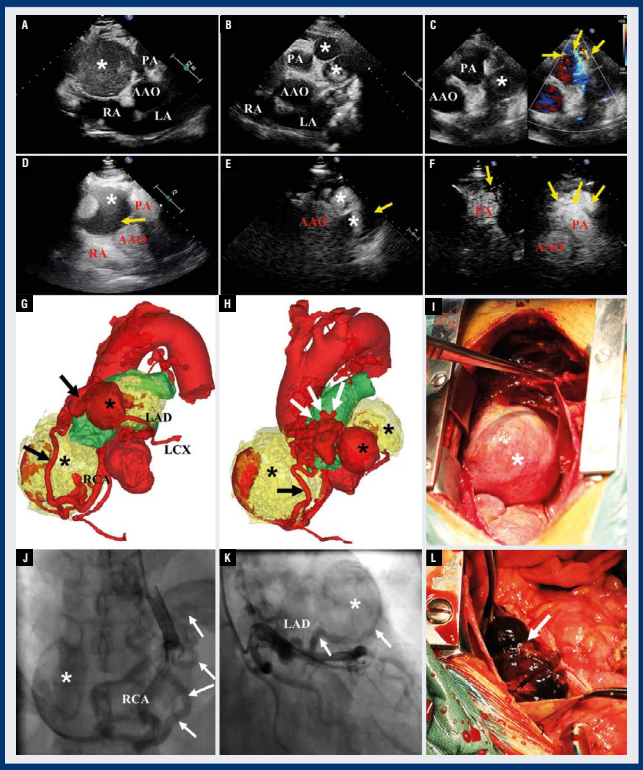
CARDIOLOGY JOURNAL

Impact Factor: 3.487

November 2022, Vol. 29, No. 6, pp. 891–1054 www.cardiologyjournal.org



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ORIGINAL ARTICLES

ISSN 1897–5593
eISSN 1898–018X

VIA MEDICA

CARDIOLOGY JOURNAL

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"Cardiology Journal", a bimonthly publication, is an official journal of the Working Groups on Cardiac Rehabilitation and Exercise Physiology, Congenital and Valvular Heart Disease, Echocardiography, Experimental Cardiology, Heart Diseases in Women, Heart Failure, Heart Rhythm, Invasive Cardiology, Noninvasive Electrocardiology and Telemedicine, Pediatric Cardiology and Resuscitation and Intensive Care of the Polish Cardiac Society.

Cardiology Journal (ISSN 1897-5593, eISSN 1898–018X) is published 6 times a year by VM Media sp. z o.o. VM Group sp.k.

Subscription rates: Paper subscription, 6 issues incl. package and postage institutional — 270 euro. The above prices are inclusive of regular postage costs. Payment should be made to: VM Media sp. z o.o. VM Group sp.k., Grupa Via Medica, Bank BGŻ Paribas SA account number: 15 1600 1303 0004 1007 1035 9021; SWIFT: PPABPLPK. Single issues, subsriptions orders and requests for sample copies should be send to e-mail: prenumerata@viamedica.pl. Electronic orders option available at: https://journals.viamedica.pl/cardiology_journal.

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21-0503.006.001

CARDIOLOGY JOURNAL

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November 2022, Vol. 29, No. 6

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EDITORIAL

Cardiology Journal
2022, Vol. 29, No. 6, 891–893
DOI: 10.5603/CJ.a2022.0107

ISSN 1897–5593
eISSN 1898–018X

Chronic total occlusions in Artsakh: The last frontier

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In September 2022 a group of international health professionals visited Stepanakert Republic Hospital for a scientific exchange and educational activity, including hands-on workshops and proctorship for complex coronary interventions. This endeavour, a mixture of symposium, advanced training and humanitarian mission, was carried out to bring hope and normality to a desperate and far from normal turmoil. Stepanakert is the capital of the autonomous republic of Artsakh, according to the historical Armenian naming, also known as Nagorno Karabakh, after its soviet denomination.

Chronic total occlusions (CTO) are often considered the last frontier in percutaneous coronary interventions (PCI), as they are technically very demanding, require dedicated training over years, consume much more time and resources than standard PCIs and entail considerable risk of potentially life-threatening complications, which urge prompt reactions of the whole interventional team. During the workshop in September 2022 a group of CTO patients, carefully selected by Drs. Vahram Gabrielyan and Vardan Lalayan, were intervened in Stepanakert under the proctorship of the international experts brought by the mission. The interventions were highly didactic: both antegrade and retrograde approaches were performed, exhibiting a whole variety of dedicated CTO techniques, like parallel wiring, anchor-balloon, dissection-re-entry, reverse controlled antegrade and retrograde subintimal tracking (CART) or tip-in, among many others (Fig. 1). The result could not have been better: 100% technical and procedural success, with 0% clinical complications. The patients' gratitude and the team's motivation peaked above any preliminary expectation after these encouraging achievements, which is, of course, highly rewarding for a proctor and ineluctably tightens very special links among all the participants in the endeavour. Teaching is a true vocation that is not always easy to fulfil, especially nowadays.

Many persons must be commended for this wonder of success, especially under the stressful conditions in which it was accomplished: most especially, the whole team at Stepanakert Hospital must be warmly congratulated by their professionalism and positive attitude. No matter how skilled or experienced a CTO operator is, the success of CTO PCI requires the commitment of the whole interventional team and supporting units. There was outstanding multilateral commitment during the interventions at the Stepanakert cathlab: professional nurses and technicians, eager to learn, notwithstanding linguistic barriers; supporting clinical cardiologists, providing all meaningful

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Received: 15.10.2022 Accepted: 12.11.2022

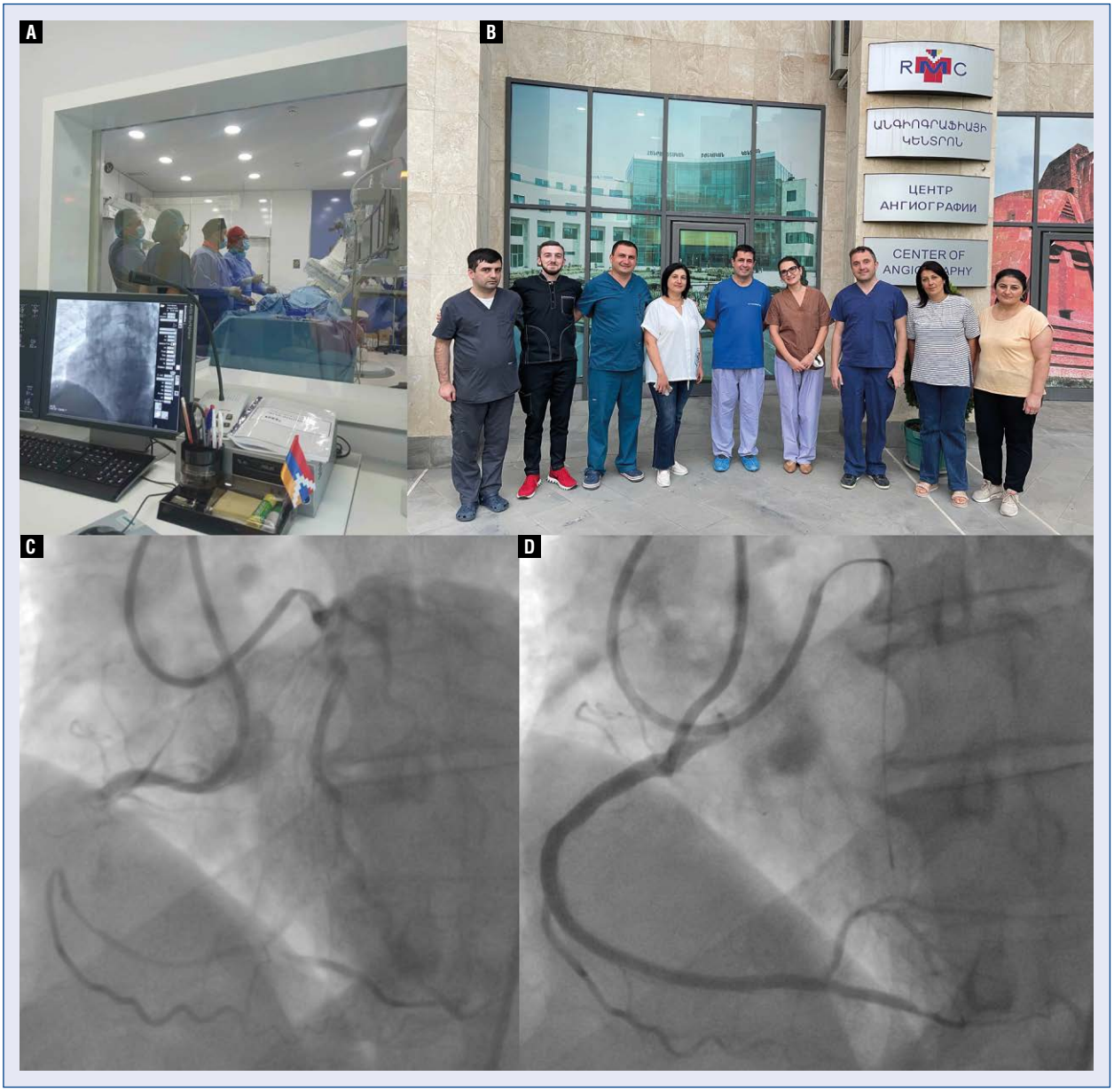

Figure 1. A. Catheterization laboratory of the Stepanakert Republic Hospital; **B.** Visiting doctors (Gutiérrez-Chico and Grigorian) with the local Interventional Cardiology Team; **C.** Example of a chronic total occlusion of the right coronary artery that was successfully treated (**D**) by means of a combined retrograde and antegrade approach in Stepanakert.

clinical and functional data and watching the procedures with genuine curiosity, while keeping the bond of trust with the patient, et cetera. Building such a professional environment is an extraordinary achievement and we are not in the position to state to whom the merit belongs, but the leadership of Drs. Lalayan and Gabrielyan for sure have something to do with it. Secondly, the board of the Hospital, especially the Director, Dr. Mher Musaelyan, for facilitating the mission in all possible means and very importantly, the Minister of Healthcare, Dr. Mikael Hayriyan and his team, who supported the participants and found room for proper institutional courtesy in the middle of such deep distress. Finally, the organizers of the International Cardiovascular Symposium in Yerevan, the scientific activity coupled with the mission, who have certainly facilitated the engagement of top international experts into this unique workshop.

Artsakh can be also considered the last frontier of our civilisation, a frontier seriously jeopardised right now, in the middle of our unconscious indif-

ference. A vast majority of Artsakh population is ethnically and culturally Armenian, even though they were ascribed to the republic of Azerbaijan during the soviet times of the USSR. After the collapse of the Soviet Union in 1992, Artsakh tried to use the existing legal mechanisms to join the newly created republic of Armenia, thus redefining a political status more conforming with the historical and *de facto* reality of the region, but Azerbaijan tried to avoid it. The result was a brutal war in which Armenians in Artsakh succeeded to obtain their independence from Azerbaijan, although with scarce international endorsement. In fact, they have been living as part of Armenia for almost 40 years. This *statu quo* was unilaterally broken by Azerbaijan in 2020 overtaking vast territories of Artsakh, which *de jure* still belonged to Azerbaijan, in a second Nagorno Karabakh war, cutting the communication with Armenia and isolating Artsakh from the rest of the world. So far everything sounds like another territorial dispute in the remnants of the old Soviet Union, but the problem in Artsakh is far more concerning. Armenians are not moved by secessionism or nationalism: they fight for their survival. Azeris are a Turkish nation and for some reason they are pervaded by an insane hate to their Armenian Christian neighbours. The few intellectuals who have raised their voice against this hatred have unfortunately not succeeded to imprint their message in the Azeri population, more prone to buy the fanatic nationalistic messages of their autocratic regime than to the self-criticism promoted by a few brave voices advocating for moderation. The Azeri soldiers share disgusting videos on social media of their inhuman atrocities and war crimes against Armenian soldiers and civilians, probably expecting the applause of their comrades or society, who seem to be fully unaware of Geneva Conventions. While the Western World prefers to ignore what is happening to Armenia, the population of Artsakh faces a bitter future, fearing another ethnic cleansing, the exsanguination in an uneven and cruel war, the slow asphyxiation in an isolated enclave sieged by unpredictable enemies, or the deportation. Sufficient material to keep the International Court of Justice in the Hague busy for quite some time, but we do not care: Azerbaijan keeps on singing in the Eurovision Song Contest, participating in all sporting competitions and we keep on buying their gas and oil, especially now, when we need it so much. Azerbaijan is affluent in resources, it has a modern and powerful Army and it is blatantly supported by Turkey, another major player in this tragedy, that has moved towards radicalisation, Islamism and nationalism in the last years. Armenia will not survive without our support, but why should we show solidarity with them? For multiple reasons. Because it is a war of civilisation vs. barbarism, of democracy vs. dictatorship, of rationalism vs. fanatism, of patriotism vs. nationalism, in summary, of the values of our free world vs. the values that enslave men. We are not so naïve as to believe in Manichean views, especially in war, where the devil always plays both sides, but a crime can never be justified by another preceding crime. We cannot simply witness the second season of the series *genocide* without reacting. We can still exert substantial diplomatic pressure to stop this carnage and force a civilised solution. If we take some distance from the immediacy of our current problems (war, energy crisis, etc.), we might admit that we have a lot to learn from the Armenian attitude in a broader perspective. In their long history, Armenians have dialogued with Russia and the USA, with Israel and Iran, with Europe and with Asia, in summary with everybody to survive. One day, hopefully soon, we will have to welcome again some countries to the international fraternity, temporarily broken by ill leaderships. We are pretty confident that Armenians will know for sure how to deal with that. Let us stand for Armenia and Artsakh, for our common roots as crane of the Christian civilisation, for a minimal sense of ethical justice in the present and for the hope in a future world, where we can live in peace with our neighbours and above all with our conscience.

Conflict of interest: None declared

VIA MEDICA

EDITORIAL

Cardiology Journal
2022, Vol. 29, No. 6, 894–896
DOI: 10.5603/CJ.2022.0108

ISSN 1897–5593
eISSN 1898–018X

The importance of experimental models in interventional cardiology. An illustration in coronary bifurcation stenting

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This editorial accompanies the article on page 899

"All models are wrong, but some are useful."

[George Box (1919-2013), "Robustness in the Strategy of Scientific Model Building", in Robustness in Statistics (1979)]

Following Vassilev et al. [1], experimental models are increasingly advocated to assess expected mechanical benefit when developing new techniques in interventional cardiology. This experimental and clinical study reports an innovative technique of percutaneous management of coronary bifurcations, proximal optimization with kissing balloon inflation (POKI): a hybrid strategy of proximal optimization technique (POT) and kissing balloon inflation (KBI). It was designed to take into account the various specificities of bifurcations and notably their fractal geometry, deriving from the law of conservation of flow, which underlies a significant difference between up- and down-stream main vessel diameter [2]. The preliminary angiographic results for POKI seemed favorable. The research strategy, moving from theoretical concept to experimental validation, exemplifies scientific method.

In coronary bifurcations, experimental models to address the clinical issue of bifurcation management were introduced in the 1990s. Ormiston et al. [3] reported the first rudimentary bench model analyzing the mechanical consequences of stent post-dilatation in a bifurcation. Subsequently, the interplay of in-vitro and in-vivo studies greatly enhanced knowledge of the anatomic specificities of bifurcations and percutaneous treatment. Bench tests clearly showed the mechanical benefit of the POT sequence [4], first proposed intuitively by Darremont and previously assessed only visually in angiography. POT enables perfect global stent apposition while limiting the metal obstruction in the side-branch ostium [4]. POT thus became the cornerstone of percutaneous bifurcation management, whether complex or not. Likewise, a numeric simulation demonstrated the mechanical benefit of rewiring toward the side branch via the most distal cell: i) balloon opening of the side-branch ostium struts while limiting metal obstruction in the carina, and ii) covering the pro-atheromatous zone lateral to the ostium [5]. In the other direc-

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Received: 10.09.2022 Accepted: 21.10.2022

tion, experimental models enriched clinical findings such as coronary imaging quantification and characterization of the fractal nature of epicardial coronary bifurcations, determining the relative diameters of the 3 vessels [2], which is fundamental to the design of coronary bifurcation bench tests.

Although experimental studies, both bench tests and numerical simulations, have clearly improved management of coronary bifurcations, implementation of models that fail to respect bifurcation physiology can mask the mechanical consequences of certain techniques. Thus, the classical KBI, which was long the sole percutaneous technique for bifurcations, never actually showed any clinical benefit in provisional stenting [6]. KBI can reduce side-branch restenosis, but at the cost of increased proximal mother-vessel restenosis [6]. This clinically adverse outcome could have been expected: proximal juxtaposition of the balloons in KBI obviously incurs a mechanical risk, with 40% overstretch [4]. The bench model initially used to validate KBI [3] by no means matched coronary physiology: it was in plexiglass, which greatly differs from the biomechanical properties of even the most pathological coronary arteries, with a Young's modulus of 3,100 10^3 kPa vs. 500 kPa for a normal artery or 1,500 kPa for a fibrous artery. Moreover, the models did not respect the fractal geometry of bifurcations, but had identical proximal and distal main vessel diameters. Thus, no observation or quantification of any deformation, malapposition or overstretch was possible. In contrast, using a model closer to actual physiology [4], although still imperfect, could have unraveled the drawbacks of KBI and its disappointing clinical results could have been partially anticipated [6]: while KBI does limit side-branch metal obstruction, balloon juxtapositioning leads both to > 30% elliptic overstretch [4], inducing restenosis [7], and to proximal stent malappositioning [4]. This negative mechanical effect was subsequently confirmed in-vivo on intracoronary imaging [8].

Bench tests and numerical models seek to mimic the anatomic and functional reality of coronary bifurcations. The quality of the design is thus essential in order to optimally approximate the real-life physiological data before attempting any clinical translation. In the case of coronary bifurcations, recommendations summarizing the basic points are needed before setting up an experimental model [9]. Respecting fractal geometry and the distributive properties of bifurcations with a model close to real arterial physiology is now indispensable. Likewise, our quantification tools have to be carefully chosen, with resolution 5 to 10 times greater than the parameter to be measured. Presently, it is OCT, with a resolution of 13 μm, which best meets this metrological requirement [10]. Coronary angiography, with an image based on projection and summation and a resolution of 180 μm, is insufficiently precise and gives ambiguous images. Exploration of the novel POKI technique in a model closer to physiological reality should be undertaken before moving on to large-scale clinical study.

What is needed, is to proceed rigorously and methodically with the requirement that any new theoretical concept should first undergo experimental validation on bench test and/or numerical simulation before being implemented on a large-scale clinical registry or in randomized controlled trials.

Conflict of interest: None declared

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EDITORIAL COMMENT

Cardiology Journal
2022, Vol. 29, No. 6, 897–898
DOI: 10.5603/CJ.2022.0109

ISSN 1897–5593
eISSN 1898–018X

Inquiries about a patient with a "snail-like" takotsubo syndrome variant

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This editorial accompanies the article on page 1051

A fascinating case report by Genc et al. [1], accompanied by a very impressive video of a patient with a "snail-like" focal takotsubo syndrome (TTS) variant underscores the contribution of videos in the appreciation of regional myocardial contraction abnormalities (RMCAs) in patients with TTS, and particularly in patients with "focal" abnormalities where such RMCAs are expected to be limited in extent. In addition, an inherent differential diagnosic problem (not encountered in the present case) is that "focal" TTS often needs to be differentiated from RMCAs related to an acute coronary syndrome, conventionally associated with a single culprit coronary artery occlusion or atherosclerotic plaque destabilization, while RMCAs in patients with non-focal TTS are more extensive occupying myocardial regions subtended by more than one coronary artery (e.g., apical, midventricular, and reverse TTS variants) comprise component RMCAs involving septal, anterior, inferior, and lateral myocardial territories, which would not be expected to be associated with a blood flow-limited occlusion or critical stenosis of a single coronary artery. I understand that the format of the paper presenting this case report was such that did not permit the authors [1] to include more details regarding this 70-year-old woman with TTS; however due to the rarity of the "focal" TTS variant, a few details provided by the authors, may be of value to the readers and investigators alike. This belief prompts me to request the authors' kind response on the following comments and inquiries: 1) The patient's lack of symptoms fits with the low troponin I and B-type natriuretic peptide, particularly the latter, value levels; 2) Was there a repeat echocardiogram done during hospitalization, and what were the findings?; 3) Was there a regional longitudinal strain (Bull's Eye Plot) carried out in the follow-up echocardiogram(s)?; 4) Was the patient on any drug therapy prior to her presentation, including hormones like estrogens or progestins [2]?; 5) Did the QTc shorten in subsequent electrocardiograms, and when, in the follow-up course?; 6) The electrocardiogram changes of ST-segment elevation in leads II, III, and aVF are incongruent with the topography of the left ventricular "focal" RMCAs (e.g., one would have expected such RMCAs to be associated with some changes in the precordial electrocardiogram leads and/or leads I and aVL [3, 4]; 7) What was the electrocardiogram evolution during hospitalization?; 8) Did the patient develop inverted T-waves, and in what electrocardiogram leads?

Conflict of interest: None declared

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Received: 13.05.2022 Accepted: 31.08.2022

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ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 6, 899–905
DOI: 10.5603/CJ.a2022.0078

ISSN 1897–5593
eISSN 1898–018X

A novel technique of proximal optimization with kissing balloon inflation in bifurcation lesions

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Abstract

Background: *Percutaneous coronary interventions (PCI) of bifurcation lesions poses a technical challenge with a high complication rate. Kissing balloon inflation (KBI) and proximal optimization technique (POT) are used to correct bifurcation carina after stenting. However, both may still lead to uncomplete strut apposition to the side branch (SB) lateral wall. Proposed herein, is a new stent-optimization technique following bifurcation stenting consisting of a combination of POT and KBI called proximal optimization with kissing balloon inflation (POKI).*

Methods: *Bench and in-vivo evaluations were performed. For the bench visualization bifurcated silicone mock vessel was used. The POKI technique was simulated using a 3.5 mm POT balloon. For the in-vivo evaluation patients with angiographic bifurcation lesions in a native coronary artery with diameter ≥ 2.5 mm and ≤ 4.5 mm, SB diameter ≥ 2.0 mm, and percentage diameter stenosis (%DS) more than 50% in the main vessel (MV) were included. Provisional stenting was the default strategy.*

Results: *In total 41 vessels were evaluated. The target vessel was left main in 9 (22.0%) patients, left anterior descending artery — in 26 (63.4%), left circumflex artery — in 4 (9.8%) and right coronary artery — in 2 (4.9%). The predominant type of bifurcation was Medina 1-1-1 (61.8%). Baseline proximal MV DS% was 60.0 ± 23.7%, distal MV DS% — 58.8 ± 28.9% and SB DS% 53.0 ± 32.0%. The application of POKI was feasible in 41 (100%) of the vessels. Post-PCI residual DS at proximal MV was 11.5 ± 15.4%, distal MV — 6.6 ± 9.3%, and SB — 22.9 ± 28.5%. Both procedural and angiographic success was 100%.*

Conclusions: *POKI is a novel stent-optimization technique for bifurcation lesions. It showed excellent feasibility and success rate both in bench and in-vivo evaluation.* (Cardiol J 2022; 29, 6: 899–905)

Key words: coronary bifurcations, stent optimization, procedural outcome

The article is accompanied by the editorial on page 894

Introduction

Coronary bifurcation lesions correspond to nearly 20–25% of all percutaneous coronary interventions (PCI) [1, 2]. Interventions in this subset of lesions pose a technical challenge with high early and late complication rates [3]. PCI of bifurcation lesions can be performed using a variety of techniques, depending on the plaque distribution across the main and daughter branches, and the bifurcation geometry [4]. The fractal geometry of coronary

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Received: 24.05.2022 Accepted: 14.06.2022 Early publication date: 16.08.2022

bifurcations defines a discrepancy in diameters between the proximal main vessel (MV) and the daughter branches — the distal MV (main branch, MB) and side branch (SB) [5]. Kissing balloon inflation (KBI) has been one of the first proposed stent-optimization techniques specific for bifurcation lesions and continues to play an essential role in bifurcation PCI by optimizing stent apposition and improving SB access. However, the application of KBI requires SB recrossing after main vessel stenting, which adds additional procedure and fluoroscopy time, as well as contrast. It also requires certain operator experience, especially in cases with SB occlusion after stenting. Additional disadvantages of KBI are the elliptical deformation of the proximal MV, which can further compromise long-term results [6]. Proximal optimization technique (POT) has been proposed as a stent-optimization technique able to adjust the tubular design of the coronary stent to the natural bifurcation anatomy [7]. It was expected that POT could correct stent apposition, respecting fractal vessel anatomy, without compromising and even improving SB patency. However, studies demonstrated that for the preservation of SB patency, without any functional vessel flow compromise, an additional SB balloon dilation is required [8]. The optimal result of POT is highly dependent on the precise balloon positioning, and inaccurate placing of the balloon may lead to uncomplete strut apposition to the SB lateral wall [9, 10]. Moreover, it is currently demonstrated that even an appropriately positioned POT balloon (according to the current criteria [4]) could cause further elliptical deformation at SB ostium thus additionally stenosing it [11]. Therefore, proposed herein is a new stent-optimization technique following bifurcation stenting consisting of a combination of POT and kissing-balloon inflation.

Methods

Proximal optimization with kissing balloon inflation (POKI) technique

After stent deployment in MV (sized according to the distal vessel diameter) the POKI technique includes the following steps: (1) Proximal optimization technique with a non-compliant (NC) balloon sized according to the proximal MV diameter; (2) SB recrossing with a wire and removal of jailed wire; (3) Kissing balloon inflation using a NC balloon in the SB, with proximal marker of the balloon into the stent borders and an NC POT balloon in the MV, with distal balloon marker positioned parallel to carina tip.

Bench visualization

For the bench visualization custom bifurcated silicone model, with proximal MB internal diameter (ID) 3.5 mm, distal MB ID 3.0 mm, SB ID 2.5 mm, and 3.0 mm. Three types of models were used according to distal branching angle — 30°, 45° and 60° models. The POKI technique has been simulated using a dedicated 3.5 mm diameter to 6 mm length non-compliant POT balloon (Brosmed, China). The balloon is specifically designed for the POT technique with shortened balloon shoulders and specific cylindrical shape. This prevents inappropriate stent deformations at the place of inflation. Following deployment, the models were visualized using fluoroscopy and fluorography (Innova, GE Healthcare).

In-vivo procedure

Stable patients with angiographic bifurcation lesions in a native coronary artery with diameter ≥ 2.5 mm and ≤ 4.5 mm and SB diameter ≥ 2.0 mm and percentage diameter stenosis (%DS) more than 50% in MV were included. PCI was performed according to the current guidelines [12]. Provisional stenting was the default PCI procedure in all patients. All lesions were stented with second-generation drug-eluting stents. Angiographic success was defined as end procedural MV %DS < 20% and SB stenosis < 50% without significant dissection and flow impairment. Procedure success included angiographic success in the absence of in-hospital major adverse cardiac events (MACE; death, stroke, and myocardial infarction). All patients received double antiplatelet therapy with acetylsalicylic acid 75–100 mg and a P2Y2 inhibitor (clopidogrel, prasugrel, or ticagrelor).

Angiographic analysis

Dedicated bifurcation quantitative coronary angiography (QCA) analysis was performed according to the recommendation of the consensus on QCA methods for bifurcation lesions using General Electric QCA software and MicroDicom QCA software [13]. True bifurcation lesions were defined as visual percent diameter stenosis (%DS) > 50% at the SB. The minimal luminal diameter (MLD), reference vessel diameter (RVD), and %DS were measured for every segment of the bifurcation (i.e., proximal, and distal MV and SB) pre-and post-intervention. Lesion length was measured from the proximal main vessel to the distal main branch (i.e., we considered beginning and ending points where hypothetically the stent will be implanted). SB lesion length was measured from the ostium to the first normal-appearing part of the vessel. All analyzes were

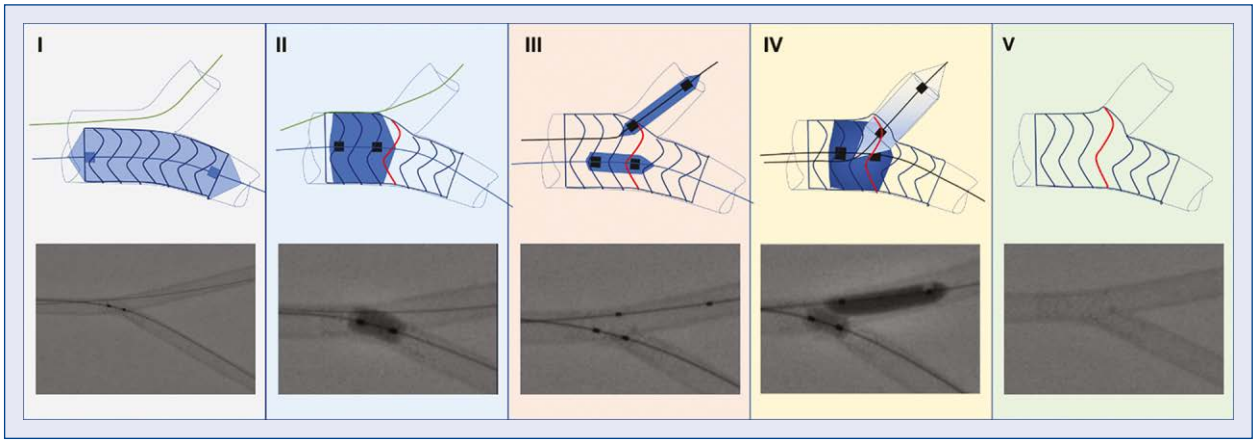

Figure 1. Schematic representation (above) and bench visualization (below) of each step of the proximal optimization with kissing balloon inflation (POKI) technique. I) The stent is implanted in main vessel (MV). Stent sizing is performed according to the distal reference diameter. II) Proximal optimization balloon is inflated in the proximal MV. The exact positioning is made by placing the distal balloon marker proximal from the carina tip. The proximal optimization technique (POT) balloon is inflated several times to ensure complete stent strut apposition in proximal region. III) The balloon positioning for POKI — in MV the distal balloon marker touches the carina tip, the side branch balloon is positioned with proximal marker exactly at the stent struts borders. The proximal SB balloon marker and MV balloon distal marker could be in parallel or MV balloon marker could be a little bit distally in the direction to the carina tip (depending on anatomy in practice). IV) During balloon inflation the stent is optimally deformed to achieve maximum apposition to the side branch ostium. V) Final result.

performed by two investigators (N.M. and P.P.) and in case of disagreement, a consensus was formed with additional analysis from the first author (D.V.).

Statistical analysis

Normality distribution of continuous variables was assessed visually with histograms and with the Shapiro–Wilk test. Continuous variables were summarized using the median and interquartile range. Categorical variables are presented as frequency counts and percentages. An independent sample T-test was performed to assess the difference between the study group and previously reported data. A p value < 0.05 was considered statistically significant. The study was investigator-initiated, funded by the local institution. The local ethics committee approved the study. All statistical calculations were performed via SPSS version 23 (SPSS, PC version, Chicago, IL, USA).

Results

Bench simulation

The POKI procedure was performed adhering to the following steps:

— **Step I: The stent is implanted in MV.** Stent sizing is performed according to the distal reference diameter.

— **Step II: POT in proximal MV.** Proximal optimization balloon is inflated in proximal MV. The exact positioning is made by placing the distal balloon marker proximal from the carina tip. The POT balloon is inflated several times to ensure complete stent strut apposition in the proximal region.

— **Step III: Balloon's positioning for POKI.** In MV the distal balloon marker is exactly at the carina tip. SB balloon is positioned with proximal marker exactly at the stent struts borders. The proximal SB balloon marker and MV balloon distal marker could be in parallel or MV balloon marker could be a little bit distally in the direction to the carina tip (depending on the specific anatomy).

— **Step IV: Simultaneous balloon inflation.** During balloon inflation the stent is optimally deformed to achieve maximum apposition to the SB. A schematic representation of the POKI procedure is illustrated in Figure 1.

In-vivo evaluation

In total 41 patients (41 vessels) were evaluated. Two case examples are illustrated in Figure 2. The mean age was 72.5 ± 8.4, and 70.6% were males. Patient clinical characteristics are shown in Table 1. The target vessel was left main in

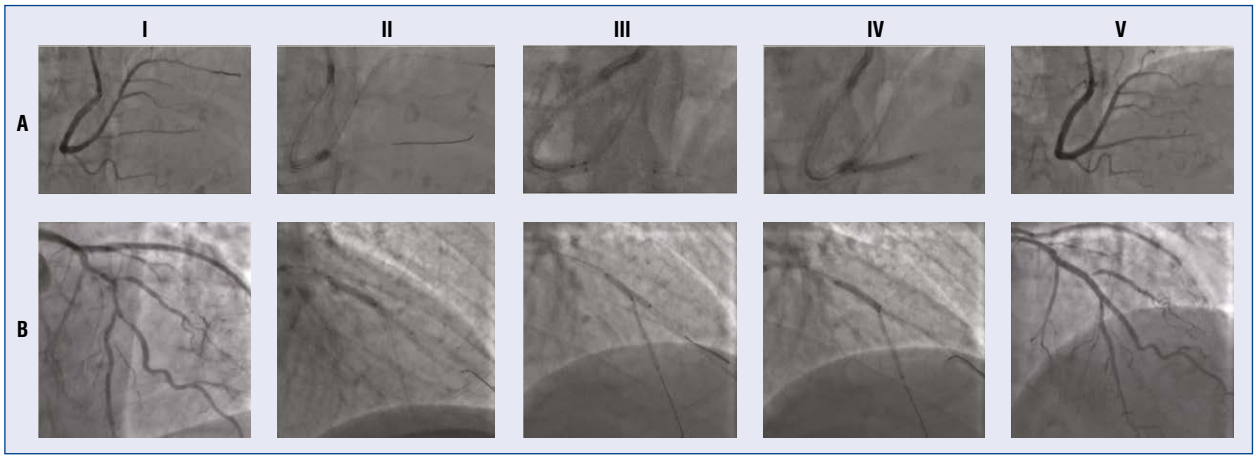

Figure 2. Clinical examples of proximal optimization with kissing balloon inflation (POKI) procedures. **A.** Percutaneous coronary intervention (PCI) of right coronary artery; **B.** PCI of left anterior descending artery. Procedural steps are the same as described in Figure 1.

Table 1. Patient demographic and clinical characteristics.

Variables	Overall (n = 41)
Age [years]	72.5 ± 8.40
Sex, male	24 (70.6%)
Body mass index [kg/m^2]	29.7 ± 5.86
Dyslipidemia	38 (92.7%)
Hypertension	41 (100.0%)
Diabetes mellitus	13 (31.7%)
Current smoker	10 (24.4%)
Previous MI	11 (26.8%)
Previous PCI in non-target vessel	22 (53.7%)
Cerebro-vascular disease	4 (9.8%)
Peripheral-artery disease	2 (4.9%)
Clinical presentation:	
Stable angina CCS II	2 (6%)
Stable angina CCS III	16 (47%)
Stable angina CCS IV	15 (44%)
Acute coronary syndrome	1 (3%)
Non-anginal symptoms	10 (50.0%)
Creatinine clearance	74.8 ± 10.1
LVEF	51.7 ± 11.0
Hospitalization days	2.62 ± 0.88

Data are shown as mean ± standard deviation or number (percentage); MI — myocardial infarction; PCI — percutaneous coronary intervention; CCS — Canadian Cardiovascular Society; LVEF — left ventricular ejection fraction

9 (22.0%) patients, left anterior descending artery — in 26 (63.4%), left circumflex artery — in 4 (9.8%) and right coronary artery — in 2 (4.9%).

Table 2. Patient's procedural characteristics.

Variables	Value
Target vessel:	41
LM	9 (22.0%)
LAD	26 (63.4%)
LCX	4 (9.8%)
RCA	2 (4.9%)
Multivessel disease	34 (82.9%)
Radial access	38 (92.7%)
SYNTAX	17.1 ± 6.66
Contrast	252.5 ± 82.6
Procedural time	91.6 ± 24.5
Scopic time	22.6 ± 11.0
Number of stents	1.5 ± 0.78
Stent length	11.25 ± 3.21
Stent diameter	6.65 ± 1.35

Data are shown as mean ± standard deviation or number (percentage); LM — left main; LAD — left anterior descending artery; LCX — left circumflex artery; RCA — right coronary artery

The predominant type of bifurcation lesion was Medina 1-1-1 (62.6%). Eight (19.5%) patients presented with chronic total occlusions of the target vessels. Patient procedural characteristics are shown in Table 2.

The mean MV lesion length was 38.6 ± 20.5 and the mean SB lesion length was 9.18 ± 2.24. Baseline proximal MV DS% was 60.0 ± 23.7%, distal MV DS% — 58.8 ± 28.9% and SB DS% 53.0 ± 32.0%. The application of the POKI technique was feasible in 41 (100%) of the vessels.

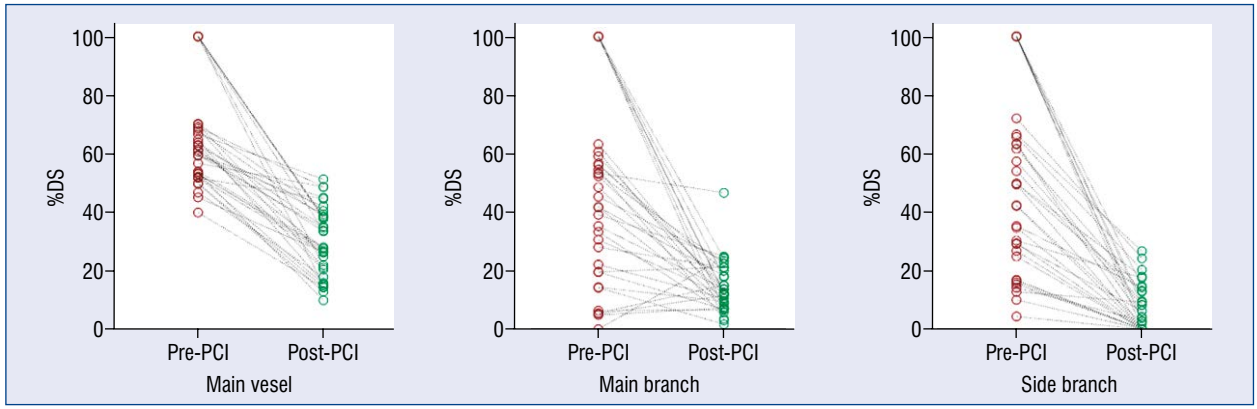

Figure 3. Changes in percentage diameter stenosis before and after percutaneous coronary intervention (PCI) in the main vessel (**A**), main branch (**B**), and side branch (**C**) of the bifurcation lesion; %DS — percentage diameter stenosis.

Table 3. Patient's procedural characteristics.

Variables	Value
MV lesion length	38.6 ± 20.5
SB lesion length	9.18 ± 2.24
MV MLD [mm]	1.31 ± 0.23
MV RVD [mm]	3.20 ± 0.46
MV DS [%]	60.0 ± 23.7
MB MLD [mm]	1.36 ± 0.45
MB RVD [mm]	2.23 ± 0.35
MB DS [%]	58.8 ± 28.9
SB MLD [mm]	1.44 ± 0.51
SB RVD [mm]	2.33 ± 0.44
SB DS [%]	53.0 ± 32.0
POKI MB balloon diameter	3.65 ± 0.5
POKI MB balloon length	10.3 ± 5.2
POKI SB balloon diameter	2.60 ± 0.42
POKI SB balloon length	18.3 ± 4.97
Maximum pressure	16 ± 1.7
Post-PCI	
MV MLD [mm]	2.20 ± 0.32
MV RVD [mm]	3.40 ± 0.40
MV DS [%]	11.5 ± 15.4
MB MLD [mm]	1.99 ± 0.35
MB RVD [mm]	2.31 ± 0.30
MB DS [%]	6.6 ± 9.3
SB MLD [mm]	2.34 ± 0.37
SB RVD [mm]	2.47 ± 0.52
SB DS [%]	22.9 ± 28.5

Data are shown as mean ± standard deviation; MV — main vessel; SB — side branch; MLD — minimal luminal diameter; RVD — reference vessel diameter; DS — diameter stenosis; MB — main branch; POKI — proximal optimization with kissing balloon inflation; PCI — percutaneous coronary intervention

Post-PCI residual DS at proximal MV was 11.5 ± ± 15.4%, distal MV — 6.6 ± 9.3%, and SB — 22.9 ± 28.5% (Fig. 3). Patient QCA characteristics are shown in Table 3. Both procedural and angiographic success were 100%.

Discussion

The main findings of the present study are the following: i) A novel stent optimization technique combining proximal optimization balloon inflation and kissing balloon technique was introduced and was found to be feasible both in bench-test and in-vivo evaluation; ii) Procedural and angiographic success after POKI in the current patient series, was excellent; iii) The immediate angiographic result after the procedure was significantly better compared with previously reported data assessing stent optimization techniques in bifurcation lesions.

Stent underexpansion and malapposition are responsible for unsatisfactory post-PCI results and are associated with target lesion failure and stent thrombosis, therefore contemporary interventional practice uses stent optimization techniques to prevent these events [14, 15]. Current expert recommendations accept POT as mandatory step in bifurcation PCI as it enhances stent apposition in the proximal MV, and reduces stent deformation [4, 16]. However, inappropriate distal positioning of the POT balloon bears the risk of distal MV overstretch and carina shift to the SB. On the other hand, incorrect proximal positioning may lead to stent malapposition and underexpansion near the carina [17]. The present analysis demonstrated that POT could be a source of additional ostial SB ste-

nosis, due to ostial stretch in elliptical fashion [11]. Concerning carina shift, KBI has shown to have an advantage over POT followed by SB balloon dilation [18]. However, KBI bears a risk of ellipsoid stent distortion of proximal MV and its overexpansion [19], which has been associated with higher rates of MV reintervention [20]. Furthermore, randomized clinical trials comparing provisional stent strategies with or without KBI failed to report any advantage on clinical outcomes for KBI [21, 22]. Finally, when comparing KBI and POT with a consequent SB dilation, randomized multicenter trial failed to show significant advantage for any of the two techniques over the other [23]. In the present view, these results could be justified by the improper choice of balloon diameters or inadequate balloon positioning which lead to insufficient correction of the stent deformation. The POT — SB dilatation — POT technique sounds logical, but in practice, as already mentioned, it did not correct SB ostial compromise. As mentioned above, POT at the level of SB ostium stretches SB perimeter in ellipse, which eliminates the positive effect of POT on carina shifting. Thus, in the end, regarding SB compromise, the final effect could be neutral.

Therefore, the current findings have important clinical implications. This novel stent optimization technique combines the benefits from POT and KBI and may provide improved post-PCI results in bifurcation lesions. POKI technique shortens the procedure time by combining POT and KBI in a one-step approach. The operator should not be concerned about further carina shifting as SB ostium is dilated simultaneously. Furthermore, the visualization of the SB balloon at the stent border provides a firm marker of the carina position and facilitates the positioning of the MV POT balloon. If during inflation the POT balloon slips proximally, it should be positioned one marker distally after deflation, without doubting excessive carina shifting.

What would be the clinical consequences and if a better angiographic result translates into better clinical result is currently under investigation by the present group.

Limitations of the study

The study has the following limitations to be considered: first, bench models fail to truly replicate the geometry and elasticity of diseased coronary vessels. Balloon inflation in diseased coronary vessels with differential distribution of fibrosis and calcification may behave differently to silicon. However, the results from this in-vivo evaluation were confirmatory of the on-bench findings. Second, the findings include a relatively low sample size of 41 vessels. Third, for the present study intravascular imaging was not performed. Lastly, presented herein are the immediate angiographic and QCA results after the index procedure. Further follow-up study with intravascular ultrasound assessment is currently performed to evaluate the long-term procedural result.

Conclusions

Proximal optimization with KBI is a novel stent-optimization technique for bifurcation lesions. It showed excellent feasibility and success--rate both in bench and in-vivo evaluation.

Funding

The study was investigator-initiated, and funded by the local institution (Medica Cor Hospital, Russe, Bulgaria).

Conflict of interest: Carlos Collet reports receiving research grants from Biosensor, Coroventis Research, Medis Medical Imaging, Pie Medical Imaging, Cathworks, Boston Scientific, Siemens, HeartFlow Inc., and Abbott Vascular; and consultancy fees from Heart Flow Inc., Opsens, Abbott Vascular, and Philips Volcano. The other authors have nothing to disclose.

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ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 6, 906–916
DOI: 10.5603/CJ.a2022.0106

ISSN 1897–5593
eISSN 1898–018X

Metal free percutaneous coronary interventions in all-comers: First experience with a novel sirolimus-coated balloon

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Abstract

Background: *Limus-eluting stents have become the mainstay for percutaneous coronary intervention (PCI). However, even with the latest generation drug-eluting stent, in-stent restenosis and very late stent thrombosis remain a concern. The Selution SLR™ drug-coated balloon (DCB) is a novel sirolimus-coated balloon that provides a controlled release of the antiproliferative drug. Herein we evaluated its performance in a real-world patient cohort with complex coronary artery lesions.*

Methods: *Patients undergoing PCI using the Selution SLR™ DCB were analyzed from the prospective SIROOP registry. We evaluated procedural success and clinical outcomes, including major adverse cardiovascular event (MACE), cardiac death, target vessel myocardial infarction and target lesion revascularization.*

Results: *From September 2020 to April 2021, we enrolled 78 patients (87 lesions) treated using a "DCB only" strategy. The mean age was 66.7 ± 10.4 years and 28 (36%) presented with an acute coronary syndrome. Almost all lesions were type B2/C 86 (99%) and 49 (63%) had moderate to severe calcifications. Procedural success was 100%. After a median follow-up of 11.2 months (interquartile range: 10.0–12.6), MACE occurred in 5 (6.8%) patients. No acute vessel closure was observed.*

Conclusions: *In complex coronary lesions, a "DCB only" strategy using the Selution SLR™ DCB is not just safe and feasible, but also seems to be associated with a low rate of MACE at 1-year follow-up. Our promising results warrant further evaluation in a dedicated comparative trial.* (Cardiol J 2022; 29, 6: 906–916)

Key words: drug-coated balloons, sirolimus, complex coronary lesions, percutaneous coronary interventions, drug-eluting stent

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Received: 24.06.2022 Accepted: 29.09.2022 Early publication date: 7.11.2022

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#Those two authors should be considered as shared last authors.

Introduction

Nowadays, drug-eluting stents (DES) represent the gold standard device used for treatment of the majority of de-novo coronary artery lesions [1]. Despite technical advancements and improved medical therapy, in-stent restenosis (ISR) and very late stent thrombosis (ST) remain a concern, even with the latest generation of DES [2, 3]. Recent reports have indicated an annual stent failure rate up to 2%, especially in complex and long lesions [4–7]. The persistence of metallic platforms, leaving the vessel "caged" after stent implantation, plays an important role in this context [4, 5].

Therefore, drug-coated balloons (DCBs) may have the potential to overcome some of the limitations associated with use of contemporary DES, by releasing an anti-restenotic drug and not leaving a permanent metallic implant behind [8]. With paclitaxel-coated balloons, good outcomes have been reported in ISR, which led to their incorporation as class IA indication in the latest European Society of Cardiology (ESC) guidelines [1, 9–12]. Moreover, several randomized trials have indicated non-inferiority of DCB compared to DES for treatment of de-novo lesions in small sized coronary vessels [13–16].

Albeit there is growing evidence highlighting the utility of DCBs in treatment of coronary artery disease (CAD), data about their performance in large vessels (> 3 mm) and especially complex coronary lesions remains scarce. The Selution SLR™ balloon (MedAlliance SA, Nyon, Switzerland) represents a novel DCB, which carries sirolimus as antiproliferative drug. Sirolimus coated balloons have not been widely studied yet, but some early small studies have suggested promising results in simple coronary lesion [17–19]. In fact, the potential of sirolimus resides, among others, in its stronger suppression of neointimal growth and wider therapeutic window [20].

The aim of the present study was to assess the safety and efficacy of an approach using the novel Selution SLR™ DCB in a real-world CAD population requiring treatment of complex coronary artery lesions, including chronic total occlusions (CTOs) and ISR lesions. Herein, we report 1-year outcome data.

Methods

The analyzed patients were those included in the prospective SIROOP Registry (Prospective Registry Study to Evaluate the Outcomes of Coronary Artery Disease Patients Treated With SIROlimus Or Paclitaxel Eluting Balloon Catheters) (ClinicalTrials.gov identifier: NCT04988685), which was designed to describe the management and outcomes of patients with acute coronary syndrome (ACS) and chronic coronary syndrome (CCS) undergoing percutaneous coronary intervention (PCI) with contemporary DCBs in native coronary and/or ISR lesions. For the current analysis, patients had been treated with the novel Selution SLR™ DCB at the Heart Center of the Luzerner Kantonsspital (Lucerne, Switzerland), which represents a tertiary cardiology facility for the central part of Switzerland.

Selution SLR™ device

The drug coating of the Selution SLR™ DCB is a formulation consisting of sirolimus as the active pharmaceutical ingredient and four excipients. The specifics of this device are summarized in the **Supplemental Figure 1**. The first excipient is a biodegradable polymer (poly-lactic-co-glycolic acid [PLGA]) that encapsulates the sirolimus into spherical homogenous micro-reservoirs (4 μm in size), which provides a controlled and sustained drug release up to 90 days. The remaining three excipients constitute a phospholipid blend, the proprietary Cell Adherent Technology (CAT™), which contains and protects the micro-reservoirs during delivery, allowing for a maximum drug transfer to the vessel wall during inflation, and with the aim to reduce wash-off of the micro-reservoirs into the bloodstream and help to adhere the drug coating to the surrounding tissues. The drug concentration is 1 μg/mm^2. Available balloon sizes range from 1.5 to 5.0 mm in diameter and 10–40 mm in length [21, 22].

Study population

Consecutive patients from the SIROOP registry, who had been treated with the Selution SLR™ DCB, were analyzed. Since this registry aims to enroll a representative — real-world — CAD population, patients with a CCS as well as ACS were included. Moreover, no angiographic exclusion criteria were applied, which allowed us not only to include the full range of coronary lesions (e.g., long, calcified, thrombotic and chronically occluded lesions), but also bifurcations and ISR lesions.

From every study participant, demographic and procedural data were collected using a dedicated database (REDCap©, Version 10.6.28, established by the Vanderbilt University, Tennessee, USA).

Prospective follow-up information was collected. Clinical follow-up information was obtained from the studied subjects by clinic visits or telephone interviews at 30 days, 6 months and 1 year after the index procedure.

PCI procedure

Device sizing and lesion preparation was performed at the discretion of the involved interventional cardiologists. Noteworthy, internal practice recommendations were established for use of DCB in CAD treatment, which emphasize vigorous lesion preparation using at least scoring/cutting and/or dedicated non-compliant (NC) balloons. This practice is in line with the 3rd DCB consensus paper [9]. To achieve optimal luminal gain, we almost routinely use the highly NC, twin-layer OPN NC® balloon (SIS Medical, Frauenfeld, Switzerland) for lesion preparation and/or post-dilatation following DCB treatment [23]. Moreover, we liberally use optical coherence tomography (OCT) with the Dragonfly® catheter (Abbott Vascular, Santa Clara, CA, USA) for lesion preparation.

Following successful lesion preparation, and in the absence of a major complication(e.g., flow limiting dissections, abrupt vessel closure, perforations), the target lesion/vessel was treated with the Selution SLR™ DCB. Conservative sizing of the DCB was advocated in order to mitigate the risk of dissecting the vessel by overstretching it with the semi-compliant balloon. Each DCB inflation was performed according to device instructions for use, meaning inflating the DCB for at least 45 s was attempted, optimally at least 90–120 s, in order to achieve optimal drug transmission to treated vessel segments. Lesions with suboptimal PCI results after DCB treatment (e.g., flow-limiting dissection, residual stenosis > 30% or a fractional flow reserve value of < 0.80) were treated with a 3rd generation DES.

Regarding the antithrombotic regimen, current antiplatelet guidelines were followed [1, 9, 24]. Patients were pretreated with acetylsalicylic acid (ASA) prior to PCI, if tolerated. At the discretion of the treating physician, the patients were loaded with either clopidogrel, ticagrelor or prasugrel during or after PCI. PCI was performed using heparin (70–100 U/kg body weight, target activated clotting time > 230–250 s during PCI). In patients presenting with CCS, a dual antiplatelet therapy (DAPT) regimen consisting of ASA and clopidogrel was generally prescribed. In complex procedures, including for instance thrombotic or long lesions, the DAPT regimen may have involved ASA and ticagrelor. The duration of the DAPT varied between 1 and 3 months, according to Third Report of the International DCB Consensus Group and patient bleeding and thrombotic risk [9]. In ACS, a DAPT regimen including ASA and ticagrelor or prasugrel for a duration of 12 months [24] was generally aimed for.

In patients, which required oral anticoagulation, the administration of direct oral anticoagulant in combination with ASA maximally for 1 week and clopidogrel for 1 to 12 months was recommended, depending upon the presentation and lesion complexity (CCS vs. ACS) [1].

Angiographic analyzes

All angiograms were analyzed by an independent core laboratory (MedStar Cardiovascular Research Network [MCRN], Washington DC, USA). The lesions were classified according to the American College of Cardiology/American Heart Association (ACC/AHA) lesion classification [25]. Bifurcation lesions were categorized according Medina classification [26]. The reader then scored the calcium based on the three-tier classification system: Minimal or no calcification; calcium covering ≤ 50% of the circumference of the vessel is classified as "Moderate calcification"; calcium covering 50–100% of the circumference of the vessel is classified as "Severe calcification". Dissections were classified according to the National Heart, Lung and Blood Institute (NHLBI) classification system for intimal tears, consisting of type A through type F [27].

Quantitative angiographic analysis (QCA) was performed before and after DCB inflation using CASS Workstation, Version 8.1 (Pie Medical, Maastricht, The Netherlands). Measurements were taken on cine-angiograms recorded after intracoronary nitroglycerine administration. Baseline measurements were taken in the single worst view projection, without foreshortening, nor overlapping and brisk contrast filling. The contrast-filled non-tapered catheter tip was used for calibration or autocalibration in case the former was not successful. The analyst marked the target segment manually and the software automatically outlined the contours of the lumen. As a result, the calculation of the lumen diameters (mean, minimum and maximum) was provided in addition to the interpolated reference vessel diameter and percent diameter stenosis in the treated segment and 5-mm proximal and distal to this.

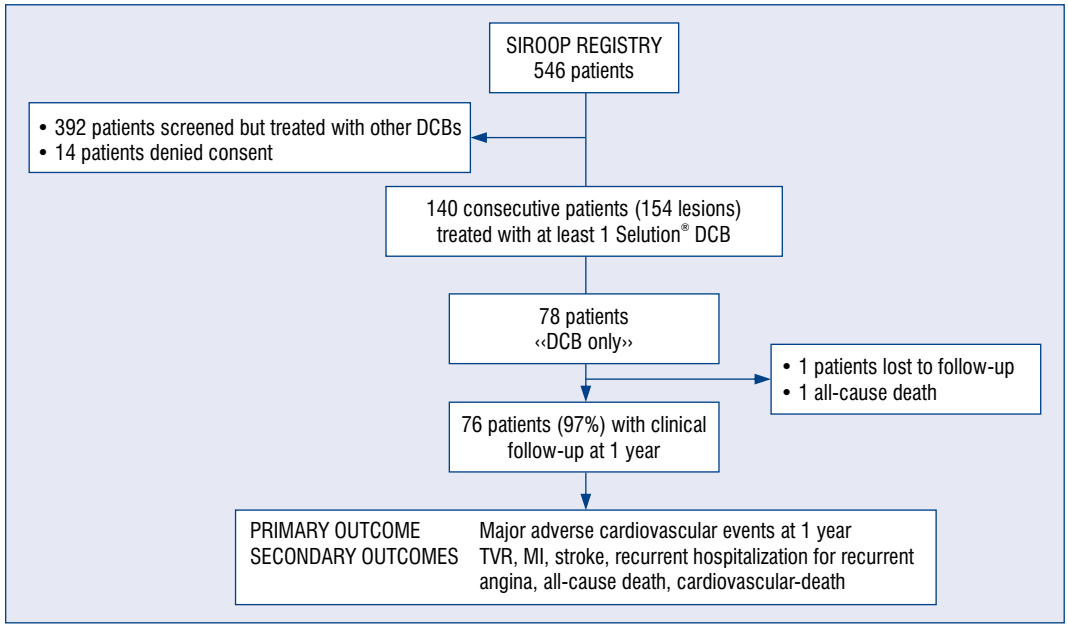

Figure 1. Study flow chart; DCB — drug coated balloon; MI — myocardial infarction; TVR — target vessel revascularization.

Study endpoints

The primary outcome was major adverse cardiovascular event (MACE) defined as composite of cardiac death, target vessel myocardial infarction (TV-MI) and target lesion revascularization (TLR). The secondary endpoints included target vessel revascularization (TVR) and all-cause death according to the criteria of the Academic Research Consortium [28]. Heart failure was defined as an ejection fraction < 40%. Procedural success was defined as < 30% stenosis remaining after PCI with a Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 at the end of the procedure

Statistical method

Categorical variables are displayed as frequencies and percentages, and continuous variables are presented as means (± standard deviations) or medians (interquartile ranges [IQR]), as appropriate. P-values were calculated using paired t-tests and Wilcoxon rank-sum test, where applicable. A two-tailed p-value < 0.05 was considered statistically significant. The analyzes were conducted using STATA version 16 (College Station, Texas, USA).

Results

Between September 2020 and April 2021, a total of 204 patients were treated with the Selution SLR™ DCB at the Luzerner Kantonsspital. Of these, 78 patients were treated with a "DCB only" strategy, see study flow chart (Fig. 1). Most patients were males, just over a third of patients presented with ACS and around 1/3 of patients had diabetes. The mean prescribed duration of DAPT was 8.6 ± 4.2 months. Further details about baseline characteristics can be found in Table 1.

A total of 87 lesions were successfully treated using a "DCB-only" strategy. The majority of lesions were located in the left anterior descending artery (57%). About half of the lesions had moderate to severe calcifications, 6.9% were ISR and 13% were CTO lesions. In bifurcation lesions, we only treated the main branch using a DCB.

Mean lesion length was 16.7 ± 13.7 mm and minimal lumen diameter was 0.82 ± 0.43 mm. The cumulative curve for minimal lumen diameter pre- and post-PCI is depicted in Figure 2. Lesion preparation was predominately carried out using the OPN NC® balloon (83%) at a mean inflation pressure of 25 ± 8 atm. A total of 35 (45%) lesions were pretreated using a cutting balloon (Wolverine®, Boston Scientific, Minneapolis) in combination with OPN NC®. Mean DCB diameter was 2.7 ± ± 0.7 mm, whereas mean inflation pressure was 8 ± 3 atm. Intravascular imaging with OCT was used in 24% of the cases. At index procedure, there were 4 (6.1%) dissections, 2 type A, 1 type C and 1 type D dissection Notably, all dissections were observed after lesion preparation. Further angiographic and procedural characteristics as well as QCA analysis are reported in Tables 2 and 3, respectively.

Table 1. Baseline characteristics of the study population.

Baseline characteristics	Number of patients (n = 78)
Age [years]	66.7 ± 10.4
Males	68 (89%)
Median follow-up time [months]	11.2 [10;12.6]
Presentation:	
Chronic coronary syndrome	50 (64%)
Acute coronary syndrome:	28 (36%)
NSTEMI	27 (96%)
STEMI	1 (4%)
Cardiovascular risk factors:	
Arterial hypertension	56 (72%)
Diabetes mellitus	18 (23%)
Dyslipidemia	57 (73%)
Current smoking	18 (23%)
Previous MI	30 (38%)
Previous CABG	4 (5%)
Heart failure (EF < 40%)	11 (14%)
Antithrombotics:	
ASA	76 (97%)
Clopidogrel	32 (41%)
Ticagrelor	20 (26%)
Prasugrel	21 (27%)
Oral anticoagulant	11 (14%)

Data are mean (standard deviation), median (interquartile range) or number (percentage), as appropriate; ASA — acetylsalicylic acid; CABG — coronary artery bypass grafting; EF — ejection fraction; MI — myocardial infarction; NSTEMI — non-ST segment elevation myocardial infarction; STEMI — ST-segment elevation myocardial infarction

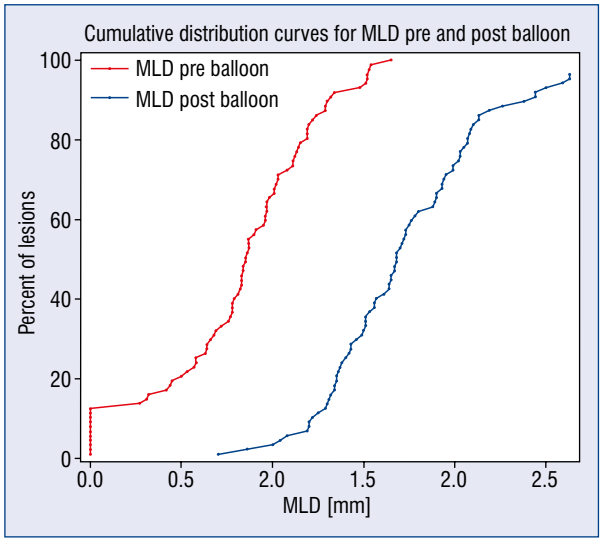

Figure 2. Graph depicting minimal lumen diameter (MLD) pre- (red line) and post-percutaneous coronary intervention (blue line).

Table 2. Lesion characteristics of the study population.

Lesion and periprocedural characteristics	Number of patients/ /lesions (n = 78/n = 87)
Access:	
Radial	70 (90%)
Femoral	8 (10%)
Vessel treated:	
Left anterior descending artery	44 (57%)
Left circumflex artery	23 (29%)
Right coronary artery	20 (26%)
Mean Syntax score	17.1 ± 11.9
Lesion classification ACC/AHA:	
Type B1	1 (1.3%)
Type B2	48 (55%)
Type C	38 (44%)
Aorto-ostial lesion	4 (5.1%)
Bifurcation:	69 (79%)
Medina (1,1,1)	31 (36%)
Medina (1,1,0)	15 (17%)
Medina (0,1,1)	10 (11%)
In-stent restenosis	6 (7.7%)
Chronic total occlusion	11 (14%)
Moderate to severe calcification	49 (63%)
Type of pre-dilatation balloon:	
SC-balloon	9 (12%)
NC-balloon	48 (62%)
Super NC-balloon	65 (83%)
Cutting balloon	35 (45%)
IVL	2 (2.3%)
Rotablation	1 (1.1%)
Lesion preparation:	
Mean diameter of larger pre-dilatation balloon [mm]	2.87 ± 0.6
Mean maximal pre-dilatation pressure [atm]	25 ± 8
Mean DCB diameter [mm]	2.66 ± 0.7
Mean DCB inflation pressure [atm]	8 ± 3
Use of intravascular imaging:	
OCT	19 (24%)
IVUS	1 (1.3%)
Dissections post-DCB:	
Type A	2 (2.3%)
Type B	0 (0%)
Type C	1 (1.1%)
Type D	1 (1.1%)

Data are mean ± standard deviation or number (percentage), as appropriate; ACC/AHA — American College of Cardiology/American Heart Association; DCB — drug coated balloon; DES — drug eluting stents; IVUS — intravascular ultrasound; IVL — intravascular lithotripsy; NC — non-compliant; OCT — optical coherence tomography; SC — semi-compliant balloon

Table 3. Quantitative coronary analysis (QCA).

