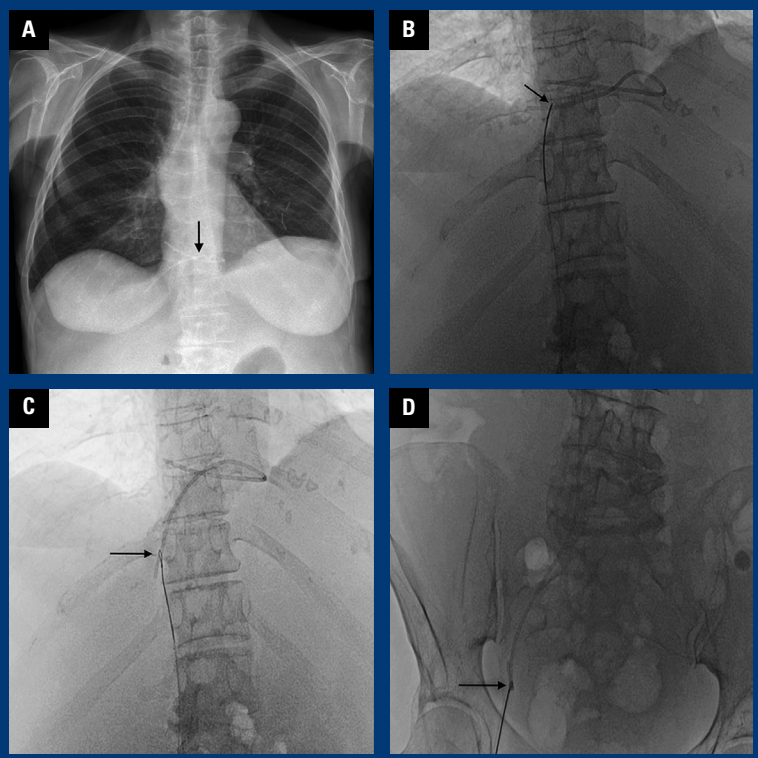
Cardiology Journal 2021, Vol. 28, No. 6, pp. 801–1006

CARDIOLOGY JOURNAL

Impact Factor: 2.737

November 2021, Vol. 28, No. 6, pp. 801–1006 www.cardiologyjournal.org



Arkadiusz Pietrasik et al., see figure legend on page 998

ISSN 1897–5593
eISSN 1898–018X

VIA MEDICA

CARDIOLOGY JOURNAL

www.cardiologyjournal.org

CARDIOLOGY JOURNAL

www.cardiologyjournal.org

"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.

Editorial address: VM Media sp. z o.o. VM Group sp.k., ul. Swietokrzyska 73, 80–180 Gdansk, tel: (+48 58) 320 94 94, fax: (+48 58) 320 94 60, www.cardiologyjournal.org, e-mail: cj@viamedica.pl

Journal has an international indexation in CrossRef, EBSCO, EMBASE, FMJ, Google Scholar, Science Citation Index Expanded, Index Copernicus (160.44 points), MEDLINE, Scopus, SJR, Ulrich's Periodicals Directory, Web of Science CC and WorldCat database, Polish Ministry of Education and Science (100 points). Current Impact Factor of "Cardiology Journal" (2020) is 2.737.

20-0801.006.001

CARDIOLOGY JOURNAL

www.cardiologyjournal.org

November 2021, Vol. 28, No. 6

Table of Contents

RESEARCH LETTERS

COVID-19

Clinical cardiology

IMAGES IN CARDIOVASCULAR MEDICINE

COVID-19

Interventional cardiology

Clinical cardiology

LETTERS TO THE EDITOR

COVID-19

VIA MEDICA

EDITORIAL

Cardiology Journal
2021, Vol. 28, No. 6, 801–803
DOI: 10.5603/CJ.2021.0140

ISSN 1897–5593
eISSN 1898–018X

An Apple Watch a day keeps the doctor away?

Mikołaj Basza[1]*, Bartosz Krzowski[2]*, Paweł Balsam[2], Marcin Grabowski[2], Grzegorz Opolski[2], Łukasz Kołtowski[2]

[1]Medical University of Silesia in Katowice, Poland
[2]1st Department of Cardiology, Medical University of Warsaw, Poland

The high prevalence of cardiovascular diseases and an increasing health workforce shortage are major challenges that cardiology will face in the decades to come. New technologies supporting physicians in screening and patient monitoring are considered a potential solution to help fill this gap. For example, the average smartwatch user generates millions of basic vital sign data points each day, observed almost continuously 7 days a week in a patient's natural environment. 2019 ended with more than 500 million wearable users, and according to the market forecasts, this number will have reached over 1 billion by 2022 [1]. Apple dominates the smartwatch market with Apple Watch (AW), which is recognized as a Food and Drug Asscoiation class-2 medical device; nevertheless, its applications and reliability in medicine remain unclear.

The AW collects various biosignals based on two core technologies, photoplethysmography (PPG) and single-lead electrocardiography (ECG) [2]. Using green or infrared light, PPG is used to measure heart rate (HR) and HR variability, relying on blood volume changes in tissue. According to manufacturer information, the AW supports an HR range of 30–210 bpm. Measurements of HR are taken in the background during rest, but a user can also perform it on-demand. In many studies with similar conclusions, HR measurement accuracy has been validated on a healthy population during different activities. Overall accuracy during rest, low and moderate activity is comparable to standard 12-lead ECG and decreases near range thresholds with motion artifacts [3–5]. These findings suggest a possible use of AW HR monitoring during therapy and cardiac rehabilitation. Apple offers an HR notification function that informs the user when the HR in a 10 min resting period is out of the previously set range. The irregular rhythm notification function is widely described in the Apple Heart Study [6]. AW showed a 34% diagnostic yield in detecting

Address for correspondence: Łukasz Kołtowski, MD, PhD, FESC, 1st Chair and Department of Cardiology, Medical University of Warsaw, ul. Banacha 1a, 02–097 Warszawa, Poland, tel: +48 22 599 29 58, fax: +48 22 599-19-57, e-mail: lukasz@koltowski.com

Received: 29.10.2020 Accepted: 5.05.2021

Equal contribution

Figure 1. Main Apple Watch options are available for everyday use; AF — atrial fibrillation; HR — heart rate; ECG — electrocardiogram; PPG — photoplethysmography.

atrial fibrillation (AF), 35% in the population over 65 years old and 18% in the cohort younger than 40 years of age. 89% of true positives had AF episodes lasting at least 1 hour. The positive predictive value of individual notification was 84%. The high false-positive rate was the main allegation in this study. However, ECG patches used for validation were worn for an average of 6.3 days and a few days after initial notification and by a limited number of study participants, so the absence of AF during validation does not indicate that the notification was false. Especially in paroxysmal and infrequent episodes of arrhythmia. This study's findings imply the potential benefits of irregular pulse notification in AF screening in a population over 65 years old when AF screening is cost-effective. According to the European Society of Cardiology (ESC) 2020 guidelines, methods based on PPG require additional ECG confirmation, which is possible in Apple Watch Series 4 and higher and occasionally, in case of doubt, needs to be verified with traditional 12-lead ECG tracing (Fig. 1).

The Apple Watch Series 4 and higher have built-in two electrodes, a titanium electrode in the Digital Crown, and a chromium silicon carbon nitride layer applied on the back of the AW. They allow obtaining a single lead ECG corresponding to lead I in standard ECG. In a validation study, Apple showed high morphology agreement between Apple Watch ECG and 12-lead ECG (lead I) waveforms at rest and after exercise. Sub-study of the Leipzig Apple Heart Rhythm Study compared three leads obtained using alternative positioning of Apple Watch to leads I, II, III of standard 12-lead ECG with the correlation between 97% and 99% for a duration (ms) of P wave, PR interval, QRS complex, QT interval and T wave in all three leads. The polarity concordance of P wave, QRS complex, and T wave was 98–100%. However, a lower correlation — 72–90% — has been observed for those parameters' amplitude (mV). In 2020 Spaccarotella et al. [7] obtained leads I, II, III, V_1, V_2, V_3, V_4, V_5, and V_6 using AW and compared it to 12-lead ECG on 100 patients admitted to the coronary care unit. Bland-Altmann did not show a significant difference in millimeters of ST-segment deviation. The feasibility of AW ECG interpretation in AF detection has been confirmed with 96% sensitivity and 100% specificity [8]. Those studies have shown that Apple Watch ECG waveform is a clinically relevant biosignal and meets the criteria of ESC 2020 guidelines for AF definitive diagnosis, which is especially important in patients at high risk of stroke. Single lead ECG is the basis of the Apple Watch ECG app 1.0 algorithm that, according to the manufacturer, is characterized by

98.3% sensitivity and 99.6% specificity in detecting AF. Still, this data requires cautious interpretation. An independent study conducted on 50 patients, who had undergone cardiac surgery, monitored by telemetry, showed 41% specificity in detecting AF by an algorithm and 5 times higher unreadable ECGs rate [8]. Apple Watch ECG app 2.0 algorithm interprets the rhythm automatically and classifies it into sinus rhythm, AF, low or high heart rate, inconclusive and poor recording. Apple's internal study demonstrated 98% correctly classified sinus rhythms and AF in the HR range of 50–99 bpm and 93% for sinus rhythm, and 83% for AF in HR range 100–150 bpm. There are no other studies that confirmed the results of the ECG 2.0 Clinical Validation Study.

One of the AW ECG waveform's possible applications is screening and monitoring therapy with a cardiac adverse effect. In 2020 Strik et al. [9] validated QT interval measurements using AW ECG to assess potential usefulness in patients with COVID-19 on hydroxychloroquine/azithromycin treatment. He revealed that adequate QT measurements were possible from AW ECG in 85% of patients. However, using additionally lead II and V_6 obtained using AW increased that score to 94%.

Year by year, the manufacturers of wearables are getting deeper into healthcare by providing new medical features and conducting further studies in collaboration with leading medical institutions. In Apple Watch Series 6, optical sensors were redesigned to provide oxygen saturation and VO_2 max measurements. Although the blood oxygen level app is officially not intended for medical use, it might be a medical-grade feature in the future. Apple recently has launched two new studies investigating the feasibility of the AW in cardiology. One is related to monitoring heart failure patients, and the second is focusing on the correlation between physical activity and heart health [10].

Though there is a need for further validation, studies have shown that wearables such as AW should not be viewed just like gadgets. Still, they may become a reliable source of medical data. In addition, professional guidance and clinical experience could provide enormous potential in screening arrhythmias, supporting therapy, and cardiac rehabilitation.

Conflict of interest: None declared

References

1. Thomas Barnett J, Shruti Jain, Usha Andra, Taru Khurana. Cisco Visual Networking Index (VNI) Global and Asia Pacific Mobile Data Traffic Forecast, 2017-2022. 2019.
2. Apple Inc. Using Apple watch for arrhythmia detection. 2020.
3. Khushhal A, Nichols S, Evans W, et al. Validity and reliability of the Apple Watch for measuring heart rate during exercise. Sports Med Int Open. 2017; 1(6): E206–E211, doi: 10.1055/s-0043-120195, indexed in Pubmed: 30539109.
4. Falter M, Budts W, Goetschalckx K, et al. Accuracy of Apple Watch measurements for heart rate and energy expenditure in patients with cardiovascular disease: cross-sectional study. JMIR Mhealth Uhealth. 2019; 7(3): e11889, doi: 10.2196/11889, indexed in Pubmed: 30888332.
5. Nelson BW, Allen NB. Accuracy of consumer wearable heart rate measurement during an ecologically valid 24-hour period: intraindividual validation study. JMIR Mhealth Uhealth. 2019; 7(3): e10828, doi: 10.2196/10828, indexed in Pubmed: 30855232.
6. Perez MV, Mahaffey KW, Hedlin H, et al. Large-Scale assessment of a smartwatch to identify atrial fibrillation. N Engl J Med. 2019; 381(20): 1909–1917, doi: 10.1056/NEJMoa1901183, indexed in Pubmed: 31722151.
7. Spaccarotella CA, Polimeni A, Migliarino S, et al. Multichannel electrocardiograms obtained by a smartwatch for the diagnosis of ST-segment changes. JAMA Cardiol. 2020; 5(10): 1176–1180, doi: 10.1001/jamacardio.2020.3994, indexed in Pubmed: 32865545.
8. Seshadri DR, Bittel B, Browsky D, et al. Accuracy of Apple Watch for detection of atrial fibrillation. Circulation. 2020; 141(8): 702–703, doi: 10.1161/CIRCULATIONAHA.119.044126, indexed in Pubmed: 32091929.
9. Strik M, Caillol T, Ramirez FD, et al. Validating qt-interval measurement using the Apple Watch ECG to enable remote monitoring during the COVID-19 pandemic. Circulation. 2020; 142(4): 416–418, doi: 10.1161/CIRCULATIONAHA.120.048253, indexed in Pubmed: 32478565.
10. MacRae CA. Apple Heart & Movement Study (NCT04198194). 2019.

VIA MEDICA

EDITORIAL

Cardiology Journal
2021, Vol. 28, No. 6, 804–806
DOI: 10.5603/CJ.2021.0141

ISSN 1897–5593
eISSN 1898–018X

Are we ready to withdraw acetylsalicylic acid after complex percutaneous coronary intervention?

Gabriella Bufano[1, 2], Marco Zimarino[1, 3]

[1]Institute of Cardiology, "G. d'Annunzio" University, Chieti, Italy
[2]Department of Medical, Oral and Biotechnological Sciences, University "Gabriele d'Annunzio", Chieti, Italy
[3]Cath Lab, Ospedale SS. Annunziata, ASL 2 Abruzzo, Chieti, Italy

This editorial accompanies the article on page 855

Dual antiplatelet therapy (DAPT) with acetylsalicylic acid (ASA) and a $P2Y_{12}$ receptor inhibitor is the cornerstone treatment both in patients with acute coronary syndromes (ACS) and in those undergoing percutaneous coronary intervention (PCI). At the beginning of the drug-eluting stent (DES) era, stent thrombosis (ST) emerged as the most relevant complication, and therefore more powerful $P2Y_{12}$ inhibition and DAPT prolongation were recommended [1, 2].

With technological refinements, newer thinner-strut DES now show dramatically improved safety profiles compared with their ancestors [3]. The increased safety of third generation DES has encouraged the treatment of complex lesions in older and more fragile patients, in whom the bleeding risk still carries relevant prognostic implications [4].

For the definition of the complex PCI, we commonly refer to the so-called "Giustino's criteria" [5]: either 3 vessel or ≥ 3 lesions treated, ≥ 3 stents implanted, bifurcation with 2 stents, total stent length > 60 mm or treatment of a chronic total occlusion, with most of the ischemic risk driven by double bifurcation stenting. In the setting of bifurcation PCI, a single "provisional" stenting is currently recommended by the European Bifurcation Club (EBC) consensus document [6], but careful planning is mandatory, as the ischemic risk is heightened when the second stent is placed in "bail-out", beyond the planned strategy [7].

In addition, the identification of high bleeding risk (HBR) patients [8, 9] has become crucial to define the DAPT strategy [10]. In HBR patients, the overlap between ischemic and bleeding features is common and therefore the evaluation of the net clinical benefit of DAPT duration becomes tricky. Costa et al. [11] documented that those patients enrolled in the PRECISE-DAPT study who underwent complex PCI had a higher risk of ischemic events, but benefitted from long-term DAPT only if HBR features were not present. In order to obtain an optimal balancing between the ischemic and the thrombotic risk, a modulation of antithrombotic strategy has been proposed, with an initial DAPT period to reduce the ST risk during the phase of strut endothelialization, followed by long-term antiplatelet monotherapy with either ASA or a $P2Y_{12}$ receptor inhibitor to contain the bleeding risk [12]. In the subgroup of patients with complex lesions

Address for correspondence: Marco Zimarino, MD, PhD, Cath Lab and Institute of Cardiology, ASL2 Abruzzo and "G. d'Annunzio" University of Chieti, c/o Ospedale SS. Annunziata, Via dei Vestini, 66100 Chieti, Italy, tel: +39-0871-41512, fax: +39-0871-402817, e-mail: m.zimarino@unich.it

Received: 17.08.2021 Accepted: 20.08.2021

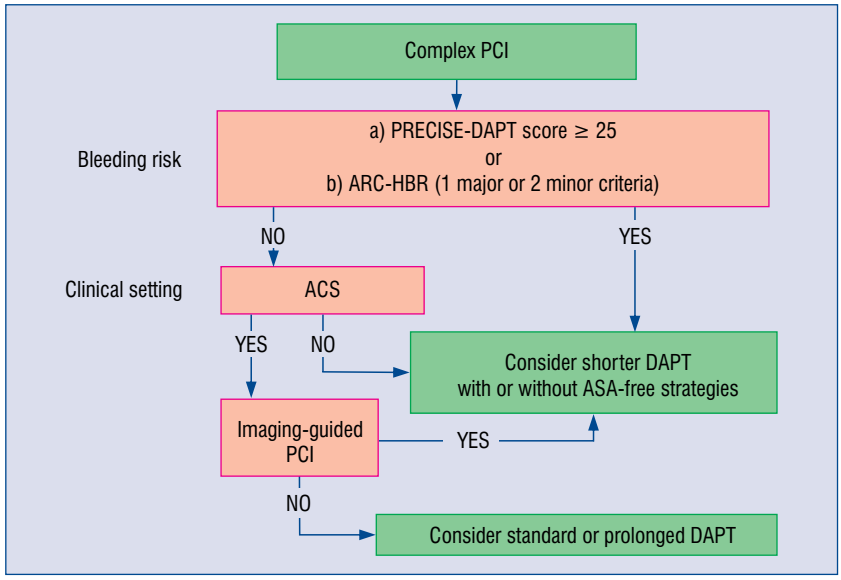


Figure 1. Decisional algorithm proposed for antiplatelet duration after complex percutaneous coronary intervention (PCI); ACS — acute coronary syndrome; ARC — Academic Research Consortium; ASA — acetylsalicylic acid; HBR — high-bleeding risk; DAPT — dual antiplatelet therapy; PRECISE-DAPT — PREdicting bleeding Complications in patients undergoing stent Implantation and SubsequEnt Dual AntiPlatelet Therapy. Bleeding risk stratification according to PRECISE-DAPT score and ARC-HBR score is defined as a 1-year risk of a BARC (bleeding ARC) type 3 or 5 ≥ 4% or of intracranial hemorrhage ≥ 1%.

enrolled in the TWILIGHT trial, Dangas et al. [13] showed that, after 3-month DAPT, continuation of ticagrelor monotherapy was associated with a lower incidence of bleeding without increasing the risk of ischemic events compared with continuing DAPT.

The multicentric, randomized, open-label SMART-CHOICE trial [14] enrolled 2,993 patients — with ACS in 60% of cases — undergoing PCI with second generation DES in Korea to receive 12-month DAPT vs. 3-month DAPT followed by $P2Y_{12}$ monotherapy (mostly clopidogrel). At 12 months of follow-up, shorter DAPT followed by $P2Y_{12}$ monotherapy was non-inferior to 12-month DAPT for the primary endpoint of major adverse cardiac and cerebrovascular events, with a lower rate of bleeding events expressed as Bleeding Academic Research Consortium (BARC) bleeding type 2–5. In the current issue of the Cardiology Journal, Roh et al. [15] performed a post-hoc analysis of the SMART-CHOICE trial among the 498 patients who underwent complex PCI, with intravascular ultrasound guidance used in 31.5% of cases. Similary to the TWILIGHT trial, also in the SMART-CHOICE complex, the $P2Y_{12}$ inhibitor monotherapy showed adverse event rates comparable to the DAPT group.

Two recent meta-analyses [16, 17] showed that shorter DAPT regimens followed by $P2Y_{12}$ monotherapy appear safe in containing bleeding events, without a significant increase in ischemic risk among unselected patients.

Looking ahead, complex PCI undoubtedly deserves careful planning, with single stenting recommended in bifurcations, and when double stenting is needed, imaging becomes vital to optimize strut overlapping and reduce the risk of strut malapposition. In this view, the EBC proposed a modulated DAPT duration strategy according to clinical presentation, HBR, stenting strategy and the use of intraprocedural imaging [18].

At present, the optimal DAPT duration after complex PCI is still under debate. ASA-free strategies, in light of the limited evidence, cannot be routinely recommended and should be restricted to selected patients. A meaningful approach should take into account both clinical and procedural risk variables (Fig. 1).

In the nearest future, without doubt we will witness several trials focusing various de-escalation antiplatelet therapeutic approaches after PCI or ACS [19].

Conflict of interest: None declared

References

1. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018; 39(3): 213–260, doi: 10.1093/eurheartj/ehx419, indexed in Pubmed: 28886622.
2. Zimarino M, Renda G, De Caterina R. Optimal duration of antiplatelet therapy in recipients of coronary drug-eluting stents. Drugs. 2005; 65(6): 725–732, doi: 10.2165/00003495-200565060-00001, indexed in Pubmed: 15819586.
3. Serruys PW, Farooq V, Kalesan B, et al. Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: final 5-year report of the LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating) randomized, noninferiority trial. JACC Cardiovasc Interv. 2013; 6(8): 777–789, doi: 10.1016/j.jcin.2013.04.011, indexed in Pubmed: 23968698.
4. Eikelboom JW, Mehta SR, Anand SS, et al. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation. 2006; 114(8): 774–782, doi: 10.1161/CIRCULATIONAHA.106.612812, indexed in Pubmed: 16908769.
5. Giustino G, Chieffo A, Palmerini T, et al. Efficacy and safety of dual antiplatelet therapy after complex PCI. J Am Coll Cardiol. 2016; 68(17): 1851–1864, doi: 10.1016/j.jacc.2016.07.760, indexed in Pubmed: 27595509.
6. Burzotta F, Lassen JF, Lefèvre T, et al. Percutaneous coronary intervention for bifurcation coronary lesions: the 15 consensus document from the European Bifurcation Club. EuroIntervention. 2021; 16(16): 1307–1317, doi: 10.4244/EIJ-D-20-00169, indexed in Pubmed: 33074152.
7. Zimarino M, Briguori C, Amat-Santos IJ, et al. Mid-term outcomes after percutaneous interventions in coronary bifurcations. Int J Cardiol. 2019; 283: 78–83, doi: 10.1016/j.ijcard.2018.11.139, indexed in Pubmed: 30528620.
8. Costa F, Klaveren Dv, James S, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet. 2017; 389(10073): 1025–1034, doi: 10.1016/s0140-6736(17)30397-5.
9. Urban P, Mehran R, Colleran R, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. Eur Heart J. 2019; 40(31): 2632–2653, doi: 10.1093/eurheartj/ehz372, indexed in Pubmed: 31116395.
10. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021; 42(14): 1289–1367, doi: 10.1093/eurheartj/ehaa575, indexed in Pubmed: 32860058.
11. Costa F, Van Klaveren D, Feres F, et al. Dual antiplatelet therapy duration based on ischemic and bleeding risks after coronary stenting. J Am Coll Cardiol. 2019; 73(7): 741–754, doi: 10.1016/j.jacc.2018.11.048, indexed in Pubmed: 30784667.
12. Capodanno D, Mehran R, Valgimigli M, et al. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. Nat Rev Cardiol. 2018; 15(8): 480–496, doi: 10.1038/s41569-018-0049-1, indexed in Pubmed: 29973709.
13. Dangas G, Baber U, Sharma S, et al. Ticagrelor with or without aspirin after complex pci. J Am Coll Cardiol. 2020; 75(19): 2414–2424, doi: 10.1016/j.jacc.2020.03.011, indexed in Pubmed: 32240761.
14. Hahn JY, Song YB, Oh JH, et al. Effect of P2Y12 Inhibitor Monotherapy vs Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention: The SMART-CHOICE Randomized Clinical Trial. JAMA. 2019; 321(24): 2428–2437, doi: 10.1001/jama.2019.8146, indexed in Pubmed: 31237645.
15. Roh JW, Hahn JY, Oh JH, et al. $P2Y_{12}$ inhibitor monotherapy in complex percutaneous coronary intervention: A post-hoc analysis of SMART-CHOICE randomized clinical trial. Cardiol J. 2021; 28(6): 855–863, doi: 10.5603/CJ.a2021.0101.
16. O'Donoghue ML, Murphy SA, Sabatine MS. The Safety and Efficacy of Aspirin Discontinuation on a Background of a P2Y Inhibitor in Patients After Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis. Circulation. 2020; 142(6): 538–545, doi: 10.1161/CIRCULATIONAHA.120.046251, indexed in Pubmed: 32551860.
17. Giacoppo D, Matsuda Y, Fovino LN, et al. Short dual antiplatelet therapy followed by P2Y12 inhibitor monotherapy vs. prolonged dual antiplatelet therapy after percutaneous coronary intervention with second-generation drug-eluting stents: a systematic review and meta-analysis of randomized clinical trials. Eur Heart J. 2021; 42(4): 308–319, doi: 10.1093/eurheartj/ehaa739, indexed in Pubmed: 33284979.
18. Zimarino M, Angiolillo DJ, Dangas G, et al. Antithrombotic therapy after percutaneous coronary intervention of bifurcation lesions. EuroIntervention. 2021; 17(1): 59–66, doi: 10.4244/EIJ-D-20-00885, indexed in Pubmed: 32928716.
19. Kubica J, Adamski P, Niezgoda P, et al. A new approach to ticagrelor-based de-escalation of antiplatelet therapy after acute coronary syndrome. A rationale for a randomized, double-blind, placebo-controlled, investigator-initiated, multicenter clinical study. Cardiol J. 2021; 28(4): 607–614, doi: 10.5603/CJ.a2021.0056, indexed in Pubmed: 34096012.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2021, Vol. 28, No. 6, 807–815
DOI: 10.5603/CJ.a2021.0104

ISSN 1897–5593
eISSN 1898–018X

Troponin T in COVID-19 hospitalized patients: Kinetics matter

Maria-Luiza Luchian[1], Andreea Iulia Motoc[1], Stijn Lochy[1], Julien Magne[2], Bram Roosens[1], Dries Belsack[3], Karen Van den Bussche[1], Berlinde von Kemp[1], Xavier Galloo[1], Clara François[1], Esther Scheirlynck[1], Sven Boeckstaens[1], Tom De Potter[4], Lucie Seyler[5], Johan van Laethem[5], Sophie Hennebicq[6], Caroline Weytjens[1], Steven Droogmans[1], Bernard Cosyns[1]

[1]Department of Cardiology, Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel, (Centrum voor Hart- en Vaatziekten), Brussels, Belgium
[2]CHU Limoges, Hôpital Dupuytren, Service Cardiologie, Limoges, France
[3]Department of Radiology, Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel, Brussels, Belgium
[4]Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel (VUB), Brussels, Belgium
[5]Department of Internal Medicine and Infectious Diseases, Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel, Brussels, Belgium
[6]Department of Nephrology, University Hospital of Ambroise Pare, Mons, Belgium

Abstract

Background: *Coronavirus disease 2019 (COVID-19) emerged as a worldwide health crisis, overwhelming healthcare systems. Elevated cardiac troponin T (cTn T) at admission was associated with increased in-hospital mortality. However, data addressing the role of cTn T in major adverse cardiovascular events (MACE) in COVID-19 are scarce. Therefore, we assessed the role of baseline cTn T and cTn T kinetics for MACE and in-hospital mortality prediction in COVID-19.*

Methods: *Three hundred and ten patients were included prospectively. One hundred and eight patients were excluded due to incomplete records. Patients were divided into three groups according to cTn T kinetics: ascending, descending, and constant. The cTn T slope was defined as the ratio of the cTn T change over time. The primary and secondary endpoints were MACE and in-hospital mortality.*

Results: *Two hundred and two patients were included in the analysis (mean age 64.4 ± 16.7 years, 119 [58.9%] males). Mean duration of hospitalization was 14.0 ± 12.3 days. Sixty (29.7%) patients had MACE, and 40 (19.8%) patients died. Baseline cTn T predicted both endpoints ($p = 0.047$, hazard ratio [HR] 1.805, 95% confidence interval [CI] 1.009–3.231; $p = 0.009$, HR 2.322, 95% CI 1.234–4.369). Increased cTn T slope predicted mortality ($p = 0.041$, HR 1.006, 95% CI 1.000–1.011). Constant cTn T was associated with lower MACE and mortality ($p = 0.000$, HR 3.080, 95% CI 1.914–4.954, $p = 0.000$, HR 2.851, 95% CI 1.828–4.447).*

Conclusions: *The present study emphasizes the additional role of cTn T testing in COVID-19 patients for risk stratification and improved diagnostic pathway and management.* (Cardiol J 2021; 28, 6: 807–815)

Key words: myocardial injury, cardiac troponin, kinetics, mortality, COVID-19, major cardiovascular adverse events

Address for correspondence: Maria Luiza Luchian, MD, Department of Cardiology, Universitair Ziekenhuis Brussel (Centrum voor Hart- en Vaat ziekten), Laerbeeklaan 101, 1090, tel: +32468531461, Brussels, Belgium, e-mail: marialuiza.luchian@uzbrussel.be

Received: 18.06.2021 Accepted: 11.08.2021 Early publication date: 23.09.2021

Introduction

Coronavirus disease 2019 (COVID-19) emerged as a worldwide health crisis, overwhelming healthcare systems and especially the intensive care units, due to high numbers of critical cases in a short period of time [1, 2]. Initial publications reported elevated cardiac troponin T (cTn T) at admission to be associated with a worse prognosis and increased in-hospital mortality, possibly due to myocardial injury [3, 4]. However, most of these series evaluated one troponin assay and focused on non-cardiovascular adverse events, for example intensive care unit admissions, and the need for ventilation or vasopressor support [5–7]. Current data addresses insufficiently the association between cTn T and adverse cardiovascular events in COVID-19 patients. By analogy with acute coronary syndromes, the change of cardiac biomarkers levels over time may indicate myocardial injury [8–11], which may develop at any point during hospitalization. Thus, serial cTn T testing might play a key role in the assessment of disease severity [9]. Moreover, it has been suggested that constant values of cTn T during hospitalization convey an improved prognosis in COVID-19 patients, whereas a continuous increase in cTn T values implies a worse outcome [9]. However, few data are available to support this hypothesis.

Therefore, we aimed to assess the additional prognostic value of baseline cTn T and cTn T kinetics in the prediction of major adverse cardiovascular events (MACE) and in-hospital mortality in COVID-19 hospitalized patients.

Methods

We prospectively included 310 patients admitted to the Universitair Ziekenhuis Brussel (University Hospital of Brussels), Belgium between March 2020 and April 2020. COVID-19 was confirmed by real-time reverse transcription polymerase chain reaction test. One hundred and eight patients with incomplete information on comorbidities, treatment history, lack of systematic evaluation of the clinical status or biomarkers, and/or short period of hospitalization (< 48 h in hospital stay) were excluded from the analysis. Clinical information was collected at admission and during hospitalization by the physicians in charge. Data included demographics, medical history, comorbidities, clinical evaluation, laboratory exams, in-hospital treatment, complications, and outcomes. Two hundred and two (65.1%) patients had at least two cTn T values assessed during hospitalization, systematically at 24–48 hours intervals, after hospital admission. cTn T-values > 0.011 μg/L were considered elevated, according to hospital laboratory cut-offs. cTn T evolution was analyzed by calculating the slope of change as the ratio of the cTn T change and the change in time (ΔcTn T/Δ time). ΔcTn T was defined as the difference between the highest value of cTn T during hospitalization and the baseline value. Baseline cTn T was considered the first cTn T assessment in the first 48 hours after hospital admission.

Patients were divided into three groups according to their cTnT kinetics profile, as follows: group 1 representing ascending cTn T profile, formed by patients with a variation of cTn T values from admission to discharge, with increased slope (ΔcTn T/Δ time $\geq$ 1); group 2, descending cTn T profile included patients with a decrease of cTn T values from admission to discharge (ΔTn T/Δ time < 1); and group 3, constant cTn T profile, included patients with a stable value of cTn T during hospitalization (ΔcTn T/Δ time = 0). MACE was considered as the primary endpoint, composed of all-cause mortality, acute heart failure, acute coronary syndrome, pericarditis, myocarditis, atrial fibrillation or flutter, and pulmonary embolism. In-hospital mortality was considered as the secondary endpoint. All cardiovascular events were defined according to current practice guidelines of cardiology [11–15].

Ethical approval

This study was approved by the local Ethical Committee and was carried out in accordance with the ethical principles for medical research involving human subjects established by the Helsinki Declaration, protecting the privacy of all participants, as well as the confidentiality of their personal information.

Statistical analyses

Descriptive statistics were performed for all study variables. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile [IQR]) for skewed variables. Categorical variables were expressed as percentages. Normality of data was tested using the Kolmogorov-Smirnov test. Comparison of continuous variables was performed using Student's t-test or the Mann-Whitney U-test, and of binominal variables using the χ^2 or Fisher exact test, respectively. Comparison between three groups was performed using one-way ANOVA for continuous data. Univariable and multivariable Cox regression models

Table 1. Cox regression analysis for major adverse cardiovascular events (MACE) and for in-hospital mortality in COVID-19 patients for baseline cardiac troponin T (cTn T).

Parameter	Univariable analysis			Multivariable analysis		
	HR	95% CI	P	HR	95% CI	P
MACE predictors						
Age	1.056	1.032–1.081	0.000	1.054	1.025–1.084	0.000
cTn T	1.966	1.225–3.154	0.005	1.805	1.009–3.231	0.047
Neutrophil-lymphocyte ratio	1.059	1.025–1.093	0.001	0.997	0.955–1.040	0.877
C-reactive protein	1.004	1.002–1.007	0.002	1.004	1.001–1.007	0.021
History of diabetes mellitus	1.232	0.689–2.201	0.482	1.238	0.276–5.551	0.780
History of arterial hypertension	1.502	0.864–2.614	0.150	0.889	0.428–1.847	0.752
History of dyslipidemia	1.194	0.689–2.071	0.527	0.894	0.202–3.968	0.883
In-hospital mortality						
Age	1.069	1.040–1.098	0.000	1.061	1.029–1.094	0.000
Neutrophil-lymphocyte ratio	1.069	1.034–1.106	0.000	1.003	0.958–1.049	0.911
C-reactive protein	1.005	1.002–1.008	0.001	1.007	1.003–1.012	0.000
cTn T	2.138	1.338–3.416	0.001	2.322	1.234–4.369	0.009
History of diabetes mellitus	1.320	0.688–2.532	0.404	0.845	0.383–1.864	0.676

CI — confidence interval; HR — hazard ratio

were used to evaluate potential predictors of in-hospital mortality and MACE.

Kaplan-Meier survival curves were used to compare event-free and survival rates for COVID-19 patients by the log-rank test. Receiver operating characteristics (ROC) curves were constructed to determine the ability of baseline cTn T to predict mortality and MACE and to identify its sensitivity and specificity.

Data were analyzed using IBM SPSS Statistic for Windows, Version 26.0 (Armonk, NY: IBM Corp.). A p value < 0.05 was considered significant.

Results

Global population: Baseline characteristics

Two hundred and two patients were included in the analysis (mean age 64.4 ± 16.7 years, 119 [58.9%] males). The mean duration of hospitalization was 14.0 ± 12.3 days.

The prevalence of cardiovascular risk factors was the following: hypertension in 102 (50.5%) patients, dyslipidemia in 83 (41.1%) patients, diabetes mellitus in 61 (30.2%) patients, and obesity in 56 (27.9%) patients. Chronic kidney disease was observed in 29 (14.4%) patients.

Baseline characteristics of the global study population and the comparison between patients with and without primary and secondary endpoints are shown in **Supplemental Material Table 1**.

Clinical outcomes of the main population

Major adverse cardiovascular events occurred in 60 (29.7%) patients. Twenty-three (11.4%) patients developed acute heart failure, 5 (2.6%) patients developed acute coronary syndrome (1 acute myocardial infarction with ST segment elevation, 2 patients with acute myocardial infarction without ST segment elevation and 2 Takotsubo syndrome), 4 (2%) patients developed pericarditis, 4 (2%) developed myocarditis, and 3 (1.3%) developed pulmonary embolism. Fourteen (6.9%) patients had acute onset of atrial fibrillation, and 1 (0.5%) patient had atrial flutter.

The in-hospital mortality rate was 40 (19.8%) patients.

Factors associated with MACE and in-hospital mortality in the main population

Baseline cTn T. Univariable and multivariable Cox regression analyses for MACE and in-hospital mortality are shown in Table 1. Baseline cTn T independently predicted MACE ($p = 0.047$, hazard ratio [HR] 1.805, 95% confidence interval [CI] 1.009–3.231) and in-hospital mortality ($p = 0.009$, HR 2.322, 95% CI 1.234–4.369).

For MACE, sensitivity and specificity of baseline cTn T (best cut-off value 0.014 μg/mL) were 92.6% and 60.1%, respectively, with an area under the curve of 0.80 (95% CI 0.73–0.87) (Fig. 1A), and for in-hospital mortality: sensitivity 77.1%

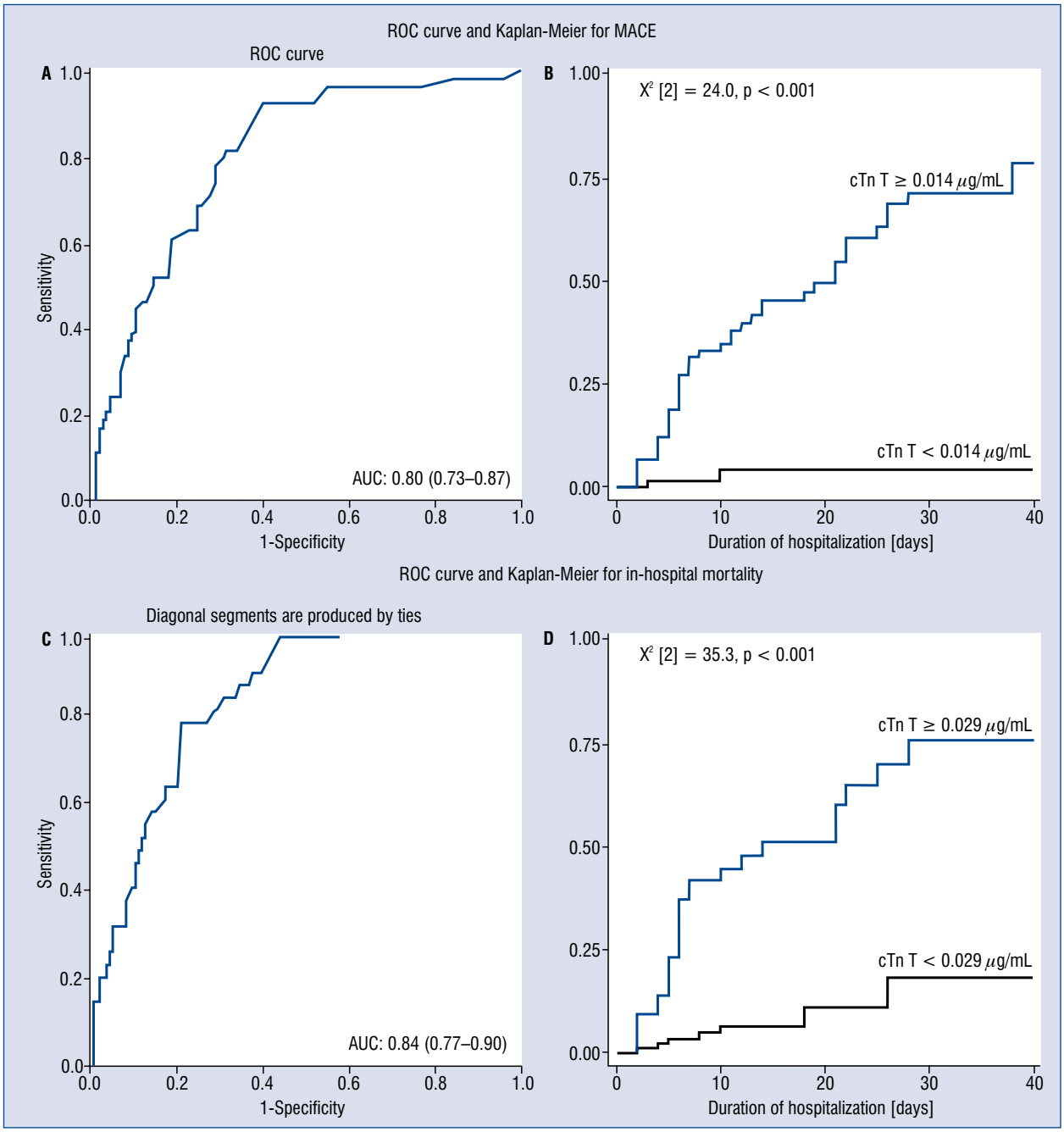


Figure 1. Receiver operating characteristics (ROC) and Kaplan-Meier analysis illustrating the role of baseline cardiac troponin T (cTn T) in major adverse cardiovascular events (MACE) and in-hospital mortality in COVID-19 patients. ROC analysis for baseline cTn T for predicting MACE (**A**) and in-hospital mortality (**C**). Kaplan-Meier survival curve analysis for MACE, Log Rank (Matel-Cox) value = 0.000 (**B**) and in-hospital mortality, Log Rank (Matel-Cox) value = 0.000 (**D**).

and specificity 78.8%; area under the curve 0.84 (95% CI 0.77–0.90); and best cut-off value 0.029 μg/mL (Fig. 1C).

Kaplan-Meier survival analysis for MACE and in-hospital mortality showed significant differences between patients with a baseline cTn T more than 0.014 μg/mL for MACE and more than 0.029 μg/mL for in-hospital mortality (X^2 [2] = 24.0, p < 0.001, X^2 [2] = 35.3, p < 0.001, respectively, Fig. 1B, D).

cTn T kinetics. Characteristics of groups according to cTn T kinetics are detailed in **Supplemental Material Table 2.**

Table 2. Cox regression analysis for major adverse cardiovascular events (MACE) and for in-hospital mortality in COVID-19 patients with constant cardiac troponin T (cTn T) profile and Cox regression analysis for in-hospital mortality in COVID-19 patients with an ascending cTn T slope.

Parameter	Univariable analysis			Multivariable analysis		
	HR	95% CI	P	HR	95% CI	P
MACE predictors in COVID-19 patients with constant cTn T profile						
Age	0.891	0.969–0.992	0.001	0.994	0.979–1.008	0.402
C-reactive protein	0.998	0.996–1.000	0.103	1.000	0.998–1.003	0.805
Neuthropil-lymphocyte ratio	0.964	0.933–0.997	0.035	1.011	0.969–1.054	0.615
Constant cTn T profile	3.133	2.140–4.589	0.000	3.080	1.914–4.954	0.000
History of diabetes mellitus	0.573	0.383–0.857	0.007	0.337	0.183–0.776	0.008
History of arterial hypertension	0.835	0.576–1.211	0.341	1.107	0.719–1.703	0.646
History of dyslipidemia	0.690	0.469–1.014	0.059	1.766	0.884–3.526	0.107
In-hospital mortality in COVID-19 patients with constant cTn T profile						
Age	0.983	0.972–0.994	0.003	0.999	0.986–1.012	0.854
C-reactive protein	0.999	0.997–1.001	0.154	1.000	0.998–1.002	0.991
Neutrophil-lymphocyte ratio	0.967	0.937–0.999	0.041	1.006	0.968–1.045	0.769
Constant cTn T profile	3.076	2.131–4.440	0.000	2.851	1.828–4.447	0.000
History of diabetes mellitus	0.598	0.408–0.877	0.009	0.690	0.462–1.030	0.070
In-hospital mortality in COVID-19 patients with an ascending cTn T slope						
Age	0.983	0.972–0.994	0.003	1.100	1.017–1.190	0.018
C-reactive protein	0.999	0.997–1.001	0.154	1.007	1.000–1.015	0.056
Neutrophil-lymphocyte ratio	0.967	0.937–0.999	0.041	1.045	0.957–1.142	0.327
Ascending slope	3.076	2.131–4.440	0.000	1.006	1.000–1.011	0.041
History of diabetes mellitus	0.598	0.408–0.877	0.009	0.629	0.141–2.811	0.544

CI — confidence interval; HR — hazard ratio

Predictors of MACE and in-hospital mortality according to cTn T kinetics pattern

A constant cTn T profile was independently associated with lower MACE and in-hospital mortality rates comparing to the other two groups ($p = 0.000$, HR 3.080, 95% CI 1.914–4.954, $p = 0.000$; HR 2.851, 95% CI 1.828–4.447, respectively).

Conversely, a positive ascending slope was an independent predictor of in-hospital mortality ($p = 0.041$, HR 1.006, 95% CI 1.000–1.011).

The univariable and multivariable Cox regression analyses for MACE and in-hospital mortality are shown in Table 2.

Kaplan-Meier survival analysis for MACE and in-hospital mortality, showed significant differences between patients with a constant cTn T profile and other cTn T profiles, ($X^2[2] = 43.4$, $p < 0.001$, $X^2[2] = 41.9$, $p < 0.001$, respectively, Fig. 2A, B; 3).

Discussion

The main findings of this study were the following: 1) baseline cTn T independently predicted MACE and in-hospital mortality in COVID-19 hospitalized patients; 2) a constant cTn T profile was independently associated with a lower risk of MACE and in-hospital mortality; and 3) a rapid increase of cTn T during hospitalization was associated with higher mortality rate but not with higher MACE rate in hospitalized COVID-19 patients.

The characteristics of our study population are similar to earlier reports [16]. Patients diagnosed with COVID-19 are older, implicitly more fragile, and have more cardiac risk factors, which predispose them to developing major cardiovascular events [17–19].

Previous studies primarily focused on the role of baseline cTn T in predicting non-cardiac major

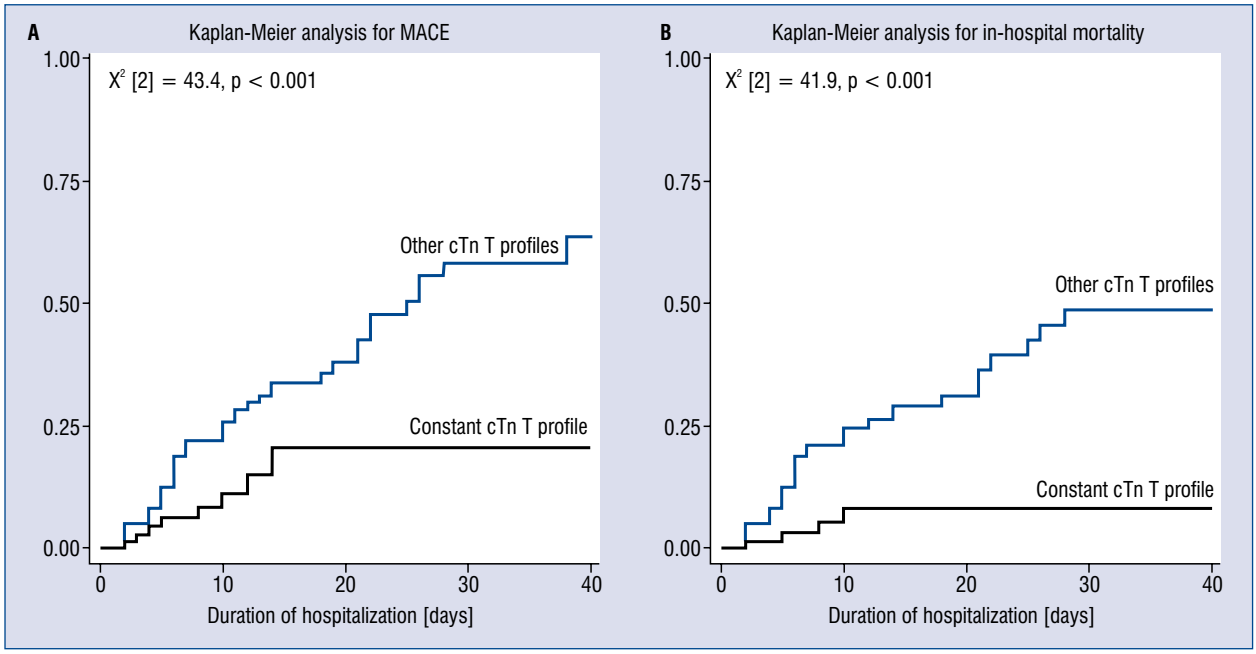


Figure 2. Kaplan-Meier survival analysis on the role of constant troponin profile in major adverse cardiovascular events (MACE) and in-hospital mortality in COVID-19 patients. Kaplan-Meier survival curve analysis for MACE, Log Rank (Matel-Cox) value = 0.000 (**A**) and in-hospital mortality, Log Rank (Matel-Cox) value = 0.000 (**B**).

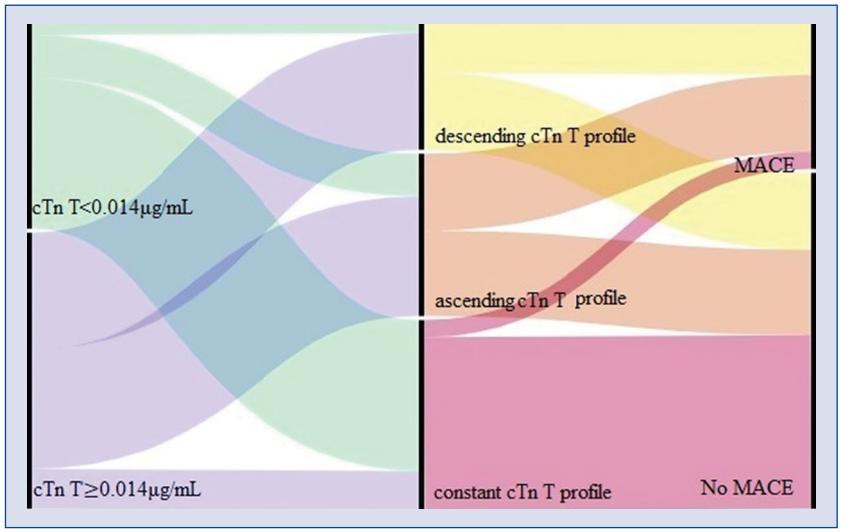


Figure 3. Alluvial plot illustrating the distribution of values of baseline cardiac troponin T (cTn T) in COVID-19 patients divided into three kinetics profiles according on the values during hospitalization of cardiac troponin (ascending cTn T, descending cTn T, and constant cTn T) and the association with major cardiovascular events. First column: patients were divided into two groups based on the best cut-off value of baseline cTn T of 0.014 μg/mL (green: cTn T< 0.014 μg/mL, purple: cTn T ≥ 0.014 μg/mL), which was shown as an independent predictor for major adverse cardiovascular events (MACE). Second column: patients were separated into three cTn T kinetics profiles: ascending troponin profile (orange), descending troponin profile (yellow), constant troponin profile (pink). Third column: Patients without MACE. Patients with MACE.

events such as intensive care unit admission, need for invasive ventilation or extracorporeal membrane oxygenation, and in-hospital mortality [6, 7, 10, 20]. Elevated cardiac biomarkers, especially cardiac troponin, were identified in about 10% to 20% of hospitalized COVID-19 patients, especially

in those with a more severe form of the disease and non-survivors [21]. Both cardiovascular comorbidities and high values of cTn T were correlated to higher morbidity and mortality in COVID-19 patients [21]. However, the small number or even the complete absence of cTn T measurements at baseline and during hospitalization were among the most frequently encountered limitations of earlier reports. Thus, data on the cardiac involvement and potential mechanisms of myocardial injury in COVID-19 are still scarce.

Possible mechanisms attributed to myocardial damage and previously observed in other viral infections such as influenza were: severe inflammation, oxygen mismatch supply-demand, thrombosis, and microvascular injury [6, 8, 22]. This is further supported by recent pathological reports on the presence of severe acute respiratory syndrome-coronavirus-2 in heart specimens, proving the cardiac tropism [23].

In the current study, elevated troponin levels at baseline were linked not only to higher mortality rates confirming the results of earlier reports [16], but they also independently predicted major cardiovascular events, with a high sensitivity and specificity. These findings emphasize the susceptibility to myocardial injury related to COVID-19 infection.

Sandoval et al. [9] postulated that in addition to baseline cTn T, stable concentrations of cTn T over time convey a lower risk of cardiovascular complications, such as myocarditis, pericarditis, or acute coronary syndromes, whereas a more in-depth approach is advised in patients with an increase in cTn T values in time. The present study reinforces this statement, by showing that a rapid increase of cTn T over a short period of time was independently associated with in-hospital mortality. The increase in cTn T values may reflect the severity of myocardial injury and may be linked to the amplitude of inflammatory response [18, 21, 24].

In our cohort, higher values of C-reactive protein were associated with increased cTn T values during hospitalization. Moreover, baseline C-reactive protein was significantly associated with both major endpoints, suggesting that inflammation acts as a trigger for acute cardiac damage and increases morbidity and mortality in these patients [25].

These findings are further supported by previous studies on severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which showed that an exaggerated immune response with release of inflammatory cytokines may cause myocardial damage with high levels of cardiac biomarkers [26].

Interestingly, patients with constant troponin values during hospitalization had lower rates of death or major cardiovascular events, even though they might have had elevated baseline cTn T.

This finding suggests that the increase in cTn T at admission might be caused by extra cardiac factors, unrelated to cardiac events, supporting the additional role of serial cTn T testing in these patients [27, 28].

Nevertheless, worse outcomes were also attributed to COVID-19 patients with cardiovascular comorbidities and risk factors, such as arterial hypertension, obesity, or diabetes mellitus [5, 29]. However, in the present study, no significant differences in terms of cardiac risk factors or pathologies between cTn T groups according to cTn T kinetics were found, except for diabetes mellitus. Nonetheless, it was not linked to higher mortality or major cardiovascular events.

Hence, these results underline that the clinical significance of serial testing in COVID-19 patients should not be overlooked, irrespective of the presence of cardiovascular disease or risk factors. The findings of the present study emphasize the additional role of troponin testing, not only on admission, but also during hospitalization, for a better risk stratification and an improved diagnostic pathway. Moreover, patients with cardiac injury during hospitalization should be routinely monitored for mid- and long-term outcomes, following COVID-19 infection.

Limitations of the study

This study has several limitations. This is a single-center study with a limited number of patients. It might be argued that cardiac troponin was assessed in more severe forms of COVID-19. Due to logistical restriction at the beginning of the pandemic, some data regarding echocardiography, cardiac magnetic resonance, or systematic measurements of cardiac biomarkers were lacking in some patients. Cardiovascular examinations were performed in selected cases based on the clinical and biological status of the patients, according to current guideline recommendations to avoid the risk of cross-infections [27, 30]. Therefore, serial echocardiographic evaluation was not available in all COVID-19 patients.

Nonetheless, patients who died were more likely to have missing data, including serial cardiac troponin testing. Thus, patients with incomplete data were excluded from the final analysis.

Also, in the present study less sensitive cardiac troponin assays were used. However, the value of troponin in distinguishing patients with worse outcome was obvious.

Multicenter research on a larger population with a standardized protocol is necessary to confirm our results.

Conclusions

Elevated cTn T at admission independently predicted MACE and in-hospital mortality in COVID-19 hospitalized patients. Moreover, a rapid increase in the value of cTn T was associated with higher mortality rates.

Conversely, a constant cTn T profile was linked to lower rates of MACE and in-hospital mortality. These findings emphasize the additional value of serial troponin testing in COVID-19 patients, for risk stratification and improved diagnosis pathways and management.

Conflict of interest: None declared

References

1. WHO, Aylward, Bruce (WHO); Liang W (PRC). Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). WHO-China Jt Mission Coronavirus Dis 2019. 2020.
2. Shi S, Qin Mu, Shen Bo, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020; 5(7): 802–810, doi: 10.1001/jamacardio.2020.0950, indexed in Pubmed: 32211816.
3. Shi S, Qin Mu, Cai Y, et al. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. Eur Heart J. 2020; 41(22): 2070–2079, doi: 10.1093/eurheartj/ehaa408, indexed in Pubmed: 32391877.
4. Kuno T, Takahashi M, Obata R, et al. Cardiovascular comorbidities, cardiac injury, and prognosis of COVID-19 in New York City. Am Heart J. 2020; 226: 24–25, doi: 10.1016/j.ahj.2020.05.005, indexed in Pubmed: 32425197.
5. Guan Wj, Liang Wh, Zhao Yi, et al. Comorbidity and its impact on 1,590 patients with COVID-19 in China: A Nationwide Analysis. Eur Respir J. 2020, doi: 10.1101/2020.02.25.20027664.
6. Guo T, Fan Y, Chen M, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). JAMA Cardiology. 2020; 5(7): 811, doi: 10.1001/jamacardio.2020.1017.
7. Sabatino J, De Rosa S, Di Salvo G, et al. Impact of cardiovascular risk profile on COVID-19 outcome. A meta-analysis. PLoS One. 2020; 15(8): e0237131, doi: 10.1371/journal.pone.0237131, indexed in Pubmed: 32797054.
8. Lala A, Johnson KW, Januzzi JL, et al. Prevalence and Impact of Myocardial Injury in Patients Hospitalized with COVID-19 Infection. medRxiv. 2020; 76(5): 533–546, doi: 10.1101/2020.04.20.20072702, indexed in Pubmed: 32511658.
9. Sandoval Y, Januzzi JL, Jaffe AS. Cardiac troponin for assessment of myocardial injury in COVID-19: JACC review topic of the week. J Am Coll Cardiol. 2020; 76(10): 1244–1258, doi: 10.1016/j.jacc.2020.06.068, indexed in Pubmed: 32652195.
10. Lorente-Ros A, Monteagudo Ruiz JM, Rincón LM, et al. Myocardial injury determination improves risk stratification and predicts mortality in COVID-19 patients. Cardiol J. 2020; 27(5): 489–496, doi: 10.5603/CJ.a2020.0089, indexed in Pubmed: 32589258.
11. Collet JP, Thiele H. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2020; 41(37): 3495–3497, doi: 10.1093/eurheartj/ehaa624.
12. Meguro S, Ishibashi M, Takei I. [The significance of high sensitive C reactive protein as a risk factor for cardiovascular diseases]. Rinsho Byori. 2012; 60(4): 356–361, indexed in Pubmed: 22686046.
13. Yancy C, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure. J Cardiac Failure. 2017; 23(8): 628–651, doi: 10.1016/j.cardfail.2017.04.014.
14. Konstantinides SV, Meyer G, Becattini C, et al. ESC Scientific Document Group, The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Heart J. 2020; 41(4): 543–603, doi: 10.1093/eurheartj/ehz405, indexed in Pubmed: 31504429.
15. Brugada J, Katritsis DG, Arbelo E, et al. 2019 ESC Guidelines for themanagement of patients with supraventricular tachycardia. Eur Heart J. 2020; 41(5): 655–720, doi: 10.1093/eurheartj/ehz467, indexed in Pubmed: 31504425.
16. Majure DT, Gruberg L, Saba SG, et al. Usefulness of elevated troponin to predict death in patients with COVID-19 and myocardial injury. Am J Cardiol. 2021; 138: 100–106, doi: 10.1016/j.amjcard.2020.09.060, indexed in Pubmed: 33058800.
17. Xu H, Hou K, Xu R, et al. Clinical characteristics and risk factors of cardiac involvement in COVID-19. J Am Heart Assoc. 2020; 9(18): e016807, doi: 10.1161/JAHA.120.016807, indexed in Pubmed: 32806998.
18. Raad M, Dabbagh M, Gorgis S, et al. Cardiac injury patterns and inpatient outcomes among patients admitted with COVID-19. Am J Cardiol. 2020; 133: 154–161, doi: 10.1016/j.amjcard.2020.07.040, indexed in Pubmed: 32829913.
19. Núñez-Gil IJ, Fernández-Ortiz A, Maroud Eid C, et al. Underlying heart diseases and acute COVID-19 outcomes. Cardiol J. 2021; 28(2): 202–214, doi: 10.5603/CJ.a2020.0183, indexed in Pubmed: 33346365.
20. Deng Q, Hu Bo, Zhang Y, et al. Suspected myocardial injury in patients with COVID-19: Evidence from front-line clinical observation in Wuhan, China. Int J Cardiol. 2020; 311: 116–121, doi: 10.1016/j.ijcard.2020.03.087, indexed in Pubmed: 32291207.
21. Mueller C, Giannitsis E, Jaffe AS, et al. Cardiovascular biomarkers in patients with COVID-19. Eur Heart J Acute Cardiovasc Care. 2021; 10(3): 310–319, doi: 10.1093/ehjacc/zuab009, indexed in Pubmed: 33655301.
22. Chow EJ, Rolfes MA, O'Halloran A, et al. Acute cardiovascular events associated with influenza in hospitalized adults: a cross-

sectional study. Ann Intern Med. 2020; 173(8): 605–613, doi: 10.7326/M20-1509, indexed in Pubmed: 32833488.
23. Pesaresi M, Pirani F, Tagliabracci A, et al. SARS-CoV-2 identification in lungs, heart and kidney specimens by transmission and scanning electron microscopy. Eur Rev Med Pharmacol Sci. 2020; 24(9): 5186–5188, doi: 10.26355/eurrev_202005_21217, indexed in Pubmed: 32432787.
24. Giustino G, Croft L, Stefanini G, et al. Characterization of myocardial injury in patients with COVID-19. J Am Coll Cardiol. 2020; 76(18): 2043–2055, doi: 10.1016/j.jacc.2020.08.069.
25. Li JJ, Fang CH. C-reactive protein is not only an inflammatory marker but also a direct cause of cardiovascular diseases. Med Hypotheses. 2004; 62(4): 499–506, doi: 10.1016/j.mehy.2003.12.014, indexed in Pubmed: 15050096.
26. Park JE, Jung S, Kim A, et al. MERS transmission and risk factors: a systematic review. BMC Public Health. 2018; 18(1): 574, doi: 10.1186/s12889-018-5484-8, indexed in Pubmed: 29716568.
27. Cosyns B, Lochy S, Luchian ML, et al. The role of cardiovascular imaging for myocardial injury in hospitalized COVID-19 patients. Eur Heart J Cardiovasc Imaging. 2020; 21(7): 709–714, doi: 10.1093/ehjci/jeaa136, indexed in Pubmed: 32391912.
28. Mahajan VS, Jarolim P. How to interpret elevated cardiac troponin levels. Circulation. 2011; 124(21): 2350–2354, doi: 10.1161/CIRCULATIONAHA.111.023697, indexed in Pubmed: 22105197.
29. Li X, Guan Bo, Su T, et al. Impact of cardiovascular disease and cardiac injury on in-hospital mortality in patients with COVID-19: a systematic review and meta-analysis. Heart. 2020; 106(15): 1142–1147, doi: 10.1136/heartjnl-2020-317062, indexed in Pubmed: 32461330.
30. Skulstad H, Cosyns B, Popescu BA, et al. COVID-19 pandemic and cardiac imaging: EACVI recommendations on precautions, indications, prioritization, and protection for patients and healthcare personnel. Eur Heart J Cardiovasc Imaging. 2020; 21(6): 592–598, doi: 10.1093/ehjci/jeaa072, indexed in Pubmed: 32242891.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2021, Vol. 28, No. 6, 816–824
DOI: 10.5603/CJ.a2021.0168

ISSN 1897–5593
eISSN 1898–018X

Impact of COVID-19 on in-hospital cardiac arrest outcomes: An updated meta-analysis

Karol Bielski[1, 2], Katarzyna Makowska[3], Adam Makowski[3], Tomasz Kopiec[3], Aleksandra Gasecka[3], Mariola Malecka[4], Michal Pruc[5], Zubaid Rafique[6], Frank W. Peacock[6], Andrea Denegri[7], Lukasz Szarpak[5, 8]

[1]Research Unit, Polonia University, Czestochowa, Poland
[2]Provincial Emergency Medical Service Dispatcher, Warsaw, Poland
[3]First Chair and Department of Cardiology, Medical University of Warsaw, Poland
[4]Institute of Outcomes Research, Maria Sklodowska-Curie Medical Academy, Warsaw, Poland
[5]Research Unit, Polish Society of Disaster Medicine, Warsaw, Poland
[6]Henry JN Taub Department of Emergency Medicine, Baylor College of Medicine, Houston, TX, USA
[7]Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy
[8]Research Unit, Maria Sklodowska-Curie Bialystok Oncology Center, Bialystok, Poland

Abstract

Background: *The main purposes of this meta-analysis are to update the information about the impact of coronavirus disease 2019 (COVID-19) pandemic on outcomes of in-hospital cardiac arrest (IHCA) and to investigate the impact of being infected by by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) on IHCA outcomes.*

Methods: *The current meta-analysis is an update and follows the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).*

Results: *In analyses, pre- and intra-COVID-19 periods were observed for: shockable rhythms in 17.6% vs. 16.2% (odds ratio [OR]: 1.11; 95% confidence interval [CI]: 0.71–1.72; p = 0.65), return of spontaneous circulation (ROSC) in 47.4% vs. 44.0% (OR: 1.36; 95% CI: 0.90–2.07; p = 0.15), 30-day mortality in 59.8% vs. 60.9% (OR: 0.95; 95% CI: 0.75–1.22; p = 0.69) and overall mortality 75.8% vs. 74.7% (OR: 0.80; 95% CI: 0.49–1.28; p = 0.35), respectively. In analyses, SARS-CoV-2 positive and negative patients were observed for: shockable rhythms in 9.6% vs. 19.8% (OR: 0.51; 95% CI: 0.35–0.73; p < 0.001), ROSC in 33.9% vs. 52.1% (OR: 0.47; 95% CI: 0.30–0.73; p < 0.001), 30-day mortality in 77.2% vs. 59.7% (OR: 2.08; 95% CI: 1.28–3.38; p = 0.003) and overall mortality in 94.9% vs. 76.7% (OR: 3.20; 95% CI: 0.98–10.49; p = 0.05), respectively.*

Conclusions: *Despite ROSC, 30-day and overall mortality rate were not statistically different in pre- vs. intra-COVID-19 periods, a lower incidence of ROSC and higher 20-day mortality rate were observed in SARS-CoV-2 (+) compared to SARS-CoV-2 (–) patients.* (Cardiol J 2021; 28, 6: 816–824)

Key words: coronavirus disease 2019, COVID-19, SARS-CoV-2, pandemic, in-hospital cardiac arrest, cardiopulmonary resuscitation, outcome, meta-analysis

Address for correspondence: Lukasz Szarpak, Assoc Prof., PhD, DPH, DBA, MBA, LL.M., Maria Sklodowska-Curie Bialystok Oncology Center, ul. Ogrodowa 12, 15–027 Białystok, Poland, tel: +48 500 186 225, e-mail: lukasz.szarpak@gmail.com

Received: 26.07.2020 Accepted: 2.08.2021 Early publication date: 17.12.2021

Introduction

The emergence of the world pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) began in Wuhan, China in December 2019 [1–3]. In November 2021, respectively over 250 million confirmed cases and 5 million total deaths were reported globally [4].

The COVID-19 manifests itself as an asymptomatic or with a broad spectrum of features commonly regarding symptoms from the respiratory system, including even severe respiratory failure or death [5–7]. The most frequent symptoms involve: fever, cough, and dyspnea then myalgia or rhinorrhea [8–10]. In 14% of patients with pneumonia caused by SARS-CoV-2 hospitalization is required [5]. Subsequently in 15% of patients with initially severe outcomes of COVID-19 multi-organ failure or acute respiratory distress syndrome may occur [6, 11].

Nevertheless, the coexistence of chronic conditions from other systems such as: diabetes mellitus, hypertension, obstructive pulmonary disease, cardiovascular diseases or even obesity was related with worse predictions [8, 12–14].

To date a specific treatment has not been discovered [15]. However, the vaccinations may contribute to limiting the spread of SARS-CoV-2 [16, 17].

Research of the literature presented on the mortality rate in intensive care units may be higher than 35% and according to this data, in-hospital cardiac arrest (IHCA) is described to be the main factor of this score [18, 19]. The IHCA prior to and throughout the COVID-19 pandemic was higher in number, but indistinguishable in outcomes [20]. The survival rate in intra-hospital cardiac arrest was much higher than in out-of-hospital cardiac arrest (OHCA) [20]. Moreover, as pointed out by Shao et al. [18] the survival of patients with non-shockable rhythms is below 0.8%. This is more disturbing, as cardiac arrests in COVID-19 patients occur much more often resulting from a respiratory failure mechanism than in patients with negative COVID-19 results [21, 22]. Because of the risk of SARS-CoV-2 infection, resuscitation of a patient with suspected or confirmed COVID-19 should be carried out using personal protective equipment (PPE) [23, 24]. However, as shown by many studies [25, 26], the use of PPE for aerosol generating procedures (AGPs) may adversely affect the quality of chest compression. In order to improve the quality of the conducted resuscitation, Malysz et al. [27] compared two techniques of manual chest compression — demonstrating that paramedics wearing PPE-AGP achieved better chest compression depth for over-the-head position compared to the standard chest position, however, over-the-head position resuscitation causes a lower full chest relaxation. It is therefore reasonable to use mechanical chest compression systems during resuscitation of a patient with COVID-19, both in pre-hospital and inpatient settings, which allow for standardization of chest compressions even during prolonged cardiopulmonary resuscitation [28].

The primary aim of this systematic review and meta-analysis is to assess the impact of the COVID-19 pandemic on outcomes due to IHCA. The secondary aim is to investigate the effect of SARS-CoV-2 infection of IHCA outcomes during the COVID-19 period.

Methods

The current systematic review and meta-analysis follows the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for conducting and reporting its results [29]. A protocol of this meta-analysis has not been registered. Ethical approval and consent were waived because this study was a systematic review and meta-analysis of published literature. This meta-analysis is an update of the analysis previously published by the authors [20].

Methodology of systematic review and meta-analysis was described in a previous article [20]. The primary outcome was overall mortality. Secondary outcomes were return of spontaneous circulation (ROSC) as well as 30-day mortality.

The polled analysis was performed using RevMan 5.4 software (The Nordic Cochrane Center, Copenhagen, Denmark), using the odds ratio (OR) with 95% confidence interval (CI) for dichotomous outcomes, and the mean difference (MD) with 95% CI for continuous outcomes. When the continuous outcome was reported in a study as median, range, and interquartile range, means and standard deviations were estimated using the formula described by Hozo et al. [30]. A quantified heterogeneity in each analysis utilized the tau-squared and I-squared statistics. Heterogeneity was detected with the chi-squared test with n – 1 degree of freedom, which was expressed as I^2. Values of $I^2 > 50\%$ and $> 75\%$ were considered to indicate moderate and significant heterogeneity among studies, respectively. A random-effects model was used to pool study results independently of the p-value for heterogeneity or I^2 [31]. All p values were two-tailed and considered significant if < 0.05.

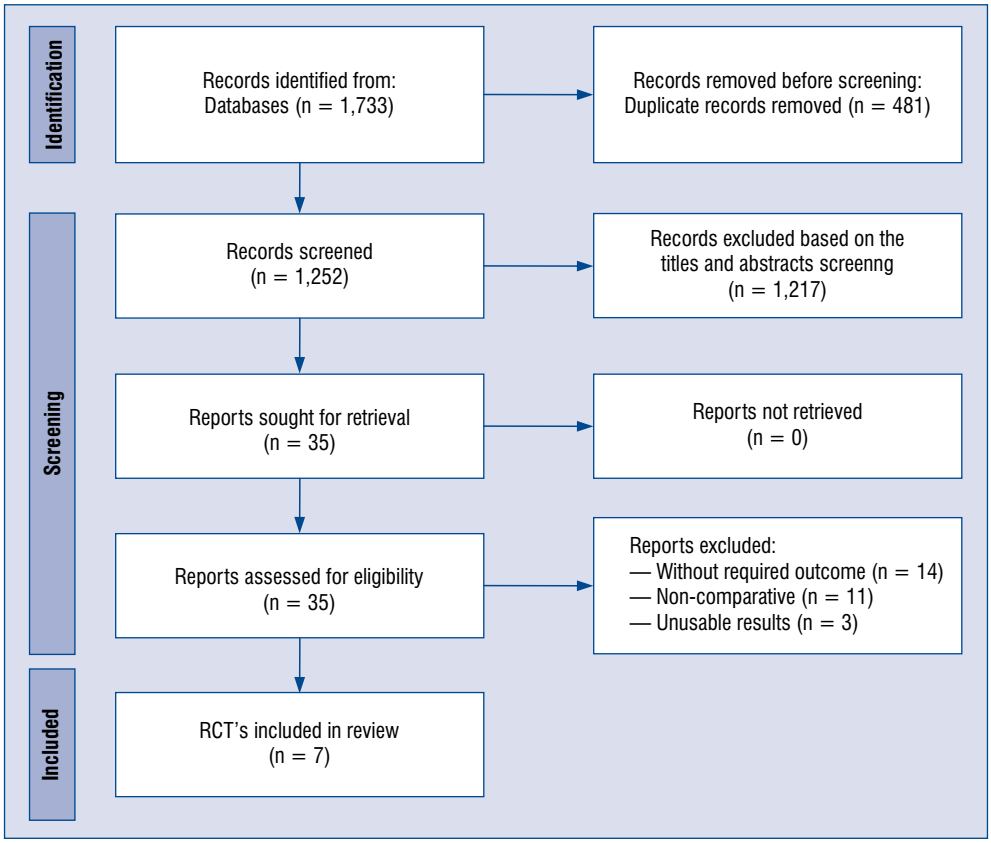


Figure 1. Flow diagram showing stages of the database search and study selection as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines; RCT — randomized controlled trials.

Results

Characteristics of studies included in the meta-analysis

A total of 1,733 articles were identified from the Medline (PubMed), Embase, Cochrane library, and a manual search as described above. After excluding duplicates, 1,252 articles remained. In the next step (screening the titles and abstracts of all retrieved articles), 1,217 articles were excluded. Thereafter, the full text was reviewed, and 28 studies were excluded because they contained pediatrics, which does not present a comparative group, report unusable results or were reviews or meta-analyses. Finally, 7 studies published from 2020 to 2021 including 3,049 IHCA patients were included in this meta-analysis (Fig. 1) [32–38]. Detailed characteristics of the studies included in the meta-analysis are presented in Table 1.

Five studies reported IHCA outcomes in pre- vs. intra-COVID-19 periods [32, 34–37] and 3 in COVID-19 period, dividing participants as SARS-CoV-2 positive vs. negative patients [33, 36, 38]. Each study was then screened for risk of bias and methodological quality using the Cochrane Collaboration tool for assessing the risk of bias (Figs. 2, 3).

Analyses in pre- vs. intra-COVID-19 periods

Patient age in the pre- vs. intra-COVID-19 periods varied and amounted to 71.6 ± 13.3 vs. 69.9 ± 14.4 years, respectively (MD: 0.62; 95% CI: –0.71 to 1.95; p = 0.36). Characteristics of patients with IHCA in pre vs. intra-COVID-19 periods and resuscitation process are presented in Table 2.

Shockable rhythms were observed in 17.6% of cases in the pre-COVID-19 period compared to 16.2% for the in COVID-19 period (OR: 1.11; 95% CI: 0.71–1.72; p = 0.65).

Five studies reported ROSC in pre- vs. intra-COVID-19 periods. Polled analysis of ROSC varied and amounted to 47.4% vs. 44.0%, respectively (OR: 1.36; 95% CI: 0.90–2.07; p = 0.15).

Thirty-day mortality was observed in 1 study and was 59.8% for pre-COVID-19 period compared to 60.9% for COVID-19 period (OR: 0.95; 95% CI: 0.75–1.22; p = 0.69). In turn, overall mortality was indicated in 5 studies, and was occurring 75.8%

Table 1. Participant characteristics in included trials.

Study	Country	Pre-COVID-19 period			COVID-19 period							
					Total			COVID-19 positive patients			COVID-19 negative patients	
		No.	Age	Sex, female	No.	Age	Sex, female	No.	Age	Sex, female	No.	Age	Sex, female
Aldabagh et al. 2021	USA	–	–	–	–	–	–	450	66.4 (13.1%)	179 (39.8%)	334	66.8 (15.5%)	148 (44.3%%)
Lyu et al. 2021	Singapore	10	NS	NS	17	NS	NS	–	–	–	–	–	–
Miles et al. 2020	USA	117	66.3 (3.5%)	50 (42.7%%)	125	66.8 (3.2%)	43 (34.4%)	–	–	–	–	–	–
Roedl et al. 2021	Germany	84	69.8 (3.5%)	24 (28.6%%)	93	67.8 (3.5%)	33 (35.5%)	–	–	–	–	–	–
Sultanian et al. 2021	Sweden	532	70.1 (18.2%)	205 (38.5%%)	548	67.8 (18.9%)	197 (35.9%)	72	67.8 (13.0%)	23 (31.9%)	285	67.0 (20.8%)	93 (32.6%)
Tong et al. 2021	China	362	75.8 (3.2%)	122	267	76.3 (3.2%)	113	–	–	–	–	–	–
Yuriditsky et al. 2020	USA	–	–	–	110		29 (26.4%)	55	69.8 (3.8%)	7 (12.7%)	55	68.9 (5.9%)	22 (40.0%)

NS — not specified

for pre-COVID-19 period compared to 74.7% for COVID-19 period (OR: 0.80; 95% CI: 0.49–1.28; p = 0.35).

Analyses in SARS-CoV-2 positive vs. negative patients

Mean age among IHCA patients with SARS-CoV-2 positive and negative amounted to 66.9 ± ± 12.5 vs. 67.1 ± 17.5 years respectively (MD: 0.37; 95% CI: –0.93 to 1.67; p = 0.57). Shockable rhythms in the group of patients with confirmed SARS-CoV-2 were observed in 9.6% of cases and it was statistically significantly lower than in the group of patients with negative results of the SARS-CoV-2 test (19.8%; OR: 0.51; 95% CI: 0.35–0.73; p < 0.001). Detailed characteristics of the patients and the resuscitation process are presented in Table 3.

The ROSC in the SARS-CoV-2 positive patients was observed in 33.9% of IHCA cases which was statistically significantly less than with SARS-CoV-2 negative patients — 52.1% (OR: 0.47; 95% CI: 0.30–0.73; p < 0.001). 30-day mortality in the case of SARS-CoV-2 positive vs. negative patients varied and amounted to 77.2% vs. 59.7% (OR: 2.08; 95% CI: 1.28–3.38; p = 0.003). A similar trend was observed for overall mortality, but it was not statistically significant (94.9% vs. 76.7%, respectively; OR: 3.20; 95% CI: 0.98–10.49; p = 0.05).

Discussion

In this meta-analysis outcomes were compared of IHCA during the COVID-19 pandemic to outcomes of IHCA that happened before the SARS-CoV-2 outbreak. Depending on the study, primary outcomes were defined differently. Some considered actual survival to that predicted by the GO-FAR score which is a validated prediction model for determining survival following IHCA [33, 36, 38]. Other studies considered ROSC, which was defined as sustained ROSC or palpable pulse that lasted over 20 min and did not require cardiopulmonary resuscitation to be performed [38].

Contradictory to the results of our previous meta-analysis which showed no significant impact of COVID-19 pandemic to survivability ratio, most studies that we analyzed now show that the rate of survival is lower during the COVID-19 pandemic than in the pre-pandemic period. It was observed in a cohort study performed by Lyu et al. [32] that IHCA was more commonly observed during the ongoing pandemic and, what is more important, the survivability ratio in patients that underwent

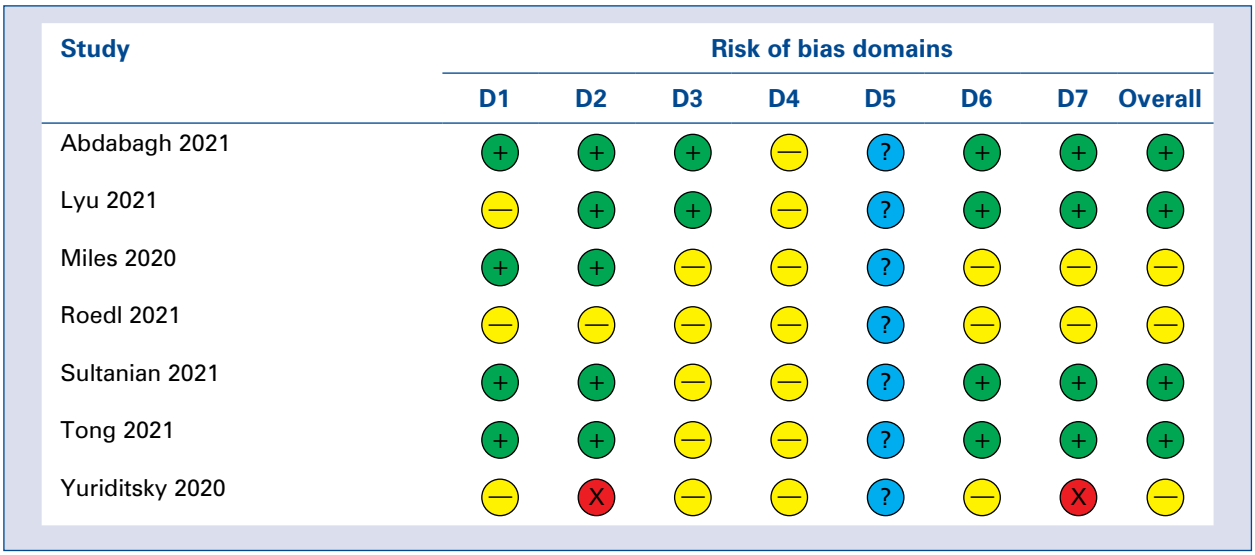


Figure 2. A summary table of review authors' judgements for each risk of bias item for each study. Domains: D1 — bias due to confounding; D2 — bias due to selection of participants; D3 — bias in classification of interventions; D4 — bias due to deviations from intended interventions; D5 — bias due to missing data; D6 — bias in measurement of ourcomes; D7 — bias in selection of the reported result; Judgement: Serious; Moderate; Low; No information.

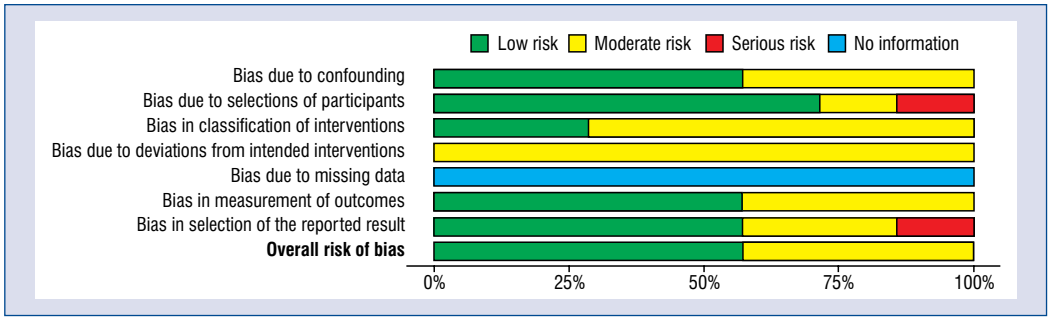


Figure 3. A plot of the distribution of review authors' judgements across randomized studies for each risk of bias item.

IHCA had decreased. This corresponds to a study performed by Miles et al. [34] in which there is statistically significant difference of survival rate of patients who suffered from IHCA during the COVID-19 pandemic and before the COVID-19 pandemic (3% vs. 13%; p = 0.007). Studies that consider both OHCA and IHCA reveal that during the pandemic phase, no less than 10% of all OHCAs and 16% of IHCAs were caused by SARS-CoV-2 infection. In these cases, mortality was higher, accordingly 3.4-fold in OHCA cases, and 2.3-fold in IHCA cases.

Sometimes results were ambiguous, as in the case of Yuriditsky et al. [38] where SARS-CoV-2 infection status did not bear any significance while considering ROSC as well as 30-day survivability rate. In comparison to some earlier publications, ROSC and 30-day survival was greater in IHCA that happened in COVID-19.

In some instances, such as in an analysis performed by Roedl et al. [35] even though the pandemic caused a decrease in number of hospital admissions, the incidence of IHCA was amplified and was occurring frequently in patients with COVID-19. Interestingly, contrary to other studies that are presented in the present meta-analysis, while compared to patients with non-COVID-19-related respiratory failure, the outcome was improved.

An interesting result comes from Tong et al. [37], which states that even after regulating for decreased comorbidity and elevated time to resuscitation team arrival, under the pandemic circumstances, ROSC in IHCA was hugely affected and its rate was considerably lower. It is worth

Table 2. Polled analysis of in-hospital cardiac arrest (IHCA) characteristics among pre- vs. intra-coronavirus disease 2019 (COVID-19) periods.

Parameter	No. of studies	Events		Events		Heterogeneity between trials		P-value for differences across groups
		Pre-COVID-19 period	COVID-19 period	OR	95% CI	P-value	I^2 statistic	
Female sex	4	36.6%	37.4%	0.95	0.68–1.32	0.04	63%	0.76
IHCA location:								
ICU	3	24.7%	17.5%	1.93	1.05–3.56	0.01	77%	0.03
ED	2	12.2%	17.1%	0.73	0.42–1.27	0.12	60%	0.27
Ward	3	39.0%	40.6%	0.58	0.58–2.49	< 0.001	95%	0.46
Comorbidities:								
Hypertension	1	58.3%	74.2%	0.49	0.26–0.92	NA	NA	0.03
CAD	2	25.3%	11.1%	2.69	2.00–3.63	0.38	0%	< 0.001
Diabetes	3	25.6%	16.4%	1.51	0.79–2.88	0.008	79%	0.21
Cancer	3	15.7%	10.8%	1.44	0.65–3.22	0.004	82%	0.37
Previous MI	2	13.3%	5.5%	2.84	1.18–6.80	0.28	13%	0.02
CKD	2	28.4%	27.5%	1.01	0.60–1.70	0.25	24%	0.96
Etiology:								
RI	2	9.7%	19.5%	0.31	0.03–3.51	< 0.001	98%	0.34
Acute MI	2	17.6%	6.4%	3.14	2.16–4.56	0.55	0%	< 0.001
Acute HF	1	3.4%	2.4%	1.44	0.32–6.57	NA	NA	0.64
Stroke	2	0.2%	0.6%	0.35	0.05–2.20	0.99	0%	0.26
Sepsis	2	10.8%	4.6%	3.34	2.04–5.48	0.77	0%	< 0.001
Witnessed arrest	2	76.0%	75.1%	1.13	0.90–1.42	0.83	0%	0.28
Shockable rhythm	5	17.6%	16.2%	1.11	0.71–1.72	0.10	48%	0.65
ALS treatment:								
Defibrillation	2	32.1%	28.9%	0.83	0.29–2.35	0.004	88%	0.72
Intubation	2	48.8%	41.2%	1.37	1.10–1.70	0.74	0%	0.005
MV	3	61.0%	49.1%	1.42	0.82–2.45	0.01	77%	0.22
Adrenaline	2	67.3%	67.9%	0.97	0.74–1.29	0.31	3%	0.86
Antiarrhythmics	2	13.9%	10.8%	1.32	0.95–1.84	0.88	0%	0.10
MCC	2	12.8%	10.8%	1.27	0.80–2.01	0.27	19%	0.31
TTM	2	7.1%	5.3%	1.82	0.54–6.07	0.04	76%	0.33
ECPR	1	6.0%	4.3%	1.41	0.37–5.43	NA	NA	0.33
Outcomes								
Cardiac re-arrest	2	25.4%	17.9%	1.61	0.89–2.89	0.23	32%	0.11
ROSC	5	47.4%	44.0%	1.36	0.90–2.07	0.007	71%	0.15
30-day mortality	1	59.8%	60.9%	0.95	0.75–1.22	NA	NA	0.69
Overall mortality	5	75.8%	74.7%	0.80	0.49–1.28	0.06	55%	0.69

ALS — advanced life support; CAD — coronary artery disease; CKD — chronic kidney disease; CI — confidence interval; ECPR — extracorporeal cardiopulmonary resuscitation; ED — emergency department; HF — heart failure; ICU — intensive care unit; MCC — mechanical chest compression; MI — myocardial infarction; MV — mechanical ventilation; NA — not applicable; OR — odds ratio; RI — respiratory failure; ROSC — return of spontaneous circulation; TTM — targeted temperature management

mentioning is that even patients who were not directly suffering from SARS-CoV-2 infection were also affected by the new resuscitation practice that was implemented in IHCA cases.

According to Aldabagh et al. [33] people suffering from COVID-19 are more prone to be more seriously affected by IHCA. Even the GO-FAR score underestimates the seriousness of SARS-CoV-2 in-

Table 3. Polled analysis of in-hospital cardiac arrest (IHCA) characteristics among severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) positive vs. negative groups.

Parameter	No. of studies	Events		Events		Heterogeneity between trials		P-value for differences across groups
		SARS-CoV-2 positive	SARS-CoV-2 negative	OR	95% CI	P-value	I^2 statistic	
Female sex	3	36.2%	39.0%	0.65	0.35–1.21	0.02	73%	0.17
IHCA location:								
ICU	3	36.4%	27.4%	1.69	0.62–4.56	< 0.001	86%	0.30
ED	3	13.0%	10.3%	1.55	1.05–2.27	0.36	2%	0.03
Ward	3	47.5%	46.3%	0.76	0.44–1.33	0.04	70%	0.34
Comorbidities:								
Hypertension	2	75.0%	69.2%	1.33	0.99–1.79	0.76	0%	0.06
CAD	3	19.2%	27.7%	0.34	0.14–0.84	0.008	79%	0.02
Diabetes	3	49.9%	26.6%	1.40	0.67–2.90	0.01	78%	0.37
Cancer	2	4.7%	7.4%	0.40	0.03–5.50	0.02	80%	0.50
Previous MI	1	1.4%	7.0%	0.58	0.17–1.99	NA	NA	0.38
CKD	1	9.1%	30.9%	0.22	0.08–0.66	NA	NA	0.007
Etiology:								
RI	1	12.5%	5.3%	2.57	1.08–6.14	NA	NA	0.03
Acute MI	2	1.4%	8.2%	0.16	0.04–0.65	0.97	0%	0.01
Stroke	1	1.4%	0.8%	1.99	0.18–22.29	NA	NA	0.58
Sepsis	1	0.0%	1.4%	0.43	0.02–8.10	NA	NA	0.57
Witnessed arrest	1	76.4%	82.8%	0.67	0.36–1.25	NA	NA	0.21
Shockable rhythm	3	9.6%	19.8%	0.51	0.35–0.73	0.62	0%	< 0.001
ALS treatment:								
Defibrillation	1	20.8%	30.2%	0.61	0.33–1.13	NA	NA	0.12
Intubation	1	48.6%	39.6%	1.44	0.86–2.42	NA	NA	0.17
MV	1	27.8%	49.1%	0.40	0.23–0.70	NA	NA	0.001
Adrenaline	1	68.1%	61.8%	1.32	0.76–2.29	NA	NA	0.32
Antiarrhythmics	1	8.3%	11.9%	0.67	0.27–1.67	NA	NA	0.39
MCC	1	8.3%	11.6%	0.69	0.28–1.73	NA	NA	0.43
TTM	1	0.0%	1.1%	0.56	0.03–10.90	NA	NA	0.70
Outcomes								
ROSC	2	33.9%	52.1%	0.47	0.30–0.73	0.32	1%	< 0.001
30-day mortality	2	77.2%	59.7%	2.08	1.28–3.38	0.85	0%	0.003
Overall mortality	3	94.9%	76.7%	3.20	0.98–10.49	0.02	73%	0.05

ALS — advanced life support; CAD — coronary artery disease; CKD — chronic kidney disease; CI — confidence interval; ED — emergency department; ICU — Intensive Care Unit; MCC — mechanical chest compression; MI — myocardial infarction; MV — mechanical ventilation; NA — not applicable; OR — odds ratio; RI — respiratory failure; ROSC — return of spontaneous circulation; TTM — targeted temperature management

fection and the rate of survival to hospital discharge is remarkably lower than in non-COVID-19 patients. In the current article, it is suggested that all these findings might be reasonably helpful in educating patients as well as healthcare professionals about risk factors that coincide with SARS-CoV-2 infection and may be useful in establishing new standards of treatment and the setting of code status designation.

Limitations of the study

There are several limitations to this review. Firstly, there is the small number of studies included in the meta-analysis, however, compared to the author's previous study, the number of patients included in the analysis was increased from 1,609 to 3,049 IHCA patients. The second limitation is the fact that in 4 studies, the authors truthfully point

to IHCA data during the COVID-19 period, but do not classify these patients as SARS-CoV-2 positive and negative patients [32, 34, 35, 37].

Conclusions

In conclusion, in pre- vs. intra-COVID-19 periods no statistical difference was observed in ROSC, 30-day or overall mortality rate. However, during the COVID-19 pandemic, a positive SARS-CoV-2 result was associated with a lower incidence of ROSC and a higher 30-day mortality rate compared to SARS-CoV-2 negative patients.

