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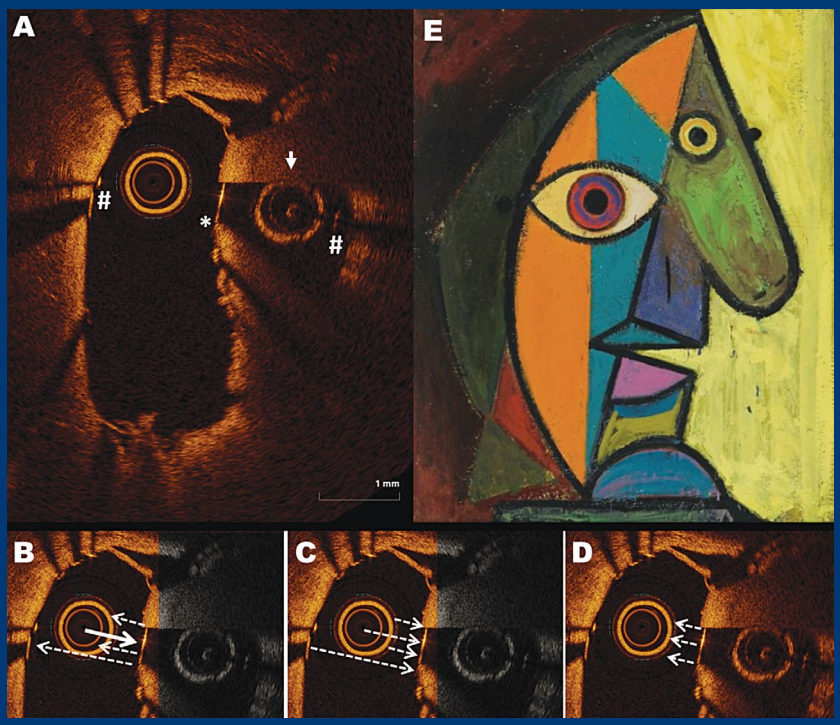

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EDITORIAL

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To drop or not to drop the antiplatelet agent, that is the question for patients with atrial fibrillation and chronic coronary syndrome undergoing percutaneous coronary intervention

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Article p. 8



The prevalence of atrial fibrillation (AF) in patients who undergo percutaneous coronary intervention (PCI) is 5–15%, and optimal antithrombotic therapy should be decided based on a balance between serious bleeding and atherothrombotic complications in these patients [1]. Recently, several randomized multicenter trials have demonstrated that compared with vitamin K antagonist (VKA)-based triple therapy (VKA in combination with a $P2Y_{12}$ inhibitor and acetylsalicylic acid [ASA]), dual therapy with non-vitamin K antagonist oral anticoagulant (NOAC) and a $P2Y_{12}$ inhibitor was associated with a lower incidence of bleeding complications without increasing ischemic risks [2–5]. These trials focused on the first 6–14 months post-PCI and therefore do not inform physicians on the optimal strategy in AF patients with chronic coronary syndromes (CCS), defined as stable state beyond 1 year after PCI. Despite a lack of data regarding the benefits of oral anticoagulant (OAC: either VKA or NOAC) alone, the current guidelines recommend OAC monotherapy in AF patients with underlying CCS and previous PCI [1]. Dual therapy with an OAC and single antipla-telet therapy (SAPT) (ASA or clopidogrel) may be considered only in selected cases with Complex High-Risk Indicated Procedure/ /Patients (CHIP) features such as complex PCI, diabetes, chronic kidney disease, or prior myocardial infarction (MI; class IIb).

Recently, two randomized clinical trials evaluating the optimal antithrombotic strategy in AF patients with CCS have been published [6, 7]. Optimizing Antithrombotic Care in Patients with Atrial Fibrillation and Coronary Stenting (OAC-ALONE) failed to demonstrate non-inferiority of OAC monotherapy to a combined regimen with OAC and SAPT in AF patients with CCS beyond 1 year after coronary stenting, since this trial was underpowered and inconclusive as patient enrollment was prematurely terminated (following recruitment of only 36% of the prespecified sample size) [6]. Another randomized clinical trial, Atrial Fibrillation and Ischemic Events with

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Table 1. Baseline characteristics and clinical outcomes in the OAC-ALONE and AFIRE trials [7, 8].

	OAC-ALONE	AFIRE
OAC monotherapy vs. combined OAC and SAPT	OAC monotherapy (n = 344) vs. combined OAC and SAPT (n = 346)	Rivaroxaban monotherapy (n = 1107) vs. combined rivaroxaban and SAPT (n = 1108)
Study population	Japan	Japan
Follow-up duration	30 months	23 months
Age [year]	74.9 vs. 75.2	74.3 vs. 74.4
Coronary stenting	100% vs. 100%	65.3% vs. 65.1%
Left main coronary stenting	6.7% vs. 6.4%	Not available
Multivessel stenting	34.6% vs. 35.0%	Not available
CHA_2DS_2-VASc score	4.6 vs. 4.6	4.0 vs. 4.0 (median)
HAS-BLED score ≥ 3	43.6% vs. 44.8%	25.6% vs. 26.2%
Combination regimen with ASA	85.9%	70.2%
TTR (INR 2.0–3.0) for VKA	54.9% vs. 47.9%	Not available
Ischemic endpoints (for noninferiority)	15.7% vs.13.6% (HR: 1.16, 95% CI: 0.79–1.72)‡	8.0% vs. 10.9% (HR: 0.72, 95% CI: 0.55–0.95)§
Bleeding endpoints (ISTH major bleeding)	7.8% vs. 10.4% (HR: 0.73, 95% CI: 0.44–1.20)	3.2% vs. 5.2% (HR: 0.59, 95% CI: 0.39–0.89) superiority
Myocardial infarction	2.3% vs. 1.2% (HR: 2.03, 95% CI: 0.64–7.59)	1.2% vs. 0.7% (HR: 1.60, 95% CI: 0.67–3.87)

‡All-cause death, myocardial infarction, stroke, or systemic embolism
§All-cause death, myocardial infarction, stroke, systemic embolism, or unstable angina requiring revascularization
AFIRE — Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease; ASA — acetylsalicylic acid; CI — confidential interval; HR — hazard ratio; INR — international normalized ratio; ISTH — International Society on Thrombosis and Hemostasis; OAC — oral anticoagulant; OAC-ALONE — Optimizing Antithrombotic Care in Patients with Atrial Fibrillation and Coronary Stenting; SAPT — single antiplatelet therapy; TTR — time in therapeutic range; VKA — vitamin K antagonist

Rivaroxaban in Patients with Stable Coronary Artery Disease (AFIRE), evaluated the benefit of rivaroxaban monotherapy in AF patients with CCS who had undergone PCI or coronary artery bypass grafting more than 1 year earlier or who had a history of angiographically confirmed coronary artery disease without revascularization [7]. This trial demonstrated that compared with rivaroxaban plus SAPT combination therapy, the rivaroxaban monotherapy was non-inferior for prevention of ischemic events. In addition, rivaroxaban monotherapy showed a significantly lower rate of major bleeding and extrapolated to clinical practice. However, the results of those trials should be carefully interpreted in some points (Table 1). Firstly, the OAC-ALONE and AFIRE trials were conducted only in Japan. It is acknowledged that East Asian patients treated with anti-thrombotics are more vulnerable to bleeding complications when compared with Caucasians ("East Asian Paradox") [8]. In addition, the occurrence of MI related with AF appeared low in East Asian vs. Caucasian patients. Secondly, patients enrolled in the AFIRE trial received low dose rivaroxaban, approved in Japan based on pharmacokinetic and clinical trials (15 mg or 10 mg once daily) and warfarin was mainly administered in the OAC-ALONE trial, (74.1%). In these studies, the preferred SAPT was ASA (86.4% in OAC-ALONE and 70.2% in AFIRE) whereas clopidogrel is preferred in non-Japanese clinical practice. Therefore, a randomized multi-national trial will be required for patients with AF and CCS in Europe or America. Thirdly, not all patients in the AFIRE study had undergone previous PCI (only two-thirds) and procedural details were not described. Finally, it is important to acknowledge that the incidence of MI during follow-up was numerically higher in the OAC monotherapy groups in both trials (0.93 vs. 0.46 percent/patient-year in OAC-ALONE and 0.59 vs. 0.37 percent/patient-year in AFIRE, respectively).

In this issue of "Cardiology Journal", Franchina et al. [9] report a case review of ST-segment-elevation myocardial infarction (STEMI) in AF patients with CCS beyond 1 year after PCI, in the context of various antithrombotic regimens (OAC monotherapy in 3 cases, discontinuation of OAC due to a planned prostate biopsy in 1 case,

combined OAC and SAPT in 1 case, and no antithrombotic therapy in 1 case). This case review reflects the "real-world" situation and challenges of antithrombotic strategy in daily practice. Despite OAC therapy, STEMI was observed in 4 patients, highlighting the complex and co-morbid nature of this patient population. High risk features included low left ventricular ejection fraction and mechanical valve replacement, and the majority of patients had multiple co-morbidities (hypertension [6 patients], diabetes mellitus [5 patients], dyslipidemia [4 patients], or smoking [current smoker in 3 patients and ex-smoker in 3 patients], respectively).

These anecdotal events and the numerical increase in MI observed with OAC monotherapy in the most contemporary trials provide persisting uncertainty regarding the optimal antithrombotic strategy for AF patients with CCS and previous PCI. Prolongation of combined OAC and SAPT may provide protection against MI but a delicate balance between ischemic and bleeding complications remains. Ideally, a tailored antithrombotic strategy should be determined according to a balanced evaluation of PCI complexity (e.g., CHIP scoring), bleeding risk (e.g. High Bleeding Risk criteria [10]) and a patients' hemostatic measurement (e.g., coagulation activity, platelet activation), which would be the right road to "precision medicine".

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EDITORIAL

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The role of intravascular ultrasound in the treatment of chronic total occlusion with percutaneous coronary intervention

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Article p. 81

Intravascular ultrasound (IVUS) facilitates the interventional treatment of chronic total occlusion (CTO) by percutaneous coronary intervention (PCI) and optimizes primary angiographic results with relevant clinical impact [1, 2]. There are several indications, where IVUS may be useful during CTO-PCI: 1) to define the entry point of an ambiguous proximal cap; 2) to simplify the reverse controlled antegrade-retrograde tracking (rCART) maneuver; 3) for IVUS controlled antegrade reentry techniques; and 4) finally for optimizing the primary result after stent implantation. Focusing on the rCART maneuver, there are four potential scenarios of antegrade and retrograde wire position: 1) antegrade and retrograde wires are in the intraplaque position; or 2) in the subintimal position. In both situations the connection of both wires can mostly be performed with a polymer-jacket lower gram tip-loaded wire after antegrade balloon inflation and facilitated with a mother-in-child catheter. Further possible scenarios are; 3) when the antegrade wire is intraplaque and the retrograde wire is subintimal; or 4) vice versa. Once the antegrade wire has entered the intraplaque position, antegrade balloon angioplasty may be very helpful for reconnection, nevertheless a penetrative higher gram tip-loaded wire is often mandatory. The most complex rCART scenario represents the subintimal position of the antegrade wire, especially after creating antegrade hematoma, and the retrograde wire is intraplaque. In this setting the antegrade dilatation of the subintimal space is often useless, since the external elastic lamina is compressed from the subintimal balloon inflation, followed by an immediate collapse of the subintimal space. This may even cause further enlargement of antegrade hematoma after multiple balloon dilatations, reducing the chance for reconnecting both wires prior to externalization. Therefore, IVUS guidance is specifically recommended after rCART failure to define another level of reconnection for antegrade and retrograde wires during retrograde CTO-PCI.

In this issue of 'Cardiology Journal', Chu et al. [3] evaluated the usage of high definition intravascular ultrasound (HD-IVUS) with a 60 MHz catheter to understand the position of the antegrade and retrograde wire during rCART maneuver. In their particular case the anatomy of the vessel during rCART appeared divided in two halfs reflecting the characteristic 'yin-yang' sign: One half dark due to intraplaque wire position, and the other whitish due to subintimal hematoma. This distinctive IVUS

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sign is easy to remember. It is important to understand that the 'ying-yang' sign may affect rCART failure. Once the antegrade wire (IVUS probe) is in the subintimal (whitish half) and the retrograde wire is in the intraplaque space (dark half), using HD-IVUS revealed another reconnection scenario more proximally to the 'ying-yang' sign.

The clear understanding of IVUS imaging during CTO-PCI is an essential diagnostic tool to decrease complications, while improving both success rates and both short- and long-term PCI results. Implementation of IVUS use should be recommended to all CTO-PCI operators.

Conflict of interest: None declared

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EDITORIAL

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Left ventricular ejection fraction… What else?

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Article p. 97



The main terminology used to describe heart failure (HF) is based on the measurement of the left ventricular ejection fraction (LVEF), and current guidelines divide patients into three subgroups: heart failure with preserved ejection fraction (HFpEF) if LVEF > 50%, heart failure with mid-range ejection fraction (HFmrEF) if LVEF is between 40% and 49% and heart failure with reduced ejection fraction (HFrEF) if LVEF is < 40% [1]. LVEF has been the main selection criteria for most clinical trials during the past three decades, however, improved morbidity and mortality rates have only been shown in patients with HFrEF.

On the contrary, despite a long history of clinical trials on HFpEF, there has been no proof of any single drug which improves survival rates in this subset of patients. There is a common understanding that this lack of success could be linked to the fact that HFpEF is comprised of a wide variety of unrelated pathologies.

In this issue of 'Cardiology Journal', Junbo Ge proposes a new classification for HFpEF into five categories based on their etiology and pathophysiology: 1) vascular related HFpEF, 2) cardiomyopathy-related HFpEF, 3) right-heart and pulmonary-related HFpEF, 4) valvular and rhythm related HFpEF, and 5) extracardiac-disease related HFpEF [2]. This new categorization could potentially allow more targeted clinical trials, and hopefully achieve some benefit in certain subgroups.

However, the main problem may not be HFpEF itself, but by the way HF is diagnosed and classified. The concept of LVEF, which is defined by dividing the stroke volume by the end-diastolic volume, was developed in the 1960s [3], and has become a cornerstone in cardiology since then. Nonetheless, HF patients, disease phenotypes and technology have evolved significantly since then, and nowadays the information provided by the LVEF is inadequate or insufficient in many situations.

There are various setbacks to two-dimensional echocardiography measured LVEF [4]. First and foremost, there is a 10% of interobserver variability [5], which may lead to the same patient falling into different categories depending on the echocardiographer who reads the study, and it varies depending on the imaging method used and on the cut-planes. Secondly, it is widely influenced by geometry, which is particularly important in ischemic cardiomyopathy, and by ventricular loading, especially afterload. Moreover, it does not take into account the complexity of myocardial mechanics or the speed of contraction, and its assessment in patients with mechanical dyssynchrony, which

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is still under debate. Last, but not least, ejection fraction (EF) has proven prognostic significance in patients with EF < 40%, but in patients with EF > 40% there is no correlation between higher EF and better outcomes [6].

Taking into account the abovementioned statements, certain doubts arise regarding the suitability of LVEF as the best method to classify HF patients. What if LVEF were too simple a classification for such a complex disease?

Changing the current classification would probably shake the foundations of HF as we know it today, since most clinical trials that have shown benefit were based on this concept. However, having said this, there is clearly room for improvement.

Left ventricular mechanics (as measured by two-dimensional speckle-tracking echocardiography), three-dimensional echocardiography or cardiac magnetic resonance (CMR) all allow for an improved assessment of myocardial function. Global longitudinal strain has been shown to correlate with prognosis in all patients with HF, regardless their LVEF, and provides the greatest incremental information when the LVEF is relatively preserved and regional wall motion scores are normal [7]. On the other hand, CMR plays an important role in the diagnosis of many HFpEF pathologies, such as hypertrophic cardiomyopathy or cardiac amyloidosis, and its role on prognosis in many others has already been stablished [8].

On top of that, CMR is the most reliable method to identify inflammation, which is the main histopathological substrate of many different causes of HFpEF. Sustained inflammation leads to interstitial fibrosis and myocardial hypertrophy, that cause impaired left ventricular relaxation and coronary microvascular dysfunction [9].

The point of view herein, is that it is not only necessary to identify the etiology of HF, as Junbo Ge [2] proposes in his article, but also to create new diagnostic and prognostic scores that include all the aforementioned tools, allowing a better classification of HF patients. It is highly probable that treatments based on integrating all this information will provide better clinical results than those based solely on LVEF. Recent drugs that have failed to prove benefit in HFpEF may have a role in a subset of patients with reduced left ventricular mechanics or active inflammation.

In conclusion, it seems that the actual concept of LVEF is set in stone, but perhaps it is time to think out of the box and rewrite the basics of heart failure.

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Mechanisms of ST-segment elevation myocardial infarction in patients with atrial fibrillation, prior stenting and long-standing chronic coronary syndrome

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Abstract

Background: *The optimal antithrombotic regimen for patients with atrial fibrillation (AF) and chronic coronary syndromes beyond 1 year after percutaneous coronary intervention (PCI) is a matter of debate. For these patients, guidelines recommend oral anticoagulation (OAC) alone, but the risk of thrombotic complications remains a concern. The aim of this study was to characterize the incidence, presentation and use of antithrombotic therapy in patients with AF, prior stenting > 12 months and new ST-segment elevation myocardial infarction (STEMI).*

Methods: *Consecutive patients were selected from an institutional registry over a 3-year period if they matched the following criteria: 1) STEMI undergoing primary PCI; 2) AF; 3) chronic coronary syndrome with prior stenting > 12 months.*

Results: *Among 852 consecutive STEMI patients undergoing primary PCI, the prevalence of AF was 4.1%, and 6 (0.9%) patients met all the inclusion criteria. Substantial heterogeneity in antithrombotic treatment for these patients was noted (e.g., OAC alone, OAC plus a single antiplatelet agent, no antithrombotic therapy). In 50% of patients, the STEMI episode was linked to a previously stented lesion or documented plaque.*

Conclusions: *This case review illustrates the wide heterogeneity in antithrombotic pharmacotherapy among AF patients presenting with STEMI > 12 months after PCI. The underlying reason for STEMI is only partly related to disease progression or stent-related events. This finding suggests that multiple mechanisms of recurrence may be advocated, and are not only limited to antithrombotic therapy but may be explained by the natural history of coronary artery disease in remote vessels.* (Cardiol J 2020; 27, 1: 8–15)

Key words: atrial fibrillation, oral anticoagulation, percutaneous coronary intervention, chronic coronary syndromes, antithrombotic therapy, dual antiplatelet therapy, ST-segment elevation myocardial infarction

Editorial p. 1

Introduction

Based on current guidelines and recent evidence from randomized trials and meta-analyses, patients with atrial fibrillation (AF) and chronic coronary syndromes (CCS) undergoing percutaneous coronary intervention (PCI) should receive oral anticoagulation (OAC) lifelong (preferably with a non-vitamin K antagonist oral anticoagulant), a $P2Y_{12}$ inhibitor for 12 months (generally clopidogrel), and a variable term of acetylsalicylic acid

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(ASA; from a few days to 6 months) depending on the individual balance of bleeding and thrombotic risks [1, 2].

According to recent European guidelines, a patient who is event-free for 12 months after PCI was performed, regardless of the initial clinical context for revascularization (e.g., elective or acute coronary syndrome) is described as having a long standing CCS [1]. When these patients have AF, it is broadly accepted that OAC should be continued alone, without concomitant antiplatelet therapy [1, 3, 4]. The AFIRE trial recently showed that adding ASA to OAC monotherapy exposes patients to an unacceptable and possibly life-threatening increased risk of bleeding [5]. However, some physicians are afraid that routinely stopping any antiplatelet therapy would expose some patients to the risk of catastrophic consequences that outweigh the risk of bleeding, e.g., those with prior PCI of the left main or the proximal left anterior descending artery (LAD). Current guidelines for CCS, published before the AFIRE trial, allow for the combination of an antiplatelet with OAC in selected circumstances [1].

When patients with AF, prior PCI and long-standing CCS present with ST-segment elevation myocardial infarction (STEMI), the question arises on the mechanisms for the new event, which may include very late stent thrombosis, progression of coronary artery disease (CAD), and lack of adequate antithrombotic protection. According to available research, there are no studies characterizing the angiographic presentation and use of antithrombotic therapy before and at the time of STEMI in patients with AF, prior PCI or long-standing CCS. A better understanding of these correlations is meaningful to inform the rationale for future studies of dual antithrombotic therapy at 12 months or longer from PCI.

Given this background, it is herein reported a review of STEMI cases with the following objectives: 1) defining the frequency of STEMI as the consequence of stent thrombosis or CAD progression by matching the angiographic presentation before and at the time of the STEMI episode; 2) identifying potential causes of pharmacological failure and areas for improvement by describing the antithrombotic regimen before, (time 0 [T0]) and at the time of STEMI presentation (time 1 [T1]).

Methods

A total of 852 consecutive STEMI patients undergoing primary PCI between December 2015 and January 2019 were retrospectively analyzed from the documented institutional registry. The screening flow chart is reported in Figure 1. Patients were included if they presented with AF and if a prior PCI with implantation of at least a coronary stent was performed at least 12 months before STEMI presentation. A total of 166 (19%) patients were excluded because no complete information was available on AF status, antithrombotic regimen or prior PCI. Of the remaining subset, 28 (4.1%) patients presented with AF at the time of STEMI. Of these, 6 (21.4%) patients presented with a prior PCI performed at least 12 months earlier (i.e., 0.9% of the analyzable STEMI cohort). For these cases, clinical charts, angiographic outcomes and antithrombotic therapy at the time of the prior PCI (T0) and at the time of STEMI (T1) were reviewed in detail. Case summaries of the 6 patients included are provided below. Basic descriptive statistics for baseline characteristics and outcomes of interest (very late stent thrombosis, CAD progression, withdrawal of antithrombotic therapy) were cal-

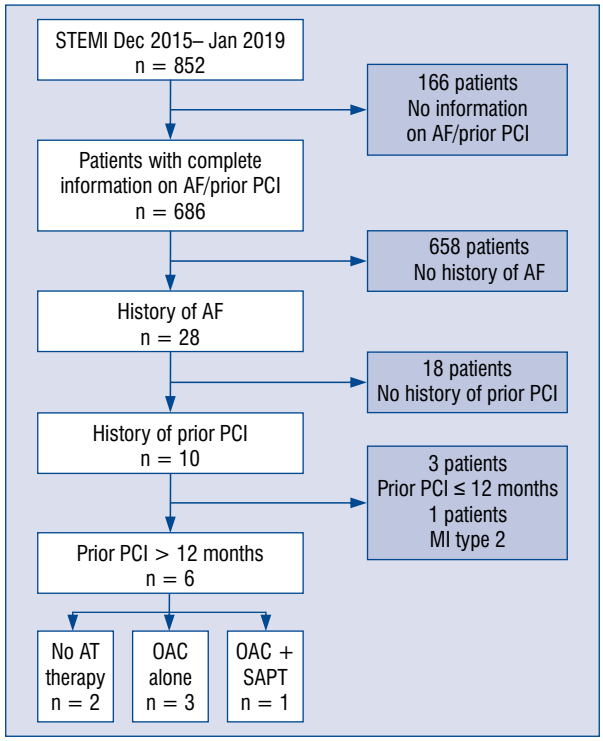

Figure 1. Flow diagram of patients selected according to pre-specified inclusion and exclusion criteria; AF — atrial fibrillation; AT — antithrombotic; MI — myocardial infarction; OAC — oral anticoagulation; PCI — percutaneous coronary intervention; SAPT — single antiplatelet therapy; STEMI — ST-segment elevation myocardial infarction.

Table 1. Baseline clinical characteristics at the time of ST-segment elevation myocardial infarction presentation.

	Case no. 1	Case no. 2	Case no. 3	Case no. 4	Case no. 5	Case no. 6
Age [years]	78	61	62	56	71	69
Gender	Male	Male	Male	Male	Male	Male
BMI	NA	30.1	33	27.1	25	37.2
Cardiovascular risk factors:						
Hypertension	Yes	Yes	Yes	Yes	Yes	Yes
Diabetes	No	Yes	Yes	Yes	Yes	Yes
Dyslipidemia	Yes	Yes	No	Yes	Yes	No
Current smoker	Yes	Yes	Yes	No	No	No
Former smoker	No	No	No	Yes	Yes	Yes
Clinical history:						
Prior stroke	No	No	No	Yes	No	No
PAD	No	Yes	No	No	No	No
CKD	No	No	No	Yes	No	No
Prior PCI	Yes	Yes	Yes	Yes	Yes	Yes
Prior CABG	No	No	No	Yes	No	No
Prior MVR	No	Yes	No	Yes	No	Yes
Other valvular disease	No	No	No	No	No	No
Pattern of AF	Paroxysmal	Paroxysmal	Permanent	Permanent	Permanent	Permanent
AF at presentation	No	No	Yes	Yes	Yes	Yes
LVEF [%]	45	43	42	NA	28	37

AF — atrial fibrillation; BMI — body mass index; CABG — coronary artery bypass grafting; CKD — chronic kidney disease (defined as glomerular filtration rate < 60 mL/min); LVEF — left ventricular ejection fraction; MVR — mechanical valve replacement; NA — not available; PAD — peripheral artery disease; PCI — percutaneous coronary intervention

culated with the Statistical Package for Social Sciences (SPSS) v. 24.0 (IBM Corporation, NY, USA). Results are reported as count and percentage for binary variables and mean ± standard deviation or median (interquartile range) for continuous variables, as appropriate based on normality distribution according to the Kolmogorov-Smirnov test.

Results

Baseline characteristics of patients included in this case series as determined at T1 are listed in Table 1. All patients were male, the mean age was 66 ± 8 years, the mean CHA_2DS_2-VASc score was 4.0 ± 0.9, and the mean HAS-BLED score was 0.8 ± ± 0.8. All patients had a reduced left ventricular ejection fraction, and 5 out of 6 (83%) presented with diabetes mellitus and a history of a prior acute coronary syndrome. Summarized in Tables 2 and 3 are the procedural details of PCI at T0 and T1, respectively. The mean time from the prior PCI to STEMI presentation (i.e., T1–T0) was 6.5 ± 4.8 years. Table 4 summarizes antithrombotic therapy at T1 (admission and discharge). Two patients out of 6 (33.3%) were not on OAC despite their CHA_2DS_2-VASc score and current, relevant guideline recommendations.

Overall, very late stent thrombosis occurred in 2 out of 6 patients (33.3%). In another patient (16.7%), progression of a documented untreated plaque was the likely mechanism of STEMI at play. Recent withdrawal of antithrombotic therapy was documented in 2 (33.3%) patients. One (16.7%) patient had very late stent thrombosis in the context of recent withdrawal of antithrombotic therapy. Case summaries for all 6 patients are reported below.

Case no. 1. A 78-year-old man with paroxysmal AF underwent stent implantation of a ramus in 2003 due to unstable angina (T0). The other vessels were free of disease with the exception of the mid-proximal right coronary artery (RCA), which presented with a 50% stenosis left untreated. In 2006 and 2010 he underwent angiographic follow-up that showed the relative patency of the stent, with subcritical narrowing (< 50%) due to

Table 2. Procedural details of last percutaneous coronary intervention before current ST-segment elevation myocardial infarction (STEMI) presentation.

	Case no. 1	Case no. 2	Case no. 3	Case no. 4	Case no. 5	Case no. 6
Time from last PCI to T1* [years]	14	2	7	3	3	10
Clinical presentation	ACS	ACS	ACS	Stable CAD	ACS	ACS
Stented vessel	Ramus	Mid LAD	OM	Prox RCA	Mid LAD	Diagonal
Number of implanted stents	NA	NA	NA	1	1	1
Other lesions ≥ 50% in remote vessels	50% mid RCA	No	No	No	No	No
Time from last coronary angiography to T1* [years]	7	2	5	2	1	9
Lesions ≥ 50% at follow-up	50% ISR ramus; 50% mid RCA	–	NA	–	50% OM	–

*T1 refers to the time of primary PCI for STEMI. ACS — acute coronary syndrome; CAD — coronary artery disease; ISR — in-stent restenosis; LAD — left anterior descending; NA — not available; OM — obtuse marginal; PCI — percutaneous coronary intervention; RCA — right coronary artery

Table 3. Procedural details of primary percutaneous coronary intervention (PCI) at the time of ST-segment elevation myocardial infarction presentation.

	Case no. 1	Case no. 2	Case no. 3	Case no. 4	Case no. 5	Case no. 6
Date	April 2017	November 2017	November 2018	September 2017	January 2019	March 2018
Culprit lesion	Mid-prox RCA	Diagonal	LMCA	Mid LAD	Prox RCA	Diagonal
Stent thrombosis	No	Yes	No	No	No	Yes
Other lesions ≥ 50% in remote vessels	50% ISR ramus	100% LCx	100% mid LAD	100% LIMA--LAD; 70% mid RCA	100% PL 50% OM	100% LAD; 100% diagonal
PCI procedure	3 BMS on the RCA	1 DES on the diagonal	1 DES on the LMCA	1 DES on the LAD; 1 DES on the mid RCA	POBA on the prox RCA; 1 DES on the PL	1 DES on the prox LAD; POBA on the diagonal
$P2Y_{12}$-inhibitors loading dose	ticagrelor 180 mg	clopidogrel 600 mg	clopidogrel 600 mg	ticagrelor 180 mg	clopidogrel 600 mg	ticagrelor 180 mg
i.v. antithrombotic drugs administered before or during the procedure	UFH; abciximab	UFH	UFH	UFH	UFH	UFH

BMS — bare metal stent; DES — drug eluting stent; ISR — in-stent restenosis; iv, intravenous; LAD — left anterior descending; LCx — left circumflex; LIMA — left internal mammary artery; LMCA — left main coronary artery; OM — obtuse marginal; PCI — percutaneous coronary intervention; PL — posterolateral; POBA — plain old balloon angioplasty; RCA — right coronary artery; UFH — unfractionated heparin

in-stent neointimal proliferation and no disease progression at the level of the RCA and the LAD. In 2017 (T1), he qualified for primary PCI due to an inferior STEMI. At entry, the patient was not taking any antithrombotic drug, including OAC. He mentioned a deliberate discontinuation of ASA approximately 2 weeks earlier. Coronary angiography showed evidence of a large thrombus at the level of the occluded mid-proximal RCA. He underwent primary PCI with implantation of 3 meshed bare metal stents. The stent of the ramus presented with the same degree of narrowing already shown in 2010, and the LAD presented with a new 40% stenosis of the proximal segment. The patient, presenting with a CHA_2DS_2-VASc score of 4 and a HAS-BLED score of 1 at T1, was discharged on dual antiplatelet therapy (DAPT) with ASA 100 mg/die and ticagrelor 90 mg bid.

Case no. 2. A 61-year-old man with paroxysmal AF and prior aortic valve replacement with

Table 4. Antithrombotic (AT) therapy and ischemic/hemorrhagic risk (T1).

	Case no. 1	Case no. 2	Case no. 3	Case no. 4	Case no. 5	Case no. 6
AT therapy at admission	No AT therapy	No AT therapy	OAC alone	OAC alone	OAC plus SAPT	OAC alone
Specific AT therapy	–	–	dabigatran 110 mg bid	warfarin 5 mg	dabigatran 110 mg bid; ASA 75 mg/die	warfarin 5 mg
CHA_2DS_2-VASc score at entry	4	3	3	5	5	4
HAS-BLED score at entry	1	0	0	1	2	1
AT therapy prescribed at discharge	DAPT (ASA and ticagrelor)	DAPT (ASA and clopidogrel) plus acenocumarol 4 mg	DAPT (ASA and clopidogrel) plus dabigatran 110 mg bid	NA (patient transferred to another ICU)	DAPT (ASA and clopidogrel) plus dabigatran 110 mg bid	DAPT (ASA and clopidogrel) plus warfarin 5 mg

ASA — acetylsalicylic acid (i.e. aspirin); DAPT — dual anti-platelet therapy; ICU — intensive care unit; OAC — oral anticoagulant; SAPT — single antiplatelet therapy

a mechanical prosthesis in 2005, underwent PCI and drug-eluting stent (DES) implantation of the mid LAD in 2015 due to unstable angina (T0). The other vessels were free of disease. In 2017, he qualified for primary PCI due to an anterior STEMI (T1). At entry, the patient was not on antithrombotic drugs due to discontinuation of OAC 3 days earlier due to a planned prostate biopsy. The coronary angiography showed a thrombotic stenosis of the ostium of the second diagonal, at the level of the LAD stent. The patient underwent primary PCI of the diagonal with implantation of a DES at the bifurcation level. The patient, presenting with a CHA_2DS_2-VASc score of 3 and a HAS-BLED score of 0 at T1, was discharged on DAPT (ASA 100 mg/die and clopidogrel 75 mg/die) plus OAC.

Case no. 3. A 62-year-old man with permanent AF underwent PCI with DES implantation of the first obtuse marginal in 2011 due to an inferior STEMI (T0). The LAD presented a chronic total occlusion in the mid portion. In 2018, he qualified for primary PCI due to a new anterior STEMI (T1). At entry, the patient was on OAC with dabigatran 110 mg bid. Coronary angiography showed a complicated atherosclerotic plaque of the left main, with signs of rupture and dissection. Primary PCI of the left main with implantation of a DES was performed. The LAD was chronically occluded and the left circumflex artery presented two new intermediate stenoses at the proximal and distal segments, whereas the stent in the first obtuse marginal was patent. The patient, presenting with a CHA_2DS_2-VASc score of 3 and a HAS-BLED score of 0 at the time of STEMI, was discharged on DAPT (ASA 100 mg/die and clopidogrel 75 mg/die) plus dabigatran 110 mg bid.

Case no. 4. A 56-year-old man with permanent AF and a history of ischemic stroke, underwent elective stent implantation of the RCA in 2014 (T0), 1 month after mitral and aortic valve replacement with mechanical prostheses and concomitant bypass of the LAD with the left internal mammary artery. In 2017 (T1), he qualified for primary PCI because of an anterior STEMI complicated by defibrillated ventricular tachycardia. At entry, the patient was on OAC only. The coronary angiography showed a subocclusive stenosis of the mid LAD with occluded left internal mammary artery and a critical stenosis of the mid RCA. The patient underwent primary PCI with implantation of a DES on the mid segment of the LAD and another DES in the mid segment of the RCA during the same procedure. After the intervention, the patient was brought back to the intensive care unit of another hospital, where he died a few days later for unknown reasons. His CHA_2DS_2-VASc and HAS-BLED scores at T1 were 5 and 1, respectively.

Case no. 5. A 71-year-old man with permanent AF underwent DES implantation of the mid segment of the LAD in 2016 due to a non-STEMI (T0). The patient underwent a follow-up coronary angiography in December 2018, which showed mild in-stent restenosis (< 50%) of the LAD and a new 50–70% stenosis of the obtuse marginal, whereas the RCA was free of disease. In January 2019 (T1), he presented with an inferior STEMI.

At entry the patient was on antithrombotic therapy with ASA plus OAC (dabigatran 110 mg bid). The coronary angiography showed evidence of a thrombotic occlusion of the proximal RCA. Primary PCI was performed with plain old balloon angioplasty of the proximal RCA segment and implantation of 1 DES at the level of the posterolateral branch. The patient, presenting with a CHA_2DS_2-VASc score of 5 and an HAS-BLED score of 2 at T1, was discharged on DAPT (ASA 100 mg/die, clopidogrel 75 mg/die) plus OAC with dabigatran 110 mg bid.

Case no. 6. A 69-year-old man with permanent AF underwent DES implantation of the first diagonal in 2008 (T0). In 2009 he underwent aortic valve replacement with a mechanical prosthesis. In 2018, he presented with an anterior STEMI (T1). At entry, the patient was on OAC with warfarin. Coronary angiography showed an occlusion of the first diagonal and the proximal segment of the LAD due to a relevant thrombus. Primary PCI was performed with the implantation of 1 DES on the proximal segment of the LAD and plain old balloon angioplasty of the diagonal. The patient, presenting with a CHA_2DS_2-VASc score of 4 and an HAS-BLED score of 1 at the time of STEMI, was discharged on DAPT (ASA 100 mg/die and clopidogrel 75 mg/die) plus OAC.

Discussion

Among patients with established CAD, the prevalence of concurrent AF is estimated at 6–8% [6, 7]. Yet, AF is more frequently encountered in the setting of STEMI, encompassing approximately 14% of patients [8], and a review from Gorenek et al. [9] reported that in about 2.5–4.4% of STEMI patients the arrhythmia existed prior to hospital admission. This is consistent with the present findings. In fact, among 852 STEMI patients screened for the purpose of the current study, 4.1% had history of AF. Of the 10 patients with AF and a history of prior PCI, 6 (60%) had a long-standing CCS according to 2019 guidelines of the European Society of Cardiology [1].

For AF patients such as those included in this case series, current European guidelines recommend chronic OAC alone [1]. This recommendation is supported by registry data [10–12], and has been recently reinforced by the results of two randomized trials [5, 13]. In the OAC-ALONE trial, the efficacy and safety of OAC monotherapy compared with dual antithrombotic therapy with OAC and an antiplatelet was investigated in patients with AF and long-standing CCS (i.e., beyond 1 year after coronary stenting) [13]. The trial failed to establish non-inferiority of OAC alone likely due to low power because patient enrollment was prematurely terminated due to slow recruitment. In the AFIRE trial, rivaroxaban monotherapy was non-inferior to combination therapy with ASA for efficacy and was superior for safety in a similar, larger population [5]. The trial was discontinued early because of increased mortality in the combination-therapy group. While the superior safety of using one rather than two antithrombotic agents is obvious, the efficacy of such an approach in preventing coronary events is less established. Indeed, good-quality OAC in patients with AF is associated with lower risk of myocardial infarction, which makes concomitant use of antiplatelet agents of uncertain added utility [14, 15]. However, a systematic review of 21 observational studies and 10 clinical trials suggests that AF patients with CCS have a substantial annual residual risk of myocardial infarction despite OAC [16].