QCA	Pre-PCI	Post-PCI	P*
Lesion length [mm]	16.7 ± 13.7	–	
Minimal lumen diameter [mm]	0.82 ± 0.43	1.7 ± 0.40	< 0.01
Diameter stenosis [%]	62.7 ± 17.9	16.6 ± 9.8	< 0.01
Reference vessel diameter [mm]	2.10 ± 0.71	2.04 ± 0.42	0.6

Data are mean ± standard deviation or number (percentage), as appropriate; *P values were based on student t-tests or the Mann-Whitney U-tests, as appropriate; PCI — percutaneous coronary intervention

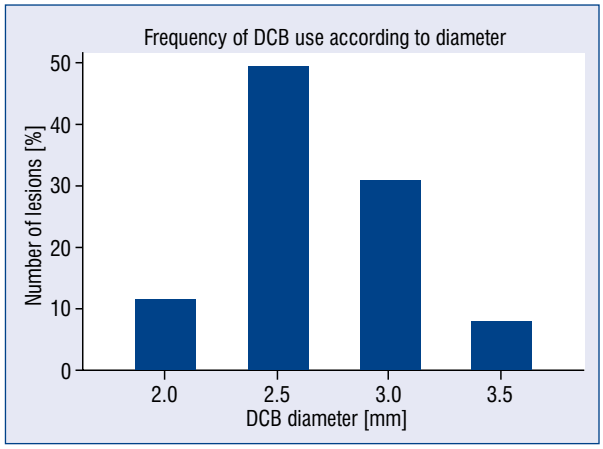

Figure 3. Diagram depicting the frequency of each drug coated balloon (DCB) used according to its diameter.

Furthermore, the percentage of DCB used according to their diameter is depicted in Figure 3. Figure 4 illustrate three representative cases, which were successfully treated using the Selution SLR™ DCB.

After a median follow-up time of 11.2 (IQR 10.0;12.6) months, the primary endpoint MACE occurred in 5 (6.8%) patients, which were all TLR. The leading mechanism of TLR was restenosis most likely attributable to recoil (3 cases, 3.9%), followed by intimal hyperplasia (2 cases, 2.8%). The narratives of the 5 patients presenting with MACE can be found in Table 4. One death secondary to pneumonia was also observed. The details about clinical outcomes are summarized in Table 5.

Discussion

According to available literature, this is the first study investigating outcomes of a real-world CAD population treated with a "DCB only" strategy in complex coronary lesions using the novel Selution SLR™ balloon. In fact, the use of DCBs for treatment of native and moreover complex coronary lesions (including calcified, CTO and ISR lesions) is not widely adopted yet. The present data not only indicates safety of a strategy using sirolimus-coated balloons for CAD treatment, but also highlights a low 1-year MACE rate (< 7%), which is lower than previously reported [6, 29, 30].

A standard PCI includes the implantation of at least one metallic stent. However, even the latest generation DES have a permanent risk of target lesion failure due restenosis or stent thrombosis ranging between 0.8% and 1% per year in simple lesions, and much higher in complex lesions, reaching up to 15% 3 years after stent implantation [6]. Several factors related to adverse long-term outcomes after stent implantation, particulary ISR and ST, have been attributed to the presence of a metallic stent, whose scaffolding properties are often only needed for a short period of time [31]. The implantation of bioresorbable scaffolds, particularly the Absorb™, was supposed to eliminate many of the limitations associated with DES, but unfortunately, those expectations have not been met. Albeit the early results were rather promising, the Absorb™ has been withdrawn from the market, since it showed to be inferior to contemporary DES for treatment of CAD [32–34]. In this context, DCBs represent an attractive alternative for a "leaving nothing behind" strategy.

It is common sense that adequate lesion preparation is key when using DCB in CAD. Especially in complex lesions, it is often challenging to achieve sufficient acute luminal gain without creating flow-limiting dissections, requiring the implantation of a stent. In order to achieve optimal luminal gain, we generally aim for adequate lesion preparation, if necessary, even combining cutting balloons (Wolverine®) and super non-compliant OPN NC® balloons. This approach led to only few flow-limiting dissections and moreover to excellent acute luminal gain, as highlighted in Table 2.

The Selution SLR™ DCB utilizes micro-reservoirs, which encapsulate the sirolimus drug.

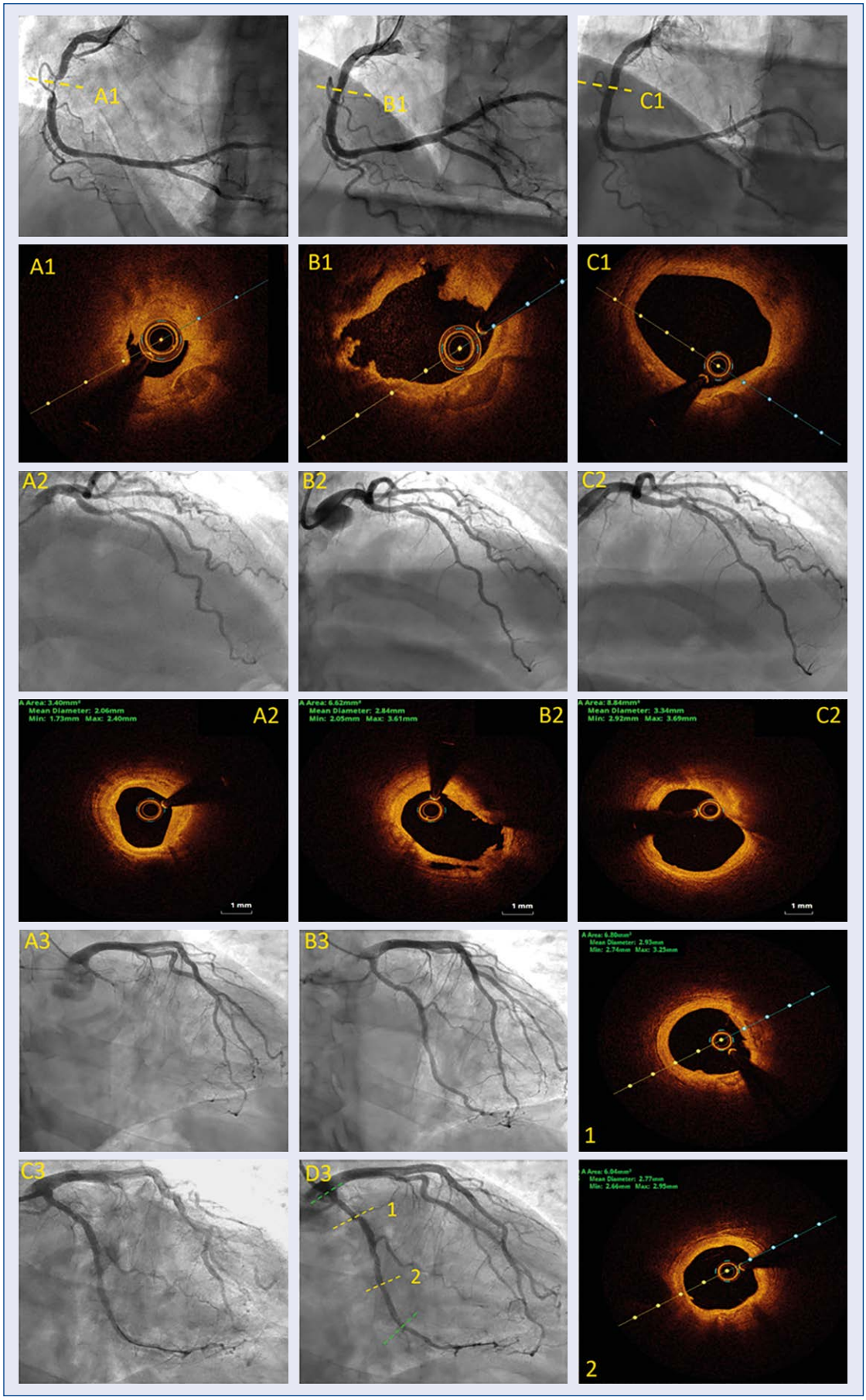
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Figure 4. Three representative cases of patients undergoing drug coated balloon-percutaneous coronary intervention (DCB-PCI) in different clinical settings, depicting angiographic and optical coherence tomography (OCT) findings at index procedure and follow-up undergoing; **A1–C1.** Patient with non-ST segment elevation myocardial infarction undergoing PCI of a subtotal stenosis of the mid right coronary artery (99% stenosis, arrow): **A1.** Initial angiogram and OCT of the culprit segment showing a heavy calcified and thrombus rich lesion; **B1.** Final angiogram and OCT after PCI with 4.0 OPN® NC (24 atm) and 1 × 4.0 × 30 mm Selution™-DCB (120 s, 10 atm) showing good acute luminal gain and no-flow limiting dissection; **C1.** Angiogram and OCT after 2 months follow-up showing both angiographic and OCT acute luminal gain and positive vessel remodeling; **A2–C2.** Patient with chronic coronary syndrome undergoing DCB-PCI of a bifurcation lesion of the proximal left anterior descending artery (LAD); **A2.** Angiogram at index procedure showing a bifurcation lesion Medina (1,0,0) of the proximal LAD. In the corresponding OCT, a mixed lipid/fibrous plaque is identified; **B2.** Angiogram and OCT findings after treatment of the main branch only, using 3.25 × 10 mm Wolverine® (20 atm), 3.5 × 15 mm (26 atm) OPN® NC and finally 1 × 3.0 × 20 mm Selution™-DCB (120 s, 6 atm) depicting an acute luminal gain with minimal luminal area (MLA) 6 mm^2 and a non-flow limiting dissection; **C2.** Angiogram and OCT at 3 months follow-up showing complete vessel healing with further luminal gain (MLA 8.8 mm^2); **A3–D3.** Patient with a chronic total occlusion (CTO) of the left circumflex artery (LCX) treated with DCB-PCI; **A3.** Angiogram showing a CTO of the LCX before PCI; **B3.** Angiogram after DCB-PCI depicting successful antegrade recanalization of the artery and treatment with 2.0 × 10 mm Wolverine® (18 atm), 2.5 × 10 mm OPN® NC (18 atm) and 1 × 2.5 × 40 mm Selution™-DCB (120 s, 6 atm) and 1 × 3.0 × 30 mm (120 s, 6 atm); **C3.** Angiogram at 6-month follow-up showing nice results with good luminal gain; **D3.** Angiogram and corresponding OCT runs (**1, 2**) at 18-month follow-up depicting persistent late luminal gain (**1, 2**).

Those micro-reservoirs are supposed to provide a sustained drug release up to 90-days [22]. Thus, the "cuts" and "cracks" created in the intima and media layers by the combined use of cutting and NC balloon represents an excellent entry port for penetration of the antiproliferative agent sirolimus.

The BASKET-SMALL II was a large trial indicating the non-inferiority of DCBs compared to DES up to 3-years follow-up [16, 35]. However, this trial was very selective and only included small vessels (< 3 mm) and rather simple coronary lesions. In contrast, the present cohort comprised a large portion of highly calcified lesions (63%), bifurcations (79%) and even CTOs (14%). Despite its complexity, this cohort showed similar MACE rate at 1-year as the pivotal BASKET-SMALL II Trial (6.8% vs. 7.5%, respectively) [16]. Likewise, the PICCOLETTO-II trial, which included mostly simple lesions and vessels with even smaller diameters than the BASKET--SMALL II trial (diameters ranged between 2.0 and 2.75 mm), reported a MACE rate of 5.6% at 1 year, which was slightly lower than observed in the present study cohort [15].

Considering the target lesion failures in the current cohort, 5 (6.8%) patients had a MACE after a median time of 187 (IQR: 140; 198) days and presented mainly with stable angina. Restenosis most likely attributable to recoil was present in 3 (3.9%) patients and intimal hyperplasia was responsible for the other 2 (2.8%) cases. While the final angiographic result at the end of the index procedure was very good in patients with intimal hyperplasia, lesion recoil was already obvious at the end of the procedure and further aggravated in the following months (**Suppl. Fig. 2**). Nonetheless, one needs to take into account that none of the studied patients required urgent revascularization. This is reassuring and indicates that in the absence of a freshly implanted DES, the treated coronary lesions may be more "forgiving" and the risk for acute vessel closure may be negligible, as long as there is good flow after DCB treatment. Although angiographic follow-up was obtained in only in a small sub-set of patients, those cases demonstrated early luminal gain and comparative OCT-imaging (at index and follow-up) showed good vascular healing, as described in a recent case report [36].

The application of DCBs in such complex lesions is relatively new and many more lessons about adequate optimal lesion preparation, plaque morphology, choice of DCB and combination with DES, remain to be learned. Furthermore, it is of paramount importance that patient safety is not compromised when applying new therapeutic approaches. This study demonstrates that the Selution® DCB is safe and effective when applied in a complex lesions with dedicated lesion preparation.

Limitations of the study

There are several limitations which apply to the present study. First, this is an observational single-center study, which may limit its generalizability and does not allow drawing firm inferences. Second, a relatively small cohort of patients was

Table 4. Narratives of the patients with a major adverse cardiovascular events (MACE).

MACE number	Time to MACE [days]	MACE presentation	Presumed cause of MACE	Indication for index PCI	Targeted vessels	Type of lesion	Target vessel	DCB diameter [mm]	DCB length [mm]	P2Y12 inhibitor
1	122	UA	Restenosis*	UA	1	No BL	Mid LAD	3.5	20	Prasugrel
2	159	Stable CAD	Restenosis*	Stable CAD	1	No BL	Mid LAD	2.5	30	Clopidogrel
3	187	Control angiography	Intimal hyperplasia	Stable CAD	1	BL (1,1,1)	Proximal LCX	2.5	30	Prasugrel
4	191	Stable CAD	Restenosis*	Stable CAD	1	BL (1,0,0)	Proximal LAD	2.5	30	Clopidogrel
5	205	Control angiography	Intimal hyperplasia	Stable CAD	1	BL (1,0,0)	Ostial LAD	3.5	20	Clopidogrel

*Most likely attributable to recoil BL — bifurcation lesion; CAD — coronary artery disease; CV-death — cardiovascular death; DCB — drug-coated balloon; NSTEMI — non-ST-segment elevation myocardial infarction; LAD — left anterior descending coronary artery; LCX — left circumflex coronary artery; PCI — percutaneous coronary intervention; RCA — right coronary artery; UA — unstable angina

Table 5. Clinical outcomes.

Clinical outcomes	6 months	1 year
Patients at follow-up	78 (100%)	76 (97%)
Primary endpoint:		
MACE	3 (3.8%)	5 (6.8%)
TLR	3 (3.8%)	5 (6.8%)
TV-MI	0 (0%)	0 (0%)
Cardiac death	0 (0%)	0 (0%)
Secondary endpoints:		
TVR	0 (0%)	1 (1.4%)
All-cause death	0 (0%)	1 (1.4%)
CABG	0 (0%)	0 (0%)
Re-hospitalisation for HF	2 (2.6%)	3 (4.0%)

Data are presented as number (percentage) and represent cumulative event rate; CABG — coronary artery bypass grafting; MACE — major adverse cardiac events; HF — heart failure < 40%; TLR — target lesion revascularization; TV-MI — target vessel myocardial infarction; TVR — target vessel revascularization

included. Third, angiographic follow-up was not routinely performed. In hindsight, this might have been helpful for better understanding vascular healing characteristics after DCB-PCI. Finally, there was no control group.

Conclusions

The present study provides important insights into the safety and feasibility of an approach using the novel sirolimus-coated Selution SLR™ balloon only for treatment of complex coronary lesions. By studying a real-world CAD cohort treated with this DCB, not only a very high rate of procedural success is highlighted (e.g., no acute vessel closure), but moreover a low rate of MACE at 1 year follow-up (< 7%). This promising signal warrants further investigation in a dedicated randomized trial comparing the Selution SLR™ balloon with contemporary DES.

Conflict of interest: Adrian Attinger-Toller has received consulting and speaker fees from SIS Medical. Richard Kobza received institutional grants from, Abbott, Biosense-Webster, Biotronik, Bostin-Scientific, Medtronic and SIS Medical and serves as a consultant for Biosense-Webster, Biotronik and Medtronic. Hector M. Garcia-Garcia received institutional grant support from Biotronik, Boston Scientific, Medtronic, Abbott, Neovasc, Shockwave, Philips, and CorFlow. Matthias Bossard has received consulting and speaker fees from Abbott Vascular, Abiomed, Amgen, Astra-

Zeneca, Bayer, Daichii, Mundipharma and SIS Medical. Florim Cuculi has received consulting and speaker fees from Abbott Vascular, Abiomed and SIS Medical. All other authors report no conflicts of interest.

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VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 6, 917–926
DOI: 10.5603/CJ.a2020.0180

ISSN 1897–5593
eISSN 1898–018X

Posterior wall substrate modification using optimized and contiguous lesions in patients with atrial fibrillation

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Abstract

Background: *Radiofrequency (RF) linear ablation at the left atrial (LA) roof and bottom to isolate the LA posterior wall using contiguous and optimized RF lesions was evaluated. Achieving isolation of the LA posterior wall is challenging as two continuous linear lesion sets are necessary.*

Methods: *Forty consecutive patients with symptomatic atrial fibrillation (AF) and arrhythmia substrates affecting the LA posterior wall underwent posterior wall isolation by linear lesions across the roof and bottom. The cohort was divided into two groups: group 1 (20 patients) linear ablation guided by contact force (CF) only; group 2 (20 patients) guided by ablation index (AI) and interlesion distance.*

Results: *Bidirectional block across the LA roof and bottom was achieved in 40/40 patients. Additional endocardial RF applications in 5 patients from group 1 vs. 3 patients from group 2 resulted in posterior wall isolation in all patients. Procedure duration was almost equal in both groups. CF and AI were significantly higher in group 2 for the roof line, whereas no statistical difference was found for the bottom line. AI-guided LA posterior wall isolation led to a significantly lower maximum temperature increase. The mean AI value as well as the mean value for catheter-to-tissue CF for the roof line were significantly higher when AI-guided ablation was performed. Standard deviation in group 2 showed a remarkably lower dispersion.*

Conclusions: *Ablation index guided posterior wall isolation for substrate modification is safe and effective. AI guided application of the posterior box lesion allows improved lesion formation.* (Cardiol J 2022; 20, 6: 917–926)

Key words: atrial fibrillation, catheter ablation, posterior wall isolation, ablation index, contact force

Introduction

Catheter ablation for persistent atrial fibrillation (PERS) is challenging and is associated with only a moderate outcome [1–4]. The mechanisms initiating and perpetuating atrial fibrillation (AF) are still not completely understood and therefore, ablation strategies are heterogeneous [1, 2, 5]. Several observations have led to individual mechanistic insights in AF management and arrhythmia associated cardiac remodeling which emphasizes

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Received: 8.07.2020 Accepted: 13.10.2020 Early publication date: 16.12.2020

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the need for personalized paths in AF management. The posterior left atrial (LA) wall has a common embryological origin with the pulmonary veins (PVs) and therefore a comparable arrhythmogenic potential, especially when there is evidence of myocardial fibrosis [3, 6, 7]. A beneficial effect of the LA posterior wall isolation (PWI) has been demonstrated among patients who underwent surgical AF therapy [8], whereas conflicting outcome data exist regarding the value of LA PWI adjunctive to or beyond PV isolation (PVI) performing endocardial ablation [9–12]. However, there is sparse data reporting the feasibility, safety and efficacy of LA PWI as performing linear ablation in the LA remains challenging. Bidirectional block across LA lines should be the ablation endpoint [13], but this is only achieved in a limited number of patients [14] and incomplete electrical block can contribute to the development of an iatrogenic arrhythmia substrate [15]. One of the most relevant drawbacks in performing posterior wall substrate modification is the risk of collateral damage to the esophagus [16]. Consequently, the theoretical advantages of PWI have to be balanced against the undisputed risk of major complications or incomplete electrical block across the applied lines resulting in proarrhythmic effects and arrhythmia recurrence [6]. Recently, new studies have reported an ablation approach in performing anatomical point-by-point radiofrequency (RF) ablation based on an indirect evaluation of lesion depth and delivery of contiguous RF lesions [17, 18]. Focusing on PVI, it has been shown that acute and late PV reconnection resulted from an insufficient ablation index (AI) and/or from interlesion distance being too far [17]. This has also been reported from catheter ablation procedures performing linear lesion sets across the LA roof, anterior wall and mitral isthmus [19, 20]. However, these criteria on minimal AI and maximal interlesion distance have not yet been evaluated and not been validated for substrate modification at the LA posterior wall. Thus, the aim of this study was to evaluate feasibility and efficacy of AI-guided isolation of the posterior wall in patients suffering from PERS.

Methods

A total of 40 consecutive patients with drug-refractory PERS and a relevant amount of bipolar low-voltage affecting the LA posterior wall were included in this prospective observational analysis. AF was defined as persistent if episodes lasted > 7 days or required electrical or pharmacological cardioversion after ≥ 48 h from onset [13]. The mean AF duration before the procedure was assessed by comprehensive review of the patients' records including 12-lead-electrocardiograms and doctors' letters. In this study AI was assessed and evaluated exclusively for PWI by means of linear lesion sets across the LA roof and bottom beyond proof or successful PVI. All patients were ablated at our institution. Written informed consent was obtained from each patient and the current study complies with the Declaration of Helsinki and was approved by the institutional review board. LA thrombus formation was ruled out prior to ablation in all patients. All procedures were performed on uninterrupted oral vitamin K anticoagulants with a target international normalized ratio of 2.0–3.0 on the day of the procedure, direct oral anticoagulants were discontinued the day of the procedure and resumed the same day after ruling out pericardial effusion. Catheter ablation was performed under deep sedation with bolus of midazolam and fentanyl and a continuous infusion of propofol. In all patients, preprocedural magnetic resonance imaging was performed to guide the intervention and to visualize the anatomical location and course of the esophagus. A 6 F diagnostic catheter was inserted distal into the coronary sinus (CS) via the right femoral vein. Double transseptal puncture using 8.5 F SL1 sheaths (SJM, St. Paul, Minnesota, USA) and a modified Brockenbrough technique was performed as previously described in detail [21]. Unfractionated heparin was administered according to the patient's weight to maintain an activated clotting time ≥ 300 s.

Map acquisition

After transseptal puncture, a multipolar mapping catheter (Lasso or PentaRay, Biosense-Webster Inc., Diamond Bar, CA, USA) and an open-tip irrigated RF catheter (8 Fr) with tip-integrated contact force (CF) sensor (Thermocool SmartTouch SF, Biosense-Webster Inc.) were positioned in the LA. Subsequent calibration of CF catheter, respiratory gating, and three-dimensional geometry of the LA (Carto System®, Biosense Webster Inc.) were performed using ultra high-density mapping aiming for > 1000 mapping points for the estimation of bipolar LA voltage (Fig. 1). Bipolar voltage maps were created during sinus rhythm. In patients with PERS, sinus rhythm was restored by transthoracic direct electrical cardioversion at the beginning of the procedure. For the LA voltage map, the bipolar voltage reference interval was set between 0.05 and 0.5 mV. The definition of low-voltage areas included one of the two following

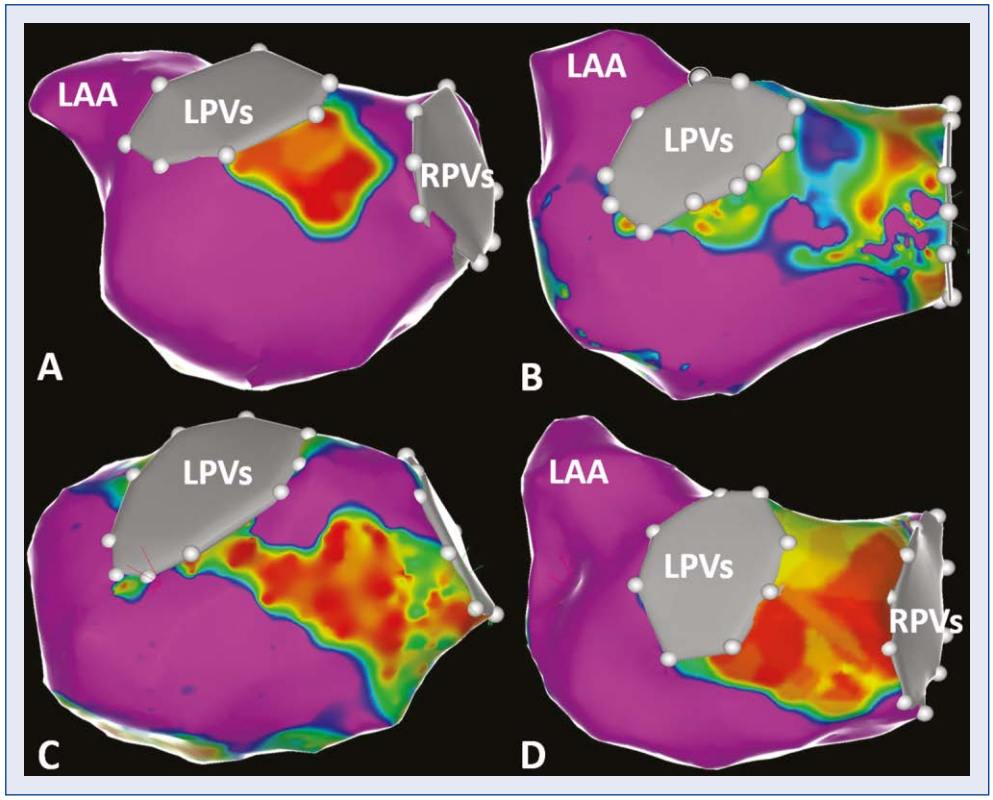

Figure 1. Typical examples for areas with left atrial bipolar low voltage using ultra-high density mapping; **A.** Native bipolar low-voltage suggestive for fibrosis, **B.** Bipolar low voltage at the posterior wall after previous radiofrequency--guided pulmonary vein isolation (PVI); **C.** Diffuse distribution of native bipolar low voltage; **D.** Localization of bipolar low voltage following previous cryoballoon-guided PVI; posterior-anterior view; bipolar voltage reference interval was set as < 0.5 mV; LAA — left atrial appendage; LPVs — left-sided pulmonary vein; RPVs — right-sided pulmonary veins.

criteria: (1) absence of voltage or a bipolar voltage amplitude ≤ 0.05 mV, indistinguishable from noise; (2) low-voltage "abnormal" areas were defined with an amplitude ≤ 0.5 mV, as previously reported [22]. The total individual amount of LA bipolar low voltage was measured using the area measurement tool. Patients with PERS undergoing a first catheter ablation procedure underwent PVI first. In patients undergoing a repeated ablation procedure, electrical isolation of the PVs was checked with the Lasso or PentaRay catheter and electrical reisolation of the PVs was performed if reconnection had occurred. Afterwards LA linear ablation at the roof and the bottom was subsequently performed to achieve posterior wall isolation if low-voltage areas were detected.

Ablation procedure

Catheter ablation was performed with an open-irrigated tip catheter (Thermocool SmartTouch SF, Biosense Webster Inc.). After reconstruction of the LA, each PV ostium was identified by selective PV angiography and ablation was performed. Following PV ablation, PWI started with a linear lesion set across the LA roof from the superior aspect of the left PVs to the superior aspect of the right-sided PVs (Fig. 2). Irrigated RF was delivered, targeting a maximum temperature of 43°C, a maximum power level of 35 W and an infusion rate of 20 mL/min. The bottom line was drawn from the most inferior aspect of the left-sided PVs to the inferior aspect of the right PVs aiming for coverage the complete area of bipolar low-voltage within posterior wall (Fig. 2). The bottom line was applied with a maximum power limited to 30 W. Patients were divided into two groups according to the ablation protocol. In patients of group 1 (n = 20), lesion creation was guided by contact force targeting 10–40 g, aiming for local signal attenuation of ≥ 80% at each point [23, 24]. These procedures were used to calculate an individual AI for posterior wall isolation. However, the performing physician was blinded to all AI values. In patients of group 2 (n = 20), all procedures were guided by AI target values (AI roof

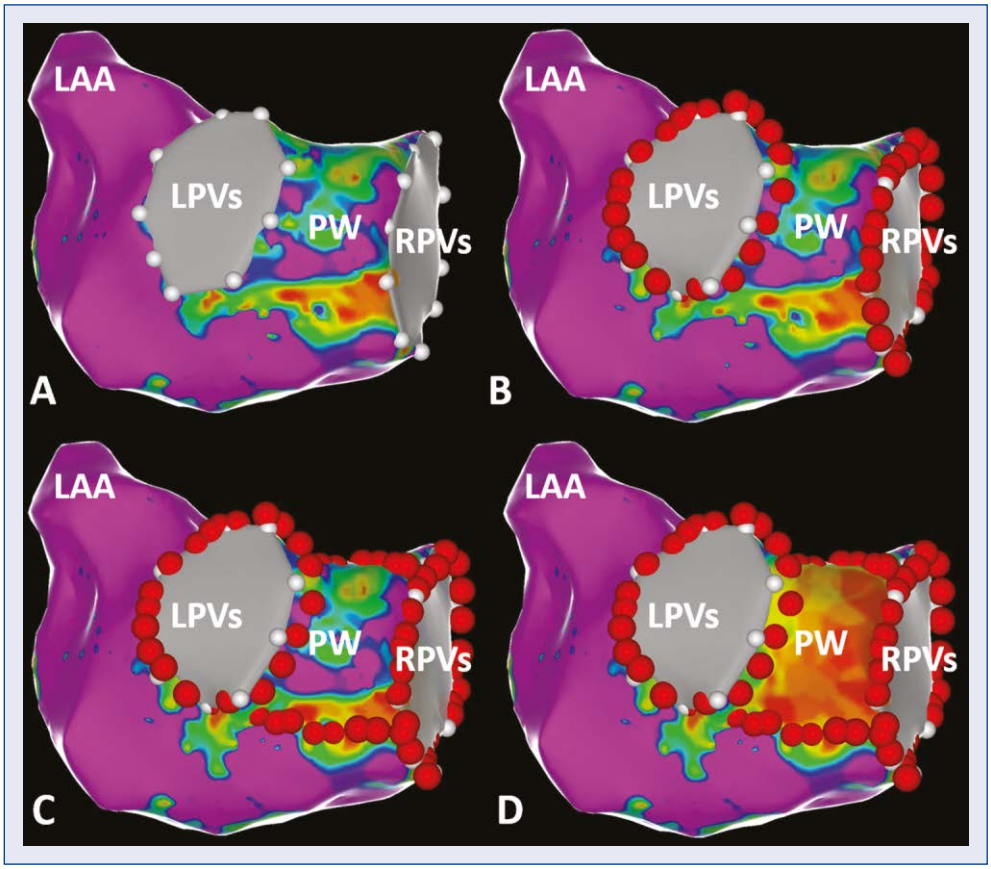

Figure 2. Patient specific example for ablation index (AI)-guided posterior wall isolation; **A.** After reconstruction of the left atrial (LA), each pulmonary vein (PV) ostium was identified; **B.** Pulmonary vein isolation was performed using AI; **C.** Posterior wall (PW) isolation started with a linear lesion set across the LA roof from the superior aspect of the left PVs (LPVs) to the superior aspect of the right-sided PVs (RPVs). The inferior line was drawn from the most inferior aspects of the left-sided PVs to the inferior aspects of the right PVs aiming for coverage of the complete area of bipolar low-voltage within PW isolation; **D.** Repeat voltage mapping to confirm isolation of the posterior box; LAA — left atrial appendage.

line: 550; AI bottom line: 400), and targeting an interlesion distance ≤ 6 mm (Fig. 2). Conduction block along the lines was validated in sinus rhythm by widely spread double potentials along the whole lines, pacing manoeuvres (including entrance- and exit-block) and repeated voltage mapping,including area measurement, of the isolated posterior box (Fig. 2D). Procedural success was subsequently reconfirmed after a minimum waiting period of 30 min. All patients were followed-up in the outpatient clinic 3, 6 and 12 months after ablation. At each visit they were asked for any symptoms suggestive for arrhythmia recurrence or discomfort during respiration. Moreover, a 72 h-Holter electrocardiogram was routinely performed in all patients to monitor arrhythmia recurrence and AF burden. Following a 3-month blanking period, recurrence was defined as any symptomatic episode of atrial tachycardia/AF lasting > 30 s.

Statistical methods

Continuous variables are reported as means ± standard deviation and were compared with the Student t test for unpaired groups as required, and dichotomic variables as percentage and compared with χ^2 test of the Fisher test as required. A p value < 0.05 was considered as statistically significant.

Results

Patients' characteristics

Forty consecutive patients (65% male), mean age 64 ± 9 years, that were routinely referred to our hospital for LA ablation procedures due

Table 1. Baseline characteristics of all patients and their respective p-values.

	Group 1 (CF)	Group 2 (AI)	P
Age [years]	63 ± 8	64 ± 17	0.37
Male	10 (50%)	16 (80%)	0.09
Left ventricular ejection fraction [%]	52 ± 13	53 ± 4	0.37
Left atrial diameter [mm]	44.3 ± 0.7	45 ± 1.9	0.22
Mean AF-duration prior ablation [months]	7 ± 2	8 ± 3	0.14
Amount of bipolar low voltage of the PW [%]	18 ± 12	20 ± 10	0.46
Ejection fraction [%]	53.8 ± 0.6	54.0 ± 0.7	0.83
Arterial hypertension	13 (65%)	15 (76%)	0.73
Congestive heart failure	2 (10%)	2 (10%)	1.0
Diabetes mellitus	2 (10%)	3 (15%)	1.0
Coronary artery disease	5 (25%	4 (20%)	1.0
CHA_2DS_2VASC Score	1.3±1.1	1.±1.2	0.16
Previous AAD	12 (60%)	14 (70%)	0.74
Beta-blockers	16 (80%)	17 (85%)	1.0
Previous ablations:			
Pulmonary vein isolation	9 (45%)	12 (60%)	0.53
LAMRT	1 (5%)	0	1.0
Cavotricuspid isthmus	3 (15%)	6 (30%)	0.45

AAD — antiarrhythmic drugs; AF — atrial fibrillation; LAMRT — left atrial macro-reentrant tachycardia; PW — posterior wall

to PERS. Mean left ventricular ejection fraction was 53 ± 5% and LA diameter was 45 ± 7 mm. A significant low-voltage area at the posterior LA wall was detected in all patients. The groups did not differ significantly in terms of age, sex and cardiovascular risk factors. Baseline characteristics are reported in Table 1.

Procedural data and success

For this study, analysis of the procedural data of all patients included a total of 601 RF applications. The whole procedure duration was comparable between both groups with 98 ± 23 min in group 1 and 92 ± 9 min in group 2, respectively (p = 0.10). This was also the fact for the mean fluoroscopy time (group 1: 4.2 ± 1.6 min; group 2: 4.1 ± 1.9 min; p = 0.87). Although there was no significant difference in terms of procedural duration, a remarkably lower variation in the AI-guided ablations was observed.

Acute isolation of the posterior wall was achieved in all cases. Bidirectional block of the roof line required a total of 5 ± 3 RF applications in group 1 and 4 ± 1 RF applications in group 2 (p = 0.44). For the bottom line, a mean of 10 ± 7 RF applications was required in group 1 and 10 ± 5 RF applications in the AI-guided group (p = 0.84). There was no significant difference focussing on ablation duration for bidirectional block across the roof (1.9 ± 1.1 min group 1 vs. 1.5 ± 0.8 min group 2; p = 0.14) or the bottom line (3.5 ± 3.1 min group 1 vs. 3.5 ± 1.6 min group 2; p = 0.95). First-pass block of the roof line was achieved in the majority of patients (n = 17 in CF-group and n = 18 in AI group). First-pass block of the bottom line, resulting in LA posterior wall isolation was observed in 15/20 patients in group 1 (75%) and 17/20 patients in group 2 (85%; p = 0.43). No electrical reconduction of the posterior wall was found after the waiting period of 30 min in patients who underwent AI-guided posterior box isolation. In contrast, reconduction requiring reablation was observed in 3 (15%) patients from group 1. Gaps in the ablation lines were identified from signal mapping and pacing maneuvers in all cases. RF applications inside the box were not necessary.

Of note, AI-guided LA PWI led to significantly lower maximum temperature rises measured at the catheter tip (roof line: 27 ± 1.4°C group 1 vs. 25 ± 1.7°C group 2; p < 0.01; bottom line: 27 ± 1.2 group 1 vs. 25 ± 1.7°C group 2; p < 0.01). Furthermore, the mean AI value (roof line: 482 ± 108 group 1 vs. 549 ± 74 group 2; p < 0.01; bottom line: 442 ± 127 group 1 vs. 428 ± 99 group 2; p < 0.01)

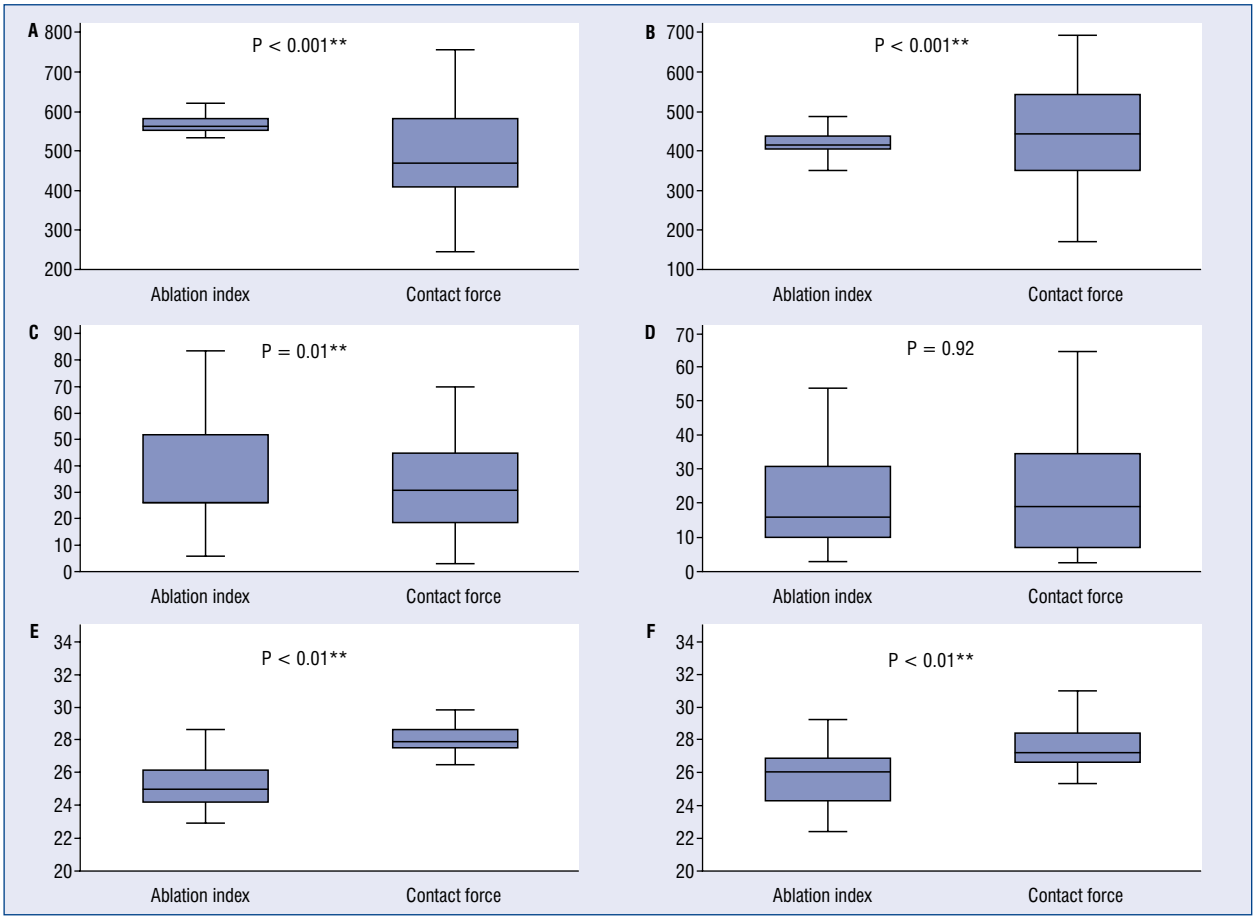

Figure 3. Box-plots depicting the mean values for ablation index (AI), catheter-tip to tissue contact force and maximum temperature rising for both groups. Values for the roof line are listed on the left side, values for the bottom lines are shown on the right. **A.** Ablation index roof line; **B.** Ablation index bottom line; **C.** Catether tip-to-tissue contact force roof line [g]; **D.** Catether tip-to-tissue contact force bottom line [g]; **E.** Maximum temperature roof line [°C]*; **F.** Maximum temperature bottom line [g]. The AI was significantly higher in the AI-group and the maximum temperature rise was significantly lower, respectively (for both $p < 0.01$). In addition, the contact force administered for the roof line was significantly higher in the AI-guided group. Of note, the variance in the AI-guided group was very small indicating a very good reproducibility of lesion application and formation using the AI; *As measured from the catheter tip; **Significant.

as well as the mean value for catheter-to-tissue contact force for the roof line (32 ± 18 group 1 vs. 39 ± 17 group 2; $p = 0.01$) were significantly higher when performing AI-guided catheter ablation. Besides these statistically significant differences mentioned above, the data highlighted even more the important benefit of using AI-guided posterior wall isolation in terms of safety and reproducible efficacy, as the AI variance creating each ablation lesion was remarkably low (Fig. 3). All procedural parameters are summarized in Table 2. No relevant complications were recorded during or after the intervention.

During a mean follow-up period of 12.1 ± 1.8 months, 16/20 (80%) and 18/20 (90%) patients were free of any arrhythmia recurrence in both group 1 and group 2, respectively. Focusing on arrhythmia recurrence, 2/4 patients from group 1 presented with LA macro-reentrant tachycardia (LAMRT), one patient presented with AF and LAMRT and another patient with AF. In contrast, 2 patients with AF recurrence were observed in group 2.

Discussion

Main findings

This is the first study systematically evaluating the use of AI guided LA posterior wall substrate modification aiming for electrical isolation of the posterior wall. Four major findings are reported in this study: First, AI guided PWI for substrate modification in AF patients is safe and reproducibly

Table 2. Procedural data and their respective p-value.

	Group 1 (CF)	Group 2 (AI)	P
Procedure duration [min]	98 ± 23	92 ± 9	0.10
Fluoroscopy time [min]	4.2 ± 1.6	4.1 ± 1.9	0.87
Ablation time [total]	2.7 ± 2.5	2.5 ± 1.6	0.67
Ablation time [min]:			
Roof line	1.9 ±1.1	1.5 ± 0.8	0.14
Bottom line	3.5 ± 3.1	3.5 ± 1.6	0.95
Length [mm]:			
Roof line	115 ± 70	90 ± 50	0.06
Bottom line	207 ± 98	210 ± 186	0.73
No of RF applications:			
Roof line	4 ± 3	4 ± 1	0.92
Bottom line	10 ± 7	10 ± 5	0.84
Contact force [g]:			
Roof line	32 ± 18	39 ± 17	0.01*
Bottom line	21 ± 16	22 ± 16	0.92
Ablation index:			
Roof line	482 ± 108	549 ± 74	< 0.01*
Bottom line	442 ± 127	428 ± 99	< 0.01*
Maximal temperature:			
Roof line	27 ± 1.4	25 ± 1.3	< 0.01*
Bottom line	27 ± 1.2	25 ± 1.7	< 0.01*

*Significant; AI — ablation index; CF — contact force; RF — radiofrequency

effective. Second, performing AI-guided LA linear lesions across the LA roof and bottom in patients with PVI results in a high rate of first-pass PWI. Third, using target AI values results in a significant decrease of temperature exposure during lesion formation at the posterior wall. Fourth, AI guided application of the posterior box lesion set is assigned by improved lesion formation focussing on CF and AI.

Left atrial posterior wall isolation: Technically challenging

The STAR AF trial [1, 25] failed to demonstrate a relevant benefit of LA lines and ablation of complex fractionated atrial electrograms beyond PVI in patients with PERS. However, catheter ablation aiming for LA PWI was not part of the study. Approaches of PWI include box isolation, single ring isolation, and debulking ablation [9]. A recent meta-analysis from Thiyagarajah et al. [9] demonstrated that acute LA PWI as a procedural endpoint was achieved in 78.5% with a pooled estimate of 70.9% in 12 studies [26–37]. The authors reported pooled estimates for 12-months freedom from any arrhythmia recurrence of 65.3% and 61.9% for patients with PERS, respectively. In the present study acute procedural success was achieved in all patients and recurrence free survival during the follow-up period was 80% and 90%, respectively. In this context, it is well known that incomplete bidirectional conduction block has been associated with an increase in subsequent arrhythmia during follow-up [14, 15]. In the recent study, even respecting the criteria for contiguity and AI in group 2, complete block across the roof in 90% of patients and in 85% at the bottom line after a single linear lesion set was achieved. The very high success rate of first-pass block of both LA lines in the current study can probably be explained by the specific anatomy of the LA roof with a thin wall thickness ranging from 3.5 to 6 mm and relatively smooth inferior parts of the posterior wall [38], which finally render the posterior wall quite suitably for a strategy aiming at transmurality and contiguity of RF lesions. Moreover, and as demonstrated in Figure 3A and B, AI-guided ablation lesions were created with a remarkably lower variance in target values at the roof and bottom line as compared to CF-guided ablation alone (Fig. 3).

Left atrial posterior wall ablation: The narrow ridge between effectiveness and risk

Hypothesized herein, that AI-guided lesion formation at the LA posterior wall could be helpful in avoiding complications in these high-risk procedures. In their meta-analysis Thiyagarajah et al. [9] reported that 15 major complications were found across 1667 ablation procedures aiming for PWI. Pericardial effusion requiring drainage or cardiac tamponade were observed in 10 patients, cerebrovascular events in 3 patients, and atrio-esophageal fistulas in 2 patients [9, 33]. There are multiple approaches to PWI with different strategies of power delivery, RF application time, image integration, endpoints and in the context of temperature monitoring for the esophagus [9]. In the present study, no major complication was observed using an AI of 400 for ablation at the posterior wall. In this context, Figure 3E and F emphasize that a significant lower maximum temperature rise was observed performing ablation guided by AI in line with improved lesion formation (Fig. 3E, F). In studies focusing on RF ablation in the canine heart, Nakagawa et al. [39, 40] found that the RF lesion depth was accurately (± 1 mm) described by a logarithmic function of CF, RF power and application time. However, today AI-guided AF ablation does not take into account atrial wall thickness and individual distribution of fibrosis in the logarithmic function, although these factors may play an important role in the initialization and maintenance of PERS [41, 42]. Based on the current findings and those discussed above we would like to address the need for personalized paths in catheter based PERS management in terms of efficacy and safety and therefore suggest a shift to the current AI approach to a substrate-based index taking into account the individual LA architecture as well as the amount and distribution of fibrosis.

The potential benefit of both continuous and optimized RF lesions

Recently, several studies reported beneficial effects of AI-guided ablation approaches for PVI with respect to periprocedural workflow, acute procedural success (first-pass PVI) and freedom from arrhythmia recurrence [18, 43–45]. Focusing on LA RF lesions, Taghji et al. [18] demonstrated that for durable PVI, the maximum interlesion distance should not exceed 6 mm and the minimal AI should be ≥ 400 at the posterior and ≥ 550 at the anterior aspects of the PVs. Beyond PVI, Santoro et al. [20] reported interesting data about the feasibility and safety of LA anterior line ablation using AI and interlesion distance measurement with shorter ablation time, shorter overall RF application time and a reduced number of RF applications to achieve anterior line bidirectional block. Another study by Wolf et al. [19] evaluated LA linear ablation using contiguous and optimized RF lesions for linear ablation across the LA roof and the posterior mitral isthmus. The authors concluded, that their ablation approach resulted in a high rate of first-pass block at the roof but not at the mitral isthmus. The present data confirms the results from Wolf et al. [19] with respect to linear lesion sets across the LA roof and also emphasizes the beneficial effects of an AI-guided approach in terms of workflow improvement, transmural lesion formation and estimation of reproducible AI target values (Fig. 3). The same effect was observed for the bottom line leading to consecutive LA PWI (Fig. 3). Consequently, this AI-guided approach resulted in PWI as a consequence of roof and inferior lines without the additional need of ablation inside the box. Based on these findings, we hypothesize that AI-guided linear ablation aiming for LA PWI respecting strict criteria of contiguity and indirect lesion assessment would also improve achievement of both acute and durable bidirectional block across linear lesion sets resulting in persistent PWI.

Limitations of the study

This is a single-center study with a limited number of patients. Although no safety-related issues were observed, larger studies are necessary to validate the safety and efficacy of this protocol for LA posterior wall substrate modification. Previous ablation for PVI may have affected the atrial tissue at the posterior wall differently according to previous RF- or cryoballoon-guided PVI (Fig. 1). However, high density mapping was performed in all patients to visualize the area of bipolar low voltage on the posterior wall representing scarred or fibrotic tissue. Another limitation might be the lack of a direct luminal esophageal temperature monitoring during PWI in the present study. Luminal esophageal temperature is not performed in clinical routine during AF ablation at our center due its potential compound role in the context of lesion formation.

Conclusions

Ablation index-guided LA PWI for substrate modification in AF patients is safe and reproducibly effective. Furthermore, AI-guided application of the posterior box lesion set is featured by improved lesion formation with respect to CF, AI and temperature development. The present find-

ings suggest AI-guided ablation is safe, effective and transmural linear LA RF lesions across the posterior LA wall.

Acknowledgments

We acknowledge support by the DFG Open Access Publication Funds of the Ruhr-Universität Bochum, Germany.

Conflict of interest: None declared

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VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 6, 927–935
DOI: 10.5603/CJ.a2020.0078

ISSN 1897–5593
eISSN 1898–018X

NT-proBNP increase during stress echocardiography predicts significant changes in ischemic mitral regurgitation severity in patients qualified for surgical revascularization

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Abstract

Background: *In many patients, significant changes in ischemic mitral regurgitation (IMR) severity during exercise can be observed independent of the degree of IMR at rest. This study aimed to investigate the correlations between N-terminal fragment B-type natriuretic peptide (NT-proBNP) and echocardiography measurements at rest and at peak exercise in patients with moderate IMR who qualified for surgical revascularization.*

Methods: *A total of 100 patients eligible for coronary artery bypass grafting, were included in this prospective study. All patients underwent exercise echocardiography. Additionally, the levels of NT-proBNP were measured at rest and after peak exercise.*

Results: *A positive correlation of absolute NT-proBNP levels with effective regurgitant orifice area (EROA) were observed and with tricuspid regurgitant peak gradient (TRPG) at peak exercise. Absolute ΔNT-proBNP during exercise and the tenting area at rest were independent predictors of severe IMR at peak exercise. The level of absolute ΔNT-proBNP during exercise and coaptation height at rest were the most important predictors of significant increases in TRPG. The best cutoff value for ΔNT-proBNP as a predictor for increases in EROA at peak exercise was 68.9 pg/mL and to predict an increase in TRPG ≥ 50 mmHg at peak exercise was 68 pg/mL.*

Conclusions: *The level of ΔNT-proBNP during exercise was the most important parameter in predicting significant changes in IMR severity and pulmonary pressure. Based on the present data, it can be speculated that integration of the assessment of NT-proBNP at rest and at exercise might improve patient selection for valve surgery.* (Cardiol J 2022; 29, 6: 927–935)

Key words: natriuretic peptides, ischemic mitral regurgitation, exercise echocardiography

Introduction

Secondary ischemic mitral regurgitation (IMR) has a dynamic nature. In many patients, significant changes in IMR severity during exercise can be observed independent of the degree of IMR at rest [1–3]. An exercise-induced increase in IMR severity is related to left ventricle (LV) remodeling and mitral valve deformation indices, namely, tenting area (TA) and coaptation height (CH), as well as LV synchronicity [4–6].

Natriuretic peptides such as B-type natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP) are released from ventricular and atrial myocardium in response to increased wall stress (left and right ventricle) and left atrial pressures due to increasing severity of mitral regurgitation [7–11]. Previous studies have suggested that BNP

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Received: 8.03.2019 Accepted: 21.04.2020 Early publication date: 3.06.2020

or NT-proBNP levels increase with exercise in patients with coronary artery disease [12], heart failure [13], organic mitral regurgitation [14], and mitral stenosis [15]. However, NT-proBNP levels during exercise do not provide new information on the severity of aortic stenosis [16]. The value of serial measurements of NT-proBNP at rest and during exercise in patients with IMR has not yet been evaluated.

Optimal management of moderate IMR in patients qualified for coronary artery bypass grafting (CABG) is still controversial [17, 18]. Hypothesized herein, that the absolute increase in NT-proBNP with exercise is a reliable parameter in predicting a significant increase in IMR severity and pulmonary systolic artery pressure and may help in the identification of high-risk patients with moderate IMR qualified for CABG. This would help improve risk stratification and identification of the subgroups of patients who could benefit from various surgical strategies (CABG or CABG with mitral repair).

The main purpose of the present study was to assess the correlation between NT-proBNP levels and echocardiography measurements at rest and at peak exercise in patients with moderate IMR, qualified for surgical revascularization.

Methods

Study population

A total of 100 patients (mean age 64.4 ± 7.9 years) with a history of myocardial infarction (MI) and were eligible for CABG were included in a prospective study. The time frame for enrollment of patients into the study was 24 months. All patients had moderate IMR caused by restrictive systolic leaflet motion (Carpentier's type IIIb), with or without annular dilatation, which occurred in ≥ 16 days from MI, with no evidence of primary leaflet, chordal, or papillary muscle pathology, excluding mechanical complications of MI.

The study inclusion criterion was the presence of a significant area of viable myocardium, as seen in the improvement in wall motion of at least four dysfunctional segments during dobutamine stress echocardiography (DSE). Exclusion criteria included left bundle branch block, unstable angina, prosthetic heart valve, other valvular or congenital heart diseases, renal failure (creatinine > 2 mg/dL), history of CABG, severe heart failure symptoms (New York Heart Association [NYHA] IV), clinical limitations to exercise testing, and atrial fibrillation before exercise testing.

Echocardiographic and clinical assessment were performed before surgery.

Each patient signed an informed consent form, and the study was approved by the institutional review board of the Medical University of Warsaw. The study had been conducted according to the principles stated in the Declaration of Helsinki.

Clinical data

Clinical assessment was comprised of a careful exploration of patient history and physical examination and was performed at the time of enrollment. Experienced cardiologists blinded to the results of NT-proBNP measurements and echocardiographic findings assessed the functional status. Clinical status was determined according to the criteria of the NYHA classification system and the Canadian Cardiovascular Society (CCS) functional class for heart failure and angina symptoms, respectively.

Echocardiographic measurements and calculations

Transthoracic echocardiograms (TTE) were performed within 2 days before surgery. All patients underwent TTE in the left lateral decubitus position at rest and during DSE. For accuracy purposes, the images obtained at rest and during stress tests were independently analyzed with a blinded method by two experienced echocardiographers.

All examinations were carried out using the iE33 system manufactured by Philips, a broadband transducer for TTE of 2.5 to 3.5 MHz frequencies. Echocardiographic measurements were averaged over three cardiac cycles.

Ischemic mitral regurgitation severity was assessed by measuring the effective regurgitant orifice area (EROA), with EROA > 10 mm^2 and < 20 mm^2 considered moderate and EROA ≥ 20 mm^3 considered severe, as well as mitral regurgitation volume (MRvol) with MRvol ≥ 30 mL considered severe [18–20]. EROA and MRvol was calculated using flow convergence (proximal isovelocity surface area-proximal isovelocity surface area [PISA] method). The radius of the PISA (r) is measured from the vena contracta level to the point of color Doppler aliasing. EROA is calculated as: $6.28 \times r^2 \times Va/Peak\ V\ RegJet$, where Va is aliasing velocity and VRegJet is the peak velocity of the regurgitant jet by Continuous Wave Doppler. The MRvol is calculated as EROA × VTI RegJet where VTI RegJet is the VTI of the regurgitant jet. Wall motion abnormalities were evaluated in accordance with the recommendations of the American Society

of Cardiology. The wall motion score index was calculated according to a 17-segment model [21]. The left ventricular volumes and ejection fraction (EF) were assessed by the biapical Simpson disk method [22]. Sphericity indices (SI) were obtained at end-diastole (SId) and end-systole (SIs) in the apical view. Pulmonary systolic arterial pressure can be estimated from the maximal tricuspid regurgitant peak gradient (TRPG) using the simplified Bernoulli equation ($\Delta P = 4V^2$, where V = maximal tricuspid regurgitant velocity [TRV] in m/s), adding an assumed right atrial pressure which can be estimated by echocardiography based on the diameter and respiratory variation in diameter of the inferior vena cava. However, TRV > 3.4 m/s indicates a high probability of pulmonary hypertension. In the present analysis it was assumed that TRPG ≥ 50 mmHg means significant pulmonary hypertension [23]. Mitral valve deformation was evaluated by measuring TA, i.e., the area enclosed between mitral leaflets and the line of annular plane, and CH, i.e., the distance between leaflet coaptation and mitral annular plane from the parasternal long-axis view at mid-systole [24].

Low-dose DSE was used in IMR patients to distinguish akinetic viable segments from nonviable myocardial regions of the LV [25]. DSE was performed in accordance with current guidelines [26]. A graded dobutamine infusion started at 5 μg/kg/min and was increased at 3-min intervals to 10, 20 μg/kg/min.

Exercise echocardiography

All subjects underwent a symptom-limited graded exercise echocardiography test to assess the dynamics of IMR changes and TRPG, the latter as the exponent of right ventricle overload. The symptom-limited grade exercise echocardiography was performed according to the following protocol: the initial workload of 25 watts (W) was maintained for 3 min, and then the workload was increased every 2 min by 25 W. Blood pressure and a 12-lead electrocardiogram was recorded every 2 min. Two-dimensional and Doppler echocardiographic recordings were available throughout the test. Exercise was interrupted when ischemic electrocardiographic signs, fatigue, or intolerable dyspnea appeared [24].

NT-proBNP measurements

Venous blood samples were collected from an antecubital vein and placed into chilled EDTA tubes before and immediately after exercise. The specimens were centrifuged within half an hour at –4°C and then plasma was frozen at –80°C until analysis. NT-proBNP was measured by an electrochemiluminescence immunoassay (ProBNP Elecsys®, Roche Diagnostics GmbH). The absolute increase in NT-proBNP during exercise (absolute ΔNT-proBNP) was calculated as the difference between NT-proBNP at peak exercise and NT-proBNP at rest. An NT-proBNP value of 125 pg/mL was used to differentiate between normal and abnormal NT-proBNP levels.

Statistical analysis

All data were prospectively recorded using the institution's database. Continuous variables are presented as mean ± standard deviation (SD), and categorical variables are presented as either absolute numbers or percentages. The Spearman correlation coefficient was used to assess the relation between NT-proBNP changes and exercise echo parameters. Multiple linear regression analysis was used to identify important predictors of significant increase of IMR severity (EROA exe ≥ 20 mm^2) and probability of pulmonary hypertension (TRPG ≥ 50 mmHg) at peak exercise echocardiography examination. Stepwise logistic regression analysis included age, NT-proBNP at rest and at peak exercise, and ΔNT-proBNP, as well as some echocardiography parameters at rest and at peak exercise, namely, EROA, MRvol, TRPG, TA, CH, left ventricular end-systolic volume (ESV), EF, and SIs. A receiver-operating characteristic (ROC) curve analysis was performed to identify the optimal cutoff point of NT-proBNP levels (at which sensitivity and specificity were maximal) to predict the increase in IMR severity and pulmonary systolic arterial pressure at peak exercise. Optimal cutoff values were determined as the rounding cutoff that gives the maximum sum of sensitivity and specificity. This value should be the shoulder at the top left of the ROC curve. The area under the curve (AUC) value was calculated as a measure of accuracy of the test. ROC analysis was performed for NT-proBNP at rest, NT-proBNP at peak exercise (NT-proBNP exe), and absolute ΔNT-proBNP as predictors of reaching the above-mentioned echo endpoints (EROA exe ≥ 20 mm^2 and TRPG ≥ 50 mmHg at peak exercise). The AUCs of the ROC curve for NT-proBNP at rest, NT-proBNP exe, and ΔNT-proBNP are given together with their 95% confidence intervals (95% CI) and are compared by the nonparametric test proposed by DeLong et al. [27]. A p value of < 0.05 was considered significant. Statistical analyses were performed with SAS software version 8.02 (SAS Institute Inc., Cary, NC).

Table 1. Baseline clinical characteristics — all groups (n = 100).

Age [years]	64.4 ± 7.9
BMI [kg/m^2]	27.1 ± 4.0
Sex, male	56 (56%)
NT-proBNP at rest, median [pg/mL]	769.5 (395.5–1334)
NT-proBNP exe, median [pg/mL]	789.9 (429.9–1478)
ΔNT-proBNP, median [pg/mL]	30.1 (14.7–89)
NYHA:	2.0 ± 0.8
I	28 (28%)
II	47 (47%)
III	25 (25%)
EuroSCORE Logistic [%]	7.1 ± 5.1
Smoking (actual)	15 (15%)
Hypertension	67 (67%)
Diabetes mellitus	32 (32%)
Hyperlipidemia	67 (67%)
Atrial fibrillation	17 (17%)
Two-vessel disease	27 (27%)
Three-vessel disease	70 (70%)
ACEI	94 (94%)
Beta-adrenolytics	96 (96%)
Statins	96 (96%)
Acetylsalicylic acid	91 (91%)

Data are presented as mean ± standard deviation or number (percentage) as shown; ACEI — angiotensin converting enzyme inhibitors; BMI — body mass index; exe — at peak exercise; NT-proBNP — N-terminal fragment B-type natriuretic peptide; ΔNT-proBNP — difference between NT-proBNP level at peak exercise and NT-proBNP level at rest; NYHA — New York Heart Association

Table 2. Baseline echocardiographic characteristics — all groups (n = 100).

ECHO rest	
LVDD [mm]	54.0 ± 6.0
LVDS [mm]	40.5 ± 7.4
LVEDV [mL]	125.8 ± 46.9
LVESV [mL]	73.9 ± 38.6
EF rest [%]	44.0 ± 9.3
WMSI rest	1.57 ± 0.3
TRPG rest [mmHg]	23.7 ± 8.5
EROA rest [mm^2]	15.0 ± 2.0
MRvol rest [mL]	22.5 ± 5.5
CH rest [cm]	0.8 ± 0.2
TA rest [cm^2]	2.0 ± 0.6
TAPSE [mm]	15.0 ± 4.1
SIs	0.38 [0.3–0.45]
ECHO exercise	
EF exe [%]	44.8 ± 9.8
TRPG exe [mmHg]	33.6 ± 14.7
EROA exe [mm^2]	18.0 ± 8.0
MRvol exe [mL]	26.8 ± 11.7

Data are presented as mean ± standard deviation. CH — coaptation height; EF — ejection fraction; EROA — effective regurgitant orifice area; exe — exercise; LVDD — left ventricular end-diastolic dimension; LVDS — left ventricular end-systolic dimension; LVEDV — left ventricular end-diastolic volume; LVESV — left ventricular end-systolic volume; SIs — sphericity index at end-systole; MRvol — mitral regurgitation volume; TA — tenting area; TAPSE — tricuspid annular plane systolic excursion; rest — echo examination at rest; TRPG — maximal tricuspid regurgitant peak gradient; WMSI — wall motion score index

Results

The mean age of the patients was 64.4 ± ± 7.9 years. Of the 100 patients analyzed, 56 were men and 44 were women. The mean logistic EuroSCORE was 7.1 ± 5.1%. All the patients were given optimal pharmacological treatment. Table 1 shows the clinical characteristics and NT-proBNP levels, and Table 2 the echocardiographic variables at rest and at peak exercise of the IMR patients. Table 3 presents correlation coefficients for associations between NT-proBNP (rest, exercise, and delta) and echocardiographic measures at rest and at peak exercise. Significant negative correlations were found between the plasma level of NT-proBNP and EF both at rest and after exercise ($p < 0.0001$), whereas positive moderate correlations were found between NT-proBNP and ESV ($p < 0.0001$) and TA ($p < 0.0001$) both at rest and after exercise. The correlation coefficients were similar for NT-proBNP at rest and NT-proBNP exe. There were also weak, but significant, correlations between NT-proBNP and other resting or post exercise measurements of LV dimensions (LV end-diastolic dimension, LV end-systolic dimension), right ventricle function assessed using tricuspid annular plane systolic excursion, severity of IMR (EROA, MRvol), and probability of pulmonary hypertension assessed using TRPG. The correlation coefficients for the above-mentioned parameters were similar for NT-proBNP at rest and NT-proBNP exe, and no statistically significant correlation existed between NT-proBNP and patient age. Furthermore, significant changes in IMR severity and maximal TRPG during an exercise test were strongly associated with the level of absolute ΔNT-proBNP after exercise. A significant positive correlation was found between the level of abso-

Table 3. Correlation between the plasma level of NT-proBNP and clinical and echocardiographic measures at rest and at peak exercise.