Acknowledgments

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

Conflict of interest: None declared

References

1. Rodriguez-Morales AJ, Bonilla-Aldana DK, Balbin-Ramon GJ, et al. History is repeating itself: Probable zoonotic spillover as the cause of the 2019 novel Coronavirus Epidemic. Infez Med. 2020; 28(1): 3–5, indexed in Pubmed: 32009128.
2. Dzieciatkowski T, Szarpak L, Filipiak KJ, et al. COVID-19 challenge for modern medicine. Cardiol J. 2020; 27(2): 175–183, doi: 10.5603/CJ.a2020.0055, indexed in Pubmed: 32286679.
3. Attila K, Ludwin K, Evrin T, et al. The impact of COVID-19 on airway management in prehospital resuscitation. Dis Emerg Med J. 2020; 5(4): 216–217, doi: 10.5603/demj.a2020.0047.
4. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020; 20(5): 533–534, doi: 10.1016/S1473-3099(20)30120-1, indexed in Pubmed: 32087114.
5. Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus Disease 2019 Case Surveillance — United States, January 22-May 30, 2020. MMWR Morb Mortal Wkly Rep. 2020; 69(24): 759–765, doi: 10.15585/mmwr.mm6924e2, indexed in Pubmed: 32555134.
6. Li G, Saguner A, An J, et al. Cardiovascular disease during the COVID-19 pandemic: Think ahead, protect hearts, reduce mortality. Cardiol J. 2020; 27(5): 616–624, doi: 10.5603/cj.a2020.0101, indexed in Pubmed: 32789839.
7. Kulak K, Wieczorek K, Krupski A, et al. SARS-CoV-2 as a real threat for healthcare workers. Dis Emerg Med J. 2020, doi: 10.5603/demj.a2020.0018.
8. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020; 8(5): 475–481, doi: 10.1016/S2213-2600(20)30079-5, indexed in Pubmed: 32105632.
9. Ruetzler K, Szarpak L, Filipiak K, et al. The COVID-19 pandemic — a view of the current state of the problem. Dis Emerg Med J. 2020, doi: 10.5603/demj.a2020.0015.
10. Kowalik MM, Trzonkowski P, Łasińska-Kowara M, et al. COVID-19 — Toward a comprehensive understanding of the disease. Cardiol J. 2020; 27(2): 99–114, doi: 10.5603/CJ.a2020.0065, indexed in Pubmed: 32378729.
11. Tajbakhsh A, Gheibi Hayat SM, Taghizadeh H, et al. COVID-19 and cardiac injury: clinical manifestations, biomarkers, mechanisms, diagnosis, treatment, and follow up. Expert Rev Anti Infect Ther. 2021; 19(3): 345–357, doi: 10.1080/14787210.2020.1822737, indexed in Pubmed: 32921216.
12. Wańha W, Wybraniec M, Kapłon-Cieślicka A, et al. Myocardial infarction in the shadow of COVID-19. Cardiol J. 2020; 27(5): 478–480, doi: 10.5603/CJ.2020.0152, indexed in Pubmed: 33165896.
13. Sip M, Puslecki M, Dabrowski M, et al. Implementation of extended cardiopulmonary resuscitation procedure in in-hospital cardiac arrest: a preliminary simulated study. Dis Emerg Med J. 2021; 6(1): 10–20, doi: 10.5603/demj.a2021.0002.
14. Lorente-Ros A, Monteagudo Ruiz JM, Rincón LM, et al. Myocardial injury determination improves risk stratification and predicts mortality in COVID-19 patients. Cardiol J. 2020; 27(5): 489–496, doi: 10.5603/CJ.a2020.0089, indexed in Pubmed: 32589258.
15. Fan L, Jiang S, Yang X, et al. COVID-19 drug treatment in China. Curr Pharmacol Rep. 2020 [Epub ahead of print]: 1–9, doi: 10.1007/s40495-020-00218-5, indexed in Pubmed: 32837851.
16. Khuroo MS, Khuroo M, Khuroo MS, et al. COVID-19 vaccines: a race against time in the middle of death and devastation! J Clin Exp Hepatol. 2020; 10(6): 610–621, doi: 10.1016/j.jceh.2020.06.003, indexed in Pubmed: 32837093.
17. Gozhenko A, Szrpk L, Jguszewski MJ. COVID-19 vccine — third dose, booster dose? Wht is it nd is it necessry? Dis Emerg Med J. 2021, doi: 10.5603/DEMJ.a2021.0027.
18. Shao F, Xu S, Ma X, et al. In-hospital cardiac arrest outcomes among patients with COVID-19 pneumonia in Wuhan, China. Resuscitation. 2020; 151: 18–23, doi: 10.1016/j.resuscitation.2020.04.005, indexed in Pubmed: 32283117.
19. Armstrong RA, Kane AD, Kursumovic E, et al. Mortality in patients admitted to intensive care with COVID-19: an updated systematic review and meta-analysis of observational studies. Anaesthesia. 2021; 76(4): 537–548, doi: 10.1111/anae.15425, indexed in Pubmed: 33525063.
20. Szarpak L, Borkowska M, Peacock FW, et al. Characteristics and outcomes of in-hospital cardiac arrest in COVID-19. A systematic review and meta-analysis. Cardiol J. 2021; 28(4): 503–508, doi: 10.5603/CJ.a2021.0043, indexed in Pubmed: 33942278.
21. Borkowska MJ, Smereka J, Safiejko K, et al. Out-of-hospital cardiac arrest treated by emergency medical service teams during COVID-19 pandemic: A retrospective cohort study. Cardiol J. 2021; 28(1): 15–22, doi: 10.5603/CJ.a2020.0135, indexed in Pubmed: 33140396.
22. Lim D, Park SYi, Choi B, et al. The comparison of emergency medical service responses to and outcomes of out-of-hospital cardiac arrest before and during the COVID-19 pandemic in an area of Korea. J Korean Med Sci. 2021; 36(36): e255, doi: 10.3346/jkms.2021.36.e255, indexed in Pubmed: 34519188.
23. Ludwin K, Bialka S, Czyzewski L, et al. Video laryngoscopy for endotracheal intubation of adult patients with suspected/confirmed COVID-19. A systematic review and meta-analysis of randomized controlled trials. Dis Emerg Med J. 2020, doi: 10.5603/demj.a2020.0023.
24. Szarpak L, Ruetzler K, Dabrowski M, et al. Dilemmas in resuscitation of COVID-19 patients based on current evidence. Cardiol J. 2020; 27(3): 327–328, doi: 10.5603/CJ.a2020.0066, indexed in Pubmed: 32419130.
25. Małysz M, Smereka J, Jaguszewski M, et al. An optimal chest compression technique using personal protective equipment during resuscitation in the COVID-19 pandemic: a randomized

crossover simulation study. Kardiol Pol. 2020; 78(12): 1254–1261, doi: 10.33963/KP.15643, indexed in Pubmed: 33047942.
26. Malysz M, Dabrowski M, Böttiger BW, et al. Resuscitation of the patient with suspected/confirmed COVID-19 when wearing personal protective equipment: A randomized multicenter crossover simulation trial. Cardiol J. 2020; 27(5): 497–506, doi: 10.5603/CJ.a2020.0068, indexed in Pubmed: 32419128.
27. Malysz M, Jaguszewski M, Szarpak L, et al. Comparison of different chest compression positions for use while wearing CBRN-PPE: a randomized crossover simulation trial. Dis Emerg Med J. 2020, doi: 10.5603/demj.a2020.0034.
28. Bhatnagar A, Khraishah H, Lee J, et al. Rapid implementation of a mechanical chest compression device for in-hospital cardiac arrest during the COVID-19 pandemic. Resuscitation. 2020; 156: 4–5, doi: 10.1016/j.resuscitation.2020.08.122, indexed in Pubmed: 32866550.
29. Page MJ, McKenzie JE, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021; 372: n160, doi: 10.1136/bmj.n160, indexed in Pubmed: 33781993.
30. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005; 5: 13, doi: 10.1186/1471-2288-5-13, indexed in Pubmed: 15840177.
31. Ades AE, Lu G, Higgins J. The interpretation of random-effects meta-analysis in decision models. Med Decis Making. 2016; 25(6): 646–654, doi: 10.1177/0272989x05282643, indexed in Pubmed: 16282215.
32. Lyu T, Khan F, Sajeed S, et al. In-hospital cardiac arrest incidence and outcomes in the era of COVID-19: an observational study in a Singapore hospital. Int J Emerg Med. 2021; 14(1): 33, doi: 10.1186/s12245-021-00356-7, indexed in Pubmed: 34058983.
33. Aldabagh M, Wagle S, Cesa M, et al. Survival of in-hospital cardiac arrest in COVID-19 infected patients. Healthcare (Basel). 2021; 9(10), doi: 10.3390/healthcare9101315, indexed in Pubmed: 34682995.
34. Miles JA, Mejia M, Rios S, et al. Characteristics and outcomes of in-hospital cardiac arrest events during the COVID-19 pandemic: a single-center experience from a new york city public hospital. Circ Cardiovasc Qual Outcomes. 2020; 13(11): e007303, doi: 10.1161/CIRCOUTCOMES.120.007303, indexed in Pubmed: 32975134.
35. Roedl K, Söffker G, Fischer D, et al. Effects of COVID-19 on in-hospital cardiac arrest: incidence, causes, and outcome — a retrospective cohort study. Scand J Trauma Resusc Emerg Med. 2021; 29(1): 30, doi: 10.1186/s13049-021-00846-w, indexed in Pubmed: 33557923.
36. Sultanian P, Lundgren P, Strömsöe A, et al. Cardiac arrest in COVID-19: characteristics and outcomes of in- and out-of-hospital cardiac arrest. A report from the Swedish Registry for Cardiopulmonary Resuscitation. Eur Heart J. 2021; 42(11): 1094–1106, doi: 10.1093/eurheartj/ehaa1067, indexed in Pubmed: 33543259.
37. Tong SKi, Ling L, Zhang JZ, et al. Effect of the COVID-19 pandemic on cardiac arrest resuscitation practices and outcomes in non-COVID-19 patients. J Intensive Care. 2021; 9(1): 55, doi: 10.1186/s40560-021-00570-8, indexed in Pubmed: 34507622.
38. Yuriditsky E, Mitchell OJL, Brosnahan SB, et al. Clinical characteristics and outcomes of in-hospital cardiac arrest among patients with and without COVID-19. Resusc Plus. 2020; 4: 100054, doi: 10.1016/j.resplu.2020.100054, indexed in Pubmed: 33403368.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2021, Vol. 28, No. 6, 825–830
DOI: 10.5603/CJ.a2021.0093

ISSN 1897–5593
eISSN 1898–018X

Transfermoral transcatheter aortic valve implantation using self-expanding Allegra bioprosthesis: One-year single-center outcomes

Joanna Milan[1]*, Mirosław Gozdek[2, 3, 4]*, Radosław Targoński[8], Mariusz Kowalewski[4, 5, 6], Aleksandra Stańska[8], Marcin Fijałkowski[1], Romuald Lango[7], Miłosz Jaguszewski[1], Dariusz Jagielak[8]

[1]1st Department of Cardiology, Medical University of Gdansk, Poland; [2]Department of Cardiology and Internal Medicine, Nicolaus Copernicus University, Collegium Medicum in Bydgoszcz, Poland; [3]Department of Cardiac Surgery, Medinet Heart Center Ltd., Wroclaw, Poland; [4]Thoracic Research Center, Collegium Medicum, Nicolaus Copernicus University, Innovative Medical Forum, Bydgoszcz, Poland; [5]Clinical Department of Cardiac Surgery, Central Clinical Hospital of the Ministry of Interior and Administration, Center of Postgraduate Medical Education, Warsaw, Poland; [6]Department of Cardio-Thoracic Surgery, Heart and Vascular Center, Maastricht University Medical Center, Maastricht, The Netherlands; [7]Department of Cardiac Anesthesiology, Medical University of Gdansk, Poland [8]Department of Cardiac and Vascular Surgery, Medical University of Gdansk, Poland

Abstract

Background: *The NAUTILUS study aimed to evaluate the safety and performance of the Allegra bioprosthesis in high-risk recipients undergoing transcatheter aortic valve implantation and previously reported 30-day outcomes. In the current investigation 1-year results of the trial are presented.*

Methods: *Twenty-seven recipients with severe, symptomatic aortic valve stenosis at high surgical risk, who underwent treatment using the next-generation self-expanding Allegra via transfemoral approach were prospectively enrolled. Clinical endpoints assessed were: mortality, stroke, permanent pacemaker implantation, New York Heart Association class and re-hospitalizations. Prosthetic valve performance evaluation comprised of: mean gradient, effective orifice area and paravalvular leak.*

Results: *Patients were elderly (82.8 ± 4.2 years) and predominantly female (n = 19, 70.4%). All of them were deemed to be at high surgical risk with a mean logistic EuroSCORE of 12.5 ± 6.7. The bioprosthesis was successfully implanted in 92.6% of the cases (n = 25). At 1-year, all-cause mortality was 12.0% (n = 3) and stroke was 4.0% (n = 1). Three (12%) of patients developed complete atrioventricular block and received permanent pacemakers. 84% of patients were in New York Heart Association class II or lower. Need for subsequent hospitalization arose in 48% patients. The echocardiographic assessment confirmed an acceptable hemodynamic profile of the Allegra with low mean transprosthetic gradient (9.5 ± 3.4 mmHg), absence of severe paravalvular leak and a 20%-presence of moderate paravalvular leak.*

Conclusions: *The current follow-up observation study shows that the Allegra was associated with a satisfactory safety profile and hemodynamic performance at 1-year after implantation.* (Cardiol J 2021; 28, 6: 825–830)

Key words: Allegra, NAUTILUS clinical study, transcatheter aortic valve implantation

Address for correspondence: Dr. Mirosław Gozdek, Department of Cardiology and Internal Medicine, Nicolaus Copernicus University, Collegium Medicum in Bydgoszcz, ul. M. Skłodowskiej-Curie 9, 85–094 Bydgoszcz, Poland, e-mail: gozdekm@wp.pl

Received: 29.04.2020 Accepted: 25.01.2021 Early publication date: 17.08.2021

**Both authors equally contributed to the study.*

Introduction

Since its introduction by Cribier in 2007 [1], transcatheter aortic valve implantation (TAVI) has complemented surgical aortic valve replacement (SAVR) in patients with severe symptomatic aortic valve stenosis (AVS). This minimally invasive technique at first presented an opportunity to treat inoperable individuals and ultimately has become common and standard in higher-risk patients. The Allegra TAVI System (NVT, Germany) bioprosthesis is a next-generation, self-expanding device, dedicated for TAVI and is designed to overcome the limitations of first-generation systems including firstly, paravalvular leak (PVL) and the necessity for permanent pacemaker implantation (PPI). The first-in-human clinical trial with implantations of the Allegra took place in 2013 by Wenaweser et al. [2]. To date, several conducted studies showed encouraging short-term outcomes in treating patients with severe aortic native valve stenosis using New Valve Technology (NVT) devices [2–4], but longer-term results are lacking. Herein, are presented 1-year single-center results with the Allegra.

Methods

NAUTILUS (NVT trAnsfemoral mUlticentric aorTIc valve pivotaL stUdy for Safety and effectiveness — DRKS00006042) is a single-arm clinical study conducted at 8 centers in 3 countries (Switzerland, Poland, and Brazil), designed to assess the safety and performance of the Allegra and, as it has been described in detail before, along with implantation protocol [3].

In brief, we previously reported on a single-center's early outcomes with the Allegra (**Suppl. Fig. 1**) implanted in 26 patients accepted by the Heart Team to undergo transfemoral TAVI. All patients suffered from severe, symptomatic AVS and met the NAUTILUS eligibility criteria. The main inclusion criteria were: 1) age ≥ 75 years; 2) symptomatic (New York Heart Association [NYHA] class II or greater), severe degenerative native aortic stenosis (mean transvalvular pressure gradient > 40 mmHg and/or aortic jet velocity > 4.0 m/s and/or aortic valve area of < 1.0 cm^2 [or aortic valve area index ≤ 0.6 cm^2/m^2]); 3) high risk for surgical aortic valve replacement with a logistic EuroSCORE ≥ 20% or documented agreement of the Heart Team that the patient is at high risk for surgery due to frailty and/or coexisting comorbidities. Amongst others, the protocol defined exclusion criteria comprised: 1) unicuspid or bicuspid valve disease; 2) non-calcified aortic valve disease; 3) mixed valve disease with predominant aortic regurgitation greater than 3+ or with associated severe (greater than 3+) mitral regurgitation; 4) aortic annulus size < 19 mm or > 29 mm; 5) type of femoral access, or any other anatomical conditions that prevented the safe placement of an 18 French introducer sheath and manipulation of the TAVI system (e.g. severe femoral-iliac obstructive calcification or tortuosity).

Patients were followed-up for 1 year. Written informed consent was obtained from each participant. The study was approved by the local ethics committee.

The data for the clinical trial was collected prospectively in an outpatient setting by using a dedicated electronic case report form. End points in the analysis included all-cause mortality, stroke, PPI, re-hospitalizations, re-hospitalizations for cardiovascular causes. Most patients underwent transthoracic echocardiography. Hemodynamic prosthesis performance assessment included mean pressure gradient, effective orifice area, presence and grade of PVL. Continuous variables are presented as mean ± standard deviation. Categorical variables are given as frequencies and percentages and were compared by the Fisher exact test. A two-sided p-value < 0.05 was considered statistically significant if applicable. Statistical analysis was performed using STATISTICA 12.0 PL (StatSoft).

Results

Baseline characteristics of the study group is listed in Table 1. The patients' population was elderly with a mean age of 82.8 ± 4.2 years, 70.4% were female and the mean logistic EuroSCORE was 12.5 ± 6.7. Twenty-six patients were implanted with the Allegra valve. The procedure was successfully completed in 25 (92.6%) of them. One individual required open-heart aortic valve replacement due to dislocation of the prosthesis into the left ventricle. The patient selection process and reasons for exclusion of proportions of them are described in **Supplementary Figure 2**. Mean follow-up was 12.4 ± 2.3 months. Three (12%) patients died within the study period. Stroke was recorded in 1 (4%) individual. Three (12%) recipients developed complete atrioventricular block and received permanent pacemakers. Lasting improvement in patients' functional class was noted (Fig. 1). Most individuals (84%) were in II or less NYHA class. Twelve patients (48%) needed rehospitalization during follow-up period.

Table 1. Baseline characteristics and parameters (n = 27).

Age [years]	82.8 ± 4.2
Male	8 (29.6%)
Female	19 (70.4%)
Logistic EuroSCORE [%]	12.5 ± 6.7
Hypertension	22 (81.5%)
Diabetes	14 (51.8%)
COPD	5 (18.5%)
Coronary artery stenosis > 50%	2 (7.4%)
Previous myocardial infarction	7 (25.9%)
Previous coronary surgery	4 (14.8%)
Previous coronary angioplasty	12 (44.4%)
Previous stroke or TIA	1 (3.7%)
Creatinine clearance (< 60 mL/min)	7 (25.9%)
NYHA:	
I	0 (0%)
II	3 (11.1%)
III	23 (85.2%)
IV	1 (3.7%)
Conduction disorders (LBBB, RBBB, AVB)	2 (7.4%)
Pre-existing permanent pacemaker	3 (11.1%)
Aortic valve insufficiency (≥ mild)	11 (40.7%)
Mitral valve insufficiency (≥ mild)	18 (66.7%)

AVB — atrioventricular block; COPD — chronic obstructive pulmonary disease; LBBB — left bundle branch block; NYHA — New York Heart Association functional class; RBBB — right bundle branch block; TIA — transient ischemic attack

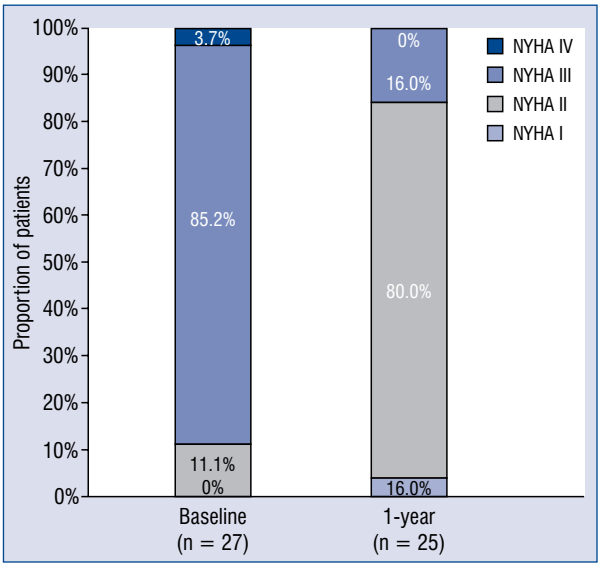


Figure 1. New York Heart Association (NYHA) functional class at baseline and after 1 year of follow-up.

Table 2. Clinical outcomes and adverse events at 1-year follow-up (n = 25).

All-cause mortality	3 (12%)
Cardiovascular mortality	3 (12%)
Myocardial infarction	0 (0%)
Stroke and/or TIA	1 (4%)
Minor bleeding	1 (4%)
Renal failure	1 (4%)
Vascular complication	0 (0%)
Sepsis	2 (8%)
Endocarditis	0 (0%)
Permanent pacemaker implantation	3 (12%)
Valve-related dysfunction requiring repeat procedure	0 (0%)
NYHA:	
I	1 (4%)
II	20 (80%)
III	4 (16%)
IV	0 (0%)
Readmission	12 (48%)
Cause of readmission	
Cardiovascular:	
CHF exacerbation	2 (8%)
Hypertension	2 (8%)
Complete AVB	1 (4%)
Supraventricular arrhythmia	1 (4%)
Stroke	1 (4%)
Other:	
Sepsis	1 (4%)
Delirium	1 (4%)
Dehydration	1 (4%)
Bronchitis	1 (4%)
Infection of the wound	1 (4%)

AVB — atrioventricular block; CHF— chronic heart failure; NYHA — New York Heart Association; TIA — transient ischemic attack

Seven individuals (58%) had cardiovascular reason for subsequent hospital stay, but none was prosthesis-related. The cardiovscular causes were: chronic heart failure exacerbation in two patients, hypertension in another two, complete atrio-ventricular block, supraventricular arrhythmia and stroke (Table 2).

The echocardiographic assessment on follow-up showed excellent hemodynamic performance. The study group had a low mean transprosthetic gradient (9.5 ± 3.4 mmHg) and suitable effective aortic orifice area (1.48 ± 0.39 cm^2). The major-

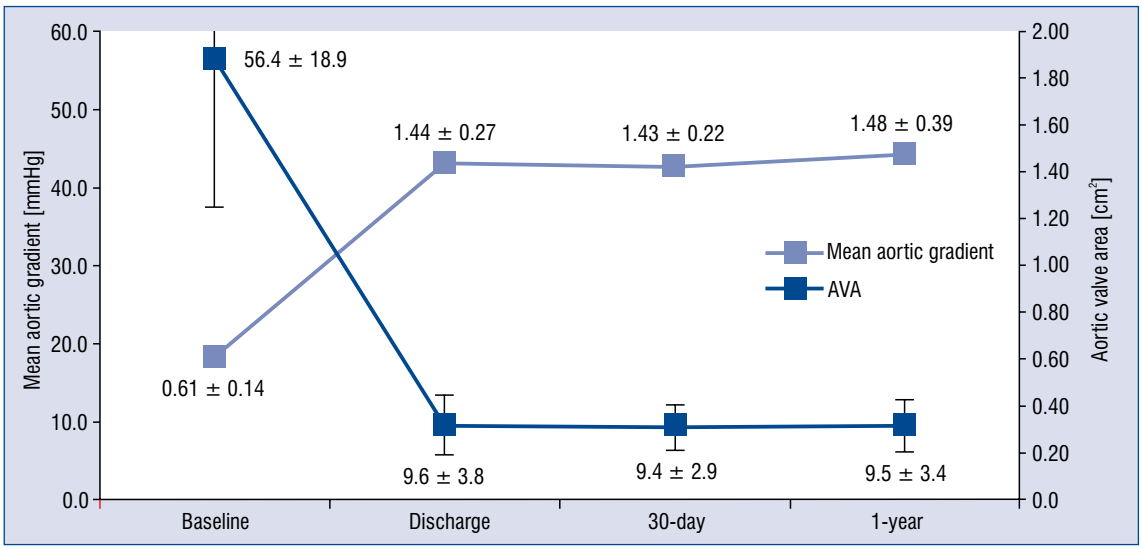


Figure 2. Analysis of mean transprosthetic gradient and aortic valve area (AVA) before and after transcatheter aortic valve implantation.

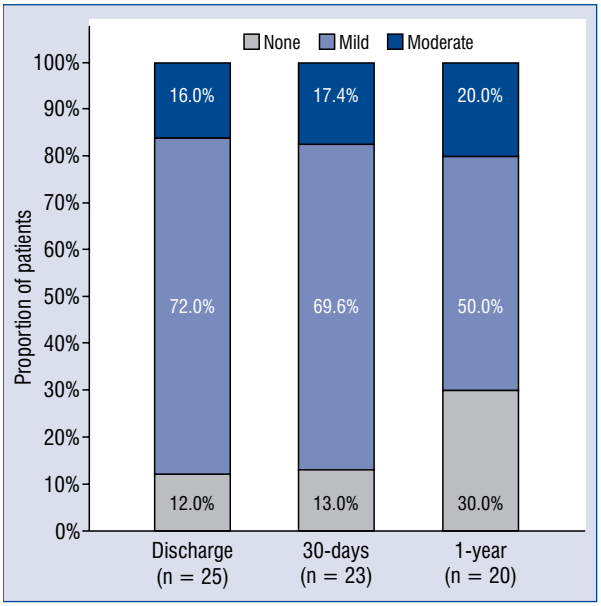


Figure 3. Analysis of paravalvular leak in observations.

ity of patients (80.0%) had only mild or less PVL, while 20% moderate and 0% severe were noted. Figures 2 and 3 present changes of prosthetic aortic valve area, mean transprosthetic gradient and paraprosthetic leak in the study population during observation.

Discussion

The current study is the single-center experience of the next-generation, self-expanding, transcatheter and transfemoral Allegra bioprosthesis and, according to available research, is the only one that presents outcomes in long-term follow-up. The study revealed a favorable valve hemodynamic profile with low transvalvular gradient and no severe PVLs. Three deaths, one cerebrovascular incident, as well as a low rate of permanent pacemaker implantation (12%) were recorded during the follow-up period. Twelve patients needed subsequent hospitalization.

The study revealed no severe PVL. However, 20% moderate and 50% mild PVLs occurred in the Allegra recipients at 1-year. Only two transcatheter devices were commercially available within the initial few years after the first procedure: the self-expandable CoreValve (Medtronic, USA) and the balloon-expandable Sapien (Edwards Lifesciences Corporation, USA). Early-generation transcatheter valves, despite providing good clinical outcomes, were not free from shortcomings such as a high rate of conduction abnormalities demanding PPI, vascular complications or more importantly a higher incidence of PVL, which was consequently associated with increased late mortality and higher rate of other adverse clinical incidents as compared to SAVR [5, 6]. Several potential causes of PVL such as severe native valve calcification, suboptimal artificial valve sizing, positioning and deployment, and prosthesis construction itself are universally reported across available literature. To minimize these shortcomings technological innovations, with respect to both delivery systems and the valve itself were developed in next-generations

devices, including the Allegra. The outer part of the valve's stent is covered by 12-mm bovine pericardial sealing skirt reducing the risk of significant paravalvular leak. The NVT system is able to reposition and retrieve the prosthesis in case of malposition or a suboptimal result. The Allegra valve has features allowing for very precise positioning. The presence of radiopaque markers in the delivery system as well as at the transition between the annular skirt and the bottom of the leaflets markedly facilitates the procedure, by enabling direct and clear visualization of the optimal implantation height and the limits of the sealing skirt.

A different grade of PVL was a common complication of early-generation TAVI devices and was associated with worse survival [7, 8]. Moreover, long-term follow-up data suggested that even mild paravalvular regurgitation was associated with increased late mortality with the balloon-expandable Sapien [5] and with the self-expandable CoreValve, early-generation valves [9, 10]. Moderate to severe PVL occurred in 7.8% of CoreVale implantations and mild paravalvular aortic regurgitation was reached in one-third of cases in 1-year observation by Adams et al. [11] as well as 4.2% and 29.1%, respectively, in a study by Popma et al. [12]. The next iteration of the Medtronic valve, the Evolut R, was associated with 1.2% of moderate PVL at 1-year observation by Manoharan et al. [13]. Newer-generation, self-expanded the Acurate neo (Boston Scientific) in study by Mauri et al. [14] presented no severe, 3.9% moderate and 47.1% mild PVL at 1-year follow-up.

Popma et al. [12] revealed that the frequency of moderate or severe PVL was lower 12 months after CoreValve TAVI (4.2%) than at discharge (10.7%). Oh reported 83% of CoreValve recipients have at least one degree of regression in PVL during 1-year follow-up [15]. Structural properties of nitinol-based frame are probably the explanation of this phenomenon. Progressive expansion of the self-expanding valve improved paravalvular sealing. Results of the current study confirm the trend of decreasing PVL frequency over time, but only concerning mild PVL.

The overall risk of the early permanent atrioventricular conduction disturbances and need for PPI following TAVI procedures varies, but remains around 17% [16]. In comparison to the balloon-expandable valves, the self-expandable TAVI prostheses have a slightly higher rate of postprocedural atrio-ventricular conduction block requiring pacemaker implantation (28%) [17, 18]. In our study only 12% of patients required PPI in longer follow-up compared to 8% in 30-day observation. In comparison to other self-expandable older and newer-generation prostheses. This is a very promising result. Adams et al. [11] and Popma et al. [12] reported 22.3% and 26.2% need of PPI for CoreValve, Manoharan [13] 19.7% for Evolut R recipients in 1-year. Such a good result may be related to a high valve implantation facilitated by refined deployment technology and the Allegra design. However, it seems atrio-ventricular conduction disturbances revealed a month after the procedure are rather not related to TAVI.

The effect of PPI on long-term outcomes after TAVI remains inconclusive [19, 20]. Post-TAVI PPI was reported as an independent predictor of 1-year mortality [19] and was also associated with a longer duration of hospitalization and higher rates of re-hospitalization at 1 year [21]. In contrast, an analysis including more than 1500 TAVI procedures the need for PPI did not increase overall mortality, cardiovascular death or re-hospitalization for heart failure within 2 years [22]. Moreover, Engborg et al. [23] reported even higher survival rate in TAVI--patients with a permanent pacemaker implanted.

The present study revealed 12% of mortality. In the article by Adams et al. [11] as well as by Popma et al. [12] concerning 1-year results after TAVI utilizing the early-generation self-expandable CoreValve, mortality was estimated at 13.9% and 24.3%, respectively. With regards to the next-generation devices, Manoharan et al. [13] reported 8.9% of mortality among Evolut R self-expandable prosthetic valve recipients at high or greater surgical risk. In turn, Barth et al. [24] and Mauri et al. [14] in studies with the self-expandable Acurate neo implanted in the high surgical risk patients revealed 16.9% and 8.3% mortality ratios in 1-year observations, respectively.

In the current investigation, despite a disturbingly high rate of moderate and mild PVL, mortality remains low, lower than recorded in early generation self-expandable valves and is comparable with the other next-generation devices.

These results suggest that the Allegra has an acceptable efficacy profile in treating elderly patients with severe symptomatic AVS, although further studies are warranted to fully elucidate this issue.

The present study has some important limitations. It is an observational, single-arm study of a small sample size which, per se, precludes any in-depth comparison against a control group or detailed analyses related to uncommonly occurring events.

Conclusions

This prospective study shows a good safety and performance profile of the Allegra. The valve has a satisfactory hemodynamic performance and encouraging clinical results with a low rate of pacemaker implantations.

Conflict of interest: None declared

References

1. Cribier A, Eltchaninoff H, Bash A, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation. 2002; 106(24): 3006–3008, doi: 10.1161/01.cir.0000047200.36165.b8, indexed in Pubmed: 12473543.
2. Wenaweser P, Stortecky S, Schütz T, et al. Transcatheter aortic valve implantation with the NVT Allegra transcatheter heart valve system: first-in-human experience with a novel self-expanding transcatheter heart valve. EuroIntervention. 2016; 12(1): 71–77, doi: 10.4244/EIJV12I1A13, indexed in Pubmed: 27173865.
3. Jagielak D, Stanska A, Klapkowski A, et al. Transfermoral aortic valve implantation using self-expanding New Valve Technology (NVT) Allegra bioprosthesis: A pilot prospective study. Cardiol J. 2021; 28(3): 384–390, doi: 10.5603/CJ.a2019.0019, indexed in Pubmed: 30761515.
4. Cuevas O, Moreno R, Pascual-Tejerina V, et al. The Allegra transcatheter heart valve: European multicentre experience with a novel self-expanding transcatheter aortic valve. EuroIntervention. 2019; 15(1): 71–73, doi: 10.4244/EIJ-D-18-00861, indexed in Pubmed: 30777839.
5. Kodali S, Williams M, Smith C, et al. Two-Year Outcomes after Transcatheter or Surgical Aortic-Valve Replacement. N Engl J Med. 2012; 366(18): 1686–1695, doi: 10.1056/nejmoa1200384.
6. Jones BM, Tuzcu EM, Krishnaswamy A, et al. Prognostic significance of mild aortic regurgitation in predicting mortality after transcatheter aortic valve replacement. J Thorac Cardiovasc Surg. 2016; 152(3): 783–790, doi: 10.1016/j.jtcvs.2016.05.023, indexed in Pubmed: 27321435.
7. Tamburino C, Capodanno D, Ramondo A, et al. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. Circulation. 2011; 123(3): 299–308, doi: 10.1161/CIRCULATIONAHA.110.946533, indexed in Pubmed: 21220731.
8. Athappan G, Patvardhan E, Tuzcu EM, et al. Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: meta-analysis and systematic review of literature. J Am Coll Cardiol. 2013; 61(15): 1585–1595, doi: 10.1016/j.jacc.2013.01.047, indexed in Pubmed: 23500308.
9. Jones BM, Tuzcu EM, Krishnaswamy A, et al. Prognostic significance of mild aortic regurgitation in predicting mortality after transcatheter aortic valve replacement. J Thorac Cardiovasc Surg. 2016; 152(3): 783–790, doi: 10.1016/j.jtcvs.2016.05.023, indexed in Pubmed: 27321435.
10. Little SH, Oh JK, Gillam L, et al. Self-Expanding transcatheter aortic valve replacement versus surgical valve replacement in patients at high risk for surgery: a study of echocardiographic change and risk prediction. Circ Cardiovasc Interv. 2016; 9(6), doi: 10.1161/CIRCINTERVENTIONS.115.003426, indexed in Pubmed: 27313280.
11. Adams DH, Popma JJ, Reardon MJ, et al. U.S. CoreValve Clinical Investigators. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med. 2014; 370(19): 1790–1798, doi: 10.1056/NEJMoa1400590, indexed in Pubmed: 24678937.
12. Popma J, Adams D, Reardon M, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. J Am Coll Cardiol. 2014; 63(19): 1972–1981, doi: 10.1016/j.jacc.2014.02.556.
13. Manoharan G, Van Mieghem NM, Windecker S, et al. 1-Year outcomes with the evolut r self-expanding transcatheter aortic valve: from the international FORWARD study. JACC Cardiovasc Interv. 2018; 11(22): 2326–2334, doi: 10.1016/j.jcin.2018.07.032, indexed in Pubmed: 30466832.
14. Mauri V, Kim WK, Abumayyaleh M, et al. Short-Term outcome and hemodynamic performance of next-generation self-expanding versus balloon-expandable transcatheter aortic valves in patients with small aortic annulus: a multicenter propensity-matched comparison. Circ Cardiovasc Interv. 2017; 10(10), doi: 10.1161/CIRCINTERVENTIONS.117.005013, indexed in Pubmed: 28951395.
15. Oh JK, Little SH, Abdelmoneim SS, et al. CoreValve U.S. Pivotal Trial Clinical Investigators. Regression of Paravalvular Aortic Regurgitation and Remodeling of Self-Expanding Transcatheter Aortic Valve: An Observation From the CoreValve U.S. Pivotal Trial. JACC Cardiovasc Imaging. 2015; 8(12): 1364–1375, doi: 10.1016/j.jcmg.2015.07.012, indexed in Pubmed: 26508386.
16. Siontis GCM, Jüni P, Pilgrim T, et al. Predictors of permanent pacemaker implantation in patients with severe aortic stenosis undergoing TAVR: a meta-analysis. J Am Coll Cardiol. 2014; 64(2): 129–140, doi: 10.1016/j.jacc.2014.04.033, indexed in Pubmed: 25011716.
17. Hayashida K, Morice MC, Chevalier B, et al. Sex-related differences in clinical presentation and outcome of transcatheter aortic valve implantation for severe aortic stenosis. J Am Coll Cardiol. 2012; 59(6): 566–571, doi: 10.1016/j.jacc.2011.10.877, indexed in Pubmed: 22300690.
18. Khawaja MZ, Rajani R, Cook A, et al. Permanent pacemaker insertion after CoreValve transcatheter aortic valve implantation: incidence and contributing factors (the UK CoreValve Collaborative). Circulation. 2011; 123(9): 951–960, doi: 10.1161/CIRCULATIONAHA.109.927152, indexed in Pubmed: 21339482.
19. Buellesfeld L, Stortecky S, Heg D, et al. Impact of permanent pacemaker implantation on clinical outcome among patients undergoing transcatheter aortic valve implantation. J Am Coll Cardiol. 2012; 60(6): 493–501, doi: 10.1016/j.jacc.2012.03.054, indexed in Pubmed: 22726632.
20. Dizon JM, Nazif TM, Hess PL, et al. PARTNER Publications Office. Chronic pacing and adverse outcomes after transcatheter aortic valve implantation. Heart. 2015; 101(20): 1665–1671, doi: 10.1136/heartjnl-2015-307666, indexed in Pubmed: 26261157.
21. Nazif TM, Dizon JM, Hahn RT, et al. Predictors and clinical outcomes of permanent pacemaker implantation after transcatheter aortic valve replacement: the PARTNER (placement of aortic transcatheter valves) trial and registry. J Am Coll Cardiol Intv. 2015; 8: 60–69, doi: 10.1016/j.jcin.2014.07.022, indexed in Pubmed: 25616819.
22. Urena M, Webb JG, Tamburino C, et al. Permanent pacemaker implantation after transcatheter aortic valve implantation: impact on late clinical outcomes and left ventricular function. Circulation. 2014; 129(11): 1233–1243, doi: 10.1161/CIRCULATIONAHA.113.005479, indexed in Pubmed: 24370552.
23. Engborg J, Riechel-Sarup C, Gerke O, et al. Effect of permanent pacemaker on mortality after transcatheter aortic valve replacement. Scand Cardiovasc J. 2017; 51(1): 40–46, doi: 10.1080/14017431.2016.1236982, indexed in Pubmed: 27624406.
24. Barth S, Reents W, Zacher M, et al. Multicentre propensity-matched comparison of transcatheter aortic valve implantation using the ACURATE TA/neo self-expanding versus the SAPIEN 3 balloon-expandable prosthesis. EuroIntervention. 2019; 15(10): 884–891, doi: 10.4244/EIJ-D-18-01120, indexed in Pubmed: 31270034.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2021, Vol. 28, No. 6, 831–841
DOI: 10.5603/CJ.a2021.0080

ISSN 1897–5593
eISSN 1898–018X

Optimal fluoroscopic viewing angles for stenting of the coronary aorto-ostial lesions

Radosław Targoński[1], Jarosław Meyer-Szary[2], Bartosz Baścik[3], Edyta Szurowska[3], Aleksandra Gąsecka[4], Dariusz Jagielak[1], Miłosz J. Jaguszewski[5]

[1]Department of Cardiac and Vascular Surgery, Medical University of Gdansk, Poland
[2]Department of Pediatric Cardiology and Congenital Heart Diseases, Medical University of Gdansk, Poland
[3]Department of Radiology, Medical University of Gdansk, Poland
[4]First Chair and Department of Cardiology, Medical University of Warsaw, Poland
[5]First Department of Cardiology, Medical University of Gdansk, Poland

This paper was guest edited by Prof. Zenon Huczek

Abstract

Background: *Long-term results after stenting aorto-coronary ostial lesions (AOL) are worse than those achieved in non-ostial locations. AOL interventions still pose a substantial challenge for interventional cardiologists. The aim of the study was to determine the optimal fluoroscopic viewing angles of the left and right coronary ostia, based on multislice computed tomography (MSCT) data.*

Methods: *Cardiac MSCT exams of 30 patients with clinical suspicion of coronary artery disease were analyzed. En face angles of both coronary ostia, as well as their optimal projection curves, were determined by 2 independent observers in a standard Dicom viewer, without any additional, specialized software add-ons, using a systematic, step-by-step approach. Spatial relations between the ostial plane and the aorta were also assessed.*

Results: *The average en face angle of the left coronary ostium was RAO 23°, CAU 45°; for the right coronary ostium RAO 18°, CRA 5°. The mean inter-observer differences for the en face angles of the left and right coronary arteries were 5° and 7°, respectively.*

Conclusions: *Multislice computed tomography data provide precise spatial information on the orientation of the coronary ostia and their relation to the aortic root. Their utilization for determining the patient-specific viewing angle may substantially facilitate percutaneous coronary interventions in AOL.*
(Cardiol J 2021; 28, 6: 831–841)

Key words: aorto-ostial lesions, coronary intervention, optimal projection curves, multislice computed tomography, cardiovascular imaging

Introduction

Despite constant advances in technology, interventions of the coronary ostia still pose a substantial challenge for interventional cardiologists. Long-term results after stenting of the aorto-coronary ostial lesions (AOL) are worse than those achieved in non-ostial locations [1, 2]. The gap results partly from differences in the plaque composition, which is more rigid, calcified, and bulky in the case of AOL [3, 4]. A lot of target lesion failures are due to technical problems during

Address for correspondence: Radosław Targoński, MD, PhD, Department of Cardiac and Vascular Surgery, Medical University of Gdansk, ul. Sklodowskiej-Curie 3a, 80–210 Gdańsk, Poland, tel: +48 607 921 300, fax: +48 58 584 42 10, e-mail: rtargonski@gmail.com

Received: 15.03.2021 Accepted: 16.07.2021 Early publication date: 2.08.2021

the procedure, resulting in overly deep stent implantation and incomplete coverage of the treated lesion [5]. On the other hand, excessive protrusion of the stent into the aorta also has negative consequences because it can hinder re-engagement of the vessel with the catheter or seriously complicate subsequent interventions on the aortic valve [6, 7]. Over the last several years, multi-sliced computed tomography (MSCT) has emerged as a useful tool in the assessment of coronary artery disease (CAD) [8–10]. This diagnostic modality offers a unique view into the spatial relationships of different cardiac structures and has been proved to be critical in procedure planning and device selection in structural heart interventions [11–14]. However, three-dimensional (3D) data provided by MSCT are still rarely used to facilitate percutaneous coronary interventions (PCI) [15, 16].

The aim of this study was to determine the optimal fluoroscopic viewing angles for AOL stenting with the use of MSCT examinations of patients with CAD. Patient-specific optimization of the viewing angle can potentially decrease/eliminate parallax error [12] and improve the precision of stent implantation in the coronary ostium. We propose a simple, step-by-step approach to find individually optimized projections with the use of patient MSCT data.

Methods

Setting and image acquisition

Multislice computed tomography examinations of 30 patients with clinical suspicion of CAD were retrospectively analyzed. MSCT was performed according to the established institutional protocol, i.e. in spiral/helical acquisition mode with retrospectively electrocardiogram-gated reconstruction, with a tube voltage of 100–120 kV, and tube current adjusted for patient size. 80–110 mL of contrast was injected into the antecubital vein at a rate of 5 mL/s. The dataset of contrast-enhanced scans was reconstructed in the diastolic phase. Images were reconstructed with a slice thickness of 0.6 mm and a reconstruction interval of 0.4 mm.

Image analysis

Multislice computed tomography exams were then analyzed with a standard DICOM viewer (Osirix Pixmeo SARL, Geneva, Switzerland). A step-by-step approach, described in detail in Figure 1, was used to calculate the *en face* angles of the coronary aorto-ostial orifice plane. Based on the determined *en face* angles, optimal projection curves (S-curve) (Fig. 2A) were then calculated in an Excel (Microsoft Corporation Redmond, WA, USA) spreadsheet using the following formula described earlier by the Nicolo Piazza group [17]:

$$Ø = -\arctan\left[\frac{\cos\theta - \theta_{en\ face}}{\tan Ø_{en\ face}}\right]$$

where Ø is the cranio-caudal angle of the optimal projection curve at RAO/LAO angle θ, and $Ø_{en\ face}$ and $\theta_{en\ face}$ are the cranio-caudal and RAO/LAO angles of the structure viewed *en face*, respectively (online version of the S-curve generator is available at https://smartheart.pl/plane-calculator/). The multiplanar reconstruction mode was applied again to define the range of the S-curve in which the adjacent aorta does not overlap with the coronary ostium in the orthogonal angiographic view (Figs. 2B, 3). Each exam was analyzed independently by two cardiologists with experience in cardiac computed tomography (CT) interpretation.

Statistical analysis

En face angles are expressed as mean with 95% confidence interval (CI), taking the average value from both observers. Discrepancies between the investigators were assessed by measuring the average angle between the S-curves produced by each investigator.

The institutional review board approved the study with a waiver of informed consent.

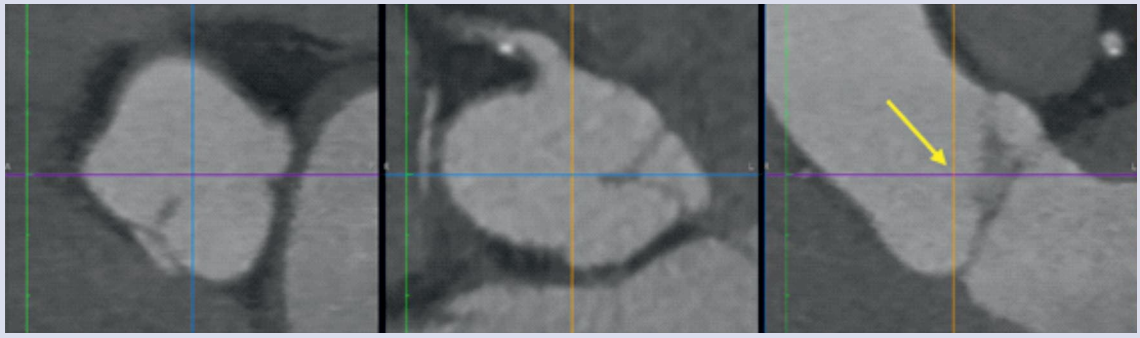
The numerical data underlying this article and the anonymized CT scan data will be shared on reasonable request to the corresponding author.

Results

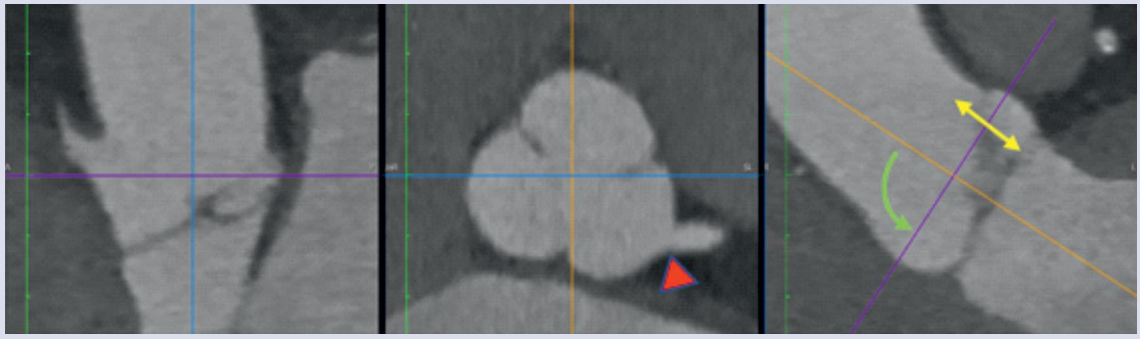
Table 1 presents mean *en face* angles of the left and right coronary ostial planes (RAO 29°, CAU 50°; and RAO 18°, CRA 5°, respectively). The mean inter-observer differences for the *en face* angles of the left and right coronary arteries (LCA, RCA) were 5° and 7°, respectively. The average range of the optimal projection curve in which the left coronary ostium does not overlap with the adjacent aorta was RAO 0° to LAO 68°. In the case of the right coronary ostium S-curve, that range was outside of the RAO 37° to LAO 48° zone (Fig. 4).

Figure 5 shows individual projection curves for each patient, the range of "unobstructed" view, and *en face* angles. Mean optimal projection curves, mean "unobstructed" view ranges, and mean *en face* angles for the left and right coronary ostia with 95% CI are presented in Figure 4.

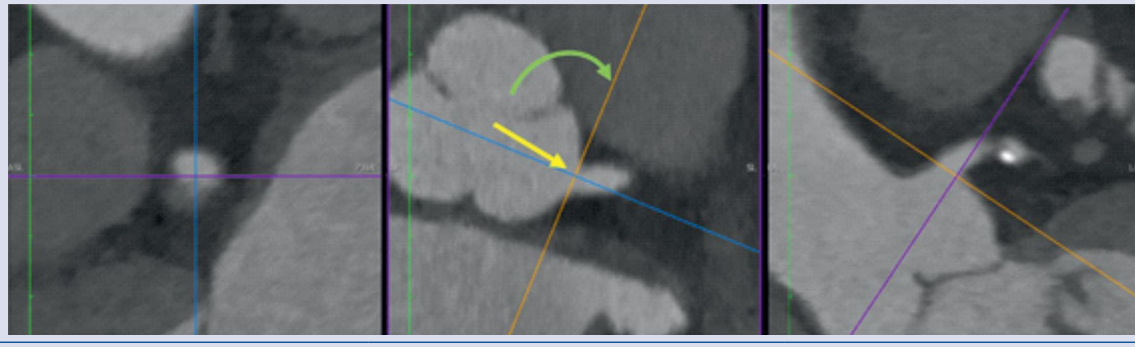
Sagittal plane	Horizontal plane	Coronal plane



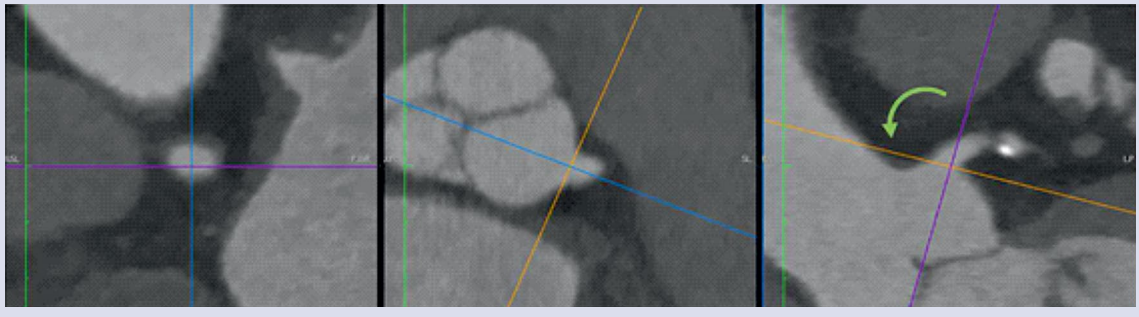
Step 1. Place the crosshair at the center of the aortic root (arrow).



Step 2. In the coronal view window — adjust the horizontal plane (purple line) to be roughly parallel to the aortic annulus (green arrow), then adjust the horizontal plane's position (yellow arrow) to the level of the coronary ostium of interest (red arrowhead).



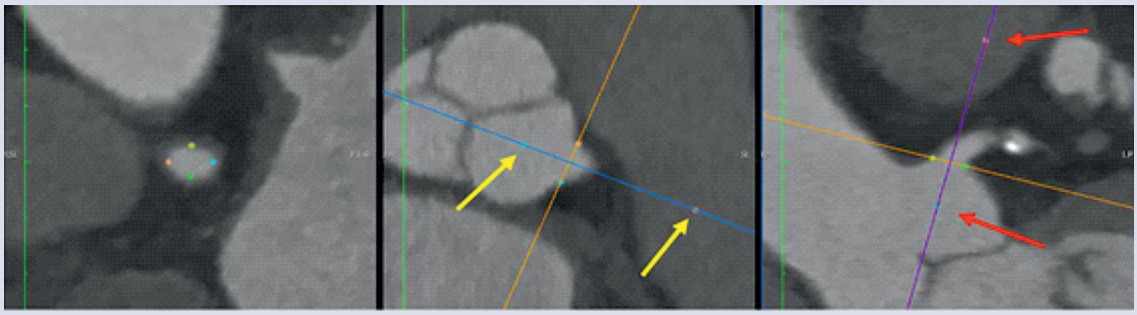
Step 3. In the horizontal view window — move the crosshairs to the center of the coronary ostium (yellow arrow), and align the sagittal plane tangentially (green arrow) to the aortic root at the level of the ostium.



Step 4. In the frontal view window — adjust the sagittal plane tangentially to the aortic root at the level of the ostium (green arrow).

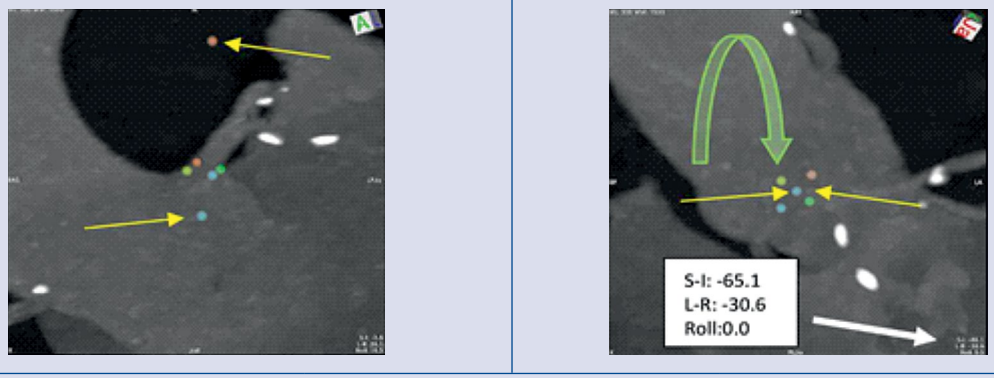
→

Sagittal plane	Horizontal plane	Coronal plane



Step 5. In the frontal view window, place two region of interest (ROI) points on the horizontal plane (purple line, red arrows) — they will also appear on the frontal plane (blue line, yellow arrows) in the horizontal view window. In the sagittal plane, put ROI points at the edges of the coronary ostium.

Before alignment	After alignment



Step 6. Change the view to a three-dimensional maximal intensity projection (3D-MIP) and adjust the brightness and contrast settings to visualize optimally the point region of interest (ROI), then align together the two ROIs marking the axis of the ostial plane (yellow arrows). After the alignment, correct the Roll to 0.0. At that point, the superior-inferior (S-I) angle will reflect the CAU/CRA angulation of the coronary ostium *en face* angle, and the left-right (L-R) angle will reflect the RAO/LAO angulation of the coronary ostium *en face* angle (RAO and CAU angles are in the negative range). Based on the determined *en face* angle, the optimal projection curve (S-curve) is drawn (Fig. 2A); CAU — caudal; CRA — cranial; RAO — right anterior oblique; LAO — left anterior oblique.

Figure 1. Systematic step-by-step approach for identifying the coronary aorto-ostial plane.

Discussion

The present study determined for the first time the optimal fluoroscopic viewing angles of the LCA and RCA based on MSCT data. This study is interesting from many perspectives: i) first and foremost, we propose a systematic step-by-step approach to determine individual optimal angiographic viewing angles for stenting of the coronary ostia based on patient angio-CT data; and ii) it provides a detailed description of the method, together with a graphic illustration of the concept. Our approach does not need any dedicated software and, thus, can be applied widely in the routine clinical practice.

Percutaneous coronary interventions of aorto-ostial lesions remain challenging

Aorto-ostial lesions are usually defined as coronary artery stenosis greater than 50%, within 3 mm of its origin [18]. They constitute around 3% of all percutaneously treated lesions. The procedural success and clinical outcomes of these lesions are inferior to those of non-ostial locations. The difference results partly from the lesions' distinct plaque composition, causing them to be more bulky, non-compliant, and with a greater tendency towards elastic recoil. The lack of adventitia in the transmural segment may also play a role [2, 3, 19]. However, a suboptimal result is very often caused by the challenges of ostial intervention and imprecise stent positioning.

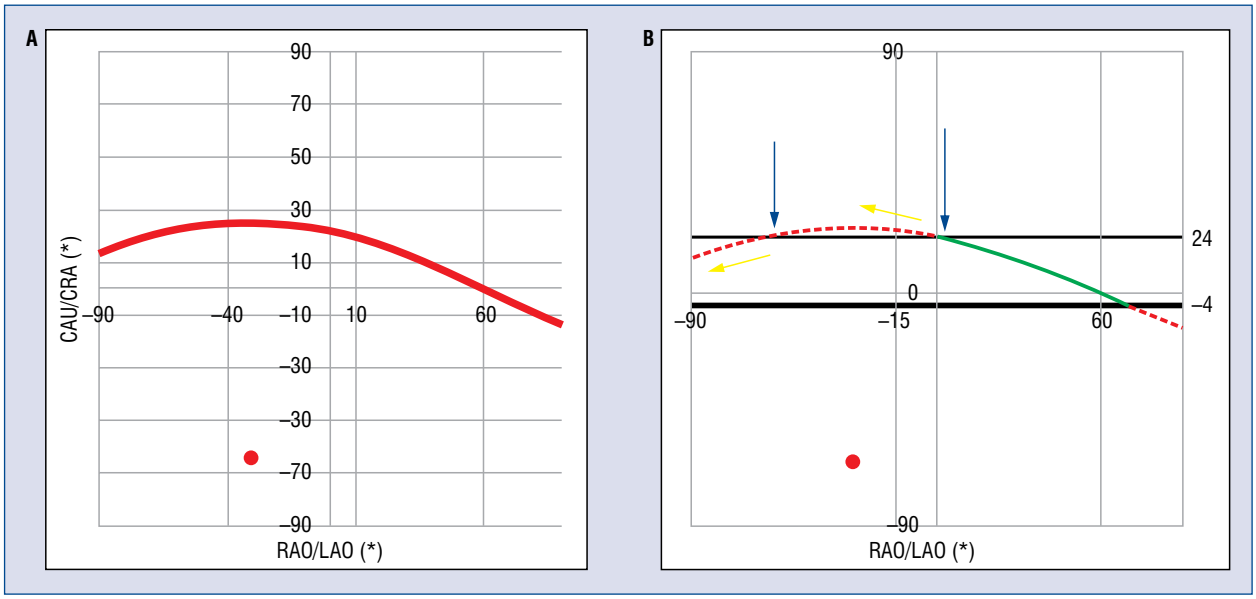
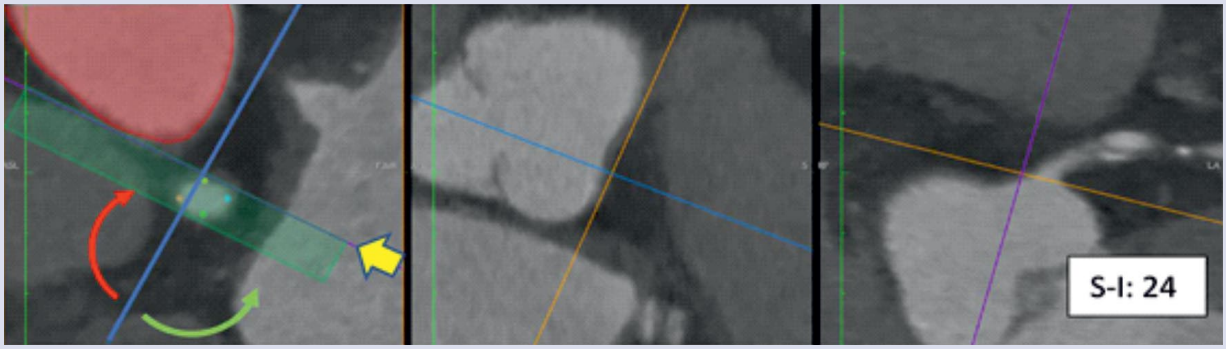


Figure 2. The optimal projection curve based on the determined *en face* angle; **A.** The optimal projection curve (red line) corresponding to the determined *en face* angle of the coronary ostium (red dot); **B.** The range of the optimal projection curve in which the coronary ostium does not overlap with the adjacent aorta. Because determining this range is based on the caudal/cranial (CAU/CRA) angulation, it is crucial to notice that two different points on the S-curve can have the same CAU/CRA angulation value (blue arrows). They can be identified by their relation to the maximal angulation of the curve (yellow arrows). Red dotted lines — "obstructed" view, green line — "unobstructed" view.

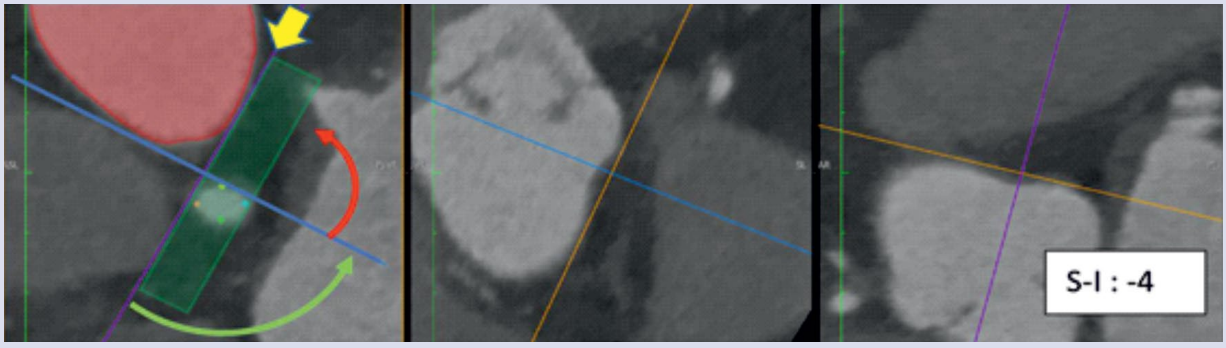
The implanted stent of choice in non-ostial lesions is usually long enough to secure a reasonably safe margin on both sides of the lesion and minimize the risk of a geographic miss. In the case of ostial stenoses, one of the margins is completely absent. A deliberate decision to protrude the stent into the aorta may result in many long-term serious consequences. First, the protruding stent makes all subsequent interventions on that vessel much more difficult. It is harder to engage the vessel with the guiding catheter [20], and attempts to do so can deform the protruding struts, potentially increasing thrombotic risk. A recent analysis from the EXCEL trial clearly showed that PCI of a target vessel after left main (LM) stenting was a strong predictor of overall and cardiovascular mortality at 3 years [21]. Secondly, stent protrusion into the aorta could be a serious problem in patients who require surgical intervention in the future. The inability to selectively cannulate coronary vessels prevents antegrade cardioprotection. Stent struts can also make aortic valve replacement surgery extremely difficult. Intraoperative stent trimming poses the risk of deformation of the intracoronary part of the stent [6]. Finally, there is a continuously growing population of patients admitted for transcatheter aortic valve replacement (TAVR) procedures. In these patients, the protruding stent can be crushed by the delivery balloon or by the valve itself. That risk is best illustrated in Figure 6C, D, where the stent protruding from the LM was crushed by the bulky, calcified valve leaflet during transapical TAVR. The only available arterial access (right radial) was used for pig-tail catheter insertion, preventing LM protection with safety wire and coronary balloon. Despite the patent LIMA-LAD and Ao-Diagonal grafts, the complications turned out to be lethal.

On the other hand, in cases when the operator tries to place the stent precisely, without any protrusion, unintended incomplete coverage of the ostium is common, resulting in a greatly enhanced risk of subsequent restenosis (Fig. 6A, B). In one short series of patients after LM stenting, control MSCT revealed that the stent had been implanted optimally in relation to the ostium only in 3 out of 23 cases [5]. The precise positioning of stents in the coronary ostia is of paramount importance because it can substantially affect long-term clinical success. Unfortunately, angiographic views are plagued with parallax error, and finding a projection orthogonal to the individual aorto-ostial plane is very challenging.

Sagittal plane	Horizontal plane	Coronal plane



Sagittal view from Figure 1, step 6 — the left image — represents the *en face* plane of the coronary ostium. The X-ray source is marked with the yellow arrow. The coronal plane window presents a "slice" of the projected angiographic view. Rotating the horizontal and frontal planes in the sagittal plane window, adjust the axes to the angle where further clockwise rotation (red arrow) would cause the silhouettes of the ostium (green rectangle) and the adjacent aorta (red area) to overlap. The superior-inferior (S-I) angle from the coronal plane window shows the real caudal/cranial (CAU/CRA) angulation of this borderline angiographic projection. Note: During rotation of the horizontal and frontal plane, the S-I angulation shown in the coronal plane window can indicate the same number twice (refer to Figure 2B, blue arrows). It is important to relate this point to the peak S-I angulation of the S-curve. Observing whether further clockwise rotation and overlapping the silhouettes of the ostium and the aorta would cause the S-I value to increase or to decrease (refer to Figure 2B, yellow arrows) enables identification of the correct point on the S-curve.



In the sagittal view window, rotate the horizontal and coronal planes counterclockwise to the angle where further rotation (red arrow) would cause the silhouettes of the ostium (green rectangle) and the adjacent aorta (red area) to overlap. The S-I angle from the coronal plane view shows the real CAU/CRA angulation of this borderline angiographic projection. The range between those two S-I angulations from the coronal plane view window corresponds to the range of the CAU/CRA angle of the optimal projection curve in which the coronary ostium does not overlap with the adjacent aorta (Fig. 2B).

Figure 3. Finding the range of S-curve in which the ostium and the aorta do not overlap with each other.

Table 1. Mean and 95% confidence intervals of *en face* angles of the coronary ostia, and interobserver difference.

En face view	Overall	Observer 1	Observer 2	Difference between observers	Average range of "unobstructed" view
LCA ostium	RAO 29; CAU 50 (RAO 24 – RAO 34; CAU 42 – CAU 58)	RAO 28; CAU 49 (RAO 23 – RAO 33; CAU 41 – CAU 57)	RAO 29; CAU 50 (RAO 24 – RAO 34; CAU 42 – CAU 58)	5 (4–6)	RAO 0 – LAO 68
RCA ostium	RAO 18; CRA 5 (RAO 13 – RAO 23; CAU 2 – CRA 12)	RAO 19; CRA 5 (RAO 14 – RAO 23; CAU 1 – CRA 12)	RAO 18; CRA 5 (RAO 12 – RAO 24; CAU 2 – CRA 12)	7 (6–8)	RAO 90 – RAO 37 and LAO 48 – LAO 90

CAU — caudal angulation; CRA — cranial angulation; LAO — left anterior oblique angulation; RAO — right anterior oblique angulation

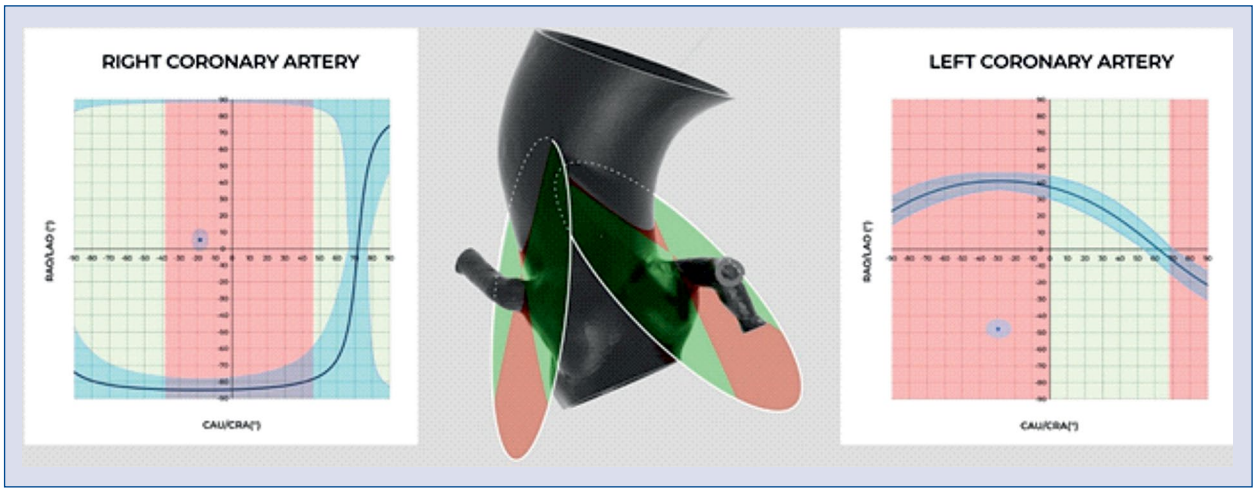


Figure 4. *En face* angles of the right and left coronary ostia and their corresponding optimal projection curves (mean and 95% confidence interval). *En face* angle — blue dot. Optimal projection curve — blue line. The red area indicates the range in which the coronary ostium and the aortic root overlap. Central panel represents schematic illustration of coronary ostia plane in relation to the aortic root.

Accurate image acquisition by using MSCT facilitates PCIs of ostial lesions

Multislice computed tomography provides complete information about the spatial relations between the aortic root, ascending aorta, and coronary vasculature. MSCT data are successfully used for device sizing, procedure planning, and angiographic view optimization during structural cardiac procedures. However, their utilization to facilitate coronary interventions has hitherto been limited, although promising [15, 22]. There are no publications defining an accurate angiographic view for a subsequent coronary procedure based on MSCT image acquisition.

In our study, we propose a simple way of establishing the *en face* angle of the aorto-ostial plane and the corresponding optimal projection curve using a standard DICOM viewer. Results from a group of 30 patients show that the angle of the coronary aorto-ostial plane and its relation to the adjacent aorta are highly variable and patient-specific. In some patients, a large portion of the optimal projection curve of the coronary ostium overlaps with the adjacent aorta, so the range of the "clear" viewing angle is quite limited. In such cases, the ostium is located in the concave part of the aortic root complex (Fig. 7A, C). In other patients in whom the coronary artery has its origin at the convex part of the sinus of Valsalva, it does not overlap with the aorta at any point (Fig. 7B, C). In these scenarios, one should opt for the projection with the smallest CRA/CAU angle.

Taking into account the high variability of coronary ostial planes and aortic configurations, an individual S-curve of the treated ostium should be calculated if an MSCT examination is available. Sometimes in the case of a funnel-shaped ostium, it may be difficult to precisely define anatomical borders. The specific ostium definition can then be fine-tuned according to the planned stenting strategy, i.e. orthogonal to the ostium at the level of the desired stent edge position.

Hitherto, the data regarding the spatial and anatomical location of the coronary ostia in patients admitted for PCI were often not available. However, since MSCT is now a first-line tool for diagnosing CAD in patients with chronic coronary syndromes [23], the availability of these data will be expanding as well. MSCT image interpretation should, therefore, be another skill in the interventional cardiologist's pocket. Nowadays, PCI operators should not just rely on the radiologist's report but should also be able to review MSCT exams by themselves, in order to assess anatomical subtleties of every individual patient and optimize the treatment strategy and viewing angles.

However, in most patients admitted for PCI of the LCA or RCA ostium, procedures are performed routinely only based on the clinical experience and judgment of the operator. This also applies to the choice of angiographic projection. The mean *en face* angles and corresponding optimal projection curves from our study roughly reflect current clinical practice. The optimal projection for stenting the

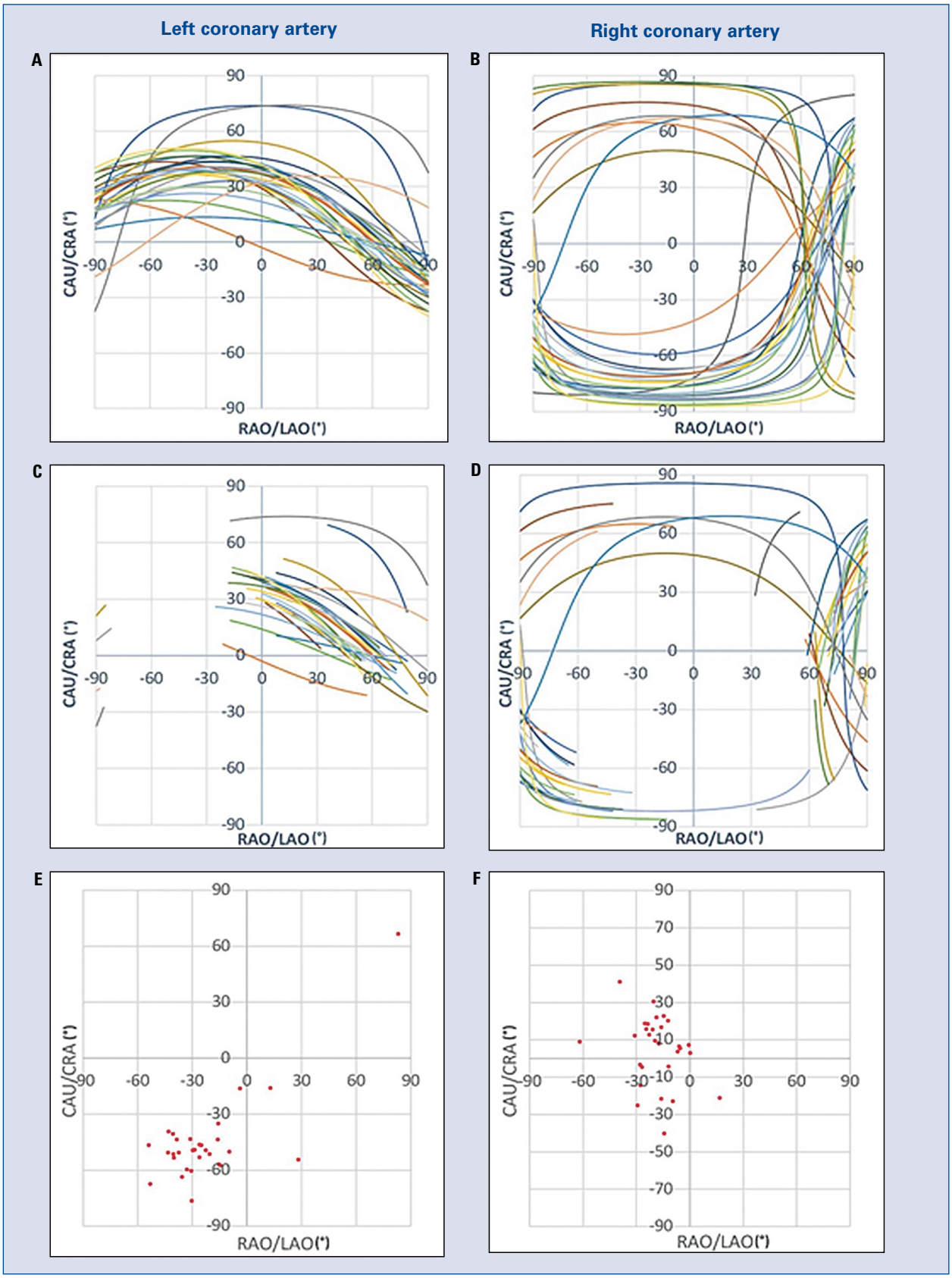


Figure 5. Individual optimal projection curves and *en face* angles in the study cohort. Optimal projection curves for the ostia of the left (**A**) and right coronary arteries (**B**). The range of the optimal projection curves in which neither the left (**C**) nor right coronary ostium (**D**) overlaps with the adjacent aorta. *En face* angles of left (**E**) and right coronary ostia (**F**).

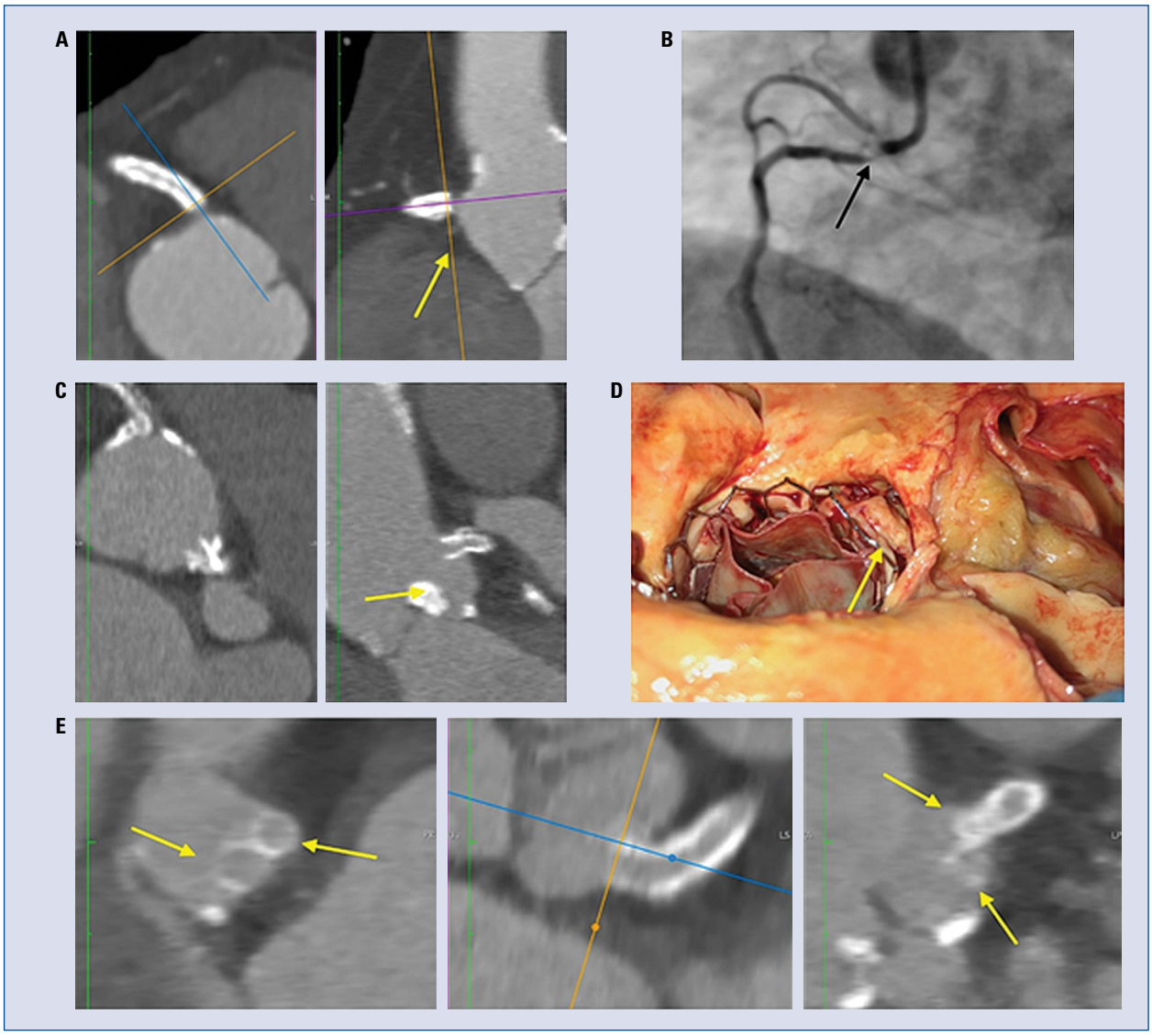


Figure 6. Clinical examples of the suboptimal stent placement in the aorto-coronary ostial lesions. Geographic miss (arrow), stent in the right coronary artery (RCA) implanted too deeply (**A**); subsequent restenosis in the RCA (arrow) (**B**); stent protruding from left main into the aorta (arrow) (**C**); protruding stent crushed (arrow) by the calcified, widened aortic leaflet on postmortem examination (**D**); two stents protruding from the left coronary artery to the aorta (arrows) accidental finding in the patient admitted for transcatheter aortic valve replacement (**E**).

LM ostium is usually in the LAO projection with cranial angulation. The best strategy for finding this optimal projection is to start at around LAO 30–40°, CRA 30° and proceed caudally. In the case of the right coronary ostium plane, most optimal projections will be between LAO 60° and 80° with slight cranial angulation. The best strategy seems to be to start in LAO 60°, CRA 10° and then move east toward LAO 90°.

Although two-dimensional (2D) angiographic images are completely spatially unoriented compared to MSCT data, there is a "life hack" solution for finding a projection perpendicular to the coronary ostium plane. If one aligns the tip of the guiding catheter with the coronary ostium and then finds the projection in which the catheter looks like a straight line with its tip circular, then this corresponds roughly to the ostial plane *en face* angle.

No matter what the CRA/CAU angulation of that ostial plane *en face* angle is, the perpendicular projection will always be located at the position of CRA/CAU 0°, with RAO/LAO angulation equal to the *en face* plane RAO/LAO value plus or minus 90. That may be the starting point for finding the optimal projection and/or calculating the expected/ /approximated S-curve. However, one should keep

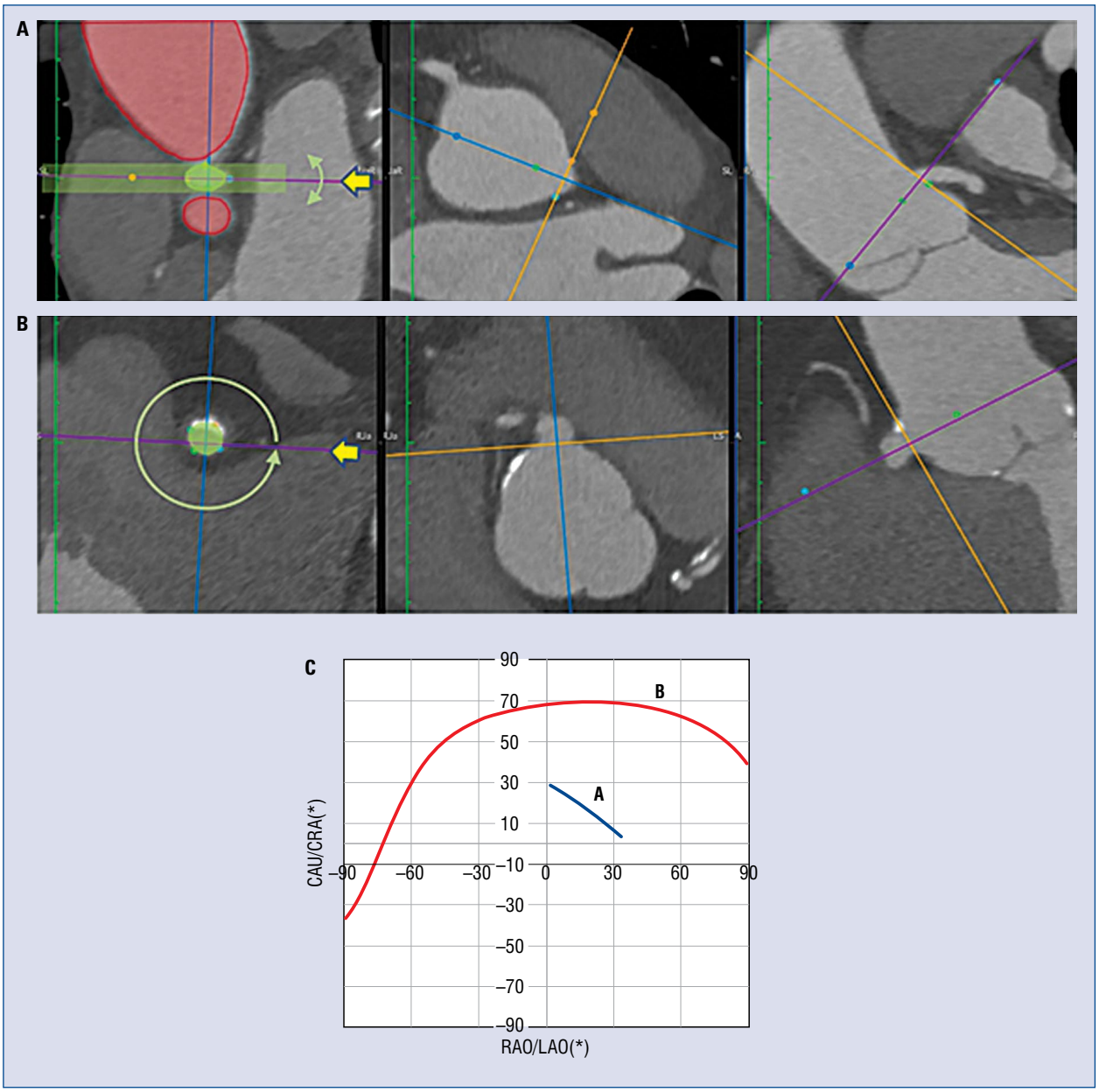


Figure 7. Examples of different aortic root configurations and their impact on the S-curve. Two examples of different aortic root configurations; **A.** A narrow "angiographic window" of the left coronary artery (LCA) ostium (green oval) with a very limited range of possible angulation (green arrow) of the X-ray source (yellow arrow) (adjacent aorta — red area); **B.** A wide "angiographic window" of the right coronary artery (RCA) ostium (green circle), offering a 360-degree view; **C.** The range of the corresponding S-curves in which the coronary ostium does not overlap with the adjacent aorta. In the case of the LCA (blue curve), angiographic viewing angles are limited, but are paradoxically "standard" and easy to achieve, while in the case of the RCA ostium (orange curve), its S-curve is quite atypical and, despite the full range, the degree of cranial angulation in standard left anterior oblique projections makes them unfeasible.

in mind that the tip of the catheter engaged in the coronary ostium is usually oriented upwards. This tendency can be corrected by pushing on the coronary guidewire for better alignment.

Limitations of the study

The main limitation of our study is that the study population consisted of a small group of patients with suspected coronary disease, admitted

for diagnostic CTA, who did not have aorto-ostial lesions, mandating intervention. Thus, the presented data remain experimental. In addition, the data has not been prospectively validated. Third, the method itself is cumbersome. Dedicated software would greatly facilitate the determination of the optimal angle of the coronary ostia. Finally, in the case of structural interventions, a predefined "implantation" projection can easily be corrected during the procedure. This may not be the case with the coronary ostial plane, due to its small size. Altogether, the clinical significance of our method remains to be established.

Conclusions

To overcome the technical challenges of aorto-ostial PCIs, we propose the first systematic step-by-step approach to determine individual fluoroscopic viewing angles for precise stenting by using MSCT image acquisition. The present study shows that, given the substantial variability of the aortic root anatomy, patient-specific implantation angles determined before intervention may essentially facilitate the procedure. The question of whether we should perform MSCT before aorto-ostial PCI for the sake of procedure planning and optimizing its results remains open and needs further prospective investigations.

Conflict of interest: None declared

References

1. Mavromatis K, Ghazzal Z, Veledar E, et al. Comparison of outcomes of percutaneous coronary intervention of ostial versus nonostial narrowing of the major epicardial coronary arteries. Am J Cardiol. 2004; 94(5): 583–587, doi: 10.1016/j.amjcard.2004.05.020, indexed in Pubmed: 15342287.
2. Freeman M, Clark DJ, Andrianopoulos N, et al. Outcomes after percutaneous coronary intervention of ostial lesions in the era of drug-eluting stents. Catheter Cardiovasc Interv. 2009; 73(6): 763–768, doi: 10.1002/ccd.21941, indexed in Pubmed: 19309731.
3. Jokhi P, Curzen N. Percutaneous coronary intervention of ostial lesions. EuroIntervention. 2009; 5(4): 511–514, doi: 10.4244/eijv5i4a81, indexed in Pubmed: 19755342.
4. Vaduganathan M, Harrington RA, Stone GW, et al. Cangrelor with and without glycoprotein iib/iiia inhibitors in patients undergoing percutaneous coronary intervention. J Am Coll Cardiol. 2017; 69(2): 176–185, doi: 10.1016/j.jacc.2016.10.055, indexed in Pubmed: 28081827.
5. Rubinshtein R, Ben-Dov N, Halon DA, et al. Geographic miss with aorto-ostial coronary stent implantation: insights from high-resolution coronary computed tomography angiography. EuroIntervention. 2015; 11(3): 301–307, doi: 10.4244/EIJV11I3A57, indexed in Pubmed: 24694540.
6. Nakamura M, Minakata K, Yamazaki K, et al. Aortic valve replacement in patients with protruding coronary artery stents. J Cardiol Cases. 2014; 10(6): 213–215, doi: 10.1016/j.jccase.2014.07.013, indexed in Pubmed: 30534246.
7. Wintzer-Wehekind J, Larose E, Rodés-Cabau J, et al. Coronary Stent Protruding in the Ascending Aorta: Multimodality Imaging Evaluation. JACC Cardiovasc Interv. 2020; 13(2): 263–264, doi: 10.1016/j.jcin.2019.07.052, indexed in Pubmed: 31563684.
8. Achenbach S. Cardiac CT: state of the art for the detection of coronary arterial stenosis. J Cardiovasc Comput Tomogr. 2007; 1(1): 3–20, doi: 10.1016/j.jcct.2007.04.007, indexed in Pubmed: 19083871.
9. Saremi F, Achenbach S. Coronary plaque characterization using CT. AJR Am J Roentgenol. 2015; 204(3): W249–W260, doi: 10.2214/AJR.14.13760, indexed in Pubmed: 25714309.
10. Hoffmann U, Truong Q, Schoenfeld D, et al. Coronary CT Angiography versus Standard Evaluation in Acute Chest Pain. N Engl J Med. 2012; 367(4): 299–308, doi: 10.1056/nejmoa1201161.
11. Blanke P, Weir-McCall JR, Achenbach S, et al. Computed tomography imaging in the context of transcatheter aortic valve implantation (tavi)/transcatheter aortic valve replacement (TAVR): an expert consensus document of the society of cardiovascular computed tomography. JACC Cardiovasc Imaging. 2019; 12(1): 1–24, doi: 10.1016/j.jcmg.2018.12.003, indexed in Pubmed: 30621986.
12. Thériault-Lauzier P, Andalib A, Martucci G, et al. Fluoroscopic anatomy of left-sided heart structures for transcatheter interventions: insight from multislice computed tomography. JACC Cardiovasc Interv. 2014; 7(9): 947–957, doi: 10.1016/j.jcin.2014.06.002, indexed in Pubmed: 25129665.
13. Pighi M, Thériault-Lauzier P, Alosaimi H, et al. Fluoroscopic Anatomy of Right-Sided Heart Structures for Transcatheter Interventions. JACC Cardiovasc Interv. 2018; 11(16): 1614––1625, doi: 10.1016/j.jcin.2018.03.050, indexed in Pubmed: 30139469.
14. Thériault-Lauzier P, Spaziano M, Vaquerizo B, et al. Computed Tomography for Structural Heart Disease and Interventions. Interv Cardiol. 2015; 10(3): 149–154, doi: 10.15420/ICR.2015.10.03.149, indexed in Pubmed: 29588693.
15. Pesenti-Rossi D, Chouli M, Gharbi M, et al. Coronary aorto-ostial stenosis analysed by multislice computed tomography: a new tool for percutaneous coronary intervention? EuroIntervention. 2011; 6(6): 717–721, doi: 10.4244/EIJV6I6A121, indexed in Pubmed: 21205594.
16. Hammas S, Amato A, Amabile N, et al. Use of multislice computed tomography angiography in percutaneous coronary intervention. Int Cardiol. 2011; 3(4): 483–492, doi: 10.2217/ica.11.55.
17. Xiong TY, Pighi M, Thériault-Lauzier P, et al. Optimal fluoroscopic viewing angles of right-sided heart structures in patients with tricuspid regurgitation based on multislice computed tomography. EuroIntervention. 2019; 15(10), doi: 10.4244/EIJ-D-19-00618, indexed in Pubmed: 31746757.
18. Zampieri P, Colombo A, Almagor Y, et al. Results of coronary stenting of ostial lesions. Am J Cardiol. 1994; 73(12): 901–903, doi: 10.1016/0002-9149(94)90822-2, indexed in Pubmed: 8184820.
19. Rathore S, Terashima M, Katoh O, et al. Predictors of angiographic restenosis after drug eluting stents in the coronary arteries: contemporary practice in real world patients. EuroIntervention. 2009; 5(3): 349–354, doi: 10.4244/v5i3a55, indexed in Pubmed: 19736160.
20. Uehara Y, Shimizu M, Yoshimura M. A novel technique for catheter engagement of protruding aorto-ostial stent. Catheter Cardiovasc Interv. 2014; 83(7): 1093–1096, doi: 10.1002/ccd.25274, indexed in Pubmed: 24174303.
21. Giustino G, Serruys P, Sabik J, et al. Mortality after repeat revascularization following PCI or CABG for left main disease. JACC: Cardiovascular Interventions. 2020; 13(3): 375–387, doi: 10.1016/j.jcin.2019.09.019.
22. Jones DA, Castle EV, Beirne AM, et al. Computed tomography cardiac angiography for planning invasive angiographic procedures in patients with previous coronary artery bypass grafting. EuroIntervention. 2020; 15(15): e1351––e1357, doi: 10.4244/EIJ-D-18-01185, indexed in Pubmed: 31235457.
23. Knuuti J, Wijns W, Achenbach S, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020; 41(3): 407–477, doi: 10.1093/eurheartj/ehz425, indexed in Pubmed: 31504439.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2021, Vol. 28, No. 6, 842–848
DOI: 10.5603/CJ.a2021.0045

ISSN 1897–5593
eISSN 1898–018X

A Prospective, observational, Italian multi-center registry of self-aPposing® cOronary Stents in patients presenting with ST-segment Elevation Myocardial InfarcTION: The iPOSITION registry

Livio Giuliani[1], Federico Archilletti[2], Giuseppe Andò[3], Serena Rossi[1], Giorgio Sacchetta[4], Giuseppe De Iaco[5], Francesco Saporito[3], Marco Contarini[4], Rosario Parisi[6], Sabina Gallina[2], Marco Zimarino[1, 2], Juan Luis Gutiérrez-Chico[7], Nicola Maddestra[1]

[1]Interventional Cardiology Unit, "SS. Annunziata" Hospital, Chieti, Italy
[2]Institute of Cardiology, "G. d'Annunzio" University, Chieti-Pescara, Italy
[3]Policlinico "Gaetano Martino" Hospital — University of Messina, Italy
[4]Cardiology Unit, "Umberto I" Hospital, Siracusa, Italy
[5]Interventional Cardiology Unit, "Cardinal G. Panico" Hospital, Tricase (Lecce), Italy
[6]Interventional Cardiology Unit, "S. Salvatore" Hospital, "Ospedali riuniti Marche Nord", Pesaro, Italy
[7]Cardio Care Heart Center, Marbella, Spain

This paper was guest edited by Prof. Krzysztof J. Filipiak

Abstract

Background: *Primary percutaneous coronary intervention (pPCI) in ST-segment elevation myocardial infarction (STEMI) can be challenging for high thrombus burden and catecholamine-induced vasoconstriction. The Xposition-S stent was designed to prevent stent undersizing and minimize strut malapposition. We evaluated 1-year clinical outcomes of a nitinol, self-apposing®, sirolimus-eluting stent, pre-mounted on a novel balloon delivery system, in de novo lesions of patients presenting with STEMI undergoing pPCI.*

Methods: *The iPOSITION is a prospective, multicenter, post-market, observational study. The primary endpoint, target lesion failure (TLF), was defined as the composite of cardiac death, recurrent target vessel myocardial infarction (TV-MI), and clinically driven target lesion revascularization (TLR).*

Results: *The study enrolled 247 STEMI patients from 7 Italian centers. Both device and procedural success occurred in 99.2% of patients, without any death, TV-MI, TLR, or stent thrombosis during the hospital stay and at 30-day follow-up. At 1 year, TLF occurred in 2.6%, cardiac death occurred in 1.7%, TV-MI occurred in 0.4%, and TLR in 0.4% of patients. The 1-year stent thrombosis rate was 0.4%.*

Conclusions: *The use of an X-position S self-apposing® stent is feasible in STEMI pPCI, with excellent post-procedural results and 1-year outcomes.* (Cardiol J 2021; 28, 6: 842–848)

Key words: acute myocardial infarction, ST-segment elevation myocardial infarction, clinical trials, self-apposing stent, nitinol stent, interventional device/innovation, percutaneous coronary intervention (PCI), complex, primary PCI, drug-eluting stent

Address for correspondence: Livio Giuliani, MD, PhD, Interventional Cardiology Unit, "SS. Annunziata" Hospital, Via dei Vestini, 66100 Chieti (CH), Italy, tel: +39347369009, e-mail: lvgiuliani@gmail.com

Received: 20.08.2020 Accepted: 24.12.2020 Early publication date: 23.04.2021

Introduction

Ischemic heart disease is the leading cause of death worldwide. The incidence of ST-segment elevation myocardial infarction (STEMI) ranges from 43 to 144 new cases per 100,000 per year in Europe, with 116 per 100,000 cases per year in Italy [1]. In STEMI, prompt reperfusion by primary percutaneous coronary intervention (pPCI) and drug-eluting stent (DES) implantation is the recommended strategy, within indicated timeframes [2, 3]. In the acute phase, catecholamine-induced vasoconstriction and high thrombus burden can interfere with proper lumen diameter evaluation and stent sizing. Subsequently, the dissolution of jailed thrombotic material and vessel relaxation can result in strut malapposition, with increased risk of stent thrombosis over time [4–6]. A self-apposing® stent, which dynamically adapts to the vessel wall after the index procedure with a continuous radial force, can be a promising therapeutic option [7–9]. This observational study aimed to collect clinical data to evaluate the safety and efficacy of a nitinol, self-apposing®, sirolimus-eluting stent, pre-mounted on a novel balloon delivery system, in de novo lesions of native coronary arteries of patients presenting with STEMI.

Methods

Study overview

The iPOSITION Registry (Prospective, observational, Italian multi-center registry of self-aPposing® cOronary Stent in patients presenting with ST-segment Elevation Myocardial Infarction) was an Italian, prospective, multicenter, post-market, observational study. The study was conducted in full conformity with the Declaration of Helsinki and approved by the local medical ethics committees of all participating sites. Written informed consent was obtained before inclusion. The iPOSITION study was registered to the National Institutes of Health database with reference number NCT02979236 (full details available at https://clinicaltrials.gov).

Patient selection and procedural instructions

Patients older than 18 years, presenting with STEMI, undergoing pPCI, in which use of the Xposition S (STENTYS S.A., Paris, France) stent was planned at the operator's discretion, were eligible for inclusion. Patients with at least one of the following criteria were excluded: cardiogenic shock at presentation, severe tortuous vessels, highly calcified lesions, intrastent pathology, multiple lesions requiring stenting in the target vessel, known allergies to stent components, inability to comply with dual antiplatelet therapy (DAPT), known comorbidities conditioning life expectancy to less than 1 year, known pregnancy or childbearing potential, and inability to provide written informed consent. Accurate lesion preparation with pre-dilation was encouraged, when deemed feasible, to obtain a residual stenosis diameter < 30%. Post-dilation was recommended, preferably using a non-compliant balloon of the same size of the reference vessel diameter. After the pPCI procedure, all patients were transferred to a coronary intensive care unit and treated according to local protocols.

Device description

The Xposition S, available on the market since the beginning of 2016, is a new generation self-apposing® DES, pre-mounted on a novel balloon delivery system (Fig. 1). The stent is made of a Z-shaped mesh of nitinol (nickel/titanium alloy) and incorporates 1.4 μg/mm^2 of sirolimus in a durable polymer matrix (ProTeqtor®) of polysulfone and soluble polyvinylpyrrolidone. Small interconnections between stent struts allow disconnections for easy side branch access in bifurcation setting. The stent is available in four lengths (17, 22, 27, and 37 mm) and three sizes suitable for reference vessel diameters of 2.5–3.0 mm (small), 3.0–3.5 mm (medium), and 3.5–4.5 mm (large), compatible with a maximum vessel diameter of 6 mm (Fig. 1E). Strut thickness ranges from 103 μm (small size) to 133 μm (medium and large sizes). The stent is folded on a delivery balloon, which is covered with a distal "splitable" sheath assembly. The nominal diameter of the delivery balloon is the same as the smallest diameter for which the stent is suitable. When the semi-compliant delivery balloon is inflated within the sheath with a pressure of at least 12 atmospheres, the sheath assembly splits, and the stent is deployed. The sheath is then withdrawn together with the balloon.

Endpoints

The primary endpoint was the occurrence of target lesion failure (TLF) at 1-year follow-up. TLF was defined as the composite of cardiac death (CD), recurrent target vessel myocardial infarction (TV-MI), and clinically driven target lesion revascularization (TLR). Secondary endpoints included the following: 30-day TLF, procedural success during the hospital stay, death from any cause, 30-day and 1-year stent thrombosis (ST), and any

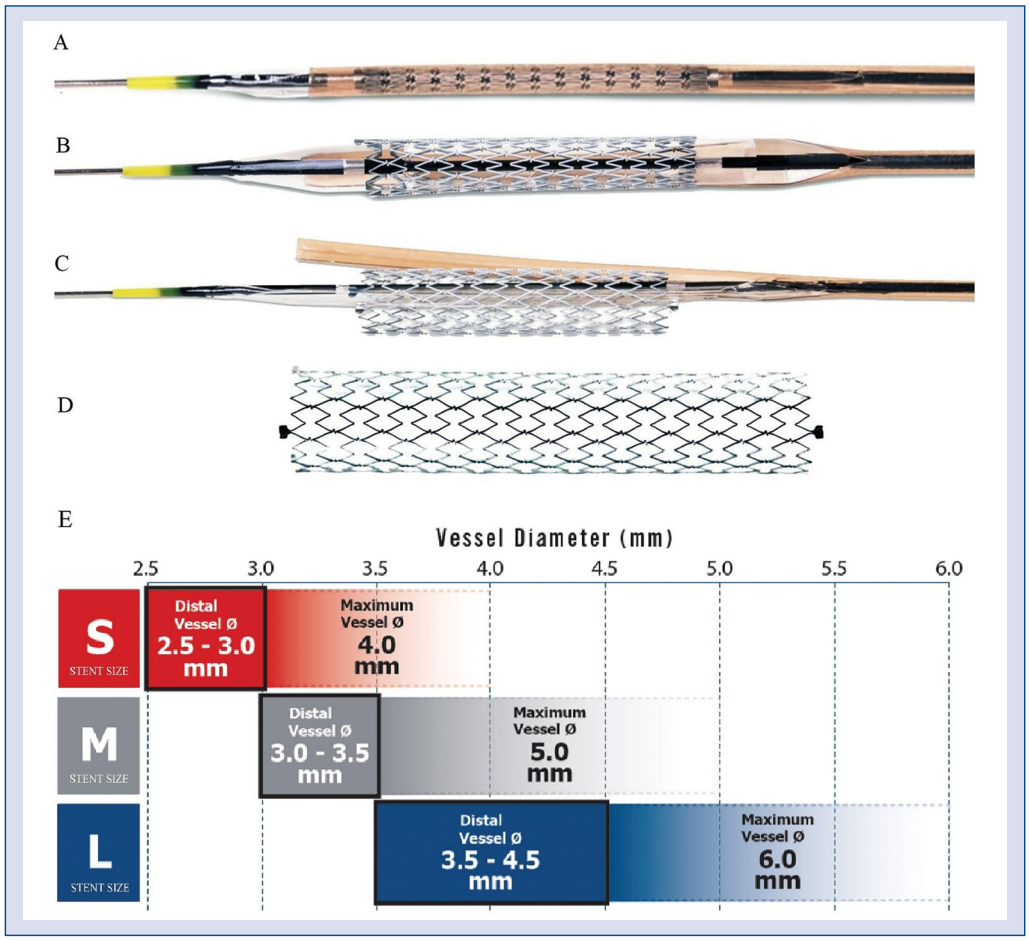


Figure 1. The Xposition S drug-eluting stent; **A.** The stent is pre-mounted on a semi-compliant balloon and is restrained by a pre-cut sheath; **B.** Balloon inflation splits the stent from distal to proximal and releases the self-apposing® stent; **C.** The balloon is then deflated; **D.** The balloon and the sheath are then withdrawn leaving the stent apposed to the vessel wall; **E.** Xposition S stent sizes.

individual component of the primary endpoint. Procedural success was defined as any device success with the obtainment of vessel recanalization (Thrombolysis in Myocardial Infarction [TIMI] grade 2–3 flow), a diameter stenosis ≤ 30% and without the occurrence of death, reinfarction, or repeated revascularization of the target vessel during the hospital stay. DAPT compliance was also investigated. A detailed overview of endpoint definition is provided in **Supplementary Appendix 1**.

Sample size calculation

The predicted rate of 1-year TLF primary endpoint was 2.5% on the basis of data reported by a previous registry [10]. Hence, a minimum sample size of 235 patients was considered enough to provide a ± 2% estimation of the primary outcome with a type-I error of 5% and a power of 80%. Taking into account 5% as a possible rate of loss at follow-up, a total of 247 patients were finally enrolled.

Statistical methods

Continuous variables were presented as mean ± standard deviation in the case of a normal distribution; conversely; when they were non-normally distributed, medians and quartiles were reported. Categorical variables were presented as frequencies and percentages. Time-to-event analysis was performed using Kaplan-Meier survival curves; the comparison between curves was obtained with the log-rank test. We considered $p < 0.05$ for statistical significance. Variables associated with 1-year TLF were identified by univariate Cox proportional hazard regression. Hazard ratios (HR), 95% confidence intervals (95% CI), and p-values were reported. All the analyses were performed with SPSS (IBM Corp., IBM SPSS Version 24.0.,

Armonk, NY, US), Med-Calc (MedCalc Software bv, Ostend, Belgium), and R-project (Core Team 2013, R Foundation for Statistical Computing, Vienna, Austria); $p < 0.05$ was considered as the threshold for statistical significance.