After 12 months from PCI, antiplatelet agents are still used by some physicians in combination with OAC, due to concerns of residual thrombotic risk [17, 18]. Current guidelines endorse this practice with a class IIb recommendation [1]. Conversely, there is also a proportion of patients with AF who do not receive adequate prevention for thromboembolism in daily practice, as also reinforced by the observation that at least 15% to 30% of AF patients are treated with ASA only, or do not receive any antithrombotic treatment [19, 20]. As a matter of fact, substantial heterogeneity has been reported in antithrombotic treatment regimens for AF patients with long-standing CCS and prior PCI [17]. This uncertainty is also reflected in the current series: 3 patients (case no. 3, case no. 4 and case no. 6) were on OAC therapy alone (yet, 2 had a mechanical prosthesis); 1 patient (case no. 5) was on OAC plus a single antiplatelet agent; 2 patients (case no. 1 and case no. 2) were on no antithrombotic therapy. Despite these differences, all patients presented with STEMI, suggesting the existence of other explanations that go beyond lack of optimal antithrombotic protection. Indeed, in case no. 1, STEMI developed on a plaque previously left untreated in a patient with no antithrombotic therapy on board and recent ASA disruption. In case no. 2, the patient presented with stent thrombosis, was not on antithrombotic therapy and had recently interrupted OAC. In these two cases, withdrawal of antithrombotic protection cannot be excluded. In contrast, in case no. 6, the patient was on OAC with warfarin (with uncertain time in

the therapeutic range) and thrombosis occurred 10 years after stent implantation with no apparent explanation. Whether the addition of an antiplatelet agent would have prevented this very late event is speculative at best. In aggregate, only 2 (33.3%) cases were related to prior PCI (i.e., very late stent thrombosis) and only 1 (16.7%) case was related to a previously-described untreated lesion. In all other cases there was an inability to correlate the occurrence of STEMI with any previously documented angiographic substrate and other causes can be inferred, such as plaque rupture in segments previously free from disease and/or inadequate control of cardiovascular risk factors (e.g., 83% of patients were diabetics).

The results of this case review are exploratory and should be carefully interpreted with a note of caution in the context of the following limitations. Firstly, the small sample size prevented drawing robust conclusions on the issue of antithrombotic therapy for AF patients with long-standing CCS and prior stenting. Indeed, this is an area of uncertainty where larger studies are lacking. Secondly, 166 patients out of 852 (i.e., almost 20% of the STEMI patients in the documented database) were excluded upfront due to incomplete information. As such, the chance of selection bias cannot completely be ruled out.

Conclusions

Among patients presenting with STEMI, a history of AF and prior PCI > 12 months is infrequent. Although these patients were theoretically candidates for OAC alone prior to the STEMI episode, substantial heterogeneity in antithrombotic regimens at entry was observed in real practice. Stent thrombosis or CAD progression explained only half of the STEMI episodes and a clear association with lack of antithrombotic therapy protection could not be inferred. Larger studies are needed to define optimal strategies for STEMI prevention in AF patients with prior stenting and long-standing CCS.

Conflict of interest: None declared

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Epidemiology and chronobiology of out-of-hospital cardiac arrest in a subpopulation of southern Poland: A two-year observation

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Abstract

Background: *Although recent studies indicate temporal variations in the incidence of out-of-hospital cardiac arrest (OHCA), the Polish experience in this research is scarce to date. We evaluated the epidemiology of OHCA and circadian, weekly and seasonal variations of OHCA frequency among the adult population of the Opole district, Poland.*

Methods: *The retrospective analysis of 815 OHCA cases with presumed cardiac etiology was made based on dispatch cards from the Emergency Medical Center in Opole registered during a 2 year period (2006–2007).*

Results: *The incidence of OHCA in the studied population was 1.56/1000 inhabitants per year. Mean age of the group was 69.2 ± 14.2 years, with the majority of men (63%), younger than women (66.1 vs. 74 years, $p = 0.0001$). The OHCA occurrence increased with age reaching a peak between 71 and 75 years. The incidence of OHCA stayed at stable low levels between 22:00 and 4:59 and started to increase at 5:00, with trimodal peaks: 8:00–10:59, 14:00–15:59 and 18.00–21.59. The lowest number of OHCA occurred from 00:00 to 5:59, the highest from 6:00 to 11:59 (13% vs. 32.4%, $p < 0.001$). The day with the lowest occurrence of OHCA was Friday, the highest Saturday (10.9% vs. 16%, $p = 0.01$). Summer was the season of the lowest incidence of OHCA, while winter — the highest (22.6% vs. 26%, $p = 0.04$). These seasons were the warmest and the coldest one, respectively (average temperature 18.5°C vs. 0°C, $p < 0.001$).*

Conclusions: *Circadian and less marked, weekly variability in OHCA occurrence were confirmed. Existing seasonal differences may be affected by temperature. This is the first Polish analysis of a large subpopulation, which also includes seasonal temperature data.* (Cardiol J 2020; 27, 1: 16–24)

Key words: circadian, weekly, seasonal, cardiac arrest, variability

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Introduction

Out-of-hospital cardiac arrest (OHCA) constitutes a significant medical issue because of both its unexpected characteristics and still low survival rate. The occurrence of cardiac arrest in Europe is estimated as 0.5–1 per 1000 inhabitants per year [1] while in Poland it is approximately 1.7 per 1000 inhabitants [2]. The majority of patients with OHCA represents a cardiac etiology [3].

There exists an impact of rhythmical factors on humans physiology, and therefore its effects on human health have been demonstrated in many studies. The diurnal variations of blood pressure [4, 5], vascular tone [5], urinary catecholamines levels [6], endothelial function, and circulating levels of humoral signals [5], were described in various studies. The levels of plasma cortisol [6], and fibrinogen [7] showed weekly variations and blood pressure [6] with the plasma fibrinogen [7] level have presented seasonal variations in previous studies. The relationship between the chronological factors and the occurrence of acute cardiac events was noted [8]. Previous studies have shown temporal variability in the rate of acute cardiac events, depends on the hour of day [9, 10], day of week [9], month [11], season [9, 11], and day of public holidays (e.g. Christmas, New Year's Day) [12]. Time variations have also been demonstrated for the incidence of cardiac arrest, including circadian, circaseptan and circannual variability in the frequency of OHCA [9]. Environmental factors such as cold temperature and higher snowfall have been hypothesized to affect OHCA risk however studies exploring seasonal variability of the occurrence of OHCA in various places around the world have given diverse results [9, 13–15]. Although recent studies indicate chronological variations of OHCA incidence but to date, Polish experience is scarce. Knowledge about trends in the occurrence of OHCA in a particular population may facilitate the development of management strategies aimed at improving survival. With this regard, objective assessment can only be made by collective reports of data from particular populations and territories as well as their comparisons.

Therefore, the aim of this study was to examine the epidemiology of OHCA as well as temporal variations in the incidence of OHCA (in terms of hour of the day, day of the week, month of the year and season) among the adult population of Opole district, Poland.

Methods

A retrospective analysis was performed of dispatch cards from Emergency Medical Services (EMS) in Opole (Poland) covering a 2-year period from January 1st, 2006 to December 31th, 2007. Dispatch cards were compatible with the Utstein template. Cards without data regarding the study criteria were not considered for analysis. Opole district is located in the south of Poland. According to the Statistical Office in Opole [16, 17] the district occupies 1683 km^2 and during the study period it was inhabited by approximately 262,000 citizens (47.8% of men). The district includes 129 km^2 of urban areas inhabited by 56% of the population and 1554 km^2 of suburban areas.

During the time analyzed there were 47,549 ambulance departures, including 870 (1.83%) departures due to OHCA. An OHCA was defined as an event with obvious cardiac arrest features happening suddenly and unexpectedly and the mechanism of cardiac arrest was set based on the first recorded heart rhythm: shockable (ventricular fibrillation [VF] or ventricular tachycardia [VT]) or non-shockable (asystole or pulseless electrical activity [PEA]). Patients with traumatic OHCA (n = 47) and under 18 years old (n = 7) were excluded from the analysis. Patients with late signs of death, defined by the presence of decomposition, rigor mortis or livor mortis were also excluded. A total of 815 OHCA cases (406 subjects in 2006 and 409 in 2007) were selected for the study.

The circadian variation was evaluated among 24, 1-hour intervals, and four 6-hour time blocks: 'night'(0:00–5:59), 'morning' (6:00–11:59), 'afternoon' (12:00–17:59) and 'evening' (18:00–23:59). In order to maintain comparability a similar pattern of division was used as in previous reports. The weekly variation was analyzed for days of the week. The marginal week days (Saturday, Sunday, Monday) were compared with middle week days (Tuesday, Wednesday, Thursday, Friday). Two definitions of season were used: meteorological season (Spring: March, April, May. Summer: June, July, August. Autumn: September, October, November. Winter: December, January, February) and astronomical season (Spring: 21.03–21.06, Summer: 22.06–22.09, Autumn: 23.09–21.12, Winter: 22.12–20.03).

Statistical analysis

The normality for all variables was verified with the Shapiro-Wilk test. Data are expressed

as mean ± standard deviation (SD) for continuous variables and as counts (percentages) for categorical variables. Statistical analysis was performed using χ^2 test for categorical variables and t-Student or Mann-Whitney U test for continuous data depending on distribution. For analysis of more than two variables ANOVA or Kruskal-Wallis test was performed as appropriate according to data distribution. The comparison of groups divided by gender (males vs. females) and age (≤ 65 years vs. > 65 years) was made. We assumed, in concordance with other reports that people aged 65 years or less are more likely to be pre-retirement and are part of the workforce. For all subgroups we checked circadian, weekly, monthly and seasonal variability. Statistical significance level was adopted for $p < 0.05$. Analysis was performed using IBM SPSS Statistics version 23.

Results

General characteristics

The incidence of OHCA in the present population was 1.56 per 1000 inhabitants per year. The above mentioned parameter for men and women accounted for 2.02 and 1.09 per 1000 inhabitants per year, respectively ($p < 0.001$). Of the 815 OHCA cases, the majority were men (63%, $p = 0.0001$). The mean patient age was 69.2 ± 14.2 years. Additional information regarding the studied population is presented in Table 1. Men suffering from OHCA were younger than women (66.1 ± 13.4 vs. 74 ± ± 14.1 years, $p = 0.0001$). OHCA incidence increased with age, reaching a peak in the 71–75 age group (Fig. 1). Non shockable rhythm (asystole, PEA) was diagnosed in 88.71% cases, whereas shockable rhythm (VF or VT) was present in 11.04% patients. There were no statistical differences regarding initial OHCA rhythms between men and women. The higher occurrence of OHCA

Table 1. Basic characteristics of the studied population.

Variable	Studied population
Number of cases	815
Mean age [years]	69.2 ± 14.2
Male sex	63%
Initial rhythm:	
Asystole	87.8%
VT/VF	11%
Location:	
Urban	63.7%
Suburban	36.3%

VT/VF — ventricular tachycardia/ventricular fibrillation

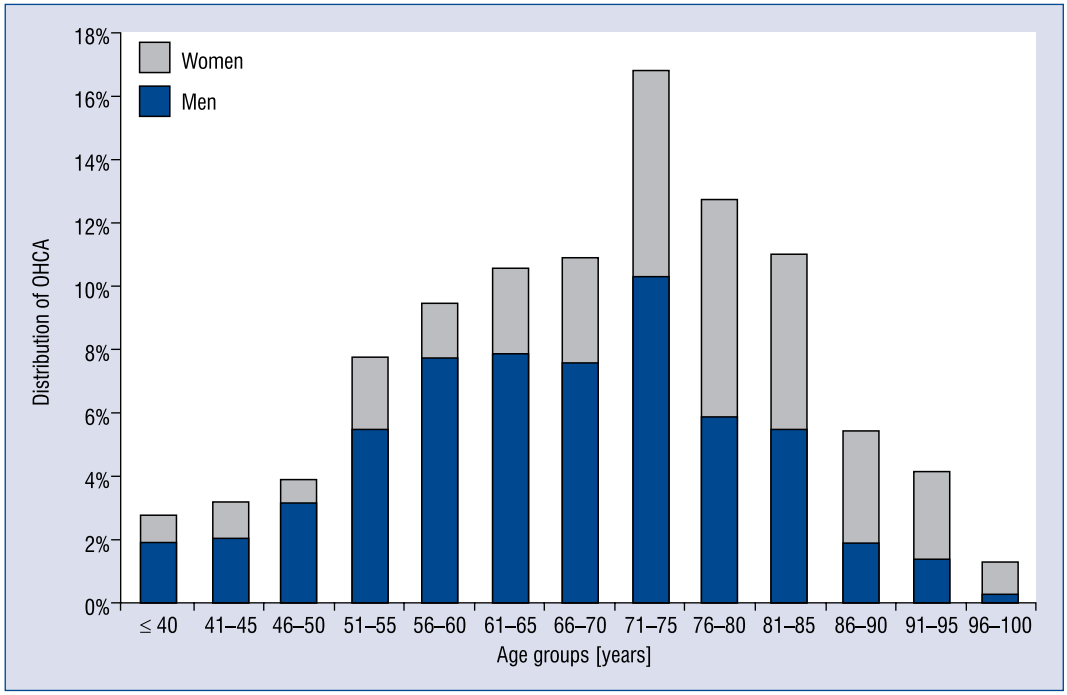

Figure 1. Distribution of out-of-hospital cardiac arrest (OHCA) occurrence depending on age group and gender categories.

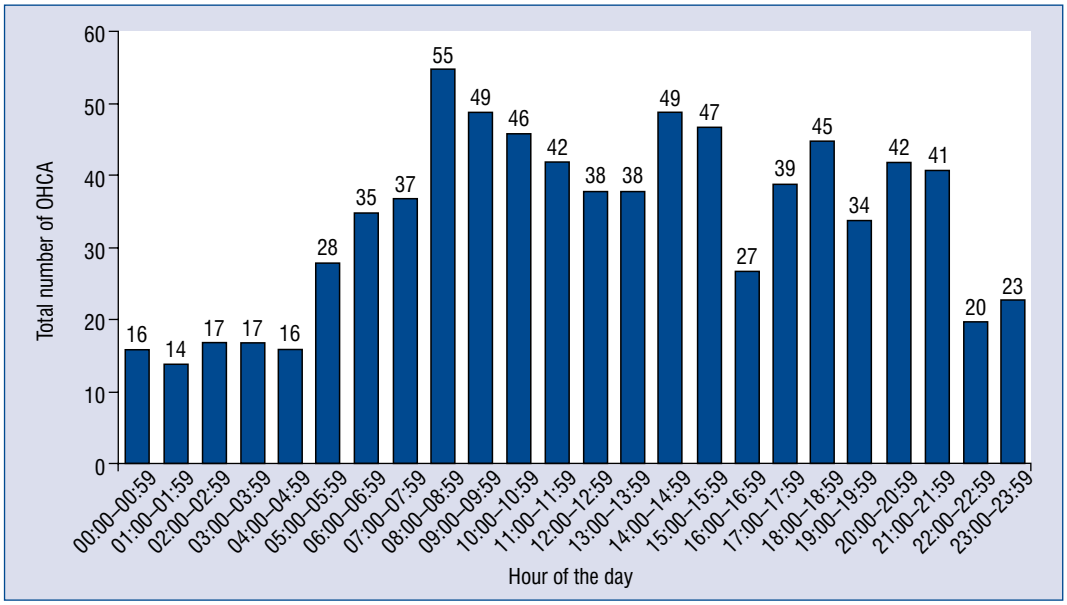

Figure 2. Circadian distribution of out-of-hospital cardiac arrest (OHCA) occurrence divided into 1-hour periods within 24 hours.

was observed in the population aged > 65 years (53.4%, p < 0.001). The subgroup of patients younger than 65 years old had a higher proportion of men (74.8% vs. 51.3%, p < 0.001) and more frequently was diagnosed with VF or VT (13.7% vs. 7.6%, p = 0.008). The majority (63.68%, p < 0.001) of OHCAs took place in urban areas.

Circadian variation of OHCA

Figure 2 shows the histogram of the circadian distribution of OHCA. It demonstrates progressive increase in the incidence of OHCA from 05:00 am with trimodal daily peak: between 8:00 and 10:59 am and between 14:00 and 15:59, less marked 18:00–21:59. It also shows a night time nadir, when the incidence of OHCA stayed at a relatively stable, low level (22:00–4:59). After division into 6-hour intervals (Fig. 3) the lowest number of OHCA occurred at 'night' (00:00–05:59 am; n = 108, 13%, p < 0.001), while the highest number was noted in the 'morning' period (6:00–11:59 am; n = 264, 32.4%). It was also a significantly higher number of OHCA in comparison to the 'evening' period (n = 205, p = 0.046), but not to the 'afternoon' period (n = 238, p = 0.8). The circadian variation characterized by the lowest number of OHCA occurring at 'night' was observed both in men (p = 0.001) and women (p = 0.002), and there was no difference between both gender groups. The circadian variation of OHCA in both age subgroups (≤ 65 years vs. > 65 years) presented the similar

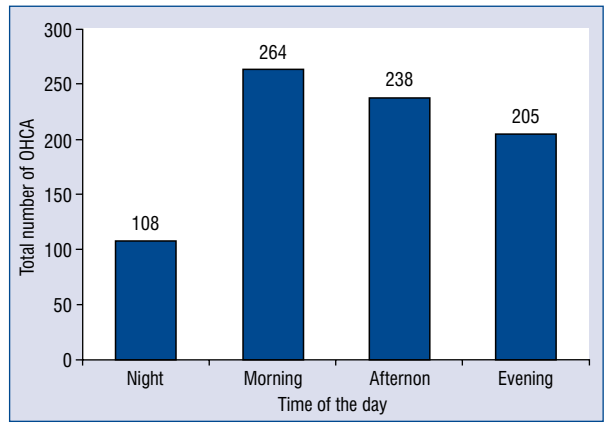

Figure 3. Number of out-of-hospital cardiac arrest (OHCA) in 6-hour intervals within 24 hours. Night vs. Morning: p < 0.001; Night vs. Afternoon: p < 0.001; Night vs. Evening: p < 0.001; Morning vs. Evening: p = 0.046.

pattern of occurrence as described for the entire group, with a morning peak and a night-time nadir (p < 0.001).

Weekly variation of OHCA

The lowest number of OHCA was noted on Friday (n = 89, 10.9%, Fig. 4) while the highest on Saturday (n = 131, 16.1%, p = 0.01), Sunday (n = 124, 15.2%, p = 0.02), and Monday (n = 128, 15.7%, p = 0.01). The OHCA occurrence was de-

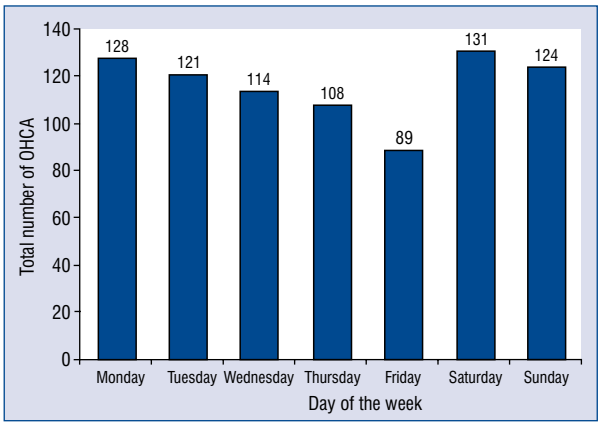

Figure 4. Distribution of out-of-hospital cardiac arrest (OHCA) occurrence in subsequent days of the week; p = 0.11. Friday vs. Saturday: p = 0.013; Friday vs. Sunday: p = 0.024; Friday vs. Monday: p = 0.01; Saturday, Sunday, Monday vs. Tuesday, Wednesday, Thursday, Friday: p = 0.021.

creasing gradually from Monday to Friday, however the variability in subsequent days did not reach statistical significance (p = 0.11). OHCA was noticed more often on marginal week days than on middle week days (p = 0.021).

With respect to age subgroups, the lowest number of OHCA events occurred on Friday, both in the group ≤ 65 years old and older, but the statistical significance was achieved only in the non-elderly group (p = 0.03).

Monthly and seasonal variation of OHCA

Figure 5 shows monthly distribution of mean daily number of OHCA. August was the month with the lowest average amount of OHCA, October and February — the highest (0.77 vs. 1.26 and 1.25 cases, p = 0.03 and p = 0.02, respectively), however the variability in subsequent months was statistically insignificant (p = 0.3). Division to astronomical and meteorological seasons gave us different results (Fig. 6). Although there was no significant difference in seasonal variability of OHCA occurrence in either astronomical (p = 0.16) or meteorological (p = 0.35) seasons, a significant difference was noticed between astronomical winter and summer. Astronomical summer was the season of the lowest incidence of OHCA, while winter — the highest (22.6% vs. 26%, p = 0.04). These seasons were the warmest and the coldest one, respectively (average temperature 18.5 vs. 0°C, p < 0.001, Fig. 6). In both age groups as well as gender groups the monthly and seasonal variability did not reach the statistical significance (p > 0.05).

Discussion

This retrospective study of OHCA affecting the population of southern Poland confirms a cir-

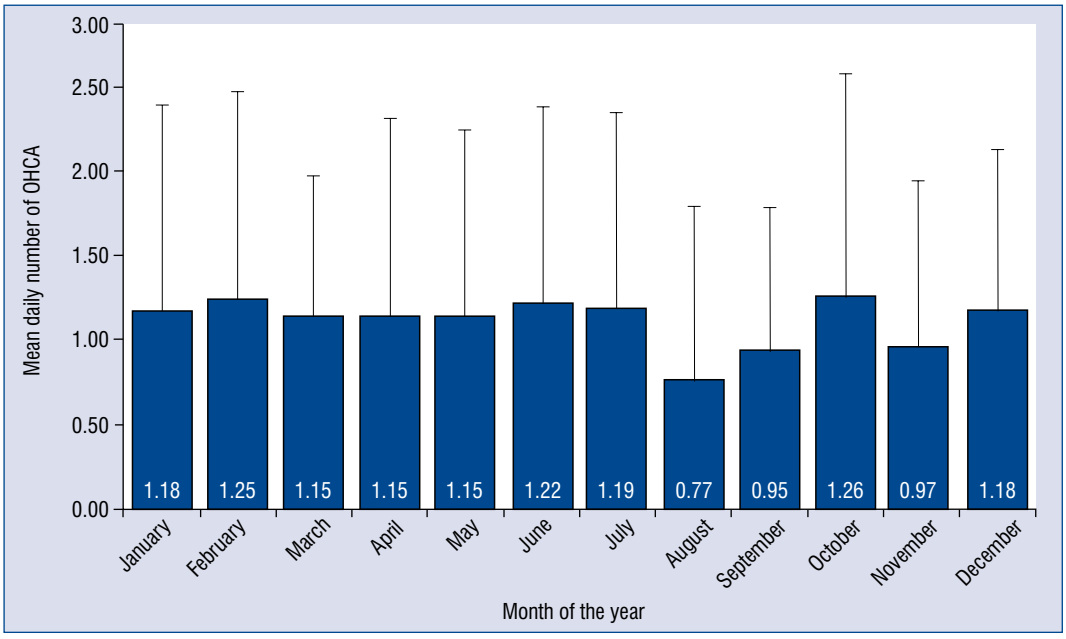

Figure 5. Monthly rhythm of mean daily number of cardiac arrests; p = 0.33. August vs. February: p = 0.024; August vs. October: p = 0.027.

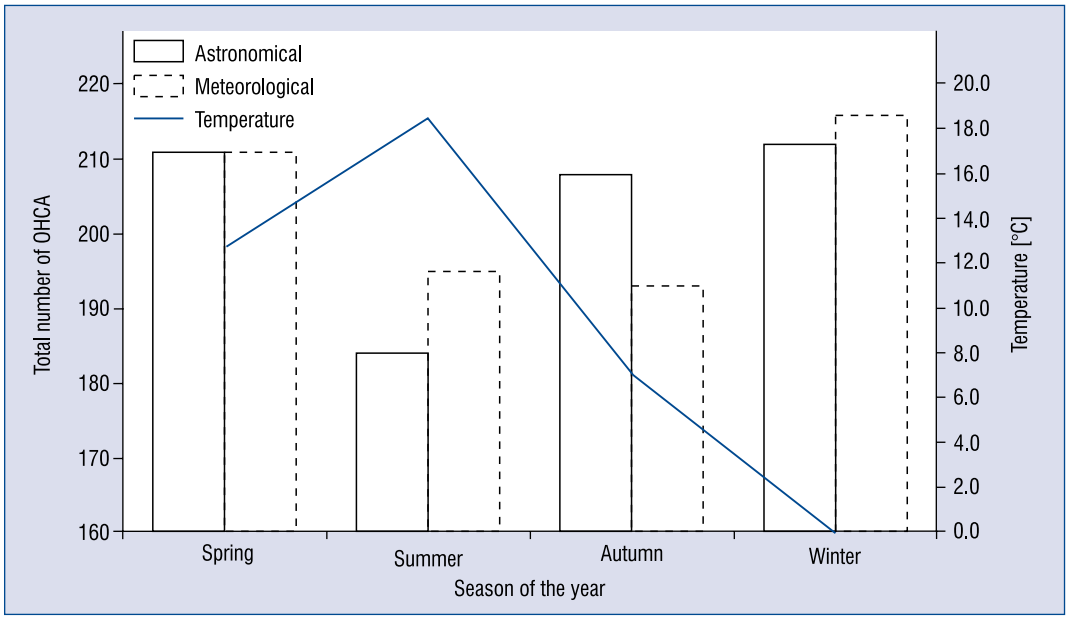

Figure 6. Seasonal rhythm of cardiac arrest with astronomical and meteorological division and with average temperatures during those seasons. Astronomical: p = 0.16; Meteorological: p = 0.35; Summer vs. Winter: p = 0.04; Summer temperature vs. Winter temperature: p = 0.0001.

cadian rhythm of OHCA occurrence, observed in previous studies. Analysis of circaseptan rhythm of events has emerged much less marked OHCA variability, with Friday being a day with the lowest case incidence. Moreover, monthly and seasonal variation of OHCA with respect to seasonal temperature was explored and this is the first report among Polish studies. The results of this work advances the knowledge about the chronobiology of OHCA in Poland and might serve as a basic source of information about the true situation of this phenomenon. To date, no previous studies have been conducted in this particular setting.

The incidence of OHCA presented in European studies range from 0.36 to 1.28/1000 inhabitants per year [1, 3]. In the present study a higher incidence of 1.56/1000 inhabitants per year was noticed, but even higher value was presented in another Polish study (1.7/1000 per year, 2.43 in men and 0.99 in women) [2]. The same tendency regarding gender was observed where the incidence rate is almost two times higher among men in comparison to women. The occurrence of OHCA increases with age, which is supported by our data, although there are visible differences between men and women. Women make up the minority of patients younger than 75 years and they reach the peak value of OHCA occurrence 5–10 years later than men.

Circadian variation of the occurrence of OHCA was widely described in the literature. The present results, in accordance with other studies, confirms the lowest occurrence of OHCA during night hours (from 00:00 to 06:00) and increasing rate of incidents in the early morning hours — the highest from 06:00 to 09:00 [9, 18]. In the majority of cases the occurrence curve presented two peaks [13–15, 18–20] in the morning (08:00–10:00) and in the late afternoon (16:00–20:00). This study observed three peaks: between 8.00 and 10.59 am, between 14.00 and 15.59, less marked 18.00–21.59 and similar observation was made by Soo et al. [21]. The distribution of OHCA with the low occurrence rate during night hours and typical increase in the morning hours may be the result of diurnal changes in blood pressure [4, 5], vascular tone [5], heart rate, endothelial function [5], platelet aggregability [22], and catecholamines concentration [6] which all are potential triggers of acute myocardial infarction. The autopsy data suggests that the majority of sudden cardiac deaths are the consequence of acute myocardial infarction or ischemia and related arrhythmias. It is supported by the fact that the incidence of myocardial infarction also exhibits a morning time excess, occurring much more frequently during the 6.00–12.00 am time block. Similar patterns of frequency exist for other cardiovascular events, like pulmonary

embolism or ischemic stroke [15]. Nevertheless, this trimodal phenomenon is difficult to explain, especially with respect to the afternoon and evening peaks. The observed variability could be driven both by patients who were found dead in the morning after some time of having a cardiac arrest and the patients who have died during the day and were found dead by family members returning home. The data concerning witnessed and non-witnessed OHCA were not analyzed, but unwitnessed cases were proven to occur more likely during the night and at private home than witnessed OHCA [18]. It might be a source of misclassification of time of arrest in the present study in some percentage of cases, but on the other hand it alone cannot explain the morning peak of OHCA.

Some previous studies showed statistically significant weekly variation of the occurrence of OHCA [9, 15, 23] although Nakanishi et al. [13] did not report such significance. If did, the majority indicated the highest number of OHCA was on Monday [9, 13, 14, 24]. Prior studies suggested a Monday excess for employed subjects [9, 25] nevertheless the present data do not confirm this observation, both in the subgroup of < 65 years old as well as the older group. Though, a tendency was demonstrated for a higher incidence rate from Saturday to Monday. Allegra et al. [23] and Brooks et al. [15] presented the results where the highest number of OHCA appeared on Saturday. The day with the lowest occurrence rate varied depending on the study: Tuesday [9, 15, 23], Wednesday [13], Thursday [14], Saturday [24]. The most commonly observed increase of risk on Mondays could be the result of increased cortisol [6] levels induced by stress due to returning to work, but it does not explain the Saturday excess in this setting. The latter might be partly explained by the probable influence of participating in strenuous activities on weekends and altered medication compliance [23]. However, the abovementioned diverse observations of weekly OHCA variation may arise presumably from the diversity of the studied populations in terms of age distribution or behavioral patterns, like alcohol intake, leisure activities, and time and type of workload among others.

The seasonal variability of the occurrence of OHCA was studied in different places around the globe, e.g. Japan [13], Singapore [14], Sweden [9], United States of America and Canada [15]. The months with the highest number of OHCA were usually: December, January and February [9, 13, 15, 23, 24]. July and August turned out to have the lowest occurrence rate in the majority of compared studies [13, 14, 23, 24], which concurs with the present research. Exposure to low temperature is considered to be one of the main factors influencing cardiac arrest incidence, also it significantly determines morbidity and mortality of acute cardiovascular events. Some authors did not divide the year into seasons but compare the three warmest and coldest months showing 71.2% more OHCA during the coldest period [13]. Not all previous publications presented statistically significant variation between the months suggesting the impact of climate, geographic specificity, climate-related behavior on analyzed data [14]. Poland lies in a moderate climate zone with mixed continental and oceanic influences and it evidently differs from other countries located not only in equatorial or subtropical climate, but also European ones. Temperature differences during the year between seasons are marked, but there are some other factors potentially influencing the results like seasonal migration. Probably not only the absolute temperatures are essential but day-to-day or month-to-month temperature changes could also have a potential significance. Moreover, the present research indicates the importance of defining seasons precisely when comparing to other outcomes because the same data divided into astronomical or meteorological seasons could give different results and patterns.

There are only a few Polish publications considering the epidemiology of cardiac arrest but, according to available research, this study is the first presenting the results of diurnal, weekly and seasonal OHCA variability collectively with various whether indices. Gach et al. [2] analyzed a smaller population from 1-year period (2013) and reported similar diurnal variation in OHCA incidence, however significant discrepancy exists when comparing days of the week and months with the lowest and the highest OHCA frequencies (May and December, respectively and no statistical significance of weekly variation, the highest rate being on Tuesday). Presented dissimilarity strengthens the need for more and large-scaled research, although the influence of multiple population and territory specific factors affecting every result cannot be neglected.

Limitations of the study

The retrospective and observational nature of this study is one of the main limitations in the analysis, together with the lack of the possibility to collect more essential data (e.g. patient medical history, comorbidities or medical treatment).

Neither analysis of the data concerning witnessed and non-witnessed OHCA nor the survival was considered. On the other hand emphasis of the characteristics of OHCA phenomenon in this subpopulation was sought in terms of various temporal and meteorological factors. Another limitation was the difficulty in the assessment of the precise time of event occurrence mainly due to the adopted methodology. The present study is also limited by the fact that the Opole district is a relatively small territory. However the observation that 63.7% of OHCAs took place in the urban area demonstrates the heterogeneity of this territory, which could result in a more accurate presentation of the phenomenon. The homogenous territory could result in a bias of selecting a specific group of patients. Thus, although we consider our data valuable, it still should be taken with caution and require both the amplification and confirmation in larger-scaled studies.

Conclusions

The studied population is characterized by circadian rhythm of OHCA incidence and less marked circaseptan differences in OHCA occurrence. These results are in agreement with the most of the previous reports. Seasonal differences in OHCA incidence was also observed, and this phenomenon may be affected by temperature. Moreover, OHCA incidence increases with patient age, but temporal variations in these events occur independent of age. This is the first Polish analysis of such a large group of cases, which also includes seasonal temperature data. We assume that it both constitutes the substantial source of knowledge as well as complements Polish experience in this research area, which had previously been rather scarce.

Conflict of interest: None declared

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In-hospital heart rate reduction and its relation to outcomes of heart failure patients with sinus rhythm: Results from the Polish part of the European Society of Cardiology Heart Failure Pilot and Long-Term Registries

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Abstract

Background: *Currently, there is no information on whether in-hospital heart rate (HR) reduction has an influence on risk of death or rehospitalization. The study evaluates the relation between in-hospital HR reduction in heart failure (HF) patients on mortality and rehospitalization within 1-year observation.*

Methods: *The analysis included patients hospitalized in Poland with sinus rhythm from the European Society of Cardiology Heart Failure Pilot (ESC-HF-Pilot) and ESC Heart Failure Long-Term Registries (ESC-HF-LT), who were divided into two groups: reduced HR and not-reduced HR. HR reduction was defined as a reduced value of HR at discharge compared to admission HR. The primary endpoint was 1-year all-cause death, the secondary endpoint was 1-year all-cause death or rehospitalization for worsening HF.*

Results: *The final analysis included 747 patients; 491 reduced HR (65.7%) and 256 not-reduced HR (34.3%). The primary endpoint occurred in 58/476 (12.2%) from reduced HR group and in 26/246 (10.5%) from not-reduced HR group ($p = 0.54$). In the reduced HR group, independent predictors of primary endpoint were age, New York Heart Association class at admission, serum sodium level at admission and systolic blood pressure at discharge. In the not-reduced HR group the independent predictor of primary endpoint was diastolic blood pressure at discharge. The secondary endpoint was observed in 180 patients, 124/398 (31.2%) from reduced HR and 56/207 (27.1%) from the not-reduced HR group ($p = 0.30$). In the not-reduced HR group only angiotensin converting-enzyme inhibitor usage at discharge was independently associated with lower risk of the secondary endpoint.*

Conclusions: *In-hospital HR reduction did not influence on the outcomes of HF patients in sinus rhythm.* (Cardiol J 2020; 27, 1: 25–37)

Key words: heart failure, registry, prognosis, heart rate, hospitalization

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Introduction

Although the treatment of heart failure (HF) has been improving in recent decades, the outcome of HF patients is still not satisfactory [1, 2]. Increasing prevalence of HF in developing countries is a great challenge for contemporary cardiology. Proper identification of risk factors of death or rehospitalization is crucial for the management of HF patients.

The most comprehensive and reliable data concerning the risk factors and outcome of patients with HF come from international observation registries. The European Society of Cardiology (ESC) created the Heart Failure Pilot (ESC-HF-Pilot) and Heart Failure Long-Term (ESC-HF-LT) Registries to assess the clinical characteristics and outcome of HF patients in clinical practice in European countries. Recently published analyses of data from both Registries revealed several risk factors associated with 1-year outcomes in hospitalized HF patients [1, 3–6]. One of the modifiable predictors of cardiovascular mortality and morbidity is heart rate (HR), which is associated with poor prognosis in general population, patients with hypertension, coronary artery disease and HF [2, 7–11]. Laskey et al. [12] reported, that higher HR at discharge in hospitalized HF patients significantly increased the risk of death or rehospitalization. However, there is still no information on whether in-hospital reduction of HR modifies risk of death or rehospitalization.

The aim of the current analysis was to evaluate the influence of in-hospital HR reduction in HF patients with sinus rhythm (SR) on mortality and/or rehospitalization over a 1-year observation period.

Methods

Study population

In the present analysis, data from two prospective, multicenter registries were included: ESC-HF-Pilot and ESC-HF-LT [1, 2, 13, 14]. The ESC-HF-Pilot Registry included data gathered between October 2009 and May 2010 in 136 European centers, including 29 centers localized in Poland. The ESC-HF-LT Registry consists of three phases, including data from 211 centers in 21 European countries. The I phase of the ESC-HF-LT Registry was conducted between May 2011 and April 2013 and enrolled patients 1 day per week for the whole year. Adult patients (at least 18 years old) with newly-diagnosed HF (using clinical, biochemical and echocardiographic findings) or worsening of HF were enrolled in the Registries. The ESC-HF-Pilot and ESC-HF-LT Registries recruited patients hospitalized for HF and outpatients seen in ambulatory care. Exclusion criteria were not specified. All patients signed an informed consent. The study was approved by the local Ethical Review Board.

In the current analysis only hospitalized patients enrolled in the ESC-HF-Pilot Registry and in phase I of the ESC-HF-LT Registry in SR were taken into account. Atrial fibrillation/atrial flutter and/or paced rhythm on 12-lead electrocardiogram (ECG), as well as lack of ECG recording during index hospitalization were excluded from the current analysis.

All data according to the medical history, concomitant diseases and clinical status at admission and hospital discharge were obtained. Follow-up of the patients lasted 1 year. During the follow-up data regarding all-cause death and readmission for HF worsening were collected.

Study groups

Patients were divided into two groups according to HR difference during index hospitalization from admission to discharge: with or without HR reduction. HR values were assessed during standard physical examination. HR reduction was defined as a reduced value of HR recorded at discharge in comparison to the value observed upon admission. Patients with HR reduction (reduced-HR group) and without HR reduction (not-reduced-HR group) during index hospitalization were compared in regard to demographics, medical history, clinical status and pharmacotherapy at the moment of admission, during index hospitalization and at hospital discharge.

Endpoints

In both Registries, the primary endpoint was 1-year all-cause death, whereas the secondary endpoint was composed of 1-year all-cause death or rehospitalization for worsening HF.