	NT-proBNP at rest, r value	P value	NT-proBNP exe, r value	P value	ΔBNP, r value	P value
Age	0.11389	0.2617	0.11966	0.2381	0.00469	0.9633
WAT	–0.29797	0.0027	–0.28685	0.0040	0.00170	0.9867
LVDD	0.25969	0.0094	0.25200	0.0119	0.19841	0.0490
LVDS	0.34539	0.0005	0.33043	0.0008	0.19839	0.0490
SIs	0.33863	0.0006	0.33315	0.0008	0.19755	0.05
LVESV	0.43340	< 0.0001	0.42522	< 0.0001	0.26054	0.0092
EF rest	–0.51588	< 0.0001	–0.50414	< 0.0001	–0.28304	0.0045
EF exe	–0.57531	< 0.0001	–0.57102	< 0.0001	–0.37037	0.0002
TAPSE	–0.21553	0.0322	–0.21390	0.0335	–0.06326	0.5339
TRPG rest	0.2	0.0471	0.20376	0.0431	0.21811	0.0301
TRPG exe	0.34616	0.0004	0.36661	0.0002	0.44151	< 0.0001
EROA rest	0.27049	0.0068	0.26598	0.0078	0.24631	0.0140
EROA exe	0.29030	0.0036	0.31848	0.0013	0.49240	< 0.0001
MRvol rest	0.17308	0.0867	0.17990	0.0748	0.32621	0.001
MRvol exe	0.31338	0.0016	0.33844	0.0006	0.47944	<0.0001
CH rest	0.3487	0.0004	0.35787	0.0003	0.44185	< 0.0001
TA rest	0.43884	< 0.0001	0.44	< 0.0001	0.42485	< 0.0001

WAT — workload in watts; rest abbreviations — see Tables 1 and 2

Table 4. Multivariate stepwise logistic regression analysis for the prediction of a significant increase in mitral regurgitation severity and pulmonary arterial pressure during exercise.

	F value	P value
EROA ≥ 20 mm²		
TA rest	28.48	0.0001
ΔNT-proBNP	4.66	0.03
TRPG ≥ 50 mmHg		
CH rest	12.76	0.0006
ΔNT-proBNP	4.65	0.03

Abbreviations — see Tables 1 and 2

lute ΔNT-proBNP and EROA, MRvol, and TRPG at peak exercise ($p < 0.001$ for each). There was also a positive moderate correlation between ΔNT-proBNP and TA at rest ($p < 0.0001$). Multivariate stepwise logistic regression analysis showed that the levels of absolute ΔNT-proBNP and TA at rest were the only independent predictors of the development of severe IMR at peak exercise ($p = 0.033$ and $p < 0.0001$, respectively). Absolute ΔNT-proBNP and CH were independent predictors of a significant increase in TRPG at peak exercise ($p = 0.033$ and $p = 0.0006$, respectively) (Table 4).

The AUC for ΔNT-proBNP predicting an increased EROA of ≥ 20 mm² was 0.812 (95% CI 0.721–0.884; $p = 0.0001$; Fig. 1). The absolute increase in NT-proBNP level of > 68.9 pg/mL was the optimal cutoff, with a sensitivity of 67% and a specificity of 90%. For NT-proBNP exe, the AUC was 0.702 (95% CI 0.602–0.790; $p = 0.0003$), with an optimal cutoff of 924 pg/mL, sensitivity of 67%, and specificity of 74%. For NT-proBNP at rest, the AUC was 0.685 (95% CI 0.583–0.774; $p = 0.0012$); the optimal cutoff was 596 pg/mL, with sensitivity of 83% and specificity of 55%. The AUC that predicted an increased TRPG of ≥ 50 mmHg at peak exercise for ΔNT-proBNP was 0.842 (95% CI 0.756–0.908; $p = 0.0001$; Fig. 2). The absolute increase of NT-proBNP level of > 68 pg/mL was the optimal cutoff, with a sensitivity of 80% and specificity of 76%. For NT-proBNP exe, the AUC was 0.768 (95% CI 0.672–0.847; $p = 0.004$), with an optimal cutoff of 1015 pg/mL, sensitivity of 87%, and specificity of 74%. For NT-proBNP at rest, the AUC was 0.756 (95% CI 0.659–0.837; $p = 0.0008$), with an optimal cutoff of 926 pg/mL, sensitivity of 87%, and specificity of 73%. The

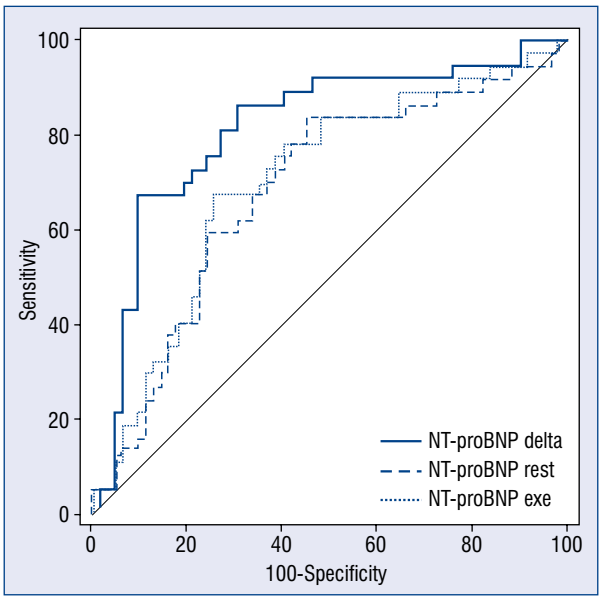

Figure 1. Receiver-operating characteristic curve analysis for N-terminal fragment B-type natriuretic peptide (NT-proBNP) at rest, NT-proBNP exe, and ΔNT-proBNP as predictors of reaching exercise-induced severe mitral regurgitation (EROA ≥ 20 mm^2).

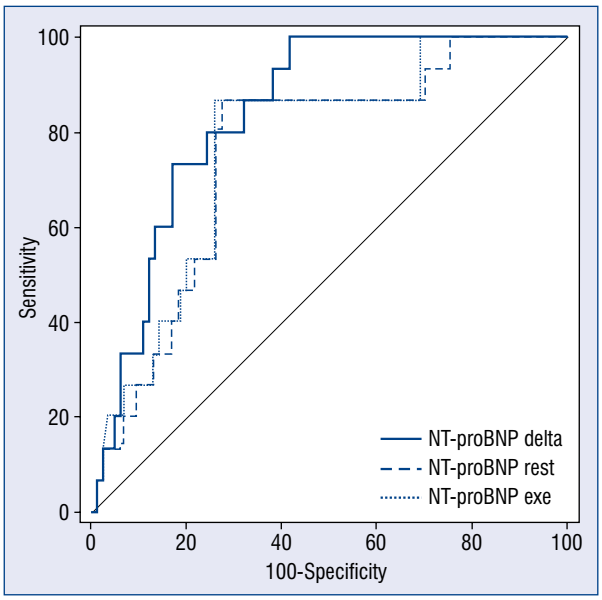

Figure 2. Receiver-operating characteristic curve analysis for N-terminal fragment B-type natriuretic peptide (NT-proBNP) at rest, NT-proBNP exe, and ΔNT-proBNP as predictors of reaching exercise-induced significant pulmonary hypertension (TRPG ≥ 50 mmHg).

Table 5. Sensitivity, specificity, and area under the curve (AUC) of NT-proBNP at rest, NT-proBNP exe, and ΔNT-proBNP for prediction of exercise-induced pulmonary hypertension and severe mitral regurgitation.

	Cutoff [pg/mL]	Sensitivity [%]	Specificity [%]	AUC
EROA ≥ 20 mm^2				
NT-proBNP at rest	596	83	55	0.685
NT-proBNP exe	924	67	74	0.702
ΔNT-proBNP	68.9	67	90	0.812
TRPG ≥ 50 mmHg				
NT-proBNP at rest	926	87	73	0.756
NT-proBNP exe	1015	87	74	0.768
ΔNT-proBNP	68	80	76	0.842

Abbreviations — see Tables 1 and 2

ROC analysis confirmed the high predictive value of ΔNT-proBNP at peak exercise for reaching the analyzed endpoints (increased EROA of ≥ 20 mm^2 and TRPG ≥ 50 mmHg at peak exercise). Table 5 presents the sensitivity, specificity, and AUC of the ΔNT-proBNP level for predicting abnormal peak-exercise pulmonary pressure thresholds and a significant increase in IMR severity (EROA ≥ 20 mm^2) at peak exercise.

Analyses of the ROC curves for EROA ≥ 20 mm^2 also indicated differences in the AUCs for NT-proBNP at rest, NT-proBNP exe, and ΔNT-proBNP. Pairwise comparisons of the ROC curves showed significant differences between ΔNT-proBNP and NT-proBNP at rest ($p = 0.006$), as well as between ΔNT-proBNP and NT-proBNP exe ($p = 0.011$). Similar results were not observed in the analysis of the ROC curves for TRPG ≥ 50 mmHg (Figs. 1, 2).

Discussion

Secondary IMR considerably worsens the prognosis of patients after acute MI, both in the short- and long-term follow-up [1, 5]. It is difficult to elaborate on uniform treatment standards in this group of patients because of the complex mechanism and dynamic nature of IMR. In many patients, significant changes in IMR severity during exercise can be observed independent of the degree of IMR at rest [1–3]. Surgical correction should be considered in patients with severe secondary IMR undergoing CABG, but optimal management of moderate IMR in patients qualified for CABG remains controversial [17–18, 28, 29].

When the complex and dynamic nature of IMR is taken into consideration, it seems that a more precise qualification of a patient to a proper surgical procedure should be broadened by the evaluation of the IMR variability in the exercise test as well as myocardial viability during DSE. The most important element of the analysis was the assessment of the relationships of the NT-proBNP levels, LV function, IMR severity, and maximal TRPG changes at rest and during exercise, observed through echocardiography.

It was hypothesized that the NT-proBNP level with exercise could be a reliable parameter in predicting a significant increase in IMR severity and pulmonary systolic artery pressure and may help in the identification of high-risk patients with moderate IMR qualified for surgical revascularization. The presumption was that this would help in identifying subgroups of patients who could benefit from better qualification to different surgical strategies (CABG alone or CABG with mitral repair).

In the present study, observations revealed a significant correlation of NT-proBNP levels at rest and at peak exercise with LV volumes and function. Yusoff et al. [11] reported statistically significant associations between the plasma level of N-terminal-BNP and LV end systolic volumes in patients with severe non-ischemic mitral regurgitation. Detaint et al. [30] found LV end-systolic volume index as the major determinant of the plasma level of BNP. Herein, it was shown that in patients with moderate IMR, an absolute increase in the NT-proBNP level at peak exercise was significantly correlated with changes in IMR severity and maximal TRPG at peak exercise. It has been shown that BNP concentrations are strictly associated with hemodynamic status in patients with heart failure [31]. It was known that in some patients with moderate IMR at rest, an increase in mitral regurgitation severity and TRPG is associated with an increase in NT-proBNP levels during exercise. Natriuretic peptides are usually produced by ventricular and atrial myocytes in response to increases in LV stress, and by atrial myocytes in response to increased atrial wall stress [8, 9, 32]. In patients with IMR, the predominant pressure load in mitral regurgitation is on the left atrium; in some patients it is on the right ventricle if there is an increase in pulmonary pressure [10–11]. The strong association between an exercise-induced absolute increase in NT-proBNP levels and pulmonary artery pressure also raises the possibility of increased NT-proBNP secretion from the right ventricle. The present data supports those obtained by Kerr et al. [14], who demonstrated that in patients with moderate to severe or severe MR and preserved resting LV EF, an increase in BNP level is associated with pulmonary artery hypertension on exercise and left atrial enlargement. The results of the current study suggest that in the analyzed models, only ΔNT-proBNP and TA at rest as well as ΔNT-proBNP and CH value at rest were good predictors of an increase in TRPG of ≥ 50 mmHg and in EROA of ≥ 20 mm^2 at peak exercise, respectively. An absolute increase in the NT-proBNP level was a more important predictor of the analyzed endpoint than were the levels of NT-proBNP at rest and at peak exercise.

According to available research, this is the first prospective study to investigate the relation between changes in NT-proBNP with exercise and IMR severity, as well as the pulmonary pressure at rest and at peak exercise in patients with moderate IMR qualified for CABG. At this time combined surgery is more likely to be considered if myocardial viability as well as exercise-induced symptoms and increase in IMR severity are present.

Based on the present data, it can be speculated that integration of the assessment of NT-proBNP at rest and at exercise might improve patient selection for valve surgery

Limitations of the study

A limitation of this study is that it does not include follow-up for clinical outcome or reassessment of NT-proBNP level after surgery.

The study was a part of a grant from the Ministry of Science and Higher Education and not every routine echo parameter was analyzed.

Although the relationships between NT-proBNP and both pulmonary pressures and IMR severity are statistically significant, the predictive value of NT-proBNP for individual pa-

tients requires further study using a larger cohort. Therefore, larger prospective studies should be conducted and the use of NT-proBNP in the diagnostic workup of patients with moderate IMR should be considered.

The present study used EROA and MRvol as reference parameters to estimate the degree of mitral regurgitation. Unfortunately, the regurgitant orifice is often non-spherical shaped in ischemic mitral regurgitation. In such cases, using two-dimensional PISA method may result in underestimation of IMR. Moreover, when IMR is not holosystolic, the degree of IMR may be overestimated [33]. However, EROA and MRvol are the most repeatable parameters of mitral regurgitation and using of three-dimensional echocardiography is very difficult in exercise echocardiography. Moreover, previous studies suggest that absolute measurements of EROA and MRvol provide the strongest predictors of outcome.

Conclusions

The level of absolute ΔNT-proBNP during exercise has been found to be the most important parameter in predicting significant changes in IMR severity and pulmonary pressure following exercise. Thus, data herein suggests that NT-proBNP measurement during exercise might be of diagnostic value with therapeutic implications. This hypothesis must be confirmed in larger multicenter studies.

Funding

The study was supported by a grant from the Ministry of Science and Higher Education (No. 2 P 05B 080 29).

Conflict of interest: None declared

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VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 6, 936–947
DOI: 10.5603/CJ.a2022.0091

ISSN 1897–5593
eISSN 1898–018X

Impact of heart failure on the clinical profile and outcomes in patients with atrial fibrillation treated with rivaroxaban. Data from the EMIR study

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Abstract

Background: *The aim of this study was to analyze the impact of the presence of heart failure (HF) on the clinical profile and outcomes in patients with atrial fibrillation (AF) anticoagulated with rivaroxaban.*

Methods: *Observational and non-interventional study that included AF adults recruited from 79 Spanish centers, anticoagulated with rivaroxaban ≥ 6 months before inclusion. Data were analyzed according to baseline HF status.*

Results: *Out of 1,433 patients, 326 (22.7%) had HF at baseline. Compared to patients without HF, HF patients were older (75.3 ± 9.9 vs. 73.8 ± 9.6 years; p = 0.01), had more diabetes (36.5% vs. 24.3%; p < 0.01), coronary artery disease (28.2% vs. 12.9%; p < 0.01), renal insufficiency (31.7% vs. 22.6%;*

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Received: 20.05.2022 Accepted: 4.09.2022 Early publication date: 4.10.2022

p = 0.01), higher CHA_2DS_2-VASc (4.5 ± 1.6 vs. 3.2 ± 1.4; p < 0.01) and HAS-BLED (1.8 ± 1.1 vs. 1.5 ± 1.0; p < 0.01). After a median follow-up of 2.5 years, among HF patients, annual rates of stroke/ /systemic embolism/transient ischemic attack, major adverse cardiovascular events (MACE) (non-fatal myocardial infarction, revascularization and cardiovascular death), cardiovascular death, and major bleeding were 1.2%, 3.0%, 2.0%, and 1.4%, respectively. Compared to those patients without HF, HF patients had greater annual rates of MACE (3.0% vs. 0.5%; p < 0.01) and cardiovascular death (2.0% vs. 0.2%; p < 0.01), without significant differences regarding other outcomes, including thromboembolic or bleeding events. Previous HF was an independent predictor of MACE (odds ratio 3.4; 95% confidence interval 1.6–7.3; p = 0.002) but not for thromboembolic events or major bleeding.

Conclusions: *Among AF patients anticoagulated with rivaroxaban, HF patients had a worse clinical profile and a higher MACE risk and cardiovascular mortality. HF was independently associated with the development of MACE, but not with thromboembolic events or major bleeding.* (Cardiol J 2022; 29, 6: 936–947)

Key words: atrial fibrillation, bleeding, EMIR, heart failure, MACE, rivaroxaban, stroke

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in adults worldwide, and it is expected to increase, mainly due to the extended longevity in the overall population as well as the increasing burden of other comorbidities such as hypertension, diabetes, or heart failure (HF) [1–3]. Despite anticoagulation markedly decreasing the risk of stroke, patients remain at risk of cardiovascular disease, including coronary artery disease, HF and cardiovascular death [4, 5].

Heart failure and AF are two common conditions that frequently coexist. In fact, the presence of one entity may precipitate/exacerbate the other [5–7]. Remarkably, the increased risk of AF occurs in both, HF with reduced left ventricular ejection fraction (LVEF) (HFrEF) and HF with preserved LVEF (HFpEF) [8]. This is not surprising, as AF and HF share common risk factors and comorbidities. In addition, dilatation of left atrium, left atrial and ventricular fibrosis, chronic inflammation, neurohormonal hyperactivation, and electrophysiologic remodeling also play a relevant role [9, 10]. The concomitance of both conditions translates into higher morbidity and mortality rates, including a greater risk of thromboembolic events, and consequently, anticoagulation is recommended [6, 11–13]. Although a number of studies have analyzed the impact of HF on patients with AF taking vitamin K antagonists, the information currently available among patients treated with direct oral anticoagulants, particularly in clinical practice remains scarce [14–18].

In ROCKET-AF, rivaroxaban was noninferior to warfarin for the prevention of stroke and systemic embolic events and significantly reduced intracranial hemorrhage in patients with AF at high thromboembolic risk [19]. In a specific analysis of the ROCKET-AF trial, the relative efficacy and safety of rivaroxaban versus warfarin was independent of HF status [20]. However, data about the role of rivaroxaban among patients with HF and AF in clinical practice are warranted [21].

The EMIR (Estudio observacional para la identificación de los factores de riesgo asociados a eventos cardiovasculares mayores en pacientes con fibrilación auricular no valvular tratados con un anticoagulante oral directo [Rivaroxaban] ["Observational study to identify risk factors associated with major cardiovascular events in patients with nonvalvular atrial fibrillation treated with a direct oral anticoagulant [rivaroxaban]") study [22, 23] was aimed to evaluate the performance of the cardiovascular risk 2MACE score in AF patients treated with rivaroxaban. In this study, the impact of the presence of HF at baseline on the clinical profile and outcomes in AF patients anticoagulated with rivaroxaban was analyzed.

Methods

The design and methods of the EMIR study have been extensively described in previous publications [22, 23]. Briefly, EMIR was a non-interventional and observational study that included patients 18 years or older, with an established diagnosis of AF (either paroxysmal, persistent or permanent), anticoagulated with rivaroxaban according to clinical practice ≥ 6 months before being enrolled and they provided written informed consent. Patients were recruited from 79 Spanish

centers (hospitals and private clinics). By contrast, patients with prosthetic heart valves, any severe valvopathy, severe cognitive impairment, chronic infections or systemic autoimmune diseases, active cancer or severe liver insufficiency were excluded from the study. The study was approved by each participating Institutional Review Board.

Patients were followed-up during 2.5 years with 4 visits (baseline, 12 months, 24 months, and study end) that should coincide with any of the patients' routine visits for HF management. No additional visits, laboratory tests, other diagnostic tests or treatments were specifically performed or prescribed for being included in the EMIR study. All data were recorded using an electronic case report form specifically created for the EMIR study.

At baseline, biodemographic data (age, sex, permanent AF, body mass index), risk stratification (CHA_2DS_2-VASc, HAS-BLED, and 2MACE score), cardiovascular risk factors (hypertension, diabetes), vascular disease (previous coronary artery disease, prior cerebrovascular disease, peripheral artery disease) and renal insufficiency were recorded. Data were collected from the clinical history of the patients and during the interview with the patient during the patients' routine visit. The presence of HF was considered when it was reflected in the clinical history of the patient. Data were analyzed according to the presence of previous HF and the HF subtypes. HFrEF was defined as HF with a LVEF < 40%, HF with mildly reduced LVEF (HFmrEF) as HF with LVEF 40 – < 50% and HFpEF as HF with LVEF ≥ 50%. Renal insufficiency was defined as an estimated glomerular filtration rate < 60 mL/min/1.73 m^2 by the MDRD-4 formula.

Events (major adverse cardiovascular events [MACE], thromboembolic events, myocardial infarction [MI], revascularization, cardiovascular death, death from any cause and major bleeding) during the study were evaluated. MACE events were defined as a combination of non-fatal MI, revascularization and cardiovascular death (death for coronary events, progressive HF death and sudden cardiac death). Thromboembolic events included stroke, systemic embolism and transient ischemic attack. Major bleedings were defined following the International Society of Thrombosis and Hemostasis definition [24]. The information source was in all cases the medical record and the patient. The investigator collected the study data from medical records or from personal interviews performed during the study follow-up. Before the present study started at the sites, all investigators were sufficiently trained on the background and objectives of the study. All outcome variables and covariates were recorded in a standardized electronic case report form. Medical review of the data was performed according to the medical review plan. A scientific committee independently evaluated and classified the events. Events were analyzed according to HF status and the HF subtypes. In addition, predictors of MACE, ischemic stroke and major bleeding in the EMIR population were analyzed.

Statement of ethics

This study protocol was reviewed and approved firstly by CAEIG (Comité Autonómico de Etica de Galicia) on July 14th, 2016, approval number 2016/348.

Patients were recruited from 79 Spanish centers (hospitals and private clinics). The study was approved by each participating Institutional Review Board.

Patients provided written informed consent.

Statistical methods

Qualitative variables were presented as absolute and relative frequencies and quantitative variables were described with measures of central tendency (mean and median) and dispersion (standard deviation and interquartile range). Qualitative variables were compared using the χ^2 test or the Fisher exact test, as required. When 2 means were compared, the t test or the Mann-Whitney test was used, when appropriate and 3 means (HF subtypes) by the Kruskal-Wallis test. Annual event rates were calculated. To assess predictors of MACE, thromboembolic events and major bleeding (dependent variables), multivariate analyzes were performed. The multivariate models began to be constructed by introducing those factors with a significance of $p < 0.15$ in the bivariates by the automatic variable selection method by steps forward and backward. Only the significant factors ($p < 0.05$) were finally considered to build the model. Odd ratios (OR) along with the 95% confidence interval (CI) were calculated. The following independent variables were considered: age (continuous variable), sex (female vs. male), body mass index (continuous variable), previous bleeding, diabetes, permanent AF, ischemic heart disease, coronary revascularization, antiplatelet agents, previous cerebrovascular disease, dependence level (dependent vs. autonomous), hypertension, hyperlipidemia, smoking, pulmonary disease, renal insufficiency, liver dysfunction, cancer, peripheral

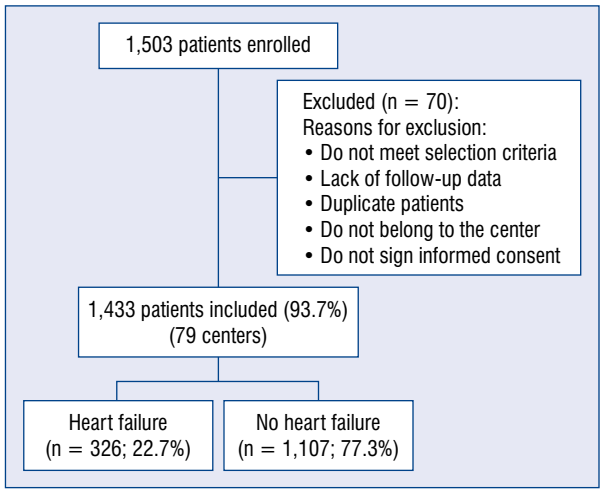

Figure 1. Flow chart of the study population.

artery disease, alcohol use, non-severe dementia, HF, CHA_2DS_2-VASc (continuous variable), HAS-BLED (continuous variable) and 2MACE ≥ 3. A level of statistical significance of 0.05 was applied in all the statistical tests. The data were analyzed using the statistical package SPSS (v18.0 or superior).

Results

A total of 1,503 patients were initially enrolled. After the exclusion of 70 patients, 1,433 (93.7%) patients from 79 Spanish centers, were included for the final analysis, of whom 326 (22.7%) had HF at baseline (Fig. 1).

The baseline clinical characteristics of the overall study population and according to HF status are presented in Table 1A. Overall, mean age was 74.2 ± 9.7 years, 55.5% of patients were men, 37.5% had permanent AF, mean CHA_2DS_2-VASc score was 3.5 ± 1.5, mean HAS-BLED was 1.6 ± 1.0 and 26.9% had a 2MACE score ≥ 3. In addition, 79.3% of patients had hypertension, 27.1% diabetes, 28.3% vascular disease, 24.7% renal insufficiency (defined by MDRD-4 < 60 mL/min/1.73 m^2), 16.4% ischemic heart disease and 12.5% prior cerebrovascular disease.

Among patients with HF (n = 326), 94 had HFrEF, 59 HFmrEF and 173 HFpEF. In patients with HF, mean LVEF was 48.0 ± 14.3%. Baseline clinical characteristics were analyzed according to HF status (Table 1A). Compared to patients without HF, patients with HF were older (75.3 ± 9.9 vs. 73.8 ± 9.6 years; p = 0.01), had more diabetes (36.5% vs. 24.3%; p < 0.01), permanent AF (50.9% vs. 33.3%; p < 0.01), previous coronary artery disease (28.2% vs. 12.9%; p < 0.01), renal insufficiency (MDRD-4: 31.7% vs. 22.6%; p = 0.001), as well as higher CHA_2DS_2-VASc score (4.5 ± 1.6 vs. 3.2 ± 1.4; p < 0.01), HAS-BLED score (1.8 ± ± 1.1 vs. 1.5 ± 1.0; p < 0.01) and more patients had a 2MACE score ≥ 3 (46.0% vs. 21.2%; p < 0.01). With regard to the baseline clinical characteristics according to HF subtype, patients with HFpEF were older, more commonly women, had a higher CHA_2DS_2-VASc score and more hypertension. By contrast, patients with HFrEF were more commonly men, had a higher 2MACE score ≥ 3 and more previous MI (Table 1B).

The mean follow-up was 2.2 ± 0.6 years (median 2.5 years, interquartile range 2.2–2.6 years). The annual rates of relevant events were calculated over 1,425 patients (323 out of 326 patients with HF and 1,102 out of 1,107 patients without HF) (Table 2A). Overall, 87 (6.1%) patients died during the study period, of whom 20 (1.4%) had a cardiovascular origin, where 13 (0.9%) were due to progressive chronic HF. As a result, 70.0% of cardiovascular deaths were caused by progressive HF. Among patients with baseline HF, annual rates of (stroke + systemic embolism + transient ischemic attack), MACE, cardiovascular death, death from any cause and major bleeding were 1.2%, 3.0%, 2.0%, 5.5% and 1.4%, respectively. Compared to those patients without HF at baseline, those patients with HF had greater annual rates of MACE (3.0% vs. 0.5%; p < 0.01), cardiovascular death (2.0% vs. 0.2%; p < 0.01) and death from any cause (5.5% vs. 2.0%; p < 0.01), without significant differences regarding other outcomes, including thromboembolic or bleeding events. With regard to events during the follow-up according to HF subtype, patients with HFpEF had more thromboembolic events and patients with HFrEF more MACE, MI and cardiovascular death (Table 2B).

A multivariate logistic regression analysis was performed to study the potential predictors of MACE events, thromboembolic events and major bleeding (Table 3). The presence of ischemic heart disease, renal insufficiency and HF were independent predictive factors associated to MACE in the global population. Type of AF did not have an impact on MACE risk (p = 0.662). On the other hand, the use of antiplatelet agents, non-severe dementia and CHA_2DS_2-VASc score were independently associated with the development of thromboembolic events and a score 2MACE ≥ 3, dependency and HAS-BLED score with major bleeding. The main results of the study are presented in Figure 2.

Table 1A. Clinical characteristics of the study population at baseline according to heart failure (HF) status.

	Total population (n = 1,433; 100%)	HF population (n = 326; 22.7%)	No HF population (n = 1,107;77.3%)	P
Biodemographic data				
Age [years]	74.2 ± 9.7	75.3 ± 9.9	73.8 ± 9.6	0.01
≥ 75 years	691 (48.2%)	173 (53.1%)	518 (46.8%)	0.05
Sex (men)	795 (55.5%)	193 (59.2%)	602 (54.4%)	0.12
Permanent atrial fibrillation	535 (37.5%)	166 (50.9%)	369 (33.3%)	< 0.01
Body mass index [kg/m^2]	29.1 ± 4.9	29.8 ± 5.3	28.9 ± 4.8	0.03
Risk stratification				
CHA_2DS_2-VASc score	3.5 ± 1.5	4.5 ± 1.6	3.2 ± 1.4	< 0.01
2MACE score ≥ 3	385 (26.9%)	150 (46.0%)	235 (21.2%)	< 0.01
HAS-BLED score	1.6 ± 1.0	1.8 ± 1.1	1.5 ± 1.0	< 0.01
Cardiovascular risk factors				
Hypertension	1,137 (79.3%)	261 (80.1%)	876 (79.1%)	0.72
Diabetes	388 (27.1%)	119 (36.5%)	269 (24.3%)	< 0.01
Vascular disease				
Vascular disease	406 (28.3%)	127 (39.0%)	279 (25.2%)	< 0.01
Previous coronary disease	235 (16.4%)	92 (28.2%)	143 (12.9%)	< 0.01
Prior cerebrovascular disease	179 (12.5%)	42 (12.9%)	137(12.4%)	0.81
Peripheral artery disease and/or aortic plaque	96 (6.7%)	33 (10.1%)	63 (5.7%)	0.005
Peripheral artery disease	58 (4.0%)	22 (6.7%)	36 (3.3%)	0.005
Other conditions/comorbidities				
Renal insufficiency (MDRD-4: < 60 mL/min/1.73 m^2)	350 (24.7%)	103 (31.7%)	247 (22.6%)	0.01
Renal insufficiency (Cockcroft-Gault: < 60 mL/min/1.73 m^2)	498 (35.1%)	133 (40.8%)	365 (33.0%)	0.01

Discussion

The present study showed that in a wide sample of real-life patients with AF anticoagulated with rivaroxaban compared to those patients without HF at baseline, individuals with previous HF have a worse clinical profile and a higher risk of MACE (cardiac mortality, coronary revascularization, non-fatal MI) and cardiovascular mortality. In addition, the history of HF is independently associated with the development of MACE, but not with stroke or major bleeding. Despite that, rates of MACE and death remained low in HF patients, indicating that anticoagulation with rivaroxaban may be a good choice in this population. This information is relevant, as although previous studies have analyzed the impact of HF on outcomes in anticoagulated AF patients, very scarce information is available in those patients taken rivaroxaban [21].

In the EMIR study, nearly 23% of AF patients presented with HF at baseline. This is in line with previous studies performed in Spain that have shown that the concomitance of both conditions is very common in clinical practice. Thus, in the PAULA study, that included AF patients treated in a primary care setting and anticoagulated with vitamin K antagonists, approximately 24% of patients had HF [25]. More recently, in the FANTASIIA study that included AF patients in a specialized cardiology setting and anticoagulated with direct oral anticoagulants or vitamin K antagonists, nearly 30% of patients also had HF [26]. In the international GLORIA-AF registry, in which AF patients anticoagulated with a direct oral anticoagulant were enrolled, 24% of patients had HF at baseline [27]. Conversely, different studies have shown that approximately one third of patients with HF also have AF [28, 29]. As each entity enhances the development of the other one [5, 6], an active search should be promoted to rule out the concomitance of both conditions [1].

In the current study, more patients had HFpEF than HFrEF or HFmrEF. Although some authors

Table 1B. Clinical characteristics of the study population at baseline according to heart failure (HF) subtype.

	HFpEF	HFmrEF	HFrEF	P
Biodemographic data				
N	173	59	94	
Proportion in the overall population	12.1%	4.1%	6.6%	–
Proportion in the HF population	53.1%	18.1%	28.8%	
Age [years]	77.5 ± 9.3	73.3 ± 9.8	72.6 ± 10.2	< 0.001
≥ 75 years	111 (64.2%)	23 (39.0%)	39 (41.5%)	< 0.001
Sex (men)	79 (45.7%)	42 (71.2%)	72 (76.6%)	< 0.001
Permanent atrial fibrillation	79 (45.7%)	30 (50.8%)	51 (54.3%)	0.39
Body mass index [kg/m^2]	30.6 ± 5.5	29.0 ± 5.3	28.8 ± 4.7	0.016
Risk stratification				
CHA_2DS_2-VASc score	4.9 ± 1.4	4.0 ± 1.5	4.2 ± 1.8	< 0.001
2MACE score ≥ 3	71 (41.0%)	21 (35.6%)	58 (61.7%)	0.001
HAS-BLED score	1.9±1.0	1.7±1.1	1.6±1.2	0.15
Cardiovascular risk factors				
Arterial hypertension	149 (86.1%)	45 (76.3%)	67 (71.3%)	0.011
Diabetes	65 (37.6%)	21 (35.6%)	33 (35.1%)	0.91
Vascular disease				
Vascular disease	59 (34.1%)	24 (40.7%)	44 (46.8%)	0.12
Previous coronary disease	39 (22.5%)	20 (33.9%)	33 (35.1%)	0.053
Previous myocardial infarction	12 (6.9%)	10 (16.9%)	25 (26.6%)	< 0.001
Previous cerebrovascular disease	23 (13.3%)	5 (8.5%)	14 (14.9%)	0.50
Peripheral artery disease and/or aortic plaque	17 (9.8%)	8 (13.6%)	8 (8.5%)	0.59
Peripheral artery disease	9 (5.2%)	7 (11.9%)	6 (6.4%)	0.21
Other conditions/comorbidities				
Renal insufficiency (MDRD-4: < 60 mL/min/1.73 m^2)	51 (29.5%)	19 (32.2%)	33 (35.5%)	0.60
Renal insufficiency (Cockcroft-Gault: < 60 mL/min/1.73 m^2)	70 (40.5%)	24 (40.7%)	39 (41.9%)	0.97

HFmrEF — heart failure with mildly reduced ejection fraction; HFpEF — heart failure with preserved ejection fraction; HFrEF — heart failure with reduced ejection fraction

have not shown significant differences in the strength of an association between AF and the type of HF [8], other authors have reported that among HF patients, AF is progressively more common with increasing LVEF [28, 30, 31]. Despite previous studies showing that HFpEF accounts for at least half of the cases of HF, it is very likely that due to the ageing of the population, this proportion will increase in the following years, as well as the number of patients with AF and HF concomitantly [32, 33]. Remarkably, the present study showed that there were relevant differences in the clinical profile of patients according to HF subtype, particularly related with age, sex and some comorbidities. These differences are in line with previous studies of HF population [34, 35].

Compared to patients without HF, patients with HF had a worse clinical profile, with more risk factors, and comorbidities, as well as a greater thromboembolic and bleeding risk. This high-risk profile in patients with HF has also been observed in previous studies [29]. As a result, to reduce the disease burden in this population, all patients with HF and AF should receive in addition to anticoagulation, guideline-adherent HF therapy [36].

Remarkably, different studies have shown that the superiority of direct oral anticoagulants over vitamin K antagonists remain in patients

Table 2A. Events during the follow-up according to heart failure (HF) status.

	Total	HF (n = 326)	No HF (n = 1,107)	P
Stroke + SE + TIA:				
Number patients (%)	23 (1.6)	8 (2.5)	15 (1.4)	0.17
Annual rate events (%)*	0.7	1.2	0.6	0.22
Major bleeding:				
Number patients (%)	29 (2.0)	8 (2.5)	21 (1.9)	0.53
Annual rate events (%)*	1.0	1.4	0.9	0.33
MACE:				
Number patients (%)	30 (2.1)	17 (5.2)	13 (1.2)	< 0.01
Annual rate events (%)*	1.1	3.0	0.5	< 0.01
Myocardial infarction:				
Number patients (%)	5 (0.3)	3 (0.9)	2 (0.2)	0.08
Annual rate events (%)*	0.2	0.4	0.1	0.15
Revascularization:				
Number patients (%)	9 (0.6)	4 (1.2)	5 (0.5)	0.13
Annual rate events (%)*	0.3	0.6	0.2	0.22
Cardiovascular death:				
Number patients (%)	20 (1.4)	13 (4.0)	7 (0.6)	< 0.01
Annual rate events (%)*	0.6	2.0	0.2	< 0.01
Death from any cause:				
Number patients (%)	87 (6.1)	38 (11.7)	49 (4.4)	< 0.01
Annual rate events (%)*	2.7	5.5	2.0	< 0.01

*Event/100 patients/year; MACE — major adverse cardiovascular event; SE — systemic embolism; TIA — transient ischemic attack

with HF, in both, clinical trials and real-life studies [16–18]. In addition, it is more difficult to attain an adequate time in therapeutic range among patients taking vitamin K antagonists in patients with HF, leading to a lower protection [15]. In the current study, all patients were taking rivaroxaban. After a median follow-up of 2.5 years, among patients with previous HF, annual rates of thromboembolic events, cardiovascular death, death from any cause and major bleeding were 1.2%, 2.0%, 5.5%, and 1.4%, respectively. In the rivaroxaban arm of the ROCKET-AF trial, these numbers were 1.9%, 3.4%, 5.1%, and 14.2% for major or nonmajor clinically relevant bleeding, respectively [20]. A retrospective study performed in the United States that analyzed patients with HF and AF taking rivaroxaban between 2011 and 2016 showed that after a median follow-up of 1.4 years, rates of stroke or systemic embolism, ischemic stroke, major bleeding and intracranial hemorrhage were 1.0, 0.7, 3.9, and 0.3 events per 100 person-years, respectively [21]. As a result, in clinical practice, rates of outcomes in patients with HF and AF seem lower than those reported in the ROCKET-AF trial [20].

Although in non-anticoagulated patients the most devastating consequence related to AF is stroke and its associated complications (death and disability), anticoagulation changes mortality and outcome patterns in AF patients. Thus, in the anticoagulated AF population, most deaths are cardiac-related (cardiovascular death, MI and HF), and only a small proportion are associated with stroke and bleeding [37]. This has also been described in the AF population with HF, including those patients with HF enrolled in the ROCKET-AF trial [18, 20, 38]. Likewise, in the present study, compared to those patients without HF at baseline, those patients with HF had greater annual rates of MACE and cardiovascular death, but with similar rates of thromboembolic and bleeding events. In addition, the multivariate analyzes showed that previous HF was independently associated with the development of MACE, but not with thromboembolic events or major bleeding. Therefore, anticoagulation is not only important in AF patients with HF, but also choosing an oral anticoagulant that effectively reduces MACE events [1]. In this context, experimental and clinical studies have shown that

Table 2B. Events during the follow-up according to heart failure subtype.

	Type of heart failure			P
	HFpEF (n = 173) Annual rate of events (n = 171; accumulated time = 386.81 years)	HFmrEF (n = 59) Annual rate of events (n = 58; accumulated time = 128.29 years)	HFrEF (n = 94) Annual rate of events (n = 94; accumulated time = 179.80 years)	
Stroke + SE + TIA:				
Number patients (%)	8 (4.6)	0	0	0.036
Annual rate events (%)*	2.07	0	0	HFpEF vs. HFrEF: $p < 0.05$
Major bleeding:				
Number patients (%)	6 (3.5)	0	2 (2.1)	0.392
Annual rate events (%)*	1.81	0	1.67	No statistically significant difference
MACE:				< 0.001
Number patients (%)	2 (1.2)	1 (1.7)	14 (14.9)	HFpEF vs. HFrEF: $p < 0.001$
Annual rate events (%)*	0.78	0.78	9.45	HFmrEF vs. HFrEF: $p < 0.001$
Myocardial infarction:				
Number patients (%)	0	0	3 (3.2)	0.029
Annual rate events (%)*	0	0	1.67	HFpEF vs. HFrEF: $p < 0.05$
Revascularization:				
Number patients (%)	1 (0.6)	0	3 (3.2)	0.110
Annual rate events (%)*	0.26	0	1.67	No statistically significant difference
Cardiovascular death:				< 0.001
Number patients (%)	2 (1.2)	1 (1.7)	11 (11.7)	HFpEF vs. HFrEF: $p < 0.001$
Annual rate events (%)*	0.52	0.78	6.12	HFmrEF vs. HFrEF: $p < 0.05$
Death from any cause:				
Number patients (%)	14 (8.1)	6 (10.2)	18 (19.1)	0.025
Annual rate events (%)*	3.62	4.68	10.01	HFpEF vs. HFrEF: $p < 0.05$

*Event/100 patients/year; HFmrEF — heart failure with mildly reduced ejection fraction; HFpEF — heart failure with preserved ejection fraction; HFrEF — heart failure with reduced ejection fraction; MACE — major adverse cardiovascular event; SE — systemic embolism; TIA — transient ischemic attack

Table 3. Predictors of MACE, ischemic stroke and major bleeding in the EMIR population.

Independent variables	Univariate analyzis			Multivariate analyzis		
	P	OR	95% CI	P	OR	95% CI
Dependent variable "MACE events"						
Antiplatelet agents	< 0.01	13.6	6.3–29.6			
Heart failure	**< 0.01**	**4.7**	**2.2–10.1**	**0.002**	**3.4**	**1.6–7.3**
Coronary revascularization	< 0.01	4.6	2.1–10.1			
Ischemic heart disease	< 0.01	4.6	2.2–9.8	0.002	3.4	1.6–7.3
2MACE ≥ 3	0.002	3.2	1.5–6.9			
Renal insufficiency	0.007	3.0	1.4–6.5	0.02	2.5	1.2–5.5
Peripheral artery disease	0.08	2.9	0.9–10.1			
Diabetes	0.15	1.8	0.8–3.8			
HAS-BLED (continuous variable)	0.02	1.5	1.1–2.1			
CHA_2DS_2-VASC (continuous variable)	0.05	1.3	1.0–1.6			
Sex (female vs. male)	0.02	0.3	0.1–0.8			
Dependent variable "Thromboembolic events"						
Antiplatelet agents	< 0.01	9.2	3.7–22.7	< 0.01	9.0	3.5–23.0
Non-severe dementia	0.002	7.7	2.2–27.5	0.02	5.5	1.3–22.7
2MACE ≥ 3	< 0.01	4.5	1.9–11.1			
Heart failure	**0.002**	**3.8**	**1.6–9.1**			
Previous bleeding	0.12	3.3	0.7–14.5			
Diabetes	0.01	3.0	1.3–7.2			
Previous stroke	0.03	2.8	1.1–7.4			
Coronary revascularization	0.04	2.8	1.1–7.3			
Ischemic heart disease	0.04	2.6	1.0–6.5			
CHA_2DS_2-VASc (continuous variable)	0.002	1.5	1.2–1.9	0.01	1.4	1.1–1.8
Age (continuous variable)	0.15	1.0	1.0–1.1			
Dependent variable "Major bleeding"						
Arterial hypertension	0.049	7.5	1.0–55.0			
Non-severe dementia	0.009	5.3	1.5–18.4			
Previous bleeding	0.003	5.2	1.7–15.6			
Patient autonomy (dependent vs. autonomous)	< 0.01	4.7	2.1–10.7	0.03	2.6	1.1–6.1
2MACE ≥ 3	< 0.01	4.6	2.2–9.9	0.02	2.6	1.1–6.1
Renal insufficiency	< 0.01	4.4	2.1–9.3			
Previous stroke	0.004	3.2	1.4–7.2			
Antiplatelet agents	0.03	3.0	1.1–8.0			
HAS-BLED (continuous variable)	< 0.01	2.2	1.6–3.0	0.01	1.9	1.3–2.7
Coronary revascularization	0.07	2.2	0.9–5.3			
Diabetes	0.08	1.9	0.9–4.1			
Hyperlipidemia	0.14	1.8	0.8–4.1			
CHA_2DS_2-VASc (continuous variable)	< 0.01	1.6	1.3–2.0			
Age (continuous variable)	< 0.01	1.1	1.0–1.1			

CI — confidence interval; MACE — major adverse cardiovascular event; OR — odds ratio

rivaroxaban decreases the progression of ischemic cardiomyopathy, as well as the risk of MI and cardiovascular death [39–42]. Of note, the use of antiplatelet agents was independently associated with the development of thromboembolic events. In the AFIRE trial, rivaroxaban monotherapy was

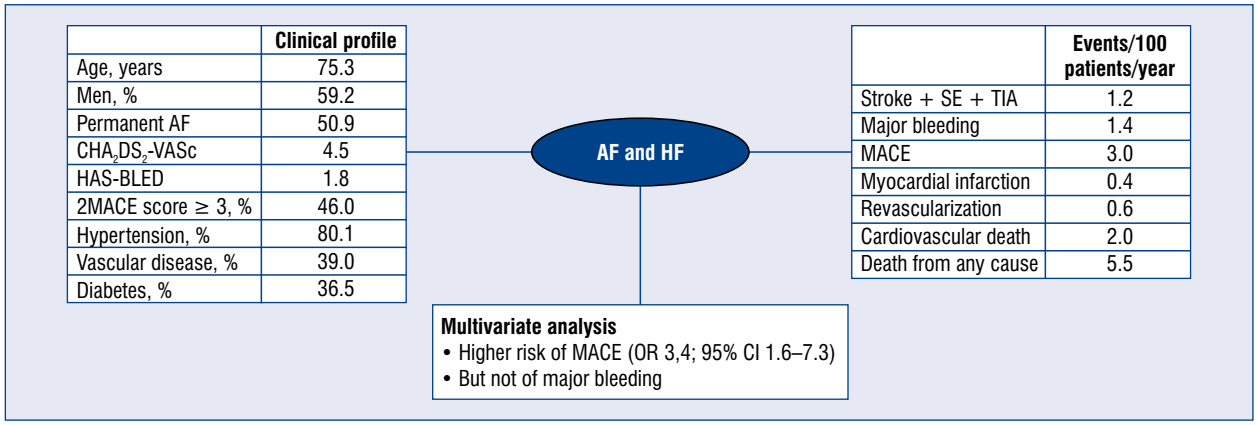

Figure 2. Graphical abstract; AF — atrial fibrillation; CI — confidence interval; HF — heart failure; MACE — major adverse cardiovascular events; OR — odds ratio; SE — systemic embolism; TIA — transient ischemic attack.

noninferior to a combination of rivaroxaban with an antiplatelet agent for thromboembolic events or death, and superior for major bleeding in AF patients with stable coronary artery disease, and this occurred irrespective of their risk for stroke and bleeding [43]. Therefore, all these data indicate that rivaroxaban in monotherapy should be considered in patients with HF and AF, not only to reduce the risk of thromboembolic events, but also the risk of MACE and cardiovascular mortality, leading to a comprehensive management of this population. On the other hand, despite the AMADEUS study, which showed that the risk of cardiovascular death, stroke, or systemic embolism increased among patients with permanent AF (vs. nonpermanent AF), regardless the presence of HF [44], in the present study the type of AF was not associated with an increased risk of outcomes. However, it should be noted that idraparinux and vitamin K antagonists were the anticoagulants used in AMADEUS, compared with rivaroxaban in the study herein. On the other hand, the current study showed that the risk of events varied according to HF subtype (thromboembolic events in HFpEF and MACE, MI and cardiovascular death in HFrEF). Other studies have also shown differences in outcomes according to HF subtype [45]. As a result, these particularities should be taken into account to provide a comprehensive approach in the management of patients with AF and HF.

Limitations of the study

As this was an observational study, no control group was available, and the presence of some confounding factors could not be excluded. However, the high number of patients included, as well as that the recruitment was performed consecutively after office consultation, may reduce possible selection bias. On the other hand, it should be considered that the patients were recruited after at least 6 months under rivaroxaban treatment. Therefore, the results of this study can only be extended to a similar population.

Conclusions

Nearly 1 out of 4 patients with AF anticoagulated with rivaroxaban in clinical practice have HF concomitantly. After a median follow-up of 2.5 years, annual rates of thromboembolic events, MACE, cardiovascular death, and major bleeding in HF population are 1.2%, 3.0%, 2.0%, and 1.4%, respectively. Compared to patients without HF, HF patients are older, have a greater baseline risk profile, and a higher risk of developing MACE and cardiovascular mortality, but not thromboembolic or bleeding events. The management of patients with HF and AF requires a comprehensive approach, with the aim to reduce not only the stroke risk, but also cardiovascular-related complications. In this context, rivaroxaban should be considered as a first-line therapy in the treatment of patients with HF and AF in clinical practice.

Acknowledgments

Writing and editorial assistance was provided by Content Ed Net (Madrid, Spain) with funding from Bayer Hispania.

Funding

The EMIR Study was funded by Bayer Hispania SL.

Conflict of interest: Manuel Anguita Sánchez has received funding for consulting and conference services from Bayer, Daiichi-Sankyo and Pfizer; Francisco Marín has received consultancy/lecturing fees from Bayer, Boehringer Ingelheim, Pfizer, Bristol Myers Squibb, Daiichi Sankyo and AFNET; Jaime Masjuan has received consultancy/lecturing fees from Bayer, Boehringer Ingelheim, Pfizer, Bristol Myers Squibb y Daiichi Sankyo; Juan Cosín-Sales has received consultancy/lecture fees from Bayer, BMS/Pfizer, Boehringer Ingelheim, and Daiichi Sankyo; José Manuel Vázquez Rodríguez has received lecturing fees from Bayer, Pfizer and Daiichi Sankyo; Vivencio Barrios has received consultancy/ /lecture fees from Bayer, BMS/Pfizer, Boehringer Ingelheim, and Daiichi Sankyo; Gonzalo Barón--Esquivias has received honoraria as advisor from Bayer, Daiichi-Sankyo, BMS-Pfizer and Rovi; and honoraria as speaker from Boehringer-Ingelheim, Bayer, Daiichi-Sankyo, BMS and Pfizer; Iñaki Lekuona has received honoraria for presentations from Bayer, Boehringer Ingelheim, Daiichi Sankyo, and Pfizer-BMS; Alejandro I. Pérez-Cabeza has received personal fees for educational activities or participation in boards from Daiichi Sankyo, Bayer, Boehringer Ingelheim and Bristol Myers Squibb; Román Freixa-Pamias has received honoraria for presentations from Bayer, Boehringer Ingelheim, Daiichi Sankyo, and Pfizer-BMS; Francisco Javier Parra Jimenez has received financial compensation from Bayer for participating in the EMIR study; Mohamed Monzer Khanji Khatib has received financial compensation from Bayer for participating in the EMIR study; Carles Rafols Priu is an employee Bayer Hispania SL; Marcelo Sanmartín Fernández has received speaker and advisory fees from the following companies in the past 3 years: Bayer, Boehringer Ingelheim, BMS and Pfizer.

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VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 6, 948–953
DOI: 10.5603/CJ.a2020.0139

ISSN 1897–5593
eISSN 1898–018X

Flow-mediated skin fluorescence: A novel method for the estimation of sleep apnea risk in healthy persons and cardiac patients

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Abstract

Background: *A pilot study revealed a relationship between the results of flow mediated skin fluorescence (FMSF) and of ECG-Holter-based estimated apnea/hypopnea index (eAHI) in asymptomatic individuals. The aim of this study was to test whether the results of FMSF show a relationship with the eAHI in patients with coronary artery disease or aortic stenosis.*

Methods: *Twenty-one patients (12 coronary disease, 9 aortic stenosis) and 37 healthy volunteers were included. FMSF was assessed before, during and after the pressure occlusion of the brachial artery, using a prototype device allowing the quantification of skin fluorescence. The values of FMSF expressed as baseline (BASE), maximum (MAX), and minimum (MIN) were analyzed. The percentages of ischemic response (IR) and hyperemic response (HR) were calculated. The eAHI was assessed from night ECG-Holter recordings. Differences between the groups and the relationships between the parameters were analyzed statistically.*

Results: *Mean ± standard deviation of BASE, MAX, MIN and IR were not significantly different in both groups ($p > 0.05$). HR was significantly lower in cardiac patients (14.7 ± 7.5 vs. 11.8 ± 5.1; $p = 0.048$), whose eAHI was significantly higher (11.0 ± 7.4 vs. 36.3 ± 16.5; $p < 0.01$). Negative correlation for MAX and eAHI was found in volunteers and patients: $r = –0.38$, $p = 0.02$ and $r = –0.47$, $p = 0.03$, respectively. In volunteers, HR had a negative correlation with eAHI: $r = –0.34$, $p = 0.04$.*

Conclusions: *This pioneer study confirms that FMSF can be used to detect the negative correlation between MAX fluorescence and eAHI not only among healthy volunteers, but also among cardiac patients with coronary artery disease or aortic stenosis.* (Cardiol J 2022; 29, 6: 948–953)

Key words: autofluorescence, obstructive sleep apnea, screening

Introduction

Sleep disordered breathing has significant medical implications [1]. A reliable noninvasive method would be valuable for the screening of this condition in ambulatory patients. A pilot study with healthy volunteers revealed a promising potential for the assessment of flow mediated skin fluorescence (FMSF) in the selection of individuals with episodes of obstructive apnea during sleep [2]. FMSF is a method of assessing the redox balance in epithelial cells [3]. The question arises whether

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Received: 18.03.2020 Accepted: 13.10.2020 Early publication date: 26.10.2020

nocturnal episodes of hypoxia caused by short periods of cessation of breathing can affect mitochondrial metabolism of the most superficial and distal organ such as skin — not only in healthy individuals, but also in cardiac patients, in whom the prevalence of obstructive sleep apnea is alarmingly high. The source of fluorescence (light of frequency 340 nm) in this pilot study were the mitochondrial molecules of NADH — a reduced form of NAD^+ (nicotinamide adenine dinucleotide) — after absorption of light energy emitted by the device Angiotester (Angionica Ltd., Lodz, Poland) [4]. The changes of the mitochondrial concentration of NADH are a consequence of hypoxia [5].

The aim of this study was to assess the relationship between the FMSF parameters and the values of the estimated apnea/hypopnea index (eAHI) in a group of healthy volunteers and cardiac patients with aortic stenosis or coronary artery disease (CAD).

Methods

Thirty-seven healthy individuals were enrolled into the study. The inclusion criteria were:

— age 18–40 years;
— the absence of any treated or diagnosed chronic diseases;
— no antibiotics, pain relievers, or vaccinations during the prior 2 weeks;
— signing a written consent to participate in the study.

Twenty-one cardiac patients hospitalized at the Department of Cardiology at the Medical University of Lodz were included, using the following criteria:

— age > 40 years;
— diagnosis of CAD confirmed in coronary angiography showing stenoses > 70% or aortic stenosis with transaortic mean gradient ≥ 40 mmHg;
— completed treatment — surgical or transvascular;
— an obtained written consent for participation.

Patients with arrhythmia, after the implantation of devices for electrotherapy, with diagnosed sleep apnea syndrome or those reporting spontaneous symptoms suggesting sleep apnea were excluded.

All the participants signed a written consent before enrollment into the study. The protocol of the study was approved by the Local Ethics Committee at the Medical University of Lodz and was concordant with the Declaration of Helsinki.

Flow mediated skin fluorescence was measured on the forearm skin after 15-minute acclimatization in a temperature-controlled room (20 ± ± 1°C). First, the basic FMSF was measured for at least 2 minutes, followed by a measurement during a 100-second period of brachial artery occlusion and then again at least a 3-minute measurement was started. The flow of the blood in the left brachial artery was occluded by a cuff inflated around the arm up to 50 mmHg above systolic blood pressure. The following parameters were measured: baseline fluorescence (BASE), maximum fluorescence (MAX) observed during occlusion, minimum fluorescence (MIN) after cuff release, and the following parameters were calculated: ischemic response (IR) defined as percentage difference between MAX and BASE (an increase in fluorescence intensity during occlusion), and hyperemic response (HR) defined as percentage difference between BASE and MIN (a decrease in intensity after the cuff release). Sample protocols of measurements performed in a healthy volunteer and in a cardiac patient are shown in Figures 1 and 2, respectively.

Coronary catheterization was performed according to the standard protocol using the INNOVA 2000 angiography system (General Electric). Two-dimensional echocardiography was performed by means of the (ViVid 7 device, GE), with the probe emitting ultrawaves of 2.5–4 MHz frequency according to the guidelines of the Working Group on Echocardiography of the Polish Cardiac Society. All patients and volunteers underwent a 24-hour electrocardiogram (ECG) Holter monitoring (Pathfinder 700, DelMar Reynolds, Hertford, UK). A three-channel recorder Lifecard CF was used. It was followed by further analysis with the Pathfinder 700 software and evaluation of the eAHI with Lifescreen Apnea (Spacelabs Healthcare, Issaquah WA, USA). An apneic event triggers the autonomic nervous system activation, which results in a specific sinus heart rhythm modulation. Lifescreen Apnea is a screening tool which calculates the probability of apneic events on the basis of changes in the beat-to-beat intervals and the ECG-derived respiration signal. A detailed description of the method was given by de Chazal et al. [6].

A statistical analysis of mutual relationships between the eAHI and the parameters obtained from FMSF was performed using the Student t-test and correlation co-efficient with p value < 0.05 regarded as significant.

Results

In the group of healthy volunteers there were 5 (13.5%) cases of the eAHI above 15, whereas

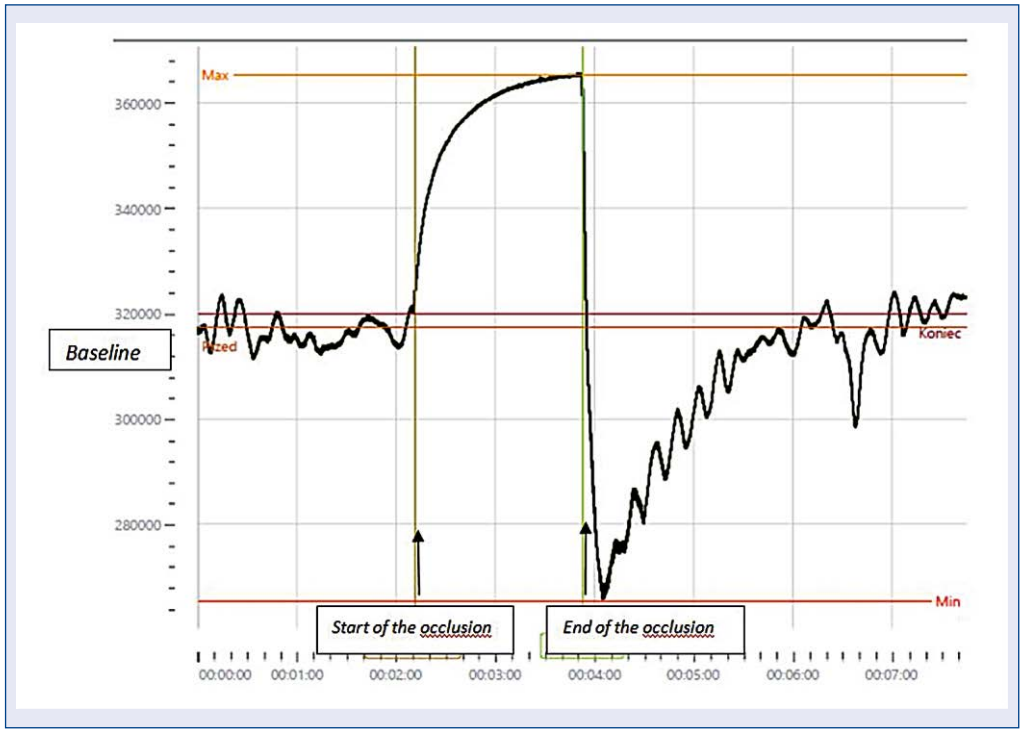

Figure 1. A sample protocol of measurement of flow mediated skin fluorescence in a healthy volunteer — baseline fluorescence (BASE) — 316200 arbitrary units, maximum fluorescence (MAX) — 364100, arbitrary units, minimum fluorescence (MIN) — 262400 arbitrary units, ischemic response — 15.1% and hyperemic response — 17.0%; Przed — the beginning; Koniec — the end.

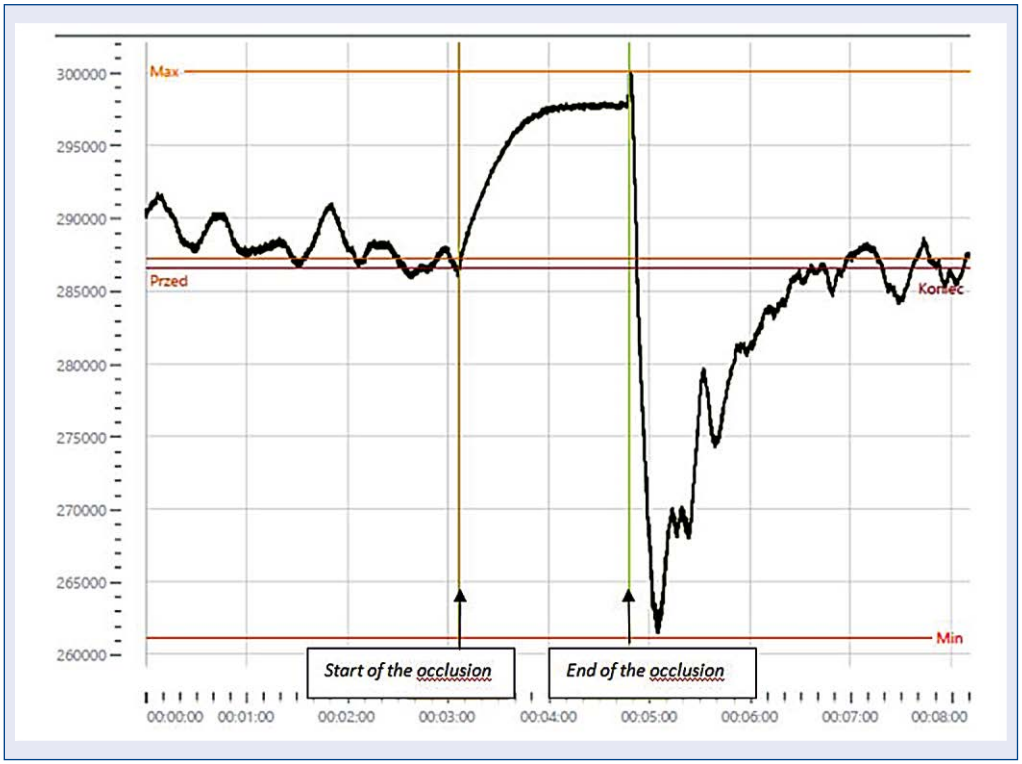

Figure 2. A sample protocol of measurement of flow mediated skin fluorescence in a cardiac patient — baseline fluorescence (BASE) — 286500 arbitrary units, maximum fluorescence (MAX) — 299400 arbitrary units, minimum fluorescence (MIN) — 261000 arbitrary units, ischemic response — 4.5% and hyperemic response — 8.9%; Przed — the beginning; Koniec — the end.

