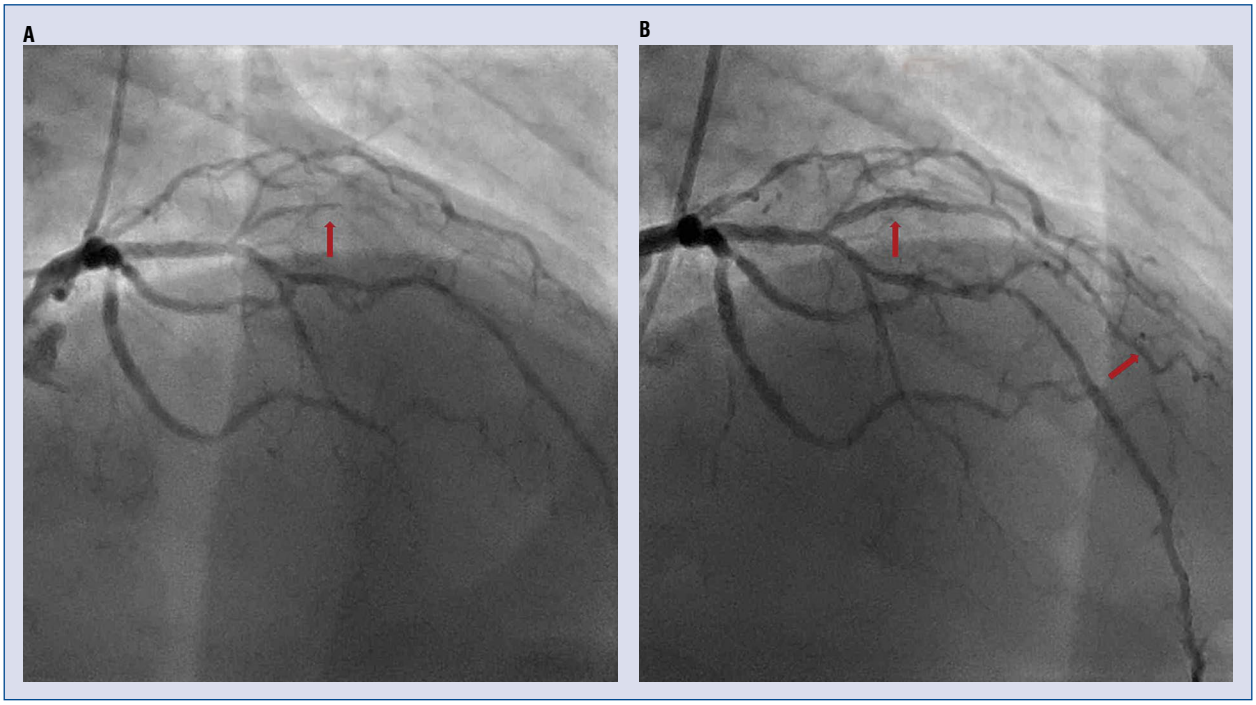

Figure 1. Example of small vessel disease amenable to percutaneous coronary intervention (RAO 30°; CRA°). **A.** Acute occlusion of small (1.5 mm) diagonal branch (arrow); **B.** Final angiographic result; percutaneous coronary intervention with 2.0 × 18 mm everolimus-eluting stent implantation in the proximal part of the vessel with slight oversize (left arrow); the image shows considerable length and extensive area supplied by the initially occluded vessel (right arrow).

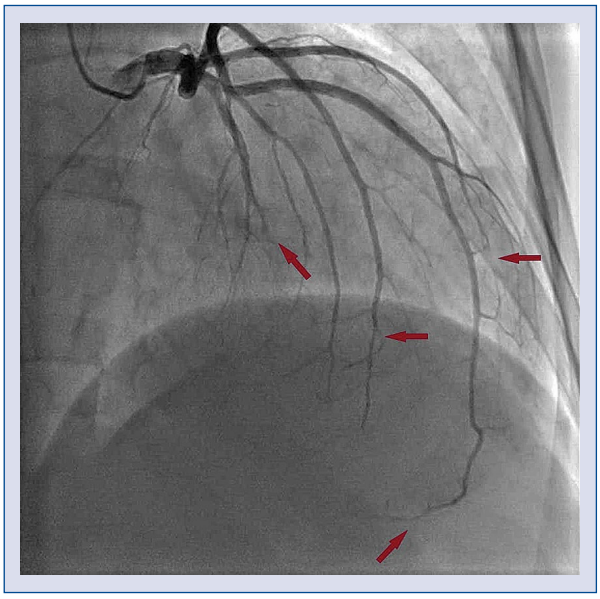

Figure 2. Example of diffuse small coronary artery atherosclerosis suitable for medical management (LAO 15°, CRA 30°); widespread significant lesions located predominantly in the peripheral and narrow parts of the coronary vessels (arrows).

impaired quality of life, and malignant ventricular arrhythmias [12]. On the other hand, an attempt of PCI may expose patients to the risk of coronary artery perforation, cardiac tamponade, and periprocedural myocardial infarction (MI) [13, 14]. However, the most important limitation of PCI in SVD is related with a higher rate of hemodynamically significant restenosis [15], which is primarily conditioned by lower initial lumen gain, rather than greater lumen loss as compared to PCI within vessels with larger diameter [2]. A large body of evidence suggests that smaller stent diameter suitable for SVD also constitutes a strong predictor of acute stent thrombosis (ST) [16]. Small stent diameter, along with increased total stent length and larger strut thickness, constitute powerful periprocedural predictors of long-term outcome [17].

The clinical profile of SVD patients, as well as higher rate of short- and long-term procedural complications, translates into poor long-term outcomes [3, 5]. Despite the use of new-generation drug-eluting stents (DES), an accumulating body of evidence suggests that PCI of coronary arteries < 2.5 mm is associated with a high rate of target lesion failure (TLF) or cardiovascular death [5]. Given the clinical significance of SVD, in the present article we will attempt to summarize the current knowledge on the definition, different approaches to interventional management, and outcomes of small coronary artery atherosclerosis.

Methods

This paper was based on systematic assessment of randomized controlled trials, observational and cohort studies, and meta-analyses comparing different strategies for the treatment of coronary stenoses located exclusively in small diameter vessels. The PubMed, EMBASE, Cochrane Library, and Clinical trial registries databases were searched using a combination of relevant text terms and key words: small coronary artery disease, small vessel coronary artery disease, small vessel disease, percutaneous coronary intervention, small coronary vessels, small coronary arteries, treatment, revascularization strategies, drug-coated balloons, drug-eluting stents, clinical trial, randomized trial, and meta-analysis. No language or sample size restrictions were applied. The review covered studies published between 1978 and April 2020.

Definition and characteristics

The greatest limitation of research in the field of SVD is the unclear definition of small coronary vessels used in the literature, which has evolved over the years. On the other hand, on closer examination, the small vessel diameter may be misleading and may derive from high plaque burden and diffuse disease.

Based on the meta-analysis by Agostoni et al. [18], SVD was liberally defined as atherosclerosis within the artery < 3.0 mm. Also, the recent BASKET-SMALL 2 trial arbitrarily adopted the diameter threshold of < 3.0 mm as SVD [19]. Early trials progressively identified vessels ≤ 2.9 mm or ≤ 2.75 mm in diameter as SVD [20, 21]. It is vital to note that these studies used these cut-off values as inclusion criteria, which were not validated against comparator cut-off values. A sub-study of the DUTCH-PEERS trial showed that a diameter of 2.5 mm appropriately stratifies patients in terms of risk of TLF [5]. Coronary arteries with diameter 2.5–3.0 were characterized by low risk of long-term complications as compared to vessels > 3.0 mm. Conversely, the risk was far greater in vessels < 2.5 mm [5]. In the IRIS-DES registry, everolimus-eluting stent < 2.78 mm and biolimus-eluting stent < 3.20 mm corresponded with increased risk of composite endpoint of cardiac death, target-vessel MI, and revascularization [17]. Very small vessel CAD was defined by Biondi-Zoccai et al. [7]; the definition considers vessels amenable to intervention using a 2.25 mm balloon or stent.

One should take into consideration the fact that the impact of vessel diameter on prognosis, including the risk of in-stent restenosis (ISR) or ST, is not categorical, and it should be regarded as a continuous variable (Fig. 3).

Diagnostic work-up and indication for myocardial revascularization

The decision-making process in patients with SVD should in general follow the same rules as described in European Society of Cardiology Guidelines for Myocardial Revascularization [22]. Depending on the clinical scenario, patients with acute coronary syndrome (ACS) should proceed to emergent invasive coronary angiography in cases of ST-segment elevation MI or non-ST-segment ACS with signs of hemodynamic or electrical instability or refractory angina. According to the guidelines on the management of chronic coronary syndromes (CCS), prior to invasive coronary angiography, all patients should be adequately verified in terms of the presence of ischemia using a non-invasive stress test [23].

Functional assessment

Prior to decision of myocardial revascularization, regardless of the vessel size, hemodynamic significance should be verified using fractional flow reserve (FFR) or instantaneous wave-free ratio measurements [24]. The PHANTOM trial provided evidence that purely angiographic assessment of SVD remains suboptimal and the use of functional assessment defers PCI in the majority of patients [25]. Only 30% of all SVD stenoses that had been alleged to be hemodynamically significant based on angiography alone were further confirmed to be truly significant [25]. Appropriate selection of affected vessels is crucial because of increased risk of long-term complications of PCI. Puymirat et al. [26] compared FFR-guided PCI with angiography-guided strategies in SVD and demonstrated a lower rate of target lesion revascularization (TLR), nonfatal MI, and major adverse cardiovascular events (MACE; 15% vs. 29%, p = = 0.002) in patients treated with FFR-guided PCI as compared with angio-guided PCI. Procedural costs were also reduced in the FFR-guided strategy (€3253 ± 102 vs. €4714 ± 37, p < < 0.0001) [26]. In the angio-guided group, the number of vessels treated per patient was significantly higher, whereas minimal lumen diameter was significantly lower as compared with the FFR-guided group [26]. These data suggest that FFR improves clinical decision-making and outcome in SVD and reduces procedural costs. One of the possible drawbacks of this method is the possibility of distal

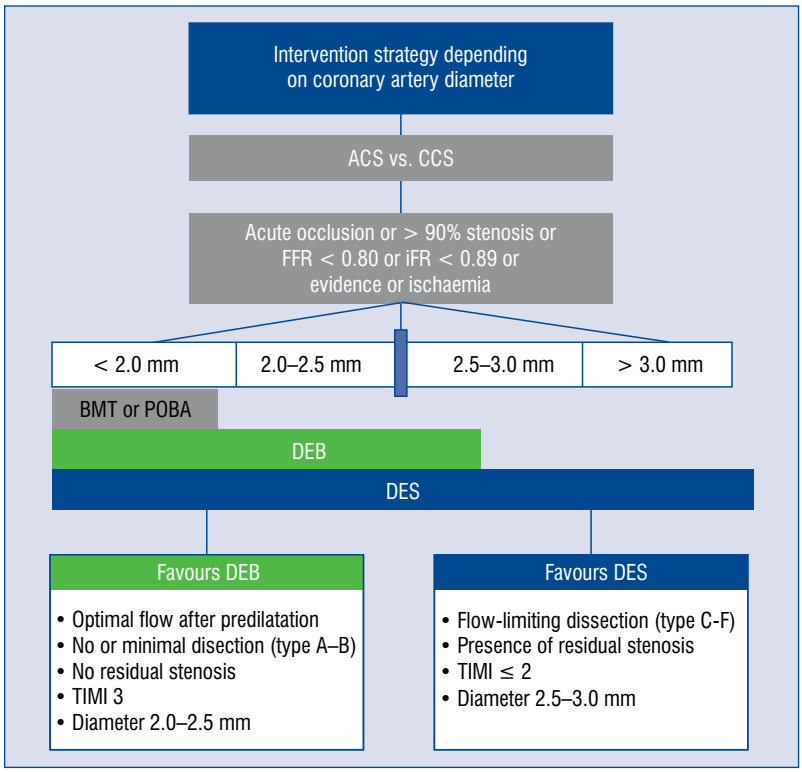

Figure 3. Classification of coronary arteries and the management of hemodynamically significant lesions depending on vessel diameter; SVD — small vessel disease; ACS — acute coronary syndrome; CCS — chronic coronary syndrome; FFR — fractional flow reserve; iFR — instantaneous wave-free ratio; BMT — best medical therapy; POBA — plain old balloon angioplasty; DEB — drug-eluting balloon; DES — drug-eluting stent; TIMI — Thrombolysis in Myocardial Infarction score.

perforation with the functional wire especially in small tortuous vessels.