Statistical analysis

Normality of distribution of variables was assessed using the Shapiro-Wilk test. Continuous non-normally distributed variables were presented as median values and interquartile range (IQR). Categorical data were presented as percentage and absolute frequencies. Statistical significance of differences between groups was assessed: for quantitative variables with U Mann-Whitney test and for qualitative variables — with Fisher exact test. Cox proportional hazard regression models were used to determine predictors of the primary

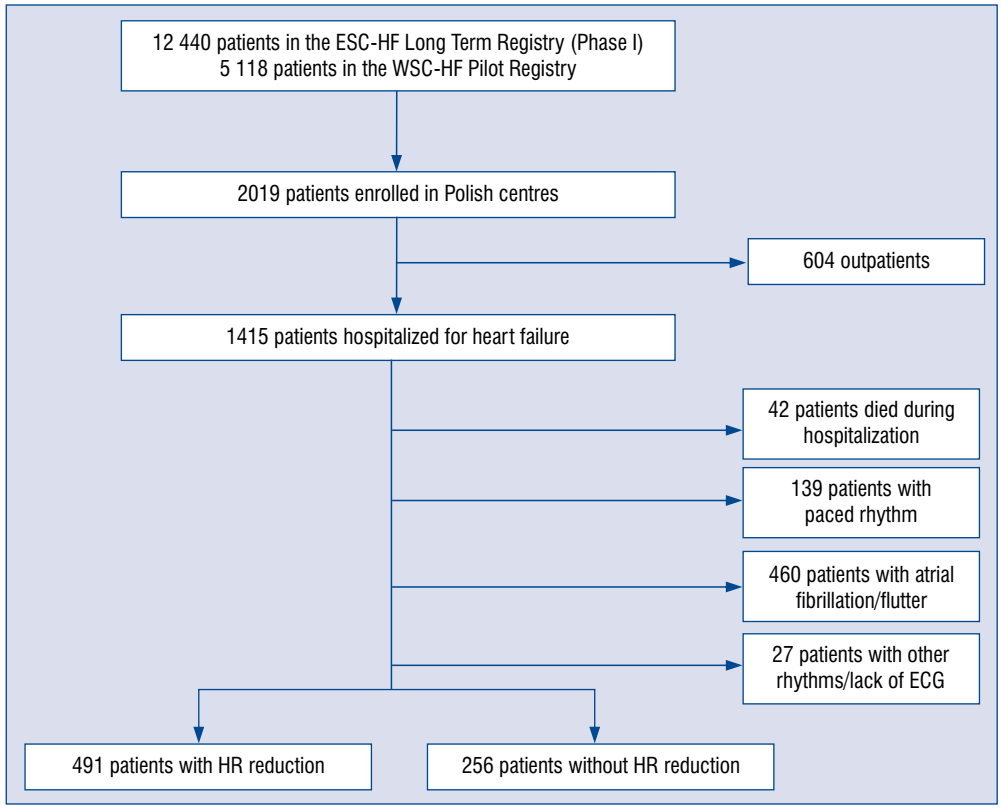

Figure 1. The flow chart of patient recruitment in the study; HR — heart rate; ECG — electrocardiogram.

and secondary endpoints. Only variables with $p < 0.1$ in univariate analysis were included in multivariate analysis. A value of $p < 0.05$ was considered significant for all tests. Statistical analysis performed using SAS® software, version 9.4.

Study group selection

Overall, in all European countries 5118 patients were enrolled in the ESC-HF-Pilot Registry and 12,440 patients in the ESC-HF-LT Registry. The Polish cohorts of the ESC-HF-Pilot and ESC-HF-LT Registries included 630 and 743 HF patients who were discharged after index hospitalization, respectively. Firstly, 139 patients were excluded from the current analysis, because of paced rhythm observed in ECG recording. Secondly, 460 patients with present atrial fibrillation/atrial flutter during index hospitalization were excluded from further analysis. Other rhythms or lack of ECG were noted in 27 patients. Finally, ECG recordings on admission and discharge were available for 747 (100%) patients. The flow chart of patient enrollment in the analysis is shown in Figure 1. HR reduction was observed in 491 of 747 (65.7%) patients, while lack of HR reduction in 256/747 (34.3%) patients included in the study. Follow-up data was excluded for 25 patients, resulting from a lack of response after direct, investigator contact.

Results

Study group characteristics

Median age in the group analyzed was 67.0 (57.6–77.0) years, 68.5% of patients were male. Median HR value at admission in the total population was 80 (70–90) beats per minute (bpm). In the reduced HR group median HR at admission was 84 (75–100) bpm, whereas in the not-reduced HR group 70 (60–75) bpm ($p < 0.0001$). Furthermore, median HR value at discharge was 70 (64–78) bpm in the population analyzed, 70 (62–75) bpm in the reduced HR group and 72 (68–80) bpm in the not-reduced HR group ($p < 0.0001$). Median value of HR reduction in the reduced HR group was 15 bpm (IQR: 8–25 bpm). The reduced HR group more frequently had hypertension (71.0% vs. 63.3%; $p = 0.04$) and less frequently used antiplatelets before the index hospitalization (58.2% vs. 69.4%; $p = 0.003$) in comparison to the not-reduced HR group. According to clinical status at admission,

the reduced HR group had higher New York Heart Association (NYHA) class (3 [2–4] vs. 3 [2–3]; p = 0.02), higher systolic blood pressure (SBP) (131 [120–150] vs. 130 [110–140]; p = 0.002), higher diastolic blood pressure (DBP) (80 [70–90] vs. 80 [70–84]; p = 0.0005) and more frequently were admitted because of acute coronary syndrome ([ACS] 27.5% vs. 20.7%; p = 0.04). Moreover, reduced HR group had a longer duration of index hospitalization (7 [4–11] vs. 6 [3–9]; p = 0.004), in comparison to the not-reduced HR group. A full comparison of both groups in regard to baseline characteristics, clinical course of index hospitalization, in-hospital and long-term outcomes are presented in Table 1. As shown in Table 2, HR at admission was significantly higher in the ESC-HF-Pilot Registry population in comparison to the group enrolled in the ESC-HF-LT Registry (80 [70–95] vs. 78 [68–90]; p = 0.02). The comparison between these two Registries did not show significant differences in regard to HR at discharge, mean HR reduction during hospitalization or the percentage of patients who achieved HR reduction (Table 2).

One-year outcomes

Moreover, no significant differences were observed between groups in occurrence of primary and secondary endpoints. In comparison of reduced HR and not-reduced HR groups, hazard ratios of prevalence of primary and secondary endpoints were 1.16 (95% confidence interval [CI] 0.73–1.84; p = 0.54) and 1.15 (95% CI 0.85–1.56; p = 0.38), respectively. Kaplan-Meier curves present outcomes of reduced HR and not-reduced HR groups are shown in Figure 2.

Primary endpoint

In the population analyzed, 722 patients completed 1-year follow-up and primary endpoint occurred in 84/722 patients (11.6%). In the reduced HR group, primary endpoint was observed more frequently (58/476, 12.2%), than in the not-reduced HR group (26/246, 10.5%; p = 0.54). Tables 3 and 4 present risk factors for 1-year all-cause death in univariate analysis in the reduced HR and not-reduced HR groups, respectively. In the multivariate analysis only older age, higher NYHA class at admission, lower serum sodium at admission and lower SBP at discharge were revealed to be independent predictors of primary endpoint in the reduced HR group (Table 5). In multivariate analysis only lower DBP at discharge remained to be a statistically significant predictor of 1-year all-cause death in the not-reduced HR group, as shown in Table 6.

Secondary endpoint

In the total population, data on 1-year follow-up were available for 605 patients. In the whole analyzed group, secondary endpoint was observed in 180 (29.8%) patients, 124/398 (31.2%) from the reduced HR and 56/207 (27.1%) from the not-reduced HR group (p = 0.30). Tables 3 and 4 present risk factors for secondary endpoint in univariate analysis in the reduced HR and not-reduced HR groups, respectively. In the reduced HR group, the multivariate analysis did reveal these factors to reach statistical significance (Table 5). However, there were trends for diabetes, history of stroke, higher NYHA class at admission and lower serum sodium at admission towards independent prediction of secondary endpoint in the reduced HR group. In the not-reduced HR only the use of angiotensin converting enzyme inhibitor at discharge was independently associated with lower risk of all-cause death or rehospitalization for worsening HF, as presented in Table 6.

Discussion

The current study has revealed that HR reduction during the hospitalization for HF was not associated with benefits in patients with SR. Moreover, predictors of all-cause death or combined endpoint (death or rehospitalization for worsening HF) at 1 year were partly comparable in patents with and without HR reduction during index hospitalization.

Among numerous demographic and clinical factors, only a few of them differed between patients with and without in-hospital HR reduction. In the reduced-HR group higher NYHA class was observed. Not much is known about the correlation between NYHA class and HR at hospital admission. However, Ahmed et al. [15] revealed no significant differences in HR at admission and NYHA class I–II vs. III–IV in patients with HF with preserved function of the left ventricle. Moreover, results from the current analysis showed that in the reduced HR group, higher NYHA class at admission is significantly related to all-cause death at 1 year. These findings are consistent with results of previous analyses performed in hospitalized HF patients enrolled in the ESC-HF-Pilot and ESC-HF-LT Registries [1, 3, 4].

In the present analysis, the reduced HR group less frequently used beta-blockers (BBs) prior to

Table 1. Baseline characteristics, clinical course of index hospitalization, in-hospital and long-term outcomes of the reduced HR and not-reduced HR groups.

	Total (n = 747)	Not-reduced HR (n = 256)	Reduced HR (n = 491)	P
Demographics				
Age [years]	67.0 (57.6–77.0); n = 747	67.0 (58.0–76.7); n = 256	67.0 (57.6–77.0); n = 491	0.92
Male	68.5%; *512/747*	70.7%; *181/256*	67.4%; *331/491*	0.41
BMI [kg/m^2]	27.7 (24.7–31.2); n = 708	27.7 (24.9–30.6); n = 244	27.7 (24.5–31.6); n = 464	0.76
Heart failure				
LVEF [%]	35 (25–50); n = 669	37 (26–50); n = 213	35 (25–50); n = 456	0.70
Medical history				
Hypertension	68.4%; *510/746*	63.3%; *162/256*	71.0%; *248/490*	**0.04**
Coronary artery disease	61.5%; *459/746*	64.5%; *165/256*	60.0%; *294/490*	0.33
Peripheral artery disease	12.5%; *92/747*	11.3%; *29/256*	12.8%; *63/491*	0.64
Diabetes	33.7%; *252/747*	33.2%; *85/256*	34.0%; *167/491*	0.87
Chronic kidney disease	18.2%; *136/746*	17.2%; *44/256*	18.8%; *92/490*	0.62
COPD	16.4%; *122/745*	12.6%; *32/255*	18.4%; *90/490*	0.05
Stroke	7.8%; *58/746*	5.5%; *14/256*	9.0%; *44/490*	0.11
Previous pharmacotherapy				
Diuretics	62.2%; *452/727*	66.3%; *167/252*	60.0%; *285/475*	0.11
Aldosterone antagonist	40.0%; *291/727*	43.7%; *110/252*	38.1%; *181/475*	0.15
ACEI	62.6%; *455/727*	65.1%; *164/252*	61.3%; *291/475*	0.33
ARB	9.8%; *71/725*	8.4%; *21/251*	10.6%; *50/474*	0.43
Beta-blocker	72.6%; *527/726*	75.4%; *190/252*	71.1%; *337/474*	0.22
Statins	57.2%; *415/726*	61.5%; *165/252*	54.9%; *260/474*	0.10
Ivabradine	0.3%; *1/391*	0.0%; *0/145*	0.4% *1/246*	1.00
Antiplatelets	62.1%; *451/726*	69.4%; *175/252*	58.2%; *276/474*	**0.003**
Clinical status at admission				
Cardiogenic shock	1.8%; *13/708*	1.3%; *3/237*	2.1%; *10/471*	0.56
NYHA class	3 (2–4); n = 743	3 (2–3); n = 256	3 (2–4); n = 487	**0.02**
NYHA I	1.4% *10/719*	1.6% *4/256*	1.3% *6/487*	
NYHA II	28.7% *206/719*	31.3% *80/256*	27.5% *129/487*	
NYHA III	44.1% *317/719*	48.1% *123/256*	43.1% *201/487*	
NYHA IV	35.9% *186/719*	19.1% *49/256*	28.1% *137/487*	
SBP [mmHg]	130 (114–150); n = 745	130 (110–140); n = 255	131 (120–150); n = 490	**0.002**
DBP [mmHg]	80 (70–90); n = 745	80 (70–84); n = 255	80 (70–90); n = 490	**0.0005**
HR [bpm]	80 (70–90); n = 747	70 (60–75); n = 256	84 (75–100); n = 491	**< 0.0001**
QRS duration [ms]	102 (91–120); n = 673	102 (92–121); n = 227	102 (90–120); n = 446	0.67
ACS as a cause of admission	25.2%; *188/746*	20.7%; *53/256*	27.5%; *135/490*	**0.04**
Laboratory findings at admission				
Serum sodium [mmol/L]	139.0 (136.0–141.0); n = 738	139.0 (136.0–141.0); n = 252	139.0 (136.6–141.0); n = 486	0.39
Serum potassium [mmol/L]	4.4 (4.1–4.8); n = 738	4.49 (4.12–4.83); n = 252	4.40 (4.06–4.76); n = 486	0.06
Serum creatinine [mg/dL]	1.05 (0.87–1.32); n = 725	1.01 (0.85–1.30); n = 248	1.07 (0.89–1.33); n = 477	0.11
Hemoglobin [g/dL]	13.4 (12.3–14.6); n = 734	13.4 (12.1–14.7); n = 251	13.4 (12.4–14.6); n = 483	0.61

→

Table 1 (cont.). Baseline characteristics, clinical course of index hospitalization, in-hospital and long-term outcomes of the reduced HR and not-reduced HR groups.

	Total (n = 747)	Not-reduced HR (n = 256)	Reduced HR (n = 491)	P
Major management and pharmacotherapy during index hospitalization, clinical status at discharge				
PCI/CABG during hospitalization	16.8%; *125/745*	16.1%; *41/254*	17.1%; *84/491*	0.76
Beta-blocker	89.9% (670/745)	87.4% (222/254)	91.2% (448/491)	0.12
Digoxin	15.0% (112/745)	14.1% (36/254)	15.5% (76/491)	0.67
Amiodarone	10.6% (79/745)	8.7% (22/254)	11.6% (57/491)	0.26
Antiarrhythmics	4.0% (30/745)	5.1% (13/254)	3.5% (17/491)	0.33
HR [bpm]	70 (64–78); n = 747	72 (68–80); n = 256	70 (62–75); n = 491	**< 0.0001**
SBP [mmHg]	120 (110–130); n = 744	120 (110–130); n = 255	120 (110–130); n = 489	0.91
DBP [mmHg]	70 (65–80); n = 742	70 (65–80); n = 254	70 (65–80); n = 488	0.16
Pharmacotherapy at hospital discharge				
Diuretics	82.1%; *613/747*	79.3%; *203/256*	83.5%; *410/491*	0.16
Aldosterone antagonist	63.1%; *471/746*	65.2%; *167/256*	62.0%; *304/490*	0.42
ACEI	77.5%; *579/747*	77.3%; *198/256*	77.6%; *381/491*	0.93
ARB	10.6%; *79/745*	9.2%; *23/255*	11.4%; *56/490*	0.38
Beta-blocker	89.3%; *667/747*	87.1%; *223/256*	90.4%; *444/491*	0.17
Statins	74.7%; *558/747*	73.4%; *188/256*	75.4%; *370/491*	0.60
Antiplatelets	78.9%; *589/747*	78.9%; *202/256*	78.8%; *387/491*	1.00
Ivabradine	0.5%; *2/391*	0.0%; *0/145*	0.8; *2/246*	0.53
In-hospital outcome				
Hospitalization length [days]	7 (4–10); n = 722	6 (3–9); n = 246	7 (4–11); n = 476	**0.004**
One-year outcome				
One-year all-cause death	11.6%; *84/722*	10.5%; *26/246*	12.2%; *58/476*	0.54
One-year all-cause death or rehospitalization due to the HF worsening	29.8%; *180/605*	27.1%; *56/207*	31.2%; *124/398*	0.30

Bolded values indicate p-values < 0.05. ACEI — angiotensin converting enzyme inhibitor; ACS — acute coronary syndrome; ARB — angiotensin receptor blocker; BMI — body mass index; CABG — coronary artery bypass grafting; COPD — chronic obstructive pulmonary disease; DBP — diastolic blood pressure; HF — heart failure; HR — heart rate; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; PCI — percutaneous coronary intervention; SBP — systolic blood pressure

Table 2. Comparison of patients enrolled in the ESC-HF-Pilot and ESC-HF-LT Registries in regard to heart rate (HR) values.

	ESC-HF-Pilot Registry	ESC-HF-LT Registry	P
HR at admission [bpm]	80 (70–95)	78 (68–90)	**0.02**
HR at discharge [bpm]	70 (65–78)	70 (62–77)	0.16
Median HR reduction during hospitalization [bpm]	10 (0–20)	6 (0–20)	0.06
Patients who achieved HR reduction	68.9%	62.9%	0.09

Bolded values indicates p-values < 0.05. ESC-HF-Pilot — European Society of Cardiology Heart Failure Pilot; ESC-HF-LT — European Society of Cardiology Long-Term

admission in comparison to the not-reduced HR group, however this observation did not reach the statistical significance. Moreover, without significance, the analysis of in-hospital pharmacotherapy showed a higher percentage of patients receiving BBs in the reduced HR group. At discharge, the

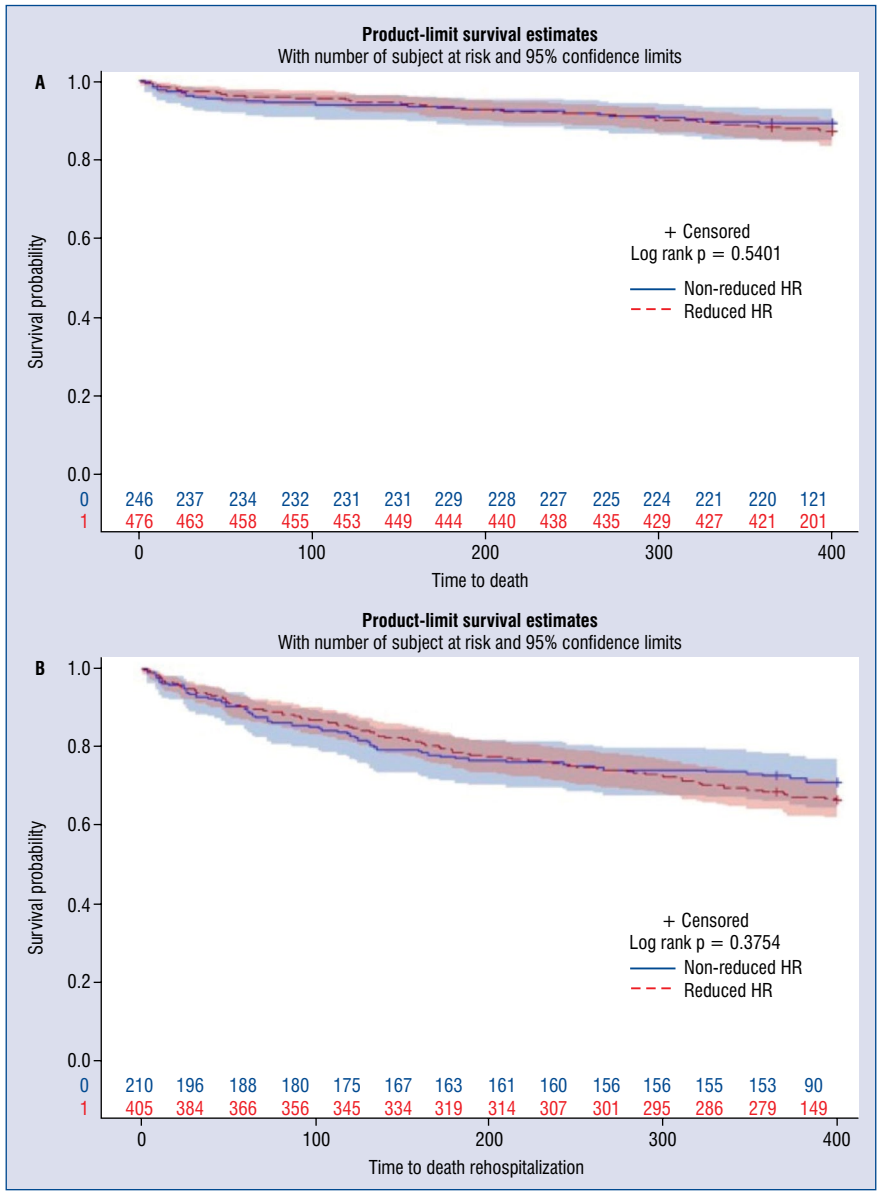

Figure 2. Kaplan-Meier curves in the reduced HR and not-reduced HR groups; **A.** For all-cause 12-month mortality; **B.** For all-cause 12-month mortality or hospitalization; HR — heart rate.

reduced HR group more often had been prescribed BBs. A lower percentage of patients receiving BBs during index hospitalization and at discharge may, at least partially, result from a higher occurrence of chronic obstructive pulmonary disease in this group.

Additionally, in the HR reduction group a higher percentage of patients presented with ACS as a cause of admission. Myftiu et al. [16] reported that, in patients presenting with acute myocardial infarction (AMI) the group with HF upon admission had significantly higher HR at admission in comparison to the AMI without HF group. Moreover, myocardial infarction may be a reason for BB implementation, which contributes to a reduction of HR.

Several recent clinical trials and population-based studies reported significant associations between HR and outcomes in patients with HF. Previous analysis of the ESC-HF Pilot Registry showed that higher HR at admission was associated with worse clinical course during index hospitalization [5]. The placebo-subgroup analysis of patients with stable coronary artery disease and left-ventricular dysfunction enrolled in the BEAUTIFUL (morBidity — mortality EvAlUaTion of the

Table 3. Univariate analysis of predictors of primary and secondary endpoints at 1 year in the reduced heart rate (HR) group.

	Primary endpoint		Secondary endpoint	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Demographics				
Age, per 10 years	1.71 (1.34–2.17)	**< 0.0001**	1.12 (0.97–1.28)	0.12
Male	0.77 (0.45–1.29)	0.32	0.81 (0.57–1.16)	0.26
BMI, per 1 kg/m^2	0.93 (0.88–0.98)	**0.01**	0.99 (0.96–1.02)	0.63
Heart failure				
LVEF, per 5%	0.98 (0.89–1.08)	0.67	0.83 (0.74–0.94)	**0.004**
Medical history				
Hypertension	1.04 (0.58–1.85)	0.90	0.77 (0.53–1.12)	0.17
Coronary artery disease	0.99 (0.58–1.67)	0.96	1.30 (0.91–1.86)	0.15
Peripheral artery disease	1.76 (0.92–3.40)	0.09	1.27 (0.77–2.09)	0.35
Diabetes	1.41 (0.83–2.37)	0.20	1.43 (1.01–2.03)	**0.04**
Chronic kidney disease	2.02 (1.16–3.52)	**0.01**	1.78 (1.22–2.60)	**0.003**
COPD	1.29 (0.70–2.39)	0.42	1.33 (0.89–2.00)	0.17
Stroke	0.94 (0.37–2.34)	0.89	1.91 (1.16–3.14)	**0.01**
Clinical status at admission				
NYHA class, per 1 class	2.09 (1.44–3.04)	**0.0001**	1.66 (1.32–2.10)	**< 0.0001**
SBP, per 10 mmHg	0.95 (0.87–1.04)	0.28	0.89 (0.84–0.95)	**0.0004**
DBP, per 10 mmHg	0.97 (0.82–1.14)	0.68	0.90 (0.81–1.01)	0.07
HR, per 10 bpm	1.10 (0.98–1.23)	0.11	1.05 (0.97–1.13)	0.25
QRS reduction, per 10 ms	1.06 (0.96–1.18)	0.25	1.05 (0.98–1.12)	0.20
Cardiogenic shock	1.53 (0.37–6.27)	0.56	1.36 (0.50–3.67)	0.55
VF or VT as a cause of admission	0.96 (0.35–2.65)	0.94	0.90 (0.46–1.76)	0.75
ACS as a cause of admission	1.30 (0.75–2.26)	0.32	1.06 (0.72–1.58)	0.77
Laboratory findings at admission				
Serum sodium, per 1 mmol/L	0.89 (0.85–0.94)	**< 0.0001**	0.94 (0.90–0.97)	**0.001**
Serum potassium, per 1 mmol/L	0.90 (0.57–1.42)	0.64	0.83 (0.61–1.14)	0.25
Serum creatinine, per 1 mg/dL	1.27 (0.94–1.72)	0.13	1.28 (1.03–1.59)	**0.02**
Hemoglobin, per 1 g/dL	0.83 (0.72–0.94)	**0.004**	0.88 (0.81–0.97)	**0.01**
Major management during index hospitalization, clinical status and laboratory findings at discharge				
PCI/CABG during hospitalization	0.84 (0.41–1.82)	0.70	1.04 (0.63–1.71)	0.88
HR, per 10 bpm	1.31 (1.02–1.68)	**0.03**	1.15 (0.97–1.37)	0.10
SBP, per 10 mmHg	0.72 (0.60–0.85)	**0.0001**	0.78 (0.70–0.88)	**< 0.0001**
DBP, per 10 mmHg	0.70 (0.54–0.91)	**0.008**	0.74 (0.62–0.88)	**0.0006**
Pharmacotherapy at hospital discharge				
Diuretics	1.31 (0.62–2.75)	0.48	1.44 (0.88–2.72)	0.15
Aldosterone antagonist	0.84 (0.50–1.42)	0.52	1.24 (0.87–1.77)	0.24
ACEI	0.60 (0.34–1.03)	0.06	0.69 (0.48–1.01)	0.05
ARB	0.73 (0.29–1.82)	0.50	1.12 (0.66–1.89)	0.70
Beta-blocker	0.47 (0.24–0.91)	**0.02**	0.82 (0.49–1.38)	0.45
Pharmacotherapy prior hospital admission				
Diuretics	1.27 (0.73–2.21)	0.40	1.66 (1.13–2.42)	**0.009**
Aldosteron antagonist	0.84 (0.48–1.45)	0.52	1.13 (0.79–1.60)	0.51
ACEI	1.35 (0.77–2.37)	0.29	1.03 (0.72–1.47)	0.89
ARB	1.00 (0.43–2.34)	0.99	1.07 (0.62–1.83)	0.81
Beta-blocker	0.91 (0.52–1.61)	0.75	1.07 (0.72–1.60)	0.72
Statins	0.65 (0.38–1.10)	0.11	1.09 (0.77–1.56)	0.62
Antiplatelets	1.19 (0.69–2.07)	0.54	1.22 (0.85–1.76)	0.28

Bolded values indicate p-values < 0.05. ACEI — angiotensin converting enzyme inhibitor; ACS — acute coronary syndrome; ARB — angiotensin receptor blocker; BMI — body mass index; CABG — coronary artery bypass grafting; CI — confidence interval; COPD — chronic obstructive pulmonary disease; DBP — diastolic blood pressure; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; PCI — percutaneous coronary intervention; SBP — systolic blood pressure; VF — ventricular fibrillation; VT — ventricular tachycardia

Table 4. Univariate analysis of predictors of primary and secondary endpoints at 1 year in the not-reduced heart rate (HR) group.

	Primary endpoint		Secondary endpoint	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Demographics				
Age, per 10 years	1.46 (1.05–2.02)	**0.02**	1.13 (0.92–1.38)	0.24
Male	0.81 (0.36–1.82)	0.61	0.88 (0.51–1.51)	0.63
BMI, per 1 kg/m^2	0.95 (0.87–1.04)	0.24	0.97 (0.92–1.02)	0.24
Heart failure				
LVEF, per 5%	0.78 (0.56–1.07)	0.12	0.80 (0.65–0.98)	**0.03**
Medical history				
Hypertension	1.66 (0.70–3.96)	0.25	0.84 (0.50–1.41)	0.50
Coronary artery disease	2.35 (0.89–6.23)	0.09	2.45 (1.27–4.72)	**0.01**
Peripheral artery disease	1.57 (0.54–4.56)	0.41	1.33 (0.63–2.80)	0.45
Diabetes	1.81 (0.84–3.92)	0.14	1.06 (0.61–1.82)	0.84
Chronic kidney disease	1.97 (0.83–4.69)	0.13	1.85 (1.03–3.32)	**0.04**
COPD	2.10 (0.84–5.23)	0.11	1.47 (0.74–2.89)	0.27
Stroke	0.00 (0.00→999)	0.99	0.97 (0.30–3.10)	0.96
Clinical status at admission				
NYHA class, per 1 class	1.93 (1.13–3.31)	**0.02**	1.38 (0.97–1.94)	0.07
SBP, per 10 mmHg	0.98 (0.84–1.13)	0.75	0.95 (0.85–1.06)	0.36
DBP, per 10 mmHg	0.69 (0.52–0.91)	**0.009**	0.87 (0.72–1.06)	0.17
HR, per 10 bpm	0.96 (0.68–1.37)	0.83	1.30 (1.03–1.64)	**0.03**
QRS duration, per 10 ms	1.08 (0.96–1.22)	0.18	1.04 (0.94–1.14)	0.42
Cardiogenic shock	0.00 (0.00→999)	0.99	0.00 (0.00→999)	0.99
VF or VT as a cause of admission	0.30 (0.04–2.18)	0.23	0.61 (0.25–1.53)	0.30
ACS as a cause of admission	0.63 (0.22–1.83)	0.40	0.88 (0.46–1.69)	0.70
Laboratory findings at admission				
Serum sodium, per 1 mmol/L	0.90 (0.82–0.99)	**0.03**	0.90 (0.84–0.97)	**0.003**
Serum potassium, per 1 mmol/L	1.52 (0.85–2.72)	0.15	1.19 (0.77–1.83)	0.43
Serum creatinine, per 1 mg/dL	1.89 (1.27–2.80)	**0.002**	1.42 (1.03–1.97)	**0.04**
Hemoglobin, per 1 g/dL	0.84 (0.72–0.99)	**0.04**	0.89 (0.79–0.996)	**0.04**
Major management during index hospitalization, clinical status and laboratory findings at discharge				
PCI/CABG during hospitalization	0.44 (0.10–0.87)	0.27	0.67 (0.30–1.48)	0.32
HR, per 10 bpm	1.05 (0.87–1.28)	0.59	1.06 (0.95–1.19)	0.31
SBP, per 10 mmHg	0.79 (0.62–1.00)	0.053	0.80 (0.68–0.93)	**0.005**
DBP, per 10 mmHg	0.56 (0.42–0.82)	**0.0015**	0.97 (0.57–0.94)	**0.016**
Pharmacotherapy at hospital admission				
Diuretics	2.31 (0.87–6.12)	0.09	2.61 (1.36–5.03)	**0.004**
Aldosterone antagonist	1.16 (0.53–2.55)	0.71	1.82 (1.08–3.06)	**0.02**
ACEI	0.97 (0.43–2.21)	0.95	0.96 (0.56–1.65)	0.89
ARB	0.46 (0.06–3.39)	0.44	0.95 (0.38–2.38)	0.92
Beta-blocker	1.36 (0.51–3.62)	0.54	1.28 (0.68–2.41)	0.45
Pharmacotherapy prior hospital discharge				
Diuretics	0.93 (0.37–2.32)	0.88	1.22 (0.63–2.35)	0.55
Aldosterone antagonist	1.21 (0.32–2.78)	0.65	1.59 (0.89–2.86)	0.12
ACEI	0.38 (0.18–0.84)	**0.02**	0.42 (0.25–0.72)	**0.001**
ARB	0.40 (0.06–2.97)	0.37	0.82 (0.33–2.04)	0.67
Beta-blocker	0.68 (0.26–1.81)	0.44	0.71 (0.37–1.38)	0.31
Statins	0.87 (0.38–1.99)	0.74	1.04 (0.58–1.84)	0.90
Antiplatelets	0.75 (0.31–1.78)	0.51	1.04 (0.56–1.92)	0.91

Bolded values indicate p-values < 0.05. ACEI — angiotensin converting enzyme inhibitor; ACS — acute coronary syndrome; ARB — angiotensin receptor blocker; BMI — body mass index; CABG — coronary artery bypass grafting; COPD — chronic obstructive pulmonary disease; DBP — diastolic blood pressure; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; PCI — percutaneous coronary intervention; SBP — systolic blood pressure; VF — ventricular fibrillation; VT — ventricular tachycardia

Table 5. Multivariate analysis of predictors of primary and secondary endpoints at 1 year in the reduced heart rate group.

Primary endpoint	HR (95% CI)	P	Secondary endpoint	HR (95% CI)	P
Age, per 10 years	1.58 (1.22–2.07)	**< 0.001**	LVEF, per 5%	0.96 (0.90–1.02)	0.209
BMI, per 1 kg/m^2	0.96 (0.91–1.02)	0.217	Diabetes	1.40 (0.96–2.05)	0.080
Chronic kidney disease	1.44 (0.74–2.81)	0.280	Chronic kidney disease	1.34 (0.85–2.10)	0.206
NYHA class at admission	1.66 (1.09–2.54)	**0.019**	Stroke	1.62 (0.92–2.85)	0.096
Serum sodium at admission, per 1 mmol/dL	0.91 (0.86–0.97)	**0.003**	NYHA class at admission	1.29 (0.98–1.68)	0.065
Hemoglobin at admission, per 1 g/dL	0.98 (0.82–1.16)	0.790	SBP at admission, per 10 mmHg	0.89 (0.76–1.04)	0.297
Heart rate at discharge, per 10 bpm	0.98 (0.72–1.33)	0.886	Serum sodium at admission, per 1 mmol/dL	0.96 (0.92–1.00)	0.058
SBP at discharge, per 10 mmHg	0.67 (0.51–0.87)	**0.003**	Serum creatinine at admission, per 1 mg/dl	1.07 (0.77–1.49)	0.688
DBP at discharge, per 10 mmHg	1.27 (0.85–1.89)	0.242	Hemoglobin at admission, per 1 g/dL	0.99 (0.85–1.03)	0.188
Beta-blocker at discharge	0.84 (0.35–2.01)	0.697	SBP at discharge, per 10 mmHg	0.89 (0.76–1.04)	0.140
Statins at discharge	0.52 (0.26–1.02)	0.057	DBP at discharge, per 10 mmHg	1.03 (0.81–1.31)	0.827
			Prior diuretics usage	1.23 (0.82–1.87)	0.320

Bolded values indicates p-values < 0.05. BMI — body mass index; CI — confidence interval; DBP — diastolic blood pressure; HR — hazard ratio; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; SBP — systolic blood pressure

Table 6. Multivariate analysis of predictors of primary and secondary endpoints at 1 year in the not–reduced heart rate group.

Primary endpoint	HR (95% CI)	P	Secondary endpoint	HR (95% CI)	P
Age, per 10 years	1.25 (0.88–1.78)	0.213	LVEF, per 5%	0.95 (0.83–1.08)	0.422
NYHA class at admission	1.73 (0.93–3.21)	0.082	Coronary artery disease	2.13 (0.92–4.93)	0.078
DBP at admission, per 10 mmHg	0.90 (0.69–1.18)	0.432	Chronic kidney disease	1.38 (0.68–2.83)	0.377
Serum sodium at admission, per 1 mmol/dL	0.96 (0.85–1.07)	0.434	Serum sodium at admission, per 1 mmol/dL	0.95 (0.86–1.04)	0.259
Serum creatinine at admission, per 1 mg/dL	1.62 (0.98–2.70)	0.061	Serum creatinine at admission, per 1 mg/dL	1.02 (0.59–1.77)	0.942
Hemoglobin at admission, per 1 g/dL	0.93 (0.74–1.17)	0.543	Hemoglobin at admission, per 1 g/dL	0.97 (0.82–1.14)	0.684
DBP at discharge, per 10 mmHg	0.64 (0.43–0.95)	**0.026**	SBP at discharge, per 10 mmHg	0.90 (0.68–1.19)	0.441
ACEI at discharge	0.79 (0.30–2.04)	0.619	DBP at discharge, per 10 mmHg	1.09 (0.70–1.69)	0.705
			Prior aldosterone antagonist usage	1.22 (0.60–2.49)	0.584
			Prior diuretics usage	1.99 (0.84–4.72)	0.118
			ACEI at discharge	0.48 (0.23–0.99)	**0.047**

Bolded text indicates p-values < 0.05. ACEI — angiotensin converting enzyme inhibitor; BMI — body mass index; CI — confidence interval; DBP — diastolic blood pressure; HR — hazard ratio; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; SBP — systolic blood pressure

I_f inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) study revealed, that a baseline resting HR ≥ 70 bpm in comparison to HR < 70 bpm is associated with a significantly higher risk of several outcomes, including cardiovascular death, admission to hospital for HF, admission to hospital for myocardial infarction and coronary revascularization [9]. Moreover, in the SHIFT (Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial) trial conducted on patients with chronic HF, the placebo-treated group with HR values ≥ 87 bpm had significantly higher risk for the primary composite endpoint (cardiovascular death or hospital admission for worsening HF) in comparison to the placebo-treated patients with HR from 70 to 72 bpm [17]. In the ivabradine-treated group patients with HR < 60 bpm at 28 days of treatment the primary composite endpoint occurred less frequently during the observation in comparison to the group of patients with higher values of HR and the observed effect of ivabradine was shown to be HR reduction-dependent [17]. The ESC-HF-Pilot and ESC-HF-LT Registries did not include information concerning the in-hospital use of ivabradine.. The analysis of hospitalized HF with reduced ejection fraction (HFrEF) patients enrolled in the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan) trial showed, that baseline HR was not associated with all-cause mortality. However at the level of ≥ 70 bpm, each 5-beat increase observed at 1 and 4 weeks following discharge was a predictor of all-cause mortality [18]. The study conducted by Kapoor et al. [19] enrolled patients with HF with preserved ejection fraction (HFpEF) revealed that all-cause mortality at one year is significantly higher in patients with HR ≥ 60 bpm or more in comparison to the group with HR < 60 bpm. An interestingly high prevalence of digoxin usage was observed in both subgroups in the present analysis, however no difference between subgroups was observed. It is worth noting, that patients with paroxysmal atrial fibrillation were not excluded from the analysis and overall frequency of digoxin usage during the first years of data gathering was higher.