Table 1. The clinical characteristics of the studied groups.

Variable	Healthy volunteers (n = 37)	Cardiac patients (n = 21)	Significance (P)
Age [years]	32.9 ± 5.2	65.9 ± 8.8	< 0.001
Sex, female	12 [32.4]	7 [33.3]	1.0
Body mass index	26.13 ± 2.9	27.6 ± 4.1	0.065
Systolic blood pressure [mmHg]	125.62 ± 9.38	131.12 ± 16.04	0.002
Diastolic blood pressure [mmHg]	78.97 ± 6.72	80.57 ± 12.48	< 0.001
Fasting glucose [mg/dL]	89.56 ± 8.06	108.92 ± 32.5	< 0.001
LDL-cholesterol [mg/dL]	109.14 ± 31.8	99.1 ± 38.7	0.238
Hemoglobin concentration [g/L]	15.98 ± 1.17	13.71 ± 1.54	< 0.001
Estimated apnea/hypopnea index	11.0 ± 7.4	36.3 ± 16.5	< 0.001
Left ventricular ejection fraction [%]	62.29 ± 2.71	51.07 ± 8.21	< 0.001
Peak aortic jet velocity [m/s]	1.26 ± 0.11	2.34 ± 1.51	< 0.001

LDL — low-density lipoprotein

Table 2. Results of flow mediated skin fluorescence measurements.

Variable	Healthy volunteers (n = 37)	Cardiac patients (n = 21)	Significance (P)
Baseline fluorescence [$\times 10^3$ arbitrary units]	360.2 ± 122.9	384.2 ± 182.9	0.505
Maximal fluorescence [$\times 10^3$ arbitrary units]	394.3 ± 140.1	395.1 ± 206.1	0.986
Minimal florescence [$\times 10^3$ arbitrary units]	300.5 ± 103.4	336.3 ± 206.0	0.240
Ischemic response [%]	2.4 ± 9.8	0.15 ± 4.9	0.176
Hyperemic response [%]	14.7 ± 7.5	11.8 ± 5.1	0.048

among cardiac patients there were 18 (85.7%) such cases.

The comparison of characteristics of volunteers and cardiac patients is presented in Table 1. All the cardiac patients received beta-blockers, angiotensin-converting enzyme inhibitors and statins, 12 (57.1%) patients were on antidiabetic medication.

No significant differences were found between the values of basic, maximal, and minimal fluorescence, and in the IR between the cardiac patients and volunteers; however, HR was significantly higher in the volunteers — 14.7 ± 7.5 vs. 11.8 ± 5.1 (p = 0.048). The detailed data are presented in Table 2. Interestingly, despite similar average fluorescence values between the two investigated groups, significant negative correlation coefficients were found between the values of maximal fluorescence and the eAHI in both groups. Additionally, significant negative correlation was found for HR and the eAHI in healthy volunteers (Table 3).

Table 3. The correlations between flow mediated skin fluorescence and the estimated apnea/hypopnea index (eAHI).

Correlated variables	Healthy volunteers	Cardiac patients
Maximal fluorescence and eAHI	r = –0.38 p = 0.02	r = –0.47 p = 0.03
Hyperemic response and eAHI	r = –0.34 p = 0.04	r = –0.07 p = 0.75

Discussion

The main finding of the present study is that the severity of sleep apnea assessed by means of the eAHI derived from 24-hour Holter monitoring is correlated with noninvasive measurements of redox parameters obtained in vivo in a simple rapid test, i.e., FMSF. This was observed both in healthy volunteers and in cardiac patients.

This finding is especially practical in the context of very high prevalence of abnormal eAHI in cardiac patients, in the absence of self-reported sleepiness or the presence of risk factors for sleep-disordered breathing. This observation is concordant with the results of previous studies by Ben Ahmed et al. [7] and by Mehra et al. [8], and it underlines a strong need for reliable and easy tools for sleep apnea screening.

The reference method — polysomnography — is a costly procedure, time-consuming and less available, and therefore it cannot be used as a screening test. Therefore, Holter monitoring is often proposed for first-step diagnostics of sleep apnea. Recent publications confirm the reliability of a simpler diagnosis of obstructive respiratory disorders on the basis of 24-hour Holter monitoring by means of the Lifescreen Apnea software making use of eAHI in various groups of patients for screening purposes. This approach was used in our study and it was observed previously that the cut-off value of eAHI set at 17 was optimal for the differentiation between patients with or without sleep-related breathing disorders [9, 10]. The existing evidence confirms the repeatability of the results of Holter-based eAHI derived from two consecutive nights on the basis of 48-hour ECG monitoring [11]. The critical advantage of FMSF over 24-hour Holter monitoring as a screening tool for sleep apnea is the much shorter duration of the test, which takes only 25 minutes.

The application of FMSF for the detection of abnormal microvascular function in healthy controls and patients with stable CAD was already described by Hellmann et al. [12]. Those authors reported both the excellent reproducibility of FMSF examination performed day by day and a significantly lower IR and HR when cardiac patients were compared with healthy volunteers. The same relationship was found in the present groups, but the difference was significant only for HR. The next study of that team, published by Tarnawska et al. [13], emphasizes a significant inverse correlation of HR with the blood concentration of ADMA (asymmetric dimethyl arginine — endogenous competitive inhibitor of nitric oxide synthase), and of IR with the concentration of endothelin-1 — vasoconstrictor and mitogen produced in response to hypoxia and vascular wall stress [13]. Nevertheless, the problem of night periods of hypoxia due to sleep apnea was not investigated in that previous study and the current report seems to be the first in this field of investigations.

The potential impact of night periods of hypoxia on the status of mitochondria on the following morning was described by two independent teams — Lacedonia et al. [14] and Kim et al. [15] — who found that people with obstructive sleep apnea have a higher concentration of damaged mitochondrial DNA than people without this disease. Since mitochondria are the only organelle where NADH — the source of fluorescence — is present, and since they have limited DNA repair capacity, impaired mitochondrial function could explain the linkage between sleep apnea and the lower values of HR observed with FMSF in the individuals participating in the present study.

The lack of polysomnography to diagnose sleep apnea and the relatively small groups participating in the study should be regarded as the main limitation of this study. Further investigations of this phenomenon on a larger sample of participants and with the use of methods directly assessing sleep apnea should be performed.

Conclusions

This pioneer study confirmed in a relatively small study group that a noninvasive test — FMSF can be used to detect a negative correlation between maximum FMSF and the eAHI not only among healthy volunteers, but also among cardiac patients with CAD or aortic stenosis.

Funding

The study was performed within the framework of the project "Novel technique for assessing microvascular circulation: Flow-Mediated Skin Fluorescence. Constructing a prototype of the device and its clinical verification" and it was supported from European Funds — project no. POIR.01.01.01-00-0540/15. All authors received remuneration from this project.

Conflict of interest: None declared

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VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 6, 954–965
DOI: 10.5603/CJ.a2020.0185

ISSN 1897–5593
eISSN 1898–018X

Sex difference after acute myocardial infarction patients with a history of current smoking and long-term clinical outcomes: Results of KAMIR Registry

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Abstract

Background: *The contribution of sex as an independent risk factor for cardiovascular disease still remains controversial. The present study investigated the impact of sex on long-term clinical outcomes in Korean acute myocardial infarction (AMI) patients with a history of current smoking on admission after drug-eluting stents (DESs).*

Methods: *A total of 12,565 AMI patients (male: n = 11,767 vs. female: n = 798) were enrolled. Major adverse cardiac events (MACEs) comprising all-cause death, recurrent myocardial infarction (Re-MI), and any repeat revascularization were the primary outcomes that were compared between the two groups. Probable or definite stent thrombosis (ST) was the secondary outcome.*

Results: *After adjustment, the early (30 days) cumulative incidences of MACEs (adjusted hazard ratio [aHR]: 1.457; 95% confidence interval [CI]: 1.021–2.216; p = 0.035) and all-cause death (aHR: 1.699; 95% CI: 1.074–2.687; p = 0.023) were significantly higher in the female group than in the male group. At 2 years, the cumulative incidences of all-cause death (aHR: 1.561; 95% CI: 1.103–2.210; p = 0.012) and Re-MI (aHR: 1.800; 95% CI: 1.089–2.974; p = 0.022) were significantly higher in the female group than in the male group. However, the cumulative incidences of ST were similar between the two groups (aHR: 1.207; 95% CI: 0.583–2.497; p = 0.613).*

Conclusions: *The female group showed worse short-term and long-term clinical outcomes compared with the male group comprised of Korean AMI patients with a history of current smoking after successful DES implantation. However, further studies are required to confirm these results.* (Cardiol J 2022; 29, 6: 954–965)

Key words: myocardial infarction, sex, smoking

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Received: 25.03.2020 Accepted: 6.12.2020 Early publication date: 31.12.2020

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Introduction

As age increases, the incidence and mortality rates of cardiovascular disease (CVD) also increases. Moreover, other factors affecting the long-term prognosis of CVD are of utmost importance for public heath investigators and cardiologists. Previously, based on sex difference, a higher mortality rate of myocardial infarction (MI) was observed in women than in men [1, 2]. However, the contribution of sex as an independent risk factor for CVD still remains controversial. Proposed explanations for higher mortality rate among women are advanced age and increased incidence of diabetes mellitus (DM), chronic heart failure (HF), and hypertension prior to MI [3]. Cigarette smoking is an important correctable risk factor and a major causative factor of recurrent MI and death after percutaneous coronary intervention (PCI) [4]. According to a recent report, the estimated prevalence of cigarette smoking was not strongly associated with sex difference [5]. In 2012, the estimated prevalence rates of smokers were greater than 40% among men and lower than 5% in women [5]. Additionally, controversy exists whether sex difference is associated with smoking and adverse cardiovascular clinical outcomes [6]. To date, the cumulative incidences of acute myocardial infarction (AMI) are increasing in South Korea [7]. In real-world practice, the use of bare-metal stent (BMS) is limited. Therefore, we investigated the impact of sex difference on the 2-year clinical outcomes in Korean AMI patients with a history of current smoking on admission who underwent successful PCI with drug-eluting stents (DESs).

Methods

Study design and population

This study was a nonrandomized, multicenter, observational retrospective cohort study, and the study population was obtained from the Korea AMI Registry (KAMIR). Detailed information about the KAMIR has already been published [7, 8]. A total of 20,174 AMI patients who were active smokers on admission between November 2005 and June 2015 were evaluated. Patients with the following characteristics were excluded from the study: (1) patients who underwent fibrinolysis (n = 609, 3.0%), (2) patients who did not undergo PCI (n = 616, 3.1%), (3) patients with failed PCI (n = 415, 2.1%), (4) patients who underwent coronary artery bypass graft (n = 55, 0.3%), (5) patients with BMS (n = 942, 4.7%), (6) patients with incomplete laboratory results (n = 3562, 17.6%), and (7) patients who were lost to follow-up (n = 1410, 7.0%). Finally, a total of 12,565 AMI patients who were active smokers at the time of admission who underwent successful PCI with DESs were enrolled. They were grouped based on their sex; male (n = 11,767, 93.6%) and female groups (n = 798, 6.4%) (Fig. 1, Table 1). This study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki. This study protocol was approved by the ethics committee of each participating center, and informed consent was obtained from all individual participants prior to their enrollment. All 12,565 AMI patients completed a 2-year clinical follow-up, and were tracked the enrolled patients via direct interviews, telephone contact, and chart reviews [9]. All clinical events were evaluated by an independent event adjudication committee. The event adjudication processes were described in a previous publication established by the KAMIR investigators [8].

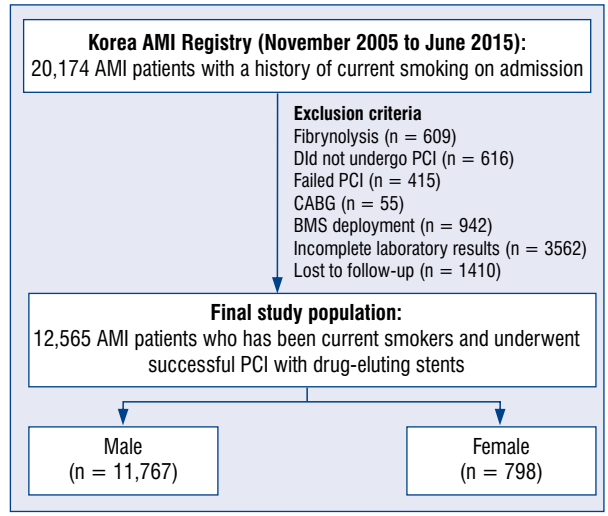

Figure 1. Flow chart; AMI — acute myocardial infarction; BMS — bare-metal stent; CABG — coronary artery bypass grafting; PCI — percutaneous coronary intervention.

Percutaneous coronary intervention procedure and medical treatment

Coronary angiography and PCI were performed as described before [10]. Before PCI, 200 to 300 mg of acetylsalicylic acid (ASA) and 300 to 600 mg of clopidogrel was administered. If possible, 180 mg of ticagrelor or 60 mg of prasugrel was administered. After discharge, 100 to 200 mg/ /day of ASA was continued indefinitely, and 75 mg/ /day of clopidogrel was maintained for at least

Table 1. Baseline clinical, laboratory, and procedural characteristics.

Variables	Male (n = 11,767)	Female (n = 798)	P	SD
Age [years]	56.7 ± 11.2	68.3 ± 11.5	< 0.001	1.21
LVEF [%]	52.6 ± 11.0	52.5 ± 11.8	0.724	–0.09
LVEF < 40%	1256 (10.7%)	96 (12.6%)	0.232	0.70
BMI [kg/m^2]	24.3 ± 3.1	23.3 ±3.6	<0.001	–2.98
SBP [mmHg]	130.0 ± 27.2	128.4 ± 28.9	0.103	–0.57
DBP [mmHg]	80.2 ± 16.6	77.5 ± 17.2	< 0.001	–1.60
STEMI	7480 (63.6%)	468 (58.6%)	0.005	–1.33
Primary PCI	6919 (92.5%)	429 (91.7%)	0.508	–0.33
NSTEMI	4287 (36.4%)	330 (41.4%)	0.005	1.34
PCI within 24 h	3342 (78.0%)	250 (75.8%)	0.354	–0.66
Hypertension	4237 (36.3%)	410 (51.4%)	< 0.001	3.99
Diabetes mellitus	2510 (21.3%)	216 (27.1%)	< 0.001	1.70
Dyslipidemia	1273 (10.8%)	80 (10.0%)	0.484	–0.31
Previous MI	338 (2.9%)	15 (1.9%)	0.101	–0.60
Previous PCI	476 (4.0%)	29 (3.6%)	0.567	–0.22
Previous CABG	27 (0.2%)	2 (0.3%)	0.904	0.07
Previous CVA	431 (3.7%)	51 (6.4%)	< 0.001	1.23
Previous HF	59 (0.5%)	11 (1.4%)	0.001	0.58
Cardiogenic shock	454 (3.9%)	48 (6.0%)	0.003	0.97
CPR on admission	364 (3.1%)	27 (3.4%)	0.648	0.16
CK-MB [mg/dL]	152.9 ± 149.4	140.4 ± 173.1	0.177	–0.77
Troponin-I [ng/mL]	52.1 ± 91.4	44.0 ± 41.5	0.473	–1.14
NT-ProBNP [pg/mL]	1042.6 ± 1119.8	3008.0 ± 3822.9	< 0.001	6.98
hs-CRP [mg/dL]	9.4 ± 51.0	8.6 ± 39.9	0.716	–0.17
Serum creatinine [mg/L]	1.1 ± 1.3	0.9 ± 0.6	0.001	–1.85
Total cholesterol [mg/dL]	187.4 ± 43.6	195.9 ± 48.2	< 0.001	1.98
Triglyceride [mg/L]	151.2 ± 129.5	137.2 ± 106.7	0.003	–1.18
HDL cholesterol [mg/L]	42.7 ± 18.5	45.0 ± 11.8	0.001	1.48
LDL cholesterol [mg/L]	119.5 ± 41.1	125.0 ± 42.7	< 0.001	1.31
Discharge medications:				
Acetylsalicylic acid	11410 (97.0%)	757 (94.9%)	0.001	–1.02
Clopidogrel	10473 (89.0%)	744 (93.2%)	< 0.001	1.88
Ticagrelor	648 (5.5%)	24 (3.0%)	0.002	–1.38
Prasugrel	485 (4.1%)	16 (2.0%)	0.003	–1.25
Cilostazole	2798 (23.8%)	194 (24.3%)	0.733	0.15
BBs	9563 (81.3%)	594 (74.4%)	< 0.001	–2.05
ACEIs	7207 (61.2%)	464 (58.1%)	0.082	–0.82
ARBs	2465 (20.9%)	160 (20.1%)	0.546	-0.25
CCBs	674 (5.7%)	56 (7.0%)	0.132	0.58
Lipid lowering agents	9669 (82.2%)	624 (78.2%)	0.005	-1.24
Angiographic and procedural characteristics				
Infarct-related artery				
Left main	174 (1.5%)	10 (1.3%)	0.608	–0.13
Left anterior descending	5765 (48.9%)	324 (40.6%)	< 0.001	–2.23
Left circumflex	2033 (17.3%)	133 (16.6%)	0.659	–0.24
Right coronary artery	3795 (32.3%)	331 (41.5%)	< 0.001	2.46

→

Table 1 (cont.). Baseline clinical, laboratory, and procedural characteristics.

Variables	Male (n = 11,767)	Female (n = 798)	P	SD
Treated vessel:				
Left main	249 (2.1%)	18 (2.3%)	0.791	0.12
Left anterior descending	6655 (56.6%)	403 (50.5%)	0.001	–1.61
Left circumflex	2956 (25.1%)	190 (23.8%)	0.408	–0.40
Right coronary artery	4530 (38.5%)	377 (47.2%)	< 0.001	2.30
ACC/AHA lesion type:				
Type B1	1801 (15.3%)	126 (15.8%)	0.714	0.17
Type B2	3554 (30.2%)	215 (26.9%)	0.052	–0.96
Type C	5148 (43.7%)	379 (47.5%)	0.039	1.00
Extent of coronary artery disease:				
1-vessel	5962 (50.7%)	369 (46.2%)	0.016	–1.19
2-vessel	3695 (31.4%)	233 (29.2%)	0.293	-0.63
≥ 3-vessel	2110 (17.9%)	196 (24.6%)	< 0.001	2.01
Drug-eluting stents:				
SES	2155 (18.3%)	168 (21.1%)	0.054	0.88
PES	1866 (15.9%)	141 (17.6%)	0.177	0.56
ZES	2866 (24.4%)	204 (25.6%)	0.332	0.36
EES	3640 (30.9%)	217 (27.2%)	0.027	–1.08
BES	1085 (9.2%)	56 (7.0%)	0.036	–0.98
Others	155 (1.3%)	12 (1.5%)	0.656	0.12
Stent diameter [mm]	3.2 ± 0.4	3.1 ± 0.4	< 0.001	–2.50
Stent length [mm]	26.1 ± 9.5	25.7 ± 8.9	0.327	–0.43
Number of stents	1.4 ± 0.8	1.5 ± 0.8	0.011	1.25

Values are mean ± standard deviation or number (%). The p values for continuous data were obtained from the analysis of the unpaired t-test. The p values for categorical data were obtained from the chi-square test. SD — standardized difference; LVEF — left ventricular ejection fraction; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; STEMI — ST-segment elevation myocardial infarction; NSTEMI — non-STEMI; PCI — percutaneous coronary intervention; MI — myocardial infarction; CABG — coronary artery bypass grafting; CVA — cerebrovascular accidents; HF — heart failure; CPR — cardiopulmonary resuscitation; CK-MB — creatine kinase myocardial band; NT-proBNP — N-terminal pro-B-type natriuretic peptide; HDL — high-density lipoprotein; LDL — low-density lipoprotein; BBs — beta-blockers; ACEIs — angiotensin converting enzyme inhibitors; ARBs — angiotensin receptor blockers; CCBs — calcium channel blockers; ACC/AHA — American College of Cardiology/American Heart Association; SES — sirolimus-eluting stents; PES — paclitaxel-eluting stents; ZES — zotarolimus-eluting stents; EES — everolimus-eluting stents; BES — biolimus-eluting stents

12 months. Triple antiplatelet therapy (TAPT) (100 mg of cilostazol [Pletaal®, Otsuka Pharmaceutical Co., Tokyo, Japan] twice a day added on a dual antiplatelet therapy) was left to the discretion of the individual operators [9].

Study definitions and clinical outcomes

Acute myocardial infarction was defined according to the current guidelines [11, 12]. Current smoking was defined as cigarette smoking within 1 year before the index PCI [9, 13]. Smoking history was assessed based on patient medical records. In this study, the occurrence of major adverse cardiac events (MACEs) was the primary endpoint. MACEs comprised all-cause death, recurrent myocardial infarction (Re-MI), and any repeat revascularization during a 2-year follow-up period. All-cause death was classified as a cardiac death (CD) or a non-CD. Re-MI was defined as the reoccurrence of AMI [14]. Any repeat revascularization comprised target lesion revascularization (TLR), target vessel revascularization (TVR), and non-TVR. Previously, the definitions of TLR, TVR, and non-TVR were published [14]. The secondary endpoint, the cumulative incidences of definite or probable stent thrombosis (ST), was defined according to the onset of this event as follows: acute (0–24 h), subacute (24 h–30 days), late (30 days–1 year), and very late (> 1 year) [14, 15].

Statistical analyses

The Statistical Package for the Social Sciences software version 20 (International Business Machines Corporation, Armonk, NY, USA) was used during the statistical analyses of this study. In case of continuous variables, differences between the

groups were evaluated using the unpaired t-test, and the data are expressed as the mean ± standard deviations. In case of categorical variables, the differences between two groups were analyzed with the χ^2 test, or, if not applicable, the Fisher exact test, and data are expressed as counts and percentages. Various clinical outcomes of this study were evaluated using the Kaplan-Meier method, and differences between two groups were compared using the log-rank test. Among the total covariates, only significant confounding covariates ($p < 0.001$ or those having predictive values) were included when performing multivariate Cox regression analysis, as shown in Table 2. For all analyses, two-sided p values < 0.05 were considered statistically significant [13].

Results

Baseline clinical, laboratory, angiographic, and procedural characteristics

The baseline, laboratory, angiographic, and procedural characteristics of the present study population are summarized in Table 1. The mean age of the patients in the female group was higher than that of the male group (68.3 ± 11.5 years vs. 56.7 ± 11.2 years, $p < 0.001$). The average level of left ventricular ejection fraction (LVEF) was similar and well preserved between the two groups (52.6 ± ± 11.0% vs. 52.5 ± 11.8, $p = 0.724$). The proportion of patients who had decreased LVEF (< 40%) was also similar between the two groups. The following values were higher in the male group than in the female group: number of ST-segment elevation myocardial infarction (STEMI); mean value of body mass index, diastolic blood pressure; serum creatinine level; triglyceride level; prescription rates of ASA, ticagrelor, prasugrel, beta-blockers, and lipid-lowering agents; and numbers of left anterior descending (LAD) artery as the infarct-related artery (IRA) or treated vessel; single-vessel disease; and the deployment of everolimus-eluting stents and biolimus-eluting stents. By contrast, the female group showed higher values than the male group for the following: number of non-STEMI; proportion of hypertension, DM, previous cerebrovascular accident (CVA), and HF; mean values of serum N-terminal pro-B-type natriuretic peptide, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol; prescription rates of clopidogrel; numbers of right coronary artery (RCA) as the IRA and treated vessel; ACC/ /AHA type C lesion; ≥ three-vessel disease; and number of deployed stent.

Clinical outcomes

Table 2 and Figure 2 show the clinical outcomes at 30 days, 1 year, and 2 years. During 1 month, the cumulative incidences of MACEs and all-cause death were significantly higher in the female group than in the male group. At 1 year after the index PCI, the cumulative incidences of MACEs, all-cause death, and Re-MI were also higher in the female group in the male group. Moreover, at 2 years, the cumulative incidences of all-cause death (adjusted hazard ratio [aHR]: 1.561; 95% confidence interval [CI]: 1.103–2.210; $p = 0.012$) and Re-MI (aHR: 1.800; 95% CI: 1.089–2.974; $p = 0.022$) were significantly higher in the female group than those in the male group. However, the cumulative incidences of ST, any repeat revascularization, TLR, TVR, and non-TVR were similar between the two groups.

Table 3 shows independent predictors for all-cause death and Re-MI at 2 years. Figure 3 shows the subgroup analyses for MACEs. In cases of over 40% of LVEF, non-hypertensive patients, ACC/ /AHA non-type C lesion, and patients who had non--RCA as IRA, who received lipid-lowering agents, and who currently smoke on admission showed worse outcomes for the female group compared with the male group in terms of MACEs.

Discussion

The main findings of the current study are as follows: 1) During 1 month, the cumulative incidences of MACEs and all-cause death were significantly higher in the female group than those in the male group; 2) At 1 year, the cumulative incidences of MACEs, all-cause death, and Re-MI were also higher in the female group than those in the male group; 3) At 2 years, the cumulative incidences of all-cause death and Re-MI were significantly higher in the female group than those in the male group; 4) However, the cumulative incidences of ST, any repeat revascularization, TLR, TVR, and non-TVR were similar between the two groups after adjustment.

To date, sex difference for MACEs and mortality showed debatable results [16, 17]. Other studies have reported that women have smaller arterial diameter and lower sensitivity to cardiac function tests and receive a more suboptimal medical treatment compared with men [18–20]. In the present cohort, before risk adjustment, the female group had less favorable baseline characteristics for CVD risk factor profiles such as old age, higher proportions of hypertension, DM, previous history

Table 2. Clinical outcomes by the Kaplan-Meier analysis and the Cox-proportional hazard ratio analysis up to 2 years.

Outcomes	Cumulative events (%)			Unadjusted		Adjusted*	
	Male (n = 11,767)	Female (n = 798)	Log--rank	HR (95% CI)	P	HR (95% CI)	P
30 days							
MACE	221 (1.9)	32 (4.0)	< 0.001	2.155 (1.487–3.122)	< 0.001	1.457 (1.021–2.216)	0.035
All-cause death	155 (1.3)	22 (2.8)	0.001	2.105 (1.347–3.289)	0.001	1.699 (1.074–2.687)	0.023
Cardiac death	145 (1.2)	19 (2.4)	0.006	1.942 (1.204–3.134)	0.007	1.505 (0.921–2.457)	0.102
Re-MI	47 (0.4)	6 (0.8)	0.133	1.896 (0.810–4.434)	0.140	1.806 (0.757–4.310)	0.183
Any revascularization	31 (0.3)	5 (0.6)	0.060	2.409 (0.937–6.196)	0.068	2.045 (0.865–3.374)	0.345
TLR	9 (0.1)	2 (0.3)	0.104	3.314 (0.716–15.34)	0.125	2.702 (0.539–13.56)	0.227
TVR	16 (0.1)	4 (0.5)	0.011	3.737 (1.249–11.18)	0.018	2.433 (0.990–8.502)	0.076
Non-TVR	14 (0.1)	1 (0.1)	0.951	1.066 (0.140–8.103)	0.951	1.131 (0.144–8.910)	0.907
ST (definite or probable)							
Acute	10 (0.1)	0 (0.0)	0.410	—	—	—	—
Subacute	29 (0.2)	3 (0.4)	0.483	1.342 (0.409–4.410)	0.627	1.031 (0.266–3.991)	0.965
Total	39 (0.3)	3 (0.4)	0.833	1.004 (0.310–3.249)	0.995	1.173 (0.322–4.264)	0.809
1 year							
MACEs	660 (5.7)	70 (8.9)	< 0.001	1.585 (1.239–2.028)	< 0.001	1.402 (1.090–1.803)	0.009
All-cause death	245 (2.1)	35 (4.4)	< 0.001	2.121 (1.489–3.023)	< 0.001	1.660 (1.153–2.390)	0.006
Cardiac death	204 (1.7)	24 (3.0)	0.009	1.747 (1.144–2.666)	0.010	1.238 (0.831–1.980)	0.261
Re-MI	107 (0.9)	16 (2.1)	0.002	2.229 (1.318–3.770)	0.003	2.040 (1.189–3.501)	0.010
Any revascularization	340 (3.0)	23 (3.0)	0.980	1.005 (0.659–1.534)	0.980	0.974 (0.635–1.495)	0.905
TLR	97 (0.9)	7 (0.9)	0.857	1.073 (0.498–2.311)	0.857	1.011 (0.464–2.204)	0.978
TVR	166 (1.5)	12 (1.6)	0.812	1.072 (0.598–1.929)	0.812	1.048 (0.578–1.900)	0.877
Non-TVR	177 (1.6)	11 (1.5)	0.794	1.084 (0.590–1.994)	0.794	1.174 (0.636–2.176)	0.608
ST (definite or probable)							
Late	35 (0.3)	4 (0.5)	0.316	1.885 (0.667–5.329)	0.232	1.343 (0.403–4.479)	0.631
Total (0–365 days)	74 (0.6)	7 (0.9)	0.397	1.372 (0.631–2.984)	0.424	1.116 (0.481–2.591)	0.799
2 years							
MACEs	819 (7.2)	78 (10.0)	0.003	1.419 (1.125–1.790)	0.003	1.264 (1.001–1.598)	0.052
All-cause death	283 (2.5)	38 (4.8)	< 0.001	1.988 (1.417–2.789)	< 0.001	1.561 (1.103–2.210)	0.012
Cardiac death	224 (1.9)	25 (3.2)	0.016	1.654 (1.094–2.500)	0.017	1.216 (0.797–1.857)	0.364
Re-MI	142 (1.3)	18 (2.4)	0.010	1.885 (1.154–3.078)	0.011	1.800 (1.089–2.974)	0.022
Any revascularization	444 (4.0)	27 (3.6)	0.594	1.111 (0.754–1.639)	0.594	1.161 (0.785–1.717)	0.453
TLR	121 (1.1)	8 (1.1)	0.956	1.021 (0.499–2.087)	0.956	1.008 (0.471–1.982)	0.982
TVR	228 (2.1)	14 (1.9)	0.726	1.101 (0.642–1.889)	0.726	1.094 (0.626–1.864)	0.745
Non-TVR	223 (2.0)	13 (1.7)	0.602	1.160 (0.663–2.030)	0.602	1.273 (0.725–2.235)	0.400
ST (definite or probable)							
Very late	15 (0.1)	1 (0.1)	0.988	1.021 (0.131–9.274)	0.684	1.042 (0.967–11.23)	0.280
Total (0–730 days)	89 (0.8)	8 (1.0)	0.445	1.104 (0.533–2.285)	0.790	1.207 (0.583–2.497)	0.613

*Adjusted by age, BMI, SBP, DBP, hypertension, diabetes, previous CVA, cardiogenic shock, NT-proBNP, total cholesterol, LDL cholesterol, clopidogrel, beta-blockers, lipid lowering agents, infarct-related artery (LAD and RCA), treated vessel (RCA), ≥ 3-vessel, stent diameter. HR — hazard ratio; CI — confidence interval; MACEs — major adverse cardiac events; Re-MI — re-myocardial infarction; TLR — target lesion revascularization; TVR — target vessel revascularization; ST — stent thrombosis

of CVA, HF, cardiogenic shock, and smaller mean diameter of deployed stents and showed significantly higher cumulative incidences of MACEs compared with the male group. These study results are consistent with the results of Bell's and Nappi's study [3]. The unfavorable effects of smoking on

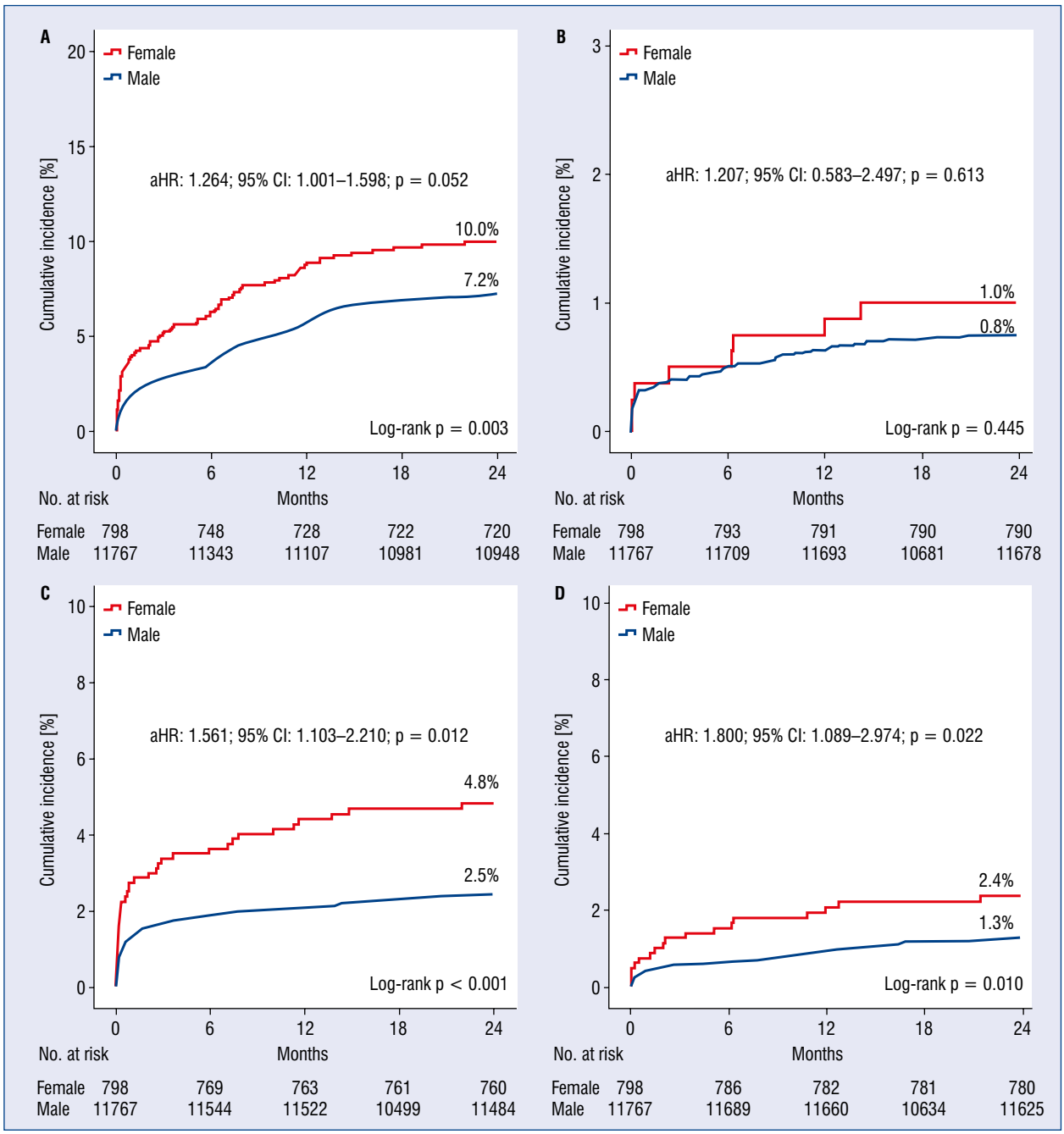

Figure 2. Kaplan-Meier Analysis for major adverse cardiac events (MACEs) (**A**), stent thrombosis (**B**), all-cause (**C**) and recurrent myocardial infarction (**D**); CI — confidence interval; aHR — adjusted hazard ratio.

CAD include increasing plasma fibrinogen level, reducing high-density lipoprotein cholesterol level, increasing carboxyhemoglobin level, and increasing platelet stickiness and aggregation under the milieu of AMI [21, 22]. Furthermore, endothelial dysfunctions, including reduced nitric oxide release [23] and inflammations [24], are involved in this process.

In this study, the cumulative incidence of all-cause death, both early (30 days) and late (1 year and 2 year), and the cumulative incidence of Re-MI after 1 month of the index PCI, were higher in the female group than that in the male group after adjustment (Fig. 2). The possible explanation for these worse clinical outcomes in the female smokers' group is related with the decreased estrogen activity or production [25]. Additionally, a Danish report suggested that women may be more sensitive compared with men to the

Table 3. Multivariable Cox-proportional regression analysis for predictors of all-cause death and recurrent myocardial infarction (Re-MI) at 2 years.

Variables	All-cause death				Re-MI			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Male vs. female	1.988 (1.417–2.789)	< 0.001	2.642 (1.984–3.327)	< 0.001	1.885 (1.154–3.078)	0.011	1.733 (1.035–2.902)	0.037
Age ≥ 65 years	3.656 (2.931–4.560)	< 0.001	2.507 (1.974–3.183)	< 0.001	1.335 (0.959–1.858)	0.087	1.128 (0.788–1.616)	0.510
LVEF < 40%	5.173 (4.127–6.483)	< 0.001	3.596 (2.831–4.568)	< 0.001	1.752 (1.159–2.650)	0.008	1.422 (0.927–2.180)	0.106
Diastolic blood pressure	0.989 (0.982–0.995)	0.001	1.005 (0.997–1.012)	0.242	1.001 (0.991–1.010)	0.863	1.002 (0.991–1.012)	0.756
STEMI	1.020 (0.813–1.279)	0.864	1.114 (0.945–1.281)	0.711	1.195 (0.859–1.664)	0.291	1.217 (0.862–1.720)	0.265
Hypertension	1.372 (1.101–1.710)	0.005	1.025 (0.813–1.291)	0.837	1.054 (0.766–1.450)	0.748	1.121 (0.801–1.568)	0.507
Diabetes mellitus	1.743 (1.380–2.202)	< 0.001	1.386 (1.085–1.771)	0.009	1.520 (1.082–2.136)	0.016	1.412 (0.991–2.010)	0.056
Previous CVA	2.896 (2.020–4.152)	< 0.001	1.772 (1.225–2.564)	0.002	2.441 (1.411–4.225)	0.001	2.178 (1.238–3.831)	0.007
Cardiogenic shock	3.103 (2.194–4.389)	< 0.001	2.829 (1.863–4.296)	< 0.001	1.132 (1.531–2.415)	0.748	1.226 (0.534–2.817)	0.631
Primary PCI	1.030 (0.825–1.286)	0.793	1.239 (0.706–2.174)	0.455	1.173 (0.852–1.615)	0.329	1.034 (0.480–2.226)	0.933
PCI within 24 h	1.069 (0.841–1.357)	0.586	1.423 (0.873–2.322)	0.157	1.288 (0.830–1.699)	0.346	1.190 (0.576–2.456)	0.639
Clopidogrel	1.344 (0.886–2.038)	0.165	1.075 (0.706–1.639)	0.735	1.199 (0.724–1.986)	0.480	1.322 (0.793–2.203)	0.284
Beta-blockers	3.796 (3.049–4.727)	< 0.001	3.153 (2.521–3.944)	< 0.001	1.007 (0.695–1.555)	0.849	1.061 (0.706–1.592)	0.777
LAD (IRA)	1.147 (0.921–1.428)	0.220	1.054 (0.779–1.406)	0.735	1.657 (1.207–2.275)	0.002	1.639 (1.203–2.626)	0.040
RCA (IRA)	1.221 (0.958–1.555)	0.106	1.657 (1.042–2.635)	0.033	1.478 (0.784–2.114)	0.032	1.237 (0.608–2.014)	0.284
RCA (treated)	1.108 (0.813–1.274)	0.879	1.248 (0.858–1.817)	0.247	1.260 (0.908–1.749)	0.166	1.141 (0.654–1.991)	0.642
ACC/AHA type B2/C lesion	1.266 (0.973–1.648)	0.079	1.256 (0.963–1.639)	0.093	1.059 (0.743–1.510)	0.751	1.019 (0.712–1.457)	0.919
≥ 3-vessel	2.013 (1.590–2.550)	< 0.001	1.329 (1.034–1.708)	0.027	1.429 (0.996–2.049)	0.053	1.291 (0.883–1.887)	0.188

HR — hazard ratio; CI — confidence interval; LVEF — left ventricular ejection fraction; STEMI — ST-segment elevation myocardial infarction; CVA — cerebrovascular accidents; PCI — percutaneous coronary intervention; LAD — left anterior descending coronary artery; IRA — infarct-related artery; RCA — right coronary artery; ACC/AHA — American College of Cardiology/American Heart Association

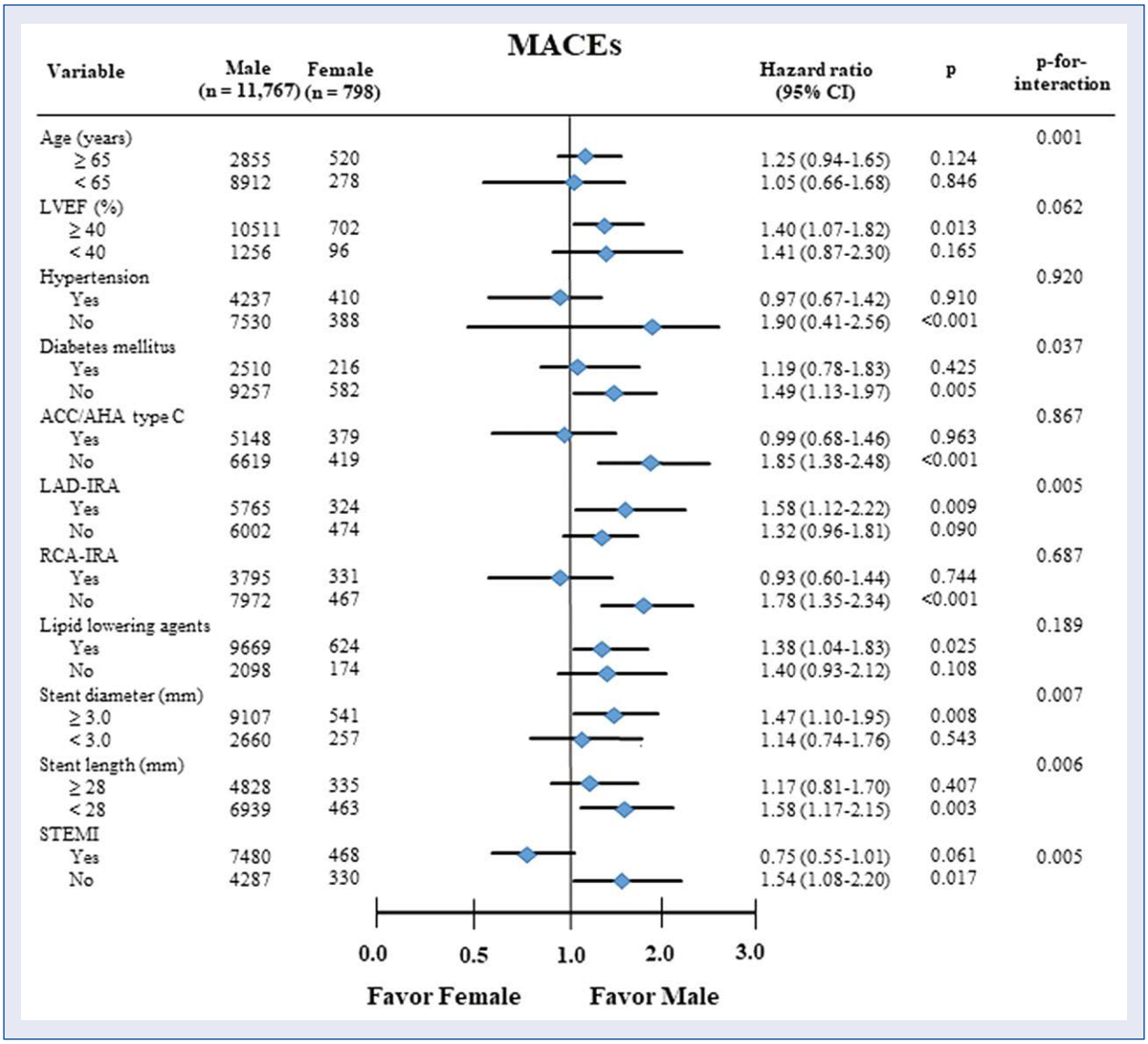

Figure 3. Subgroup analyses for major adverse cardiac events (MACEs). CI — confidence interval; LVEF — left ventricular ejection fraction; ACC/AHA — American College of Cardiology/American Heart Association; LAD — left anterior descending coronary artery; RCA — right coronary artery; IRA — infarct-related artery; STEMI — ST-segment elevation myocardial infarction.

deleterious effects of smoking [6]. According to other studies [21, 26], women are more susceptible to the effects of nicotine consumption, which causes vasoconstriction, compared with men. Although previous studies [20, 27] have reported that less aggressive treatment of acute coronary syndrome may be a causative factor to poorer outcomes in women than in men, in this study, the proportions of primary PCI (92.5% vs. 91.7%, p = 0.508) and PCI within 24 h (78.0% vs. 75.8%, p = 0.354) were similar at baseline (Table 1). Moreover, both primary PCI and PCI within 24 h were not predictors of all-cause death and Re-MI in our study (Table 3).

In the GUSTO-1 trial, single-vessel disease was more frequently observed in smokers compared with nonsmokers (63% vs. 55%) [28]. In the current study, singe-vessel disease was also more frequently observed compared with multivessel disease in both sexes (Table 1). It is highly likely that the mortality rate for RCA as an IRA is lower than for LAD [29]. Despite the number of RCA as an IRA was higher in the female group than that in the male group (47.2% vs. 43.7%, p = 0.039), all-cause death was significantly higher in the female group than that in the male group after adjustment. Hence, sex difference for the major clinical outcomes was strongly suggested in this cohort study.

Approximately 23% of patients who quit smoking at 30 days had relapsed at 12 months [30]. One Asian study showed that a total of 34.1% of smokers continued to smoke or relapsed after a period of time of quitting smoking [31]. Therefore, it can be assumed that greater than 30% of the enrolled patients continued to smoke after the index PCI during the follow-up period.

In the present cohort study, the proportion of women was relatively smaller compared to the total number of men (93.6% vs. 6.4%). This proportional difference of enrolled patients between the two groups is consistent with the previous studies [32, 33]. In the previous studies, the number of smokers is relatively lower in women than in men with some regional variations, specifically in Asian regions where the prevalence of women smoking is less than 10% [32, 33]. Moreover, the KAMIR is a nationwide, prospective, observational multicenter registry in South Korea, and more than 50 high-volume university or community hospitals participated in this study [7, 8]. Therefore, we believe that in this study, the study population is not small for providing reasonably accurate results.

Limitations of the study

This study has the following limitations. First, due to the characteristics of the nonrandomized retrospective nature of the study, there may be some incomplete variables. Second, the smoking status of the study population was assessed on admission, and the registry data did not include full detailed data concerning the status of smoking including before admission and during the follow-up period [9, 13]. Therefore, these factors may contribute bias. Third, this study assessed the discharge medications. Fourth, it was not possible to compare the initial laboratory results with the serial follow-up results because of the limited registry data, subsequently introducing bias. Fifth, although multivariate Cox proportional regression analysis was performed, the results of the present study are relatively different according to the variables included or excluded when performing this analysis. Sixth, the strategy of antiplatelet therapy (e.g., dual antiplatelet therapy or TAPT) was left to the physician's discretion, which may have influenced the major clinical outcomes [9]. Finally, AMI was defined according to the current guidelines including the 3rd universal definition of MI [11, 12] in this study. However, the fourth universal definition of MI [34] contains more updated and accurate diagnostic criteria than those of the third universal definition of MI.

Conclusions

In conclusion, the female group showed worse short-term and long-term clinical outcomes compared with the male group comprising Korean AMI patients with history of current smoking who underwent successful DES implantation. However, additional studies are required to determine the clinical implications of these results.

Acknowledgments

This research was supported by a fund (2016-ER6304-02) by Research of Korea Centers for Disease Control and Prevention.

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Conflict of interest: None declared

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VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 6, 966–977
DOI: 10.5603/CJ.a2020.0134

ISSN 1897–5593
eISSN 1898–018X

Efficacy and safety of hypertonic saline solutions fluid resuscitation on hypovolemic shock: A systematic review and meta-analysis of randomized controlled trials

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This paper was guest edited by Prof. Togay Evrin

Abstract

Background: *Fluid resuscitation is a fundamental intervention in patients with hypovolemic shock resulting from trauma. Appropriate fluid resuscitation in trauma patients could reduce organ failure, until blood components are available, and hemorrhage is controlled. We conducted a systematic review and meta-analysis assessing the effect of hypertonic saline/dextran or hypertonic saline for fluid resuscitation on patient outcomes restricted to adults with hypovolemic shock.*

Methods: *We conducted a search of electronic information sources, including PubMed, Embase, Web of Science, Cochrane library and bibliographic reference lists to identify all randomized controlled trials (RCTs) investigating outcomes of crystalloids versus colloids in patients with hypovolemic shock. We calculated the risk ratio (RR) or mean difference (MD) of groups using fixed or random-effect models.*

Results: *Fifteen studies including 3264 patients met our inclusion criteria. Survival to hospital discharge rate between research groups varied and amounted to 71.2% in hypertonic saline/dextran group vs. 68.4% for isotonic/normotonic fluid (normal saline) solutions (odds ratio [OR] = 1.19; 95% confidence interval [CI] 0.97–1.45; I^2 = 48%; p = 0.09). 28- to 30-days survival rate for hypertonic fluid solutions was 72.8% survivable, while in the case of isotonic fluid (normal saline) — 71.4% (OR = 1.13; 95% CI 0.75–1.70; I^2 = 43%; p = 0.56).*

Conclusions: *This systematic review and meta-analysis, which included only evidence from RCTs hypertonic saline/dextran or hypertonic saline compared with isotonic fluid did not result in superior 28- to 30-day survival as well as in survival to hospital discharge. However, patients with hypotension who received resuscitation with hypertonic saline/dextran had less overall mortality as patients who received conventional fluid.* (Cardiol J 2022; 29, 6: 966–977)

Key words: fluid resuscitation, hypovolemic shock, trauma, injury, hypertonic saline, normal saline, treatment, crystalloid, colloid fluid

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Received: 28.08.2020 Accepted: 2.09.2020 Early publication date: 22.10.2020

Introduction

Fluid resuscitation is a fundamental intervention in patients with hypovolemic shock resulting from trauma. The main purpose of undertaking fluid therapy is to stabilize post-traumatic circulation disorders [1, 2]. Baroreceptor-mediated, catecholamine-induced venoconstriction acts on the venous capacitance system to increase venous return and maintain cardiac output, moreover the renin–angiotensin–aldosterone and adrenocortical systems produces an antidiuretic response to retain water [3]. The hypovolemic shock caused by acute hemorrhage occurs when intravascular volume loss exceeds the capacity of these compensatory mechanisms, resulting in the compromise of vital organ perfusion [4].

Advanced trauma life support recommends the prehospital assessment of a patient's circulation status and to resuscitate with intravenous fluids in patients with obvious hemorrhage or systolic blood pressure (SBP) below 90 mmHg [5]. A particularly important problem of fluid therapy is observed in patients with multi-organ injuries, including those affecting the central nervous system, which is extremely susceptible to osmolality changes. For this reason, hypotonic solutions that increase intracerebral water and exacerbate post-traumatic brain edema are not recommended in patients treated for head injuries [6, 7]. As indicated by Reddy et al. [8] most infusion solutions exhibit hypoosmotic effects, since only some components of crystalline solutions are active in plasma and their osmotic coefficient is 0.92.

Crystalloid is a broad term that can encompass many different types of solutions from hypertonic normal saline (NS) to lactated Ringer's solution to 5% dextrose and half NS. 0.9% sodium chloride (NS) is one of the most frequently administered solutions. It is also the basis for the preparation of many colloids, including hypertonic saline/dextran, human albumins or gelatins.

When infused, crystalloids with a sodium concentration close to that of intravascular fluid (140 mmol/L) produce a transient increase in intravascular volume before equilibrating with the extracellular fluid. Crystalloids can be used either as resuscitation fluids (to increase or maintain intravascular volume) or as maintenance fluids (to maintain hydration and basic electrolyte balance) in persons unable to tolerate enteral administration of fluid [9]. As indicated by the meta-analysis published by Safiejko et al. [10] hypotensive fluid resuscitation significantly reduced the mortality of traumatic hemorrhagic shock patients. Rapid administration of a large volume will cause hyperchloremic metabolic acidosis. This is because in the case of a standard 0.9% NaCl strong ion difference between 0.9% NaCl fluid solution and plasma (respectively 0 vs. 40 mEq/L). Therefore, it is important to know the effect of using both isotonic vs. hypertonic fluid solutions during fluid resuscitation of trauma patients.

The present study is a systematic review and meta-analysis assessing the effect of hypertonic saline fluid resuscitation on patient outcomes restricted to adults with hypovolemic shock.

Methods

This review was conducted and presented according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement standards [11]. We did not publish a prior protocol for this review.

Literature searches

A computerized literature search was conducted from the PubMed, Embase, Web of Science, and the Cochrane library data bases from their inception to August 20th 2020. In addition to the reference lists of the selected articles they were hand-searched to identify additional relevant reports. Google Scholar and other Internet search engines were also used to search for additional information.

The search terms comprised the followings: (crystalloid* OR normal saline* OR saline OR Ringers OR Ringer's OR Hartmanns OR Hartmann's OR hypertonic OR 7.5% saline OR NaCl OR sodium chloride) AND (Emergency medicine OR Emergency treatment OR Emergency department OR Emergency room OR Emergency medical service OR EMS OR Hemorrhagic shock OR Hypovolemic shock OR trauma).

Selection and exclusion criteria

Two reviewers (K.S. and A.S.) independently screened the titles and abstracts of all citations retrieved during the literature search based on inclusion criteria. Disagreements were resolved through discussion until consensus was reached. Inclusive criteria: (a) Research types: randomized controlled trials (RCTs) and quasi-randomized trials; (b) Research subjects: human studies involved adult patients needing fluid resuscitation were involved in the meta-analysis. Also included were studies which were in preprint. Observational stud-

ies, case-control studies, non-trials conducted on simulated models, editorials, reviews, guidelines, meta-analysis, and theoretical models were excluded from the review. The search was limited to English language studies and adult patients needing fluid resuscitation. The data were recorded using Review Manager.

Data extraction

Two authors (K.S. and J.R.L.) independently reviewed all identified titles and abstracts against the prespecified eligibility criteria using a standardized form piloted before the study. The reviewers then independently evaluated the full texts of the selected articles, applied the selection criteria to them, and compared decisions for all the included and excluded studies. Disagreements were resolved by discussion with the other authors (J.S.). The duplicate publications of the same trial were excluded from the present study.

The clinical data were extracted as the following: the name of the first author, the year published, the country of the author, the types of study design, the number of patients, type of fluid infused, and follow-up time. The primary outcome herein, was survival to hospital discharge or at 28 to 30 days. Other mortality periods were also extracted as defined by the authors.

Outcome measures

The primary endpoint was short-term survival (hospital discharge or 28 to 30 days). Secondary outcomes included long-term mortality (≥ 3 months), 24-hour mortality, overall mortality, adverse outcome, length of stay in an intensive care unit and hospital, laboratory parameters at patient admission, the Glasgow Outcome Scale Extended score.

Risk of bias assessment

Two authors independently assessed the methodological quality and risk of bias of the included articles using the method outlined in the Cochrane Collaboration Handbook for Systematic Reviews of Interventions [12]. Risk of bias was assessed as high, low, and unclear for each of selection bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. The review authors' judgments about each risk of bias item are provided in **Supplementary Digital File 1**.

Statistical analysis

All analyses were performed by the Review Manager Version 5.4. (The Cochrane Collaboration, Oxford, Copenhagen, Denmark). Dichotomous data were presented as risk ratios using the Mantel–Haenszel method. Continuous data were presented as means with standard deviations and analyzed using the inverse variance. The random-effects model was used for $I^2 > 50\%$; otherwise, the fixed effects model was employed. When continuous data were presented as medians with ranges, the data were converted for inclusion into the meta-analysis using the method described by Hozo et al. [13]. Heterogeneity among the studies was assessed using the Cochran Q test (χ^2). Inconsistency was quantified by calculating I^2 and was interpreted using the following guide: no heterogeneity, $I^2 = 0–25\%$; moderate heterogeneity, $I^2 = 25–50\%$; large heterogeneity, $I^2 = 50–75\%$; extreme heterogeneity, $I^2 = 75–100\%$. Where appropriate, subgroup analyses were performed based on the study design and methodological quality.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Study selection

The comprehensive search yielded 1271 potentially relevant articles; after exclusion of duplicates and assessment of titles and/or abstracts, 43 articles were chosen for complete review. Finally, 15 studies including 3264 patients met our inclusion criteria, published between 1987 and 2011 [14–28]. Figure 1 shows the flow of studies through the review.

Characteristics of included studies

The studies comprised a total of 3264 participants, of whom 54.9% were exposed to hypertonic saline solutions (Table 1).

All studies were RCTs. Eight studies were conducted in the United States of America [15, 18–20, 24–26], two in Brazil [27, 28], two in Canada [21, 22], one in the United Kingdom [14], and one in Australia [17]. One study was multi-county [16]. In general, the studies were judged as being of good quality. **Supplementary Digital File 1** presents

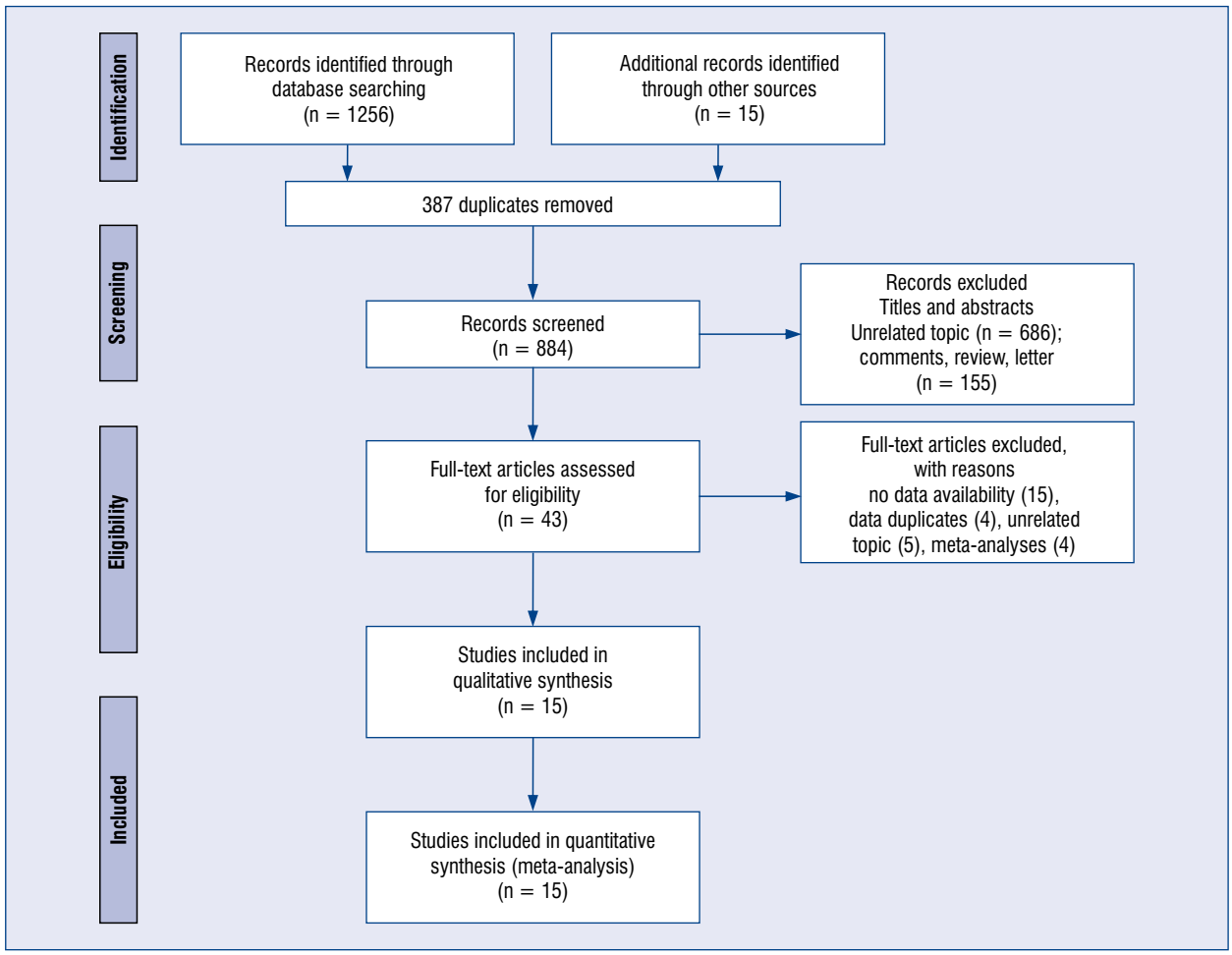

Figure 1. Flow diagram showing stages of database searching and study selection as per PRISMA guidelines.

inclusion and exclusion criteria, primary outcome as well as 28- to 30-day survival rate with an odds ratio (OR) (95% confidence interval [CI]).

Primary endpoint

In summary, 9 studies reported survival to hospital discharge including 2081 patients [16, 17, 21–27]. Survival to hospital discharge rate between research groups varied and amounted to 71.2% in hypertonic saline/dextran (HSD) group vs. 68.4% for isotonic fluid (NS) solutions (OR = 1.19; 95% CI 0.97–1.45; I^2 = 48%; p = 0.09).

Subgroup analysis is shown in Figure 2. Eight studies reported a comparison between HSD and control group [16, 21–27]. The differences in terms of survival to hospital discharge were not significant and were respectively 72.8% vs. 72.3% (OR = 1.13; 95% CI 0.89–1.44; I^2 = 36%; p = 0.30). In turn, 4 studies [16, 17, 25, 27] reported analyzed comparison between hypertonic saline and isotonic saline (68.8% vs. 68.1%, respectively; OR = 1.10; 95% CI 0.83–1.44; I^2 = 0%; p = 0.51).

28- to 30-day survival rate was reported by 5 studies [15, 16, 19, 21, 28]. Pooled analysis showed that the use of hypertonic fluid solutions was 72.8% survivable, while in the case of isotonic fluid (NS) — 71.4% (OR = 1.13; 95% CI 0.75–1.70; I^2 = 43%; p = 0.56).

As shown in Figure 3 in the HSD subgroup, 4 studies indicated that hypertonic/dextran solutions infusion [15, 16, 19, 21] was associated with a survival rate of 72.6% and NS with 72.8% (OR = = 1.06; 95% CI 0.64–1.77; I^2 = 56%; p = 0.81). Analysis in the subgroup where the infusion of hypertonic saline vs. isotonic saline [16, 28] was used showed survival at the level of 73.1% vs. 71.9%, respectively (OR = 1.14; 95% CI 0.71–1.83; I^2 = 49%; p = 0.59).

Table 1. Characteristics of included studies.