Recently, a new quantitative flow ratio method of functional evaluation of coronary arteries was introduced, which is based on wire-free and adenosine-independent analysis of coronary angiography [27]. This promising new diagnostic tool was demonstrated to be as effective in vessels with diameter of 2.3–2.7 mm as in larger arteries with diameter 3.0–3.6 mm [28]. Similar technology based on non-invasive fractional flow reserve derived from computed tomography (FFR_{CT}) has been introduced, but no data regarding its accuracy depending on vessel diameter have been published [29].

Intravascular imaging

Intravascular ultrasound (IVUS) is mostly recommended to guide revascularization of left main disease or in cases of stent-related complications [22]. Evidence on IVUS-guided PCI in SVD is less convincing, although one study suggested that it led to a reduction of the number and length of implanted stents, median stent diameter, and high-pressure balloon use [30]. Of note, the number of ISRs on 2-year follow-up and MACE was significantly lower in the IVUS-guided than in the angio-guided group [30].

The use of IVUS and optimal coherence tomography (OCT) is also decisive in the diagnosis of unusual causes of ACS, including spontaneous coronary dissection, intramural hematoma, coronary embolism and thrombosis, or angiographically missed eroded plaque. Some data show that precise OCT-based calculation of post-intervention minimal stent area < 3.5 mm^2 in patients treated with a 2.5 mm everolimus-eluting stent predicts the 9-month risk of ISR [31]. Nevertheless, the use of IVUS and OCT in vessels < 2.25 mm may be challenging and increases the risk of iatrogenic plaque destabilization, coronary dissection, thrombosis, and coronary perforation [32].

Options of myocardial revascularization

The final decision about the revascularization should depend on the symptomatic presentation. The primary goal of PCI of narrow and frequently

peripheral coronary arteries in CCS patients is to provide symptomatic relief. This belief was endorsed by recently presented results of the pivotal ISCHEMIA trial (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) [33], which compared an invasive strategy with conservative pharmacological management of patients with moderate–severe ischemia based on non-invasive stress test [33]. The study showed that in a median follow-up time of 3.3 years, patients treated conservatively had similar outcomes to patients managed invasively, as reflected by comparable rates of composite endpoint of death, MI, resuscitated cardiac arrest, hospitalization for unstable angina, or heart failure (15.5% vs. 13.3%, p = 0.34) [33]. Nonetheless, the invasive group was characterized by significant reduction of symptoms, but only if angina was present at baseline [33]. This landmark trial provided sound evidence for a more lenient approach to revascularization in CCS, especially in patients with peripheral SVD.

In cases of ACS, PCI or coronary artery bypass grafting (CABG) should generally be pursued, which is addressed in subsequent sections of the manuscript. It should be noted, however, that some evidence adjudicates in favor of conservative management in very specific clinical situations. In the EROSION study Jia et al. [34] found that antithrombotic therapy without stenting is a reasonable clinical option, provided that plaque erosion (not rupture) has been confirmed in OCT imaging. This was confirmed by reduction of thrombus burden or its disappearance on OCT at 1-month [34] and 12-month follow-up [35]. It is vital to note that nearly 25% of all patients presented with this etiology of ACS [34], which may be regarded as a rationale for conservative management of patients with ACS due to eroded plaque in small vessels, especially if the PCI is at risk because of small vessel diameter.

Plain old balloon angioplasty

Since the beginning of invasive cardiology, PCI has evolved from plain old balloon angioplasty (POBA) and bare-metal stents (BMS) to drug-coated balloons (DCB) and drug-eluting stents (DES), which result in better clinical outcomes [36]. Although POBA should be regarded as a viable option within coronary arteries < 2.0 mm (Fig. 3), in which stent implantation is technically impossible or could increase the risk of vessel rupture, a number of studies have proven that stent implantation confers significantly lower risk of restenosis as compared with POBA [7, 18]. According to some reports, balloon-only PCI with optimal postprocedural angiographic flow can achieve comparable results to BMS implantation in small coronary vessels [18].

Technological development has led to the introduction of commonly available 1.5 mm or even smaller balloons; however, no prospective data on the results of POBA with this kind of device are available. Examples of the smallest balloons include the 1.5 mm APEX® Dilatation Catheter [37], 1.25 Sprinter® Legend RX, 1.5 mm Euphora® Semicompliant Dilatation Catheter [38], 1.0 mm Ryurei® Dilatation Catheter [39], and 1.25 Sapphire® Coronary Dilatation Catheter [40], which are dedicated to dilatation of the most stenotic part of the lesion. The even smaller 0.85 mm NIC Nano balloon was introduced for PCI of chronic total occlusion [41]. All the above-mentioned balloon catheters share different technical specifications, and an overview is beyond the scope the current manuscript. Nowadays these dilatation catheters are primarily used for stepped lesion preparation prior to stenting of larger coronary arteries. Randomized controlled trials are warranted to assess the safety and feasibility of these devices for POBA in SVD.

BMS and DES

Stent implantation has become the core element of PCI in the majority of procedures, including SVD [18]. Accordingly, with the advent of DES showing better efficacy in terms of lower rates of ISR and TLR, combarable risk of ST and mortality, second-generation DES implantation is the state-of-the-art management of patients with CAD within vessels large enough to accommodate a stent [42]. Although the ISR rate has generally diminished, the efficacy of DES within small coronary arteries is lower [43, 44]. A wall injury induced by stent implantation initiates a vasculoproliferative cascade with smooth muscle cell proliferation and neointimal hyperplasia [45]. This protrusion is independent of nominal vessel size, so smaller coronary arteries are more prone to late luminal loss and are less able to accommodate neointimal tissue without blood flow limitation [46, 47]. The DUTCH PEERS randomized trial assessed novel DES (zotarolimus and everolimus) in patients with SVD [5]. The rates of TLF were significantly higher in patients with target lesion being < 2.5 mm than in those that were ≥ 2.5 mm (8.6% vs. 5.4%, p = = 0.01), and acute myocardial infarction (AMI) was numerically, but not significantly, higher (2.7% vs. 1.2%, p = 0.04) [5]. Another study with a sirolimus-

Table 1. Overview of available evidence concerning percutaneous coronary interventions of small coronary vessels.

Trial	Type	Sample size	Reference diameter [mm]	Intervention	Target lesion revascularization
BMS vs. POBA					
LASMAL I [76]	RCT	246	2.0–2.9	BMS vs. POBA	0.8% vs. 6.6%, p = 0.018
DES vs. BMS					
C-SIRIUS [49]	RCT	100	2.5–3.0	SES vs. BMS	4% vs. 18%, p = 0.05
SES-SMART [21]	RCT	257	≤ 2.75	SES vs. BMS	9.8% vs. 53.1%, p < 0.001
E-SIRIUS [77]	RCT	352	2.5–3.0	SES vs. BMS	4% vs. 20.9%, p < 0.0001
DES vs. DES					
ISAR-SMART 3 [78]	RCT	360	< 2.8	PES vs. SES	14.7% vs. 6.6%, p = 0.008
DCB vs. POBA/BMS/DES					
PICCOLETO [79]	RCT	57	≤ 2.75	DCB vs. PES	10.3%, vs. 32.1%, p = 0.043
BELLO [63]	RCT	182	< 2.8	DCB vs. PES	4.4% vs. 7.6%, p = 0.37
BASKET-SMALL 2 [19]	RCT	758	< 3.0	DCB vs. DES	3.4% vs. 4.5%, p = 0.4375
Giannini et al. [64]	Cohort study	181	< 2.8	DCB vs. EES	4.4% vs. 5.6%, p = 0.720
Sim et al. [80]	Cohort study	87	2.0	DCB vs. DES	7.0% vs. 8.2%, p = 0.73
Nishiyama et al. [81]	RCT	60	< 3.0	DCB vs. DES	0.0% vs. 6.1%, p = 0.169
Funatsu et al. [82]	RCT	135	< 2.8	DCB vs. POBA	2.3% vs. 10.3%, p = 0.07
Her et al. [83]	Case-control study	72	2.5–3.0	DCB vs. POBA	0% vs. 13%, p = 0.033
Sinaga et al. [65]	Case-control study	335	≤ 2.5	DCB vs. DES	5.2% vs. 3.7%, p = 0.601
Shin et al. [84]	Cohort study	66	< 3.0	DCB vs. DES/BMS	0% vs 5%, p = NS
RESTORE SVD [66]	RCT	256	2.0–2.75	DCB vs. ZES	2 years: 5.2% vs. 2.8%, p = 0.5
SCAAR Report [67]	Cohort study	14,788	≤ 2.5	DCB vs. DES	4.1% vs. 1.8%, p < 0.001

DCB — drug-coated balloon; DES — drug-eluting stent; POBA — plain old balloon angioplasty; RCT — randomized controlled trial; BMS — bare metal stent; EES — everolimus-eluting stent; PES — paclitaxel-eluting stent; SES — sirolimus-eluting stent; ZES — zotarolimus-eluting stent

eluting stent (SES) and angiographic follow-up showed higher restenosis rates in patients with lesions smaller than 2.41 mm, as compared with those over ≥ 2.41 mm [48].

The current evidence regarding the use of BMS/DES is summarized in Table 1. According to the C-SIRUS trial, deployment of SES instead of BMS has improved TLR from 52% to only 2% [49]. Similar results were confirmed in other trials with a very low late loss ranging between 0.05 and 0.20 mm [21, 48, 49]. Moreover, the median TLR rate was 7% for SES in comparison to 15% and 13% for a paclitaxel-eluting stent (PES) and DCB, respectively [50]. SES significantly reduced the odds of TLR compared to PES (odds ratio [OR] 0.39), DCB (OR 0.34) and BMS (OR 0.21), but there were no differences in the rate of AMIs among patients [50].