Analysis performed by Bui et al. [20] of HF hospitalized patients enrolled in the Get With The Guidelines-Hart Failure program showed a J-shaped correlation of in-hospital mortality and HR, whereas the lowest mortality rate was observed within HR values between 70 bpm and 75 bpm, moreover, higher HR at admission is independently associated with higher in-hospital mortality [20]. The analysis of the Acute Decompensated Heart Failure Syndromes [21] Registry revealed, that in patients hospitalized for acute HF lower baseline HR is associated with a significantly higher rate of in-hospital cardiac death [22]. Moreover, Lancellotti et al. [23] reported, that increased HR at 24–36 h following admission for acute HF is related to a higher risk of in-hospital mortality. The impact of higher HR at discharge on poor prognosis of HF patients has also been reported [24]. Habal et al. [24] analyzed a group of discharged HF patients and revealed a significant increase in all-cause 1-month mortality for the value of discharge HR ≥ 81 bpm in comparison to the control group with HR 61–70 bpm. Moreover, the group of patients with HR > 90 bpm had significantly increased risk of one-year all-cause mortality when compared to the controls (HR 40–60 bpm) and also had higher rate of HF readmissions and cardiovascular disease within 30 days [24].

Laskey et al. [12] reported, in patients with SR HR ≥ 75 bpm at hospital discharge increased the risk of 1-month and 1-year mortality and composite outcome of mortality and all-cause rehospitalization. The data concerning the impact of HR reduction on the prognosis of HF patients remains controversial. The results of the BEAUTIFUL study revealed no significant difference in the primary composite endpoint (cardiovascular death, admission to hospital for AMI and admission to hospital for new-onset or worsening HF) between ivabradine- and placebo-treated group [25]. However, in the subgroup of patients with HR ≥ 70 bpm, treatment with ivabradine significantly reduced the occurrence of coronary endpoints — admission to hospital for myocardial infarction (fatal and non-fatal), admission to hospital for myocardial infarction or unstable angina and coronary revascularization. In the present study only 1 patient from the HR reduction group was using ivabradine and this difference between the two analyzed groups of patients did not reach statistical significance. The Cardiac Insufficiency BIsoprolol Study II (CIBIS II) revealed, that the lowest baseline HR and greatest HR changed during 2 months following inclusion due to bisoprolol usage in HF patients significantly reducing 1-year mortality and HF admission rate [10]. Li et al. [26] reported, that in- and outpatients with HFrEF in SR, who were enrolled in the Swedish Heart Failure Registry, had significant relation of higher HR with increased mortality. BB use significantly reduced HR in comparison to non-treated group and was related to reduced mortality, however, treatment with BBs did not change the association between HR and all-cause mortality [26].

In the present analysis, differences in usage of BB were observed. Compared with the not-reduced HR group, in the HR reduced group fewer patients used BBs before admission and more of them used BBs at discharge from the hospital. However, these discrepancies did not reach statistical significance.

Conclusions

The current study evaluates the impact of in-hospital HR reduction during hospitalization in HF patients on 1-year mortality and rehospitalization. The results of the present study revealed that HR reduction during hospitalization for HF is not associated with outcome of patients with SR. Moreover, predictors of primary endpoint and secondary endpoint were similar in patients with and without HR reduction during index hospitalization.

Conflict of interest: None declared

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The comparison of endothelial function between conduit artery and microvasculature in patients with coronary artery disease

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Abstract

Background: *Flow-mediated dilation (FMD) and reactive hyperemia-peripheral arterial tonometry (RH-PAT) are both established modalities to assess vascular endothelial function. However, clinical significance of FMD and RH-PAT may be different because these methods measure vascular function in different vessels (conduit arteries and resistance vessels).*

Methods: *To elucidate differences in the clinical significance of FMD and RH-PAT, a simultaneous determination of FMD was performed and reactive hyperemia index (RHI) measured by RH-PAT in 131 consecutive patients who underwent coronary angiography for suspicion of coronary artery disease (CAD).*

Results: *There was no significant correlation between FMD and RHI in patients overall. When patients were divided into four groups: FMD ≥ 6%/RHI ≥ 1.67 group, FMD ≥ 6%/RHI < 1.67 group, FMD < 6%/RHI ≥ 1.67 group and FMD < 6%/RHI < 1.67 group, the highest incidence of multivessel CAD was seen in the FMD < 6%/RHI < 1.67 group (52%). Multiple logistic regression analysis showed that a prevalence of both FMD < 6% and RHI < 1.67 was an independent predictor of multivessel CAD (odds ratio: 4.160, 95% confidence interval: 1.505–11.500, p = 0.006). RHI was negatively correlated with the baseline vessel diameter (R = –0.268, p = 0.0065) and maximum vessel diameter (R = –0.266, p = 0.0069) in patients with FMD < 6%, whereas these correlations were absent in patients with FMD ≥ 6%.*

Conclusions: *Present results suggest that noninvasive assessment of vascular endothelial functions provide pathophysiological information on both conduit arteries and resistance vessels in patients with CAD.* (Cardiol J 2020; 27, 1: 38–46)

Key words: flow mediated-dilation, reactive hyperemia-peripheral arterial tonometry, reactive hyperemia index, vascular endothelial function, coronary artery disease

Introduction

The endothelium plays a seminal role in the regulation of vascular tone, new vessel growth, thrombogenicity, and inflammation [1]. Moreover, endothelial dysfunction is associated with cardiovascular events. Brachial artery flow-mediated dilation (FMD) and reactive hyperemia-peripheral arterial tonometry (RH-PAT) are established methods to assess vascular endothelial function. FMD measures the ability of the brachial artery to release endothelial nitric oxide (NO) during reactive hyperemia after a 5-min occlusion of the artery with a blood pressure cuff [2, 3]. Celermajer et al. [4] first observed this response in vivo by using ultrasound to measure changes in the diameter of the brachial artery, and later demonstrated this response to be mainly NO-dependent [5]. Importantly, peripheral vascular endothelial function as assessed by FMD correlates with coronary artery endothelial function [6]. In addition, FMD has independent prognostic value to predict future

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cardiovascular events that may exceed the predictive ability of traditional risk factors [7]. On the other hand, RH-PAT has been recently introduced as a new surrogate marker to evaluate endothelial function. RH-PAT is a noninvasive, automatic, and quantitative method of clinical assessment based on digital measurements of the hyperemic response [8]. Although FMD reflects endothelial function of large conduit arteries [9]. Reactive hyperemia index (RHI) as measured by RH-PAT reflects endothelial function of the microvasculature (i.e., resistance vessels) [10] and depends more on endothelium-derived hyperpolarizing factor (EDHF) than NO [11, 12]. However, endothelial function measured by RH-PAT also predicts cardiovascular events [13].

Although both FMD and RH-PAT can predict cardiovascular events, it was hypothesized that the clinical significance of these two vascular endothelial function tests in patients with cardiovascular diseases are different because these methods measure vascular function in different vessels (conduit arteries or resistance vessels). In this study, both FMD and RH-PAT-based RHI were simultaneously measured in patients with coronary artery disease (CAD) to elucidate differences in clinical significance of each method for assessment of vascular endothelial function.

Methods

Subjects and study outline

Simultaneous measurement of FMD and RH-PAT were performed in 131 consecutive patients, who underwent diagnostic coronary angiography due to suspicion of CAD (including stable angina pectoris, old myocardium infarction, coronary spastic angina and chest pain syndrome) at Dokkyo Medical University Hospital. Patients were excluded if they had acute coronary syndrome, valvular heart disease, atrial fibrillation/flutter, permanent pacemaker implantation, impaired left ventricular systolic function (left ventricular ejection fraction < 40%), aortic dissection, malignancy or serious liver diseases, or were on hemodialysis. The Dokkyo Medical University review board approved the study protocol, and written informed consent was obtained from each patient.

Simultaneous measurement of FMD and RHI

Simultaneous measurement of FMD and RHI was performed in the morning of the day before coronary angiography, according to the method previously described by Tomiyama et al. [14]. In brief, the subjects were instructed to fast overnight and to abstain from alcohol, smoking, caffeine and antioxidant vitamins for at least 12 h before the measurements. They were asked to rest in the sitting position in a quiet, dark, air-conditioned room (22°C to 25°C) for 5 min. Then, they were asked again to rest for at least 15 min in the supine position in the same room before FMD and RH-PAT procedures. Blood pressure was measured in the left arm using a mercury sphygmomanometer with an appropriately sized cuff and recorded to the nearest 2 mmHg. After blood pressure was measured, a 10-MHz linear array ultrasound transducer (Unex EF 18G, UNEX Corp., Nagoya, Japan) was placed on the proximal right brachial artery to measure FMD, and the manchette was rolled at the forearm. For the RH-PAT procedure (EndoPAT-2000, Itamar Medical Ltd., Caesarea, Israel), a peripheral arterial tonometry probe was placed on the right index finger and a control tonometry probe was also placed on the left index finger to eliminate sympathetic nerve effects. The RH-PAT probes were exchanged for each patient. For FMD measurement, ultrasound longitudinal images were recorded at baseline and continuously from 30 s before to ≥ 2 min after cuff deflation following compression with a cuff pressure that was 50 mmHg above the systolic blood pressure of the right forearm for 5 min. The diastolic diameter of the brachial artery was determined semi-automatically using an instrument equipped with software for monitoring the brachial artery diameter. FMD was estimated as percent change of brachial artery diameter at maximal dilation during hyperemia compared with the baseline value. In the RH-PAT procedure, the RHI value was calculated as the ratio of reactive hyperemia between two hands. Moreover, other parameters obtained during the FMD procedure such as baseline vessel diameter, maximum vessel diameter and blood flow velocity increase (maximum blood flow velocity/baseline blood flow velocity) were also measured after forearm cuff deflation following compression.

Assessment of the results of coronary angiography

The angiographic findings were visually assessed for all atherosclerotic coronary lesions by an investigator who was unaware of the study design. According to the classification of the American Heart Association, the percent diameter stenosis was evaluated for each lesion and the lesion location was assessed. The number of affected vessels

was assessed, considering that ≥ 75% diameter stenosis was a significant atherosclerotic coronary lesion. If there were no significant stenotic lesions, provocation of coronary artery spasm was performed with an intracoronary injection of acetylcholine. Acetylcholine chloride was injected in incremental doses of 25 and 50 μg into the right coronary artery and of 25, 50, and 100 μg into the left coronary artery over 20 s, with at least a 3 min interval between each injection. The patients who had a positive acetylcholine test were diagnosed with coronary spastic angina and those with a negative acetylcholine test were diagnosed with chest pain syndrome.

Coronary risk factor assessment

Prior to FMD and RH-PAT procedures, information on coronary risk factors such as hypertension, diabetes, dyslipidemia and smoking habit were obtained from each patient, as well as information on medication usage. Height and body weight were measured, and body mass index (BMI) was calculated as body weight (kg)/(height [m])^2. Blood pressure was measured using a mercury sphygmomanometer with an appropriately sized cuff and recorded to the nearest 2 mmHg. Just after FMD and RH-PAT procedures, peripheral blood samples were taken via the antecubital vein. Serum creatinine level was measured using an enzymatic method, and the estimated glomerular filtration rate (eGFR) was calculated by a formula provided by the Japanese Society of Nephrology Chronic Kidney Disease (CKD) Practice Guide: eGFR (mL/min/1.73 m^2) = 194 × (serum creatinine level [mg/dL])$^{-1.094}$ × (age [y])$^{-0.287}$. The product of this equation was multiplied by a correction factor of 0.739 for women [15]. Total cholesterol (TC) and triglyceride (TG) levels were determined using enzymatic methods, high-density lipoprotein cholesterol (HDL-C) was measured using the precipitation method and low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula: LDL-C = TC – HDL-C – (TG/5). The LDL-C could not be calculated in those patients with a triglyceride level over 400 mg/dL. Hemoglobin A1c was measured by high-performance liquid chromatography and values were expressed according to the National Glycohemoglobin Standardization Program.

Statistical analysis

Data were expressed as the mean ± standard deviation (SD) or median and interquartile range. Normality for distribution of continuous variables was assessed using the Shapiro-Wilk test. Multiple group comparisons were performed using one-way analysis of variance followed by the post-hoc Bonferroni test for continuous variables and the Fisher exact test for categorical variables. Intra-group comparisons for normally distributed continuous variables were performed using an unpaired t test. The correlation between two variables was determined by the Pearson correlation coefficient. Logistic regression analysis was performed to predict multi-vessel CAD using age, gender, various risk factors and vascular endothelial function parameters as independent variables. Variables that could predict multi-vessel disease using a simple logistic regression model were first we determined, then multiple regression analysis was performed using the variables identified by the simple logistic regression model. All statistical analyses were performed using the statistical package for Social Science (Dr. SPSS II for Windows, SPSS Inc., Tokyo, Japan). $P < 0.05$ was considered significant.

Results

Relationship between both values of FMD and RHI

In all 131 patients, there was no significant correlation between FMD and RHI ($R = 0.119$). Then, the patients were divided into four groups, based on cut off values of 6% for FMD and 1.67 for RHI, according to previous reports [16, 17], i.e., FMD ≥ 6%/RHI ≥ 1.67 group (n = 22; 17%), FMD ≥ 6%/RHI < 1.67 group (n = 7; 5%), FMD < 6%/ /RHI ≥ 1.67 group (n = 81; 62%) and FMD < 6%/ /RHI < 1.67 group (n = 21; 6%) (Fig. 1). Baseline characteristics were compared among these four groups. There were no significant differences among the four groups in age, sex, traditional risk factors and medications. All patients in groups with RHI < 1.67 had significant coronary artery stenosis. In the FMD < 6%/RHI ≥ 1.67 group, 86% of patients had stable angina. The incidence of old myocardial infarction and multi-vessel CAD (≥ 2 vessels) were both higher in FMD < 6% groups, compared with FMD ≥ 6% groups. Among the four groups, the highest incidence of multi-vessel CAD was seen in the FMD < 6%/RHI < 1.67 group (52% of patients in this group) (Table 1).

Prediction of multi-vessel CAD using FMD and RHI

In all 131 patients, multi-vessel CAD was seen in 34 (26.0%) patients. Logistic regression analysis was performed to try to discriminate the

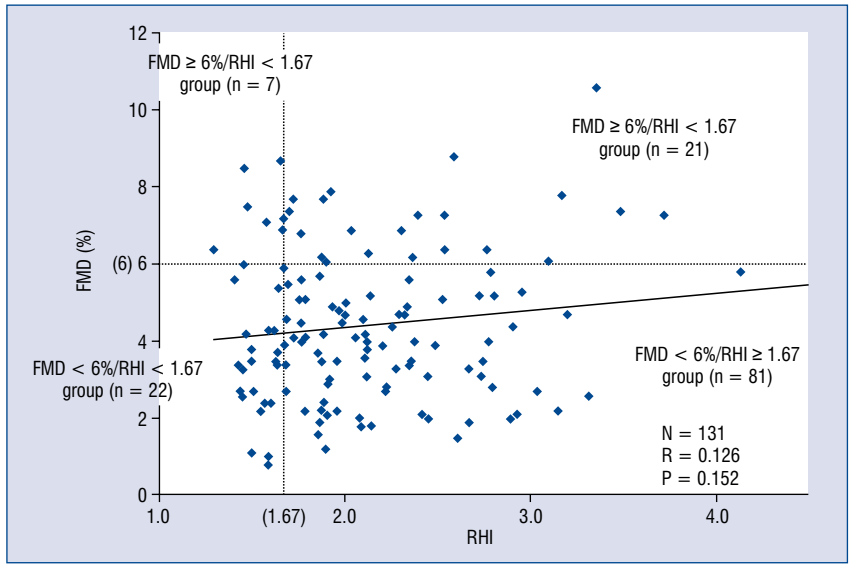

Figure 1. The relationship between flow-mediated dilation (FMD) and reactive hyperemia index (RHI) measured by reactive hyperemia-peripheral arterial tonometry in all patients. There was no significant correlation between FMD and RHI. Then, patients were divided into four groups, according to cut-off values of 6% for FMD and 1.67 for RHI: FMD ≥ 6%/ /RHI ≥ 1.67 group, FMD ≥ 6%/RHI < 1.67 group, FMD < 6%/ RHI ≥ 1.67 group and FMD < 6%/RHI < 1.67 group.

34 multi-vessel CAD patients from the remaining 97 patients who had no coronary artery stenosis or just single-vessel disease. In simple logistic regression analysis, age, gender, coronary risk factors and vascular endothelial function parameters to predict multi-vessel disease were used. These analyses showed that the prevalence of both FMD < 6% and RHI < 1.67 was a significant predictor of multi-vessel disease (odds ratio [OR]: 4.161, 95% confidence interval [CI]: 1.574–10.998, p = 0.004); and age (OR: 1.026, 95% CI: 0.986–1.067, p = 0.206), BMI (OR: 1.077, 95% CI: 0.974–1.190, p = 0.149), systolic blood pressure (OR: 1.020, 95% CI: 0.996–1.045, p = 0.109), hemoglobin A1c (OR: 1.439, 95% CI: 0.892–2.322, p = 0.136) and eGFR (OR: 0.981, 95% CI: 0.957–1.006, p = 0.128) were potential predictors (p < 0.3) (Fig. 2). Multiple logistic regression analysis using all of these variables showed that only the prevalence of both FMD < 6% and RHI < 1.67 independently predicted multi-vessel CAD (OR: 4.160, 95% CI: 1.505–11.500, p = 0.006) (Table 2).

RHI and the other parameters measured with FMD

Next, other parameters measured during the FMD procedure separately in 29 patients with FMD ≥ 6% and 102 patients with FMD < 6% were assessed. In the patients with FMD ≥ 6%, there were no significant differences in baseline vessel diameter, maximum vessel diameter and blood flow velocity increase between 22 patients with RHI ≥ 1.67 and 7 patients with RHI < 1.67. In patients with FMD < 6%, there were also no significant differences in these other parameters among 81 patients with RHI ≥ 1.67 and 21 patients with RHI < 1.67 (Table 3). However, RHI was negatively correlated with the baseline vessel diameter (R = –0.268, p = 0.0065) and maximum vessel diameter (R = –0.266, p = 0.0069) in the patients with FMD < 6%, whereas these correlations were absent in patients with FMD ≥ 6% (Fig. 3).

Discussion

In the present study, it was first demonstrated that FMD and RHI were not correlated in patients who underwent coronary angiography for the suspicion of CAD. Next, patients were divided into four groups, based on cut off values of 6% for FMD and 1.67 for RHI. As a result, 62% of the patients showed FMD < 6% but RHI ≥ 1.67, and 52% of patients with FMD < 6% and RHI < 1.67 had multi-vessel CAD. Multiple regression analysis showed that the prevalence of both FMD < 6% and RHI < 1.67 independently predicted multi-vessel CAD. Finally, the relationship was assessed between other parameters measured during the FMD procedure and RHI. As a result, RHI was negatively correlated with brachial artery diameter in patients

Table 1. Baseline characteristics.

	Normal FMD/ /normal RHI (n = 22)	Normal FMD/ /low RHI (n = 7)	Low FMD/ /normal RHI (n = 81)	Low FMD/ /low RHI (n = 21)	P
Age [years]	64 ± 10	70 ± 7	67 ± 12	69 ± 8	0.413
Male gender	17 (77%)	5 (71%)	62 (77%)	20 (95%)	0.266
Body mass index [kg/m^2]	25.2 ± 4.1	25.5 ± 3.3	23.6 ± 3.6	24.8 ± 3.2	0.137
Risk factors:					
Hypertension	16 (73%)	5 (71%)	55 (68%)	13 (62%)	0.891
Diabetes	10 (45%)	2 (29%)	36 (44%)	14 (67%)	0.218
Dyslipidemia	19 (83%)	19 (83%)	12 (80%)	12 (80%)	0.207
Smoking	16 (72%)	4 (57%)	53 (65%)	14 (67%)	0.874
Systolic blood pressure [mmHg]	131 ± 17	128 ± 14	134 ± 18	132 ± 14	0.959
LDL-cholesterol [mg/dL]	94 ± 23	79 ± 13	82 ± 23	78 ± 24	0.103
HDL-cholesterol [mg/dL]	48 ± 13	43 ± 12	50 ± 14	45 ± 13	0.911
Triglyceride [mg/dL]	111 ± 75	74 ± 38	88 ± 52	75 ± 57	0.166
Hemoglobin A1c [%]	6.3 ± 0.9	6.1 ± 0.5	6.3 ± 0.8	6.5 ± 0.7	0.700
Creatinine [mg/dL]	0.79 ± 0.16	0.77 ± 0.17	0.8 ± 0.2	0.9 ± 0.2	0.226
eGFR [mL/min/1.73 m^2]	75.4 ± 15.1	71.8 ± 9.3	73.1 ± 17.2	67.2 ± 16.6	0.399
Medications:					
ACEI/ARBs	8 (36%)	5 (71%)	33 (41%)	7 (33%)	0.090
Sulfonylureas	3 (14%)	0 (0%)	10 (12%)	3 (14%)	0.777
Insulins	1 (5%)	0 (0%)	3 (4%)	0 (0%)	0.762
Statins	16 (73%)	6 (86%)	64 (79%)	21 (100%)	0.096
Basal disease:					
Stable angina pectoris	6 (27%)	6 (86%)	21 (68%)	5 (23%)	0.009
Old myocardial infarction	11 (50%)	1 (14%)	48 (59%)	16 (76%)	0.030
Coronary spastic angina	4 (18%)	0 (0%)	7 (9%)	0 (0%)	0.150
Chest pain syndrome	1 (5%)	0 (0%)	5 (6%)	0 (0%)	0.611
Affected vessel number:					
No stenotic lesion	5 (23%)	0 (0%)	12 (15%)	0 (0%)	0.099
Single vessel disease	16 (73%)	4 (57%)	49 (60%)	10 (48%)	0.364
Multi-vessel disease	1 (5%)	3 (43%)	20 (25%)	11 (52%)	0.005

ACEI — angiotensin converting enzyme inhibitors; ARB — angiotensin receptor blocker; eGFR — estimated glomerular filtration rate; FMD — flow-mediated dilation; HDL — high density lipoprotein; LDL — low density lipoprotein; RHI — reactive hyperemia index

with low FMD, whereas a correlation was absent in patients with normal FMD.

Flow-mediated dilation and RH-PAT are both extremely effective noninvasive methods of evaluating vascular endothelial function, but have some physiological and clinical differences that depend on the vessels evaluated with each method. There are only a few studies that examined the relationship between FMD and RH-PAT based on RHI. Dhindsa et al [18]. demonstrated that FMD was significantly and positively associated with RHI in apparently healthy normotensive subjects. The Framingham Heart Study demonstrated that FMD and RHI were not correlated in multivariable models [19], whereas the Gutenberg Heart Study showed a modest correlation [20]. However, in both of these studies, FMD, which represents endothelial function of large conduit arteries, and was particularly sensitive to impairment by traditional risk factors. In contrast, RHI, which represents endothelial function of resistance vessels, was more sensitive to metabolic risk factors, such as diabetes and obesity. Moreover, endothelial dysfunction in the conduit arteries and resistance vessels could also reflect different stages of atherosclerosis. Endothelial dysfunction in conduit arteries might

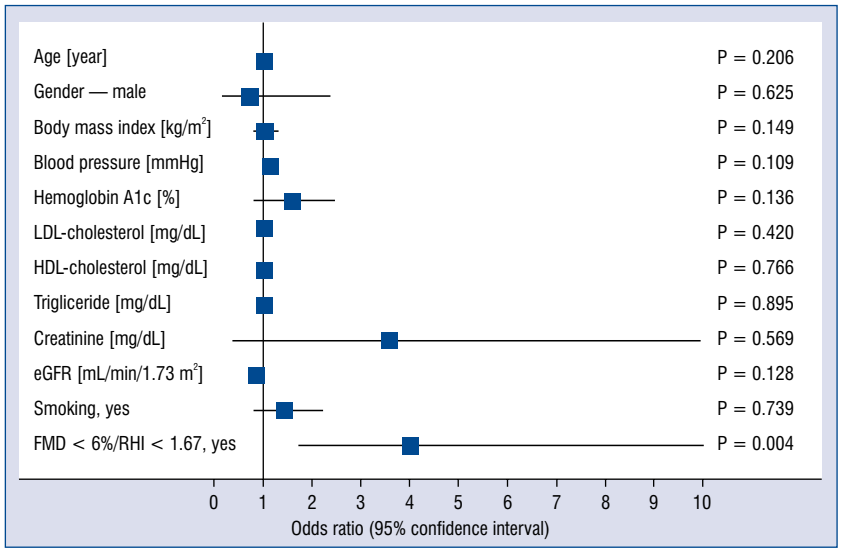

Figure 2. Simple logistic regression model to determine variables that predicted multi-vessel coronary artery disease. The prevalence of both flow-mediated dilation (FMD) < 6% and reactive hyperemia index (RHI) < 1.67 was a significant predictor of multi-vessel disease; age, body mass index, systolic blood pressure, hemoglobin A1c and estimated glomerular filtration rate (eGFR) were also potential predictors of multi-vessel disease; HDL — high density lipoprotein; LDL — low density lipoprotein.

Table 2. Multiple logistic regression analysis for prediction of multi-vessel coronary artery disease.

	Wald λ^2	Odds ratio	95% CI	P
Age [years]	0.609	1.002	0.968–1.079	0.435
Body mass index [kg/m^2]	1.151	1.068	0.947–1.204	0.283
Systolic blood pressure [mmHg]	1.133	1.016	0.987–1.045	0.287
Hemoglobin A1c [%]	1.200	1.346	0.791–2.289	0.273
eGFR [mL/min/1.73 m^2]	0.183	0.993	0.964–1.024	0.669
FMD < 6%/RHI < 1.67, yes	7.549	4.160	1.505–11.500	0.006

CI — confidence interval; eGFR — estimated glomerular filtration rate; FMD — flow-mediated dilation; RHI — reactive hyperemia index

Table 3. Other parameters measured during flow-mediated dilation (FMD) procedure.

	FMD ≥ 6% (n = 29)			FMD < 6% (n = 102)		
	RHI ≥ 1.67 (n = 22)	RHI < 1.67 (n = 7)	P	RHI ≥ 1.67 (n = 81)	RHI < 1.67 (n = 21)	P
Baseline vessel diameter [mm]	3.93 ± 0.53	3.69 ± 0.60	0.313	4.31 ± 0.56	4.46 ± 0.64	0.313
Maximum vessel diameter [mm]	4.21 ± 0.56	3.95 ± 0.63	0.314	4.47 ± 0.57	4.60 ± 0.64	0.380
Blood flow velocity increase	5.68 ± 2.42	4.17 ± 1.46	0.133	4.83 ± 2.00	4.93 ± 2.55	0.844

RHI — reactive hyperemia index

be more important in patients with existing atherosclerosis, whereas that in resistance vessels might be an early indicator of arteriosclerosis risk [19–21]. Recently, Tomiyama et al. [14] found no correlation between FMD and RH-PAT when the two parameters were measured simultaneously, and results were similar to the present results. They demonstrated that autonomic nervous activation, especially sympathetic nerve activation induced by reactive hyperemia, affected RHI more than FMD.

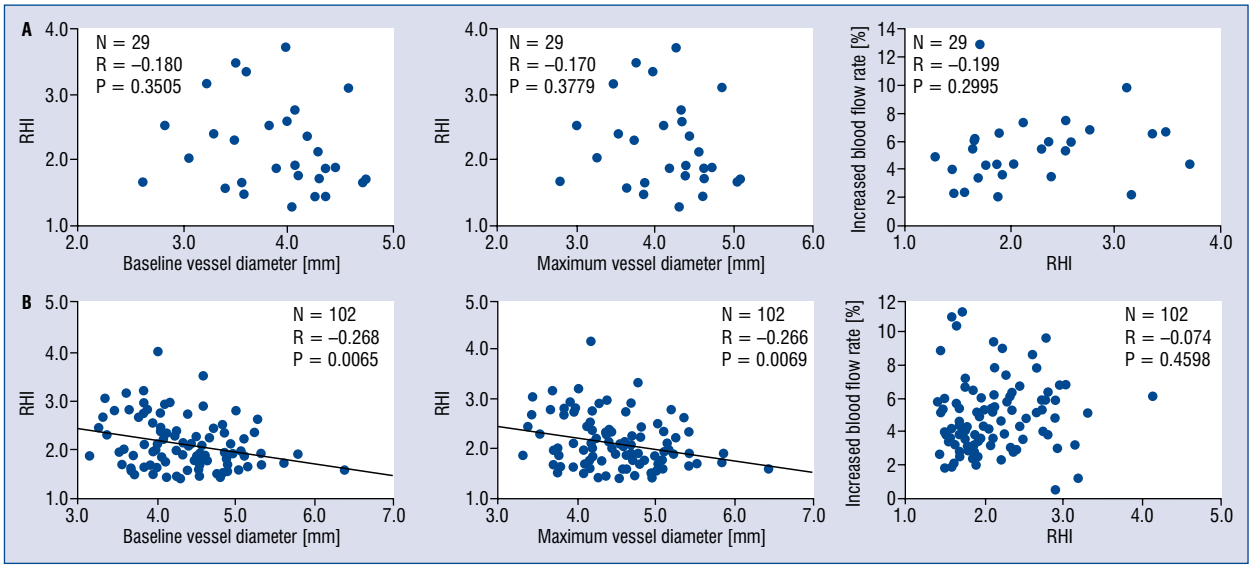

Figure 3. The correlation between reactive hyperemia index (RHI) and the other parameters obtained during flow-mediated dilation (FMD) procedure. **A.** In patients with FMD ≥ 6%, there were no significant correlations; **B.** In patients with FMD < 6%, however, RHI was negatively correlated with the baseline vessel diameter and maximum vessel diameter.

Although the relationship between FMD and RHI is controversial as described above, there was no correlation between these two parameters In all patients in the present study. However, analysis herein, after dividing patients into four groups provided some new information. Patients with stenotic lesions (i.e., coronary spastic angina or chest pain syndrome) were present in groups with low RHI. In addition, the highest incidence of multi-vessel CAD was seen in the group with the prevalence of both FMD < 6% and RHI < 1.67. This result suggests that the presence of low values of both FMD and RHI would be a strong risk factor for severe CAD. Furthermore, multiple regression analysis showed that the incidence of both FMD < 6% and RHI < 1.67 could independently predict multi-vessel CAD also supports this suggestion. Woo et al. [22] compared FMD and RHI in patients with CAD and demonstrated that the value of each parameter was significantly lower in patients with multi-vessel and complex CAD. Their receiver-operating characteristic curve analysis showed that both FMD and RHI had a similar value for predicting the presence of CAD and its complexity. They concluded that RH-PAT would be a more useful method for evaluating vascular endothelial function in patients with CAD, because it is less operator-dependent and it is noninvasive compared with FMD. According to the present results, however, it is envisioned herein that the assessment of vascular endothelial functions of both conduit arteries and resistance vessels using the simultaneous measurement of FMD and RH-PAT would be more sensitive for the prediction of severe CAD.

Another novel finding of the present study is that RHI was negatively correlated with brachial artery diameter at baseline as well as at the maximum response after forearm cuff deflation following compression in patients with FMD < 6%, whereas these correlations were absent in patients with FMD ≥ 6%. Thus, lower RHI is associated with larger baseline brachial artery diameter, since the change in vessel diameter at maximum response after forearm cuff deflation was small in cases with low FMD. This result suggests that reactive hyperemic flow response of resistance vessels might depend on vascular remodeling in the conduit artery. Endothelial function contributes to the maintenance of vasodilator tone by endothelium-dependent relaxing factors, including NO and EDHF [11, 12]. Endothelium-dependent vasodilation in the conduit artery is mediated mainly by NO, whereas the dilation of resistance vessels is mediated by NO and EDHF together [23]. In patients with low FMD, basal NO bioavailability might decrease. Since decreased NO bioavailability leads to positive vessel remodeling [24], it is postulated that EDHF contributes more to the endothelium-dependent vascular response in resistance vessels than NO in CAD patients with low FMD.

Limitations of the study

The present study has several potential limitations. First, the sample size was too small to draw definitive conclusions. Although it was suggested that both low FMD and low RHI are risk factors for severe CAD, the number of patients in this group was small. In addition, a negative correlation was observed between RHI and brachial artery diameter in patients with FMD < 6%, but not in those with FMD ≥ 6%. However, the number of patients with FMD ≥ 6% was small (n = 29), whereas there were 81 patients with FMD < 6%, so the absence of a correlation in patients with FMD ≥ 6% may be a type II error. Further assessment using a larger number of patients is needed. Second, this study was a cross-sectional study, and logistic regression analysis was used to discriminate patients with multi-vessel disease from others. To evaluate the value of FMD and RH-PAT to predict severe CAD, a prospective observational study is required. Finally, the mechanism for correlation between RHI and brachial artery diameter in patients with FMD < 6% may be somewhat speculative. Even considering these limitations, however, it is believed that this study showed important and clinically significant differences between FMD and RHI, and the advantages of simultaneous measurement of both values.

Conclusions

From the present study it can be envisioned that noninvasive assessment of vascular endothelial functions provide pathophysiological information on both conduit arteries and resistance vessels, and that this information is relevant to CAD. A unique classification by simultaneous measurement of FMD and RHI would allow the prediction of the severity of the coronary artery lesions and the presence of advanced atherosclerotic CAD.

Conflict of interest: None declared

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Implantation of the Micra transcatheter pacing system: Single Polish center experience with the real costs of hospitalization analysis

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Abstract

Background: *The Micra transcatheter pacing system (TPS) is a miniaturized, single-chamber pacemaker system. Study reported herein is an initial experience with implantation of the Micra TPS.*

Methods: *The leadless pacemaker was implanted in 10 patients with standard indications for a permanent pacemaker implantation. All hospitalization costs were calculated for all patients.*

Results: *The mean age of the patients was 75 ± 7.1 years, 6 were men and 4 were women. Four patients had permanent atrial fibrillation as the basal rhythm and 6 patients had sinus rhythm. All patients had at least one relative contraindication that precluded the use of a traditional pacing system. Mean intraoperative ventricular sensing amplitude was 10.6 ± 5.4 mV, impedance 843 ± 185 ohms, and pacing threshold at 0.24 ms was 0.56 ± 0.23 V. At discharge, those values were 13.9 ± 5.6 mV, 667 ± 119 ohms and 0.47 ± 0.17, respectively. The mean duration of implantation procedure was 82 min, while mean fluoroscopy time was 3.5 min. Two patients developed hematoma at the groin puncture site post-implantation. In 1 case there was a need for erythrocyte mass transfusion and surgical intervention. Mean total time of hospitalization was 26 days and time from procedure to discharge 12 days. Average cost of hospitalization per 1 patient was 11,260.15 EUR minimal cost was 9,052.68 EUR, while maximal cost was 16,533.18 EUR.*

Conclusions: *Implantation of leadless pacemakers is feasible, safe and provides advantages over the conventional system. Hospitalization costs vary for individual patients in wide range.* (Cardiol J 2020; 27, 1: 47–53)

Key words: leadless pacemakers, complications, procedure cost, hospitalization cost

Introduction

Recent advances in miniaturization technologies and battery chemistries have made it possible to develop a pacemaker small enough to implant within the heart while still aiming to provide similar effectiveness and durability to conventional pacemakers. The Micra transcatheter pacing system (Micra TPS) (Medtronic, USA) is a miniaturized single-chamber pacemaker system that is implanted directly to the right ventricle, eliminating the need for device pocket creation or insertion of a pacing lead, thereby avoiding some of the complications associated with traditional

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pacing systems [1, 2]. This emerging technology has the potential to significantly improve outcomes associated with a need for long-term pacing and can help patients get back to work and limit disability or restrictions to lifestyle [3, 4].

In the present single-center observational study, an initial experience with implantation of the Micra TPS is reported.

Methods

Procedure

The Micra TPS is a single chamber ventricular pacemaker. The device is attached to a steerable catheter delivery system with catheter and is inserted through a femoral vein with the use of a 23-French (outer diameter 27 F) introducer sheath. The delivery system is advanced into the right ventricle (RV), and the device is affixed to the myocardium with four electrically inactive nitinol tines located at the distal end of the device. If optimal electrical measurement results are not achieved the system is fully repositionable while the device is still connected to the delivery system. After verification of adequate electrical parameters and device fixation to the endocardium the device is released and delivery system is removed. According to this local strategy vascular access site was closed with subcutaneous absorbable double 'figure-of--eight' suture followed by 4 h bandage compression used for the access site in the groin [5].

Duration of procedure (from femoral vein puncture to venous access closure), fluoroscopy time, number of device repositions, periprocedural electrical measurements (sensing, threshold and impedance) and in-hospital adverse events related to procedure were evaluated.

Patients

All patients had classic indications for permanent pacing system implantation. Patients with sinus rhythm were not excluded if they had relative or absolute contraindication to traditional pacemaker implantation. Prior to procedure patients and their family members were informed of the characteristics of the new system, indications and potential complications. Informed consent was obtained.

Costs of hospitalization analysis

All costs of hospitalization were calculated and summed up for each patient. Costs were divided into following categories: Micra TPS device, medical materials excluding Micra TPS (disposable materials related to the procedure, pacemaker introducer), pharmaceuticals (e.g. oral drugs, antibiotics, disinfectants, analgesics), operating theatre staff (e.g. electrophysiologists, scrub nurse, personal costs of analgesia), cardiology department staff (e.g. cardiologists, nurses), additional laboratory tests (e.g. blood group, morphology, electrolytes, C-reactive protein, procalcitonin, natriuretic peptides, viral antigens and antibodies, clotting), additional non-laboratory tests (e.g. echocardiography, X-ray), additional non-medical costs (e.g. materials and energy, linen, maintenance materials, office supplies, informatics and information technology, laboratory reagents, medical gases, electricity, heat, water, permanent foreign services, minor repair of hardware, postage and telephone charges — non-medical indirect costs, management).

Results

Baseline characteristics

The Micra TPS implantation was attempted in 10 patients with 100% success rate. All patients had standard indication for a permanent pacemaker implantation, i.e. third-degree atrioventricular block (40%), second-degree atrioventricular block (30%), symptomatic sick sinus syndrome (20%), bradycardia-tachycardia syndrome (10%). The mean age of patients was 75 ± 7.6 years, 6 were men and 4 were women. Four patients had permanent atrial fibrillation (AF) as basal rhythm and 4 patients had paroxysmal AF or atrial flutter. Over half of the patients had a previously implanted cardiac electronic device including cardiac resynchronization therapy. In addition, all patients had at least one condition that precluded the use of a traditional pacing system, i.e. history of implantable cardiac electronic device (ICED) related infection (60%), lack of vascular access on one site and the need to preserve venous system for hemodialysis on opposite site (20%) and post mastectomy bilateral upper limb lymphedema (10%). Patien characteristics and basic procedural data are summarized in Table 1.