Results

A total of 247 STEMI patients were enrolled in 7 Italian centers from June 2016 to July 2018. Eighteen patients were lost at 1-year follow-up, so the final analysis was performed on 229 patients.

Baseline characteristics

Demographic characteristics are presented in Table 1. The mean age was 61 ± 11 years, with the majority being male (83%). More than half of the patients had systemic arterial hypertension (51%), and almost one in two was an active cigarette smoker (46%), 30% had coronary artery disease, a quarter had hypercholesterolemia (25%), and 13% had diabetes mellitus. Most of the patients presented in Killip class I (88.7%), with more than a half less than 3 h from symptom onset (54%). Culprit lesions were identified predominantly in the right coronary artery (43%) and the left anterior descending coronary artery (41%). Only a minority of patients required a pPCI of the left main (n = 4). High thrombus burden (TIMI thrombus burden 4–5) was identified in 41% of lesions and required thrombus aspiration in 30% of cases; 24% of lesions involved a bifurcation site. A complete overview of angiographic and procedural characteristics is summarized in Table 1.

Primary endpoint

Eighteen (7.3%) patients were lost at 1-year follow-up. The primary endpoint of 1-year TLF occurred in 6 patients (2.6%; 95% CI 0.53–4.67). Four patients died, and all events were attributed to a cardiac cause, resulting in a 1-year cardiac death rate of 1.7% (95% CI 0.03–3.37). Recurrent TV-MI was observed in 1 patient (0.4%; 95% CI 0.0–1.22). Clinically indicated TLR was performed in 1 patient (0.4%; 95% CI 0.0–1.22). Freedom from TLF at 1-year follow-up was 97.4% ± 1.1%; it was significantly higher in patients whose lesions were treated with pre-dilation (98.4% ± 0.9% vs. 92.5% ± 4.2%, p = 0.03; Fig. 2A) and lower with thrombus aspiration (94.1% ± 2.9% vs. 98.7% ± ± 0.9%, p = 0.04; Fig. 2B). At univariate Cox regression, performing pre-dilation was associated with better freedom from TLF (HR = 0.21, 95% CI 0.04–0.97); conversely, thrombus aspiration was associated with worse freedom from TLF

Table 1. iPOSITION baseline demographic characteristics, clinical history, cardiovascular risk factors, clinical presentation, and procedural characteristics.

BASELINE CHARACTERISTICS	
Age [years]	60.9 ± 10.9
Sex (male)	204 (82.6%)
Clinical history	
Previous MI (> 30 days)	9 (3.6%)
Previous CABG	3 (1.2%)
Previous PCI	11 (4.5%)
Previous stroke/TIA	4 (1.6%)
Cardiovascular risk factors	
Hypertension	126 (51.0%)
Diabetes mellitus	33 (13.4%)
Renal dysfunction (GFR < 60 mL/ /min/1.73 m^2)	7 (2.8%)
Smoker:	
Active smoker	113 (45.7%)
Former smoker	33 (13.4%)
Family history CAD	74 (30%)
Hypercholesterolemia	62 (25.1%)
Time from onset of symptoms	
< 3 h	134 (54.3%)
≥ 3 h and < 6 h	74 (30.0%)
≥ 6 h and <12 h	28 (11.3%)
≥ 12 h	11 (4.5%)
Killip class	
I	219 (88.7%)
II	19 (7.7%)
III	4 (2.0%)
IV	0 (0.0%)
Unknown	4 (1.6%)
Lesion location	
RCA	107 (43.3%)
LM	4 (1.6%)
LAD	101 (40.9%)
LCX	34 (13.8%)
Ramus	2 (0.8%)
Lesion characteristics	
Reference vessel diameter [mm]	3.40 ± 0.46
Length [mm]	26.1 ± 10.5
High thrombus burden (TIMI thrombus grade ≥ 4)	101 (40.9%)
Ostial lesion	18 (7.3%)
Bifurcation	58 (23.5%)
Calcifications (≥ mild)	37 (15.0%)
Tortuosity (≥ mild)	12 (4.9%)
Xposition S size	
S (2.5–3.0 mm)	60 (24.3%)

→

Table 1 (cont.). iPOSITION baseline demographic characteristics, clinical history, cardiovascular risk factors, clinical presentation, and procedural characteristics.

M (3.0–3.5 mm)	127 (51.4%)
L (3.5–4.5 mm)	60 (24.3%)
Xposition S length	
17 mm	30 (12.1%)
22 mm	86 (34.8%)
27 mm	73 (29.6%)
37 mm	58 (23.5%)
Techniques used	
QCA assessment	12 (4.9%)
Intravascular imaging (IVUS or OCT)	6 (2.4%)
Thrombus aspiration	73 (29.6%)
Pre-dilation	204 (82.6%)
Post-dilation	186 (75.3%)
POST-PROCEDURAL OUTCOMES	
Procedural outcomes	
TIMI flow post:	
0	0 (0.0%)
1	2 (0.8%)
2	16 (6.5%)
3	227 (92.7%)
Postprocedural vessel dissection	3 (1.2%)

Variables have been reported as mean ± standard deviation or number (%). MI — myocardial infarction; CABG — coronary artery by-pass graft; PCI — percutaneous coronary intervention; TIA — transient ischemic attack; GFR — glomerular filtration rate; CAD — coronary artery disease; RCA — right coronary artery; LM — left main; LAD — left anterior descending coronary artery; LCX — left circumflex coronary artery; TIMI —Thrombolysis in Myocardial Infarction; QCA — quantitative coronary analysis; IVUS — intravascular ultrasound; OCT — optical coherence tomography

(HR = 4.9, 95% CI 1.1–26.5). All the other variables reported in Table 1 were also tested, but none of them was significantly associated with 1-year TLF.

Secondary endpoint

Both device and procedural success occurred in 99.2% (95% CI 98.09–100%) of patients, without any death, recurrent TV-MI, TLR, or ST during the hospital stay and at 30-day follow-up. A single event of possible ST occurred, resulting in a 1-year ST rate of 0.4% (95% CI 0.0–1.22%).

DAPT compliance

Almost all patients were on DAPT after discharge (99%), 94% with a potent P_2Y_{12} inhibitor (ticagrelor or prasugrel) and acetylsalicylate (n = 232). A total of 95% of patients (n = 213) were still on DAPT at 1-year follow-up. Three patients had switched to oral anticoagulation for atrial fibrillation or mechanical heart valve implantation. The remaining 4% of patients (n = 9) had switched to a single antiplatelet therapy, four with acetylsalicylate and five with a P_2Y_{12} inhibitor.

Discussion

Main findings

The present post-marketing registry clearly shows that the use of the Xposition S self-apposing® stent is feasible in pPCI, with an excellent result in almost all STEMI patients. Good mid-term outcomes corroborate such findings, with a significant TLF risk reduction when lesions were prepared with pre-dilation, without thrombus

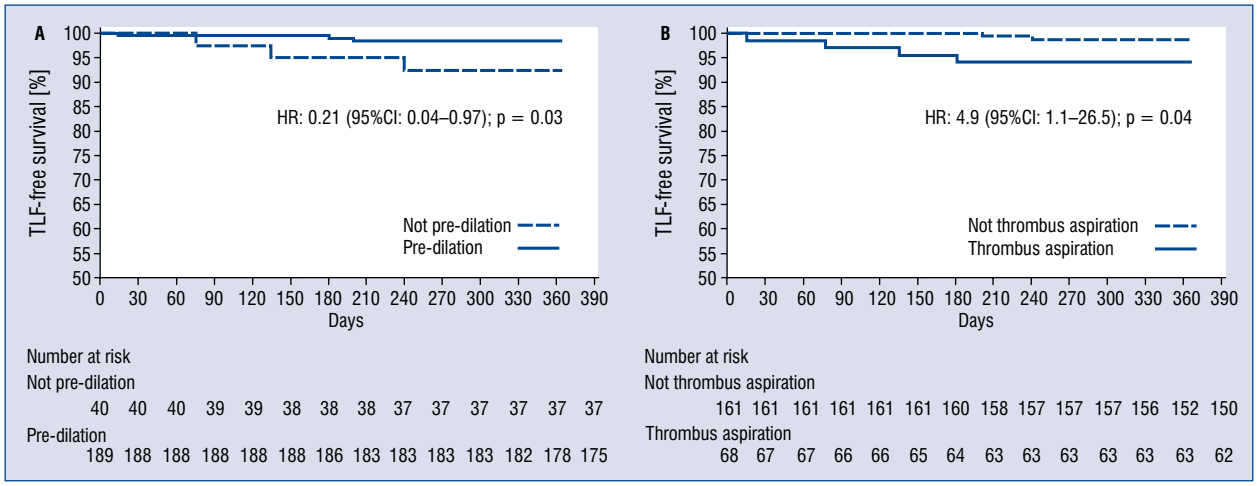


Figure 2. A. Freedom from target lesion failure at 1 year; comparison between patients whose lesions were treated with pre-dilation (solid line) and those whose were not (dashed line); **B.** Freedom from target lesion failure at 1 year; comparison between patients whose lesions were treated with thrombus aspiration (solid line) and those whose were not (dashed line).

aspiration. Procedural and clinical outcomes were comparable to other currently available balloon--expandable DES in the same setting [11–13]. The APPOSITION III study [9, 10] investigated clinical outcomes in STEMI pPCI with the previous version of the same device. Although a direct comparison cannot be performed, we here document a much lower ST, leading to a lower 1-year TLF rate, because only a single possible ST event was observed. Several factor potentially contributed to this notable outcome improvement. First, the introduction and the extensive use of the more potent P_2Y_{12} inhibitors could have strongly reduced thrombotic events [14]. Secondly, as we learned from the APPOSITION III itself [9, 10], a higher post-dilation rate might have reduced events by the improvement of strut apposition. Thirdly, even when post-dilation was not performed, the new releasing system in the iPOSITION may have guaranteed a larger stent expansion because of the balloon inflation, whereas in the APPOSITION III the stent expansion was left solely to its elastic properties, with an increasing risk of stent under-expansion [15–18].

We observed a high rate of 1-year DAPT compliance in our study, and patients with inability to comply with DAPT were excluded as per the protocol. Therefore, our results cannot be extended to a high bleeding risk population [19].

Unfortunately, we have to acknowledge that the Xposition S self-apposing® stent is currently no longer available in the market. The Stentys Company claimed that its search for a strategic partner failed, and subsequently its shareholders voted for dissolution.

Technical insight

Statistic regression with univariate Cox model and subgroup analysis (Fig. 2) revealed lesion predilation and avoidance of thrombus aspiration were associated with a lower 1-year TLF rate. The lack of clinical benefits of thrombus aspiration in STEMI pPCI has already been proven in randomized clinical trials [20–22]. Pre-dilation may favor lesion preparation before stenting, but concerns about the risk of no-reflow phenomenon due to thrombotic debridement and microcirculatory impairment often discourage this approach in STEMI [23–26]. The clinical benefit of pre-dilation in our study could be a hypothesis-generating result for further future investigations.

Limitations of the study

The results should be interpreted with caution because of several limitations: 1) iPOSITION enrolled non-randomized and non-consecutive patients, so a selection bias cannot be excluded, 2) variables associated with 1-year TLF events were not tested in a multivariate model for low event rates, 3) clinical follow-up was limited to 1 year, and a longer observation would be advisable to explore the response to DAPT demodulation, 4) no data on the completeness of revascularization were collected [27], 5) events were not adjudicated by an independent clinical event committee, and 6) a slightly high rate of patients were lost at follow-up.

Conclusions

To the best of our knowledge, this is the first multicenter Italian registry evaluating the performance of the nitinol self-apposing DES in a STEMI population and the first worldwide study weighing up the self-apposing DES novel balloon delivery system. Both procedural success and 1-year clinical outcomes were excellent. Although acknowledging the current unavailability of the device on the market, we should further investigate such a promising device in order to better define the role of self-apposing® DES in STEMI pPCI.

Acknowledgments

The authors would like to thank Dr M. Di Biasi from Interventional Cardiology Unit of "L. Sacco" Hospital, Milano, Italy and Dr. A. Ferraro from Interventional Cardiology Unit of "P. Ciaccio" Hospital, Catanzaro, Italy for their patient screening and enrolment.

Conflict of interest: None declared

References

1. Widimsky P, Wijns W, Fajadet J, et al. Reperfusion therapy for ST elevation acute myocardial infarction in Europe: description of the current situation in 30 countries. Eur Heart J. 2010; 31(8): 943–957, doi: 10.1093/eurheartj/ehp492, indexed in Pubmed: 19933242.
2. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019; 40(2): 87–165, doi: 10.1093/eurheartj/ehy394, indexed in Pubmed: 30165437.
3. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST -segment elevation. Eur Hear J. 2018; 39: 119–177, doi: 10.1093/eurheartj/ehx393, indexed in Pubmed: 28886621.
4. Cook S, Windecker S. Early stent thrombosis: past, present, and future. Circulation. 2009; 119(5): 657–659, doi: 10.1161/CIRCULATIONAHA.108.842757, indexed in Pubmed: 19204315.
5. van Werkum JW, Heestermans AA, Zomer AC, et al. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Regi-

stry. J Am Coll Cardiol. 2009; 53(16): 1399–1409, doi: 10.1016/j.jacc.2008.12.055, indexed in Pubmed: 19371823.
6. van der Hoeven BL, Liem SS, Jukema JW, et al. Sirolimus-eluting stents versus bare-metal stents in patients with ST-segment elevation myocardial infarction: 9-month angiographic and intravascular ultrasound results and 12-month clinical outcome results from the MISSION! Intervention Study. J Am Coll Cardiol. 2008; 51(6): 618–626, doi: 10.1016/j.jacc.2007.09.056, indexed in Pubmed: 18261680.
7. Spaulding C, Amoroso G, Verheye S, et al. Assessment of the safety and performance of the stentys self-expanding coronary stent system in acute myocardial infarction. J Am Coll Cardiol. 2010; 55(10): A105.E977, doi: 10.1016/s0735-1097(10)60978-3.
8. van Geuns RJ, Tamburino C, Fajadet J, et al. Self-expanding versus balloon-expandable stents in acute myocardial infarction: results from the APPOSITION II study: self-expanding stents in ST-segment elevation myocardial infarction. JACC Cardiovasc Interv. 2012; 5(12): 1209–1219, doi: 10.1016/j.jcin.2012.08.016, indexed in Pubmed: 23257368.
9. Lu H, Grundeken MJ, Vos NS, et al. Clinical outcomes with the STENTYS self-apposing coronary stent in patients presenting with ST-segment elevation myocardial infarction: Two-year insights from the APPOSITION III registry. EuroIntervention. 2017; 13: e572–e577.
10. Koch KT, Grundeken MJ, Vos NS, et al. One-year clinical outcomes of the STENTYS Self-Apposing¨ coronary stent in patients presenting with ST-segment elevation myocardial infarction: results from the APPOSITION III registry. EuroIntervention. 2015; 11(3): 264–271, doi: 10.4244/EIJY15M02_08, indexed in Pubmed: 25692610.
11. Hofma SH, Brouwer J, Velders MA, et al. Second-generation everolimus-eluting stents versus first-generation sirolimus-eluting stents in acute myocardial infarction. 1-year results of the randomized XAMI (XienceV Stent vs. Cypher Stent in Primary PCI for Acute Myocardial Infarction) trial. J Am Coll Cardiol. 2012; 60(5): 381–387, doi: 10.1016/j.jacc.2012.01.073, indexed in Pubmed: 22835668.
12. Tu D, Lu TF, Matter CM, et al. Effect of biolimus-eluting stents with biodegradable polymer vs bare-metal stents. JAMA. 2012; 308: 777–787.
13. Sabate M, Cequier A, Iñiguez A, et al. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. Lancet. 2012; 380(9852): 1482–1490, doi: 10.1016/s0140-6736(12)61223-9.
14. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. Eur J Cardio-Thoracic Surg. 2017: 213–254.
15. Kimura M, Mintz GS, Carlier S, et al. Outcome after acute incomplete sirolimus-eluting stent apposition as assessed by serial intravascular ultrasound. Am J Cardiol. 2006; 98(4): 436–442, doi: 10.1016/j.amjcard.2006.02.050, indexed in Pubmed: 16893693.
16. Fujii K, Carlier SG, Mintz GS, et al. Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: an intravascular ultrasound study. J Am Coll Cardiol. 2005; 45(7): 995–998, doi: 10.1016/j.jacc.2004.12.066, indexed in Pubmed: 15808753.
17. Hong MK, Mintz GS, Lee CW, et al. Intravascular ultrasound predictors of angiographic restenosis after sirolimus-eluting stent implantation. Eur Heart J. 2006; 27(11): 1305–1310, doi: 10.1093/eurheartj/ehi882, indexed in Pubmed: 16682378.
18. Cheneau E, Leborgne L, Mintz GS, et al. Predictors of subacute stent thrombosis: results of a systematic intravascular ultrasound study. Circulation. 2003; 108(1): 43–47, doi: 10.1161/01.CIR.0000078636.71728.40, indexed in Pubmed: 12821553.
19. Corpataux N, Spirito A, Gragnano F, et al. Validation of high bleeding risk criteria and definition as proposed by the academic research consortium for high bleeding risk. Eur Heart J. 2020; 41(38): 3743–3749, doi: 10.1093/eurheartj/ehaa671, indexed in Pubmed: 33029615.
20. Svilaas T, Vlaar PJ, van der Horst IC, et al. Thrombus aspiration during primary percutaneous coronary intervention. N Engl J Med. 2008; 358(6): 557–567, doi: 10.1056/NEJMoa0706416, indexed in Pubmed: 18256391.
21. Fröbert O, Lagerqvist Bo, Olivecrona GK, et al. Thrombus aspiration during ST-segment elevation myocardial infarction. N Engl J Med. 2013; 369(17): 1587–1597, doi: 10.1056/NEJMoa1308789, indexed in Pubmed: 23991656.
22. Jolly SS, Cairns JA, Yusuf S, et al. TOTAL Investigators. Randomized trial of primary PCI with or without routine manual thrombectomy. N Engl J Med. 2015; 372(15): 1389–1398, doi: 10.1056/NEJMoa1415098, indexed in Pubmed: 25853743.
23. Dziewierz A, Siudak Z, Rakowski T, et al. Impact of direct stenting on outcome of patients with ST-elevation myocardial infarction transferred for primary percutaneous coronary intervention (from the EUROTRANSFER registry). Catheter Cardiovasc Interv. 2014; 84(6): 925–931, doi: 10.1002/ccd.25266, indexed in Pubmed: 24155092.
24. Bessonov I, Zyrianov I, Kuznetsov V, et al. TCTAP A-024 comparison of direct stenting versus pre-dilation in ST-elevation myocardial infarction. J Am Coll Cardiol. 2016; 67(16): S10, doi: 10.1016/j.jacc.2016.03.035.
25. Azzalini L, Millán X, Ly HQ, et al. Direct stenting versus pre-dilation in ST-elevation myocardial infarction: a systematic review and meta-analysis. J Interv Cardiol. 2015; 28(2): 119–131, doi: 10.1111/joic.12190, indexed in Pubmed: 25884895.
26. Mahmoud KD, Jolly SS, James S, et al. Clinical impact of direct stenting and interaction with thrombus aspiration in patients with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention: Thrombectomy Trialists Collaboration. Eur Heart J. 2018; 39(26): 2472–2479, doi: 10.1093/eurheartj/ehy219, indexed in Pubmed: 29688419.
27. Zimarino M, Curzen N, Cicchitti V, et al. The adequacy of myocardial revascularization in patients with multivessel coronary artery disease. Int J Cardiol. 2013; 168(3): 1748–1757, doi: 10.1016/j.ijcard.2013.05.004, indexed in Pubmed: 23742927.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2021, Vol. 28, No. 6, 849–854
DOI: 10.5603/CJ.a2020.0097

ISSN 1897–5593
eISSN 1898–018X

Assessment of the conventional radial artery with optical coherent tomography after the snuffbox approach

Yongcheol Kim[1, 2], Sang Yeub Lee[3, 4], Dae In Lee[3], Ju-Hee Lee[3], Sang Min Kim[3], Jang-Whan Bae[3, 4], Kyung-Kuk Hwang[3, 4], Dong-Woon Kim[3, 4], Myeong-Chan Cho[3, 4], Myung Ho Jeong[2]

[1]Division of Cardiology, Department of Internal Medicine, Yonsei University College of Medicine and Cardiovascular Center, Yongin Severance Hospital, Yongin, Korea
[2]Division of Cardiology, Chonnam National University Hospital, Gwangju, Korea
[3]Regional Cardiovascular Disease Center, Chungbuk National University Hospital, Cheongju, Korea
[4]Department of Internal Medicine, College of Medicine, Chungbuk National University, Cheongju, Korea

Abstract

Background: *This study aimed to evaluate acute injuries of the radial artery (RA) using optical coherence tomography (OCT) in patients who underwent coronary intervention via the snuffbox approach.*

Methods: *Forty-six patients, who underwent coronary intervention and assessment of the conventional RA using OCT via the snuffbox approach, were enrolled from two university hospitals between August 2018 and August 2019.*

Results: *The mean age of the patients was 65.1 years. In this study population, 6-French (Fr) sheaths were used. The mean diameter of the conventional RA was 2.89 ± 0.33 mm, and the mean lumen area of the conventional RA was 6.68 ± 1.56 mm^2. Acute injuries of the conventional RA, after the snuffbox approach, were observed in 5 (10.9%) patients. Intimal tear was observed in the RA in 1 (2.2%) case. Intraluminal thrombi, without vessel injuries, were detected in the RA in 4 (8.7%) cases. However, medial dissection was not observed in the OCT analysis.*

Conclusions: *This retrospective OCT-based study showed that the diameter of the conventional RA was 2.89 mm and acute vessel injury of the conventional RA was rare in patients who underwent coronary intervention via the snuffbox approach.* (Cardiol J 2021; 28, 6: 849–854)

Key words: anatomical snuffbox, radial artery occlusion, optical coherence tomography

Introduction

The transfemoral approach has traditionally been used as the route for coronary intervention as a larger guiding catheter can be used and good back-up support is available for this approach; moreover, the approach is also convenient for the operator. Since the first percutaneous coronary intervention (PCI) via the conventional transradial approach (cTRA) performed by Kiemeneij and Laarman in 1993, the use of cTRA has gradually increased [1]. The cTRA is associated with a lower rate of serious access-site complications and improved patient comfort compared to the transfemoral approach [2, 3]. The cTRA has become essential for coronary angiography (CAG) and PCI and is the default access-site route used in daily practice. It is recommended as the standard

Address for correspondence: Sang Yeub Lee, MD, PhD, Division of Cardiology, Department of Internal Medicine, College of Medicine, Chungbuk National University, 776, 1Sunhwan-ro, Seowon-gu, Cheongju-si, Chungcheongbuk-do 28644, Korea, e-mail: louisahj@gmail.com

Received: 14.03.2020 Accepted: 13.07.2020 Early publication date: 21.07.2020

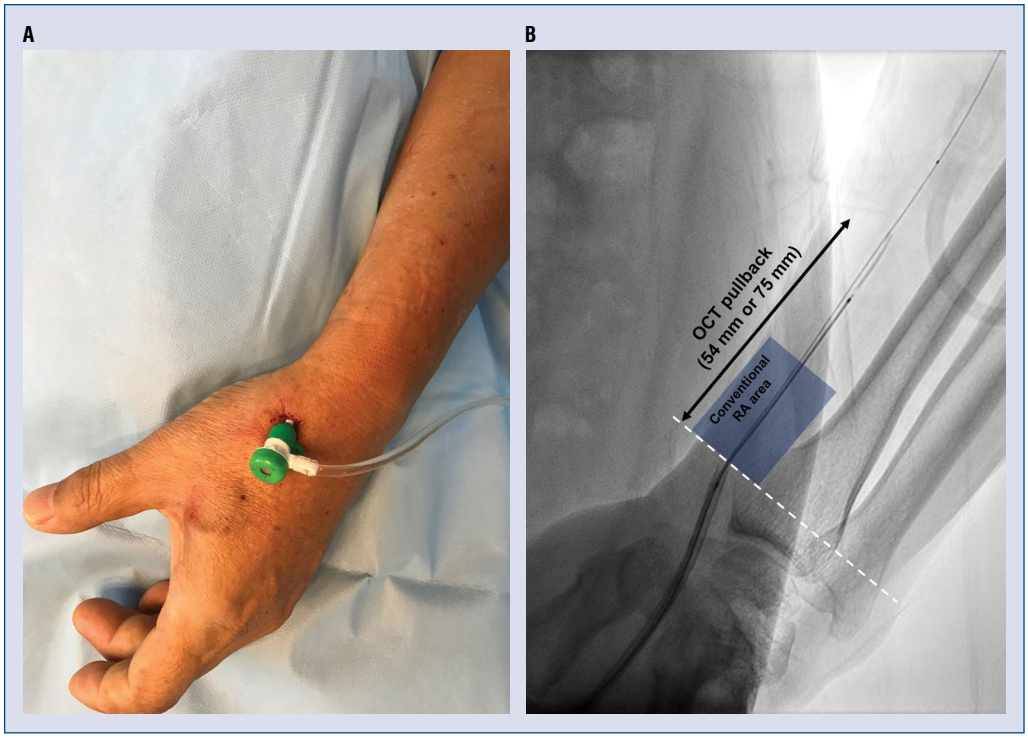


Figure 1. A 6-Fr sheath is inserted via the distal radial approach (**A**) and the conventional radial artery (RA) is assessed with optical coherence tomography (OCT; **B**). (White dotted line: distal margin of the conventional RA).

approach for PCI in most clinical settings, including acute myocardial infarction [4, 5]. However, damage to the puncture site is inevitable, and there is still concern for radial arterial occlusion (RAO) [6]. In addition, the cTRA is associated with potential risks of functional and anatomical injuries in future candidates of hemodialysis access and bypass grafts for surgical revascularization [7].

The distal radial approach, called the snuffbox approach, is a relatively novel technique that has attracted the interest of interventional cardiologists [8]. The incidence of RAO may decrease using this approach due to the availability of a dual supply system with no direct cannulation injury of the conventional radial artery (RA) [9]. However, limited data are available regarding the incidence of complications with this new puncture technique, especially acute injury of the RA after coronary intervention via the snuffbox approach.

Optical coherence tomography (OCT) is an imaging technique and is currently the best modality for assessing subtle damages (e.g., intimal and medial layer injuries) at high-resolution (10 μm) [10, 11]. This imaging modality can clearly reveal significant acute injuries and chronic intimal thickening of the RA after the cTRA [12]. However, the assessment of acute RA injuries after the snuffbox approach using OCT has not been reported to date. Therefore, this study aimed to evaluate the conventional RA after the snuffbox approach by qualitative and quantitative OCT analysis.

Methods

Study population

Patients who underwent coronary intervention under OCT guidance via the snuffbox approach at two hospitals were included. Those who had previously undergone CAG or PCI via the conventional radial approach were excluded. A single operator at each hospital performed the snuffbox approach in patients who had a palpable distal RA in the anatomical snuffbox area. The study protocol was approved by the Institutional Review Board of Chungbuk National University Hospital and Chonnam National University Hospital (approval number: CNUH-2019-272, CBNUH-2019-10-019).

Puncture and cannulation at the anatomical snuffbox

After local anesthesia, with 1 mL lidocaine hydrochloride using a 26-gauge needle, was administered to the anatomical snuffbox area, the puncture was performed using a 21-gauge open

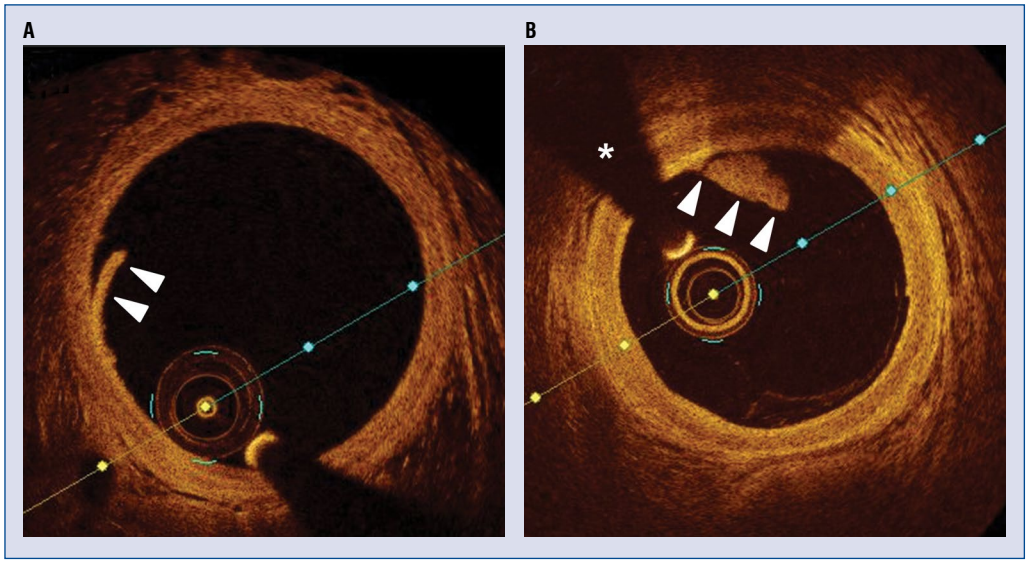


Figure 2. Optical coherence tomography image of the conventional radial artery, showing an intimal tear (**A**, arrowheads), intraluminal thrombus (**B**, arrowheads; wire artifact — asterisk).

needle using the anterior puncture technique. A 0.018-inch hair wire was then introduced after successful puncture, followed by the insertion of a 6-French (Fr) radial sheath (Prelude Radial®, Merit Medical, Utah, USA) (Fig. 1A). Following successful cannulation in the snuffbox area, a solution containing 0.2 mg of nitroglycerin, 2.5 mg of verapamil, and 3,000 units of unfractionated heparin (diluted in 10 mL of saline solution) was injected in all study participants to prevent arterial spasms and thrombosis. Anticoagulation with a bolus of unfractionated heparin (75–100 U/kg) was administered to achieve an activated clotting time > 300 s during PCI.

Hemostasis

After the puncture procedure was completed, hemostasis was achieved by applying sterile 4"×4" gauze and self-adherent bandages for 3 h. Hemostasis was evaluated by the operator; when hemostasis was successfully achieved, the bandage could be removed. If hemostasis was not achieved, the gauze and bandages were applied for an additional 30–60 min.

OCT image acquisition and analysis

The OCT system used in this study was The Dragonfly™ OPTIS™ Imaging Catheter (Abbott, St. Paul, Minnesota, USA) with OPTIS analysis software. Obtaining an OCT image of RA was done in patients who underwent successful PCI. Before the OCT examination for conventional RA, the introducer sheath was pulled out when the tip reached the dorsal tubercle of the radius; this was defined as the distal margin of the conventional RA area, based on a previous study (Fig. 1B) [13]. Then, 54 mm or 75 mm OCT pullback was conducted. During the OCT pullback, 5 cc of contrast media was manually injected via the radial sheath. After acquisition of the OCT images of the RA, cross-sectional OCT images on conventional RA area were analyzed at 1-mm intervals of the intravascular image core laboratory at the Chonnam National University Hospital. An intimal tear was defined as luminal surface discontinuity, with or without an intimal flap, that was restricted within the intima (Fig. 2A). Medial dissection was defined as luminal surface disruption that extended into the media, either in the radial or the circumferential direction [12]. The presence of a thrombus was also assessed; a thrombus was defined as high-backscattering protrusions inside the lumen of the artery in the OCT image (Fig. 2B) [14]. Qualitative assessment of acute injury of the conventional RA was performed using whole OCT pullback images for each patient. With respect to the quantitative assessment, the regions within 30 mm of the conventional RA area were assessed on the OCT images, as shown Figure 1B.

Data collection and statistical analysis

Patient demographic data, including age, gender, height, weight, body mass index, current smoking status, and medical history, including

prevalence of hypertension, diabetes mellitus, and dyslipidemia were recorded. The data on coronary angiographic and procedural characteristics during the snuffbox approach were recorded.

The continuous variables were analyzed using the paired t-test; they were expressed as the mean with standard deviation. For categorical variables, data were expressed as counts with percentages. Statistical analysis was performed using SPSS 22.0 for Windows (SPSS-PC, Chicago, IL, USA).

Results

Baseline and procedural characteristics

Forty-six patients who underwent coronary intervention and assessment of the conventional RA with OCT via the snuffbox approach were enrolled from two university hospitals between August 2018 and August 2019. The baseline clinical and procedural characteristics of the study population are summarized in Table 1. The mean age of the patients was 65.1 years, and 84.8% were male. A total of 30 (65.2%) patients underwent coronary intervention for acute coronary syndrome, including 4 patients with ST-segment elevation myocardial infarction. The left snuffbox approach was selected for 31 (67.4%) patients. All coronary interventions via the snuffbox approach were performed using a 6-Fr sheath. There were 26 (59.1%) patients with lesions in the left anterior descending coronary artery and 3 (6.8%) patients with lesions in the left main artery.

Qualitative and quantitative assessment of the conventional RA with OCT (Table 2)

The number of total cross-sections analyzed for the study population was 2491 frames. For each RA, the mean number of RA cross-sections analyzed was 27.7 ± 5.1 frames. The mean diameter of the conventional RA was 2.89 ± 0.33 mm, and the mean lumen area of the conventional RA was 6.68 ± 1.56 mm^2.

Acute injuries of the conventional RA after the snuffbox approach were observed in 5 (10.9%) patients. Intimal tears were observed in the RA in 1 (2.2%) case. Intraluminal thrombi, without vessel injury, were detected in the RA in 4 (8.7%) cases. However, medial dissections were not observed in the OCT analyses.

Table 1. Baseline and procedural characteristics of the study population.

Clinical characteristics (n = 46)	Value
Age [years]	65.1 ± 10.3
Male	39 (84.85)
BMI [kg/m^2]	24.0 ± 2.9
BSA [m^2]	1.78 ± 0.16
Hypertension	49 (49.0%)
Diabetes mellitus	30 (30.0%)
Dyslipidemia	33 (33.0%)
Current smoking	51 (51.0%)
LVEF [%]	63.7 ± 10.7
Serum creatinine [mg/dL]	1.0 ± 0.8
Indication:	100 (100%)
Stable angina pectoris	16 (34.8%)
NSTE-ACS	26 (56.5%)
STEMI	4 (8.7%)
Left snuffbox approach	31 (67.4%)
Use of 6-Fr sheath	46 (100%)
Target vessel (n = 44):	
Left anterior descending artery	26 (59.1%)
Left circumflex artery	7 (15.9%)
Right coronary artery	8 (18.2%)
Left main artery	3 (6.8%)
Stent implantation	42 (91.3%)

Values are presented as mean ± standard deviation or number (%); BMI — body mass index; BSA — body surface area; LVEF — left ventricular ejection fraction; NSTE-ACS — non-ST-segment elevation acute coronary syndrome; STEMI — ST-segment elevation myocardial infarction

Table 2. Evaluation of radial artery (RA) by optical coherence tomography (n = 46).

Parameters	Value
Number of total analyzed cross sections [frame]	2491
Mean length of cross sections of analyzed RA [mm]	27.7 ± 5.1
Mean diameter of conventional RA [mm]	2.89 ± 0.33
Mean lumen area of conventional RA [mm^2]	6.68 ± 1.56
Acute injury of RA after snuffbox approach:	5 (10.9%)
Intimal tear	1 (2.2%)
Intraluminal thrombus	4 (8.7%)
Medial dissection	0 (0%)

Values are presented as mean ± standard deviation or number (%).

Discussion

In the present study, the diameter and the lumen area of the conventional RA, as assessed by OCT, were 2.89 ± 0.33 mm and 6.68 ± 1.56 mm^2, respectively. Moreover, among 46 OCT pullback

images of the RA, acute vessel injury of the conventional RA was rarely observed. There was only 1 case of intimal tear (2.2%); although, 4 cases of intraluminal thrombi, without vessel injury (8.7%), were observed. According to available research, this is the first study to evaluate acute injury of the conventional RA with OCT after coronary intervention via the snuffbox approach.

Several studies have reported on the diameter of the RA. In a previous study, the diameter of the conventional RA was 2.72 mm in Korean patients, as noted with quantitative coronary angiography (QCA) [13]. In other studies, the diameter of the conventional RA was reported to be 2.7–3.1 mm, as assessed by vascular ultrasonography [15–17]. These findings were similar to the present RA diameter findings. However, several studies reported the lumen diameter measured using QCA was significantly smaller, approximately 5% smaller, compared to that determined using OCT [18, 19]. Therefore, the accurate RA diameter measured using OCT in the present study is expected to aid interventional cardiologists.

Several studies have reported that the occurrence of conventional RAO was rare, confirmed by vascular ultrasonography, after the snuffbox approach (0.27%, 1/366) [8, 16, 17]. Mizuguchi et al. [16] reported that the incidence of conventional RAO at 1-month, as evaluated by vascular sonography, was very rare (0.4%, 1/228). Moreover, snuffbox approach does not lead to direct damage of the conventional RA by arterial puncture and sheath insertion. Therefore, it is expected that the snuffbox approach would be beneficial for patients with end-stage renal disease (ESRD) or chronic kidney disease (CKD) in whom the RA must be preserved for the creation of the arteriovenous fistula. The protection of the RA by the snuffbox approach is expected; however, no studies have assessed the conventional RA using intravascular imaging modalities. OCT can provide superior resolution (10 μm) for the visualization of the three layers of the artery: the intima, media, and adventitia [20, 21]. OCT evaluated the whole RA at the conventional radial puncture site in the present study and it clearly demonstrated that acute vessel injury of the RA after the snuffbox approach was infrequent. Therefore, this study reaffirms the potential benefits of the snuffbox approach in terms of the preservation of the conventional RA and the feasible access-site for CAG or PCI in patients with CKD or ESRD.

Limitations of this study

There are several limitations of the present study. First, for each patient, the snuffbox approach was performed by a single experienced radial operator at each hospital. Second, this study did not have a control group. Therefore, some selection bias may have influenced the results. Third, inter-observer and intra-observer variability of OCT analysis were not evaluated. Fourth, only Korean patients were enrolled in this study. Fifth, short-term or long-term patency of RA with using vascular ultrasound was not evaluated. Thus, the present results should be carefully interpreted. Despite these limitations, the study findings are expected to aid physicians in understanding the feasibility of the snuffbox approach for the preservation of the conventional RA.

Conclusions

This retrospective OCT-based study indicated that the diameter of the conventional RA was 2.89 ± 0.33 mm and that acute vessel injury of the conventional RA was rare in patients who underwent coronary intervention via the snuffbox approach. In the future, a large prospective multi-national study is needed to evaluate the long-term patency of conventional RA after the snuffbox approach.

Acknowledgments

The authors would like to thank the staff, especially Young Hun Jin, at the cardiac catheterization laboratories at Chonnam National University Hospital and Chungbuk National University Hospital for their commitment to this study.

Conflict of interest: None declared

References

1. Kiemeneij F, Laarman GJ. Percutaneous transradial artery approach for coronary stent implantation. Cathet Cardiovasc Diagn. 1993; 30(2): 173–178, doi: 10.1002/ccd.1810300220, indexed in Pubmed: 8221875.
2. Agostoni P, Biondi-Zoccai GGL, de Benedictis ML, et al. Radial versus femoral approach for percutaneous coronary diagnostic and interventional procedures; Systematic overview and meta-analysis of randomized trials. J Am Coll Cardiol. 2004; 44(2): 349–356, doi: 10.1016/j.jacc.2004.04.034, indexed in Pubmed: 15261930.
3. Valgimigli M, Gagnor A, Calabró P, et al. MATRIX Investigators. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. Lancet. 2015; 385(9986): 2465–2476, doi: 10.1016/S0140-6736(15)60292-6, indexed in Pubmed: 25791214.

4. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018; 39(2): 119–177.
5. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019; 40(2): 87–165.
6. Avdikos G, Karatasakis A, Tsoumeleas A, et al. Radial artery occlusion after transradial coronary catheterization. Cardiovasc Diagn Ther. 2017; 7(3): 305–316, doi: 10.21037/cdt.2017.03.14, indexed in Pubmed: 28567356.
7. Possati G, Gaudino M, Prati F, et al. Long-term results of the radial artery used for myocardial revascularization. Circulation. 2003; 108(11): 1350–1354, doi: 10.1161/01.CIR.0000087402.13786.D0, indexed in Pubmed: 12939220.
8. Kiemeneij F. Left distal transradial access in the anatomical snuffbox for coronary angiography (ldTRA) and interventions (ldTRI). EuroIntervention. 2017; 13(7): 851–857, doi: 10.4244/EIJ-D-17-00079, indexed in Pubmed: 28506941.
9. Babunashvili A, Dundua D. Recanalization and reuse of early occluded radial artery within 6 days after previous transradial diagnostic procedure. Catheter Cardiovasc Interv. 2011; 77(4): 530–536, doi: 10.1002/ccd.22846, indexed in Pubmed: 20939038.
10. Kim Y, Johnson TW, Akasaka T, et al. The role of optical coherence tomography in the setting of acute myocardial infarction. J Cardiol. 2018; 72(3): 186–192, doi: 10.1016/j.jjcc.2018.03.004, indexed in Pubmed: 29650398.
11. Kim Y, Hong Y, Kim S, et al. Impact of combination therapy with ezetimibe/simvastatin treatment on the neointimal response to biodegradable polymer biolimus-eluting stent implantation in patients with acute myocardial infarction: serial assessment with optical coherence tomography. Applied Sciences. 2018; 8(10): 1968, doi: 10.3390/app8101968.
12. Yonetsu T, Kakuta T, Lee T, et al. Assessment of acute injuries and chronic intimal thickening of the radial artery after transradial coronary intervention by optical coherence tomography. Eur Heart J. 2010; 31(13): 1608–1615, doi: 10.1093/eurheartj/ehq102, indexed in Pubmed: 20413398.
13. Kim Y, Jeong MHo, Kim MC, et al. Feasibility of coronary angiography and percutaneous coronary intervention via left snuffbox approach. Korean Circ J. 2018; 48(12): 1120–1130, doi: 10.4070/kcj.2018.0181, indexed in Pubmed: 30088362.
14. Kume T, Akasaka T, Kawamoto T, et al. Assessment of coronary arterial thrombus by optical coherence tomography. Am J Cardiol. 2006; 97(12): 1713–1717, doi: 10.1016/j.amjcard.2006.01.031, indexed in Pubmed: 16765119.
15. Lee JW, Park SW, Son JW, et al. Real-world experience of the left distal transradial approach for coronary angiography and percutaneous coronary intervention: a prospective observational study (LeDRA). EuroIntervention. 2018; 14(9): e995–e99e1003, doi: 10.4244/EIJ-D-18-00635, indexed in Pubmed: 30222122.
16. Mizuguchi Y, Izumikawa T, Hashimoto S, et al. Efficacy and safety of the distal transradial approach in coronary angiography and percutaneous coronary intervention: a Japanese multicenter experience. Cardiovasc Interv Ther. 2020; 35(2): 162–167, doi: 10.1007/s12928-019-00590-0, indexed in Pubmed: 31127474.
17. Norimatsu K, Kusumoto T, Yoshimoto K, et al. Importance of measurement of the diameter of the distal radial artery in a distal radial approach from the anatomical snuffbox before coronary catheterization. Heart Vessels. 2019; 34(10): 1615–1620, doi: 10.1007/s00380-019-01404-2, indexed in Pubmed: 30972548.
18. Kubo T, Akasaka T, Shite J, et al. OCT compared with IVUS in a coronary lesion assessment: the OPUS-CLASS study. JACC Cardiovasc Imaging. 2013; 6(10): 1095–1104, doi: 10.1016/j.jcmg.2013.04.014, indexed in Pubmed: 24011777.
19. Gutiérrez-Chico JL, Serruys PW, Girasis C, et al. Quantitative multi-modality imaging analysis of a fully bioresorbable stent: a head-to-head comparison between QCA, IVUS and OCT. Int J Cardiovasc Imaging. 2012; 28(3): 467–478, doi: 10.1007/s10554-011-9829-y, indexed in Pubmed: 21359517.
20. Kim Y, Jeong MHo, Kim MC, et al. Assessment for ambiguous angiographic finding in patient with acute myocardial infarction by optical coherence tomography. Cardiol J. 2018; 25(4): 536–537, doi: 10.5603/CJ.2018.0086, indexed in Pubmed: 30211933.
21. Kim Y, Johnson TW, Park SH, et al. Optical coherence tomography findings of non-st elevation myocardial infarction with multivessel disease. Korean Circ J. 2020; 50(1): 88–90, doi: 10.4070/kcj.2019.0222, indexed in Pubmed: 31854159.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2021, Vol. 28, No.6, 855–863
DOI: 10.5603/CJ.a2021.0101

ISSN 1897–5593
eISSN 1898–018X

$P2Y_{12}$ inhibitor monotherapy in complex percutaneous coronary intervention: A post-hoc analysis of SMART-CHOICE randomized clinical trial

Ji Woong Roh[1, 2], Joo-Yong Hahn[3], Ju-Hyeon Oh[4], Woo Jung Chun[4], Yong Hwan Park[4], Woo Jin Jang[5], Eul-Soon Im[6], Jin-Ok Jeong[7], Byung Ryul Cho[8], Seok Kyu Oh[9], Kyeong Ho Yun[9], Deok-Kyu Cho[2], Jong-Young Lee[10], Young-Youp Koh[11], Jang-Whan Bae[12], Jae Woong Choi[13], Wang Soo Lee[14], Hyuck Jun Yoon[15], Seung Uk Lee[16], Jang Hyun Cho[17], Woong Gil Choi[18], Seung-Woon Rha[19], Hee-Yeol Kim[1], Joo Myung Lee[2], Taek Kyu Park[2], Jeong Hoon Yang[2], Jin-Ho Choi[2], Seung-Hyuck Choi[2], Sang Hoon Lee[2], Hyeon-Cheol Gwon[2], Dong-Bin Kim[1], Young Bin Song[2]

[1]Division of Cardiology, Department of Internal Medicine, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]Division of Cardiology, Department of Internal Medicine, Yonsei University College of Medicine and Cardiovascular Center, Yongin Severance Hospital, Yongin, Korea; [3]Division of Cardiology, Department of Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [4]Division of Cardiology, Samsung Changwon Hospital, Department of Internal Medicine, Sungkyunkwan University School of Medicine, Korea; [5]Division of Cardiology, Department of Internal Medicine, Ewha Womans University Medical Center Seoul Hospital, Seoul, Republic of Korea; [6]Division of Cardiology, Dongsuwon General Hospital, Suwon, Korea; [7]Department of Internal Medicine, Chungnam National University Hospital, Chungnam National University School of Medicine, Daejeon, Korea; [8]Division of Cardiology, Kangwon National University Hospital, Chuncheon, South Korea; [9]Department of Cardiology, Wonkwang University School of Medicine, Iksan, South Korea; [10]Division of Cardiology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Korea; [11]Division of Cardiology, Department of Internal Medicine, Chosun University Hospital, Gwangju, Korea; [12]Department of Internal Medicine, Chungbuk National University College of Medicine, Cheongju, Korea; [13]Department of Cardiology, Seoul Eulji Hospital, Eulji University College of Medicine, Seoul, Korea; [14]Department of Internal Medicine, College of Medicine, Chung-Ang University, Seoul, Korea; [15]Division of Cardiology, Department of Internal Medicine, Keimyung University Dongsan Medical Center, Daegu, South Korea; [16]Division of Cardiology, Kwangju Christian Hospital, Gwangju, Korea; [17]Division of Cardiology, Department of Internal Medicine, Saint Carollo Hospital, Suncheon, Korea; [18]Division of Cardiology, Department of Internal Medicine, Konkuk University Chungju Hospital, Konkuk University College of Medicine, Chungju, Korea; [19]Department of Cardiology, Cardiovascular Center, Korea University Guro Hospital, Seoul, Korea

Address for correspondence: Dong-Bin Kim, MD, Division of Cardiology, Department of Internal Medicine, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, tel: 82-32-340-7019, fax: 82-32-340-7227, e-mail: dbkimmd@catholic.ac.kr; Young Bin Song, MD, Division of Cardiology, Department of Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, tel: 82-02-3410-3419, fax: 82-02-3410-3849, e-mail: youngbin.song@gmail.com

Received: 12.07.2021 Accepted: 21.08.2021 Early publication date: 8.09.2021

Abstract

Background: *It remains unclear whether $P2Y_{12}$ monotherapy, especially clopidogrel, following short-duration dual antiplatelet therapy (DAPT) is associated with favorable outcomes in patients undergoing complex percutaneous coronary intervention (PCI). Therefore, this study analyzed the efficacy and safety of $P2Y_{12}$ inhibitor monotherapy, mostly clopidogrel (78%), in complex PCI following short-term DAPT.*

Methods: *The post-hoc analysis of the SMART-CHOICE trial involving 2,993 patients included 498 cases of complex PCIs, defined by at least one of the following features: 3 vessels treated, ≥ 3 stents implanted, ≥ 3 lesions treated, bifurcation with ≥ 2 stents implanted, and a total stent length of ≥ 60 mm. The primary endpoint was major adverse cardiac and cerebrovascular event (MACCE), defined as the composite of all-cause death, myocardial infarction, and stroke. The primary safety endpoint included bleeding, defined as Bleeding Academic Research Consortium (BARC) types 2 to 5.*

Results: *Complex PCI group had a higher risk of MACCE (4.0% vs. 2.3%, hazard ratio [HR] = 1.74, 95% confidence interval [CI]: 1.05–2.89, p = 0.033) and a similar risk of BARC types 2–5 bleeding (2.6% vs. 2.6%, HR = 1.02, 95% CI: 0.56–1.86, p = 0.939) compared with those without complex PCIs. Patients undergoing complex PCIs, followed by $P2Y_{12}$ inhibitor monotherapy and 12 months of DAPT exhibited similar rates of MACCE (3.8% vs. 4.2%, HR = 0.92, 95% CI: 0.38–2.21, p = 0.853).*

Conclusions: *$P2Y_{12}$ inhibitor monotherapy, mostly clopidogrel, following 3 months of DAPT did not increase ischemic events in patients with complex PCIs.* (Cardiol J 2021; 28, 6: 855–863)

Key words: clopidogrel, high-risk, percutaneous coronary intervention

This article is accompanied by the editorial on page 804

Introduction

With the development of new-generation drug-eluting stents (DES), several studies including GLOBAL-LEADERS, TWILIGHT, TICO, and the SMART-CHOICE trial have reported the safety and effectiveness of $P2Y_{12}$ monotherapy following short-term dual antiplatelet therapy (DAPT) [1–4]. However, short-term DAPT therapy in complex percutaneous coronary intervention (PCI) remains a concern. The concept of complex PCI has been recently proposed [5]. However, there is currently no universal definition of a complex PCI. In general, complex PCI includes bifurcation with 2 stent implants, ≥ 3 stents implanted, ≥ 3 lesions treated, and total stent length ≥ 60 mm or stent with chronic total occlusion lesions [6]. Patients with complex PCIs carry a higher risk of ischemic adverse events that is proportional to their burden and severity of coronary artery disease [7], and require longer DAPT to prevent ischemic events [8]. Although prolonged DAPT is associated with a potential benefit in preventing ischemic events, it also increases bleeding risk, which is correlated with the morbidity and mortality of patients [9]. Sub-group analyses of complex PCI focusing on monotherapy with ticagrelor, but not clopidogrel which is used more in real-world practice showing favorable ischemic outcomes [6, 10].

The aim of this present sub-study of the SMART-CHOICE trial was to investigate the effectiveness and safety of $P2Y_{12}$ inhibitor monotherapy, mostly clopidogrel (78%), following short-term DAPT in patients with complex PCI compared with 12 months of DAPT.

Methods

Study design

This study involved a post-hoc analysis of the SMART-CHOICE trial, a multicenter, prospective open-label randomized clinical trial (NCT02079194). The study design and protocol have been reported in detail elsewhere [2]. In brief, the trial randomly assigned patients to two groups before PCI: (i) 3 months of DAPT (acetylsalicylic acid [ASA] and a $P2Y_{12}$ inhibitor), followed by 9 months of $P2Y_{12}$ inhibitor monotherapy, and (ii) 12 months of DAPT. The trial was designed and coordinated by the Academic Clinical Research Organization of Samsung Medical Center (Seoul, Korea). The trial randomized a total of 2,993 patients at 33 hospitals. This trial was approved by the Institutional Review Board of each center. The study followed the ethical principles of the Declaration of Helsinki. All patients provided written informed consent before participating in the trial. Patients and the public were not involved in the design of conduct in this research.

Study proceedings

In the present analysis, complex PCI was defined by at least one of the following angiographic characteristics: 3 vessels treated, ≥ 3 stents implanted, ≥ 3 lesions treated, bifurcation PCI with ≥ 2 stents, and a total stent length of ≥ 60 mm. These five high-risk features of complex percutaneous procedures for ischemic events have been reported in previous studies [10].

Study endpoints

The primary efficacy endpoint included major adverse cardiac and cerebrovascular event (MACCE) defined as a composite of all-cause death, myocardial infarction (MI), and stroke at 1 year after the index procedure. The primary safety endpoint was bleeding defined as Bleeding Academic Research Consortium (BARC) types 2 to 5 at 12 months after the index procedure.

Definitions

Unless a definite noncardiac cause could be established, cardiac disease was assumed as the default cause of death. Myocardial infarction was defined as elevated cardiac enzyme levels (cardiac troponin or myocardial band fraction of creatine kinase) above the upper reference limits with ischemic symptoms or electrocardiographic findings indicative of ischemia. However, periprocedural enzyme elevations within 48 hours after the index procedure without concomitant ischemic symptoms or electrocardiographic findings indicative of ischemia were excluded from the endpoint assessment. Stroke was defined as any nonconvulsive focal or global neurologic deficit of abrupt onset lasting more than 24 hours or leading to death caused by cerebral ischemia or hemorrhage. Stent thrombosis was defined as definite or probable type according to the Academic Research Consortium classification [11]. Major bleeding was defined as BARC types 3, 4, and 5 [12].

Statistical analysis

Categoric variables are presented as numbers and percentages and were compared using the χ^2 test or the Fisher exact test. Continuous variables are presented as the mean ± standard deviation and compared using the Student t-test. The cumulative incidence of clinical events up to 1 year was calculated using the Kaplan-Meier method and compared using the log-rank test. The hazard ratio (HR), with a 95% confidence interval (CI) was derived from a Cox regression model. Subgroup analyses of the outcomes were performed to evaluate the effects of P2Y$_{12}$ inhibitor monotherapy compared with DAPT using Cox regression models with tests for interaction. All tests were two-sided and a p-value of < 0.05 was considered statistically significant. All analyses were performed using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

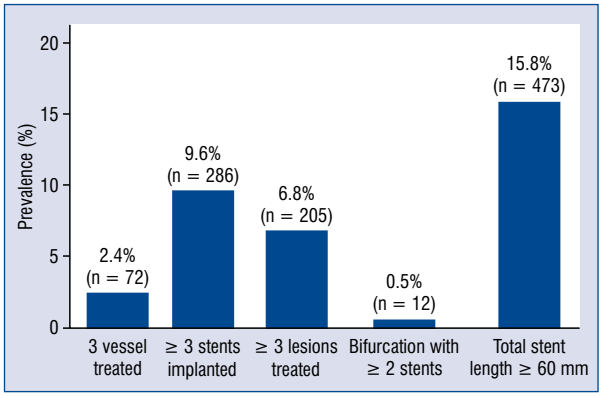


Figure 1. Prevalence of complex percutaneous coronary intervention components.

Results

The SMART-CHOICE trial randomized a total of 2,993 patients including 498 treated with complex PCIs and 2,495 undergoing non-complex PCIs. The prevalence of complex PCI components in the overall population is shown in Figure 1. The baseline clinical and procedural characteristics according to PCI complexity are summarized in Table 1. Of the patients, 76.3% (380/498) who underwent complex PCIs and 83.8% (1961/2495) of those who underwent non-complex PCIs were exposed to clopidogrel-based therapy. Patients undergoing complex PCIs manifested higher rates of hypertension, diabetes mellitus, and chronic renal failure, but lower rate of prior revascularization, and low ejection fraction. Angiographically, the complex PCI group had more diseased, treated lesions, and total stents implanted, with increased usage of intravascular ultrasound.

At 1 year, the patients who underwent complex PCIs carried higher rates of MACCE (4.0% vs. 2.3%, HR = 1.74, 95% CI: 1.05–2.89, p = 0.033), all-cause death (2.6% vs. 1.0%, HR = 2.52, 95% CI: 1.30–4.90, p = 0.007), cardiac death (1.6% vs. 0.6%, HR = 2.51, 95% CI: 1.08–5.88, p = 0.033), and stent thrombosis (0.6% vs. 0.1%, HR = 7.53, 95% CI: 1.26–45.06, p = 0.027). However, BARC bleeding types 2–5 showed similar rates (2.6% vs. 2.6%, HR = 1.02, 95% CI: 0.56–1.86, p = 0.939) in the complex and non-complex PCI groups (Table 2, Fig. 2).

Table 1. Baseline and procedural characteristics in patients according to percutaneous coronary intervention (PCI) complexity

	Complex PCI (n = 498)	Non-complex PCI (n = 2495)	P value
Age [years]	64.4 ± 10.7	64.5 ± 10.7	0.755
Male	376 (75.5%)	1822 (73.0%)	0.220
Body mass index	24.7 ± 3.1	24.6 ± 3.1	0.340
Hypertension	340 (68.3%)	1500 (60.1%)	0.001
Diabetes mellitus	218 (43.8%)	904 (36.3%)	0.002
Dyslipidemia	222 (44.6%)	1130 (45.5%)	0.767
Current smoking	127 (25.5%)	664 (26.7%)	0.630
Prior myocardial infarction	18 (3.6%)	109 (4.4%)	0.520
Prior revascularization	44 (8.8%)	305 (12.2%)	0.037
Prior stroke	41 (8.2%)	160 (6.4%)	0.168
Chronic renal failure	28 (5.6%)	69 (2.8%)	0.002
LVEF [%]	58.1 ± 11.9	60.3 ± 10.5	< 0.001
Acute coronary syndrome	288 (57.8%)	1453 (58.3%)	0.891
Shorter DAPT	260 (52.2%)	1235 (49.5%)	0.350
Clopidogrel based therapy	380 (76.3%)	1961 (83.8%)	0.258
Procedural characteristics			
No. of diseased lesion/patient	2.39 ± 0.85	1.23 ± 0.47	< 0.001
No. of lesions stented/patient	2.37 ± 0.78	1.18 ± 0.38	< 0.001
No. of stents implanted/patient	2.75 ± 0.78	1.22 ± 0.43	< 0.001
Target vessels:			
Left main	9 (1.8%)	49 (2.0%)	0.957
Left anterior descending	382 (76.7%)	1471 (59.0%)	< 0.001
Left circumflex	235 (47.2%)	540 (21.6%)	< 0.001
Right coronary	313 (62.9%)	735 (29.5%)	< 0.001
Trans radial approach	367 (73.7%)	1815 (72.7%)	0.704
Use of IVUS	156 (31.5%)	622 (25.0%)	0.004

DAPT — dual antiplatelet therapy; IVUS — intravascular ultrasound; LVEF — left ventricular ejection fraction

Table 2. Clinical outcomes in patients according to percutaneous coronary intervention (PCI) complexity.

	Complex PCI (n = 498)	Non-complex PCI (n = 2495)	Univariate hazard ratio	P value
MACCE	20 (4.0%)	58 (2.3%)	1.74 (1.05–2.89)	0.033
Bleeding BARC type 2–5	13 (2.6%)	64 (2.6%)	1.02 (0.56–1.86)	0.939
All death:	13 (2.6%)	26 (1.0%)	2.52 (1.30–4.90)	0.007
Cardiac death	8 (1.6%)	16 (0.6%)	2.51 (1.08–5.88)	0.033
Non-cardiac death	5 (1.0%)	10 (0.4%)	2.52 (0.86–7.38)	0.091
Myocardial infarction	6 (1.2%)	22 (0.9%)	1.38 (0.56–3.40)	0.487
Stroke	3 (0.6%)	13 (0.5%)	1.16 (0.33–4.07)	0.816
Stent thrombosis	3 (0.6%)	2 (0.1%)	7.53 (1.26–45.06)	0.027
Major bleeding*	2 (0.4%)	24 (1.0%)	0.42 (0.10–1.77)	0.236

*BARC type 3 to 5 bleeding; BARC — Bleeding Academic Research Consortium; MACCE — major adverse cardiac and cerebrovascular event

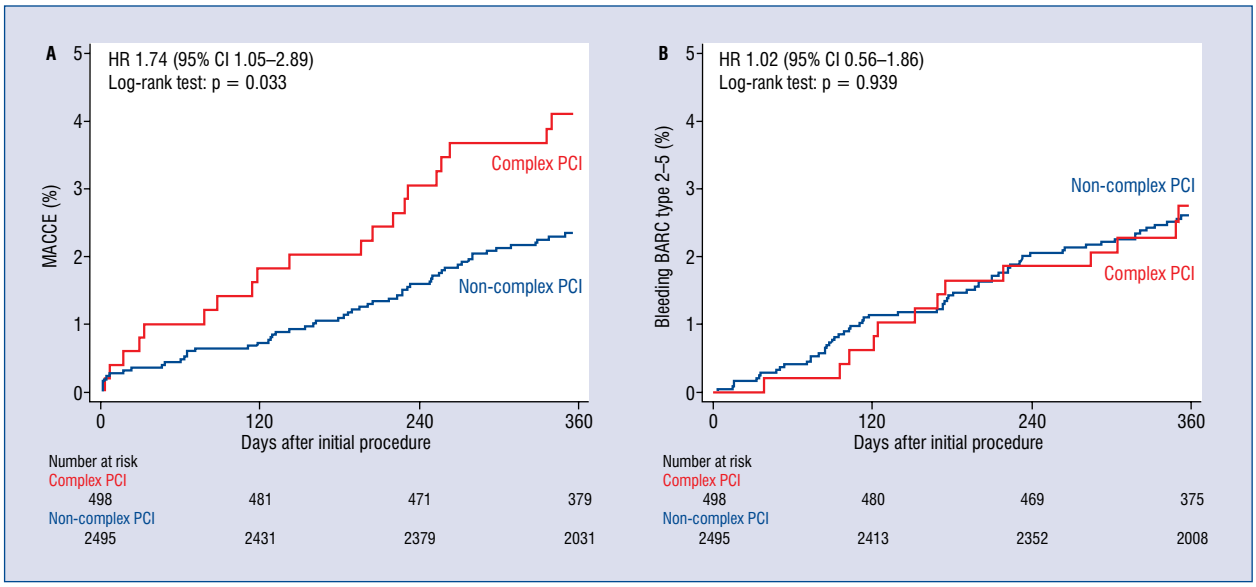


Figure 2. Cumulative incidence of events at 1 year on crude analysis according to complex and non-complex percutaneous coronary interventions (PCI); **A.** Major adverse cardiovascular and cerebrovascular events (MACCE); **B.** Bleeding Academic Research Consortium (BARC) types 2–5; CI — confidence interval; HR — hazard ratio.

Baseline characteristics according to the antiplatelet regimen used in patients with complex and non-complex PCIs are presented in Table 3. No significant differences were found in any variables. The effects of DAPT and P2Y$_{12}$ inhibitor monotherapy in the complex and non-complex PCI groups are presented in Table 4 and Figure 3. In non-complex PCI, P2Y$_{12}$ monotherapy showed similar MACCE rates (2.6% vs. 2.1%; HR = 1.27; 95% CI: 0.76–2.14; p = 0.359) and significantly lower BARC 2–5 bleeding rates (1.9% vs. 3.3%; HR = 0.57; 95% CI: 0.34–0.96; p = 0.033) compared with the DAPT group. Similar MACCE rates were found among patients exposed to P2Y$_{12}$ inhibitor monotherapy and DAPT (3.8% vs. 4.2%; HR = 0.92; 95% CI: 0.38–2.21; p = 0.853). P2Y$_{12}$ monotherapy was associated with lower BARC 2–5 bleeding rates compared with the DAPT group without statistical significance (1.9% vs. 3.4%; HR = 0.58; 95% CI: 0.19–1.77; p = 0.340). The interaction was not statistically significant between complex and non-complex PCI groups with MACCE (interaction p = 0.483) and BARC bleeding types 2–5 (interaction p = 0.904).

Discussion

The current study compared the clinical outcomes of patients treated with P2Y$_{12}$ inhibitor monotherapy, mostly clopidogrel, following 3 months of DAPT and 12 months of standard DAPT according to the PCI complexity. The findings of this study were as follows. First, patients undergoing complex PCIs carried a higher risk of ischemic and similar risk of bleeding events than those with non-complex PCIs. Second, patients with complex PCIs treated with P2Y$_{12}$ inhibitor monotherapy, mostly clopidogrel, following short-term DAPT showed favorable ischemic outcomes comparable to those 12 months of DAPT.

Regarding new-generation DESs, compared with standard DAPT, patients treated with PCI undergoing P2Y$_{12}$ inhibitor monotherapy following short-term DAPT showed non-inferior ischemic outcomes [2]. P2Y$_{12}$ inhibitor monotherapy reduced the risk of bleeding compared with DAPT [13]. These results suggest that P2Y$_{12}$ inhibitor monotherapy after short-term DAPT might be comparable to long-term DAPT for preventing ischemic events, with a lower risk of bleeding in patients undergoing PCIs with new-generation DESs. However, the risk-benefit profile of antiplatelet therapy regimens and their duration in patients with complex PCI remains disputed.

The concept of complex PCI has recently been proposed along with improvement in PCI techniques, adjunct pharmacological therapy, and the development of new-generation DES. However, currently, there is no universal definition of complex PCI in terms of angiographic or lesion characteristics. In the present study, the definition proposed by Serruys et al. [10], was used.

Table 3. Baseline and procedural characteristics stratified according to percutaneous coronary intervention (PCI) complexity and randomized regimen.

	Complex PCI (n = 498)			Non-complex PCI (n = 2495)		
	$P2Y_{12}$ monotherapy (n = 260)	DAPT (n = 238)	P	$P2Y_{12}$ monotherapy (n = 1235)	DAPT (n = 1260)	P
Age [years]	64.7 ± 10.5	64.0 ± 10.9	0.458	64.6 ± 10.8	64.4 ± 10.6	0.695
Male	191 (73.5%)	185 (77.7%)	0.316	896 (72.6%)	926 (73.5%)	0.628
Body mass index	24.6 ± 3.3	24.8 ± 2.9	0.680	24.5 ± 3.1	24.7 ± 3.2	0.101
Hypertension	177 (68.1%)	163 (68.5%)	0.978	744 (60.3%)	756 (60.0%)	0.914
Diabetes mellitus	119 (45.8%)	99 (41.6%)	0.397	451 (36.6%)	453 (36.0%)	0.766
Dyslipidemia	115 (44.2%)	107 (45.0%)	0.942	558 (45.3%)	572 (45.7%)	0.904
Current smoking	67 (25.8%)	60 (25.2%)	0.968	357 (29.0%)	307 (24.4%)	0.072
Prior myocardial infarction	9 (3.5%)	9 (3.8%)	0.987	53 (4.3%)	56 (4.4%)	0.929
Prior revascularization	19 (7.3%)	25 (10.5%)	0.272	153 (12.4%)	152 (12.1%)	0.840
Prior stroke	22 (8.5%)	19 (8.0%)	0.975	77 (6.2%)	83 (6.6%)	0.789
Chronic renal failure	16 (6.2%)	12 (5.0%)	0.731	28 (2.3%)	41 (3.3%)	0.168
LVEF [%]	58.3 ± 10.9	57.9 ± 11.6	0.657	60.2 ± 10.1	60.2 ± 9.8	0.950
Acute coronary syndrome	142 (54.6%)	146 (61.3%)	0.153	728 (58.9%)	725 (57.6%)	0.163
Clopidogrel based therapy	198 (76.2%)	182 (76.5%)	0.934	967 (78.3%)	994 (78.9%)	0.720
Procedural characteristics						
No. of diseased lesion/patient	2.39 ± 0.95	2.39 ± 0.79	0.336	1.23 ± 0.40	1.23 ± 0.51	0.307
No. of lesions stented/patient	2.37 ± 0.58	2.37 ± 0.91	0.144	1.18 ± 0.41	1.18 ± 0.36	0.381
No. of stents implanted/patient	2.75 ± 0.82	2.75 ± 0.71	0.347	1.22 ± 0.41	1.22 ± 0.45	0.662
Target vessels:						
Left main	5 (1.9%)	4 (1.7%)	0.419	20 (1.6%)	29 (2.3%)	0.279
Left anterior descending	193 (74.2%)	189 (79.4%)	0.208	710 (57.5%)	761 (60.4%)	0.151
Left circumflex	123 (47.3%)	112 (47.1%)	0.853	276 (22.3%)	264 (21.0%)	0.425
Right coronary	156 (60.0%)	157 (66.0%)	0.199	368 (29.8%)	367 (29.1%)	0.746
Trans radial approach	191 (73.5%)	176 (73.9%)	0.983	900 (72.9%)	915 (72.6%)	0.922
Use of IVUS	82 (31.7%)	74 (31.2%)	0.954	290 (23.6%)	332 (26.4%)	0.110

DAPT — dual antiplatelet therapy; IVUS — intravascular ultrasound; LVEF — left ventricular ejection fraction

The study pooled patient-level data from 6 randomized controlled trials and compared long--term (≥ 12 months) and short-term (3 or 6 months) DAPT following ASA monotherapy in patients undergoing complex PCIs. The results showed that long-term DAPT significantly reduced MACCEs compared with short-term DAPT in the complex PCI group. That study also found that the benefit of long-term DAPT was increased additively with each increase in procedural complexity. However, the ischemic benefit of extended DAPT was offset by an increased risk of bleeding [14].

$P2Y_{12}$ inhibitor monotherapy has been suggested as a new alternative antiplatelet strategy to ASA because it reduced the cardiovascular events and gastrointestinal bleeding [15]. Recently, 4 large randomized clinical trials showed favorable results with $P2Y_{12}$ inhibitor monotherapy after short-term DAPT. Among them, sub-analyses of the Global Leaders and TWILIGHT trials showed efficacy and safety of ticagrelor monotherapy in complex PCI. A post-hoc study of the Global Leaders trial revealed that 23 months of ticagrelor monotherapy following 1 month of DAPT provided a net clinical benefit for patients with complex PCIs [10]. The post-hoc study of the TWILIGHT trial showed that ticagrelor monotherapy was associated with a lower incidence of bleeding without an increased risk of ischemic events compared with continuing ticagrelor plus ASA for 12 months among patients undergoing complex PCIs [6]. In contrast to the previous 2 sub-studies, the present study used

Table 4. Comparison of clinical outcomes in patients stratified according to percutaneous coronary intervention (PCI) complexity and randomized regimen.

	Percent (number)		Hazard ratio	P value	Interaction p
	$P2Y_{12}$ monotherapy	DAPT			
MACCE:					
Complex	3.8% (10/260)	4.2% (10/238)	0.92 (0.38–2.21)	0.853	0.483
Non-complex	2.6% (32/1235)	2.1% (26/1260)	1.27 (0.76–2.14)	0.359	
Bleeding BARC type 2–5:					
Complex	1.9% (5/260)	3.4% (8/238)	0.58 (0.19–1.77)	0.340	0.904
Non-complex	1.9% (23/1235)	3.3% (41/1260)	0.57 (0.34–0.96)	0.033	
All death:					
Complex	3.1% (8/260)	2.1% (5/238)	1.48 (0.48–4.51)	0.494	0.646
Non-complex	1.1% (13/1235)	1.0% (13/1260)	1.03 (0.48–2.22)	0.942	
Cardiac death:					
Complex	1.9% (5/260)	1.3% (3/238)	1.54 (0.37–6.42)	0.557	0.671
Non-complex	0.5% (6/1235)	0.8% (10/1260)	0.62 (0.23–1.70)	0.351	
Non-cardiac death:					
Complex	1.2% (3/260)	0.8% (2/238)	1.39 (0.23–8.31)	0.719	0.210
Non-complex	0.6% (7/1235)	0.2% (3/1260)	2.40 (0.62–9.27)	0.205	
Myocardial infarction:					
Complex	0.8% (2/260)	1.7% (4/238)	0.46 (0.09–2.53)	0.375	0.306
Non-complex	0.7% (9/1235)	1.0% (13/1260)	0.71 (0.31–1.67)	0.438	
Stroke:					
Complex	0% (0/260)	1.3% (3/238)	0.01 (0.01–153.1)	0.369	0.126
Non-complex	0.9% (11/1235)	0.2% (2/1260)	5.69 (1.26–25.67)	0.024	
Stent thrombosis:					
Complex	0.8% (2/260)	0.4% (1/238)	1.82 (0.17–20.11)	0.624	0.320
Non-complex	0.1% (1/1235)	0.1% (1/1260)	1.02 (0.06–16.36)	0.987	
Major bleeding:					
Complex	0% (0/260)	0.8% (2/238)	0.01 (0.01–125.1)	0.464	0.721
Non-complex	1.0% (12/1235)	1.0% (12/1260)	1.03 (0.46–2.30)	0.939	

BARC — Bleeding Academic Research Consortium; DAPT — dual antiplatelet therapy; MACCE — major adverse cardiac and cerebrovascular event

$P2Y_{12}$ inhibitor monotherapy, mostly clopidogrel, in more than three-quarters of the total study population following 3 months of DAPT. Although clopidogrel is most often used after PCI in real-world clinical practice, clopidogrel monotherapy may be inadequate in preventing ischemic events associated with complex PCIs due to less potency and wide individual variability of the drug response.

Although the current study involved only East Asians who carry a lower ischemic risk than Westerners, $P2Y_{12}$ inhibitor monotherapy, mostly clopidogrel, did not increase the ischemic risk compared with 12 months of DAPT. However, patients with $P2Y_{12}$ monotherapy carrying non-complex lesions showed significantly lower bleeding rates (1.9% vs. 3.3%; HR = 0.57, 95% CI: 0.34–0.96; p = 0.033) than patients with 12 months of DAPT, although the patients with complex PCIs did not show significantly lower bleeding rates (1.9% vs. 3.3%; HR = 0.58, 95% CI: 0.19–0.77; p = 0.340). The p-value for the interaction between the two treatment arms was close to one, which is thought to be a type II statistical error due to the small sample size, and $P2Y_{12}$ monotherapy also might have a favorable effect on bleeding events in complex PCIs.

An expert consensus suggested that the selection and duration of the antiplatelet agents should be individualized by balancing ischemic and bleeding risks. Accordingly, three scoring systems were developed, including the PRECISE-DAPT score to

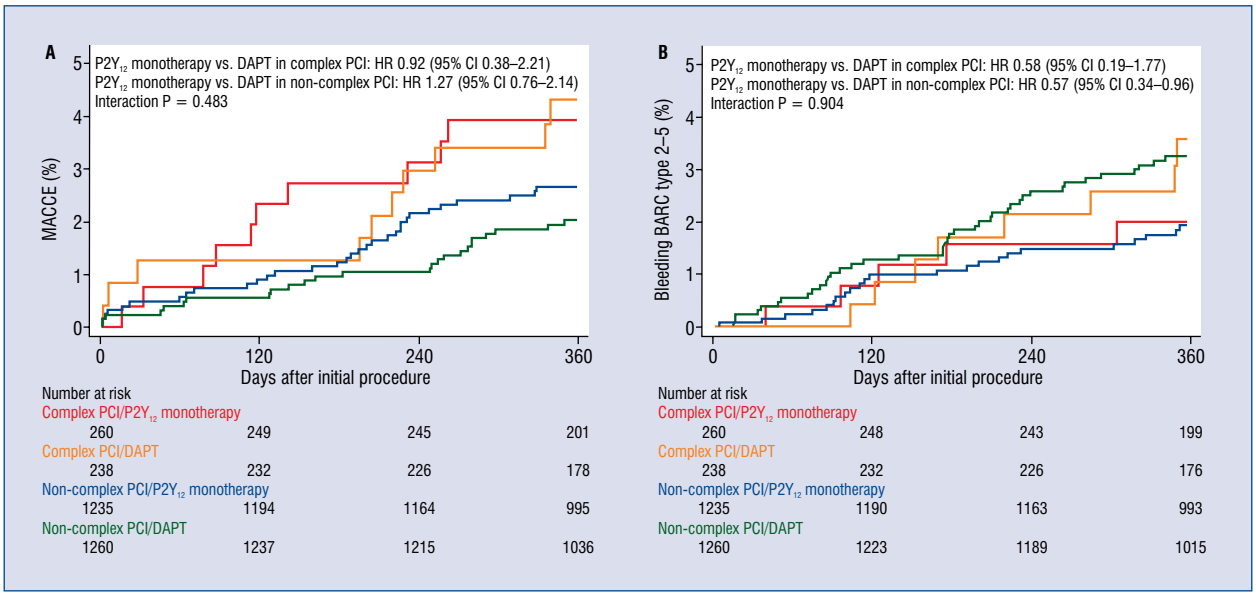


Figure 3. Cumulative incidence of events at 1 year after randomization according to randomization group (dual antiplatelet therapy [DAPT] vs. $P2Y_{12}$ monotherapy) in subjects with and without complex percutaneous coronary interventions (PCI); **A.** Major adverse cardiovascular and cerebrovascular events (MACCE); **B.** Bleeding Academic Research Consortium (BARC) types 2–5; CI — confidence interval; HR — hazard ratio.

facilitate the selection and duration of antiplatelet agents for patients with high bleeding risk (PRECISE-DAPT score ≥ 25) [16]. In a study of patients who underwent complex PCI and using PRECISE-DAPT score, the long-term DAPT was associated with net adverse clinical events (NACE) only if the bleeding risk was low (PRECISE-DAPT score < 25) and no ischemic benefit and significantly higher bleeding events in patients with high bleeding risk (PRECISE-DAPT score ≥ 25) [17]. In the present study of complex PCI stratified according to PRECISE-DAPT score, the high bleeding risk group was associated with higher rates of MACCE and NACE. In particular, the high bleeding risk group, unlike the low bleeding risk group, manifested fewer BARC type 2–5 bleeding events and a HR 0.35 in the $P2Y_{12}$ monotherapy group, without statistical significance due to the possibility of type 2 error associated with small sample size (**Suppl. Table 1**). Another significant feature in this study was that intravascular ultrasound was used more in the complex PCI group, which may have affected lower ischemic events in the $P2Y_{12}$ monotherapy group. Recently, the European Bifurcation Club proposed an algorithm for DAPT duration after PCI for bifurcation with a higher risk of both procedural and long-term adverse events. They proposed that decisions of DAPT duration should be based on the clinical presentation, bleeding risk, stenting strategy, and the possible use of intracoronary imaging. When confirming coronary imaging during PCI, the duration of DAPT should be reduced [18].

Limitations of the study

The present study has notable strengths associated with a well-randomized study design involving mainly clopidogrel but also had several limitations. First, the present study on complex PCI was not pre-specified in the protocol. Therefore, the current findings must only be interpreted as hypothesis-generating. Confirmatory randomized trials for complex PCI with proper antiplatelet therapy are still needed in the future. Second, the complexity of coronary anatomy and lesions were site-reported, not reviewed by an angiographic core laboratory. Thus, they might not have included all angiographic markers of lesion complexity or risk. Third, in bleeding events of complex PCI, $P2Y_{12}$ inhibitor monotherapy resulted in fewer bleeding events without statistical significance due to type II error associated with a small sample size. Unfortunately, the advantage of $P2Y_{12}$ monotherapy with fewer bleeding events in complex PCIs could not be established. Fourth, the study findings cannot be generalized to Western patients because all patients were East Asians who were relatively resistant to ischemic events but more susceptible to bleeding events.

Conclusions

In conclusion, compared with patients treated with non-complex PCIs, patients with complex PCIs carried a higher risk of ischemic events at 1 year. P2Y$_{12}$ inhibitor monotherapy, mostly with clopidogrel, following 3 months of DAPT resulted in favorable ischemic events comparable to the standard 12 months of DAPT regimen for complex PCIs. These findings need to be considered as hypothesis-generating. This study should be viewed as a dedicated prospective trial of proper antiplatelet regimen for complex PCI.

Acknowledgments

All authors listed met the authorship requirements in the latest guidelines of the International Committee of Medical Journal Editors. All authors agreed with the publication of the manuscript.

Funding

This study was supported by unrestricted grants from the Korean Society of Interventional Cardiology (grant 2013-3), Abbott Vascular, Biotronik, and Boston Scientific.

Conflict of interest: Dr. Hahn reports receiving grants from Abbott Vascular, Boston Scientific, Biotronik, the Korean Society of Interventional Cardiology, and Medtronic; and speaker fees from AstraZeneca, Daiichi Sankyo, and Sanofi-Aventis. Dr. Gwon reports receiving research grants from Abbott Vascular, Boston Scientific, and Medtronic; and speaker fees from Abbott Vascular Boston Scientific, and Medtronic. All other authors declare that they have no conflicts of interest.

References

1. Vranckx P, Valgimigli M, Jüni P, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet. 2018; 392(10151): 940–949, doi: 10.1016/s0140-6736(18)31858-0.
2. Hahn JY, Song YB, Oh JH, et al. SMART-CHOICE Investigators. Effect of P2Y12 Inhibitor Monotherapy vs Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention: The SMART-CHOICE Randomized Clinical Trial. JAMA. 2019; 321(24): 2428–2437, doi: 10.1001/jama.2019.8146, indexed in Pubmed: 31237-645.
3. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. N Engl J Med. 2019; 381(21): 2032–2042, doi: 10.1056/NEJMoa1908419, indexed in Pubmed: 31556978.
4. Kim BK, Hong SJ, Cho YH, et al. TICO Investigators. Effect of Ticagrelor Monotherapy vs Ticagrelor With Aspirin on Major Bleeding and Cardiovascular Events in Patients With Acute Coronary Syndrome: The TICO Randomized Clinical Trial. JAMA. 2020; 323(23): 2407–2416, doi: 10.1001/jama.2020.7580, indexed in Pubmed: 32543684.
5. Kirtane AJ, Doshi D, Leon MB, et al. Treatment of higher-risk patients with an indication for revascularization: evolution within the field of contemporary percutaneous coronary intervention. Circulation. 2016; 134(5): 422–431, doi: 10.1161/CIRCULATIONAHA.116.022061, indexed in Pubmed: 27482004.
6. Dangas G, Baber U, Sharma S, et al. Ticagrelor with or without aspirin after complex PCI. J Am Coll Cardiol. 2020; 75(19): 2414–2424, doi: 10.1016/j.jacc.2020.03.011, indexed in Pubmed: 32240761.
7. Piccolo R, Giustino G, Mehran R, et al. Stable coronary artery disease: revascularisation and invasive strategies. Lancet. 2015; 386(9994): 702–713, doi: 10.1016/S0140-6736(15)61220-X, indexed in Pubmed: 26334162.
8. Stefanini GG, Serruys PW, Silber S, et al. The impact of patient and lesion complexity on clinical and angiographic outcomes after revascularization with zotarolimus- and everolimus-eluting stents: a substudy of the RESOLUTE All Comers Trial (a randomized comparison of a zotarolimus-eluting stent with an everolimus-eluting stent for percutaneous coronary intervention). J Am Coll Cardiol. 2011; 57(22): 2221–2232, doi: 10.1016/j.jacc.2011.01.036, indexed in Pubmed: 21616282.
9. Giustino G, Baber U, Sartori S, et al. Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials. J Am Coll Cardiol. 2015; 65(13): 1298–1310, doi: 10.1016/j.jacc.2015.01.039, indexed in Pubmed: 25681754.
10. Serruys PW, Takahashi K, Chichareon P, et al. Impact of long-term ticagrelor monotherapy following 1-month dual antiplatelet therapy in patients who underwent complex percutaneous coronary intervention: insights from the Global Leaders trial. Eur Heart J. 2019; 40(31): 2595–2604, doi: 10.1093/eurheartj/ehz453, indexed in Pubmed: 31397487.
11. Cutlip DE, Windecker S, Mehran R, et al. Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007; 115(17): 2344–2351, doi: 10.1161/CIRCULATIONAHA.106.685313, indexed in Pubmed: 17470709.
12. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011; 123(23): 2736–2747, doi: 10.1161/CIRCULATIONAHA.110.009449, indexed in Pubmed: 21670242.
13. Watanabe H, Domei T, Morimoto T, et al. STOPDAPT-2 Investigators. Effect of 1-Month Dual Antiplatelet Therapy Followed by Clopidogrel vs 12-Month Dual Antiplatelet Therapy on Cardiovascular and Bleeding Events in Patients Receiving PCI: The STOPDAPT-2 Randomized Clinical Trial. JAMA. 2019; 321(24): 2414–2427, doi: 10.1001/jama.2019.8145, indexed in Pubmed: 31237644.
14. Giustino G, Chieffo A, Palmerini T, et al. Efficacy and safety of dual antiplatelet therapy after complex PCI. J Am Coll Cardiol. 2016; 68(17): 1851–1864, doi: 10.1016/j.jacc.2016.07.760, indexed in Pubmed: 27595509.
15. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet. 1996; 348(9038): 1329–1339, doi: 10.1016/s0140-6736(96)09457-3, indexed in Pubmed: 8918275.
16. Costa F, van Klaveren D, James S, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet. 2017; 389(10073): 1025–1034, doi: 10.1016/s0140-6736(17)30397-5.
17. Costa F, van Klaveren D, Feres F, et al. PRECISE-DAPT Study Investigators. Dual antiplatelet therapy duration based on ischemic and bleeding risks after coronary stenting. J Am Coll Cardiol. 2019; 73(7): 741–754, doi: 10.1016/j.jacc.2018.11.048, indexed in Pubmed: 30784667.
18. Zimarino M, Angiolillo DJ, Dangas G, et al. Antithrombotic therapy after percutaneous coronary intervention of bifurcation lesions. EuroIntervention. 2021; 17(1): 59–66, doi: 10.4244/EIJ-D-20-00885, indexed in Pubmed: 32928716.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2021, Vol. 28, No. 6, 864–878
DOI: 10.5603/CJ.a2020.0031

ISSN 1897–5593
eISSN 1898–018X

Stroke volume and cardiac output non-invasive monitoring based on brachial oscillometry-derived pulse contour analysis: Explanatory variables and reference intervals throughout life (3–88 years)

Yanina Zócalo[1], Victoria García-Espinosa[1], Juan M. Castro[1], Agustina Zinoveev[1], Mariana Marin[1], Pedro Chiesa[2], Alejandro Díaz[3], Daniel Bia[1]

[1]Departamento de Fisiología, Facultad de Medicina, Centro Universitario de Investigación, Innovación y Diagnóstico Arterial (CUiiDARTE), Universidad de la República, Montevideo, Uruguay
[2]Servicio de Cardiología Pediátrica, Centro Hospitalario Pereira-Rossell, ASSE – Facultad de Medicina, Universidad de la República, Montevideo, Uruguay
[3]Instituto de Investigación en Ciencias de la Salud, UNICEN, CCT-Tandil, CONICET, Argentina

Abstract

Background: *Non-invasive assessment of stroke volume (SV), cardiac output (CO) and cardiac index (CI) has shown to be useful for the evaluation, diagnosis and/or management of different clinical conditions. Through pulse contour analysis (PCA) cuff-based oscillometric devices would enable obtaining ambulatory operator-independent non-invasive hemodynamic monitoring. There are no reference intervals (RIs), when considered as a continuum in childhood, adolescence and adult life, for PCA-derived SV [SV(PCA)], CO [CO(PCA)] and CI [CI(PCA)]. The aim of the study were to analyze the associations of SV(PCA), CO(PCA) and CI(PCA) with demographic, anthropometric, cardiovascular risk factors (CVRFs) and hemodynamic parameters, and to define RIs and percentile curves for SV(PCA), CO(PCA) and CI(PCA), considering the variables that should be considered when expressing them.*

Methods: *In 1449 healthy subjects (3–88 years) SV(PCA), CO(PCA) and CI(PCA) were non-invasively obtained (Mobil-O-Graph; Germany). Analysis: associations between subject characteristics and SV(PCA), CO(PCA) and CI(PCA) levels (correlations; regression models); RIs and percentiles for SV(PCA), CO(PCA) and CI(PCA) (parametric methods; fractional polynomials).*

Results: *Sex, age, and heart rate would be explanatory variables for SV, CO, and CI levels. SV levels were also examined by body height, while body surface area (BSA) contributing to evaluation of CO and CI. CVRFs exposure did not contribute to independently explain the values of the dependent variables. SV, CO and CI levels were partially explained by the oscillometric-derived signal quality. RIs and percentiles were defined.*

Conclusions: *Reference intervals and percentile for SV(PCA), CO(PCA) and CI(PCA), were defined for subjects from 3–88 years of age, results are expressed according to sex, age, heart rate, body height and/or BSA.* (Cardiol J 2021; 28, 6: 864–878)

Key words: adolescents, adults, cardiac output, children, pulse contour analysis, reference intervals

Address for correspondence: Dr. Yanina Zócalo, MD, PhD, Physiology Department, School of Medicine, Centro Universitario de Investigación, Innovación y Diagnóstico Arterial (CUiiDARTE), Universidad de la República, General Flores 2125, 11800 Montevideo, Uruguay, tel/fax: 0598-29293414-3313, e-mail: yana@fmed.edu.uy; cuiidarte@fmed.edu.uy

Received: 4.07.2019 Accepted: 15.10.2019 Early publication date: 11.03.2020

Introduction

Non-invasive assessment of left ventricle stroke volume (SV), cardiac output (CO) and cardiac index (CI) were shown to be useful for the evaluation, diagnosis and/or management of different clinical and physiological conditions in both pediatric, and adult populations [1, 2]. Several non-invasive and/or minimally invasive approaches have been proposed to determine SV, CO and CI (i.e. transpulmonary-thermodilution, thoracic bioimpedance-bioreactance, ultrasonography). Among them, echocardiography stands out as a method widely used and recommended in clinical practice [3–5]. However, different factors contribute to circumscribe the use of echocardiography to certain contexts and conditions, limiting its widespread use (i.e. for community-based epidemiological studies). Among those factors are: (1) physical (size) restrictions and cost of the devices, (2) operator-dependency and the need for a learning-curve, (3) inability to obtain adequate records in many subjects or conditions, (4) different acquisition approaches may affect measurement variability, (5) a relatively long period of time is required to complete a study and/or (6) ambulatory records or continuous monitoring of the variables cannot be obtained [6, 7]. Pulse contour analysis (PCA) of blood pressure (BP) waveforms obtained non-invasively would enable estimating the SV, CO and CI [8–12]. Among the different approaches and devices available, the cuff-based oscillometric devices would be of choice, in cases of population studies within a community, taking into account their portability, high speed of measurement (2–3 min), operator-independence and need for minimal collaboration of the subject (e.g. children) [13–15].

In both, pediatric and adult populations, there is scarce data about normal and reference values for SV, CO and CI at rest. That is particularly true for data obtained from PCA. Furthermore, available information acquired in specific (i.e. Asian) populations cannot not be extrapolated to other populations [16, 17]. The present group of researchers have been working on the identification and definition of particular characteristics (i.e. age-related changes, percentile curves, reference intervals [RIs]) of cardiovascular variables in several populations; with special emphasis which considers childhood, adolescence and/or adult life as a continuum [18–23].

The main aims herein, were to analyze the associations of SV(PCA), CO(PCA) and CI(PCA) with demographic, anthropometric, cardiovascular risk factors (CVRFs) and hemodynamic parameters, and to define percentile curves and RIs for SV(PCA), CO(PCA) and CI(PCA), taking into account the variables that should be considered when expressing them (e.g. age, sex, body surface area [BSA]).

Methods

Healthy subjects (n = 1449; 3–88 years) from the community were considered for enrolment (Table 1) [18–22]. Hypertension, diabetes or dyslipidemia were considered present if the subject reported being in treatment and/or a previous diagnosis of their condition. Subjects were classified as sedentary when the physical activity they performed was lower than a moderate intensity of physical load. Smoking at least one cigarette per week was defined as a current smoker. Family history of cardiovascular disease was defined by the presence of first-degree relatives with premature cardiovascular disease [18–22]. Body mass index (BMI) was calculated as the weight-to-squared height ratio converted into percentiles/z-scores (subjects < 18 years) [18–22].

Pulse contour analysis

Readings were obtained after 10 min of rest. The oscillometric-cuff (Mobil-O-Graph; I.E.M.-GmbH, Germany) was placed on the left arm. The device measured peripheral (brachial) mean BP (MBP) and determined peripheral systolic BP, diastolic BP and pulse pressure (pSBP, pDBP, pPP). Peripheral waveforms were calibrated to pDBP and calculated MBP (MBP = pDBP + pPP/3). From the peripheral measurements, the Mobil-O-Graph determined the central (aortic) BP waveform and quantified [14, 15]: (1) central systolic BP, diastolic BP and pulse pressure (cSBP, cDBP, cPP); (2) heart rate (HR); (3) pulse wave analysis (PWA)-derived parameters like P1 and P2, augmented pressure (AP), augmentation index without and with normalization to a HR = 75 beats/min (AIx, AIx@75), pulse wave velocity (PWV), forward (Pf) and backward (Pb) wave components, reflection coefficient; (4) SV, CO, CI, and total systemic vascular resistance. Only data from accurate waves were considered. Record quality was consigned as an in-device quality index: (1 — excellent, 2 — good, and 3 — minimally acceptable record). Data assigned to each subject were an average of at least three measurements.

Data analysis

Data analysis was done using MedCalc (v.18.5, MedCalc Inc., Belgium) and IBM-SPSS Statistical

Table 1. Subjects characteristics.

	Entire group (n = 1449)									Male (n = 745)									Female (n = 704)								
	MV	SE	SD	Min	p25th	p50th	p75th	Max	Range	MV	SE	SD	Min.	p25th	p50th	p75th	Max	Range	MV	SE	SD	Min.	p25th	p50th	p75th	Max	Range
Sex (male)					51.4%																			Mean			
Age [years]	29.3	0.7	22.4	3.9	12.4	18.3	50.1	88.8	84.9	28.9	0.9	21.3	4.2	12.4	18.3	49.0	84.4	80.2	29.6	1.0	23.4	3.9	12.5	18.3	53.3	88.8	84.9
Body weight [kg]	61.6	0.7	22.8	13.2	48.9	61.9	76.5	134.7	121.5	67.1	1.0	24.2	14.3	53.0	69.0	82.7	134.7	120.4	56.1	0.8	19.9	13.2	46.4	57.0	67.1	115.0	101.8
Body height [cm]	157.0	0.6	20.1	97.0	149.0	162.0	171.0	197.0	100.0	1.6	0.0	0.2	1.1	1.5	1.7	1.8	2.0	0.9	1.5	0.0	0.2	1.0	1.5	1.6	1.6	1.8	0.9
BSA [m^2]	1.61	0.01	0.39	0.59	1.43	1.66	1.87	2.65	2.06	1.71	0.02	0.41	0.67	1.51	1.80	1.99	2.65	1.98	1.50	0.01	0.34	0.59	1.41	1.58	1.70	2.23	1.63
BMI [kg/m^2]	24.0	0.2	5.6	11.5	20.1	23.4	27.2	48.2	36.7	24.4	0.2	5.5	11.5	20.6	24.1	27.7	45.5	34.0	23.6	0.2	5.7	12.9	19.8	22.8	26.7	48.2	35.3
Z-score BMI* [SD]	1.10	0.08	1.93	-3.81	-0.13	0.64	1.88	9.64	13.45	1.32	0.12	2.15	–3.81	0.00	0.76	2.24	9.64	13.45	0.88	0.09	1.67	-3.00	-0.22	0.56	1.75	8.16	11.16
Sedentarism					44.2%										46.0%									55.6%			
Hypertension					20.5%										21.5%									19.6%			
Current smoke					9.8%										11.2%									10.2%			
Dyslipidemia					23.5%										24.6%									22.6%			
Diabetes					3.2%										3.4%									3.1%			
Familiar history of premature atherosclerosis-related disorder					10.8%										10.2%									12.4%			
Pharmacological treatment for hypertension					15.9%										14.9%									16.9%			
Pharmacological treatment for dyslipidemia					9.4%										12.2%									8.3%			
Pharmacological treatment for diabetes					3.7%										4.1%									3.9%			
Total cholesterol [mg/dL]	205	2	43	99	175	201	231	363	264	200	3	44	99	170	195	227	363	264	211	3	42	120	184	205	240	336	216
HDL cholesterol [mg/dL]	53	1	16	17	42	51	63	109	92	48	1	13	17	40	46	54	93	76	59	1	17	19	47	58	69	109	90
LDL cholesterol [mg/dL]	126	2	40	31	97	120	148	293	262	126	3	42	31	97	120	148	293	262	126	3	38	49	98	120	149	244	195
Triglycerides [mg/dL]	130	5	88	1	76	105	150	742	741	136	7	89	34	80	112	163	742	708	123	6	85	1	72	101	141	538	537
Glycemia [mg/dL]	95	1	20	64	86	93	100	296	232	95	1	14	65	88	94	101	172	107	95	2	25	64	85	91	99	296	232
Signal quality (continuous variable)	1.47	0.01	0.42	1.00	1.13	1.40	1.75	3.00	2.00	1.49	0.02	0.46	1.00	1.11	1.40	1.75	3.00	2.00	1.45	0.02	0.38	1.00	1.13	1.40	1.75	3.00	2.00
Signal quality (categorical variable):																											
1 ("Excellent")					61.3%										60.2%									62.4%			
2 ("Very good")					36.9%										36.7%									37.1%			
3 ("Poor")					1.8%										3.1%									0.5%			
pSBP [mmHg]	119	0.402	14	85	110	118	126	199	114	120	0.552	13	85	112	119	128	196	111	118	0.581	14	86	108	115	125	199	113
pMBP (calculated; form factor: 0.33) [mmHg]	86	0.329	11	54	79	85	93	148	94	87	0.467	11	61	79	86	93	148	87	85	0.462	11	54	78	84	91	140	86
pDBP [mmHg]	70	0.326	11	36	62	69	76	131	95	70	0.478	11	41	62	69	77	131	90	70	0.444	11	36	62	68	76	111	75
pPP [mmHg]	49	0.276	9	28	43	48	55	105	77	50	0.400	10	28	43	49	56	105	77	48	0.377	9	29	42	48	54	89	60
Heart rate (MOG) [beats/min]	73	0.410	14	33	62	71	81	135	102	70	0.539	13	33	60	68	78	121	88	76	0.595	14	41	66	74	84	135	94
aSBP [mmHg]	108	0.464	16	71	97	107	118	185	114	111	0.670	16	77	101	110	121	180	103	105	0.616	15	71	95	104	112	185	114
aDBP [mmHg]	71	0.326	11	38	63	70	78	133	95	72	0.477	11	41	64	70	79	133	92	71	0.444	11	38	63	70	77	112	74
aPP [mmHg]	37	0.332	11	15	30	35	42	88	73	40	0.503	12	15	32	38	45	88	73	35	0.409	10	15	28	33	39	82	67
P1 [mmHg]	101	0.394	13	67	92	100	109	162	95	105	0.580	14	74	96	104	112	162	88	97	0.486	12	67	89	96	104	151	84
P2 [mmHg]	108	0.464	16	71	97	107	118	185	114	111	0.669	16	77	101	110	121	180	103	105	0.616	15	71	95	104	112	185	114
AP [mmHg]	8	0.162	5	1	4	6	9	38	37	7	0.220	5	1	3	5	9	37	36	8	0.237	6	2	4	6	10	38	36
AIx [%]	19	0.320	11	–7	11	16	24	60	67	16	0.415	10	2	9	13	21	53	51	22	0.457	11	-7	14	19	28	60	67
AIx@75 [%]	18	0.342	12	–7	9	17	26	65	72	13	0.422	10	-7	5	12	20	43	50	22	0.463	11	-6	14	22	30	65	71
Pb [mmHg]	15	0.151	5	4	11	14	17	38	34	16	0.229	5	4	12	15	18	38	34	14	0.186	4	4	11	13	16	35	31
Pf [mmHg]	24	0.223	8	11	19	23	28	66	55	26	0.348	8	11	21	25	30	66	55	23	0.260	6	11	18	22	25	53	42
RC [%]	60	0.279	9	18	55	61	67	81	63	61	0.388	9	18	55	61	67	81	63	60	0.401	10	19	54	61	67	80	61
PVV [m/s]	6	0.060	2	4	5	5	7	15	12	6	0.077	2	4	5	5	7	13	9	6	0.092	2	4	5	5	7	15	12
SV [mL/beat]	73	15.981	0	33	62	73	84	125	91	78	0.646	15	40	67	80	88	125	85	67	0.609	15	33	58	68	77	114	81
CO [L/min]	5.09	0.02	0.74	3.10	4.54	5.06	5.63	7.10	4.00	5.28	0.03	0.74	3.40	4.73	5.28	5.82	7.10	3.70	4.91	0.03	0.70	3.10	4.43	4.86	5.40	6.68	3.58
SVR [s.mmHg/mL]	1.12	0.01	0.19	0.75	0.98	1.11	1.25	1.98	1.23	1.10	0.01	0.19	0.75	0.96	1.08	1.23	1.98	1.23	1.15	0.01	0.19	0.78	1.02	1.15	1.28	1.95	1.17
CI [$L.min/m^2$]	3.32	0.90	0.03	1.53	2.68	3.15	3.70	6.77	5.23	3.26	0.04	0.93	1.53	2.60	3.03	3.73	6.77	5.23	3.37	0.04	0.86	1.88	2.80	3.23	3.68	6.67	4.78

*Calculated for subjects under 18 years old. Min — minimal value; Max — maximal value; SD — standard deviation; SE —standard error; BSA — body surface area; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure, PP — pulse pressure; MBP — mean blood pressure; LDL — low-density lipoprotein; HDL — high density lipoprotein; MOG — Mobil-O-Graph; AP — augmented pressure; AIx and AIx@HR75 — augmentation index non-normalized and normalized considering a heart rate equal 75 beats/min; Prefix "p" and "a" — peripheral (brachial artery) and central (bortic); P1 and P2 — blood pressure at time 1 and 2, respectively; Pb and Pf — backward and forward aortic blood pressure component amplitude, respectively; RC — reflection coefficient; PVV — pulse wave velocity; SV — stroke volume; CO — cardiac output; SVR — systemic vascular resistances; CI — cardiac index

Software (v.20, SPSS Inc., USA). A $p < 0.05$ was considered statistically significant.