Factors such as lesion length, strut thickness, and minimum stent lumen diameter were identified as independent predictors of restenosis in DES [45, 51, 52]. The most powerful predictor of angiographic restenosis is the diameter of the vessel, with a 60% higher risk of restenosis for each decrease by 0.50 mm [53]. The TAXUS ATLAS study compared the performance of the thin strut (0.095 mm) Taxus Liberte 2.25 mm stent and the Taxus Express (0.132 mm) in small vessels [54]. Thinner stent struts significantly reduced the rate of 9-month restenosis (18.5% vs. 32.7%, p = 0.02) [54].

Technological development led to the introduction of 2.0 mm stents in order to accommodate

Table 2. Principles of percutaneous coronary intervention with drug-coated balloons (DCB) [60, 62].

1.	The lesion should be prepared prior to the use of DCB. DCB should serve only as a vector of antiproliferative drug.
2.	Predilatation with semi-compliant balloon sized 0.8–1.0 to reference vessel diameter with higher than nominal pressure.
3.	Use of non-compliant balloons or scoring/cutting balloons or rotablation in the case of complex lesions.
4.	Prior to using DCB, check the deliverability of DCB to peripheral lesions. Severe proximal calcifications can prevent the transfer of DCB to the culprit lesion.
5.	DCB should not be applied in lesions with residual stenosis > 30% or with type C–F dissection following initial predilatation. Consider DES implantation.
6.	DCB should not be exposed to or immersed into the saline as the drug can be released in the solvent, not the culprit lesion.
7.	DCB should be swiftly deployed in the lesion, as the drug can be dissolved in the catheter or in non-culprit segment of the artery.
8.	DCB should be sized 0.8–1.0 to reference vessel diameter and inflated for at least 30–60 s depending on the DCB type.
9.	Angiographic or intravascular assessment of possible complications (dissection).
10.	Dual antiplatelet therapy for as little as 1 month in patients with chronic coronary syndrome.

for smaller vessel size, but the clinical benefit of small stent implantation (≤ 2.25 mm) is vague [55]. The new portfolio of 2.0 mm DES (everolimus--eluting Xience Xpedition SV or Xience Alpine; zotarolimus-eluting Resolute Onyx) created new options of PCI in a smaller vascular territory, with promising results in retrospective analysis [55, 56].

Drug-coated balloons

Drug-coated balloon therapy (otherwise known as drug-eluting balloon, DEB) has been proposed as an alternative to DES in SVD, obviating the need for implantation of a foreign body into a small artery [57]. The technique is based on rapid delivery of an antiproliferative drug to the arterial wall from a semi-compliant balloon covered with a lipophilic matrix [58]. Therapeutic agents, most commonly paclitaxel, are delivered during single balloon inflation, which should last between 30 and 60 seconds depending on the DCB type [58]. A crucial step prior to deployment of DCB consists of adequate lesion preparation with a successful predilatation to avoid elastic recoil and flow-limiting dissections [59]. It was shown to provide a good initial angiographic result [59]. The basic principles of PCI with the use of DCB are highlighted in Table 2 [60].

In the past, DCB was primarily utilized for the treatment of ISR, which constitutes its primary indication with class IA recommendation in line with current European Society of Cardiology Guidelines on Myocardial Revascularization [22, 61]. However, numerous recent studies have focused on the possible application of DCB for the treatment of de-novo lesions within small coronary arteries. A few randomized controlled trials compared the efficacy of DCB and DES in SVD. A summary of available evidence concerning the comparison of DCB and DES in SVD is presented in Table 1 [62].

The results of the BELLO study are worth mentioning, which compared the IN.PACT Falcon paclitaxel-coated balloon with PES Taxus Liberte in vessels with a mean diameter of 2.15 mm [63]. The study showed promising lower late lumen in the DCB group than in the PES group (0.08 mm vs. 0.29 mm, $p < 0.001$), but similar event rates were reported in both groups [63]. This was confirmed in propensity score analysis of the BELLO population [64].

More recently Sinaga et al. [65] performed a retrospective analysis of 335 patients treated either with DCB or DES by means of device ≤ 2.5 mm. This real-world analysis showed that although the DCB group had lower acute lumen gain than DES group, the 1-year MACE rate (11.6% vs. 11.7%, $p = 1.0$) and TLR (5.2% vs. 3.7%, $p = 0.601$) were comparable between both cohorts [65].

Similar efficacy between DCB and DCB within relatively small coronary vessels was further corroborated by the high-volume BASKET-SMALL 2 study [19]. This open-label randomized trial comprised 758 patients with native lesions in vessels < 3.0 mm to either DCB or second-generation DES implantation [19]. The use of DCB was non-inferior

to second-generation DES in terms of MACE occurrence (cardiovascular death, non-fatal AMI, target vessel revascularization) at 12 months (7.5% vs. 7.3%, hazard ratio [HR] 0.97, p = 0.918) [19].

Also, the RESTORE SVD randomized trial compared DCB with zotarolimus-eluting stent in 256 patients with de novo lesions within vessels between 2.0 and 2.75 mm in size [66]. TLF did not differ significantly between DCB and DES group at 2 years (5.2% vs. 3.7%, p = 0.75) [66].

In contrast to former reports, doubt was cast on the efficacy of DCB in de novo SVD in the recent SCAAR report [67]. This retrospective registry-based Swedish study comprised 14,788 patients treated with either DCB or second-generation DES for stenoses in arteries ≤ 2.5 mm [67]. The propensity score-matched analysis denoted that the DCB group was characterized by significantly higher risk of restenosis at 3 years (HR 2.027, 95% confidence interval [CI] 1.537–2.674) but had comparable risk of lesion thrombosis, AMI, and all-cause death to the DES group [67]. Despite its retrospective design, the present study is the largest report concerning SVD treatment with DCB. Further high-volume prospective studies are required to verify the conflicting results of the trials.

In spite of divergent data on risk of restenosis [19, 67], DCB represents a viable interventional option in patients with native SVD, with similar risk of adverse events and mortality to contemporary DES technology. The advantages of DCB over stent implantation include significantly lower risk of acute thrombosis, potentially favorable vascular remodeling after PCI, and dual antiplatelet therapy shortened to 4 weeks in stable patients, which may reduce the risk of major bleeding and bring additional clinical benefit [19]. DCB should be applied particularly within in-stent restenosis, in de novo lesions ranging from 2.0 mm to 2.5 mm, and as an adjunct to DES implantation for side branch PCI in selected cases (Fig. 3) [68].

Bioresorbable scaffolds

Bioresorbable scaffolds (BRS) were designed to allow for gradual resorption of stent components, which seemed to be attractive in the context of possible PCI in SVD [69]. This approach was thought to provide similar benefits as DES, at same time being minimally invasive. Conversely, the first-generation lactic acid BRS was shown to confer greater risk of subacute, late, and very late stent thrombosis and a higher rate of TLR, most likely due to the design of thick lactic acid struts [70, 71]. This led to contraindication for these devices to be used in routine clinical practice outside of clinical trials and recommendation for prolonged dual antiplatelet therapy > 12 months [21]. The potential benefit of these stents in SVD was outweighed by even greater risk of poor outcome within small coronary vessels [72]. The retrospective analysis by Wiebe et al. [72] provided evidence that implantation of the smallest 2.5 mm BRS was linked to higher risk of TLF (HR 1.31, 95% CI 1.01–1.69). There are numerous ongoing trials evaluating the application of experimental bioresorbable technologies, including magnesium-based bioresorbable stents [73]. Time will show if these solutions are safe in the clinical setting of SVD.

CABG

Coronary artery bypass grafting represents a cornerstone of myocardial revascularization in patients with multivessel CAD and high SYNTAX score [74]. Multivessel CAD is frequently accompanied by the presence of SVD. Based on convincing evidence from high-volume reports, CABG is not a preferable choice of treatment in SVD due to an increased risk of technical failure and risk of MACE [75]. O'Connor et al. [75] studied the impact of gender, body size, and mid-left anterior descending artery dimeter on the in-hospital mortality of patients submitted to CABG [76]. The in-hospital mortality amounted to 15.8% in patients with a diseased vessel diameter of 1.0 mm, while it was as low as 1.5% in patients with a grafted vessel size of 2.5–3.5 mm [75]. This constitutes a strong indicator that vessel size should be regarded as one of the core variables in the decision-making process during Heart Team meetings. Unfortunately, the reference tool for evaluation of morphology and degree of CAD, namely the SYNTAX score, does not account for vessels < 1.5 mm and it does adjust risk score to vessel diameter in larger arteries, which represents a major limitation of the current approach [74].

Conclusions

Small vessel disease is a challenging condition due to its equivocal definition and abundance of different therapeutic options. Revascularization should be performed in patients with confirmed ischemia and only in cases of hemodynamically significant lesions based on functional assessment, which has proven even more important in small vessel diameter. The diameter of the diseased vessel represents the most potent variable affecting long-term outcome after PCI in SVD. The choice

between DES or DCB should be based on a number of clinical variables, including vessel size, ischemic territory, and lesion characteristics. In the group of lesions > 2.5 mm, the application of DES is associated with a more favorable clinical outcome with low rate of TLR, while both DCB and DES tend to show similar efficacy in the vessel diameter between 2.0 and 2.5 mm. In this clinical setting, DCB is an alternative to DES, with the advantage of positive vascular remodeling and shortened dual antiplatelet therapy. Very small coronary vessels < 2.0 mm should either be treated with POBA or best medical therapy, especially in the case of chronic coronary syndromes. SVD remains an unexplored clinical setting, which requires extensive research into the indications and optimal methods of myocardial revascularization.

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How to obtain diagnostic and procedural quality three-dimensional-rotational angiograms in congenital heart disease: Tips and tricks from a single center experience

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The problem

Three-dimensional rotational angiography (3DRA) is a commonly used imaging modality in congenital cardiac catheterization laboratories around the world. 3DRA research often focuses on the novelty and retrospective utility of 3DRA for a variety of procedures. Its hypothetical benefits may be through its potential to decrease radiation and contrast dose and to assist in the technical aspects of difficult cases [1–3]. There are currently no peer-reviewed guidelines on the efficient technical performance of a successful 3DRA, the key tenets of which are:

— Good quality angiography;
— Ease of 3D reconstruction;
— Minimizing catheter and foreign body artifact;
— Ability to use the resultant reconstructions to perform accurate measurements and produce a quantitatively representative image of structures;
— Accurate and rapid 3DRA reconstruction to facilitate overlay onto live fluoroscopy during procedural guidance.

The proposal

Extensive experience with current and past Philips's imaging technologies have allowed us to develop 3DRA protocols for different anatomical patient subsets, based on different structures and procedures of interest. These protocols, when used systematically provide high quality 3DRA using both the Philips' Allura and Azurion platforms. Sharing this experience may assist other centers in developing and improving their 3DRA workflows. The aim herein, was to provide guidance for other catheterization laboratories on useful tools and adjuncts that will allow them to take full advantage of the applications provided with their systems.

Technical description

Angiographic prescriptions for specific congenital lesions are summarized in Table 1. General recommendations for 3DRA include:

1. In our experience, using rapid ventricular pacing does not improve the quality of our diagnostic imaging, therefore we **do not** use it for 3DRA. Pacing alters the cardiac output, decreasing the accuracy of dimensional measurements. This can require the performance of additional 2D angiography to reliably measure structures of interest.
2. Lengthening the intravenous (IV) lines and ventilatory tubing/equipment to avoid any interaction with the C-arm during the rotational angiogram. Excellent co-operation with the anesthesia team is essential.
3. 3DRA should be acquired during cessation of mechanical ventilation (expiratory breath hold) to eliminate respiratory motion artifacts.