Procedure

All the devices were implanted through the right femoral vein to the septum of RV. In 50% of patient there was no need for any repositioning of the system and the position of the device had to be changed ≥ 2 times only in 2 patients due to suboptimal pacing threshold or sensing value. Mean procedure time in the present population was 82 min (from femoral vein puncture to vascular

Table 1. Patient characteristics and implantation data.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
CLINICAL CHARACTERISTICS										
Sex	Male	Male	Male	Male	Female	Female	Female	Female	Male	Male
Age [years]	73	66	78	79	77	80	84	63	88	78
Concomitant conditions	HTN DM CAD	CAD	HTN h/o AVR	HTN CKD stage 3	HTN CKD stage 3 COPD	DM CKD stage 5 MI (NSTEMI) CAD	DM CKD stage 3 h/o AVR h/o MVR	HTN DM h/o breast cancer (bilateral mastectomy)	HTN CKD stage 5 Kidney cancer (nephrectomy)	HTN DM CKD stage 5
Previous permanent pacemaker	Yes (VVI)	Yes (DDD)	No	Yes (VVI)	Yes (DDD)	No	Yes (VVI)	No	No	No
Previous CRT-P	No	Yes	Yes	No	No	No	No	No	No	No
Indication for MICRA	Sinus arrest with pauses > 10 s MAS	Bradycardia--tachycardia syndrome preMAS	AV block III	AV block II preMAS	AV block III MAS	AV block II MAS	AV block III	SSS MAS	AV block II (3:1)	AV block III
Contraindications for traditional pacemaker	PI LDIE	LDIE	PI	PI	PI	Thrombosis of brachio-cephalic vein (R), protection veins for hemodialysis	PI LDIE	Bilateral lymphedema	Thrombosis of arteriovenous fistula (L), protection veins for hemodialysis	Inactive arteriovenous fistula (L), dialysis catheter (R)
Basal rhythm + frequency [bpm]	AF permanent 80	SR (AF paroxysmal) 60	AF permanent 85	AF permanent 72	SR 70	SR (AF paroxysmal) 70	AF permanent 70	SR (AF/AFl paroxysmal) 60	SR 74	SR (AF paroxysmal) 40
LVEF [%]	55	62	39	60	60	60	56	60	59	34
Time from admission to implantation [days]	38	1	20	1	12	25	39	1	2	2
Time from implantation to discharge [days]	3	4	28	5	27	12	21	7	5	3
IMPLANTATION										
Total implantation time [h] (time from patient in to patient out)	1.30	1.30	1.10	1.45	0.55	1.20	1.25	1.15	1.05	1.45
Fluoroscopy time	2′18″	3′45″	1′50″	9′09″	1′58″	2′23″	2′21″	3′01″	1′54″	6′17″
No. of system repositions	0	1	0	1	0	0	2	1	0	2

→

Table 1 (cont.). Patient characteristics and implantation data.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Final position	Mid septum	Inferior septum	Mid septum	Mid septum	Mid septum	Mid septum	Mid septum	Mid septum	Mid septum	Mid septum
Device programming	VVI 60 bpm	VVI 60 bpm	VVIR 60–110 bpm	VVIR 70–110 bpm	VVI 55 bpm	VVI 60 bpm	VVIR 70–100 bpm	VVI 45 bpm	VVI 45 bpm	VVI 45 bpm
Complications	No	No	RGH, transfusion, surgical intervention	No	No	No	RGH	No	No	No
INTRAOPERATIVE ELECTRIC PARAMETERS										
Sensing [mV]	19.4	20	10.9	5.4	9.2	10.6	4.7	6.8	11.5	7.0
Impendence [Ohm]	870	1050	700	810	760	650	1200	980	620	790
Threshold at 0.24 ms [V]	0.3	0.75	0.6	0.8	0.38	0.38	0.38	1	0.63	0.38
ELECTRIC PARAMETERS AT HOSPITAL DISCHARGE										
Sensing [mV]	> 20	> 20	18.2	8.3	8.2	11.7	9.6	10.1	> 20	7.0
Impendence [Ohm]	680	740	630	710	720	480	870	570	610	790
Threshold at 0.24 ms [V]	0.38	0.75	0.34	0.5	0.5	0.5	0.25	0.75	0.38	0.38
COSTS OF HOSPITALIZATION ANALYSIS (IN EURO)										
Micra TPS	7 971	7971	7971	7971	7971	7971	7971	7971	7971	7971
Medical materials excluding Micra TPS	296	296	296	296	296	296	296	296	296	296
Intraoperative pharmaceutical costs	93	93	93	93	29	29	29	29	29	29
Operating theatre staff (calculated by hours of work)	159	159	317,27*	159	159	159	159	159	159	159
Cardiology department staff (calculated by days spent in the hospital)	2,490.55	303.73	3,093.17	364.47	2,369.06	2,247.57	3,471.28	462.84	404.98	983.53
Laboratory additional test	200.47	86.90	345.95	96.90	345.95	484	827.38	67.38	118.81	118.81
Non-laboratory additional test	105.95	50	105.95	85.71	180.95	369	505.95	67.86	67.86	67.86
Additional non-medical	755.47	92.13	884.46	110.56	718.62	681.77	1056.86	140.91	141.8	344.37
TOTAL	**12,071.44**	**9,051.78**	**13,106.80**	**9,176.64**	**12,069.58**	**12,237.34**	**14,316.47**	**9,193.99**	**9,188.45**	**9,673.57**

*Operating theatre was used for the second when surgical treatment of the groin bleeding was performed.
AF — atrial fibrillation; AFl — atrial flutter; AV — atrioventricular; AVR — aortic valve replacement; bpm — beats per minute; CAD — coronary artery disease; CKD — chronic kidney disease; COPD — chronic obstructive pulmonary disease; CRT-P — cardiac resynchronization therapy pacemaker; DM — diabetes mellitus; HTN — hypertension; IE — infective endocarditis; LDIE — lead-dependent infective endocarditis; LVEF — left ventricular ejection fraction; MI — myocardial infraction; MVR — mitral valve replacement; MAS — Morgagni-Adams–Stokes syndrome; PI — pocket infection; PLN — Polish zloty; RGH — right groin hematoma; SR — sinus rhythm; SSS — sick sinus syndrome; V — volts; h/o — history of

sheath removal) and mean fluoroscopy duration was 3.5 min. Mean procedure (from introducer insertion to introducer removal) and fluoroscopy time in post-approval registry was 34.8 min and 8.9 min, respectively.

The mean intraoperative sensing value was 10.6 ± 5.4 mV and the impedance was 843 ± 185 ohms. At discharge from hospital, those values were 13.9 ± 5.6 mV and 667 ± 119 ohms, respectively. The recommended pacing threshold value, i.e. ≤ 1 V at 0.24 ms was achieved in all patients. Mean procedure duration was 82 min (55–90 min), while mean fluoroscopy time was 3.5 min (minimal 1'50'' – maximal 9'09'').

Mean total time of hospitalization was 26 days (5–60 days) and time from procedure to discharge 12 days (3–21 days). During post-implantation period 2 (20%) patients developed hematoma at the groin puncture site. In 1 case there was a need for erythrocyte mass transfusion and surgical intervention. The second one was treated conservatively without any sequelae.

Adverse events

Two patients developed groin hematoma. The first patient developed large hematoma that was associated with anemization, required blood transfusion (6 units of blood) and surgical intervention. The second patient complained of groin pain.

Ultrasound imaging revealed relatively small hematoma that was absorbed spontaneously. What should be underlined, both patients had a history of valve replacement (mechanical aortic prosthesis in 1st case, mechanical aortic and mitral valve in 2nd case) and were under bridging anticoagulant therapy (low molecular weight heparin). In patients receiving vitamin K antagonists (VKA), treatment was continued until the international normalization rate was therapeutic (range of 2–3) and in patients on non-VKA, treatment discontinued at least 24 h before operation.

Costs of hospitalization analysis

Real costs of hospitalization for every patient are presented in Table 1. Average cost of hospitalization per 1 patient was 11,260.15 EUR (minimal = 9 051.68 EUR and maximal = 16,533.18 EUR). Average costs for each category were as follows: 8,267.66 EUR for medical materials; 54.58 EUR for pharmaceuticals; 174.5 EUR for operating theatre staff; 1,619.12 EUR (minimal = 303.73 EUR and maximal = 3,471.28 EUR) for cardiology department staff; 269.26 EUR (minimal = 67.38 EUR and maximal = 827.38 EUR) for laboratory additional test, 160.71 EUR for non-laboratory additional test; 492.69 EUR for additional non-medical costs.

Discussion

Elimination of leads and pocket with the introduction of leadless pacemakers offered potential advantages over conventional transvenous systems. Lead- and pocket-related complications are dominant adverse events associated with cardiac pacing [1, 2]. Pacing leads and the pacemaker as a high-volume foreign body become the background for CIED related infections that are associated with poor prognosis despite complete hardware removal [6, 7]. Micra's small size, reduced surface area, and lack of lead exposed to the bloodstream appear to substantially mitigate the risk of early device infection [8]. Over the long-term follow-up, these features will also promote complete device encapsulation, which may significantly reduce the risk of late infections.

Micra TPS is a full capability VVIR pacemaker. Typical indications for this system include patients with atrioventricular conduction disturbances and permanent AF. Despite that fact more and more patients are offered with the leadless system because of conditions that precludes implantation of conventional pacemaker such as history or high risk of infection, lack of axillary/subclavian vascular access, thrombosis or need to preserve the venous system for hemodialysis. This group of patients amounted 6.2% in Investigational Device Exemption (IDE) study and reached 20.9% in post-approval registry [9, 10]. In our cohort all patients, had at least one factor that precluded implantation of transvenous pacing system.

An early report of Micra TPS implantations showed very high procedural success rate of 100% [3]. It was reduced to 99.2% in a full cohort of patients in the IDE study [9]. The interim report from Micra TPS post-approval registry also showed high procedural efficacy with 99.6% successful implantations [10]. All 10 implantation attempts were completed in this study. All the devices were able to be implanted to the RV septum, which was confirmed in all patients in LAO projection with contrast medium injection. Septal positioning of the system seems to bring some benefits in terms of avoiding pericardial effusion and tamponade. In the literature a trend toward more frequent septal implantations could be observed. There were 65.9% apical implantations in the IDE study compared to 39.3% in post-approval registry [8, 9]. A similar trend could be observed with a different

transcatheter pacemaker, Nanostim (apical position in primary analysis cohort vs. total cohort, 48.4% vs. 38.1%, respectively) [11].

Although the purpose of each case was a RV septal pacing, it did not translate to significantly longer procedure duration and/or fluoroscopy time. Recommended electrical parameters in 9 patients were achieved. In 1 patient (patient no. 7) after two repositions of the system the procedure was ended with sensing value slightly lower than recommended, i.e. 4.7 mV. In accordance to observations from the trials and registry the value increased and reached 9.6 mV before hospital discharge [9, 10, 12].

Nevertheless leadless pacing reduces the rate of some procedural and long-term complications it also brings new problems that were not present with traditional pacing systems, i.e. vascular complications at the groin puncture site. In the IDE study arteriovenous fistula or pseudoaneurysm occurred in 5 (0.7%) patients [8]. A similar rate of vascular complications was observed in post-approval registry. Among total 0.75% of access site complications, there were 2 hematomas (0.25% of patients) [9]. Currently there is no data about proper periprocedural antithrombotic management in those patients.

Although implantation of single chamber VVI pacemaker is on the list of guaranteed services but total cost of Micra TPS highly exceeds reimbursement level for this category, so individual financing was implemented for each patient and this study depicts expenditures divided into a range of categories. According to available research this is the first cost analysis of the Micra implantation procedure. Hospitalization costs for individual patient with a wide range of medical conditions. The price of the Micra device was the same for all procedures, but final costs varied depending on patient. Those who had an infection or an implanted device extraction had higher expenditures than those with simple/stand alone Micra implantation procedure. Two patients had bleeding complications. One patient had pseudoaneurysm in the vascular access site, while the other had femoral artery aneurysm demanding intervention. These events prolonged hospitalization length and therefore final costs. The relatively low cost of operating theatre staff also deserves comment. This is due to the fact that the hospital calculates it from the staff costs based on the hourly wage rates, that, while calculating the actual time of treatment, gives very small amounts and does not take into account the time between procedures. In addition, current analysis did not include costs of proctors presence during first 6 procedures. According to the hospital contract these costs were covered by the device supplier.

Limitations of the study

The cost of Micra implantation varies dramatically between centers, contracts with the vendor, and country which limits the generalizability of this report. However, the primary objective of this study was to compare hospital costs between patients with different clinical profiles assuming one price of the device, mainly due to the fact that Poland is applying for Micra implantation reimbursement. Therefore a comparison was not made with a matched group undergoing transvenous pacemaker implantation, because the aim herein was not a comparison in the context of effectiveness and safety assessment between tranvenous and leadless pacemaker.

The first ten cases of Micra implantation were performed in the certificated Clinic. The introduction of a novel technology is usually accompanied by a period of learning in which operators develop and refine new skills until they achieve a "steady state" characterized by high efficiency and procedural success with low complications. This is one limitation of the present study.

Conclusions

The presented registry of Micra implantation is the first single-center observational study in Poland. Early results from this and other clinical evaluations suggest that leadless pacing is effective, safe and could gain wider adoption particularly in patients with contraindications to conventional cardiac pacing. Further studies on periprocedural antithrombotic management in patients with indications to permanent anticoagulation are warranted. Hospitalization costs for individual patients varies over a large range. Diversity of costs is mainly attributed to concomitant indications (e.g. infection), comorbidities (e.g. dialysis) and post-procedural complications (e.g. bleeding and hematoma).

Conflict of interest: Marcin Grabowski has honoraria from Medtronic.

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Fragmented endocardial signals and early afterdepolarizations during torsades de pointes tachycardia

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Abstract

Background: *Bradycardia-induced torsade de pointes (TdP) tachycardia in patients with spontaneous high-degree atrioventricular block (AVB) is common. The aim of this study was to analyze endocardial recordings during TdP in spontaneous high-degree AVB in humans to better understand the electrophysiological mechanisms underlying this phenomenon.*

Methods: *The study group consisted of 5 patients with typical episodes of TdP during spontaneous high-degree AVB. A standard (USCI) temporary bipolar endocardial catheter positioned at the apex of the right ventricle (RV) and bipolar chest leads from two precordial leads V1 and V4 were used to record the tracings during TdP.*

Results: *The presence of a wide spectrum of fragmentations was noted on endocardial electrograms (EGMs), which were invisible on the surface electrocardiogram (ECG) tracing. Endocardial signals indicated that TdP started in the proximity of the RV apex, since the local EGM began prior to the QRS complex on the surface ECG. Early afterdepolarizations (EADs) were observed in 2 out of 5 cases confirming a common opinion about the mechanism of TdP. However, this phenomenon was not observed in 3 other patients suggesting that the arrhythmia was the result of a different mechanism originating in proximity to the RV apex.*

Conclusions: *This work demonstrated early endocardial signals in the RV apex during TdP associated with high-degree AVB in humans, and exhibits a spectrum of fragmented signals in this area occurring on a single or multiple beats. These fragmentations indicate areas of poor conduction and various degrees of intramyocardial block, and therefore a new mechanism of TdP tachycardia in some patients with spontaneous high-degree AVB.* (Cardiol J 2020; 27, 1: 54–61)

Key words: early afterdepolarizations, torsades de pointes, electrocardiogram, atrioventricular block, endocardial recordings

Introduction

The exact mechanism of torsades de pointes (TdP) tachycardia in high-degree atrioventricular block (AVB) and long QT syndrome (LQTS) has been puzzling electrophysiologists over the past decades [1–5]. This syndrome or its variants are a rare but important cause of sudden death in young people with a genetically determined form of LQTS [6, 7]. The length of the QT interval

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is directly related to risk stratification of these patients modulated by genetic factors [8]. TdP is also a major concern to the pharmaceutical industry for the development of cardiac and non-cardiac drugs [9]. In these cases the role of early afterdepolarizations (EAD) has been suggested as their main trigger [10].

Therefore, it is important to understand the basic mechanisms of this form of polymorphic ventricular tachycardia (VT), originally denominated in patients with high-degree AVB in 1966. The descriptive term of "torsade de pointes" was chosen to describe the fact that QRS complexes seem to twist around the isoelectric line [11]. A German team reproduced this arrhythmia experimentally giving credit to this original mechanism of two alternating ventricular foci [12]. The aim of this study is to report on right ventricular (RV) endocardial recordings in vivo in humans presenting unexpected signals for the first time during high-degree AVB-induced TdP or its impending premature ventricular contractions (PVCs), couplets, triplets etc., which are considered as the minor equivalents of TdP. These events produce successive short-long intervals until the initiation of TdP.

Methods

This is a retrospective study. When G.H.F. carried out these studies between 1965 and 1970, there were no ethical standards of a responsible committee on human experimentation (institutional or regional). This investigation was approved by the chief of cardiology as there was a clinical need to study these patients. In those times it was important to verify that polymorphic non sustained VT (early name for TdP) [13] could be prevented by ventricular pacing in non ischemic patients with AVB-induced bradycardia, which is not possible in polymorphic VT due to myocardial ischemia. An oral informed consent by the patient was obtained before the procedure.

The population consisted of 5 patients exhibiting TdP resulting from spontaneous high-degree AVB. Most of these patients were waiting for pacemaker (PM) implantation, replacement or repair at a time when these devices were not readily available and were expensive. Therefore, they had a temporary pacing system with an endocardial electrode and external PM. A standard temporary bipolar pacing endocardial catheter (USCI, Billerica, MA USA) was positioned at the apex of the RV. A bipolar electrocardiogram (ECG) was derived from two precordial electrodes placed at the V1 and V4 positions. In fact, this bipolar recording extracts information mostly from the RV since both electrodes are put in regular place in the parasternal intercostal space (V1) and V4, which is mostly covering the RV. They were connected to a 3A9 differential amplifier with a band pass from direct current to -1 Mhz with an industrial oscilloscope (Tektronix 361A Portland, Oregon, USA) equipped with a phosphor cathodic tube and a 2B67 time base, in those times when specific electrophysiological equipment was not available. The amplifier output was connected to a tape recorder (Ampex SP 300, Redwood City, CA, USA). The tapes were subsequently reviewed with an oscilloscope (Tektronix 561A-3A72) to select episodes of TdP, which were printed on a two-channel industrial ink pressure recorder (Clevite Brush 220 Chart Recorder Cleveland, OH, USA). An external defibrillator was readily available before the disconnection of the endocardial lead. Preliminary findings from this patient population have been previously published by the present group [14]. The current study extends those findings and further elucidates on the pathophysiology of TdP tachycardia in high degree AVB.

Results

Study population

Patients were > 65 years old; 80% were females. They had no sign of coronary artery disease, but presented with AVB type II Mobitz or AVB III. Most of them had well tolerated short episodes of TdP (less than 5 s) preceded by PVCs, couplets, triplets etc.

Tracings

Tracings will be presented according to their increasing complexity.

Variable patterns of ventricular activation until reorganization of ventricular activation leading to the termination of most TdP episodes were noted on the endocardial tracings and surface ECG. The recordings allow to analyze the different apical endocardial characteristics of the initiating beat, and of the following ones.

Figure 1 shows the escape junctional rhythm followed by a ventricular triplet. The initiating endocardial signal consists of two consecutive negative high amplitude contiguous sharp potentials at the beginning of the triplet. The first sharp potential starts at the same time as the surface ECG tracing. This tracing shows no other fragmentation

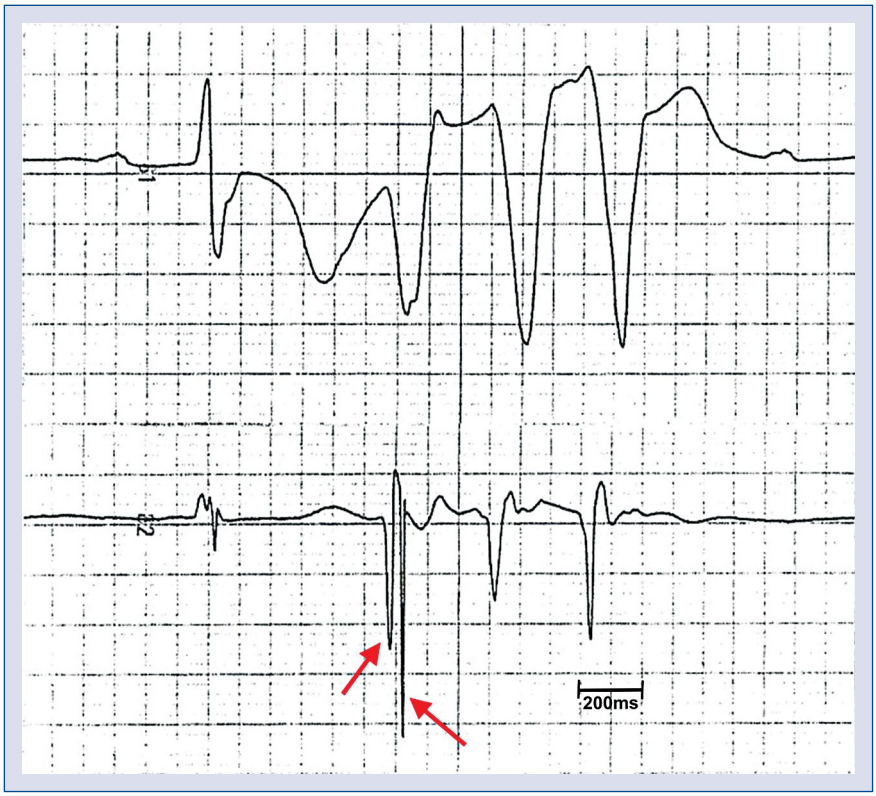

Figure 1. Two consecutive negative high amplitude contiguous sharp potentials (red arrowheads) were observed at the beginning of a triplet. There is no visible early afterdepolarization (EAD) or EAD-like pattern.

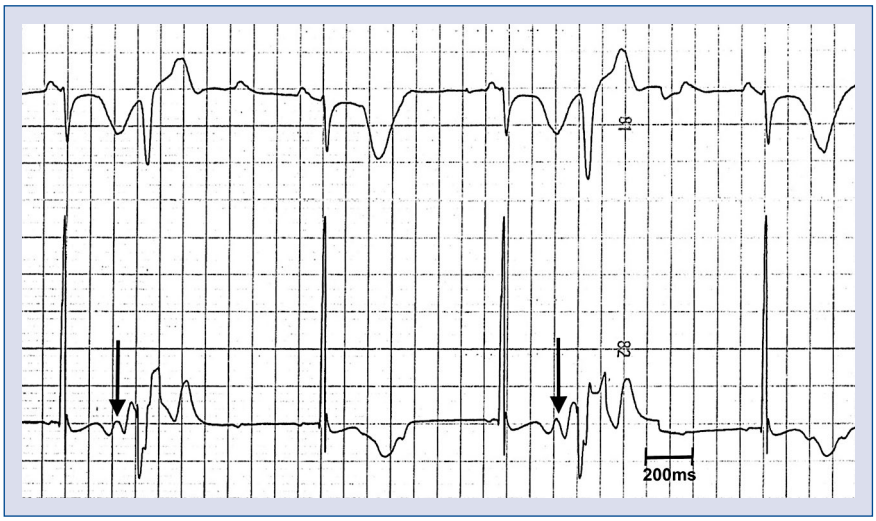

Figure 2. On this electrogram, there is a positive smooth potential occurring on the nadir of the T wave compatible with an early afterdepolarizations (black arrowheads) followed by polyphasic potentials before a smooth potential.

on the two following beats. No EAD or EAD-like pattern is visible.

In Figure 2, a second patient with a third degree AVB has an atrial tachycardia, and a ventricular bigeminus. The first QRS is followed by a PVC. Its polyphasic electrogram, synchronous to the surface ECG, is preceded by a small positive smooth potential (arrows) occurring on the nadir

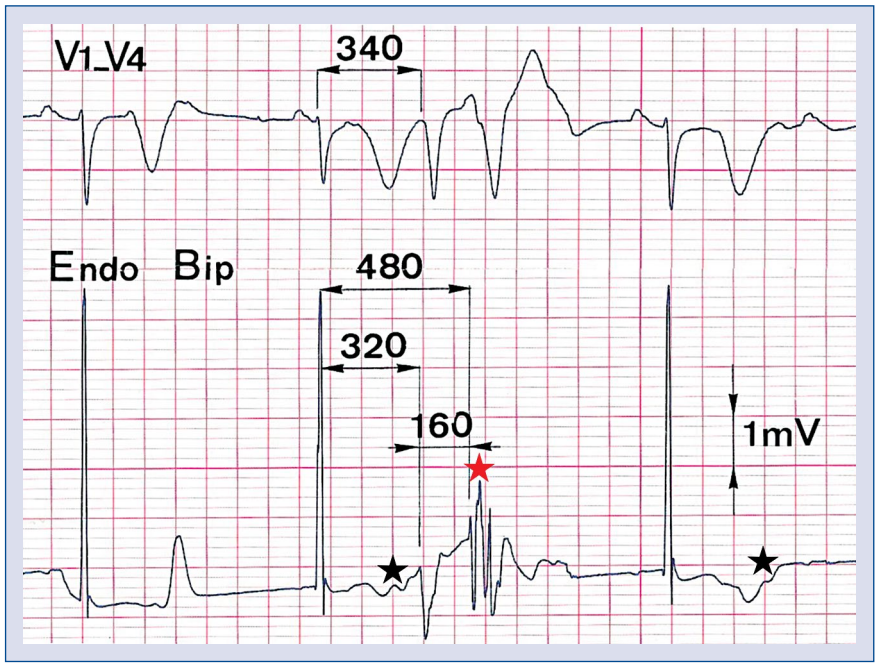

Figure 3. The second beat of a couplet is made of three consecutive sharp signals (red asterisk) with a duration of around 100 ms. Early afterdepolarization is visible in the T wave of the endocardial signal (first black asterisk) and not on the others (second black asterisk). This figure has been published in Guy Fontaine's previous work [24].

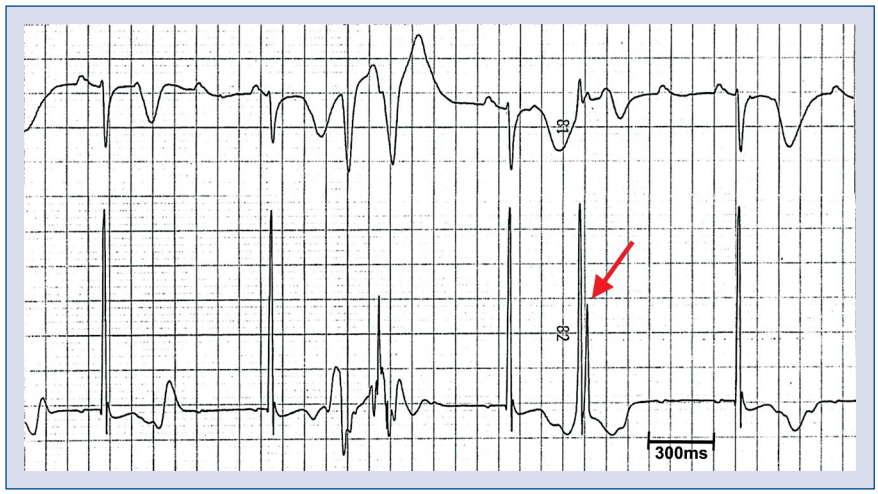

Figure 4. The same phenomenon of fragmentation with negative, positive, negative potentials with three notches on the second torsades the pointes beat with smaller amplitude is noted on this tracing. In addition, the next beat is followed by a premature ventricular contraction with double sharp positive deflections (red arrowhead) of high amplitude with no isoelectric interval in between.

of the T wave, 200 ms before PVC onset. It seems to have a second component, interrupted by multiphasic sharp deflections of PVC local activation and repolarization. Those smooth potentials could be part of a junctional repolarization wave, but, as they do not appear when the junctional complex is not followed by a PVC, they should reflect early depolarization activation.

Figure 3 (same patient as in Figures 2 and 4) shows a ventricular couplet. Its first beat is also preceded by a low amplitude signal synchronous to the nadir of the T wave as in Figure 2 (first black

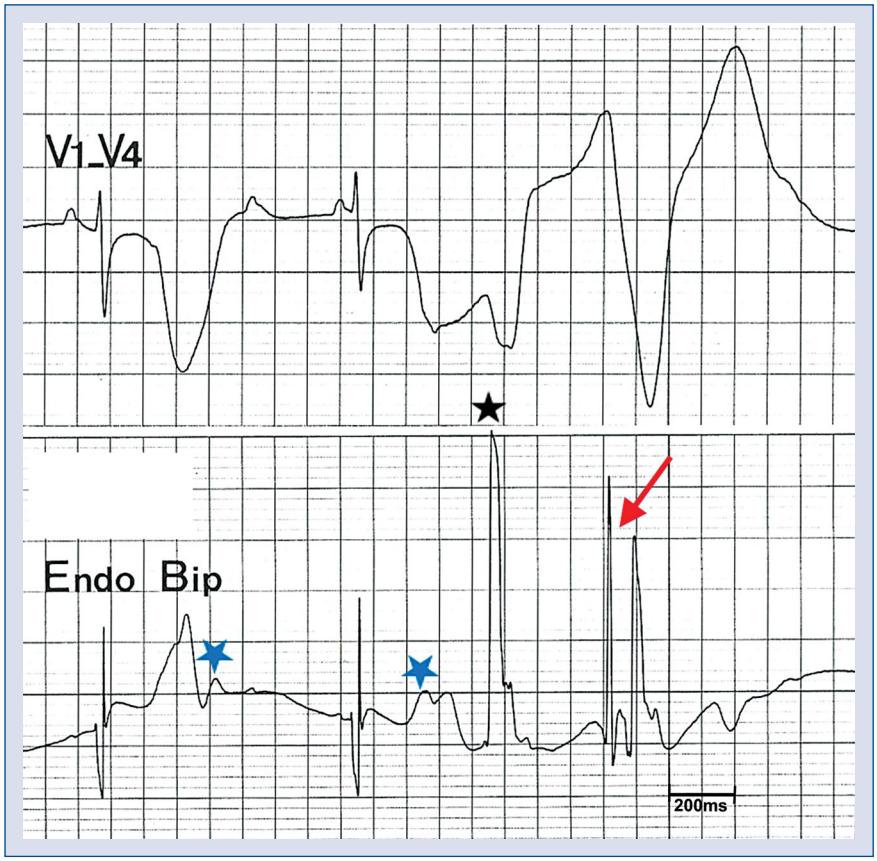

Figure 5. The same pattern with 40 ms interval between the two sharp potentials (red arrowhead) of high amplitude is illustrated on this tracing. This is preceded by a huge potential of the first torsades the pointes beat (black asterisk). The two junctional beats show a deflection compatible with early afterdepolarizations (blue asterisk).

star), and not on other single junctional QRS complexes. That first PVC has an endocardial morphology somehow different from the ones on Figure 2, suggesting a different origin. The following PVC is made of three consecutive sharp endocardial signals with a duration of around 100 ms. It is interesting to note that the endocardial signals of the couplet start 20 ms prior to the onset of the surface QRS, indicating an origin or an exit of the TdP in proximity to the RV apex, where a bipolar catheter is positioned.

In the same patient, Figure 4 illustrates another ventricular couplet with the same phenomenon of fragmentation with negative, positive, negative deflections of the endocardial signal with three notches on the second PVC. In addition, the next junctional complex is followed by a single PVC with double sharp positive deflections of high amplitude with almost no isoelectric interval in between (red arrow). The isolated junctional beats again exhibited different major repolarization trouble.

Figure 5 illustrates in a third patient a similar endocardial activation pattern when compared to Figure 4 with an interval of 40 ms between the two sharp potentials of high amplitude (red arrow). This is preceded by a huge potential of the first TdP beat (black asterisk). The T waves of the two junctional beats show a deflection compatible with EADs.

Figure 6 (the same patient as Fig. 1) shows that the first beat is the basic rhythm in high degree AVB with a long QT interval showing the typical pattern of smooth and sharp potentials on the endocardial tracing. The first TdP beat exhibits a sharp notch, which is not compatible with an EAD (first arrow). The corresponding electrogram (EGM) is exactly in synchrony with the notch also not compatible with an EAD, but suggests that the TdP starts, or has its exit in the proximity of the RV apex, since the RV endocardial signal starts approximately 20 ms prior to the surface ECG. The negative terminal part of the first EGM of the TdP has a letter V shape of 100 ms duration followed by

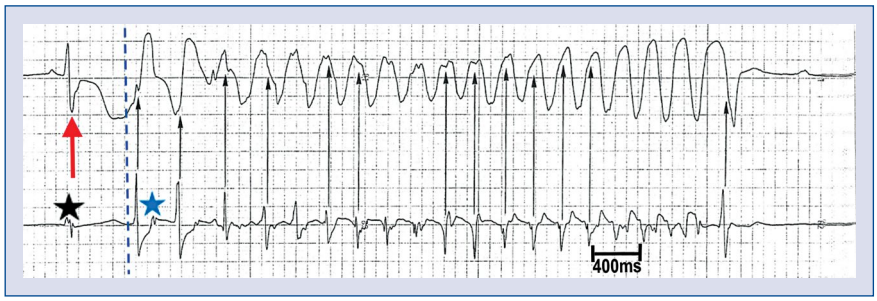

Figure 6. This tracing was the same patient as Figure 1. The endocardial signal below the surface electrocardiogram (ECG) tracing was noted. The first beat (red arrow) is the basic rhythm in high degree atrioventricular block with a long QT interval showing the typical pattern of smooth and sharp potentials. Note that the endocardial signal starts prior to the surface ECG (blue dashed line). The following beats show the narrowing of the electrograms except for the last beats, which show a fragmentation close to ventricular fibrillation. Some of the arrows stress that the local right ventricle activation can occur in diastole between two torsade de pointes beats.

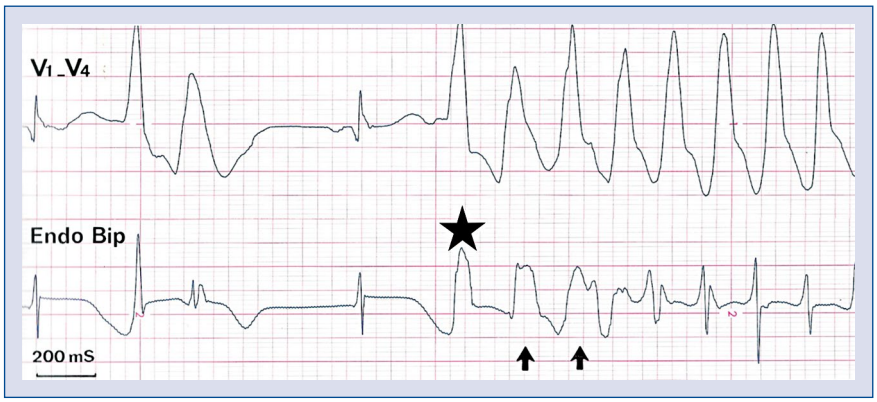

Figure 7. The tracing shows at the initiation of torsade de pointes a similar pattern such as in Figure 6 with even longer electrograms (arrows) with a reverse U-shape T wave up to 200 ms (black asterisk). This figure has been published in Guy Fontaine's previous work [24].

a small sharp notch. This again demonstrates the delayed activation of several contiguous structures also observed on the next TdP beat. The following beats show the narrowing of the EGMs except for the last beats, which show a fragmentation resembling ventricular fibrillation (VF). Some of the black arrows stress that RV activation can occur during diastole between two TdP beats.

The tracings of Figure 7 show that at the initiation of TdP a similar pattern of Figure 6 with even larger EGMs with an inverted "U" pattern of 200 ms (black asterisk). This is followed by narrowing of the EGM close to the basic AVB rhythm also located in the diastole between two TdP beats.

Discussion

Early afterdepolarizations (EADs) have been extensively studied in animal models and by computer simulation [4, 15–18]. They are an important cause of ventricular arrhythmias in the LQTS, but the mechanisms by which EADs at the cellular scale cause arrhythmias such as TdP are unclear.

This work, which is an extension of a preliminary study previously published by the present group [14], reports on endocardial signals during episodes of TdP in high-degree AVB in humans in vivo. Endocardial signals derived from the RV apex exhibit a spectrum of fragmentations occurring on a single or multiple beats prior to the initiation of TdP, which are intermittent, transient, or irregular suggesting parallel activation of uncoupled contiguous structures in proximity to the RV apex and also demonstrate that there is a major impairment of electrotonic forces. In fact, the bipolar recording V1–V4 used in this study extracts information mostly from the RV since both electrodes are put in V1 and V4, in

a parasternal anterior location mostly covering the RV. Indeed, this recording underscores the present hypothesis that the origin of these PVCs leading to TdP are from the RV.

In the early 60 s experimental animal studies from the Gordon Moe laboratory showed that prolongation of the monophasic action potential duration was time-dependent and the same group also demonstrated time-dispersion dependence of refractory periods [19, 20]. These seminal observations, which demonstrated heterogeneities, are crucial to explain a phenomenon of phase-2 reentry, which is valid only for the first TdP beat (the second beat occurs after a short coupling interval). Multipolar plunge electrodes led to construction of a 3-dimensional (3D) isochronal map demonstrating an origin in the subendocardial tissue followed by bifurcation of activation towards the right as well as the left ventricle and the septum [21].

The present results provide new insights into the mechanism of TdP in AVB stressing the presence of a spectrum of fragmentation of endocardial signals, which can be observed on the first TdP beat, the second, or during a period of up to 200 ms. The V shape or inverted U shape of endocardial signals presented at the beginning of the TdP in Figure 6 represent the most impressive pattern of activation of multiple contiguous structures. Note that it was possible to record this phenomenon without distortion because of the band-pass of the chain of apparatus including the recorders, which were going from DC to 60 Hz. All these aspects demonstrate intraventricular troubles in conduction, most likely independent of an anatomical obstacle.