Study	Country	Study design	Intervention	Hyper-saline group			Control group		
				N	Age	Males	N	Age	Males
Alpar et al. 2004	UK	RCT	Patients randomized to receive HSD or Hartmann's. HSD infused at a dose of 4 mL/kg or maximum 250 mL, with further fluid resuscitation with Hartmann's or blood transfusion. Average volume infused: HSD group: 4.5 L, Hartmann's group: 6.5 L	90	34.3 ± ± 11.3	NS	90	33.5 ± ± 11	ns
Bulger et al. 2008	USA	Double--blind RCT	Prehospital resuscitation with 250 mL either HSD or Ringer's lactate. Additional ongoing resuscitation with Ringer's lactate only	110	41 ± ± 18	69 (62.7%)	99	38 ± ± 19	68 (68.7%)
Bulger et al. 2011	Multi--country	Multi--center double--blind RCT	Patients randomized to receive a 250-mL bolus of either 7.5% HS, 7.5% HSD 70 or NS, in prehospital setting	476	37.2 ± ± 16.7	375 (78.8%)	376	36.2 ± ± 16.4	291 (77.4%)
Cooper et al. 2004	Australia	Double--blind RCT	Patients randomized to receive a 250 mL bolus of either 7.5% saline or Ringer's lactate solution	114	38 ± ± 19	75 (65.8%)	115	37 ± ± 19	76 (66.1%)
Holcroft et al. 1987	USA	RCT	Patients randomized to receive a 3% NaCl (1028 mOsm/kg, 4 mL/kg) or lactated Ringer's solution (12 mL/kg)	10	36 ± ± 13	9 (90.0%)	10	36 ± ± 21	9 (90.0%)
Holcroft et al. 1989	USA	RCT	Patients randomized to receive a 3% NaCl (1028 mOsm/kg, 4 mL/kg) or lactated Ringer's solution (12 mL/kg)	29	38 ± ± 15.6	23 (79.3%)	31	38 ± ± 19	26 (83.9%)
Mattox et al. 1991	USA	Multi--center double--blind RCT	Patients randomized to receive 250 mL either HSD or Ringer's lactate as prehospital resuscitation	211	34 ± ± 12	184 (87.2%)	211	33 ± ± 12	175 (82.9%)
Morrison et al. 2011	Canada	Randomized controlled feasibility trial	250 mL of NS or 250 mL of HSD in a single dose. If the paramedics failed to obtain an intravenous access, the study's solution could be started immediately at the arrival to the emergency department as long as this occurred within 4 h from the injury	50	46 ± ± 21	30 (60.0%)	57	43 ± ± 21	43 (75.4%)
Rizoli et al. 2006	Canada	Double--blind RCT	Patients randomized to receive a single 250-mL bolus of either HSD or normal saline. Mean (standard deviation) total volume in first 24 h; Control group: colloid 696 (773) mL, crystalloid 8080 (2736) mL; HSD group: colloid 361 (377) mL, crystalloid 7796 (3189) mL; p = 0.02 and p = 0.75 between groups for crystalloid and colloid respectively	10	49.3 ± ± 16.7	7 (70.0%)	14	47.5 ± ± 15.9	9 (64.3%)
Vassar et al. 1991	USA	Double--blind RCT	Trauma patient were given 250 mL of 7.5 HSD 70 or Ringer's lactate as prehospital resuscitation	83	30.3 ± ± 6.1	NS	83	32.3 ± ± 6.1	ns
Vassar et al. 1993 (1)	USA	Double--blind RCT	Trauma patients in prehospital transport were given 250 mL of: (1) normal saline; (2) 7.5% NaCl (HS); (3) 7.5% NaCl in 6% HSD 70	174	31.5 ± ± 14.5	NS	84	31 ± ± 12	ns

→

Table 1 (cont.). Characteristics of included studies.

Study	Country	Study design	Intervention	Hyper-saline group			Control group		
				N	Age	Males	N	Age	Males
Vassar et al. 1993 (2)	USA	Double--blind RCT	Trauma patients were given 200 mL or more of: (1) Lactate Ringer's solution, (2) 7.5% hypertonic saline solution, (3) 7.5% HS combined with 6% HSD 70, (4) 7.5 HS combined with 12% HSD 70	149	32 ± ± 13	NS	45	37 ± ± 18	ns
Wade et al. 2003	USA	Double--blind RCT	Trauma patients were given 250 mL of HSD (7.5% NaCl/6% HSD 70) or 250 mL of normal saline (0.9% NaCl)	120	32 ± ± 10.4	NS	110	32 ± ± 10.5	ns
Younes et al. 1992	Brazil	Double--blind RCT	Emergency unit patients received either an intravenous bolus infusion of 250 mL of hypertonic/ /hypertonic 7.5% NaCl + 6% HSD 70 or an isotonic 0.9% NaCl (NS) solution	70	NS	NS	35	NS	ns
Younes et al. 2002	Brazil	Double--blind RCT	Emergency unit patients received either an intravenous bolus infusion of 250 mL of hypertonic/ /hypertonic 7.5% NaCl + 6% HSD 70 or an isotonic 0.9% NaCl (IS) solution	101	39.8 ± ± 11.2	93 (92.1%)	111	40.8 ± ± 12.2	92 (82.9%)

HS — hypertonic saline; HSD — hypertonic saline/dextran; NS — normotonic/isotonic fluid; ns — not specified; RCT — randomized controlled trial

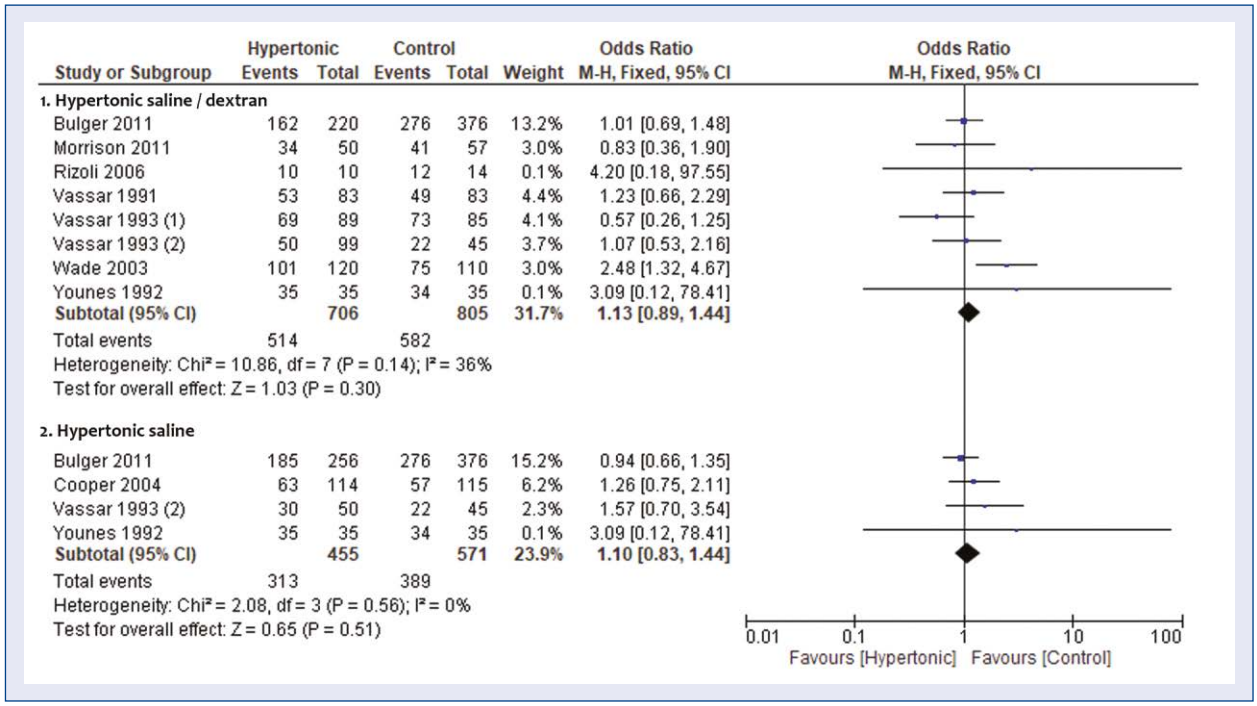

Figure 2. Forest plot of survival to hospital discharge rate while using hypertonic fluid solutions versus isotonic fluid solutions. The center of each square represents the weighted mean difference for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results.

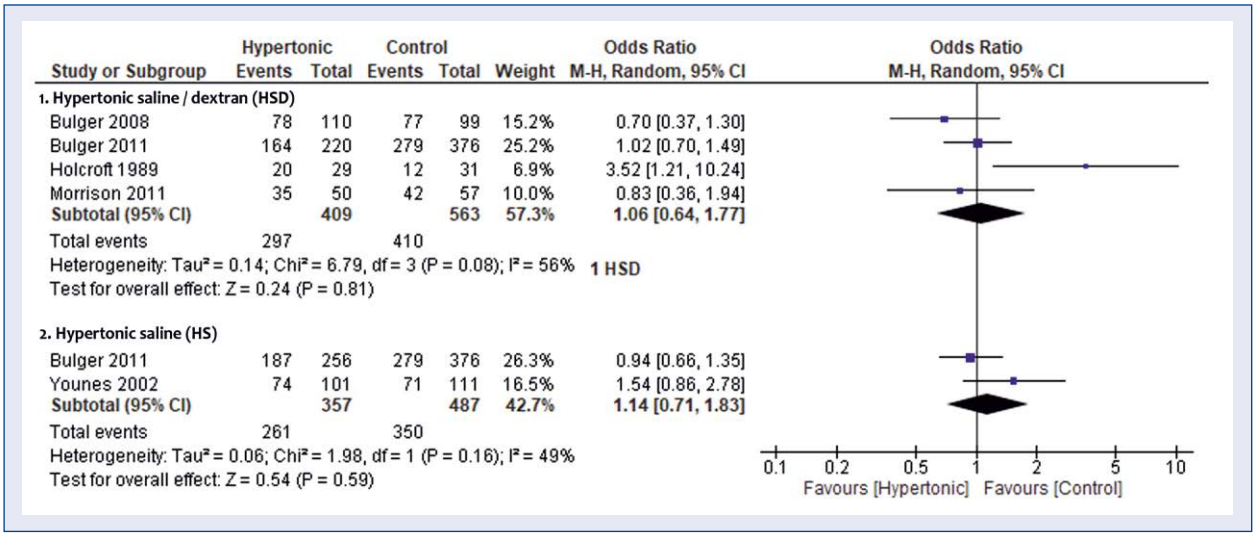

Figure 3. Forest plot of 28- to 30-days survival rate while using hypertonic fluid solutions versus isotonic fluid solutions. The center of each square represents the weighted mean difference for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results.

Secondary endpoints

The detailed results of the secondary endpoints are presented in Table 2. 24 h survival rate in case of hypertonic fluids was 88.6% and was higher than with isotonic fluids — 72.3% (OR = 2.99; 95% CI 2.04–4.39; I^2 = 0%; p < 0.001). In the case of the 3-month survival rate, there was no significant statistical difference (55.3% vs. 48.2%; OR = 1.33; 95% CI 0.79–2.23; p = 0.29).

Seven studies [14, 16, 20, 22, 26–28] reported overall mortality in the experimental group was 19.7% compared with NS group — 24.8% (OR = 0.76; 95% CI 0.61–0.94; I^2 = 33%; p = 0.01). Subgroup analysis showed higher total mortality in the HSD group (23.3% for hypertonic vs. 17.3% for isotonic group; p = 0.01) as well as in the hypertonic saline group (25.9% vs. 23.7%, respectively; p = 0.51; Fig. 4).

The use of hypertonic fluid was associated with a longer hospital stay than with isotonic fluid solutions (mean difference [MD] = 1.45; 95% CI 0.43–2.46; p = 0.005). Acute respiratory distress syndrome-free survival rate at 28 days was reported in 2 studies. The difference between hypersaline and normosaline groups was not statistically significant (OR = 1.10; 95% CI 0.85–1.44; p = 0.46).

The use of hypertonic fluid solutions was associated with higher SBP at hospital admission compared to isotonic fluids (MD = 6.71; 95% CI 1.75–11.67; I^2 = 72%; p = 0.008; **Suppl. Digital File 1**).

Polled analyses illustrated selected laboratory parameters are presented in **Supplementary Digital File 1**.

Adverse events

Pooled analysis showed no statistically significant incidence of complications between hypertonic vs. isotonic fluids solutions. Detailed analysis of particular types of adverse events is presented in Table 3. The most frequently observed nosocomial infections were pneumonia, urinary tract infection, or bloodstream infection. For non-infectious complications: abdominal compartment syndrome, cerebral infarction, or deep vein thrombosis. A summary of the injuries related and the use of fluid types is presented in **Supplementary Digital File 1**.

Publication bias

The risk of bias of all the RCTs included in the meta-analysis is shown in **Supplementary Digital File 1.** Overall, the included RCTs suggested good quality in terms of risk of bias.

Discussion

This systematic review and meta-analysis evaluated data from RCTs of hypertonic fluid solutions (HSD or hypertonic saline) and isotonic

Table 2. Characteristics of outcomes: hypertonic fluid solutions versus isotonic fluid solutions.

Type of adverse event	Number of trials	Total numer of patients	Percentage of adverse event		Treatment effect (hypertonic vs. normotonic fluid solutions) OR/MD (95% CI)	P value	I^2, statistic, %
			HSD or HS	NS			
24-h survival							
HSD	2	575	89.4%	73.8%	2.99 (1.88–4.75)	< 0.001	18%
NS	2	332	86.4%	68.6%	3.01 (1.54–5.89)	0.001	23%
Total	4	807	88.6%	72.3%	2.99 (2.04–4.39)	< 0.001	0%
28- to 30-day survival							
HSD	4	972	72.6%	72.8%	1.06 (0.64–1.77)	0.81	56%
NS	2	844	73.1%	71.9%	1.14 (0.71–1.83)	0.59	49%
Total	5	1440	72.8%	71.4%	1.13 (0.75–1.70)	0.56	54%
Survival to discharge							
HSD	8	1511	72.8%	72.3%	1.13 (0.89–1.44)	0.30	36%
NS	4	1026	68.8%	68.1%	1.10 (0.83–1.44)	0.51	0%
Total	9	2081	71.2%	69.4%	1.19 (0.97–1.45)	0.09	48%
Survival at 3 months							
HSD	–	–	–	–	–	–	–
NS	1	228	55.3%	48.2%	1.33 (0.79–2.23)	0.29	–
Total	1	228	55.3%	48.2%	1.33 (0.79–2.23)	0.29	–
Length of hospital stay (days)							
HSD	3	361	–	–	1.05 (–1.88–3.98)	0.48	0%
NS	1	222	–	–	1.50 (0.42–2.58)	0.007	–
Total	4	583	–	–	1.45 (0.43–2.46)	0.005	0%
ARDS-free survival rate to day 28							
HSD	2	805	51.8%	54.9%	1.15 (0.84–1.57)	0.39	0%
NS	1	632	66.0%	65.4%	1.03 (0.73–1.43)	0.88	–
Total	2	1061	58.0%	54.9%	1.10 (0.85–1.44)	0.46	6%
Total fluids in first 24-h							
HSD	4	1268	–	–	–1.14 (–2.15—0.13)	0.03	0%
NS	1	632	–	–	–0.70 (–2.47–1.07)	0.44	–
Total	4	1524	–	–	–1.07 (–2.03—0.12)	0.03	0%
Hypernatremia (Na > 160 mEq/L) requiring intervention							
HSD	1	596	0.9%	1.3%	0.68 (0.13–3.54)	0.65	–
NS	1	632	1.9%	1.3%	1.48 (0.42–5.16)	0.54	–
Total	1	852	1.5%	1.3%	1.11 (0.35–3.52)	0.86	–
Overall mortality							
HSD	6	1459	17.3%	23.3%	0.72 (0.55–0.94)	0.01	20%
NS	3	914	23.7%	25.9%	0.90 (0.66–1.23)	0.51	10%
Total	7	1962	19.7%	24.8%	0.76 (0.61–0.94)	0.01	33%

ARDS — acute respiratory distress syndrome; CI — confidence interval; HSD — hypertonic fluid solutions; MD — mean difference; NS — izotonic/norotonic fluid solutions; OR — odds ratio

fluid solutions (0.9% NaCl or lactated Ringer's solution) for fluid resuscitation in fluid with traumatic hypovolemic shock, encompassing 15 studies and approximately 3264 adult trauma patients. At primary timepoints assessed (including at 28- to 30-days survival rate or survival to hospital dis-

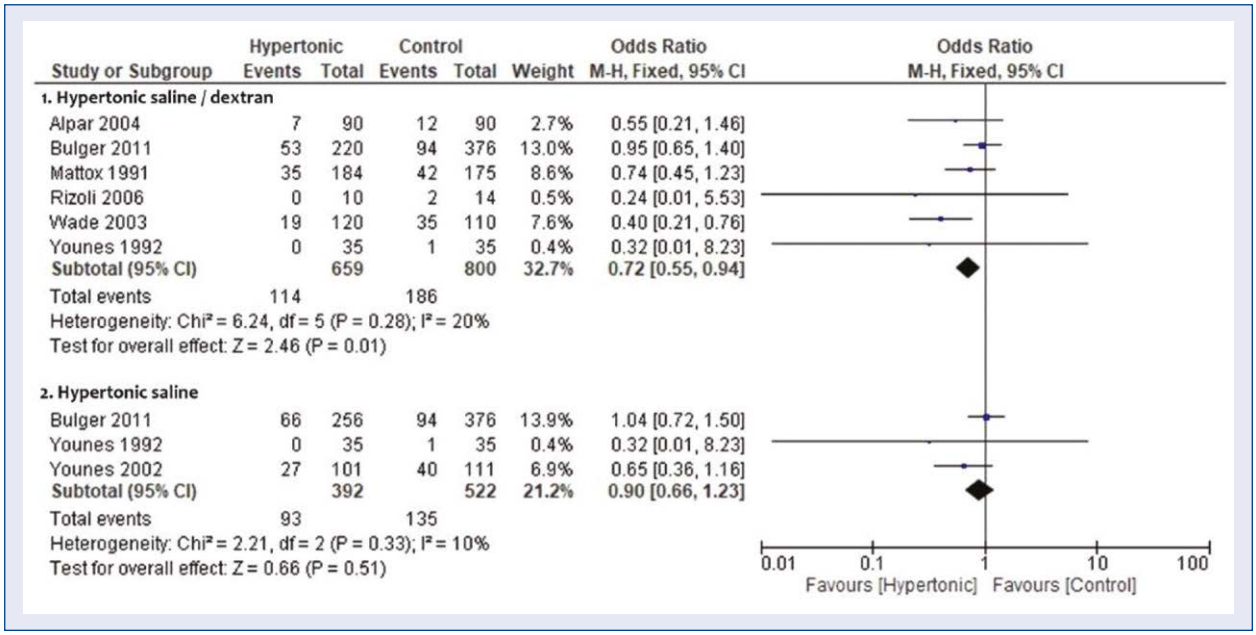

Figure 4. Forest plot of overall mortality rate while using hypertonic fluid solutions versus isotonic fluid solutions. The center of each square represents the weighted mean difference for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results.

charge), treatment with hypertonic fluid solutions was associated with a higher rate than treatment with isotonic fluid solutions). However, in the case of 24-survival rate treatment with hypertonic fluid solutions was related to a significantly higher survival rate, as well as significantly lower overall mortality.

0.9% sodium chloride solution is a basic crystalline fluid used in both pre-hospital and hospital care [29]. Due to high chlorine levels in the isotonic salt, there is a potential risk of metabolic hyperchloremic acidosis [30]. An alternative to 0.9% NaCl is Ringer's lactate, also called Hartman's solution, where the sodium and calcium concentration corresponds to the plasma concentration of these ions. However, it is important to note that the calcium contained in Ringer's lactate can bind to and interfere with some drugs. Indeed, Ringer's lactate is not free of disadvantages. Its main disadvantage is that it binds calcium to citrate anticoagulants in blood products, which can lead to clots in the bloodstream. Due to the above, Ringer's lactate is contraindicated as a diluent for blood transfusions [31, 32]. Hypertonic solutions, on the other hand, result in a slight improvement in volume and a rapid restoration of hemodynamics. The present analysis looked at hemodynamic parameters, such as SBP, and indicated that the use of hypertonic fluid solutions was associated with a statistically significant higher SBP than that of isotonic solutions ($p = 0.008$).

According to laboratory studies, hypertonic solutions especially improve the hemodynamics of microcirculation. This is due to the recruitment of intra-tissue volume by these fluids, which increases the volume of circulating blood and at the same time increases blood pressure. According to numerous studies, a 7.5% NaCl solution should be administered at 250 mL or 4 mL/kg body weight [33]. The same volume of hypertonic fluid administered compared to the isotonic solution causes a greater increase in the volume of fluid in the vascular bed, as this difference comes from the intracellular fluid, which penetrates from the cells into the extracellular space. Therefore, the use of hypertonic solutions should be reflected in the treatment of trauma patients as they allow to restore intravascular volume without increasing intravascular space [34]. Moreover, the present results showed no significant differences in adverse events between the treatment of hypertonic fluid solutions compared with isotonic solutions. However, it should be noted that many studies have not reported adverse events, which is a potential source of bias.

Limitations of the study

There are potential limitations in this systematic review and meta-analysis. One limitation is to

Table 3. Characteristics of adverse events between hypertonic fluid solutions versus isotonic fluid solutions.

Type of adverse event	Number of trials	Total numer of patients	Percentage of adverse event		OR (95%CI)	P value	I^2, statistic, %
			HSD or HS	NS			
Nosocomial inections							
Pneumonia	4	1695	9.9%	9.8%	0.95 (0.68–1.31)	0.75	0%
ARDS	1	422	0.0%	0.9%	0.20 (0.01–4.15)	0.30	–
Blood stream infection	2	1061	7.2%	6.1%	1.18 (0.72–1.93)	0.51	0%
Urinary tract infection	2	1061	6.1%	7.6%	0.79 (0.49–1.28)	0.34	0%
Wound infection	2	1061	5.8%	4.0%	1.50 (0.84–2.67)	0.17	0%
Intra-abdominal abcess	2	631	1.6%	0.3%	3.49 (0.57–21.54)	0.18	11%
Sinustis	1	209	0.9%	0.0%	2.71 (0.11–67.69)	0.54	–
Pseudomembranous colitis	1	209	1.0%	0.0%	2.73 (0.11–67.69)	0.54	–
Line infection	1	209	1.0%	0.0%	2.73 (0.11–67.69)	0.54	–
Sepsis	1	422	0.0%	1.4%	0.14 (0.01–2.74)	0.20	–
Other	1	311	3.8%	0.0%	8.27 (0.47–144.75)	0.15	–
One or more nosocomial infections	2	1061	23.0%	21.9%	1.06 (0.79–1.42)	0.70	0%
Noninfectious complications							
Acute renal failure	3	780	0.8%	1.6%	0.52 (0.14–1.95)	0.33	0%
Abdominal compartment syndrome	1	209	3.6%	8.1%	0.43 (0.13–1.47)	0.18	–
Cardiac arrest	2	568	1.0%	1.5%	0.71 (0.17–2.88)	0.63	
Myocardial infarction	3	780	1.0%	2.1%	0.52 (0.16–1.67)	0.28	0%
Cerebral infarction	2	421	4.3%	2.8%	1.61 (0.58–4.53)	0.36	0%
Dead bowel	1	359	0.0%	0.6%	0.32 (0.01–7.79)	0.48	–
Deep vein thrombolysis	1	209	0.9%	7.0%	0.12 (0.01–1.00)	0.05	–
Pulmonary embolism	2	568	0.3%	1.1%	0.39 (0.06–2.70)	0.34	0%
Coagulopathy	1	359	0.9%	0.0%	2.73 (0.11–67.69)	0.54	–

ARDS — acute respiratory distress syndrome; CI — confidence interval; HS — hypertonic saline; HSD — hypertonic fluid solutions; NS — isotonic/norotonic fluid solutions; OR — odds ratio

include only studies on the use of fluid therapy in patients with hypovolemic shock resulting from the injury. However, this was deliberate because it is a specific group of patients who require different treatment from patients with no hypovolemic shock due to the bleeding. The second limitation of the study is the fact that over the last years no randomized study has been published in the scope discussed in the article. With the development of medical technology and the creation of new guidelines of conduct, the authors believe that a multi-center study should be carried out, involving a large number of patients, which would verify the data from previous articles.

Conclusions

This systematic review and meta-analysis, which included only evidence from RCTs hypertonic saline/dextran or hypertonic saline compared with isotonic fluid did not result in superior 28- to 30-day survival as well as in survival to hospital discharge. However, patients with hypotension who received resuscitation with HSD had less overall mortality than patients who received conventional fluid. These findings highlight an urgent need for further research and guidance for physicians regarding when to administer fluid solutions to ensure optimal fluid therapy for the resuscitation of hypovolemic shock caused by acute hemorrhage.

Acknowledgments

The study was supported by the ERC Research Net and by the Polish Society of Disaster Medicine.

Conflict of interest: None declared

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VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 6, 978–984
DOI: 10.5603/CJ.a2020.0187

ISSN 1897–5593
eISSN 1898–018X

Factors and outcomes associated with improved left ventricular systolic function in patients with cardiomyopathy

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Abstract

Background: *Many patients in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) had a significant improvement (> 10%) in the left ventricular ejection fraction (LVEF) during the course of the study, but the factors and outcomes associated with such improvement are uncertain.*

Methods: *We examined factors and rates of mortality, cause-specific mortality, and implantable cardioverter-defibrillator (ICD) shocks associated with improvement in LVEF by analyzing patients in the SCD-HeFT who were randomized to placebo or an ICD and who had an LVEF checked during follow-up.*

Results: *During a median follow-up of 3.99 years, of 837 patients who had at least two follow-up LVEF measurements, 276 (33%) patients had > 10% improvement in LVEF and 561 (67%) patients had no significant change in LVEF. Factors significantly associated with LVEF improvement included female sex, white race, history of hypertension, a QRS duration < 120 ms, and beta-blocker use. Improvement in LVEF was associated with a significant improvement in survival. There was no significant association between improvement in LVEF and cause-specific death, but there was a significant association between improvement in LVEF and reduced risk of receiving appropriate ICD shocks.*

Conclusions: *About a third of patients in this analysis, who were randomized to placebo or an ICD in SCD-HeFT, had a significant improvement in LVEF during follow-up; improvement in LVEF was associated with improved survival but not with cause-specific death, and with decreased likelihood of receiving appropriate ICD shocks.* (Cardiol J 2022; 29, 6: 978–984)

Key words: defibrillator, implantable, heart failure, sudden cardiac death, arrhythmia

Introduction

Treatment guidelines for the prevention of sudden cardiac death in patients with heart failure and reduced left ventricular ejection fraction (LVEF) have been informed by the results of various groundbreaking clinical trials [1–3]. One such trial is the pivotal Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), which showed a 23% relative risk reduction in mortality with an implant-

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Received: 1.06.2020 Accepted: 2.12.2020 Early publication date: 31.12.2020

able cardioverter-defibrillator (ICD) in patients with New York Heart Association (NYHA) class II or III heart failure and LVEF ≤ 35% despite optimal medical therapy [2]. However, there is a subset of patients who receive an ICD for these criteria who later have improvement in LVEF to > 35%. The factors and outcomes associated with this improvement are not completely understood. A prior study showed that patients with heart failure with reduced ejection fraction, who later demonstrate recovery of LVEF above 40% have a lower rate of all-cause mortality and fewer hospitalizations than patients with heart failure with preserved ejection fraction (HFpEF) or heart failure with a persistently reduced ejection fraction (HFrEF) [4]. These findings suggest that an improved LVEF, even if it remains below normal, is associated with increased survival in patients with heart failure. However, this study was limited by the single-center retrospective study design. The SCD-HeFT overcomes these limitations by being a randomized clinical trial and by enrolling and following patients with a reduced LVEF from multiple medical centers. In this study, we aimed to examine factors and outcomes associated with a significant improvement in LVEF (> 10%) in SCD-HeFT. This magnitude in LVEF improvement was chosen at the inception of this analysis and was based on clinical judgment of what is considered meaningful LVEF improvement that is not due to errors in measuring LVEF while preserving a reasonable sample size.

Methods

Briefly, SCD-HeFT enrolled 2521 patients with NYHA class II or III heart failure due to ischemic or non-ischemic cardiomyopathy and an LVEF of ≤ 35%, who were randomly assigned to placebo (n = 847), amiodarone (n = 845), or a shock only, single-lead ICD (n = 829). All patients received optimal medical therapy at the time for heart failure. Patients were enrolled in SCD-HeFT from September 16, 1997, to July 18, 2001 and all patients were followed until October 31, 2003.

We selected patients from SCD-HeFT who were in the placebo or ICD arms and had at least three recorded measurements of LVEF during the course of the study with one measurement taken at baseline and at least two measurements obtained during follow-up. These follow-up LVEF measurements were performed ad hoc and were not mandated per the SCD-HeFT protocol. We required patients to have two follow-up LVEF measurements to decrease variability in these measurements and the likelihood of mis-readings.

Patients in the amiodarone arm were excluded from this analysis due to the difficulty to adequately adjust for the confounding factor that amiodarone may have on our results. In addition, prior studies have shown increased risk of mortality with amiodarone, especially in patients with NYHA class III symptoms [2, 5].

While for the primary analysis we defined LVEF improvement as > 10%, we considered another definition based on a recent report from the Journal of the American College of Cardiology (JACC) Scientific Expert Panel on Heart Failure with Recovered Left Ejection Fraction, which provided a working definition of heart failure with recovered LVEF as: (1) documentation of a decreased LVEF < 40% at baseline, (2) ≥ 10% absolute improvement in LVEF, and (3) a second measurement of LVEF > 40% [6].

In this analysis, the main outcome was all-cause mortality. Other outcomes of interest included cause-specific mortality and appropriate ICD shocks. Deaths were classified as cardiac or non-cardiac death, and when the event was cardiac, it was further classified as arrhythmic cardiac death, which includes death due to ventricular tachyarrhythmia or bradyarrhythmia, and non-arrhythmic cardiac death, which includes heart failure, non-arrhythmic non-heart failure, and other cardiac causes [7].

Per the SCD-HeFT protocol, the modality to measure LVEF at baseline and during follow-up was not specified. In the majority of patients, the baseline LVEF was measured by an echocardiogram (n = 1461), while the remainder were measured by contrast angiography (n = 436) and radionuclide angiography (n = 616). While granular data on the modality used to measure follow-up LVEF were not available, the vast majority of LVEF assessments during follow-up were done by echocardiography.

For descriptive analyses, we fit a linear mixed-effects model for the log-transformed LVEF and used the estimated slopes to stratify patients into groups consisting of patients with an increase in LVEF by > 10% vs. not. We log-transformed LVEF measurements and plotted the transformed measurements for each patient against time, and a best-fit line was obtained. The slope of the line was used to assess the overall change in LVEF over time, even if the LVEF initially decreased and then increased, or vice versa, which was then used to determine whether the patients showed > 10% or ≤ 10% improvement.

We compared these LVEF groups with descriptive statistics, with means and standard deviations

for continuous variables and counts and proportions for the categorical variables. In unadjusted analyses, we obtained Kaplan-Meier survival curves comparing the two LVEF groups and examined the mode of death with cumulative incidence functions.

In adjusted analyses, to examine all-cause mortality, we used joint longitudinal-survival models [8–10]. Such models have two components: a model for the longitudinal LVEF trajectory and a model for the survival data that incorporates features of the longitudinal LVEF model as predictors. With joint models, we note that the regression parameters for both the time-to-event and longitudinal outcomes are estimated jointly, unlike the procedure adopted for the descriptive analysis. Specifically, we modeled the log-transformed LVEF as a linear mixed--effects model regressed on time since randomization and baseline variables, and we used a Weibull proportional hazards survival regression model for time to death from all causes regressed on the subject-specific intercept and slope, dichotomized based on > 10% improvement in LVEF versus ≤ 10% improvement, from the longitudinal LVEF model and baseline variables including treatment assignment, age, sex, race, history of hypertension, diabetes, pulmonary disease, smoking, ischemic heart disease, prior myocardial infarction (MI), prior coronary artery bypass grafting (CABG), prior percutaneous coronary intervention (PCI), NYHA class of heart failure, QRS duration, baseline LVEF, and treatment with beta-blockers, diuretics, or angiotensin-converting enzyme inhibitors (ACEI).

To examine cause-specific mortality, we utilized joint longitudinal competing risks survival models, which were fit under the Bayesian approach using relatively non-informative priors with JAGS and the R-package rjags.

To examine the risk of appropriate ICD therapy, we fitted a mixed-effects model for the log-transformed LVEF regressed on time since randomization and adjusted for baseline covariates, and a logistic regression model for the outcome of appropriate shocks regressed on the subject-specific intercept and slope, dichotomized based on > 10% improvement in LVEF vs. ≤ 10% improvement. The variables included in this model were sex, age, race, presence or absence of ischemic heart disease, QRS duration, NYHA class of heart failure, history of smoking, diabetes, hypertension, pulmonary disease, prior MI, CABG, or PCI, and treatment with beta-blockers or ACEI. Patients who were classified as having received appropriate shock therapy were those who had documented evidence of appropriate shock therapy, in the presence or absence of other inappropriately delivered ICD therapy. Patients not in this group included those who received only inappropriately delivered shock therapy or no therapy at all.

All analyses were repeated in the subset of patients (n = 248) with at least one follow-up LVEF measurement of > 40%.

Results

Baseline characteristics of patients included (n = 837) and excluded (n = 839) from our analysis due to having fewer than three LVEF measurements are shown in **Supplementary Table 1**. Compared with patients who were excluded from the analysis, those who were included were more likely to be white and to have left bundle branch block and a higher baseline LVEF (25% vs. 23%). The included patients had lower rates of hypertension, diabetes, pulmonary disease, and ischemic heart disease, as well as lower baseline blood urea nitrogen and creatinine.

During a median follow-up of 3.99 years, 837 patients had at least one initial and two follow-up LVEF measurements. The average time to first follow-up LVEF was 1.02 ± 0.28 years, second follow-up was 2.39 ± 0.57 years, and third follow-up was 3.04 ± 0.98 years. The median follow-up times for patients included in this study were similar between patients with or without > 10% improvement in LVEF (4.04 vs. 3.97 years, respectively). Of these patients, 276 (33% of all patients, of whom 149 had an ICD) had a 10% improvement in LVEF and 561 (67% of all patients, of whom 267 had an ICD) had no significant change in LVEF. Of the 276 patients who demonstrated an improvement in LVEF > 10%, only 10 had a final LVEF that remained below 35%. The baseline characteristics of the patients in the two groups are listed in Table 1.

In the adjusted longitudinal model, there was a significant association between improvement in LVEF and female sex (p = 0.003, 1.09, 95% confidence interval [CI] 1.03–1.14), white race (p < 0.001, 1.13, 95% CI 1.08–1.19), history of hypertension (p < 0.001, 1.10, 95% CI 1.05–1.14), a QRS duration < 120 ms (p < 0.001, 1.16, 95% CI 1.12–1.20), and beta-blocker use (p = 0.01, 1.05, 95% CI 1.01–1.10). Notably, the type of cardiomyopathy (ischemic vs. non-ischemic) and prior coronary interventions were not associated with LVEF improvement.

In the adjusted survival model, improvement in LVEF was associated with a significant improvement in survival (hazard ratio [HR] 0.58, 95% CI

Table 1. Baseline characteristics between patient groups.

	No change in LVEF (n = 561)		Increase in LVEF > 10% (n = 276)		P
	Mean/Count	SD/Percentage	Mean/Count	SD/Percentage	
ICD	267	47.59	149	53.99	0.10
Age	59	16	58	16	0.50
Male	451	80.39	186	67.39	< 0.001
White	460	82	223	80.8	0.74
History of hypertension	285	50.8	153	55.43	0.23
History of diabetes	161	28.7	81	29.35	0.91
History of pulmonary disease	91	16.22	51	18.48	0.47
History of smoking	428	76.29	193	69.93	0.06
eGFR (0, 60) [mL/min]	175	31.36	72	26.18	0.14
eGFR ≥ 60 mL/min	383	68.64	203	73.82	—
Ischemic disease	309	55.08	115	41.67	<0.001
Prior CABG	153	27.27	59	21.38	0.08
Prior MI	275	49.02	97	35.14	< 0.001
Time MI (days)*	1652	2977.5	1510	2670	0.47
Prior PCI	126	22.46	42	15.22	0.02
History of syncope	0	0	0	0	NA
LVEF [%]	24	6	25	7	0.04
New York Heart Association 2	403	71.84	204	73.91	0.58
New York Heart Association 3	158	28.16	72	26.09	—
Anti-arrhythmic medication	0	0	0	0	NA
Beta-blockers	382	68.09	186	67.39	0.90
ACEI*	544	96.97	268	97.1	1.00
Diuretics	475	84.67	233	84.42	1.00
QRS duration [ms]	118	52	104	32	< 0.001
Right bundle branch block	30	5.35	13	4.71	0.82
Left bundle branch block	151	26.92	52	18.84	0.01

*Time MI: time from the most recent myocardial infarction to enrollment in SCD-HeFT; ACEI — angiotensin-converting enzyme inhibitor; CABG — coronary artery bypass grafting; eGFR — estimated glomerular filtration rate; ICD — implantable cardioverter-defibrillator; LVEF — left ventricular ejection fraction; MI — myocardial infarction; PCI — percutaneous coronary intervention

0.35–0.96). Additionally, there was a significant negative association between baseline LVEF and all-cause mortality. Specifically, patients with a 10% higher baseline LVEF had a lower mortality risk (HR 0.87, 95% CI 0.84–0.91). Importantly, ICD use was significantly associated with improved survival independently of change in LVEF and other clinical variables (HR 0.62, 95% CI 0.43–0.91).

Kaplan-Meier survival curves for the two groups of interest are shown in Figure 1. At 5 years, the survival probability for patients with > 10% improvement in LVEF was 0.90 (95% CI 0.85–0.95) while the survival probability for patients with no change in LVEF was 0.77 (95% CI 0.72–0.81), demonstrating that > 10% improvement in LVEF is associated with improved survival outcomes.

In the adjusted survival model, there was a significant negative association between baseline LVEF and rates of non-cardiac death, non-arrhythmic cardiac death, and arrhythmic cardiac death. Specifically, patients with a 10% higher baseline LVEF had lower rates of non-cardiac death (HR 0.95, 95% CI 0.91–0.98), non-arrhythmic cardiac death (HR 0.91, 95% CI 0.88–0.94), and arrhythmic cardiac death (HR 0.95, 95% CI 0.92–0.99). However, there was no association between improvement in LVEF and non-cardiac death (HR 0.92, 95% CI 0.61–1.41), non-arrhythmic cardiac death (HR 0.73,

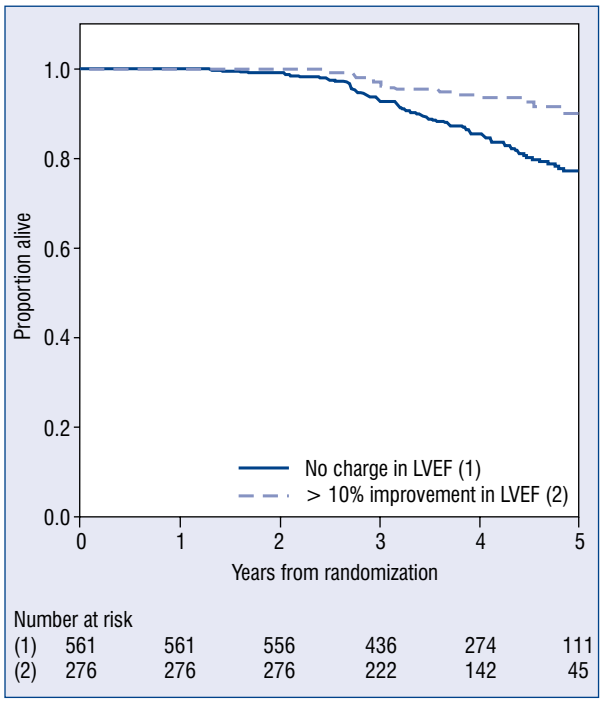

Figure 1. Kaplan-Meier survival curves for groups defined by left ventricular ejection fraction (LVEF). The number of patients at risk for each year in each LVEF category since randomization is listed below the Kaplan-Meier curve.

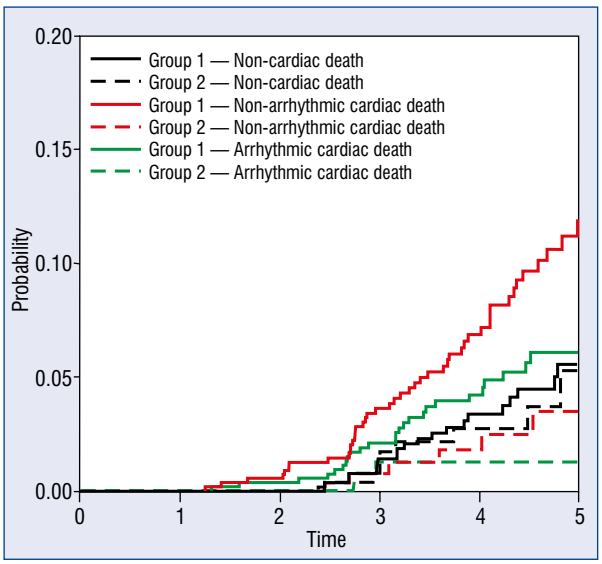

Figure 2. Cumulative incidence functions of cause-specific mode of death for left ventricular ejection fraction (LVEF) groups. Group 1 (solid lines) refers to patients who experienced no change (≤ 10% improvement) in LVEF while Group 2 (dashed lines) refers to patients who demonstrated an improvement of > 10% in LVEF.

95% CI 0.49–1.10), and arrhythmic cardiac death (HR 0.84, 95% CI 0.55–1.27). Cumulative incidence functions for cause-specific death between LVEF groups are shown in Figure 2.

Of 416 patients with an ICD, 96 received appropriate ICD therapy. There was a significant association between improvement in LVEF > 10% and decreased likelihood of receiving appropriate ICD shocks (odds ratio [OR] 0.27, 95% CI 0.08–0.77). However, there was no association between baseline LVEF and likelihood of receiving appropriate ICD shocks (OR 0.76, 95% CI 0.33–1.51).

Repeating all analyses in the subset of patients with at least one follow-up LVEF measurement of > 40% (n = 248, 206 had > 10% improvement in LVEF and 42 had ≤ 10% improvement in LVEF) showed an association between baseline LVEF and survival. However, there was no significant association between improvement in LVEF and overall survival, cause-specific death, and appropriate ICD shocks.

Discussion

This study demonstrates that a third of patients included in this analysis had > 10% improvement in LVEF, and factors associated with this improvement are female sex, white race, QRS < 120 ms, history of hypertension, and beta-blocker usage. Additionally, we demonstrated that > 10% improvement in LVEF was associated with lower risk of all-cause mortality and decreased likelihood of receiving appropriate ICD therapy.

There is a growing body of evidence demonstrating that patients with heart failure with recovered or significantly improved LVEF have a distinct clinical phenotype and physiology that are not properly captured or addressed in clinical trials [11–16]. Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF) found that patients who had a > 10% improvement in LVEF were more likely to be women, have a non-ischemic etiology of heart failure, have no prior MI, have a lower ejction fraction at baseline, and not be taking digoxin [14]. While both studies determined that factors such as age, diabetes, and renal insufficiency were not associated with LVEF improvement, some baseline patient characteristics associated with improved LVEF found in IMPROVE HF are not concordant with those found in our study, demonstrating the need for more investigations of this patient population. Prior studies have shown that patients with improved LVEF have improved survival and lower

risk of all-cause, cardiovascular, and heart failure--related hospitalizations, cardiac transplantation, or left ventricular assist device implantation when compared with patients with HFrEF [4, 14, 17]. Additionally, in a post hoc analysis of SCD-HeFT by Adabag et al. [18], patients with an improved LVEF to > 35% had a similar survival benefit from an ICD to those who did not demonstrate this improvement. It is noteworthy that using an LVEF of > 35% as a definition for LVEF improvement does not normalize the magnitude of change across patients, which Adabag et al. [18] acknowledged as a limitation. For example, a patient with LVEF improvement from 34% to 36% and a patient with improvement from 18% to 36% were analyzed as being the same by Adabag et al. [18]. We believe that our inclusion criterion of at least two follow-up LVEF measurements and our definition of a clinically significant improvement in LVEF as > 10% increase the likelihood that the measured change in LVEF and associated findings are real and clinically meaningful. Therefore, our analysis adds to prior studies by using a better definition of LVEF improvement, further identifying factors associated with LVEF improvement, and demonstrating that LVEF improvement is associated with a decreased likelihood of receiving appropriate ICD shocks.

Left ventricular ejection fraction improvement in patients with a primary prevention ICD presents a dilemma to clinicians and patients when deciding to replace the ICD generator at the end of battery life [15, 19–22]. Naksuk et al. [23] demonstrated that patients who had an LVEF improvement to > 35% and an increase in > 10% from baseline LVEF had a similar survival benefit before and after ICD replacement when compared with patients who had no improvement in LVEF. Our results support these findings by showing that ICD use was significantly associated with improved survival independent of change in LVEF and other clinical variables.

Whether LVEF improvement is associated with appropriate ICD therapies was examined by Schliamser et al. [24], who determined that while improvement in LVEF was associated with improved survival, it was not with a significant decrease in appropriate ICD shocks. These authors determined that rates of appropriate ICD therapy are similar between those with and without improvement in LVEF while we present evidence for a decreased incidence of receiving appropriate ICD therapy with improvement in LVEF. Although patients with > 10% improvement in LVEF in our study experienced a lower incidence of appropriate ICD therapy, there was still a clear survival benefit to having an ICD; therefore, this finding does not justify forgoing ICD generator replacement at the end of battery life.

Limitations of the study

There are several limitations to this analysis. This was a retrospective analysis of prospectively collected data; therefore, we cannot rule out residual confounding factors and selection bias. We were not able to examine subgroups of interest like patients who experience an improvement of > 10% yet remain beneath an LVEF of 35% (10 out of 276 patients).

Follow-up LVEF assessment was not protocol driven, potentially leading to other sources of bias. Also, the observed changes in LVEF, read at enrolling centers and not at a central core facility, may partially be the result of differences in measurement technique or user variability. Approximately 50% of patients included in this analysis had ischemic heart disease, and data regarding the revascularization procedures conducted during follow-up were unavailable. Additionally, specific data regarding heart rhythm, therapeutic procedures, and other drugs including digoxin, angiotensin receptor blockers, and aldosterone antagonists were also unavailable. Some may critique our definition of an improvement in LVEF. We note that the > 10% improvement in LVEF was chosen at the inception of this analysis because it was thought to be less prone to errors in reading (e.g. from choosing a 5% change). In fact, our analysis provides evidence that a > 10% change in LVEF is associated with changes in clinical outcomes such as mortality and rates of appropriate ICD therapy. Patients included in this analysis had at least two follow-up LVEF measurements, which may have introduced selection-bias against patients who died prior to having a repeat LVEF measurements, and it may reflect differences in overall quality of care. Although repeating the analyses in the subset of patients with at least one follow-up LVEF > 40% showed that there was no significant association between improvement in LVEF and overall survival, cause-specific death, and appropriate ICD shocks, these analyses were limited by the small sample size. Larger studies are needed to examine the association between LVEF improvement and outcomes in patients with at least one follow-up LVEF > 40%. Finally, optimal medical therapy of heart failure has significantly changed since the completion of SCD-HeFT, which may further influence factors that predict LVEF improvement and limit the applicability of these findings to heart failure patients today.

Conclusions

About a third of patients in this analysis, who were randomized to placebo or an ICD in SCD-HeFT, had > 10% improvement in LVEF during follow-up. Improvement in LVEF was associated with added survival benefit and decreased likelihood of receiving appropriate ICD shocks; however, there was no association with decreased risk of non-cardiac death and arrhythmic- and non-arrhythmic-related cardiac death. While female sex, white race, QRS < 120 ms, history of hypertension, and beta-blocker usage are associated with LVEF improvement, future studies should determine whether additional factors and tests can improve the prediction of LVEF improvement and associated outcomes.

Acknowledgments

This work was supported by the Duke University Medical Scientist Training Program (to D.S.E.) and the National Institute of General Medical Sciences at the National Institutes of Health (5T32GM007171-45 to D.S.E.).

Conflict of interest: None declared

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VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 6, 985–993
DOI: 10.5603/CJ.a2020.0104

ISSN 1897–5593
eISSN 1898–018X

Spectrum of transthyretin gene mutations and clinical characteristics of Polish patients with cardiac transthyretin amyloidosis

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Abstract

Background: *Transthyretin amyloidosis (ATTR) is a rare, life-threatening systemic disorder. We present first findings on the cardiac hereditary ATTR in Poland.*

Methods: *Sixty-eight consecutive patients with suspected or known cardiac amyloidosis were evaluated, including blood tests, standard 12-lead electrocardiography (ECG) and transthoracic echocardiography. ATTR was confirmed histologically or non-invasively using 99mTc-DPD scintigraphy. Transthyretin (TTR) gene sequencing was performed.*

Results: *In 2017–2019, 10 unrelated male patients were diagnosed with hereditary ATTR. All patients had very uncommon TTR gene mutations: 7 patients had p.Phe53Leu mutation, 2 patients had p.Glu109Lys mutation and 1 patient had p.Ala101Val mutation. The age of onset ranged from 49 to 67 years (mean [SD] age, 58.7 [6.4] years). On ECG, most patients (70%) had pseudoinfarct pattern and/or low QRS voltage. The maximal wall thickness (MWT) on echocardiography varied considerably among the patients from moderate (16 mm) to massively increased (30 mm). Most patients (90%) had decreased left ventricular ejection fraction (mean [SD], 43 [11] %). On follow-up, we observed progressive heart failure in almost all cases. The first patient with p.Phe53Leu mutation died of heart failure, the second died suddenly, the third successfully underwent combined heart and liver transplant with 15 months survival from the surgery. The patient with p.Ala101Val mutation died of stroke.*

Conclusions: *According to available data, this is the first time that the types of TTR mutations and the clinical characteristics of Polish patients with cardiac hereditary ATTR have been described. Previous literature data about Polish background in families with p.Phe53Leu mutation and the present results, suggest that this TTR mutation might be endemic in the Polish population.* (Cardiol J 2022; 29, 6: 985–993)

Key words: cardiac amyloidosis, hereditary transthyretin amyloidosis, transthyretin amyloidosis, transthyretin cardiomyopathy, transthyretin mutation

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Received: 19.12.2019 Accepted: 13.07.2020 Early publication date: 11.08.2020

Introduction

Transthyretin amyloidosis (ATTR) is a rare, life-threatening systemic disorder. It results from extracellular deposition of transthyretin (TTR)--derived amyloid fibrils leading to dysfunction of affected organs. It occurs in both a wild-type form (wtATTR) and a hereditary form (hATTR) transmitted in an autosomal dominant inheritance with a variable penetrance [1]. Without treatment the disease progresses gradually. According to recent reports, median survival of patients with cardiac ATTR is approximately 25 months to 41 months from onset of the first symptoms. The prognosis is worse in cases of hATTR [2].

More than 140 different disease-causing mutations of the *TTR* gene have been reported [3]. The prevalence of different mutations varies according to ethnicity and geographic region. Although there are endemic regions of ATTR such as Portugal, Sweden and Japan with certain high frequency mutations, the disease has been identified worldwide [1, 4–6].

Transthyretin amyloidosis is known for its heterogeneity. Some *TTR* mutations induce cardiomyopathy as a main presentation while others are associated primarily with familial amyloid polyneuropathy. Other manifestations of hATTR often include gastrointestinal, renal and ocular symptoms as well as carpal tunnel syndrome [2, 7, 8]. The phenotypic expression can vary not only among mutations but within mutations. The geographical origin and ethnic background of the patient can have implications for disease onset and initial symptoms for a given mutation [1]. Surprisingly, cases of monozygotic twins, in which one twin develops the disease and the other does not, have also been reported, proving that there are factors modulating amyloid fibrils formation [9, 10].

Screening of the *TTR* gene and differentiation hATTR from wtATTR have serious clinical implications. In contrast to wtATTR, patients with hATTR may benefit from liver transplant or combined heart and liver transplant. Information on the type of *TTR* mutation provides prognostic value not only for the proband but also for his family members. The spectrum of *TTR* gene mutations in Polish patients with cardiac ATTR and their clinical characteristics have not yet been described. Therefore, this study presents for the first time the results of genetic testing and a description of clinical heterogeneity of patients with cardiac ATTR diagnosed in our centers during the last 3 years.

Methods

The study complies with the principles outlined in the Declaration of Helsinki and was approved by the Institutional Ethics Committee.

Study population

The study included consecutive patients diagnosed with hereditary cardiac ATTR in 2017–2019. 68 consecutive patients examined with suspected or known cardiac amyloidosis were referred to two cardiology centers for further evaluation. All patients underwent routine assessment including medical history, physical examination, blood tests with N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitive cardiac troponin T (hs-cTnT) measurements, as well as standard 12-lead electrocardiography (ECG) and transthoracic echocardiography. ATTR was confirmed histologically with immunohistochemistry and/or non-invasively (intensive cardiac uptake at 99mTc-DPD bone scintigraphy) [11]. Light chain amyloidosis was excluded by free light chain testing: conventional electrophoresis and immunofixation of serum or urine. Patients underwent *TTR* gene sequencing as part of their routine workup. Neurological assessment was performed in all patients with hATTR. Informed written consent was obtained from each participant included in the study.

Analysis of *TTR* gene

Patients assessed at the Institute of Cardiology, Warsaw, Poland underwent genetic testing in a local laboratory. Genomic DNA in all patients was extracted from whole blood leukocytes with the salting-out method. The entire coding regions of the *TTR* gene together with splice sites were sequenced with the Sanger method using a 3130xL Genetic Analyzer (Life Technologies, Foster City, California, United States) and the Big Dye Terminator v1.1 Cycle Sequencing Kit (Life Technologies) according to manufacturer instructions. For chromatograms analysis Variant Reporter 1.1 (Life Technologies) was used. All patients from both centers also underwent commercially available *TTR* genetic testing developed and performed by Centogene AG, Rostock, Germany.

Results

Of the 68 patients, 10 (14.7%) male patients had cardiac hATTR, 19 (27.9%) had wtATTR, 9 (13.2%) were diagnosed with cardiac light chain amyloidosis and 30 (44.1%) had no evidence of

amyloid deposition. All patients with hATTR had very uncommon *TTR* gene mutations: p.Phe53Leu (NM_000371.3:c.157T>C, rs121918068), p.Glu109Lys (NM_000371.3:c.325G>A) and p.Ala101Val (NM_000371.3:c.302C>T). The most prevalent was p.Phe53Leu mutation identified in 7 out of 10 patients with hATTR. The baseline clinical data of the patients with hATTR was shown in Table 1.

The age of onset ranged from 49 to 67 years (mean [SD] age, 58.7 [6.4] years) and differed considerably even among patients with the same mutation. Family history suggestive of cardiac amyloidosis was positive in 6 probands. On ECG, most patients (70%) had a pseudoinfarct pattern in precordial leads. Similarly, most patients (70%) had low QRS voltage in limb leads. Echocardiography revealed concentrically increased thickness of left ventricular (LV) wall in all patients. The maximal wall thickness (MWT) varied markedly among the patients from moderate (16 mm) to massively increased (30 mm) (mean [SD] MWT, 22 [4] mm). Most patients (90%) had decreased LV ejection fraction (LVEF) (mean [SD] LVEF, 43 [11] %). Baseline laboratory examination revealed increased levels of hs-cTnT and NT-proBNP in all patients. Even individuals with initially mild symptoms of heart failure (HF) had elevated serum concentrations of examined biomarkers (Fig. 1).

Seven patients presented with mixed-phenotype and suffered also from polyneuropathy. Only 2 patients primarily presented with polineuropathy (patients with p.Phe53Leu mutation) and cardiac assessment was performed after familial amyloid polyneuropathy was confirmed. Five other patients were diagnosed with polyneuropathy during follow-up. Of the 10 patients, 7 suffered from gastrointestinal disturbances. However, it was difficult for the patients to determine at what stage of the disease the first symptoms from the gastrointestinal tract appeared and whether they preceded the appearance of cardiac manifestations. Five patients presented with carpal tunnel syndrome, the so-called 'red flag' symptom for ATTR, which evidently preceded the appearance of cardiac manifestations. One of the patients had ocular symptoms, which seem to occur frequently in patients with p.Glu109Lys mutation. Orthostatic hypotension was present in 4 patients with advanced symptoms of HF regardless of the presence of polyneuropathy.

Clinical characteristics of patients with p.Phe53Leu *TTR* mutation

Although the patients with p.Phe53Leu *TTR* mutation had heterogeneous clinical presentation and were diagnosed at various stages of the disease, ranging from accidentally discovered disease in asymptomatic patient to the advanced stages of biventricular HF, all of them had significant abnormalities on ECG and echocardiography from the first assessment. It is noteworthy that all patients except for proband 6, who was diagnosed at a very early stage of the disease, had reduced LV systolic function. Interestingly, symptoms of HF assessed in accordance to the New York Heart Association (NYHA) classification, did not reflect the impairment of LV systolic function — patients with only mild symptoms of HF had already significantly impaired LVEF (Fig. 2). Most of the patients with p.Phe53Leu mutation (71.4%), except for 2 cases, presented with mixed phenotype and had also polyneuropathy at various stages of advancement.

The case of proband 3 who was diagnosed with hATTR at a time when he was completely asymptomatic with confirmed good exercise tolerance, is particularly interesting. He was referred for cardiological assessment due to ECG abnormalities found during annual medical check-up (sinus rhythm with low QRS voltage in the limb leads and nonspecific ST-T wave changes). Physical examination and chest X-ray were normal. However, baseline levels of NT-proBNP and hs-cTnT were significantly increased from the beginning. Echocardiography revealed moderately increased LV wall thickness (MWT 16 mm), mildly enlarged left atrium and significantly reduced LV systolic function without segmental hypokinesis (LVEF 40%). Moreover, coronary computed tomography angiography, performed to reveal the reasons for the impaired LVEF, showed right coronary artery (RCA) chronic total occlusion as well as stenosis in the left main coronary artery, in the left anterior descending artery (LAD) and in the left marginal artery. The patient was diagnosed with occult multivessel coronary artery disease. Invasive coronary angiography with fractional flow reserve demonstrated that only stenosis in the LAD was hemodynamically relevant. Percutaneous coronary intervention using drug eluting stents was performed for occlusion in the RCA and for stenosis in LAD. Although at 20-month follow-up, the patient remained asymptomatic, with good exercise tolerance confirmed on ECG exercise testing, further deterioration of LV function and a significant increase of cardiac biomarkers were observed. HF symptoms progressed rapidly, however signs of polyneuropathy never appeared in this patient. Ultimately, the patient underwent successful combined heart and liver transplantation.

Table 1. Baseline clinical characteristics and outcome of patients with hereditary transthyretin (TTR) amyloid cardiomyopathy.

Patient	1	2	3	4	5	6	7	8	9	10
TTR mutation	p.Phe53Leu	p.Phe53Leu	p.Phe53Leu	p.Phe53Leu	p.Phe53Leu	p.Phe53Leu	p.Phe53Leu	p.Glu109Lys	p.Glu109Lys	p.Ala101Val
Age of onset	64	57	49	58	64	55	66	49	57	67
NYHA class	III/IV	I	I	II	IV	I	III	II	III	II/III
Positive family history	+	+	–	–	+	+	+	+	–	–
ECG	Ventricular pacing, AF	SR, SVT, nsVT	SR	SR	SR	SR	AF, nsVT	SR	AF	AF
Low QRS voltage	NA	+	+	+	+	+	–	+	–	+
Pseudoinfarct pattern	NA	+	–	–	+	+	+	+	+	+
NT-proBNP [pg/mL]	10954	1199	925	1049	10780	191	13541	394	2340	6070
hs-cTnT [ng/L]	103	98	28	51	122	26	136	19	50	78
MWT [mm]	30	20	16	18	25	20	20	24	23	27
Increased RV wall thickness	+	–	–	+	–	–	–	–	+	+
LVEF [%]	30	40	40	55	40	62	29	55	45	35
Restrictive LV filling pattern	–	–	+	–	+	–	–	+	+	–
Pericardial effusion	+	–	–	–	+	–	+	+	+	+
Orthostatic hypotension	+	–	–	–	+	–	+	–	–	+
Polyneuropathy	+	+	–	+	–	+	+	–	+	+
CNS manifestations	+	–	–	–	–	+	+	–	–	+
Small fiber neuropathy	+	+	–	+	–	+	+	–	+	+
Gastrointestinal manifestations	+	+	–	–	+	+	–	+	+	+
Ocular manifestations	–	–	–	–	–	–	–	–	–	+
Biceps tendon rapture	–	–	–	–	+	–	–	–	–	–
Chronic kidney disease	–	+	–	–	+	–	+	–	–	–
Carpal tunnel syndrome	+	+	–	–	–	–	–	+	+	+
Outcome	Death at age of 67 due to HF	SCD at age of 59	Successful combined heart and liver trans-plantation	Alive	Alive, progressive HF	Alive, progressive neuropathy	Alive	Alive	Awaiting combined heart and liver trans-plantation	Death at age of 71 due to stroke

AF — atrial fibrillation; CNS — central nervous system; ECG — electrocardiogram; HF — heart failure; hs-cTnT — high-sensitivity cardiac troponin T; LV — left ventricular; LVEF — left ventricular ejection fraction; MWT — maximal wall thickness; NA — not applicable; nsVT — nonsustained ventricular tachycardia; NT-proBNP — N-terminal pro-B-type natriuretic peptide; NYHA — New York Heart Association classification of heart failure; RV — right ventricular; SCD — sudden cardiac death; SR — sinus rhythm; SVT — supraventricular tachycardia

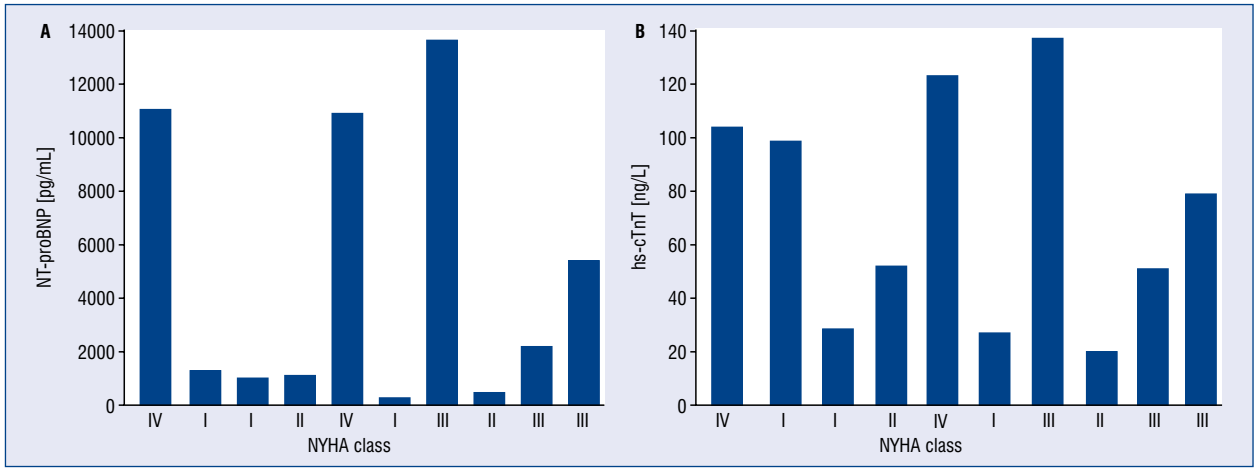

Figure 1. Baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP; normal range: 0–125 pg/mL, **A**) and high-sensitive cardiac troponin T (hs-cTnT; normal range: 0–14 ng/L, **B**) levels in the patients classified according to the New York Heart Association (NYHA) classification of heart failure.

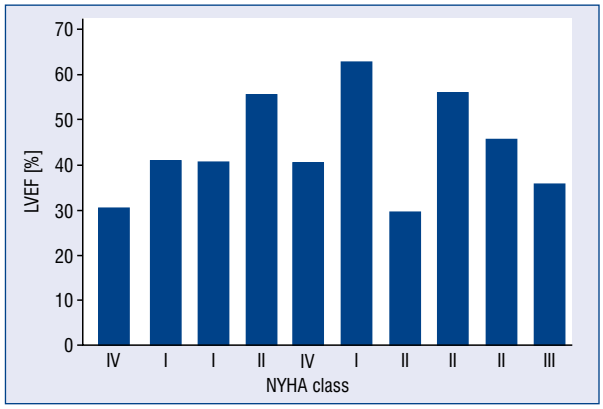

Figure 2. Left ventricular ejection fraction (LVEF) in the patients classified according to the New York Heart Association (NYHA) classification of heart failure.