Associations between the subject characteristics (demographic, anthropometric, CVRFs, hemodynamic characteristics) and the SV(PCA), CO(PCA), CI(PCA) and signal-quality index levels were evaluated. To this end, simple and point-biserial correlations (Table 2) and multiple linear regression models (MLR, Stepwise) were considered (Table 3). After age, sex, BSA and height adjustment, there were no significant associations between the exposure to CVRFs and SV, CO or CI levels. Consequently, disregarding their exposure to CVRFs, all subjects studied could be considered in constructing the RIs.

As a result of the analysis described: (1) sex and age-specific RIs for SV(PCA), CO(PCA) and CI(PCA); (2) height specific RIs for SV(PCA) and (3) BSA specific RIs for CO and CI were considered necessary (Table 3). Then, age-related, height-related and BSA-related (always discriminated by sex) equations for mean and SD values were obtained for PCA-derived parameters. To this end, parametric regression methods based on fractional polynomials (FPs) were implemented [18–21, 24–27]. Briefly (as an example), mean and SD regression curves for age-specific SV(PCA), CO(PCA) and CI(PCA) were defined as fitting FPs. Thereafter, age-specific mean and standard deviation (SD) values could be obtained. As an example, CO(PCA) mean equation would be: $= a + b \times age^{p} + c \times age^{q} + \ldots$, where a, b, and c, are coefficients, and p, q, are powers, with numbers selected from the set [–2, –1, –0.5, 0, 0.5, 1, 2, 3], estimated from the regression for the mean CO(PCA) curve. Continuing the example, FPs with powers [1, 2], that is, with $p = 1$ and $q = 2$, illustrates an equation with the form $a + b \times age + c \times age^{2}$ [24]. Residuals were used to assess the model fit, deemed appropriate if the scores were normally distributed, with a mean equal to 0 and an SD equal to 1, randomly scattered above and below 0 when plotted against age. The best fitted curves, considering visual and mathematical criteria (Kurtosis and Skewness coefficients) were selected. From the mean and SD equations, and considering the standard normal distribution (Z) age-specific, HR-specific, height-specific and BSA-specific percentiles were defined (SV(PCA): Fig. 1; **Suppl. Tables S1–S6**; CO(PCA): Fig. 2; **Suppl. Tables S7–S12**; CI(PCA): Fig. 3; **Suppl. Tables S13–S18**). The 1^{th}, 2.5^{th}, 5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, 95^{th}, 97.5^{th}, and 99^{th} percentile curves were calculated as mean + Zp × SD, where Zp assumed –2.3263, –1.9599, –1.6448, –1.2815, –0.6755, 0, 0.6755, 1.2815, 1.6448, 1.9599, and 2.3263 values, respectively.

The minimum sample size required ($n = 377$ subjects) for RIs construction (i.e. for males or females) was defined considering a normal distribution for the covariate in the sample (conservatively), a 95% and 90% limit of reference and confidence interval (two-sided), respectively; with a 95% and 10% reference range and relative margin of error, respectively [18–21, 28]. According to the central limit theorem, a normal distribution was assumed considering Kurtosis and Skewness coefficients distribution and the number of subjects studied (sample size > 30) [29].

Results

SV(PCA), CO(PCA), CI(PCA): Impact of sex, age, HR and anthropometric characteristics

Table 1 describes characteristics of the 1449 subjects included in the study. Note the wide age range considered (3–88 years old) and the balanced sex distribution (male = 51.4%).

Table 3 shows explanatory variables for SV(PCA), CO(PCA) and CI(PCA) values (MLR models). The variables considered were those with statistically significant associations with PCA-derived data in bivariate analyses (Table 2). Sex, age, and HR would be explanatory variables for dependent variables (SV, CO, CI). SV levels were also explained by height, while BSA contributed to explain CO and CI. CVRFs did not contribute to explain, independently, the values of the dependent variables. Then, data from all the studied subjects could be considered for the RIs, which should be sex-specific and expressed taking into account age, HR and height or BSA) (Table 3). It is noteworthy that variations in SV, CO and CI were partially explained by the oscillometric-derived signal quality. A higher signal quality was associated with higher SV, CO and CI (Tables 2, 3).

SV(PCA), CO(PCA), CI(PCA): Percentile curves and RIs for children, adolescents and adults

Figure 1 shows age, HR and height-specific percentile curves for SV(PCA). **Supplementary Tables S1–S6** show sex-specific RIs for SV considering age, HR and height.

Age, HR and BSA-specific percentile curves for CO(PCA) and CI(PCA) in males and females are shown in Figures 2, 3. **Supplementary Tables S7–S12** show sex-specific RIs for CO considering

Table 2. Association (unadjusted and adjusted) between stroke volume, cardiac output or cardiac index and demographic, anthropometric, cardiovascular risk factors exposition, hemodynamic and cardiovascular parameters.

Variable and units	Bivariate (unadjusted or Zero-order) correlations										Bivariate (adjusted) correlations: Sex, Age, BMI and BSA									
	SV (MOG) [mL/beat]		CO (MOG) [L/min]		CI (MOG) [L.min/m^2]		Signal quality (continuous variable)		Signal quality (categorical variable)		SV (MOG) [mL/min]		CO (MOG) [L/min]		CI (MOG) [L.min/m^2]		Signal quality (continuous variable)		Signal quality (categorical variable)	
	R	p	R	p	R	p	R	p	R	p	R	p	R	p	R	p	R	p	R	p
Sex [Female: 1; Male: 0]	–0.340	< 0.001	–0.246	< 0.001	0.060	0.042	–0.050	0.092	–0.046	0.120	—	—	—	—	—	—	—	—	—	—
Age [years]	0.229	< 0.001	–0.096	0.001	–0.596	< 0.001	0.061	0.039	0.052	0.081	—	—	—	—	—	—	—	—	—	—
Body weight [kg]	0.503	< 0.001	0.329	< 0.001	–0.787	< 0.001	–0.044	0.138	–0.031	0.302	–0.236	< 0.001	–0.228	< 0.001	0.201	< 0.001	0.115	< 0.001	0.092	0.002
Body height [cm]	0.635	< 0.001	0.407	< 0.001	–0.774	< 0.001	–0.126	< 0.001	–0.105	< 0.001	0.225	< 0.001	0.266	< 0.001	–0.177	< 0.001	–0.138	< 0.001	–0.114	< 0.001
BSA [m^2]	0.584	< 0.001	0.377	< 0.001	–0.822	< 0.001	–0.081	0.006	–0.063	0.032	—	—	—	—	—	—	—	—	—	—
BMI [kg/m^2]	0.276	< 0.001	0.215	< 0.001	–0.617	< 0.001	0.003	0.909	0.013	0.661	—	—	—	—	—	—	—	—	—	—
Z-score BMI* [SD]	–0.052	0.186	0.106	0.007	–0.050	0.202	–0.025	0.524	–0.036	0.353	0.000	0.998	–0.043	0.270	–0.243	< 0.001	–0.080	0.041	–0.108	0.006
Sedentarism [Yes: 1; No: 0]	–0.119	< 0.001	0.022	0.477	–0.038	0.226	–0.043	0.176	–0.032	0.305	–0.147	< 0.001	0.006	0.857	0.069	0.029	–0.043	0.180	–0.034	0.282
Hypertension [Yes: 1; No: 0]	0.067	0.023	0.043	0.150	–0.220	< 0.001	0.019	0.511	0.016	0.589	–0.017	0.564	0.101	0.001	0.081	0.007	–0.027	0.369	–0.025	0.392
Current smoke [Yes: 1; No: 0]	0.090	0.004	0.002	0.958	–0.092	0.003	0.010	0.736	0.011	0.724	–0.006	0.854	–0.044	0.156	0.041	0.183	0.033	0.293	0.031	0.323
Dyslipidemia [Yes: 1; No: 0]	0.033	0.261	–0.104	< 0.001	–0.321	< 0.001	0.088	0.003	0.076	0.010	–0.108	< 0.001	–0.086	0.004	–0.031	0.304	0.051	0.085	0.042	0.156
Diabetes [Yes: 1; No: 0]	0.006	0.969	–0.281	0.055	–0.471	0.001	0.182	0.220	0.246	0.096	–0.233	0.133	–0.463	0.002	–0.464	0.002	0.161	0.303	0.238	0.124
Family history of premature CVD [Yes: 1; No: 0]	0.070	0.021	–0.029	0.340	–0.152	< 0.001	0.040	0.180	0.038	0.213	0.030	0.328	0.013	0.665	0.007	0.826	0.025	0.410	0.025	0.414
Pharmacological treatment for hypertension [Yes: 1; No: 0]	0.013	0.673	–0.094	0.002	–0.258	< 0.001	0.108	< 0.001	0.081	0.009	–0.098	0.002	0.002	0.950	0.091	0.003	0.067	0.032	0.042	0.178
Pharmacological treatment for dyslipedemia [Yes: 1; No: 0]	0.032	0.301	–0.143	< 0.001	–0.288	< 0.001	0.144	< 0.001	0.122	< 0.001	–0.111	< 0.001	–0.136	< 0.001	–0.066	0.035	0.120	< 0.001	0.101	0.001
Pharmacological treatment for diabetes [Yes: 1; No: 0]	–0.048	0.122	–0.025	0.418	–0.149	< 0.001	0.031	0.321	0.017	0.585	–0.120	< 0.001	–0.012	0.706	0.013	0.680	0.005	0.883	–0.008	0.805
Total cholesterol [mg/dL]	–0.152	0.003	–0.205	< 0.001	–0.127	0.013	0.110	0.030	0.074	0.146	–0.164	0.001	–0.139	0.007	–0.096	0.063	0.091	0.077	0.057	0.268
HDL cholesterol [mg/dL]	–0.138	0.008	–0.184	< 0.001	–0.020	0.699	–0.038	0.468	–0.011	0.825	0.005	0.930	0.091	0.084	–0.054	0.305	–0.089	0.091	–0.043	0.418
LDL cholesterol [mg/dL]	–0.120	0.024	–0.156	0.003	–0.071	0.185	0.100	0.060	0.043	0.416	–0.137	0.011	–0.129	0.016	–0.085	0.115	0.078	0.145	0.024	0.660
Triglycerides [mg/dL]	–0.009	0.873	0.012	0.823	–0.116	0.031	0.076	0.156	0.067	0.210	–0.099	0.069	–0.095	0.082	–0.020	0.710	0.084	0.124	0.070	0.200
Glycemia [mg/dL]	–0.069	0.259	–0.101	0.100	–0.204	0.001	0.056	0.365	0.061	0.319	–0.149	0.016	–0.108	0.082	–0.084	0.177	0.030	0.624	0.039	0.536
Signal quality (continuous variable)	0.008	0.784	–0.296	< 0.001	0.007	0.815	1.000	—	0.877	< 0.001	0.091	0.002	–0.272	< 0.001	–0.101	0.001	—	—	0.873	< 0.001
Signal quality (categorical variable)	0.009	0.751	–0.269	< 0.001	–0.018	0.543	0.877	< 0.001	1.00	—	0.078	0.009	–0.255	< 0.001	–0.125	< 0.001	0.873	< 0.001	—	—
pSBP [mmHg]	0.252	< 0.001	0.267	< 0.001	–0.403	< 0.001	–0.025	0.397	–0.026	0.371	–0.013	0.656	0.208	< 0.001	0.087	0.003	–0.016	0.581	–0.023	0.436
pMBP (calculated; form factor: 0.33) [mmHg]	0.187	< 0.001	0.138	< 0.001	–0.450	< 0.001	0.043	0.149	0.023	0.432	–0.108	< 0.001	0.108	< 0.001	0.051	0.088	0.050	0.090	0.024	0.420
pDBP [mmHg]	0.129	< 0.001	0.042	0.159	–0.430	< 0.001	0.084	0.004	0.052	0.076	–0.152	< 0.001	0.028	0.351	0.027	0.367	0.091	0.002	0.051	0.084
pPP [mmHg]	0.213	< 0.001	0.340	< 0.001	–0.080	0.007	–0.0137	< 0.001	–0.101	0.001	0.131	< 0.001	0.241	< 0.001	0.088	0.003	–0.112	< 0.001	–0.082	0.006
Heart rate [beats/min]	–0.773	< 0.001	–0.015	0.614	0.547	< 0.001	–0.196	< 0.001	–0.187	< 0.001	–0.714	< 0.001	0.177	< 0.001	0.293	< 0.001	–0.270	< 0.001	–0.254	< 0.001
aSBP [mmHg]	0.520	< 0.001	0.192	< 0.001	–0.584	< 0.001	0.114	< 0.001	0.101	0.001	0.271	< 0.001	0.047	0.117	–0.066	0.027	0.186	< 0.001	0.160	< 0.001
aDBP [mmHg]	0.147	< 0.001	0.038	0.200	–0.430	< 0.001	0.110	< 0.001	0.071	0.016	–0.129	< 0.001	0.013	0.666	0.023	0.446	0.124	< 0.001	0.075	0.012
aPP [mmHg]	0.580	< 0.001	0.230	< 0.001	–0.392	< 0.001	0.050	0.094	0.070	0.018	0.423	< 0.001	0.042	0.159	–0.093	0.002	0.101	0.001	0.115	< 0.001
P1 [mmHg]	0.572	< 0.001	0.401	< 0.001	–0.496	< 0.001	0.038	0.203	0.029	0.326	0.299	< 0.001	0.272	< 0.001	0.103	0.001	0.099	0.001	0.075	0.011
P2 [mmHg]	0.520	< 0.001	0.192	< 0.001	–0.584	< 0.001	0.113	< 0.001	0.100	0.001	0.271	< 0.001	0.047	0.118	–0.066	0.027	0.185	< 0.001	0.159	< 0.001
AP [mmHg]	0.099	0.001	–0.422	< 0.001	–0.464	< 0.001	0.234	< 0.001	0.218	< 0.001	0.032	0.289	–0.467	< 0.001	–0.385	< 0.001	0.250	< 0.001	0.235	< 0.001
AIx [%]	–0.185	< 0.001	–0.625	< 0.001	–0.354	< 0.001	0.279	< 0.001	0.251	< 0.001	–0.207	< 0.001	–0.629	< 0.001	–0.436	< 0.001	0.298	< 0.001	0.272	< 0.001
AIx@75 [%]	–0.699	< 0.001	–0.601	< 0.001	0.057	0.056	0.136	< 0.001	0.113	< 0.001	–0.674	< 0.001	–0.451	< 0.001	–0.189	< 0.001	0.091	0.002	0.076	0.011
Pb [mmHg]	0.604	< 0.001	0.153	< 0.001	–0.456	< 0.001	0.126	< 0.001	0.131	< 0.001	0.456	< 0.001	–0.022	0.468	–0.135	< 0.001	0.179	< 0.001	0.176	< 0.001
Pf [mmHg]	0.519	< 0.001	0.234	< 0.001	–0.310	< 0.001	0.025	0.406	0.048	0.102	0.366	< 0.001	0.034	0.255	–0.083	0.005	0.077	0.009	0.094	0.002
RC [%]	0.369	< 0.001	–0.076	0.011	–0.447	< 0.001	0.244	< 0.001	0.214	< 0.001	0.302	< 0.001	–0.090	0.002	–0.140	< 0.001	0.276	< 0.001	0.241	< 0.001
PWV [m/s]	0.227	< 0.001	–0.116	< 0.001	–0.539	< 0.001	0.077	0.009	0.069	0.020	0.088	0.003	–0.056	0.059	–0.120	< 0.001	0.024	0.411	0.029	0.336
SVR [s.mmHg/mL]	–0.306	< 0.001	–0.715	< 0.001	–0.377	< 0.001	0.279	< 0.001	0.242	< 0.001	–0.425	< 0.001	–0.760	< 0.001	–0.500	< 0.001	0.269	< 0.001	0.235	< 0.001

*For subjects < 18 years. A $p < 0.05$ (red text) was considered statistically significant; CVD — atherosclerosis-related cardiovascular disease; Signal quality: 1 (excellent), 2 (good), 3 (minimum acceptable); R — Pearson coefficient; other abbreviations — see Table 1

Table 3. Pulse contour analysis-derived stroke volume, cardiac output and cardiac index data: explanatory variables (multiple linear regression models).

Dependent variable [Unit]	Model		Unstandardized coefficients		Standardized coefficients	P	95%-CI for β		VIF	R	Adjusted R^2	SE of the estimate	Change statistics	
			β	SE	β		Lower bound	Upper bound					R^2 change	P (F change)
Stroke volume [mL/beat]														
	1	(Constant)	118.631	3.604		< 0.001	111.528	125.734		0.627	0.390	9.817	0.393	8.336E-26
		Heart rate [beats/min]	–0.629	0.053	–0.627	< 0.001	–0.733	–0.526	1.000					
	2	(Constant)	119.584	3.181		< 0.001	113.315	125.854						
		Heart rate [beats/min]	–0.577	0.047	–0.575	< 0.001	–0.669	–0.485	1.020	0.728	0.526	8.659	0.136	6.848E-14
		Sex [female: 1; male: 0]	–9.384	1.172	–0.374	< 0.001	–11.694	–7.074	1.020					
	3	(Constant)	129.487	4.340		< 0.001	120.933	138.041						
		Heart rate [beats/min]	–0.654	0.051	–0.652	< 0.001	–0.755	–0.552	1.288	0.743	0.546	8.473	0.021	0.001
		Sex [female: 1; male: 0]	–8.651	1.169	–0.344	< 0.001	–10.955	–6.348	1.059					
		Age [years]	–0.100	0.031	–0.167	0.001	–0.160	–0.040	1.278					
	4	(Constant)	94.483	10.338		< 0.001	74.108	114.858						
		Heart rate [beats/min]	–0.622	0.051	–0.620	< 0.001	–0.722	–0.521	1.327					
		Sex [female: 1; male: 0]	–5.941	1.351	–0.236	< 0.001	–8.604	–3.279	1.497	0.761	0.571	8.237	0.026	0.0002
		Age [years]	–0.129	0.031	–0.216	< 0.001	–0.190	–0.069	1.367					
		Body height [cm]	20.011	5.395	0.207	< 0.001	9.377	30.644	1.610					
	5	(Constant)	101.820	10.571		< 0.001	80.984	122.655						
		Heart rate [beats/min]	–0.654	0.052	–0.652	< 0.001	–0.755	–0.552	1.406					
		Sex [female: 1; male: 0]	–5.980	1.333	–0.238	< 0.001	–8.607	–3.353	1.497	0.769	0.582	8.127	0.013	0.008
		Age [years]	–0.132	0.030	–0.221	< 0.001	–0.192	–0.072	1.369					
		Body height [cm]	19.389	5.328	0.200	< 0.001	8.888	29.891	1.613					
		Signal quality (categorical variable)	–2.806	1.063	–0.118	0.009	–4.902	–0.710	1.065					
Cardiac output [L/min]														
	1	(Constant)	3.438	0.250		< 0.001	2.945	3.931		0.401	0.157	0.681	0.160	4.923E-10
		Heart rate [beats/min]	0.024	0.004	0.401	< 0.001	0.017	0.031	1.000					
	2	(Constant)	3.497	0.227		< 0.001	3.050	3.944						
		Heart rate [beats/min]	0.027	0.003	0.456	< 0.001	0.020	0.034	1.020	0.559	0.306	0.618	0.151	3.940E-11
		Sex [female: 1; male: 0]	–0.582	0.084	–0.393	< 0.001	–0.747	–0.417	1.020					
	3	(Constant)	4.321	0.319		< 0.001	3.693	4.950						
		Heart rate [beats/min]	0.023	0.003	0.392	< 0.001	0.016	0.030	1.130	0.592	0.341	0.602	0.038	0.0004
		Sex [female: 1; male: 0]	–0.592	0.082	–0.400	< 0.001	–0.753	–0.432	1.021					
		Signal quality (categorical variable)	–0.380	0.106	–0.206	< 0.001	–0.588	–0.171	1.114					
	4	(Constant)	3.111	0.507		< 0.001	2.112	4.110						
		Heart rate [beats/min]	0.026	0.004	0.443	< 0.001	0.019	0.033	1.229					
		Sex [female: 1; male: 0]	–0.471	0.089	–0.318	< 0.001	–0.647	–0.295	1.275	0.614	0.365	0.591	0.026	0.0026
		Signal quality (categorical variable)	–0.364	0.104	–0.198	0.001	–0.569	–0.159	1.117					
		BSA [m^2]	0.511	0.168	0.191	0.003	0.179	0.842	1.386					

→

Table 3 (cont.). Pulse contour analysis-derived stroke volume, cardiac output and cardiac index data: explanatory variables (multiple linear regression models).

Dependent variable [Unit]		Model	Unstandardized coefficients		Standardized coefficients	P	95%-CI for β		VIF	R	Adjusted R^2	SE of the estimate	Change statistics	
			β	SE	β		Lower bound	Upper bound					R^2 change	P (F change)
	5	(Constant)	3.561	0.503		< 0.001	2.569	4.553						
		Heart rate [beats/min]	0.021	0.004	0.347	< 0.001	0.013	0.028	1.446					
		Sex [female: 1; male: 0]	–0.365	0.091	–0.246	< 0.001	–0.544	–0.187	1.397					
		Signal quality (categorical variable)	–0.379	0.101	–0.206	< 0.001	–0.578	–0.181	1.119	0.647	0.405	0.571	0.042	9.670E-05
		BSA [m^2]	0.696	0.169	0.261	< 0.001	0.363	1.030	1.500					
		Age [years]	–0.009	0.002	–0.242	< 0.001	–0.013	–0.004	1.387					
Cardiac index [L.min/m^2]														
	1	(Constant)	5.313	0.214		< 0.001	4.891	5.735						
		BSA [m^2]	–1.383	0.117	–0.625	< 0.001	–1.614	–1.152	1.000	0.625	0.387	0.480	0.390	3.163E-25
	2	(Constant)	3.391	0.289		< 0.001	2.821	3.962						
		BSA [m^2]	–1.082	0.107	–0.489	< 0.001	–1.293	–0.871	1.119	0.739	0.542	0.415	0.155	1.253E-15
		Heart rate [beats/min]	0.020	0.002	0.418	< 0.001	0.016	0.025	1.119					
	3	(Constant)	4.135	0.294		< 0.001	3.556	4.714						
		BSA [m^2]	–1.389	0.111	–0.627	< 0.001	–1.607	–1.170	1.403					
		Heart rate [beats/min]	0.020	0.002	0.412	< 0.001	0.016	0.025	1.119	0.784	0.608	0.3841	0.067	3.823E-09
		Sex [female: 1; male: 0]	–0.360	0.059	–0.294	< 0.001	–0.476	–0.245	1.278					
	4	(Constant)	4.403	0.292		< 0.001	3.828	4.978						
		BSA [m^2]	–1.265	0.111	–0.571	< 0.001	–1.484	–1.045	1.519					
		Heart rate [beats/min]	0.017	0.002	0.340	< 0.001	0.012	0.021	1.315	0.801	0.634	0.371	0.026	8.050-05
		Sex [female: 1; male: 0]	–0.289	0.059	–0.236	< 0.001	–0.406	–0.172	1.401					
		Age [years]	–0.006	0.001	–0.193	< 0.001	–0.008	–0.003	1.380					
	5	(Constant)	4.687	0.306		< 0.001	4.084	5.289						
		BSA [m^2]	–1.259	0.110	–0.569	< 0.001	–1.476	–1.042	1.520					
		Heart rate [beats/min]	0.015	0.002	0.310	< 0.001	0.011	0.020	1.388					
		Sex [female: 1; male: 0]	–0.286	0.058	–0.234	< 0.001	–0.402	–0.171	1.402	0.808	0.644	0.365	0.012	0.0068
		Age [years]	–0.006	0.001	–0.201	< 0.001	–0.009	–0.003	1.385					
		Signal quality (categorical variable)	–0.131	0.048	–0.114	0.007	–0.226	–0.037	1.063					

95% CI — 95% confidence interval; VIF — variance inflation factor; SV, CO, CI were obtained using the pulse contour analysis (PCA) algorithm. A p value < 0.05 (red text) was considered statistically significant; other abbreviations — see Tables 1 and 2

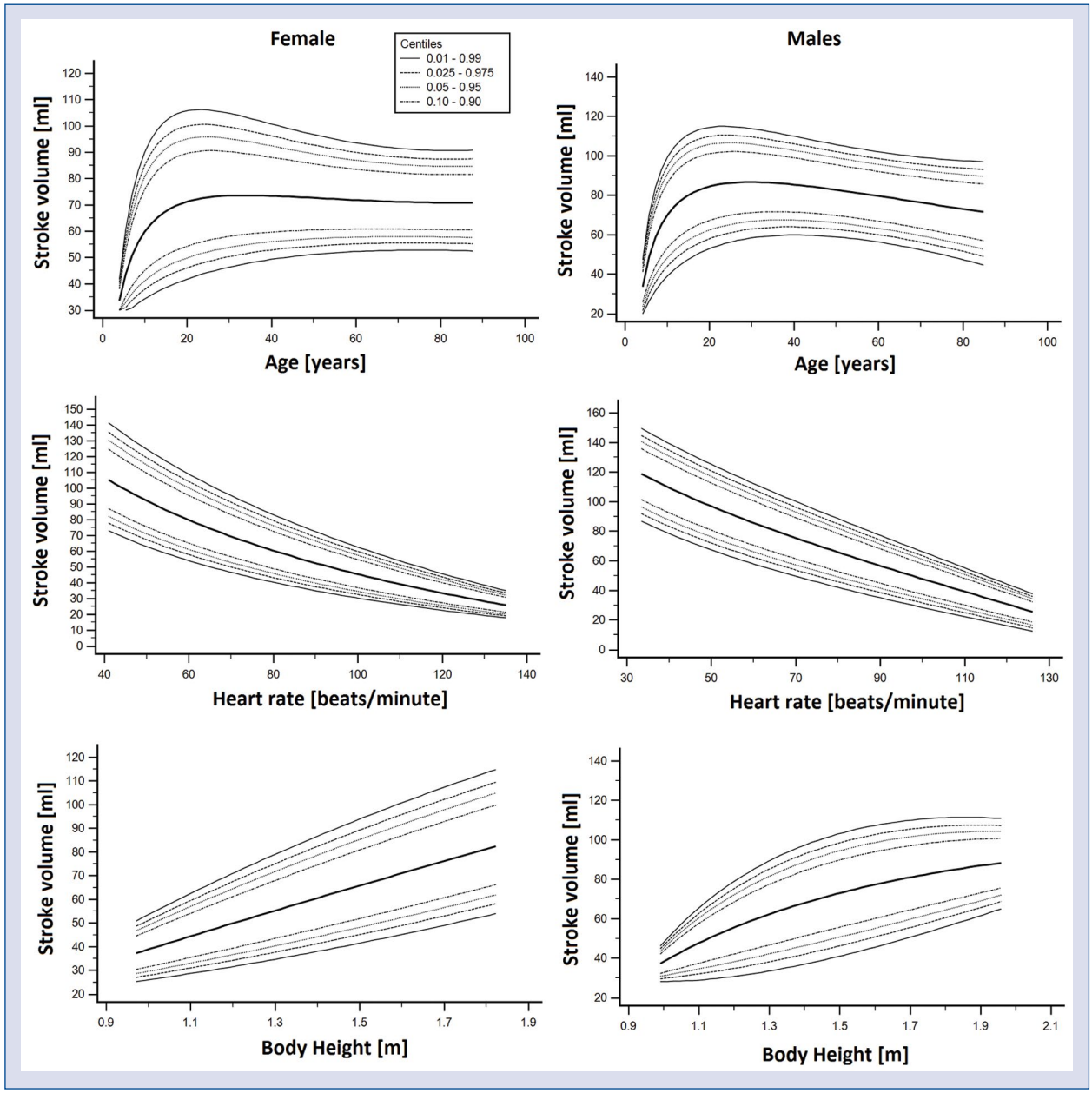


Figure 1. Age-specific, heart rate-specific and body height-specific percentiles of left ventricle stroke volume in females and males.

age, HR and BSA. **Supplementary Tables S13–S18** show sex-specific RIs for CI considering age, HR and BSA.

Discussion

The work's main findings were:

— First, in the construction of RIs for PCA-derived SV, CO and CI, not only were the age and anthropometric variables of the subjects taken into account, but also their sex and HR. The importance of the different explanatory variables varied depending on the parameter for which the RIs were constructed (SV, CO or CI) (Tables 2, 3).

— Second, this study represents the first study in which RIs and percentiles for PCA-derived SV, CO and CI are defined for children, adolescents, adults and elderly subjects (as a continuum throughout life; 3–88 years old) (Figs. 1–3; **Suppl. Tables S1–S18**).

— Third, when SV levels were analyzed it a steep rise in SV was observed during the first two decades, followed by a slow decline over the

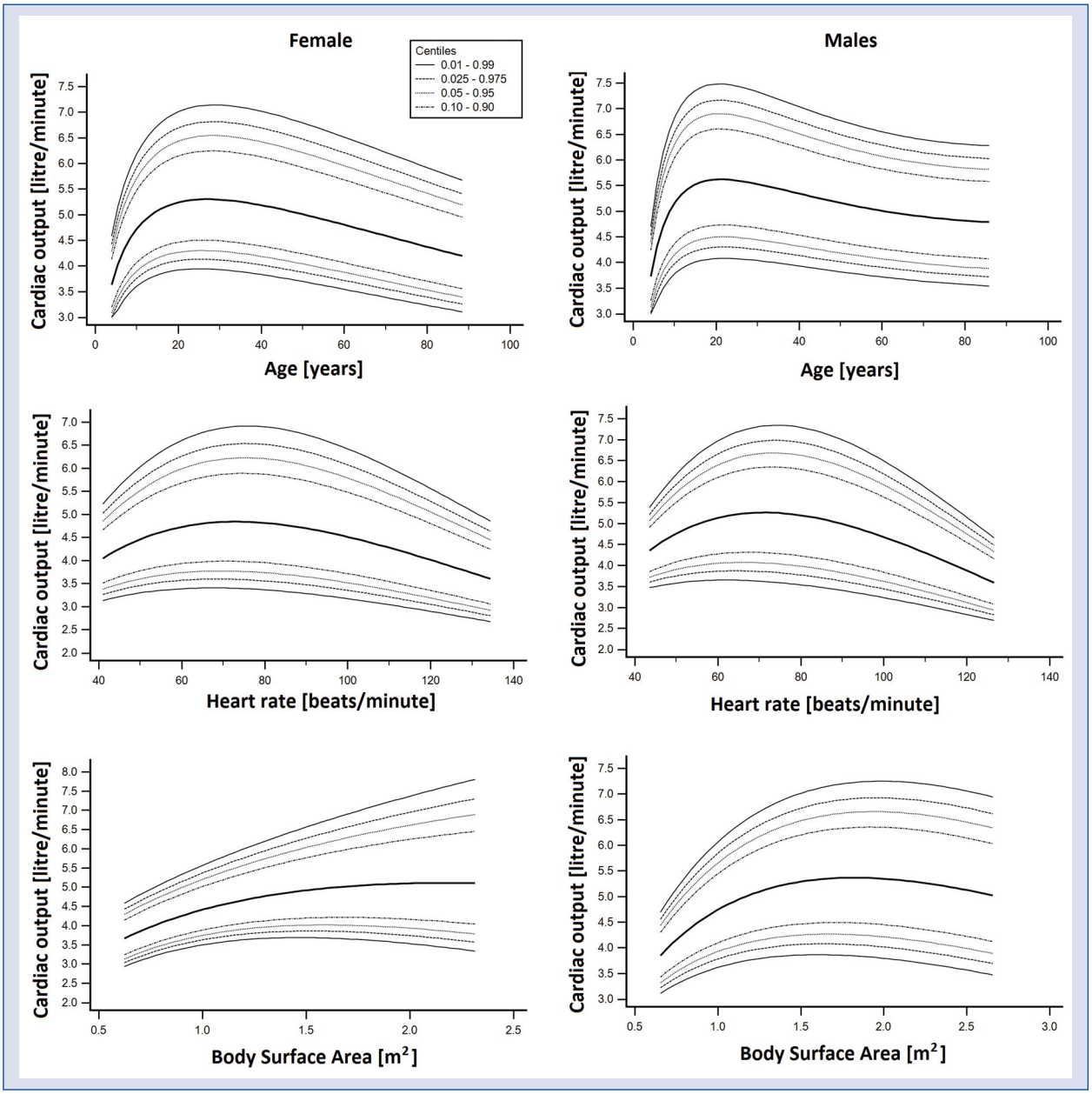


Figure 2. Age-specific, heart rate-specific and body surface area-specific percentiles of left ventricle cardiac output in females and males.

rest of their lives; additionally, the higher the HR, the lower the SV, while the higher the height, the higher the expected SV values (Fig. 1). There was a rapid increase in CO in the first two decades of life, followed by a fall throughout adult life (Fig. 2). Initially CO increases as HR increases, until HR reaches ~70–80 beats/min, then CO begins to fall in association with increases in HR; additionally, CO increases as the BSA increases (Fig. 2). CI values showed an important fall during the first two decades and then they remained practically unchanged over the rest of their lives (Fig. 3). CI increases in association with increases in HR, while lower CI values were observed in association with higher BSA values (Fig. 3).

The need to express SV, CO and/or CI values considering the age and/or anthropometric characteristics is widely known and accepted. However, it is of note that RIs constructed for a population including subjects from childhood to old age are scarce; in most works the age-groups included people of very different ages (i.e. 20 years apart)

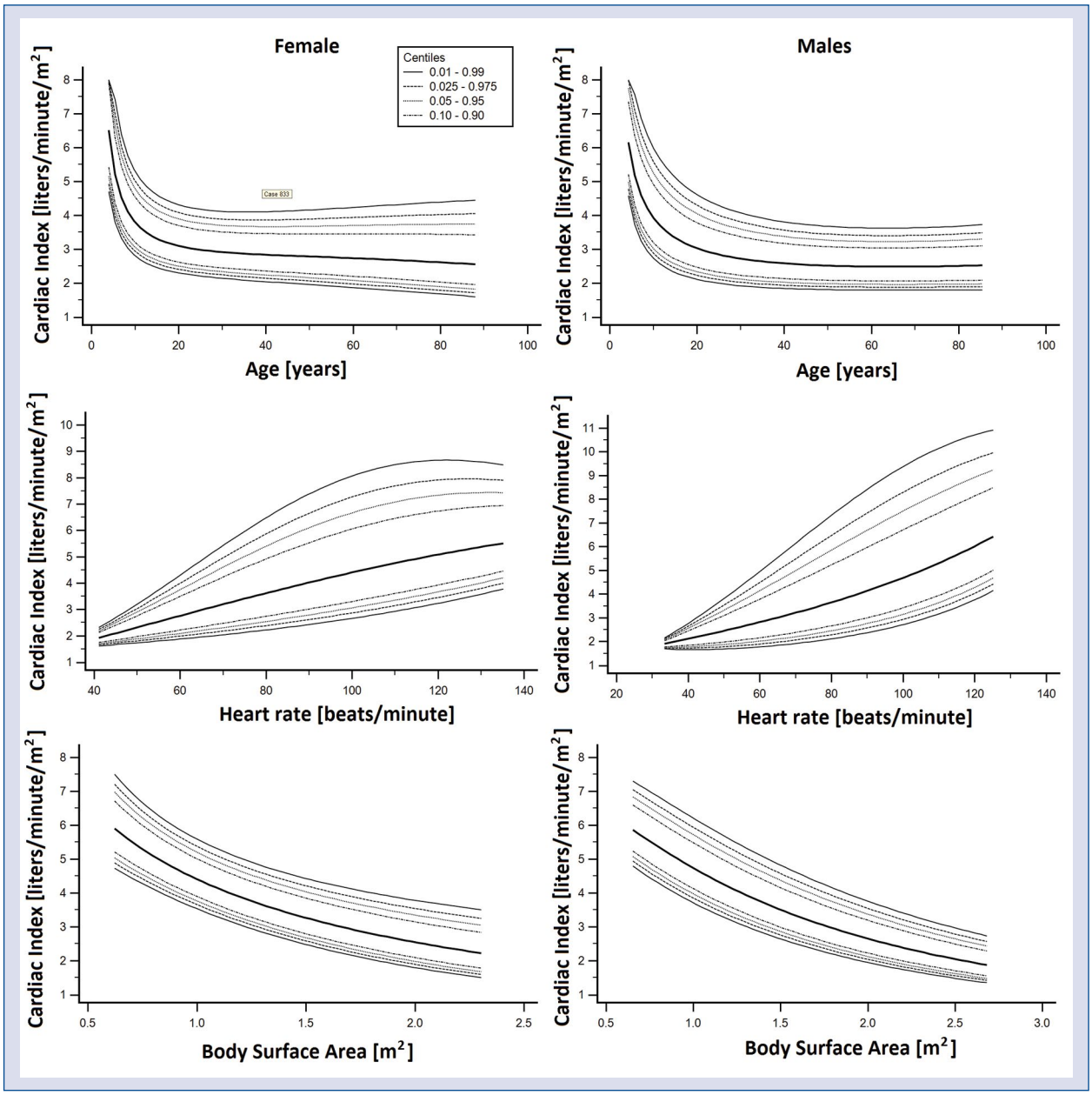


Figure 3. Age-specific, heart rate-specific and body surface area-specific percentiles of left ventricle cardiac index in females and males.

[30]; only adults were considered [5, 30, 31]; subjects aged 60–65 and older were assigned to a single group [5, 30] and/or non-uniform age ranges were considered (i.e. 0–2.9, 3–5.9, 6–11.9, 12–17.9, 18–29.9, 30–59.9, and ≥ 60 years old) [32]. The above does not allow for an adequate analysis of the age impact on hemodynamic characteristic and their variations. In addition, it does not allow for the use of accurate cut-off points in clinical practice (i.e. a 31 year old would be given reference values for a group ranging from 30 to 50.9 years old) [32].

The need to define RIs for males and females separately is not universally accepted and could even be considered controversial. There are works in which it was considered necessary to define sex-specific RIs, others in which the issue was not analyzed or was evaluated inaccurately, and finally, there are works that considered negligible the sex-related differences in the RIs of hemodynamic variables [16, 32–34]. In relation to the latter, sex-specific RIs were not defined; even when sex-related differences in hemodynamic

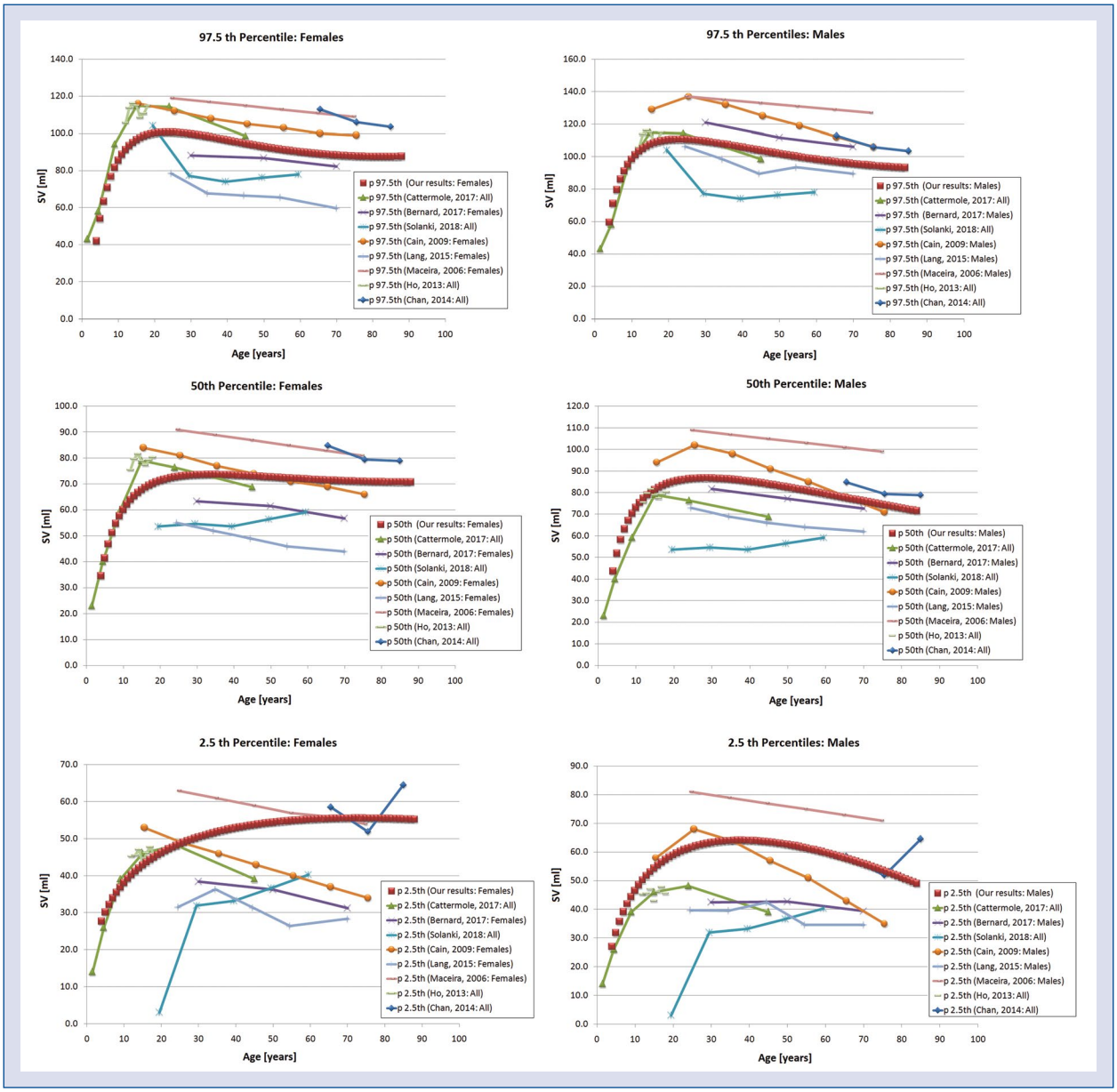


Figure 4. Age-specific percentiles (97.5th, 50th and 2.5th) of left ventricular stroke volume obtained in the present population and those reported from other authors [5, 16, 30, 31, 32, 33, 34, 35].

parameters remained statistically significant after controlling for anthropometric parameters [32]. Results herein, reinforce that the RIs in males differ for females, even after adjusting for height, weight and/or BSA (Table 3); highlighting the need for sex-specific RIs.

Finally, it is of note that oscillometric-derived signal quality was associated with SV, CO and CI values (Table 3). On average, a variation in the signal quality equal to the unit, could independently explain variations in SV, CO and CI equal to 2.8 mL/beat, 0.38 L/min and 0.13 L/min/m^2, respectively. Therefore, at least in theory, further work would be necessary to identify the specific wave characteristics required and/or the minimum quality value of an aortic waveform that would allow accurate CO values to be obtained using PCA.

Related with our second and third main result, when RIs for SV were analyzed taking into account age-related variations, a steep rise in SV was observed during the first two decades, followed by a slow decline during the rest of life (Fig. 1). In addition, the higher the HR, the lower the SV, while the greater the height, the higher the expected SV

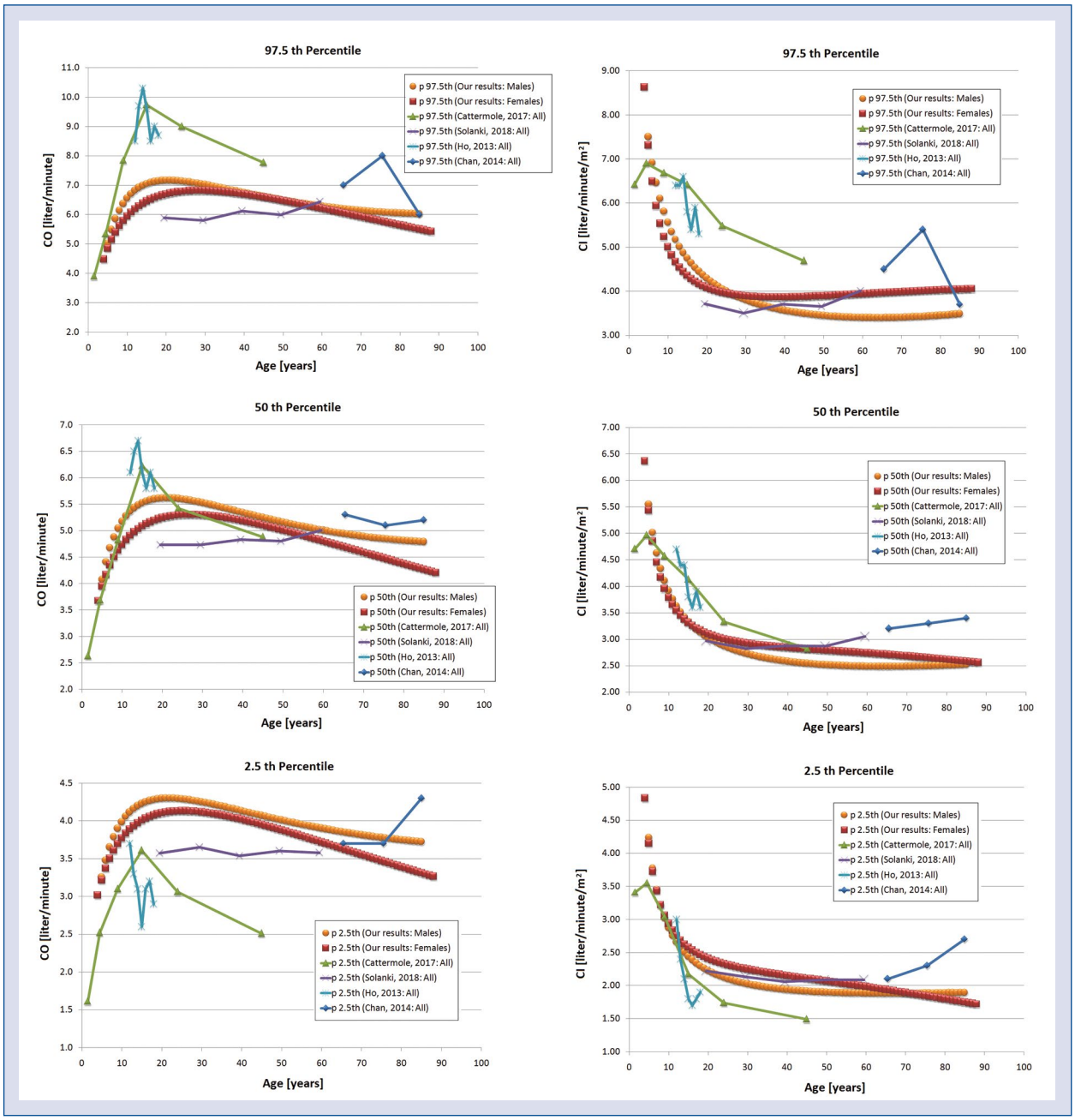


Figure 5. Age-specific percentiles (97.5th, 50th and 2.5th) of left ventricular cardiac output and cardiac index obtained in the present population and those reported from other authors [16, 32, 33, 34].

(Fig. 1). According to available research, until now there have been no reference values defined based on simultaneous or joint analysis of children, adolescents, adults or elderly subjects from a population. Since most available data correspond to values for pediatric or adult subjects it was not possible to perform direct comparisons with the present data. Therefore, a comparative analysis, from available works, an average was taken and SD values were obtained for the different ages. Then, assuming normal distribution, the 97.5th (mean +1.96 SD), 50th (mean) and 2.5th (mean –1.96 SD) percentiles were calculated (Figs. 4, 5). Being aware of the described limitation, it could be said that similar trends were observed among other studies.

Cattermole et al. [32] in a population based, cross-sectional, observational study performed in healthy Chinese subjects (n = 2218, age mean/range: 16.4/0.5–89 years old, 52% females), including data previously published by Ho et al. in 2013

(n = 590, age: 12–18 years old, 49% boys) and Chan et al. [34] in 2014 (n = 165, age groups: 61–70, 71–80, > 80 years old, 48.5% males), reported reference ranges for SV, CO and CI data obtained non-invasively (transcutaneous continuous Doppler) [32–34]. Despite methodological differences, including the non-uniformity of ranges used in the determination of age-subgroups and the lack of consideration of sex-related differences, in agreement with the present study the authors found a rapid increase in SV reaching its peak in their 20 s followed by a slow fall from the beginning of the third decade of life (Fig. 4). Time profiles and percentiles 2.5th, 50th and 97.5th reported by Cattermole et al. [32] are similar to those presented here.

Cattermole et al. [32] is almost the only study that can be fully compared with the present results (i.e. it included a large number of subjects within a wide age range). However, they studied: (1) a small number of subjects (e.g. n = 96 [31, 35]), (2) considered few age-groups and/or wide age intervals in the same group (i.e. 20–40, 40–60, ≥ 60) [30], (3) defined sex-specific analysis as unnecessary despite the sex-related differences observed [16] and/or (4) included subjects with mild chronic illness [34], also evidenced an SV tendency which decreases with age, within the heterogeneity of the reported values. The tendency of SV (percentile 50th) to decrease with age was evidenced regardless of the measurement method used: three-dimensional-echocardiography [30], PCA [16], magnetic resonance [31, 35], transcutaneous continuous-wave Doppler [32–34], biplane-echocardiography (Fig. 4) [5]. The rates of SV change with age (slope of association between SV 50th-percentile and age) were not very different when compared to results of other authors among themselves to the present data.

The analysis of age-related RIs for CO showed there was a rapid increase in CO levels over the first two decades of life, followed by a fall throughout adult life (in both, males and females) (Fig. 2). Initially CO increases as HR increases, until HR reaches ~70–80 beats/min, then CO begins to fall in association with increases in HR; CO increases as the BSA increases (Fig. 2).

Temporal profiles for CO were similar to those reported by Cattermole et al. (2017) [32]. The authors found an increase in CO, until 20 years of age. Thereafter, an age-related reduction in CO was observed. Cattermole et al. [32] values for the 50th-percentile and those from the present work almost overlap. In turn, Solanki et al. [16] and Chan et al. [34] reported average values (50th-percentile) for CO in adults and old age subjects similar to those found in the current data (Fig. 5).

Cardiac index values showed an important fall during the first two decades and then they remained practically unchanged (Fig. 3). CI values were associated with HR and BSA. CI increases in association with increases in HR, while lower CI values were observed in association with higher BSA values (Fig. 3). The described findings are in agreement with those reported by other authors (Fig. 5). In this regard, Cattermole et al. (2017) [32] and Ho et al. (2013) [33] described age-associated variations in CI, and their 50th-percentile curves were similar to the present ones. The present curves and those reported by Solanki et al. (2018) [16] and Chan et al. (2014) [34] for the 50th-percentile in adults are comparable.

Jointly analyzing the described results, it could be stated that CO rises steadily and reaches a peak in the 15–20 (teenage) years of life. Thereafter, it gradually declines. However, when considering CO adjusted for BSA (that it is to say CI), maximum (peak) would be observed < 6 years old, corresponding to a weight of 10–15 kg [32]. The variations in CO and CI could be related to and explained by the oxygen requirements of the tissues during those periods of life (i.e. those of maximum growth). High absolute CO levels in teenagers probably corresponds to accelerated growth and elevated oxygen consumption. From late teens onwards there is little or no growth, but a steadily declining level of physical activity was observed [32]. Overall, SV rises steadily until late teens then tends to decline gradually over the years, but when viewed against height (present data) or weight (Cattermole et al. data [32]), it shows a more linear positive relationship (Figs. 1, 4).

Conclusions

Sex, age, HR, and body height (for SV) or BSA (for CO and CI) are independent factors that explain PCA-derived hemodynamic values. Consequently, when constructing RIs of SV, CO and CI, it is necessary to discriminate using these variables.

This study provides the largest database concerning RIs and percentile curves of left ventricle SV(PCA), CO(PCA) and CI(PCA), obtained in children, adolescents and adults (3–88 years of age) from Latin-America (Uruguay), expressing results according to sex (males and females), age (year-to-year), HR (beats/minute), body height (in cm) and BSA (m^2).

Ethics

All procedures were in accordance with the ethical standards of the institutional and/or the national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual included in the study.

Acknowledgments

This work was supported by the Agencia Nacional de Investigación e Innovación (PRSCT-008-020; FSPI_X_2015_1_108484) and by extrabudgetary funds generated by CUiiDARTE.

Conflict of interest: None declared

References

1. García X, Mateu L, Maynar J, et al. [Estimating cardiac output. Utility in the clinical practice. Available invasive and non-invasive monitoring]. Med Intensiva. 2011; 35(9): 552–561, doi: 10.1016/j.medin.2011.01.014, indexed in Pubmed: 21411188.
2. Porter TR, Shillcutt SK, Adams MS, et al. Guidelines for the use of echocardiography as a monitor for therapeutic intervention in adults: a report from the American Society of Echocardiography. J Am Soc Echocardiogr. 2015; 28(1): 40–56, doi: 10.1016/j.echo.2014.09.009, indexed in Pubmed: 25559474.
3. Majonga ED, Rehman AM, McHugh G, et al. Echocardiographic reference ranges in older children and adolescents in sub-Saharan Africa. Int J Cardiol. 2017; 248: 409–413, doi: 10.1016/j.ijcard.2017.06.109, indexed in Pubmed: 28711335.
4. Lopez L, Colan SD, Frommelt PC, et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. J Am Soc Echocardiogr. 2010; 23(5): 465–95; quiz 576, doi: 10.1016/j.echo.2010.03.019, indexed in Pubmed: 20451803.
5. Lang R, Badano L, Mor-Avi V, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015; 16(3): 233–271, doi: 10.1093/ehjci/jev014.
6. Gottdiener JS, Bednarz J, Devereux R, et al. American Society of Echocardiography. American Society of Echocardiography recommendations for use of echocardiography in clinical trials. J Am Soc Echocardiogr. 2004; 17(10): 1086–1119, doi: 10.1016/j.echo.2004.07.013, indexed in Pubmed: 15452478.
7. Savage DD, Garrison RJ, Kannel WB, et al. Considerations in the use of echocardiography in epidemiology. The Framingham Study. Hypertension. 1987; 9(2 Pt 2): II40–II44, doi: 10.1161/01.hyp.9.2_pt_2.ii40, indexed in Pubmed: 3804399.
8. de Wilde RBP, Schreuder JJ, van den Berg PCM, et al. An evaluation of cardiac output by five arterial pulse contour techniques during cardiac surgery. Anaesthesia. 2007; 62(8): 760–768, doi: 10.1111/j.1365-2044.2007.05135.x, indexed in Pubmed: 17635422.
9. Camporota L, Beale R. Pitfalls in haemodynamic monitoring based on the arterial pressure waveform. Crit Care. 2010; 14(2): 124, doi: 10.1186/cc8845, indexed in Pubmed: 20236463.
10. Schlöglhofer T, Gilly H, Schima H. Semi-invasive measurement of cardiac output based on pulse contour: a review and analysis. Can J Anaesth. 2014; 61(5): 452–479.
11. Broch O, Bein B, Gruenewald M, et al. Accuracy of cardiac output by nine different pulse contour algorithms in cardiac surgery patients: a comparison with transpulmonary thermodilution. Biomed Res Int. 2016; 2016: 3468015, doi: 10.1155/2016/3468015, indexed in Pubmed: 28116294.
12. Grensemann J. Cardiac output monitoring by pulse contour analysis, the technical basics of less-invasive techniques. Front Med (Lausanne). 2018; 5: 64, doi: 10.3389/fmed.2018.00064, indexed in Pubmed: 29560351.
13. Weiss W, Gohlisch C, Harsch-Gladisch C, et al. Oscillometric estimation of central blood pressure: validation of the Mobil-O-Graph in comparison with the SphygmoCor device. Blood Press Monit. 2012; 17(3): 128–131, doi: 10.1097/MBP.0b013e328353ff63, indexed in Pubmed: 22561735.
14. Weber T, Wassertheurer S, Rammer M, et al. Validation of a brachial cuff-based method for estimating central systolic blood pressure. Hypertension. 2011; 58(5): 825–832, doi: 10.1161/HYPERTENSIONAHA.111.176313, indexed in Pubmed: 21911710.
15. Wassertheurer S, Kropf J, Weber T, et al. A new oscillometric method for pulse wave analysis: comparison with a common tonometric method. J Hum Hypertens. 2010; 24(8): 498–504, doi: 10.1038/jhh.2010.27, indexed in Pubmed: 20237499.
16. Solanki J, Mehta H, Shah C. Aortic blood pressure and central hemodynamics measured by noninvasive pulse wave analysis in Gujarati normotensives. Int J Clin Exp Physiol. 2018; 5(2): 75, doi: 10.4103/ijcep.ijcep_24_18.
17. Nakagomi A, Okada S, Funabashi N, et al. Age-related change in contribution of stroke volume to central pulse pressure. Clin Exp Hypertens. 2017; 39(3): 284–289, doi: 10.1080/10641963.2016.1259331, indexed in Pubmed: 28448183.
18. Díaz A, Zócalo Y, Cabrera-Fischer E, et al. Reference intervals and percentile curve for left ventricular outflow tract (LVOT), velocity time integral (VTI), and LVOT-VTI-derived hemodynamic parameters in healthy children and adolescents: Analysis of echocardiographic methods association and agreement. Echocardiography. 2018; 35(12): 2014–2034, doi: 10.1111/echo.14176, indexed in Pubmed: 30376592.
19. Díaz A, Zócalo Y, Bia D. Reference Intervals and Percentile Curves of Echocardiographic Left Ventricular Mass, Relative Wall Thickness and Ejection Fraction in Healthy Children and Adolescents. Pediatr Cardiol. 2019; 40(2): 283–301, doi: 10.1007/s00246-018-2000-y, indexed in Pubmed: 30288599.
20. Diaz A, Zócalo Y, Bia D, et al. Reference intervals and percentiles for carotid-femoral pulse wave velocity in a healthy population aged between 9 and 87 years. J Clin Hypertens (Greenwich). 2018; 20(4): 659–671, doi: 10.1111/jch.13251, indexed in Pubmed: 29532992.
21. Díaz A, Zócalo Y, Bia D, et al. Reference intervals of aortic pulse wave velocity assessed with an oscillometric device in healthy children and adolescents from Argentina. Clin Exp Hypertens. 2019; 41(2): 101–112, doi: 10.1080/10641963.2018.1445754, indexed in Pubmed: 29521547.
22. Curcio S, García-Espinosa V, Arana M, et al. Growing-Related changes in arterial properties of healthy children, adolescents, and young adults nonexposed to cardiovascular risk factors:

analysis of gender-related differences. Int J Hypertens. 2016; 2016: 4982676, doi: 10.1155/2016/4982676, indexed in Pubmed: 26989504.
23. Farro I, Bia D, Zócalo Y, et al. Pulse wave velocity as marker of preclinical arterial disease: reference levels in a uruguayan population considering wave detection algorithms, path lengths, aging, and blood pressure. Int J Hypertens. 2012; 2012: 169359, doi: 10.1155/2012/169359, indexed in Pubmed: 22666551.
24. Royston P, Wright E. A method for estimating age specific reference intervals ('normal ranges') based on fractional polynomials and exponential transformation. J R Statist Soc. 1998; 161(1): 79–101, doi: 10.1111/1467-985x.00091.
25. Engelen L, Ferreira I, Stehouwer CD, et al. Reference Values for Arterial Measurements Collaboration. Reference intervals for common carotid intima-media thickness measured with echotracking: relation with risk factors. Eur Heart J. 2013; 34(30): 2368–2380, doi: 10.1093/eurheartj/ehs380, indexed in Pubmed: 23186808.
26. Engelen L, Bossuyt J, Ferreira I, et al. Reference Values for Arterial Measurements Collaboration. Reference values for local arterial stiffness. Part A: carotid artery. J Hypertens. 2015; 33(10): 1981–1996, doi: 10.1097/HJH.0000000000000654, indexed in Pubmed: 26431185.
27. Bossuyt J, Engelen L, Ferreira I, et al. Reference Values for Arterial Measurements Collaboration. Reference values for local arterial stiffness. Part B: femoral artery. J Hypertens. 2015; 33(10): 1997–2009, doi: 10.1097/HJH.0000000000000655, indexed in Pubmed: 26431186.
28. Bellera CA, Hanley JA. A method is presented to plan the required sample size when estimating regression-based reference limits. J Clin Epidemiol. 2007; 60(6): 610–615, doi: 10.1016/j.jclinepi.2006.09.004, indexed in Pubmed: 17493520.
29. Lumley T, Diehr P, Emerson S, et al. The importance of the normality assumption in large public health data sets. Annu Rev Public Health. 2002; 23: 151–169, doi: 10.1146/annurev.publhealth.23.100901.140546, indexed in Pubmed: 11910059.
30. Bernard A, Addetia K, Dulgheru R, et al. 3D echocardiographic reference ranges for normal left ventricular volumes and strain: results from the EACVI NORRE study. Eur Heart J Cardiovasc Imaging. 2017; 18(4): 475–483, doi: 10.1093/ehjci/jew284, indexed in Pubmed: 28329230.
31. Maceira AM, Prasad SK, Khan M, et al. Normalized left ventricular systolic and diastolic function by steady state free precession cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2006; 8(3): 417–426, doi: 10.1080/10976640600572889, indexed in Pubmed: 16755827.
32. Cattermole G, Leung P, Ho G, et al. The normal ranges of cardiovascular parameters measured using the ultrasonic cardiac output monitor. Physiol Rep. 2017; 5(6): e13195, doi: 10.14814/phy2.13195.
33. Ho GYL, Cattermole GN, Chan SSW, et al. Noninvasive transcutaneous Doppler ultrasound-derived hemodynamic reference ranges in Chinese adolescents. Pediatr Crit Care Med. 2013; 14(5): e225–e232, doi: 10.1097/PCC.0b013e3182772f78, indexed in Pubmed: 23439468.
34. Chan CPY, Agarwal N, Sin KK, et al. Age-specific non-invasive transcutaneous Doppler ultrasound derived haemodynamic reference ranges in elderly Chinese adults. BBA Clin. 2014; 2: 48–55, doi: 10.1016/j.bbacli.2014.09.002, indexed in Pubmed: 26672648.
35. Cain PA, Ahl R, Hedstrom E, et al. Age and gender specific normal values of left ventricular mass, volume and function for gradient echo magnetic resonance imaging: a cross sectional study. BMC Med Imaging. 2009; 9: 2, doi: 10.1186/1471-2342-9-2, indexed in Pubmed: 19159437.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2021, Vol. 28, No. 6, 879–886
DOI: 10.5603/CJ.a2021.0022

ISSN 1897–5593
eISSN 1898–018X

Patient counselling service with the use of pictograms as the example of pharmacist intervention to improving compliance and medicine safety

Piotr Merks[1, 2, 3]*, Damian Świeczkowski[4], Marcin Balcerzak[5], Urszula Religioni[6], Ewelina Drelich[2], Jerzy Krysiński[2], Dagmara Hering[4], Miłosz Jaguszewski[4]

[1]Faculty of Medicine, Collegium Medicum, Cardinal Stefan Wyszynski University in Warsaw, Poland
[2]Department of Pharmaceutical Technology, Collegium Medicum, Bydgoszcz, Nicolaus University, Torun, Poland
[3]Piktorex, Warsaw, Poland
[4]First Department of Cardiology, Medical University of Gdansk, Poland
[5]Medink, Mysiadlo, Poland
[6]Collegium of Business Administration, Warsaw School of Economics, Warsaw, Poland

This paper was quest edited by Prof. Jan Saevels

Abstract

Background: *Pharmaceutical pictograms have been designed to help communicate medication instructions to patients. Pictograms used within a patient counseling service can significantly improve medication compliance and adherence. The study aimed to assess the improvement of adherence to therapy with the use of pictogram intervention in comparison to standard pharmacy practice in community pharmacies.*

Methods: *Pictograms informing about the proper way of using metoprolol prolonged release tablets were designed to be used on the packages of the drug in community pharmacies. Pharmacies belonging to a pharmacy practice-based research network were randomly assigned to a group using pictograms when dispensing the drug or one following their normal practice. At the first visit, all patients answered a structured questionnaire about their medication behavior in the preceding 7 days. The same questions were asked 4 weeks later to follow-up treatment adherence change and compare patients from pictogram group and standard practice group. Descriptive statistics was used to analyze the data, and the McNemar test was used to compare categorical data at baseline and follow-up.*

Results: *Of a total of 253 patients screened, 117 and 104 patients completed the study in the standard practice and pictogram groups, respectively. The use of pictograms significantly improved medication adherence in the following areas: not omitting doses ($p < 0.0001$), not crushing tablets ($p = 0.004$), number of tablets/day ($p = 0.49$), and time of use ($p = 0.001$), compared to the standard practice group.*

Conclusions: *Our results suggest that pictograms are effective in conveying messages about the proper way of using medications, and they increase treatment adherence, in comparison to standard dispensing practice.* (Cardiol J 2021; 28, 6: 879–886)

Key words: adherence, compliance, chronic disease, community pharmacy, pharmaceutical pictograms

Address for correspondence: Dr. Piotr Merks, Faculty of Medicine, Collegium Medicum, Cardinal Stefan Wyszynski University, ul. Wóycickiego 1/3, 01–938 Warszawa, Poland. tel: +48 602101979, e-mail: p.merks@uksw.edu.pl

Received: 4.01.2021 Accepted: 5.02.2021 Early publication date: 16.02.2021

Introduction

To date, many studies have addressed the problem of lack of adherence in patients diagnosed with chronic diseases. Due to the high prevalence and burden of cardiovascular diseases, adherence to prescribed treatment is considered among the most critical strategies contributing to improving health outcomes [1, 2]. Of the many factors affecting medication adherence, health care providers' factors are highlighted in particular [2]. Improving communication with the patient, patients' education, and increasing patient involvement can significantly improve medication adherence. Pharmacists' counseling is especially emphasized in this area [3]. Pharmacists play a key role in handling prescriptions, and by direct contact with patients just before the use of the drug, they have great potential to encourage patient compliance [4]. Good compliance and adherence improve health-related outcomes in many conditions [5]. On the other hand, poor medication adherence is associated with higher mortality and a greater risk of hospitalization [6].

Pharmaceutical pictograms as a supplement to pharmacy counseling are considered an effective tool facilitating the patient's understanding of the information provided [1, 7]. Pictograms are defined as visual images used in health information materials [8]. These types of drawings graphically represent instructions for the correct use and storage of medicines [7]. Pictograms enable patients to understand the instructions on how to use medicines, which is especially important in the context of health literacy. Pictograms can significantly influence the proper use of drugs among patients with low health literacy [9]. Thus, including pictograms in patient counseling could reduce the frequency of medication dosing errors. Moreover, pictograms in combination with a leaflet attached to the drug increase the patient's attention, remembering and recalling the rules of taking the drug [10]. Significantly, pictograms are culturally neutral, making them understandable regardless of language, also for people who cannot fully understand printed textual medication information [9]. Although there are many publications on pictograms in the literature, data about the utilization of pharmaceutical pictograms in a community pharmacy setting is limited. Most studies focus on design, comprehensiveness, and validation of different pictograms. High-quality studies are needed to support the routine use of any pictogram-based materials in routine practice. This study presents the results of the utilization of pharmaceutical pictograms in a community pharmacy setting. The study aimed to compare changes in adherence to treatment with metoprolol prolonged release (PR) in groups of patients who were/were not provided with pictograms when dispensing the drug at pharmacies.

Methods

Design and setting

This was a multicenter, prospective study with a control arm. The study was approved by the institutional review board of Collegium Medicum in Bydgoszcz, Poland. Patients' participation in the study was voluntary. All the patients provided written informed consent.

Patients were eligible for enrollment in the study if they were ≥ 18 years old, had a prescription of metoprolol PR tablets, had been using the drug once daily for at least 3 months, and signed an informed consent form agreeing to follow-up contact.

Metoprolol, a beta-blocking agent, belongs to the most common drugs used in the treatment of cardiovascular diseases. Patients who had just started PR metoprolol therapy, had used immediate-release metoprolol, or had been prescribed a different dosage regimen than once daily were excluded from our study. At a 1:1 ratio between groups, levels of type I error 0.05, and type II error 0.2 the study required 93 patients per group. However, these hypothetical assumptions were not reflected in the study results.

The study was conducted in Polish community pharmacies belonging to the Farenta Research pharmacy practice-based research network. Pharmacies were randomly assigned in a 1:1 ratio to dispense the products together with 3 pictograms placed on an external package showing how to use the medicine correctly, or in line with standard pharmacy practice (control group, without any pictograms). Pharmacies (n = 50) were randomized to pictogram or standard practice groups using a random sequence generator from www.random.org. The study was based on 2 interviews: an initial interview conducted during dispensation and a second interview performed no more than 30 days after first one (Fig. 1). At pharmacies randomized to the pictogram group, each patient received with the drug a set of 3 pharmaceutical pictograms with the following instructions: Take 1 tablet in the morning, do not crush the tablet, and swallow the tablet with water (Fig. 2). All pictograms were validated, as described earlier [11]. The dimension of each pictogram was

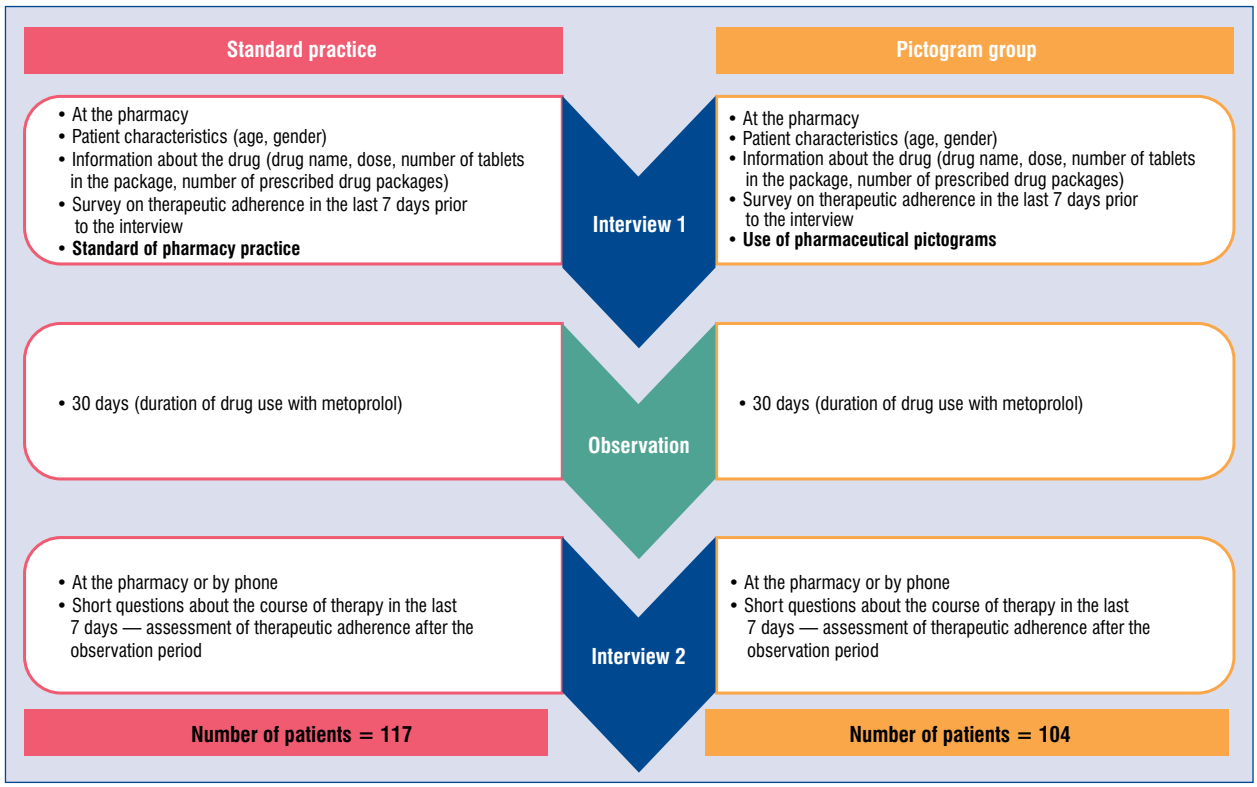


Figure 1. The use of pharmaceutical pictograms in the course of therapy with metoprolol prolonged-release tablets — the intervention chart.

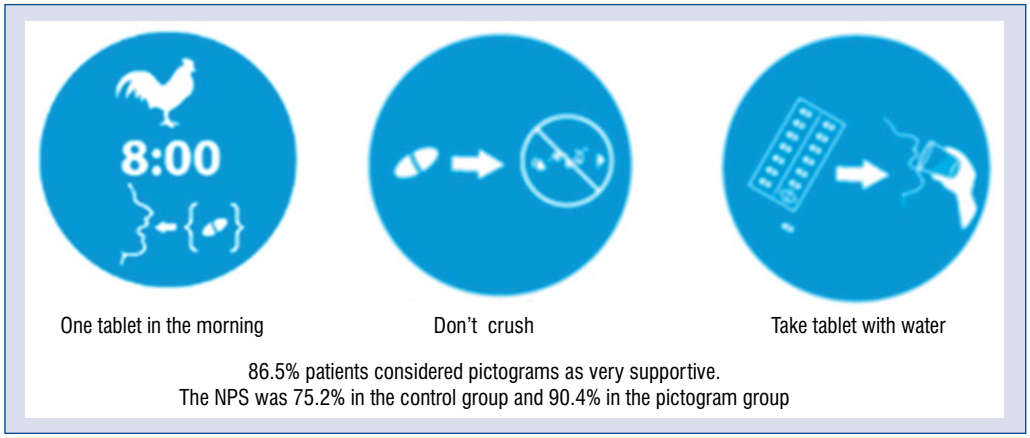


Figure 2. The set of pictograms used in the study; NPS — net promoter score.

30 × 30 mm (Fig. 2). Medical information conveyed by pictograms was consistent with the information in the local summaries of product characteristics and aligned with medication plans of patients. As recommended by the physician, the correct behavior was as follows: taking the medicine every day, taking one tablet once a day in the morning, not crushing/not chewing the tablet, swallowing the tablet with water. At pharmacies randomized to the standard practice, group patients obtained the drug without pictograms. The dispensation was ongoing according to the individual practice of pharmacists and not influenced by the study team.

Data acquisition

The first study interview was conducted during the initial visit at the pharmacy. We gave the same questionnaires to both groups. To allow us to compare the results from both interviews, during the first interview each patient received a unique identifier. The interviews were conducted by the pharmacy employee dispensing the medicines.

The questions asked in the first interview included sociodemographic information and behavior regarding use of metoprolol PR tablets in the last 7 days. Questions were related to the following dimensions of adherence: omitting doses, time of drug use, a number of tablets taken, dosing frequency, crushing/chewing tablets, and taking them with water (these 6 dimensions are understood as full adherence). The Brief Medication Questionnaire (BMQ) inspired the design of the questions [5]. The questions were adapted to assess outcomes influenced by pictogram messages. The scoring system was similar to the BMQ. The scales with multiple choices graduating the patient's adherence behavior were used to allow patients to indicate even small deviations from the target way of the use of the drug; however, the analysis was conservative, and the only full adherence to therapy was considered as a positive outcome.

The questions used in the study and their interpretation are available in Supplementary Materials. The second interview was performed 1 month after the first visit and included the same questions as in the earlier survey about adherence behavior in the preceding 7 days. Also, patients were asked to evaluate medical information received in the community pharmacy on a scale from 1 to 10, where 1 = very bad and 10 = very good. The data were recorded electronically by interviewing the employees of the participating pharmacies.

Endpoints

The primary outcome measures of the study included a change from the first to the second visit in the percentage of patients fully adherent to the main messages conveyed by the 3 pictograms: not omitting doses, not crushing tablets, swallowing tablets with water. The secondary endpoint was a change in the percentage of patients declaring the use of the correct number of individual doses during the day, the right number of tablets per dose, and taking the drug in the morning.

Data analysis

All categorical data were expressed as proportions, and continuous data were expressed as mean and standard deviation (SD). Descriptive analysis was conducted to present the results at baseline and follow up, assessing the primary and secondary outcome measures. Patients' declarations in the survey were classified as indicating full adherence (answers indicating proper behavior) or non-adherence (answers indicating any other behavior than the proper one or 'do not know'). The McNemar test was used to compare categorical data at baseline and follow-up in both groups. Intention to treat analysis was followed, and a probability value of < 0.05 was considered statistically significant for all analyses. Possible changes from the first visit to the second visit included the following: no change in adherence, improvement, and worsening of adherence. Logistic regression was used to calculate the odds of improvement or worsening adherence in every studied dimension of adherence for the patients of each group.

The net promoter score (NPS) was used to examine the patients' opinions about medical information received at a pharmacy [12]. Patients who evaluated medical information as 9 or 10 points were classified as advocates. The group of patients who responded 7–8 were classified as indifferent, and re the respondents who evaluated the information received as 1–6 points were classified as critical of the provided information.

Results

Patient disposition and characteristics

The data were collected between January and March 2017, and in total 253 patients participated in the first interview. The number of screened patients is unknown because pharmacists did not record patients refusing to participate or ineligible to participate. The data of 32 patients were not included in the analysis because they were lost to follow-up (n = 13), provided incomplete data in the first interview (n = 12), used metoprolol immediate release (n = 2), were dosed differently than according to the inclusion criteria (n = 3), or misconduct was detected (n = 2). The complete data from 117 patients in the standard practice group and 104 patients in the pictogram group were included in the analysis. The baseline characteristics by treatment group are presented in Table 1. The patient sample was 59% female. Mean age ± SD of patients was 65.2 ± 13.0 years. The sample included patients self-reporting use of metoprolol for hypertension (51%), cardiac arrhythmias (29%), prophylactic treatment following myocardial infarction (7%), angina (5%), and unknown/undeclared reasons (7%).

Table 1. Characteristics of the study population.

	Routine pharmacy practice (n = 117)	Pharmaceutical pictograms (n = 104)
Age, median (range) [years]	67 (31–94)	64 (30–91)
Woman	74 (63.2%)	58 (55.8%)
Different drugs used by patients:		
Missing	1 (0.9%)	0 (0%)
1 drug	5 (4.3%)	5 (4.8%)
2 drugs	15 (12.8%)	11 (10.6%)
3 drugs	25 (21.4%)	17 (16.3%)
≥ 4 drugs	71 (60.7%)	71 (71.2%)
Indication for use of metoprolol:		
Hypertension	60 (51.3%)	52 (50.0%)
Cardiac arrythmias	40 (34.2%)	25 (24.0%)
Prophylactic after myocardial infarction	6 (5.1%)	10 (9.6%)
Angina pectoris	5 (4.3%)	7 (6.7%)
I do not know/I do not remember	6 (5.1%)	10 (9.6%)

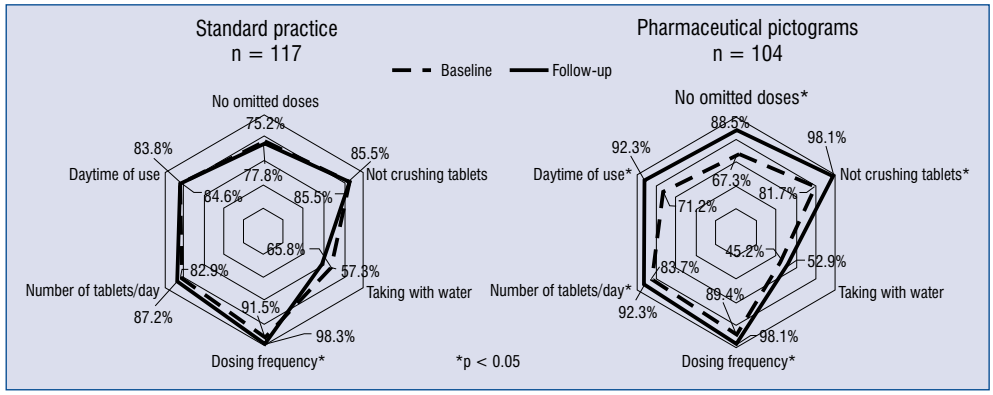


Figure 3. The percentage of patients fully adherent (proper therapeutic behavior) for each tested adherence domain in the standard practice and pictogram groups at baseline and follow-up.

The practical effectiveness of pictograms

At baseline, 74 (63.2%) patients in the standard practice group and 70 (67.3%) patients in the pharmaceutical pictograms group had ≥ 1 problem in any of the analyzed adherence dimensions. At the follow-up, the number of non-adherent patients remained stable in the standard group (n = 76, 65.0%) and decreased in the pictogram group (n = 58, 55.8%), p = 0.1636. Figure 3 presents changes in percentages of patients fully adherent in each of the 6 analyzed dimensions of adherence at baseline and follow-up. In the pictogram group an increase in the number of patients with full adherence was more common than in the standard practice group. The percentage of patients not omitting doses increased in the pictogram group from 67.3% to 88.5% (an increase of 31.5%, p < 0.0001). In the standard practice group the percentage of patients not omitting doses remained stable (from 77.8% to 75.2%; p = 0.8679). At the follow-up, 98.1% of patients in the pictogram group were not crushing tablets, compared to 81.7% at baseline (increase by 20.07%, p = 0.004). In the standard practice group, the percentages of patients not crushing tablets at baseline and follow-up did not change (85.5% vs. 85.5%, p = 0.647). Neither pictograms nor standard practice improved significantly for the swallowing tablets with water behavior (an increase from 45.2% to 52.9% of patients in the pictogram group, p = 0.322, and a decrease from

65.8% to 57.2% of patients in the standard practice group, p = 0.121; Fig. 3).

Pictograms improved adherence in all secondary endpoints. In the pictogram group the percentage of patients using metoprolol once daily was 89.4% at baseline and 98.1% at follow-up (an increase of 9.73%, p = 0.004). However, a similar improvement was also observed in the standard practice group (an increase of 7.43%, p = 0.021; Fig. 3). Pictograms significantly increased the number of patients using 1 tablet per day in line with a defined treatment plan from 83.6% to 92.3% (an increase of 10.27%, p = 0.049). The improvement was not significant in the standard practice group (p =0.359; Fig. 3). Finally, pictograms increased the percentage of patients using the drug in the morning from 71.1% at baseline to 92.3% at follow-up (an increase of 29.63%, p = 0.0001), but this was not the case in the standard practice group (p = 1).

Patients' opinions about pharmaceutical pictograms

The NPS was 75.2% in the control group and 90.4% in the pictogram group. The vast majority of patients (86.5%; n = 90) who obtained pictograms identified them as very supportive. The mean score ± SD in the pictogram group was 9.58 ± 0.69 and in the control group 9.24 ± 1.30 (p = 0.0129).

Discussion

This study provides the first comparative evidence that the use of pharmaceutical pictograms improves adherence to recommended drug therapy in routine pharmacy practice. Improvement of adherence was associated with a substantial reduction in the number of patients who missed drug doses. Importantly, pictograms have also increased awareness and knowledge about not crushing tablet medication, which has clinically relevant implications in terms of treatment effectiveness. Furthermore, patients who were using pictograms more often changed the time of taking the drug to the morning, in comparison to the standard practice. Of all these areas, only an improvement in dosing frequency was observed in the group of patients with standard practice.

The only domain of adherence that remained unchanged by pictogram use was taking tablets with water (as was recommended by the third pictogram — take a tablet with water). Because the use of tablets with water was the most compromised dimension of adherence studied, improvement of this behavior requires additional studies. In Poland, every package insert of metoprolol PR provides information about the required liquid volume recommended to assure effects (the PR form of metoprolol should be used in the morning, with a minimum half a glass of water, and it cannot be crushed). The pictogram highlighted this information; however, an improvement was not observed, and many patients swallowed medicines without or with not enough liquid.

Non-adherence to recommended therapy can lead to ineffectiveness as well as the manifestation of unintended adverse reactions [13, 14]. Taking a PR formulation requires specific patient behavior and should be considered an important matter for both physicians and pharmacists [15, 16]. At the first interview over 10% of patients from both groups crushed the tablets and over 40% of participants only sometimes swallowed the tablets with water. This observation indicates that information received from physicians and pharmacists may be insufficient for the correct use of medications.

Strategies to improve medication adherence in clinical practice are necessary, given the consequences of medication misuse [6]. Pharmacists, who provide pharmaceutical counseling, play a vital role in this respect [17–19]. The literature indicates many advantages of patient counseling; among others, patients become aware of the importance of therapy, understand doctors' recommendations, become active participants in the treatment process, and thus better follow the treatment recommendations [20].

Patients who received pictograms were able to favorably change their behavior, in contrast to those who were not using pictograms. This is particularly evident with omitting doses, crushing tablets, taking the right dose with the right frequency, and at the correct time of day. Finally, the pictograms were well accepted by the vast majority of participants, which can be understood as a good prognosis for this technology in the future.

Pictograms contribute to a better understanding of the drug's information, especially for the elderly or patients with low health literacy [9]. In our study, the patients' median age was 67 years in the standard pharmacy practice group and 64 years for patients in the pictogram group. Moreover, most of the patients in both groups were taking more than 4 drugs. For this reason, adherence to therapy for these groups of patients is particularly important.

The use of pictograms should be classified as a behavioral technique aimed at changing patient behavior by constantly reminding the patient of proper medication usage. Despite the long history

of using pictograms, their effectiveness is still a matter of controversy, particularly due to the risk of misunderstanding the pictogram [21–23]. Yin et al. [24] conducted a high-quality randomized study and that showed that pictogram-based intervention decreased the rate of dosing errors among caregivers whose children were treated at an urban pediatric emergency department. Similarly, a study from Malaysia proved the positive role of pictograms in improving the quality of use of oral liquid medicines. Another study suggests that pictograms significantly increased dosing accuracy [25]. The results of a recently published analysis of 771 studies aiming to improve therapeutic adherence showed that healthcare professionals should focus more on behavioral interventions, especially those based on the development of drug use habits, than on cognitive strategies to change the knowledge and beliefs of patients [26].

Although our study only refers to one product (metoprolol), the positive results obtained may be an incentive to extend the use of pictograms to other drugs used in cardiac diseases. Undoubtedly, all pictograms should be designed carefully and tested before their implementation to routine practice [10]. Moreover, pictograms need to be adjusted to local requirements, both formally determined by local summaries of products characteristics and social determinates, which may significantly improve understanding and acceptance levels [19]. For clarity, pictograms should be supplemented by a clear and simple oral statement provided by healthcare professionals [27]. It is worth mentioning that among illiterate populations, verbal explanations are indispensable, and in many clinical scenarios they are crucial to effective comprehension of drug-related information conveyed in pictograms [28]. While our study indicates that pictograms exert a substantial impact on patient behaviors and therapeutic adherence, we were not able to rule out the potential bias related to the study methods. Randomization of pharmacies instead of patients would affect the objectivity of findings. Moreover, the study was conducted in community pharmacies belonging to Farenta Research. These pharmacies, relying on the pharmacy standards, can provide patients with a better quality of care, which may affect the obtained results. The self-reported medication adherence measures used in the study can provide valuable information despite their limitations. Patients may tend to evaluate their adherence better than it really is. Thus, the used questionnaire offered many options to express the level of adherence, but the data analysis was conservative. It was assumed that only total adherence was considered as a positive outcome, and all other options as non-adherence. The change from non-adherence to partial adherence was not considered as an improvement.

Conclusions

Based on these results, pictograms can be an effective tool dedicated to improving patient adherence. Pictograms were accepted by patients and effectively changed most of their inappropriate behaviors. Our study certainly confirmed that pictograms significantly improve patients' compliance, particularly in the areas of non-omitted drug doses and indications not to crush tablets. Importantly, an improvement in compliance in this respect in the group of patients with standard practice was not observed. Further randomized clinical studies aimed at the evaluation of long-term effectiveness of pictograms are strongly warranted. Further clinical studies should also focus on health care providers' perception of pictograms and how pictograms influence regular work in community pharmacies. This type of research may improve the transition pictograms from research to routine settings.

Acknowledgments

The authors thanks the personnel of the pharmacies and patients who participated in the study.

Funding

This work was supported by the National Centre of Research and Development in Warsaw and the LQT Fund S.A. in Gdansk (project Bridge Alfa).

Conflict of interest: None declared

References

1. Park LG, Howie-Esquivel J, Chung ML, et al. A text messaging intervention to promote medication adherence for patients with coronary heart disease: a randomized controlled trial. Patient Educ Couns. 2014; 94(2): 261–268, doi: 10.1016/j.pec.2013.10.027, indexed in Pubmed: 24321403.
2. Yap A, Thirumoorthy T, Kwan Y. Medication adherence in the elderly. J Clin Gerontol Geriat. 2016; 7(2): 64–67, doi: 10.1016/j.jcgg.2015.05.001.
3. Kvarnström K, Airaksinen M, Liira H. Barriers and facilitators to medication adherence: a qualitative study with general practitioners. BMJ Open. 2018; 8(1): e015332, doi: 10.1136/bmjopen-2016-015332, indexed in Pubmed: 29362241.
4. Cushing A, Metcalfe R. Optimizing medicines management: From compliance to concordance. Ther Clin Risk Manag. 2007; 3(6): 1047–1058, indexed in Pubmed: 18516274.

5. Okumura LM, Rotta I, Correr CJ. Assessment of pharmacist-led patient counseling in randomized controlled trials: a systematic review. Int J Clin Pharm. 2014; 36(5): 882–891, doi: 10.1007/s11096-014-9982-1, indexed in Pubmed: 25052621.
6. Kim S, Shin DW, Yun JM, et al. Medication adherence and the risk of cardiovascular mortality and hospitalization among patients with newly prescribed antihypertensive medications. Hypertension. 2016; 67(3): 506–512, doi: 10.1161/HYPERTENSIONAHA.115.06731, indexed in Pubmed: 26865198.
7. Sletvold H, Sagmo LA, Torheim EA. Impact of pictograms on medication adherence: A systematic literature review. Patient Educ Couns. 2020; 103(6): 1095–1103, doi: 10.1016/j.pec.2019.12.018, indexed in Pubmed: 31924384.
8. Dowse R. Pharmacists, are words enough? The case for pictograms as a valuable communication tool. Res Social Adm Pharm. 2020 [Epub ahead of print], doi: 10.1016/j.sapharm.2020.10.013, indexed in Pubmed: 33139214.
9. Ng AWY, Chan AHS, Ho VWS. Comprehension by older people of medication information with or without supplementary pharmaceutical pictograms. Appl Ergon. 2017; 58: 167–175, doi: 10.1016/j.apergo.2016.06.005, indexed in Pubmed: 27633210.
10. Barros IMC, Alcântara TS, Mesquita AR, et al. The use of pictograms in the health care: a literature review. Res Social Adm Pharm. 2014; 10(5): 704–719, doi: 10.1016/j.sapharm.2013.11.002, indexed in Pubmed: 24332470.
11. Merks P, Świeczkowski D, Balcerzak M, et al. The evaluation of pharmaceutical pictograms among elderly patients in community pharmacy settings: a multicenter pilot study. Patient Prefer Adherence. 2018; 12: 257–266, doi: 10.2147/PPA.S150113, indexed in Pubmed: 29497281.
12. Reichheld FMR. The ultimate question 2.0. Now net promoter companies thrive in a customer-driven world. Harvard Business Review Press, Boston MA 2011.
13. Jankowski P, Czarnecka D, Wolfshaut-Wolak R, et al. Secondary prevention of coronary artery disease in contemporary clinical practice. Cardiol J. 2015; 22(2): 219–226, doi: 10.5603/CJ.a2014.0066, indexed in Pubmed: 25299500.
14. Kubica A, Obońska K, Kasprzak M, et al. Prediction of high risk of non-adherence to antiplatelet treatment. Kardiol Pol. 2016; 74(1): 61–67, doi: 10.5603/KP.a2015.0117, indexed in Pubmed: 26101025.
15. Swieczkowski D, Merks P, Gruchala M, et al. Pharmaceutical services as a tool to improve outcomes in patients with cardiovascular diseases. Int J Cardiol. 2016; 222(11): 238–241, doi: 10.1016/j.ijcard.2016.07.189, indexed in Pubmed: 27497101.
16. Mogielnicki M, Swieczkowski D, Bachorski W, et al. The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) perspective on cardiovascular Polypill: A multidimensional concept. Cardiol J. 2016; 23(5): 515–517, doi: 10.5603/CJ.2016.0074, indexed in Pubmed: 27723064.
17. Smith DH, Kramer JM, Perrin N, et al. A randomized trial of direct-to-patient communication to enhance adherence to beta-blocker therapy following myocardial infarction. Arch Intern Med. 2008; 168(5): 477–483; quiz 447, doi: 10.1001/archinternmed.2007.132, indexed in Pubmed: 18332291.
18. Wong MCS, Liu KQL, Wang HHX, et al. Effectiveness of a pharmacist-led drug counseling on enhancing antihypertensive adherence and blood pressure control: a randomized controlled trial. J Clin Pharmacol. 2013; 53(7): 753–761, doi: 10.1002/jcph.101, indexed in Pubmed: 23677794.
19. Rosen MI, Rigsby MO, Salahi JT, et al. Electronic monitoring and counseling to improve medication adherence. Behav Res Ther. 2004; 42(4): 409–422, doi: 10.1016/S0005-7967(03)00149-9, indexed in Pubmed: 14998735.
20. Mohiuddin AK. Patient counseling: a complete guide for compliance. J Applied Pharma Sci Res. 2019: 1–10, doi: 10.31069/japsr.v1i4.1.
21. Mansoor LE, Dowse R. Effect of pictograms on readability of patient information materials. Ann Pharmacother. 2003; 37(7-8): 1003–1009, doi: 10.1345/aph.1C449, indexed in Pubmed: 12841808.
22. Kim H, Nakamura C, Zeng-Treitler Q. Assessment of pictographs developed through a participatory design process using an online survey tool. J Med Internet Res. 2009; 11(1): e5, doi: 10.2196/jmir.1129, indexed in Pubmed: 19275981.
23. Cloutier M, Vaillancourt R, Pynn D, et al. Design and development of culture-specific pictograms for type 2 diabetes mellitus education and counselling. Can J Diabetes. 2014; 38(6): 379–392, doi: 10.1016/j.jcjd.2014.03.010, indexed in Pubmed: 25028197.
24. Yin HS, Dreyer BP, van Schaick L, et al. Randomized controlled trial of a pictogram-based intervention to reduce liquid medication dosing errors and improve adherence among caregivers of young children. Arch Pediatr Adolesc Med. 2008; 162(9): 814–822, doi: 10.1001/archpedi.162.9.814, indexed in Pubmed: 18762597.
25. Chan HK, Hassali MA, Lim CJ, et al. Improving pediatric liquid medication labeling of the hospital information system in Malaysia: qualitative analysis of pharmacists' perceptions. Pharm Pract (Granada). 2016; 14(2): 699, doi: 10.18549/PharmPract.2016.02.699, indexed in Pubmed: 27382422.
26. Conn VS, Ruppar TM. Medication adherence outcomes of 771 intervention trials: Systematic review and meta-analysis. Prev Med. 2017; 99: 269–276, doi: 10.1016/j.ypmed.2017.03.008, indexed in Pubmed: 28315760.
27. Braich PS, Almeida DR, Hollands S, et al. Effects of pictograms in educating 3 distinct low-literacy populations on the use of postoperative cataract medication. Can J Ophthalmol. 2011; 46(3): 276–281, doi: 10.1016/j.jcjo.2011.05.004, indexed in Pubmed: 21784215.
28. Joshi Y, Kothiyal P. A pilot study to evaluate pharmaceutical pictograms in a multispecialty hospital at dehradun. J Young Pharm. 2011; 3(2): 163–166, doi: 10.4103/0975-1483.80306, indexed in Pubmed: 21731363.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2021, Vol. 28, No. 6, 887–895
DOI: 10.5603/CJ.a2019.0126

ISSN 1897–5593
eISSN 1898–018X

The influence of high-density lipoprotein cholesterol on maximal lipid core burden indexing thin cap fibrous atheroma lesions as assessed by near infrared spectroscopy

Magdalena M. Dobrolińska[1], Paweł Gąsior[1], Wojciech Wańha[1], Przemysław Pietraszewski[2], Elżbieta Pociask[3], Grzegorz Smolka[1], Wojciech Wojakowski[1], Tomasz Roleder[4]

[1]Division of Cardiology and Structural Heart Diseases, Medical University of Silesia in Katowice, Poland
[2]Department of Sports Theory, Jerzy Kukuczka Academy of Physical Education in Katowice, Poland
[3]Department of Biocybernetics and Biomedical Engineering, AGH University of Science and Technology, Krakow, Poland
[4]Regional Specialist Hospital, Research and Development Center, Wroclaw, Poland

Abstract

Background: *Previous studies suggest that higher plasma concentrations of several lipid molecules are associated with higher lipid core burden index (LCBI) near infrared spectroscopy (NIRS) imaging. The aim of this study was to investigate whether an association between plasma lipids depends on plaque morphology (thin cap fibrous atheroma [TCFA] vs. non-TFCA) as measured by near-infrared spectroscopy–intravascular ultrasound (NIRS-IVUS).*

Methods: *Sixty-four patients retrospectively enrolled were diagnosed with stable coronary artery disease or acute coronary syndrome who underwent NIRS-IVUS imaging. Before percutaneous coronary intervention, blood samples were collected for measurement of serum levels of total cholesterol (TC), low-density lipoprotein cholesterol (HDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG). Patients were divided into two groups based on $maxLCBI_{4mm}$ and IVUS imaging. Those with $maxLCBI_{4mm} \geq 323$ were included into TCFA group ($n = 35$) while others were assigned to the non-TCFA group ($n = 29$).*

Results: *Thin cap fibrous atheroma lesions were significantly longer than the non-TCFA lesions (25.66 ± 9.56 vs. 17.03 ± 9.22, $p = 0.001$). TCFA characterizes greater plaque burden (78.4 [70.9, 82.2] vs. 72.70 [64.77, 76,05]; $p = 0.021$) and plaque volume (176.1 [110.75, 247.5] vs. 68.1 [55.58, 143.35]; $p = 0.000$) as compared to non-TCFA. In TCFA suspected lesions, there was no correlation between $maxLCBI_{4mm}$ and LDL levels ($r = 0.105$, $p = 0.549$) nor TC levels ($r = –0.035$, $p = 0.844$) but a negative correlation was found between HDL-C and $maxLCBI_{4mm}$ ($r = –0.453$, $p = 0.007$).*

Conclusions: *The present study showed that there was no correlation between plasma LDL-C, TC and TG level and the amount of lipids in coronary plaque assessed by NIRS in both TCFA and non-TCFA groups. Only HDL-C correlated with $maxLCBI_{4mm}$ in TCFA lesions.* (Cardiol J 2021; 28, 6: 887–895)

Key words: lipid plasma levels, NIRS-IVUS

Address for correspondence: Tomasz Roleder, MD, PhD, Provintional Specialist Hospital, Research and Development Center, ul. H.M. Kamieńskiego 73a 51–124 Wrocław, Poland, tel: +48 884096034, e-mail: tomaszroleder@gmail.com

Received: 31.03.2019 Accepted: 19.08.2019 Early publication date: 23.12.2019

Introduction

Stable coronary artery disease (SCAD) is a common cause of death. According to the European Heart Network Report from 2017 Ischemic Heart Disease (IHD) is responsible for 862,000 deaths a year (19% of all deaths) among men and 877,000 deaths (20%) among women in Europe each year [1]. Untreated SCAD may be followed by acute coronary syndrome (ACS). In most cases (approximately 75%) ACS is caused by a rupture or erosion of the vulnerable atherosclerotic plaque which leads to an occlusion of the vessel [2–4]. Vulnerable plaques are considered to be thin cap fibrous atheroma (TCFA) [5, 6]. TCFAs were defined by Burke et al. [7] as a necrotic and lipid-rich core plaque covered with fibrous cap < 65 μm measured by optical coherence tomography (OCT). The lipid-rich core containing plaques can also be detected by near-infrared spectroscopy (NIRS) [8, 9], a catheter-based intravascular imaging device based on diffuse reflectance spectroscopy. Its adjustment to intravascular ultrasound (IVUS) enables the periprocedural analysis of the chemical composition of plaque and distinguishes lipid-rich lesions. The amount of lipids is measured as a lipid core burden index ($_{max}LCBI_{4mm}$). Roleder et al. [10] and Inaba et al. [11] identified TCFA as lesions with $_{max}LCBI_{4mm} \geq 323$.