On all tracings of patients studied herein, the first endocardial signal occurs at the same time or prior to the onset of the QRS complex on the surface tracing. This highly suggests that in humans the origin of activation or exit site during AVB-induced TdP starts in the proximity of the RV apex, although a more septal or even left-sided origin cannot be ruled out since there were no catheters in place at these sites [21]. This is also in agreement with the work of Birati et al. [22]. It may be speculated that the human RV is thin enough to enable TdP, ideally a structure of less than its normal thickness of 3 mm. This led to the suspicion that RV crista supraventricularis, the thinnest structure in the ventricles, could be an ideal site for initiation of TdP [23]. Study of this anatomical region by the present group in 3 patients without cardiac disease showed a thickness of crista supraventricular of 1 mm. With this result in mind, it is now possible to interpret the fragmentation of potentials as the result of transient electrical uncoupling of contiguous structures close to RV crista supraventricularis. However, this hypothesis has to be confirmed in future 3D electroanatomical endocardial and epicardial mapping studies during TdP in humans with high degree AVB. Therefore, the safety factor of transmission of activation is weak producing a spectrum of intermittent, irregular, intramyocardial blocks. If this situation involves both ventricles it may explain that most TdP episodes are self-terminating and explain why they rarely degenerate into VF.

Early afterdepolarizations are secondary voltage depolarizations producing a low amplitude hump at the end of the phase-2 of the action potential. The presence of potentials compatible with an EAD phenomenon was observed in 2 patients, and was absent in 3. This absence can be explained by the genesis of EAD in a zone located far from the bipolar recording system because of heterogeneity. It is assumed that a bunch of 100 to 1000 EAD cells are necessary to have enough electrical force to produce the first PVC. However, induction of TdP could also be the result of a different phenomenon not involving EADs, but a local conduction disorder leading to a microreentry as suggested by this study.

Limitations of the study

This was a small study performed several decades ago, and some clinical information was missing. With today's techniques such as electroanatomical voltage mapping and modern mapping catheters, a more profound knowledge on the pathophysiology of TdP may be acquired in humans in vivo. Therefore, these results to some extent remain hypothetical and have to be confirmed and extended in future studies. Yet, these kind of studies in humans, where pacing is stopped in order to induce TdP nowadays has become almost impossible due to ethical restrictions. Furthermore, fragmented potentials in the initiating phase of TdP may be a bystander phenomenon, just representing conduction delay due to the short coupling intervals of PVCs. Yet, it is interesting to see that this phenomenon often occurred prior to PVC crescendo and prior to initiation of TdP. A way to exclude a causal role would be to ablate these regions and to see, whether TdP is rendered non-inducible.

Conclusions

This work demonstrated fragmented endocardial signals in the RV apical region in vivo during episodes

of TdP in humans with high-degree AVB, and exhibits a spectrum of fragmentations occurring on a single or multiple beats prior to initiation of TdP. These fragmentations indicate areas of poor conduction and various degrees of intramyocardial block, and therefore suggest a new mechanism of TdP tachycardia in patients with spontaneous high-degree AVB.

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Conflict of interest: None declared

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Ivabradine in acute heart failure: Effects on heart rate and hemodynamic parameters in a randomized and controlled swine trial

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Abstract

Background: *Acute heart failure patients could benefit from heart rate reduction, as myocardial consumption and oxidative stress are related to tachycardia. Ivabradine could have a clinical role attenuating catecholamine-induced tachycardia. The aim of this study was to evaluate hemodynamic effects of ivabradine in a swine model of acute heart failure.*

Methods: *Myocardial infarction was induced by 45 min left anterior descending artery balloon occlusion in 18 anesthetized pigs. An infusion of dobutamine and noradrenaline was maintained aiming to preserve adequate hemodynamic support, accompanied by fluid administration to obtain a pulmonary wedged pressure ≥ 18 mmHg. After reperfusion, rhythm and hemodynamic stabilization, the animals were randomized to 0.3 mg/kg ivabradine intravenously ($n = 9$) or placebo ($n = 9$). Hemodynamic parameters were observed over a 60 min period.*

Results: *Ivabradine was associated with a significant reduction in heart rate (88.4 ± 12.0 bpm vs. 122.7 ± 17.3 bpm after 15 min of ivabradine/placebo infusion, $p < 0.01$) and an increase in stroke volume (68.8 ± 13.7 mL vs. 52.4 ± 11.5 mL after 15 min, $p = 0.01$). There were no significant differences in systemic or pulmonary arterial pressure, or significant changes in pulmonary capillary pressure. However, after 15 min, cardiac output was significantly reduced with ivabradine (–5.2% vs. +15.0% variation in ivabradine/placebo group, $p = 0.03$), and central venous pressure increased (+4.2% vs. –19.7% variation, $p < 0.01$).*

Conclusions: *Ivabradine reduces heart rate and increases stroke volume without modifying systemic or left filling pressures in a swine model of acute heart failure. However, an excessive heart rate reduction could lead to a decrease in cardiac output and an increase in right filling pressures. Future studies with specific heart rate targets are needed.* (Cardiol J 2020; 27, 1: 62–71)

Key words: acute heart failure, heart rate, ivabradine, swine model, porcine model

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Introduction

Acute heart failure (AHF) continues to be associated with poor prognosis and high in-hospital mortality [1]. Inotropic drugs are the cornerstone in management of hypotensive (cold) AHF patients, promoting a dose-dependent increase in cardiac output (CO) and reduction of left ventricle (LV) filling pressures. The downside to these effects is an increase in heart rate (HR) with its corresponding increase in myocardial oxygen consumption [2–5]. European Society of Cardiology guidelines recommend a limited use of inotropic agents in the management of AHF [1], recognizing sinus tachycardia as possibly deleterious, as it may compromise ventricular filling efficiency by shortening diastolic duration [6]. Accordingly, reduction of HR could be an important energy-saving maneuver in AHF.

Ivabradine is a specific blocker of the I_f "funny" currently supported by hyperpolarization-activated cyclic nucleotide-gated channels, regulating sinoatrial node activity. Its pharmacological effects are deemed to be almost exclusively on the sinus node reducing HR without affecting myocardial contractility or vascular tone. Ivabradine has been shown to reduce re-hospitalization and mortality rates in patients with chronic HF and ≤ 35% left ventricular ejection fraction (LVEF) [1, 7, 8], but it has not been adequately tested in AHF. It has been postulated that ivabradine could have a role attenuating catecholamine-induced tachycardia [5, 6]. Few case series and reports suggest its safety and potential benefit, improving surrogate endpoints in AHF and cardiogenic shock (CS) [9–12]. However, the effects of rapid reduction of HR on CO or heart filling pressures in this context are not clearly understood and a comprehensive analysis of hemodynamic of ivabradine effects in this setting is warranted.

The main objective of this study was to evaluate the impact of ivabradine on hemodynamic parameters in a swine model of AHF.

Methods

Ethical approval

All procedures were performed in the Experimental Surgery Department of the Hospital Universitario La Paz (Madrid, Spain). Protocol was followed and approved by the Animal Welfare Ethics Committee. The investigation conforms to Guide for the Care and Use of laboratory Animals, published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1985) and complied with the EU Directive on experimental animals (63/2010 EU) and related Spanish legislation (RD 53/2013). PROEX 365-15.

Surgery and instrumentation

Eighteen Large White female pigs (37.6 ± 5.1 kg) were used in the study. The animals were initially treated with intramuscular ketamine (10 mg/kg, Pfizer) and midazolam (0.5 mg/kg, Braun). Anesthesia was induced by inhaled isoflurane (Abbvie Spain SLU) and maintained with continuous infusion of propofol (2 mL/kg/h, Fresenius Kabi), fentanyl (50 μg/kg/h, Kern Pharma) and diazepam (10 μg/kg/h, Roche). Animals were intubated and ventilated with 60% oxygen saturation. A central venous catheter (Swan-Ganz oximetry thermodilution catheter, Edwards Lifesciences) was placed through the right internal jugular vein to the pulmonary artery for measurement of central venous pressure (CVP), CO, pulmonary capillary wedge pressure (PCWP), pulmonary artery pressure (PAP) and mixed venous oxygen saturation (SvO_2). Systemic arterial pressure (SAP) was measured in the ascending aorta through the guiding catheter used to catheterize the left coronary artery tree. The animals received 5000 IU of heparin and amiodarone (53 μg/kg/min, Sanofi Aventis) to avoid blood clotting of catheters and malignant cardiac arrhythmias, respectively. Animals were stabilized for 15 min before baseline measurements (T0).

Experimental protocol

The experimental protocol is outlined in Figure 1. After baseline measurements, including echocardiogram and hemodynamic assessment, acute anterior myocardial infarction was induced by mid-left anterior descending artery (LAD) occlusion for 45 min using a JL 3 6 F catheter and 3.0 or 3.5 mm conventional angioplasty balloons. Hemodynamic measurements were continuously monitored and recorded at 15, 30 and 45 min during ischemia (T15, T30, T45). Noradrenaline (0.4–0.8 μg/kg/min, Braun), dobutamine (2.9–6.2 μg/kg/min, Hospira Productos farmacéuticos y Hospitalarios SL) and physiological saline (1000–2000cc, Grifols) were administered after the first 15 min of occlusion to maintain adequate systemic perfusion and titrated to obtain a HR ≥ 90 bpm and PCWP > 18 mmHg. After 45 min of coronary occlusion, the angioplasty balloon was deflated and at least 15 min of electrical and hemodynamic stabilization time was allowed before infusion of study drug or placebo. Hemodynamic measurements were recorded (T60) and

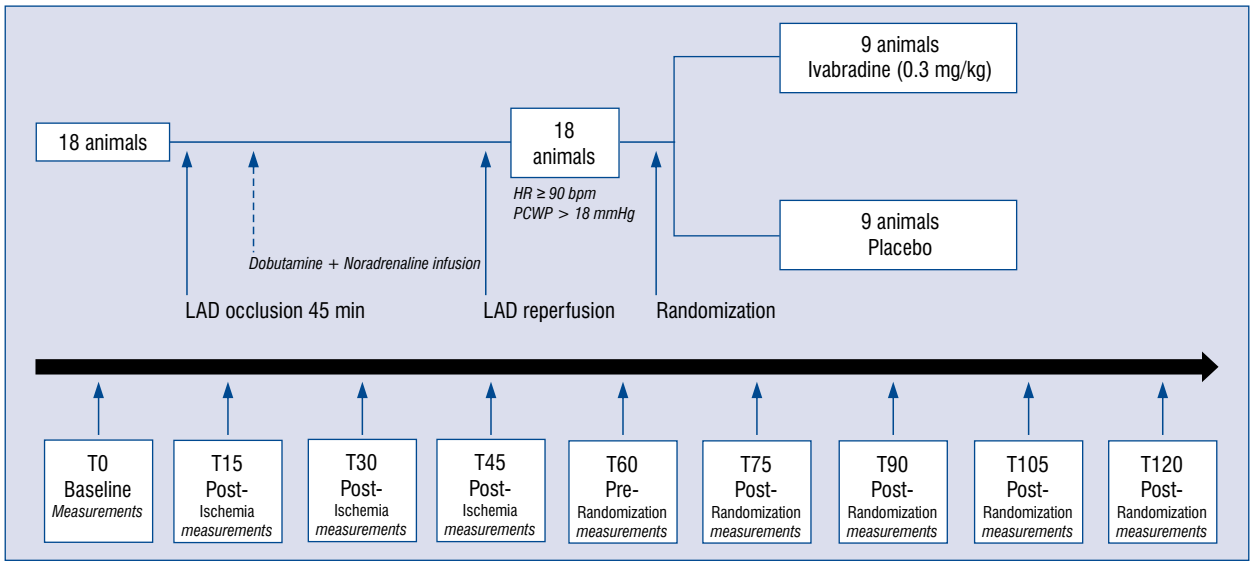

Figure 1. Outline of the experimental protocol. After baseline assessment of hemodynamics parameters, animals underwent left anterior descending artery (LAD) occlusion. Hemodynamic measurements were recorded at 15, 30 and 45 min of ischemia. After LAD reperfusion, pigs were allowed to stabilize for another 15 min before recording the pre-randomization measurements. Animals were then randomized to receive ivabradine (0.3 mg/kg) of either placebo. Hemodynamic measurements were repeated 15-30-45 and 60 min after ivabradine/placebo administration; HR — heart rate; PCWP — pulmonary capillary wedge pressure.

animals were then randomized to a control group (n = 9) or to receive ivabradine (n = 9). According to Servier laboratories instructions, ivabradine powder was diluted in distilled water in a proportion of at least 12 mg/mL and administered intravenously in slow bolus at a dose of 0.3 mg/kg. This dose was chosen based on evidence available in the literature on the effect of intravenously ivabradine in porcine and human models, with doses between 0.1 mg/kg and 0.6 mg/kg [13–16]. The control group received an equivalent volume of physiological saline. Hemodynamic measurements were repeated 15-30-45 and 60 min after ivabradine/placebo administration (T75, T90, T105, T120).

Statistical analysis

All data were analyzed with a statistical software package (Stata 13.0 statistical software (Stata Corporation, College Station, TX)). All values are given as mean ± standard deviation. A two-sided $p < 0.05$ was considered significant. Saphiro-Wilk test was used to assess variable distribution.

Statistical analysis was performed in two phases. Firstly, individual variables were assessed before and after coronary occlusion in the same animal. The Student t-test for paired data was used to analyze variables of normal distribution, and Wilcoxon test was used in non-normal distribution variables. Secondly, hemodynamic effects of ivabradine were compared with placebo. The Student t-test for unpaired data was used in variables of normal distribution, and Mann-Whitney U test was used in variables of non-normal distribution.

Results

Effects of coronary occlusion on hemodynamic parameters

The accumulated ischemia time was 45.3 ± ± 1.2 min. Ventricular fibrillation necessitating external defibrillation occurred on average 1.9 times per animal. The induction of ischemia led to a significant decline in SAP and CO in the first 15 min after LAD occlusion (Table 1). Following dobutamine and noradrenaline administration, HR, PCWP, PAP and CVP increased progressively (Table 1).

Effects of ivabradine on hemodynamic parameters

Hemodynamic variables for ivabradine-treated animals and controls are summarized in Tables 2 and 3 and Figure 2. Table 2 expresses absolute values. Study groups had comparable HR and systemic or pulmonary perfusion and filling pressures at baseline. Ivabradine administration produced a significant reduction in HR (at 15 min: –21.9% reduction vs. 2.6% increase; $p < 0.01$). Parallel to this rapid reduction in HR, we observed a sig-

Table 1. Parameters before left anterior descendent artery (LAD) occlusion; parameters 15, 30 and 45 min after LAD occlusion and 15 min after reperfusion.

Effects of coronary occlusion on hemodynamic parameters					
Hemodynamic parameters (n = 18)	**LAD occlusion**				**LAD reperfusion + DB/NA**
	Basal	**LAD 15 min**	**LAD 30 min + DB/NA**	**LAD 45 min + DB/NA**	
SAP [mmHg]	**95.1** ± 14.4	**87.2** ± 14.2*	**95.3** ± 24.3	**101.2** ± 12.5	**105.2** ± 12.3*
MAP [mmHg]	**73.6** ± 10.2	**68.1** ± 12.5	**74.7** ± 20.4	**78.3** ± 12.5	**71.2** ± 11.4
CO [l/min]	**5.2** ± 1.1	**4.6** ± 1.3*	**5.0** ± 1.2	**5.6** ± 1.1	**6.10**± 1.4*
SV [mL]	**59.9** ± 12.0	**51.6** ± 15.5**	**50.9** ± 14.0**	**56.3** ± 12.8	**51.4** ± 11.6**
HR [bpm]	**88.1** ± 17.5	**90.3** ± 13.6	**98.8** ± 13.0*	**99.9** ± 12.5*	**116.4** ± 16.5**
PCWP [mmHg]	**16.0** ± 3.0	**18.8** ± 3.0**	**21.1** ± 3.9**	**20.9** ± 3.0**	**23.4** ± 3.8**
MPAP [mmHg]	**23.7** ± 5.2	**24.4** ± 5.7	**25.7** ± 6.6	**27.9** ± 6.0**	**31.4** ± 6.5**
CVP [mmHg]	**9.9** ± 2.9	**11.4** ± 2.8*	**12.6** ± 3.1**	**13.5** ± 3.0**	**13.7** ± 3.2**
SVO_2 [%]	**69.4** ± 12.6	**65.0** ± 7.0	**72.3** ± 8.9	**77.7** ± 6.8*	**76.9** ± 7.4*

Values are expressed as mean ± standard deviation. LAD occlusion led to a significant decline in MAP, CO and SV in the first 15 min after LAD occlusion. Dobutamine and noradrenaline, along with fluids, were administered after 15 min of occlusion to preserve adequate hemodynamics during induction of myocardial infarction. *$p < 0.05$; **$p < 0.01$. N = 18 (all animals, both groups); DB — dobutamine; NA — noradrenaline; SAP — systolic arterial pressure; MAP — mean arterial pressure; CO — cardiac output; SV — stroke volume; HR — heart rate; PCWP — pulmonary capillary wedge pressure; MPAP — mean pulmonary artery pressure; CVP — central venous pressure; SVO_2 — mixed venous oxygen saturation

nificant CO reduction in response to ivabradine (at 15 min: –5.2% reduction vs. +15.0% increase; $p = 0.03$), that remained stable during the following 45 min (Table 3, Fig. 2). Despite reduction of HR and CO no significant changes in perfusion or left filling pressures were observed (SAP, PCWP and PAP in Tables 2 and 3 and Fig. 2). After ivabradine bolus there was a corresponding increase in stroke volume (SV), compared to placebo values (+21.5% vs. +13.6% increase, ivabradine and placebo respectively; $p = 0.34$), which tended to stabilize during the 60 min observation period (Table 2, Fig. 2). Finally, a significant reduction in right filling pressure was observed (CVP) in the control group, and not observed in the ivabradine-assigned group (+4.2% increase vs. –19.7% reduction after 15 min ivabradine/placebo administration, $p < 0.01$).

Discussion

This is an open-label randomized study evaluating the hemodynamic effects of ivabradine in an experimental model of AHF based on an acute myocardial infarction-reperfusion injury. LAD occlusion led to a significant decline in mean arterial pressure (MAP) and CO similar to other studies with the same characteristics [17]. The rapid reduction of HR induced by an intravenous bolus of ivabradine produced a reduction in CO with a corresponding increase in SV, with no changes in systemic or pulmonary arterial pressures. There were no acute changes in left filling pressures, while there was a spontaneous decrease in right filling pressures in control animals, not observed in the ivabradine group. An observed reduction in CO was not progressive and both perfusion and heart filling pressures tended to remain stable after the first hour of drug administration.

Tachycardia is a common and physiological response to vasodilation or reduction in effective perfusion pressures but can result in higher myocardial oxygen consumption and lower coronary filling time. Higher HR has been shown to predict a worse prognosis in both AHF and chronic decompensated HF [18, 19]. After demonstration of reduction of HR with ivabradine in chronic HF [7, 8], several studies have suggested a possible role of rapid lowering HR during hospitalization in AHF patients or CS [9–12, 20–23]. However, few data are available on the hemodynamics of rapidly reducing HR in AHF. Gallet et al. [9] evaluated the effects of combining dobutamine and ivabradine (5 mg bid) in 9 patients with refractory CS. Ivabradine not only reduced HR, but also improved SAP, CO and N-terminal pro-B-type natriuretic peptide (NT-proBNP) values. Cavusoglu et al. [22] randomized 58 patients with AHF requiring inotropic support to receive ivabradine (n = 29) or placebo (n = 29) in addition to dobutamine. In the control group, mean HR gradually and significantly increased

Table 2. Hemodynamic values after myocardial infarction and reperfusion in ivabradine (n = 9) and control (n = 9) groups. Hemodynamic parameters were measured before randomization and 15, 30, 45 and 60 min after drug (ivabradine or placebo) administration.

Variable	Group	Effects of ivabradine on hemodynamic parameters. Hemodynamic values				
		Before randomization	15 min after drug administration	30 min after drug administration	45 min after drug administration	60 min after drug administration
HR [bpm]	Control	**119.6** ± 10.0	**122.7** ± 17.3	**123.2** ± 19.4	**124.0** ± 22.2	**121.4** ± 26.6
	Ivabradine	**113.2** ± 21.3	**88.4** ± 12.0**	**88.0** ± 12.6**	**86.6** ± 13.3**	**88.1** ± 14.8**
MAP [mmHg]	Control	**70.7** ± 12.1	**68.7** ± 10.7	**73.7** ± 8.1	**70.4** ± 10.0	**71.2** ± 11.6
	Ivabradine	**71.8** ± 11.2	**66.1** ± 10.1	**70.0** ± 13.3	**72.3** ± 15.6	**65.0** ± 13.3
SV [mL]	Control	**46.2** ± 12.8	**52.4** ± 11.5	**54.2** ± 13.2	**53.5** ± 12.3	**54.5** ± 11.4
	Ivabradine	**56.7** ± 7.6	**68.8** ± 13.7*	**62.1** ± 7.5	**60.8** ± 7.9	**59.1** ± 8.5
CO [l/min]	Control	**5.5** ± 1.5	**6.5**± 1.9	**6.7** ± 2.0	**6.7** ± 2.1	**6.9** ± 2.2
	Ivabradine	**6.4** ± 1.3	**6.1** ± 1.4	**5.5** ± 1.2	**5.3** ± 1.3	**5.3** ± 1.5
PCWP [mmHg]	Control	**22.7** ± 3.4	**19.7** ± 2.7	**19.0** ± 2.5	**17.8** ± 2.3	**17.2**± 1.7
	Ivabradine	**24.2** ± 4.2	**21.3** ± 5.1	**20.2** ± 2.9	**19.4** ± 3.6	**19.8** ± 3.1
MPAP [mmHg]	Control	**31.8** ± 6.0	**30.1** ± 6.2	**29.0** ± 5.5	**27.4** ± 6.2	**28.1** ± 6.4
	Ivabradine	**31.1** ± 7.4	**30.3** ± 7.9	**29.3** ± 7.5	**27.9** ± 5.9	**27.7** ± 5.3
CVP [mmHg]	Control	**14.1** ± 3.2	**11.3** ± 3.3	**10.8** ± 3.4	**10.4** ± 3.9	**9.9** ± 3.1
	Ivabradine	**13.3** ± 3.5	**13.9** ± 3.2	**13.4** ± 2.8	**13.4** ± 2.2*	**12.8** ± 2.9
SVO_2 [%]	Control	**76.4** ± 5.9	**76.3** ± 10.9	**77.0** ± 12.7	**74.0** ± 13.1	**78.1** ± 8.2
	Ivabradine	**77.3** ± 9.0	**75.6** ± 8.7	**74.4** ± 8.9	**74.8** ± 9.4	**75.3** ± 7.8

Values are expressed as mean ± standard deviation. *$p < 0.05$ for effect of ivabradine vs. control on hemodynamic parameters; **$p < 0.01$ for effect of ivabradine vs. control on hemodynamic parameters; HR — heart rate; MAP — mean arterial pressure; SV — stroke volume; CO — cardiac output; PCWP — pulmonary capillary wedge pressure; MPAP — mean pulmonary artery pressure; CVP — central venous pressure; SVO_2 — mixed venous oxygen saturation

Table 3. Changes in hemodynamic parameters in ivabradine and control animals, after administration of study drug.

Variable	Group	Effects of ivabradine on hemodynamic parameters. Hemodynamic changes			
		15 min after drug administration	30 min after drug administration	45 min after drug administration	60 min after drug administration
HR [bpm]	Control	**3.1** ± 18.6	**3.7** ± 21.2	**4.4** ± 22.7	**1.9** ± 25.1
	Ivabradine	**–24.8** ± 16.7*	**–25.2** ± 17.3**	**–26.7** ± 17.1**	**–25.1** ± 16.3*
MAP [mmHg]	Control	**–2.0** ± 8.7	**3.0** ± 8.2	**–0.2** ± 15.2	**–0.5** ± 17.9
	Ivabradine	**–5.7** ± 6.9	**–1.8** ± 8.1	**0.6** ± 15.6	**–6.8** ± 8.2
SV [mL]	Control	**6.3** ± 9.9	**8.0** ± 10.6	**7.2** ± 9.9	**6.6** ± 11.5
	Ivabradine	**12.2** ± 10.1	**5.5** ± 9.4	**4.1** ± 9.1	**2.4** ± 10.7
CO [l/min]	Control	**1.0** ± 1.5	**1.2** ± 1.7	**1.2** ± 1.7	**1.1** ± 2.1
	Ivabradine	**–0.3** ± 0.5*	**–0.9** ± 1.0**	**–1.1** ± 1.1**	**–1.1** ± 1.2*
PCWP [mmHg]	Control	**–3.0** ± 3.3	**–3.7** ± 3.3	**–4.9** ± 2.6	**–4.4** ± 1.1
	Ivabradine	**–2.9** ± 3.3	**–4.0** ± 3.0	**–4.8** ± 4.1	**–4.4** ± 3.9
MPAP [mmHg]	Control	**–1.7** ± 5.0	**–2.8** ± 5.3	**–4.3**± 5.7	**–2.7** ± 4.7
	Ivabradine	**–0.8** ± 1.9	**–1.8** ± 2.9	**–3.2** ± 3.1	**–3.4** ± 3.4
CVP [mmHg]	Control	**–2.8** ± 2.2	**–3.3** ± 2.1	**–3.7** ± 2.6	**–4.1** ± 2.2
	Ivabradine	**0.6** ± 1.7**	**0.1** ± 1.3**	**0.1** ± 2.1**	**–0.6** ± 2.3*
SVO_2 [%]	Control	**–0.1** ± 9.0	**–0.6** ± 11.2	**–2.4** ± 12.7	**–1.4** ± 7.5
	Ivabradine	**–1.8** ± 3.5	**–2.9** ± 4.8	**–2.6** ± 3.1	**–2.0** ± 3.2

Values are expressed as mean ± standard deviation. *$p < 0.05$; **$p < 0.01$ (comparison ivabradine–placebo); HR — heart rate; MAP — mean arterial pressure; SV — stroke volume; CO — cardiac output; PCWP — pulmonary capillary wedge pressure; MPAP — mean pulmonary artery pressure; CVP — central venous pressure; SVO_2 — mixed venous oxygen saturation

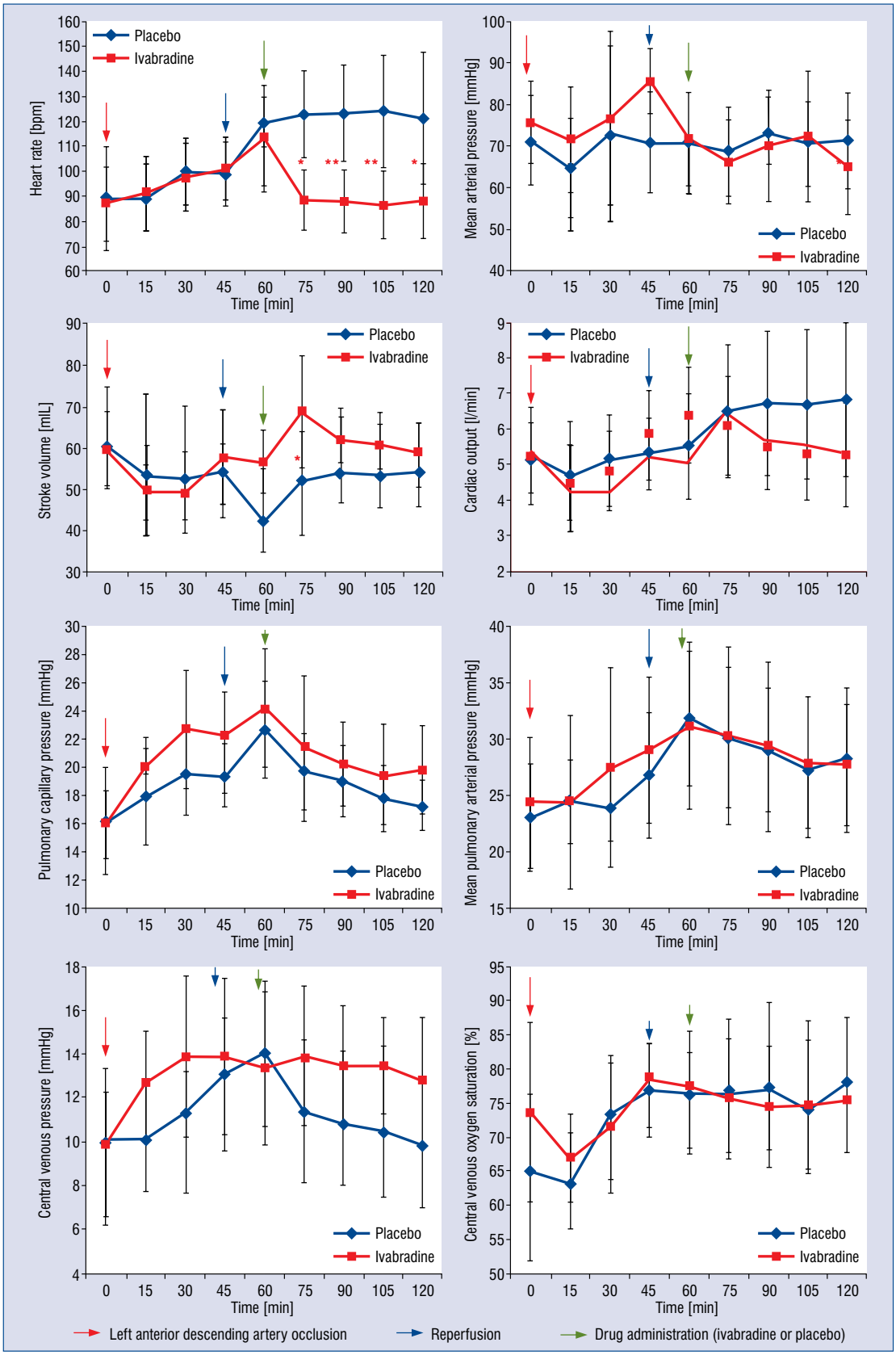

Figure 2. Ivabradine and placebo hemodynamic parameters variations; *p < 0.05 for effect of ivabradine vs. placebo on hemodynamic parameters; **p < 0.01 for effect of ivabradine vs. placebo on hemodynamic parameters; N = 9 — ivabradine group; N = 9 — placebo group.

at each step of dobutamine infusion, whereas no significant increase in HR was observed in the ivabradine group. However, important hemodynamic parameters, such as PCWP, SAP or CO were not recorded in these studies. In a study by Barillá et al [23], a total of 58 patients with CS as a complication of acute elevation myocardial infarction and HR > 75 bpm were randomized to standard treatment or to standard treatment plus ivabradine. HR was significantly reduced in ivabradine group, without modifying SAP. In-hospital mortality was doubled in the standard group in comparison with the standard plus ivabradine group, but the difference was not statistically significant. Nevertheless, invasive hemodynamic parameters such as CO or SV were not measured in this study. The MODIFY trial [24] enrolled 70 patients with multiple organ dysfunction syndrome (MODS) and HR > 90 bpm. Patients were randomized to receive standard treatment plus ivabradine or placebo. The HR reduction from enteral administration of ivabradine was not associated with an improvement in hemodynamic values or disease severity among critically ill patients with MODS. However, this study included patients with MODS but not necessarily with CS or AHF. In fact, coronary etiology was identified in only 17 patients; but important information as LVEF or filling pressure values was not registered. On the other hand, patients enrolled in the MODIFY trial received mainly vasopressor drugs instead of inotropic drugs. The present study focuses on the role of ivabradine in tachycardia induced by inotropic drugs (mainly dobutamine) in patients with AHF and depressed LVEF. Target HR may not be the same for patients with preserved or reduced cardiac inotropism, but the effect of ivabradine on hemodynamic parameters in this kind of patient have not been studied in any human clinical trial yet.

In one experimental swine model, Bakkehaug et al. [25] presented an ischemia–reperfusion protocol in 12 pigs after intermittent ligation of the left coronary arteries. Dobutamine infusion in post-ischemic heart increased CO by increasing significantly HR from 102 to 131 bpm ($p < 0.05$). The analysis demonstrated that adding ivabradine to dobutamine reported a reduction of HR to baseline values (100 bpm) without any effect on CO or MAP, with a significant increase in SV. However, in this study the hemodynamic effects of ivabradine were not determined in different groups, but the same animal was compared with itself before and after ivabradine administration. Therefore, it is impossible to overrule a "self-recovery" effect after releasing left coronary occlusion.

In the present study, ivabradine significantly reduced HR with no effect on SAP or PCWP. In contrast to previous observations and despite a rapid increase in SV, a decrease in CO values was observed when compared to control animals. However, the following limitations should be taken into consideration. First of all, the observation period (60 min) could be too short to detect a possible "catch-up" effect on CO values or stabilization of right or left filling pressures. Secondly, the experimental model in this study was unable to produce a sustained reduction in CO as in pump failure due to acute myocardial infarction and actually several animals showed a high-CO state induced by catecholamine infusion. And finally, this is a modest sample. Thus, caution is suggested in extrapolating this observed effect on CO to "clinical CS". Despite these important limitations, it is believed herein that rapid and excessive HR reduction as produced by this model might be inappropriate in a clinical scenario. Accordingly, it may be postulated that there could be a specific ideal HR target, adjusted to individual clinical scenarios, and that an excessive attenuation of tachycardia response to endogenous or therapeutic catecholamines could be deleterious, leading to increased filling pressures and reduction of CO.

Another unique finding of in the present results was higher CVP values in the ivabradine group compared with the placebo group, with no clear effects on PCWP. It is possible that preserving an adequate HR in the ischemia-reperfusion model could be more important to right-ventricle filling pressures that left-ventricle mechanics. These data should be confirmed in robust future studies with longer observation times and, ideally, clinical endpoints.

This study has some limitations that should be considered. First, anesthetic drugs could exert a vasodilatory effect not present in clinical models of AHF, although the same anesthetics were used in the ivabradine and control group. Second, dobutamine and noradrenaline were administered to induce tachycardia and maintain adequate systemic perfusion. Cathecolamine infusion produced a high-output state in some experimental animals could have had an important interaction with the hemodynamic effects of the study drug. Finally, operators were blinded to the product administered after the occlusion phase (ivabradine or saline infusion). However, masking the chronotropic effects

of ivabradine was not possible, reducing the impact of a blind design.

Conclusions

In conclusion, in a swine model of myocardial ischemia-reperfusion injury and AHF, ivabradine effectively attenuates catecholamine-induced tachycardia and acutely increases SV and diastolic filling time without affecting systemic or left-heart filling pressures. However, in this experimental model, an excessive HR reduction produced lower CO values. Future studies with more specific HR targets are needed to evaluate possible benefits of ivabradine in this context.

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Aortic stenosis and anemia with an update on approaches to managing angiodysplasia in 2018

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Abstract

Angiodyplasia and aortic stenosis are both conditions that are highly prevalent in elderly people and can often co-exist. Recent studies suggest that this association is related to subtle alterations in plasma coagulation factors. The von Willebrand factor is the strongest link between aortic stenosis and bleeding associated with gastrointestinal angiodysplasia. With an ageing population, the disease burden of aortic stenosis and its association with angiodysplasia of the bowel makes this an incredibly underdiagnosed yet important condition. Clinicians should be aware of this association when dealing with elderly patients presenting either with unexplained anemia, gastrointestinal bleeding or with aortic stenosis. A high index of suspicion and appropriate diagnostic techniques followed by appropriate and prompt treatment could be life-saving. No clear guidelines exist on management but surgical aortic valve replacement is thought to offer the best hope for long-term resolution of bleeding. With a growing number of technological armamentarium in the management of such patients, especially with the advent of transcatheter aortic valve implantation, new options can be offered even to elderly patients with comorbidities for whom conventional surgery would have been impossible. (Cardiol J 2020; 27, 1: 72–77)

Key words: aortic stenosis, Heyde's syndrome, angiodysplasia, von Willebrand factor, transcatheter aortic valve implantation

Introduction

Angiodysplasia is one of the commonest reported causes of gastrointestinal (GI) bleeding (GIB) in the elderly population [1]. It is an acquired submucosal arterio-venous malformation that arises during the ageing process due to the combination of high stress and deficiency of collagen IV that supports the connective tissue in the GI wall [2]. This condition is often associated with aortic stenosis (AS) and may be referred to by its eponymous name, Heyde's syndrome [1]. There remains an ongoing debate as to whether there is a genuine association or it is just coincidental because the mechanism connecting both pathologies remains unclear. There is however, a general consensus that aortic valve replacement (AVR) in this setting terminates GI blood loss in the majority of patients [3].

This paper aims at reviewing the evidence between aortic stenosis and anaemia with a particular focus on angiodysplasia.

Subheadings

Historical perspective

Heyde's syndrome was first described in 1958 by Edward Heyde following a series of 10 patients with AS and GI bleeding of unknown origin [1]. Subsequent reports have inferred GI angiodysplasia especially in the right colon as a probable site of the bleeding but the exact association between AS and angiodysplasia remained unclear. Later, angiodysplasia of the stomach and duodenum was

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reported in patients with AS as being a potential cause of recurrent unexplained massive upper GI hemorrhage. With the combined use of both angiography and endoscopy to identify GI lesions, AS associated with angiodysplasia has been thoroughly documented, and can include both upper GI and lower GI lesions, particularly right sided colonic lesions.

It was not until 1992 that an etiopathogenic mechanism was postulated. According to Warkentin et al. [4], this phenomenon arises due to a deficiency of high molecular weight (HMW) multimeters of the von Willebrand factor (vWF). Type 2A von Willebrand disease appears to be the nexus between two components of this condition and is reported in as many as 67–92% of patients with severe AS [5].

Epidemiology

Anemia is a common finding among patients with severe AS. Rheude et al. [6] and Tjahjadi et al. [7] reported a 45% and a 30.1% prevalence of anaemia (World Health Organization definition) among patients undergoing surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI), respectively. On the other hand, it has been postulated that the prevalence of calcific AS is much higher in patients with idiopathic GIB compared to non-idiopathic GIB and the general population. Several studies have reported a prevalence of 7–41% of AS with symptomatic GIB [7–10].

Godino et al. [11] elegantly showed that among 400 consecutive TAVI patients (Nov 2007 till Feb 2012), 37 patients had a history of GIB (9.2%). Of those, 7 (1.7%) patients had confirmed instrumental evidence of angiodysplasia and a final diagnosis of Heyde's syndrome.

Pathophysiology

Several pathological mechanisms have been hypothesized to explain this condition and these include an age-related degenerative process, genetic predisposition and hematological abnormalities.

Age related degenerative process

This condition presents in patients of advanced age, usually in the seventh decade of life (range 53–90 years old) [11]. The bleeding is normally recurrent and potentially massive. Age dependant tissue deterioration is a known risk factor of both AS and angiodysplasia and the incidence of both increases with age. Hence, angiodysplasia was thought to be due to senescence rather than AS per se [11].