Interestingly, proband 1, a 64-year-old male with advanced biventricular HF, also had a history of ischemic heart disease treated with coronary artery bypass graft surgery. The patient had many comorbidities, including atrial fibrillation (AF) with third--degree atrioventricular block requiring pacemaker implantation, subsequently upgraded to cardiac resynchronization therapy, polyneuropathy grade 1 (he was able to walk without aid), recurrent pleural effusion and bilateral carpal tunnel syndrome.

Clinical characteristics of patients with p.Glu109Lys *TTR* mutation

Two patients with features of restrictive cardiomyopathy and carpal tunnel syndrome were identified with the p.Glu109Lys *TTR* mutation. Proband 8, a 49-year-old male, was diagnosed at a very early stage of the disease (NYHA class I), without overt signs of HF, with only mildly increased levels of cardiac serum biomarkers. However, echocardiography and ECG demonstrated significant abnormalities, including mildly reduced LV systolic function, restrictive LV filling pattern, small pericardial effusion as well as pseudoinfarct pattern and low QRS voltage in limb leads. The patient had a family history suggestive of cardiac amyloidosis.

A second patient with p.Glu109Lys *TTR* mutation, proband 9, was referred to our institution due to a 3 month history of progressive exertional dyspnea (NYHA class III at initial presentation) and massive lower-limbs edema. He also suffered from periorbital purpura, weight loss, mild symptoms of polyneuropathy (predominantly paresthesias) and ocular symptoms including vitreous opacities. His family history was unremarkable. ECG demonstrated occult AF of unknown duration, pseudoinfarct pattern, nonspecific ST segment and T-wave abnormalities. QRS voltage was in the lower range of the norm. The chest X-ray showed pulmonary congestion and small left sided pleural effusion. Echocardiography revealed increased LV wall thickness (max. 23 mm at interventricular septum), sparkling echoes, restrictive LV filling pattern and decreased LVEF 45%. Right ventricle (RV) was enlarged with increased wall thickness. Both atria were augmented and small pericardial effusion was present. Diagnosis of ATTR was

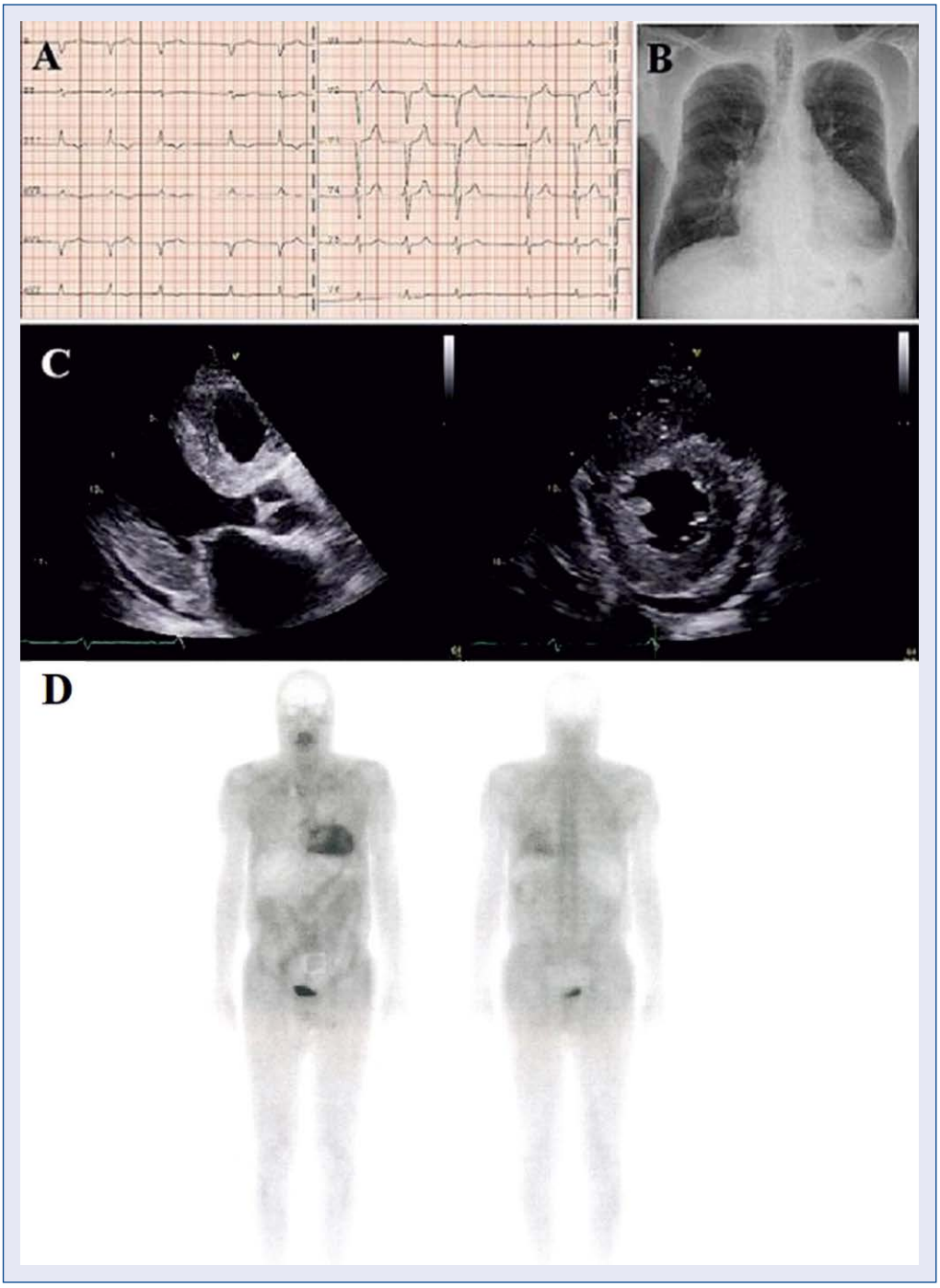

Figure 3. Clinical data of proband 9; **A.** Standard 12-lead electrocardiogram; **B.** Chest X-ray; **C.** Transthoracic echocardiography; **D.** Bone scintigraphy with 99mTc-DPD tracer confirming transthyretin amyloid cardiomyopathy in anterior (left) and posterior (right) whole body scan.

confirmed with bone scintigraphy with 99m-DPD tracer (Fig. 3A–D). Two months after initial presentation the patient was stable but with a further increase in NT-proBNP and hs-cTnT levels (3513 pg/mL and 68 ng/L, respectively). He was referred for compassionate treatment with tafamidis as a bridge to combined heart and liver transplantation.

Clinical characteristics of patients with p.Ala101Val *TTR* mutation

Only 1 patient, 67-year-old male with progressive HF (NYHA class II/III at initial presentation), permanent AF, significantly increased levels of cardiac biomarkers was identified with p.Ala101Val *TTR* mutation. Echocardiography of this patient

showed massively increased RV and LV wall thickness (max. 27 mm at interventricular septum), significantly decreased LV systolic function (LVEF 35%) and small pericardial effusion. The patient also suffered from orthostatic hypotension, bilateral carpal tunnel syndrome, mild symptoms of polyneuropathy and monoclonal gammapathy of unknown significance. Due to the presence of only microdeposits of amyloid in the tissue biopsy and no access to 99mTc-DPD scintigraphy at that time, diagnosis of ATTR in the patient was established using mass spectrometry.

Follow-up

Information about the outcome of patients with hATTR are collected in Table 1. In almost all cases progressive HF was observed. One patient with p.Phe53Leu *TTR* mutation (proband 1) died of biventricular HF, proband 2 died due to sudden cardiac death, proband 3 successfully underwent combined heart and liver transplantation with a 15-month survival from the surgery. One patient with p.Glu109Lys *TTR* mutation, proband 9, is currently waiting for combined heart and liver transplantation. Patient with p.Ala101Val *TTR* mutation (proband 10) died of stroke.

Discussion

Herein, we report for the first time the types of *TTR* mutations and the clinical characteristics of Polish patients with cardiac hATTR. Currently, literature data on Polish patients with cardiac amyloidosis concerns mainly light chain amyloidosis and consists of only a few case reports and two original papers [11–15]. The presented study, although based on the small cohort of patients from two cardiology centers, fills an important gap in diagnosis and clinical management of cardiac ATTR in Poland. This research highlights that improvements in diagnostics, in particular introducing genetic analysis of the *TTR* gene and 99mTc-DPD scintigraphy into a routine diagnostic path of patients with suspicion of ATTR, hugely facilitates diagnostics. Moreover, it allows to perform a non-invasive diagnosis [8, 16]. It is crucial to identify patients with ATTR, especially now, when the targeted treatment of ATTR is possible.

The present study reports patients with unexpectedly rare *TTR* mutations: p.Phe53Leu, p.Ala101Val and p.Glu109Lys. Surprisingly, none of the most prevalent *TTR* variants: p.Val50Met, p.Val142Ile or p.Thr80Ala, were identified [4, 17, 18]. Moreover, a high incidence of p.Phe53Leu *TTR* mutation were observed. This occurred in the majority of the patients (70%).

The phenylalanine 53 is highly conserved amino acid of the TTR protein across species [19]. Position 53 of TTR protein is not directly involved in the formation of the transthyretin tetramer, however, loss of an aromatic ring associated with phenylalanine, may change the molecule conformation and lead to fibril formation [20]. The p.Phe53Leu *TTR* mutation was described previously only in 7 unrelated families including 2 American families of Polish descent and single Swedish, Taiwanese, Chinese, Hungarian and Israeli families [19–25]. This mutation was associated mostly with late-onset, progressive polyneuropathy and simultaneous presentation of severe cardiomyopathy. Previous literature data about a Polish background in families with p.Phe53Leu mutation and our findings (another 7 unrelated Polish families identified with p.Phe53Leu mutation) imply that this *TTR* mutation might be very frequent in the Polish population [20, 21]. Of note, almost all of the patients with p.Phe53Leu mutation presented in this study (85.7%) were of south Poland origin, suggesting that this might be an endemic region, where p.Phe53Leu mutation is found with high frequency. It is also possible that this rare mutation was introduced into the population by a common ancestor. However, based on available data it is not possible to prove so-called "founder effect". The heterogeneous clinical presentation of the patients with p.Phe53Leu *TTR* mutation (different age of onset, concomitant polyneuropathy but not in all cases) suggests also that other genetic or environmental factors may be involved in the disease development and progression.

p.Glu109Lys *TTR* mutation was reported previously only in 3 families and is characterized by early onset, concomitant ocular manifestation and severe phenotype with early heart dysfunction leading to heart and liver transplantation [26–28]. A similar course of the disease was observed in the case of proband 9, including the rapid progression of HF and ocular manifestations.

p.Ala101Val *TTR* mutation is an unusually rare mutation. So far, only 2 patients were previously reported with this mutation, including 1 patient from Institute of Cardiology who was diagnosed genetically in the National Amyloidosis Center in London in 2008 [17]. The patient suffered from severe biventricular HF with massive leg edema, persistent pericardial and pleural effusion requiring recurrent hospitalizations. ECG demonstrated sinus rhythm, first degree atrioventricular block

(PR 320 ms), low QRS voltage in limb leads and regression of r waves in lateral (V5–V6) leads. Echocardiography demonstrated features of restrictive cardiomyopathy with concentrically increased LV wall thickness (max. 15 mm), moderated left atrium enlargement and mildly decreased LV systolic function (LVEF 50%). During follow-up, further deterioration of LV function was observed (LVEF 38%) as well as features of moderate pulmonary hypertension (PASP 40 mmHg), thickening of RV wall and dilatation of both atria. The patient died of advanced HF while awaiting heart transplantation.

In the present study, in line with the previous literature data, a high sensitivity of cardiac biomarkers for diagnostic and prognostic purposes was observed [29]. Even patients with only mild symptoms of HF (NYHA I) or asymptomatic patients, had already elevated serum levels of cardiac biomarkers (Fig. 1).

Conclusions

The high prevalence of p.Phe53Leu *TTR* mutation in the study group and in previous literature data suggest that a possible endemic mutation has been found among Polish patients with cardiac hATTR. Considering the fact that the diagnosis of cardiac hATTR has clinical implications and information on the presence of *TTR* mutation is useful for affected patients, pre-symptomatic carriers and their relatives, we should identify patients with this disorder and better define the disease. The emergence of novel treatments in cardiac ATTR, which may improve patient prognosis is another argument for the intensification of epidemiological and cross-sectional studies like this.

Acknowledgments

We would like to acknowledge Centogene AG, Rostock, Germany for support in genetic testing.

Conflict of interest: None declared

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VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 6, 994–1003
DOI: 10.5603/CJ.a2020.0079

ISSN 1897–5593
eISSN 1898–018X

Prediction of the hypertension risk in teenagers

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Abstract

Background: *Creation of a hypertension risk stratification model and development of an algorithm to detect hypertension in teenagers.*

Methods: *The study group consisted of 690 middle and high school students, aged 15–17 years, from the metropolitan area of Warsaw, Poland. Information concerning family history and presence of risk factors for cardiovascular disease was gathered. Three-time blood pressure measurements were taken during at least two separate visits, which were at least a week apart, using the auscultatory method, according to standard procedures. Anthropometric measurements included: body weight, height, arm, hip and abdominal circumference, skin-fold thickness measured on the rear surface of an arm, below the inferior angle of the scapula and at the belly. Following indexes were determined: body mass index, waist to hip ratio (WHR), waist to height ratio, hip to height ratio.*

Results: *A logistic regression model, describing the risk of hypertension in adolescents aged 15–17 was invented.* $\hat{\pi}(x) = \frac{e^{\hat{g}(x)}}{1 + e^{\hat{g}(x)}}$ *where* $\hat{g}(x) = -0.097 \times height + 0.085 \times weight + 7.764 \times WHR + 1.312 \times$ *× family hypertension. Family hypertension means presence of hypertension among members of the closest family. The formula was created, allowing the pre-selection of adolescents at risk of hypertension during screening. Next an algorithm for the detection of hypertension for practical use was proposed.*

Conclusions: *Body weight, WHR and incidence of hypertension in the family are the strongest predictors of hypertension in teenagers. Proposed screening algorithm can be a useful tool for selecting teenagers at risk of hypertension and in need of specialized diagnostics and care.* (Cardiol J 2022; 29, 6: 994–1003)

Key words: primary hypertension, hypertension risk stratification, hypertension in children, hypertension in teenagers, prediction of hypertension

Introduction

Hypertension is not an isolated phenomenon in pediatric populations and needs to be treated in the same way as other diseases of a chronic nature. The strategy of prevention and treatment in the light of available research should be long-term and focused on reducing the number of complications in adulthood.

Hypertension affects 20–30% of the global population and in most cases its form is essential hypertension [1–9]. Polish multicenter population based studies showed that hypertension affects about 30–35% of adult Poles and the incidence of hypertension increases with age [10–13]. The number of adolescents with essential hypertension has rapidly increased in number. According to some authors, in older age groups the problem of hypertension may affect eight or even over a dozen percent of adolescents [8, 14–17].

The incidence of hypertension in the population under 18 years of age is estimated at 2–5%. More recent epidemiological studies have revealed a marked increase in the percentage of children with primary hypertension. It is estimated that it affects 4% of the pediatric population and increases with age and that the percentage of children with high normal blood pressure (BP) valuesare more than twice as high (9%). The results of the OLAF study carried out in Poland from 2007 to 2009 with the participation of over 17,000 students aged 6.5–18.5 years, were similar to those in previous studies and showed the incidence of hypertension in the studied age group to range between 3% and

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Received: 15.07.2019 Accepted: 5.05.2020 Early publication date: 3.06.2020

3.5% [18, 19]. Essential hypertension is the predominant form of hypertension in children older than 10 years of age [20, 21].

In all developed and developing countries there is a tendency for diagnosing essential hypertension in younger and younger children, which goes hand in hand with the observed parallel increase in the prevalence of overweight and obesity in the pediatric age [22–26].

It is estimated that in Europe, 1 in 5 children is overweight or obese, and approximately 400,000 new cases of overweight and obesity are annually recognized among children and adolescents [27, 28].

With increasing rates of obesity in children and adolescents, the proportion of primary hypertension increases and it is diagnosed in about 50% of all children evaluated due to hypertension [18]. Fortunately, in recent years the percentage of obese children in developed countries has been reported to be in a plateau phase or even decreasing in number. According to recent studies, 11–12.5–14.8% of Polish teenagers are overweight and obese. Several other large population analyzes, that had been carried out in Poland in the last few years — depending on the methodology used — have revealed that 8–10.5–14.2% of boys are overweight and 7–6.8–6.4% of boys are obese. In girls, respectively — overweight is observed in 10.5–12–13%; obesity in 11–10–7.7%. Excess body weight is significantly higher in girls than boys and in children living in the cities rather than in those in countryside [29–33].

Even in the developmental age significant damage of the arteries and left ventricular hypertrophy are observed. Overall, left ventricular hypertrophy and thickening of the intima-media complex of carotid arteries are observed in even up to 40% of children at the time of diagnosis of essential hypertension, before the introduction of any antihypertensive treatment [8, 16, 20, 34–37].

The aim of the present study was the creation of a hypertension risk stratification model and development of an algorithm to detect hypertension in teenagers.

The idea behind this study was to create a simple questionnaire — based on the developed risk model — which would be accessible for each student by a dedicated website, e-mail or a smartphone application. To complete questionaire students would neither have to know or measure their BP values.

The goal was to develop an algorithm that would inform students of what the likelihood of abnormal test result means, what the potential complications are as well as to suggest further steps.

Methods

In this prospective study 690 middle school and high school students aged 15–17 years who underwent screening were enrolled. Schools were chosen at random. They were larger and smaller high schools in Warsaw and smaller cities. The tests were also conducted in two small village schools. There were sports classes in some of those schools. No student in the studied group had been diagnosed or suspected of having hypertension before.

Information concerning family history and the presence of risk factors for cardiovascular disease was gathered based on the questionnaire.

Blood pressure measurements were taken using the auscultatory Korotkoff method with the aid of a manual aneroid sphyngomanometer, according to standards contained in The Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents (4 TFBP) and Guidelines of the Pediatric Section of the Polish Society of Hypertension on diagnosis and treatment of arterial hypertension in children and adolescents [18, 36, 38]. Blood pressure measurements were taken 3 times during at least 2 separate visits, at least a week apart and the values were related to values contained in the 4 TFBP [36, 38]. In accordance with current recommendations, the criteria for diagnosing hypertension in students over 16 years of age were the same as those used in adult populations [18].

In all patients admitted to the Department of Cardiology, automatic BP measurements were performed using the oscillometric method. The results of the BP measurement using the oscillometric method were referred to standards developed during the OLAF study [19]. In all students with suspected hypertension, 24-hour arterial blood pressure monitoring (ABPM) was performed. Blood pressure values obtained by ABPM were assessed on the basis of centile charts recommended by the American Heart Association (AHA) adapted from Wühl and the team, with permission from Lippincott Williams & Wilkins [39, 40]. Arterial hypertension was diagnosed when systolic BP and/or diastolic BP $\geq 95^{th}$ percentile according to norms for sex, age and/or height were found. Students who were diagnosed with arterial hypertension on the basis of a screening test prior to being reported to the cardiology department

Table 1. Basic statistics of the study group including parameters used in the algorithm and of the control group on which the model was tested.

	Study group for which the algorithm was created, n = 690 366 boys (53%); 324 girls (47%)	Control group, n = 108 50 boys (46.3%); 58 girls (53.7%)
Age [years]	15.65 ± 0.86; min. 14; max. 17; median 15.0	15.7 ± 0.77; min. 14; max. 17; median 16.0
Weight [kg]	61.5 ± 12.4; min. 37.5; max. 119; median 59.5	62.5 ± 14.4; min. 38; max. 101; median 59.7
Hight [cm]	169 ± 8.3; min. 148; max. 191.5; median 169	167 ± 9.0; min. 140.5; max. 189; median 166
Waist circumference	72.6 ± 9.0; min. 52; max. 117; median 71	76.4 ± 10.9; min. 61; max. 110; median 74.5
Hip circumference	83.5 ± 8.6; min. 63; max. 120; median 82	95.6 ± 8.7; min. 74; max. 123; median 95
Waist to hip ratio	0.87 ± 0.06; min. 0.62; max. 1.08; median 0.87	0.8 ± 0.08; min. 0.6; max. 1.07; median 0.79
SBP [mmHg]	112.3 ± 12.2; min. 82.0; max. 158; median 112.7	118.5 ± 12.2; min. 97.5; max. 145; median 117.2
DBP [mmHg]	66.9 ± 6.9; min. 50.5; max. 101.0; median 66.0	68.7 ± 9.2; min. 50.0; max. 100.0; median 68.0
Hypertension	N = 40 (5.8%)	N = 11 (10.2%)
Family hypertension	N = 479 (69%) at least one close family member with hypertension	N = 51 (47%) at least one close family member with hypertension
	N = 163 (23.6%) more than one person in closest family with hypertension	N = 26 (24%) more than one person in closest family with hypertension

SBP — mean systolic blood pressure; DBP — mean diastolic blood pressure

for further diagnosis were advised to perform BP measurements at home.

Anthropometric measurements included: body weight, height, arm, hip and abdominal circumference. Skin-fold thickness was measured on the rear surface of the freely lowered arm, on the back below the inferior angle of the scapula, at the belly — midway between the umbilicus and the anterior superior iliac spine, and one third of the distance between the anterior superior iliac spine and the pubic symphysis.

On the basis of measurements taken, the following indexes were determined: body mass index (BMI), waist to hip ratio (WHR), waist to height ratio (WHtR), hip to height ratio — body adiposity index [36, 38, 41–43].

For analysis the following statistical methods were used: the Shapiro-Wilk test, the t-Student test, the U Mann-Whitney test (the Wilcoxon Rank Sum Test), the non-parametric χ^2 test, the Pearson correlation coefficient, the Kruskal-Wallis test in analysis of variance (ANOVA).

All hypotheses were tested with a significance level 0.05. Logistic regression analysis was conducted in order to assess probability of hypertension occurrence. Variables that could have influenced the risk of hypertension in children were searched for. The algorithm was tested for: sensitivity, specificity, positive predictive value, negative predictive value in the tested group and receiver operating characteristic (ROC) analysis was performed. For statistical analysis R software version 3.1 was used.

The study was approved by the University Bioethics Committee. Approval number of the Bioethics Committee KB/204/2009. The study was carried out according to the World Medical Association Declaration of Helsinki.

Results

In the present study 690 students aged 15–17 years were enrolled, 366 boys and 324 girls. Hypertension was diagnosed in 40 (5.8%) adolescents: 22 (3.2%) boys and 18 (2.6%) girls. Basic statistics of the study group including parameters used in the algorithm are listed in Table 1.

Afterwards the influence of selected factors on the prevalence of hypertension was evaluated. Statistically significant differences in mean values

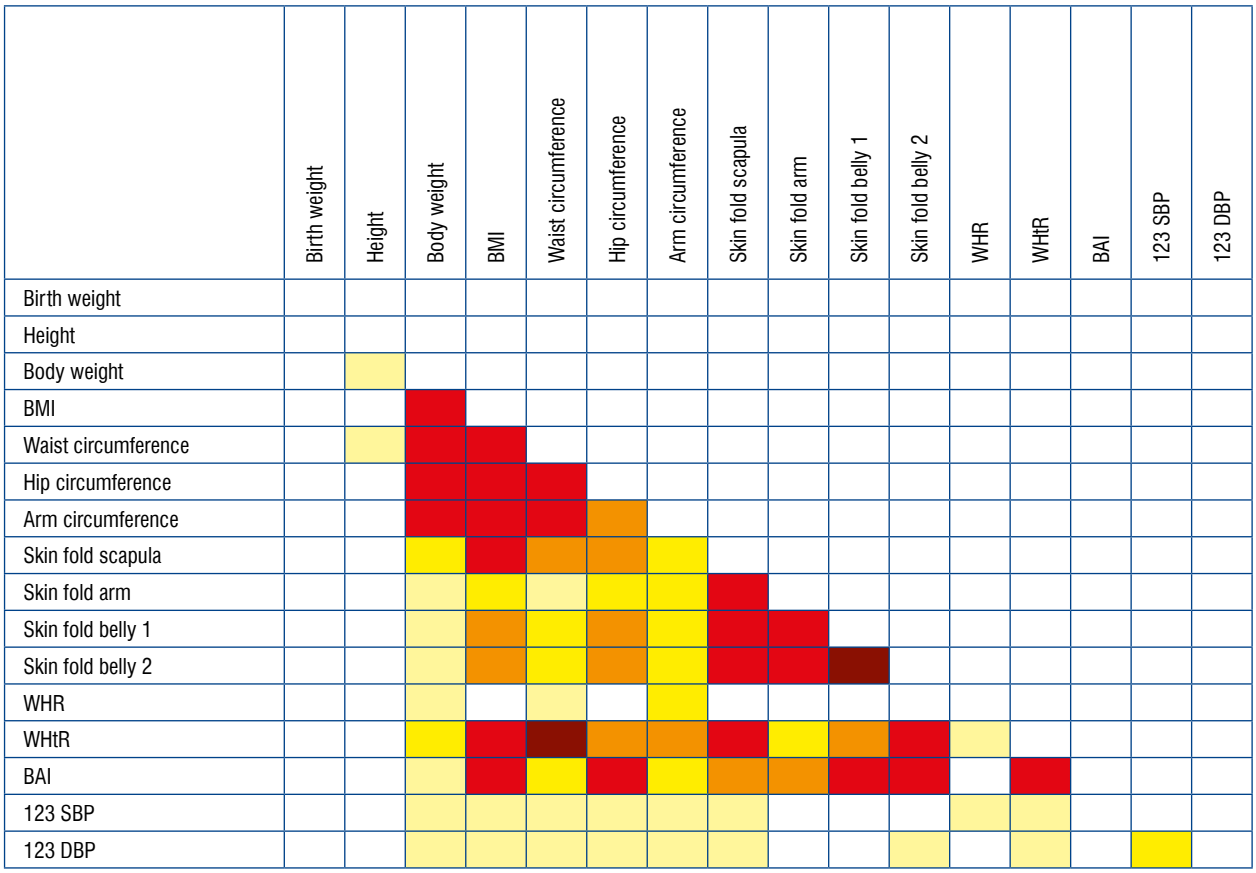

Figure 1. Correlation between analyzed parameters in the study group. Maroon — correlation power ≥ 0.9; < 0.00001; Red — correlation power ≥ 0.8; p < 0.00001; Orange — correlation power ≥ 0.75; p < 0.00001; Yellow — correlation power ≥ 0.6; p < 0.00001; Light yellow — correlation power ≥ 0.3; p < 0.001; SBP — systolic blood pressure; DBP — diastolic blood pressure; BMI — body mass index; WHR — waist to hip ratio; WHtR — waist to height ratio; BAI — body adiposity index (hip to height ratio); skin fold scapula — skin-fold thickness on the back below the inferior angle of the scapula; skin fold arm — skin-fold thickness on rear surface of freely lowered arm; skin fold belly 1 — skin-fold thickness at the belly midway between the umbilicus and the anterior superior iliac spine; skin fold belly 2 — skin-fold thickness at the belly in third of the distance between the anterior superior iliac spine and the pubic symphysis.

($p < 0.001$) of both systolic and diastolic BP values were observed, depending on weight category, as defined by BMI. The highest mean values of systolic and diastolic BP occurred in adolescents with obesity, was slightly lower among adolescents who were overweight, and was lowest in adolescents with normal body weight and body mass deficiency ($p < 0.001$). It was estimated that the risk of hypertension for an obese adolescent is over 13 times greater than that of an adolescent who is not obese.

Hypertension was more frequent ($p = 0.004$) in adolescents who had at least one parent who suffered from hypertension. Hypertension was diagnosed in 22 (10.8%) of 204 adolescents who had at least one parent with diagnosed hypertension. Among a group over twice as large, consisting of 464 adolescents whose parents did not suffer from hypertension, there were only 18 adolescents with diagnosed hypertension, representing 3.9%. What is more, among the 447 adolescents who had at least one person among their next of kin who suffered from high BP, hypertension was diagnosed in 32 (6.9%), and among the 243 adolescents who did not have anyone in their family suffering from hypertension — only 5 (2.1%) met the criteria for diagnosis of hypertension ($p = 0.030$). It has been estimated that the risk of hypertension for a pupil from a family where at least one person suffers or had suffered from hypertension, is more than 2.8 times higher than that of an adolescent, who had no history of family hypertension (Fig. 1).

A logistic regression model describing the probability of hypertension in adolescents was used to verify which of the analyzed parameters

Table 2. Results of the logistic regression model describing the probability of hypertension in adolescents.

	CE	95% CE	OR	95% CI OR	P
Body height	–0.097	(–0.13; –0.066)	0.91	(0.88; 0.93)	< 0.0001
Weight	0.085	(0.06; 0.11)	1.09	(1.06; 1.12)	< 0.0001
WHR	7.764	(2.16; 13.55)	2355	(8.66; 762608)	0.007
Family hypertension	1.312	(0.35; 2.5)	3.7	(1.41; 12.2)	0.015

Family hypertension (1 if hypertension in 1 of the family members, 2 if hypertension in 2 of the family members etc.); CE — coefficient-estimate; WHR — waist to hip ratio; OR — odds ratio; 95% CI OR — 95% confidence interval odds ratio

affect the increased risk of developing hypertension. Diagnosis of hypertension was the dependent variable.

Finally, the following set of explanatory variables was used: birth weight, height, weight, WHR, family history of hypertension, presence of obesity among members of the closest family, type II diabetes among members of the closest family, cardiovascular disease among members of the closest family. It was tested to find which variables were useful for the prediction of developing hypertension.

The results of the logistic regression model for risk of hypertension in young adults are shown in Table 2.

The final form of logistic regression model is: $\hat{\pi} = \frac{e^{\hat{g}(x)}}{1 + e^{\hat{g}(x)}}$ where $\hat{g}(x) = -0.097 \times$ height $+ 0.085 \times$ $\times$ weight $+ 7.764 \times$ WHR $+ 1.312 \times$ family hypertension, where "family hypertension" means the presence of hypertension among members of the closest family — father, mother, siblings, grandfather and grandmother — 1 if hypertension is present in 1 of the family members, 2 if in 2 of the members etc.

On the basis of a logistic regression model one can estimate the probability of a student developing hypertension.

Testing of the developed algorithm was carried out at a school on students aged 15–17. 108 students completed questionnaires by themselves. In all students BP was measured three times using the oscillometric method. The basic statistics of the control group on which the model was tested are listed in Table 1. Sensitivity and specificity of the developed algorithm was calculated for the estimated risk > 50% and > 75% as a positive result of the screening test. Predictive value for positive and negative results was also calculated. The mean of three BP measurements was analyzed. Systolic and/or diastolic BP > 95 percentile according to norms for sex age and height or > 140 and/or 90 mmHg were considered test confirmation. The results are shown in Figure 2.

For the test group ROC analysis was performed (Fig. 3). In order to demonstrate results better, sensitivity and specificity values for a greater number of thresholds can be seen in Table 3.

Based on test results obtained, an algorithm was proposed that could be suitable for practical use for detection of hypertension, using the created risk model (Fig. 4).

Discussion

Conducting epidemiological studies on the prevalence of hypertension in children and adolescents requires a different approach than in adults. This is due to the need of taking into account the specific nature of the developmental age population, in particular development of systems and organs that are involved in the complex process of BP control. Differences and difficulties in conducting screening tests for hypertension in children and adolescents arise from the need of using different cuffs, precisely matching the arm circumference, application of standards appropriate for age, sex, height, use of charts and tables to evaluate other parameters, such as height or BMI. In children one should always take into account possible measurement errors, resulting from physical activity, increased excitability and emotions during measurements taken by a school nurse at her office [44].

All of the differences and difficulties mentioned above result in screening of the studied age group being extremely laborious, difficult to perform and generates huge costs. Screening programs used in the prevention of cardiovascular diseases may take the form of organized programs or are being implemented in an opportunistic form [15, 16, 23].

One cannot forget that according to existing guidelines, BP measurement should be an integral part of any medical visit in every child over 2 years old. It should be performed at least once a year. This recommendation is usually respected in the so-called healthy children clinics during periodic

		Mean arterial pressure from 3 measurements using the oscillometric method		
		Diagnosis of hypertension SBP and/or DBP > 95 percentile or > 140 mmHg and/or 90 mmHg N = 11	Normal blood pressure SBP and/or DBP < 95 percentile or < 140/90 mmHg N = 97	
The probability of hypertension estimated using the developed formula	**Test outcome positive for risk of hypertension** > 50%, n = 13 > 75%, n = 6	**True positive** TP 50%, n = 10 TP 75%, n = 6	**False positive** FP 50%, n = 3 FP 75%, n = 0	**Positive predictive value** PPV 50% = **77%** PPV 75% = **100%**
	Test outcome negative for risk of hypertension > 50%, n = 95 > 75%, n = 102	**False negative** FN 50%, n = 1 FN 75%, n = 5	**True negative** TN 50%, n = 94 TN 75%, n = 97	**Negative predictive value** NPV 50% = **99%** NPV 75% = **94%**
		Sensitivity 50% = **91%** 75% = **54%**	**Specificity** 50% = **97%** 75% = **100%**	

Figure 2. Sensitivity, specificity, positive predictive value, negative predictive value in the tested group; SBP — systolic blood pressure; DBP — diastolic blood pressure; TP — true positive; FP — false positive; FN — false negative; TN — true negative; PPV — positive predictive value; NPV — negative predictive value.

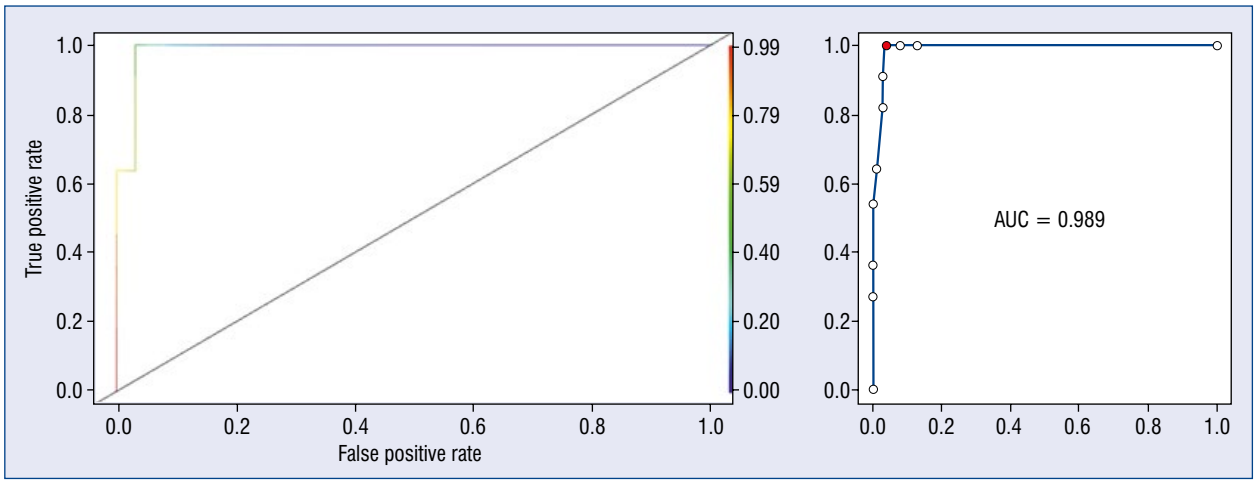

Figure 3. Receiver operating characteristic curve for risk of hypertension calculated using an algorithm. The optimal cut-off point for risk of hypertension, calculated using the algorithm is 46% area under the curve (AUC): 0.989 (0.973;1.00; cut-off: 0.4597). For this value: sensitivity = 100%; specificity = 97%; positive predictive value = 79%; negative predictive value = 100%.

Table 3. Sensitivity and specificity for different risk thresholds.

Risk thresholds	0.1	0.2	0.3	0.4	0.46	0.5	0.6	0.7	0.75	0.8	0.9
Sensitivity	1	1	1	1	**1**	0.91	0.82	0.64	0.54	0.36	0.27
Specificity	0.87	0.92	0.96	0.96	**0.97**	0.97	0.97	0.99	1	1	1

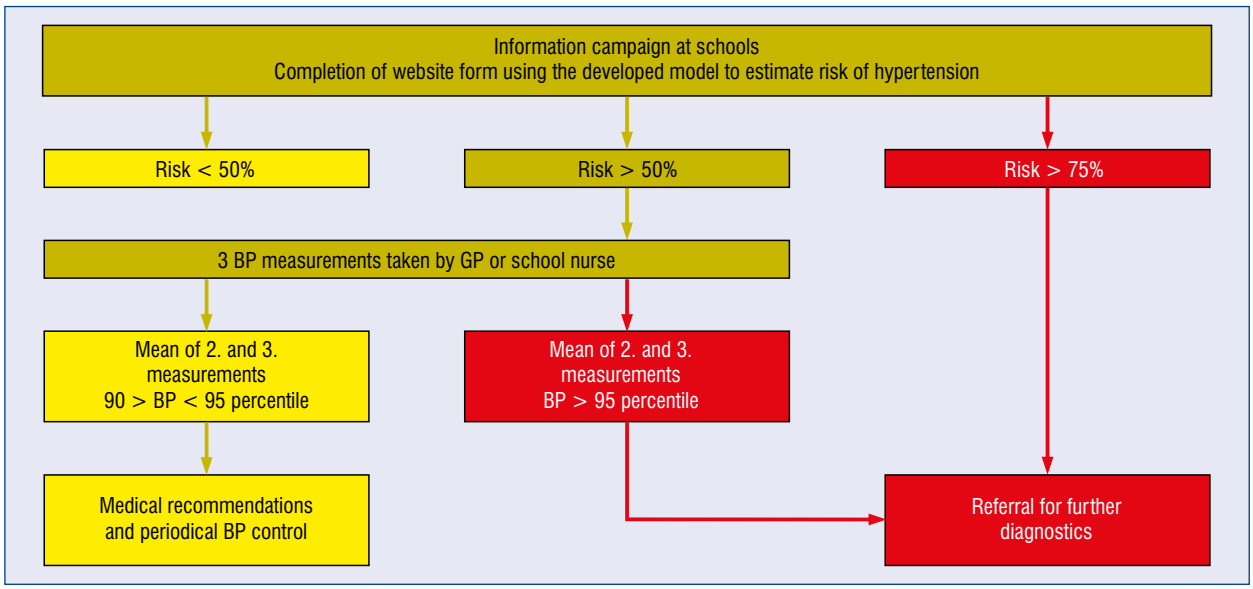

Figure 4. An algorithm to detect hypertension based on a developed model of hypertension probability; BP — blood pressure; GP — general practitioner.

health evaluation and visits and allows for the identification of younger children with hypertension at an early stage, mainly children with secondary forms of hypertension [15, 16, 36, 38, 41].

According to current recommendations, general practitioners are obliged to perform such screening tests, such as: recording history of cardiovascular diseases occurring in the family, taking BP measurements as well as measurements of body weight and height. These screening tests are classified as occasional tests (so-called opportunistic tests). In adolescents they appear to be inefficient and ineffective [36, 38, 41, 44–47].

Teenagers do not seek medical care often, because they are less susceptible to viral diseases of childhood, periodic health evaluations are carried out in schools less often, pupils do not need to undergo mandatory medical examinations in occupational medicine clinics and they suffer less often from chronic diseases than adults do [44–46].

Screening programs are another possibility. These may be smaller, locally funded actions, covering several schools, or larger projects which may for example, be financed by the Ministry of Health, that cover cities and regions. Such programs usually require large amounts of money and an enormous commitment of medical and administrative staff [44–46].

Another model is a screening test based on preselection. It involves screening of patients at risk of studied and a searched for feature — hypertension in this case — on the basis of available data, e.g. patient history, medical records or performance of a simple, noninvasive and inexpensive test [44–46].

In order to stratify risk of hypertension, a logistic regression model, describing the risk of hypertension in adolescents between 15 and 17 years of age was invented. A formula was created, allowing for the pre-selection of adolescents at risk of hypertension during the screening of hypertension.

The study needed an easy to use calculator, and one was created that gives the doctor, student or parent an opportunity to assess the risk of hypertension occurrence.

For example, probability of a diagnosis of hypertension for a student weighing 95 kg, 177 cm tall, with WHR = 0.95, having 2 family members with hypertension is ~70%.

For the same student having 3 family members with hypertension the risk is ~ 90%.

A student, weighing 75 kg, 180 cm tall and with WHR = 0.85, with no family history of hypertension has a risk of hypertension ~1%. If this student weighed 110 kg, the risk would increase to about 18%. If there were 1, 2 or 3 family members with hypertension, risk would increase to ~45% and ~75% and ~95%, respectively.

It turns out that the standard measurement of BP in children and adolescents is encumbered by a large error. Often, high BP values recorded during

the first measurement, become gradually normalized during subsequent measurements.

A large number of false positive results in this group of patients implies that patients are unnecessarily directed to diagnostic expertise, which generates additional costs and exposes the patient to unnecessary stress [14–17, 36].

Conducting screening using the developed algorithm and spreading it with the aid of social media and networking sites frequented by youth, will allow in a short time and without major financial investment or risk of obtaining a large number of false positive results associated with the measurement of BP, to extract a group of young people in which there is a high risk of essential hypertension.

There is no similar, simple algorithm to be found in available literature, that does not require measurement of BP and is useful in screening for hypertension in adolescents [45].

The National High Blood Pressure Education Program's Working Group (NHBPEP) recommended lifestyle interventions (i.e., weight reduction, increased physical activity, and adoption of healthy eating habits) to reduce BP in children and adolescents with prehypertension and hypertension, with pharmacologic approaches reserved for children and adolescents with elevated BP not responding to lifestyle interventions or for those who have secondary causes of hypertension [38]. An updated review conducted by the United States Preventive Services Task Force (USPSTF) in 2012 concluded that even though BP screening in children and adolescents could be effective in identifying high BP, there is still no sufficient evidence on routine screening, and that false positive rates might be high. Public health authorities should work with health-care providers to promote and to improve BP screening in children and adolescents. For example health-care providers can use healthy children visits and physical examinations of sports participants as opportunities to increase screening rates among children [45]. Still it remains, that routine screening is potentially more effective and less costly than selective screening or no screening [46, 48, 49].

According to the USPSTF guidelines, the primary justification for screening for hypertension in children and adolescents it is that early diagnosis of essential hypertension can lead to interventions in reducing BP in childhood and adolescence, thus reducing the risk of cardiovascular event occurrence and death in adulthood [44, 50].

The primary prevention of atherosclerosis should precede its clinical manifestation and begin in early childhood [48, 49].

Conclusions

Body weight, WHR and incidence of hypertension in the family are the strongest predictors of hypertension in teenagers. The proposed screening algorithm can be a useful tool for selecting teenagers at risk of hypertension and in need of specialized diagnostics. There is a plan to upscale research and test the algorithm on larger groups on a larger scale.

Conflict of interest: None declared

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ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 6, 1004–1012
DOI: 10.5603/CJ.a2020.0129

ISSN 1897–5593
eISSN 1898–018X

Baroreflex sensitivity but not microvolt T-wave alternans can predict major adverse cardiac events in ischemic heart failure

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Abstract

Background: *Major adverse cardiovascular events (MACE) constitutes the main cause of morbidity and mortality in ischemic heart failure (HF) patients. The prognostic value of the autonomic nervous system parameters and microvolt T-wave alternans (MTWA) in this issue has not been identified to date. The aim herein, was to assess the usefulness of the abovementioned parameters in the prediction of MACE in HF patients with left ventricular systolic dysfunction of ischemic origin.*

Methods: *Baroreflex sensitivity (BRS), heart rate variability (HRV), MTWA and other well-known clinical parameters were analyzed in 188 ischemic HF outpatients with left ventricular ejection fraction (LVEF) ≤ 50%. During 34 (14–71) months of follow-up, 56 (30%) endpoints were noted.*

Results: *Univariate Cox analyses revealed BRS (but not HRV), MTWA, age, New York Heart Association functional class III, LVEF, implantable cardioverter-defibrillator presence, use of diuretics and antiarrhythmic drugs, diabetes, and kidney insufficiency were defined as significant predictors of MACE. Pre-specified cut-off values for MACE occurrence for the aforementioned continuous parameters (age, LVEF, and BRS) were: ≥ 72 years, ≤ 33%, and ≤ 3 ms/mmHg, respectively. In a multivariate Cox analysis only BRS (HR 2.97, 95% CI 1.35–6.36, $p < 0.006$), and LVEF (HR 1.98, 95% CI 0.61–4.52, $p < 0.038$) maintained statistical significance in the prediction of MACE.*

Conclusions: *Baroreflex sensitivity and LVEF are independent of other well-known clinical parameters in the prediction of MACE in patients with HF of ischemic origin and LVEF up to 50%. BRS ≤ 3 ms/mmHg and LVEF ≤ 33% identified individuals with the highest probability of MACE during the follow-up period.* (Cardiol J 2022; 29, 6: 1004–1012)

Key words: autonomic nervous system, baroreflex sensitivity, heart rate variability, microvolt T-wave alternans, heart failure, left ventricular dysfunction, ischemic cardiomyopathy

Introduction

Major adverse cardiovascular events (MACE) constitutes the main cause of morbidity and mortality in heart failure (HF) patients, particularly when ischemic etiology is involved [1]. The role and prognostic value of the autonomic nervous system (ANS) indices: baroreflex sensitivity (BRS) and heart rate variability (HRV), as well as microvolt T-wave alternans (MTWA), have been thoroughly confirmed in patients with HF concerning cardiovascular death (CVD) [2–8]. A robust body of the previous data focused on patients with HF and reduced ejection fraction, which have the most clinical evidence with regard to therapies, and guidelines clearly define management strategies

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Received: 20.03.2020 Accepted: 28.08.2020 Early publication date: 28.09.2020

[9, 10]. However, the latest recommendations for the management of acute and chronic HF have defined a new category — HF with mid-range ejection fraction (HFmrEF), i.e. with left ventricular ejection fraction (LVEF) in the range of 40–49%. Research on HFmrEF has recently begun to appear, although, data remain scarce and the management is not clearly defined. Estimates show that HFmrEF is responsible for 13% to 24% of all HF cases [11], so from a practical point of view, it seems important to include this group of patients in clinical studies.

The role and prognostic value of ANS indices and MTWA in prediction MACE (which beside CVD involves non-fatal myocardial infarction [MI] and non-fatal stroke), especially in patients with LVEF up to 50%, requires further investigations. In this study, the authors aimed to examine this issue in HF patients with left ventricular systolic dysfunction of ischemic origin.

Methods

The protocol of the study was approved by the Local Ethics Committee at the Medical University of Gdansk, and written informed consent was obtained from all participants.

Patient's selection

Between 2009 and 2018, 188 consecutive patients with stable ischemic HF (documented by prior MI, percutaneous coronary intervention, or coronary artery by-pass grafting) and LVEF ≤ 50% who visited the outpatient clinic, were enrolled in this single-center study. The protocol of the initial visit included anamnesis with particular emphasis on pharmacological treatment and comorbidities; information on the demographic status of the patients; physical examination; two-dimensional-transthoracic echocardiographic study; laboratory blood tests; ANS and MTWA assessment. Additional inclusion criteria were as follows: sinus rhythm; a stable clinical condition for at least 3 months before enrollment; optimal medical therapy for HF and complete coronary revascularization under current guidelines [9, 12–14]. The exclusion criteria were: age < 18 years; a history of prior sustained ventricular arrhythmia or cardiac arrest; permanent atrial fibrillation/flutter; ventricular paced rhythm due to atrioventricular block; New York Heart Association (NYHA) functional class IV, clinical features of coronary instability; a revascularization (coronary angioplasty and/or surgery by-pass grafting) within 3 months before the study; incomplete coronary revascularization status (scheduled coronarography, coronary angioplasty or surgery by-pass graft); diabetes complicated by documented symptomatic peripheral neuropathy; inability to perform exercise test; poor general condition or non-cardiologic comorbidities with potential unfavorable effect on survival.

Studied parameters

MTWA assessment. Detailed skin preparation including mild abrasion was performed to reduce the impedance between skin and the electrode and minimize the risk of artifacts. Next, special electrodes (High-Res high-resolution electrodes, Cambridge Heart — Spacelab's Healthcare, Snoqualmie, WA, USA) were placed in three orthogonal Frank leads (X, Y, and Z). The exercise test was performed on a treadmill (Delmar Reynolds), in line with the protocol dedicated for MTWA testing i.e. with a gradual increment in heart rate, first to the range of 100–110 bpm and then to 110–120 bpm for at least 2 min. The data were analyzed with the CH2000 system utilizing a spectral method (Cambridge Heart, Inc., Bedford, MA, USA), and were finally verified by the physician performing the study. The detailed methodology was already precisely described in previous studies [2, 15, 16]. The results of the test were classified as negative (MTWA_neg), positive (MTWA_pos) or indeterminate (MTWA_ind), and additionally, all non-negative results were classified jointly as MTWA_non-neg and were included for further analysis.

ANS assessment. Autonomic parameters were analyzed in a quiet room with dimmed lights between 08.00 am and 1.00 pm, all patients were asked to fast (at least 4 h) and to refrain from smoking and drinking coffee (at least 12 h) before the examination. After adjustment of measuring devices, and a 15 min stabilization period, resting electrocardiogram (ECG) (Mingograf 720C) and beat-to-beat non-invasive arterial blood pressure (Finapres 2300, Ohmeda) were continuously recorded for 10 min during spontaneous breathing. The collected data were transferred to a PC workstation, processed with POLYAN software [17] and analyzed according to the described protocol [18, 19].

The information on RR interval (resolution 1 ms) and systolic arterial pressure (SAP) were obtained automatically. BRS (ms/mmHg) was computed by spectral analysis as the average value of the transfer function modulus (Blackman-Tukey method, 0.03 Hz-bandwidth Parzen window) be-

tween SAP and RR interval time series in low frequency (LF, 0.04–0.15 Hz) band, independently from coherence values [18]. Then, based on collected ECG data routine HRV frequency-domain indices such as LF (in ms^2), high frequency (HF, 0.14–0.4 Hz, in ms^2), LF to HF ratio (LF/HF), and relative spectral powers in LF bands expressed in normalized units (LFnu) were analyzed. Furthermore, time-domain HRV parameters were calculated based on RR data, such as the standard deviation of normal-to-normal RR intervals (SDNN), the square root of the mean of squared differences between successive intervals (RMSSD), and percentage of adjacent RR intervals differing by more than 50 ms (pNN50). Also, the mean heart period (HP in ms) value was included in the analysis [20].

Follow-up

The routine assessment, which took place every 6 months (or earlier if clinically necessary) involved assessing the patient's clinical condition and recorded study if any had occurred. A decision on potential implantation on an implantable cardioverter-defibrillator (ICD) as a primary prevention of sudden cardiac death (or CRT-D if needed) was at the discretion of the physician in charge. The endpoint of the study was 3-point MACE, defined as non-fatal MI, non-fatal stroke and CVD [21, 22]. Non-fatal MI was recognized according to the Fourth Universal Definition of Myocardial Infarction Guidelines [23]. Non-fatal stroke was defined according to the World Health Organization (WHO) definition as rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting 24 h (unless interrupted by surgery) with no apparent causes other than of vascular origin [24]. CVD included: fatal stroke or MI; death attributed to HF; any sudden death including unobserved and unexpected death; fatal pulmonary or systemic embolism; death following a vascular operation, vascular procedure, or amputation. All deaths were confirmed against the patient's death certificate information or medical documentation.

Statistical analysis

Database construction and statistical analysis were performed with STATISTICA 12 software (StatSoft, Poland) and R 2.15.2 environment. Continuous data were presented as the median (25^{th}–75^{th} percentiles), categorical as a number and percentage. Differences between the MACE(+) and MACE(–) groups were calculated with the Mann-Whitney U-test and for qualitative data with the χ^2 or Yates χ^2 test. The accuracy of pre-specified cut-off values for analyzed parameters was determined by area (AUC) under the receiver-operating characteristic (ROC) curve. An association between the analyzed parameters and the endpoint was assessed using the Cox univariate and multivariate proportional hazard models. The probabilities of reaching the primary endpoint over time, for pre-specified cut-off values for BRS and LVEF, were estimated using the Kaplan-Meier method and compared with the log-rank test. A p value of less than 0.05 was considered statistically significant.

Results

Clinical characteristics of the studied patients

Demographic, clinical and echocardiographic data, as well as parameters of the ANS and MTWA of the studied groups, are presented in Table 1. Briefly, the patients were approximately 64 (58–72) years old, most of them were males (92%), more than 90% underwent MI. During 34 (14–71) months of follow-up, 56 (30%) patients underwent MACE: 7 had a non-fatal stroke, 5 non-fatal MI, and 44 suffered from CVD. These patients were characterized by worse echocardiographic parameters, i.e. lower LVEF and larger atrial size, fewer negative results in MTWA assessment, worse results derived from ANS testing such as lower BRS, LFnu, and LF/HF ratio values. Furthermore, antiarrhythmic and diuretic drugs were used more frequently in these patients, and more often they had diabetes and chronic kidney disease (in stage III or higher).

Predictors of the endpoint

Univariate Cox analyses revealed age, NYHA III functional class, LVEF, ICD presence, use of diuretics and antiarrhythmic drugs, diabetes and glomerular filtration rate < 60 mL/min/1.73 m^2 as significant predictors of the MACE (Table 2). Only BRS and MTWA_non-neg, but not HRV indices (both time and frequency domain) proved to be statistically significant. Pre-specified cut-off values with a high predictive likelihood for MACE occurrence established by using area under ROC for the aforementioned continuous parameters (age, LVEF, and BRS) were: ≥ 72 years, $\leq 33\%$, and ≤ 3 ms/mmHg, respectively (Table 3). In a multivariate Cox analysis, which included all parameters which proved to be statistically significant in the univariate test, only BRS and LVEF maintained statistical significance in the prediction of MACE (Table 2). Figures 1 and 2 presents the Kaplan-

Table 1. Clinical, laboratory and echocardiographic characteristics of the study group and comparison between the major adverse cardiovascular events [MACE(+) and MACE(–)] groups.

	All (n = 188)	MACE(+) (n = 56)	MACE(–) (n = 132)	P*
Age [years]	64 (58–72)	65 (60–74)	64 (58–70)	**< 0.026**
Male	173 (92%)	53 (95%)	120 (91%)	0.406
Myocardial infarction	171 (91%)	50 (89%)	121 (92%)	0.785
Revascularization	169 (90%)	53 (95%)	116 (88%)	0.195
ICD	113 (60%)	37 (66%)	76 (58%)	0.262
CRT-D	17 (9%)	5 (9%)	12 (9%)	1
NYHA class				**< 0.001**
NYHA I	34 (18%)	3 (5%)	31 (23%)	
NYHA II	122 (65%)	36 (64%)	86 (65%)	
NYHA III	32 (17%)	17 (30%)	15 (11%)	
Laboratory parameters				
Hemoglobin [g/dL]	14 (13–15)	13.9 (13.0–14.5)	14.1 (13.3–14.8)	0.368
BNP [pg/mL]	108 (77–300)	238 (104–918)	104 (66–201)	**< 0.003**
Echocardiographic parameters				
LADs [mm]	45 (41–48)	46 (41–50)	44 (40–48)	**< 0.035**
LVEF [%]	33 (27–40)	28 (23–32)	35 (30–42)	**< 0.001**
MTWA results				
MTWA_neg	59 (31%)	10 (18%)	49 (37%)	**< 0.021**
MTWA_pos	84 (45%)	32 (57%)	52 (39%)	**< 0.021**
MTWA_ind	45 (24%)	14 (25%)	31 (23%)	**< 0.021**
MTWA_non-neg	129 (69%)	46 (82%)	83 (63%)	**< 0.010**
ANS parameters				
Mean HP [ms]	1031 (948–1136)	1021 (950–1109)	1033 (949–1148)	0.230
SDNN [ms]	25.3 (16.8–37.9)	20.2 (11.5–47.0)	25.5 (18.8–36.4)	0.229
RMSDD [ms]	17.1 (10.3–29.9)	19.7 (7.5–41.4)	16.9 (10.9–27.6)	0.470
pNN50 [%]	0.68 (0–7.9)	0.81 (0.0–10.5)	0.63 (0.0–6.9)	0.321
LFnu	51 (26.7–69.8)	31.3 (23.4–61.6)	54.1 (29.5–70.6)	**< 0.041**
LF/HF	1 (0.38–2.31)	0.53 (0.3–1.6)	1.2 (0.4–2.40	**< 0.041**
BRS [ms/mmHg]	4.2 (2.2–6.7)	2.6 (1.9–4.9)	4.6 (2.3–7.8)	**< 0.001**
Medications				
Beta-adrenolytics	179 (95%)	52 (93%)	127 (96%)	0.286
ACEI or ARB	173 (92%)	52 (93%)	121 (92%)	1
Spironolactone/eplerenone	98 (52%)	30 (54%)	68 (51%)	0.874
Antiplatelet therapy	171 (91%)	51 (91%)	120 (91%)	1
Statins	169 (90%)	52 (93%)	117 (89%)	0.596
Digoxin	6 (3%)	3 (5%)	3 (2%)	0.359
Diuretics	86 (46%)	39 (70%)	50 (36%)	**< 0.001**
Anti-arrhythmic	19 (10%)	11 (20%)	8 (6%)	**< 0.006**
Concomitant diseases				
Arterial hypertension	128 (68%)	35 (62%)	93 (70%)	0.313
Diabetes	51 (27%)	23 (41%)	28 (21%)	**< 0.012**
GFR < 60 (mL/min/1.73 m^2)	41 (22%)	23 (41%)	20 (14%)	**< 0.001**
Hypercholesterolemia	128 (68%)	40 (71%)	92 (67%)	0.612
History of atrial fibrillation/flutter	39 (21%)	14 (25%)	25 (19%)	0.441
Smoking	139 (74%)	41 (73%)	98 (74%)	1

*p value for comparison between MACE(+) and MACE(–) groups; ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor blocker; BNP — B-type natriuretic peptide; BRS — baroreflex sensitivity; CRT-D — implantable cardioverter-defibrillator with cardiac resynchronization therapy; HP — heart period; LADs — left atrium diameter; LFnu — spectral power in low-frequency range expressed in normalized units; LF/HF — LF to high frequency ratio; LVEF — left ventricular ejection fraction; GFR — glomerular filtration rate; ICD — implantable cardioverter-defibrillator; MI — myocardial infarction; MTWA_ind — indeterminate result for microvolt T-wave alternans; MTWA_neg — negative result for microvolt T-wave alternans; MTWA_non-neg — positive and indeterminate results for microvolt T-wave alternans; MTWA_pos — positive result for microvolt T-wave alternans; NYHA — classification according to the New York Heart Association; pNN50 — proportion of successive R-R intervals that differ by more than 50 ms; QRS — QRS complex width; RMSSD — square root of the mean squared difference of successive R-R intervals; SDNN — standard deviation of the average R-R intervals of the sinus rhythm

Table 2. Univariate and multivariate Cox models estimating the likelihood of major adverse cardiovascular events (MACE).

Parameter	Unadjusted		P*	Adjusted		P*
	HR	95% CI		HR	95% CI	
Age ≥ 72 [years]	2.03	1.17–3.51	**< 0.012**	0.90	0.38–2.11	0.801
NYHA class III	2.02	1.14–3.59	**< 0.016**	1.35	0.57–3.20	0.327
LVEF ≤ 33 [%]	3.65	1.93–6.93	**< 0.001**	1.98	0.61–4.52	**< 0.038**
MTWA_non-neg	2.15	1.08–4.27	**< 0.029**	1.86	0.66–5.26	0.242
BRS ≤ 3.0 [ms/mmHg]	3.78	1.85–7.73	**< 0.001**	2.97	1.35–6.36	**< 0.006**
Diuretics	2.38	1.34–4.21	**< 0.003**	1.37	0.56–2.77	0.410
Diabetes	1.76	1.03–3.00	**< 0.039**	1.78	0.77–4.69	0.165
GFR < 60 (mL/min/1.73 m^2)	2.33	1.37–3.99	**< 0.002**	1.13	0.49–2.57	0.778

*p value for comparison between MACE(+) and MACE(–) groups; BRS — baroreflex sensitivity CI — confidence interval; LVEF — left ventricular ejection fraction; GFR — glomerular filtration rate; HR — hazard ratio; MTWA_non-neg — positive and indeterminate results for microvolt T-wave alternans; NYHA — classification according to the New York Heart Association

Table 3. Prognostic accuracy of the pre-specified cut-off values for analyzed parameters as the predictors of major adverse cardiovascular events during the follow-up.

Parameters	AUC (95% CI)	Characteristics (95% CI)		Predictive value (95% CI)	
		Sensitivity (%)	Specificity (%)	Positive (%)	Negative (%)
Age ≥ 72 [years]	0.59 (0.5–0.68)	81	36	76	43
LVEF ≤ 33 [%]	0.79 (0.72–0.85)	69	79	89	51
BRS ≤ 3.0 [ms/mmHg]	0.65 (0.55–0.76)	69	64	85	41

AUC — area under the curve; BRS — baroreflex sensitivity; CI — confidence interval; LVEF — left ventricular ejection fraction

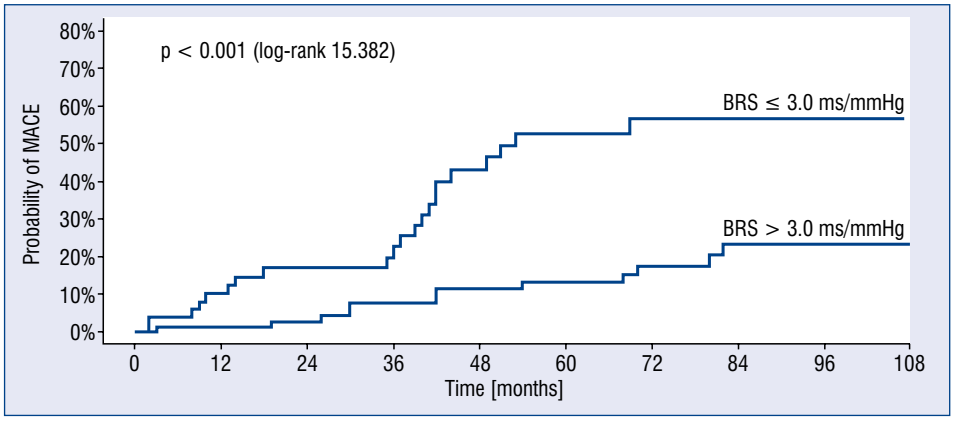

Figure 1. Kaplan-Meier curves illustrating the probability of major adverse cardiovascular events (MACE) during the follow-up period according to the cut-off value for baroreflex sensitivity (BRS).

-Meier curves illustrating the probability of MACE depending on pre-specified cut-off values for LVEF and BRS during the follow-up period, while Figure 3 illustrates the probability of endpoint for a combined parameter (LVEF and BRS jointly). As it has been presented, both LVEF ≤ 33% and BRS ≤ 3 ms/ /mmHg assessed separately or jointly, can identify patients at highest risk of MACE occurrence.