High cholesterol levels are strongly associated with SCAD [12–14]. It is known that there is a positive relation between low-density lipoprotein cholesterol (LDL-C) and SCAD [15, 16]. In contrast, there is an inverse relationship between high-density lipoprotein cholesterol (HDL-C) and the risk of SCAD [17, 18]. It was established that both LDL-C [19] and HDL-C [20] are associated with plaque volume. However, the influence of lipid plasma levels on the chemical composition of the plaque measured by NIRS remains unknown.

The aim of this study was to investigate whether an association between plasma lipids depends on plaque morphology (TCFA vs. non-TFCA) as measured by NIRS-IVUS.

Methods

Study population

All patients diagnosed with SCAD or ACS between 2012 and 2015 who underwent NIRS-IVUS imaging were screened for inclusion in this study. The SCAD and ACS management met the criteria of the European Society of Cardiology [21]. Patients with stent restenosis as a target lesion, renal failure (creatinine > 1.5 mg/dL), hemodynamic compromise and contrast allergy were excluded from the study. The percutaneous coronary intervention (PCI) was performed under angiography guidance, and NIRS-IVUS data were not used for this purpose. Analyzed segments were targeted in the imaged artery by NIRS-IVUS. None of the patients developed any complications related to NIRS-IVUS imaging.

Before or after the PCI blood samples were collected from every patient on day 1, after fasting conditions for the measurement of serum levels of total cholesterol (TC), LDL-C, HDL-C and triglyceride (TG). All of them were measured enzymatically using standard methods. Clinical demographics and medical history were obtained from hospital records. The study group consisted of 64 lesions analyzed in 64 patients. Patients were divided into two groups based on $_{max}LCBI_{4mm}$ results. Those with $_{max}LCBI_{4mm} \geq 323$ were included in the TCFA group (n = 35) while others were assigned to the non-TCFA group (n = 29). The study conformed to the Declaration of Helsinki. Due to retrospective design of the study, further application was not needed.

NIRS-IVUS analysis

The NIRS-IVUS analysis was performed in culprit lesions using standard protocol before stent implantation. All NIRS-IVUS examinations were performed after heparin anticoagulation (activated clotting time > 250 s) and following intracoronary nitroglycerine (100–200 μm) administration. The 2.4 Fr. TVC Insight Catheter (InfraReDx, TVC Imaging System™, Burlington, MA, USA) was positioned at least 10 mm distal to the imaging target lesion. Subsequently, the automated pullback was started with at 0.5 mm/s (240 rotations/min) until the TVC catheter entered the guiding catheter. Measurements were made every 1 mm in region of interest (ROI), and the target lesion was required to be at least 4 mm long. Quantitative gray-scale IVUS measurements were performed every 1 mm in the scanned coronary segment before stent implantation. Cross-sectional images were quantified for lumen diameters and area, external elastic lamina (EEM) diameters and area, total plaque area, plaque burden, and lumen and EEM eccentricity by one observer. Plaque burden was calculated as total plaque area divided by EEM CSA × 100 (%). The remodeling index (RI) was calculated by dividing EEM area at the minimal lumen area (MLA) by the reference EEM area. Lesions with RI ≤ 0.95 were defined as negatively remodeled, while

Table 1. Patient characteristics.

	TCFA (n = 35)	Non-TCFA (n = 29)	P
Clinical demographics			
Age [years]	63.2 ± 11.37	66.64 ± 9.8	0.176
Women	9 (25.7%)	9 (31%)	0.637
BMI [kg/m^2]	27.2 ± 6.07	26.4 ± 4.95	0.625
Prior MI	9 (25.7%)	10 (34.5%)	0.445
Prior PCI	13 (37.1%)	13 (37.1%)	0.533
Prior CABG	3 (8.5%)	2 (6.9%)	0.845
Dyslipidemia	35 (100%)	29 (100%)	
Hypertension	30 (85.7%)	27 (93.1%)	0.209
Diabetes mellitus	15 (42.8%)	9 (31%)	0.331
Statin use	30 (85.7%)	25 (86.2%)	0.719
Hemoglobin	12.97 ± 1.64	12.7 ± 2.5	0.635
Creatinine	1.06 ± 0.26	1.01 ± 0.25	0.514
GFR	68.62 ± 18.77	70.7 ± 16.04	0.767
Procedural findings			
Indication for coronary angiography			
ACS	8 (22.85%)	8 (27.58%)	0.664
Region of interest [mm]	25.66 ± 9.56	17.03 ± 9.22	0.001
Imaged coronary artery			
Left main artery	1 (5.7%)	0	0.05
Left descending artery	20 (57.1%)	11 (37.9%)	0.05
Circumflex artery	9 (25.7%)	5 (17.2%)	0.05
Right coronary artery	5 (14.3%)	13 (44.8%)	0.05

Variables are displayed as mean ± standard deviation when a normal distribution is present, or as median (1st–3rd quartile) when there was not a normal distribution present. For each variable, the percentage of patients involved (n%) is given. ACS — acute coronary syndrome; BMI — body mass index; CABG — coronary artery bypass grafting; GFR — glomerular filtration rate; MI — myocardial infarction; PCI — percutaneous coronary intervention; TCFA — thin cap fibrous atheroma

those with RI ≥ 1.05 were defined as positively remodeled. RI between these values was taken as a non-remodeled vessel.

The chemical composition of the plaque in ROI was acquired using NIRS. The lipid-rich plaques are displayed on chemogram on which the X-axis shows the pullback position (1 pixel every 0.1 mm) and Y-axis displays the circumferential position (1 pixel every 1 mm). Based on chemogram the LCBI in 4 mm was measured. There was a fraction of pixels indicating lipids (yellow pixels) within the ROI. The LCBI with $_{max}LCBI_{4mm}$ was measured automatically by NIRS software. TCFA suspected lesions were defined as $_{max}LCBI_{4mm} \geq 323$.

NIRS-IVUS data were analyzed off-line using CAAS intravascular software (Pie Medical Imaging BV, Maastricht, The Netherlands).

Statistical analysis

Normality of variables was assessed by the Kolmogorov-Smirnov test. For normally distributed data values were presented as the mean with a standard deviation (± SD). Non-normally distributed continuous variables were displayed as a median with interquartile intervals (IQR, 1st, 3d). Categorical data were shown as the number or percentage (%). For the normally distributed group comparison, the one-way ANOVA was used. Non-normally distributed data were compared using the Mann-Whitney test. The correlation was measured using the Pearson correlation coefficient for normally distributed values and the Spearman rank-order correlation for non-normally distributed variables. The categorical data were compared using the Fischer exact test or χ^2 test. A value of

Table 2. Summary of near-infrared spectroscopy–intravascular ultrasound (NIRS-IVUS) results.

	TCFA (n = 35)	Non-TCFA (n = 29)	P
NIRS analysis			
$_{max}LCBI_{4mm}$	551.0 (423.0, 697.0)	137 (27.0, 232.0)	0.000
IVUS analysis			
Stenosis length	25.66 ± 9.56	17.03 ± 9.22	0.001
Lumen volume	114.800 (86.100, 137.90)	75.10 (55.75, 128.60)	0.05
EEM volume	301.6 (212.9, 393.7)	153.2 (105.85, 272.1)	0.003
EEM area at MLA	11.2 (9.5, 12.6)	10.0 (7.35, 11.6)	0.056
Plaque volume	176.1 (110.75, 247.5)	68.1 (55.58, 143.35)	0.000
Plaque burden	78.4 (70.9, 82.2)	72.70 (64.77, 76,05)	0.021
MLA	2.57 (1.9, 3.4)	2.60 (2.05, 3.22)	0.69
MLD	1.6 (1.5, 1.7)	1.60 (1.50, 1.80)	0.334
MLD based on reference	1.7 (1.6, 2.0)	1.80 (1.65, 2.00)	0.047
Remodeling index	1.02 (0.8, 1.27)	1.00 (0.84, 1.44)	0.69

Variables are displayed as mean ± SD when a normal distribution is present, or as median (1^{st}–3^{rd} quartile) when there was not a normal distribution present. For each variable, the percentage of patients involved (n%) is given. EEM — external elastic lamina; MLA — minimal lumen area; MLD — minimal lumen diameter

$p < 0.05$ was considered statistically significant. SPSS version 25.0 (SPSS, Inc., Chicago, Illinois) was used for statistical analysis.

Results

Patients characteristics

The baseline characteristics are summarized in Table 1. Between 2012 and 2015 64 patients were enrolled in the study. All patients included underwent PCI followed by stent deployment. Patients from the TCFA group were not-significantly younger than patients from non-TCFA group (63.2 ± 11.37 vs. 66.64 ± 9.8; p = 0.176). All patients in both groups had dyslipidemia. There were no significant differences in the percentage of patients who had hypertension (85.7% vs. 93.1%, p = 0.209) or diabetes mellitus (42.8% vs. 31%, p = 0.331) in TCFA or non-TCFA groups. At the time of the procedure, the percentage of patients treated with statins was similar in both groups (85.7% vs. 86.2%; p = 0.719). Nine (25.7%) of TCFA patients and 10 (34.5%) of non-TCFA patients presented with a history of myocardial infarction (p = 0.445).

IVUS lesion analysis

Intravascular ultrasound results are reported in Table 2. The NIRS-IVUS analysis was performed during coronary angiography. TCFA lesions were significantly longer than non-TCFA lesions (25.66 ± 9.56 vs. 17.03 ± 9.22; p = 0.001). TCFA characterizes greater plaque burden (78.4 [70.9, 82.2] vs. 72.70 [64.77, 76,05]; p = 0.021) and plaque volume (176.1 [110.75, 247.5] vs. 68.1 [55.58, 143.35]; p = 0.000) as compared to non-TCFA. The values of lumen volume (114.800 [86.100, 137.90] vs. 75.10 [55.75, 128.60]; p = 0.05) and EEM volume (301.6 [212.9, 393.7] vs. 153.2 [105.85, 272.1]; p = 0.003) were also higher in TCFA group. According to MLA and minimal lumen diameter there were no significant differences comparing both groups (respectively, p = 0.69, p = 0.334). No difference was found in RI for both groups as well (1.02 [0.8, 1.27] vs. 1.00 [0.84, 1.44]; p = 0.69).

Association between NIRS analysis and lipid plasma levels

Comparing TCFA to non-TCFA group, the differences in the levels of LDL-C (80.00 [69.00, 111.00], vs. 72.00 [58.50, 97.50]; p = 0.43), HDL-C (39.50 [35.75, 46.00] vs. 42.00 [33.50, 53.00]; p = 0.47), TC (146.00 [122.00, 181.00] vs. 140.00 [120.50, 167.50; p = 0.80) and TG (119.00 [74.00, 160.00] vs. 102.00 [83.50, 120.50]; p = 0.34) were not statistically significant. Also, the number of patients with LDL > 70 was not significantly higher in TCFA group as compared to non-TCFA group (24 vs. 15; p = 0.223) (Fig. 1). The summary of lipid plasma levels is listed in Table 3.

In non-TCFA group there was no significant correlation between $_{max}LCBI_{4mm}$ and LDL levels (r = –0.55, p = 0.783), TC levels (r = –0.133, p = 0.498) nor HDL-C levels (r = –0.062, p = 0.754). In TCFA lesions there was also no correlation

Table 3. Summary of lipid plasma levels.

Blood lipid levels	TCFA (n = 35)	Non-TCFA (n = 29)	P
LDL-C	80.00 (69.00, 111.00)	72.00 (58.50, 97.50)	0.43
HDL-C	39.50 (35.75, 46.00)	42.00 (33.50, 53.00)	0.47
TC	146.00 (122.00, 181.00)	140.00 (120.50, 167.50)	0.80
TG	119.00 (74.00, 160.00)	102.00 (83.50, 120.50)	0.34

Variables are displayed as mean ± standard deviation when a normal distribution is present, or as median (1^{st}–3^{rd} quartile) when there was not a normal distribution present. For each variable, the percentage of patients involved (n%) is given. HDL-C — high density lipoprotein cholesterol; LDL-C — low density lipoprotein cholesterol; TC — total cholesterol; TCFA — thin cap fibrous atheroma; TG — triglycerides

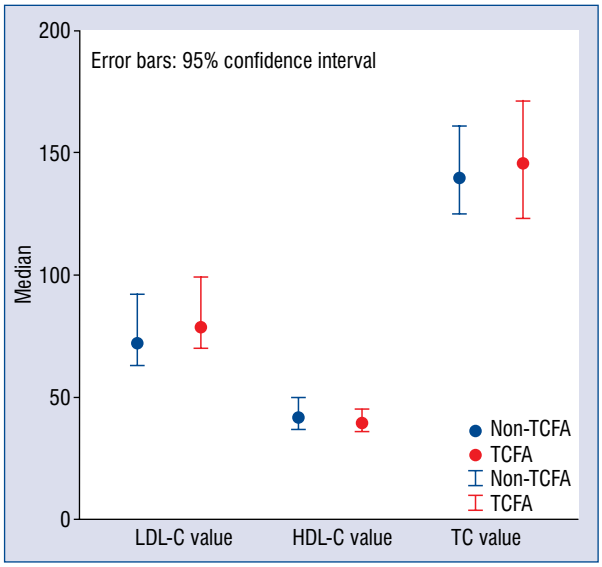


Figure 1. The relation of lipid plasma levels between thin cap fibrous atheroma (TCFA) and non-TCFA group. Variables are displayed as median with 1^{st}–3^{rd} quartile; HDL-C — high density lipoprotein cholesterol; LDL-C — low density lipoprotein cholesterol; TC — total cholesterol.

between $_{max}LCBI_{4mm}$ and LDL levels (r = 0.105, p = 0.549) nor TC levels (r = –0.035, p = 0.844) but a negative correlation was found between HDL-C and $_{max}LCBI_{4mm}$ (r = –0.453, p = 0.007) (Fig. 2).

Discussion

The major findings of the present study are as follows: 1) there was no correlation between LDL-C, TC and TG plasma levels and the number of lipids in coronary plaque assessed by NIRS in both groups, 2) HDL-C correlated with $_{max}LCBI_{4mm}$ in TCFA lesions, 3) there was no difference in LDL-C, HDL-C, TC and TG plasma levels in patients with TCFA compared to those with non-TCFA lesions, 4) based on IVUS analysis TCFA characterized greater values of plaque volume, plaque burden and stenosis length.

A large number of patients suffering from SCAD has aroused an interest in the pathology of atherosclerotic plaque. The Dynamic Registry revealed that 6% of lesions being < 50% in severity during initial angiography progressed mainly as ACS [22]. It showed that there is a need for a new diagnostic approach to finding clinically silent plaques. Pathological studies have found TCFA lesions to be the main precursor of plaque rupture in patients suffering from ACS [6, 23]. It was distinguished by a fibrous cap thickness which was < 65 μm, a small MLA, and a larger plaque burden [6]. This finding and the fact that an angiographic evaluation of the stenosis was not sufficient led to the development of intravascular imaging modalities which facilitated in vivo TCFA identification. Especially OCT imaging, due to its high resolution emerged as a favorable intravascular modality in confirming a vulnerable plaque presence. OCT measurements determined a borderline fibrous cap thickness of < 65 μm [6, 7, 24]. Also, studies evaluating multiple imaging modalities enabled TCFA identification using IVUS, NIRS-IVUS or VH-NIRS. IVUS, in contrast to OCT, IVUS enables deep penetration into the plaque. Roleder et al. [24] emphasized its superior role in the estimation of plaque burden, vessel remodeling, and plaque vulnerability identification. Based on its measurements TCFA was defined as a lesion with a plaque burden greater than 70%, and a MLA of 4 mm^2 or less [25]. Those lesions were also associated with higher major adverse cardiac event (MACE) rate [26] and positive remodeling [27]. Based on our results, TCFA characterizes greater plaque burden and plaque volume.

The adjustment of NIRS to IVUS enables the periprocedural analysis of chemical composition of the plaque and distinguishes lipid-rich lesions.

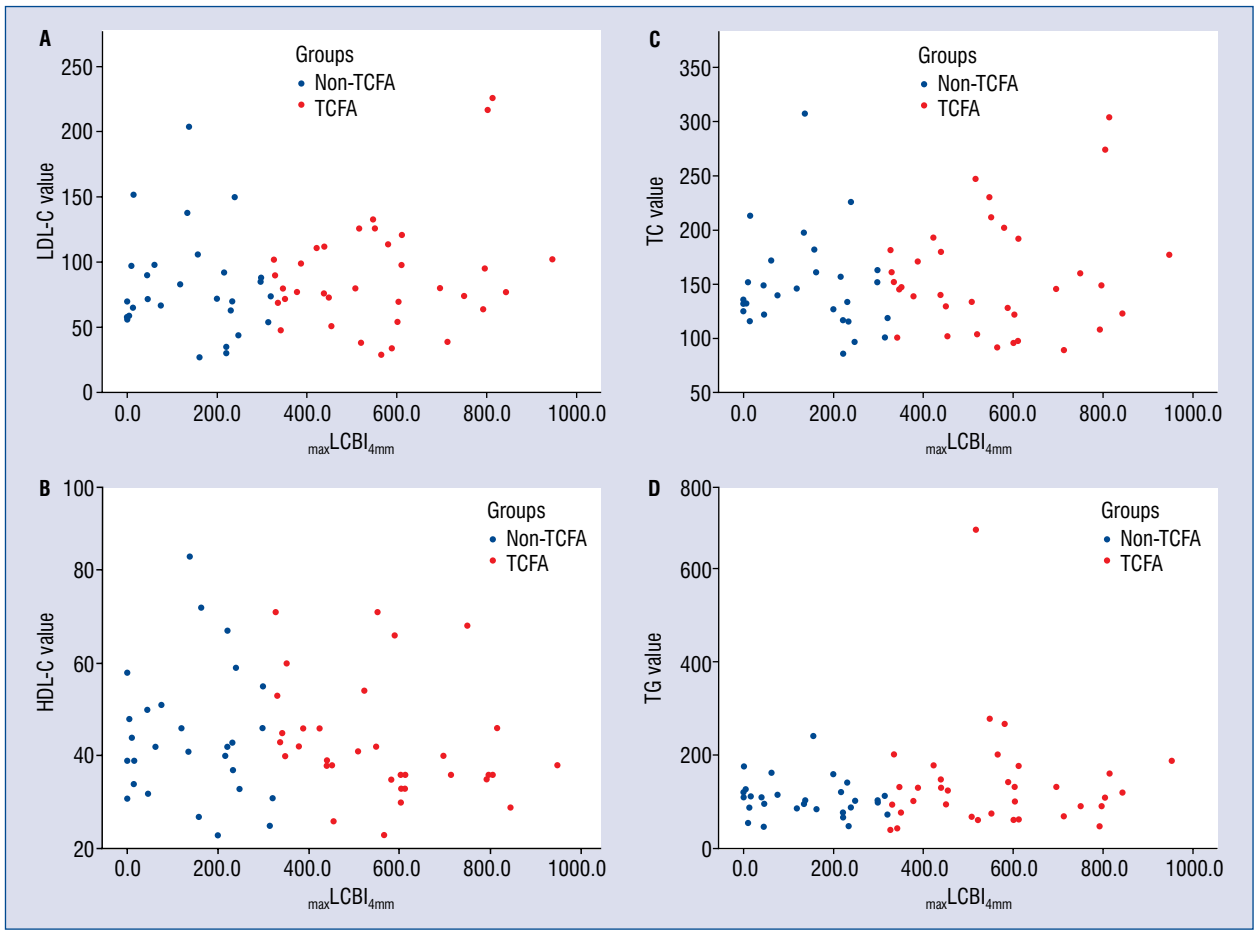


Figure 2. A–D. The correlations between low density lipoprotein cholesterol (LDL-C) (**A**), high density lipoprotein cholesterol (HDL-C) (**B**), total cholesterol (TC) (**C**), triglycerides (TG) (**D**) and $_{max}LCBI_{4mm}$. **A.** Correlation between LDL-C in thin cap fibrous atheroma (TCFA) and non-TCFA group was respectively 0.105 (p = 0.549) and –0.55 (p = 0.783); **B.** Correlation between HDL-C in TCFA and non-TCFA group was respectively –0.453 (p = 0.007) and –0.062 (p = 0.754); **C.** Correlation between TC in TCFA and non-TCFA group was respectively –0.035 (p = 0.844) and –0.133 (p = 0.498); **D.** Correlation between TG in TCFA and non-TCFA group was respectively 0.059 (p = 0.735) and –0.21 (p = 0.283).

It was also believed that identification of lipid-rich plaques based on chemical analysis might point out lesions responsive to intensive lipid-lowering therapy. It not only plays a qualitative role but also enables the quantitative measurement of lipid content as a $_{max}LCBI_{4mm}$ [9, 28]. According to NIRS results, TCFA was described by Inaba et al. [11] as a lesion with a threshold of $_{max}LCBI_{4mm} \geq 323$. A statistically significant association between $_{max}LCBI_{4mm}$ and an increased incidence of MACE was also observed [29, 30].

It is commonly known that higher LDL-C and TC plasma levels increase the risk of vulnerable plaque [18]. Some clinical trials showed that LDL-C lowering therapy decreases the risk of cardiovascular events. The influence of LDL-C reduction of lipid content measured by NIRS was found in the Yellow trial which showed a decrease in $_{max}LCBI_{4mm}$ after rosuvastatin intensive therapy [31]. Even though LDL-C is considered to be one of the main factors of SCAD, many patients presenting with SCAD have LDL-C within normal levels, which was shown in a study carried out by Sachdeva et al. [32] revealing that only 50.5% of the patients admitted with SCAD presented LDL-C levels greater than 100 mg/dL [32]. This may explain the lack of correlation between LDL-C and $_{max}LCBI_{4mm}$ for both groups in the present study. According to LDL-C plasma levels in TCFA and non-TCFA group, Nasu et al. [14] showed that in the TCFA group LDL-C levels were significantly higher than in the non-TCFA group while a study conducted by Nagasawa et al. [33] revealed no difference between those groups and this is what was also demonstrated in the current study.

High density lipoprotein cholesterol is inversely related to SCAD. Its main role is to remove the excessive cholesterol by transporting its particles from non-hepatic cells to the liver and other steroidogenic organs [34]. It is believed that it plays a pivotal role in the inhibition of atherosclerosis by reducing the migration of inflammatory cells into the artery wall and inhibiting LDL-C oxidation [35]. The Framingham Heart Study highlighted HDL-C as a risk factor for SCAD and considered it to be of greater importance as compared to LDL-C [17]. A study conducted by Honda et al. [36] revealed that independent of statin use HDL-C inversely correlated with a change in lipid plaque composition assessed by NIRS. The mentioned study and other studies did not show an association between LDL and $_{max}LCBI_{4mm,}$ which indicates the role of HDL-C in plaque composition and also agrees with the findings of the present study [37, 38]. It suggests that HDL-C may decrease the vulnerability of the plaque, but this finding requires further investigation.

As far as TG are concerned, it was shown that they were among factors inducing the plaque progression [39], but are not independently associated with CAD. Further studies focused on the relationship between lipid plasma levels and plaque morphology showed no relation between TG and $_{max}LCBI_{4mm}$ which was also found in the current study.

It needs to be highlighted that only periprocedural lipid plasma levels were measured with no insight into long-term analysis. Danek et al. [40] studied the progression of atherosclerosis in saphenous vein grafts and revealed that in contrast to the LDL-C and TG measured annually, the periprocedural measurements showed no association with $_{max}LCBI_{4mm}$. It was also found that annual measurements are more representative for the assessment of plaque morphology. It may explain the lack of correlation between lipid plasma levels and $_{max}LCBI_{4mm}$ in the present study.

According to patients who had suffered from myocardial infarction in the past, there was no significant difference between the TCFA and non-TCFA group. What was found was that all these patients had a significantly lower $_{max}LCBI_{4mm}$ value which had probably occurred due to lipid-lowering therapy.

Limitations of the study

This study involves a small number of patients which leads to an increased risk of selection bias. The main limitation of this study is the fact that the length of lipid-lowering therapy remains unknown and was not taken into account. Additionally, only the stented lesion was analyzed without insight into other plaques in the coronary tree which may have led to an inaccurate assessment of the association between lipid plasma levels and plaque morphology. A larger and prospective study is needed to verify the results of this study.

Conclusions

The major finding of the present study showed that there was no correlation between plasma LDL-C, TC, and TG level and the number of lipids in coronary plaque assessed by NIRS in both TCFA and non-TCFA group. Only HDL-C correlated with $_{max}LCBI_{4mm}$ in TCFA lesions. There was also no difference in LDL-C, HDL-C, TC, and TG in patients with TCFA compared to those with non-TCFA lesions. Based on IVUS analysis TCFA characterized greater values of plaque volume, plaque burden and stenosis length.

Conflict of interest: None declared

References

1. Wilkins E, Wilson L, Wickramasinghe K, et al. European Cardiovascular Disease Statistics 2017 edition. Eur Hear Network, Brussels. 2017, doi: 978-2-9537898-1-2.
2. Farb A, Tang AL, Burke AP, et al. Sudden coronary death. Frequency of active coronary lesions, inactive coronary lesions, and myocardial infarction. Circulation. 1995; 92(7): 1701–1709, doi: 10.1161/01.cir.92.7.1701, indexed in Pubmed: 7671351.
3. Davies MJ, Richardson PD, Woolf N, et al. Risk of thrombosis in human atherosclerotic plaques: role of extracellular lipid, macrophage, and smooth muscle cell content. Br Heart J. 1993; 69(5): 377–381, doi: 10.1136/hrt.69.5.377, indexed in Pubmed: 8518056.
4. Kolodgie FD, Burke AP, Farb A, et al. The thin-cap fibroatheroma: a type of vulnerable plaque: the major precursor lesion to acute coronary syndromes. Curr Opin Cardiol. 2001; 16(5): 285–292, doi: 10.1097/00001573-200109000-00006, indexed in Pubmed: 11584167.
5. Virmani R, Kolodgie F, Burke A, et al. Lessons from sudden coronary death. Arter Thromb Biol. 2000; 20(5): 1262–1275, doi: 10.1161/01.atv.20.5.1262.
6. Virmani R, Burke A, Willerson J, et al. The pathology of vulnerable plaque. Vulnerable Atherosclerotic Plaque. 2007: 19–36, doi: 10.1002/9780470987575.ch2.
7. Burke AP, Farb A, Malcom GT, et al. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. N Engl J Med. 1997; 336(18): 1276–1282, doi: 10.1056/NEJM199705013361802, indexed in Pubmed: 9113930.
8. Madder RD, Goldstein JA, Madden SP, et al. Detection by near-infrared spectroscopy of large lipid core plaques at culprit sites in

patients with acute ST-segment elevation myocardial infarction. JACC Cardiovasc Interv. 2013; 6(8): 838–846, doi: 10.1016/j.jcin.2013.04.012, indexed in Pubmed: 23871513.
9. Waxman S, Dixon SR, L'Allier P, et al. In vivo validation of a catheter-based near-infrared spectroscopy system for detection of lipid core coronary plaques: initial results of the SPECTACL study. JACC Cardiovasc Imaging. 2009; 2(7): 858–868, doi: 10.1016/j.jcmg.2009.05.001, indexed in Pubmed: 19608137.
10. Roleder T, Kovacic JC, Ali Z, et al. Combined NIRS and IVUS imaging detects vulnerable plaque using a single catheter system: a head-to-head comparison with OCT. EuroIntervention. 2014; 10(3): 303–311, doi: 10.4244/EIJV10I3A53, indexed in Pubmed: 24769522.
11. Inaba S, Mintz GS, Burke AP, et al. Intravascular ultrasound and near-infrared spectroscopic characterization of thin-cap fibroatheroma. Am J Cardiol. 2017; 119(3): 372–378, doi: 10.1016/j.amjcard.2016.10.031, indexed in Pubmed: 27876264.
12. Silbernagel G, Fauler G, Renner W, et al. The relationships of cholesterol metabolism and plasma plant sterols with the severity of coronary artery disease. J Lipid Res. 2009; 50(2): 334–341, doi: 10.1194/jlr.P800013-JLR200, indexed in Pubmed: 18769018.
13. Strandberg T, Tilvis R, Pitkala K, et al. Cholesterol and Glucose Metabolism and Recurrent Cardiovascular Events Among the Elderly. J Am Coll Cardiol. 2006; 48(4): 708–714, doi: 10.1016/j.jacc.2006.04.081.
14. Nasu K, Terashima M, Habara M, et al. Impact of cholesterol metabolism on coronary plaque vulnerability of target vessels: a combined analysis of virtual histology intravascular ultrasound and optical coherence tomography. JACC Cardiovasc Interv. 2013; 6(7): 746–755, doi: 10.1016/j.jcin.2013.02.018, indexed in Pubmed: 23769651.
15. MacMahon S, Duffy S, Rodgers A, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55 000 vascular deaths. Lancet. 2007; 370(9602): 1829–1839, doi: 10.1016/s0140-6736(07)61778-4.
16. Mihaylova B, Emberson J, Blackwell L, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012; 380(9841): 581–590, doi: 10.1016/S0140-6736(12)60367-5, indexed in Pubmed: 22607822.
17. Gordon T, Castelli WP, Hjortland MC, et al. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. Am J Med. 1977; 62(5): 707–714, doi: 10.1016/0002-9343(77)90874-9, indexed in Pubmed: 193398.
18. Sharrett AR, Ballantyne CM, Coady SA, et al. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: The Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2001; 104(10): 1108–1113, doi: 10.1161/hc3501.095214, indexed in Pubmed: 11535564.
19. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA. 2004; 291(9): 1071–1080, doi: 10.1001/jama.291.9.1071, indexed in Pubmed: 14996776.
20. Nicholls S, Tuzcu E, Sipahi I, et al. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. JAMA. 2007; 297(5): 499, doi: 10.1001/jama.297.5.499.
21. Thygesen K, Alpert JS, Jaffe AS, et al. Writing Group on the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction, ESC Committee for Practice Guidelines (CPG). Third universal definition of myocardial infarction. Eur Heart J. 2012; 33(20): 2551–2567, doi: 10.1093/eurheartj/ehs184, indexed in Pubmed: 22922414.
22. Glaser R, Selzer F, Faxon DP, et al. Clinical progression of incidental, asymptomatic lesions discovered during culprit vessel coronary intervention. Circulation. 2005; 111(2): 143–149, doi: 10.1161/01.CIR.0000150335.01285.12, indexed in Pubmed: 15623544.
23. Virmani R, Kolodgie FD, Burke AP, et al. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol. 2000; 20(5): 1262–1275, doi: 10.1161/01.atv.20.5.1262, indexed in Pubmed: 10807742.
24. Roleder T, Kovacic JC, Ali Z, et al. Combined NIRS and IVUS imaging detects vulnerable plaque using a single catheter system: a head-to-head comparison with OCT. EuroIntervention. 2014; 10(3): 303–311, doi: 10.4244/EIJV10I3A53, indexed in Pubmed: 24769522.
25. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011; 364(3): 226–235, doi: 10.1056/NEJMoa1002358, indexed in Pubmed: 21247313.
26. Cheng JM, Garcia-Garcia HM, de Boer SPM, et al. In vivo detection of high-risk coronary plaques by radiofrequency intravascular ultrasound and cardiovascular outcome: results of the ATHEROREMO-IVUS study. Eur Heart J. 2014; 35(10): 639–647, doi: 10.1093/eurheartj/eht484, indexed in Pubmed: 24255128.
27. Glagov S, Weisenberg E, Zarins CK, et al. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med. 1987; 316(22): 1371–1375, doi: 10.1056/NEJM198705283162204, indexed in Pubmed: 3574413.
28. Gardner CM, Tan H, Hull EL, et al. Detection of lipid core coronary plaques in autopsy specimens with a novel catheter-based near-infrared spectroscopy system. JACC Cardiovasc Imaging. 2008; 1(5): 638–648, doi: 10.1016/j.jcmg.2008.06.001, indexed in Pubmed: 19356494.
29. Schuurman AS, Vroegindewey M, Kardys I, et al. Near-infrared spectroscopy-derived lipid core burden index predicts adverse cardiovascular outcome in patients with coronary artery disease during long-term follow-up. Eur Heart J. 2018; 39(4): 295–302, doi: 10.1093/eurheartj/ehx247, indexed in Pubmed: 28531282.
30. Oemrawsingh RM, Cheng JM, García-García HM, et al. Near-infrared spectroscopy predicts cardiovascular outcome in patients with coronary artery disease. J Am Coll Cardiol. 2014; 64(23): 2510–2518, doi: 10.1016/j.jacc.2014.07.998, indexed in Pubmed: 25500237.
31. Kini AS, Baber U, Kovacic JC, et al. Changes in plaque lipid content after short-term intensive versus standard statin therapy: the YELLOW trial (reduction in yellow plaque by aggressive lipid-lowering therapy). J Am Coll Cardiol. 2013; 62(1): 21–29, doi: 10.1016/j.jacc.2013.03.058, indexed in Pubmed: 23644090.
32. Sachdeva A, Cannon CP, Deedwania PC, et al. Lipid levels in patients hospitalized with coronary artery disease: an analysis of 136,905 hospitalizations in Get With The Guidelines. Am Heart J. 2009; 157(1): 111–117.e2, doi: 10.1016/j.ahj.2008.08.010, indexed in Pubmed: 19081406.
33. Nagasawa Y, Shinke T, Toh R, et al. The impact of serum trans fatty acids concentration on plaque vulnerability in patients with coronary artery disease: Assessment via optical coherence tomography. Atherosclerosis. 2017; 265: 312–317, doi: 10.1016/j.atherosclerosis.2017.06.922, indexed in Pubmed: 28697847.

34. Rosenson RS, Brewer HB, Davidson WS, et al. Cholesterol efflux and atheroprotection: advancing the concept of reverse cholesterol transport. Circulation. 2012; 125(15): 1905–1919, doi: 10.1161/CIRCULATIONAHA.111.066589, indexed in Pubmed: 22508840.
35. Navab M, Reddy ST, Van Lenten BJ, et al. HDL and cardiovascular disease: atherogenic and atheroprotective mechanisms. Nat Rev Cardiol. 2011; 8(4): 222–232, doi: 10.1038/nrcardio.2010.222, indexed in Pubmed: 21304474.
36. Honda S, Sidharta SL, Shishikura D, et al. High-density lipoprotein cholesterol associated with change in coronary plaque lipid burden assessed by near infrared spectroscopy. Atherosclerosis. 2017; 265: 110–116, doi: 10.1016/j.atherosclerosis.2017.08.016, indexed in Pubmed: 28881268.
37. Park SJ, Kang SJ, Ahn JM, et al. Effect of statin treatment on modifying plaque composition: a double-blind, randomized study. J Am Coll Cardiol. 2016; 67(15): 1772–1783, doi: 10.1016/j.jacc.2016.02.014, indexed in Pubmed: 27081016.
38. Hong MK, Park DW, Lee CW, et al. Effects of statin treatments on coronary plaques assessed by volumetric virtual histology intravascular ultrasound analysis. JACC Cardiovasc Interv. 2009; 2(7): 679–688, doi: 10.1016/j.jcin.2009.03.015, indexed in Pubmed: 19628193.
39. Campeau L, Enjalbert M, Lespérance J, et al. The relation of risk factors to the development of atherosclerosis in saphenous-vein bypass grafts and the progression of disease in the native circulation. A study 10 years after aortocoronary bypass surgery. N Engl J Med. 1984; 311(21): 1329–1332, doi: 10.1056/NEJM198411223112101, indexed in Pubmed: 6333635.
40. Danek BA, Karatasakis A, Alame AJ, et al. Saphenous vein graft near-infrared spectroscopy imaging insights from the lipid core plaque association with clinical events near-infrared spectroscopy (ORACLE-NIRS) registry. Catheter Cardiovasc Interv. 2017; 89(6): E172–E180, doi: 10.1002/ccd.26696, indexed in Pubmed: 27535486.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2021, Vol. 28, No. 6, 896–904
DOI: 10.5603/CJ.a2019.0069

ISSN 1897–5593
eISSN 1898–018X

Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation in secondary stroke and systemic embolism prevention

Iwona Gorczyca[1, 2], Anna Michalska[2], Magdalena Chrapek[3], Olga Jelonek[1], Paweł Wałek[1], Beata Wożakowska-Kapłon[1, 2]

[1]1st Clinic of Cardiology and Electrotherapy, Swietokrzyskie Cardiology Center, Kielce, Poland
[2]Collegium Medicum, The Jan Kochanowski University, Kielce, Poland
[3]Faculty of Mathematics and Natural Sciences, The Jan Kochanowski University, Kielce, Poland

Abstract

Background: *Oral anticoagulants (OAC) are recommended in all patients with atrial fibrillation (AF) after thromboembolic events without contraindications. It is hypothesized herein, that the majority of patients with AF after thromboembolic events receive OAC and the presence of specific factors, predisposes the use of non-vitamin K antagonist oral anticoagulants (NOACs).*

Methods: *This is a retrospective study, encompassing patients with AF hospitalized in a reference cardiology center over the years 2014–2017. Thromboembolic events were defined as: ischemic stroke, transient ischemic attack and systemic embolism. Inclusion criteria were the following: diagnosis of non-valvular AF at discharge from hospital, hospitalization not resulting in death.*

Results: *Among 2834 hospitalized patients with AF, a history of thromboembolic events was identified in 347 (12.2%) patients. In the group studied, of 347 patients with AF after a thromboembolic event, 322 (92.8%) received OAC, including 133 patients on vitamin K antagonist (41.3% of patients on OAC) and 189 patients on NOACs (58.7% of patients on OAC). Among patients treated with NOACs the majority were on dabigatran (116 patients, 61.4%), followed by rivaroxaban (54 patients, 28.6%), and apixaban (19 patients, 10%). Multivariate logistic regression analysis demonstrated that the presence of arterial hypertension reduced the chance for NOACs use (odds ratio [OR] 0.4, 95% confidence interval [CI] 0.2–0.9, $p = 0.04$) and left atrial size ≤ 40 mm was a factor increasing the chance for the use of NOACs (OR 2.5, 95% CI 1.1–5.8, $p = 0.03$).*

Conclusions: *Nearly all hospitalized patients with AF received OAC in the secondary prevention of thromboembolic complications. NOACs were used for secondary prevention of stroke among patients with AF in patients with fewer comorbidities.* (Cardiol J 2021; 28, 6: 896–904)

Key words: atrial fibrillation, oral anticoagulants, secondary prevention, thromboembolic event, stroke

Introduction

Atrial fibrillation (AF) is the most common supraventricular arrhythmia. Thromboembolic events, mainly involving cerebral circulation, constitute its most serious complication [1, 2]. In developed countries nearly 85% of strokes are of ischemic origin caused by a blockage of blood flow to the brain through narrowed or closed arteries, while 15% of strokes are hemorrhagic [3]. It has been established that AF is associated with a 5-fold increase in the risk of ischemic stroke and is gen-

Address for correspondence: Iwona Gorczyca, MD, 1st Clinic of Cardiology and Electrotherapy, Swietokrzyskie Cardiology Center, ul. Grunwaldzka 45, 25–736 Kielce, Poland, tel: +48 604 407 956, fax: +48 41 367 13 96, e-mail: iwona.gorczyca@interia.pl

Received: 24.02.2019 Accepted: 23.05.2019 Early publication date: 8.07.2019

erally responsible for 15–20% of all strokes [4, 5]. A history of thromboembolism in a patient with AF is the strongest risk factor for another thromboembolic event [6]. Oral anticoagulants (OAC) should be used for prevention of thromboembolism among patients with AF and the risk factors for such events [7]. Non-vitamin K antagonist oral anticoagulants (NOACs) are used increasingly more often and are characterized by at least a similar or greater effectiveness compared to that of vitamin K antagonists (VKA) [8–11].

The aim of this study was to assess the frequency of use of NOACs among hospitalized patients with AF and a history of thromboembolism, as well as to analyze factors which predispose the choice of NOACs in this group of patients.

Methods

Study group

Patients with AF hospitalized at a reference cardiology center, over the years 2014–2017, were included in this retrospective analysis. The following inclusion criteria of the study were applied: diagnosis of AF at discharge from hospital, hospitalization not resulting in death. Patients with valvular AF (mechanical valve prosthesis, severe mitral stenosis) were excluded from the study. Thromboembolic complications were defined as: ischemic stroke, transient ischemic attack (TIA), and systemic embolism. Anticoagulation treatment was evaluated at discharge from the hospital.

Statistical analysis

Arithmetic means, standard deviations, medians and quartiles were used to describe quantitative data. Distribution of qualitative data was presented as frequency and percentages. Frequencies were compared using the χ^2 test or the exact Fisher test. Normality of distribution was tested with the Shapiro-Wilk test. If the assumption of normality of distribution was fulfilled, the distributions of quantitative variables were compared using the Student t-test, while in the absence of normality of distribution, the U Mann-Whitney test was applied. Uncorrected (crude) and corrected (adjusted) odds ratios (OR) together with 95% confidence intervals (CIs) were determined using a logistic regression model. Multivariate logistic regression analysis included variables with statistically significant OR, confirmed in univariate analysis. All statistical tests conducted were two-sided and zero hypotheses were rejected when $p < 0.05$. The R software v. 3.4.3 (R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/) and STATISTICA v. 12 were used to conduct the analyses.

Table 1. Anti-stroke prophylaxis in patients with atrial fibrillation after thromboembolic complications (n = 347).

Type of prophylaxis	Number and percentage of patients
Oral anticoagulants	322 (92.8%)
Vitamin K antagonists	133 (38.3%)
Non-vitamin K oral anticoagulant:	189 (54.5%)
Apixaban	19 (5.5%)
Dabigatran	116 (33.4%)
Rivaroxaban	54 (15.6%)
Antiplatelet medicine / medicines	9 (2.6%)
Low molecular weight heparin	7 (2%)
Without prevention	9 (2.6%)

Results

In a group of 2834 consecutively hospitalized patients with AF, a history of thromboembolic complications was noted in 347 (12.2%) patients. Among the 347 patients with AF after thromboembolic events, 245 (70.6%) patients were diagnosed with stroke, 56 (16.1%) patients with TIA, 37 (10.7%) with systemic embolism, and more than one presentation of thromboembolic complication were noted in 9 (2.6%) patients.

In the group of 347 patients examined with AF after thromboembolic event, 49.6% were male and mean patient age amounted to 75.1 years. Fifty-one (14.7%) patients were under 65 years of age, 104 (30%) patients were aged 65–74, 133 (38.3%) patients were aged 75–84 years, and 59 patients were at least 85 (17%). A 128 (36.9%) patients presented with paroxysmal AF, 48 (13.8%) patients with persistent AF, and 171 (49.3%) with permanent arrhythmia. In the study group of 347 AF patients with a history of thromboembolic events, 322 (92.8%) received an OAC at the time of discharge from the hospital, including 133 on VKA (41.3% of patients treated with OAC) and 189 on NOACs (58.7% of patients with OAC). Table 1 presents pharmacological means of stroke prevention in the study group.

In a group of 189 patients treated with NOACs dabigatran was used most frequently — 116

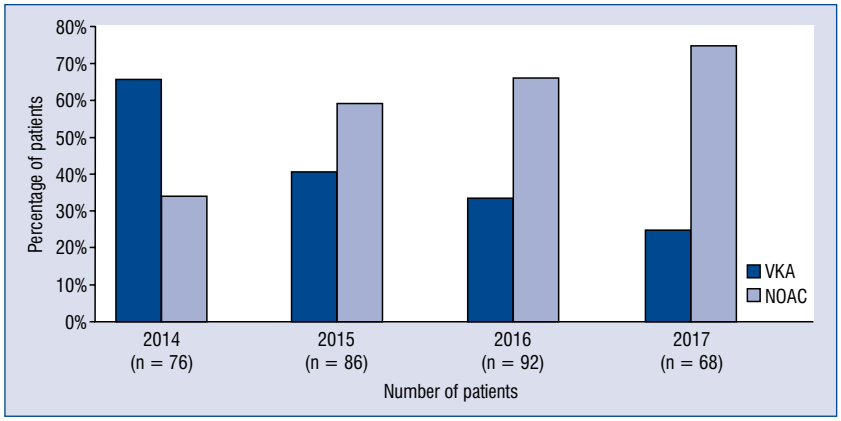


Figure 1. Percentage of patients treated with vitamin K antagonist (VKA) and non-vitamin K antagonist oral anticoagulants (NOAC) with atrial fibrillation after thromboembolic complications hospitalized between 2014 and 2017.

patients (61.4% of subjects were treated with NOACs), followed by rivaroxaban — 54 (28.6% of subjects were treated with NOACs), and apixaban — 19 patients (10% of subjects were treated with NOACs). Standard doses were administered in 76 (40.2%) patients on NOACs, while 113 (59.8%) patients received reduced doses.

The following number of patients with AF and history of thromboembolic events were hospitalized during the years 2014–2017: 76, 86, 92, and 68 patients, respectively. A significant increase in the proportion of patients on NOACs were among all OAC-treated subjects: from 34.2% in 2014 to 75% of subjects in 2017 (Fig. 1).

Patients with AF and a history of thromboembolic events treated with VKA vs. NOACs with regard to age, type of AF, and comorbidities (Table 2) were compared. Patients with AF, who were prescribed a NOACs suffered from arterial hypertension heart failure, or myocardial infarction less often than those receiving VKA. They were also characterized by lower mean $CHADS_2$ and CHA_2DS_2VASc scores as well as higher left ventricular ejection fraction and smaller left atrial dimension in echocardiographic assessment.

Univariate logistic regression analysis demonstrated that among patients after thromboembolic complications the following characteristics significantly reduced the chance of receiving a prescription for NOACs: arterial hypertension, heart failure, history of myocardial infarction, and $CHADS_2$ score ≥ 4 points. Among echocardiographic parameters ejection fraction < 50% significantly reduced chance for the use of NOACs in the group studied. However, left atrial size ≤ 40 mm was a factor significantly increasing the likelihood of being prescribed NOACs (Table 3). Multivariate logistic regression analysis showed that arterial hypertension significantly reduced the chance of NOACs use, while left atrial size ≤ 40 mm significantly increased the likelihood of NOACs administration in patients with AF and a history of thromboembolic events (Table 4).

Discussion

In the present study, encompassing almost 3000 hospitalized patients with AF, thromboembolic events were diagnosed in 12% of subjects. In the PREFER registry thromboembolic complications were noted in 8.4% of patients with AF [12]. A similar proportion of patients with a history of stroke, amounting to 10.5%, was found in the 2nd phase of the GLORIA-AF registry [13]. A higher proportion of patients after stroke/TIA than in the current study was established in the GARFIELD registry — it amounted to 15.2% in cohort I, and 21.4% in cohort II. In the Polish population of patients included in the GARFIELD registry the percentage of patients after stroke/TIA was lower and amounted to 8.3% and 7.9% in cohort I and II, respectively [14]. The population of patients in the present study was higher than in the GARFIELD registry — mean patient age was 75 years, while in the GARFIELD registry it amounted to 67 years in the Polish population; in the European population it amounted to 73 years in cohort II and 72 years in cohort I [14]. Among 2259 British patients with AF remaining under the care of general practitioners, 19% had a history of stroke. Mean age of patients in this study was similar to that in the current study — 76 years [15].

Patients with a history of thromboembolic complications have at least 2 points on the

Table 2. Clinical characteristics of patients with atrial fibrillation vitamin K antagonist (VKA) or non-vitamin K antagonist oral anticoagulant (NOAC)-treated after thromboembolic events.

Clinical feature	OAC group (n = 322)	VKA group (n = 133)	NOAC group (n = 189)	P
Age [years]				0.81
Mean ± SD	74.9 ± 9.9	74.8 ± 9.5	74.9 ± 10.9	
Median (Q1–Q3)	76 (68–83)	76 (68–83)	76 (68–83)	
Age [years]				0.61
Age < 50	3 (0.9%)	0 (0.0%)	3 (1.6%)	
Age 50–64	45 (14.0%)	18 (13.5%)	27 (14.3%)	
Age 65–74	99 (30.7%)	43 (32.3%)	56 (29.6%)	
Age > 74	175 (54.3%)	72 (54.1%)	103 (54.5%)	
Female	165 (51.2%)	71 (53.4%)	94 (49.7%)	0.52
Form of atrial fibrillation				0.59
Paroxysmal	161 (50.0%)	62 (46.6%)	99 (52.4%)	
Persistent	116 (36.0%)	51 (38.4%)	65 (34.4%)	
Permanent	45 (14.0%)	20 (15.0%)	25 (13.2%)	
Medical history				
Hypertension	258 (80.1%)	114 (85.7%)	144 (76.2%)	0.03
Heart failure	227 (70.5%)	106 (79.7%)	121 (64.0%)	0.002
Diabetes mellitus	115 (35.7%)	47 (35.3%)	68 (36.0%)	0.91
Previous stroke	234 (72.7%)	99 (74.4%)	135 (71.4%)	0.55
Previous TIA	60 (18.6%)	26 (19.5%)	34 (18.0%)	0.72
Coronary artery disease	101 (31.4%)	42 (31.6%)	59 (31.2%)	0.95
Myocardial infarction	91 (28.3%)	48 (36.1%)	43 (22.8%)	0.009
PCI	53 (16.5%)	27 (20.3%)	26 (13.8%)	0.12
CABG	31 (9.6%)	17 (12.8%)	14 (7.4%)	0.11
COPD	29 (9.0%)	13 (9.8%)	16 (8.5%)	0.69
Hyperthyroidism	21 (6.5%)	10 (7.5%)	11 (5.8%)	0.54
Hypothyroidism	31 (9.6%)	10 (7.5%)	21 (11.1%)	0.28
$CHADS_2$ [points]				
Mean ± SD	4.4 ± 1.0	4.5 ± 0.9	4.3 ± 1.0	0.04
Median (Q1–Q3)	4 (4–5)	5 (4–5)	4 (4–5)	
$CHADS_2$ 2–3	58 (18%)	15 (11.3%)	43 (22.8%)	0.008
CHADS2 > 3	264 (82%)	118 (88.7%)	146 (77.2%)	0.008
CHA_2DS_2VASc [points]				
Mean ± SD	6.5 ± 1.4	6.7 ± 1.3	6.4 ± 1.5	0.0 8
Median (Q1–Q3)	7 (6–7)	7 (6–8)	6 (5–7)	
CHA_2DS_2VASc 2–3	9 (2.8%)	1 (0.8%)	8 (4.2%)	0.09
CHA_2DS_2VASc > 3	313 (97.2%)	132 (99.2%)	181 (95.8%)	0.09
HAS-BLED				
Mean ± SD	2.6 ± 0.8	2.7 ± 0.7	2.6 ± 0.8	
Median (Q1–Q3)	3 (2–3)	3 (2–3)	3 (2–3)	
ECHOCARDIOGRAPHY				
EF [%]	[n = 250]	[n = 106]	[n = 144]	0.04
Mean ± SD	46.9 ± 12.9	44.9 ± 13.7	48.4 ± 12.2	
Median (Q1–Q3)	50 (40–55)	49,5 (38–55)	50 (43–55)	
EF > 50%	101 (40.4%)	34 (32.1%)	56 (38.9%)	
EF 50–30%	115 (46.0%)	54 (50.9%)	61 (42.4%)	
EF < 30%	101 (13.6%)	34 (32.1%)	56 (38.9%)	

→

Table 2 (cont.). Clinical characteristics of patients with atrial fibrillation vitamin K antagonist (VKA) or non-vitamin K antagonist oral anticoagulant (NOAC)-treated after thromboembolic events.

Clinical feature	OAC group (n = 322)	VKA group (n = 133)	NOAC group (n = 189)	P
LA [mm]	[n = 248]	[n = 106]	[n = 142]	< 0.0001
Mean ± SD	47.3 ± 8.2	49.6 ± 8.9	45.7 ± 7.3	
Median (Q1–Q3)	46 (42.5–52)	48.5 (45–54)	45 (41–50.7)	
LA > 40 mm	[n = 246] 205 (83.3%)	[n = 106] 97 (91.5%)	[n = 142] 108 (76.1%)	0.002
LABORATORY TESTS				
Hemoglobin [g/dL]	[n = 321]	[n = 132]	[n = 189]	0.38
Mean ± SD	13.2 ± 1.7	13.1 ± 1.7	13.2 ± 1.6	
Median (Q1–Q3)	1.2 (12.1–14.3)	13.2 (12.1–14.2)	13.2 (12.1–14.5)	
GFR [mL/min]				0.16
Mean ± SD	55.8 ± 18.6	53.7 ± 17.3	57.3 ± 19.4	
Median (Q1–Q3)	54.9 (43.8–66.3)	53.7 (42.6–65.6)	56.0 (44.3–67.4)	
GFR > 60	114 (35.4%)	43 (32.3%)	118 (37.6%)	0.43
GFR 60–46	111 (34,5%)	48 (36.1%)	63 (33.3%)	
GFR 45–30	63 (19.6%)	25 (18.8%)	38 (20.1%)	
GFR 29–15	23 (71%)	12 (9.0%)	11 (5.8%)	
GFR < 15	1 (0.3%)	0 (0.0%)	1 (0.5%)	

CABG — coronary artery bypass grafting; COPD — chronic obstructive pulmonary disease EF — ejection fraction; GFR — glomerular filtration rate; LA — left atrial; PCI — percutaneous coronary intervention; TIA — transient ischemic attack

Table 3. Factors increasing the chances of using non-vitamin K antagonist oral anticoagulant (NOAC) in patients with atrial fibrillation after thromboembolic complications — univariate logistic regression analysis.

Factors	VKA group (n = 133)	NOAC group (n = 322)	Crude OR	95% CI	P
Sex					
Female	71 (53.4%)	94 (49.7%)	Ref. level		
Male	62 (46.6%)	95 (50.3%)	1.2	0.7–1.8	0.52
Age [years]	74.8 ± 9.5	74.9 ± 10.3	1.0	0.98–1.02	0.96
< 65	18 (13.5%)	30 (15.9%)	Ref. level		
65–74	43 (32.3%)	56 (29.6%)	0.8	0.4–1.6	0.49
> 74	72 (54.1%)	103 (54.5%)	0.9	0.4–1.7	0.65
Form of AF					
Paroxysmal	51 (38.3%)	65 (34.4%)	Ref. level		
Persistent	20 (15.0%)	25 (13.2%)	1.0	0.5–2.0	0.96
Permanent	62 (46.6%)	99 (52.4%)	1.3	0.8–2.0	0.36
Form of AF					
Permanent	62 (46.6%)	99 (52.4%)	Ref. level		
Persistent	51 (38.3%)	65 (34.4%)	0.8	0.5–1.3	0.36
Paroxysmal	20 (15.0%)	25 (13.2%)	0.8	0.4–1.5	0.47
Hypertension					
No	19 (14.3%)	45 (23.8%)	Ref. level		
Yes	114 (85.7%)	144 (76.2%)	0.5	0.30–0.96	0.04
Heart failure					
No	27 (20.3%)	68 (36.0%)	Ref. level	0.3–0.8	0.003
Yes	106 (79.7%)	121 (64.0%)	0.5		

→

Table 3 (cont.). Factors increasing the chances of using non-vitamin K antagonist oral anticoagulant (NOAC) in patients with atrial fibrillation after thromboembolic complications - univariate logistic regression analysis.

Factors	VKA group (n = 133)	NOAC group (n = 322)	Crude OR	95% CI	p
Diabetes mellitus					
No	86 (64.7%)	121 (64.0%)	Ref. level		
Yes	47 (35.3%)	68 (36.0%)	1.0	0.6–1.6	0.91
Previous stroke					
No	34 (25.6%)	54 (28.6%)	Ref. level		
Yes	99 (74.4%)	135 (71.4%)	0.9	0.5–1.4	0.55
Previous transient ischaemic attack					
No	107 (80.5%)	155 (82.0%)	Ref. level		
Yes	26 (19.5%)	34 (18.0%)	0.9	0.5–1.6	0.72
Coronary artery disease					
No	91 (68.4%)	130 (68.8%)	Ref. level		
Yes	42 (31.6%)	59 (31.2%)	1.0	0.6–1.6	0.95
Myocardial infarction					
No	85 (63.9%)	146 (77.2%)	Ref. level		
Yes	48 (36.1%)	43 (22.8%)	0.5	0.3–0.9	0.009
Percutaneous coronary intervention					
No	106 (79.7%)	163 (86.2%)	Ref. level		
Yes	27 (20.3%)	26 (13.8%)	0.6	0.3–1.1	0.12
Coronary artery bypass graft					
No	116 (87.2%)	175 (92.6%)	Ref. level		
Yes	17 (12.8%)	14 (7.4%)	0.5	0.3–1.2	0.11
Chronic obstructive pulmonary disease					
No	120 (90.2%)	173 (91.5%)	Ref. level		
Yes	13 (9.8%)	16 (8.5%)	0.9	0.4–1.8	0.69
$CHADS_2$ score	4.5 ± 0.9	4.3 ± 1.0	0.8	0.6–0.97	0.029
2–3	15 (11.3%)	43 (22.8%)	Ref. level		
> 3	118 (88.7%)	146 (77.2%)	0.4	0.2–0.8	0.001
CHA_2DS_2VASC score	6.7 ± 1.3	6.4 ± 1.5	0.9	0.7–1.01	0.06
2–3	1 (0.8%)	8 (4.2%)	Ref. level		
> 3	132 (99.2%)	181 (95.8%)	0.2	0.02–1.4	0.10
HASBLED score	2.7 ± 0.8	2.6 ± 0.8	0.9	0.7–1.2	0.56
Ejection fraction [%]	44.9 ± 13.7	48.4 ± 12.2	1.02	1.001–1.04	0.037
Missing value	27 (20.3%)	45 (23.8%)	–		
> 50	34 (25.6%)	67 (35.4%)	Ref. level		
30–50%	54 (40.6%)	61 (32.3%)	0.6	0.3–0.995	0.048
< 30%	18 (13.5%)	16 (8.5%)	0.5	0.2–0.994	0.048
Left atrial group [mm]	49.6 ± 8.9	45.7 ± 7.3	0.94	0.91–0.97	0.0004
Missing value	27 (20.3%)	47 (24.9%)	–		
> 40 mm	97 (72.9%)	108 (57.1%)	Ref. level		
≤ 40 mm	9 (6.8%)	34 (18.0%)	3.4	1.5–7.4	0.002
Hemoglobin [g/dL]	13.1 ± 1.7	13.2 ± 1.6	1.1	0.9–1.2	0.38
< 12 g/dL	31 (23.3%)	38 (20.1%)	Ref. level		
≥ 12 g/dL	101 (75.9%)	151 (79.9%)	1.2	0.7–2.1	0.47
GFR [mL/min]	53.7 ± 17.3	57.3 ± 19.4	1.01	0.998–1.023	0.09
> 60 mL/min	43 (32.3%)	71 (37.6%)	Ref. level		
60–46 mL/min	50 (37.6%)	66 (34.9%)	0.8	0.5–1.4	0.41
45–30 mL/min	26 (19.5%)	40 (21.2%)	0.9	0.5–1.7	0.82
< 30 mL/min	14 (10.5%)	12 (6.3%)	0.5	0.2–1.2	0.13

Data are shown as number (percentage) or mean ± standard deviation. CI — confidence interval; GFR — glomerular filtration rate; OR — odds ratio; VKA — vitamin K antagonist

Table 4. Factors increasing the chances of using non-vitamin K antagonist oral anticoagulant in patients with atrial fibrillation after thromboembolic complications — multivariate logistic regression analysis.

Factors	Adjusted OR	95% CI	P
Hypertension			
No	Ref. level		
Yes	0.4	0.2–0.9	0.04
Heart failure			
No	Ref. level		
Yes	0.6	0.3–1.2	0.14
Myocardial infarction			
No	Ref. level		
Yes	0.6	0.3–1.1	0.13
$CHADS_2$ score			
2–3 points	Ref. level		
> 3 points	1.0	0.4–2.7	0.97
Ejection fraction			
> 50%	Ref. level		
50–30%	0.8	0.4–1.4	0.39
< 30%	0.8	0.3–1.8	0.53
Left atrial			
> 40 mm	Ref. level		
≤ 40 mm	2.5	1.1–5.8	0.03

CI — confidence interval; OR — odds ratio

CHA_2DS_2VASc scale, although usually the score is higher due to age and comorbidities. In the present study the majority of patients were over 75 years and mean CHA_2DS_2VASc of patients treated with OAC amounted to 6.5 points, thus this study group was at the highest risk of thromboembolic events.

Lopatowska et al. [16] analyzed antithrombotic management in AF implemented into practice in a group of 1556 patients. The study showed that the use of OAC increased with increasing CHA_2DS_2VASc score but was less frequent in score ≥ 4 irrespectively of whether it was primary or secondary prevention.

According to the current guidelines of the European Society of Cardiology (ESC) on the treatment of patients with AF, anticoagulation is indicated in men with at least 2 points and women with at least 3 points on the CHA_2DS_2VASc scale. Therefore, each patient who had suffered a thromboembolic complication of AF should receive an OAC [17]. Data from registries demonstrate that clinical practice differs significantly from the guidelines. It is estimated that half of patients with AF and no risk factors for thromboembolic complications receive an OAC and 1/3 of patients at high risk of thromboembolic events remain without prophylactic anticoagulation [18]. However, only about 10% with AF have absolute contraindications to anticoagulant treatment. Mazurek et al. [19] showed that in a group of 2250 patients with AF contraindications to OAC were present in only 8.3% of subjects. In the same study it was shown that among patients with AF at high risk of thromboembolic events both overtreatment, as well as undertreatment, were associated with significant increases in the risk of stroke, while undertreatment was also associated with increased total mortality [19]. In the present study OAC was administered in 93% of patients, which is in agreement with the reports of other authors, who confirmed that contraindications to OAC are present in approximately one in ten patients with AF. In Darlington Atrial Fibrillation Registry on 2259 patients with AF, a history of stroke was identified in 18.9% of subjects [20]. In this group of patients OAC in monotherapy or combined with an antiplatelet drug was applied in 61.7% of subjects, 1/3 of patients received only an antiplatelet drug, while 6.5% of subjects with AF and history of stroke had no anticoagulation therapy [20]. In the current study OAC was administered in 92.8% of patients with AF and history of stroke, an antiplatelet drug/drugs in 2.6% of subjects, low molecular weight heparin in 2%, and 2.6% of patients were left without prophylactic anticoagulation. In the present study the mean age of patients with AF after a thromboembolic event amounted to 75 years, while in a British study of patients after stroke it was 79.6%. Also, patients in the study herein were characterized by a higher mean CHA_2DS_2VASc score compared to that of the British authors. Significant differences regarding treatment of patients after thromboembolic complications in studies under comparison probably ensue from the fact that in the present study, prophylactic anticoagulation was implemented by a reference cardiac center, while in the British study, by general practitioners.

In the current study the majority of patients on OAC were treated with NOACs. Reduced NOACs doses were used in 60% of patients and dabigatran was the most frequent therapeutic choice. In the SAMURAI-NVAF Study encompassing 1116 patients after stroke/TIA discharged from neurology centers, the majority of patients received VKA compared to NOAC (58.2 vs. 41.8%) [21]. Rivaroxaban, usually a full dose, was the most frequently chosen NOAC in the SAMURAI-NVAF

Study, followed by dabigatran and apixaban, which were most often used in reduced doses [21]. In the Novel Oral Anticoagulants in Stroke Patients (NOACISP)-LONGTERM registry that included 251 patients after stroke, who were treated with an OAC, NOAC was administered in 78% of patients [22]. Over a 1-year observation period full adherence was noted in 77.1% of patients treated with NOAC and 83.3% of patients receiving VKA [23].

The data on anticoagulant therapy in the group of women and men after thromboembolic complications is not consistent. In the present study, no significant differences were noted between the sexes preferring NOACs treatment. However, in the SAMURAI-NVAF study, the group of men after thromboembolism events were treated with NOACs more often than with VKA [21].

In the current study NOACs was prescribed more frequently than VKA in patients with lower thromboembolic risk according to the CHA_2DS_2-VASc and $CHADS_2$ scales, as well as with non-dilated left atrium, while VKA was used more often than NOACs among patients with arterial hypertension, heart failure, history of myocardial infarction and reduced left ventricular ejection fraction. Multivariate logistic regression analysis demonstrated that diagnosis of arterial hypertension significantly reduced the chance for NOACs administration for secondary prevention of stroke among patients with AF. It may be inferred that NOACs are more likely to be selected in lower-risk patients with fewer comorbidities. In a study that included patients hospitalized over the years 2004–2012 at the documented center, among patients at high risk of thromboembolic complications, the proportion of subjects with a history of thromboembolic events was higher in the group treated with OAC compared to those not treated with OAC [24]. In a Danish study conducted between 2011 and 2013, history of stroke was a factor predisposing the use of NOACs over VKA [25]. In the 2016 ESC guidelines experts recommend a preference of NOAC to VKA or acetylscalicylic acid among patients after stroke [17]. In the present study significant increase was demonstrated in the use of NOACs in patients after thromboembolic events — in 2017, ¾ of patients treated with oral anticoagulation received a NOACs.

Limitations of the study

There are several limitations of the present study. As is the case for all retrospective studies, there exist potential unidentified confounders. Data sources could not ascertain symptom severity of AF and the date of thromboembolic complication. There was no adjustment for levels of socioeconomic status or education levels of patients in the study group.

Conclusions

Oral anticoagulants were administered for secondary prevention of thromboembolic events in nearly all hospitalized patients with AF. NOACs were used in the majority of patients treated with oral anticoagulation and they were more often used in reduced than standard doses. NOACs were more frequently used for secondary prevention of stroke in AF patients with fewer comorbidities.

Conflict of interest: Iwona Gorczyca — paid lecture for Bayer, Boehringer Ingelheim; Beata Wożakowska-Kapłon — paid lecture for Bayer, Boehringer Ingelheim, Pfizer.

References

1. January C, Wann L, Alpert J, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. Circulation. 2014; 130(23), doi: 10.1161/cir.0000000000000041.
2. Cheng TO. Reduced risk for thromboembolism in atrial fibrillation and mitral regurgitation. Am Heart J. 1999; 138(5 Pt 1): 998–999, doi: 10.1016/s0002-8703(99)70045-1, indexed in Pubmed: 10539836.
3. Wendelboe AM, Raskob GE. Global burden of thrombosis: epidemiologic aspects. Circ Res. 2016; 118(9): 1340–1347, doi: 10.1161/CIRCRESAHA.115.306841, indexed in Pubmed: 27126645.
4. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. Arch Intern Med. 1987; 147(9): 1561–1564, indexed in Pubmed: 3632164.
5. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991; 22(8): 983–988, indexed in Pubmed: 1866765.
6. Hijazi Z, Lindbäck J, Alexander JH, et al. ARISTOTLE and STABILITY Investigators. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. Eur Heart J. 2016; 37(20): 1582–1590, doi: 10.1093/eurheartj/ehw054, indexed in Pubmed: 26920728.
7. Kailas SD, Thambuluru SR. Efficacy and safety of direct oral anticoagulants compared to warfarin in prevention of thromboembolic events among elderly patients with atrial fibrillation. Cureus. 2016; 8(10): e836, doi: 10.7759/cureus.836, indexed in Pubmed: 27900231.
8. Connolly S, Ezekowitz M, Yusuf S, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med. 2009; 361(12): 1139–1151, doi: 10.1056/nejmoa0905561.
9. Patel M, Mahaffey K, Garg J, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. N Engl J Med. 2011; 365(10): 883–891, doi: 10.1056/nejmoa1009638.
10. Granger C, Alexander J, McMurray J, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med. 2011; 365(11): 981–992, doi: 10.1056/nejmoa1107039.

11. Giugliano R, Ruff C, Braunwald E, et al. Edoxaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med. 2013; 369(22): 2093–2104, doi: 10.1056/nejmoa1310907.
12. Kirchhof P, Ammentorp B, Darius H, et al. Management of atrial fibrillation in seven European countries after the publication of the 2010 ESC Guidelines on atrial fibrillation: primary results of the PREvention oF thromboemolic events--European Registry in Atrial Fibrillation (PREFER in AF). Europace. 2014; 16(1): 6–14, doi: 10.1093/europace/eut263, indexed in Pubmed: 24084680.
13. Huisman MV, Rothman KJ, Paquette M, et al. The Changing Landscape for Stroke Prevention in AF: Findings From the GLORIA-AF Registry Phase 2. J Am Coll Cardiol. 2017; 69(7): 777–785, doi: 10.1016/j.jacc.2016.11.061, indexed in Pubmed: 28209218.
14. Stępińska J, Kremis E, Konopka A, et al. Stroke prevention in atrial fibrillation patients in Poland and other European countries: insights from the GARFIELD-AF registry. Kardiol Pol. 2016; 74(4): 362–371, doi: 10.5603/KP.a2015.0173, indexed in Pubmed: 26365937.
15. Shantsila E, Wolff A, Lip GYH, et al. Optimising stroke prevention in patients with atrial fibrillation: application of the GRASP-AF audit tool in a UK general practice cohort. Br J Gen Pract. 2015; 65(630): e16–e23, doi: 10.3399/bjgp15X683113, indexed in Pubmed: 25548312.
16. Lopatowska P, Tomaszuk-Kazberuk A, Mlodawska E, et al. Do CHA2 DS2 VASc and HAS-BLED scores influence 'real-world' anticoagulation management in atrial fibrillation? 1556 patient registry from the reference cardiology centre. Pharmacoepidemiol Drug Saf. 2015; 24(12): 1297–1303, doi: 10.1002/pds.3878, indexed in Pubmed: 26419506.
17. Kirchhof P, Benussi S, Kotecha D, et al. ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016; 37(38): 2893–2962, doi: 10.1093/eurheartj/ehw210, indexed in Pubmed: 27567408.
18. Mazurek M, Huisman MV, Lip GYH. Registries in atrial fibrillation: from trials to real-life clinical practice. Am J Med. 2017; 130(2): 135–145, doi: 10.1016/j.amjmed.2016.09.012, indexed in Pubmed: 27746290.
19. Mazurek M, Shantsila E, Lane DA, et al. Guideline-Adherent antithrombotic treatment improves outcomes in patients with atrial fibrillation: insights from the community-based darlington atrial fibrillation registry. Mayo Clin Proc. 2017; 92(8): 1203–1213, doi: 10.1016/j.mayocp.2017.05.023, indexed in Pubmed: 28778255.
20. Mazurek M, Shantsila E, Lane DA, et al. Secondary versus primary stroke prevention in atrial fibrillation: insights from the darlington atrial fibrillation registry. Stroke. 2017; 48(8): 2198–2205, doi: 10.1161/STROKEAHA.116.016146, indexed in Pubmed: 28679859.
21. Yoshimura S, Koga M, Sato S, et al. Two-Year Outcomes of Anticoagulation for Acute Ischemic Stroke With Nonvalvular Atrial Fibrillation - SAMURAI-NVAF Study. Circ J. 2018; 82(7): 1935–1942, doi: 10.1253/circj.CJ-18-0067, indexed in Pubmed: 29863095.
22. Seiffge DJ, Traenka C, Polymeris A, et al. Early start of DOAC after ischemic stroke: Risk of intracranial hemorrhage and recurrent events. Neurology. 2016; 87(18): 1856–1862, doi: 10.1212/WNL.0000000000003283, indexed in Pubmed: 27694266.
23. Polymeris AA, Traenka C, Hert L, et al. Frequency and Determinants of Adherence to Oral Anticoagulants in Stroke Patients with Atrial Fibrillation in Clinical Practice. Eur Neurol. 2016; 76(3-4): 187–193, doi: 10.1159/000450750, indexed in Pubmed: 27705975.
24. Gorczyca I, Wożakowska-Kapłon B, Starzyk K, et al. Evaluation of the recommended prevention of thrombosis in hospitalised patients with atrial fibrillation and high thromboembolism risk. Kardiol Pol. 2018; 76(3): 625–632, doi: 10.5603/KP.a2017.0241, indexed in Pubmed: 29297187.
25. Olesen JB, Sørensen R, Hansen ML, et al. Non-vitamin K antagonist oral anticoagulation agents in anticoagulant naïve atrial fibrillation patients: Danish nationwide descriptive data 2011-2013. Europace. 2015; 17(2): 187–193, doi: 10.1093/europace/euu225, indexed in Pubmed: 25236181.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2021, Vol. 28, No. 6, 905–913
DOI: 10.5603/CJ.a2019.0033

ISSN 1897–5593
eISSN 1898–018X

Selected matrix metalloproteinases activity and hypertension-mediated organ damage in relation to uric acid serum level

Krystian Gruszka[1], Marek Rajzer[1], Tomasz Drożdż[1], Wiktoria Wojciechowska[1], Tomasz Pizoń[1], Kamila Migacz-Gruszka[2], Danuta Czarnecka[1]

[1]1st Department of Cardiology, Interventional Electrocardiology and Arterial Hypertension, Jagiellonian University Medical College, Krakow, Poland
[2]Department of Dermatology, Jagiellonian University Medical College, Krakow, Poland

Abstract

Background: *Atherosclerosis is as a systemic inflammatory disease associated with the activation of many mediators, including matrix metalloproteinases (MMPs), and may be amplified by abnormal high serum uric acid (UA) concentration (hyperuricemia, HU). The aim of the study was to determine the relationship between serum UA concentration and activity of MMPs and their correlation with the hypertension-mediated organ damage (HMOD) intensity.*

Methods: *One hundred and nine patients untreated with antihypertensive, hypolipemic or urate-lowering drugs with diagnosed stage 1–2 essential hypertension were included in this study. In all participants blood pressure (BP) was measured, carotid-femoral pulse wave velocity (PWV), intima–media thickness (IMT), echocardiography and blood tests including UA, lipids and serum concentrations of MMPs (1, 2, 3, 9) were observed. The participants were divided into hyper- and normuricemic groups.*

Results: *Uric acid concentration in the whole study group positively correlated with some HMOD parameters (IMT, PWV, left ventricular mass index, left atrial dimension). Among the studied metalloproteinases only MMP-3 activity positively correlated with serum UA concentration independently of age, body mass index and serum lipids ($R2 = 0.11$, $p = 0.048$). Multivariate regression analysis showed positive association between IMT and BP, UA concentration and MMP-3 activity, independently of waist circumference and serum lipids ($R2 = 0.328$, $p < 0.002$). Patients with HU were characterized by higher activity of MMP-3 than those without (19.41 [14.45; 21.74] vs. 13.98 [9.52; 18.97] ng/mL, $p = 0.016$).*

Conclusions: *The present results may support the thesis that UA and the increased by UA activity of MMPs may take part in the development of HMOD, especially IMT.* (Cardiol J 2021; 28, 6: 905–913)

Key words: arterial hypertension, uric acid, hyperuricemia, matrix metalloproteinases, metabolic syndrome

Introduction

Cardiovascular disorders caused by atherosclerosis remain the main cause of morbidity and death in developed countries. Currently atherosclerosis is defined as a systemic inflammatory disease associated with the activation of many mediators and effectors, including excessive activation of matrix metalloproteinases (MMPs) [1] MMPs are a large group of zinc-dependent proteolytic enzymes which play a key role in physiological and pathological inflammatory processes, including activation of

Address for correspondence: Dr. Marek Rajzer, 1st Department of Cardiology, Interventional Electrocardiology and Arterial Hypertension, Jagiellonian University Medical College, ul. Kopernika 17, 31–501 Kraków, Poland, tel: +48 12 424 73 00, fax: +48 12 424 73 20, e-mail: rajzer37@interia.pl

Received: 21.12.2018 Accepted: 20.03.2019 Early publication date: 26.03.2019

immune cells, damage and apoptosis of endothelial cells, fibrosis and remodeling of vascular wall. Increased activity of MMPs was described in many inflammatory diseases as well as in selected cardiovascular diseases [2, 3].

Under physiological conditions MMPs are inhibited by a group of tissue inhibitors of metalloproteinases (TIMPs) [4, 5]. The collagenases (MMP-1, -8, -13, -18) are capable of breaking down interstitial collagen I, II, III. Collagen fragments are further degraded by gelatinases (MMP-2, -9), MMP-2, -9 are also involved in the degradation of collagen IV, vessel remodeling, angiogenesis, inflammation and atherosclerotic plaque rupture. Stromelysin-1 (MMP-3) and stromelysin-2 (MMP-10) play the key role in extracellular matrix protein degradation by activation of MMPs cascade [6–8].

Essential hypertension is associated with vascular wall remodeling, which may be amplified by abnormal high serum uric acid (UA) concentration Increased UA concentration is called hyperuricemia (HU). HU is a common condition which may affect up to a quarter of the adult population [9, 10]. Many factors promote the development of HU, especially: the use of a high-purine diet, sedentary lifestyle, metabolic syndrome, obesity and arterial hypertension. In most cases, HU is accompanied by high estimated cardiovascular risk [11, 12].

Uric acid is an important antioxidant, but in excessive amounts it can activate the formation of reactive oxygen species. UA participates in atherogenesis process by enhancing inflammation, causing endothelium dysfunction, vascular smooth muscle proliferation, increased platelet adhesion and lipid peroxidation [13]. In subjects with arterial hypertension HU is associated with increased risk of coronary heart disease and cardiovascular mortality [14, 15].

The action mechanism of elevated UA concentration on the progression of vascular changes has yet to be clearly identified. Available data in the literature about the relationship between HU and MMPs activity is limited.

The aim of the study was to determine the relationship between serum UA concentration and selected MMPs activity and their correlation with hypertension-mediated organ damage (HMOD).

Methods

The study group consisted of consecutive patients with diagnosed essential hypertension stage 1 or 2 (blood pressure [BP] ≥ 140/90 and < <180/110 mmHg) in accordance with the 2018 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines [16]. They were admitted within a 6 month period to the hypertension outpatient department. Subjects were both women and men aged 20–80 years. The exclusion criteria included: symptomatic gout, coronary heart disease (previous myocardial infarction, coronary angioplasty procedure or coronary artery bypass surgery), atrial fibrillation, stroke history or transient ischemic attack episode, active acute or chronic inflammatory process, cancer, kidney or liver failure and reported treatment with antihypertensive, hypolipemic or urate-lowering drugs in the prior 4 weeks.

Study procedures

All participants underwent medical examination, with office BP measurements in standard conditions, after 10 min rest, in a sitting position on the non-dominant arm with the use of the Omron M5-I oscillometric device (Omron Healthcare Co., Japan). The mean of the three measurements at 1-min intervals was taken for analysis. 24-h ambulatory blood pressure monitoring (ABPM) was also performed using a SpaceLabs 90207 recorder (SpaceLabs Inc, Richmond, Washington, USA) according to ESH/ESC recommendations [16]. The SphygmoCor (AtCor Medical, Sydney, Australia) device was used to examine arterial stiffness. Carotid-femoral pulse wave velocity (PWV) and central blood pressure in the aorta were measured according to ESC expert consensus recommendations [17, 18]. Echocardiographic examination using the Vivid 7® VingMed (GE-Healthcare Chicago, IL, USA) device was performed in accordance with the ESH/ESC guidelines for the management of hypertension [16]. The left ventricular mass (LVM) was calculated according to the Devereaux formula using the Penn convention LVM = 1.04 ([left ventricular internal diameter in diastole + + posterior wall thickness in diastole + interventricular septum thickness in diastole]3 – [left ventricular internal diameter in diastole]3) – 13.6 g [19]. Ultrasound carotid arteries were examined with intima–media thickness (IMT) measurement of common carotid artery and was carried out in accordance with recommendations of the Mannheim consensus with the use of the Vivid 7® VingMed (GE-Healthcare Chicago, IL, USA) [20].

Measurements of serum concentrations of UA, creatinine, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides were performed. Blood samples from the antecubital

vein were taken for the determination of serum concentrations of metalloproteinases (MMP-1, MMP-2, MMP-3 and MMP-9) and tissue inhibitor of matrix metalloproteinases-1 (TIMP-1) in the morning hours before study procedures. Then the plasma was separated and samples stored at –75°C until analysis. TIMP-1 plasma concentrations were measured using an ELISA kit (Human TIMP-1 Immunoassay, Quantikine, R&D Systems Europe, Ltd. Abingdon, UK). The concentration of serum metalloproteinases was measured using kits from R&D Systems Europe Ltd, Abingdon, UK.

According to The Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994) hyperuricemia was defined as UA concentration > 7 mg/dL (416 μmol/L) in men and > 5.7 mg/dL (339 μmol/L) in women [21]. Based on the cut-off values, the study group was divided into hyper- and normuricemia group.

Statistical analysis

Statistical analyses were performed with STATISTICA software (StatSoft, Poland), version 13.1. Nonparametric tests were used, because some of the variables studied did not have a normal distribution and study subgroups had different numbers. Groups were compared using the Mann-Witney U test and the association between variables was studied using the Spearman rank correlation. For the evaluation of association of HMOD with UA concentration, multivariate regression analysis was used. P-values < 0.05 were considered statistically significant.

Results

Relation of UA serum concentration with the hypertension-mediated organ damage and selected biochemical parameters

The body mass index (BMI) was 27.4 (24.3; 30.1) kg/m^2, office systolic blood pressure (SBP-office) was 150 (135; 162) mmHg, office diastolic blood pressure (DBP-office) was 93 (86; 100) mmHg, heart rate (HR) was 72 (66;79) bpm, creatinine was 65.9 (58.2; 74) μmol/L, PWV was 7.8 (7.1; 9.1) m/s, IMT was 0.6 (0.55; 0.75) mm, left ventricular mass index (LVMI) was 132.2 (103.9; 144) g. UA concentration in the whole study group positively correlated with: BMI, waist circumference, BP and some HMOD parameters (IMT, PWV, LVMI, left atrial dimension) and triglyceride level. UA concentration in the study group negatively correlated with HDL-C level. Among the metalloproteinases studied, only MMP-3 activity was positively correlated with UA serum concentration (Fig. 1, Table 1). In multivariate regression analysis, after adjustment for age, BMI and serum lipids, UA associated with higher MMP-3 activity (R2 = = 0.11, beta = 0.332, p = 0.048) (Fig. 2) and PWV (R2 = 0.33, beta = 0.230, p = 0.0004), thicker IMT (R2 = 0.34, beta = 0.240, p = 0.04) and increased LVMI (R2 = 0.11, beta = 0.232, p = 0.0004).

The activity of MMP-3 correlated, like the concentration of UA, with the IMT (r = 0.292; p = 0.002) and the LVMI (r = 0.273; p = 0.009).

In further analyses, both factors, MMP-3 and UA serum activity together with waist circumference, SBP and DBP obtained in 24-h ABPM and serum lipids into the multivariate regression model were used to evaluate their influence on selected parameters of HMOD.

IMT value in this model was significantly positively associated with SBP and DBP (24-h mean values in ABPM), UA serum concentration and MMP-3 activity (R2 = 0.328, p < 0.002).

Only the SBP and DBP were significant determinants of PWV (R2 = 0.25, p = 0.0047).

The same multivariate regression model was not sufficient to explain LVMI variability in the group (p > 0.05).

Differences in clinical profiles of hypertensives with normo- or hyperuricemia

The hyperuricemic group consisted of 21 subjects (15 women, 6 men). The group with normouricaemia consisted of 88 subjects (40 women, 48 men).

Hypertensive patients with HU were characterized by higher BMI and waist circumference in comparison to patients without HU (Table 2).

In the HU group, higher SBP during daily activity and higher SBP and DBP during night-time were observed than in the normouricemic group (Table 2).

The group with HU compared to the normouricemic group had lower HDL-C values and higher triglyceride serum concentrations (Table 3).

Between-group differences in activity of selected MMPs (-1, -2, -3 and -9) and TIMP-1 were analyzed. Only for MMP-3 activity was a statistically significant difference obtained. Patients with HU were characterized by higher activity of MMP-3 in relation to patients without HU (Table 3).

There were no significant differences in the prevalence of diabetes or pre-diabetic conditions between the group with HU and the normouricamic group.

The comparison of HMOD parameters between the present groups showed a greater IMT

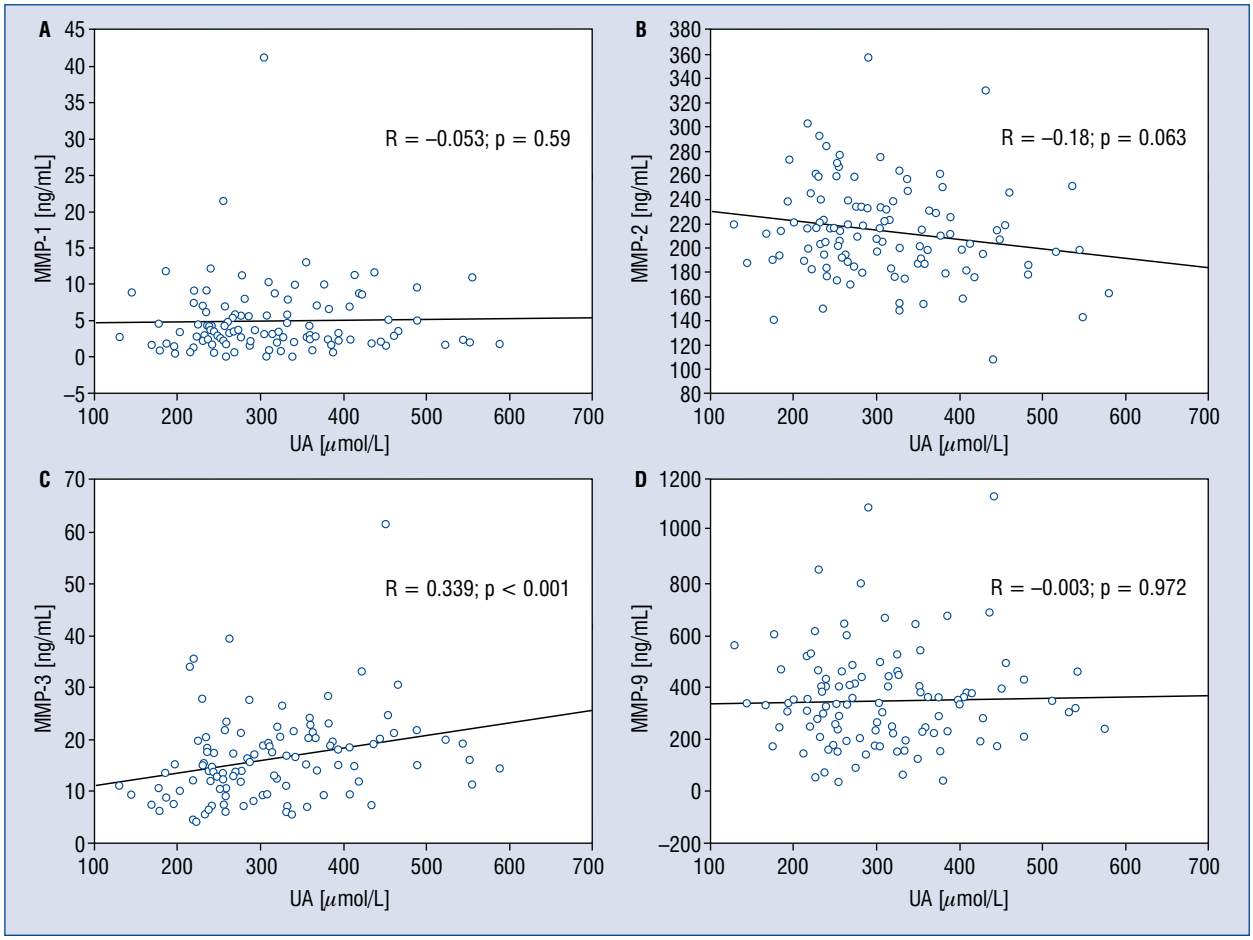


Figure 1. A–D. The relationship between selected matrix metalloproteinase (MMP-1, -2, -3, and -9) and uric acid (UA) concentration.

of the common carotid artery and larger left atrium dimension in the M-mode parasternal long axis view in the hyperuricemic group. Patients with HU were also characterized by higher LVM, however, this difference lost significance after indexing the body surface (LVMI). There were no significant differences between the groups examined in carotid-femoral pulse wave velocity (Table 4).

Discussion

The relationship between elevated serum UA level and arterial BP is well documented in the literature. The analysis of the Framingham Study population showed positive correlations between SBP and DBP and UA [22]. The current study also observed a positive correlation of UA concentration with systolic and diastolic office BP values. A new result in the present study was a higher BP at night in patients with HU compared to normouricemic patients.

Elevated UA serum level is often recognized as an integral component of metabolic syndrome [23, 24]. The metabolic syndrome, as defined by the International Diabetes Federation in 2006, consists of: increased triglycerides and reduced HDL-C serum level, arterial hypertension, raised fasting plasma glucose or previously diagnosed type 2 diabetes and of course abdominal obesity [25]. The results the study herein, showed a positive correlation of most components of the metabolic syndrome with UA serum concentration. The hyperuricemic group was also characterized by: higher BMI, waist circumference, triglyceride concentration and lower serum HDL-C level. However, differences in the frequency of diabetes and pre-diabetes between normouricemic and hyperuricemic group were not observed.

The biochemical characteristics of the group with HU and essential hypertension in the current study was completed by higher MMP-3 activity in comparison to patients without HU. MMP-3, is a proteolytic enzyme playing a main role in the

Table 1. The correlations of serum uric acid (UA) concentration with selected variables.

Selected variable	Correlation coefficient (r) with UA	P
BMI	0.376	**< 0.001**
Waist circumference	0.486	**< 0.001**
SBP office	0.104	0.308
DBP office	0.223	**0.027**
24-h SBP	0.247	**0.025**
24-h DBP	0.238	**0.032**
SBP day	0.189	0.051
DBP day	0.256	**0.008**
SBP night	0.259	**0.008**
DBP night	0.264	**0.007**
Central BP	0.235	**0.016**
IMT	0.241	**0.012**
PWV	0.203	**0.037**
AIx-c	–0.237	**0.015**
HDL-C	–0.261	**0.006**
Triglycerides	0.362	**< 0.001**
Creatinine	0.339	**< 0.001**
MMP-1	0.053	0.590
MMP-2	–0.18	0.063
MMP-3	0.339	**< 0.001**
MMP-9	–0.003	0.972
TIMP	0.051	0.605
LVMI	0.197	**0.040**
LVM	0.376	**< 0.001**
LA (PLAX)	0.487	**< 0.001**

BMI — body mass index; SBP office — office systolic blood pressure; DBP office — office diastolic blood pressure; 24-h SBP — 24-hour systolic blood pressure; 24-h DBP — 24-hour diastolic blood pressure; SBP night — systolic nighttime blood pressure; DBP night — diastolic nighttime blood pressure; SBP day — systolic blood pressure during daily activity; DBP day — diastolic blood pressure during daily activity; BP — blood pressure; ITM — intima–media thickness; PWV — pulse wave velocity; AIx-c — central augmentation index; HDL-C — high density lipoprotein cholesterol; MMP-1, -2, -3, -9 — matrix metalloproteinase 1, 2, 3, 9; TIMP — tissue inhibitor of metalloproteinases; LVMI — left ventricular mass index; LVM — left ventricular mass, LA — left atrium dimension in PLAX presentation

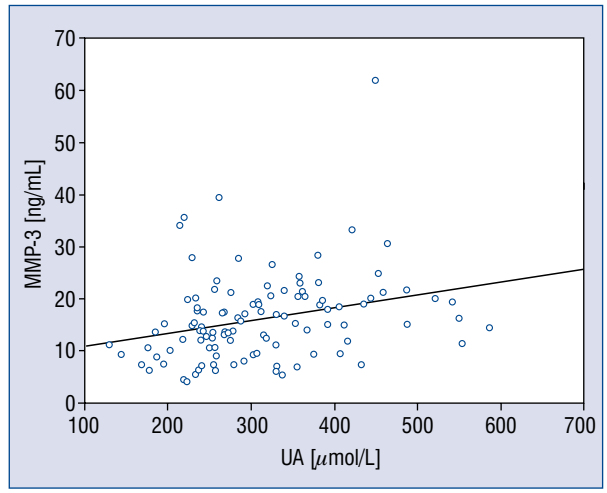


Figure 2. Association between matrix metalloproteinase 3 (MMP-3) and uric acid (UA) serum levels after adjustment to: age, waist circumference, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol and triglycerides serum concentration. Uric acid = 0.278 × MMP-3 + 259.9.

activation of other MMPs. The cascade of MMPs is responsible for the degradation of collagen and other fibrile proteins, leading to the remodeling of vascular wall, formation and destabilization of atherosclerotic plaque [26, 27].

In many diseases, MMPs are over-expressed and their over-activity leads to pathological heart and vessel remodeling, and the development of cardiovascular diseases [7, 28]. Increased activity of MMP-1, -2, -3 and -9 might also be associated with a higher risk of death independently of other typical cardiovascular risk factors [29].

The most important result of the present study is a strong, independent association between increased activity of MMP-3 UA serum concentration in patients with mild to moderate essential arterial hypertension. The data about the association of MMP-3 activity and UA concentration in the literature is limited and includes subjects with inflammatory diseases. Increased activity of MMP-3 has been reported in gout and acute arthritis [30, 31]. In patients with lupus erythematosus a positive correlation of plasma MMP-3 and UA concentration was observed. The latter is similar to present results obtained in patients with essential arterial hypertension free of acute or chronic inflammatory diseases [32]. A positive relationship between plasma activity of collagenase-2 (MMP-2) and UA concentration in men with coronary artery disease was reported [33, 34]. Tan et al. [35] showed that higher activity of MMP-9 coexists with higher concentrations of UA and higher IMT. In opposition to the above-mentioned results in an experimental animal study performed in rats showed that UA-induced inflammation led to a decrease in MMP-9 activity [36]. Similarly, UA administration during acute phase of ischemic stroke decreased the activity of proinflammatory MMP-9 [37]. In the present study MMP-2 and MMP-9 activity did not show a significant association with UA level or HMOD parameters.

Table 2. Groups characteristics. Anthropometric and clinical data.

Selected variable	Hyperuricemic group (n = 21)	Normouricemic group (n = 88)	P (the Mann-Whitney U test)
Age [years]	52 (43; 60)	54 (42; 61)	**0.030**
Sex (no. of females)	15 (71.4%)	40 (45.5%)	0.803
Weight [kg]	88 (84; 95)	75 (65; 86)	**< 0.001**
Haight [cm]	172 (170; 176)	169 (162; 176)	0.1477
BMI [kg/m^2]	30.08 (28.4; 33.53)	26.8 (23.85; 29;48)	**< 0.001**
Waist circumference [cm]	99 (92;106)	90 (81; 97)	**< 0.001**
Heart rate [bpm]	70 (64; 75)	72 (67; 80)	0.203
SBP office [mmHg]	155 (140; 178)	150 (135; 161)	0.176
DBP office [mmHg]	94 (90; 109)	92 (85; 99)	0.073
24h SBP [mmHg]	134 (123; 138)	128 (120; 132)	0.070
24h DBP [mmHg]	82 (76; 87)	77 (72; 84)	0.118
SBP day [mmHg]	136 (125; 140)	126 (119; 133)	**0.015**
DBP day [mmHg]	83 (77; 89)	80 (74; 85)	0.092
SBP night [mmHg]	119 (112; 129)	114 (107; 121)	**0.016**
DBP night [mmHg]	73 (67; 77)	68 (62; 73)	**0.022**

Values presented as medians (interquartiles ranges) or numbers (part of the group in %). Abbreviations — see Table 1.