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Table 1. Children's Hospital Colorado three-dimensional rotational angiography (3DRA) protocols per cardiac lesion for Philips Allura and Azurion systems.

	< 20 kg	20–50 kg	Adults (> 50 kg)
Aortic arch			
Catheter/size	Pigtail or Berman/4 F or 5 F	Pigtail or Berman/5 F	Pigtail or Berman/5 F or 6 F
Injection site	Ascending aorta*	Ascending aorta*	Ascending aorta*
Total volume	2 mL/kg	2 mL/kg	100 mL
Dilution (% contrast)	75%	75%	100%
Delay time [s]	1	1	1
Notes	Place catheter in LVOT instead of ascending aorta for improved coronary opacification.		
Fontan evaluation			
Catheter/size	*Long sheath/5 F Pigtail or Berman/4 F	*Long sheath/6 F Pigtail or Berman/4 F	*Long sheath/6 F Pigtail or Berman/4 F
Injection site	IVC SVC or innominate vein	IVC SVC or innominate vein	IVC SVC or innominate vein
Total volume	25% total volume by hand 1.5 mL/kg (minus the amount given by hand)	20 mL by hand 1.5 mL/kg (minus 20 mL)	20 mL by hand 40 mL (for a total of 60 mL injection)
Dilution (% contrast)	75%	75%	100%
Delay time [s]	1	1	1
Notes	Multiple site injection with IVC injections delineated in grey. Side arm injection by hand into long sheath should be performed at same time as automated pump. We have also used a short sheath for injection with good result.		
Superior cavopulmonary anastomosis (bidirectional glenn/hemifontan)			
Catheter/size	Berman or Ssheath/5 F	Berman or sheath/5 F	
Injection site	SVC or innominate vein	SVC or innominate vein	
Total volume	1 mL/kg	1 mL/kg	
Dilution (% contrast)	75%	75%	
Delay time [s]	1	1	
Notes	1 mL/kg is enough for an adequate 3DRA in a low flow system.		
Pulmonary arteries (without stenosis and/or insufficiency)			
Catheter/size	Berman or pigtail/5 F	Berman or pigtail/6 F	Berman or pigtail/6 F
Injection site	RVOT	RVOT	RVOT
Total volume	2 mL/kg	2 mL/kg	100 mL
Dilution (% contrast)	75%	75%	100%
Delay time [s]	1	1	1
Pulmonary arteries (with significant stenosis)			
Catheter/size	Berman or pigtail/5 F	Berman or pigtail/6 F	Berman or pigtail/6 F
Injection site	MPA	MPA	MPA
Total volume	2 mL/kg	2 mL/kg	100 mL
Dilution (% contrast)	75%	75%	100%
Delay time [s]	1	1	1
Notes	Catheter side holes should be placed distal to vascular narrowing.		
PPVI balloon coronary interrogation (non-selective)			
Catheter/size	Pigtail/5 F	Pigtail/5 F	Pigtail/5 F or 6 F
Injection site	Aortic root	Aortic root	Aortic root
Total volume	1.5 mL/kg	1.5 mL/kg	75 mL
Dilution (% contrast)	75%	75%	100%
Delay time [s]	1	1	1
Notes	RVOT balloon contrast should be at 50% dilution. Injection to commence at full balloon inflation. Lower injection volume in the setting of low cardiac output with RVOT balloon occlusion.		

→

Table 1 (cont.). Children's Hospital Colorado three-dimensional rotational angiography (3DRA) protocols per cardiac lesion for Philips Allura and Azurion systems.

	< 20 kg	20–50 kg	Adults (> 50 kg)
PPVI balloon coronary interrogation (selective single coronary assessment)			
Catheter/size	JR or JL/4 F	JR or JL/5 F	JR or JL/5 F
Injection site	RCA or LCA	RCA or LCA	RCA or LCA
Total volume	Manual injection	Manual injection	Manual injection
Dilution (% contrast)	100%	100%	100%
Delay time [s]	1	1	1
Notes	RVOT balloon contrast should be at 50% dilution. No pump angiography required. Injection to commence at full balloon inflation with 1 s delay on 3D acquisition. 'Coupling' should be switched off.		
PPVI (RVOT assessment in patients with stenosis or significant insufficiency)			
Catheter / size	Pigtail or multitrack/5 F	Pigtail or multitrack/6 F	Pigtail or multitrack/6 F
Injection site	MPA	MPA	MPA
Total volume	2 mL/kg	2 mL/kg	100 mL
Dilution (% contrast)	75%	75%	100%
Delay time [s]	1	1	1
Notes	If planning for overlay, perform the angiogram with your intended wire for the intervention along with a Multitrack catheter. The stiff wire doesn't introduce significant artifact and guidance is more accurate.		

*Catheters are suggestions only; F — french; IVC — inferior vena cava; JL — left Judkins catheter; JR — right Judkins catheter; LCA — left coronary artery; LVOT — left ventricular outflow tract; MPA — main pulmonary artery; PPVI — percutaneous pulmonary valve implantation; RCA — right coronary artery; RVOT — right ventricular outflow tract; SVC — superior vena cava

4. When using 3DRA for fluoroscopic overlay during procedural guidance, we recommend having the procedural guide wire in its intended position for intervention. This will increase the accuracy of the overlay by cancelling out the anatomic shift which occurs after placing a stiff wire. Stationary guide wire does not produce a significant artifact.
5. For patients < 50 kg, our contrast solution is diluted (75% contrast and 25% normal saline). Remember to agitate this solution prior to injection. For patients > 50 kg, we use straight (100%) contrast.
6. The catheter and accosted tubing should be primed with contrast prior to injection.
7. The contrast injection is given over 5 s, starting 1 s before the C-arm rotation begins (1 s delay). This time delay should be modified when injecting in the pulmonary arterial circulation and focusing on levophase structures.

The Philips platform has several available processing tools designed for vascular and solid organ imaging that we have found extremely useful in congenital cardiology (Fig. 1).

1. We perform 3D reconstructions using the **XtraVision workstation** (Philips Healthcare, Andover, Massachusetts, USA). During the reconstruction, the first step before manipulating the histogram, is to remove any clips/wires or other highly opacified artifact.
2. We use **XperCT** to create multiplanar reconstructions of our imaging dataset facilitating measurements of structures of interest. These images are similar to multiplanar reconstructions views obtained with a computed tomographic angiography. This allows cardiac anatomy evaluation and its relationship with other nearby structures.
3. If the reconstruction will be used for live guidance overlay, we use the **XperGuide** function instead of the built-in "Overlay" tool. XperGuide was developed to guide solid organ procedures like liver or tumor biopsies. It allows the reconstructed 3DRA or a computed tomography "like" view (multiplanar view); to be overlaid on live fluoroscopy.
4. Using the **"Segmentation"** tool in the XtraVision workstation, we routinely segment airway anatomy, described in a prior publication [4]. This can be viewed along with the 3DRA vascular reconstruction and also overlaid onto live fluoroscopy using XperGuide.

In our experience, these "non-cardiac" software packages work well with acquisitions from

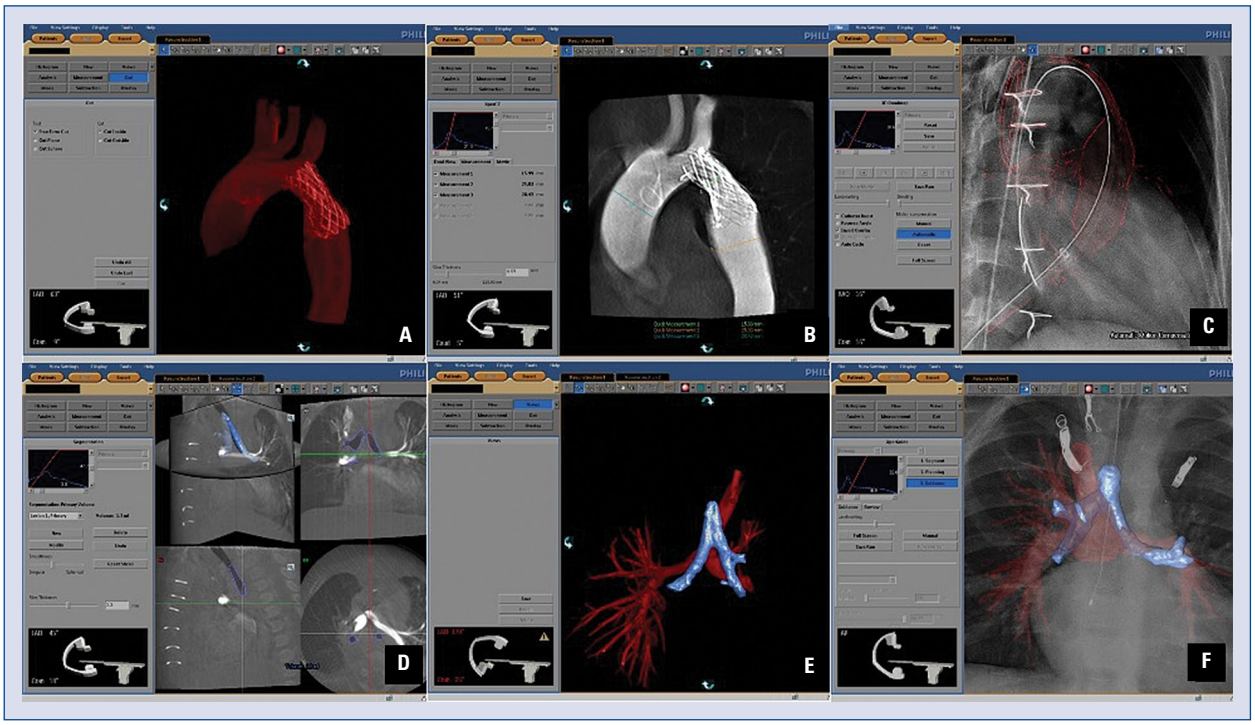

Figure 1. The multiple phases of three-dimensional rotational angiography (3DRA) acquisition, post processing, overlaying and segmentation; **A.** 3DRA reconstruction using Philips XtraVision workstation. The acquisition was in a patient with a coarctation of the aorta after stent placement. The angiogram was done with a Berman catheter to produce adequate contrast enhancement of entire aorta with minimal catheter related artifact; **B.** XperCT is used to perform measurements in the multiplanar reconstruction (MPR) view of the 3DRA dataset, facilitating non-axial evaluation of the images; **C.** 3D Roadmap tool developed for the 3DRA overlay but unable to overlay airway and only allows the mask of the 3DRA to be used which limits the anatomic details available for live guidance (not used in our center, we use XperGuide instead); **D.** Segmentation tool that allows reconstruction of the airway with an MPR view; **E.** 3DRA reconstruction after the airway has been segmented. The airway can then be hidden to assess the vascular reconstruction only if necessary; **F.** XperGuide with 3DRA vascular and airway reconstruction overlay in live fluoroscopy.

both the Allura (FD10, FD20) and Azurion (B12/12) systems. Of note, using our current configurations, 3DRA acquisitions are performed at 15 frames per second with the Azurion system and 30 frames per second with the Allura system.