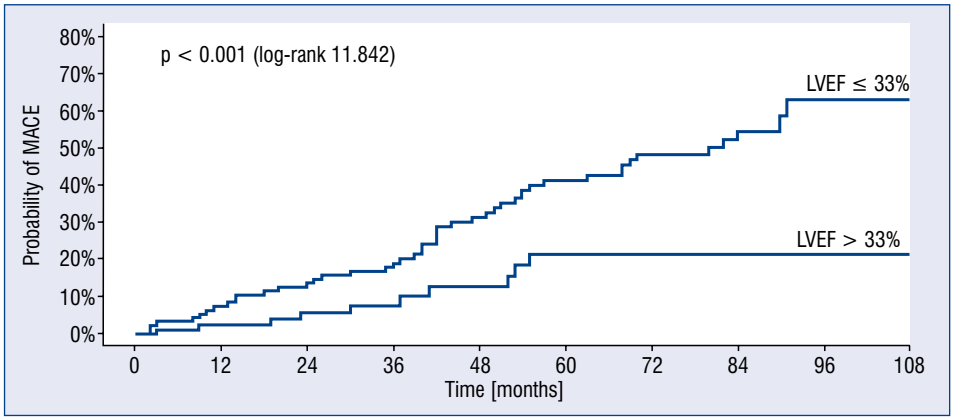

Figure 2. Kaplan-Meier curves illustrating the probability of major adverse cardiovascular events (MACE) during the follow-up period according to the cut-off value for left ventricular ejection fraction (LVEF).

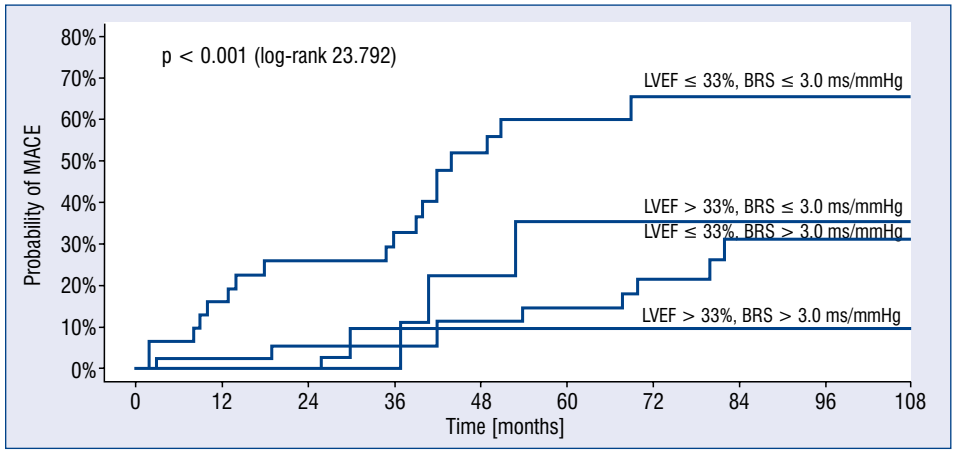

Figure 3. Kaplan-Meier curves illustrating the probability of major adverse cardiovascular events (MACE) during the follow-up period according to the combined parameter (left ventricular ejection fraction [LVEF] + baroreflex sensitivity [BRS]).

Discussion

The observation that not only LVEF but also BRS can predict MACE in patients with ischemic left ventricular systolic dysfunction, even after adjusting for other clinical parameters (such as age, NYHA functional class, ICD presence, impaired renal function, diuretics and antiarrhythmic's using, and diabetes), is the principal finding of the present study. The role of MTWA was proved only in univariate Cox analysis. According to available research, this is the first study analyses regarding the usefulness of ANS and MTWA parameters in the identification of high-risk individuals of MACE occurrence among patients with ischemic cardiomyopathy and LVEF up to 50%. Previous investigations concerning MACE risk assessment among patients with coronary artery disease were dedicated to other well-known clinical parameters [25, 26], which were also confirmed in the present study. The role of ANS indices and MTWA was previously proven for arrhythmic, cardiac and all-cause mortality [2–7, 19, 27–34], however not for MACE, which are common and relevant in this population [1]. Moreover, the vast majority of cited studies omitted patients with ejection fraction 40–50%, who have similarly poor prognosis [35–39].

Prognostic value of MTWA indices in the identification of MACE

Univariate Cox analysis showed that non-negative MTWA is a prognostic risk factor for MACE occurrence, yet it was not confirmed in the multivariate analysis (Table 2). This could be due

to the fact that abnormal MTWA, as a potential modulator of arrhythmic episodes, is mainly associated with the risk of these events [2, 31, 33, 40–42]. Several studies have shown the usefulness of MTWA in predicting cardiac and overall mortality mainly in patients with reduced LVEF [6, 7, 34, 43, 44]. However, in MACE, which is a complex endpoint, where the percentage of arrhythmias is relatively smaller, its prognostic value seems to be significantly lower. This was noted by Chow et al. [44], who stated that non-negative MTWA increases the risk of total and arrhythmic mortality but does not increase the risk of non-arrhythmic death. Another explanation may be the interpretation of indeterminate MTWA results. In patients with LVEF ≤ 35% indeterminate MTWA is associated with a poor prognosis — similar to the patients with positive MTWA [45]. Regarding the patients with higher LVEF, as it was shown in one of the largest meta-analyses, conducted by Merchant et al. [46], indeterminate MTWA results are not associated with such outcomes.

Prognostic value of ANS indices in the identification of MACE

In the present study, it was shown in both uni- and multivariate Cox analyses, the role of BRS in the prediction of MACE occurrence in patients with HF of ischemic origin and LVEF up to 50%. The pre-specified cut-off value for BRS (3 ms/mmHg) is consistent with the results acquired by other researchers, where BRS was determined by both invasive and non-invasive methods [3, 4, 19, 27, 28, 47]. In the current study, patients with BRS below 3 ms/mmHg had a relative risk for MACE threefold higher than patients above the cut-off. Moreover, as Figure 3 presents, individuals with both LVEF ≤ 33% and BRS ≤ 3 ms/mmHg had the highest MACE probability over a 34-month follow-up period. In many previous studies, BRS was proved to have prognostic value in predicting various end-points, such as hospitalization due to HF exacerbation as well as arrhythmic, cardiovascular, or all-cause mortality [3, 4, 8, 19, 27, 28, 47]. The results of our research show that BRS also has an important role in the prediction of MACE, which proves the fact that autonomic imbalance could have an enormous impact on the development of various cardiovascular complications, and that this parameter should be taken into account in risk stratification and clinical evaluation of HF patients.

Two recently published studies [48, 49], put in question earlier data from the literature regarding the role of autonomic tone parameters. However, the clinical characteristics of studied populations and duration of follow-up periods were different, therefore these results, as it was noticed in the commentary by Parati et al. [50] should be interpreted with caution and should not be extrapolated to HF patients with other clinical characteristics [49].

Limitations of the study

The authors are well aware of the potential limitations of the study. Firstly, this was a fairly small, single-center study with strict inclusion criteria, and thus needs confirmation in larger trials. Secondly, although the percentage of patients with HFmrEF is similar to that in the general population of patients with HF, it should be noted that the group of patients with HFmrEF in this article was 50. Next, due to the nature of the methodology of ANS and MTWA evaluation, only patients with sinus rhythm were included in the study. Moreover, in this paper we primarily focused on the MACE assessment rather than assessing other important endpoints, e.g. hospitalization due to HF exacerbation. Finally, during the follow-up period, ANS or MTWA evaluation was not repeated, which makes it difficult to assess the impact of potential changes occurring at that time.

Conclusions

Baroreflex sensitivity and LVEF are independent of other well-known clinical parameters (such as age, NYHA functional class, ICD presence, impaired renal function, diuretics and antiarrhythmic's using, and diabetes), in the prediction of MACE in patients with left ventricular systolic dysfunction of ischemic origin and LVEF up to 50%. BRS ≤ 3 ms/mmHg and LVEF ≤ 33% identified individuals with the highest probability of MACE during the follow-up period.

Funding

The research task was financed by the Ministry of Science and Higher Education, awarded for the development of young scientists.

Conflict of interest: None declared

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VIA MEDICA

REVIEW ARTICLE

Cardiology Journal
2022, Vol. 29, No. 6, 1013–1019
DOI: 10.5603/CJ.a2021.0073

ISSN 1897–5593
eISSN 1898–018X

Congestive heart failure clinics and telemedicine: The key to reducing hospital readmissions in the United States

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Abstract

The United States healthcare system currently faces an economic challenge related to frequent hospital readmission rates. As such, hospitals have begun implementing strategies to reduce readmission rates for specific medical conditions such as congestive heart failure, which had a 30-day readmission rate of 23.2% in 2014. Patient education and frequent monitoring of symptoms have since allowed patients to work together with doctors and nurses to take charge of their healthcare management. Due to heart failure clinics and the rise of telemedicine and telemonitoring, heart failure readmission rates have since decreased. (Cardiol J 2022; 29, 6: 1013–1019)

Key words: congestive heart failure, telemedicine, telemonitoring, heart failure clinics

Introduction

Readmission is a major concern for the United States (US) healthcare system. Under the Affordable Care Act's Hospital Readmission Reduction Program (HRRP), hospital systems are penalized monetarily if they have a higher than expected 30--day readmission for 6 conditions [1]. The Center for Medicare and Medicaid Services (CMS) can withhold anywhere from 1% to 3% of Medicare reimbursements for the readmissions of congestive heart failure (CHF), coronary artery bypass graft surgery, acute myocardial infarction, elective primary total hip/knee arthroplasty, pneumonia, and chronic obstructive pulmonary disease. Under the HRRP, CMS evaluated a total of 3129 hospitals for the fiscal year 2020, and 2583 (83%) of these hospitals will face penalties, which is estimated at $563 million dollars over the course of 1 year [2].

In a 2014 comparison of 7-day and 30-day readmissions by Fingal et al. [3], nearly 10% of Medicaid patients with a diagnosis of either CHF or schizophrenia were readmitted within 7 days of discharge. The top 5 diagnoses with the highest 30-day readmission rates (n = 27,698,101) were as follows: CHF (23.2%), schizophrenia (22.9%), respiratory failure (21.6%), alcohol-related disorders (21.5%), iron deficiency and other anemias (21.2%) (Fig. 1) [3]. In the US, CHF affects 2–3% of the population, with a slightly higher prevalence in males (10%) compared to females (8%) [1]. Given that the CMS can withhold at least 1% of Medicare reimbursement for a diagnosis such as heart failure (HF), and the 30-day readmission rate for HF is 23.2%, the American healthcare system is becoming increasingly burdened with juggling between optimizing patient care and preventing readmissions.

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Received: 9.11.2021 Accepted: 6.06.2021 Early publication date: 2.07.2021

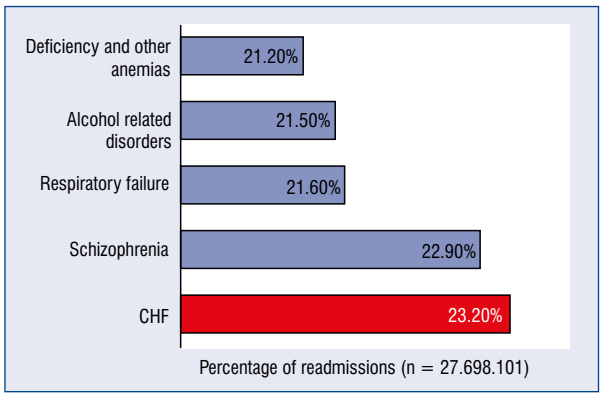


Figure 1. Top diagnoses with the highest 30-day readmission rates out of 27,698,101 readmissions. Red bar: congestive heart failure (CHF) accounts for 23.2% of all readmissions within 30 days.

Pathophysiology of congestive heart failure

Congestive heart failure is an accumulation of myocardial injury that ultimately leads to counterproductive remodeling of the heart [4]. CHF results in reduced cardiac output, leading to compensatory effects by the body through neurohumoral activation and activation of the sympathetic nervous system (Fig. 2). There are two types of HF that commonly present in patients: systolic and diastolic. Systolic heart failure is referred to as HF with reduced ejection fraction (HFrEF), which presents with lower-than-normal left ventricular ejection fraction on echocardiogram [5]. The myocardium is unable to contract adequately and, as a result, ejects less oxygen-rich blood into the body. Fatigue and shortness of breath are common symptoms. In diastolic HF, also known as HF with preserved ejection fraction (HFpEF), patients present with left ventricular diastolic dysfunction [6]. In HFpEF, the myocardium contracts normally but a thickened left ventricle reduces compliance, resulting in decreased filling capacity and thus cardiac output. Decreased cardiac output results in deactivation of the carotid baroreceptors and activation of the renin–angiotensin system [7]. Angiotensin II increases afterload by activating vasoconstriction to the blood vessels, aldosterone increases preload by increasing sodium and water retention, and antidiuretic hormone stimulates water retention [8]. Without B-type natriuretic peptide and atrial natriuretic peptide, the water retention exacerbates the symptoms of CHF, leading to damage of left ventricular remodeling to compensate for the increased peripheral resistance [7]. The body compensates by stimulating the sympathetic nervous system to increase heart rate and contractility, which increases stress on the heart. Increasing contractility increases the cardiac workload resulting in dilation and hypertrophy of the cardiac heart muscle. In a failing heart, the compromised ventricles are unable to pump the blood

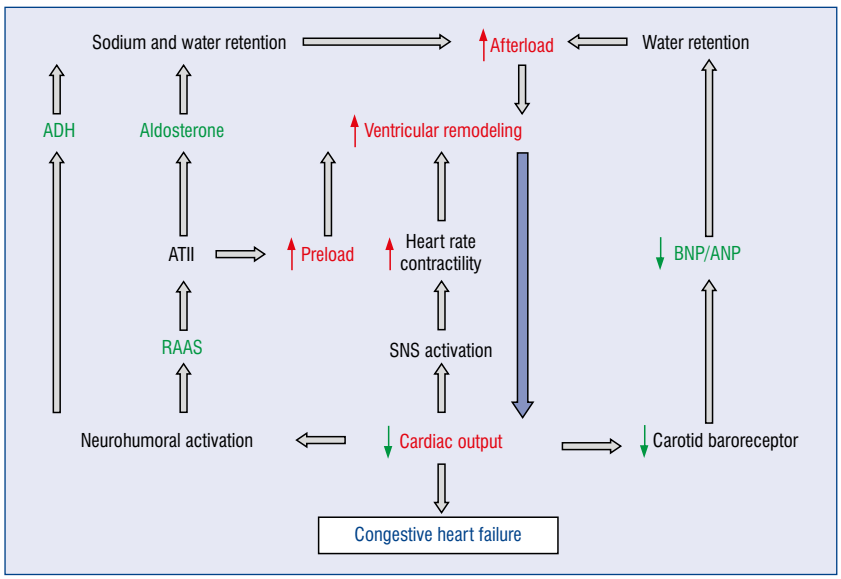


Figure 2. Mechanism of congestive heart failure; ADH — antidiuretic hormone; ANP — atrial natriuretic peptide; ATII — angiotensin II; BNP — B-type natriuretic peptide; RAAS — renin–angiotensin–aldosterone system; SNS — sympathetic nervous system.

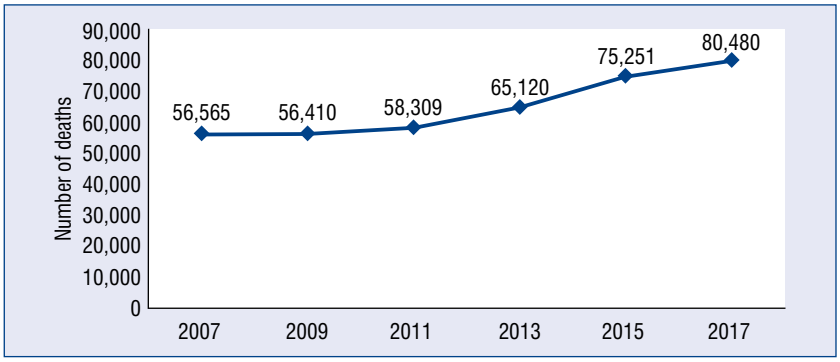


Figure 3. Heart failure mortality rates in the United States from 2007 to 2017. Trendline shows an increase in mortality over a 10-year period.

forward to the rest of the body, resulting in fluid accumulation into the lungs and the rest of the boy.

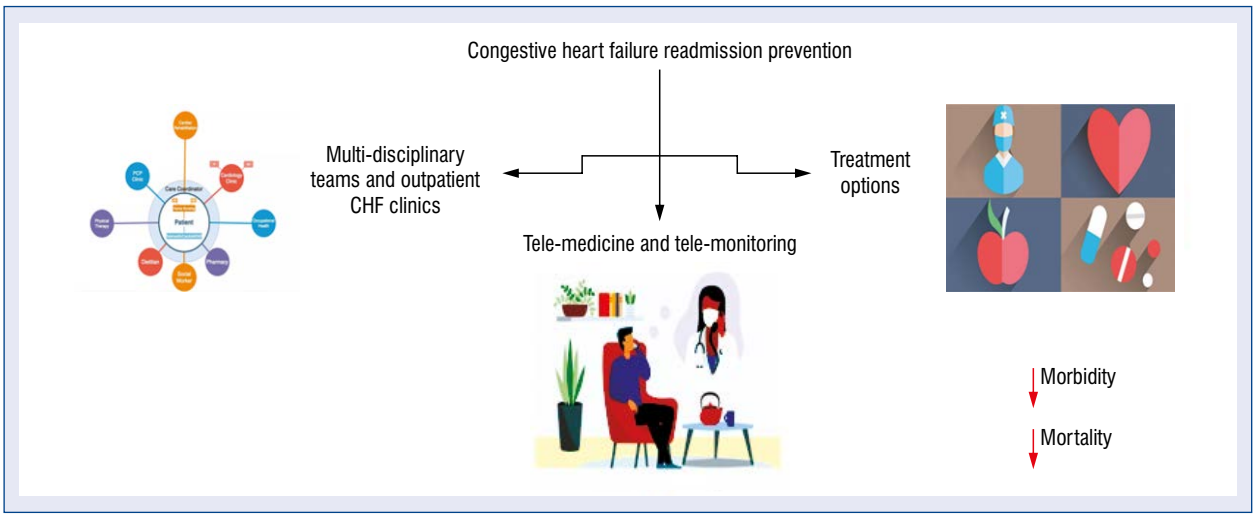
Congestive heart failure morbidity and mortality rates

In a 2020 updated report from the American Heart Association, an estimated 6.2 million Americans over the age of 20 years have HF. In 2016, hospital discharges with a diagnosis of CHF numbered 809,000, and in 2017 the mortality rate from CHF was 80,480, a 42% increase from 56,565 in 2007 [9, 10]. As has been shown, there has been a steady increase in mortality from HF (Fig. 3). Heidenreich et al. [11] estimated that the medical cost of CHF admissions will increase from $20.9 billion in 2012 to $53.1 billion in 2030, with the majority (80%) being attributed to hospitalization. Similarly, their projections show the prevalence of HF increasing by 46% from 2012 to 2030 [11]. Among Medicare patients, the prevalence of HF was 44% in 2010, with HF admissions being the costliest preventable hospitalization at an average $10,775 [12].

Several factors play roles in the high readmission rate of CHF. In an analysis done by Inamdar, some of the major causes of readmission were shown to be due to medication noncompliance, smoking, diet noncompliance, failure of documentation of discharge information and patient education, and comorbidities such as hypertension and diabetes mellitus [1]. Under the HRRP, hospitals have since been incentivized to come up with strategies to decrease the number of readmissions. Some of these strategies include multidisciplinary HF clinics, visiting nurse services, physician-directed HF transitional care programs, telemonitoring at home, and 1-week follow-ups. Inamdar also reports that HF clinics reduced all cause readmission rates by 50% [1]. During the HRRP implementation phase the 30-day risk-adjusted readmission rate declined from 20% to 18.4%; however, the 30-day mortality rate increased from 7.6% to 9.3% [13].

Congestive heart failure clinics and outcomes

An important reason why readmission rates have effectively decreased is due to outpatient HF clinics, home intervention methods, and medications. Because HF disproportionately affects the older population, the management goals focus on maintaining and optimizing patient capabilities (Central illustration). Several classes of drugs have been indicated in the treatment of HF, such as diuretics, angiotensin converting enzyme inhibitors, and more (Table 1). For CHF patients to remain stable after discharge, fluid balance, blood pressure, and heart rate must be medically optimized [14]. This can be monitored during clinic follow-up or at home via implantable devices that transmit data to healthcare providers. CHF clinics, commonly known as HF clinics, have been developed to help patients diagnosed with CHF manage their condition. By educating patients on their disease and encouraging active participation in their treatment, one goal is to reduce the need for readmission to hospitals for CHF exacerbations. It is important that patients being discharged also have a strong support system and home environment so that they can maintain functional independence. Caregivers may also accompany patients to clinic appointments, thus ensuring proper follow-up after discharge. Outpatient clinics can help in educating patients and caregivers on weight management, medication compliance, dietary changes, and exercise regimens. By seeing a multidisciplinary team



Central illustration. Key proponents in reducing readmission rates related to congestive heart failure (CHF).

Table 1. Drugs commonly used in the treatment of heart failure (HF), their mechanisms of action, and effects.

HF treatments	Drug names	Mechanism of action	Effects
Angiotensin converting enzyme (ACE) inhibitors	Captopril, enalapril, fosinopril, lisinopril, ramipril	Competitively inhibit the conversion of angiotensin I to angiotensin II, inhibit bradykinin metabolism, promote sodium and water excretion by inhibiting angiotensin II--induced aldosterone secretion	Reduces preload and afterload on the heart, exerts reno-protective effects via dilation of renal arterioles, reduces cardiac and vascular remodeling
Angiotensin receptor blockers (ARBs)	Candesartan, losartan, valsartan	Prevents angiotensin II from binding to its receptor	Prevents vasoconstriction and aldosterone secretion
Calcium channel blockers	Ivabradine	Blocks hyperpolarization-activated cyclic nucleotide (HCN) gated channel responsible for cardiac pacemaker funny current	Decreases heart rate, cardiac output and oxygen demand
Beta-blockers	Bisoprolol, metoprolol, carvedilol	Blocks response to beta-adrenergic stimulation by preventing ligand binding of the beta-adrenergic receptor by norepinephrine and epinephrine; cardio selective for beta-1 at low doses	Decreases heart rate, contractility, conduction velocity, and relaxation rate of myocardial tissues
Aldosterone antagonists	Spironolactone, eplerenone	Competitively binds receptors at aldosterone-dependent sodium--potassium (Na-K) exchange site in distal renal tubules	Increases excretion of sodium, chloride and water; increases retention of potassium and hydrogen ion
Diuretics	Furosemide, bumetanide, torsemide, chlorothiazide, hydrochlorothiazide, triamterene, metolazone, indapamide	Loop diuretics: Inhibit cotransport of Na-K-2Cl at the thick ascending loop of Henle Thiazide diuretics: Inhibit sodium--chloride transporter at the distal renal tubule Potassium sparing diuretics: Inhibit sodium channels at the cortical collecting tubules	Promotes diuresis, depletion of sodium and total body volume resulting in decreased cardiac output
Angiotensin receptor neprilysin blockers	Sacubitril/ /valsartan	Sacubitril: neprilysin inhibitor. Neprilysin degrades atrial and B-type natriuretic peptides as well as bradykinin Valsartan: angiotensin II receptor type I inhibitor	Promotes relaxation of blood vessels, sodium excretion and fluid retention

Table 2. Summary of studies done to evaluate the readmission rates between patients who had physician follow-up compared to those without follow-up.

Author	Country	Study	Outcome
Tung et al., 2017	Taiwan	13,775 patients discharged from hospitals in 2010 followed for association between 7-day follow-up and 30-day readmission	Early physician follow-up of HF patients was associated with lower readmission rates compared to no physician follow-up (HR 0.54; 95% CI 0.48–0.60)
Hernandez et al., 2010	United States	Observational analysis of patients 65 years or older with HF	Patients discharged from the hospital, who have higher early follow-up rates, also have lower 30-day readmission rates
Jain et al., 2010	United States	138 HF patients during the period June 2005 through June 2006 were evaluated for outcomes through September 2007	4 HF clinic patients (n = 27) were readmitted 5 times 85 non-HF clinic patients (n = 111) were readmitted 187 times ($p < 0.001$)
			A subgroup analysis of crossovers from the non-HF clinic to HF clinic group (n = 39) revealed a 60% reduction in readmission
Tse et al., 2018	United States	Systematic review and meta-analysis of randomized controlled trials and real-world studies	Telemonitoring reduced hospitalization rates of HF patients (n = 31,501) by 24% over a 6-month period, and by 27% over a 12-month period
Cleland et al., 2005	United States	Comparison between HTM, NTS, and usual care on improving outcomes for patients with HF who are at high risk of hospitalization or death	Similar numbers of admissions and mortality among patients in the HTM and NTS groups. Patients in the HTM group had reduced mean duration of admissions by 6 days (95% CI 1–11). Patients in the usual care group had a higher 1-year mortality (45%) than patients in the NTS (27%) and HTM (29%) groups ($p = 0.032$)

CI — confidence interval; HF — heart failure; HR — hazard ratio; HTM — home telemonitoring; NTS — nurse telephone support

at an HF clinic, a patient's care is tailored to their specific needs. Multidisciplinary teams include a cardiologist, specialized HF nurses, pharmacists, physiotherapists, social workers, dieticians, and other allied health professionals [15]. It is especially important for patients being discharged to be followed up at either their doctor's office or an outpatient clinic for management of their condition. Outpatient clinic visits with a physician or healthcare provider after discharge prove to be important in reducing readmission for HF. In a Taiwanese study of 13,577 HF patients, early follow-up with a physician within 7 days of discharge was associated with a lower readmission rate (Table 2) [16]. Similarly, an extensive observational analysis conducted by Hernandez et al. [17] showed that patients who were discharged and received early follow-up with a physician had lower 30-day readmission rates. In a study comparing patients followed in outpatient management vs. no management, only 4 (n = 27) managed outpatients were readmitted 5 times, whereas 85 (n = 111) patients who did not have follow-up accounted for a total of 187 readmissions ($p < 0.001$) [18].

Advent of telemedicine

Due to advancements in digital technology and Internet access, coupled with ever changing circumstances, telemedicine has recently become increasingly popular. Telemedicine is the use of video and audio technology, such as phones and webcams, to electronically connect a patient to a health care provider remotely [19]. Telemedicine is used to deliver patient care and provide follow-up and education to patients who may not be able to visit a doctor's office as soon as possible. It is not only cost effective but it also provides healthcare professionals the opportunity to see and talk to their patients in real time [20]. The efficacy and

ease of seeing a healthcare professional in the comfort of your own home is an opportunity many do not pass on. Not only can patients visit with a doctor, but they can also talk to behavioral health counselors, dieticians, social workers, and other professionals while at home. In the management of CHF, telemedicine could be utilized to follow up patients leaving the hospital, ensuring they are receiving adequate care. Healthcare providers can also remotely telemonitor and review vitals from patient's in-home devices such as blood pressure monitors and pulse oximetry. Telemonitoring is the continuous assessment of a medical condition by way of home monitoring systems or implantable devices that automatically transmit vital signs and other physiological data to medical professionals. Vital signs can be used to check for decompensated HF by measuring parameters such as heart rate, blood pressure, heart rate variability, urine output, and weight gain [21]. Remote data collection can also be done by patient questionnaires that monitor vital signs and symptoms daily. It is not only non-invasive but also much easier for a patient to continue care in their own home. Home telemonitoring has been found to reduce the average number of days spent in the hospital, and patients who received home telemonitoring or nurse telephone support had a better 1-year mortality outcome than patients who received usual care ($p = 0.032$) [22]. In a meta-analysis by Tse et al. [21], telemonitoring reduced hospitalization rates of HF patients ($n = 31,501$) by 24% over a 6-month period, and by 27% over a 12-month period. Providers can also utilize hemodynamic monitoring by way of implantable cardiac devices, such as CardioMEMS and HeartPOD, which continuously transmit cardiac or vascular pressures to a remote system that can be reviewed. Here, doctors can assess increases in intracardiac and pulmonary arterial pressures, which may indicate oncoming decompensation of HF [21]. Therefore, both telemedicine and telemonitoring can be utilized by healthcare professionals to effectively assess patients being discharged from the hospital. These interventions can reduce 30-day readmission rates by decreasing the likelihood of CHF exacerbations.

Conclusions

Heart failure costs the US healthcare system billions of dollars annually. Hospitalizations are expensive, and readmission rates have increased the burden on hospitals due to decreased compensation for readmissions. On the other hand, patients who are discharged and do not follow up with a provider for management often have poorer outcomes than those who do undergo follow-up. Outpatient clinics and telemedicine/telemonitoring are crucial for reducing the readmissions rates of patients with HF and for achieving better health outcomes. Given that some HF patients have significant barriers to accessing medical care outside of the hospital, such as physical inability, lack of transportation, or residing in a rural area, telemedicine provides the ability to receive the care they need. Together, clinics and telemedicine/telemonitoring interventions help to create a system that works with patients to achieve their health goals. We are hopeful that telemedicine and outpatient clinics will continue to reduce patient's readmissions and mortality and play a key role in caring for the aging population.

Conflict of interest: None declared

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VIA MEDICA

REVIEW ARTICLE

Cardiology Journal
2022, Vol. 29, No. 6, 1020–1027
DOI: 10.5603/CJ.a2021.0055

ISSN 1897–5593
eISSN 1898–018X

A systematic review of nonsynonymous single nucleotide polymorphisms in the renin–angiotensin–aldosterone system

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Abstract

In this recent publication review the authors aimed to collect evidence of impact of nonsynonymous single nucleotide polymorphisms (nsSNP) in the renin–angiotensin–aldosterone system on patients' phenotype not only regarding arterial hypertension and its complications, but also the impact on other diseases of interest outside the field of cardiovascular medicine.

PubMed database records published between 2017–2020 were searched and all positive case-control studies or positive studies with human DNA were selected.

The search identified 104 articles, of which 22 were included on the basis of the inclusion criteria. This paper presents the impact of 44 nsSNPs in panels for genes of renin, angiotensinogen, angiotensin-converting enzyme, angiotensin receptor and aldosterone on the clinical picture of investigated cohorts or on the peptide-protein interactions as consequence of nsSNPs.

Genetic variability in nsSNPs of the RAAS is involved in the pathogenesis of arterial hypertension and its complications, and surprisingly also in the pathogenesis of conditions not associated with elevated blood pressure, like neoplasms or inflammatory diseases. (Cardiol J 2022; 29, 6: 1020–1027)

Key words: nonsynonymous single nucleotide polymorphisms, renin–angiotensin–aldosterone system

Introduction

The renin–angiotensin–aldosterone system (RAAS) is strongly involved in the pathogenesis of arterial hypertension, as well as in the occurrence of its complications. The diversity of the clinical course of this disease and the acceleration of target organ damage may depend not only on the presence of concomitant diseases, on environmental factors including lifestyle, quality of health care, utilization and adherence to proven preventive therapies, but also to some extent on genetic factors. The rapid development of genetics shows that nonsynonymous single nucleotide polymorphisms (SNP) are one of many types of human genome variability, which along with changes in epigenetic modulators (e.g., microRNA) or posttranscriptional modifications (e.g., methylation of DNA), play a role in shaping the final picture of the disease. Although transcriptional errors which lead to a single nucleotide swap from a wild to a mutated variant usually have a spontaneous nature, they may be also inherited by descendants and be of importance even in fetal life. In 2017 it was suggested that the role of polymorphisms in the RAAS assessed in various population studies was overestimated during the "candidate gene era" and that there is a need to reconsider the clinical significance of RAAS variants for individuals in the framework of "precision medicine" [1]. Surprisingly, in the review prepared by Ji et al. [1], genetic variants of some genes related to the RAAS were not associ-

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Received: 30.12.2020 Accepted: 5.05.2021 Early publication date: 28.05.2021

ated with risk of cardiovascular diseases, but rather with abnormal thyroid function, schizophrenia, lead poisoning, fibrosis, angiotensin-converting-enzyme (ACE) induced cough or with lipoprotein concentrations. Additionally, some new technologies enabled using artificial intelligence for the prediction of SNPs importance with regard to the interactions of their products (protein-peptide) and, potentially — for their altered function [2]. The aim of this study was to critically review the results of studies on the most investigated RAAS SNPs published since 2017 to date.

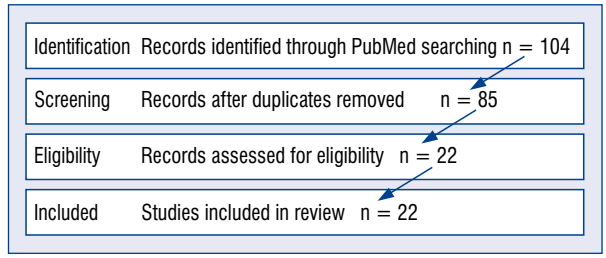


Figure 1. Flow diagram of publications selection.

Methods

Two reviewers working independently extracted from PubMed database (www.pubmed.ncbi.nlm.nih.gov) the relevant publications released between January 1, 2017 and November 30, 2020. Studies with the following keywords (as inclusion criteria): SNP, RAAS, renin, angiotensinogen, angiotensin, aldosterone, angiotensin-converting enzyme, angiotensin-receptor were extracted. Reviews, meta-analyses, case reports, basic science studies with experimental medicinal compounds and studies performed in unique or specific populations were excluded. Only English-language, positive human studies or studies with human DNA were selected for this review of the latest reports on SNP in the RAAS. Figure 1 with flow-chart shows the selection of papers qualified for the present publication.

In the first step, two authors reviewed the abstracts and excluded those not meeting eligibility criteria. The articles were included after two investigators independently recognized the article as eligible to this review. Differences between two reviewers were resolved by consensus. Twenty-two articles referring to 44 SNPs were finally chosen for inclusion in this review — these SNPs are presented on the Central illustration.

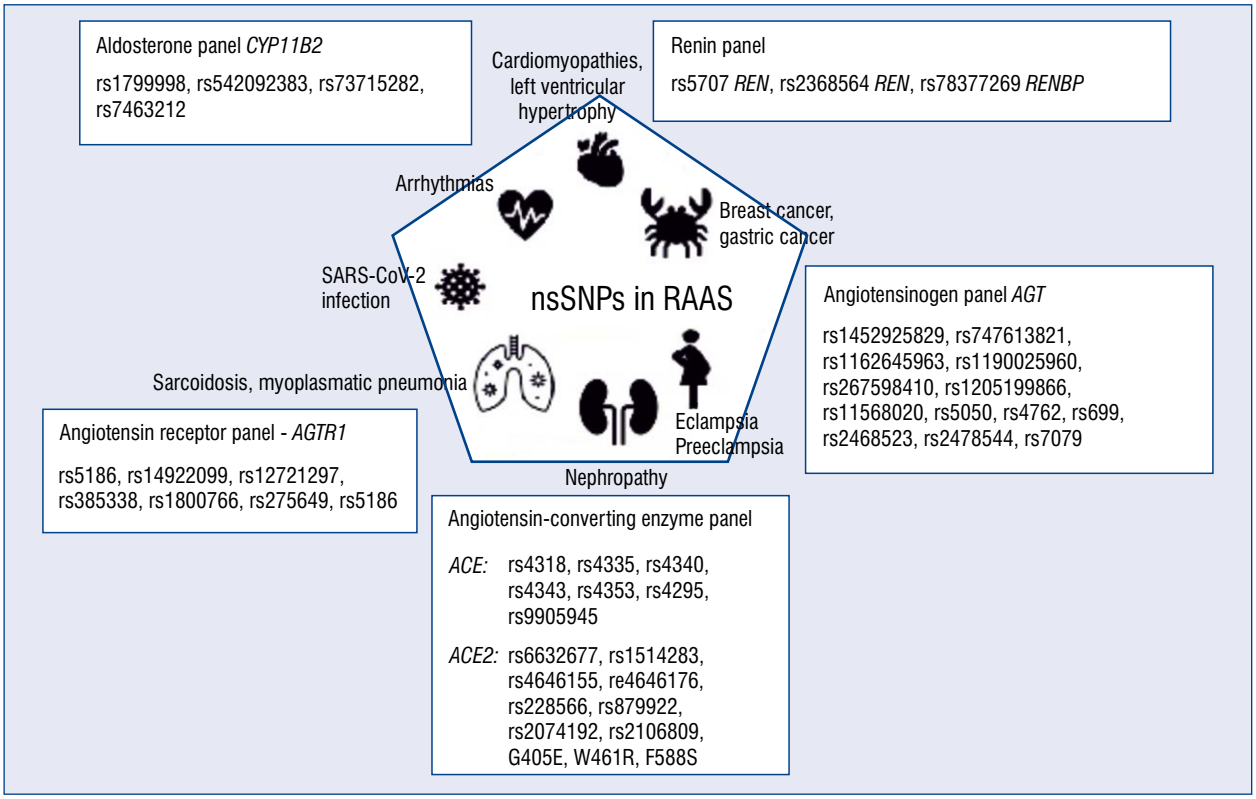
Results

The renin panel

The resequencing study conducted among the 1906 participants of the GenSalt study aimed to find SNP association with salt-sensitive arterial hypertension in a community from the Han Chinese population with a habitually high Na-intake from rural areas [3]. Gene-based analyses were performed in 300 participants selected with the highest arterial pressure dietary response (mean +11.8 mmHg) and 300 with the lowest response (mean –1.1 mmHg). The probands in salt-sensitive group had higher mean age (41.6 vs. 38.2 years) than salt-resistant probands, and the rate of females was higher (52.5% vs. 35.6%). Seven RAAS genes with potential biological effect on blood pressure regulation were selected — renin-binding protein gene (*RENBP*), angiotensin I converting enzyme 2 gene (*ACE2*) and angiotensin II type 1 receptor gene (*AGTR1*) were in this number. Within 50 single-nucleotide variants only low-frequency, missense SNP in *RENBP* gene described as rs78377269, present in exonic region of chromosome X (C to A substitution in 153941584 position) reached statistical significance in a single marker analysis ($p = 0.03$) after adjustment for multiple testing when studied subgroups were compared. Each copy of the minor allele corresponded to a 1.63 mmHg larger mean arterial pressure response to dietary sodium intervention and a 2.21-fold increased odds of salt sensitivity (95% confidence interval [CI] 1.10–4.42). The authors of that study do not exclude that the other SNPs tested in the study may explain, in aggregate, the phenomenon of salt-response hypertension.

Since renin is associated with preeclampsia and eclampsia — genetic variability of its gene located on chromosome 1, was a subject of studies with mothers and their offspring, as well as mothers alone in this respect in Chinese and Romanian centers, respectively.

Three SNPs were analyzed by Yu et al. [4] in a study which included 347 preeclampsia/eclampsia patients and 700 controls. The fetal heterozygotic genotype rs5707 in renin gene *REN* (AC) was significantly ($p = 0.004$) associated with an increased risk of preeclampsia/eclampsia when accompanied by a mother's body mass index ≥ 24 kg/m^2 — odds ratio (OR) 2.75 (95% CI 1.5–5.06) [4]. In a study by Procopciuc et al. [5] where 87 pregnant women with preeclampsia were compared with 130 con-



Central illustration. The nonsynonymous single-nucleotide polymorphisms (nsSNPs) and spectrum of diseases described in this review; ACE — angiotensin converting enzyme; RAAS — renin–angiotensin–aldosterone system; SARS-CoV-2 — severe acute respiratory syndrome coronavirus 2.

trols also SNP rs2368564 (G83A) in *REN* with a heterozygotic form were significantly associated ($p = 0.009$) with late-onset preeclampsia [5].

The angiotensinogen panel

A different approach to genetic variability evaluation was applied in a study by Goswami [6] regarding angiotensinogen gene (*AGT*). That author validated 354 SNPs of *AGT* and determined their conservation degree in a 9-step scale. Using a computational modeling, 3-dimentional structures of wild-type and mutant *AGT* variants were generated. The nature of each of the 485 amino acids of this macromolecule was defined as exposed or as buried depending on what extent it is hidden in the protein structure space, moreover their functional or structural role for the protein was predicted. Three SNPs (rs1452925829, rs746613821 and rs1162645963) were identified as being highly destabilizing for renin-angiotensinogen binding, they had also strongest impact on the change of the interface area between renin and angiotensinogen. It was proved earlier that a majority of diseases associated with nonsynonymous SNPs are caused by the instability of the proteins. The highest scores (0.808–0.919) for the prediction of the structure, function and post-translational modifications of human angiotensinogen were observed for rs1190025960, rs267598410, and rs1205199806 which lead to following swaps of amino acids in the indicated positions: G149R, R477G, and L162P, respectively. Substitutions of amino acids cause changes in some physical properties of angiotensinogen such as electrostatic potentials, nonpolar and polar solvation energy, mechanical energy and van der Waals forces. After *AGT* expression had been correlated with the survival of patients with four neoplasms, the author concluded that deregulation of angiotensinogen and des(angiotensin I)angiotensinogen is associated with survival outcomes in patients with gastric and breast cancer through their anti-angiogenic activity, as opposed to the pro-angiogenic action of angiotensin II with angiotensin II-receptor.

Returning from oncology to cardiovascular diseases, this next publication reestablishes the role of *AGT* variants and their haplotypes in the etiology of arterial hypertension and therefore

deserves attention [7]. The subject of interest in a study by Purkait et al. [7] performed in an Indian population were nine SNPs, both in 5' untranslated regions (5'UTR), in exon and in intron regions of *AGT*. Four of them (rs11568020, rs5050 — in promoter and rs4762, rs699 — in exon 2) showed a positive association with arterial hypertension ($p < 0.05$), when 256 hypertensive cases were compared with 158 normotensive controls. Additionally, from the pool of 13 analyzed haplotypes, 3 of them with 2–4/9 minor allele revealed in this study, a pro-hypertensive effect and 1 of them with all major allele — protective association with hypertension ($p < 0.01$). On the other hand, using multiple logistic regression analysis Khatami et al. [8] found a significant association of the two mentioned in the previous study SNPs — rs4762 and rs699 with ischemic heart disease when in a dominant model 148 Iranian patients with coronary artery disease (100% hypertensive as described in the patient characteristics) were compared with 135 normotensive controls without coronary artery disease — OR 1.91; 95% CI 1.16–3.15; $p = 0.01$ and OR 1.8; 95% CI 1.1–2.93; $p = 0.01$, respectively [8]. The rs4762 and rs699 were also among SNPs which underwent analysis for the purpose of verifying a hypothesis about their linkage with diabetic nephropathy. Mutated alleles of these SNPs presented an association with diabetic nephropathy with OR 10.25; $p = 0.001$ and OR 22.21; $p < 0.001$, respectively, in a comparison of 47 Tunisian type 2 diabetic patients with nephropathy and 189 without this complication [9]. A cohort of 2872 white Australians from the Victorian Family Heart Study were enrolled in a program to test the association of systolic blood pressure with 88 SNPs in *AGT*, *AGTR1*, *REN* and aldosterone synthase gen (CYP11B2). This study by Scurrah et al. [10] revealed that in this group rs2468523 and rs2478544 at *AGT* presented sex-specific association (not in women), and the presence of every minor allele resulted in an increase of systolic blood pressure in men by 1.58 and 1.63 mmHg, respectively [10]. The next paper by Wu et al. [11] presents the problem of occupational exposure on lead, of lead-related hypertension and its association with rs7079 SNP. Although rs7079 nucleotide is located in the untranslated region of the gene it is suggested that this DNA fragment is crucial for binding microRNA and that in this way influences *AGT* transcription and translation, and subsequently its serum concentration. The authors compared the frequency of minor allele and allele distribution between persons with a blood lead level $< 200\ \mu g/L$ and those with a blood lead level $\geq 400\ \mu g/L$. Heterozygotic variant (CA) and homozygotic with minor allele (AA) variant of rs7079 appeared more frequently in lead exposed than in unexposed individuals 47.4% vs. 33.3%; $p = 0.02$. Apart from this, homozygotes with major alleles (CC) had significantly higher blood concentration of angiotensinogen than heterozygotes ($p = 0.01$). This may be explained by observation that A allele decreased the binding between miRNA and the angiotensinogen gene.

The ACE gene panel

In recent years some studies on *ACE* were focused on the association of its SNPs with an inflammatory process. It is reported in many studies that *ACE* has been associated with sarcoidosis. Although the group of Lahtela et al. [12, 13] did not confirm this link in their own study on Finnish patients, they indicated an interesting trait in the association of rs9905945 with prognosis in this disease. Using generally accepted criteria of World Association of Sarcoidosis and Other Granulomas (WASOG) they divided 188 patients from pulmonary departments into two groups depending on the effects of treatment during a 2-year period: 89 patients in whom the disease resolved and 97 in whom it persisted. They discovered that the combination of rs9905945 in *ACE* and of previously reported HLA markers is helpful in predicting the course of this disease in a Finnish population more accurately than previously known. The C phenotype was statistically more frequent in the better prognosis group than the group with poor prognoses (79.8% vs. 66%; $p = 0.035$), and combining the frequencies of C phenotype with two defined HLA markers revealed a strong association with resolved versus persistent disease prognosis: 37.1% vs. 11.3%; $p < 0.001$; OR 4.61 (95% CI 2.15–9.86). Another interesting association of lung disease with *ACE* was tested in a population of Chinese children infected with *Mycoplasma pneumoniae* [14]. Polymorphism within *ACE* — rs4340 was analyzed together with SNPs within interleukin-6 gene (*IL-6*) — rs1800795, and within nitric oxide synthase gene (*NOS3*) — rs1799983 and two other genes. The gene-gene interactions were tested using Multifactor Dimensionality Reduction (MDR) and cumulative genetic risk score approaches. The results of 715 blood samples (415 cases of mycoplasmatic pneumonia and 300 healthy controls) showed that a combination of a major allele in *ACE* (D) with a minor allele in *NOS3* (T) contribute to the genetic susceptibility of this germ-related

pneumonia in children in China: p =1.86 × 10^{-6}, OR 3.44 (95% CI 2.014–5.888).

ACE SNPs were also studied for associations with cardiovascular entities. A hypothesis that SNP of angiotensin-converting enzyme 2 gene (ACE2, mapped on chromosome X), may be associated with structural atrial fibrillation (AF) was verified in 300 patients with this most frequent supraventricular arrhythmia and 300 arrhythmia-free controls (mean age in both groups 67.6 ± 12.5 and 66.1 ± 12.5, respectively; p = 0.133). In those Chinese patients the prevalence of arterial hypertension, diabetes mellitus, coronary artery disease, heart failure and nicotine-addiction were similar in the compared groups. However, the C allele in rs6632677 was more frequent in males, and when males were analyzed separately from females, the presence of the C allele increased significantly the risk of AF — OR 1.954 (95% 1.196–3.192) [15]. Additionally, an interaction was found between *ACE2* and *AGTR1* in Chinese patients with this arrhythmia in MDR analysis in a 4-locus model (1 locus in *ACE2* and 3 loci in *AGTR1*). A 3-locus model with the same SNP in *ACE2* together with SNP in the troponin I-interacting kinase gene (*TNNI3K*) and calmodulin III gene (*CALM3*) was used by Kumar et al. [16] for risk prediction of hypertrophic and dilated cardiomyopathy (HCM and DCM). On the basis of the comparison of genotypes in 130 patients with HCM, 161 — with DCM and 236 controls, the authors concluded that these 3 polymorphisms significantly influenced both cardiomyopathy phenotypes. The 3-locus model predicted the risk of HCM and DCM with a prediction error of 23.4% and 22.77%, respectively, with p = 0.03 and p = 0.04, respectively [16].

Quite a new association was described between three SNPs in the *ACE* gene located at chromosome 17 and the risk of sudden cardiac death (SCD) during a 64-month follow-up of 1852 participants in the EVOLVE study (EValuation Of Cinacalcet Hydrochloride Therapy to Lower CardioVascular Events), who were from two ancestry groups — European and African — and who were qualified for hemodialysis due to chronic kidney disease with secondary hyperthyroidism [17]. Three correlated SNPs — rs4335, rs4343 and rs4353 — in DNA from European ancestry patients were associated with a 26–27% reduction of SCD (OR 0.74 [95% CI 0.56–0.99], p = 0.004; OR 0.74 [95% CI 0.55–0.99], p = 0.04; OR 0.73 [95% CI 0.54–0.98], p = 0.036, respectively) and only one SNP — rs4318 — reduced the risk of SCD by 70% in the African ancestry patients (OR 0.3 [95% CI 0.1–0.85], p = 0.03). Some ethnic differences in alleles distribution between European and African ancestry patients were found. In the former group, A is the minor allele in rs4335 and rs4343 had a frequency of 0.47 for both of them; whereas in the latter group it was G with a frequency of 0.23. For the third SNP — rs4353 — the same G was a minor allele in both ancestry groups.

Three SNPs in the *ACE* gene were investigated among 125 genetic variants in a group of 1009 participants to evaluate influence of genetic variant on the VO_{2peak} level (as a measure of cardiorespiratory fitness) in untrained people in China [18]. Only 1 of the 3 assessed SNPs — rs4295 — was associated with VO_{2peak} (β = 0.87; p < 2.9 × 10^{-4}) and it was responsible for 1.1% of interindividual variance in VO_{2peak}.

A large-scale study (1024 hypertensive Chinese patients and 956 normotensive ones) was focused on the impact of 34 SNPs of the *ACE2* gene located on chromosome X. Interestingly, it was determined that five of them (rs1514283, rs4646155, rs4646176, rs2285666, and rs879922) were associated significantly with hypertension in women, but not in men. For instance, in rs1514283 the CC genotype and C allele were more frequent in hypertensive patients than in controls — 2.2% vs. 0.7%; OR 4.209; 95% CI 1.633–10.851; p < 0.05 and 3.7% vs. 2.2%; p = 0.01. According to available research, this study reported for the first time that rs4646155 was associated with essential hypertension in women, and homozygotes with minor allele T were significantly more frequent in patients with hypertension than in controls — 1.9% vs. 0.7%; p = 0.01; OR 3.492; 95% CI 1.324–9.212 [19]. Interestingly enough, in another study, two of the above-mentioned SNPs (rs4646155 and rs4646176) together with rs2074192, rs2106809 were investigated with regard to whether they could influence not only elevated blood pressure, but also their susceptibility to hypertensive left ventricular hypertrophy (LVH) in Chinese patients. These four SNPs were genotyped in 289 patients with arterial hypertension with LVH and 358 controls without hypertrophy. The presence of minor allele T in rs2074192 and minor allele T in rs2106809 was significantly associated with LVH, with p = 0.005 for both and OR 2.094, 95% CI 1.249–3.512; OR 2.029, 95% CI 91.235–3.333, respectively [20].

Since angiotensin converting enzyme 2 interacts with spike glycoprotein of the host to facilitate COVID-19 virus entry to the cells, Khalid et al. [21], carried out an *in-silico* study to determine the effect of SNPs at *ACE2* gene on tertiary structure

of this protein and the impact of these SNPs on binding the virus. Two variants in *ACE2* were identified as those which have an influence on the repulsion of ligands of the same negative charge (G405E, W461R), and the third was probably damaging to the protein (F588S). These findings may explain the differences in the course of severe acute respiratory syndrome coronavirus 2 (SARS--CoV-2) infection-related disease during the current pandemic [21].

Angiotensin receptor panel

Many polymorphisms listed in this panel were described already in previously cited articles, since SNPs of *AGTR1* gene were quite often studied together with SNPs of *ACE* or *AGT* genes. An exception to this was a study on the association of rs5186 SNP (A1166C) with retinal vein occlusion; the study involved 69 patients and 82 controls. The minor allele C was significantly more frequent (17.4% vs. 1.2%, $p = 0.0001$) in individuals with such complications within the ocular venous vasculature, which confirms earlier reports on the association of this SNP with other vascular events [22]. The rs5186 SNP was also studied with regard to its impact on development of diabetic nephropathy and presented positive association with this complication; $p < 0.0001$ [9]. The same SNP was studied in aforementioned EVOLVE trial, which presented a 31% increase in risk of composite endpoints (defined as death, nonfatal myocardial infarction, unstable angina leading to hospitalization, aggravation of heart failure or event related to peripheral artery disease) in patients qualified for dialysis — OR 1.31 (95% CI 1.15–1.49), $p = 4.4 \times 10^{-5}$. The molecular importance of this SNP may be explained by the fact, that AGTR1 is co-expressed with miR-155 in many tissues and the latter molecule represses the expression of AGTR1 only in the presence of a major A allele, but not in the presence of a minor C allele [23]. Additionally, as the EVOLVE study proved, the minor C allele was found more frequently in patients of European ancestry (28%) than patients of African ancestry (5%) [17]. Another *AGTR1* polymorphism — rs1492099 — was studied with respect to structural AF in a Chinese population group of 300 patients with this arrhythmia and 300 controls [15]. The authors revealed a higher frequency of minor allele A in AF-group than in controls 14.2% vs. 8.8%, $p = 0.004$ with a 72.7% increased risk of arrhythmia for the minor allele — OR 1.727 (95% CI 1.154–2.487). Of the four SNPs in *AGTR1* gene tested in the Victorian Family Study — rs12721297, rs385338, rs1800766 and rs275649 — only the first one presented an association with decreased values of systolic blood pressure with β(SE) –2.54(0.76) mmHg [10]. Finally, as it was mentioned for *ACE,* some SNPs of *AGTR* gene played a critical role in breast cancer. One hundred sixty-one women in a North Indian breast cancer cohort were compared with 152 healthy women, among others with respect to *AGTR1* — rs5186 (A1166C) and ACE insertion/deletion (I/D) polymorphism. The results of analysis suggest a significant association of two tested polymorphisms with the risk of breast cancer: individuals harboring AC or CC genotype in *AGTR1* together with DD genotype for *ACE* I/D polymorphism — present increased risk of breast cancer with OR 258 (95% CI 34.2–1944.4, $p < 0.001$) [24].

The aldosterone panel

An important rating enzyme in the process of the synthesis of aldosterone from cholesterol is aldosterone synthase (CYP11B2) and genetic variability in its gene is crucial for blood concentration of this hormone. One of the best investigated SNP of *CYP11B2* gene is rs1799998 (T344C), but Qian et al. [25], added some new aspects to existing knowledge after a study on 96 adult patients with chronic kidney disease. They confirmed not only that homozygotes with major alleles (TT) have a significantly higher aldosterone concentration when compared with homozygotes with minor alleles (CC) — 247.5 ± 93.6 pg/mL vs. 190.0 ± ± 81.7 pg/mL, $p = 0.036$, but also that the median annual decline of the estimated glomerular filtration rate during 1.5-year observation was significantly higher in the TT group (5.2 ± 16.1%) than in the CC group (32.8 ± 82.5%) with $p = 0.011$ [25]. Additionally, this group aimed to assess the impact of T344C on incidence of cardiovascular events defined as ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction and unstable angina in this group. The distribution of cardiovascular events was significantly different from random, and it was highest in the TT group (25%), lowest in the CC group (0%), and intermediate in the CT group (7.8%), with $p = 0.033$. Lesser known polymorphisms of *CYP11B2* were the subject of investigation in 1024 patients with essential hypertension and 956 normotensive controls [26]. Only one of seven SNPs selected for this study — rs542092383 — was found to increase the risk of essential hypertension — OR 3.48 (95% CI 1.407–8.597), $p = 0.004$. An interesting result was also obtained for the

next two SNPs — rs73715282 and rs7463212 after adding them to the haplotype analysis with rs542092383. When major alleles in rs73715282 and rs7463212 were accompanied by a minor allele in rs542092383 (this was observed in 1.1% of patients with essential hypertension and in 0.2% of normotensive controls) the OR reached 5.729 (95% CI 1.889–17.371), with p values < 0.0005.

Discussion

Some practitioners may be disappointed by a very weak impact of SNPs on phenotype in some publications mentioned in this review, e.g., significant but small differences in allele frequency between various study groups. It is important to be aware, however, that such is the nature of SNPs, and a stronger association with clinical manifestation is only possible when a higher number of unbeneficial SNP coexists in an analyzed individual. So, with respect to a benefit for public health, it is prudent to identify individuals at high risk of a given disease, hence it was proposed to consider inclusion of so-called polygenic scores in this procedure. Such scores are already determined for the five most common diseases, including coronary artery disease, AF, diabetes mellitus type 2, inflammatory bowel disease and breast cancer [27]. Their potential advantage over the assessment based on clinical risk factors relies on a possibility to assess them directly after birth, so that primary prevention could be started at the earliest stages of the disease. However, a complex, multifactorial disease such as essential hypertension will probably be even more difficult to predict in childhood on the basis of genetic tests than the already studied diseases.

Limitations of the study

This review has some limitations: first of all, this article was focused only on SNPs. Other polymorphisms like an insertion/deletion polymorphism or the polymorphism of variable number tandem repeats were ignored, although they also belong in genetic studies of proteins involved in the RAAS [28, 29]. Apart of this, epigenetic changes — DNA methylation, histone modifications or translational control with microRNA may alter the RAAS function. Furthermore, to some extent also enzymatic posttranslational modifications of proteins play a role in the function of the RAAS, although predisposition to protein destabilization depends also on nonsynonymous SNP as was explained by Goswami [6].

Conclusions

In conclusion, individual susceptibility to hypertension and its associations with genetic variability remain a subject of investigation, which also involve the proteins and enzymes not analyzed in this review. Generally, it should be emphasized that many regions of the genome are still unexplored and knowledge about the importance of underestimated regions will be deepened. Especially, the noncoding regions of the described genes deserve detailed research, as they are expected to constitute 35 times more genetic material than the coding regions [30].

Acknowledgments

The authors would like to thank Mr. Janusz Wróblewski for his linguistic consultation.

Conflict of interest: None declared

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VIA MEDICA

TECHNOLOGY NOTE

Cardiology Journal
2022, Vol. 29, No. 6, 1028–1030
DOI: 10.5603/CJ.a2022.0097

ISSN 1897–5593
eISSN 1898–018X

Laser speckle contrast imaging to assess microcirculation

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Microcirculation plays a crucial role in tissue oxygenation and nutrient supply. Indeed, microvascular dysfunction may precede endothelial impairment in large arteries and clinical manifestations. It is becoming apparent that microcirculation is essentially involved in a variety of pathological conditions, and that microvascular dysfunction may be a biomarker in the development of cardiovascular disease [1]. Recently, accumulating evidence suggests that coronavirus disease 2019 (COVID-19) should be considered as a systemic microvascular endothelial disease with different clinical manifestations from severe and acute to completely asymptomatic course [2]. Hence, non-invasive and reliable methods for microcirculation status monitoring are still strongly needed.

Several methods are available to study the human microcirculation and to quantify microvascular blood flow. Among them, the recent non-invasive laser speckle contrast imaging (LSCI) provides a real-time monitoring of microvascular perfusion. Using LSCI, we showed that topical administration of treprostinil, a prostacyclin analog, increases cutaneous microvascular blood flow in diabetic patients [3]. Indeed, LSCI enables a precise quantification of variations of skin blood flow in two-dimension. LSCI measurements coupled with acetylcholine and sodium nitroprusside iontophoresis showed that for both agents the vasodilatation is reduced in early-onset coronary artery disease patients suggesting concurrent endothelial-dependent and -independent skin microvascular dysfunction [4]. Taken together, in clinical studies, LSCI is mainly used to assess skin microcirculation (Fig. 1) [5]. However, quite recently, LSCI was applied intraop-

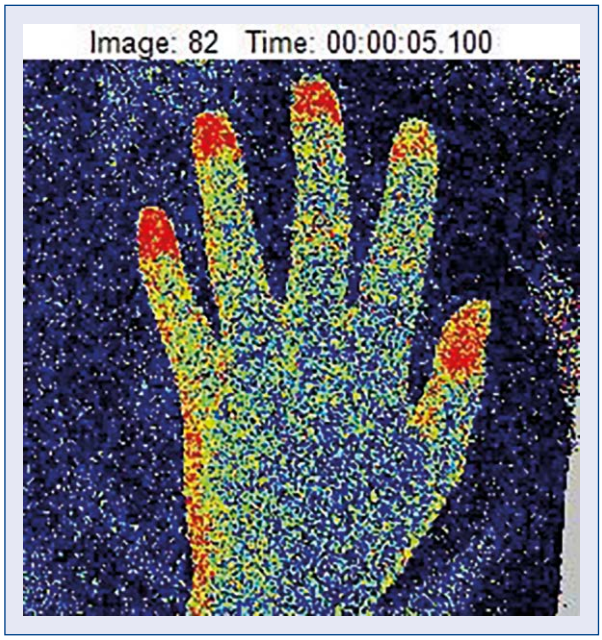

Figure 1. Skin microvascular perfusion on laser speckle contrast imaging with colours ranging from blue (low perfusion) to red (high perfusion).

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Received: 9.09.2022 Accepted: 19.10.2022 Early publication date: 27.10.2022

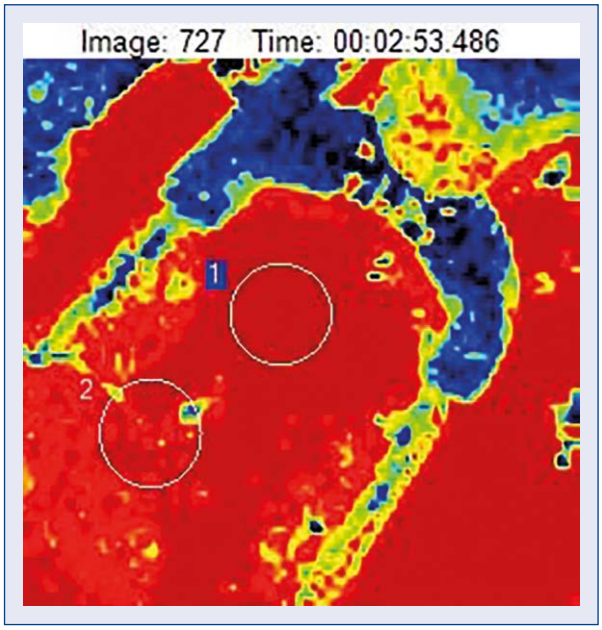

Figure 2. Dynamic two-dimensional microvascular quantification during coronary artery bypass grafting surgery by laser speckle contrast imaging. The blue part corresponds to the myocardial tissue stabilizer (Octopus) used during beating heart surgery.

eratively to estimate parathyroid viability [6]. Using two-dimensional LSCI, we recently performed non-invasive real-time microcirculation imaging on the beating heart (Fig. 2) in a patient undergoing coronary artery bypass grafting surgery [7].

Laser speckle contrast imaging is a recently developed technique based on speckle contrast analysis that provides an index of blood flow. When motionless tissue is illuminated with a laser, a random interference pattern, or speckle, is observed independent of the structure of the tissue surface. Speckle contrast is calculated as the ratio of its standard deviation to its mean intensity. When the laser light is scattered by moving red blood cells, the speckle pattern decorrelates. LSCI is based on the two-dimensional quantification of variations in this speckle contrast. Due to the movement of red blood cells, each single speckle intensity will fluctuate as a function of their velocity, and the time-integrated speckle contrast will be reduced. The penetration depth of LSCI measurements is about 300 μm, whereas it is deeper (about 1–1.5 mm) with laser Doppler techniques. Therefore, LSCI mostly records blood flow in the skin's superficial papillary plexus while laser Doppler techniques record deeper dermal blood flow [8].

Laser speckle contrast imaging does not provide an exact measure of flow (mL/min). Measurements are therefore often expressed as arbitrary perfusion units or as cutaneous vascular conductance, which is flux divided by mean arterial pressure. The latter approach is more physiological as it takes into account differences and variations in blood pressure. Importantly, LSCI measurements can be carried out continuously, but are sensitive to movement artefacts.

In summary, LSCI allows non-invasive real-time monitoring of peripheral microcirculatory perfusion on a wide area of tissue with a very good spatial and temporal resolution and an excellent reproducibility. Therefore, LSCI combines the advantages of laser Doppler flowmetry and laser Doppler imaging [9]. As mentioned above, LSCI is mainly used in clinical studies to assess skin microcirculation [5]. However, LSCI is also successfully applied to animal studies and angiogenesis measurements [10].

A number of common clinical conditions are closely associated with microvascular dysfunction. The monitoring of the microvascular perfusion is therefore of essential interest in various experimental and clinical studies. LSCI measurements are reproducible and highly sensitive to acute changes in tissue perfusion. Of note, this technique coupled with vascular reactivity tests enables assessment of endothelial function. Additionally, LSCI can be easily applied in pharmacological studies aimed at assessing drug safety, efficacy and influence on microcirculation in cardiovascular diseases [3].