Table 3. Group characteristics. Biochemical blood tests.

Selected variable	Hyperuricemic group (n = 21)	Normouricemic group (n = 88)	P (the Mann-Whitney U test)
Uric acid [μmol/L]	449 (416; 487)	268 (235; 324)	**< 0.001**
MMP-1 [ng/mL]	3.51 (2.13; 8.64)	3.43 (1.99; 5.76)	0.350
MMP-2 [ng/mL]	203.8 (186.2; 218.8)	214.7 (189; 239.4)	0.233
MMP-3 [ng/mL]	19.41 (14.45; 21.74)	13.98 (9.52; 18.97)	**0.016**
MMP-9 [ng/mL]	350.1 (245.1; 432.3)	335.6 (209.9; 442.9)	0.417
TIMP [ng/mL]	92.9 (81.2; 106.8)	86.8 (80; 101.3)	0.335
Creatinine [μmol/L]	68.9 (64.2; 78.9)	65.15 (57.65; 72.55)	**0.027**
Urea [mmol/L]	6.1 (5.2; 6.8)	5.5 (4.55; 6.3)	0.0739
Total cholesterol [mmol/L]	5.43 (4.87; 5.99)	5.27 (4.57; 6.08)	0.563
LDL-C [mmol/L]	3 (2.71; 3.86)	3.21 (2.44; 3.75)	0.482
HDL-C [mmol/L]	1.17 (1.09; 1.5)	1.44 (1.19; 1.7)	**0.029**
Triglycerides [mmol/L]	1.56 (1.16; 2.18)	1.2 (0.94; 1.57)	**0.018**

Values presented as medians (interquartiles ranges). LDL-C — low density lipoprotein cholesterol; other abbreviations — see Table 1.

Lien et al. [38] studied various plasma metalloproteinase activity in atherosclerosis. Only increased MMP-3 activity showed a significant relationship with the degree of atherosclerosis in the carotid arteries. A similar result was obtained in our study. The severity of atherosclerosis in carotid arteries evaluated by IMT was related to UA and MMP-3 concentrations. Kawamoto et al. [39] showed that UA in men may increase carotid atherosclerosis independent of other factors. The authors concluded that people with hypertension and hyperuricemia are characterized by greater IMT than hypertensive patients without HU. Increased IMT in this study correlated with UA concentration independently of the BP level. Hyperuricemia may also negatively affect other HMOD indicators [40].

In a population of more than 4,000 healthy participants selected from the Generation 3 Framing-

Table 4. Selected hypertension-mediated organ damage (HMOD).

Selected HMOD	Hyperuricemic group (n = 21)	Normouricemic group (n = 88)	P (the Mann-Whitney U test)
LVMI [g/m^2]	129.32 (114.72; 156.53)	123.1 (102.03; 138.93)	0.145
LVM [g]	268.62 (220.77; 331.19)	226.41 (185.76; 261.6)	**0.006**
LA (PLAX) [mm]	45 (42; 46)	40 (36; 43)	**< 0.001**
IMT [mm]	0.65 (0.6; 0.8)	0.6 (0.5; 0.75)	**0.038**
PWV [m/s]	8.4 (7.4; 8.9)	7.7 (7.1; 9.2)	0.258
c-AIx [%]	24 (14; 29)	25 (14; 33)	0.524
eGFR [mL/min/1.73 m^2]	95 (82; 109)	97.5 (86; 108)	0.514

Values presented as medians (interquartiles ranges). LVMI — left ventricular mass index; LVM — left ventricular mass; LA — left atrium dimension in PLAX presentation; IMT — intima–media thickness; PWV — pulse wave velocity, c-AIx — central augmentation index; eGFR — estimated glomerular filtration rate

ham cohort, an independent positive relationship between UA level and carotid-femoral PWV was proved [41]. In a much smaller study, carried out with a group of 222 subjects with essential hypertension, a positive correlation of PWV with UA in hypertensive patients was also observed [42]. In the current study, the group of patients with essential hypertension showed a positive correlation of arterial stiffness (evaluated by carotid-femoral PWV) with UA concentration.

There are existing reports in the literature indicating that UA serum concentration is associated with decreased left ventricular function and left ventricle hypertrophy [43, 44]. In the patients of this study a positive correlation was observed between UA and LVMI and UA and the left atrium dimension. Similar results have been described by Tavil et al. [45]. The current study also performed a multivariate regression analysis of the simultaneous effect of UA and MMP-3 concentrations on the other HMODs. Analysis for LVMI did not show statistical significance. In the case of PWV, BP values played the main role, and the effects of UA and MMP-3 were not significant.

Based on these results and data from the literature, it was suspected that among different indicators of HMOD (except for) hypertension there are big differences in factors determining their development and advancement. IMT is the HMOD most closely reflecting atherosclerosis; in the present study it was associated with proinflammatory factors like UA concentration and MMP-3 activity. Results obtained herein may support the thesis that UA and increased by UA activity of MMPs may take part in the development of HMOD, especially IMT. These results are consistent with the inflammatory and free radicals hypothesis of UA side effects.

However UA may play both pro- and antioxidative roles, depending on its concentration, solubility and place of action (plasma or cells) [46], free radicals formed in various mechanisms in hyperuricemia [47] have a great potential to activate various inflammatory mechanisms, including the activation of metalloproteinases cascade [48].

Conclusions

In patients with primary arterial hypertension UA concentration is associated with higher MMP-3 serum activity and selected hypertension-mediated organ damage advancement, especially carotid IMT. Patients with HU and arterial hypertension are characterized by a symptom cluster typical for metabolic syndrome and more advanced structural changes in the heart and vessels as well as higher activity of MMP-3.

Funding

This study was supported by the Polish Ministry of Science and Higher Education grant No. NN402367333.

Conflict of interest: None declared

Reference

1. Galis ZS, Khatri JJ. Matrix metalloproteinases in vascular remodeling and atherogenesis: the good, the bad, and the ugly. Circ Res. 2002; 90(3): 251–262, indexed in Pubmed: 11861412.
2. Matsuyama A, Sakai N, Ishigami M, et al. Matrix metalloproteinases as novel disease markers in Takayasu arteritis. Circulation. 2003; 108(12): 1469–1473, doi: 10.1161/01.CIR.0000090689.69973.B1, indexed in Pubmed: 12952836.
3. Vitlianova K, Georgieva J, Milanova M, et al. Blood pressure control predicts plasma matrix metalloproteinase-9 in diabetes mellitus type II. Arch Med Sci. 2015; 11(1): 85–91, doi: 10.5114/aoms.2015.49208, indexed in Pubmed: 25861293.

4. Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. Circ Res. 2003; 92(8): 827–839, doi: 10.1161/01.RES.0000070112.80711.3D, indexed in Pubmed: 12730128.
5. Johnson JL. Matrix metalloproteinases: influence on smooth muscle cells and atherosclerotic plaque stability. Expert Rev Cardiovasc Ther. 2007; 5(2): 265–282, doi: 10.1586/14779072.5.2.265, indexed in Pubmed: 17338671.
6. Johnson J. Metalloproteinases in atherosclerosis. Eur J Pharmacol. 2017; 816: 93–106, doi: 10.1016/j.ejphar.2017.09.007.
7. Raffetto J, Khalil R. Matrix metalloproteinases and their inhibitors in vascular remodeling and vascular disease. Biochem Pharmacol. 2008; 75(2): 346–359, doi: 10.1016/j.bcp.2007.07.004.
8. Jaiswal A, Chhabra A, Malhotra U, et al. Comparative analysis of human matrix metalloproteinases: Emerging therapeutic targets in diseases. Bioinformation. 2011; 6(1): 23–30, indexed in Pubmed: 21464841.
9. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum. 2011; 63(10): 3136–3141, doi: 10.1002/art.30520, indexed in Pubmed: 21800283.
10. Kumar A U A, Browne LD, Li X, et al. Temporal trends in hyperuricaemia in the Irish health system from 2006-2014: A cohort study. PLoS One. 2018; 13(5): e0198197, doi: 10.1371/journal.pone.0198197, indexed in Pubmed: 29852506.
11. Thiele P, Schröder HE. Epidemiology of hyperuricemia and gout. Z Gesamte Inn Med. 1982; 37(13): 406–410.
12. Abeles AM. Hyperuricemia, gout, and cardiovascular disease: an update. Curr Rheumatol Rep. 2015; 17(3): 13, doi: 10.1007/s11926-015-0495-2, indexed in Pubmed: 25740704.
13. Johnson RJ, Kang DH, Feig D, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension. 2003; 41(6): 1183–1190, doi: 10.1161/01.HYP.0000069700.62727.C5, indexed in Pubmed: 12707287.
14. Li M, Hu X, Fan Y, et al. Hyperuricemia and the risk for coronary heart disease morbidity and mortality a systematic review and dose-response meta-analysis. Sci Rep. 2016; 6: 19520, doi: 10.1038/srep19520, indexed in Pubmed: 26814153.
15. Qin T, Zhou X, Wang Ji, et al. Hyperuricemia and the Prognosis of Hypertensive Patients: A Systematic Review and Meta-Analysis. J Clin Hypertens (Greenwich). 2016; 18(12): 1268–1278, doi: 10.1111/jch.12855, indexed in Pubmed: 27247021.
16. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. J Hypertens. 2018; 36(10): 1953–2041, doi: 10.1097/hjh.0000000000001940.
17. Laurent S, Cockcroft J, Bortel LV, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. European Heart Journal. 2006; 27(21): 2588–2605, doi: 10.1093/eurheartj/ehl254.
18. Van Bortel LM, Laurent S, Boutouyrie P, et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. J Hypertens. 2012; 30(3): 445–448, doi: 10.1097/hjh.0b013e32834fa8b0.
19. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. Circulation. 1977; 55(4): 613–618, indexed in Pubmed: 138494.
20. Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim Carotid Intima-Media Thickness and Plaque Consensus (2004–2006–2011). Cerebrovasc Dis. 2012; 34(4): 290–296, doi: 10.1159/000343145.
21. Gunter EW, Lewis BG, Koncikowski SM. Laboratory procedures used for the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994. U.S. Department Of Health And Human Services. 1996. .https://www.cdc.gov/nchs/data/nhanes/nhanes3/cdrom/nchs/manuals/labman.pdf.
22. Sundström J, Sullivan L, D'Agostino RB, et al. Relations of serum uric acid to longitudinal blood pressure tracking and hypertension incidence. Hypertension. 2005; 45(1): 28–33, doi: 10.1161/01.HYP.0000150784.92944.9a, indexed in Pubmed: 15569852.
23. Silva HA, Carraro JC, Bressan J, et al. Relation between uric acid and metabolic syndrome in subjects with cardiometabolic risk. Einstein (Sao Paulo). 2015; 13(2): 202–208, doi: 10.1590/S1679-45082015AO3194, indexed in Pubmed: 26018145.
24. Wang H, Zhang H, Sun L, et al. Roles of hyperuricemia in metabolic syndrome and cardiac-kidney-vascular system diseases. Am J Transl Res. 2018; 10(9): 2749–2763, indexed in Pubmed: 30323864.
25. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med. 2006; 23(5): 469–480, doi: 10.1111/j.1464-5491.2006.01858.x, indexed in Pubmed: 16681555.
26. Woessner JF. Matrix metalloproteinases and their inhibitors in connective tissue remodeling. FASEB J. 1991; 5(8): 2145–2154, indexed in Pubmed:1850705.
27. Ye S. Influence of matrix metalloproteinase genotype on cardiovascular disease susceptibility and outcome. Cardiovasc Res. 2006; 69(3): 636–645, doi: 10.1016/j.cardiores.2005.07.015, indexed in Pubmed: 16122719.
28. Heagerty AM, Aalkjaer C, Bund SJ, et al. Small artery structure in hypertension. Dual processes of remodeling and growth. Hypertension. 1993; 21(4): 391–397, indexed in Pubmed: 8458640.
29. Peeters SA, Engelen L, Buijs J, et al. Plasma matrix metalloproteinases are associated with incident cardiovascular disease and all-cause mortality in patients with type 1 diabetes: a 12-year follow-up study. Cardiovasc Diabetol. 2017; 16(1): 55, doi: 10.1186/s12933-017-0539-1, indexed in Pubmed:28446168.
30. Zucker S, Lysik RM, Zarrabi MH, et al. Elevated plasma stromelysin levels in arthritis. J Rheumatol. 1994; 21(12): 2329–2333, indexed in Pubmed:7699637.
31. Ribbens C, Martin y Porras M, Franchimont N, et al. Increased matrix metalloproteinase-3 serum levels in rheumatic diseases: relationship with synovitis and steroid treatment. Ann Rheum Dis. 2002; 61(2): 161–166, indexed in Pubmed: 11796404.
32. Kotajima L, Aotsuka S, Fujimani M, et al. Increased levels of matrix metalloproteinase-3 in sera from patients with active lupus nephritis. Clin Exp Rheumatol. 1998; 16(4): 409–415, indexed in Pubmed: 9706420.
33. Leyva F. Uric acid in chronic heart failure: a marker of chronic inflammation. Eur Heart J. 1998; 19(12): 1814–1822, doi: 10.1053/euhj.1998.1188.
34. Wingrove CS, Garr ED, Leyva F, et al. Elevated circulating matrix metalloproteinase-2 in coronary heart disease (abstr). Eur Hear J Abstr. 1998; 19(Suppl.): 613.
35. Tan C, Liu Yi, Li W, et al. Associations of matrix metalloproteinase-9 and monocyte chemoattractant protein-1 concentrations with carotid atherosclerosis, based on measurements of plaque and intima-media thickness. Atherosclerosis. 2014; 232(1): 199–203, doi:10.1016/j.atherosclerosis.2013.11.040, indexed in Pubmed: 24401238.
36. Wang Y, Guo W, Li Y, et al. Hypothermia induced by adenosine 5'-monophosphate attenuates injury in an L-arginine-induced acute pancreatitis rat model. J Gastroenterol Hepatol. 2014; 29(4): 742–748, doi: 10.1111/jgh.12448, indexed in Pubmed: 24224980.

37. Amaro S, Obach V, Cervera A, et al. Course of matrix metalloproteinase-9 isoforms after the administration of uric acid in patients with acute stroke. J Neurol. 2009; 256(4): 651–656, doi: 10.1007/s00415-009-0153-6.
38. Lien LM, Hsieh YC, Bai CH, et al. Association of blood active matrix metalloproteinase-3 with carotid plaque score from a community population in Taiwan. Atherosclerosis. 2010; 212(2): 595–600, doi: 10.1016/j.atherosclerosis.2010.05.040, indexed in Pubmed: 20609440.
39. Kawamoto R, Tomita H, Oka Y, et al. Relationship between serum uric acid concentration, metabolic syndrome and carotid atherosclerosis. Intern Med. 2006; 45(9): 605–614, indexed in Pubmed: 16755091.
40. Li Y, Lu J, Wu X, et al. Serum uric acid concentration and asymptomatic hyperuricemia with subclinical organ damage in general population. Angiology. 2014; 65(7): 634–640, doi: 10.1177/0003319713513143, indexed in Pubmed: 24327770.
41. Mehta T, Nuccio E, McFann K, et al. Association of Uric Acid With Vascular Stiffness in the Framingham Heart Study. Am J Hypertens. 2015; 28(7): 877–883, doi: 10.1093/ajh/hpu253, indexed in Pubmed: 25552515.
42. Mulè G, Riccobene R, Castiglia A, et al. Relationships between mild hyperuricaemia and aortic stiffness in untreated hypertensive patients. Nutr Metab Cardiovasc Dis. 2014; 24(7): 744–750, doi: 10.1016/j.numecd.2014.01.014, indexed in Pubmed: 24675008.
43. Fang X, Pan C, Chen Y, et al. Assessment of subclinical left ventricular changes in essential hypertensive patients with hyperuricemia: A three-dimensional speckle-tracking echocardiography study. Clin Exp Hypertens. 2017; 39(1): 93–99, doi: 10.1080/10641963.2016.1210626, indexed in Pubmed: 28072551.
44. Krishnan E, Hariri A, Dabbous O, et al. Hyperuricemia and the echocardiographic measures of myocardial dysfunction. Congest Heart Fail. 2012; 18(3): 138–143, doi: 10.1111/j.1751-7133.2011.00259.x, indexed in Pubmed: 22587743.
45. Tavil Y, Kaya MG, Oktar SO, et al. Uric acid level and its association with carotid intima-media thickness in patients with hypertension. Atherosclerosis. 2008; 197(1): 159–163, doi: 10.1016/j.atherosclerosis.2007.03.008, indexed in Pubmed: 17416371.
46. Sautin YY, Johnson RJ. Uric acid: the oxidant-antioxidant paradox. Nucleosides Nucleotides Nucleic Acids. 2008; 27(6): 608–619, doi:10.1080/15257770802138558, indexed in Pubmed: 18600514.
47. Pasalic D, Marinkovic N, Feher-Turkovic L. Uric acid as one of the important factors in multifactorial disorders--facts and controversies. Biochem Med (Zagreb). 2012; 22(1): 63–75, indexed in Pubmed: 22384520.
48. Rajagopalan S, Meng XP, Ramasamy S, et al. Reactive oxygen species produced by macrophage-derived foam cells regulate the activity of vascular matrix metalloproteinases in vitro. Implications for atherosclerotic plaque stability. J Clin Invest. 1996; 98(11): 2572–2579, doi: 10.1172/JCI119076, indexed in Pubmed: 8958220.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2021, Vol. 28, No. 6, 914–922
DOI: 10.5603/CJ.a2019.0065

ISSN 1897–5593
eISSN 1898–018X

Could autonomic nervous system parameters be still helpful in identifying patients with left ventricular systolic dysfunction at the highest risk of all-cause mortality?

Damian Kaufmann[1], Grzegorz Raczak[1], Małgorzata Szwoch[1], Dariusz Kozłowski[1], Joanna Kwiatkowska[2], Ewa Lewicka[1], Ludmiła Daniłowicz-Szymanowicz[1]

[1]Department of Cardiology and Electrotherapy, Medical University of Gdansk, Poland
[2]Department of Pediatric Cardiology and Congenital Heart Defect, Medical University of Gdansk, Poland

Abstract

Background: *Autonomic imbalance is associated with poor prognosis of patients with systolic dysfunction. Most of the previous data were written several years ago and constituted to cardiovascular or arrhythmic mortality. The current treatment of these patients has improved substantially over the last decades, and thus, the population at risk of death may have altered as well. Consequently, data on high-risk patients with systolic dysfunction in the modern era are sparse and those from previous trials may no longer be applicable. The aim herein, was to verify whether well-known autonomic indices — baroreflex sensitivity (BRS) and heart rate variability (HRV) — remain accurate predictors of mortality in patients with systolic dysfunction.*

Methods: *Non-invasively obtained BRS and HRV were analyzed in 205 clinically stable patients with left ventricular ejection fraction (LVEF) ≤ 40%. 28 patients died within 28 ± 9 month follow-up.*

Results: *Baroreflex sensitivity, low-frequency (LF) in normalized units, LF to high-frequency ratio and standard deviation of average R-R intervals were significantly associated with mortality; cut-off values of the highest discriminatory power for abovementioned parameters were ≤ 3.0 ms/mmHg, ≤ 41, ≤ 0.7 and ≤ 25 ms, respectively. In bivariate Cox analyses (adjusted for LVEF, New York Heart Association [NYHA] or absence of implantable cardioverter-defibrillator [ICD]) autonomic indices remain significant predictors of death.*

Conclusions: *Baroreflex sensitivity and HRV — may still be helpful in identifying patients with left ventricular systolic dysfunction at the highest risk of all-cause mortality, independently of LVEF, NYHA class, and ICD implantation.* (Cardiol J 2021; 28, 6: 914–922)

Key words: baroreflex sensitivity, heart rate variability, all-cause mortality, left ventricular dysfunction

Introduction

Heart failure (HF) is a constantly growing global pandemic, and according to the most recent data may affect between 26 and almost 38 million people worldwide [1, 2]. Future forecasts are even more alarming, in the United States alone, morbidity due to HF is projected to increase from current 5.7 million to almost 8 million by 2030 [3]. Despite continuous progress in pharmacotherapy [4, 5], widespread use of implantable cardioverter-defibrillators (ICD) and resynchronization therapy,

Address for correspondence: Dr. Ludmiła Daniłowicz-Szymanowicz, Department of Cardiology and Electrotherapy, Medical University of Gdansk, ul. Dębinki 7, 80–952 Gdańsk, Poland, tel: +48 58 349 39 10, fax: +48 58 349 39 20, e-mail: ludwik@gumed.edu.pl

Received: 3.03.2019 Accepted: 23.05.2019 Early publication date: 27.06.2019

all-cause mortality among patients with HF remains high [6, 7]. Persons with significant left ventricular (LV) systolic dysfunction (LV ejection fraction [LVEF] < 40%) have the worst prognosis of all patients with HF [8], therefore, further evaluation, risk stratification and new therapy options for these patients remains of important clinical value. Novel treatment methods, based on autonomic nervous system (ANS) modulation [9–12], seem to be particularly promising in this context, as these treatments were shown to contribute to better quality of life and exercise capacity i.e., improvement of the New York Heart Association (NYHA) functional class and longer 6-minute walking distance. However, these beneficial effects were not associated with a decrease in all-cause mortality [9–14]. Possibly an appropriate selection of these patients, taking into account the initial ANS parameters that reveal the patients at the highest risk of all-cause mortality, could improve the results of these therapies. The majority of previous studies dealing with the ANS testing in HF constituted cardiovascular and arrhythmic mortality, and were conducted several years ago when both pharmacotherapy and electrotherapy differed substantially from those presently used [15–26]. The treatment of such individuals with HF has improved substantially over the last decades, and thus, the patient population at risk of death may have been altered as well. As a result, available data on high-risk patients with systolic dysfunction in the modern era are sparse and data from previous trials may no longer be applicable.

The aim of the present study was to verify whether simple, non-invasive autonomic parameters, such as baroreflex sensitivity (BRS) and short-term heart rate variability (HRV), could be valuable predictors of all-cause mortality in patients with significant LV systolic dysfunction, and to identify the most accurate cut-off values for these parameters.

Methods

Patient selection

In this prospective study, 205 patients with reduced LVEF (≤ 40%) were enrolled between October 2009 and June 2014. 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. Additional inclusion criteria: sinus rhythm, optimal pharmacological therapy, stable clinical condition for at least 3 months before enrollment, and without significant features of hypervolemia at the moment of enrollment. The patients were excluded if they were younger than 18 years old had: a history of sustained ventricular arrhythmia (ventricular tachycardia or ventricular fibrillation) or cardiac arrest, NYHA functional class IV, permanent atrial fibrillation/flutter, permanent second- or third-degree atrioventricular block, implanted pacemaker, clinical features of coronary instability at the moment of enrolment, a revascularization (coronary angioplasty or/and surgery by-pass) within 3 months prior to the study, or incomplete coronary revascularization status (scheduled control coronarography, coronary angioplasty or surgery by-pass), clinical evidence of autonomic neuropathy, concomitant terminal disease and non-cardiologic comorbidities with a potentially unfavorable effect on survival.

ANS parameters

Autonomic nervous system tests were performed according to the protocol precisely described in our previous studies [27, 28] with the use of Mingograf 720C for ECG and Finapres 2300 (Ohmeda) for beat-to-beat non-invasive arterial blood pressure, which was recorded continuously for 8 min, but in comparison to abovementioned studies [27, 28] during breathing with a controlled interval (0.25 Hz). Data received were converted from analog to digital signals, processed with dedicated software [29] and analyzed according to the protocol [15, 30]. BRS (ms/mmHg) was computed by spectral analysis exactly as it was previously described [27, 28]. Furthermore, routine HRV indices: low-frequency (LF) to high-frequency (HF) ratio (LF/HF), relative spectral powers in LF (LFnu expressed in normalized units), as well as time-domain HRV parameters (standard deviation of normal-to-normal RR intervals [SDNN], the square root of the mean of squared differences between successive intervals [RMSSD], and the percentage of adjacent RR intervals differing by more than 50 ms [pNN50]) were analyzed [16].

Follow-up

All patients were followed-up at the university outpatient clinic with the first visit scheduled within 3 months of enrolment; the patients were checked every 6 months thereafter, or earlier if clinically required. During each visit, patient clinical status was evaluated and all adverse events were recorded, if any. The primary endpoint of the study was death of any cause. All deaths were verified against medical documentation of the patient and/or death certificate information.

Statistical analysis

The variables were expressed as medians (Q25–Q75 intervals), or numbers (n) and percentages (%). Comparisons between dead and living patients were made by the U Mann-Whitney test, the χ^2 test or the Yates χ^2 test. The accuracy of analyzed parameters as potential predictors of the study end-point was determined by area (AUC) under the receiver-operating characteristic (ROC) curve. An association between analyzed parameters and the end-point was assessed using the Cox hazard models, after the dichotomization of the measurements according to their cut-off values that maximized the hazard ratio (HR). For this purpose, HR for progressively increasing appropriate values were comprised between the 20^{th} and 50^{th} percentiles (to have an adequate number of patients in each subgroup) was calculated and the point at which HR attained its maximum was identified. The time course of the end-point, stratified according to the aforementioned cut-off values, was estimated using the Kaplan-Meier method, and the association between compared groups was estimated by the log-rank test. All results were considered statistically significant at $p \leq 0.05$. The statistical analysis was conducted with R 2.15.2 environment.

Results

Demographic, clinical and autonomic data of the group studied is presented in Table 1. Patients were approximately 63 years old, most patients had coronary artery disease and were in NYHA II class. Those with an ICD (including devices with cardiac resynchronization function) were approximately 70% of the patients. 29 (14%) patients had LVEF > 35%, and 36 (17%) patients were in NYHA I class. Pharmacotherapy in both groups did not differ statistically. The average follow-up period was 28 ± 9 months, during which 28 (14%) patients died, and they were characterized by significantly lower LVEF, more often presented with NYHA class III and digoxin use and less had an ICD implantation. SDNN, LFnu, LF/HF and BRS were significantly lower in patients who died in comparison to other, living patients.

Predictors of all-cause mortality

Baroreflex sensitivity was the best predictor of all-cause mortality in the studied patients (AUC 72.0% [95% CI 61.2–82.2]), whereas other autonomic parameters and LVEF had lower discriminatory powers: AUC 67.5 [95% CI 56.8–78.2] for SDNN, AUC 68.8% [95% CI 60.7–76.9] for LFnu, AUC 69.0 [95% CI 60.8–77.1] for LF/HF and AUC 67.9% [95% CI 56.8–79.1] for LVEF. The Cox-hazard regression analyses revealed that cut-off values maximally identifying patients at increased risk of death were 3.0 ms/mmHg for BRS, 41 for LFnu, 0.7 for LF/HF, 25 ms for SDNN and 25% for LVEF. All these values, as well as NYHA class III, were significantly associated with the incidence of the end-point in univariate Cox analyses (Fig. 1).

The absence of ICD implantation was also a strong indicator risk of death (HR 3.21 [95% CI 1.53–6.75], $p < 0.002$). Accuracy of the above-mentioned cut-off values of BRS, LFnu, LF/HF, SDNN and LVEF in predicting the risk of death is presented in Table 2 — it was noted BRS ≤ 3.0 ms/mmHg had the highest power in prediction of all-cause mortality in the patients studied. No other parameters from Table 1 were significant in predicting all-cause mortality in the Cox hazard regression analyses.

Kaplan-Meier curves illustrate the probability of all-cause mortality after dichotomization according to cut-off values BRS (Fig. 2), SDNN (Fig. 3), LFnu (Fig. 4) and LF/HF (Fig. 5).

Due to a relatively small number of end-points, the maximum number of predictors that could be used in a multivariate model without the risk of its overfitting was 2. Therefore, bivariate combinations of LVEF, NYHA III and ICD presence with above-mentioned cut-off values for analyzed autonomic parameters were checked: BRS, SDNN, LFnu, and LF/HF turned-out to be independent significant predictors of the all-cause mortality (Table 3).

Discussion

The observation that decreased values of BRS, SDNN, LFnu and LF/HF are accurate predictors of all-cause mortality in clinically stable patients with reduced LVEF, even after adjusting for other well-known clinical parameters (such as LVEF, NYHA class, ICD implantation) is the principal finding of the present study. The cut-off values determined in this study (BRS ≤ 3.0 ms/mmHg, SDNN ≤ 25 ms, LFnu ≤ 41 and LF/HF ≤ 0.7) accurately identified patients who were at increased risk of all-cause mortality during an average 2-year follow-up period. The novelty of the present study can be found in the demonstration that in the group of HF patients treated according to the current guidelines, in the era of widespread use of electrotherapy with ICD, the simple, non-invasive autonomic indices obtained from short-term systolic arterial pressure and electrocardiography signals are still accurate predictors of all-cause mortality.

Table 1. Clinical and demographic characteristics of the studied patients.

	All (n = 205)	Dead patients (n = 28)	Alive patients (n = 177)	P*
Age [years]	63 (57–71)	64 (56–71)	61 (57–71)	0.442
Male	175 (85%)	25 (89%)	150 (85%)	0.771
CAD history	128 (62%)	16 (57%)	112 (63%)	0.532
Revascularization	129 (63%)	17 (61%)	113 (64%)	0.843
LVEF [%]	30 (25–35)	25 (20–33)	30 (25–35)	**< 0.032**
QRS ≥ 120 ms	130 (63%)	18 (64%)	112 (63%)	1.000
NYHA class:				**< 0.041**
I	36 (17%)	2 (7%)	34 (19%)	
II	130 (63%)	16 (57%)	114 (64%)	
III	39 (19%)	10 (36%)	29 (16%)	
Beta-adrenolytics	197 (96%)	28 (100%)	169 (95%)	0.602
ACEI, ARB	193 (94%)	26 (93%)	167 (94%)	0.668
Spironolactone, eplerenone	115 (56%)	16 (57%)	99 (56%)	1.000
Antiplatelet therapy	159 (78%)	22 (79%)	137 (78%)	1.000
Amiodarone	21 (10%)	4 (14%)	17 (10%)	0.502
Statins	163 (80%)	20 (71%)	143 (81%)	0.309
Digoxin	11 (5%)	4 (14%)	7 (4%)	**< 0.047**
Diuretics	110 (54%)	20 (71%)	90 (51%)	0.072
Arterial hypertension	120 (59%)	11 (39%)	109 (62%)	**< 0.038**
Diabetes	51 (25%)	6 (21%)	45 (25%)	0.821
Renal function				0.092
GFR > 60 mL/min/1.73 m^2	154 (75%)	19 (68%)	135 (76%)	
GFR 30–59 mL/min/1.73 m^2	44 (21%)	6 (21%)	38 (21%)	
GFR < 30 mL/min/1.73 m^2	7 (3%)	3 (11%)	4 (2%)	
Hypercholesterolemia	114 (56%)	15 (54%)	99 (56%)	0.836
ICD	145 (71%)	14 (50%)	131 (77%)	**< 0.012**
Autonomic parameters				
Mean HP [ms]	1040 (966–1133)	996 (929–1122)	1050 (969–1133)	0.071
SDNN [ms]	25.8 (16.6–36.5)	15.0 (12.2–24.4)	27.2 (18.2–38.0)	**< 0.012**
RMSSD [ms]	21.0 (13.2–34.0)	16.9 (9.0–26.8)	21.3 (13.6–36.0)	0.063
pNN50 [%]	1.84 (0–11.58)	0.78 (0–5.24)	2.31 (0–13.38)	0.088
LFnu	32.15 (15.35–52.7)	17.95 (11.27 –28.6)	35.8 (17.88–57.5)	< 0.009
LF/HF	0.48 (0.19–1.12)	0.22 (0.12–0.40)	0.58 (0.23–1.38)	< 0.008
BRS [ms/mmHg]	3.89 (2.24–6.55)	2.28 (1.51–3)	4.66 (2.74–7.98)	< 0.015

*P value for comparison between patients who died and alive patients. CAD — coronary artery disease; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; ACEI — angiotensin converting enzyme inhibitors; ARB — angiotensin receptor blockers GFR — glomerular filtration rate; ICD — implantable cardioverter-defibrillator; HP — heart period; SDNN — standard deviation of the average R-R intervals of the sinus rhythm; RMSSD — square root of the mean squared difference of successive R-R intervals; pNN50 — proportion of successive R-R intervals that differ by more than 50 ms; LFnu — spectral power in low-frequency range expressed in normalized units; LF/HF — LF to HF ratio; BRS — baroreflex sensitivity

In two recent studies [27, 28], the usefulness of BRS and short-term HRV in prognosis, an increased risk of hospitalization due to HF decompensation [27], and identification of low-arrhythmic risk patients [28] was discovered. It needs to be noted, that cut-off values for BRS established in the abovementioned [27, 28], and other studies [15, 16, 31–33], are similar, at well-known 3.0 ms/mmHg cut-off on BRS estimates, which presents, according to Gouveia et al. [32], a natural partition of HF patients at risk.

Noticeably, the present study showed that BRS and short-term HRV were independent

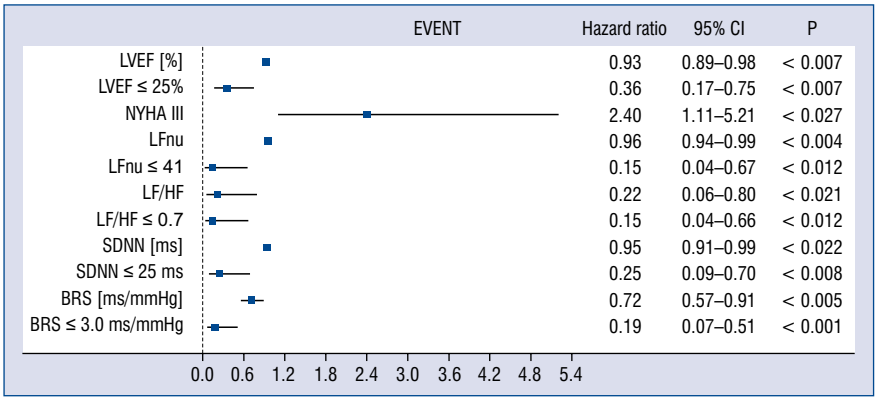


Figure 1. The Cox hazard regression analysis for pre-specified cut-off values of analyzed parameters as predictors of all-cause mortality during follow-up period; CI — confidence interval; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association functional class; LFnu — spectral power in low-frequency range expressed in normalized units; LF/HF — low-frequency to high-frequency ratio; SDNN — standard deviation of average R-R intervals of sinus rhythm; BRS — baroreflex sensitivity.

Table 2. Prognostic accuracy of the cut-off values of BRS, LFnu, LF/HF, SDNN, LVEF and NYHA III as predictors of death.

Parameters	AUC (%)	Characteristics (%) (95% CI)		Predictive value (%) (95% CI)	
		Sensitivity	Specificity	Positive	Negative
LVEF ≤ 25%	62.4	53.57 (35.81–70.47)	71.19 (64.12–77.35)	22.73 (14.29–34.17)	90.65 (84.66–94.45)
NYHA III	60.0	47.71 (20.71–54.17)	83.62 (77.46–88.34)	25.64 (14.57–41.08)	89.16 (83.51–93.03)
BRS ≤ 3.0 ms/mmHg	72.0	76.19 (54.91–89.37)	67.80 (58.92–75.55)	29.63 (19.14–42.83)	94.12 (86.96–97.46)
SDNN ≤ 25 ms	67.5	75.00 (53.13–88.81)	60.00 (51.06–68.32)	23.81 (14.99–35.64)	93.51 (85.68–97.19)
LFnu ≤ 41	68.8	90.00 (69.90–97.21)	47.50 (38.78–56.37)	22.22 (14.54–32.42)	96.61 (88.46–99.07)
LF/HF ≤ 0.7	69.0	90.00 (69.90–97.21)	47.90 (39.13–56.80)	22.50 (14.73–32.79)	96.61 (88.46–99.07)

AUC — area under the receiver-operating characteristic (ROC) curve; CI — confidence interval; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association functional class; BRS — baroreflex sensitivity; SDNN — standard deviation of the average R-R intervals of the sinus rhythm; LFnu — spectral power in low-frequency range expressed in normalized units; LF/HF — low-frequency to high-frequency ratio

risk factors of death regardless of LVEF and NYHA class, and, even more importantly, irrespective of ICD use, which can be considered a particularly important and novel finding. In the light of current discussions in the literature on the validity of ICD implantation in all patients with LV systolic dysfunction [34, 35], as well as in light of new methods of treatment of HF patients based on ANS modulation, the analyses presented in this paper seem to be of particular clinical significance.

In comparison to two recent studies [27, 28], in the present paper, BRS and HRV estimation were performed during breathing with a controlled interval (0.25 Hz), which is well-known methodological modification allowing the exclusion of the breathing rate influences on spontaneous BRS and HRV parameters in HF patients [36, 37].

Limitations of the study

There are potential limitations in the present study. Firstly, this was a small, single-center study,

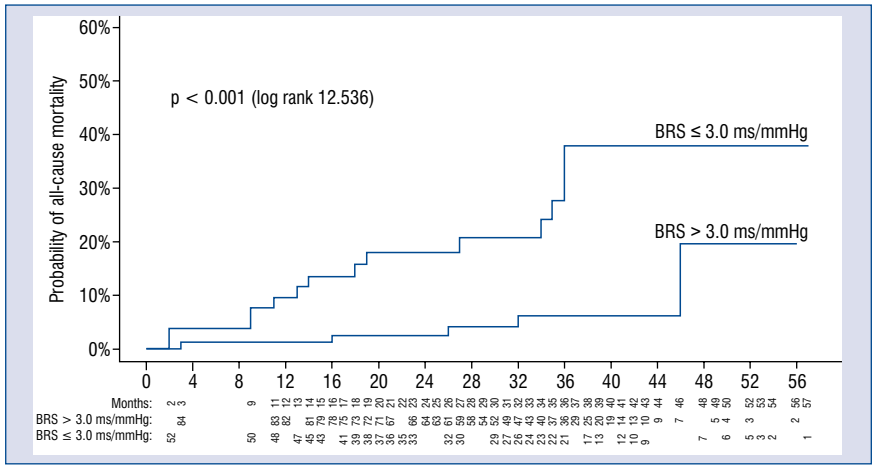


Figure 2. Kaplan-Meier curves illustrating the probability of the EVENT during the follow-up period depending on pre-specified cut-off values for baroreflex sensitivity (BRS).

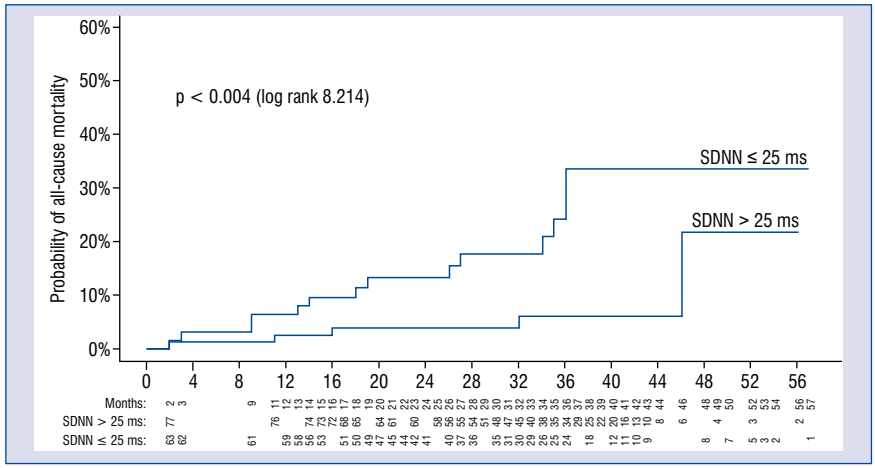


Figure 3. Kaplan-Meier curves illustrating the probability of the EVENT during follow-up period depending on pre-specified cut-off values for standard deviation of the average R-R intervals of the sinus rhythm (SDNN).

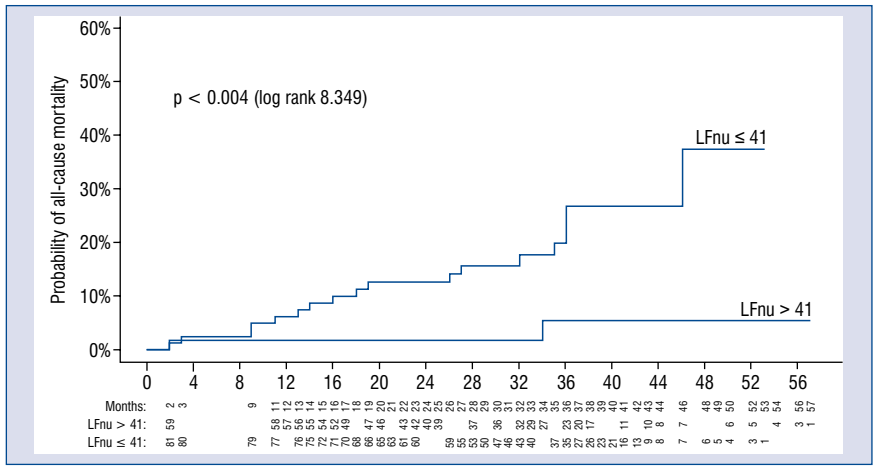


Figure 4. Kaplan-Meier curves illustrating the probability of the EVENT during follow-up period depending on pre-specified cut-off values for spectral power in low-frequency range expressed in normalized units (LFnu).

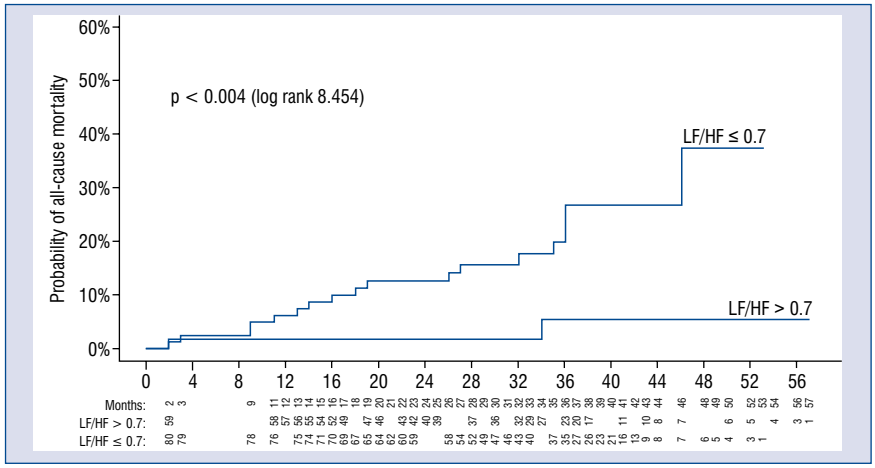


Figure 5. Kaplan-Meier curves illustrating the probability of the EVENT during follow-up period depending on pre-specified cut-off values for low-frequency to high-frequency ratio (LF/HF).

Table 3. Bivariate Cox models for EVENTs for BRS and HRV indexes during follow-up period (adjusted to LVEF, NYHA III, or presence of ICD).

	Hazard ratio	95% CI	P
LVEF-adjusted HR for BRS ≤ 3.0 ms/mmHg	6.52	2.36–17.96	**< 0.0001**
LVEF-adjusted HR for SDNN ≤ 25 ms	3.68	1.32–10.25	**< 0.013**
LVEF-adjusted HR for LF/HF ≤ 0.7	6.18	1.43–26.73	**< 0.015**
LVEF-adjusted HR for LFnu ≤ 41	6.12	1.42–26.50	**< 0.015**
NYHA III-adjusted HR for BRS ≤ 3.0 ms/mmHg	5.24	1.92–14.36	**< 0.001**
NYHA III-adjusted HR for SDNN ≤ 25 ms	3.77	1.37–10.40	**< 0.010**
NYHA III-adjusted HR for LF/HF ≤ 0.7	5.67	1.29–24.81	**< 0.021**
NYHA III-adjusted HR for LFnu ≤ 41	5.61	1.28–24.57	**< 0.022**
ICD-adjusted HR for BRS ≤ 3.0 ms/mmHg	5.48	2.01–14.99	**< 0.0001**
ICD-adjusted HR for SDNN ≤ 25 ms	3.88	1.41–10.70	**< 0.009**
ICD-adjusted HR for LF/HF ≤ 0.7	6.56	1.52–28.33	**< 0.012**
ICD-adjusted HR for LFnu ≤ 41	6.52	1.51–28.15	**< 0.012**

CI — confidence interval; LVEF — left ventricular ejection fraction; BRS — baroreflex sensitivity; SDNN — standard deviation of the average R-R intervals of sinus rhythm; LFnu — relative spectral power in LF range, expressed in normalized units; LF/HF — low-frequency to high-frequency ratio; NYHA — New York Heart Association functional class; ICD — implantable cardioverter-defibrillator

with a relatively short follow-up period; the results need to be confirmed in a larger group of patients with a longer observation periods. Secondly, some patients, apart from the fact that they were clinically stable, were not optimally treated concerning the three groups of drugs (ACEI/ARB, BB and MRA): some of them due to the significant contraindications or intolerance symptoms, another reason could be connected with the period of enrollment, which took place a few years ago and since then there has been further progress in pharmacological treatment of patients with HF. Additionally, the authors did not analyse the influence of diuretics doses on mortality. The next limitation concerns BRS and HRV indices, which were not possible to measure in the patients with permanent atrial fibrillation/flutter, permanent second- or third-degree atrioventricular block, and persons with paced rhythm; these patients are at the high risk of death, therefore further investigations concerning the prognosis of all-cause mortality amongst all HF patients with reduced LVEF are still needed.

Conclusions

The results of the present study suggest that simple, non-invasively obtained parameters of ANS activity, such as BRS and short-term HRV (SDNN, LFnu and LF/HF), remains helpful in the identification of persons with increased risk of all-cause mortality amongst clinically stable patients with LV systolic dysfunction treated in line to current guidelines, even after adjusting for other basic clinical parameters, such as LVEF, NYHA class, and ICD implantation.

Conflict of interest: None declared

References

1. Ponikowski P, Anker SD, AlHabib KF, et al. Heart failure: preventing disease and death worldwide. ESC Heart Fail. 2014; 1(1): 4–25, doi: 10.1002/ehf2.12005, indexed in Pubmed: 28834669.
2. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; 380(9859): 2163–2196, doi: 10.1016/S0140-6736(12)61729-2, indexed in Pubmed: 23245607.
3. Mozaffarian D, Benjamin E, Go A, et al. Heart Disease and Stroke Statistics—2016 Update. Circulation. 2016; 133(4), doi: 10.1161/cir.0000000000000350.
4. Ponikowski P, Voors A, Anker S, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Journal of Heart Failure. 2016; 18(8): 891–975, doi: 10.1002/ejhf.592.
5. Tomaszuk-Kazberuk A, Bolińska S, Młodawska E, et al. Does admission anaemia still predict mortality six years after myocardial infarction? Kardiol Pol. 2014; 72(6): 488–493, doi: 10.5603/KP.a2014.0046, indexed in Pubmed: 24526561.
6. Murad K, Goff DC, Morgan TM, et al. Burden of Comorbidities and Functional and Cognitive Impairments in Elderly Patients at the Initial Diagnosis of Heart Failure and Their Impact on Total Mortality: The Cardiovascular Health Study. JACC Heart Fail. 2015; 3(7): 542–550, doi: 10.1016/j.jchf.2015.03.004, indexed in Pubmed: 26160370.
7. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation. 2015; 131(4): e29–322, doi: 10.1161/CIR.0000000000000152, indexed in Pubmed: 25520374.
8. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. Eur Heart J. 2011; 33(14): 1750–1757, doi: 10.1093/eurheartj/ehr254.
9. Premchand RK, Sharma K, Mittal S, et al. Autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure: results of the ANTHEM-HF trial. J Card Fail. 2014; 20(11): 808–816, doi: 10.1016/j.cardfail.2014.08.009, indexed in Pubmed: 25187002.
10. Zannad F, De Ferrari GM, Tuinenburg AE, et al. Chronic vagal stimulation for the treatment of low ejection fraction heart failure: results of the NEural Cardiac TherApy foR Heart Failure (NECTAR-HF) randomized controlled trial. Eur Heart J. 2015; 36(7): 425–433, doi: 10.1093/eurheartj/ehu345, indexed in Pubmed: 25176942.
11. Abraham W, Zile M, Weaver F, et al. Baroreflex activation therapy for the treatment of heart failure with a reduced ejection fraction. JACC: Heart Failure. 2015; 3(6): 487–496, doi: 10.1016/j.jchf.2015.02.006.
12. Gronda E, Seravalle G, Brambilla G, et al. Chronic baroreflex activation effects on sympathetic nerve traffic, baroreflex function, and cardiac haemodynamics in heart failure: a proof-of-concept study. Eur J Heart Fail. 2014; 16(9): 977–983, doi: 10.1002/ejhf.138, indexed in Pubmed: 25067799.
13. De Ferrari GM, Stolen C, Tuinenburg AE, et al. Long-term vagal stimulation for heart failure: Eighteen month results from the NEural Cardiac TherApy foR Heart Failure (NECTAR-HF) trial. Int J Cardiol. 2017; 244: 229–234, doi: 10.1016/j.ijcard.2017.06.036, indexed in Pubmed: 28663046.
14. Gold M, Veldhuisen DV, Hauptman P, et al. Vagus Nerve Stimulation for the Treatment of Heart Failure. J Am Coll Cardiol. 2016; 68(2): 149–158, doi: 10.1016/j.jacc.2016.03.525.
15. Pinna GD, Maestri R, Capomolla S, et al. Applicability and clinical relevance of the transfer function method in the assessment of baroreflex sensitivity in heart failure patients. J Am Coll Cardiol. 2005; 46(7): 1314–1321, doi: 10.1016/j.jacc.2005.06.062, indexed in Pubmed: 16198850.
16. Camm AJ, Bigger JT, Breithardt G, et al. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J. 1996; 93(5): 1043–1065.
17. La Rovere MT, Bigger JT, Marcus FI, et al. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Lancet. 1998; 351(9101): 478–484, doi: 10.1016/s0140-6736(97)11144-8, indexed in Pubmed: 9482439.
18. La Rovere MT, Pinna GD, Maestri R, et al. Prognostic implications of baroreflex sensitivity in heart failure patients in the beta-blocking era. J Am Coll Cardiol. 2009; 53(2): 193–199, doi: 10.1016/j.jacc.2008.09.034, indexed in Pubmed: 19130988.
19. La Rovere MT, Maestri R, Robbi E, et al. Comparison of the prognostic values of invasive and noninvasive assessments of baroreflex sensitivity in heart failure. J Hypertens. 2011; 29(8): 1546–1552, doi: 10.1097/HJH.0b013e3283487827, indexed in Pubmed: 21666492.
20. Perkiömäki JS, Hämekoski S, Junttila MJ, et al. Predictors of long-term risk for heart failure hospitalization after acute myocardial infarction. Ann Noninvasive Electrocardiol. 2010; 15(3): 250–258, doi: 10.1111/j.1542-474X.2010.00372.x, indexed in Pubmed: 20645968.
21. Raczak G, Pinna GD, Maestri R, et al. Different predictive values of electrophysiological testing and autonomic assessment in patients surviving a sustained arrhythmic episode. Circ J. 2004; 68(7): 634–638, indexed in Pubmed: 15226627.
22. La Rovere MT, Pinna GD, Maestri R, et al. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. Circulation. 2003; 107(4): 565–570, indexed in Pubmed: 12566367.
23. La Rovere MT, Pinna GD, Maestri R, et al. Autonomic markers and cardiovascular and arrhythmic events in heart failure patients: still a place in prognostication? Data from the GISSI-HF

trial. Eur J Heart Fail. 2012; 14(12): 1410–1419, doi: 10.1093/eurjhf/hfs126, indexed in Pubmed: 22851700.
24. Nolan J, Batin P, Andrews R, et al. Prospective study of heart rate variability and mortality in chronic heart : results of the United Kingdom heart failure evaluation and assessment of risk trial (UK- heart). Circulation. 1998; 98(15): 1510–1516, doi: 10.1161/01.cir.98.15.1510.
25. Ponikowski P, Anker SD, Chua TP, et al. Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol. 1997; 79(12): 1645–1650, indexed in Pubmed: 9202356.
26. Powell BD, Saxon LA, Boehmer JP, et al. Survival after shock therapy in implantable cardioverter-defibrillator and cardiac resynchronization therapy-defibrillator recipients according to rhythm shocked. The ALTITUDE survival by rhythm study. J Am Coll Cardiol. 2013; 62(18): 1674–1679, doi: 10.1016/j.jacc.2013.04.083, indexed in Pubmed: 23810882.
27. Daniłowicz-Szymanowicz L, Suchecka J, Niemirycz-Makurat A, et al. Autonomic Predictors of Hospitalization Due to Heart Failure Decompensation in Patients with Left Ventricular Systolic Dysfunction. PLoS One. 2016; 11(3): e0152372, doi: 10.1371/journal.pone.0152372, indexed in Pubmed: 27015089.
28. Daniłowicz-Szymanowicz L, Kaufmann D, Rozwadowska K, et al. Microvolt T-wave alternans and autonomic nervous system parameters can be helpful in the identification of low-arrhythmic risk patients with ischemic left ventricular systolic dysfunction. PLoS One. 2018; 13(5): e0196812, doi: 10.1371/journal.pone.0196812, indexed in Pubmed: 29723261.
29. Maestri R, Pinna G. POLYAN: A computer program for polyparametric analysis of cardio-respiratory variability signals. Comput Methods Programs Biomed. 1998; 56(1): 37–48, doi: 10.1016/s0169-2607(98)00004-2.
30. Pinna GD, Maestri R, Raczak G, et al. Measuring baroreflex sensitivity from the gain function between arterial pressure and heart period. Clin Sci (Lond). 2002; 103(1): 81–88, doi: 10.1042/, indexed in Pubmed: 12095408.
31. Ranucci M, Porta A, Bari V, et al. Baroreflex sensitivity and outcomes following coronary surgery. PLoS One. 2017; 12(4): e0175008, doi: 10.1371/journal.pone.0175008, indexed in Pubmed: 28384188.
32. Gouveia S, Scotto MG, Pinna GD, et al. Spontaneous baroreceptor reflex sensitivity for risk stratification of heart failure patients: optimal cut-off and age effects. Clin Sci (Lond). 2015; 129(12): 1163–1172, doi: 10.1042/CS20150341, indexed in Pubmed: 26432088.
33. Schwartz PJ, La Rovere MT, De Ferrari GM, et al. Autonomic modulation for the management of patients with chronic heart failure. Circ Heart Fail. 2015; 8(3): 619–628, doi: 10.1161/CIRCHEARTFAILURE.114.001964, indexed in Pubmed: 25991804.
34. Køber L, Thune JJ, Nielsen JC, et al. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. N Engl J Med. 2016; 375(13): 1221–1230, doi: 10.1056/NEJMoa1608029, indexed in Pubmed: 27571011.
35. Haugaa KH, Tilz R, Boveda S, et al. Implantable cardioverter defibrillator use for primary prevention in ischaemic and non-ischaemic heart disease-indications in the post-DANISH trial era: results of the European Heart Rhythm Association survey. Europace. 2017; 19(4): 660–664, doi: 10.1093/europace/eux089, indexed in Pubmed: 28431077.
36. Rahman F, Pechnik S, Gross D, et al. Low frequency power of heart rate variability reflects baroreflex function, not cardiac sympathetic innervation. Clin Auton Res. 2011; 21(3): 133–141, doi: 10.1007/s10286-010-0098-y, indexed in Pubmed: 21279414.
37. Harada D, Asanoi H, Takagawa J, et al. Slow and deep respiration suppresses steady-state sympathetic nerve activity in patients with chronic heart failure: from modeling to clinical application. Am J Physiol Heart Circ Physiol. 2014; 307(8): H1159–H1168, doi: 10.1152/ajpheart.00109.2014, indexed in Pubmed: 25128165.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2021, Vol. 28, No. 6, 923–931
DOI: 10.5603/CJ.a2019.0066

ISSN 1897–5593
eISSN 1898–018X

Improvement of left ventricular function after percutaneous coronary intervention in patients with stable coronary artery disease and preserved ejection fraction: Impact of diabetes mellitus

Malgorzata Sikora-Frac, Beata Zaborska, Pawel Maciejewski, Andrzej Budaj, Bronislaw Bednarz

Department of Cardiology, Center of Postgraduate Medical Education, Grochowski Hospital, Warsaw, Poland

Abstract

Background: *Many patients with stable coronary artery disease (CAD) have no visual segmental wall motion abnormalities and a left ventricular (LV) ejection fraction (LVEF) ≥ 50% at rest despite significant coronary artery stenosis. Here, the aim was to determine the impact of percutaneous coronary intervention (PCI) on LV function assessed by enhanced echocardiography in patients with stable CAD with or without diabetes mellitus type 2 and a preserved LVEF.*

Methods: *Sixty-six consecutive patients with CAD and LVEF ≥ 50%, admitted to the hospital for planned coronary angiography, were prospectively assessed. PCI was performed for coronary artery stenosis > 70%. CAD extent was assessed using SYNTAX and EXTENT scores. To assess LV function, LVEF, global longitudinal strain (GLS), and LV peak systolic myocardial velocity (S') were measured and Tei index was calculated before and 3 months after PCI.*

Results: *Before PCI, LVEF, GLS, and Tei index were significantly worse in diabetic patients. LV functional indices improved significantly after PCI in all patients ($p < 0.001$). Multivariate linear regression analyses were performed to evaluate the impact of selected factors on LV function after PCI expressed as changes (Δ) of LVEF, GLS, S', and Tei index. LV function improvement expressed as ΔGLS was associated only with SYNTAX score. Higher SYNTAX scores were related to greater GLS improvement ($\beta = 0.003$, 95% confidence interval: 0.0004–0.005; $p = 0.02$).*

Conclusions: *Percutaneous coronary intervention significantly improved LV function in diabetic and non-diabetic CAD patients with preserved LVEF. Enhanced echocardiography allowed an assessment of subtle changes in LV function.* (Cardiol J 2021; 28, 6: 923–931)

Key words: coronary artery disease, left ventricular function, percutaneous coronary intervention, echocardiography, diabetes mellitus

Introduction

Stable coronary artery disease (CAD) is one of the most common cardiovascular diseases. Acute and chronic myocardial ischemia leads to systolic and diastolic left ventricular (LV) dysfunction resulting in the development of heart failure [1]. Percutaneous coronary intervention (PCI) is a widely used invasive treatment for CAD that eliminates symptoms, improves LV function and quality of life, and, in selected groups of patients, reduces the incidence of death [2, 3]. However,

Address for correspondence: Malgorzata Sikora-Frac, MD, PhD, Grochowski Hospital, Center of Postgraduate Medical Education, Department of Cardiology, ul. Grenadierów 51/59, 04–073 Warszawa, Poland, tel: +48 22 515 26 60, fax: +48 22 515 26 71, e-mail: msikora-frac@wp.pl

Received: 8.04.2019 Accepted: 9.06.2019 Early publication date: 27.06.2019

an optimal revascularization strategy for patients with diabetes mellitus type 2 (DM) remains under discussion [4, 5]. Most patients with stable CAD have no visual segmental wall motion abnormalities and an LV ejection fraction (LVEF) ≥ 50% at rest despite significant coronary artery stenosis. Limited data are available concerning the effects of elective PCI on LV function in patients with stable CAD (especially in diabetic patients), without myocardial infarction (MI), and with preserved LVEF. The value of single echocardiographic parameters in the assessment of LV function before and after PCI has been analyzed [6–9]. Standard echocardiography with an LVEF assessment does not reflect all aspects of LV systolic function. The use of advanced echocardiographic techniques including tissue Doppler echocardiography and LV strain measurement (e.g. global longitudinal strain [GLS]) enables the demonstration of LV systolic dysfunction despite preserved LVEF. Information obtained through advanced echocardiography may allow clinicians to decide whether to perform PCI in stable CAD patients with preserved LVEF and comorbid DM. The study aims were to determine the impact of PCI on LV function assessed by enhanced echocardiography in patients with stable CAD and preserved LVEF and evaluate the impact of DM on LV systolic function in patients with CAD before and after PCI.

Methods

Study population

Two hundred and fourteen consecutive patients were prospectively selected with symptomatic CAD without acute coronary syndrome in whom coronary angiography and PCI were performed. Patients with prior MI, symptomatic heart failure, segmental LV wall motion abnormalities, an LVEF < 50%, arrhythmias, or poor acoustic windows were excluded from the study. To exclude acute ischemia, electrocardiography was performed in each patient prior to coronary angiography and compared with previous electrocardiograms (ECG). Patients were referred for coronary angiography by treating physicians and then qualified for PCI according to the European Society of Cardiology Guidelines for CAD [2]. All patients included in our study complained of cardiac ischemic pains (CCS I–III). Myocardial ischemia was confirmed by resting ECG (chronic ST-changes) or ambulatory ECG (Holter) monitoring (myocardial ischemia during normal activities) and/or treadmill exercise testing (ST-segment abnormality). Diagnostic tests were conducted in 40 patients (21 CAD patients, 19 diabetic CAD patients).

Percutaneous coronary intervention was considered successful when Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow and residual stenosis < 20% were achieved [10]. The decision concerning PCI and use of coronary stents was left to the treating cardiologists. Coronary angiography was recorded in digital form and assessed for ongoing study by an independent invasive cardiologist blinded to the patient history and ECG and echocardiographic data. CAD extent was assessed using SYNTAX [11] and EXTENT [12] scores.

N-terminal pro B-type natriuretic peptide, fasting blood glucose, creatinine, lipids, glycated hemoglobin concentrations, and glomerular filtration rate were assessed before the angiography was performed. To exclude DM, glucose tolerance tests were performed in patients without DM.

Echocardiography

Two-dimensional echocardiography with LV systolic and diastolic function assessments were performed. The first echocardiographic examination was performed before PCI (< 12 h) in all patients who qualified for the study. The second echocardiographic examination was performed in all patients included in the study 3 months after the last PCI. Echocardiography was performed in the standard parasternal and apical views using a VIVID 9 (GE Medical System, Horten, Norway; 1.7–3.3-MHz transducer) and VIVID 4 (GE Medical System, Haifa, Israel; 1.5–2.5-MHz transducer) devices. All images were stored digitally for later analysis. LV function was expressed as LVEF, LV GLS, LV S', and Tei index. The Tei index was calculated as a sum of isovolumetric contraction time and isovolumetric relaxation time divided by LV ejection time as described by Tei [13]. LVEF was calculated using the modified Simpson method [14].

Apical four- and two-chamber and long-axis views were used for quantification of LV GLS by automated function imaging of two-dimensional speckle tracking analysis. All analyzed images were recorded with a frame rate > 55 frames per second. Data were subsequently transferred for offline analysis using EchoPack Sw Only BT version 110.0.x (GE Medical System). For each of three views, mean longitudinal strain was calculated according to current standards [15]. LV GLS was calculated as the arithmetical mean of these three values. The division of LV into 17 segments was applied and presented graphically in the form of curves and bullseye plots (Fig. 1A, 1B). Territorial

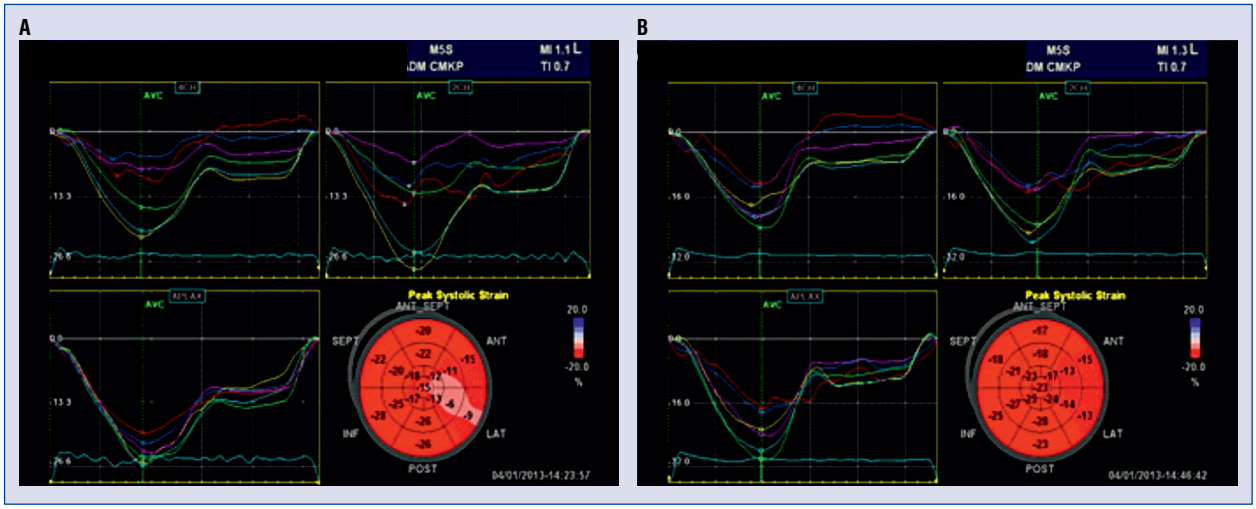


Figure 1. Assessment of global longitudinal strain with automated function imaging before percutaneous coronary intervention (PCI) (**A**) and after PCI for circumflex coronary artery (**B**). The polar maps show the improvement in segmental longitudinal strain in the mid and apical anterior segments and basal, mid, and apical lateral segments.

longitudinal strain (TLS) was calculated based on perfusion territories of the three major coronary arteries in a 17-segment LV model by averaging all segmental peak systolic strain values within each territory [15]. For comparison with the angiographic findings, segments were correlated with the arterial supply as follows: basal anterior and anteroseptal, mid-anterior and anteroseptal, apical anterior, septal and apex were assigned to the left anterior descending (LAD) coronary artery distribution; basal inferoseptal and inferior, mid-inferoseptal and inferior, and apical inferior were assigned to the right coronary artery (RCA); and basal inferolateral and anterolateral, mid-inferolateral and anterolateral, and apical lateral were assigned to the left circumflex artery (LCX).

S' was assessed from the apical four- and two-chamber view for basal segments septal, lateral, anterior, and inferior LV wall by pulsed tissue Doppler echocardiography. The average of these four basal velocities was used to calculate mean basal S'. Three consecutive beats were measured and averaged for all S' measurements.

Statistical analysis

The statistical analysis was preceded by an analysis of the group size. The sample size of patients in the study group was estimated based on the differences between S' and GLS values before and after PCI. Based on available literature, the minimum clinically meaningful differences for S' and GLS values before and after PCI were 0.7 ± 1.1 cm/s [4, 6] and –2.5 ± 3% [16, 17], respectively. To prove the impact of PCI on LV function with a 5% level of significance and ensure that the power of the test was 80%, to detect these differences, the minimum number of patients enrolled to this study should be 43 and 26 for S' and GLS, respectively. The data are expressed as mean value ± standard deviation or median value (interquartile range) for continuous variables and frequency tables for discrete parameters. Mean values were compared with the t-test or the nonparametric Mann-Whitney U test. Proportions were compared using the χ^2 test. Medians were compared with the Kruskal-Wallis test. Multivariate linear analyses were performed to evaluate the impact on LV function after PCI, expressed as changes of GLS, S', and Tei index between the measurements before and after PCI (ΔGLS, ΔS', ΔTei index). The correlation between the statistically significant parameters and the analysed parameters (GLS, S', Tei index) was expressed by the β coefficient with a 95% confidence interval (CI). For p values > 0.1, β coefficient and CI were not indicated. P values < 0.05 were considered significant. The Spearman correlation coefficients were calculated to assess the relationship between LV GLS and SYNTAX and EXTENT scores. Statistical analysis was performed using Stata version 10.

Results

Clinical data

Of the 214 patients screened, 66 were enrolled in the study (34 with DM); the other 148 subjects

Table 1. Demographic and clinical characteristic of the study population.

Parameter*	All patients (n = 66)	CAD + DM (n = 34)	CAD (n = 32)	P (CAD + DM vs. CAD)
Age [years]	67 ± 8.2	67 ± 8.7	66.2 ± 7.7	NS
Sex:				
Female	23 (35%)	12 (35%)	11 (34%)	NS
Male	43 (65%)	22 (65%)	21 (66%)	NS
BMI [kg/m^2]	29.3 ± 4.0	30.4 ± 4.0	28.2 ± 3.7	0.05
Current smoking	12 (18%)	6 (18%)	6 (19%)	NS
Smoking cessation	27 (48%)	14 (48%)	13 (48%)	NS
Hypertension	59 (89%)	33 (93%)	26 (81%)	NS
DM duration [years]	–	6 ± 3.2	–	–
TC [mg/dL]	175.1 ± 38.2	171.3 ± 39.8	179.2 ± 36.5	NS
LDL-C [mg/dL]	95.8 ± 35.5	88.8 ± 3.0	103.3 ± 31.6	NS
TG [mg/dL]	136.4 ± 63.8	157.8 ± 75.1	113.8 ± 38.7	0.01
HDL-C [mg/dL]	49.2 ± 13	45.6 ± 11.5	53.1 ± 13.6	0.05
GFR > 60 mL/min × 1.72 m^2	20 (30.3%)	9 (25%)	11 (34.3%)	NS
NT-proBNP (pg/mL), median (min, max)	145 (73, 273)	136 (64, 293)	151 (104, 238)	NS
Medication:				
ACEI or ARB	52 (79%)	29 (85%)	23 (72%)	NS
BB	63 (95%)	31 (91%)	32 100%)	NS
ASA	66 (100%)	34 (100%)	32 (100%)	NS
Clopidogrel	65 (98%)	33 (97%)	32 (100%)	NS
Statins	59 (89%)	28 (82%)	31 (97%)	NS
DM treatment:				
Diet	–	5 (15%)	–	–
Diet + OAD	–	24 (70%)	–	–
Diet + OAD + insulin	–	5 (15%)	–	–
HbA_{1c} [%]	–	6.81 ± 0.94	–	–

*Continuous variables are presented as mean ± standard deviation and categorical variables are presented as number (percentage). CAD — coronary artery disease; DM — diabetes mellitus type 2; NS — statistically nonsignificant; BMI — body mass index; TC — total cholesterol; LDL-C — low density lipoprotein cholesterol; TG — triglycerides; HDL-C — high density lipoprotein cholesterol; GFR — glomerular filtration rate; NT-proBNP — N-terminal pro B-type natriuretic peptide; ACEI — angiotensin converting enzyme inhibitors; ARB — angiotensin receptor blockers; BB — beta-adrenergic receptor blockers; ASA — acetylsalicylic acid; OAD — oral antidiabetic medication; HbA1c — glycated hemoglobin

did not meet the entry criteria. All 66 patients underwent successful PCI. The mean duration of DM was 6 ± 3.2 years. The mean HbA1c level of patients with DM was 6.8 ± 0.9%. The patient demographic and clinical characteristics are presented in Table 1.

Angiographic data

Patient angiographic characteristics are shown in Table 2. The mean EXTENT score was greater in patients with CAD and DM than in those with CAD only, but the differences were not statistically significant. There were no differences in SYNTAX score among diabetic and non-diabetic patients. In all patients who qualified for the study, complete revascularization of all coronary lesions qualified for PCI was performed. Thirty patients underwent two-step revascularization (16 with CAD, 14 with CAD and DM). There was no difference in stent type used for revascularization between patients with or without DM. Second-generation drug-eluting stents were mainly used (88% and 89% for diabetic and non-diabetic patients, respectively).

Echocardiographic data

Two-dimensional echocardiography was performed in all 66 patients. LVEF, S', and Tei index were assessed in the whole group, while GLS was assessed in 53 patients. GLS was not assessed in 13 patients because anatomic conditions precluded the registration of an appropriate echocardiogram quality. Baseline echocardiographic parameters

Table 2. Baseline angiographic characteristics.

Parameter	CAD + DM (n = 34)	CAD (n = 32)	P (CAD + DM vs. CAD)
Stenotic coronary artery:			
LAD	8	9	NS
LCX	3	3	NS
RCA	7	6	NS
LAD+RCA	6	9	NS
LAD+LCX	7	3	NS
LCX+RCA	2	2	NS
LAD+LCX+RCA	1	0	NS
EXTENT score:			
Minimum, maximum	3, 90	3, 58	
Median (Q1, Q3)	24 (6, 43)	17 (12, 32)	NS
SYNTAX score:			
Minimum, maximum	2, 39	2, 34	
Median (Q1, Q3)	9 (6, 16)	10 (6, 18)	NS
Stent type:			
DES	44 (86%)	37 (79%)	NS
BMS	7 (14%)	10 (21%)	NS
Treated vessels per patient	1.5	1.4	NS

CAD — coronary artery disease; DM — diabetes mellitus type 2; LAD — left anterior descending artery; NS — statistically nonsignificant; LCX — left circumflex coronary artery; RCA — right coronary artery; DES — drug-eluting stents; BMS — bare metal stents

Table 3. Baseline echocardiographic parameters.

Parameter	All patients (n = 66)	CAD + DM (n = 34)	CAD (n = 32)	P (CAD + DM vs. CAD)
LVEDD [mm]	44.7 ± 5.4	44.4 ± 5.1	45 ± 5.7	NS
LVEDV [mL]	85 ± 21	85 ± 23	85 ± 18	NS
LVEF [%]	59 ± 5	58 ± 4	60 ± 4	0.028
IVS [mm]	11.1 ± 1.4	11.4 ± 1.3	10.8 ± 1.4	NS
PW [mm]	10.1 ± 1.3	10.2 ± 1.4	10 ± 1.2	NS
LA [mm]	33.3 ± 3.7	34 ± 4.4	32.7 ± 2.7	NS
RV [mm]	28.5 ± 2.9	28.9 ± 2.9	28 ± 2.9	NS
E/A	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	NS
DT [ms]	262 ± 72	267 ± 87	257 ± 52	NS
E′ [cm/s]	8.1 ± 1.4	7.9 ± 1.4	8.4 ± 1.4	NS

Data are presented as mean ± standard deviation. CAD — coronary artery disease; DM — diabetes mellitus type 2; LVEDD — left ventricular end-diastolic diameter; NS — statistically nonsignificant; LVEDV — left ventricular end-diastolic volume; LVEF — left ventricular ejection fraction; IVS — intraventricular septum; PW — posterior wall; LA — left atrium; RV — right ventricle; E/A — ratio E/A (E, A waves — mitral inflow velocities); DT — E wave deceleration time; E′— mean early diastolic tissue velocity in the basal segments

before PCI are summarized in Table 3. LV function parameters differed between diabetic and non-diabetic patients. LVEF, GLS, and Tei index were significantly worse in diabetic patients before PCI (Table 4). All echocardiographic parameters of LV function improved significantly after PCI in all patients (Table 5). However, the differences in GLS and LVEF between the subgroups of patients with CAD and DM and those with CAD without DM were maintained (Table 4). GLS values increased by 18% in CAD patients and DM and by 14% in CAD patients without DM but were significantly

Table 4. Parameters of left ventricular (LV) function before and after percutaneous coronary intervention (PCI) by subgroup.

	LVEF [%]			GLS [%]			S' [cm/s]			Tei index		
	CAD + DM	CAD	P*	CAD + DM	CAD	P*	CAD + DM	CAD	P*	CAD + DM	CAD	P*
Before PCI	58 ± 4	60 ± 4	0.028	–16.6 ± 0.9	–18.6 ± 2.3	< 0.001	6.8 ± 1	7.2 ± 0.9	NS	0.6 ± 0.1	0.53 ± 0.06	0.0006
After PCI	61 ± 5	63 ± 5	0.045	–19.4 ± 2.3	–21.1 ± 1.7	0.003	7.6 ± 0.9	8 ± 0.9	NS	0.44 ± 0.1	0.4 ± 0.05	NS
P**	< 0.0001	< 0.0001	–	< 0.0001	< 0.0001	–	< 0.0001	< 0.0001	–	< 0.0001	< 0.0001	–

Data are presented as mean ± standard deviation. *CAD + DM vs. CAD, **before vs. after PCI. LVEF — left ventricular ejection fraction; GLS — global longitudinal strain; S' — left ventricular peak systolic myocardial velocity; CAD — coronary artery disease; DM — diabetes mellitus type 2; NS — statistically nonsignificant

worse in diabetic patients than in non-diabetic patients (p = 0.003).

There were high correlations between GLS and intraobserver and interobserver variation (correlation coefficient, 0.98 and 0.96, respectively; p < 0.001).

S' increased significantly after PCI in all patients (Tables 4 and 5). The range of S' changes was similar in both groups of patients (increase by 0.8 cm/s). Tei index improved significantly in all patients and in both subgroups of patients (p < < 0.0001; Tables 4 and 5). The improvement in Tei index was more evident in patients with CAD and DM than in patients with CAD only (–0.17 ± 0.07 vs. –0.12 ± 0.05, respectively; p = 0.002).

The average TLS for LAD, LCX, and RCA significantly improved after PCI (Table 6).

The patient group with one-vessel disease was also separated and the strain assessed before and after revascularization for territory distribution of this coronary artery and other LV segments. TLS after PCI increased in both territories (–16.3 ± ± 2.9% vs. –19.7 ± 2.6% and –17.8 ± 1.9% vs. –19.6 ± 2.2%, respectively), but the change (Δ) was greater in the revascularized area (Δ–3.5 ± ± 1.5% vs. Δ–1.8 ± 1.5%; p = 0.0001).

Relationship between selected parameters and LV function

Multivariate linear regression analyses were performed to evaluate the impact of selected factors on LV function after PCI are expressed as changes (Δ) of GLS, S', and Tei index. The selected factors included DM presence, DM duration, SYNTAX and EXTENT scores, sex, and age. The ΔGLS was associated with SYNTAX score. Higher SYNTAX scores were related to greater improvement in GLS and led to greater LV function improvement after revascularization (β = 0.003, 95% CI 0.0004–0.005; p = 0.02). No significant impacts of other variables on ΔGLS or any tested factors on the ΔS' and the ΔTei index were revealed.

Discussion

The present study showed that PCI significantly improved LV function in CAD patients with or without DM with preserved LVEF and no visual segmental wall motion abnormalities or heart failure symptoms. Advanced echocardiography with assessment of GLS, S', and Tei index enabled the diagnosis of subclinical impairment of LV systolic function in patients with stable CAD despite the absence of evident LV systolic dysfunction in con-

Table 5. Parameters of left ventricular (LV) function before and after percutaneous coronary intervention (PCI) in all patients.

	LVEF [%] (n = 66)	GLS [%] (n = 53)	S' [cm/s] (n = 66)	Tei index (n = 66)
Before PCI	59 ± 5	–17.5 ± 2.34	7.0 ± 0.96	0.57 ± 0.09
After PCI	62 ± 5	–20.5 ± 2.26	7.8 ± 0.95	0.42 ± 0.08
P*	0.001	0.001	0.001	0.001

Data are presented as mean ± standard deviation. *Before vs. after PCI. LVEF — left ventricular ejection fraction; GLS — global longitudinal strain; S' — left ventricular peak systolic myocardial velocity

Table 6. Territorial longitudinal strain (TLS) of the three major coronary arteries.

	TLS before PCI [%]	TLS after PCI	P*
LAD	–16.3 ± 2.3	–19.6 ± 2.2	< 0.0001
LCX	–16.9 ± 2.7	–19.8 ± 2.7	0.001
RCA	–16.8 ± 3.3	–20.3 ± 2.6	< 0.0001

Data are presented as mean ± standard deviation; *Before vs. after PCI. LAD — left anterior descending artery; LCX — left circumflex coronary artery; PCI — percutaneous coronary intervention; RCA — right coronary artery

ventional two-dimensional echocardiography and revealed LV functional improvement after PCI.

According to the literature, there are several mechanisms responsible for myocardial damage in patients with stable CAD. The most important are: reduced coronary flow, chronic ischemia [1], small-vessel microembolization, and endothelial dysfunction. Myocardial fibres consist of three different anatomical layers. The innermost subendocardial layer has an oblique clockwise orientation in the longitudinal direction. The subendocardial layer mainly contributes to cardiac long-axis function. Myocardial fibres of the subendocardial layer are more vulnerable to ischemic damage than those in the midmyocardium and subepicardium. Previous studies have demonstrated that, in the presence of the epicardial flow restriction, the subendocardial layer tends to have less blood flow than the subepicardial layer [18, 19]. Choi et al. [20] suggested that repetitive ischemic episodes of LV myocardium due to significant coronary stenosis might reduce longitudinal function despite normal resting or a regional wall motion. This may explain why longitudinal measures such as GLS and S' are sensitive markers of ischemia and LV function impairments. Biering-Sorensen et al. [21] revealed differences between GLS values in patients with and without stable CAD and an LVEF > 50%. GLS values were significantly lower in patients with ≥ 70% stenosis in at least one coronary artery compared to patients without coronary stenosis. Agarwal et al. [22] performed a systematic review and meta-analysis to assess the efficacy of tissue Doppler echocardiography indices in the diagnosis of CAD and demonstrated that LV S' was significantly decreased among patients with CAD compared to those without CAD. Ischemia is associated with a rapid and massive increase in the concentration of endogenous catecholamines in the myocardial interstitial fluid with a deleterious effect on cardiac myocytes culminating in myocardial apoptosis and fibrosis [23].

Limited data are available on the effects of PCI on LV function in patients with a preserved LVEF. The majority of studies examined the way in which PCI affects LV diastolic function or LV systolic function in patients with acute MI or complete coronary artery occlusion. In patients without a MI assessment of LV function after revascularization, testing was limited to the evaluation of LV contraction at rest and during dobutamine stress echocardiography or demonstrating enhanced performance in the exercise test [24, 25].

In the present study, LV function was assessed simultaneously by four echocardiographic parameters: LVEF in the assessment of global LV function; GLS and S' in the assessment of systolic longitudinal function; and Tei index in the assessment of combined systolic and diastolic myocardial performance. This enabled a sensitive and comprehensive assessment of LV function before and after PCI.

In all patients included in the study, GLS values were significantly higher after, than before PCI. There are limited data on GLS changes after elective PCI in patients with stable CAD and a preserved LVEF. Ryo et al. [26] showed LV function improvements expressed as GLS in 35 patients 1 month after PCI. Antoni et al. [17] assessed LV function after acute MI using GLS during 1 year of follow-up. Patients with an increase in GLS ≥ 10% are recognized as improvers. In the present study, the increase in GLS after PCI was 17% in all groups of patients despite their lack of MI and having less LV dysfunction.

Percutaneous coronary intervention significantly improved S' values in all patients. Diller et al. [8] studied 24 patients with normal systolic LV function undergoing elective PCI and showed that S' improved in all investigated ventricular areas compared to pre-interventional values. Surucu et al. [27] did not found any improvement in S' values after revascularization. These differences may be due to different time spans between PCI and the re-assessment of S' in the present study.

Another important finding was that PCI significantly reduced the Tei index. A change in the Tei index was more beneficial in diabetic patients with CAD than in patients with CAD only. The data of Tei index before and after elective PCI are scarce and limited to patients with MI. According to available research, the Tei index has not been used to assess LV function changes after revascularization in cases of stable CAD. The improvement in TLS confirms the beneficial effect of PCI on LV function in patients with stable CAD and a preserved LVEF.

Tei index, LVEF, and GLS values before PCI were worse in patients with CAD and DM compared to patients with CAD only despite the lack of statistically significant differences in the extent of atherosclerosis in the coronary arteries assessed using SYNTAX and EXTENT scores. This finding is in accordance with the hypotheses of increased myocardial stiffness, increased resting myocyte tension, and the deposition of advanced glycated end products associated with diabetic cardiomyopathy and worse systolic and diastolic LV function in diabetic patients [28].

The improvement of LV function after PCI observed in the current study was similar in non-diabetic and diabetic patients. However, LVEF and GLS values were still worse after PCI in patients with CAD and DM compared to those with CAD but without DM. This may suggest that PCI improved LV function similarly in all patients enrolled in the study and differences resulted from worse baseline LV function in patients with DM.

In the present study, higher SYNTAX scores were associated with greater improvement in GLS. According to available research, this is a new finding. SYNTAX score is considered a parameter of anatomical CAD complexity; therefore, it could be used as an indirect marker of plaque burden [29]. A greater plaque burden indicated by a higher SYNTAX score may lead to a more beneficial effect of complete revascularization in this group of patients.

The improvement of LV function noted in the present study may have clinical consequences i.e., reduced future heart failure. This paper opens the door to future investigations assessing the importance of small but detectable LV function changes in patients with and without DM.

Limitations of the study

The current study has some limitations. First, the number of patients enrolled is relatively small. Second, the severity of atherosclerosis in the coronary arteries was assessed by one investigator. And finally, SYNTAX and EXTENT scores are subjective [30].

Conclusions

Percutaneous coronary intervention significantly improved LV function in diabetic and non-diabetic CAD patients with a preserved LVEF. Enhanced echocardiography allows the assessment of subtle beneficial changes in LV function in patients with no wall motion visual abnormalities, i.e. candidates for PCI. These results support the indication for PCI in diabetic and non-diabetic patients.

Acknowledgments

The study was supported by research grant 501-2-1-09-38 from the Center of Postgraduate Medical Education, Warsaw, Poland.

Conflict of interest: None declared

References

1. Gheorghiade M, Sopko G, De Luca L, et al. Navigating the crossroads of coronary artery disease and heart failure. Circulation. 2006; 114(11): 1202–1213, doi: 10.1161/CIRCULATIONAHA.106.623199, indexed in Pubmed: 16966596.
2. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery

disease of the European Society of Cardiology. Eur Heart J. 2013; 34(38): 2949–3003, doi: 10.1093/eurheartj/eht296, indexed in Pubmed: 23996286.
3. Windecker S, Stortecky S, Stefanini GG, et al. Revascularisation versus medical treatment in patients with stable coronary artery disease: network meta-analysis. BMJ. 2014; 348: g3859, doi: 10.1136/bmj.g3859, indexed in Pubmed: 24958153.
4. Li X, Kong M, Jiang D, et al. Comparing coronary artery bypass grafting with drug-eluting stenting in patients with diabetes mellitus and multivessel coronary artery disease: a meta-analysis. Interact Cardiovasc Thorac Surg. 2014; 18(3): 347–354, doi: 10.1093/icvts/ivt509, indexed in Pubmed: 24345688.
5. Dai X, Luo ZC, Zhai Lu, et al. Reassessing Coronary Artery Bypass Surgery Versus Percutaneous Coronary Intervention in Patients with Type 2 Diabetes Mellitus: A Brief Updated Analytical Report (2015-2017). Diabetes Ther. 2018; 9(5): 2163–2171, doi: 10.1007/s13300-018-0504-3, indexed in Pubmed: 30220039.
6. Strotmann JM, Richter A, Kukulski T, et al. Doppler myocardial imaging in the assessment of regional myocardial function in longitudinal direction pre- and post-PTCA. Eur J Echocardiogr. 2001; 2(3): 178–186, doi: 10.1053/euje.2001.0091, indexed in Pubmed: 11882451.
7. Labovitz AJ, Lewen M, Kern MJ, et al. The effects of successful PTCA on left ventricular function: assessment by exercise echocardiography. Am Heart J. 1989; 117(5): 1003–1008, indexed in Pubmed: 2523633.
8. Diller GP, Wasan BS, Thom SA, et al. Evidence of improved regional myocardial function in patients with chronic stable angina and apparent normal ventricular function--a tissue Doppler study before and after percutaneous coronary intervention. J Am Soc Echocardiogr. 2009; 22(2): 177–182, doi: 10.1016/j.echo.2008.10.018, indexed in Pubmed: 19022622.
9. Gasior Z, Drzewiecki J, Wita K, et al. [Left ventricular systolic function after PTCA--recent and late assessment by exercise echocardiography]. Pol Arch Med Wewn. 1994; 92(4): 307–312, indexed in Pubmed: 7854958.
10. Smith SC, Feldman TE, Hirshfeld JW, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). Circulation. 2006; 113(7): e166–286.
11. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention. 2005; 1(2): 219–227, indexed in Pubmed: 19758907.
12. Sullivan DR, Marwick TH, Freedman SB. A new method of scoring coronary angiograms to reflect extent of coronary atherosclerosis and improve correlation with major risk factors. Am Heart J. 1990; 119(6): 1262–1267, indexed in Pubmed: 1972310.
13. Tei C. New non-invasive index for combined systolic and diastolic ventricular function. J Cardiol. 1995; 26(2): 135–136, indexed in Pubmed: 7674144.
14. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr. 1989; 2(5): 358–367, indexed in Pubmed: 2698218.
15. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015; 28(1): 1–39.e14, doi: 10.1016/j.echo.2014.10.003, indexed in Pubmed: 25559473.
16. Nakai H, Takeuchi M, Nishikage T, et al. Subclinical left ventricular dysfunction in asymptomatic diabetic patients assessed by two-dimensional speckle tracking echocardiography: correlation with diabetic duration. Eur J Echocardiogr. 2009; 10(8): 926–932, doi: 10.1093/ejechocard/jep097, indexed in Pubmed: 19622532.
17. Antoni ML, Mollema SA, Atary JZ, et al. Time course of global left ventricular strain after acute myocardial infarction. Eur Heart J. 2010; 31(16): 2006–2013, doi: 10.1093/eurheartj/ehq198, indexed in Pubmed: 20566488.
18. Bache RJ, McHale PA, Greenfield JC. Transmural myocardial perfusion during restricted coronary inflow in the awake dog. Am J Physiol. 1977; 232(6): H645–H651, doi: 10.1152/ajpheart.1977.232.6.H645, indexed in Pubmed: 879303.
19. Yao GH, Zhang C, Sun FR, et al. Quantification of transmural gradient of blood flow in myocardial ischemia with real-time myocardial contrast echocardiography and dipyridamole stress test. Ultrasound Med Biol. 2008; 34(1): 22–30, doi: 10.1016/j.ultrasmedbio.2007.06.019, indexed in Pubmed: 17854984.
20. Choi JO, Cho SW, Song YB, et al. Longitudinal 2D strain at rest predicts the presence of left main and three vessel coronary artery disease in patients without regional wall motion abnormality. Eur J Echocardiogr. 2009; 10(5): 695–701, doi: 10.1093/ejechocard/jep041, indexed in Pubmed: 19401300.
21. Biering-Sørensen T, Hoffmann S, Mogelvang R, et al. Myocardial strain analysis by 2-dimensional speckle tracking echocardiography improves diagnostics of coronary artery stenosis in stable angina pectoris. Circ Cardiovasc Imaging. 2014; 7(1): 58–65, doi: 10.1161/CIRCIMAGING.113.000989, indexed in Pubmed: 24186963.
22. Agarwal R, Gosain P, Kirkpatrick JN, et al. Tissue Doppler imaging for diagnosis of coronary artery disease: a systematic review and meta-analysis. Cardiovasc Ultrasound. 2012; 10: 47, doi: 10.1186/1476-7120-10-47, indexed in Pubmed: 23199010.
23. Tomai F, Crea F, Chiariello L, et al. Ischemic preconditioning in humans: models, mediators, and clinical relevance. Circulation. 1999; 100(5): 559–563, indexed in Pubmed: 10430772.
24. Klisiewicz A, Michałek P, Szymański P, et al. Changes in the response of hibernated myocardium to inotropic stimulation after angioplasty: a Doppler myocardial imaging study. Clin Cardiol. 2003; 26(11): 503–507, doi: 10.1002/clc.4960261105, indexed in Pubmed: 14640464.
25. Parisi AF, Folland ED, Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. Veterans Affairs ACME Investigators. N Engl J Med. 1992; 326(1): 10–16, doi: 10.1056/NEJM199201023260102, indexed in Pubmed: 1345754.
26. Ryo K, Tanaka H, Kaneko A, et al. Efficacy of longitudinal speckle tracking strain in conjunction with isometric handgrip stress test for detection of ischemic myocardial segments. Echocardiography. 2012; 29(4): 411–418, doi: 10.1111/j.1540-8175.2011.01621.x, indexed in Pubmed: 22329730.
27. Sürücü H, Tatli E, Okudan S, et al. Evaluation of subendocardial and subepicardial left ventricular functions using tissue Doppler imaging after complete revascularization. Echocardiography. 2009; 26(2): 203–210, doi: 10.1111/j.1540-8175.2008.00765.x, indexed in Pubmed: 19054027.
28. Aneja A, Tang WH, Bansilal S, et al. Diabetic cardiomyopathy: insights into pathogenesis, diagnostic challenges, and therapeutic options. Am J Med. 2008; 121(9): 748–757, doi: 10.1016/j.amjmed.2008.03.046, indexed in Pubmed: 18724960.
29. Stuart HJ, Farooq V, Serruys PW, et al. The SYNTAX score and its clinical implications. Heart. 2014; 100(2): 169–177, doi: 10.1136/heartjnl-2012-302482, indexed in Pubmed: 23539552.
30. Généreux P, Palmerini T, Caixeta A, et al. SYNTAX score reproducibility and variability between interventional cardiologists, core laboratory technicians, and quantitative coronary measurements. Circ Cardiovasc Interv. 2011; 4(6): 553–561, doi: 10.1161/CIRCINTERVENTIONS.111.961862, indexed in Pubmed: 22028472.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2021, Vol. 28, No. 6, 932–940
DOI: 10.5603/CJ.a2019.0032

ISSN 1897–5593
eISSN 1898–018X

Diastolic dyssynchrony and its exercise-induced changes affect exercise capacity in patients with heart failure with reduced ejection fraction

Jakub Stępniewski, Grzegorz Kopeć, Wojciech Magoń, Piotr Podolec

Department of Cardiac and Vascular Diseases, Jagiellonian University Medical College, John Paul II Hospital, Krakow, Poland

Abstract

Background: *Left ventricular diastolic dyssynchrony is common in patients with heart failure with reduced ejection fraction (HFREF). Little is known however, about its pathophysiology and clinical effects. Herein is hypothesized that presence of diastolic dyssynchrony at rest or at exercise may importantly contribute to HF symptoms. The aim was to investigate the influence of diastolic dyssynchrony and its exercise-induced changes on exercise capacity in HFREF patients.*

Methods: *Patients with stable, chronic HF, left ventricular ejection fraction < 35%, sinus rhythm and QRS ≥ 120 ms were eligible for the study. Rest and cyclo-ergometer exercise echocardiography were performed. Diastolic dyssynchrony was defined as opposing-wall-diastolic-delay ≥ 55 ms measured in tissue-Doppler imaging. Exercise capacity was assessed by peak oxygen consumption (VO_{2peak}). Association between diastolic dyssynchrony and VO_{2peak} was assessed in univariate regression analysis and further adjusted for possible confounders.*

Results: *Fourty eight patients were included (aged 63.7 ± 12.2). Twenty-seven (56.25%) had diastolic dyssynchrony at rest and 13 (27%) at exercise. Twenty-two (46%) experienced a change in diastolic dyssynchrony status during exercise. In univariate models diastolic dyssynchrony at rest or at exercise were associated with lower VO_{2peak} (beta coefficient = –3.8, p = 0.004; beta coefficient = –3.6, p = 0.02, respectively). However, the ability to restore diastolic synchronicity during exercise was associated with higher VO_{2peak} (beta coefficient = 3.4, p = 0.04) and remained an important predictor of exercise capacity after adjustment for age and HF etiology.*

Conclusions: *The ability to restore diastolic synchronicity at exercise predicts exercise capacity in patients with HFREF.* (Cardiol J 2021; 28, 6: 932–940)

Key words: stress echocardiography, cardiopulmonary exercise test, ischemic cardiomyopathy, QRS prolongation, cardiac resynchronization therapy

Introduction

Mechanical dyssynchrony results from the incoordinate wall motion of different ventricular segments. It may occur not only in systole, but also in diastole. While systolic dyssynchrony has been shown to be an important contributor to the left ventricular (LV) dysfunction in a wide spectrum of heart failure (HF) patients, little is known on the pathophysiology and clinical effects of diastolic dyssynchrony, although diastolic dyssynchrony has been frequently observed both in HF patients with reduced (HFREF) and preserved (HFPEF) ejection fraction [1–5].

Most evidence regarding diastolic dyssynchrony come from studies on patients with HFPEF.

Address for correspondence: Jakub Stępniewski, MD, Department of Cardiac and Vascular Diseases, Jagiellonian University Medical College, John Paul II Hospital, ul. Prądnicka 80, 31–202 Kraków, Poland, tel: +48 12 614 22 87, fax: +48 12 423 43 76, e-mail: jakub.stepniewski@gmail.com

Received: 2.01.2019 Accepted: 5.02.2019 Early publication date: 26.03.2019

Diastolic dyssynchrony in this population was found to aggravate LV diastolic dysfunction [5]. It was associated with the LV hypertrophy and increased LV mass [5]. Interestingly, initiation of medical therapy has shown to favor improvement of diastolic dyssynchorny. Patients with HFPEF, in whom treatment with diuretics, when beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists were initiated, experienced a significant decrease in diastolic dyssynchrony [5].

In contrast, an understanding of the pathophysiology and clinical effects of diastolic dyssynchrony in HFREF patients remains deficient. It was found, that diastolic dyssynchrony occurs at least as frequent as systolic, although the coexistence of systolic and diastolic dyssynchrony is low, suggesting that the mechanisms of these two phenomena may exhibit some differences [3]. The presence of diastolic dyssynchrony was observed more often in patients with wider QRS duration and was linked to worse diastolic LV function [1]. It was also associated with an adverse prognosis in children with dilated cardiomyopathy [6]. Eventually, cardiac resynchronization therapy (CRT) was found to improve diastolic dyssynchrony, however the role of diastolic dyssynchrony in CRT patient selection is less clear [3].

Data on the influence of diastolic dyssynchrony on exercise capacity in patients with HFREF is lacking. It was also unknown as to whether diastolic dyssynchrony is prone to change during exercise as had previously been reported with regard to systolic dyssynchrony [7].

Limitation of exercise capacity is the main symptom of HF, hence the aim in the present study to investigate the influence of diastolic dyssynchrony on exercise capacity in HFREF patients with prolonged QRS duration, and to analyse the effect of exercise on the presence of LV diastolic dyssynchrony.

Methods

Study population

Consecutive HFREF patients considered for CRT device implantation at a single tertiary cardiology department between 2013 and 2014 were included in this study. Patients were enrolled in the study if they classified in the New York Heart Association (NYHA) functional class II–IV despite optimal medical therapy and had no further coronary revascularization options, presented with LV ejection fraction (LVEF) ≤ 35%, were in sinus rhythm and had QRS duration ≥ ≥ 120 ms on a 12-lead electrocardiogram. Patents with any HF exacerbations within past 3 months were not eligible for the study. Exclusion criteria also included a history of any cardiac implantable electronic devices, persistent atrial fibrillation, significant respiratory, neurological or orthopaedic disorder limiting exercise capabilities. Ischemic etiology (ischemic cardiomyopathy [ICM]) of the HF was defined based on a history of myocardial infarction, coronary revascularization or presence of angiographically significant stenotic coronary lesions. Otherwise the patients were diagnosed with non-ischemic cardiomyopathy (DCM).

All patients provided written informed consent to participate in this study. The study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Ethical Committee at the Jagiellonian University in Krakow, Poland (KBET/110/B/2013).

All measurements and patient medical records were prospectively acquired by the authors themselves.