Conclusions

These simple guidelines on the proficient use of 3DRA with the Philips system have been developed over years of work with their angiographic platforms. They should act as guidance to clinicians who feel they are not utilizing their imaging systems fully as well as providing a technical platform for continued improvements generated by interested clinicians around the world.

Conflict of interest: None declared

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Outcomes associated with lidocaine and amiodarone administration in pediatric in-hospital cardiac arrest

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Pediatric in-hospital cardiac arrest is a devastating condition with the average annual incidence of 15,200 cases in the United States [1]. The survival rate after hospital discharge remains poor (~55%) [2], although it shows an increasing trend in the last decade [3]. In the pediatric population, around 10% of patients have initial shockable rhythms (ventricular fibrillation or pulseless ventricular tachycardia) following cardiac arrest, and 15% of patients develop them during resuscitation. The rate of shockable rhythms varies depending on the patient age and is lowest for infants, followed by children and adolescents [4]. Early defibrillation and high-quality cardiopulmonary resuscitation are the core of treatment for cardiac arrests caused by shockable rhythms, followed by administration of adrenaline and antiarrhythmic drugs [5].

Amiodaron and lidocaine are used in the treatment of pediatric cardiac arrest with shockable rhythms refractory to defibrillation. Previously, amiodaron was recommended by the American Heart Association (AHA) Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care 2010: Pediatric Advanced Life Support [6], and by the European Resuscitation Council (ERC) 2010: Pediatric Life Support Guidelines [7] as the preferred antiarrhythmic. Currently, both AHA 2020 [8] and ERC 2021 Guidelines [5] state that amiodaron and lidocaine can be used interchangeably, depending on the physician's preferences. However, data regarding the outcomes associated with amiodarone and lidocaine administration in pediatric cardiac arrest are very limited. Therefore, this study is a systematic review and meta-analysis to determine the efficacy of amiodarone and lidocaine in pediatric cardiac arrest.

This present review and meta-analysis were performed following the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines. The search of data included the Embase, Medline and the Cochrane from the databases' inception to April 15, 2021. Studies included in this meta-analysis met the following PICOS criteria: (1) Participants: patients < 18 years of age with cardiac arrest due to any cause; (2) Intervention: amiodarone treatment; (3) Comparison: treatment with lidocaine; (4) Outcomes: detailed information for survival; (5) Study design: randomized controlled trials, observational trials comparing lidocaine and amiodarone in pediatric resuscitation. Studies were excluded if they were reviews, guidelines or articles not containing original data.

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Table 1. Pooled analysis of pediatric cardiac arrest outcomes in patients treated with lidocaine and amiodarone.

Adverse event type	No. of studies	Events/ /participants		Events		Heterogeneity between trials		P-value for differences across groups
		Lidocaine group	Amiodarone group	OR	95% CI	P-value	I^2 statistic	
Full cohort data								
ROSC	2	307/430 (71.4%)	140/237 (59.1%)	1.96	1.39–2.77	0.45	0%	**< 0.001**
Survival to 24 h	2	232/430 (54.0%)	94/237 (39.7%)	1.94	1.39–2.69	0.82	0%	**< 0.001**
SHD	2	138/429 (32.2%)	55/235 (23.4%)	1.68	1.16–2.44	0.99	0%	**0.006**
SHD with favorable neurological outcome	1	39/186 (21.0%)	30/141 (21.3%)	0.98	0.57–1.68	NA	NA	0.95
Matched cohort data								
ROSC	2	203/303 (67.0%)	107/179 (59.8%)	1.51	0.64–3.55	0.04	76%	0.35
Survival to 24 h	2	145/303 (47.9%)	71/179 (39.7%)	1.48	0.77–2.83	0.10	64%	0.24
SHD	2	82/302 (27.2%)	43/179 (24.0%)	1.31	0.84–2.05	0.27	16%	0.23
SHD with favorable neurological outcome	1	12/78 (15.4%)	20/85 (23.5%)	0.59	0.27–1.31	NA	NA	0.19

CI — confidence interval; NA — not applicable, OR — odds ratio; ROSC — return of spontaneous circulation; SHD — survival to hospital discharge

Following identification and selection of the relevant studies for the present meta-analysis and removal of duplicates and nonrelevant trials, two studies were included in the analysis [9, 10]. Both studies focused on in-hospital cardiac arrest (IHCA).

Results of the pooled analysis of IHCA outcomes is presented in Table 1. In the full cohort, the use of lidocaine in pediatric resuscitation was associated with a higher incidence of return of spontaneous circulation (71.4% vs. 59.1%, respectively; odds ratio [OR] 1.96; 95% confidence interval [CI] 1.39–2.77; $p < 0.001$), survival to 24 h (54.0% vs. 39.7%; OR 1.94; 95% CI 1.39–2.69; $p < 0.001$) and survival to hospital discharge (32.2% vs. 23.4%; OR 1.68; 95% CI 1.16–2.44; $p = 0.006$), compared to amiodaron. There were no differences regarding favorable neurological outcome at hospital discharge in patients who received lidocaine and amiodarone (21.0% vs. 21.3%, respectively; OR 0.98; 95% CI 0.57–1.68; $p = 0.95$). In the propensity-score matched cohort data (comparison of propensity-matched patients from the first study [9] and all patients from the second study [10], no significant differences between the use of lidocaine and amiodarone were found in terms of all researched outcomes.

In conclusion, despite better IHCA outcomes associated with lidocaine in the full cohort analysis, analysis of the propensity-matched data showed no significant differences between the treatment arms. Although the small number of studies included in this meta-analysis and lack of access to individual patient data is a limitation, the meta-analysis herein, implies that results of previous studies comparing lidocaine and amiodarone in pediatric cardiac arrest should be interpreted which caution, as the observed differences might be due to substantial differences in patient baseline and clinical characteristics. Further randomized controlled trials are warranted to establish which treatment strategy is associated with better outcomes.

Conflict of interest: None declared

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Novel polygenetic variants evidenced in a patient with Jervell and Lange-Nielsen syndrome

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Jervell and Lange-Nielsen syndrome (JLNS) is an ion channel-caused cardioauditory syndrome characterized by a congenital neurosensorial bilateral deafness and a long QT interval. JLNS is inherited in an autosomal recessive manner and is caused by mutations in the *KCNQ1* gene (potassium voltage-gated channel subfamily Q member 1) [1].

The proband was an 8-year-old male who presented with a family history of sudden death and congenital sensorineural deafness. Initial clinical evaluation of the proband showed a mild cranial trauma and minor occipital subgaleal hematoma. No significant cardiovascular findings were noted, but electrocardiography (ECG) analysis (ECG Edan SE-1200, USA) revealed a prolonged QT/QTc in the lead II (420/460 ms) (Fig. 1A, left). Despite the use of beta-blocker (2 mg/kg/day) therapy at home, the patient experienced a syncopal event related to emotional stress.

Viskin test [2] was performed, and the results did not support an long QT syndrome (LQTS)--related orthostatic event (baseline QTc 465 ms in resting phase, QTc MHR of 492 ms, and QTc recovery of 444 ms). An adrenaline test [3] was performed at doses of 0.025 μg/kg/min, enabling a QTc of 550 ms without an arrhytmic event (Fig. 1A, right), and met LQTS electrocardiographic criteria. QTc 686 ms was observed under stress after placement of the implantable cardioverter-defibrillator (ICD) and beta-blockers. At follow up, the patient was ventricular arrhytmia-free or shock therapy during the 4 years after ICD implantation. After clinical and cardiac electrophysiology, the patient was diagnosed with JLNS.

Molecular genetic analysis was performed by next generation sequencing in the proband, and 4 family members were clinically affected (Fig. 1B). Electrocardiographic assessment of the mother and maternal grandparents revealed borderline QTc values. The electrocardiographies were measured by the Bazett formula. Only the index case was genotyped and the family members declined to do genetic testing until there was more evidence that genetic testing had to be recommended by a genetic counselor.

High throughput DNA sequencing was performed using an Ion Torrent Personal Genome Machine to target and sequence 87 candidate genes linked with inhereted cardiac arrhythmia syndromes. These candidate genes were selected based on their relative expression in the human heart and their ability to modulate ion channel

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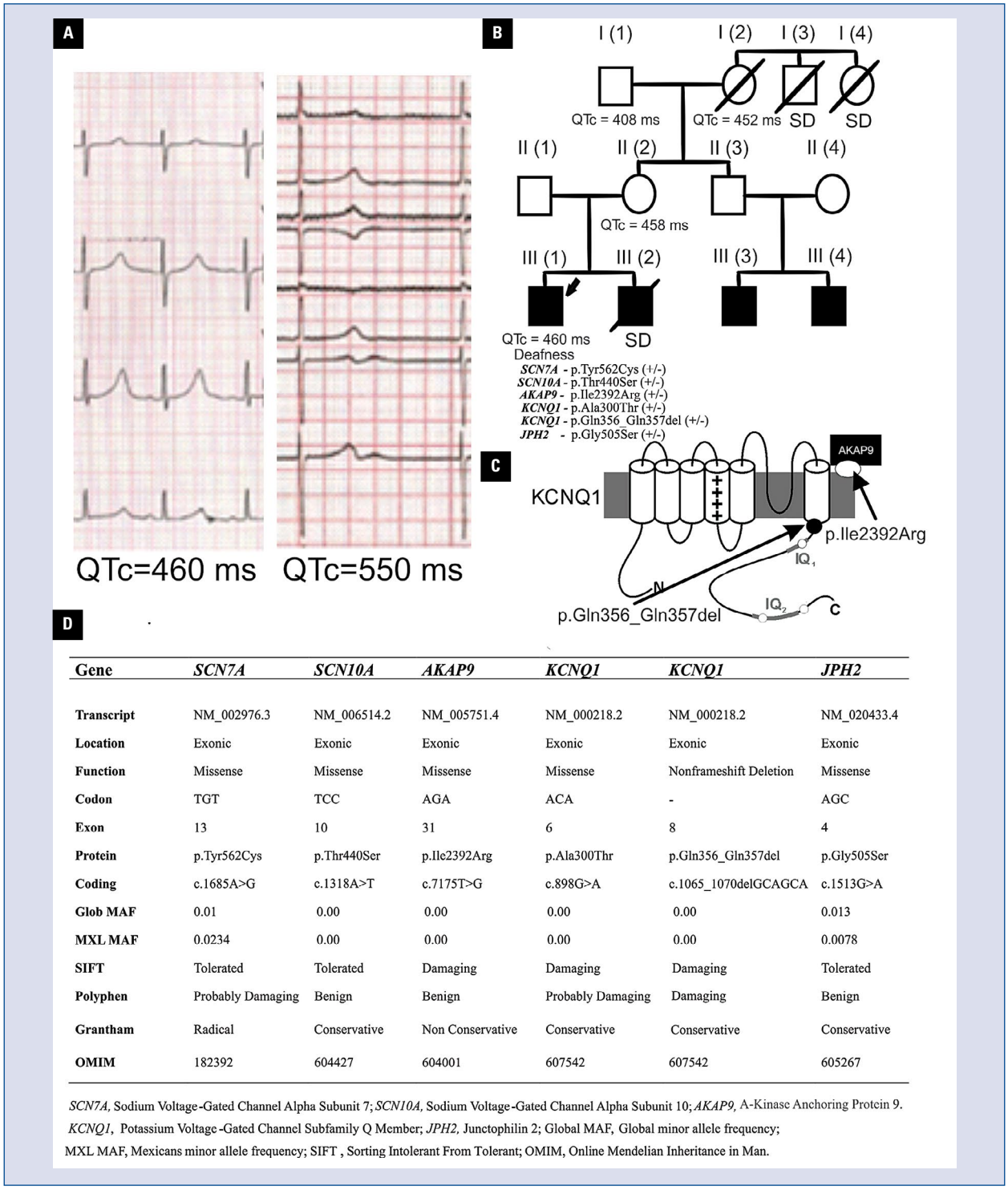