Genetic predisposition

Heyde's syndrome may be attributed to a common genetic predisposition for an underlying defect in connective tissue disease, particularly a deficiency of collagen type IV. Congenital connective tissue defects may aggravate age dependant tissue degradation essentially due to high tension and weak supporting tissue particularly in the colon [12]. Likewise, congenital abnormalities of the aortic valve, namely the bicuspid valve are other risk factors to induce calcification of the aortic valve [13].

Hematological abnormalities

Hematological disorders, especially defects of vWF can play a key role in Heyde's syndrome [14]. vWF is a multimeric glycoprotein that controls adhesion of platelets to the subendothelium of damaged blood vessels. Any cardiovascular disease that induces rapid clearance of HMW multimers (multimers of vWF $\geq$ 10 dimers are known as HMW multimers) could cause bleeding from angiodysplasia. It is therefore understandable that the high shear in vasculature present in patients with AS is responsible for the decrease in size of the vWF mulitimers. Conversely, substantial improvement is noted in the amount of HMW multimers after surgical valve replacement [5] and TAVI [15, 16].

Other

Boss and Rosenbaum [16] described distension of intestinal mucosal vessels in post-mortem subjects with AS as the cause of GI blood loss. This reflex vasodilation is believed to be caused via the sympathetic system due to low-grade hypoxia. There is relaxation of the vascular smooth muscle, which with chronicity results in distension. It has also been postulated that in AS there is a redistribution of the splanchnic blood flow with associated mesenteric ischemia along with high intestinal intramural pressure. Pulse wave arterial patterns in the final portion of the superior mesenteric conduit have shown a significant drop in arterial pressure in patients with AS compared to controls [17]. Ultimately the above pathological processes result in mucosal ischemia and bleeding due to loss of gut integrity.

Clinical presentation

Most patients are elderly, more than 65 years old with known valvular heart disease or who have undergone heart valve replacement [11]. Patients with AS can present with unexplained chronic lower GIB which can cease and recur after several years. Angiodysplasia can be diagnosed as an incidental finding in an otherwise asymptomatic patient with valvular heart diseases or who has had an acute massive hemorrhage [11]. Another presentation is unexplained chronic iron deficiency [18].

Diagnostic modalities

Diagnosis remains a challenge because most patients do not exhibit generalized hemostatic deficit and bleeding is generally confined to GI tract but we believe that diagnosis should consist of a triad of cardiovascular, GI and hematological investigations.

Cardiovascular investigation

A transthoracic echocardiogram is the first line investigation to confirm the presence of AS and assess its severity.

GI investigation

Colonoscopy, either alone, or alongside angiography can be both diagnostic and therapeutic.

Whenever feasible, colonoscopy and gastroduodenoscopy are the initial diagnostic modalities of choice [19]. Selective mesenteric angiography may serve as a useful diagnostic technique for angiodysplasia, particularly in patients with a massive hemorrhage where a colonoscopic diagnosis is difficult. Before establishing a diagnosis of Heyde's syndrome in an elderly patient with unexplained or unrevealed bleeding, other diagnoses such as GI malignancy, celiac disease, vitamin B12 or folate deficiency must be excluded. However, presence of angiodysplasia on sigmoidoscopy or colonoscopy should raise suspicions of Heyde's syndrome particularly in patients with known echocardiographic evidence of AS or classical auscultatory findings of AS [19].

Wireless capsule endoscopy (CE) and double balloon enteroscopy (DBE) are newer techniques that allow diagnostic enteroscopy of the entire small intestine. CE is a painless, non-invasive procedure that facilitates visualization of the small intestine and indicates the route for enteroscope insertion [20]. However, CE is not a reliable method to detect all the lesions especially during active bleeding and does not offer a therapeutic intervention. DBE however can overcome the disadvantages of CE as it can visualize most of the small bowel by providing superior quality images compared to CE, enables diagnostic manoeuvres and therapeutic intervention such as achieving hemostasis, performing polypectomies, stricture dilatation and stenting. Radionuclide methods such as labelled red cell scintigraphy can also be used to image the GI tract over a prolonged period as GIB in this condition, whilst episodic is usually recurrent [21]. Endoscopic Doppler sonography has also been used to identify intestinal angiodysplasias and has also been used to indicate efficacy of treatment [22].

Despite significant advances in endoscopic technology as well as standardization of training and lesion recognition, the lesion can potentially be missed in about 35% of cases despite all investigations. Diagnostic laparotomy could be the only option and may be life-saving in such cases [23].

Hematological investigations

Heyde's syndrome is usually associated with one of the acquired forms of vWF deficiency and the recommended guidelines for diagnosis and management which involves measurement of vWF levels. Immunoblot analysis or gel electrophoresis can detect a low level of HMW vWF multimers. vWF antigen levels and ristocetin co-factor activity are abnormal when where is severe deficit of the largest vWF multimers [24]. Likewise, patients with AS have a higher incidence of prolonged bleeding time with an otherwise normal coagulation state compared to normal subjects. However, tests performed to detect von Willebrand diseases are not always confirmatory, as the abnormality may be subtle [24]. Moreover, multiple blood transfusions can also make vWF levels inconclusive [2].

Management

As of now, there are no recommended guidelines or universally accepted unified treatment or protocol for the management of Heyde's syndrome. One should consult guidelines for management of unexplained GI blood loss, AS and vWF-deficiency before treating patients with Heyde's syndrome. Therapeutic options for Heyde's syndrome include AVR, surgery, angiographic intervention, double or single balloon endoscopy and medical therapy particularly hormonal and thalidomide treatment.

Aortic valve replacement

Aortic valve replacement is recommended as the first line treatment in this condition as it reduces or terminates GI blood loss [23]. Cessation of bleeding after AVR was found in 95% as compared to 5% managed by laparotomy with or without bowel resection [23]. Following AVR, it was also found that patients had improved levels of HMW multimers of vWF. AVR ameliorates mucosal blood supply and corrects the hematological abnormality [23, 24]. GI angiodysplasia could cease following AVR as shown by endoscopy, hence, elective GI surgery for bleeding angiodysplasias in patients with co-existing AS needs to be rescheduled until AVR has been attempted [25]. Moreover, in the presence of chronic anemia requiring multiple blood transfusions coupled with reduced levels of vWF, AVR should be considered even in asymptomatic but hemodynamically significant AS patients [26]. Further studies are needed to clarify whether Heyde's syndrome should be considered as an indication for valve surgery in the absence of cardiac symptoms, anemia or GIB.

Valve replacement can result in almost immediate cessation of bleeding and remission of GIB, a theoretically, mechanical valve replacement warrants lifelong anticoagulation and this could promote GI bleeding from angiodysplastic lesions. Hence, biological valve replacement has been preferred over mechanical valves [27]. Some studies report no recurrence of bleeding in patients despite having had a mechanical valve with oral anticoagulant therapy. Indeed, some authors suggest that choice between a biological and a mechanical valve makes no difference so long as AS is treated promptly and effectively [28].

Of note, patient-prosthesis mismatch and structural valve deterioration usually lead to recurrence of angiodysplasia and bleeding [29].

Transcatheter aortic valve implantation

The new paradigm shift in the management of AS, after the recent update of the European and American guidelines to include TAVI as a treatment option for intermediate risk cases, means that many of these patients will undergo TAVI rather than SAVR. However, very few studies have investigated the effect of using TAVI to treat patients with co-existing HMW multimers of vWF and severe AS. Spangenberg et al. [30] enrolled 95 patients for elective TAVI of which 40 had abnormal multimers with 42% of these patients experiencing an average HMW multimers content of 16.2 ± 3.3%. TAVI led to a normalization of HMW multimers content in patients with prior abnormal multimers and also left HMW multimers in the remainder of the study population unaltered [30]. Similar findings were reported by Caspar et al. [31] and Marggraf et al. [32]. Spangenberg et al. [30] did not show any increase in bleeding of transfusion requirements in patients with severe vWF deficiency undergoing TAVI as opposed to surgical valve repair.

Based on the above studies, one can assume that TAVI is likely to be a curative option for Heyde's syndrome and its associated GIB just like SAVR. Godino et al. [11], as mentioned above, reported on 7 cases of Heyde's syndrome that underwent TAVI. Of those, one had failed TAVI due to access issues, the others had successful implants. A median follow up of 22 ± 15 months of this small group of patients demonstrated that no patients had recurrence of GIB and the only patient that had failed TAVI required repeated transfusions.

Para-valvular leak (PVL) post TAVI, yet again, is this treatment's Achilles' heel. PVL cases tend to have inferior HMW multimers recovery, and potentially this could abate the potential curative effect TAVI has over Heyde's syndrome [30]. Thus TAVI deserves consideration as the primary approach for patients with severe acquired von Willebrand syndrome or abnormal multimers.

GI surgery/endoscopy

Treatment of bleeding GI angiodysplasia may require surgical resection of the affected part or frequently endoscopic laser photocoagulation with good initial results but recurrence occurs in a third of patients. Previously, segmental bowel resection of angiodysplasia lesions was the recommended treatment for patients with Heyde's syndrome. In the absence of any colonic abnormalities observed intra-operatively, a blind right colectomy was recommended [33]. Ogano et al. [34] highlighted the need for elective bowel resection once a restricted bleeding site had been identified in patients at high risk of cardiac surgery. However, bleeding recurs in about a third of patients possibly due to lesions elsewhere in the GI tract which continues or starts to bleed in contrast to patients who undergo AVR who usually have long-term durable remissions [34]. GI surgery is only recommended if hemorrhage persists after a period of observation in patients who have demonstrable vascular ectasia on selective mesenteric angiography. A few case reports have described massive GI hemorrhage after SAVR, hence this strategy might not be ideal treatment in every patient with Heyde's syndrome [35].

In patients deemed unfit for AVR or surgical resection, endoscopic management has been the mainstay of treatment. Endoscopic destruction is usually performed using non-contact techniques with APC considered superior to Nd:YAG laser treatment due to lower risk of perforation [36].

Medical management

Replacement of clotting factors, vWF supplementations or Contact F (combination of vWF and factor VIII) can be effective for acute control of GIB [17, 18]. Other alternatives include desmopressin, cryoprecipitate or the pan haemostatic agent recombinant factor VIIa transfusion that can augment circulating levels of vWF [37]. Other forms of medical therapy include use of somatostatin or octreotide that potentially reduces venous pressure in the portal venous system [38, 39]. This can aid in controlling bleeding, although the long-term benefit of Octreotide is still undergoing evaluation [40]. Hormonal replacement therapy in the form of low doses of ethinyl estradiol and norethisterone can reduce transfusion requirements by 50% [41]. However, the mechanism of action behind this remains unknown.

Other

Angiographic embolization of the source artery of the bleeding site could be an option to surgery [41]. Some studies recommend this approach only for high-risk surgical patients while others argue that this procedure can be considered in all patients presenting with massive GIB. The endoscopic treatment of angiodysplasia in the form of electrocoagulation sclerotherapy and laser photocoagulation has been shown to be effective [42], however several treatment attempts may be required due to a high bleeding recurrence rate.

Thus, angiography and embolization, whilst often used as a rescue approach for the management of GIB following failed endoscopic therapy may have a larger role to play.

Future work: Biomarkers predicting risk

The vascular growth factor, angiopoeitin-2 which plays an important role in embryonic angiogenesis may also have a role as a biomarker in predicting patients at risk of bleeding. Angiopoeitin-2 levels (both serum and mucosal levels) have been found to be elevated in patients with sporadic small bowel angiodysplasia [43]. It remains to be seen whether these levels are affected by AVR.

Conclusions

The nexus between aortic valve stenosis and GIB still remains poorly understood. Its potentially life-threatening nature and uncertainty renders it a difficult condition to treat. However, a high index of suspicion must alert any clinician especially in the emergency department while treating an elderly patient with co-existing gastrointestinal hemorrhage and AS. A multi-disciplinary approach can be comprised of a gastroenterologist, cardiologist, cardiac surgeon and a hematologist to best treat such patients. Besides, further studies must be carried out to explore the pathophysiology and management options for this condition.

Conflict of interest: None declared

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TECHNOLOGY NOTE

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Kissing-Watchman technique applied in single-lobulated left atrial appendage anatomy with giant ostia

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The only commercially available device in the documented institution is the Watchman (Boston Scientific, Marlborough, MA, USA) occluder which is the predominant occluder in China. The single device approach may not always fit the great anatomic variability of the left atrial appendage (LAA). Adequate closure may require more than a single device. The commercially available Watchman device only fits LAAs with a maximum diameter of 30 mm [1–3]. In patients with bilobulated LAA, the one-stop implantation of double Watchman is feasible as reported by a previous study [4]. However, it is unknown whether this approach is feasible in the setting of a single-lobulated LAA with a giant ostium (> 30 mm). Reported herein, is a consecutive case series of patients in whom kissing-Watchman was performed to achieve adequate closure of the single-lobulated LAA with large-ostium.

Three out of 100 consecutive patients underwent kissing-Watchman occlusion under the guidance of transesophageal echocardiography (TEE). This experimental procedure was preceded with the patient's acceptance. Before intervention, TEE was performed to exclude thrombi in the LAA. The procedures were performed via femoral access under general anesthesia, and were controlled by the angiography and TEE. At the beginning of the intervention, 5000 units of heparin were given. After transseptal passage, TEE measurement of the LAA diameter at the intended implantation site was performed at four different angles. According to the three cases, the maximal LAA ostia diameters were 35, 36, and 33 mm, respectively. The first occluder was deemed to cover half of the estimated LAA orifice area (d1 = LAAmax/√2). Additionally, the size of the first Watchman device should be greater than or equal to the size of the second device. The second occluder was chosen based on residual space. The first Watchman device was pre-released and held still at the intended implantation site (Fig. 1A). After another transseptal puncture via the same femoral site, the pigtail catheter with the second access sheath was delivered carefully to the uncovered space parallel to the first access sheath and contrast injection was made (Fig. 1B). Excessive adjustment was avoided in order to minimize the sheath-sheath interplay. The second Watchman device was chosen according to the residual stump and was carefully placed next to the first device in a kissing fashion. Two Watchman devices were deployed adjacently. Therefore, complete LAA closure was achieved. Fluoroscopy and TEE were used to confirm the position, size and seal of the kissing device. The tug-test was performed on the two devices by pulling the parallel deliver system simultaneously to avoid dislocation (Fig. 1C). The two devices were released respectively after the Position, Anchor, Size and Seal (PASS) criteria had been met (Fig. 1D). The final diameters of each kissing-Watchman deployed were measured by TEE and the maximum device compression ratio of the kissing-Watchman LAA closure should be larger than a single device LAA closure technique (the upper limit was not limited to 30%). This higher compression ratio contributed to a more radical deformation of the

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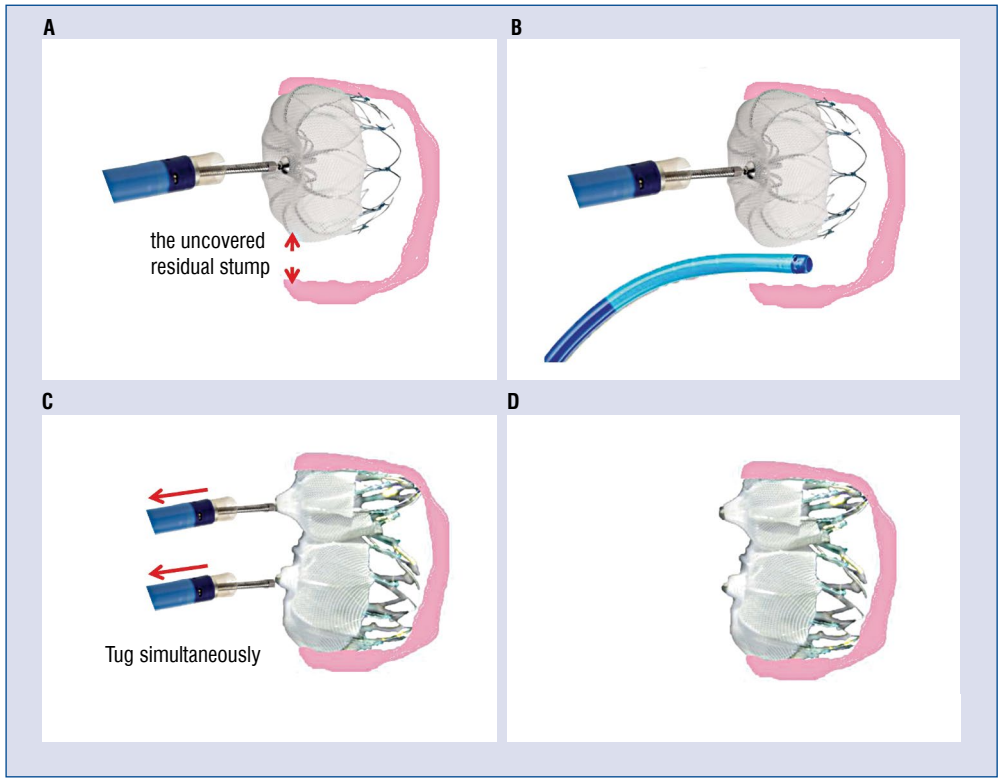

Figure 1. Diagram of kissing-Watchman technique; **A.** The first device is pre-released and held still at the intended implantation site, leaving a residual stump uncovered; **B.** The second access sheath is delivered to the uncovered space parallel to the first access sheath; **C.** The tug test is performed on the kissing-devices simultaneously; **D.** The two devices are released after the Position, Anchor, Size and Seal (PASS) criteria have been met.

kissing-device on the mutual compression side reducing the possibility of inter-device residual flow. Larger endotheliazation area of the kissing device contributes to prolongation of antithrombotic/antiplatelet therapy (3-month antithrombotic therapy or 12-month antiplatelet therapy). TEE 3-month and 12-month was scheduled after kissing-Watchman implantation.

The first patient was a 70-year-old male with a CHA_2DS_2-VASc score of 3. He was referred for LAA closure due to gastrointestinal bleeding on warfarin. TEE showed a single lobe LAA with a maximum LAA ostium of 35 mm (**Suppl. Fig. 1A**). In a single intervention, the giant LAA was partially closed by the implantation of a 27 mm Watchman, and the remaining ostium with a diameter of 12.3 mm was closed by implantation of another 21 mm Watchman (**Suppl. Fig. 1B**). TEE showed that the maximum device compression ratio of the kissing-Watchman LAA closure was 19% and a complete LAA closure was achieved (**Suppl. Fig. 1C, D**). The patient was placed on full dose rivaroxaban for 3 months after the intervention and dual antiplatelet therapy daily afterwards. A TEE performed 3 months later showed good position of both devices, with a newly formed gap of 4.6 mm (**Suppl. Fig. 1E**). The patient remained asymptomatic. Twelve months after the intervention, TEE confirmed an adequate occlusion with a remarkably shrinking peri-device flow of 1.8 mm and no device related thrombus was identified (**Suppl. Fig. 1F**).

The second patient was a 55-year-old male who underwent closure of a giant single-lobulated LAA due to paroxysmal atrial fibrillation, a CHA_2DS_2-VASc score of 4, and recurrent stroke under warfarin. TEE showed a single lobe LAA with a maximum LAA ostium of 36 mm without a ridge-like pectinate muscle inside (**Suppl. Fig. 2A**). Knowing that two devices would be necessary, the giant LAA was partially closed by implantation of a 27 mm Watchman leaving a 24 mm opening stump (**Suppl. Fig. 2B**). Therefore, complete LAA closure was achieved by the subsequent implantation with an additional 27 mm Watchman (**Suppl. Fig. 2C, D**). The maximum device compression ratio of the kissing-Watchman system was 33.3%. The patient was discharged on 110 mg dabigatran bid for the

first 3 months post-operation and dual antiplatelet therapy for the following 8 months. TEE 3-month and 1-year post-operation follow-up showed adequate LAA sealing, with a persistent residual flow of 1.6 mm in the LAA and no device related thrombus was identified (**Suppl. Fig. 2E, F**). One year after the intervention the patient remained free of symptoms on acetylsalicylic acid 100 mg daily indefinitely.

The third patient was a 78-year-old man with a previous stroke, a CHA_2DS_2-VASc score of 4, and chronic kidney disease precluding the use of warfarin. TEE demonstrated a large single-lobulated LAA with a 33 mm ostium and many pectinate muscles deep inside (**Suppl. Fig. 3A**). Knowing that two devices would be necessary, 27 mm Watchman was placed at the entrance of the LAA. It partially occluded LAA with a 14 mm residual stump uncovered (**Suppl. Fig. 3B**). A subsequent implantation with an additional 21 mm Watchman was achieved to completely occlude this large LAA (**Suppl. Fig. 3C–E**). The maximum compression ratio of the kissing-Watchman system was 28.6%. The patient was prescribed with dual antiplatelet daily for the following 12 months, post-implantation. TEE performed after 3 months showed good position of both devices, with no evidence of residual shunt (**Suppl. Fig. 3F**). The clinical follow-up was uneventful.

There is a myriad of variations of LAA anatomy in terms of number of lobes and size of orifices [5]. One restriction inherent in single-device LAA occlusion technique concerns the maximum LAA body size suitable for intervention. Though there are larger sizes in other devices nowadays, the largest commercially available Watchman device only fits LAA with a maximum diameter of 30 mm [1]. Therefore, for an LAA ostium > 31 mm, it is difficult to obtain complete closure with a single Watchman device. The implantation of double Watchman is recommended in bilobulated LAA anatomy [1–3]. It remains controversial whether kissing-device, deployed adjacently in the same lobe is safe. Some scientists argue that there are several potential procedural risks [4]: 1) a severe residual flow between devices can exist; 2) the fixation barbs may injure the permeable polyester polyethylene membrane of the first device while deploying the second device; 3) due to the long-term mechanical interaction, device embolization may occur. In a considered opinion, to avoid potential peri-operative complications, it is important to: 1) select the kissing-device of identical or similar size to facilitate closer contact between the two devices minimizing residual shunting between them; 2) a more liberal oversizing technique (higher compression ratio) helps to minimize inter-device flow and also contributes to a greater radial force for stability; 3) deformation of the kissing-device on the mutual compression side contributes to minimizing potential leak between the kissing-devices.

No device dislocation, severe residual flow (> 5 mm) or device related thrombosis was observed, aside from the minor (< 3 mm) peri-device leakage identified at both 3-month and 12-month TEE follow-up. It was reported that, in patients who had undergone single Watchman LAA closure, an intraprocedural gap could persist, and could close or close and reopen during the follow-up period [6]. Therefore, in patients who underwent kissing-Watchman implantation, a mild peri-device leak during TEE follow-up may not be related to interaction between the devices. Additionally, a peri-device gap with mild blood leak may not affect the stability of the Watchman device inside LAA, as evidenced by the fact that no device dislodgement occurred in patients of the present study.

Due to individual anatomic variations, a single Watchman device may not always adequately seal the LAA. In these cases, implantation of kissing-Watchman in single-lobulated LAA with giant ostia may afford a good anatomical result. Larger cohorts are needed to corroborate the safety and efficacy of this technical innovation.

Conflict of interest: None declared

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The yin-yang sign in the detection of subintimal hematoma with high-definition intravascular ultrasound

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This paper was guest edited by Prof. Cheol Woong Yu and Prof. Yongcheol Kim

Editorial p. 4

A 60-year-old male patient, with severe ischemic ventricular dysfunction underwent revascularization of a chronic total occlusion (CTO) in the proximal right coronary artery (Fig. 1A, **Suppl. Video 1**) with retrograde epicardial approach (**Suppl. Video 2**). A reverse controlled-antegrade-retrograde tracking (rCART) technique was performed (Fig. 1B, **Suppl. Video 3**) and the retrograde wire progressed up to the tip of the antegrade catheter, but it could not be externalized, bending continuously near the catheter tip. The intervention was then guided by high definition intravascular ultrasound (HD-IVUS) with a 60 MHz Opticross-HD catheter (Boston Scientific, Marlborough, MA), showing a scenario of antegrade intraplaque / retrograde subintimal (Fig. 1C, arrow pointing retrograde wire, **Suppl. Video 4**), with hematoma (Fig. 1D, arrow-heads) near the antegrade catheter, probably created by wire manipulation in externalization attempts. The speckle of static blood appears enhanced in HD-IVUS as compared with 40-MHz IVUS, thus giving the hematoma a characteristic whitish appearance, in contrast with the dark appearance of the plaque and t he true lumen, thus resembling the yin-yang symbol (Fig. 1D). After rCART with a larger balloon (**Suppl. Video 5**), the wire could be externalised (**Suppl. Video 6**) and a second HD-IVUS was acquired (Fig. 1E–H, **Suppl. Videos 7, 8**), from distal (Fig. 1E) to proximal true lumina (Fig. 1H). The yin-yang sign enabled easy recognition of the subintimal course (Fig. 1F, G), pointing out sharply the entry and exit points. After sizing the stents according to HD-IVUS, the CTO was successfully revascularized (Fig. 1I, **Suppl. Video 9**). According to available research, this is the first report of HD-IVUS in a CTO, suggesting an advantage over other techniques in detecting subintimal hematoma.

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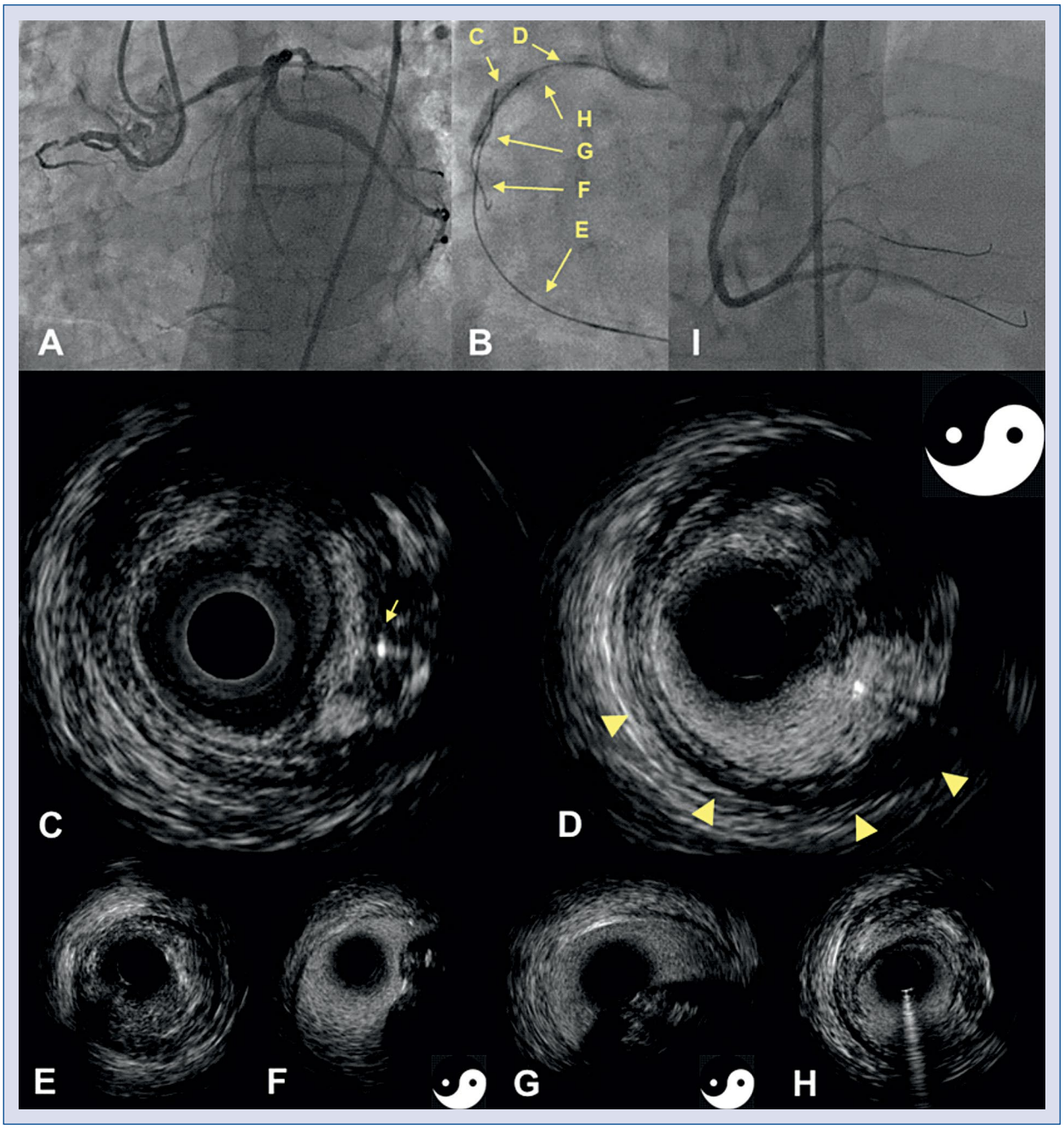

Figure 1. A chronic total occlusion of the proximal right coronary artery (**A**) was percutaneously treated via the retrograde approach with controlled-antegrade-retrograde tracking (rCART) technique (**B**), but the retrograde wire had problems externalizing. Intravascular ultrasound (IVUS)-guided rCART was then performed with a 60 MHz high definition IVUS (**C**, **D**), finding a scenario of antegrade intraplaque/retrograde subintimal (**C**, arrow; **D**, arrow heads). Since the speckle of static blood appears enhanced in 60 MHz IVUS as compared to lower frequencies, the subintimal hematoma appears whitish (**D**), producing a characteristic yin-yang sign: the anatomy of the vessel appears divided in two, with one half dark (true lumen/intraplaque) and the other half whitish (subintimal). After externalization of the wire a final 60-MHz IVUS pullback was acquired (**E**–**H**). The yin-yang sign (**F**, **G**) enables unambiguous and accurate recognition of the subintimal course. An excellent final result was, in the end, achieved (**I**).

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Echoes from Picasso: Explanation of an unusual artefact in optical coherence tomography

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This paper was guest edited by Dr. Evelyn Regar

A patient referred for primary percutaneous coronary intervention presented with severe stenosis in the distal left main. After implanting a bifurcation-dedicated sirolimus-eluting stent (BIOSS-LIM™, Balton, Warsaw, PL) angiography showed an apparently good angiographic result but with somewhat hazy appearance, requiring clarification by means of optical coherence tomography (OCT). OCT showed a region of severe underexpansion and a high ellipticity index (2.9) [1], corresponding with the hazy image (Fig. 1A). An interesting circular structure could be observed outside the vessel (Fig. 1A, arrow), mirroring the sheath of the optical catheter. This corresponds to an unusual expression of an artefact known as *echo*, happening when a strut is perpendicularly aligned with the OCT scan plane for a fairly large angle (Fig. 1A, asterisk). The light is then backscattered in the strut (Fig. 1B), and subsequently back to the catheter and to the opposite wall (Fig. 1B, dashed arrow), where it is reflected again, then back to the strut (Fig. 1C) and back to the catheter, where it is now detected (Fig. 1D), This creates echoes of the backscattered structures throughout the beam pathway. The result is a mirror image where the optical catheter (normally absent from the OCT image; Fig. 1A, arrow) and the strut at the opposite wall (Fig. 1A, hash) can be recognised. The vicinity of structures, due to the severe underexpansion, favours the appearance of this artefact within the OCT field of view.

The curious image resembles a cubist artwork, like Picasso's portrait of Dora Maar (Fig. 1E), although attending to the physics underneath it would match better with Picasso's *Girl before a Mirror*.

Conflict of interest: None declared

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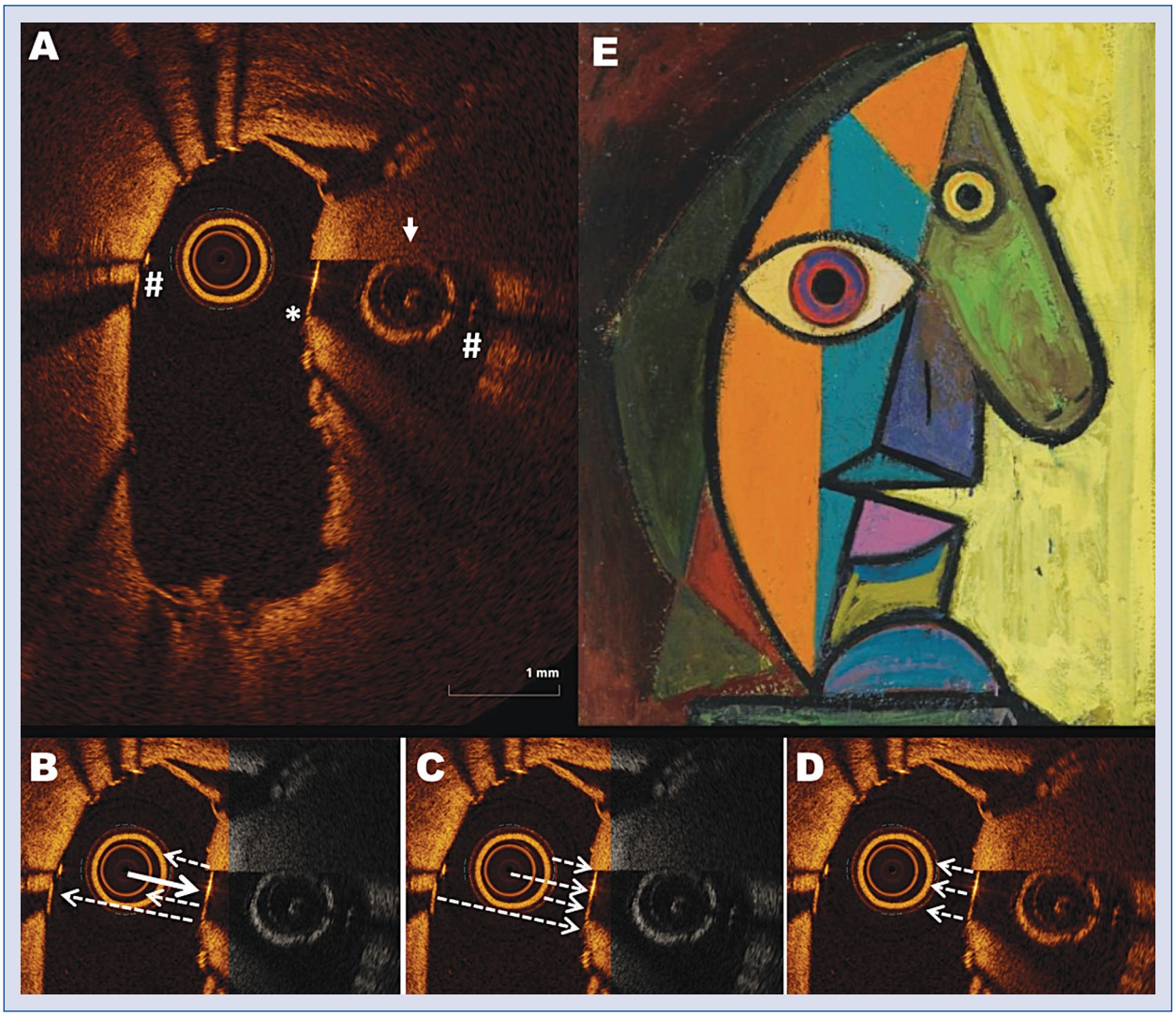

Figure 1. Marked echo artefact due to the vicinity of a large strut (*) to the optical catheter (#), depicting the optical catheter in the echo (arrow), usually absent from an optical coherence tomography image, and resembles an unusual cubist portrait.

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A case of drug-coated balloon treatment for three-vessel stenosis with left main bifurcation lesion

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A 62-year-old man who was a current smoker presented with a 2-month history of effort angina. His treadmill exercise test was positive with significant ST-segment depression at stage 2. Coronary angiography showed a subtotal occlusion of mid right coronary artery (RCA) and 90% stenosis at the distal left main (LM) bifurcation (Fig. 1A–C). He declined bypass surgery or stent implantation but agreed to treat with drug-coated balloon (DCB) with bailout stenting only in the event of a flow limiting dissection. He was carefully evaluated and provided informed consent.

The RCA lesion was successfully treated with a DCB after balloon angioplasty (Fig. 1D). The lesion of LM to proximal left anterior descending artery (LAD) was dilated with a non-compliant 3.5 × 15 mm balloon at 14 atm and a 3.5 × 20 mm DCB was inflated at 8 atm for 60 s. The ostium of the left circumflex (LCX) was not treated. The final angiogram showed normal flow in both LAD and LCX and no significant dissection (Fig. 1E, F). Post-intervention his symptoms resolved, and his follow-up treadmill test was negative.

Six months later, follow-up coronary angiography confirmed adequate patency of the DCB treated segments and reassuringly the LM bifurcation looked better (Fig. 1G–I). He remains symptom-free 12-month post-intervention.

Drug-coated balloon has shown good results in controlling neointimal hyperplasia in the coronary arteries including side branch ostium, although its role in treating LM bifurcation stenosis is still unknown. Even though long-term outcome data are lacking, this case of DCB treatment for distal LM bifurcation stenosis is promising, patency was demonstrated at 6-month, with no evidence of angina at 1-year. These findings suggest that distal LM bifurcation stenosis may be a potential novel indication for DCB, especially when patients are unsuitable for long-term antiplatelet therapy or are unwilling to undergo coronary bypass grafting or stenting.