Echocardiography

A Vivid 7 device (GE Medical System, Horten, Norway) was used, equipped with phased-array 3.5-MHz transducer and tissue Doppler imaging (TDI) software to perform echocardiographic examinations in all patients. The recordings were analysed offline on EchoPac software (GE Vingmed, Horten, Norway) after digital storage. Conventional 2-dimensional and Doppler parameters were calculated in apical 4-, 3- and 2-chamber views. TDI data were recorded with the highest attainable frame rate. Six basal LV time-velocity curves (TVI) were reproduced offline from stored TDI color images to analyse LV systolic and diastolic dyssynchrony. All measurements were performed by experienced echocardiographers by averaging at least 3 consecutive heart beats.

The LV systolic function was determined by LVEF, calculated using the Simpson biplane method [8]. The LV diastolic function was quantified by the ratio of the early diastolic mitral velocity (E) acquired with the pulsed-wave Doppler, to the mean septal and lateral mitral annulus early diastolic velocity (e') obtained by the TDI-derived pulsed-wave (E/e') [9].

Exercise stress echocardiography

Symptom-limited exercise echocardiography was performed on cycle ergometer (Ergoline 9000 Ergoline GmbH, Bitz, Germany) in a semi-recum-

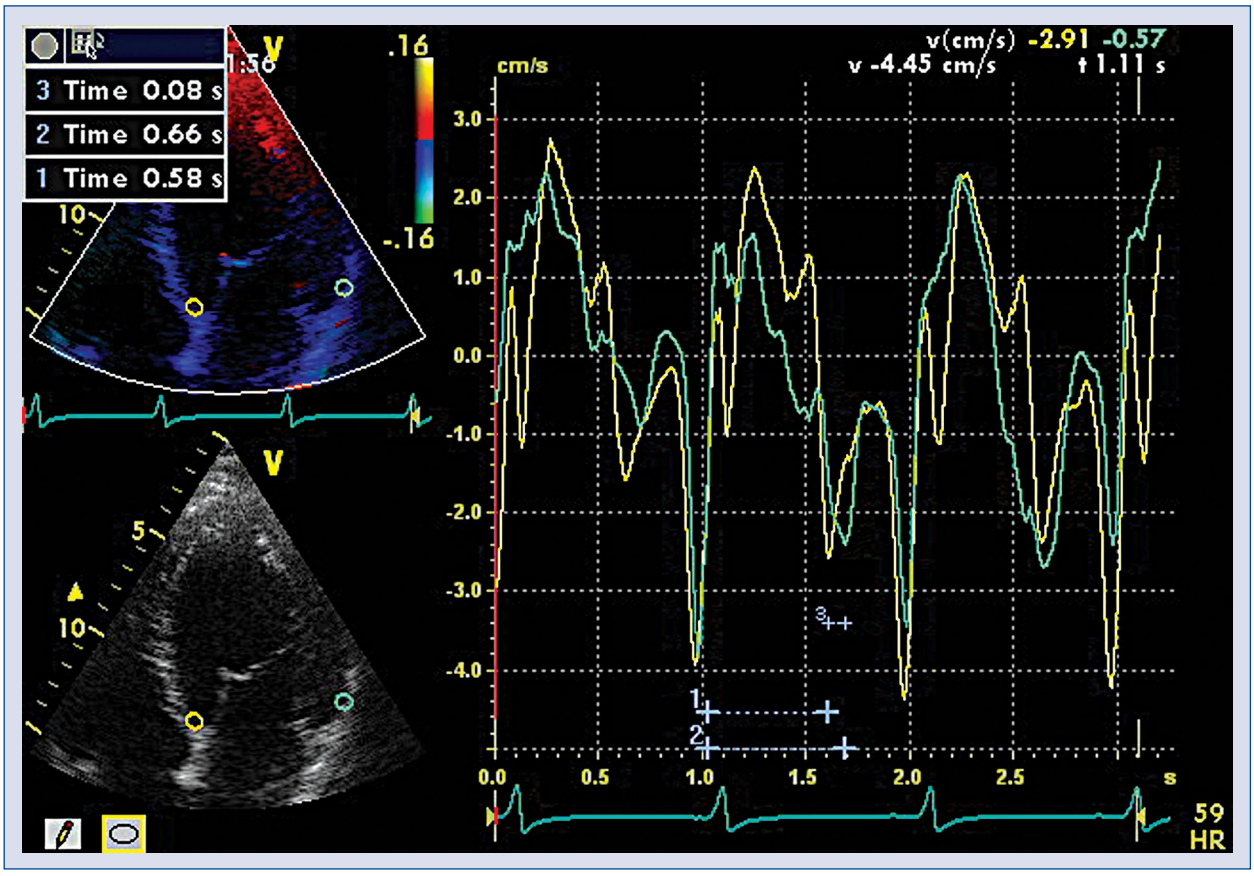


Figure 1. An example of diastolic dyssynchrony evaluation on the myocardial velocity imaging curves. The yellow curve represents basal segment of the interventricular septum (IVS) and the green, a basal segment of the lateral wall (LAT). Line 1 and 2 measure the time-to-peak early diastolic myocardial velocity interval (Te) of the IVS (line 1) and the LAT (line 2) from the onset of the QRS. Line 3 shows the difference between the IVS Te and the LAT Te representing an opposing wall Te delay.

bent position with the initial workload of 20 Watts increasing every 2 min by 20 Watts. Echocardiographic data were recorded throughout the exercise and stored for subsequent off-line analysis. Peak exercise measurements were derived from at least 3 heart beats in the last 2-min cycle and are expressed as means. Pharmacotherapy was continued without change at the time of stress tests.

Diastolic and systolic LV dyssynchrony

Calculations of the LV diastolic and systolic dyssynchrony were performed at rest and at peak exercise for each patient. 6 LV basal TVIs were applied to measure time-to-peak early diastolic myocardial velocity intervals (Te) from the onset of QRS complex to the peak early diastolic myocardial velocity to analyse diastolic dyssynchrony (Fig. 1), and time-to-peak systolic velocity intervals (Ts) from the onset of QRS complex to the peak myocardial systolic velocity in order to analyse systolic dyssynchrony. The differences between Te and Ts of opposing wall segments were calculated to determine opposing wall diastolic and systolic delays. In order to eliminate the effect of heart rate on measurements of dyssynchrony parameters and to allow for comparison of rest and exercise dyssynchrony status, Te and Ts delays were corrected for RR intervals using the Bazzet formula [10]. At least one corrected opposing wall diastolic delay greater or equal to 55 ms was indicative for rest and exercise diastolic dyssynchrony, as previously described [3]. Similarly, at least one corrected opposing wall systolic delay greater or equal to 65 ms was indicative for rest an exercise systolic dyssynchrony [11].

Exercise-induced diastolic resynchronization was defined as change from the presence of diastolic dyssynchrony at rest to absence of diastolic dyssynchrony at exercise. In contrast, occurrence of diastolic dyssynchrony during exercise if not

present at rest was indicative of exercise-induced diastolic dyssynchronization.

Cardiopulmonary exercise test

The treadmill cardiopulmonary exercise test (CPET) was employed to determine exercise capacity. The tests were conducted on a separate day than stress echocardiography. The CPET was performed using Reynolds Medical TMX425 TRACKMASTER treadmill unit with continuous breath-by-breath measurement of oxygen consumption (VO_2), carbon dioxide production (VCO_2), and minute ventilation (VE) on Reynolds Medical ZAN-600 respiratory gas analyzer. Modified Naughton protocol was applied in all patients [12]. VO_{2peak} was defined as the highest value of oxygen uptake attained in the final 30 s of exercise and was presented as a weighted variable (mL/kg/min) and as a percentage of age and sex predicted maximal exercise oxygen consumption. Anaerobic threshold was defined as the submaximal VO_2 level when there is a dislinear rise in VE and VCO_2 and expressed as mL/kg/min. Respiratory exchange ratio was calculated as the VCO_2/VO_2.

Statistical analysis

Categorical variables were described as counts and percentages and continuous variables as means ± standard deviations or median and interquartile range. the unpaired Student's t-test was used for normally distributed variables, the Mann-Whitney U-test for non-normally distributed continuous data, and the χ^2 test for categorical data to compare patients with and without diastolic dyssynchrony. With the use of univariate regression analysis the association between VO_{2peak} (dependent variable) were examined and its potential modifiers (independent variables) including age, sex (0 — male, 1 — female), HF etiology (0 — DCM, 1 — ICM), serum hemoglobin level, PR interval, QRS duration and morphology (0 — non-left bundle branch block [LBBB], 1 — LBBB), markers of the LV systolic (LVEF) and diastolic function (E/e' ratio), the presence of rest and exercise diastolic and systolic dyssynchrony (0 — not present, 1 — present) and the presence of exercise-induced diastolic resynchronization and exercise-induced dyssynchronization. Significant associations were further adjusted the for age and etiology. The significance level was set at $p < 0.05$. Statistical analyses were performed with Statistica PL software (StatSoft, Inc. 2017, STATISTICA, data analysis software system, version 13.1; www.statsoft.com) and MedCalc version 11.6.1.0 (MedCalc Software, Mariakerke, Belgium).

Results

Characteristics of the patients studied

Between 2013 and 2014 we recruited 54 patients. Further analyses were based on 48 patients aged 63.7 ± 12.2 (39; 81.3% males) with a sufficient quality of echocardiographic data. The majority of patients (30; 62.5%) were in NYHA class III. Medical treatment of the patients studied complied with contemporary guidelines [13]. A summary of clinical characteristics of the study group is presented in Table 1.

Rest and stress echocardiography

The mean LVEF was reduced (23.6 ± 6%) and the LV diastolic function was decreased with the mean E/e' ratio of 17.1 ± 8.

Exercise cardiac echo studies were performed without significant adverse events. Stress examinations were terminated at the mean workload of 76.2 ± 30.5 Watts and the mean heart rate of 115.4 ± 22.1 bpm. Echocardiographic parameters are presented in Table 1.

Diastolic LV dyssynchrony at rest and at exercise

Diastolic dyssynchrony at rest was identified in 27 (56.3%) patients, mainly in males (25; 93%) and patients with ICM were (17; 63%). The group with diastolic dyssynchrony compared to the group without had similar LV systolic and diastolic function and a similar proportion of patients with systolic dyssynchrony. A detailed comparison of clinical parameters between patients with and without diastolic dyssynchrony is summarized in Table 1.

Exercise echocardiography revealed the presence of exercise diastolic dyssynchrony in 13 (27%) patients. Twenty-two (46%) patients experienced a change in the diastolic dyssynchrony status under exercise. Exercise-induced diastolic resynchronization was present in 18 (66.6%) patients and provoked diastolic dyssynchrony in 4 (19%) patients (Fig. 2). A detailed comparison of clinical parameters between patients who remained synchronized during exercise or became dyssynchronized and between patients who remained dyssynchronized or resynchronized during exercise is presented in **Supplementary Table 1**.

Diastolic dyssynchrony and exercise capacity

The CPET was performed in every patient but the full protocol was obtained in 41 (85%).

Table 1. Characteristics of the patients studied.

Variable	All patients (n = 48)	Without diastolic dyssynchrony (n = 21)	With diastolic dyssynchrony (n = 27)	P
Age [years]	63.7 ± 12.2	63.5 ± 9.6	63.8 ± 14	0.93
Women/men	9 (18.7%)/39 (81.3%)	7 (33%)/14 (67%)	2 (7%)/25 (93%)	0.02
Body mass index [kg/m^2]	26.5 ± 3.8	25.9 ± 4.2	26.9 ± 3.5	0.37
Ischemic/non-ischemic	23 (47.9%)/25 (52.1%)	6 (29%)/15 (71%)	17 (63%)/10 (37%)	0.02
NYHA:				0.58
II	12 (25%)	6 (29%)	6 (22%)	
III	30 (62.5%)	13 (62%)	17 (63%)	
IV	6 (12.5%)	2 (9%)	4 (15%)	
NT-proBNP [pg/mL]	1667 [503–3309]	1206 [532–2665]	1744 [479–4888]	0.47
Hemoglobin [g/dL]	14.4 ± 1.2	14.4 ± 1	14.3 ± 1.3	0.7
Heart rate [bpm]	70.6 ± 8.9	71.2 ± 8.8	70,1 ± 9.1	0.69
QRS duration [ms]	150 [120–160]	160 [120–160]	140 [120–160]	0.51
PR [ms]	200 [160–220]	180 [160–200]	200 [160–220]	0.08
LBBB/non-LBBB	28 (58.3%)/20 (41.7%)	11 (52%)/10 (48%)	17 (63%)/10 (37%)	0.46
Beta-blocker	47 (97.9%)	21 (100%)	26 (96%)	0.37
ACEI or ARB	47 (97.9%)	20 (96%)	27 (100%)	0.25
Aldosterone receptor antagonist	43 (89.6%)	18 (86%)	25 (93%)	0.44
Loop diuretics	44 (91.6%)	18 (86%)	26 (96%)	0.18
LVEF [%]	23.6 ± 6.0	23.5 ± 6.6	23.7 ± 5.7	0.91
E/e' ratio	17.1 ± 8.1	15.3 ± 6.2	18.5 ± 9.2	0.17
Max Te delay [ms]	60 [40–80]	40 [30–45]	80 [60–98]	< 0.001
Systolic dyssynchrony	32 (66.6%)	15 (71%)	17 (63%)	0.54

NYHA — New York Heart Association; NT-proBNP — N-terminal prohormone of B-type natriuretic peptide; LBBB — left bundle branch block; ACEI — angiotensin converting enzyme inhibitor; ARB — angiotensin receptor blocker; LVEF — left ventricular ejection fraction; E/e' — ratio of early diastolic mitral velocity to early diastolic velocity of the mitral annulus; max Te delay — maximal opposing wall diastolic delay

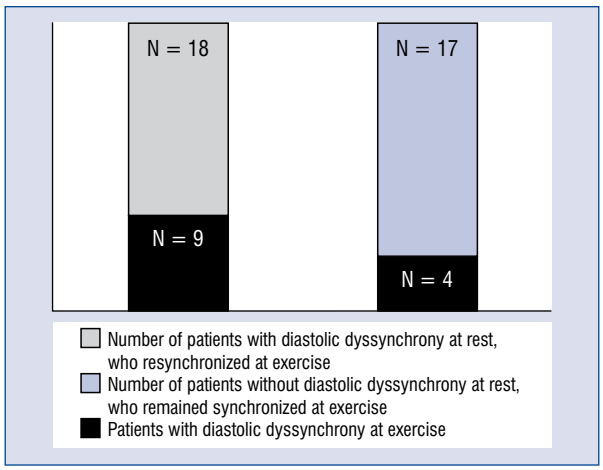


Figure 2. Exercise related changes of diastolic dyssynchrony. The first column shows proportion of patients with diastolic dyssynchrony at rest, who restored synchronicity at exercise (gray square) and those, who remained dyssynchronized (black square); The second column shows proportion of patients without diastolic dyssynchrony at rest, who remained synchronized at exercise (blue square) and those who dyssynchronized (black square).

Seven patients refused to complete the test due to anxiety for exercising on the treadmill or lightheadedness. Detailed CPET results are shown in Table 2. Lower VO_{2peak} was associated with more advanced age, ischemic etiology of HF, longer PR interval, higher E/e' ratio, the presence of rest and exercise diastolic dyssynchrony and lack of diastolic resynchronization at exercise (Table 3). After adjustment for age and etiology, exercise induced diastolic resynchronization (beta coefficient = 3.4; 95% confidence interval [CI] 0.17 to 6.6; p = 0.04), E/e' (beta coefficient = –2.0; 95% CI –0.06 to –0.34; p = 0.006) and PR interval (beta coefficient = –0.05; 95% CI –0.02 to –0.08, p = 0.004) were significantly associated with VO_{2peak} (Table 3). A comparison of mean VO_{2peak} between patients without rest diastolic dyssynchrony, who remained synchronized at exercise and those who dyssynchronized at exercise, and between patients with rest diastolic dyssynchrony, who remained dyssnchronized at exercise and those who resynchronized at exercise is shown in Figure 3.

Table 2. Cardiopulmonary exercise tests parameters.

Variable	All patients (n = 41)	Without diastolic dyssynchrony (n = 17)	With diastolic dyssynchrony (n = 24)	P
Time of exercise [s]	555 ± 234	661 ± 247	510 ± 218	0.14
Exercise load [METs]	5.4 [4.4–6.3]	5.4 [4.4–7.4]	4.7 [3.4–5.4]	0.16
VO_{2peak} [mL/kg/min]	15.5 ± 4.3	17.8 ± 4	13.9 ± 4	0.004
Percentage of predicted VO_{2max} [%]	57.9 ± 18.6	65.4 ± 23.5	52.4 ± 11.6	0.04
Anaerobic threshold [mL/kg/min]	11 [7.1–14.5]	11.7 [8.9–16.7]	7.8 [6.9–12.1]	0.14
VE/VCO_2	31 [27.3–37]	28 [25.1–30.4]	33.3 [30.1–39.5]	< 0.001
Respiratory exchange ratio	1.03 [0.96–1.12]	1.03 [0.96–1.09]	1.03 [0.95–1.14]	0.62

VO_{2peak} — peak oxygen uptake; VO_{2max} — maximal exercise oxygen consumption; VE/VCO_2 — minute ventilation to carbon dioxide production ratio

Table 3. Associations between clinical, electro- and echocardiographic variables and VO_{2peak}.

Variable	Univariate analysis		Associations after adjustment for age and etiology	
	Beta coefficient (95% CI)	P	Beta coefficient (95% CI)	P
Age [years]	–0.17 (–0.3 to 0.05)	0.006		
Etiology [0 — non-ischemic; 1 — ischemic]	–4.7 (–6.8 to –2.1)	0.0005		
PR interval [ms]	–0.06 (–0.1 to –0.03)	0.0013	–0.05 (–0.08 to –0.02)	0.004
QRS duration [ms]	0.05 (–0.01 to 0.12)	0.1		
LBBB [0 — absent; 1 — present]	0.4 (–2.4 to 3.2)	0.78		
LVEF [%]	0.09 (–0.13 to 0.32)	0.38		
E/e'	–0.27 (–0.4 to –0.12)	0.0006	–2.0 (–0.34 to –0.06)	0.006
Rest diastolic dyssynchrony	–3.8 (–6.35 to –1.3)	0.004		
Exercise diastolic dyssynchrony	–3.6 (–6.6 to –0.6)	0.02		
Exercise-induced diastolic resynchronization	3.4 (0.2 to 6.6)	0.04	3.4 (0.17 to 6.6)	0.04
Rest systolic dyssynchrony	1.5 (–1.3 to 4.4)	0.28		

VO_{2peak} — peak oxygen consumption; LBBB — left bundle branch block; LVEF — left ventricular ejection fraction; E/e' — ratio of early diastolic mitral velocity to early diastolic velocity of the mitral annulus

Discussion

There are two major findings in this study. First, diastolic dyssynchrony may change during exercise. Some patients with diastolic dyssynchrony at rest experienced diastolic resynchronization during exercise, while some of those without diastolic dyssynchrony at rest, became dyssynchroneous at exercise. Although such dynamic features have previously been attributed to systolic dyssynchrony in patients with HFREF [7, 14]. According to available research this is the first report on the dynamic nature of diastolic dyssynchrony.

The presence of diastolic dyssynchrony was also found, both at rest and exercise, was associated with decreased exercise capacity in HFREF patients, but diastolic resynchronisation during exercise improved this.

Similarly, a negative effect of diastolic dyssynchrony on exercise capacity was reported in hypertensive patients with LV hypertrophy. In this group of patients diastolic dyssynchrony was also associated with decreased exercise capacity [15].

Impaired LV synchronicity may occur not only during ventricular contraction, but also during ventricular relaxation. In fact, diastolic dyssynchrony was found to be at least as frequent as systolic. The prevalence of LV diastolic dyssynchrony in patients with HFREF and prolonged QRS duration ranged from 52% to 73% as compared to systolic (46–73%)

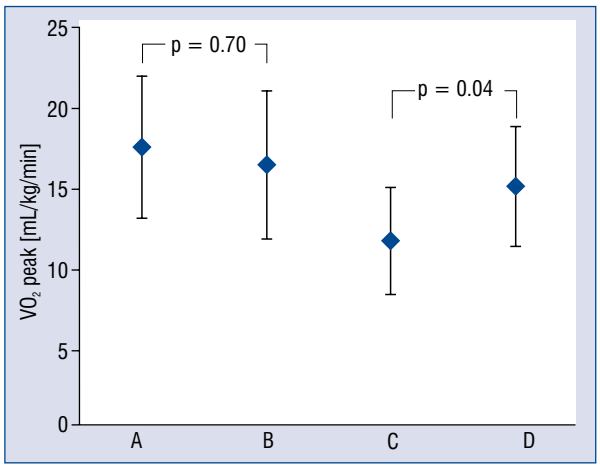


Figure 3. Comparison of mean VO_{2peak} between patients without rest diastolic dyssynchrony, who remained synchronized at exercise (A) and those who dyssynchronized at exercise (B); and between patients with rest diastolic dyssynchrony, who remained dyssnchronized at exercise (C) and those who resynchronized at exercise (D).

[1–3]. In the present study diastolic dyssynchrony was present in more than a half of the patients. A concurrent presence of systolic and diastolic dyssynchrony in the current study was seen in 35% of patients. A similar coincidence was shown in previous observations [1, 2]. This would suggest that systolic and diastolic dyssycnhrony may have some different pathophysiologies.

Intraventricular diastolic dyssynchrony reflects inhomogeneous timing of relaxation in different myocardial segments [16]. In healthy hearts, all LV segments relax in an organized fashion producing suction forces at the most efficient energy consumption level. This is achieved by synchronous interplay between uninterrupted stimulation and undisturbed regional relaxability of cardiac myocytes. In the presence of diastolic dyssynchrony, relaxation of the LV becomes inefficient. Early diastolic discoordinate motion of the LV walls may cause impairment of the LV filling dynamics decreasing left atrial function, aggravating mitral regurgitation, adversely affecting right-to-left ventricular interaction and concomitantly hinder ejection properties [17, 18]. As cardiac output is dependent not only on systolic emptying but also on diastolic filling, diastolic dyssynchrony may cause additive hemodynamic compromise in a failing heart. Decreased global performance of the heart at an increased workload promotes consequently, in chronic unfavourable cardiac remodelling leading to a worsening of symptoms [19].

The causes of diastolic dyssynchrony has been less well understood. As systole and diastole are closely linked, it would be most expected that systolic asynchrony determined the presence of diastolic dyssynchrony. However, as discussed earlier, less than one-half of the HFREF patients have a coexistent systolic and diastolic dyssynchrony. This lack of concurrence may in part be attributed to the regional heterogeneity of the load-induced relaxation delay. It has been previously demonstrated in experimental studies, that global LV afterload translates to regional loading conditions in an ununiformed fashion [20, 21]. It was shown, that regional myocardial load correlates with the timing of local relaxation [22]. Differences in regional loading conditions may thus result in regional discoordinate diastolic motion.

In relation to this, the LV diastolic dysfunction and its regional differences may also play a role in the pathophysiology of diastolic dyssynchrony. It has been shown, that diastolic dyssynchrony correlated with the degree of LV diastolic dysfunction, prolonged relaxation and elevated pulmonary capillary wedge pressure in patients with HFPEF, but also in HFREF [1, 5, 23]. The present study found that, although not statistically significant, patients with diastolic dyssynchrony had higher estimated LV filling pressure than those without. Several studies have additionally proposed, that right-to-left ventricular diastolic interaction from raised right ventricular diastolic pressure could explain delayed onset of myocardial diastolic motion [24, 25]. Differences in serum fibrosis markers representing different LV diastolic dysfunction stages might thus help to indicate patient with advanced diastolic dyssynchrony [26].

Another potential circumstance for the occurrence of diastolic dyssynchrony may include myocardial ischemia. It the present study, it was observed that a majority of patients with diastolic dyssynchrony had ischemic origin of HF, whereas DCM was more prevalent among those without. Data from several studies on diastolic dyssynchrony in coronary artery disease come in line with the current observations. In 1 study diastolic dyssynchrony was evident in patients with ischemic heart disease and preserved ejection fraction and correlated with lower diastolic LV function [27, 28]. In another, LV diastolic synchronicity was shown to be disrupted in patients with ST segment elevation myocardial infarction [29]. Interestingly, diastolic dyssynchrony recovered after successful coronary revascularization. Additionally, a study investigating the occurrence of diastolic dyssynchrony during

dobutamine stress echocardiography found that diastolic dyssynchrony imaging at peak dobutamine yielded high sensitivity and specificity in predicting significant coronary artery disease [30]. This might imply, that diastolic dyssynchrony is related to the presence of viable myocardium and could partly explain dynamic changes of diastolic dyssynchrony observed in the present study. In contrast to the previously cited study, diastolic dyssynchrony has been shown to improve during dobutamine stress echocardiography in patients with LV hypertrophy, demonstrating that the lusitropic effect of dobutamine improve LV regional diastolic asynchrony led to an improvement of global LV diastolic filling [31]. Furthermore, CRT and medical therapy has been found to restore diastolic synchronicity. Wang et al. [5] who explored the effect of medical therapy on the extent of diastolic dyssynchrony in HF patients with preserved ejection fraction has shown, that the initiation of treatment with diuretics, beta-blockers and angiotensin-converting enzyme inhibitors or receptor blockers resulted in an improvement of diastolic dyssynchrony [5]. Accordingly, as wider QRS has been associated with the presence of diastolic dyssynchrony, it has been hypothesized, that CRT may also lead to diastolic resynchronization. Shanks et al. [3] observed a high incidence of diastolic dyssynchrony in CRT responders, and its sustained improvement with biventricular pacing. Although diastolic together with systolic dyssynchrony has been shown to normalise with CRT in some patients, it is questionable whether the presence of diastolic dyssynchorny improves CRT patient selection.

Diastolic dyssynchrony and its changes appear to have multifactorial pathophysiology, which include electrical and local mechanical properties of the myocardium, but the exact mechanism or clinical meaning remains uncertain. As discussed earlier, the presence of diastolic dyssynchrony may be attributed to myocardial ischemia or myocardial viability, as well as suboptimal medical therapy. Whether exercise-induced diastolic resynchronization could serve as a marker to guide therapy optimization requires further study.

Limitations of the study

The main strength of the present study is that it enriches a limited body of literature on the clinical implications of diastolic LV dyssynchrony and its exercise-induced changes in patients with HFREF and helps to improve our understanding of this phenomenon.

Despite these advantages there are several limitations. It was a pilot, single-center study with a limited number of participants. A limited number of LV dyssynchrony parameters were used. Measurement of dyssynchrony at peak exercise may pose some difficulties caused by insufficient quality of echocardiographic recordings in up to 10% of patients. There was no attempt to evaluate the causes of diastolic dyssynchrony and its exercise-induced changes. Despite these drawbacks, it is believed that the consistency of the results validates the observations. Larger scale prospective studies are needed to validate the present results.

Conclusions

Diastolic dyssynchrony may change during exercise in half of HFREF patients. The ability to restore diastolic synchronicity at exercise predicts better aerobic capacity, whereas advanced age, ischemic etiology, prolonged PR interval and more advanced diastolic dysfunction are associated with lower exercise tolerance.

Conflict of interest: None declared

References

1. Yu CM, Lin H, Zhang Q, et al. High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. Heart. 2003; 89(1): 54–60, indexed in Pubmed: 12482792.
2. Schuster I, Habib G, Jego C, et al. Diastolic asynchrony is more frequent than systolic asynchrony in dilated cardiomyopathy and is less improved by cardiac resynchronization therapy. J Am Coll Cardiol. 2005; 46(12): 2250–2257, doi: 10.1016/j.jacc.2005.02.096, indexed in Pubmed: 16360054.
3. Shanks M, Bertini M, Delgado V, et al. Effect of biventricular pacing on diastolic dyssynchrony. J Am Coll Cardiol. 2010; 56(19): 1567–1575, doi: 10.1016/j.jacc.2010.01.077, indexed in Pubmed: 21029873.
4. Yu CM, Zhang Q, Yip GWK, et al. Diastolic and systolic asynchrony in patients with diastolic heart failure: a common but ignored condition. J Am Coll Cardiol. 2007; 49(1): 97–105, doi: 10.1016/j.jacc.2006.10.022, indexed in Pubmed: 17207728.
5. Wang J, Kurrelmeyer KM, Torre-Amione G, et al. Systolic and diastolic dyssynchrony in patients with diastolic heart failure and the effect of medical therapy. J Am Coll Cardiol. 2007; 49(1): 88–96, doi: 10.1016/j.jacc.2006.10.023, indexed in Pubmed: 17207727.
6. Friedberg MK, Roche SL, Mohammed AF, et al. Left ventricular diastolic mechanical dyssynchrony and associated clinical outcomes in children with dilated cardiomyopathy. Circ Cardiovasc Imaging. 2008; 1(1): 50–57, doi: 10.1161/CIRCIMAGING.108.782086, indexed in Pubmed: 19808514.

7. Stępniewski J, Kopeć G, Magoń W, et al. Ischaemic aetiology predicts exercise dyssynchrony in patients with heart failure with reduced ejection fraction. Kardiol Pol. 2018; 76(10): 1450–1457, doi: 10.5603/KP.a2018.0148, indexed in Pubmed: 30067277.
8. Lang R, Badano L, Mor-Avi V, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015; 16(3): 233–271, doi: 10.1093/ehjci/jev014.
9. Galderisi M, Henein MY, D'hooge J, et al. European Association of Echocardiography. Recommendations of the European Association of Echocardiography: how to use echo-Doppler in clinical trials: different modalities for different purposes. Eur J Echocardiogr. 2011; 12(5): 339–353, doi: 10.1093/ejechocard/jer051, indexed in Pubmed: 21555455.
10. Stoylen A. Left Ventricular Mechanics During Exercise: A Doppler and Tissue Doppler Study. Eur J Echocardiogr. 2003; 4(4): 286–291, doi: 10.1016/s1525-2167(03)00008-8.
11. Gorcsan J, Abraham T, Agler DA, et al. American Society of Echocardiography Dyssynchrony Writing Group, American Society of Echocardiography Dyssynchrony Writing Group, Heart Rhythm Society. Echocardiography for cardiac resynchronization therapy: recommendations for performance and reporting: a report from the American Society of Echocardiography Dyssynchrony Writing Group endorsed by the Heart Rhythm Society. J Am Soc Echocardiogr. 2008; 21(3): 191–213, doi: 10.1016/j.echo.2008.01.003, indexed in Pubmed: 18314047.
12. Balady GJ, Arena R, Sietsema K, et al. American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, Interdisciplinary Council on Quality of Care and Outcomes Research. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation. 2010; 122(2): 191–225, doi: 10.1161/CIR.0b013e3181e52e69, indexed in Pubmed: 20585013.
13. McMurray JJV, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012; 33(14): 1787–1847, doi: 10.1093/eurheartj/ehs104, indexed in Pubmed: 22611136.
14. Lafitte S, Bordachar P, Lafitte M, et al. Dynamic ventricular dyssynchrony: an exercise-echocardiography study. J Am Coll Cardiol. 2006; 47(11): 2253–2259, doi: 10.1016/j.jacc.2005.11.087, indexed in Pubmed: 16750692.
15. Jung IH, Seo HS, Kim MJ. P569. Diastolic dyssynchrony is associated with exercise intolerance in hypertensive patients with left ventricular hypertrophy. Eur Heart J Cardiovasc Imaging. 2016; 17(suppl_2): ii102–ii109, doi: 10.1093/ehjci/jew248.002, indexed in Pubmed: 28415098.
16. Cheng A, Helm RH, Abraham TP. Pathophysiological mechanisms underlying ventricular dyssynchrony. Europace. 2009; 11 Suppl 5: v10–v14, doi: 10.1093/europace/eup272, indexed in Pubmed: 19861385.
17. Kasner M, Westermann D, Schultheiss HP, et al. Diastolic heart failure and LV dyssynchrony. Curr Pharm Biotechnol. 2012; 13(13): 2539–2544, indexed in Pubmed: 22280429.
18. Kass DA. An epidemic of dyssynchrony: but what does it mean? J Am Coll Cardiol. 2008; 51(1): 12–17, doi: 10.1016/j.jacc.2007.09.027, indexed in Pubmed: 18174030.
19. Zhang Q, Yu CM. Clinical implication of mechanical dyssynchrony in heart failure. J Cardiovasc Ultrasound. 2012; 20(3): 117–123, doi: 10.4250/jcu.2012.20.3.117, indexed in Pubmed: 23185653.
20. Miura T, Bhargava V, Guth BD, et al. Increased afterload intensifies asynchronous wall motion and impairs ventricular relaxation. J Appl Physiol (1985). 1993; 75(1): 389–396, doi: 10.1152/jappl.1993.75.1.389, indexed in Pubmed: 8376290.
21. Yano M, Kohno M, Konishi M, et al. Influence of left ventricular regional nonuniformity on afterload-dependent relaxation in intact dogs. Am J Physiol. 1994; 267(1 Pt 2): H148–H154, doi: 10.1152/ajpheart.1994.267.1.H148, indexed in Pubmed: 8048579.
22. Aoyagi T, Iizuka M, Takahashi T, et al. Wall motion asynchrony prolongs time constant of left ventricular relaxation. Am J Physiol. 1989; 257(3 Pt 2): H883–H890, doi: 10.1152/ajpheart.1989.257.3.H883, indexed in Pubmed: 2782445.
23. Waggoner AD, Rovner A, de las Fuentes L, et al. Clinical outcomes after cardiac resynchronization therapy: importance of left ventricular diastolic function and origin of heart failure. J Am Soc Echocardiogr. 2006; 19(3): 307–313, doi: 10.1016/j.echo.2005.10.014, indexed in Pubmed: 16500494.
24. Bleeker GB, Mollema SA, Holman ER, et al. Left ventricular resynchronization is mandatory for response to cardiac resynchronization therapy: analysis in patients with echocardiographic evidence of left ventricular dyssynchrony at baseline. Circulation. 2007; 116(13): 1440–1448, doi: 10.1161/CIRCULATIONAHA.106.677005, indexed in Pubmed: 17785624.
25. Atherton J, Moore T, Lele S, et al. Diastolic ventricular interaction in chronic heart failure. Lancet. 1997; 349(9067): 1720––1724, doi: 10.1016/s0140-6736(96)05109-4.
26. Wiśniowska-Śmiałek S, Dziewięcka E, Holcman K, et al. Kinetics of selected serum markers of fibrosis in patients with dilated cardiomyopathy and different grades of diastolic dysfunction of the left ventricle. Cardiol J. 2018 [Epub ahead of print], doi: 10.5603/CJ.a2018.0143, indexed in Pubmed: 30484268.
27. Bonow RO, Vitale DF, Bacharach SL, et al. Asynchronous left ventricular regional function and impaired global diastolic filling in patients with coronary artery disease: reversal after coronary angioplasty. Circulation. 1985; 71(2): 297–307, indexed in Pubmed: 3155499.
28. Lee PW, Zhang Q, Yip GWK, et al. Left ventricular systolic and diastolic dyssynchrony in coronary artery disease with preserved ejection fraction. Clin Sci (Lond). 2009; 116(6): 521–529, doi: 10.1042/CS20080100, indexed in Pubmed: 18684109.
29. Turan B, Daşli T, Erkol A, et al. Diastolic dyssynchrony in acute ST segment elevation myocardial infarction and relationship with functional recovery of left ventricle. J Cardiovasc Ultrasound. 2016; 24(3): 208–214, doi: 10.4250/jcu.2016.24.3.208, indexed in Pubmed: 27721951.
30. Onishi T, Uematsu M, Watanabe T, et al. Objective interpretation of dobutamine stress echocardiography by diastolic dyssynchrony imaging: a practical approach. J Am Soc Echocardiogr. 2010; 23(10): 1103–1108, doi: 10.1016/j.echo.2010.06.031, indexed in Pubmed: 20719470.
31. Liu J, Murata K, Fujino T, et al. Effect of dobutamine on regional diastolic left ventricular asynchrony in patients with left ventricular hypertrophy. Circ J. 2003; 67(2): 119–124, indexed in Pubmed: 12547992.

VIA MEDICA

REVIEW ARTICLE

Cardiology Journal
2021, Vol. 28, No. 6, 941–953
DOI: 10.5603/CJ.a2021.0086

ISSN 1897–5593
eISSN 1898–018X

COVID-19, long flights, and deep vein thrombosis: What we know so far

Zbigniew Krasiński, Andre Chou, Hubert Stępak

Department of Vascular and Endovascular Surgery, Angiology, and Phlebology, Poznan University of Medical Sciences, Poznan, Poland

Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease 2019 [COVID-19]) pandemic has presently stunted the growth of the airline industry. Despite the setbacks, pre-COVID-19 passenger numbers are forecasted to return by as early as 2024. As the industry recovers, the number of long-distance flights will surely continue to increase like it did before the pandemic. The incidence of venous thromboembolism (VTE) following air travel is also likely to increase. Although not common, the unique environment of air travel exposes individuals with particular health conditions to an elevated risk of acquiring VTEs. Numerous factors increasing the risk of developing VTE related to air travel have been identified, including inherited and acquired flight-related aspects. Non-pharmacological approaches to reduce air travel-related VTEs involve simple foot movements, compression socks and stockings, intermittent pneumatic compression devices, a novel modified airline seat, and foot exercisers. Pharmacological methods include heparins and direct oral anticoagulants. More than 30 reliable articles were evaluated to present the current knowledge regarding air travel-related VTEs, their risk factors, and prophylactic methods. Issues in research methodologies found in the literature were identified and discussed. Further research involving international collaboration projects is recommended. The authors' perspectives regarding long flights in previously infected COVID-19 individuals are also included. (Cardiol J 2021; 28, 6: 941–953)

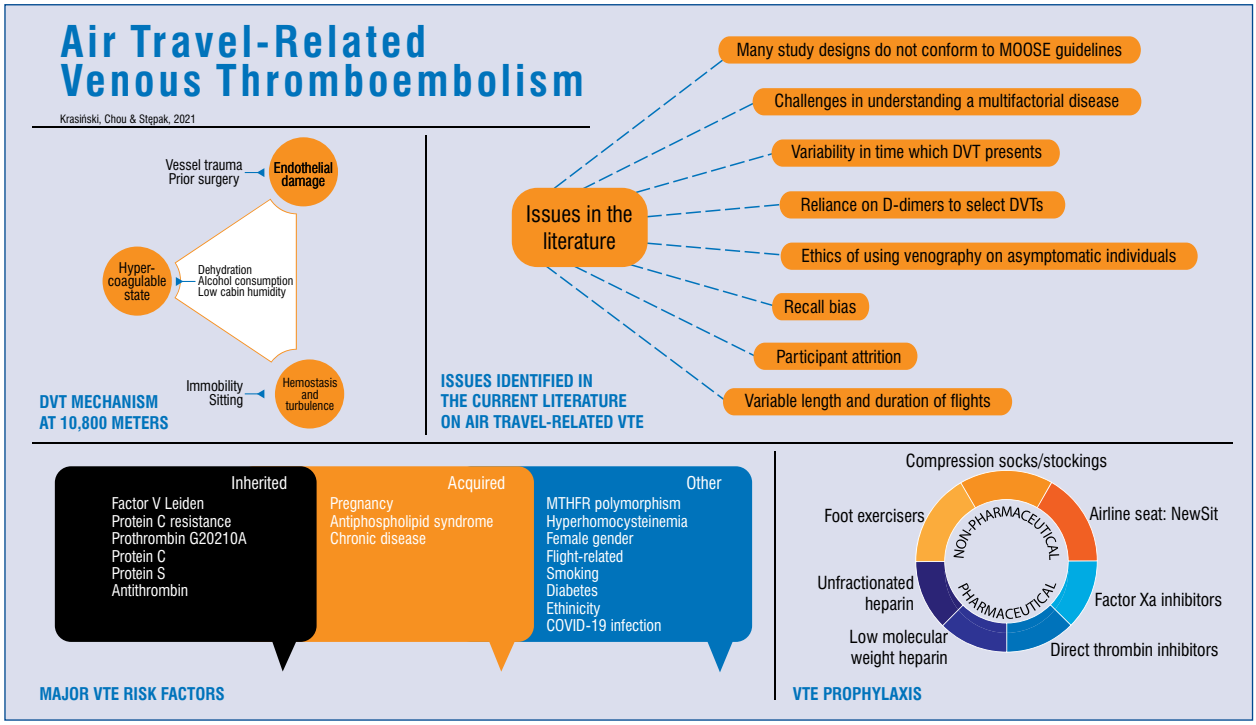
Key words: deep vein thrombosis, economy class syndrome, pulmonary embolism, travel-related illness, venous thromboembolism, COVID-19

Introduction

Despite the effects of the ongoing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease 2019 [COVID-19]) pandemic, the airline industry is projected to recover by 2024. New estimates from the International Air Transport Association predict passenger numbers to double by the year 2039, compared to pre-COVID-19 years [1]. As new technologies allow for more affordable travel over long distances, a yearly passenger growth rate of 7% since 2015 had been recorded until the onset of COVID-19 [2, 3]. The long periods of immobility and cramped conditions seen in most air travelers is reflected in the term "economy class syndrome" [4–6]. Therefore, the growing number of long-range routes and passenger numbers is likely to increase the incidence of pulmonary embolism caused by deep vein thrombosis (DVT) [7]. It is estimated that in other automotive forms of transport, the risk for venous thromboembolism (VTE) amounts to between 0.5% and 10% after travelling longer than 12 and 24 hours, respectively [7, 8]. The findings of the article are summarized in the Central illustration.

Address for correspondence: Dr. Hubert Stępak, MD, PhD, Department of Vascular and Endovascular Surgery, Angiology, and Phlebology, Poznan University of Medical Sciences, ul. Długa 1/2, 61–848 Poznań, Poland, tel: +48 61 854 91 41, e-mail: hstepak@gmail.com

Received: 26.01.2021 Accepted: 5.07.2021 Early publication date: 2.08.2021



Central Illustration. Graphical summary of the article's findings on air travel-related venous thromboembolism (VTE); DVT — deep vein thrombosis.

Review methods

Reviews of medical articles relating to air travel-related VTE, risk factors, and prophylaxis were conducted. Medical journals in the English language were selected for review using PubMed and Google Scholar. The keywords used included "economy class syndrome", "pulmonary embolism", "deep vein thrombosis", "venous thromboembolism", "venous thromboembolism prophylaxis", and "air travel-related illness" either as standalone searches or in combination. Additional publications not recovered in the preliminary searches were reviewed and added if deemed suitable to the topic. Finally, 30 articles were selected for review. Additional literature not previously captured was added to supplement the review based on its relevance to the scope of interest.

Mechanism

Virchow's triad details the conditions contributing to venous thrombosis, i.e. endothelial injury, venous hemodynamic changes (stasis and turbulence), and hypercoagulability [9, 10]. Damage to the endothelium causes platelets to bind to the injury site, forming a hemostatic plug, which may become the nidus of thrombosis [9]. Two common causes of vascular injury include surgery and major trauma. Hypobaric hypoxia, low humidity, and immobility are commonly seen in air travel [9, 11].

Hypobaric hypoxia and low humidity

At 10,800 m, airplanes are pressurized to create a livable environment, which equates to an altitude of between 1524 and 2134 m, and a cabin pressure of 75.8 kPa (101 kPa AMSL) [11]. In such conditions, the oxygen saturation in healthy individuals can decrease to 90–93%, whereas in the elderly and passengers suffering from cardiac or pulmonary disorders, it may be as low as 80% [9]. Although coagulation in hypobaric and normobaric hypoxia conditions have been the subject of a number of studies, there remains a lack of consensus regarding thrombin formation in the aforementioned conditions [12].

The humidity level in an aircraft is approximately 10% (compared to sea level 30–40%) [13]. This effect is exacerbated by decreased fluid intake, which may result in dehydration [9]. In a simulated long flight study, no evidence concerning dehydration was found, although fluid retention corresponding to an approximate increase of 1 kg in body weight was observed [14]. An increase in urinary and plasmatic osmolarity associated with a low humidity combined

with the diuretic effect of beverages, such as coffee, tea, or alcohol contribute to hemoconcentration promoting VTE formation [9].

Immobility

The endothelium can be deprived of its non-thrombogenic state without direct injury [10]. Immobility causes stasis, which forms a chemotactic gradient across the endothelium, triggering major leukocyte migration. Furthermore, leukocyte trapping can occur between the basement membrane and the endothelium, resulting in endothelial cell separation and desquamation, which further leads to the exposure of subendothelial layers and thrombus formation [10]. Thus, the immobility of passengers in long-distance travel is referred to as "economy class syndrome" [5]. As experienced by passengers mainly in economy class, those in window seats would have a twofold increase in risk for a VTE compared to those seated by the aisle [15].

Endurance athletes

Individuals in excellent physical condition can also be at risk of a travel-related VTE. In particular, endurance athletes and long-distance runners experience repeated microtrauma, which may induce endothelial injury. Additionally, dehydration can lead to hemoconcentration while immobility during travel to and from events contribute to VTE formation [16]. In Paget-Schrötter syndrome, heavy upper extremity activities can activate coagulation in the axillo-subclavian vein [17]. Rare iliofemoral DVT known as May-Thurner syndrome has been described in a runner [18]. Indeed, a report of a triathlete diagnosed with DVT upon completion of a half-ironman triathlon indicates that DVT risk factors, such as microtrauma, immobility, and dehydration may also be present in this population [16].

Risk factors

The most common risk factors for flight-related VTEs are thrombophilic abnormalities and the occurrence of previous DVT [11]. Others include obesity (body mass index [BMI] > 30 kg/m^2), age (> 40 years old), tall and short stature (> 1.90 m or < 1.60 m), chronic disease, oestrogen administration, female gender, pregnancy, and immobility [19–21]. A new risk factor for VTE is undoubtedly related to COVID-19 infection [22]. At present, data are scarce regarding the implications for long-haul flights in individuals who are or have previously been infected with COVID-19, although the coagulopathy observed in the disease may increase the risk of VTE [23]. Because this is a developing topic within the literature, the authors offer some perspectives in the section "COVID-19: Authors' perspectives".

In general, although most sufferers of air travel-related VTEs are older, young and physically fit individuals can also be at risk [16, 24]. In a study, travelers' absolute VTE risk was evaluated, and the identified risks were as follows: 1/109 for pregnant travelers, 1/140 for travelers in a plaster cast, 1/141 for travelers with malignancies, 1/164 for travelers following a recent surgery, 1/259 for travelers on contraceptives, and 1/405 for female travelers on hormone replacement therapy [25].

Inherited factors

Inherited thrombophilias predispose individuals to hypercoagulable states [26]. The prothrombin gene constitutes the most frequent cause of hereditary hypercoagulable conditions, comprising 50–60% of VTE cases, whereas factor V Leiden mutations with antithrombin, and protein C and S represent the remainder [26]. A study showed that in 72% of travel-related VTE cases thrombophilic irregularities were present [11].

Factor V Leiden and activated protein C resistance

There is an elevated VTE risk in individuals with factor V Leiden (FVL) (in which insensitivity to activated protein C [APC] is observed) [9]. Moreover, APC resistance was detected in 47% of individuals with travel-related VTE [11]. Thus, even without FVL, APC resistance constitutes a risk factor for VTE, and it was observed in 15% of patients with travel-related VTE [11].

Prothrombin G20210A

Mutations to prothrombin constitute the second most frequently inherited thrombophilia after FVL [11]. Combined mutations of FVL and prothrombin gene 20210A are linked with a greater risk of VTE [27]. In a travel-related VTE study, a synergistic increase in the risk for DVT was found in FVL individuals, although the VTE risk for prothrombin mutations was less pronounced [28].

Protein C and protein S

Protein C is a vitamin K-dependent anticoagulant protein, circulating as a zymogen. Anticoagulant effects are exerted following the activation to APC which, in turn, inactivates factors Va and VIIIa, further activating factor X for thrombin formation

[27]. Protein C deficiency was identified in 4.8% of individuals with travel-related VTE [11]. Protein S is a cofactor for APC and regulates clot formation [29]. Deficiencies of protein S were found in 7% of patients experiencing travel-related VTE. Protein C and protein S levels are decreased by vitamin K deficiency, warfarin, and liver failure [30].

Antithrombin

Antithrombin is an inhibitor of thrombin, factors IXa and Xa, and other serine proteases. Deficiency of antithrombin is either inherited or acquired. Inherited deficiencies result from mutations, whereas acquired deficiencies are primarily caused by impaired production of viable antithrombin, increased utilization, or protein losses [31]. Antithrombin deficiency may result in an elevated thrombotic risk and heparin insensitivity. In an air travel-related VTE study, 3 (< 2%) subjects with VTE suffered from antithrombin deficiencies [32].

Other

According to the literature, non-O blood groups have higher plasma levels of von Willebrand factor and factor VIII, which may lead to an elevated risk for thrombosis [13]. Fibrinogen gene mutation C10034T is known to produce variant fibrinogen linked with increased venous thrombosis [13]. Furthermore, lupus anticoagulant, anti-β2-glycoprotein I, and antiprothrombin antibodies participate in prolonged coagulation in vitro [33].

Acquired factors

Pregnancy

Many adaptive changes occur in the hemostatic system as the body prepares for placental expulsion and vascular disruption [34]. The body enters a state of hypercoagulability and hypofibrinolysis in order to prevent excessive bleeding [34]. Although VTE risk during pregnancy is low, the postpartum risk is 5 times higher than during pregnancy [35]. However, the risk for VTE is estimated to be between 0.03% and 0.1% when the two factors, i.e. air travel and pregnancy, are combined [36]. Indeed, pregnant women on 4- to 5-hour flights have a VTE risk 5 to 10 times greater than non-pregnant women, and the risk increases to 4 and 8 times in flights longer than 8 and 12 hours, respectively [9].

Trophoblastic injury triggered by flight-related hypoxic conditions leading to premature birth and intrauterine death were reported [37]. Therefore, airlines have introduced restrictions on pregnant women, allowing travel only up to the 36th week of pregnancy [13]. Following findings presented by the Royal College of Obstetricians and Gynecologists, it is accepted that pregnancy is at least a moderate risk factor and requires further investigation [38]. Pharmacological prevention should also be evaluated in this group of travelers [24].

Antiphospholipid syndrome

Antiphospholipid syndrome is an autoimmune disorder in which antibodies against proteins are bound to anionic phospholipids on plasma membranes [26]. Secondary antiphospholipid syndrome was observed in rheumatic diseases such as systemic lupus erythematosus or as a standalone disease [26]. Although VTE occurrences were reported in nearly all locales of the vascular tree in antiphospholipid syndrome patients, the most frequently reported are lower extremity DVTs and pulmonary embolisms [39].

Chronic disease

Numerous cases of VTE are associated with chronic disease [19]. Chronic lung or cardiovascular diseases can be exacerbated by the hypoxic conditions in air travel (i.e. induction of the coagulation system during a flight) [40]. Arthritis and inflammatory bowel disease were also identified as potential risk factors together with neoplastic diseases and chronic kidney disease [9, 21]. Indeed, the death of New Zealand international rugby icon Jonah Lomu, who had been diagnosed with nephrotic syndrome, was suspected to be caused by a VTE shortly after a long-distance flight from the United Kingdom to New Zealand [41].

Obesity (BMI > 30 kg/m^2) is a widely reported risk factor in several VTE studies [9, 21]. In fact, a relative risk of 2.4 for DVT was determined when comparing non-obese and obese women [42].

Other factors

MTHFR polymorphism and hyperhomocysteinemia

5,10-methylenetetrahydrofolate is reduced to 5-methyltetrahydrofolate using methylene tetrahydrofolate reductase (MTHFR). Methyl tetrahydrofolate is required in the re-methylation of homocysteine to methionine, a process that requires folate and vitamin B_{12} [43].

Indeed, MTHFR polymorphisms were linked to an increased VTE risk [27]. MTHFR compound mutations entail a greater risk for VTE compared to heterozygous, homozygous C677T, or A1298C variants which constitute an intermediate risk [44]. It has been demonstrated that geographic

and ethnic variations exist in the population. Homozygosity for C677T in North America is most prevalent in Hispanics (21–25%), followed by Whites (10–14%), and Blacks (1–2%, particularly in the USA and Brazil), whereas homozygosity for A1298C is found more in Whites (7–12%) followed by Hispanics (4–5%) and Asians (1–4%) [45]. In contrast, heterozygosity was not considered a risk factor for VTE [11].

Hyperhomocysteinemia is another important risk factor for initial and recurring VTE, especially when fasting levels exceed 20 μmol/L [46]. The most commonly known genetic cause of hyperhomocysteinemia is MTHFR gene polymorphism [27]. Acquired hyperhomocysteinemia can stem from chronic renal failure, or it can be induced by drugs such as cyclosporine and methotrexate [11]. Additionally, folate, vitamin B_6, and vitamin B_{12} deficiencies due to a low dietary intake can also result in mild to moderate hyperhomocysteinemia [47].

Female gender

Female gender is an independent risk factor for flight-related VTE. According to Lapostolle et al. [6], 75% (42 of 56) of confirmed VTE patients were female. Additionally, a large cohort study found the VTE risk for females is 3 times higher than for men [20]. Moreover, an increased VTE risk is also observed in menopausal women receiving hormone replacement therapy; in individuals undergoing estrogen therapy, the risk of VTE is nearly 20 times higher [21, 48]. The use of the oral contraceptive pill (OCP) in healthy women increases VTE risk fourfold [49]. According to the Centers for Disease Control and Prevention, 12.6% of women between 15 and 49 years of age take the OCP in the USA [50]. Worldwide, 65 million women take the OCP, which amounts to 6% of all women of reproductive age [11]. Indeed, the increased risk of VTE events when using OCP is well established in the literature [49].

Flight-related

Long-distance flights are defined as lasting 7 to 15 hours or more [51, 52]. According to the literature, the risk of DVT for such flights equals 3–12% and is 3 times higher in comparison to shorter travels [53].

Arya et al. [51] found that long-haul flights (> 8 h) were associated with DVT only if one additional risk factor was present.

Window and central seating locations are significant. Belcaro et al. [54] observed that 18 of 19 thromboses were formed in subjects sitting by the window or in central seats. In their subsequent study, all 22 DVT cases (of 422 subjects) were reported in passengers seated by the window or in central seats. As for so-called "economy class syndrome", the risk was the same for business and economy class travelers [48, 55]. Therefore, the term "traveler's thrombosis" has been suggested as a more appropriate term [56].

As discussed previously, alcohol contributes to the diuretic effect, thereby increasing the risk of VTE. Interestingly, 66% more alcohol is consumed in business class than in economy class [55].

Other

A hypercoagulable state in type I and II diabetes has been established. Chronic hyperglycemia can lead to endothelial dysfunction and is crucial for the progression of vascular complications in diabetic patients [57]. In several studies diabetes was frequently used as an indicator or as an exclusion criterion of high-risk VTE in long-haul flights [58–60].

Smoking is reportedly a risk factor for travel-related VTE because it causes hypoxia and increases blood viscosity [13, 57, 61]. In women taking OCPs, smoking acts synergistically in increasing VTE risk [62]. Interestingly, while one study demonstrated that smoking was unrelated to D-dimer development and found little evidence of its association with VTE, while another study classified smoking as a low risk for VTE [55, 63]. Nevertheless, cessation of smoking to decrease VTE risk was recommended in other studies [6, 61].

Recent surgery represents a well-described risk for VTE [9, 21, 64]. Surgery risk was divided into low (minor surgery within 3 days of a flight) and high risk (major surgery within 6 weeks of a flight) [13].

An individual with a history of previous DVT or pulmonary embolism is at high risk of developing VTE [6, 27].

The impact of race and ethnicity on VTE risk has been scarcely investigated. According to White and Kenan, African Americans had a notably higher rate of VTE, particularly following events which include surgery, illness, and trauma [65]. Pacific Islanders and Asians had between 3 and 5 times lower risk for cancer-associated VTE, and idiopathic first-time symptomatic and secondary VTE [65]. Using Caucasians as the reference ethnic group for any first-time VTE risk, the less vulnerable groups were Hispanics (50%) and Asians/Pacific Islanders (70%), whereas African Americans were 35% more vulnerable to VTE [66]. Al-

though genetic factors are more present in some ethnic groups, the data regarding air travel-related VTEs remain insufficient.

Prevention: Non-pharmacological

General advice on inflight exercises for travelers is available from airline websites and on-board entertainment systems and includes stretching, foot exercises, standing up, removing bags from under the seat for more leg space, and avoiding restrictive clothing [59, 67]. Foot exercises increase the mean peak velocity in the popliteal vein and can be activated by frequent plantarflexion and dorsiflexion [68]. However, data concerning the compliance and efficacy of such exercises are scarce.

For higher-risk individuals, compression socks/stockings, intermittent pneumatic compression devices, and active foot movements have been shown to be effective [21]. The mechanism is attributed to the high flow pulsatility induced by the vessel collapse due to distal compression (by muscle contraction) allowing deep veins to drain more readily, thereby reducing venous stasis [69]. External mechanical compression does not affect coagulation; hence, the risk of increased bleeding with this method is minimal.

Compression stockings

Passengers using compression stockings have reduced incidences of DVT and lower extremity edema [54]. In LONFLIT 2, the frequency of DVT among high-risk individuals in long-haul routes was reduced 18.5 times when wearing stockings [54]. The LONFLIT 4 Concorde Edema-SSL study evaluated Scholl (UK) Flight Socks (below knee, 14–17 mmHg compression at the ankles) and found a distal DVT in less than 1% of the study group compared to 6% in the controls [54, 70]. In the LONFLIT 4 Concorde ECO-TRAS study, similar results were found regarding Sigvaris Traveno (Ganzoni, Switzerland) elastic stockings (below knee, 12–18 mmHg compression the ankles) [71]. Thigh-length socks were found to have equivalent effectiveness compared with knee-length although the latter has better compliance and a lower cost [72]. Similar efficacy was also reported in graded compression stockings [73].

Intermittent pneumatic compression devices

Intermittent pneumatic compression devices, calf muscle pump-facilitating devices, and simple foot movements were compared [74]. Calf muscle pump facilitating devices did not present a higher efficacy than simple foot movements, whereas the use of intermittent pneumatic compression devices was found to be justifiable for sleeping, or immobile patients [74]. The use of intermittent pneumatic compression devices on flights is restricted due to the external power source, size, and weight requirements; thus, compression stockings are preferred [75].

Modified airline seat

A modified standard airline seat (NewSit) was proposed, which elevates the feet, assisting leg mobility and allowing intermittent calf compression [76]. Improvement in venous emptying was observed in 23 out of 25 subjects whilst sitting for 5 hours, in comparison to a conventional airline seat [76]. Currently, this is the only published paper concerning this technology.

Foot exercisers

Physical foot exercisers, such as the Airogym Exerciser (Airogym Ltd., UK) and travel footrest hammocks (various brands), are less common, although they do promote blood flow through deep veins [77].

Prevention: Pharmacological

Pharmacological methods aim to decrease coagulation and clot formation. Common drugs include low-molecular-weight heparin (LMWH), unfractionated heparin (UFH), factor Xa inhibitors, direct thrombin inhibitors, and acetylsalicylic acid (ASA) [24, 48]. Such methods to decrease or prevent DVT can be employed when compression, or other physical methods are contraindicated, as in the case of severe arterial claudication, drug allergies, or high hemorrhage risk [78]. The main advantages of the pharmacological measures are the increased compliance when compared to non-pharmacological methods [78]. Crucially, for individuals undergoing long-term anticoagulant therapy with a proven prevention of recurring VTE (following an unprovoked first event), the same effect cannot be presumed when administering these medications shortly before travel [79].

Heparins

Conventional evidence-based guidelines for the treatment and prevention of DVT are with heparins [79]. Data regarding UFH use for pre-flight DVT prophylaxis is scarce because it is normally used instead in the treatment of acute VTE in controlled settings due to the intensive activated partial thromboplastin time demands [24, 80].

Low-molecular-weight heparin has replaced UFH as the drug of choice for VTE prophylaxis [64]. The efficacy of LMWH is well documented and recommended for high-risk individuals on long--distance flights [81]. LMWH has certain advantages over heparin, such as a lower risk of heparin-induced thrombocytopenia at 0.2% vs. 2.6%, respectively, and better pharmacokinetic profile [82]. In a study, a LMWH group who were administered 1 mg/kg of enoxaparin between 2 and 4 hours before a long-distance flight reported 0.61% of thrombotic events in the extremities compared to 4.8% in the control group and 2.9% in the ASA group ($p = 0.002$ when compared to the two other groups). Additionally, recommendations for a single 40 mg dose of enoxaparin or 5000 IU of dalteparin subcutaneously prior to departure have also been made [24]. LMWH's route of administration is not the most convenient, which decreases its compliance [83].

Direct oral anticoagulants: Factor Xa and direct thrombin inhibitors

Due to minimal food and drug interactions, direct oral anticoagulants are a safer alternative than the previous methods [61]. Furthermore, there is no evidence suggesting direct oral anticoagulants cannot be used as prophylaxis for travel-related VTE. However, as primary prophylaxis, LMWH is still preferred due to the novelty and thereby lack of data regarding direct oral anticoagulants [83].

Factor Xa transforms prothrombin to thrombin and thus is essential for coagulation. rivaroxaban is a direct inhibitor of factor Xa [83]. Oral administration of 10 mg was recommended for the prevention of VTE [84]. Another direct factor Xa inhibitor is apixaban, but there are no data on its safety or efficacy for long-haul flight VTE prophylaxis [85].

An indirect factor Xa inhibitor is fondaparinux [86]. In comparison to LMWH, fondaparinux may increase the risk for fatal hemorrhage; on the other hand, when compared to UFH, it increases all-cause mortality, simultaneously reducing VTE events [87]. An informal cost analysis of the drug indicated fondaparinux to be more expensive than LMWH [80]. A recommendation for pre-flight VTE prevention is 2.5 mg subcutaneously [24]. Contraindications for factor Xa inhibitors are renal insufficiency (creatinine clearance < 30 mL/ /min) and hemodialysis [24].

Dabigatran etexilate is a thrombin inhibitor with a similar efficacy to enoxaparin and a comparable safety profile to LMWH [24]. It has predictable pharmacokinetics, a rapid onset of action, and minimal drug and food interactions. A recommended prophylactic dosage is reported as 220 mg once per day [88].

Acetylsalicylic acid

Acetylsalicylic acid inhibits platelet activation by the inactivation of cyclooxygenase. ASA used in combination with stockings has proven to be beneficial, although very few studies support ASA use for VTE prophylaxis [56, 89]. Subjects of the LONFLIT 3 study were administered 400 mg once daily for 3 days, beginning the first dose 12 hours prior to the flight. The results indicated a small decrease of 3.6% in subjects with DVT compared with 4.8% in the control group; however, this result was not statistically significant [81]. The efficacy of ASA as a standalone drug in VTE prevention is doubtful; hence, the American College of Chest Physicians have advised against its use for thromboprophylaxis [56].

Discussion

It is generally accepted that air travel is related to VTE [53, 90, 91]. However, the issue of heterogeneity in the literature remains problematic, although explicable. Despite various definitions of a "long-distance" flight, the research performed has been extensive in methodology, variables, sampled populations, and locations, offering various opinions on the inclusion or exclusion criteria [51, 92]. Major papers and findings are summarized in Table 1.

The conundrum of air travel-related VTE is that it constitutes a multifactorial disease [9]. Distance or length traveled, individual variables, air travel conditions, passenger behaviors during travel, and recent events prior to travel such as trauma and surgery, all interact to produce different outcomes [56]. Thus, it is very challenging to identify the exact factors resulting in travel-related VTE.

The great variety of study designs in the literature is encouraging [56]. However, the variability in the study protocols has in some cases impeded subsequent meta-analyses [53]. Numerous studies do not meet the criteria for inclusion to meta-analyses (such as the MOOSE guidelines) and thus are unable to contribute to the existing literature [53, 93]. Chandra et al. [53] reported issues with study design, in particular regarding the use of control participants. The idea that control participants should be similar to the case patients is

Table 1. Major papers on air travel-related venous thromboembolism (VTE).

Authors	Year	Study type	Findings
Ferrari et al. [90]	1999	Case control	Travel is a risk factor for VTE
Kraaijenhagen et al. [91]	2000	Case control	No association between VTE and long-distance travel
Arya et al. [51]	2002	Case control	DVT risk only increased in long-haul travelers if additional risk factors are present — prophylaxis recommended
Martinelli et al. [32]	2003	Case control	Air travel doubles the risk for VTE, and the presence of thrombophilia or oral contraceptives increases the risk 16 and 14 times, respectively
Schwarz et al. [102]	2002	Cohort pilot	Passengers with isolated calf vein thrombosis reported other risk factors for thrombosis
Schwarz et al. [48]	2003	Cohort	Flights longer than 8 hours double the risk for isolated calf muscle venous thrombosis
Lapostolle et al. [6]	2001	Retrospective	A greater distance traveled is a significant contributor to air travel-related PE
Pérez-Rodríguez et al. [52]	2003	Retrospective	Air travel is a risk factor for VTE, and its incidence increases with the journey duration
Scurr et al. [7]	2001	Randomized trial	Asymptomatic DVT in up to 10% of long-haul air travelers. Wearing compression stockings associated with a reduction in asymptomatic DVT
Belcaro et al., LONFLIT 1 [59]	2001	Cross-sectional	Flight related DVTs were found in individuals who presented a high risk or sitting in the window and central seats
Belcaro et al., LONFLIT 2 [59]	2001	Randomized trial	Compression therapy (stockings) decreased DVT incidence in long-haul flights
Cesarone et al., LONFLIT 3 [81]	2002	Randomized trial	LMWH use almost eradicated thrombotic events
Belcaro et al., LONFLIT 4 Concorde Edema-SSL [103]	2002	Randomized trial	Scholl Flight Socks are effective in controlling edema and reducing DVT incidence in low to medium risk subjects on long-haul flights
Cesarone et al., LONFLIT 4 ECO-TRAS [71]	2003	Randomized trial	Sigvaris Traveno Stockings are effective in controlling edema in long-haul flights
Cesarone et al., LONFLIT 4 Concorde DVT Edema [104]	2003	Randomized trial	Kendall Travel Socks are effective in controlling edema and reducing DVT incidence in low- and medium-risk subjects
Belcaro et al., LONFLIT 5 JAP [70]	2003	Randomized trial	Scholl Flights Socks are effective in reducing DVT incidence in high-risk subjects

DVT — deep vein thrombosis; LMWH — low-molecular-weight heparin; PE — pulmonary embolism

erroneous because individuals who develop VTEs or DVTs will always have more risk factors for the disease than those who remain disease-free [53]. This selection bias leading to the underrepresentation and, therefore, incorrect conclusions requires attention for future studies [53].

The literature shows a reliance on the D-dimer to determine the presence of DVT. For instance, in the New Zealand Air Traveler's Thrombosis study, only participants with elevated D-dimer scores were included for further investigation [89]. Having a high sensitivity, D-dimer levels are well established, although the false positive rate for other conditions compromises their specificity [94]. Furthermore, a third of the 878 subjects had been administered ASA. Hence, it was suggested that either the patients taking ASA were at high-risk for VTE, or the ASA falsely elevated D-dimers due to gastritis [55]. In another study, 12 subjects were evaluated for asymptomatic thrombosis detected by ultrasound. In 6 of these subjects, no elevation in D-dimer was observed. However, the authors note that the short half-life of D-dimers (6 h) and the long time (up to 48 h) between the

end of the journey and collecting blood samples could be contributing factors [7]. Schwarz et al. [48] noted 11 out of 27 DVTs, or isolated calf muscle vein thromboses, to have elevated D-dimers. In fact, the high negative predictive value of the D-dimer was reportedly so high that it has been clinically used to exclude DVT in low-risk patients [95]. Even though the role of D-dimers as a VTE marker has been well investigated, its continued role should be revised [28, 55].

Although using venography to detect DVTs is considered a gold standard by some researchers, others consider its use unethical in asymptomatic patients. Therefore, alternative methods, such as duplex ultrasonography, have also been used [7]. However, there is a potential to underestimate thromboses due to the specificity, which is reportedly between 79% and 99% [7]. Furthermore, duplex ultrasonography sensitivity and specificity decrease for distal DVT when compared to venography [94].

The variability in the time in which the DVT presents (from during the flight to several weeks after) poses a challenge for capturing data outside the normal ranges [53]. Optimal timing of ultrasound scans then should be considered when investigating travel-related VTE. In the BEST study, compressive ultrasonography (CUS) was used in addition to D-dimers to improve detection accuracy. However, most participants declined the CUS after the journey. Only half of the participants who presented elevated D-dimer agreed to a CUS. Additionally, because the scans were performed on arrival, it was not possible to detect developing thrombi. Interestingly, 90% of subjects with elevated D-dimers reported no VTE symptoms in the follow-up 6 months later [55].

Participant attrition can affect the statistical power of the study. Because the literature largely depends on volunteer recall, many subjects do not continue with subsequent phases of the research. Dropouts due to flight connection problems or other non-medical issues have the potential to affect results, depending on the study design, e.g. in LONFLIT 1 and 2, out of the original 1663 participants, 1577 subjects did not complete the study [59, 92, 96]. Another study by Belcaro et al. [60] showed that only 198 out of 244 individuals completed the study due to logistical problems. Critically, the size of the dropout effect may be difficult to determine. Although it is conceivable that participants will be tired after the journey and dropouts may occur for a multitude of reasons, every possibility to retain subjects should be explored.

Recall bias can be managed with careful study design [28, 53]. Although difficult to eliminate, recall bias from questionnaires can be decreased with clear guidelines and timely administration of questionnaires [32]. Particular items, such as the exact amount of water/alcohol/fluid intake and the amount of inflight exercise, are available only from the most determined research subjects.

The varying length and duration of flights may need to depend on randomization of data for meaningful statistics [92]. The unpredictable nature of flights and airborne delays or re-routing, which can be difficult to report accurately, may result in inaccuracies in the subsequent analyses.

It is vital then to conduct a series of large international collaborations where uniformity in data collection methodology and consistency in study designs can definitively capture the correct data. To date, the BEST study is an example of such a collaboration, where subjects flew directly from point A to point B, with data collection at both locations eliminating the concern regarding stopovers [6, 92]. In terms of recall biases, the aforementioned large-scale studies could even involve airlines through flight attendants, who could remind the participants to record the datapoints at the best junctures.

Pre- or post-surgery considerations

Endothelial damage can be a proponent for platelet aggregation, causing thrombus formation and increasing the risk of VTE after surgery. It is possible that the danger of VTE is enhanced when surgery and long-haul travel are combined. In fact, the risk of VTE increases nearly 20 times in passengers who had a surgery within a 3-month period [25]. Conversely, in a study involving 1465 total joint arthroplasty patients, 220 traveled by air at a mean of 2.9 days after the surgery and demonstrated no differences between flying and non-flying patients. The study concluded that air travel following total joint arthroplasty is safe [97]. Furthermore, another study also found that preoperative air travel did not influence the risk of VTE after total hip and knee arthroplasty [98].

A case report described a 37-year-old male who traveled from Europe to the USA for elective pelvic surgery. Six days postoperatively, the man died from an acute pulmonary embolism despite having heparin prophylaxis [99]. The authors suggested he had developed a DVT during travel and the symptoms appeared following the surgery. However, the patient did present additional VTE risk factors, including heavy smoking, obesity, and dehydration due to pre-operative preparations [99].

Indeed, long-haul travel prior to a major surgery increases the risk of perioperative VTE [99].

COVID-19: Authors' perspectives

When is it safe to travel long distances by air given a previous COVID-19 infection? The thrombotic risk in COVID-19 is well documented, and in many cases, it is a determinant of disease severity or fatality [100, 101]. However, to begin answering this question, the issue of the severity with which the individual suffered from the disease should first be evaluated. The introduction of vaccinations brings yet another set of uncertainties to the equation, which adds much complexity to the issue. This question unfortunately cannot be answered scientifically without data and large-scale studies, as described in the previous sections. Given the fluidity of the situation and the amount of new information being learned about the disease every week, the authors are hesitant and reluctant to provide any real opinions.

In any case, exercising the rule of "best judgment" and conservative management, we recommend that those previously infected with COVID-19 wait at least 6 months after resolution of the disease. This includes cases of long COVID-19 where it is not advisable to travel at all until disease-free. Furthermore, flights in these individuals should be limited to less than 6 hours duration. Should the essential need for longer journeys arise, it is advisable to arrange multi-stop journeys with a travel break in between. Lastly, the general methods of VTE prevention as described in this review should be strictly followed:

- Take pharmacological prophylaxis under direction of the individual's physician;
- Choose an aisle seat if possible and/or seat with more legroom;
- Strictly adhere to on-board airline guidance regarding DVT prevention strategies, i.e. calf exercises, periodic foot movements, and frequent ambulation;
- Drink plenty of water and refrain from alcohol, coffee, or other diuretics before, during, and after the flight;
- Purchase and wear recommended compressive flight stockings as directed.

Conclusions

Great interest in the literature regarding air travel-related VTE reflects global trends. The conditions in which people travel by air over long distances are likely to facilitate VTE formation, most frequently in higher-risk individuals with predisposing factors. As such, preventative measures should be evaluated to decrease the possibility of developing VTE in at-risk individuals. It is likely that as a result of lockdowns and travel restrictions imposed throughout the pandemic, the post-COVID-19 era may well see a sharp rise in air travel as borders reopen. Because long-distance airline travel is mostly international, larger prospective research on an international level should be supported. In particular, studies relating to individuals with post SARS-CoV-2 infection, infection severity, and vaccination effects will be of exceptional value.

Conflict of interest: None declared

References

1. International Air Transport Association. 20 Year Passenger Forecast [Internet]. www.iata.org. 2020. https://www.iata.org/en/publications/store/20-year-passenger-forecast/.
2. Bowler T. Carbon fibre planes: Lighter and stronger by design. BBC News [Internet]. 2014 Jan 28. https://www.bbc.com/news/business-25833264 (cited 2018 Jul 7).
3. Annual growth in global air traffic passenger demand from 2005 to 2018. Statista [Internet]. 2018 Jun 1. https://www.statista.com/statistics/193533/growth-of-global-air-traffic-passenger-demand/ (https://www.bbc.com/news/business-25833264).
4. Simpson K. Shelter deaths from pulmonary embolism. Lancet. 1940; 236(6120): 744, doi: 10.1016/s0140-6736(00)92078-6.
5. Homans J. Thrombosis of the deep leg veins due to prolonged sitting. N Engl J Med. 1954; 250(4): 148–149, doi: 10.1056/NEJM195401282500404, indexed in Pubmed: 13119864.
6. Lapostolle F, Surget V, Borron SW, et al. Severe pulmonary embolism associated with air travel. N Engl J Med. 2001; 345(11): 779–783, doi: 10.1056/NEJMoa010378, indexed in Pubmed: 11556296.
7. Scurr J, Machin S, Bailey-King S, et al. Frequency and prevention of symptomless deep-vein thrombosis in long-haul flights: a randomised trial. The Lancet. 2001; 357(9267): 1485–1489, doi: 10.1016/s0140-6736(00)04645-6.
8. Watson HG. Travel and thrombosis. Blood Rev. 2005; 19(5): 235–241, doi: 10.1016/j.blre.2004.08.001, indexed in Pubmed: 15963832.
9. Sándor T. Travel thrombosis: Pathomechanisms and clinical aspects. Pathophysiology. 2008; 15(4): 243–252, doi: 10.1016/j.pathophys.2008.10.001, indexed in Pubmed: 19019640.
10. Nicolaides AN. Thromboembolism: etiology, advances in prevention, and management. University Park Press, Baltimore 1975: 348.
11. Parsi K, McGrath MA, Lord RSA. Traveller's Venous Thromboembolism: A Review of World Literature, a Survey of World Airlines and an Australian Perspective. Australian New Zealand J Phlebology. 2001; 5(1): 32–53.
12. Schobersberger W, Schobersberger B, Mittermayr M, et al. Air travel, hypobaric hypoxia, and prothrombotic changes. JAMA. 2006; 296(19): 2313–4; author reply 2314, doi: 10.1001/jama.296.19.2313-b, indexed in Pubmed: 17105791.

13. Dusse LM, Silva MV, Freitas LG, et al. Economy class syndrome: what is it and who are the individuals at risk? Rev Bras Hematol Hemoter. 2017; 39(4): 349–353, doi: 10.1016/j.bjhh.2017.05.001, indexed in Pubmed: 29150108.
14. Landgraf H, Vanselow B, Schulte-Huermann D, et al. Economy class syndrome: rheology, fluid balance, and lower leg edema during a simulated 12-hour long distance flight. Aviat Space Environ Med. 1994; 65(10 Pt 1): 930–935, indexed in Pubmed: 7832736.
15. Schreijer AJM, Cannegieter SC, Doggen CJM, et al. The effect of flight-related behaviour on the risk of venous thrombosis after air travel. Br J Haematol. 2009; 144(3): 425–429, doi: 10.1111/j.1365-2141.2008.07489.x, indexed in Pubmed: 19036084.
16. Tao K, Davenport M. Deep venous thromboembolism in a triathlete. J Emerg Med. 2010; 38(3): 351–353, doi: 10.1016/j.jemermed.2008.07.030, indexed in Pubmed: 19128915.
17. Getzin AR, Silberman MR. Iliac artery flow limitations in endurance athletes. Curr Sports Med Rep. 2010; 9(6): 334–337, doi: 10.1249/JSR.0b013e3181fc7250, indexed in Pubmed: 21068564.
18. Béliard S, Feuvrier D, Ducroux E, et al. May Thurner syndrome revealed by left calf venous claudication during running, a case report. BMC Sports Sci Med Rehabil. 2018; 10: 3, doi: 10.1186/s13102-018-0092-6, indexed in Pubmed: 29435334.
19. Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. J Thromb Thrombolysis. 2016; 41(1): 3–14, doi: 10.1007/s11239-015-1311-6, indexed in Pubmed: 26780736.
20. Lapostolle F, Le Toumelin P, Chassery C, et al. Gender as a risk factor for pulmonary embolism after air travel. Thromb Haemost. 2009; 102(6): 1165–1168, doi: 10.1160/TH09-06-0407, indexed in Pubmed: 19967147.
21. Geerts W, Bergqvist D, Pineo G, et al. Prevention of venous thromboembolism. Chest. 2008; 133(6): 3815–4535, doi: 10.1378/chest.08-0656.
22. Nopp S, Moik F, Jilma B, et al. Risk of venous thromboembolism in patients with COVID-19: A systematic review and meta-analysis. Res Pract Thromb Haemost. 2020; 4(7): 1178–1191, doi: 10.1002/rth2.12439, indexed in Pubmed: 33043231.
23. Parker S, Mahomed O. Hypoxia and thrombosis in COVID-19: new considerations for air passengers. J Travel Med. 2020; 27(8), doi: 10.1093/jtm/taaa122, indexed in Pubmed: 32710617.
24. Bartholomew JR, Schaffer JL, McCormick GF. Air travel and venous thromboembolism: minimizing the risk. Cleve Clin J Med. 2011; 78(2): 111–120, doi: 10.3949/ccjm.78a.10138, indexed in Pubmed: 21285343.
25. Kuipers S, Venemans A, Middeldorp S, et al. The risk of venous thrombosis after air travel: contribution of clinical risk factors. Br J Haematol. 2014; 165(3): 412–413, doi: 10.1111/bjh.12724, indexed in Pubmed: 24428564.
26. Bauer KA, Lip GY, Leung LLK, et al. Overview of the causes of venous thrombosis. Post TW, ed [Internet]. https://www.uptodate.com/contents/overview-of-the-causes-of-venous-thrombosis/ (cited 2019 Jul 13).
27. Iqbal O, Eklof Bo, Tobu M, et al. Air travel-associated venous thromboembolism. Med Princ Pract. 2003; 12(2): 73–80, doi: 10.1159/000069121, indexed in Pubmed: 12634460.
28. Cannegieter SC, Doggen CJM, van Houwelingen HC, et al. Travel-related venous thrombosis: results from a large population-based case control study (MEGA study). PLoS Med. 2006; 3(8): e307, doi: 10.1371/journal.pmed.0030307, indexed in Pubmed: 16933962.
29. Bauer KA, Leung LLK, Mahoney DH, Tirnauer JS. Protein S deficiency. Post TW, ed [Internet]. https://www.uptodate.com/contents/protein-s-deficiency/ (cited 2019 Jul 13).
30. Presgrave P, Ma D. Genetic predisposition to venous thromboembolism: molecular basis and a practical guide to management. Australian New Zealand J Phlebology. 2000; 4: 39–45.
31. Bauer KA, Leung LLK, Tirnauer JS. Antithrombin deficiency. Post TW, ed [Internet]. https://www.uptodate.com/contents/antithrombin-deficiency/.
32. Martinelli I, Taioli E, Battaglioli T, et al. Risk of venous thromboembolism after air travel: interaction with thrombophilia and oral contraceptives. Arch Intern Med. 2003; 163(22): 2771–2774, doi: 10.1001/archinte.163.22.2771, indexed in Pubmed: 14662632.
33. de Groot PG, Lutters B, Derksen RH, et al. Lupus anticoagulants and the risk of a first episode of deep venous thrombosis. J Thromb Haemost. 2005; 3(9): 1993–1997, doi: 10.1111/j.1538-7836.2005.01485.x, indexed in Pubmed: 16102105.
34. Alemzadeh-Ansari MJ, Kazemisaleh D, Moshkani-Farahani M, et al. Do pregnant women have a higher risk for venous thromboembolism following air travel? Adv Biomed Res. 2015; 4: 60, doi: 10.4103/2277-9175.151879, indexed in Pubmed: 25802829.
35. Heit JA, Kobbervig CE, James AH, et al. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med. 2005; 143(10): 697–706, doi: 10.7326/0003-4819-143-10-200511150-00006, indexed in Pubmed: 16287790.
36. Cannegieter SC, Rosendaal FR. Pregnancy and travel-related thromboembolism. Thromb Res. 2013; 131 Suppl 1: S55–S58, doi: 10.1016/S0049-3848(13)70023-9, indexed in Pubmed: 23452744.
37. Brenner B. Interventions to prevent venous thrombosis after air travel, are they necessary? Yes. J Thromb Haemost. 2006; 4(11): 2302–2305, doi: 10.1111/j.1538-7836.2006.02181.x, indexed in Pubmed: 16938123.
38. Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium [Internet]. Royal College of Obstetricians and Gynaecologists; 2015. https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37a.pdf (cited 2019 Jul 13).
39. Meroni PL, Moia M, Derksen RH, et al. Venous thromboembolism in the antiphospholipid syndrome: management guidelines for secondary prophylaxis. Lupus. 2003; 12(7): 504–507, doi: 10.1191/0961203303lu389oa, indexed in Pubmed: 12892388.
40. Naouri D, Lapostolle F, Rondet C, et al. Prevention of medical events during air travel: a narrative review. Am J Med. 2016; 129(9): 1000.e1–1000.e6, doi: 10.1016/j.amjmed.2016.05.013, indexed in Pubmed: 27267286.
41. Long haul flight may have led to Jonah Lomu's death. The New Zealand Herald [Internet]. 2015 Nov 23. https://www.nzherald.co.nz/sport/long-haul-flight-may-have-led-to-jonah-lomus-death/DWWBA7BFLUMHBEHVAYY5SNAECM/ (cited 2020 Dec 9).
42. Abdollahi M, Cushman M, Rosendaal FR. Obesity: risk of venous thrombosis and the interaction with coagulation factor levels and oral contraceptive use. Thromb Haemost. 2003; 89(3): 493–498, indexed in Pubmed: 12624633.
43. Liu F, Silva D, Malone MV, et al. MTHFR A1298C and C677T Polymorphisms Are Associated with Increased Risk of Venous Thromboembolism: A Retrospective Chart Review Study. Acta Haematol. 2017; 138(4): 208–215, doi: 10.1159/000480447, indexed in Pubmed: 29212064.
44. Guba SC, Fink LM, Fonseca V. Hyperhomocysteinemia. An emerging and important risk factor for thromboembolic and car-

diovascular disease. Am J Clin Pathol. 1996; 106(6): 709–722, doi: 10.1093/ajcp/106.6.709, indexed in Pubmed: 8980346.
45. Botto LD, Yang Q. 5,10-Methylenetetrahydrofolate reductase gene variants and congenital anomalies: a HuGE review. Am J Epidemiol. 2000; 151(9): 862–877, doi: 10.1093/oxfordjournals.aje.a010290, indexed in Pubmed: 10791559.
46. den Heijer M, Koster T, Blom HJ, et al. Hyperhomocysteinemia as a risk factor for deep-vein thrombosis. N Engl J Med. 1996; 334(12): 759–762, doi: 10.1056/NEJM199603213341203, indexed in Pubmed: 8592549.
47. Lievers KJ, Boers GH, Verhoef P, et al. A second common variant in the methylenetetrahydrofolate reductase (MTHFR) gene and its relationship to MTHFR enzyme activity, homocysteine, and cardiovascular disease risk. J Mol Med (Berl). 2001; 79(9): 522–528, doi: 10.1007/s001090100253, indexed in Pubmed: 11692165.
48. Schwarz T, Siegert G, Oettler W, et al. Venous thrombosis after long-haul flights. Arch Intern Med. 2003; 163(22): 2759––2764, doi: 10.1001/archinte.163.22.2759, indexed in Pubmed: 14662630.
49. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet. 1995; 346(8990): 1575–1582, indexed in Pubmed: 7500748.
50. Contraceptive Use. In: National Survey of Family Growth [Internet]. https://www.cdc.gov/nchs/fastats/contraceptive.htm.
51. Arya R, Barnes JA, Hossain U, et al. Long-haul flights and deep vein thrombosis: a significant risk only when additional factors are also present. Br J Haematol. 2002; 116(3): 653–654, doi: 10.1046/j.0007-1048.2001.03330.x, indexed in Pubmed: 11849227.
52. Pérez-Rodríguez E, Jiménez D, Díaz G, et al. Incidence of air travel-related pulmonary embolism at the Madrid-Barajas airport. Arch Intern Med. 2003; 163(22): 2766–2770, doi: 10.1001/archinte.163.22.2766, indexed in Pubmed: 14662631.
53. Chandra D, Parisini E, Mozaffarian D. Meta-analysis: travel and risk for venous thromboembolism. Ann Intern Med. 2009; 151(3): 180–190, doi: 10.7326/0003-4819-151-3-200908040-00129, indexed in Pubmed: 19581633.
54. Belcaro G, Cesarone MR, Dugall M, et al. Venous Thromboembolism from Air Travel: The LONFLIT Studies. In: Shirato K, editor. Venous Thromboembolism [Internet]. Tokyo: Springer-Verlag; 2005, p. 103-116. http://link.springer.com/10.1007/4-431-27121-X_10 (cited 2018 Nov 24).
55. Jacobson BF, Münster M, Smith A, et al. The BEST study: a prospective study to compare business class versus economy class air travel as a cause of thrombosis. S Afr Med J. 2003; 93(7): 522–528, indexed in Pubmed: 12939926.
56. Chee YL, Watson HG. Air travel and thrombosis. Br J Haematol. 2005; 130(5): 671–680, doi: 10.1111/j.1365-2141.2005.05617.x, indexed in Pubmed: 16115122.
57. Domingueti CP, Dusse LM, Carvalho Md, et al. Diabetes mellitus: The linkage between oxidative stress, inflammation, hypercoagulability and vascular complications. J Diabetes Complications. 2016; 30(4): 738–745, doi: 10.1016/j.jdiacomp.2015.12.018, indexed in Pubmed: 26781070.
58. Belcaro G, Stansby G, Nicolaides AN. The Venous Clinic. Imperial College Press, London 1999.
59. Belcaro G, Geroulakos G, Nicolaides AN, et al. Venous thromboembolism from air travel: the LONFLIT study. Angiology. 2001; 52(6): 369–374, doi: 10.1177/000331970105200601, indexed in Pubmed: 11437026.
60. Belcaro G, Cesarone MR, Rohdewald P, et al. Prevention of venous thrombosis and thrombophlebitis in long-haul flights with pycnogenol. Clin Appl Thromb Hemost. 2004; 10(4): 373––377, doi: 10.1177/107602960401000410, indexed in Pubmed: 15497024.
61. Bartholomew JR, Evans NS. Travel-related venous thromboembolism. Vasc Med. 2019; 24(1): 93–95, doi: 10.1177/1358863X18818323, indexed in Pubmed: 30747601.
62. Pomp ER, Rosendaal FR, Doggen CJM. Smoking increases the risk of venous thrombosis and acts synergistically with oral contraceptive use. Am J Hematol. 2008; 83(2): 97–102, doi: 10.1002/ajh.21059, indexed in Pubmed: 17726684.
63. Morio H. Pulmonary Thromboembolism Associated with Air Travel in Jaan. In: Shirato K, editor. Venous Thromboembolism. Springer, Tokyo 2005: 87–93.
64. Parsi K. Traveller's Venous Thromboembolism [Master of Science (Medicine)]. University of New South Wales, Sydney 2001.
65. White R, Keenan C. Effects of race and ethnicity on the incidence of venous thromboembolism. Thromb Res. 2009; 123: S11–S17, doi: 10.1016/s0049-3848(09)70136-7.
66. Keenan CR, White RH. The effects of race/ethnicity and sex on the risk of venous thromboembolism. Curr Opin Pulm Med. 2007; 13(5): 377–383, doi: 10.1097/MCP.0b013e3281eb8ef0, indexed in Pubmed: 17940480.
67. Inflight wellbeing. Air New Zealand [Internet]. https://www.airnewzealand.co.nz/inflight-wellbeing (cited 2018 Aug 7).
68. Hitos K, Cannon M, Cannon S, et al. Effect of leg exercises on popliteal venous blood flow during prolonged immobility of seated subjects: implications for prevention of travel-related deep vein thrombosis. J Thromb Haemost. 2007; 5(9): 1890–1895, doi: 10.1111/j.1538-7836.2007.02664.x, indexed in Pubmed: 17723128.
69. Chen AH, Frangos SG, Kilaru S, et al. Intermittent pneumatic compression devices -- physiological mechanisms of action. Eur J Vasc Endovasc Surg. 2001; 21(5): 383–392, doi: 10.1053/ejvs.2001.1348, indexed in Pubmed: 11352511.
70. Belcaro G, Cesarone MR, Nicolaides AN, et al. Prevention of venous thrombosis with elastic stockings during long-haul flights: the LONFLIT 5 JAP study. Clin Appl Thromb Hemost. 2003; 9(3): 197–201, doi: 10.1177/107602960300900303, indexed in Pubmed: 14507107.
71. Cesarone MR, Belcaro G, Nicolaides AN, et al. The LONFLIT4--Concorde — Sigvaris Traveno Stockings in Long Flights (EcoTraS) Study: a randomized trial. Angiology. 2003; 54(1): 1–9, doi: 10.1177/000331970305400101, indexed in Pubmed: 12593490.
72. Sajid MS, Tai NRM, Goli G, et al. Knee versus thigh length graduated compression stockings for prevention of deep venous thrombosis: a systematic review. Eur J Vasc Endovasc Surg. 2006; 32(6): 730–736, doi: 10.1016/j.ejvs.2006.06.021, indexed in Pubmed: 16931066.
73. Cesarone MR, Belcaro G, Nicolaides AN, et al. Prevention of venous thrombosis in long-haul flights with Flite Tabs: the LONFLIT-FLITE randomized, controlled trial. Angiology. 2003; 54(5): 531–539, doi: 10.1177/000331970305400502, indexed in Pubmed: 14565628.
74. Lurie F, Kistner RL, Eklof Bo, et al. Prevention of air travel-related deep venous thrombosis with mechanical devices: active foot movements produce similar hemodynamic effects. J Vasc Surg. 2006; 44(4): 889–891, doi: 10.1016/j.jvs.2006.06.019, indexed in Pubmed: 17012016.

75. Comerota AJ, Katz ML, White JV. Why does prophylaxis with external pneumatic compression for deep vein thrombosis fail? Am J Surg. 1992; 164(3): 265–268, doi: 10.1016/s0002-9610(05)81083-9, indexed in Pubmed: 1415927.
76. Abramowitz HB, Gertz SD. Venous stasis, deep venous thrombosis and airline flight: can the seat be fixed? Ann Vasc Surg. 2007; 21(3): 267–271, doi: 10.1016/j.avsg.2007.03.007, indexed in Pubmed: 17484958.
77. Coleridge PD. Independent Clinical Trials. https://airogym.com/en/content/17-independent-clinical-trials (cited 2018 Nov 24).
78. Paydar S, Sabetian G, Khalili H, et al. Management of Deep Vein Thrombosis (DVT) Prophylaxis in Trauma Patients. Bull Emerg Trauma. 2016; 4(1): 1–7, indexed in Pubmed: 27162921.
79. Pai M, Douketis JD. Prevention of venous thromboembolism in adult travelers. Post TW, ed [Internet]. https://www.uptodate.com/contents/prevention-of-venous-thromboembolism-in-adult-travelers (cited 2019 Jul 7).
80. Bevis P, Smith F. Deep vein thrombosis. Surgery (Oxford). 2016; 34(4): 159–164, doi: 10.1016/j.mpsur.2016.02.001.
81. Cesarone MR, Belcaro G, Nicolaides AN, et al. Venous thrombosis from air travel: the LONFLIT3 study — prevention with aspirin vs low-molecular-weight heparin (LMWH) in high-risk subjects: a randomized trial. Angiology. 2002; 53(1): 1–6, doi: 10.1177/000331970205300101, indexed in Pubmed: 11863301.
82. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood. 2005; 106(8): 2710–2715, doi: 10.1182/blood-2005-04-1546, indexed in Pubmed: 15985543.
83. Chamnanchanunt S, Rojnuckarin P. Direct Oral Anticoagulants and Travel-related Venous Thromboembolism. Open Med (Wars). 2018; 13: 575–582, doi: 10.1515/med-2018-0085, indexed in Pubmed: 30519635.
84. Weitz JI, Bauersachs R, Beyer-Westendorf J, et al. EINSTEIN CHOICE Investigators. Two doses of rivaroxaban versus aspirin for prevention of recurrent venous thromboembolism. Rationale for and design of the EINSTEIN CHOICE study. Thromb Haemost. 2015; 114(3): 645–650, doi: 10.1160/TH15-02-0131, indexed in Pubmed: 25994838.
85. Clark SL, Onida S, Davies A. Long-haul travel and venous thrombosis: What is the evidence? Phlebology. 2018; 33(5): 295–297, doi: 10.1177/0268355517717423, indexed in Pubmed: 28650273.
86. Zhu Q, Zhou S, Liu Z. Fondaparinux and Direct Oral Anticoagulants. J Am Coll Cardiol. 2018; 71(15): 1710, doi: 10.1016/j.jacc.2017.12.067.
87. National Clinical Guideline Centre (UK). Venous Thromboembolic Diseases: The Management of Venous Thromboembolic Diseases and the Role of Thrombophilia Testing [Internet]. London: Royal College of Physicians (UK); 2012. (National Institute for Health and Clinical Excellence: Guidance). http://www.ncbi.nlm.nih.gov/books/NBK132796/ (cited 2018 Jul 9).
88. Wolowacz SE, Roskell NS, Plumb JM, et al. Efficacy and safety of dabigatran etexilate for the prevention of venous thromboembolism following total hip or knee arthroplasty. A meta-analysis. Thromb Haemost. 2009; 101(1): 77–85, indexed in Pubmed: 19132192.
89. Hughes RJ, Hopkins RJ, Hill S, et al. Frequency of venous thromboembolism in low to moderate risk long distance air travellers: the New Zealand Air Traveller's Thrombosis (NZATT) study. Lancet. 2003; 362(9401): 2039–2044, doi: 10.1016/s0140-6736(03)15097-0.
90. Ferrari E, Chevallier T, Chapelier A, et al. Travel as a risk factor for venous thromboembolic disease: a case-control study. Chest. 1999; 115(2): 440–444, doi: 10.1378/chest.115.2.440, indexed in Pubmed: 10027445.
91. Kraaijenhagen R, Haverkamp D, Koopman M, et al. Travel and risk of venous thrombosis. Lancet. 2000; 356(9240): 1492–1493, doi: 10.1016/s0140-6736(00)02878-6.
92. Aryal KR, Al-Khaffaf H. Venous thromboembolic complications following air travel: what's the quantitative risk? A literature review. Eur J Vasc Endovasc Surg. 2006; 31(2): 187–199, doi: 10.1016/j.ejvs.2005.08.025, indexed in Pubmed: 16230037.
93. Stroup DF. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. JAMA. 2000; 283(15): 2008.
94. Tovey C, Wyatt S. Diagnosis, investigation, and management of deep vein thrombosis. BMJ. 2003; 326(7400): 1180–1184, doi: 10.1136/bmj.326.7400.1180, indexed in Pubmed: 12775619.
95. Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med. 2003; 349(13): 1227–1235, doi: 10.1056/NEJMoa023153, indexed in Pubmed: 14507948.
96. Bell ML, Kenward MG, Fairclough DL, et al. Differential dropout and bias in randomised controlled trials: when it matters and when it may not. BMJ. 2013; 346: e8668, doi: 10.1136/bmj.e8668, indexed in Pubmed: 23338004.
97. Cooper HJ, Sanders SA, Berger RA. Risk of symptomatic venous thromboembolism associated with flying in the early postoperative period following elective total hip and knee arthroplasty. J Arthroplasty. 2014; 29(6): 1119–1122, doi: 10.1016/j.arth.2014.01.005, indexed in Pubmed: 24556112.
98. Citak M, Klatte TO, Suero EM, et al. Are patients with preoperative air travel at higher risk for venous thromboembolism following primary total hip and knee arthroplasty? Technol Health Care. 2015; 23(3): 307–311, doi: 10.3233/THC-150893, indexed in Pubmed: 25669208.
99. Gajic O, Sprung J, Hall BA, et al. Fatal acute pulmonary embolism in a patient with pelvic lipomatosis after surgery performed after transatlantic airplane travel. Anesth Analg. 2004; 99(4): 1032–1034, doi: 10.1213/01.ANE.0000131725.40714.9F, indexed in Pubmed: 15385344.
100. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med. 2020; 58(7): 1116–1120, doi: 10.1515/cclm-2020-0188, indexed in Pubmed: 32172226.
101. Helms J, Tacquard C, Severac F, et al. CRICS TRIGGERSEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis). High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020; 46(6): 1089–1098, doi: 10.1007/s00134-020-06062-x, indexed in Pubmed: 32367170.
102. Schwarz T, Langenberg K, Oettler W, et al. Deep vein and isolated calf muscle vein thrombosis following long-haul flights: pilot study. Blood Coagul Fibrinolysis. 2002; 13(8): 755–757, doi: 10.1097/00001721-200212000-00013, indexed in Pubmed: 12441916.
103. Belcaro G, Cesarone MR, Shah SSG, et al. Prevention of edema, flight microangiopathy and venous thrombosis in long flights with elastic stockings. A randomized trial: The LONFLIT 4 Concorde Edema-SSL Study. Angiology. 2002; 53(6): 635–645, doi: 10.1177/000331970205300603, indexed in Pubmed: 12463616.
104. Cesarone MR, Belcaro G, Errichi BM, et al. The LONFLIT4--Concorde Deep Venous Thrombosis and Edema Study: prevention with travel stockings. Angiology. 2003; 54(2): 143–154, doi: 10.1177/000331970305400202, indexed in Pubmed: 12678188.