Gene	*SCN7A*	*SCN10A*	*AKAP9*	*KCNQ1*	*KCNQ1*	*JPH2*
Transcript	NM_002976.3	NM_006514.2	NM_005751.4	NM_000218.2	NM_000218.2	NM_020433.4
Location	Exonic	Exonic	Exonic	Exonic	Exonic	Exonic
Function	Missense	Missense	Missense	Missense	Nonframeshift Deletion	Missense
Codon	TGT	TCC	AGA	ACA	-	AGC
Exon	13	10	31	6	8	4
Protein	p.Tyr562Cys	p.Thr440Ser	p.Ile2392Arg	p.Ala300Thr	p.Gln356_Gln357del	p.Gly505Ser
Coding	c.1685A>G	c.1318A>T	c.7175T>G	c.898G>A	c.1065_1070delGCAGCA	c.1513G>A
Glob MAF	0.01	0.00	0.00	0.00	0.00	0.013
MXL MAF	0.0234	0.00	0.00	0.00	0.00	0.0078
SIFT	Tolerated	Tolerated	Damaging	Damaging	Damaging	Tolerated
Polyphen	Probably Damaging	Benign	Benign	Probably Damaging	Damaging	Benign
Grantham	Radical	Conservative	Non Conservative	Conservative	Conservative	Conservative
OMIM	182392	604427	604001	607542	607542	605267

SCN7A, Sodium Voltage-Gated Channel Alpha Subunit 7; *SCN10A,* Sodium Voltage-Gated Channel Alpha Subunit 10; *AKAP9,* A-Kinase Anchoring Protein 9. *KCNQ1,* Potassium Voltage-Gated Channel Subfamily Q Member; *JPH2,* Junctophilin 2; Global MAF, Global minor allele frequency; MXL MAF, Mexicans minor allele frequency; SIFT , Sorting Intolerant From Tolerant; OMIM, Online Mendelian Inheritance in Man.

Figure 1. A. Clinical electrocardiography analysis; **Left.** Electrocardiography during the first syncopal event with QTc of 460 ms by Bazett formula; **Right.** Electrocardiography during the adrenaline test with QTc 550 ms by Bazett formula at the second syncopal event; **B.** Patient's pedigree; I (1). Maternal grandfather; I (2). Maternal grandmother; I (3). Maternal granduncle; I (4). Maternal grandaunt; II (1). Patient's father; II (2). Patient's mother; II (3). Maternal uncle; III (1). Patient; III (2). Patient's brother; III (3). Patient's cousin; III (4). Patient's cousin; SD — sudden death; **C.** Schematic molecular genetics and localization of *KCNQ1* mutation and *AKAP9* novel genetic variant. Long QT syndrome, like severe Jervell and Lange-Nielsen syndrome, is associated with sudden cardiac death syndromes. *KCNQ1* mutation and *AKAP9* variant and proteins location and possible interaction in the C-Terminus in the plasma membrane that maybe expressed in the brain, muscle and heart tissues; **D.** Molecular genetics of novel genetic variants (*AKAP9*; *JPH2*; *SCN10A*; *SCN7A*) and *KCNQ1* mutations using bioinformatics.

expression and function: *ABCC8*, *ABCC9*, *ACTC1*, *ACTN2*, *AGTR1*, *AKAP9*, *ANK2*, *CACNA1C*, *CACNA2D1*, *CACNA2D2*, *CACNB1*, *CACNB2*, *CACNB3*, *CACNB4*, *CACNG4*, *CACNG5*, *CACNG6*, *CALM1*, *CALM2*, *CASQ2*, *CAV1*, *CAV2*, *CAV3*, *DSG2*, *DSP*, *DPP6*, *DPP7*, *DPP8*, *DPP9*, *DPP10*, *FGF12*, *FGF13*, *GATAD1*, *GJA5*, *GLA*, *GPD1L*, *HCN2*, *HCN4*, *HEY2*, *IRX3*, *IRX4*, *IRX5*, *JPH2*, *KCNA4*, *KCNA5*, *KCNN1*, *KCNN2*, *KCNN3*, *KCNK1*, *KCNK2*, *KCNK3*, *KCND3*, *KCNE1*, *KCNE2*, *KCNE3*, *KCNE4*, *KCNE5*, *KCNH2*, *KCNIP2*, *KCNJ2*, *KCNJ8*, *KCNJ9*, *KCNJ10*, *KCNQ1*, *KCNQ2*, *PKP2*, *PRKAG2*, *PXDNL*, *RYR2*, *SCN1A*, *SCN2A*, *SCN3A*, *SCN4A*, *SCN5A*, *SCN7A*, *SCN10A*, *SCN1B*, *SCN2B*, *SCN3B*, *SCN4B*, *SEMA3C*, *SNTA1*, *SUR1A*, *SUR2A*, *TBX5*, *TRPM4*, *TTN*. All genetic variants uncovered were confirmed using the gold standard Sanger sequencing. Polymerase chain reaction (PCR) products were purified with a commercial enzyme (ExoSAP- IT, USB, Cleveland, OH) and directly sequenced from both directions using BigDye Terminator v3.1 chemistry on an Applied Biosystems 3730DNA Analyzer (Life Technologies, Carlsbad, CA).

After signal processing and basecalling, the Ion Torrent Suite software was used to map the sequencing reads to the DNA reference sequence (hg19) and identify variants through the Variant Caller plugin as well as the Ion Reporter analysis tool. Ion Reporter compares all variations identified against NCBI's dbSNP to rule out common SNPs, as well as the 1000 Genomes Project and Exome Sequencing Project to get published frequencies. All variations uncovered were probed in 200–400 healthy ethnically matched controls. Genetic variant under 0.05% minor allele frequency were considered mutations and above 0.05–2.5% rare variants, following American College of Medical Genetics (ACMG) recommendations [4]. All variants were analyzed using several pathogenicity *in silico* prediction tools such as PolyPhen-2, SIFT and Grantham.

Three novel heterozygous exonic were identified, likely benign variants to be associated in this index patient diagnosed with JLNS, *AKAP9*(p.Ile2392Arg); *JPH2*(p.Gly52Ser); *SCN10A*(p.Thr440Ser), and one moderate pathogenic rare variant *SCN7A*(p.Tyr562Cys) [4]. Two mutations in *KCNQ1* were already discovered in the patient (p.Gln356_Gln357del and p.Ala300Thr) [5, 6]. According to available research, this is the first evidence of polygenic variants in a confirmed case of clinically severe JLNS. In this case, polygenic variants may be explained by consanguineous relations among the patient's relatives, consistent with local traditions still prevalent in small populations. Surprisingly, the ECG abnormalities manifested only in the index patient who carried the mutations and genetic variants in five different genes with a very interesting double deletion in *KCNQ1* with a close physical protein–protein interaction with the *AKAP9* gene (Fig. 1C). Based on the clinical and ECGs phenotype associated with LQTS one of the main culprit genes could be the doble mutations in the *KCNQ1* gene and genetic variant in *AKAP9* to induce QT prolongation. It has been described that multiple genes identified could play together a role in the development of the LQTS phenotype at the same time or to be associated with any cardiac arrhythmia syndrome [6].

Genetic variants found in the case reported have been rarely associated with disease in previous reports. The observed variant *JPH2* (p.Gly505Ser) has been related to hypertrophic cardiomyopathy [7], whereas the relationship of the observed variants in *SCN10A* and *SCN7A* genes have not been previously characterized for a JLNS--related phenotype. In another context, almost 30 pathogenic genetic variants of *KCNQ1* gene have been associated with JLNS [8], meanwhile, both deletion and duplication of one or more exons of *KCNQ1* are known to cause LQTS [9]. In the present study the two mutations in *KCNQ1* have been related with LQTS and sudden unexpected death syndromes [5, 6]. *KCNQ1* also has been found to co-interact with *AKAP9* by reducing the IKs channels, and it has been associated with prolongation of the QT interval as a potential marker for long QT type 1-modified effects [10].

Localization of the *KCNQ1* mutations and *AKAP9* genetic variant in the proband are shown in Figure 1D. The hypothesis herein, is based on the possible loss-of-function in the potassium in comparison to WT channels when predicted by *in silico* prediction [11]; however, *in vitro* functional studies may need it to clarify the ionic mechanisms. These potential pathophysiological deficiencies may alter the phenotypic manifestation of LQTS as well as the responsiveness to pharmacological therapies.

In summary, four novel genetic variants were found [*AKAP9*(p.Ile2392Arg); *JPH2*(p.Gly52Ser); *SCN10A*(p.Thr440Ser) and *SCN7A*(p.Tyr562Cys)] and two known mutations in *KCNQ1* in a patient with ventricular arrhythmias with similarities to long QT type 1-modified effects. Moreover, none of these variants has been linked to either LQTS or other sudden cardiac death syndromes.

Conflict of interest: None declared

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A successful transcatheter aortic valve implantation in an extremely tortuous S-shaped aorta due to chest deformation

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A 65-year-old woman was admitted to the hospital for interventional treatment of aortic stenosis. Echocardiography confirmed severe aortic stenosis and a normal left ventricular ejection fraction (60%). Computed tomography demonstrated an extremely tortuous, S-shaped descending aorta and a significant scoliosis with chest wall deformation (Figs. 1A, B). Considering the complex anatomy, the Heart Team qualified the patient for transcatheter aortic valve implantation (TAVI), despite the low peri-operative risk (1.54% in the EuroScore II).

Transcatheter aortic valve implantation was performed in a standard manner, under local anesthesia, from the right femoral artery. Once the Confida Brecker Curve guidewire was placed in the aortic arch, the valve was predilated with 20 mm balloon. A 26 mm Evolut PRO valve (Medtronic Inc., Minneapolis, Minnesota) was slowly advanced into the aorta, which was technically challenging (Fig. 1C, **Suppl. Video 1**). The valve was correctly aligned and deployed under rapid pacing (120/min). Aortogram at the end of the procedure showed no evidence of aortic injury or paravalvular leak (Fig. 1D). Procedural success was confirmed by control transthoracic echocardiography.

The indications for transfemoral TAVI are expanding. The final decision considering the type of procedure should be made by the Heart Team, based on an individual's evaluation. Despite the low risk of mortality following surgery, the patient suffered from the extreme chest wall deformation which made successful sternotomy and latter rehabilitation improbable. Given the flexibility of second generation TAVI delivery systems, it is possible to safely perform the procedure even in a severely tortuous anatomy, which was initially considered a contraindication for TAVI.