Conflict of interest: None declared

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STUDY PROTOCOL

Cardiology Journal
2022, Vol. 29, No. 6, 1031–1036
DOI: 10.5603/CJ.a2022.0103

ISSN 1897–5593
eISSN 1898–018X

Rationale and design of SAN.OK randomized clinical trial and registry: Comparison of the effects of evidence-based pacemaker therapy and cardioneuroablation in sinus node dysfunction

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Background

Sinus node dysfunction (SND) is considered a progressive, incurable, but manageable disease and has conventionally been treated with definitive pacemaker (PM) implantation, according to current European Society of Cardiology (ESC) guidelines [1–3]. However, there is lack of evidence that PM therapy results in improved prognosis and increased expectancy of life [1]. Moreover, the essential number of complications of PM implantation and relatively high rate of rejection by young patients constitute a common clinical dilemma in SND management [4].

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Received: 2.07.2022 Accepted: 31.10.2022 Early publication date: 7.11.2022

**Sebastian Stec and Beata Jankowska-Polańska are co-primary investigators of the study.*

Cardioneuroablation (CNA) is an emerging treatment, a novel method of bradyarrhythmia management [5–8], which is by endocardial radiofrequency (RF) catheter ablation, causing targeted neuromodulation of the cardiac autonomic nervous system, enabling a sudden postprocedural increase in sinus rhythm, thereby providing an attractive treatment option without the necessity for PM implantation in SND, atrioventricular blocks (AVB) and vasovagal syncope (VVS).

The main principle of CNA is a catheter-based destruction of parasympathetic postganglionic neurons of vagal nerve located in ganglionated plexi (GP) in atrial myocardium and epicardium, which induces cardio-neuromodulation of the sino-atrial node (SAN) and/or atrio-ventricular node (AVN), as it has been proven that SAN dysfunction and AVB can be directly related to vagal nerve hyperactivity [5–9].

The CNA technique was introduced by Jose Carlos Pachon over two decades ago and has been refined and improved along the way [5–8]. Currently many investigators worldwide reproduce CNA results with the immediate CNA endpoints including total abolition of atropine response and elimination or significant reduction of vagal response, confirmed by a vagal stimulation [9–16].

The implementation of comprehensive diagnostic assessment including the atropine challenge test, autonomic tests (head-up tilt test, Valsalva maneuver, carotid sinus massage, forced breathing test) and extracardiac vagal nerve stimulation (ECVS), with recently introduced ultrasound-guided ECVS (US-ECVS), enables validation of early and late success rate of vagal nerve ablation and positive impact on automaticity of SAN and conduction of the heart [15].

Despite promising results and relatively high (92%) short- and long-term efficacy of CNA and low risk of complications of the procedure (1–3% vs. 3–5% in PM implantation) [4–7], concerns about the performance of the new non-standardized method, its safety and clinical benefits still exist. In the 2018 ESC guidelines on the diagnosis and management of syncope and 2021 ESC guidelines on cardiac pacing CNA was considered an experimental method and did not receive ESC recommendations, mainly due to the lack of randomized clinical trials.

Therefore, a prospective randomized clinical trial (RCT) evaluating CNA application in SND management and feasibility of non-invasive and invasive diagnostic techniques to facilitate patients for CNA may influence the decision-making process to avoid long-term PM therapy and may have a major impact on future recommendations.

This manuscript is the study protocol of SAN.OK trial and registry, one of the first prospective randomized trials, designed to compare the effects of PM implantation and CNA in patients with SND.

Methods

Study design

SAN.OK study is a multicenter, noncommercial, physician-initiated, proof-of-concept, prospective, randomized, controlled, unblinded clinical trial and registry designed to compare two methods of SND treatment: optimized guideline-recommended PM therapy and a novel method, CNA, preceded by autonomic and interdisciplinary assessment, electrophysiological study (EPS) and ECVS with the goal of achieving post-procedure and maintaining a target heart rate > 50 beats per minute. Subjects who will choose to opt-out of randomization will be included in the registry and will undergo patient-tailored intervention through shared decision-making with a possibility of either PM implantation, CNA or observation only. The study design is presented in Figure 1.

Recruitment will take place in four study sites (**Suppl. Table S1**), in two distinct phases. First, the investigators will identify potential participants. Their medical records will be analyzed by the Scientific Committee (symptoms evaluation, physical examination, documentation of bradyarrhythmia). In the second phase eligible patients will be invited by the investigator to participate in the trial during medical consultation. After detailed explanations describing the study protocol, including the risk and benefits, they will sign the written informed consent to participate in the study or will choose to opt-out of randomization to be included in the registry only. Informed consent will be obtained only if it is clear that the patient truly understands the nature of the study. Alternatively, the patient will be encouraged to take a copy of the consent form home to contemplate enrolment in the study. Only patients who voluntarily consent will be included. Patients will be able to withdraw at any time without compromising their medical care. All measured parameters, as well as demographic and clinical data will be recorded in the study database.

Patients enrolled in the SAN.OK trial will be randomized in a 1:1 allocation to either an optimized guideline-recommended PM therapy (group A) or CNA (group B). Randomization will

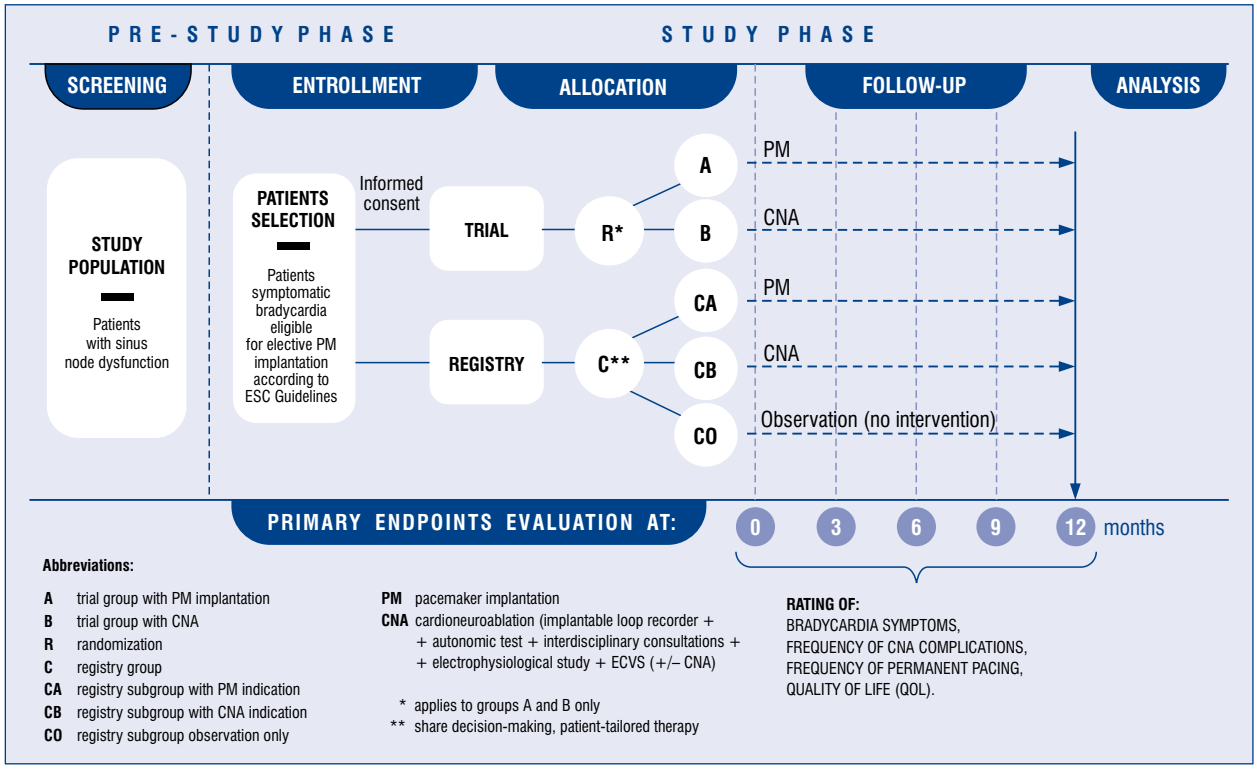

Figure 1. Study design of SAN.OK trial and registry; ECVS — extracardiac vagal nerve stimulation; ESC — European Society of Cardiology.

be performed centrally and assigned automatically to each patient via the internet. The randomization list will be blocked per center, with randomly varying block sizes of 2 and 4. The centers will not be aware of the block sizes. The PM implantation and treatment allocation will not be blinded to the patient or follow-up physician.

Patients in either arm of the study will be followed-up at regular intervals for a minimum of 12 months. The schedule of interventions and assessments of the SAN.OK study and registry is summarized in **Supplementary Tables S2 and S3**. During the 12-month study duration, the use of effective contraception will be recommended for women of child-bearing age.

The SAN.OK study protocol was approved by the independent Ethics Committee of Institutional Board Review (Bioethics Committee at the Lower Silesian Medical Chamber, Wroclaw, Poland, KBE 6/BOBD/2021). The study is registered at clinicaltrials.gov [https://www.clinicaltrials.gov/], identifier NCT05196126. Enrolment began on June 1, 2022. The SAN.OK trial is independently managed by KCRI (www.kcri.org), Krakow, Poland and the Scientific Steering Committee. Members of the latter are the exclusive authors of this manuscript.

Study population

SAN.OK trial will enroll a minimum of 29 patients in each group, 18–75 years old with indications for elective PM implantation according to 2021 ESC guidelines on cardiac pacing. The registry is expected to include up to 120 patients. The recruitment will take place at four study sites in Poland by medical referral (**Suppl. Table S1**). Patient enrollment time is anticipated to last 1 year. Inclusion and exclusion criteria are summarized in Table 1. The population of elderly patients > 75 years, frequently with concomitant heart disease, is excluded, since the demonstration of a clear cause–effect relationship between symptoms and SND is difficult to achieve.

Interventions

Patients in group A (PM, n = 29) will receive care on the basis of the 2021 ESC guidelines on cardiac pacing recommendations. They will be implanted with PM.

Patients in group B (CNA, n = 29) will be implanted with the same type of implantable loop recorder (ILR) device (Biotronic, Biomonitor 3m) with remote tele-monitoring, with the same thresholds for automatic episode recording. A central

Table 1. Inclusion and exclusion criteria of SAN.OK trial and registry.

Inclusion criteria
Male and female patients, age 18–75 years
Sinus node dysfunction/disease fulfilling criteria for elective pacemaker implantation according to current ESC guidelines (I, IIa, and IIb)
Optimization of chronic disease treatment
Ability to provide informed consent to participate in the study
Ability to understand patient information
Exclusion criteria
Contraindications to invasive and non-invasive procedures used in the study
Uncontrolled systemic and endocrine disorders
Persistent atrial fibrillation
Dilated cardiomyopathy
Severe congenital heart valve disease or cardiomyopathy
Functional NYHA class III/IV
Left ventricular ejection fraction < 35%
Left atrial diameter > 50 mm
Previous catheter ablation
Contraindications to anticoagulant treatment
Contraindications to catheter ablation
Chronic advanced (II or III degree) AV block associated with structural heart disease
Contraindications to non-invasive tests
Pregnancy and lactation
Previous cardiac surgery
Implanted pacemaker device
Neck and chest abnormalities
Myocardial infarction in the previous 6 months
Percutaneous coronary intervention in the previous 3 months
Estimated survival < 24 months
Participation in another drug or medical device program
Limited capacity to understand the study protocol or psychological disorders precluding informed consent to participate in the study
Any other uncontrolled chronic diseases, neck and chest abnormalities, or disorders that constitute a contraindication to catheter ablation, antiarrhythmic treatment, general anesthesia, or ECVS
Severe obesity (BMI ≥ 40 kg/m^2)

AV — atrioventricular; BMI — body mass index; ECVS — extracardiac vagal nerve stimulation; ESC — European Society of Cardiology; NYHA — New York Heart Association

committee will be responsible for remote tele-monitoring. The major reason for ILRs implantation is to provide electrocardiogram documentation of clinical bradycardia, as well as monitoring of patients before and after CNA (or PM implantation, if accepted). In case of severe bradycardia, the emergency system will always be called. Patients in group B will be accepted for CNA (or PM implantation) based on complex data including ILRs interrogation and multidisciplinary assessment.

Multidisciplinary assessment in group B will include: a) symptoms evaluation on VAS; b) documentation of bradyarrhythmias on ILR with remote monitoring; c) autonomic tests: atropine challenge, Valsalva maneuver, carotid sinus massage, head-up tilt test, forced breathing test; d) interventional assessment: EPS, ECVS; e) interdisciplinary consultations: sleep medicine, otolaryngology, vascular surgery, bruxism-orthodontic.

Cardioneuroablation will be performed in group B under general anesthesia by highly trained operators according to previous case reports [14, 15]. After EPS biatrial, binodal, anatomically-guided CNA will be performed with ECVS guidance, with demonstration of vagal response by ECVS at the beginning of CNA and its complete disappearance after successful CNA. Additional substrates for ablation will also be investigated. If CNA is unsuccessful, a second session of CNA is planned. In case of an inefficient second attempt, patients will be referred for PM implantation. They will cross-over to the PM arm.

Patients in the registry (group C) will undergo patient-tailored intervention through shared decision-making with a possibility of either PM implantation (subgroup CA), CNA (subgroup CB), or observation only (subgroup CO).

All patients in the trial and registry will be asked to complete questionnaires on health-related quality of life; (QOL) (EQ-5D-5L, SF-36), bradycardia symptoms; (Visual Analog Scale [VAS]), fatigue; (Modified Fatigue Impact Scale [MFIS]), depression (Modified Hospital Anxiety and Depression Scale; [HADS-M]) and sleep disorders (Epworth Sleep Scale [ESS]; Athens Insomnia Scale-8 [AIS-8]).

The safety of the interventions will be assessed weekly, with monitoring of major adverse cardiovascular events (MACE). All outcome events will be adjudicated by The Central Adjudication Committee, which does not include members of the Scientific Steering Committee.

Endpoints

The primary endpoint is to determine the efficacy of CNA in the treatment of bradyarrhythmia in comparison to PM therapy within 6 months of PM implantation/CNA procedure.

The secondary endpoints include: 1) occurrence of MACE, defined as peri-procedural and long-term complications: death, stroke, myocardial infarction, pericardial effusion requiring drainage, AVB, venous thrombosis, infection, hemorrhage, hematoma, fistula, pseudoaneurysm, surgical intervention; 2) assessment of the effect of CNA and PM implantation on bradycardia symptoms on VAS, health-related QOL (EQ-5D-5L, SF-36 questionnaires), fatigue (MFIS), depression/anxiety (HADS-M), sleep disorders questionnaire (ESS, AIS-8) at 0, 3, 6, 12 months (**Suppl. Table S4**).

Statistical analysis

Statistical analysis includes descriptive analysis of the primary and secondary endpoints. There are two types of endpoints in this study concerning the nature of the parameters tested: objective and subjective.

The objective endpoint examining the onset of bradyarrhythmia episodes after PM/CNA will be assessed at 6 months. It will specify the number of pauses > 3.0 s in the ILR for group B (occurrence of > 1 pause or the need for earlier (0–6 months) PM implantation will be an indicator of the failure of the CNA procedure), assuming the presence of PM stimulation in group A at the level between 93–100% (equates to the continued duration of the bradyarrhythmia treated with PM).

The subjective endpoint examining symptoms such as QOL, fatigue, depression/anxiety, sleep disorders using questionnaires will be assessed at 0, 3, 6, 12 months.

For both endpoints descriptive statistics (parametric and non-parametric) will be determined for the parameters tested. In addition, a comparative analysis between groups for the objective parameters at timepoints 0, 6 months and the subjective parameters at timepoints 0, 3, 6, 9, 12 months will be carried out with non-parametric tests of statistical significance using the Bonferroni correction.

The effectiveness of CNA vs. PM will be considered statistically significant at the level of $p < 0.01$ if there is an absence of pauses > 3.0 s within 6 months after the CNA procedure in 33% of patients (12/30) — assuming 90% statistical power, with simultaneous assumption of the presence of PM and 100% effectiveness of stimulation in group A. Such a result will mean a reduction in the need for PM implantation in 33% of respondents.

Statistical significance is expected in the difference between groups A and B in both objective and subjective endpoints, meaning:

- reduction in the number of patients requiring PM implantation in group B compared to group A (all patients with implanted PM);
- a significant improvement in the quality of life of patients in group B as measured by bradycardia symptoms on VAS, QOL (EQ-5D-5L, SF-36), fatigue (MFIS), depression/anxiety (HADS-M), sleep disorders (ESS, AIS-8) questionnaires.

Assuming the incidence of PM implantation at 6-month follow-up as 28/30 (93%) and 18/30 (60%) in groups A and B, respectively, and statistical power of 90%, the group size should be 29 patients each to obtain a statistical level of 0.01. This translates into a 33% reduction of the need for PM implantation.

Discussion

The autonomic nervous system plays a distinctive role in the pathophysiology of bradyarrhythmia [8]. Neuraxial modulation of vagal nerve is an important avenue of scientific inquiry and novel therapeutic intervention [5–18]. Treatment of SND by ablation technique seems a very attractive method, especially in young patients in whom a prosthesis is highly undesirable. Therefore, CNA has a potential to revolutionize cardiac electrophysiology and become a minimally invasive method of functional bradycardia and SND treatment. According to available research, SAN.OK RCT is one of the first clinical studies investigating optimal decisions on invasive strategy in SND and/or chance to avoid PM therapy with the use of ECVS as the most rational peri-procedural endpoint of CNA [19, 20]. In comparison to other registered ongoing trials, such as GAPS [19] and DINERVAPACE [20], in the SAN.OK study patients allocated to the CNA group will be monitored by ILR and ECVS. Moreover, the SAN.OK study is the first to compare measurable indicators of QOL and associated symptoms before and after CNA and PM implantation. According to current ESC guidelines quality of life is an essential metric for measuring a patient's clinical status and outcome, and provides a holistic picture of clinical treatment effectiveness [1]. In summary, SAN.OK prospective trial may influence the decision-making process to avoid long-term PM therapy, provided that an alternative treatment is available with demonstrated non-inferiority.

Clinical Trial Registration: URL: https://www.clinicaltrials.gov/; unique identifier: NCT05196126.

Limitations of the study

Owing to differences in techniques of PM implantation and CNA the present study is unable to be blinded.

Acknowledgments

The authors appreciate the support of Adrianna Szalonka MSc, Aleksandra Wróblewska MD, Aleksandra Banc-Wilczek MD, Łukasz Dobaj MD, Maciej Kluk MD, Justyna Mach RN, Aleksandra Buchta-Nitecka MD, Daker Al-Soori MD, Andrzej Kutarski MD, PhD, Anna Polewczyk MD, PhD, Marzena Krawiec CEO, Kinga Gościńska-Bis MD, Joanna Jędrzejczyk-Spaho MD, Łukasz Partyka MD, CEO, Przemysław Guzik MD, PhD and Jacek Gajek MD, PhD. We are grateful to Mrs Paulina Rymer for graphical editing of the study design.

Funding

The study is funded by Medikard and co-sponsored by Telemedycyna Polska SA. Regarding economic impact on subjects there are no additional costs related to involvement in this study. Since the cost of ILRs and the diagnostic tests will be covered by study sponsors and costs related to invasive procedures (PM implantation, CNA) will be included within the National Fund of Health charge, the patient will not incur additional costs.

Conflict of interest: Sebastian Stec is the author of several patents and shareholder of Medicine S.A. and Tracess A.B. No specific product of any company will be used in this trial. Artur Fedorowski has received speaker fees from Medtronic Inc, Biotronik, Finapres Medical Systems, and Bristol-Myers-Squibb, and is a consultant to Medtronic Inc. and Argenx B.V. All other authors declare that they have no conflicts of interest.

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VIA MEDICA

RESEARCH LETTER

Cardiology Journal
2022, Vol. 29, No. 6, 1037–1039
DOI: 10.5603/CJ.a2022.0088

ISSN 1897–5593
eISSN 1898–018X

The role of cardiometabolic risk factors and endothelial dysfunction in serum albumin levels of patients with COVID-19

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With more than 500 million cases and 6.2 million deaths worldwide, coronavirus disease 2019 (COVID-19) is the biggest global challenge the world is facing in modern times. Growing evidence focuses on the role of hypoalbuminemia in the COVID-19 course and on the role of vascular inflammation in the progression to capillary leak syndrome (CLS) [1]. Hypoalbuminemia is more common in patients with severe COVID-19, and is indicative of a poor prognosis [2, 3]. CLS is characterized by the combination of severe hypoalbuminemia with diffuse pitting edema, exudative serous cavity effusions, non-cardiogenic pulmonary edema, and hypotension which can progress to resistant hypovolemia and shock in the most severe cases. Insulin resistance and overt diabetes mellitus, obesity, dyslipidemia, hypertension, and coronary artery disease all fall under the umbrella of cardiometabolic disease [4]. The common ground between these disorders is endothelial dysfunction, which may be attributed to hereditary and environmental factors, but it also shares various mechanisms with metabolic derangement, especially insulin resistance [5]. The aim of this study is to investigate the role of cardiometabolic risk factors (CRFact) in the endothelial dysfunction-related hypoalbuminemia of hospitalized COVID-19 patients.

In this study, conducted in the "Sotiria" General Hospital for Chest Diseases, Athens, Greece, 73 patients admitted for COVID-19 were enrolled. COVID-19 was confirmed by real-time reverse transcriptase-polymerase chain reaction assay of nasopharyngeal or bronchial swabs, in at least one biological sample. Study parameters, medical history, and laboratory examinations were collected in the acute phase of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (between 24 and 72 h after hospital admission). Endothelial function was evaluated by estimating the flow-mediated dilation (FMD) in the brachial artery. According to the presence of obesity (body mass index > 30 kg/m^2), history of hypertension, dyslipidemia, and diabetes mellitus, COVID-19

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Received: 11.04.2022 Accepted: 24.08.2022 Early publication date: 16.09.2022

patients were categorized as those with CRFact or without CRFact (no-CRFact). From the study population, subjects excluded were with a) established cardiovascular disease, b) end-stage renal failure, c) active malignancy, d) previous or current autoimmune diseases.

All individuals were informed about the study's aims and provided written informed consent.

The study was approved by the hospital's Ethics Committee and conformed to the ethical guidelines of the 2008 Declaration of Helsinki.

All statistical calculations were performed using IBM SPSS software Version 26.0. Categorical variables were presented as frequencies and percentages. The Student t-test or Mann-Whitney test were used to assess the differences between groups of normally and non-normally distributed continuous variables, respectively. Differences between categorical variables were tested by forming contingency tables and performing χ^2 tests. The Pearson and Spearman coefficients were used for parametric and nonparametric correlations, respectively. All reported p-values were based on two-tailed tests, with a p-value < 0.05 being considered statistically significant.

The 73 patients enrolled were (male: 63%), hospitalized for COVID-19 in the present study, with a mean age of 60.6 years. Patients with CRFact (50 patients) were significantly older (63.8 ± ± [standard deviation] 10.9 years vs. 53.8 ± 14.4 years, p = 0.002), with lower FMD (1.2 ± 2.1% vs. 2.7 ± 2.4%, p = 0.006) and higher interleukin-6 (IL-6) (16.1 [5.7, 81.9] pg/mL vs. 3.5 [1.5, 36.8] pg/mL, p = 0.01) compared to those without CRFact. No differences in C-reactive protein (CRP) were noted (6.7 [3.4, 10.7] mg/dL vs. 6.4 [2.5, 12.5] mg/dL, p = 0.71). As far as serum albumin is concerned, significantly lower concentrations were found in patients with CRFact compared to those without CRFact (3.1 ± 0.7 g/dL vs. 3.6 ± ± 0.3 g/dL, p = 0.003) (Fig. 1). Interestingly, serum albumin in patients with CRFact was significantly lower than the lower reference limit (3.5 g/dL) of albumin (p < 0.001), a finding which was not confirmed in patients without CRFact (p = 0.28). Furthermore, regression analysis revealed that, irrespective of age, the presence of CRFact was associated with decreased serum albumin levels (by 0.34 g/dL, 95% confidence interval: –0.65 to –0.03, p = 0.03). Finally, significant correlations of serum albumin with FMD (R = 0.30, p = 0.03) and inverse correlations of albumin with inflammatory biomarkers (IL6: rho = –0.68, p < 0.001 and CRP: rho = –0.47, p < 0.001) were only detected in subjects with CRFact.

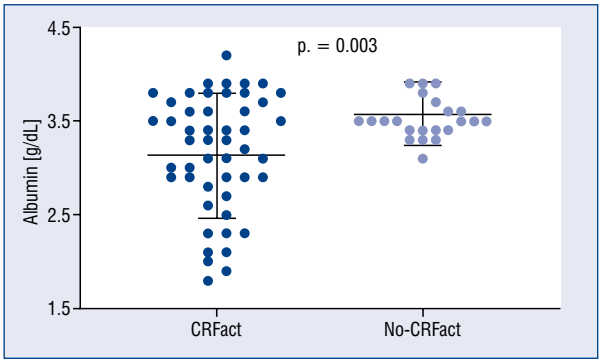

Figure 1. Serum albumin levels in patients with and without cardiovascular risk factors (CRFact).

In this cross-sectional study, patients with CRFact hospitalized for COVID-19 presented with significantly lower serum albumin levels compared to COVID-19 patients without CRFact. Importantly, albumin levels in this group of patients were associated with impaired endothelial function and inflammatory response.

Albumin appears to be a critical mediator of COVID-19 course and outcome. Even though the mechanisms of hypoalbuminemia in COVID-19 have not been elucidated, it is believed that systemic inflammation may precipitate to leakage of albumin to the interstitial space due to increased capillary permeability, the so-called CLS. Hepatocellular injury-induced hypoalbuminemia is unlikely since albumin's half-life (21 days) is much longer than the time from symptom onset in the current study (median 6 days). As decreased serum albumin levels may be related to the hyperinflammatory state and endothelial cell dysfunction in COVID-19 [6–8], a pre-existing inflammatory state paired with impaired endothelial function in the setting of cardiometabolic diseases (obesity, hypertension, diabetes mellitus, dyslipidemia) could be a contributing factor, as we have reported. As serum albumin levels were correlated with indices of dysfunctional endothelium and pro-inflammatory markers only in the group of patients with cardiometabolic risk factors, it may be hypothesized that capillary leakage of albumin is another pathophysiologic mechanism of increased disease severity in these patients. Existing evidence highlights the association of hypoalbuminemia with poor COVID-19 prognosis [9]. At the same time, decreased serum albumin may be observed more frequently in hy-

pertensive or diabetic patients [10], as also seen in the present study.

To conclude, serum albumin levels may be an important clue of capillary leakage in patients with cardiometabolic risk factors, which is associated with inflammation and endothelial dysfunction. Capillary leakage of albumin, through the routine measurement of its serum levels, at least the first few days of hospital admission, should be promptly identified. This is important especially in patients at risk of poor COVID-19 outcome, who may benefit from early advanced treatment modalities and possibly by immunomodulatory or anti-inflammatory therapy. Whether hypoalbuminemia correction may benefit patients merits further research.

Conflict of interest: None declared

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VIA MEDICA

RESEARCH LETTER

Cardiology Journal
2022, Vol. 29, No. 6, 1040–1042
DOI: 10.5603/CJ.a2022.0096

ISSN 1897–5593
eISSN 1898–018X

Hybrid method of large bore arterial access closure: Single-center initial experience based on percutaneous coronary artery interventions assisted with left ventricle support device

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Introduction

Despite advancement in surgical techniques, cardiologic patients are often not good candidates for surgery due to a large burden of comorbidities or frailty syndrome. Transcatheter aortic valve replacement, endovascular aortic repair and percutaneous coronary interventions (PCI) assisted with percutaneous left ventricle assist devices (pLVAD) are gaining in popularity, gradually replacing alternative surgical methods [1].

The aim of the present study is to delineate initial experience of vascular closure device application based on a series of patients undergoing high-risk PCI with pLVAD.

Twenty-one consecutive patients treated with high-risk PCI with pLVAD were included in accordance with the Heart Team opinion. Data were collected retrospectively. The procedures were performed by highly experienced operators and were elective, except for 1 case. The efficacy endpoint was successful vascular closure. The safety endpoint were in-hospital complications with special regard for hemorrhagic events which remained in line with the criteria proposed by the Bleeding Academic Research Consortium (BARC) [2]. Additional vascular access site imaging examinations were performed in the case of suspecting arterial dissection, false aneurysm or retroperitoneal hemorrhage. Perclose Proglide (PP; Abbott Vascular, California, USA) and Angio-Seal VIP (AS; Terumo Corporation, Tokyo, Japan) were used for vascular closure in the presented series of cases. Vascular closure failure was defined as an inability to fully deploy the closure devices or the necessity to implement adjunctive procedures at an access site other than additional vascular puncture site compression. The large bore arteries (LBA) was defined as vascular access exceeding 8-French. Nonetheless, in the present study, in all assessed puncture sites 14-French sheaths were inserted, except for 1, where a 19-French sheath was used. The closure method was chosen at the discretion of the operator by his experience. All LBA were obtained under the control of fluoroscopy and managed applying 1 of the following methods.

Double Angio-Seal VIP

After the insertion of the pLVAD, 2 0.035” guidewires are introduced into the femoral lumen

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Received: 1.02.2022 Accepted: 31.08.2022 Early publication date: 4.10.2022

Table 1. Patient baseline characteristics and procedural outcomes.

	AS + PP (n = 12)	PP + PP, AS + AS (n = 9)
Patient characteristics		
Age [years]	63.9 ± 7.7	69.8 ± 10.2
Gender, males	10 (83.3%)	9 (100%)
Body mass index [kg/m^2]	25.7 ± 4.0	28.4 ± 3.9
LVEF [%]	18.4 ± 3.9	23.2 ± 9.1
Arterial hypertension	9 (75%)	7 (77.8%)
Diabetes mellitus	5 (41.7%)	2 (22.2%)
Peripheral artery disease	0 (0%)	2 (22.2%)
eGFR < 60 mL/min/1.73 m^2	3 (25%)	4 (44.4%)
Peri- and postprocedural outcomes		
LBA closure failure	0 (0%)	2 (22.2%)
HNF during PCI, 1000 U	10 ± 1.5	11.1 ± 2.2
Contrast administration [mL]	388.2 ± 119.1	316.7 ± 148
Inotropes or vasopressors during PCI	3 (25%)	1 (11.1%)
Hemoglobin drop during hospitalization [g/dL]	2 ± 2	3.5 ± 2.5
BARC:		
1	4 (33%)	3 (33.3%)
2	1 (8.3%)	0 (0%)
3	2 (16.6%)	4 (44.4%)
Cases of RCP transfusions	1 (8.3%)	0 (0%)
Pseudo-aneurysm treated with thrombin injection	0 (0%)	1 (11.1%)
VCD deployment failure	0 (0%)	2 (22.2%)
Surgical management of hemorrhagic complication	0 (0%)	0 (0%)
Arterial puncture site infection	0 (0%)	0 (0%)

AS — AngioSeal VIP; BARC — bleeding classification system definitions; Data presented as mean ± standard deviation for continuous variables and counts (percentages) for nominal variables; HNF — non-fractioned heparin; LBA — large bore access; LVEF — left ventricular ejection fraction; PCI — percutaneous coronary intervention; PP — Perclose Proglide; RCP — red cell package; VCD — vascular closure device

and a 14-French sheath is explanted. Subsequently, shafts of 2 AS systems are put into the femoral artery. After the deployment of the first AS, manual compression is applied for a couple of minutes. Then, the second system is deployed with subsequent manual compression.

Double Perclose Proglide

Both PP systems should be partially deployed before insertion of a large sheath, in concordance to the instructions available on the producer's website [3]. The main difference compared to a single PP deployment is an imperative of 30-degree PP rotation in opposing directions before opening a "foot" inside the femoral artery. There is also the technically demanding maneuver of large sheath protrusion and simultaneous advancement of the PP's knots in order to be deployed. In the case of lack of hemostasis, there is a possibility to use an additional vascular closure device (VCD) (if the wire is still in the vessel), a compression device or manual compression could also be introduced.

Angio-Seal VIP + Perclose Proglide

Perclose Proglide is deployed in a "perclose" manner before insertion of a large sheath. After the PCI and explantation of the pLVAD, the large sheath is protruded under the control of the artery manual compression proximally to the arterial puncture. The compression aims to limit blood loss during sheath protrusion and, at the same time, it must not hinder advancement of the knot. Afterwards, a 6-French sheath is inserted, and if a hemostasis is achieved, the 6-French or 8-French AS is deployed in a standard manner. The process is finalized with the PP knot tightening (white stitch).

Baseline patient characteristics are shown in Table 1. The most frequently chosen technique was

LBA closure with AS + PP (57.1%), then PP + PP (33.3%) and AS + AS (9.5%). Closure failure occurred in 2 double PP cases due the stitch rupture. The most common complication was a hematoma not demanding surgical management. In 1 case in the AS + PP group, the procedure was complicated by a retroperitoneal hematoma that was treated pharmacologically and by transfusion of 2 units of packed red blood cells. In this case, the LBA was not a source of the bleeding, but the contralateral femoral 7-French access closed by a single AS. One procedure with the double PP technique was complicated by a pseudoaneurysm which was treated with thrombin injection. In 2 cases of hybrid closure, despite successful deployment of devices, the Femostop (Medline Industries, Illinois, Northfield, USA) was applied due to local oozing. There were no cases of arterial puncture infection or the need for surgical intervention.

Overall efficacy of the vascular closure in the presented series was 90.4%, which was comparable to the data reported by other authors. In the literature, the success rate varies from 91.4% to 100% [4–8]. Nonetheless, Toggwailer et al. [9] described the necessity of additional surgery in almost 28% of early patients due to vascular complications, with an impressive reduction to 2% at the end of the study. A decrease in arterial complications in the access site over time was also observed in other studies regarding procedures with LBA [10]. Thus, lower success rate in the present study could be mainly attributed to the initial nature of the series and the learning curve. Contrary to the PP system, the AS is not meant to be mixed with other VCDs by the instruction of use. Nonetheless, available literature provided reliable and favorable outcomes of this method [6, 7]. Based on our experience, comparing the hybrid method with others, it seems to have a higher efficacy and lower rate of bleeding complications in class > 2 according the BARC classification.

Summary

The main finding of this study is that initial experience of the hybrid LBA closure technique gives promising results and is more effective compared to other methods analyzed in the presented work. While the patient sample size is too small to draw definitive conclusions, the present outcomes are consistent with those reached in other studies, showing high effectiveness and safety of the hybrid closure method. Nonetheless, further investigation in randomized controlled trials is needed to compare different methods of LBA closure.

Conflict of interest: None declared

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VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

Cardiology Journal
2022, Vol. 29, No. 6, 1043–1044
DOI: 10.5603/CJ.2022.0110

ISSN 1897–5593
eISSN 1898–018X

Added value of contrast echocardiography for the evaluation of multiple giant coronary artery aneurysms with coronary to pulmonary arterial fistulas

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A 55-year-old man was admitted to our hospital for transient headache. Twelve-lead surface electrocardiogram (ECG) revealed rapid atrial fibrillation and premature ventricular beat. Transthoracic echocardiography revealed a huge hypoechoic mass adjacent to the aorta and two cystic masses located in the left anterolateral aspect of the pulmonary artery (PA), which were initially suspected as pseudoaneurysms of PA (Fig. 1A, B). Color Doppler flow imaging showed multiple bilateral flows between masses and PA (Fig. 1C). Subsequent contrast echocardiography was performed, which displayed no origination of masses from the aorta or the PA, suggesting giant coronary artery aneurysms (Fig. 1D, E).

In addition, a great quantity of intraluminal thrombi was evident on contrast echocardiography. Furthermore, contrast agent provided better delineation of tortuous coronary arteries with fistulas to the PA (Fig. 1F). Three-dimensional volume-rendered reconstruction images of cardiac coronary computed tomographic angiography (CTA) demonstrated multiple giant coronary artery aneurysms originating from the right coronary artery (RCA) and the left anterior descending artery (LAD) with bilateral coronary artery fistulas to the PA (Fig. 1G, H).

Invasive coronary angiography confirmed the presence of huge coronary artery aneurysms arising from the RCA and the LAD, associated with coronary-pulmonary fistulas (Fig. 1J, K). During operation, large aneurysms with intramural thrombus arising from the LAD and the RCA and coronary artery fistulas to the PA were observed (Fig. 1I, L). The aneurysms were resected; orifices of fistulae were closed, and the RCA and the LAD were reconstructed. The patient recovered well after the surgery.

Funding

This work was supported by the National Natural Science Foundation of China (No. 81727805; 81922033; 81401432).

Conflict of interest: None declared

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Received: 4.01.2022 Accepted: 5.09.2022

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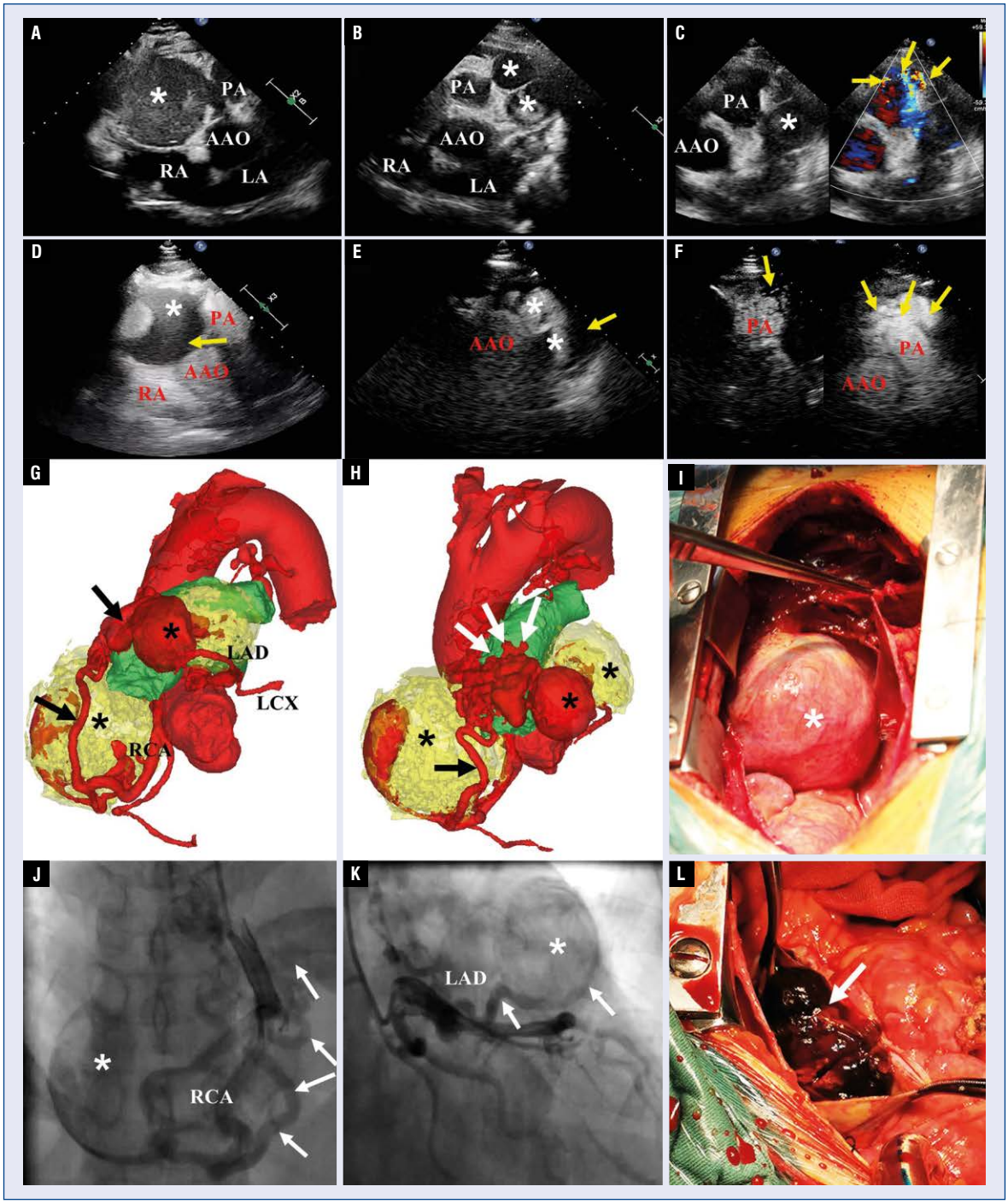

Figure 1. A, B. Two-dimensional echocardiography showing a huge hypoechoic mass (asterisk) adjacent to the aorta and two cystic or solid-cystic masses (asterisk) located in the left anterolateral aspect of the pulmonary artery (PA); **C.** Color Doppler flow imaging demonstrating a continuous shunt from the coronary artery into the PA (yellow arrows); **D, E.** Contrast echocardiography clearly displaying the giant coronary artery aneurysm with intramural thrombus (yellow arrows); **F.** Contrast echocardiography confirms the communication between the tortuous coronary arteries (yellow arrows) and the main PA; **G, H.** Three-dimensional volume-rendered reconstruction images of cardiac computed tomographic angiography shows multiple giant aneurysms of coronary arteries with intramural thrombi (asterisk), connected by fistulas (black arrows) to the PA (white arrows). (Yellow color indicates aneurysmal thrombus); **J, K.** Coronary angiography showing the huge coronary artery aneurysms (asterisk) with fistulas from the right coronary artery (RCA) and left anterior descending artery (LAD) to the PA (white arrow); **I, L.** Intraoperative photographs displaying the huge aneurysm of RCA (asterisk) and thrombus within the aneurysm of LAD (white arrow); AAO — ascending aorta; LA — left atrium; RA — right atrium; LCX — left circumflex.

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

Cardiology Journal
2022, Vol. 29, No. 6, 1045–1046
DOI: 10.5603/CJ.2022.0111

ISSN 1897–5593
eISSN 1898–018X

Coronary artery embolism as a silent killer due to asymptomatic paroxysmal atrial fibrillation

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A previously healthy 48-year-old man presented to the emergency department with chest pain of sudden onset. Electrocardiography showed complete atrioventricular block and an elevated ST-segment in the inferior limb leads. Emergency coronary angiography showed occlusion of the right coronary artery (Fig. 1A). Thrombus aspiration followed by crushing thrombi by balloon dilation and recovered favorable blood flow (Fig. 1B). Optical coherence tomography (OCT) and intravascular ultrasound demonstrated neither evidence of plaque rupture nor erosion at the culprit lesion (Fig. 1C). Asymptomatic paroxysmal atrial fibrillation was detected during the hospital stay and a huge thrombus was identified in the left atrial appendage (LAA) with transesophageal echocardiography (Fig. 1D). These findings indicate acute myocardial infarction (AMI) caused by highly likely thromboembolism from the LAA thrombus. Administration of a direct oral anticoagulant agent dissolved the LAA thrombus and no thromboembolic event has since been observed.

Although many cases of coronary artery embolism (CE) have been reported, the present case was the first to demonstrate both a clear embolic source in LAA and an OCT finding indicating no atherosclerotic origin of the culprit lesion. CE is the underlying cause of 2.9% of cases of de novo AMI. Considering the poorer long-term outcomes of CE patients than non-CE patients, it must be recognized that they are a high-risk subpopulation of AMI patients. Atrial fibrillation is the most frequent cause of CE, and the recurrence of systemic thromboembolism is also noted in patients with atrial fibrillation. Therefore, CE patients must be appropriately diagnosed and optimize management to improve their prognoses.

Conflict of interest: None declared

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Received: 7.08.2022 Accepted: 10.10.2022

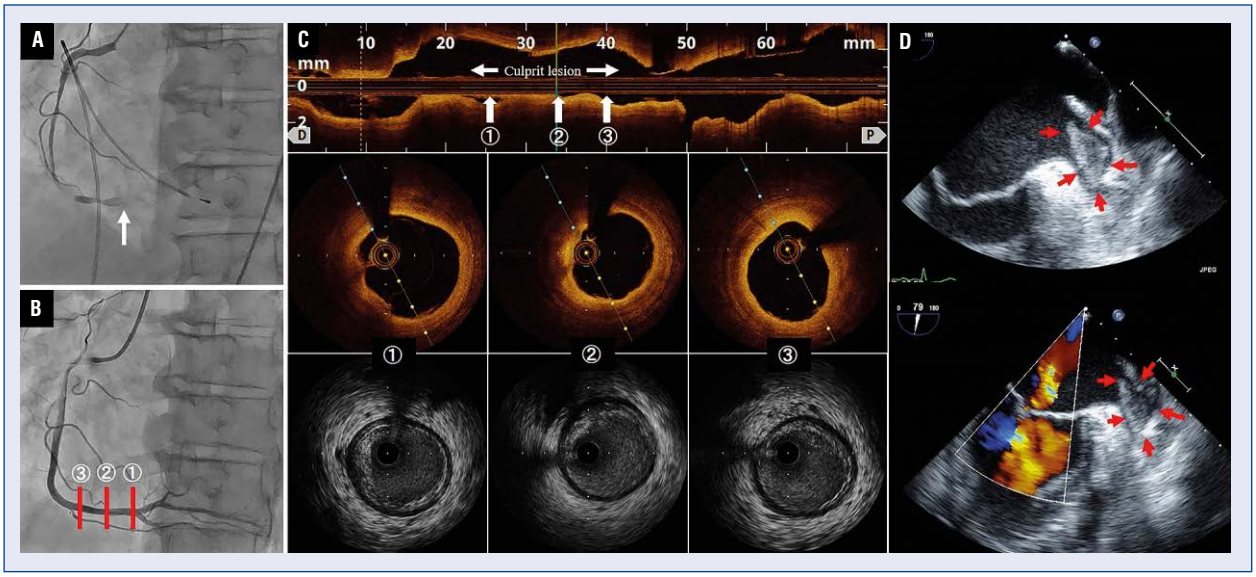

Figure 1. A. Coronary angiography showing an occlusion of the right coronary artery (RCA) (arrow); **B.** Absence of organized stenosis at the culprit lesion of RCA after recanalization; **C.** Optical coherence tomography and intravascular ultrasound showing neither evidence of plaque rupture nor erosion at the culprit lesion; **D.** Transesophageal echocardiography showing the presence of a huge thrombus in left atrial appendage.

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

Cardiology Journal
2022, Vol. 29, No. 6, 1047–1048
DOI: 10.5603/CJ.2022.0112

ISSN 1897–5593
eISSN 1898–018X

Cardiac imaging high-risk features of malignant mitral valve prolapse

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Mitral valve prolapse (MVP) is an underappreciated cause of sudden cardiac death (SCD). There are some imaging test signs that can help identify high-risk cases which may result in serious outcomes.

A 35-year-old woman suffered sudden loss of consciousness at home. Emergency services observed a ventricular fibrillation rhythm, and after the delivery of electric shocks, sinus rhythm returned, showing negative T waves in inferolateral leads (Fig. 1A). Two-dimensional echocardiogram showed prolapse and thickness of mitral leaflets and mitral annulus disjunction (separation of mitral leaflet and left atrial junction from left ventricular posterior wall during systole) (Fig. 1B). Doppler echocardiography showed tissue supranormal longitudinal strain in left ventricle posterolateral wall (Fig. 1C). Cardiac magnetic resonance (CMR) confirmed mitral annulus disjunction and showed pathological late gadolinium enhancement (LGE) in papillary muscles and inferolateral left ventricular wall (Fig. 1D, E). Pickelhaube sign (mitral annulus velocity > 16 cm/s) was also observed in the Doppler study (Fig. 1F). This sign is so called because of its similarity to an old Prussian soldiers' helmet (Pickelhaube, in German) (Fig. 1G). Coronary artery disease was ruled out, and an implantable cardioverter-defibrillator was implanted. The substrate for ventricular arrhythmia is the presence of fibrosis, identified by LGE in CMR, in papillary muscles and inferobasal wall, due to an abnormal systolic mechanical stretch of the myocardium adjacent to the valve. Fortunately, most patients with these signs do not experience such a malignant course, but the finding of the described characteristics in MVP patients should alert us to the risk of SCD and lead to a careful monitoring and evaluation of the patients.

Conflict of interest: None declared

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Received: 6.09.2022 Accepted: 13.10.2022

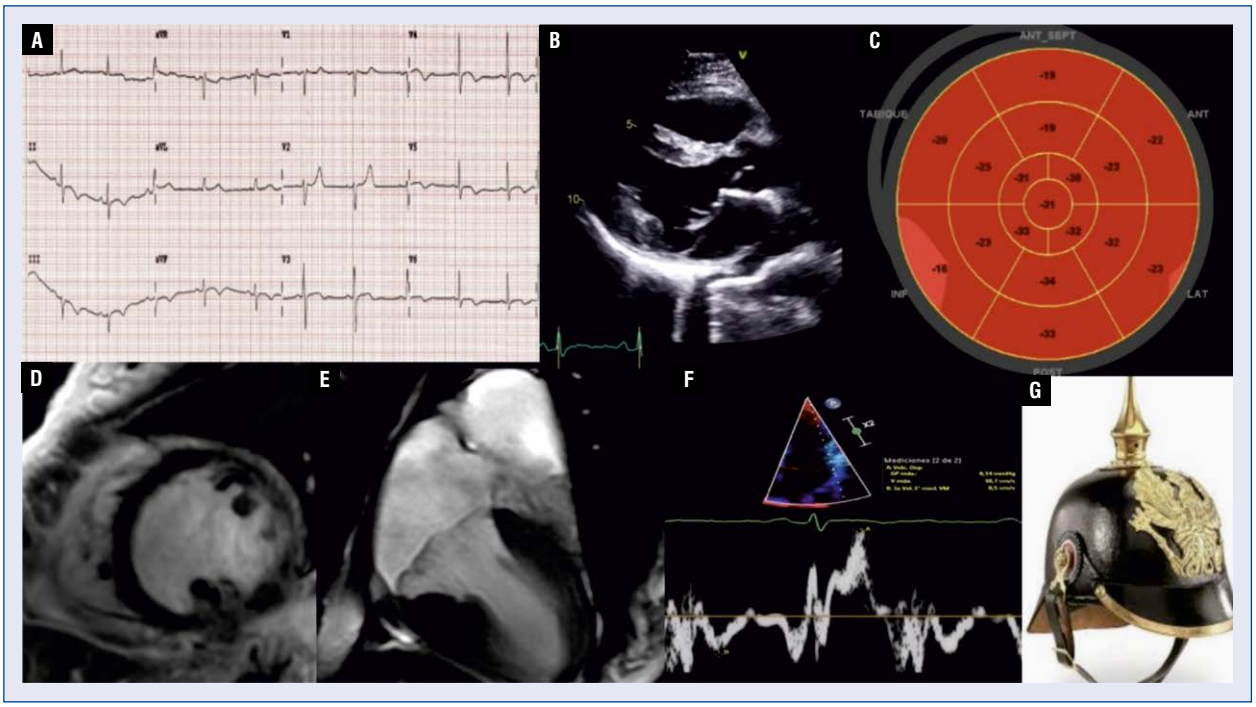

Figure 1. A. Baseline electrocardiogram in sinus rhythm, showing negative T waves in inferior and lateral leads; **B.** Two-dimensional echocardiogram (parasternal long-axis view), showing prolapse and thickness of both mitral leaflets and mitral annulus disjunction; **C.** Doppler echocardiography showing tissue supranormal longitudinal strain in left ventricle posterolateral wall; **D**, **E.** Cardiac magnetic resonance, showing pathological late gadolinium enhancement in papillary muscles and inferolateral left ventricular wall (**D**) and mitral annulus disjunction (**E**); **F.** Doppler study with the Pickelhaube sign (mitral annulus velocity > 16 cm/s), so called because of its similarity to an old Prussian soldiers' helmet (Pickelhaube, in German) (**G**).

VIA MEDICA

LETTER TO THE EDITOR

Cardiology Journal
2022, Vol. 29, No. 6, 1049–1050
DOI: 10.5603/CJ.a2022.0099

ISSN 1897–5593
eISSN 1898–018X

Chosen laboratory markers as a determinant of COVID-19 severity

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We read with great attention the article by Fialek et al. [1] titled "Diagnostic value of lactate dehydrogenase in COVID-19: A systematic review and meta-analysis" in which the authors try to define the relationship between lactate dehydrogenase (LDH) values as a predictor of coronavirus disease 2019 (COVID-19) severity. According to available research, this is the largest meta-analysis in this field throughout the world. Since December 2019, when the first mention of the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appeared, the world has been struggling with the new COVID-19 disease, which has taken the form of a global pandemic [2, 3]. Even though vaccines are now available, COVID-19 should still be considered a highly contagious disease, as we never know whether its subsequent mutations will pose a potential risk of their failure to work. We must also remember that vaccination does not protect against infection, but only prevents a severe course, so this virus will continue to spread throughout society [4]. Searching for markers that are able to identify patients at high risk of severe disease and/or death due to COVID-19 in a fast and highly predictable manner is a key element of screening [5, 6]. An important issue is also the development of effective methods of predicting complications in long-COVID-19 syndromes as well as those with which patients will be exposed as post-COVID-19 syndrome. As a result, the medical staff is able to implement specialist treatment already at the initial stage of treatment of these patients, which is to prevent the progression of the patient to a serious condition [7]. The currently available meta-analyzes indicate the potential importance of various markers, however, it is necessary to conduct extensive research as well as research of new markers, the sensitivity and specificity of which will be as high as possible. Meta-analysis performed by Fialek et al. [1] showed that elevated LDH was associated with a poor outcome in COVID-19. It should be kept in mind that therapy and medications used for treatment may affect the levels of markers in patients — this is a possible limitation that the authors of the meta-analysis did not address. How the currently utilized medication groups in COVID-19 affect the changes in concentrations of specific markers is one of the aspects that should be taken into consideration and in the context of which research should be conducted. This will allow us to adapt the prediction scales as precisely as possible. It is worth emphasizing here, that typical cardiac biomarkers are also of great importance in predicting the severity of a patient with COVID-19. An example is the confirmed predictive value of cytokines, including interleukin 6 [8], D-dimers, high-sensitivity troponin I [9] or creatine kinase-MB [10]. However, the use of biomarkers that have not been routinely used in medical practice so far should also be considered, and whose accuracy and functions will also provide us with insight into the pathogenesis of COVID-19 — an example is mid-regional pro-adrenomedullin and its function showing endothelial damage. Due to the high costs of this determination, they are not routinely per-

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Received: 16.06.2022 Accepted: 29.09.2022 Early publication date: 27.10.2022

formed, but the reduction of costs and work on the cheapest tests consisting in marking markers will bring us closer to detailed diagnostics and possible complications, which will enable identification at the stage of their early beginnings.

Conflict of interest: None declared

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VIA MEDICA

LETTER TO THE EDITOR

Cardiology Journal
2022, Vol. 29, No. 6, 1051–1052
DOI: 10.5603/CJ.2022.0113

ISSN 1897–5593
eISSN 1898–018X

Inquiries about a patient with a "snail-like" takotsubo syndrome variant. Authors' reply

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This article is accompanied by the editorial on page 897

We appreciate John E. Madias' interest and comments on our case report recently published in the Cardiology Journal, which generated great interest [1]. We would like to dispel any doubts about the course of the disease and the echocardiography and electrocardiography (ECG) findings in our patient with the "snail-like" takotsubo variant. Unfortunately, Images in Cardiovascular Medicine have a restrictive word limit; however, herein, we can kindly provide further details on our case.

The patient suffered from recurrent chest pain for 2 days, provoked by stress and released after nitroglycerin intake. The troponin level was the highest on admission to the hospital (3.4 ng/mL), then it decreased. The maximum marked B-type natriuretic peptide concentration (120 pg/mL) occurred the day after hospital admission when the patient reported no symptoms. A discharge echocardiogram revealed residual akinesis of the medium segment of the anterior wall and the anterior part of an intraventricular septum. The patient was followed-up twice. The echocardiography showed a contractility improvement, but the hypokinesis was still present 3 weeks after discharge. After 5 weeks, the echo examination was without any abnormalities. The regional longitudinal strain during the 5-week follow-up improved but was still slightly worse in the hypokinetic segments (see: Bull's Eye Plot, Fig. 1). Among the drugs taken before hospitalization were: sotalol, candesartan, hydrochlorothiazide, lercanidipine, rosuvastatin, acenocoumarol, levothyroxine, and metformin. The QTc was slightly shortened during hospitalization, but interestingly on the 4th day of hospitalization, there was an episode of atrial fibrillation. After electrical cardioversion, the QTc interval extended to 479 ms. Certainly, QTc was shortened after a 3-week follow-up; it was 421 ms.

The ST segment elevations in leads II, III, and aVF revealed the importance of repeated examinations and appropriate interpretation. We reanalyzed the available ECGs thanks to Madias' question and concluded that the ECG leads had been switched in the Emergency Department. The ST segment elevations in II, III, and aVF were only observed in the first ECG. The next ECGs revealed ST segment elevations in I, aVL and T waves inversions in I, aVL, and positive-negative T waves in V2–V4 (Fig. 1). At discharge, T waves were inverted in V1 and positive-negative in V2. Interestingly, in a 3-week follow-up, negative T waves in I, aVL, V2 and positive-negative T waves in V3–V5 were observed.

We presented this unique case not only because of localization but also because monitoring laboratory parameters and serial ECGs affect the overall course of the disease.

Conflict of interest: None declared

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Received: 24.08.2022 Accepted: 3.09.2022

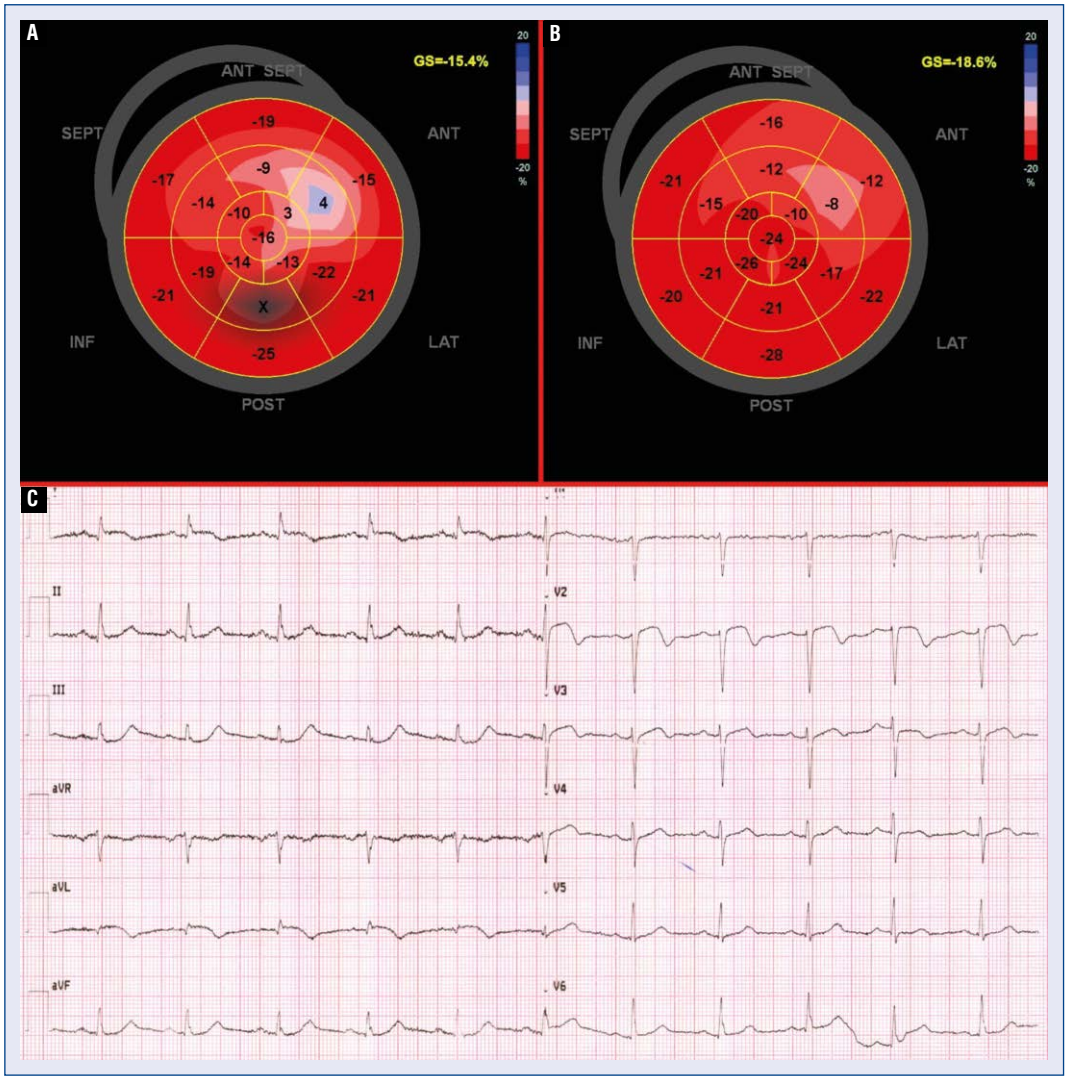

Figure 1. A. Bull's Eye Plot presenting global longitudinal strain (GLS) on the day of admission to the hospital; **B.** Bull's Eye Plot presenting GLS after 5-week follow-up, **C.** Electrocardiogram done on the day of admission to the hospital.

VIA MEDICA

LETTER TO THE EDITOR

Cardiology Journal
2022, Vol. 29, No. 6, 1053–1054
DOI: 10.5603/CJ.a2022.0098

ISSN 1897–5593
eISSN 1898–018X

Mild therapeutic hypothermia or targeted temperature management for cardiac arrest survivors?

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Out-of-hospital cardiac arrest (OHCA) is burdened with a high risk of death [1–5]. Following the results of the The Targeted Temperature Management Trial (TTM trial) — a randomized study published by Nielsen et al. [6] suggesting equivalent results of targeted temperature management (TTM) at 33°C and 36°C in comatose patients after OHCA, current guidelines recommend TTM in this subset of patients [7]. TTM covers a wider body's core temperature range (between 32°C and 36°C) than mild therapeutic hypothermia (MTH) (between 32°C and 34°C) [8–10]. However, while favorable clinical outcome of MTH was proven in several clinical studies [11–13], the impact of TTM remains less clear. A favorable effect of MTH on survival and neurological outcome was confirmed in a meta-analysis of data pooled from randomized and non-randomized studies [14]. Recently, Sobczyk et al. [15] published another report showing benefits of MTH in cardiac arrest survivors in the early phase of myocardial infarction. Taking into account the results of studies on MTH, it should be noted that the methodology of the TTM study — the largest available randomized trial — is questionable [6, 10]. The limitations were related to the non-uniform methodology of cooling (intravascular cooling was used in only 24% of patients) and the heterogeneity of the trial population (40% of patients with myocardial infarction). Moreover, a substantial proportion of patients in the MTH arm did not reach the target temperature, and the duration of hypothermia induction was unacceptably long (a mean of 8 h) [6]. These important shortcomings of the TTM study could have negatively affected the results, with a survival rate and neurological outcome being much worse than observed in MTH arms and similar to control arms of MTH studies [6, 11–15]. Nevertheless, European Society of Cardiology recommendations are based on results of the TTM study [6, 7]. Of note, also registries accepting the MTH's methodological diversity are burdened with a serious risk of result misinterpretations [16]. These observations strongly suggest the need for a new multicenter, methodologically uniform trial, free from the hoaxes of the TTM study. Acute coronary syndrome is the most common cause of OHCA [17]. In this context, when planning a new trial, the routine use of cangrelor in patients undergoing MTH should be considered due to the diminished antiplatelet effect of oral P2Y12 inhibitors [18–22].

Conflict of interest: None declared

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Received: 21.08.2022 Accepted: 29.09.2022 Early publication date: 27.10.2022

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