Conflict of interest: None declared

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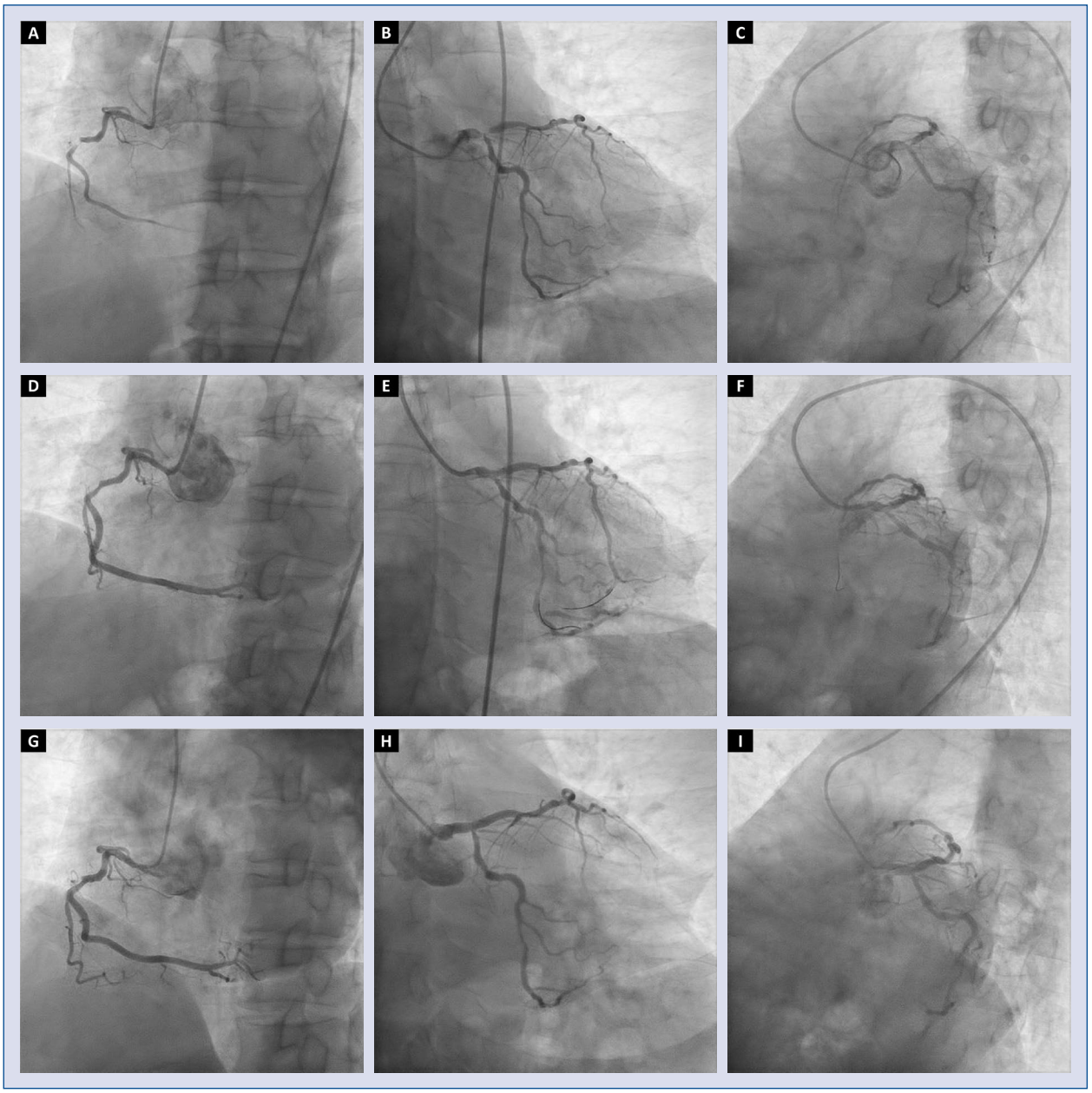

Figure 1. Coronary artery angiography; **A–C.** Before intervention; **D–F.** Right after treatment with a drug-coated balloon; **G–I.** Follow-up angiography at 6-month.

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Valve in valve procedure and left main stent: To deliver or not to deliver

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A 82-year-old woman was admitted for severe aortic regurgitation due to degenerated Mitroflow-21. Redo surgery was rejected and transcatheter valve-in-valve was planned.

There was a short distance from the bioprosthesis to the coronary ostia (Fig. 1A). Considering the risk of coronary obstruction, two undeployed drug-eluting stents were positioned at the left anterior descending and right coronary artery (Fig. 1B). Subsequently, a 23 mm Allegra bioprosthesis was implanted and since right coronary artery was patent, the gear was removed (Fig. 1C). Although there was no angiographic impairment of the left main, a guidewire deformation at the ostium was observed (Fig. 1D; asterisk). Moreover, the guiding catheter was non-deeply engaged and coaxial alignment was not viable. Due to the possibility of not retrieving the stent through the prosthesis and a likely delayed coronary obstruction, a stent at the left main was successfully deployed (Figs. 1E, F).

The present case highlights the importance of careful planning and the need for protecting coronary arteries with a guidewire, balloon or stent in valve-in-valve procedures to prevent coronary obstruction. However, it remains unknown which method is best. It is also controversial as to when stents should be deployed, since late vessel obstruction may occur. The difficulty of recovering the stent if the guiding catheter is not coaxial is another factor which should be kept in mind. For these reasons, if in doubt, a recommendation presented herein, is to deploy the stent to ensure coronary flow. Further investigation is required to know the best stent deployment technique: "chimney" versus "optimal ostial stent placement".

Conflict of interest: Ariana Gonzálvez-García, Harold Hernández-Matamoros, Alfonso Jurado-Román, Guillermo Galeote and Santiago Jiménez-Valero declare no conflict of interest. Raúl Moreno is Allegra valve proctor for NVT.

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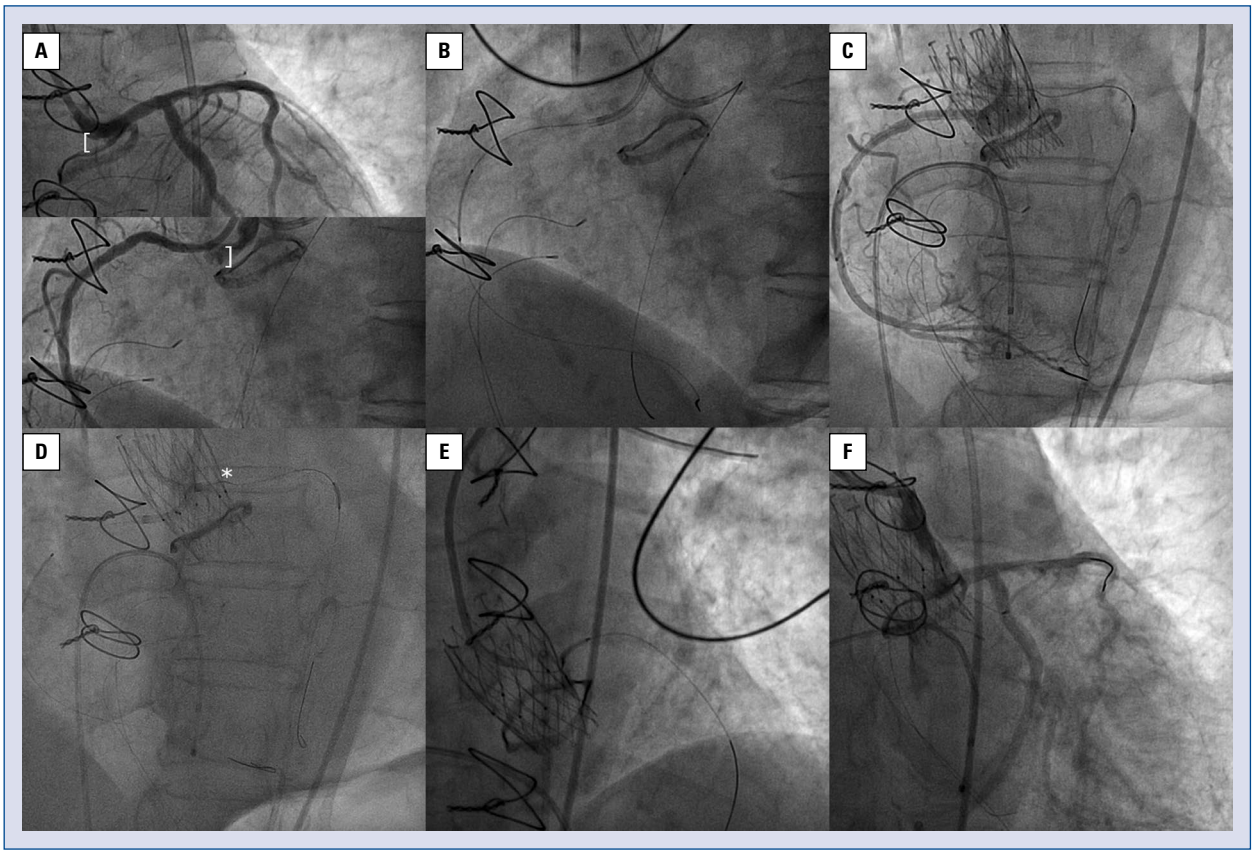

Figure 1. A. Distance between the bioprosthesis and coronary arteries; **B.** Undeployed stents at mid-left anterior descending and right coronary arteries; **C.** Patent right coronary artery after Allegra implantation; **D.** Asterisk: Deformed guidewire at ostial left main. Guiding catheter at the left main non-deeply engaged; **E.** Stent deployment in left main ostium; **F.** Patent left coronary tree.

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Lithotripsy and ultrasound: Useful armamentarium in the case of ostial calcified stenosis of the right coronary artery

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An 88-year-old female was admitted for angioplasty of the right coronary artery (RCA) (Fig. 1A). Two months prior an unsuccessful angioplasty of the RCA was undertaken — a 3.0 × 20 mm non-compliant (NC) balloon was unable to dilate ostial stenosis and ruptured during inflation. Intravascular ultrasound (IVUS) showed long, diffuse and a heavily calcified narrowing with two concentric calcified plaques in the ostial and medial portion of RCA with a minimal lumen area (MLA) of 1.7 mm^2 and 2.1 mm^2, respectively (Fig. 1D1–F1, **Suppl. Video 1**). The shockwave balloon (3.0 × 12 mm) was delivered, several applications had been performed throughout the RCA and finally the shockwave balloon was fully opened (Fig. 1B). The second IVUS run showed multiple cracks in calcified plaques with new acoustic shadowings, especially in a calcified ring of the medial RCA (Fig. 1D2–F2, **Suppl. Video 1**). Lithotripsy was followed by dilatation with NC balloon in the ostium of the RCA. Then two drugs eluting stents were implanted. Post-dilatation with an NC balloon was performed and consequently the angiographic result was good (Fig. 1C). The final IVUS demonstrated a complete stent apposition and acceptable stent expansion in the ostium of RCA with MLA of 12.0 mm^2 (Fig. 1D3–F3, **Suppl. Video 1**).

Coronary lithotripsy is a novel method for calcified lesion modification, i.e. pulsatile sonic pressure waves generate cracks in both intimal and medial part of the artery wall and enable vessel compliance. Compared with rotablation, this tool is easier to apply and causes fewer complications, e.g. coronary perforation and slow/no-flow phenomenon. Shockwave balloon allows simultaneous guidewire placement during bifurcation intervention. The limitation of this technique is a relatively bulky device therefore some lesions are uncrossable.

Herein, is described the use of lithotripsy for treatment of heavily calcified and undilatable ostial RCA stenosis with a satisfactory procedural result.

Conflict of interest: None declared

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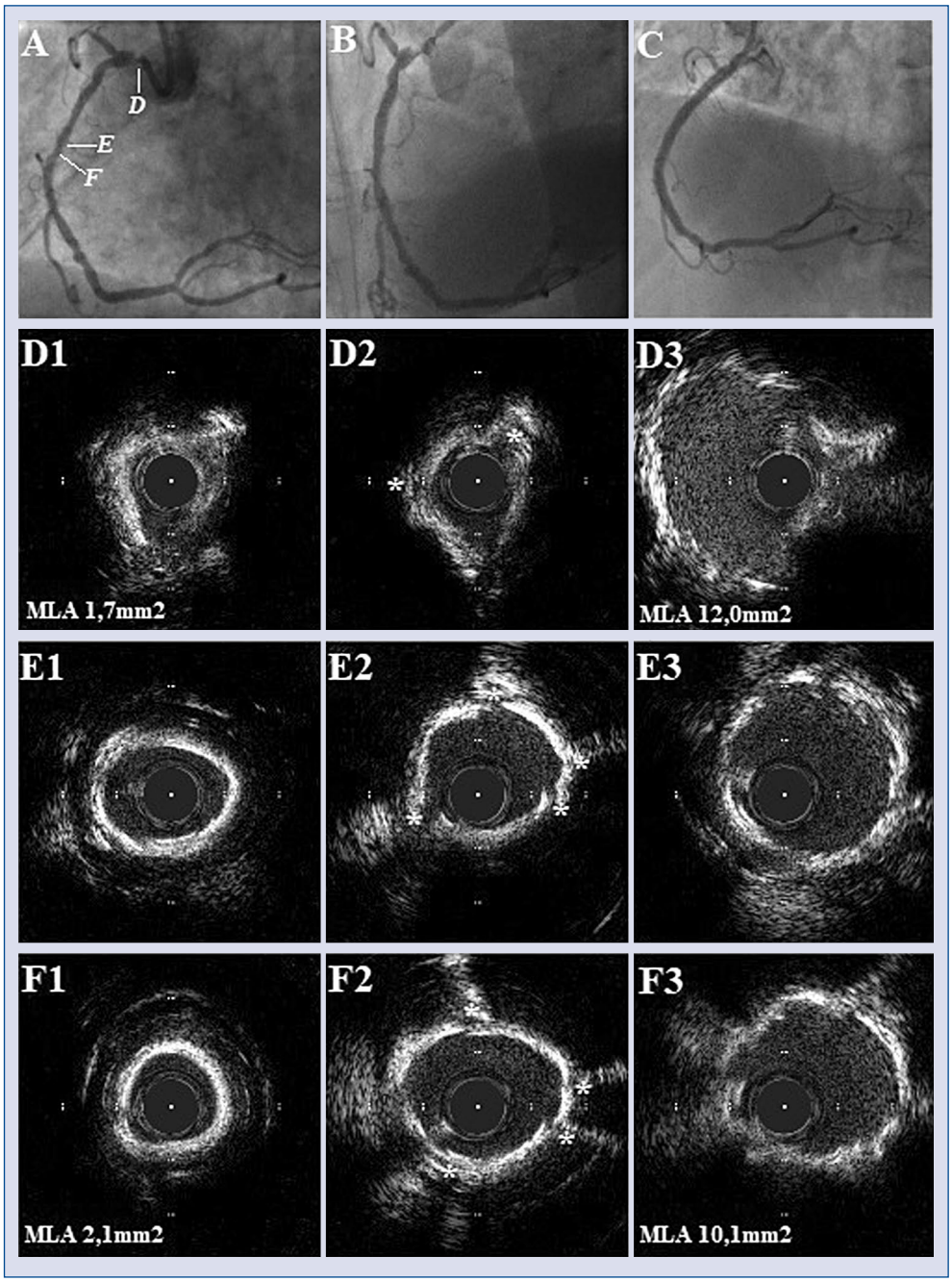

Figure 1. Baseline angiography shows long and diffuse stenosis of the right coronary artery (RCA) involving its aortic ostium (**A**). Angiography of the RCA after Schockwave balloon modification (**B**). Final angiographic result after stent implantation (3.0 × 44 mm distally and 3.5 × 18 mm proximally) and non-compliant balloons post-dilatation (3.25 × 12 mm distally and 4.0 × 12 mm proximally at 24 atm) (**C**). The intravascular ultrasound (IVUS) images: baseline (D1, E1, F1), after shockwave balloon modification (D2, E2, F2) and final result (D3, E3, F3). Small white lines in Figure 1A point to placement of IVUS images on the RCA angiography, respectively D, E and F. Small white stars (*) in the Figure 1D2–F2 show cracks in calcified plaques with concomitant acoustic shadowings; MLA — minimal lumen area.

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How to retrieve a ruptured micro-catheter tip stuck in a tight lesion?

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A 63-year-old male underwent percutaneous coronary intervention of the distal left circumflex artery due to effort angina. The target lesion showed critical stenosis with severe calcification and tortuosity. A 6-French guiding catheter was engaged to the left coronary artery via right radial artery. A SION blue wire (Asahi Intecc, Japan) could pass the lesion, however, a Caravel MC (Asahi Intecc, Japan) micro-catheter could not pass the lesion. When the Caravel MC was pulled out strongly, its tip was twisted off and left in the lesion.

Although there are some possible methods to retrieve it (e.g. use of a snaring catheter, twisted guide wire and so on), it was thought that these methods would not work well because of the very tight lesion.

It was thought that inserting a balloon with a tip diameter smaller than the ruptured tip might enable retrieving both the balloon and the damaged tip.

First, a 1.0 × 5 mm balloon was inserted but did not reach the ruptured tip. Consequently, a 1.25 × 10 mm diameter balloon was inserted and pushed to the ruptured tip, then the balloon was attached to it. Then the connected tip and balloon catheter were carefully pulled out into the guiding catheter, and was successfully retrieved.

After crossing a Rotawire (Boston Scientific, USA), rotational atherectomy and balloon dilatation were performed, then a drug-eluting stent was implanted. The final angiography showed good results.

When a ruptured micro-catheter tip is stuck in a tight lesion, this balloon attached technique may be effective (Fig. 1, **Suppl. Video 1**).

Conflict of interest: None declared

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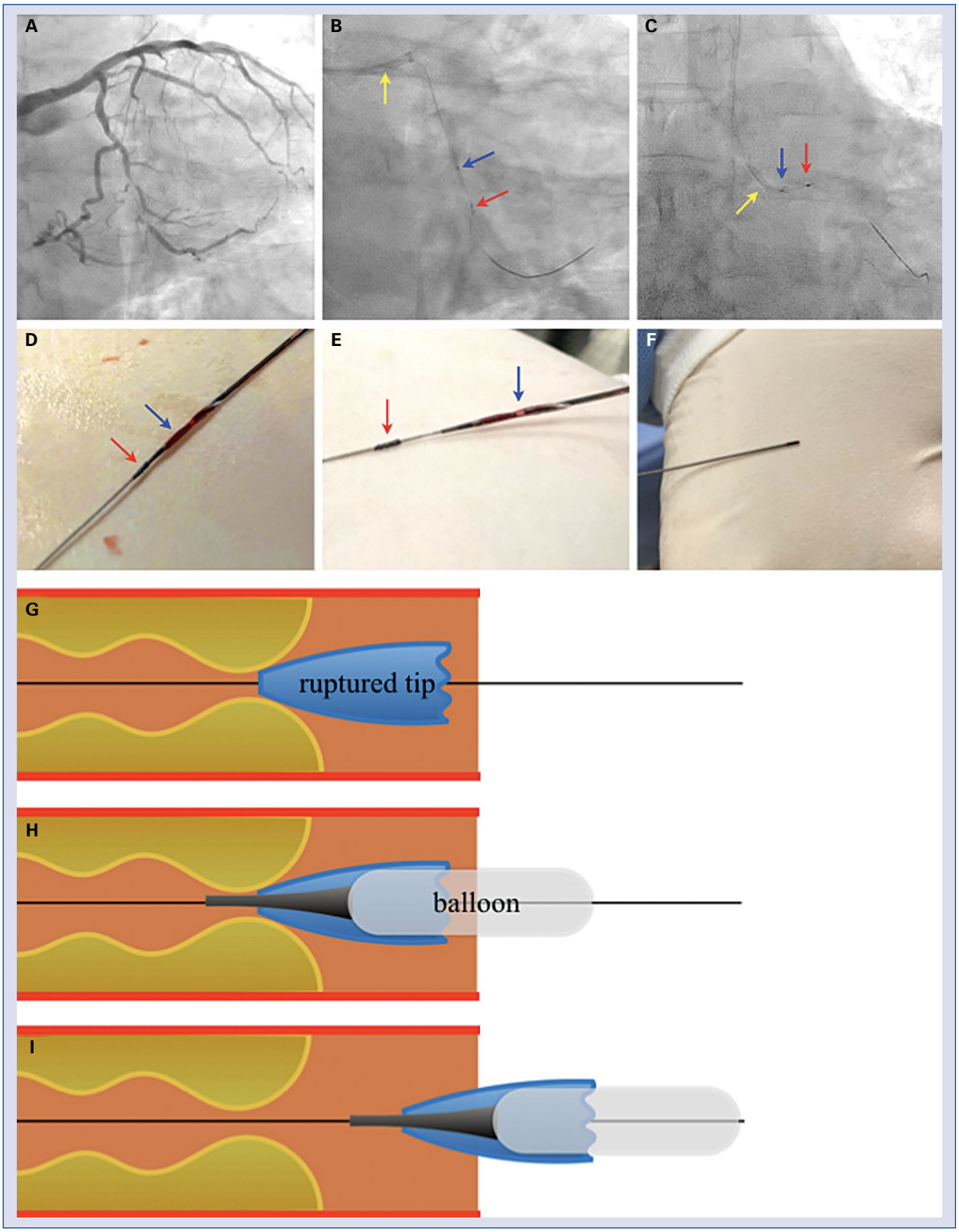

Figure 1. A. Initial angiography; **B.** Balloon is inserted and pushed to the ruptured tip; **C.** Retrieving the ruptured tip attached to the balloon into the guiding catheter; **D.** Ruptured tip attached to the balloon after retrieval from the guiding catheter; **E.** Ruptured micro-catheter tip is pulled out from the balloon tip; **F.** Ruptured micro-catheter; **G.** Illustration of micro-catheter left in a tight lesion; **H.** Illustration of balloon which was inserted and attached to the ruptured tip; **I.** Illustration of ruptured tip retrieval using a balloon. Red arrow: a ruptured tip, blue arrow: a 1.25 mm balloon, yellow arrow: a guiding catheter.

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Dilated cardiomyopathy with severe arrhythmias in Emery-Dreifuss muscular dystrophy

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Herein presented is the case of a 51-year-old male with Emery-Dreifuss muscular dystrophy (EDMD) with a history of rapid progression heart failure (HF) and heart rhythm disturbances over an 8 year period. EDMD is a rare genetic condition that primarily affects skeletal muscles. The patient presented with muscle weakness since childhood. Family history was negative. At the age of 43 atrial fibrillation was diagnosed and 2 years later a single chamber pacemaker was implanted due to third atrioventricular block. After another 2 years, the patient was admitted due to ventricular tachycardia. Transthoracic echocardiography (TTE) revealed moderately reduced left ventricular function (ejection fraction [EF] 48%). A single-chamber cardioverter-defibrillator (ICD-VR) was implanted. After 2 years of well-being, he was admitted to the hospital due to an electrical storm. TTE revealed dilated cardiomyopathy with severe left ventricular dysfunction (EF 15%). Due to clinical presentation, a high percentage of right ventricular pacing, and wide QRS complex (paced QRS 200 ms) the patient qualified for cardiac resynchronization therapy with defibrillator (CRT-D). The left ventricular electrode was implanted and ICD was upgraded to CRT-D resulting in a correct VVI-BiV stimulation with narrowing of QRS complexes to 140 ms. TTE performed after another few months showed significantly improved EF (30%). After another year a right ventricular lead malfunction occurred — myopotential oversensing and inappropriate detection of ventricular tachycardia. Connection of the right ventricular pace/sense lead to the pace-sense header resulted in proper sensing. Since then the patient has remained stable. EDMD leads to HF, arrhythmias and conduction disturbances in about 30% of cases. It is thus believed that implantation of CRT-D in an early stage of cardiac involvement may both treat arrhythmias and slow HF progression (Fig. 1).

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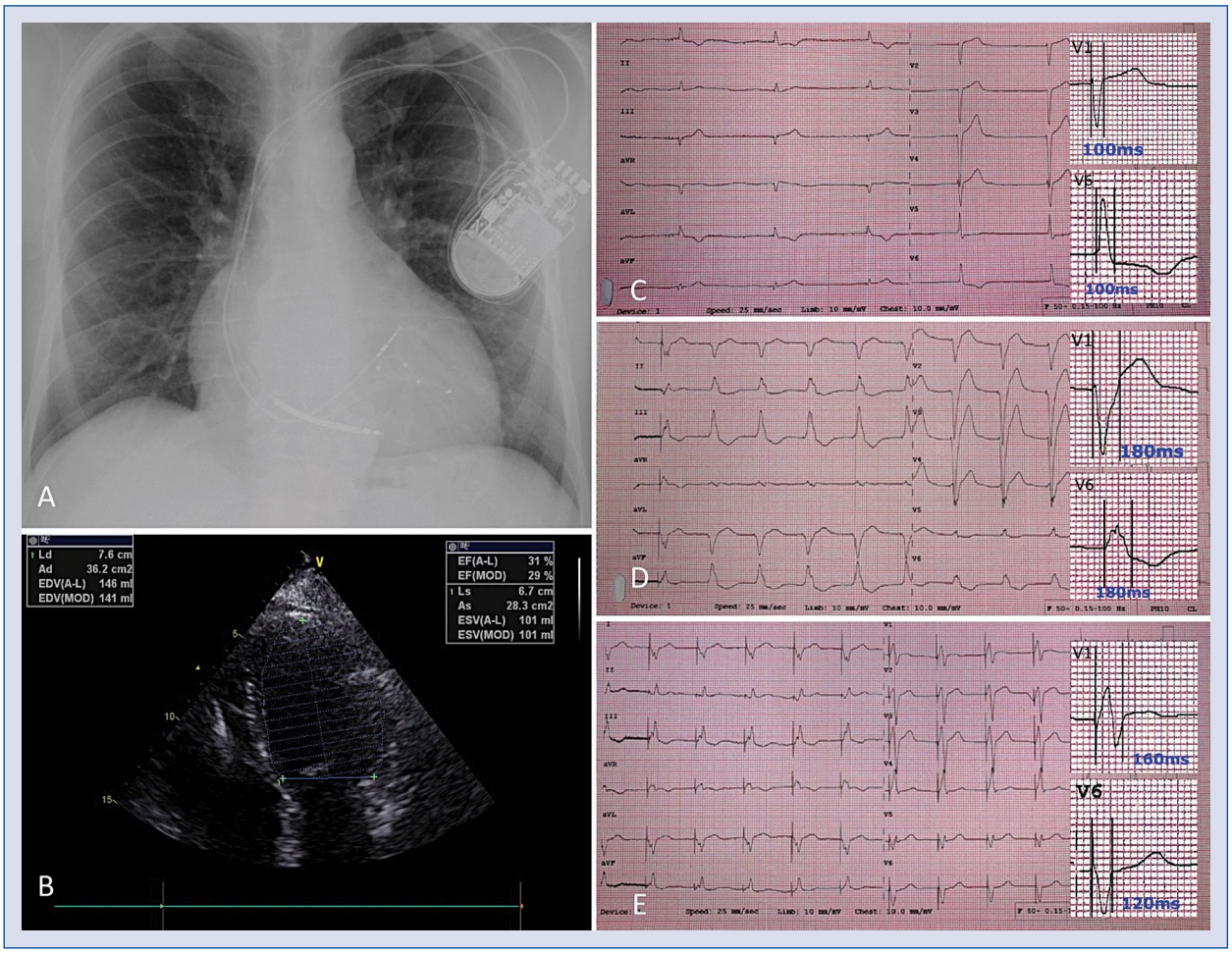

Figure 1. A. Chest X-ray after cardiac resynchronization therapy (CRT) implantation; **B.** Dilated cardiomyopathy in transthoracic echocardiography; **C.** Native rhythm electrocardiogram with atrial fibrillation and complete atrioventricular block; **D.** Electrocardiogram after single-chamber implantable cardioverter-defibrillator implantation; **E.** Electrocardiogram after up-grade to CRT-D with VVI-BiV mode stimulation.

VIA MEDICA

LETTER TO THE EDITOR

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Left atrial appendage closure using the Watchman device in patients with off-label anatomy: "No man left behind"

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The Watchman (Boston Scientific, Marlborough, MA, USA) occluder is specifically designed to be permanently implanted at or slightly distal to the left atrial appendage (LAA) ostia trapping thrombus before they exit the LAA. With accumulating proof that LAA closure using the Watchman device is effective in reducing the risk of thromboembolism in patients with atrial fibrillation, it is becoming a worldwide predominant occluder. There are five different sizes: 21, 24, 27, 30 and 33 mm, and are labeled for patients with an LAA ostial diameter between 17 and 31 mm [1]. However, LAA anatomy is highly heterogeneous, with a range of ostia diameters from 5 to 40 mm [2]. The currently available devices are far from ideal, and in some patients, the conventional practice of LAA closure with a Watchman device could not obtain optimal anatomic results, which requires no peri-device leakage of clinical significance (> 5 mm) due to a suboptimal match between the device and a complex LAA morphology [3]. Therefore, the technical challenges of percutaneous LAA occlusion relate to the morphology of LAA, including the number of lobes, and the maximum and minimum of ostia suitable for intervention. An off-label attempt is necessary to widen the indication of Watchman in a complex LAA anatomy in order to leave no man behind. Giant single-lobulated LAA, multilobed LAA and small LAA present a real challenge for conventional Watchman-based LAA closure. Herein, is summarized the latest reports regarding Watchman-based technique innovations, focusing on patients with off-label LAA anatomy.

A single-device LAA occlusion technique concerns the maximum LAA body size suitable for intervention. Therefore, in patients with the single-lobulated LAA and giant ostia > 31 mm, complete closure of the LAA could not be achieved with a single Watchman implantation. Clinically obvious residual flow > 5 mm in the LAA is associated with an increasing risk of thromboembolism which requires prolonged antithrombotic therapy thereby defeating the purpose of an LAA closure [4]. Accordingly, adequate closure of this giant LAA is essential. In the current issue of the 'Cardiology Journal' [5], a technology note was published reporting three successful attempts using a kissing--Watchman strategy by deploying two Watchman devices adjacently in a kissing-fashion to achieve complete LAA occlusion in patients with single-lobulated LAA and giant ostia (> 31 mm). Despite a more liberal oversizing technique, favorable anatomic results were achieved in all 3 patients. Image follow-up showed adequate LAA sealing (peri-device leakage < 5 mm), without device-related thrombosis or obvious device dislocation. There were no major adverse events including device embolism, pericardial tamponade, stroke/ /transient ischemic attack/systemic embolism, death or major bleeding during a 1-year clinical follow-up. This technical innovation shows that a more liberal oversizing technique contributes to greater stability rather than a hazard for device dislocation and provides a reasonable LAA closure strategy in this single-lobulated LAA with giant ostia anatomy.

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Owing to the variations of LAA anatomy, in terms of number of lobes, it is impossible to completely close LAA with a single Watchman device. The LAA uncovered lobe was deemed to be a nidus for thrombus formation, because of slow blood flow caused by a ridge-like pectinate muscle which separates the LAA into two lobes. Accordingly, adequate closure may require more than a single device in LAA morphology with two outgoing lobes. Liu et al. [6] and Jiang et al. [7], respectively, reported their initial experience on either one-stop or staged double-Watchman implantation. This anatomic structure warranted that the two devices were implanted separately rather than adjacently, reducing the possibility of direct mechanical interaction between the two devices. Sealing both the lobes was essential to effectively reducing the risk of thrombus formation. According to clinical observations and image follow-up, none of the patients had severe complications or major adverse events. Their reports provide a feasible and safe strategy avoiding incomplete LAA closure due to a single Watchman implantation in this bilobulated-LAA anatomy.

According to Food and Drug Administration labelling, it is recommended in patients with a maximal LAA ostial diameter of 17 mm in order to accommodate the smallest Watchman device (21 mm) currently available for LAA occlusion. Deploying a round occluder into a relatively small ostium may lead to excessive radial force, which could theoretically result in endocardium perforation or device embolization. Additionally, shoulder protrusion of Watchman device out of the LAA may interfere with the surrounding structure (circumflex coronary artery, mitral valve, pulmonary vein). In the issue of 'Journal of Cardiovascular Electrophysiology', Venkataraman et al. [8] reported their experience in 31 out of 32 patients with the mean maximal LAA ostial width range from 14 mm to 16 mm who successfully underwent Watchman implantation. Although the maximum compression ratio was numerically greater than manufacturer recommendations (20%) [9], no adverse events of clinical significance occurred during a 45 day follow-up. Their experience again substantiated the fact that over-compression to some extent is not a hazard for device dislocation. Additionally, moderate shoulder protrusion of the Watchman device would not interfere with the surrounding structure of LAA. This report provides first-hand evidence that Watchman implantation is safe in occluding smaller LAA with a maximal LAA ostial width < 17 mm.

There is a kaleidoscope of variations concerning LAA anatomy in terms of the diameter of ostia and plane of lobes, and no occluder fits them all. While those technical innovations can be useful, a word of caution should be issued since late mechanical interaction is unknown and the number of patients and follow-up duration are limited in all these reports. More intense imaging follow-up may be considered, when dealing with LAAs with these complex anatomic features. The authors mentioned above should be congratulated for their effort in these technical innovations, however, the safety and efficacy of these strategies remain to be verified by larger cohorts. Nevertheless, these technique innovations of LAA closure may overcome the anatomic limitation and potentially widen Watchman-based LAA occlusion indications in all candidates for percutaneous LAA closure.

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LETTER TO THE EDITOR

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Coding proposal on phenotyping heart failure with preserved ejection fraction: A practical tool for facilitating etiology-oriented therapy

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Editorial p. 6

With the publication of the PARAGON-HF (The Prospective Comparison of ARNI [angiotensin receptor–neprilysin inhibitor] with ARB [angiotensin-receptor blockers] Global Outcomes in Heart Failure with Preserved Ejection Fraction) trial during the European Society of Cardiology Congress 2019 [1], cardiologists again faced the reality that there remains no convincing evidence-proven strategy that can bring definitive benefit for heart failure (HF) with preserved ejection fraction (HFpEF). After hearing the news, many of the attendees' mood turned as blue as the sky over Paris. Certainly, we should keep moving forward, but before that, why not wait a minute and think about where the problem of HFpEF is.

To date, therapies tested in clinical trials on HFpEF have all been adopted from successful therapy concepts of heart failure with reduced ejection fraction (HFrEF). However, it seems to have been ignored that HF is a heterogeneous disease or syndrome, especially for HFpEF [2]. The heterogeneity in etiology and pathophysiology, alone or in combination, of HFpEF patients might explain why successful approaches in HFrEF patients failed however in HFpEF. One way to solve the HFpEF problem might be to go back to an etiology-oriented therapy principle and get rid of "one-size-fits-all" thinking mode. As early as 2012, it was pointed out that HFpEF patients should be phenotyped according to etiology in order to make targeted therapies in HFpEF subgroups [2]. Shah et al. [3] once introduced a clinical phenotypic classification of HFpEF, which included: (1) "garden-variety" HFpEF; (2) coronary artery disease-HFpEF; (3) right heart failure-predominant HFpEF; (4) atrial fibrillation-predominant HFpEF; (5) hypertrophic cardiomyopathy-like HFpEF; (6) valvular HFpEF; (7) high output HFpEF; and (8) rare cause of HFpEF. Although this classification is oriented by the etiology and risk factors of HFpEF, its intrinsic complexity has prevented its widespread clinical use. Hence, here I proposed a new coding method on phenotyping HFpEF, following principles of simplicity, practicality, and comprehensiveness.

The view expressed herein is that HFpEF can be classified into five subtypes (Table 1):

1. Vascular-related HFpEF. It includes HFpEF related to hypertension, coronary artery disease (CAD), and coronary microvascular dysfunction. Systemic and cardiac vascular abnormalities are both common in HFpEF, and that hypertension and CAD are considered the most prevalent cardiovascular comorbidities in HFpEF [4]. Furthermore, coronary microvascular dysfunction is also a common pathophysiological mechanism of HFpEF [4]. In these patients, hypertension or ischemia resulting from epicardial CAD or microvascular dysfunction plays a crucial role in the pathophysiology of HFpEF, so these patients might benefit from the HFrEF therapy strategy.
2. Cardiomyopathy-related HFpEF. These patients may have hypertrophic cardiomyopathy, infiltrative cardiomyopathies like cardiac amyloidosis and Fabry cardiomyopathy, etc. Diastolic dysfunction and elevation of left

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Table 1. New phenotypic coding for heart failure with preserved ejection fraction (HFpEF).

Phenotypic coding	Brief description
HFpEF-1. Vascular--related HFpEF	Hypertension, coronary artery disease, and coronary microvascular dysfunction related HFpEF.
HFpEF-2. Cardiomyopathy-related HFpEF	These patients may have hypertrophic cardiomyopathy, infiltrative cardiomyopathies like cardiac amyloidosis and Fabry cardiomyopathy which induced the HFpEF.
HFpEF-3. Right heart- and pulmonary-related HFpEF	Patients in this subtype often have pulmonary hypertension with or without right ventricular dysfunction.
HFpEF-4. Valvular- and rhythm-related HFpEF	It mainly refers to HFpEF resulting from valvular disease and atrial fibrillation.
HFpEF-5. Extracardiac disease-related HFpEF	Extracardiac diseases involve: (1) metabolic diseases, such as diabetes mellitus, obesity, or metabolic syndrome; (2) diseases that often cause high output state, such as anemia, liver disease, hyperthyroidism, and arteriovenous fistula; (3) other diseases, such as chronic kidney disease, radiotherapy for cancer, etc.

ventricular filling pressure should be the underlying pathophysiology in these patients. Specific therapies, like targeted surgery or intervention in obstructive hypertrophic cardiomyopathy, tafamidis for transthyretin amyloidosis, enzyme replacement for Fabry should be considered in these cases.

3. Right heart- and pulmonary-related HFpEF. Patients in this subtype often have pulmonary hypertension with or without right ventricular dysfunction. Actually, pulmonary hypertension and right ventricular dysfunction could result from increased left ventricular filling pressure and left atrial hypertension, resulting in HFpEF in turn [3, 4]. Combined therapy from cardiologists and pulmonary specialists might be the key option for these patients.
4. Valvular- and rhythm-related HFpEF. Valvular diseases could lead to hemodynamic disorder in left and/or right heart, influencing the filling pressure and diastolic function further. Rhythm-related HFpEF mainly refers to HFpEF in which atrial fibrillation is predominant. Patients in this category might benefit from surgical or interventional valve therapy and rhythm control therapy.
5. Extracardiac disease-related HFpEF. The extracardiac diseases involve: (1) metabolic diseases, such as diabetes mellitus, obesity, or metabolic syndrome; (2) diseases that often cause a high output state, such as anemia, liver disease, hyperthyroidism, and arteriovenous fistula; (3) other diseases, such as chronic kidney disease, radiotherapy for cancer, etc. [5]. Again, etiology-oriented therapy options are needed for these patients, for instance, sodium-dependent glucose transporters 2 (SGLT2) inhibitor, weight-reduction efforts and exercise might be effective for metabolic HFpEF.

The new phenotype proposal for HFpEF is more structured than previously suggested [3]. The phenotypic coding not only helps introduce a better understanding about the risk factors, etiology, pathophysiology and clinical course of HFpEF, but also contributes to guide targeted treatment. The PARAGON-HF study confirmed again that, until now, no single therapy could treat HFpEF once and for all. Targeted treatment for etiologies and/or comorbidities may be the best choice. Proposed herein, it is high time to test the therapy principle by randomized clinical trials in HFpEF patients with identical or major etiologies according to the present coding proposal. It should be noted that an HFpEF patient could belong to one or more subtypes, and they can be defined as HFpEF-1, HFpEF-2, or a combination of HFpEF-13, HFpEF-135 for example.

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