Conflict of interest: None declared

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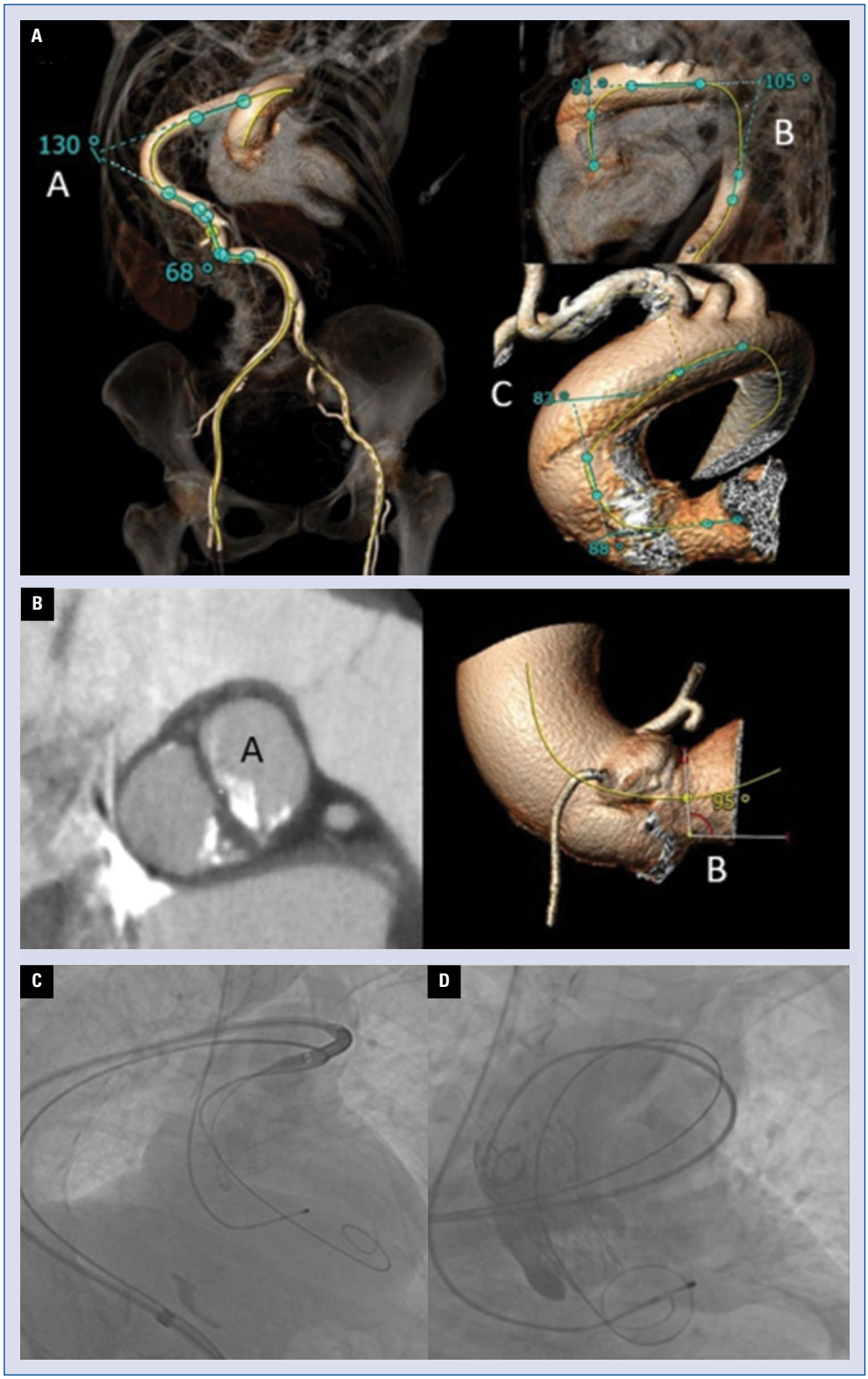

Figure 1. A. Preprocedural multi-slice computer tomography. Three-dimensional reconstruction of access arteries. Severe angulation in descending aorta (A), aortic arch (B) and ascending aorta (C); **B.** Preprocedural multi-slice computer tomography. Bicuspid anatomy type 0 (A), with severely horizontal aorta (B); **C.** Fluoroscopy images demonstrating advancement of a 26 mm Evolut PRO valve (Medtronic Inc., Minneapolis, Minnesota) along the tortuous path of the aorta; **D.** Fluoroscopy image demonstrating the correct position of 26 mm Evolut PRO valve (Medtronic Inc., Minneapolis, Minnesota) with no evidence of aortic injury or paravalvular leak.

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Protamine induced right ventricular dysfunction and systemic hypotension during transcatheter aortic valve replacement

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Presented herein, is the case of a 73-year-old male who underwent an uneventful transcatheter aortic valve replacement (TAVR) for severe non-rheumatic aortic valve stenosis. Protamine was administered intravenously to reverse anticoagulation, followed by large bore sheath removal. Immediately following protamine infusion, the patient developed profound hypotension with a systolic blood pressure of 60 mmHg. Transthoracic echocardiogram was being performed simultaneously to assess the prosthetic aortic valve which revealed a significant dilation of the right ventricle (RV) with reduction in RV systolic function (Fig. 1C, D). Clinical assessment of the patient ruled out arteriotomy site bleeding or valvular dysfunction as the cause of hypotension. Approximately 90 s later, the patient's hemodynamics recovered spontaneously without the use of vasopressors or any further intervention. Repeat echocardiogram revealed RV size and function had returned to baseline which were normal (Fig. 1A, B). While the precise mechanism of protamine induced systemic hypotension has not been determined, vasodilation or protamine induced pulmonary vasoconstriction secondary to an anaphylactic response may occur as a result of histamine release and increased nitric oxide production. This case presents a novel finding of protamine induced hypotension without features of shock observed during a TAVR procedure along with RV dilation that resolved spontaneously. The patient had a repeat echocardiogram at 3-month follow-up which showed normal biventricular size and function, normal pulmonary artery pressures and prosthetic valve function. We recommend that the RV should be adequately monitored during protamine administration and echocardiograms should be recorded before and after protamine administration to assess for sustained RV compromise.

Conflict of interest: None declared

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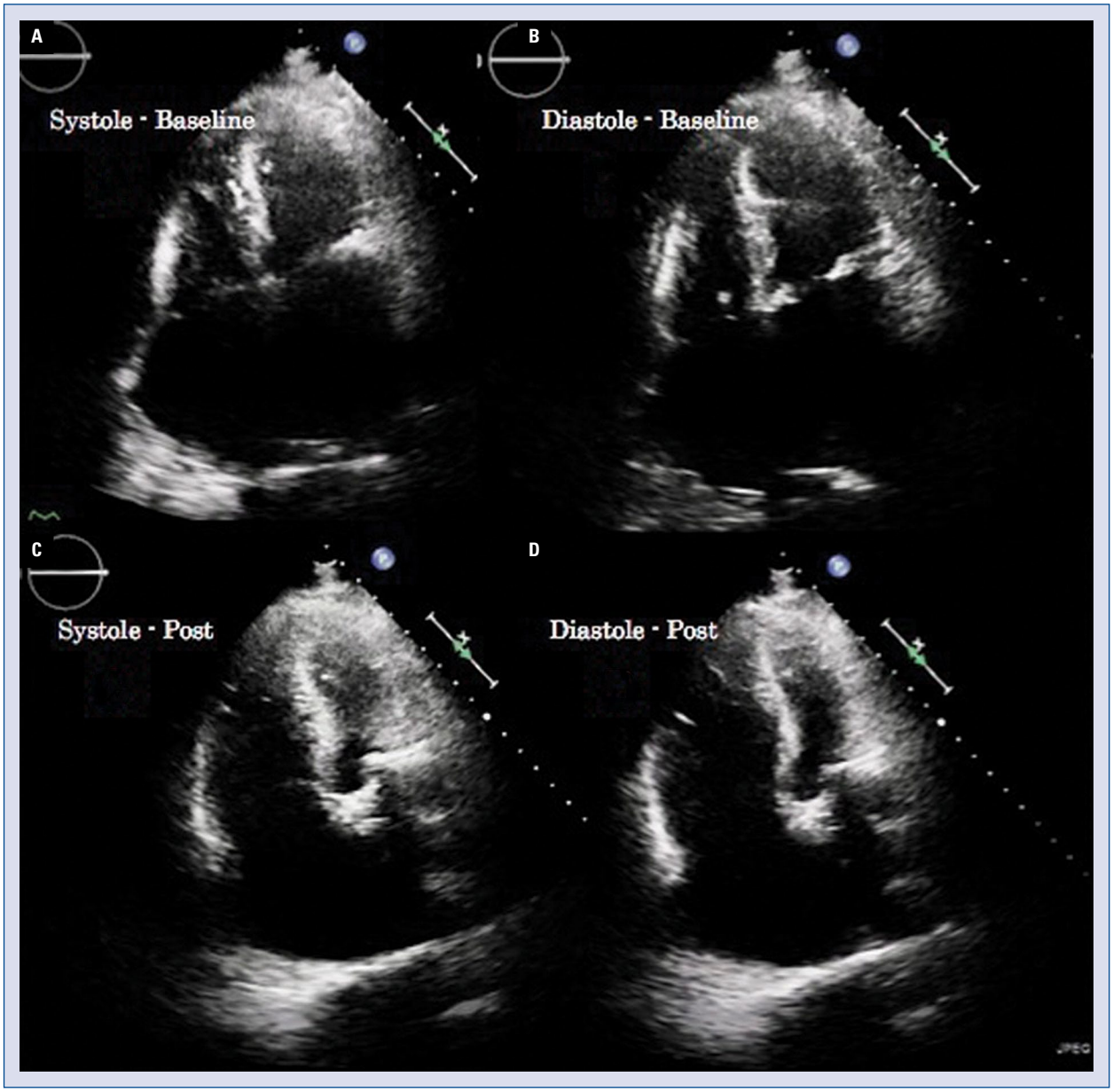

Figure 1. Transthoracic echocardiogram images at baseline (**A**, **B**) and after protamine administration (**C**, **D**). Image shows normal right ventricle (RV) size at baseline (**A**, **B**) and RV dilation after protamine administration (**C**, **D**).

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The effectiveness of drug-coated balloons for two dissimilar calcific lesions assessed by near-infrared spectroscopy intravascular ultrasound and optical coherence tomography

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A 63-year-old woman, who had undergone an everolimus-eluting stent implantation in the middle right coronary artery (mRCA) 3 years ago, was referred to our hospital for chest pain. Coronary angiography revealed 90% stenosis of the proximal right coronary artery (pRCA, Fig. 1A, white arrow) and mRCA (Fig. 1A, white arrowhead). Near-infrared spectroscopy-intravascular ultrasound (NIRS-IVUS) showed a fibro-fatty plaque (thick yellow arrow) with deep calcification (thin yellow arrow) in the pRCA (Fig. 1B, a). A calcified nodule (yellow arrowhead) was found in the mRCA (Fig. 1B, b). Angioplasties with paclitaxel-coated balloons 3.5/15 mm and 3.0/20 mm intra-stent were performed for pRCA and mRCA, respectively. Final angiography showed no significant RCA stenosis (Fig. 1C). However, 6 months later, significant in-stent restenosis was observed (Fig. 1D). Optical coherence tomography (OCT) showed no significant restenosis in the pRCA (Fig. 1E, c). Meanwhile, a calcified nodule protruding intra-stent was detected in the mRCA (Fig. 1E, d, yellow arrowhead). Recent studies have shown that the stent-less strategy using drug-coated balloon (DCB) might be an effective option for calcific lesions in patients with coronary artery disease. Paclitaxel-coated balloon can inhibit the growth of smooth muscle cells, thus inhibiting neointimal proliferation. This case highlighted that DCB treatment was more effective for deep calcification with superficial fibrous plaques than for calcified nodules. NIRS-IVUS and OCT were useful for identifying different types of coronary calcifications and for predicting the effectiveness of DCB treatment.

Conflict of interest: None declared

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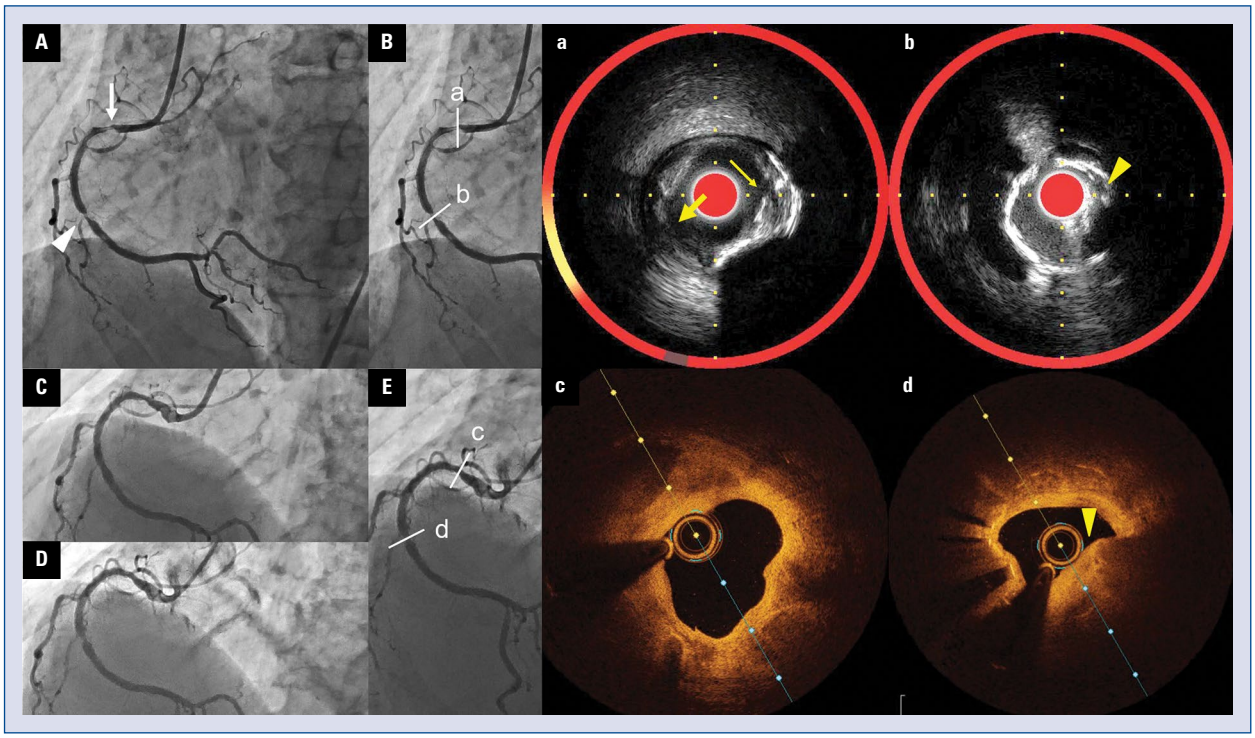

Figure 1. A. The initial coronary angiogram (CAG); **B.** Near-infrared spectroscopy-intravascular ultrasound; **C.** Final CAG; **D.** CAG at 6 month-follow-up; **E.** Optical coherence tomography.

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Large bowel occlusion from fecal impaction: An unusual cause of obstructive cardiogenic shock

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A 69-year-old woman was admitted to the orthopedic department with a femoral shaft fracture requiring osteosynthesis. On the third post-operative day, the patient developed abdominal distension and became progressively tachycardic, hypotensive (76/40 mmHg) and anuric. Upon arrival in the intensive care unit, hyperlactatemia was noticed (4.4 mmol/L). Transthoracic echocardiography revealed an extrinsic compression of the left ventricle at the level of the mid-anterolateral wall with a compromise of preload (Fig. 1A), not responding to fluid resuscitation. Computed tomography showed massive fecal impaction extending from the descending colon to the rectum with significant large bowel distension proximally (Fig. 1C), causing a compression of the left ventricle (Fig. 1D). During emergent exploratory laparotomy, ischemia of the colon with necrosis of the cecum was found. No anatomic anomaly of the left diaphragm was identified. A right-sided damage-control colectomy was performed, the fecaloma was manually evacuated, and the abdomen was temporarily closed with a negative pressure dressing, resulting in complete resolution of the circulatory shock. The intestinal continuity was re-established 2 days later and the patient fully recovered. Post-operative ultrasound showed normal cardiac cavities (Fig. 1B). Common causes of extra-pericardial tamponade are hematomas, tumors, ascites and hernias. This is a rare case of a trans-diaphragmatic cardiac compression without structural anomaly of the diaphragm.

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Figure 1. A. Transthoracic apical four chambers echography: extrinsic compression of the left ventricle; **B.** Transthoracic apical four chambers echography: post-operative normal cardiac cavities; **C.** Computer tomography, anteroposterior scout; **D.** Computer tomography, thoracic axial view: dilated large bowel with compression of the left ventricle.

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LETTER TO THE EDITOR

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Mortality reduction with levosimendan in patients with heart failure: Current evidence is underpowered

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It is with great interest that we read the meta-analysis by Jaguszewski et al. [1] comparing the effects of levosimendan and dobutamine in patients with heart failure (HF). This meta-analysis is relevant and it confirms a possibly preferential role for levosimendan in this population of patients considering the significant reduction in hospital (or 30-day) mortality, as shown by the pooled analysis on the 10 included studies. This finding is not surprising, since this ino-dilator has shown a reduction in mortality for patients with severely reduced left ventricular systolic function and/or low cardiac output syndrome undergoing cardiac surgery. Moreover, levosimendan also reduced the need for renal replacement therapy after high-risk cardiac surgery [2].

However, before drawing firm conclusions on the use of levosimendan in patients with HF, an analysis of the robustness of the findings by Jaguszewski et al. [1] is needed. Therefore, it was thought that the manuscript would greatly benefit from the addition of a trial-sequential analysis (TSA), which would allow calculation of the required sample ("information size"), estimating the power of the meta-analysis on the reduction of mortality by levosimendan, as well as the need for further research.

Hereby, we would like to offer a contribution. We imported the same data provided by the authors in the TSA Software (Copenhagen Trial Unit's TSA Software®; Copenhagen, Denmark). The information size was computed assuming an alpha risk of 5% with a power of 80%. The estimated mortality was computed using weighted averages from the included studies (levosimendan 8.4% vs. dobutamine 12.6%). We used a random effect model with mortality analyzed as odds ratio (OR). Further details on TSA and its interpretation are available elsewhere [3].

The TSA showed that current evidence is severely underpowered to determine whether levosimendan reduces mortality in patients with HF as compared to dobutamine. Indeed, the ratio between number of patients recruited and sample needed (n = 2263/8366; 27%; Fig. 1). Therefore, more research is certainly warranted on mortality in this population of patients.

Another minor (statistical) consideration is on the authors' choice to perform their meta-analysis using a fixed effect model, which assumes that the true effect is the same across studies. However, it is unlikely that all included studies have "identical" true effect, especially when there is statistical heterogeneity (47% in the meta-analysis Jaguszewski et al. [1]). In such cases it is advisable to use a random effect model, which better balances the weights of the included studies [4]. For instance, moving from the fixed to the random effect model, the weight of the largest study (Mebazaa et al. [5]) on the overall results passed from 62% to 28.6%. Nonetheless, our consideration does not change the meta-analysis results since levosimendan still shows significant reductions in mortality also using the random effect model (OR: 0.45; 95% confidence interval: 0.24–0.84; p = 0.01).

In summary, in their meta-analysis Jaguszewski et al. [1] showed benefits of levosimendan over dobutamine for patients with HF with a significant reduction in hospital (or 30-day) mortality. However, current evidence is severely underpowered

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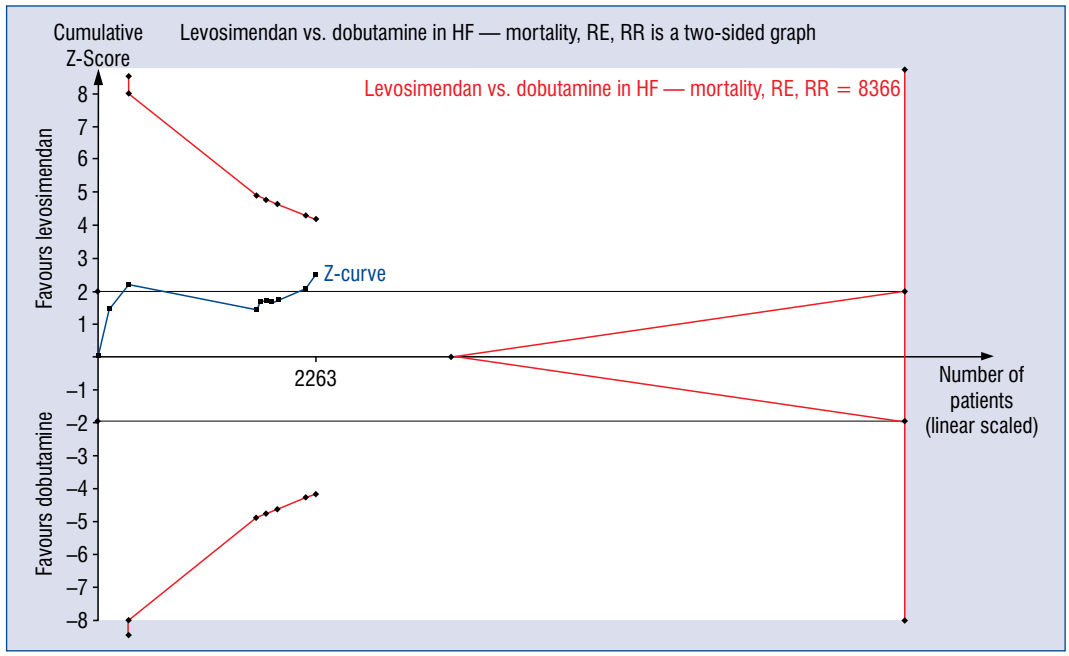

Figure 1. Trial sequential analysis on hospital (30-day) mortality in patients with heart failure (HF), comparing treatment with levosimendan versus dobutamine; RE — random effect; RR — risk reduction.

and further randomized research is required before drawing firm conclusions.

Conflict of interest: None declared

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