VIA MEDICA

REVIEW ARTICLE

Cardiology Journal
2021, Vol. 28, No. 6, 954–961
DOI: 10.5603/CJ.a2020.0164

ISSN 1897–5593
eISSN 1898–018X

Antiplatelet effects of prostacyclin analogues: Which one to choose in case of thrombosis or bleeding?

Sylwester P. Rogula[1]*, Hubert M. Mutwil[1]*, Aleksandra Gąsecka[1], Marcin Kurzyna[2], Krzysztof J. Filipiak[1]

[1]1st Chair and Department of Cardiology, Medical University of Warsaw, Poland
[2]Department of Pulmonary Circulation, Thromboembolic Diseases and Cardiology, Center of Postgraduate Education Medical, European Health Center Otwock, Poland

Abstract

Prostacyclin and analogues are successfully used in the treatment of pulmonary arterial hypertension (PAH) due to their vasodilatory effect on pulmonary arteries. Besides vasodilatory effect, prostacyclin analogues inhibit platelets, but their antiplatelet effect is not thoroughly established. The antiplatelet effect of prostacyclin analogues may be beneficial in case of increased risk of thromboembolic events, or undesirable in case of increased risk of bleeding. Since prostacyclin and analogues differ regarding their potency and form of administration, they might also inhibit platelets to a different extent. This review summarizes the recent evidence on the antiplatelet effects of prostacyclin and analogue in the treatment of PAH, this is important to consider when choosing the optimal treatment regimen in tailoring to an individual patients' needs. (Cardiol J 2021; 28, 6: 954–961)

Key words: prostacyclin analogues, pulmonary arterial hypertension, platelets, antiplatelet effect, thrombosis, bleeding

Introduction

Since 1935 when prostaglandin was isolated for the first time [1], many scientists have focused on a thorough study of arachidonic acid transformation products and their various biological functions. One of the major prostaglandins is prostacyclin (PGI_2), which was discovered by John R. Vane in 1976 [2]. Endogenous PGI_2 binds to prostacyclin receptor (IP) on pulmonary vessels smooth muscle cells and platelets. Activated IP receptor induces production of cyclic adenosine monophosphate (cAMP), which activates protein kinase A (PKA) and results in smooth muscle relaxation, inhibition of platelet aggregation and reduction of cell proliferation [3]. Synthetic PGI_2 analogues have a similar effect on cells as does natural PGI_2. Nowadays, PGI_2 and its analogues are being used due to their vasodilating, antithrombotic and antiproliferative effects [4]. The main indication for PGI_2 and analogues is advanced pulmonary arterial hypertension (PAH) and peripheral vascular disorders [5]. Treprostinil, iloprost and beraprost are the most frequently used prostacyclin analogues [4]. Selexipag is a non-prostanoid IP receptor agonist and a promising new alternative for classic PGI_2 analogues [6].

As PGI_2 analogues vary depending on the way of administration, pharmacokinetics, binding and affinity for IP receptors, they may also inhibit platelets to a different extent [5]. These differences result in various side effects and complications associated with the of PGI_2 analogues and implicate the need to tailor the treatment according to a patient's individual needs. Because the intensity of antiplatelet effect of PGI_2 analogues have not been clarified, choosing the best therapeutic option for individual patients at high risk, or with

Address for correspondence: Dr. Aleksandra Gąsecka, 1st Chair and Department of Cardiology, Medical University of Warsaw, ul. Banacha 1a, 02-097 Warszawa, Poland, tel: +48 518 343 599, e-mail: aleksandra.gasecka@wum.edu.pl

Received: 1.07.2020 Accepted: 12.10.2020 Early publication date: 9.11.2020

**Sylwester P. Rogula and Hubert M. Mutwil share the first authorship.*

Table 1. Receptors for prostacycline and its analogues on platelets.

Receptor	G-protein coupled	Effect of activation	Agonist
DP [25, 49]	Gs	cAMP↑	epoprostenol, iloprost, treprostinil
IP [23, 24, 25, 48]	Gs > Gq	cAMP↑	epoprostenol, iloprost, treprostinil, beraprost, selexipag
TP [22]	Gq > Gs = Gi	cAMP↓↓	iloprost
EP_3 [23, 24]	Gi > Gq = Gs	cAMP↓	epoprostenol, iloprost, beraprost

cAMP — cyclic adenosine monophosphate

a history of thrombosis or bleeding remains challenging. This review (i) describes the role of PGI_2 in hemostasis, (ii) summarizes the recent evidence on the antiplatelet effect of PGI_2 analogues in the treatment of PAH, and (iii) provides recommendations regarding the choice of the optimal PGI_2 analogue in case of thrombosis or bleeding.

Role of prostacyclin in hemostasis

PGI_2 plays a prominent role in hemostasis, both due to its effect on vascular endothelium, smooth muscle cells and platelets. When a blood vessel wall is damaged, collagen and von Willebrand factor (vWF) are exposed enabling platelets adherence to the subendothelium and granule content release [7]. Thromboxane A2 (TxA2) and adenosine diphosphate (ADP) released from, or produced by activated platelets contribute to platelet aggregation, which temporarily repairs vascular injury. ADP also induces the conformation change of glycoprotein (GP) IIb/IIIa type receptor, allowing binding of fibrinogen to GP IIb/IIIa and cross-linking of the adjacent platelets. The released calcium ions (Ca^{2+}) bind to phospholipids that are exposed on the surface of activated platelets and provide a co-factor for the assembly of coagulation factors, facilitating thrombus formation [8]. The processes of primary hemostasis are counteracted by PGI_2, which is a thromboxane receptor antagonist. The main task of PGI_2 is to limit the coagulation to the small area where it is needed, and to sustain patency of the blood vessel [9].

Following platelet-rich thrombus formation, further steps include activation of plasma coagulation factors and formation of crosslinked fibrin by two pathways: extrinsic and intrinsic. The extrinsic pathway is activated by the tissue factor (TF) exposed by vessel injury and released from platelets, which is necessary for activation of factor VII. The complex consisting of Ca^{2+}, TF and factor VII can then activate factor X, which starts the common pathway [10]. In the intrinsic pathway, factor XII is activated by contact with the damaged vascular surface, high molecular weight kininogen and kallikrein. This complex initiates the cascade of activation of factor XI and IX. The next step is the activation of factor X, which starts the common pathway. Finally, factors Xa, Va and Ca^{2+} form a complex that converts prothrombin to thrombin, which then converts fibrinogen to fibrin to form a fibrin polymer. After that, plasma transglutaminase (factor XIII) stabilises the clot. Although PGI_2 is not directly involved in clot formation, appropriate platelet aggregation is a prerequisite for clotting. Hence, PGI_2 may affect secondary hemostasis and clot formation as well.

Prostacyclin receptors

Prostacyclin receptors (IP) are seven-transmembrane G protein-coupled receptors, exposed on vascular smooth muscle cells and platelets [11]. The main characteristics of the IP receptors are summarized in Table 1. There are four types of IP receptors on platelets: IP, DP, TP, and EP_3. The IP and DP receptors have anti-aggregatory effects, whereas the TP, EP_3 have pro-aggregatory effects [12].

Figure 1 shows the function of IP and DP receptors. The IP receptor works in two ways. First, it activates Gs protein, associated with adenylyl cyclase (AC) to produce cAMP [13], resulting in phosphorylation of the vasodilator-stimulated phosphoprotein (VASP) by protein kinase A. VASP suppresses the activation of the membrane GP IIb/IIIa, thus preventing platelet aggregation [14]. Second, IP activates Gq protein [15]. Activation of Gq protein stimulates phospholipase C to synthesize second messengers which increases the intracellular Ca^{2+} concentration. Increases Ca^{2+} reduces the amount of cAMP, which might facilitate platelet aggregation [16]. However, the Gq-mediated effect of PGI_2 is less significant, so that the net effect of PGI_2 binding to IP receptor is anti-aggregatory. The DP receptor activates Gs protein only, therefore raising the intracellular cAMP concentration and potentiating platelet inhibition.

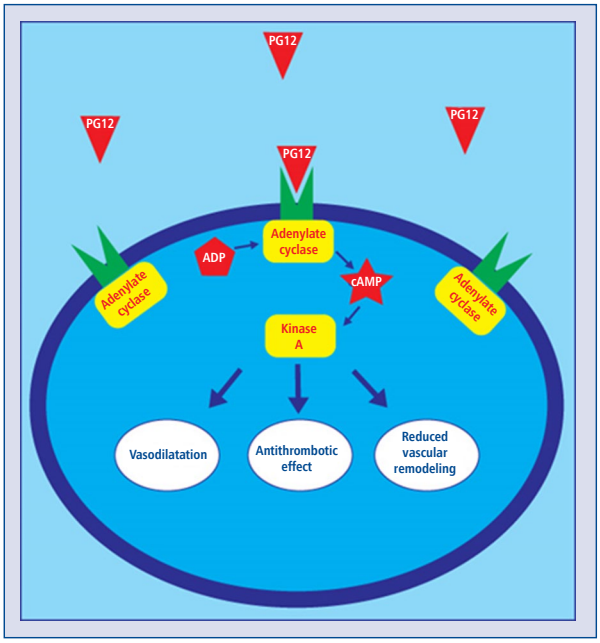


Figure 1. Effects of activation of IP and DP for prostacyclin receptors on platelets; abbreviations — see text.

TP receptor affects the activity of three G proteins: Gq protein strongly, and both Gi and Gs in a less significant way. Since the effect of TP on Gi and Gs are contradictory, the net effect of this receptor is executed via Gq protein, resulting in reduced cAMP concentration and a pro-aggregatory effect [17, 18]. However, the TP receptor can also form heterodimers with the TP receptor [19]. The IP-TP heterodimer function is similar to the IP receptor (anti-aggregatory), since the TP compound is overpowered. The EP_3 receptor activates the same G proteins as TP receptor, but most significantly the Gi protein, resulting in reduced cAMP and platelet aggregation [20].

Due to the fact that the IP receptors have both anti- and pro-aggregatory modes of action, the net clinical effect (thrombosis and bleeding) of PGI_2 and analogues are difficult to predict. Recently, there has been a search for a substance, which would specifically bind to the IP receptor, resulting in the introduction of selexipag [21]. Selexipag has a much higher affinity to platelet-inhibiting receptors (IP and DP), and none to platelet-activating receptors (TP and EP_3). However, whether this specificity is associated with a higher bleeding tendency remains to be investigated.

Differences in pharmacodynamics and pharmacokinetics of prostacyclin and analogues

PGI_2 and analogues are available in parenteral and oral form. Different routes of administration result in differing pharmacokinetics of each drug. PGI_2 and analogues are primarily metabolized by cytochromes P450 in the liver, especially by CYP2C8. Selexipag is the only PGI_2 analogue which has an active metabolite. Short half-life of PGI_2 and analogues often requires continuous infusions by external or implantable intravenous infusion pumps. Epoprostenol, iloprost and beraprost bind both to the antiaggregatory IP and DP receptors and to the pro-aggregatory EP_3 [22–24]. Iloprost also binds to the pro-aggregatory TP receptor [22]. Treprostinil binds only to the anti-aggregatory IP and DP receptors [25]. Selexipag is a specific IP receptor agonist [24]. Consequently, the route of administration, metabolism of PGI_2 and analogues and their binding profile may define their side effects, including thrombosis and bleeding. The comparison of pharmacokinetics, pharmacodynamics and side effects of the most commonly used drugs PGI_2 analogue are thoroughly summarized in Table 2.

Table 2. Comparison of pharmacokinetics, side effects, contraindications of the most commonly used drugs which target the prostacyclin pathway.

Drug[1]	Route of administration	Pharmacokinetics	Side effects related to the route of administration	Side effects not related to the route of administration
Epoprostenol [50, 51]	i.v. infusion (Flolan®, Veletri®)	**Bioavailability:** 100% **Metabolism:** Spontaneous degradation in blood Enzymatic degradation in the liver **Elimination:** Mainly urine (84%) T½ < 6 min	Bleeding Infection (catheter-related) Malfunction of the infusion pump Pain Sepsis Thromboembolic event	Anorexia Diarrhoea Dizziness Flushing Headache Hypotension Jaw pain Musculoskeletal pain Nausea Vomiting Tachycardia Vasodilatation

→

Table 2 (cont.). Comparison of pharmacokinetics, side effects, contraindications of the most commonly used drugs which target the prostacyclin pathway.

Drug[1]	Route of administration	Pharmacokinetics	Side effects related to the route of administration	Side effects not related to the route of administration
Treprostinil [52, 53, 54]	s.c. infusion[2] (Remodulin®, Tresuvi®, Trepulmix®)	**Bioavailability:** 100% **Metabolism:** Degradation in the liver (primarily CYP2C8) **Elimination:** Mainly urine (79%) T½ 2–4 h	Abscess Bleeding/bruising Infection (infusion pump-related) Malfunction of the infusion pump Pain Other site reactions (erythema, induration, rash)	Bleeding Diarrhoea Dizziness Headache Hypotension Jaw pain Nausea Edema Vomiting Tachycardia Vasodilatation
	i.v. infusion[3] (Remodulin® Tresuvi®)	**Bioavailability:** 100% **Metabolism:** Degradation in the liver (primarily CYP2C8) **Elimination:** Mainly urine (79%) T½ 2–4 h	Abscess Bleeding/bruising Infection (catheter-related) Malfunction of the infusion pump Pain Sepsis Thrombophlebitis Other site reactions (swelling, paraesthesia's, erythema, induration, rash)	
	Inhalation (Tyvaso®)	**Bioavailability:** 64–72% **Metabolism:** Degradation in the liver (primarily CYP2C8) **Elimination:** Mainly urine (70%) T½ 3–4 h	Cough Epistaxis Hemoptysis Nasal discomfort throat irritation Throat pain Wheezing	Diarrhoea Dizziness Flushing Headache Nausea Tachycardia Vasodilatation
	p.o. (Orenitram®)	**Bioavailability:** 17% **Metabolism:** Degradation in the liver (primarily CYP2C8) **Elimination:** Mainly urine (70%) T½ *1*–1.5 h	Abdominal discomfort Diarrhoea Nausea Vomiting	Flushing Headache Jaw pain Hypokalemia
Iloprost [55]	Inhalation (Ventavis®)	**Bioavailability:** 63% **Metabolism:** Oxidation in the liver **Elimination:** Mainly urine (68%) T½ *20*–30 min	Cough Epistaxis Hemoptysis Nasal discomfort throat irritation Throat pain	Diarrhoea Dizziness Flushing Headache Hypotension Insomnia Jaw pain Nausea Vomiting Tachycardia Vasodilatation
Beraprost [56]	p.o. (Beraprost®)	**Bioavailability:** 50–70% **Metabolism:** Degradation in the liver **Elimination:** Mainly faeces (75%) T½ 30–40 min	Diarrhoea Nausea	Flushing Headache Increased bilirubin, lactate dehydrogenase, triglycerides
Selexipag [34, 57]	p.o. (Uptravi®)	**Bioavailability:** 49% **Metabolism:** Hydrolysis in the liver and intestine (primarily CYP2C8) **Elimination:** Mainly feaces (93%) T½ 3–4 h	Diarrhoea Decreased appetite Nausea Vomiting	Anaemia Arthralgia Headache Hyperthyroidism Flushing Myalgia Rash

[1]Contraindications to the use of any of the PGI_2 analogues: heart failure with reduced left ventricular ejection fraction, severe hepatic impairment (Child Pugh class C), concomitant use of strong inhibitors of CYP2C8 (e.g. gemfibrozil), hypersensitivity to the drug; [2]The preferred administration route of treprostinil; [3]External or implantable intravenous infusion pump

Thrombosis and bleeding during prostacyclin and analogues therapy

Epoprostenol

Epoprostenol not only inhibits platelet reactivity, but also decreases platelet count [26]. It was reported that epoprostenol induces thrombocytopenia in 35–65% of patients [27, 28]. Hence, bleeding complications may occur during treatment with epoprostenol. For example, among 31 patients with idiopathic PAH (iPAH), who were treated both with epoprostenol and anticoagulants, 11 bleeding episodes occurred (35%), 9 of which were alveolar hemorrhages [29]. However, the concomitant anticoagulation may have biased the results. In a prospective, randomized, multicenter, open-label clinical trial which compared the efficacy of the continuous intravenous infusion of epoprostenol on top of conventional therapy versus conventional therapy alone in 81 patients with severe iPAH (New York Heart Association [NYHA] class III or IV), 4 out of 41 patients treated with epoprostenol (9.8%) experienced bleeding at the catheter site, and 1 experienced a thrombotic event (paradoxical embolism) [30]. However, the rate of bleeding and thrombotic events in the control group were not reported [30]. Herrero et al. [31] described 3 cases of severe PAH in pregnancy, treated with epoprostenol and complicated with thrombocytopenia, caesarean section wound hematoma and postpartum hemorrhage. Louis et al. [32] described 3 cases of nontraumatic subdural hematomas during treatment with PGI_2 and analogues (1 with epoprostenol, 1 with iloprost and 1 with treprostinil). However, all episodes occurred in patients with low platelet count, and all patients received concomitant anticoagulantion, making it impossible to determine the real cause of bleeding events. Altogether, it seems that epoprostenol may increase the risk of bleeding. However, since the hitherto studies were prone to confounding factors such concomitant anticoagulation, lack of control group and small sample size, more research is needed to draw firm conclusions.

Treprostinil

In a prospective study including 860 patients with PAH treated with subcutaneous treprostinil with or without warfarin, the incidence of bleeding was 35% (206/590) in patients on combined therapy, and 42% (112/270) in patients only receiving treprostinil (13 severe, 29 moderate and 70 mild bleeding episodes) [33, 34]. Similarly, in a double-blind, placebo-controlled, multicenter trial comprising 470 patients with PAH, either idiopathic or associated with connective tissue disease or congenital heart disease, 34% patients experienced infusion site bleeding or bruising with treprostinil (79/233), and as much as 44% with a placebo (102/236) during 12 weeks of treatment [35]. The incidence of gastrointestinal (GI) bleeding was only 0.01% (3/233) on treprostinil, and 2 out of 3 patients who experienced GI bleeding had increased international normalized ratio (INR; 3.1 and 4.0). In another study, the estimated incidence of GI bleeding with subcutaneous administration of treprostinil was 1.3% [36]. However, in a case series of 5 infants with PAH associated with chronic lung disease and treated with subcutaneous treprostinil, there were no bleeding or bruising episodes [37]. Altogether, although the treatment with subcutaneous treprostinil seems to be associated with relatively high rate of small and local bleeding, this rate was comparable to the placebo, which implies an effect of the infusion system, but not the drug itself. Recently, a double-blind, phase 3, randomised controlled trial was conducted, where 105 patients with chronic thromboembolic pulmonary hypertension, classified as non-operable, or with persistent or recurrent pulmonary hypertension after pulmonary endarterectomy, on chronic anticoagulation were divided into high-dose (~30 ng/kg/min, n = 53) and low-dose (~3 ng/kg/min, n = 52) of subcutaneously administered treprostinil. There were no severe bleeding adverse events in the low dose group and single episodes of hemoptysis and hematoma in the high-dose group. Noteworthy, 3 (5.8%) episodes of epistaxis were observed in the low-dose group, and only 1 (1.9%) episode in the high-dose group, implying that the bleeding on subcutaneous treprostinil is not dose-related [38].

Besides subcutaneous infusion, which is the preferred administration route of treprostinil, it may also be administered intravenously. In a retrospective, multi-center study involving 12 patients with PAH treated with subcutaneous infusion of treprostinil, with intolerable pain at the infusion site, an intravenous infusion pump was implanted. During the postoperative period, 4 (33%) patients experienced a small hematoma in the implantation site that required a single evacuation by puncture. In 1 patient, puncturing of the pump area was required 3 times due to a recurrence of the hematoma. However, this patient had concomitant coagulopathy due to splenomegaly associated with liver cirrhosis resulting in thrombocytopenia [39]. However, intravenous infusion might increase the bleeding risk, although no head-to-head compari-

sons between the routes of treprostinil administration are available.

The efficacy and safety of inhaled treprostinil was evaluated in 9 patients with pulmonary hypertension and concomitant chronic obstructive pulmonary disease [40]. After 16 weeks of treatment, none of the patients experienced a clinically significant bleeding episode, and 1 patient reported blood in sputum [40]. Hence, it seems that treprostinil administered in inhalation may be safer than administered subcutaneously or intravenously, but the heterogeneity and small sample size of the study groups require caution when interpreting the results.

Iloprost

Intravenous iloprost was investigated in a prospective study in 30 patients with systemic sclerosis, leading to only 1 bleeding episode (intracranial hemorrhage) during 3 years follow-up. The same patient had previously suffered a central retinal vein thrombosis [41]. Intravenous iloprost was also evaluated in a randomized, placebo-controlled study in 300 patients as adjuvant to surgery for acute ischemia of lower limbs, with similar incidences of bleeding in patients treated with iloprost and placebo at 3 month follow-up [42]. Inhaled iloprost, in turn, was used to treat PAH due to preterm rupture of foetal membranes in 4 extremely low-birthweight neonates (23–25 weeks gestation, 448–645 gram weight) under spontaneous breathing, supported by nasal continuous positive airway pressure. There was no prolonged bleeding incident noted in any of the patients [43]. Altogether, it seems that both intravenous and inhaled iloprost may be safe, but there is too little data to draw firm conclusions.

Beraprost

In a prospective clinical trial comprising 308 patients with acute ischemic stroke, patients were divided into an experimental group (n = 154) treated with beraprost (40 μg, twice daily) on top of acetylsalicylic acid (100 mg, once daily) and a control group (n = 154) treated with acetylsalicylic acid only (100 mg, once daily). Both treatment regimens were administered orally and continued for 6 months after hospital discharge. At 6 months, the coagulation parameters (activated partial thromboplastin time, prothrombin time, INR and fibrinogen) and bleeding rates were comparable between the groups [44]. Similarly, in a prospective clinical study including 55 patients with end-stage renal disease on hemodialysis, beraprost (n = 23, 120 μg per day) did not increase the rate of bleeding, compared to the standard therapy (n = 32) [45]. Altogether, the preliminary data implicate that treatment with beraprost does not increase the rate of bleeding, but this conclusion needs to be confirmed in future studies.

Selexipag

The GRIPHON (PGI_2 Receptor Agonist In Pulmonary Arterial Hypertension) study took place in 181 centres and was the biggest clinical trial in patients with PAH. In this double-blind, randomized, placebo-controlled study, the efficacy and safety of selexipag was investigated in 1156 patients in different stadiums of PAH [21]. Selexipag did not increase the rate of bleeding, including gastrointestinal hemorrhage [46], and did not have a substantial effect on platelet aggregation [47]. Based on this study, selexipag seems to be a safe treatment regimen in PAH.

Discussion

PGI_2 and analogues are widely used in treatment of PAH, but their antiplatelet effect and related bleeding complications are still insufficiently investigated. Experimental data suggests that the IP and DP receptors have antiaggregatory effects, whereas the TP and EP_3 have pro-aggregatory effects by modulating the intracellular concentration of cAMP [23–25, 48, 49]. Consequently, drugs which bind to the IP and DP receptors only (treprostinil, selexipag) are expected to have higher antiplatelet activity than those which bind to IP, DP and EP_3 receptors (epoprostenol, beraprost) and to all receptors (iloprost). However, data from clinical studies do not always comply with experimental insights. For example, it seems that epoprostenol and treprostinil may increase bleeding risk, especially if treprostinil is administered subcutaneously or intravenously [33–35, 39]. In addition, a randomized controlled trial on 105 patients treated with treprostinil administered subcutaneously showed that the frequency of bleeding complications was not dose-related [38]. On the contrary, no increased bleeding tendency was seen with iloprost, beraprost and selexipag. Hence, one could consider avoiding epoprostenol and treprostinil, and rather choose iloprost, beraprost or selexipag in patients with increased bleeding risk, or with a history of bleeding. However, since the hitherto studies were prone to confounding factors such concomitant anticoagulation, lack of control group, small sample size and heterogeneity, the previous

results should be interpreted with caution, and more evidence is needed to draw firm conclusions. Especially, large-scale, randomized clinical studies to compare different PGI_2 analogues head-to-head are urgently needed to determine the optimal treatment regimen in patients with increased risk of thrombosis or bleeding, tailored to an individual patients' needs.

Acknowledgments

Aleksandra Gąsecka acknowledges funding from National Science Center, research program PRELUDIUM (2018/31/N/NZ7/02260).

Conflict of interest: None declared

References

1. Von Euler US. Über die Spezifische Blutdrucksenkende Substanz des Menschlichen Prostata- und Samenblasensekretes. Klin Wochenschr. 1935; 14(33): 1182–1183, doi: 10.1007/bf01778029.
2. The Nobel Prize. https://www.nobelprize.org/prizes/medicine/1982/press-release/ (Accessed: 7 April 2020).
3. Woodward DF, Jones RL, Narumiya S. International Union of Basic and Clinical Pharmacology. LXXXIII: classification of prostanoid receptors, updating 15 years of progress. Pharmacol Rev. 2011; 63(3): 471–538, doi: 10.1124/pr.110.003517, indexed in Pubmed: 21752876.
4. Mubarak KK. A review of prostaglandin analogs in the management of patients with pulmonary arterial hypertension. Respir Med. 2010; 104(1): 9–21, doi: 10.1016/j.rmed.2009.07.015, indexed in Pubmed: 19683911.
5. Safdar Z. Treatment of pulmonary arterial hypertension: the role of prostacyclin and prostaglandin analogs. Respir Med. 2011; 105(6): 818–827, doi: 10.1016/j.rmed.2010.12.018, indexed in Pubmed: 21273054.
6. Uptravi® Full Prescribing Information. https://www.uptravi.com/assets/pdf/UPTRAVI-full-prescribing-information.pdf (Accessed 7 April 2020).
7. Heemskerk JWM, Bevers EM, Lindhout T. Platelet activation and blood coagulation. Thromb Haemost. 2002; 88(2): 186–193, indexed in Pubmed: 12195687.
8. Palta S, Saroa R, Palta A. Overview of the coagulation system. Indian J Anaesth. 2014; 58(5): 515–523, doi: 10.4103/0019-5049.144643, indexed in Pubmed: 25535411.
9. Winter WE, Flax SD, Harris NS. Coagulation testing in the core laboratory. Lab Med. 2017; 48(4): 295–313, doi: 10.1093/labmed/lmx050, indexed in Pubmed: 29126301.
10. Lasne D, Jude B, Susen S. From normal to pathological hemostasis. Can J Anaesth. 2006; 53(6 Suppl): S2–11, doi: 10.1007/BF03022247, indexed in Pubmed: 16766787.
11. Gomberg-Maitland M, Olschewski H. Prostacyclin therapies for the treatment of pulmonary arterial hypertension. Eur Respir J. 2008; 31(4): 891–901, doi: 10.1183/09031936.00097107, indexed in Pubmed: 18378784.
12. Armstrong RA. Platelet prostanoid receptors. Pharmacol Ther. 1996; 72(3): 171–191, doi: 10.1016/s0163-7258(96)00103-9, indexed in Pubmed: 9364574.
13. Boie Y, Sawyer N, Slipetz DM, et al. Molecular cloning and characterization of the human prostanoid DP receptor. J Biol Chem. 1995; 270(32): 18910–18916, doi: 10.1074/jbc.270.32.18910, indexed in Pubmed: 7642548.
14. Deep A, Zoha M, Dutta Kukreja P. Prostacyclin as an anticoagulant for continuous renal replacement therapy in children. Blood Purif. 2017; 43(4): 279–289, doi: 10.1159/000452754, indexed in Pubmed: 28118627.
15. Boie Y, Rushmore TH, Darmon-Goodwin A, et al. Cloning and expression of a cDNA for the human prostanoid IP receptor. J Biol Chem. 1994; 269(16): 12173–12178, indexed in Pubmed: 7512962.
16. Berridge MJ. Inositol trisphosphate and calcium signaling. Nature. 1993; 361(6410): 315–325.
17. Hirata M, Hayashi Y, Ushikubi F, et al. Cloning and expression of cDNA for a human thromboxane A2 receptor. Nature. 1991; 349(6310): 617–620, doi: 10.1038/349617a0, indexed in Pubmed: 1825698.
18. Nagy Z, Smolenski A. Cyclic nucleotide-dependent inhibitory signaling interweaves with activating pathways to determine platelet responses. Res Pract Thromb Haemost. 2018; 2(3): 558–571, doi: 10.1002/rth2.12122, indexed in Pubmed: 30046761.
19. Chakraborty R, Pydi SP, Gleim S, et al. New insights into structural determinants for prostanoid thromboxane A2 receptor- and prostacyclin receptor-G protein coupling. Mol Cell Biol. 2013; 33(2): 184–193, doi: 10.1128/MCB.00725-12, indexed in Pubmed: 23109431.
20. Kotani M, Tanaka I, Ogawa Y, et al. Structural organization of the human prostaglandin EP3 receptor subtype gene (PTGER3). Genomics. 1997; 40(3): 425–434, doi: 10.1006/geno.1996.4585, indexed in Pubmed: 9073510.
21. Sitbon O, Channick R, Chin K, et al. Selexipag for the Treatment of Pulmonary Arterial Hypertension. N Engl J Med. 2015; 373(26): 2522–2533, doi: 10.1056/nejmoa1503184.
22. Abramovitz M, Adam M, Boie Y, et al. The utilization of recombinant prostanoid receptors to determine the affinities and selectivities of prostaglandins and related analogs. Biochim Biophys Acta. 2000; 1483(2): 285–293, doi: 10.1016/s1388-1981(99)00164-x, indexed in Pubmed: 10634944.
23. Kiriyama M, Ushikubi F, Kobayashi T, et al. Ligand binding specificities of the eight types and subtypes of the mouse prostanoid receptors expressed in Chinese hamster ovary cells. Br J Pharmacol. 1997; 122(2): 217–224, doi: 10.1038/sj.bjp.0701367, indexed in Pubmed: 9313928.
24. Kuwano K, Hashino A, Asaki T, et al. 2-[4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy]-N-(methylsulfonyl)acetamide (NS-304), an orally available and long-acting prostacyclin receptor agonist prodrug. J Pharmacol Exp Ther. 2007; 322(3): 1181–1188, doi: 10.1124/jpet.107.124248, indexed in Pubmed: 17545310.
25. Whittle BJ, Silverstein AM, Mottola DM, et al. Binding and activity of the prostacyclin receptor (IP) agonists, treprostinil and iloprost, at human prostanoid receptors: treprostinil is a potent DP1 and EP2 agonist. Biochem Pharmacol. 2012; 84(1): 68–75, doi: 10.1016/j.bcp.2012.03.012, indexed in Pubmed: 22480736.
26. Gomberg-Maitland M, Tapson VF, Benza RL, et al. Transition from intravenous epoprostenol to intravenous treprostinil in pulmonary hypertension. Am J Respir Crit Care Med. 2005; 172(12): 1586–1589, doi: 10.1164/rccm.200505-766OC, indexed in Pubmed: 16151039.
27. Chin KM, Channick RN, de Lemos JA, et al. Hemodynamics and epoprostenol use are associated with thrombocytopenia in pul-

monary arterial hypertension. Chest. 2009; 135(1): 130–136, doi: 10.1378/chest.08-1323, indexed in Pubmed: 18719056.
28. Hargett C, Ahearn G, Krichman A, et al. Thrombocytopenia associated with chronic intravenous epoprostenol therapy. Chest. 2004; 126(4), doi: 10.1378/chest.126.4_meetingabstracts.760s-b.
29. Ogawa A, Matsubara H, Fujio H, et al. Risk of alveolar hemorrhage in patients with primary pulmonary hypertension--anticoagulation and epoprostenol therapy. Circ J. 2005; 69(2): 216–220, doi: 10.1253/circj.69.216, indexed in Pubmed: 15671616.
30. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med. 1996; 334(5): 296–301, doi: 10.1056/NEJM199602013340504, indexed in Pubmed: 8532025.
31. Herrero T, Martin E, Poch DS, et al. Anti-coagulation complications in pregnancies with severe pulmonary arterial hypertension. J Matern Fetal Neonatal Med. 2018; 31(9): 1209–1213, doi: 10.1080/14767058.2017.1312329, indexed in Pubmed: 28353362.
32. Louis L, Bair N, Banjac S, et al. Subdural hematomas in pulmonary arterial hypertension patients treated with prostacyclin analogs [corrected]. Pulm Circ. 2012; 2(4): 518–521, doi: 10.4103/2045-8932.105041, indexed in Pubmed: 23372937.
33. Ascha M, Zhou X, Rao Y, et al. Impact on survival of warfarin in patients with pulmonary arterial hypertension receiving subcutaneous treprostinil. Cardiovasc Ther. 2017; 35(5), doi: 10.1111/1755-5922.12281, indexed in Pubmed: 28643420.
34. Barst RJ, Galie N, Naeije R, et al. Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil. Eur Respir J. 2006; 28(6): 1195–1203, doi: 10.1183/09031936.06.00044406, indexed in Pubmed: 16899485.
35. Simonneau G, Barst RJ, Galie N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med. 2002; 165(6): 800–804, doi: 10.1164/ajrccm.165.6.2106079, indexed in Pubmed: 11897647.
36. Mindus S, Pawlowski J, Nisell M, et al. Intra-abdominal bleeding during treprostinil infusion in a patient with pulmonary arterial hypertension. BMJ Case Rep. 2013; 2013, doi: 10.1136/bcr-2013-008677, indexed in Pubmed: 23446048.
37. Ferdman DJ, Rosenzweig EB, Zuckerman WA, et al. Subcutaneous treprostinil for pulmonary hypertension in chronic lung disease of infancy. Pediatrics. 2014; 134(1): e274–e278, doi: 10.1542/peds.2013-2330, indexed in Pubmed: 24982101.
38. Sadushi-Kolici R, Jansa P, Kopec G, et al. Subcutaneous treprostinil for the treatment of severe non-operable chronic thromboembolic pulmonary hypertension (CTREPH): a double-blind, phase 3, randomised controlled trial. Lancet Respir Med. 2019; 7(3): 239–248, doi: 10.1016/S2213-2600(18)30367-9, indexed in Pubmed: 30477763.
39. Kurzyna M, Małaczyńska-Rajpold K, Koteja A, et al. An implantable pump Lenus pro® in the treatment of pulmonary arterial hypertension with intravenous treprostinil. BMC Pulm Med. 2017; 17(1): 162, doi: 10.1186/s12890-017-0474-7, indexed in Pubmed: 29195500.
40. Bajwa AA, Shujaat A, Patel M, et al. The safety and tolerability of inhaled treprostinil in patients with pulmonary hypertension and chronic obstructive pulmonary disease. Pulm Circ. 2017; 7(1): 82–88, doi: 10.1086/689291, indexed in Pubmed: 28680567.
41. Bettoni L, Geri A, Airò P, et al. Systemic sclerosis therapy with iloprost: a prospective observational study of 30 patients treated for a median of 3 years. Clin Rheumatol. 2002; 21(3): 244–250, doi: 10.1007/pl00011223, indexed in Pubmed: 12111631.
42. de Donato G, Gussoni G, de Donato G, et al. The ILAILL study: iloprost as adjuvant to surgery for acute ischemia of lower limbs: a randomized, placebo-controlled, double-blind study by the italian society for vascular and endovascular surgery. Ann Surg. 2006; 244(2): 185–193, doi: 10.1097/01.sla.0000217555.49001.ca, indexed in Pubmed: 16858180.
43. Eifinger F, Sreeram N, Mehler K, et al. Aerosolized iloprost in the treatment of pulmonary hypertension in extremely preterm infants: a pilot study. Klin Padiatr. 2008; 220(2): 66–69, doi: 10.1055/s-2007-984370, indexed in Pubmed: 17710738.
44. Chen S, Xie S, He W, et al. Beneficial effect of beraprost sodium plus aspirin in the treatment of acute ischemic stroke. Med Sci Monit. 2017; 23: 4401–4407, doi: 10.12659/msm.902825, indexed in Pubmed: 28898204.
45. Kim M, Kim JiU, Kim SoMi, et al. Effectiveness of beraprost sodium in maintaining vascular access patency in patients on hemodialysis. Int Urol Nephrol. 2017; 49(7): 1287–1295, doi: 10.1007/s11255-017-1586-y, indexed in Pubmed: 28409403.
46. Krause A, Machacek M, Lott D, et al. Population Modeling of Selexipag Pharmacokinetics and Clinical Response Parameters in Patients With Pulmonary Arterial Hypertension. CPT Pharmacometrics Syst Pharmacol. 2017; 6(7): 477–485, doi: 10.1002/psp4.12202, indexed in Pubmed: 28556581.
47. Bruderer S, Hurst N, Kaufmann P, et al. Multiple-dose up-titration study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of selexipag, an orally available selective prostacyclin receptor agonist, in healthy subjects. Pharmacology. 2014; 94(3-4): 148–156, doi: 10.1159/000367630, indexed in Pubmed: 25277144.
48. Stitham J, Arehart E, Gleim SR, et al. New insights into human prostacyclin receptor structure and function through natural and synthetic mutations of transmembrane charged residues. Br J Pharmacol. 2007; 152(4): 513–522, doi: 10.1038/sj.bjp.0707413, indexed in Pubmed: 17704830.
49. Wright DH, Metters KM, Abramovitz M, et al. Characterization of the recombinant human prostanoid DP receptor and identification of L-644,698, a novel selective DP agonist. Br J Pharmacol. 1998; 123(7): 1317–1324, doi: 10.1038/sj.bjp.0701708, indexed in Pubmed: 9579725.
50. Flolan® Full Prescribing Information. https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Flolan/pdf/FLOLAN-PI-PIL.PDF (Accessed 7 April 2020).
51. Veletri® Full Prescribing Information. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/VELETRI-pi.pdf (Accessed 7 April 2020).
52. Orenitram® Full Prescribing Information. https://www.orenitram.com/pdf/Orenitram_Full_Prescribing_Information.pdf (Accessed 7 April 2020).
53. Remodulin® Full Prescribing Information. https://www.remodulin.com/downloads/remodulin-prescribinginformation.pdf (Accessed 7 April 2020).
54. Tyvaso® Full Prescribing Information. https://www.tyvaso.com/hcp/pdf/Tyvaso-PI.pdf (Accessed 7 April 2020).
55. Ventavis® Full Prescribing Information. https://www.4ventavis.com/pdf/Ventavis_PI.pdf (Accessed 7 April 2020).
56. Melian EB1, Goa KL. Beraprost: a review of its pharmacology and therapeutic efficacy in the treatment of peripheral arterial disease and pulmonary arterial hypertension. Drugs. 2002; 62(1): 107–133.
57. Kingman M, Archer-Chicko C, Bartlett M, et al. Management of prostacyclin side effects in adult patients with pulmonary arterial hypertension. Pulm Circ. 2017; 7(3): 598–608, doi: 10.1177/2045893217719250, indexed in Pubmed: 28632002.

VIA MEDICA

REVIEW ARTICLE

Cardiology Journal
2021, Vol. 28, No. 6, 962–969
DOI: 10.5603/CJ.a2021.0165

ISSN 1897–5593
eISSN 1898–018X

Iron deficiency as an emerging therapeutic target in patients stabilized after an episode of acute heart failure

Michał Tkaczyszyn[1, 2], Tomasz Skrzypczak[3], Jakub Michałowicz[3], Piotr Ponikowski[1, 2], Ewa A. Jankowska[1, 2]

[1]Institute of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland
[2]Institute of Heart Diseases, University Hospital, Wroclaw, Poland
[3]Faculty of Medicine, Wroclaw Medical University, Wroclaw, Poland

Abstract

Acute heart failure (AHF) syndromes are among the most frequent causes of hospitalization in the elderly and put a heavy financial burden on healthcare systems, mainly due to high early readmission rates. The understanding of AHF has evolved over the years from a significant hemodynamic failure to a multi-organ disease in the course of which peripheral mechanisms such as dysregulated cardiorenal axis or inflammation also play essential roles. A few available observational studies investigating iron deficiency (ID) in patients hospitalized for AHF indicate that this comorbidity is more prevalent than in chronic heart failure, and iron status presents some dynamics in these subjects. ID in AHF predicts increased mortality, greater risk for early readmission and is related to prolonged hospitalization. This paper reviews the results of the first multicenter, double-blind, randomized clinical trial on ferric carboxymaltose in patients who were stabilized after an episode of AHF who had concomitant ID (AFFIRM-AHF), and potential pathophysiological links between dysregulated iron status and AHF syndromes are discussed. (Cardiol J 2021; 28, 6: 962–969)

Key words: acute heart failure, cardiac decompensation, iron deficiency, ferric carboxymaltose

Introduction

Acute heart failure (AHF) syndromes constitute one of the most frequent causes of hospitalization in the elderly and, analyzed in total, put a heavy financial burden on healthcare systems in developed countries [1–4]. Importantly, 30-day readmission rates exceed 25% in this patient population and it has been demonstrated that among these frequent early re-hospitalizations, a significant proportion will also be due to heart failure (HF) (recurrent episodes) [5]. From a clinical perspective, hospitalization due to AHF should always be considered a highly important adverse health event because such an episode represents the "inflection point" [6] in the natural history of the disease. The perception of AHF (in both observational and interventional trials overrepresented by the form of decompensation of pre-existing or de novo heart failure — ADHF) has evolved over the years from a hemodynamic failure (most frequently with fluid overload/congestion) to a multi-organ disease during which peripheral mechanisms such as dysregulated cardiorenal axis (acute "cardiorenal syndrome") or systemic (pro-)inflammation also play important pathophysiological roles [7, 8]. It needs to be acknowledged that the unsatisfactory results of randomized clinical trials (RCTs) investigating short- to mid-term effects of different intravenous (i.v.) vasodilators or cardiac calcitropes adminis-

Address for correspondence: Prof. Ewa A. Jankowska, MD, PhD, FESC, FHFA, Institute of Heart Diseases, Wroclaw Medical University, ul. Borowska 213, 50–556 Wrocław, Poland, tel: +48 71 736 42 52, e-mail: ewa.jankowska@umw.edu.pl

Received: 30.10.2021 Accepted: 28.11.2021 Early publication date: 9.12.2021

Table 1. Major large clinical trials investigating the impact of early pharmacological interventions in acute on "hard" clinical outcomes (morbidity and mortality).

Trial acronym, year of publication [reference number]	Population	Intervention and comparator	Outcomes analyzed and results
SURVIVE, 2007 [9]	1327 patients hospitalized with ADHF requiring inotrope agents	Levosimendan (inodilator/ /cardiac calcitrope) vs. dobutamine	All-cause mortality at 180 days; NS
ASCEND-HF, 2011 [10]	7141 patients with AHF	Nesiritide (vasodilator) or placebo for 24 to 168 h	Rate of re-hospitalization for HF or death from any cause within 30 days; NS
TRUE-AHF, 2017 [11]	2157 patients with AHF	Ularitide (vasodilator) or placebo for 48 h	CV death during a median follow-up of 15 months; NS
RELAX-AHF-2, 2019 [12]	6545 patients with AHF	48 h infusion of serelaxin (vasodilator) or placebo within 16 h after presentation	Death from CV causes at 180 days; NS, and worsening HF at 5 days; NS

AHF — acute heart failure; ADHF — acute decompensated heart failure; CV — cardiovascular; HF — heart failure; NS — not significant

tered in hospital to impact 'hard' clinical outcomes in AHF (Table 1) [9–12] have highlighted the need to search for other interventions than modulating cardiac inotropy, fluid (re-)distribution or vascular tone during the acute phase of the disease.

Indeed, available evidence from well-designed clinical trials in AHF implies that the concept of short but intensive support for cardiovascular hemodynamics presumably does not impact mid--to-long-term morbidity and mortality significantly in such patients. The only positive clinical trial in the broadly understood setting of AHF refers to subjects with acute decompensated heart failure (ADHF) and diabetes who were assigned early (before or shortly after discharge) to a chronic HF (CHF) drug sodium-glucose co-transporter 2 inhibitor (sotagliflozin) vs. placebo [13]. Therefore, there is still a need to test substances administered as a specific intervention for this acute state to improve outcomes. Moreover, it seems reasonable that a potential pharmaceutical should first act longer than in a hospital (ideally for weeks/ /months following one or a few easy administrations during the acute phase). Secondly, it is essential to target mechanisms involved in a complex AHF pathophysiology other than hemodynamics [14].

Iron deficiency in the setting of acute heart failure: Data from observational studies and evidence from clinical trials

Iron deficiency (ID), defined as reduced serum ferritin and/or transferrin saturation index (TSAT, serum iron divided by total iron-binding capacity), is highly prevalent in HF (in CHF it affects up to 50% patients) and worsens both symptoms and outcomes in these subjects independently of anemia [15–17]. There is evidence from multicenter, double-blind, RCTs (also aggregated in a few meta-analyses) that in patients with CHF with reduced to mid-range ejection fraction and concomitant ID (defined as serum ferritin < 100 μg/L or 100–299 μg/L if TSAT < 0.2) the administration of i.v. ferric carboxymaltose (FCM) improves exercise capacity, symptoms and the quality of life [18–21]. A few available observational studies investigating ID in patients hospitalized for AHF (Table 2) indicate that this comorbidity not only may even be more frequent in this clinical setting, but also iron status presents somewhat dynamics in AHF (Table 2) [16, 22–27].

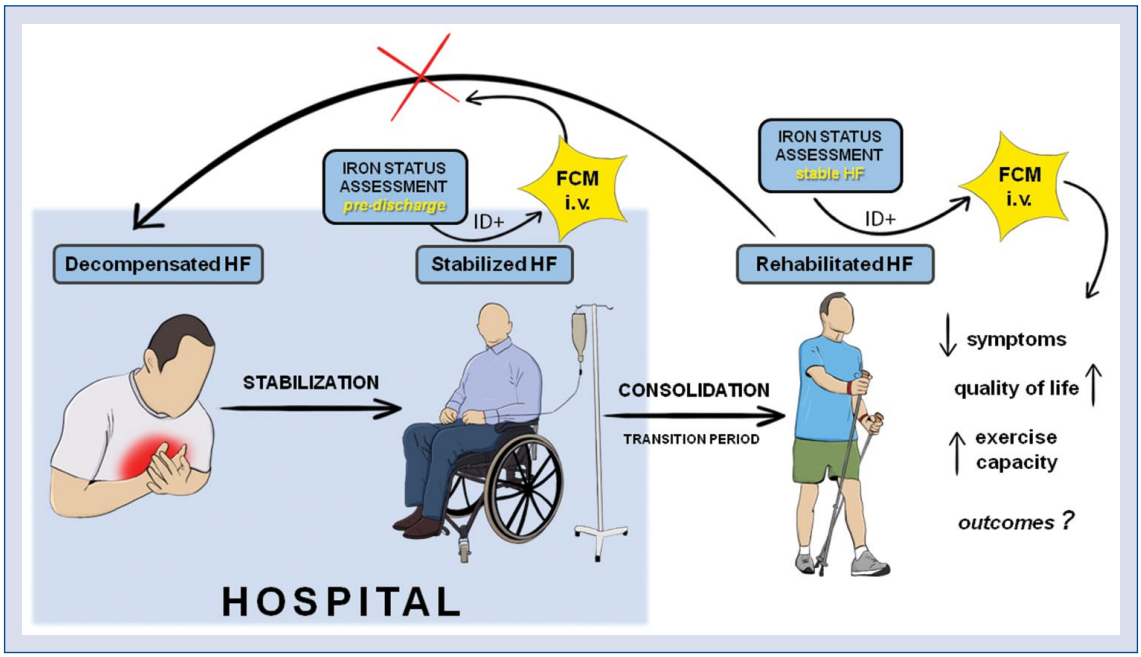
Not surprisingly, ID in patients with AHF predicted increased mortality, greater risk for early unplanned readmission, and prolonged in-hospital stay. Although there were attempts to define ID more precisely and pathophysiology-oriented in AHF [16], most observational studies on the prevalence of ID in AHF used classical iron biomarkers implemented from CHF — serum ferritin and TSAT. Regarding i.v. iron therapy in patients hospitalized for AHF, data was limited until recently. In one small RCT PRACTICE-ASIA-HF conducted in two centers in Singapore yielding a total number of 50 patients hospitalized due to ADHF, there was a trend towards greater distance in 6-minute walking test distance over the 12-week study period in subjects given a single-dose FCM pre-discharge compared to placebo, and the drug was well-tolerated [28].

AFFIRM-AHF trial (NCT02937454) was designed to investigate the effects of i.v. FCM on

Table 2. Summary of observational studies investigating the prevalence, clinical correlates and consequences of iron deficiency in patients with acute heart failure.

Number of study (chronologically)	Authors	Number of patients	Females	LVEF (%, mean ± SD unless otherwise stated)	Natriuretic peptides (median and interquartile range for NT-proBNP unless otherwise stated)	Definition of ID	Prevalence of ID	Prevalence of anemia	Clinical correlates of ID	Impact ID on outcomes
1	Jankowska et al., 2014 [16]	165	19%	33 ± 13	4800 (2471–8056) pg/mL	Serum ferritin < 100 μg/L or serum ferritin 100–299 μg/L with TSAT < 20% (standard definition)*	65%	37%	Peripheral edema, higher NT-proBNP, higher uric acid, anemia	↑ 12-month mortality
2	Cohen-Solal et al., 2014 [22]	832	51%	Preserved LVEF: 16% men, 36% women	Mean values for ID+: men 8933 pg/mL, women 8047 pg/mL	Standard definition	Men: 69% Women: 75%	60%	Men: anemia and antiplatelets Women: diabetes and low CRP	Not analyzed
3	Núñez et al., 2016 [23]	626	48%	Preserved LVEF: 52% of patients	3756 (1634–7566) pg/mL,	Standard definition	74%	54%	Dyslipidemia and diabetes, anemia, higher troponin T	↑ early readmissions (absolute ID)
4	Van Aelst et al., 2017 [24]	47	32%	39 ± 16	BNP: 1004 (652–1676) pg/mL	Standard definition	83% (on admission)	N/A	Soluble suppression of tumorigenicity 2, IL-6, galectin-3	Not analyzed
5	Beale et al., 2019 [25]	430	43%	48 ± 16	Mean ± SD: 3926 ± 6763 pg/mL	Serum ferritin < 100 μg/L or 100–200 μg/L with TSAT < 20%	HFrEF: 54% HFpEF: 56%	N/A	HFpEF: female, gender, COPD, CRP	↑ LOS (HFpEF)
6	Beattie et al., 2020 [26]	78 805 HF admissions were analyzed of which 91% were classified as emergency	ID/IDA: 34%	–	–	ICD-10 codes: D50.0, D50.8, D50.9, D64.9 (ID/IDA)	66%	N/A	–	↑ readmissions ↑ mortality ↑ LOS and costs
7	Jacob et al., 2020 [27]	221	61%	–	Mean ± SD: 5092 ± 6125 pg/mL	Standard definition	86%	30%	Female gender, anemia	No differences; 83% of patients with ID were treated with ferric carboxymaltose

*Additional definition of ID based on low serum hepcidin and high serum soluble transferrin receptor was applied in this study. BNP — B-type natriuretic peptide; CHF — chronic heart failure; CKD — chronic kidney disease; COPD — chronic obstructive pulmonary disease; CRP — C-reactive protein CV — cardiovascular; HF — heart failure; HFpEF — heart failure with preserved ejection fraction; HFrEF — heart failure with reduced ejection fraction; ID — iron deficiency; IDA — iron deficiency anemia; IL — interleukin; LOS — length of stay; LVEF — left ventricular ejection fraction; NT-proBNP — N-terminal prohormone of B-type natriuretic peptide; SD — standard deviation; TSAT — transferrin saturation; N/A — not available



Central illustration. Positioning and beneficial effects of intravenous (i.v.) ferric carboxymaltose (FCM) therapy in patients with heart failure (HF) and iron deficiency (ID) based on published randomized clinical trials.

morbidity and mortality in iron-deficient patients hospitalized for AHF [29]. In this multicenter, multinational, double-blind RCT, more than 1100 patients aged > 18 years who were hospitalized for AHF (with reduced or mildly reduced in-hospital left ventricular ejection fraction [LVEF], i.e. < 50%) and had ID detected during index hospitalization (standard definition implemented from nephrology through RCTs in stable HF based on serum ferritin and TSAT) were randomized before hospital discharge (after achieving clinical stabilization) in a 1:1 proportion to receive i.v. FCM or placebo for up to 24 weeks (dosing based on ID severity) [30]. The primary outcome in the trial was a composite of total hospitalizations for HF and cardiovascular death up to 52 weeks. Although the primary endpoint did not reach the statistical significance (293 primary events in FCM arm vs. 372 in the placebo group with a rate ratio [RR] of 0.79, 95% confidence interval [CI] 0.62–1.01, p = 0.059), there were fewer HF hospitalizations in an active treatment arm (217 total hospitalizations in FCM group vs. 294 in subjects assigned for placebo [RR 0.74; 95% CI 0.58–0.94, p = 0.013]) [30]. Notably, such therapy resulted in clinically meaningful beneficial effects on health-related quality of life (assessed using Kansas City Cardiomyopathy Questionnaire) as early as 4 weeks after the first dose of iron, lasting up to week 24 [31]. Additionally, based on a modeling methodology, it has been estimated that FCM is homogeneously cost-effective in patients with AHF in different countries characterized by variant healthcare system design [32]. Based on the results of the AFFIRM-AHF trial in the recently published 2021 European Society of Cardiology Guidelines for the diagnosis and treatment of AHF and CHF [33], the indications for i.v. iron supplementation with FCM have been extended beyond stable, CHF. Namely, such therapy should be considered in symptomatic HF patients with LVEF ≤ 50% and ID (guidelines recommend the definition based on serum ferritin and TSAT — see above) and recently hospitalized for HF to improve symptoms and reduce the risk of HF hospitalization — as an element of peri-discharge management (class or recommendation IIa, level of evidence B) [33]. The guidelines also emphasize the need to actively screen for ID and anemia in all subjects with HF by clearly recommending the assessment of iron parameters (ferritin and TSAT as well as hemoglobin concentration/complete blood count) regularly (class of recommendation I, level of evidence C) [33].

Acute heart failure and iron deficiency: Pathophysiological links

The concept of modulating adverse clinical trajectories after an episode of acute HF (Cen-

tral illustration) in terms of improving indices of morbidity and mortality by administering i.v. iron already in-hospital after clinical stabilization is based on a few (patho)physiological assumptions. There have also been discussions regarding, e.g., the appropriateness of the definition of ID in AHF borrowed from stable HF or the safety of such intense iron load in an acute setting.

Analogously to CHF, the exact mechanisms of clinical benefits of i.v. iron (FCM) after an episode of AHF are not fully elucidated. The one hypothesized mechanism is linked with the energetic hypothesis of AHF. It emphasizes the critical involvement of iron in energy generation within all types of cells/tissues. Indeed, the chemical properties of iron warrant its crucial role in comprehensive cellular energetics through effective mitochondrial respiration [34]. Apart from oxygen transportation and storage as the constituent of hemoglobin and myoglobin, iron is an element of two key groups of proteins involved in cellular energy production — hemoproteins (e.g., cytochromes), and non-heme iron-containing proteins such as citric acid cycle enzyme aconitase [35, 36]. Just as stable HF is associated with a chronic cardiac energetic dysfunction and/ /or deficit, AHF is characterized by a rapid energetic imbalance within the myocardial muscle. Chronic (stable) HF has long been associated with energetic disturbances within the heart as a muscle that is undeniably energetically demanding [37, 38]. The so-called "metabolic remodeling" of a chronically failing heart is visible functionally in terms of abnormal substrate utilization and impaired metabolism of high-energy phosphates and structurally through abnormal mitochondria that present with decreased biogenesis [39, 40]. For AHF, which is an acute and particularly dynamic process, less data is available, even experimental data. In one of the few available animal models of a pacing-induced decompensated HF, in dogs developing severe HF in this (patho)mechanism rapidly (within a few weeks), metabolic derangements were already observed in terms of substrate utilization shift in favor of glucose at the expense of free fatty acids [41]. Some information can also be obtained from hearts explanted during the orthotopic transplantation to treat refractory HF from life indications. The morpho-functional and energetic end-stage state of these organs reflects the acute phase of cardiac dysfunction in AHF/ADHF. For example, Leszek et al. [42] have demonstrated a notable reduction in left and right ventricular myocardial iron content in 33 explanted failing hearts compared to 11 non-failing organs.

Historically, depleted iron has been associated with anemia. However, experimental and clinical evidence shows that i.v. iron therapy in HF is about more than just elevating hemoglobin concentration. Moreover, this intervention exerts therapeutic effects longer than hours/days following its administration. It is worth noting that parenteral iron supplementation is simpler compared to infusion of vasoactive drugs/inotropes (requiring supervised and blood pressure-guided control of infusion in the setting of an acute cardiac care unit). Characteristics mentioned above of i.v. iron is known from clinical trials on FCM in stable HF with reduced ejection fraction (HFrEF) with concomitant ID. For example, in the CONFIRM-HF trial demonstrating sustained beneficial effects of FCM on functional capacity in subjects with HFrEF and ID during the 1-year study period, as much as over 75% of patients assigned for FCM required only 1–2 administrations of the study drug at week 0 and optionally at week 6 [19]. Importantly, FCM brings clinical benefits in HF patients with concomitant ID regardless of anemia [21]. How i.v. iron improves functional capacity in HF has not been fully elucidated (oral does not work due to poly-etiological low absorption). We have proposed an explanation that i.v. iron could improve the functioning of skeletal muscles [43–45]. Charles-Edwards et al. [46] have demonstrated in an interventional study that in iron-deficient CHF patients, iron repletion indeed can improve skeletal muscle energetics (assessed in vivo using phosphorus magnetic resonance spectroscopy). Still, it is unknown whether such a mechanism may play a role in the myocardial muscle.

Until recently, it was not unequivocally clear if the CHF definition of ID would be appropriate for AHF patients (whose iron status is dynamic to some extent, as mentioned previously) in terms of differentiating potential beneficiaries of i.v. iron therapy group vs. subjects not requiring i.v. iron. There were also some doubts whether the definition of ID in AHF could be firmly based on serum ferritin, an acute phase reactant protein, and whether ferritin-guided referral for i.v. iron (the threshold for ID: < 100 μg per litre or 100–299 with TSAT $< 20\%$) will be appropriate in AHF analogously to stable disease. The latter for cutoffs above were introduced based on nephrology expertise. Although not fully understood, hyperferritinemia in the course of inflammation (e.g. progressive bacterial infection leading to septic shock) is considered a protective mechanism through diverse immunomodulatory and anti-microbial effects [47].

There is no doubt that AHF is related to increased inflammatory processes within the organism. The roles of diverse circulating inflammatory biomarkers are still discussed for direct pathogenesis of acute myocardial dysfunction and the subsequent injury of other organs such as kidneys and lungs or liver [48]. The magnitude of systemic inflammation in the course of AHF is less expressed than, e.g., in sepsis. For example, in the sub-analysis of the ASCEND-HF trial investigating the effects of vasodilator nesiritide vs. placebo in more than 7 thousand patients hospitalized for AHF, it was demonstrated that high sensitivity C-reactive protein is significantly increased within the first days of index hospitalization, followed by the general decline through the first month after admission (median concentrations for baseline, 48–72 h, and 30-day follow-up: 12.6, 11.0, and 4.7 mg/L, respectively) [49]. Regardless of some doubts if CHF definition of ID will be valid for AHF subjects, another question arose if such therapy will be safe as in chronic, stable conditions. Cellular iron status is tightly controlled as cellular viability represents a U-shaped relationship with amounts of iron. Some authors express their doubts whether an intensive iron load is unequivocally safe in terms of potential overproduction of reactive oxygen species in particular tissues [50]. The results of the AFFIRM-AHF trial confirm the safety of FCM in patients hospitalized for AHF and add to our knowledge regarding clinical benefits of i.v. iron at different stages of the natural history of HF.

Conclusions

In the AFFIRM-AHF trial recruiting subjects with AHF and ID, there have been demonstrated treatment benefits of i.v. iron beyond what is known about the chronic stage of HF, namely the administration of FCM vs. placebo initiated pre-discharge has been shown to reduce the risk of HF hospitalizations. The exact mechanisms of how intravenous iron improves outcomes in this clinical setting are not fully understood. Further translational research is needed to elucidate the acute and long-term myocardial vs. peripheral effects of such therapy. The results of sufficiently powered (to assess the impact on morbidity and mortality) RCTs on i.v. iron in chronic HF with ID is awaited.

Conflict of interest: Wroclaw Medical University received an unrestricted grant from Vifor Pharma. Michał Tkaczyszyn reports personal fees from V-Wave Ltd., Eidos Therapeutics, Cytokinetics, Impulse Dynamics, outside the submitted work. Tomasz Skrzypczak and Jakub Michałowicz report no conflict of interest. Piotr Ponikowski reports grants, personal fees and other from Vifor Pharma; personal fees and other from Amgen, Bayer, Novartis, Abbott Vascular, Boehringer Ingelheim, Pfizer, Servier, AstraZeneca, Cibiem, BMS, Impulse Dynamics; personal fees from Berlin Chemie; and other from Cardiac Dimensions; outside the submitted work. Ewa A. Jankowska reports grants and personal fees from Vifor Pharma, Bayer, Novartis, Abbott, Boehringer Ingelheim, Pfizer, Servier, AstraZeneca, Berlin Chemie, Cardiac Dimensions, Takeda, Gedeon Richter, outside the submitted work. Both Piotr Ponikowski and Ewa A. Jankowska have been co-PIs in the AFFIRM-AHF trial sponsored by Vifor Pharma.

References

1. Krumholz HM, Parent EM, Tu N, et al. Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. Arch Intern Med. 1997; 157(1): 99–104, indexed in Pubmed: 8996046.
2. Chioncel O, Mebazaa A, Maggioni AP, et al. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. Eur J Heart Fail. 2017; 19(10): 1242–1254, doi: 10.1002/ejhf.890, indexed in Pubmed: 28463462.
3. Dharmarajan K, Hsieh A, Lin Z, et al. Diagnoses and timing of 30-day readmissions after hospitalization for heart failure, acute myocardial infarction, or pneumonia. JAMA. 2013; 309(4): 355, doi: 10.1001/jama.2012.216476.
4. Tymińska A, Ozierański K, Grabowski M, et al. Feasibility of sacubitril/valsartan initiation early after acute decompensated heart failure. Cardiol J. 2020; 27(5): 625–632, doi: 10.5603/CJ.a2020.0094, indexed in Pubmed: 32648251.
5. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. N Engl J Med. 2009; 360(14): 1418–1428, doi: 10.1056/NEJMsa0803563, indexed in Pubmed: 19339721.
6. Yancy CW. Acute heart failure: searching for a new evident truth. J Am Coll Cardiol. 2017; 69(11): 1420–1423, doi: 10.1016/j.jacc.2017.01.018, indexed in Pubmed: 28302293.
7. Cotter G, Felker GM, Adams KF, et al. The pathophysiology of acute heart failure--is it all about fluid accumulation? Am Heart J. 2008; 155(1): 9–18, doi: 10.1016/j.ahj.2006.02.038, indexed in Pubmed: 18082483.
8. Doehner W, Frenneaux M, Anker SD. Metabolic impairment in heart failure: the myocardial and systemic perspective. J Am Coll Cardiol. 2014; 64(13): 1388–1400, doi: 10.1016/j.jacc.2014.04.083, indexed in Pubmed: 25257642.
9. Mebazaa A, Nieminen MS, Packer M, et al. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. JAMA. 2007; 297(17): 1883–1891, doi: 10.1001/jama.297.17.1883, indexed in Pubmed: 17473298.
10. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure.

N Engl J Med. 2011; 365(1): 32–43, doi: 10.1056/NEJMoa1100171, indexed in Pubmed: 21732835.
11. Packer M, O'Connor C, McMurray JJV, et al. Effect of ularitide on cardiovascular mortality in acute heart failure. N Engl J Med. 2017; 376(20): 1956–1964, doi: 10.1056/NEJMoa1601895, indexed in Pubmed: 28402745.
12. Metra M, Teerlink JR, Cotter G, et al. Effects of serelaxin in patients with acute heart failure. N Engl J Med. 2019; 381(8): 716––726, doi: 10.1056/NEJMoa1801291, indexed in Pubmed: 31433919.
13. Bhatt D, Szarek M, Steg P, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med. 2021; 384(2): 117–128, doi: 10.1056/nejmoa2030183.
14. Njoroge JN, Teerlink JR. Pathophysiology and therapeutic approaches to acute decompensated heart failure. Circ Res. 2021; 128(10): 1468–1486, doi: 10.1161/CIRCRESAHA.121.318186, indexed in Pubmed: 33983837.
15. Jankowska EA, Rozentryt P, Witkowska A, et al. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. Eur Heart J. 2010; 31(15): 1872–1880, doi: 10.1093/eurheartj/ehq158, indexed in Pubmed: 20570952.
16. Jankowska EA, Kasztura M, Sokolski M, et al. Iron deficiency defined as depleted iron stores accompanied by unmet cellular iron requirements identifies patients at the highest risk of death after an episode of acute heart failure. Eur Heart J. 2014; 35(36): 2468–2476, doi: 10.1093/eurheartj/ehu235, indexed in Pubmed: 24927731.
17. Klip IT, Comin-Colet J, Voors AA, et al. Iron deficiency in chronic heart failure: an international pooled analysis. Am Heart J. 2013; 165(4): 575–582.e3, doi: 10.1016/j.ahj.2013.01.017, indexed in Pubmed: 23537975.
18. Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med. 2009; 361(25): 2436–2448, doi: 10.1056/NEJMoa0908355, indexed in Pubmed: 19920054.
19. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency†. Eur Heart J. 2015; 36(11): 657–668, doi: 10.1093/eurheartj/ehu385, indexed in Pubmed: 25176939.
20. van Veldhuisen DJ, Ponikowski P, van der Meer P, et al. Effect of ferric carboxymaltose on exercise capacity in patients with chronic heart failure and iron deficiency. Circulation. 2017; 136(15): 1374–1383, doi: 10.1161/CIRCULATIONAHA.117.027497, indexed in Pubmed: 28701470.
21. Jankowska EA, Tkaczyszyn M, Suchocki T, et al. Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials. Eur J Heart Fail. 2016; 18(7): 786–795, doi: 10.1002/ejhf.473, indexed in Pubmed: 26821594.
22. Cohen-Solal A, Damy T, Terbah M, et al. High prevalence of iron deficiency in patients with acute decompensated heart failure. Eur J Heart Fail. 2014; 16(9): 984–991, doi: 10.1002/ejhf.139, indexed in Pubmed: 25065368.
23. Núñez J, García-Blas S, Comín-Colet J, et al. Iron deficiency and risk of early readmission following a hospitalization for acute heart failure. Eur J Heart Fail. 2016; 18(7): 798–802, doi: 10.1002/ejhf.513, indexed in Pubmed: 27030541.
24. Van Aelst LNL, Abraham M, Sadoune M, et al. Iron status and inflammatory biomarkers in patients with acutely decompensated heart failure: early in-hospital phase and 30-day follow-up. Eur J Heart Fail. 2017; 19(8): 1075–1076, doi: 10.1002/ejhf.837, indexed in Pubmed: 28516737.
25. Beale A, Carballo D, Stirnemann J, et al. Iron deficiency in acute decompensated heart failure. J Clin Med. 2019; 8(10): 1569, doi: 10.3390/jcm8101569, indexed in Pubmed: 31581494.
26. Beattie JM, Khatib R, Phillips CJ, et al. Iron deficiency in 78 805 people admitted with heart failure across England: a retrospective cohort study. Open Heart. 2020; 7(1): e001153, doi: 10.1136/openhrt-2019-001153, indexed in Pubmed: 32201585.
27. Jacob J, Miró Ò, Ferre C, et al. Iron deficiency and safety of ferric carboxymaltose in patients with acute heart failure. AHF-ID study. Int J Clin Pract. 2020; 74(10): e13584, doi: 10.1111/ijcp.13584, indexed in Pubmed: 32533907.
28. Yeo TJ, Yeo PS, Hadi FA, et al. Single-dose intravenous iron in Southeast Asian heart failure patients: a pilot randomized placebo-controlled study (PRACTICE-ASIA-HF). ESC Heart Fail. 2018; 5(2): 344–353, doi: 10.1002/ehf2.12250, indexed in Pubmed: 29345426.
29. Ponikowski P, Kirwan BA, Anker SD, et al. Rationale and design of the AFFIRM-AHF trial: a randomised, double-blind, placebo-controlled trial comparing the effect of intravenous ferric carboxymaltose on hospitalisations and mortality in iron-deficient patients admitted for acute heart failure. Eur J Heart Fail. 2019; 21(12): 1651–1658, doi: 10.1002/ejhf.1710, indexed in Pubmed: 31883356.
30. Ponikowski P, Kirwan BA, Anker SD, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. Lancet. 2020; 396(10266): 1895–1904, doi: 10.1016/S0140-6736(20)32339-4, indexed in Pubmed: 33197395.
31. Jankowska EA, Kirwan BA, Kosiborod M, et al. The effect of intravenous ferric carboxymaltose on health-related quality of life in iron-deficient patients with acute heart failure: the results of the AFFIRM-AHF study. Eur Heart J. 2021 [Epub ahead of print]: 3011–3020, doi: 10.1093/eurheartj/ehab234, indexed in Pubmed: 34080008.
32. McEwan P, Ponikowski P, Davis JA, et al. Ferric carboxymaltose for the treatment of iron deficiency in heart failure: a multinational cost-effectiveness analysis utilising AFFIRM-AHF. Eur J Heart Fail. 2021; 23(10): 1687–1697, doi: 10.1002/ejhf.2270, indexed in Pubmed: 34191394.
33. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contributio. Eur Heart J. 2021; 42(36): 3599–726, doi: 10.1093/eurheartj/ehab368, indexed in Pubmed: 34447992.
34. Dev S, Babitt JL. Overview of iron metabolism in health and disease. Hemodial Int. 2017; 21 Suppl 1: S6–SS20, doi: 10.1111/hdi.12542, indexed in Pubmed: 28296010.
35. Cairo CW, Mirchev R, Golan DE. Cytoskeletal regulation couples LFA-1 conformational changes to receptor lateral mobility and clustering. Immunity. 2006; 25(2): 297–308, doi: 10.1016/j.immuni.2006.06.012, indexed in Pubmed: 16901728.
36. Ponka P. Cell biology of heme. Am J Med Sci. 1999; 318(4): 241–256, doi: 10.1097/00000441-199910000-00004, indexed in Pubmed: 10522552.
37. Mettauer B, Zoll J, Garnier A, et al. Heart failure: a model of cardiac and skeletal muscle energetic failure. Pflugers Arch. 2006; 452(6): 653–666, doi: 10.1007/s00424-006-0072-7, indexed in Pubmed: 16767467.

38. Neubauer S. The failing heart — an engine out of fuel. N Engl J Med. 2007; 356(11): 1140–1151, doi: 10.1056/NEJMra063052, indexed in Pubmed: 17360992.
39. Rosano GMc, Vitale C. Metabolic modulation of cardiac metabolism in heart failure. Card Fail Rev. 2018; 4(2): 99–103, doi: 10.15420/cfr.2018.18.2, indexed in Pubmed: 30206484.
40. Tuunanen H, Knuuti J. Metabolic remodelling in human heart failure. Cardiovasc Res. 2011; 90(2): 251–257, doi: 10.1093/cvr/cvr052, indexed in Pubmed: 21372005.
41. Recchia FA, McConnell PI, Bernstein RD, et al. Reduced nitric oxide production and altered myocardial metabolism during the decompensation of pacing-induced heart failure in the conscious dog. Circ Res. 1998; 83(10): 969–979, doi: 10.1161/01.res.83.10.969, indexed in Pubmed: 9815144.
42. Leszek P, Sochanowicz B, Szperl M, et al. Myocardial iron homeostasis in advanced chronic heart failure patients. Int J Cardiol. 2012; 159(1): 47–52, doi: 10.1016/j.ijcard.2011.08.006, indexed in Pubmed: 21899903.
43. Tkaczyszyn M, Drozd M, Węgrzynowska-Teodorczyk K, et al. Depleted iron stores are associated with inspiratory muscle weakness independently of skeletal muscle mass in men with systolic chronic heart failure. J Cachexia Sarcopenia Muscle. 2018; 9(3): 547–556, doi: 10.1002/jcsm.12282, indexed in Pubmed: 29573220.
44. Stugiewicz M, Tkaczyszyn M, Kasztura M, et al. The influence of iron deficiency on the functioning of skeletal muscles: experimental evidence and clinical implications. Eur J Heart Fail. 2016; 18(7): 762–773, doi: 10.1002/ejhf.467, indexed in Pubmed: 26800032.
45. Tkaczyszyn M, Comín-Colet J, Voors AA, et al. Iron deficiency contributes to resistance to endogenous erythropoietin in anaemic heart failure patients. Eur J Heart Fail. 2021; 23(10): 1677–1686, doi: 10.1002/ejhf.2253, indexed in Pubmed: 34050579.
46. Charles-Edwards G, Amaral N, Sleigh A, et al. Effect of iron isomaltoside on skeletal muscle energetics in patients with chronic heart failure and iron deficiency. Circulation. 2019; 139(21): 2386–2398, doi: 10.1161/CIRCULATIONAHA.118.038516, indexed in Pubmed: 30776909.
47. Kernan KF, Carcillo JA. Hyperferritinemia and inflammation. Int Immunol. 2017; 29(9): 401–409, doi: 10.1093/intimm/dxx031, indexed in Pubmed: 28541437.
48. Murphy SP, Kakkar R, McCarthy CP, et al. Inflammation in Heart Failure: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020; 75(11): 1324–1340, doi: 10.1016/j.jacc.2020.01.014, indexed in Pubmed: 32192660.
49. Kalogeropoulos AP, Tang WH, Hsu A, et al. High-sensitivity C-reactive protein in acute heart failure: insights from the ASCEND-HF trial. J Card Fail. 2014; 20(5): 319–326, doi: 10.1016/j.cardfail.2014.02.002, indexed in Pubmed: 24530944.
50. Ghafourian K, Chang HC, Ardehali H. Intravenous iron therapy in heart failure: a different perspective. Eur J Heart Fail. 2019; 21(6): 703–714, doi: 10.1002/ejhf.1434, indexed in Pubmed: 30884037.

VIA MEDICA

TECHNOLOGY NOTE

Cardiology Journal
2021, Vol. 28, No. 6, 970–972
DOI: 10.5603/CJ.a2021.0100

ISSN 1897–5593
eISSN 1898–018X

Remote proctoring for cryoballoon ablation of atrial fibrillation: A challenge or an opportunity in the COVID-19 era?

Andrzej Glowniak[1], Myroslav Petkanych[2], Katarzyna Wojewoda[1, 3], Vladimir Komiaty[4], Marcin Sudol[5], Oksana Dyomenko[6], Kamil Torres[7], Andrzej Wysokinski[1], Antonio Sorgente[8], Gian-Battista Chierchia[8], Carlo de Asmundis[8]

[1]Department of Cardiology, Medical University of Lublin, Poland
[2]Amosov National Institute of Cardiovascular Surgery, Kyiv, Ukraine
[3]Doctoral School, Medical University of Lublin, Poland
[4]Transcarpathian Regional Cardiology Clinic, Uzhhorod National University, Ukraine
[5]Medtronic Poland, Warsaw, Poland
[6]Medtronic Ukraine, Kyiv, Ukraine
[7]Medical Simulation Center, Medical University of Lublin, Poland
[8]Heart Rhythm Management Center, Postgraduate Program in Cardiac Electrophysiology and Pacing, Universitair Ziekenhuis Brussel-Vrije Universiteit Brussel, Brussels, Belgium

During the past year, the fast-spreading new coronavirus disease 2019 (COVID-19) [1] has led to the outbreak of a pandemic that has changed our lives. The increase in the overall mortality [2] results from the viral infection itself but also derives from the lack of access to vital medical treatments, and the health systems being utterly challenged by the worldwide pandemic. On top of this, social distancing and travel limitations have impeded the physical presence of proctors during innovative procedures in developing centers, reducing the spread of medical knowledge and patients' access to cutting-edge technologies.

The idea of telemedicine and remote proctoring emerged already in the pre-covid era [3], as a solution to uneven distribution of up-to-date medical treatments in the modern-day world. In cardiology, there are reports on successful teleproctored catheter-based atrial fibrillation (AF) ablations [4] and transcatheter aortic valve implantations [5]. However, to our knowledge, there are no reports on cryoballoon (CB) remote-proctored AF ablations. We believe that CB technology is perfectly suited to remote training thanks to its "single-shot" feature and reduced operator dependency compared with other AF ablation techniques.

At the beginning of the pandemic, a CB ablation proctor affiliated to the Department of Cardiology of the Medical University of Lublin, Poland (A.G.) was scheduled to visit the Cardiac Center in Uzhhorod, Zakarpattia Oblast, Ukraine, to provide expert support with the first-in-site CB AF ablation procedures. Considering the consecutive waves of the pandemic, we decided to perform the cases with the "remote-presence" technique [3]. To ensure maximum safety and effectiveness of the training, two main issues had to be addressed: the on-site presence of a skilled operator, and a high-quality, real-time audiovisual connection. The first issue was overcome by inviting an operator experienced in classic AF ablation from the Amosov National Institute of Cardiovascular Surgery in Kyiv, Ukraine (M.P.), who had no travel restrictions within Ukraine. The second was solved by arranging a pre-procedural "sham" (no patient-involved) remote ablation, which allowed

Address for correspondence: Andrzej Glowniak, MD, PhD, Department of Cardiology, Medical University of Lublin, ul. Jaczewskiego 8, 20–954 Lublin, Poland, tel/fax: +48 724 41 51, e-mail: andrzej.glowniak@gmail.com

Received: 20.06.2021 Accepted: 22.08.2021 Early publication date: 8.09.2021

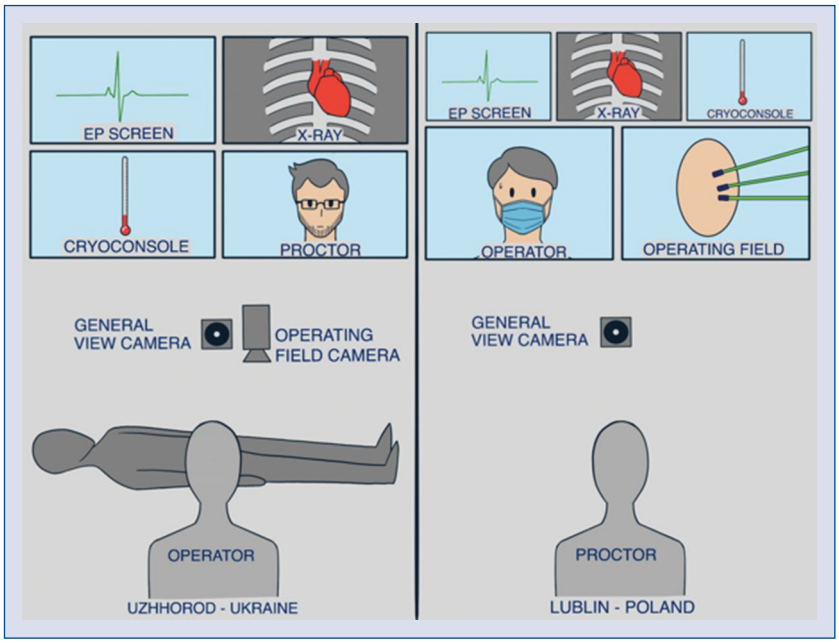


Figure 1. Visual transmission scheme between the operating room in Uzhhorod, Ukraine (**left panel**) and virtual operating room in the Medical Simulation Center in Lublin, Poland (**right panel**) with all live screens available to the operator and the proctor. Additional transmission of a high-definition operating field view is important to closely monitor all the operator's maneuvers.

us to test the audiovisual connection between the virtual operating room (vOR) in the Medical Simulation Center in Lublin (Poland) and the real operating room (rOR) in the Cardiology Clinic at Uzhhorod (Ukraine), separated by a distance of 400 km, which showed that we had a reliable high-resolution real-time audio-visual connection between the two centers. Dell™ (Dell Inc., US) and Apple™ portable computers (Apple Inc., US) together with compatible external camera-microphone units, smartphones (iPhone XS, Apple Inc, US), and a dedicated protected health information (PHI-secure) Zoom platform providing end-to-end 256-bit encryption (Zoom Video Communications Inc., US) with a backup Internet connection were used to ensure audio-visual communication. In the vOR in Poland, the transmitted images from the EP system (CardioLab, GE Prucka, US), fluoroscopy screen (Philips Healthcare, Amsterdam, Netherlands), cryoconsole (Medtronic, USA), and the operation site view were combined in one 60-inch high-resolution flat screen (LG Corp., South Korea) to provide the proctor with full audiovisual access to the procedure (Fig. 1). Three patients with paroxysmal symptomatic AF were recruited for remotely proctored CB ablation. The patient characteristics and procedural data are presented in Table 1. All CB-based pulmonary vein isolation procedures were performed in accordance with European Society of Cardiology guidelines [6], as thoroughly described previously [7, 8].

We present herein a first report on remote proctoring of CB-based AF ablations. The procedures were performed by an experienced point-by-point AF ablation operator under the remote guidance of an experienced cryoballoon ablation operator. All pulmonary veins were isolated, and there were no complications.

We believe that there are multiple advantages of a tele-proctoring approach. The most important is that it overcomes travel limitations and cuts travel expenditures [9], ensuring the access to novel cutting-edge procedures to virtually any place with access to a fast and reliable Internet connection [10]. Secondly, it eases the search for an available proctor. With fast Internet connection and readily available technical equipment, remotely-proctored services can be provided even by a quarantined physician, who otherwise would not be able to conduct any medical procedure — either on-site or remotely.

The key disadvantage of remote-presence-based teleproctoring is the lack of the physical presence of the proctor in the operating room. In the case of potential difficulties, he/she cannot take over the case with his/her own hands. This

Table 1. Patients' characteristics and procedural data of the remotely proctored cryoballoon ablations.

Patients' characteristics					
Patient	**Age**	**Sex**	**EHRA score**	**LA diameter [cm]**	**LVEF [%]**
1	55	Male	2b	4.5	63
2	48	Male	3	4.1	60
3	60	Male	2b	4.3	56
Procedural parameters					
Patient	**Procedure time [min]**	**LA dwell time [min]**	**Fluoro time [min]**	**Number of PVs isolated**	**Complications**
1	165	110	24	4/4	No
2	130	35	18	4/4	No
3	160	57	20	4/4	No

EHRA — European Heart Rhythm Association; LA — left atrium; LVEF — left ventricular ejection fraction; PVs — pulmonary veins

essential disadvantage can be, however, turned into an important benefit. Firstly, even with on-site proctoring for novel techniques, the trainee is usually a highly qualified operator, who should easily manage all procedure-related complications. Apparently, this is even more true with remote proctoring, which will result in the finest trainee preparation. Secondly, being aware of an attentive, yet not physically present proctor, and thus realizing that the procedure outcome depends literally on his/her own hands, the trainee might acquire the specific skills faster, which may result in a steeper learning curve. Our case series of remote monitoring of CB ablation demonstrates that teleproctoring in cardiac electrophysiology can be easily performed. However, its feasibility and safety are yet to be demonstrated, and further data are needed.

Conflict of interest: Andrzej Glowniak reports speaking and proctoring honoraria from Medtronic and Abbott; Marcin Sudol and Oksana Dyomenko are the Medtronic company employees; Gian-Battista Chierchia and Carlo de Asmundis reports speaker fees for Medtronic, Biotronik, Biosense Webster, Abbott, and proctoring honoraria from Medtronic. All other autors declare that they have no conflicts of interest.

References

1. Guan Wj, Ni Zy, Hu Yu, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020; 382(18): 1708–1720, doi: 10.1056/nejmoa2002032.
2. Cannatà A, Bromage DI, McDonagh TA. The collateral cardiovascular damage of COVID-19: only history will reveal the depth of the iceberg. Eur Heart J. 2021; 42(15): 1524–1527, doi: 10.1093/eurheartj/ehab097, indexed in Pubmed: 33624020.
3. Smith CD, Skandalakis JE. Remote presence proctoring by using a wireless remote-control videoconferencing system. Surg Innov. 2005; 12(2): 139–143, doi: 10.1177/155335060501200212, indexed in Pubmed: 16034503.
4. Shinoda Y, Sato A, Adach T, et al. Early clinical experience of radiofrequency catheter ablation using an audiovisual telesupport system. Heart Rhythm. 2020; 17(5 Pt B): 870–875, doi: 10.1016/j.hrthm.2020.01.018, indexed in Pubmed: 32354452.
5. Arslan F, Gerckens U. Virtual support for remote proctoring in TAVR during COVID-19. Catheter Cardiovasc Interv. 2021 [Epub ahead of print], doi: 10.1002/ccd.29504, indexed in Pubmed: 33527578.
6. Hindricks G, Potpara T, Dagres N, et al. ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021; 42(5): 373–498, doi: 10.1093/eurheartj/ehaa612, indexed in Pubmed: 32860505.
7. Reissmann B, Heeger CH, Opitz K, et al. Clinical outcomes of cryoballoon ablation for pulmonary vein isolation: Impact of intraprocedural heart rhythm. Cardiol J. 2020 [Epub ahead of print], doi: 10.5603/CJ.a2020.0147, indexed in Pubmed: 33140384.
8. Glowniak A, Tarkowski A, Fic P, et al. Second-generation cryoballoon ablation for recurrent atrial fibrillation after an index procedure with radiofrequency versus cryo: Different pulmonary vein reconnection patterns but similar long-term outcome-Results of a multicenter analysis. J Cardiovasc Electrophysiol. 2019; 30(7): 1005–1012, doi: 10.1111/jce.13938, indexed in Pubmed: 30938917.
9. Hollander JE, Carr BG. Virtually Perfect? Telemedicine for Covid-19. N Engl J Med. 2020; 382(18): 1679–1681, doi: 10.1056/NEJMp2003539, indexed in Pubmed: 32160451.
10. Goel SS, Greenbaum AB, Patel A, et al. Role of Teleproctoring in Challenging and Innovative Structural Interventions Amid the COVID-19 Pandemic and Beyond. JACC Cardiovasc Interv. 2020; 13(16): 1945–1948, doi: 10.1016/j.jcin.2020.04.013, indexed in Pubmed: 32819483.

VIA MEDICA

RESEARCH LETTER

Cardiology Journal
2021, Vol. 28, No. 6, 973–975
DOI: 10.5603/CJ.a2021.0102

ISSN 1897–5593
eISSN 1898–018X

Atrial fibrillation is related to higher mortality in COVID-19/SARS-CoV-2 pneumonia infection

Andrea Denegri[1], Marianna Morelli[2], Giuseppe Pezzuto[2], Vincenzo Livio Malavasi[1], Giuseppe Boriani[1]

[1]Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy
[2]Emergency Department, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy

Coronavirus disease 2019 (COVID-19) due to a novel coronavirus (CoV-2) has rapidly spread worldwide, with over 110,7 million cases and 2.4 million deaths have been reported globally as of February 25th, with 420,000 new cases and nearly 10,000 new deaths reported over the last 24 hours [1]. Cardiac involvement in COVID-19 patients has been described and associated with worse outcomes [2] and atrial fibrillation (AF) has been correlated with ventilator use and increased mortality [3]. The aim of the present study was to assess the impact of AF at admission on outcome in all-comer COVID-19 patients admitted to the Emergency Department of Modena University Hospital.

We retrospectively analyzed the patients diagnosed with COVID-19 pneumonia (symptoms, positive nasopharyngeal swab and typical radiological feature) admitted to the Emergency Department of Modena University Hospital from March the 16th to April the 15th 2020, after obtaining local EC approval. Clinical data, including outcome, were extracted from medical records. 12-lead ECGs with 25 mm/s and 1 mV/cm calibration and 0.05–150 Hz filter setting were recorded and analyzed off-line. Continuous variables were expressed as mean ± standard deviation while categorical data were expressed as absolute values and proportions. The Fisher exact test and the t-test or the Mann–Whitney U test were applied as appropriate. Survival curves were plotted using the Kaplan–Meier method with log-rank test and COX-regression model was applied. Analyses were performed with SPSS, Statistical Package for Social Science) software (v26, SPSS Inc., Chicago, IL, USA). For all the statistical analyses, a two tailed $p < 0.05$ was considered significant.

Atrial fibrillation patients (30/201, 14.9%) were older (78.5 ± 12.6 vs. 66.8 ± 14.4, $p < 0.001$), with a more complex cardiovascular history (hypertension [86.7% vs. 51.2%, $p < 0.001$], coronary artery disease [CAD, 46.7% vs 12.4%, $p < 0.001$], peripheral artery disease [20.0% vs. 5.9%, $p = 0.019$] and chronic kidney disease [CKD 30.0% vs. 10.1%, $p = 0.006$]) and positive myocardial injury markers (troponin I 1042.7 ± 4534.5 vs. 55.6 ± 172.3 ng/L). The mean CHA_2DS_2VASc score was 4.23 ± 1.71 vs. 2.27 ± 1.76, $p < 0.001$ (Fig. 1A). AF-patients presented a 5-fold higher risk of mortality (odds ratio [OR] 5.33, 95% confidence interval [CI] 2.34–12.17, $p < 0.001$), which rose 12-fold (OR 12.74, 95% CI 3.65–44.48, $p < 0.001$) for those with AF at 12-lead electrocardiogram (ECG) at admission. Patients with the highest CHA_2DS_2VASc score presented the highest rate of mortality (Fig. 1B). After adjustment for confounding factors such as age, sex, hypertension, CAD and CKD, AF was confirmed to be an independent predictor of all-cause mortality (hazard ratio 0.48, 95% CI 0.24–0.93, $p = 0.030$; Fig. 1C).

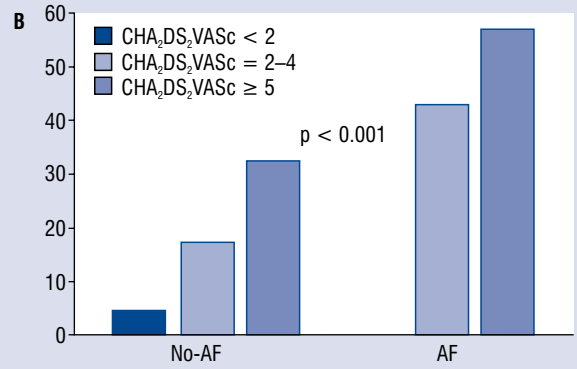
Electrocardiogram alterations, including AF, are quite common in COVID-19 infection and related to worse clinical outcome [4]. AF is detected in COVID-19 patients at 12-lead baseline ECG in up to one fifth of the cases [5]. Particularly, new-

Address for correspondence: Dr. Andrea Denegri, MD, PhD, FESC, Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Azienda Ospedaliero-Universitaria di Modena, Largo del Pozzo 71, 41125, Modena, Italy, tel: +393286574387, e-mail: denegri.andrea@aou.mo.it

Received: 28.02.2021 Accepted: 30.07.2021 Early publication date: 10.09.2021

A

	AF (n = 30)	No-AF (n = 171)	P value
Age	78.5 ± 12.6	66.8 ± 14.4	0.003
Female sex	40.0	35.1	0.681
Hypertension	86.7	51.2	< 0.001
Diabetes	33.3	15.9	0.038
CAD	46.7	12.4	< 0.001
PAD	20.0	5.9	0.019
CKD	30.0	10.1	0.006
SO_2	90.7 ± 5.3	93.1 ± 4.4	0.009
Troponin I	1042.7 ± 4534.3	55.6 ± 172.3	< 0.001



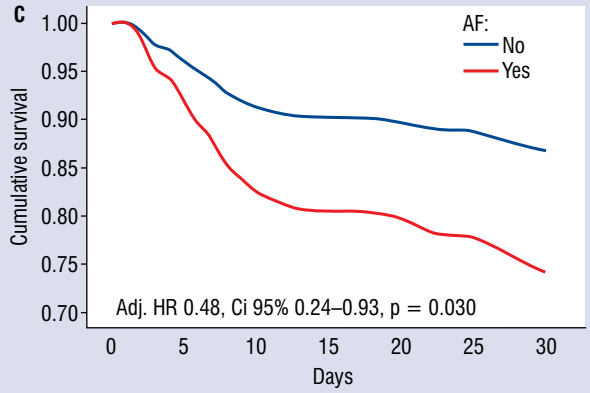


Figure 1. A. Baseline characteristics; **B.** 30-day mortality rate according to CHA_2DS_2VASc score in atrial fibrillation (AF)- and no-AF-patients; **C.** 30-day mortality according to presence/absence of AF after adjustment for age, sex, history of hypertension, coronary artery disease (CAD) and chronic kidney disease (CKD); PAD — peripheral artery disease; HR — hazard ratio; CI — confidence interval.

onset AF has been related to worse cardiovascular outcome [6]. These patients may benefit from a more intensive treatment for primary prevention of thrombo-embolic events, representing, among all cardiovascular-diseased COVID-19 patients, a high-risk group. Although further studies from larger population cohorts are required to assess the prognostic role of AF in COVID-19, these patients are potentially fragile and vulnerable, characterized by a higher risk of death, thus suitable for a careful clinical monitoring and more intensive treatment [7]. The CHA_2DS_2VASc score may be useful in further risk stratification of COVID-19 [8] and early identification of AF with routine ECG evaluation may be helpful in risk assessment and therapy approach individualization.

As of today, COVID-19 infection treatment is based on supportive therapies and mechanical ventilation. Despite our small cohort size, a higher 30-day mortality was observed in COVID-19 patients with AF at baseline 12-lead ECG; thus, routine ECG evaluation, in COVID-19 pneumonia, may be helpful in risk stratification and therapeutic approach targeting.

Conflict of interest: None declared

References

1. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200928-weekly-epi-update.pdf?sfvrsn=9e354665_6.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395(10223): 497–506, doi: 10.1016/s0140-6736(20)30183-5.
3. Elias P, Poterucha TJ, Jain SS, et al. The prognostic value of electrocardiogram at presentation to emergency department in patients with COVID-19. Mayo Clin Proc. 2020; 95(10): 2099–2109, doi: 10.1016/j.mayocp.2020.07.028, indexed in Pubmed: 33012341.
4. Denegri A, Pezzuto G, D'Arienzo M, et al. Clinical and electrocardiographic characteristics at admission of COVID-19/SARS-CoV2 pneumonia infection. Intern Emerg Med. 2021; 16(6): 1451–1456, doi: 10.1007/s11739-020-02578-8, indexed in Pubmed: 33398608.

5. Bertini M, Ferrari R, Guardigli G, et al. Electrocardiographic features of 431 consecutive, critically ill COVID-19 patients: an insight into the mechanisms of cardiac involvement. Europace. 2020; 22(12): 1848–1854, doi: 10.1093/europace/euaa258, indexed in Pubmed: 32944767.
6. Pardo Sanz A, Salido Tahoces L, Ortega Pérez R, et al. New-onset atrial fibrillation during COVID-19 infection predicts poor prognosis. Cardiol J. 2021; 28(1): 34–40, doi: 10.5603/CJ.a2020.0145, indexed in Pubmed: 33140386.
7. Sanchis-Gomar F, Perez-Quilis C, Lavie CJ. Should atrial fibrillation be considered a cardiovascular risk factor for a worse prognosis in COVID-19 patients? Eur Heart J. 2020; 41(32): 3092–3093, doi: 10.1093/eurheartj/ehaa509, indexed in Pubmed: 32688380.
8. Ruocco G, McCullough PA, Tecson KM, et al. Mortality risk assessment using CHA(2)DS(2)-VASc scores in patients hospitalized with coronavirus disease 2019 infection. Am J Cardiol. 2020; 137: 111–117, doi: 10.1016/j.amjcard.2020.09.029, indexed in Pubmed: 32991860.

VIA MEDICA

RESEARCH LETTER

Cardiology Journal
2021, Vol. 28, No. 6, 976–978
DOI: 10.5603/CJ.a2021.0139

ISSN 1897–5593
eISSN 1898–018X

Spectrum of lesions visualized in cardiac magnetic resonance imaging in COVID-19-related myocarditis: Findings from a pilot study of the TRICITY-CMR trial

Dagmara Wojtowicz[1]*, Karolina Dorniak[2]*, Marzena Ławrynowicz[1], Joanna Rejszel-Baranowska[1], Jadwiga Fijałkowska[3], Dorota Kulawiak-Gałąska[4], Edyta Szurowska[3], Marek Koziński[1]

[1]Department of Cardiology and Internal Diseases, Institute of Maritime and Tropical Medicine, Medical University of Gdansk, Gdynia, Poland
[2]Department of Noninvasive Cardiac Diagnostics, Medical University of Gdansk, University Clinical Center in Gdansk, Poland
[3]Department of Radiology II, Medical University of Gdansk, University Clinical Center in Gdansk, Poland
[4]Department of Radiology, Medical University of Gdansk, University Clinical Center in Gdansk, Poland

Myocardial injury with an elevated concentration of cardiac troponins is a prevalent condition associated with increased in-hospital mortality in patients with coronavirus disease-2019 (COVID-19) [1]. Myocarditis may be the underlying pathology in some patients with COVID-19-related myocardial injury. Additionally, a substantial proportion of patients who have recovered from COVID-19 pneumonia present with persistent symptoms indicating sustained cardiac involvement. Therefore, it is of major clinical importance to investigate the association between cardiac symptoms and possible myocardial lesions in post-COVID-19 patients.

Cardiac magnetic resonance (CMR) is considered the gold standard to assess cardiac morphology and function. Moreover, unlike other imaging modalities, it allows for detailed tissue characterization.

In this research letter, we report on the findings of a pilot study including patients with a history of recent COVID-19 pneumonia confirmed by a positive real-time polymerase chain reaction test and referred to our outpatient post-COVID-19 cardiology clinic. This paper is focused on types of lesions and their prevalence observed in CMR imaging. The TRICITY-CMR trial was designed as a prospective, cohort study including patients presenting with symptoms suggesting the involvement of the heart (e.g., chest pain, palpitations, dyspnea). In all the study participants, extracardiac etiology of symptoms seemed unlikely based on available test results. We excluded patients with any known previous cardiac pathology except essential hypertension as well as those with contraindications for CMR imaging. Clinical data and CMR imaging were analyzed. The study protocol was approved by the local ethics committee, and subsequently all patients provided informed written consent. Patients were recruited between December 2020 and March 2021. CMR was performed on a 1.5-T scanner (Magnetom Aera or Magnetom Sola, Siemens AG, Erlangen, Germany), and the protocol included standard long-axis and short-axis cine series for anatomy and functional assessment, followed by cardiac parametric mapping (MyoMaps, Siemens Healthineers, Erlangen, Germany) and late gadolinium enhancement (LGE) (free breathing phase-sensitive inversion recovery,

Address for correspondence: Dagmara Wojtowicz, MD, PhD, Department of Cardiology and Internal Diseases, Institute of Maritime and Tropical Medicine, Medical University of Gdansk, ul. Powstania Styczniowego 9B, 81–519 Gdynia, Poland, tel: +48 58 699 84 06, e-mail: dagmara.wojtowicz@gumed.edu.pl

Received: 14.05.2021 Accepted: 23.09.2021 Early publication date: 27.10.2021

*Equal contributors.

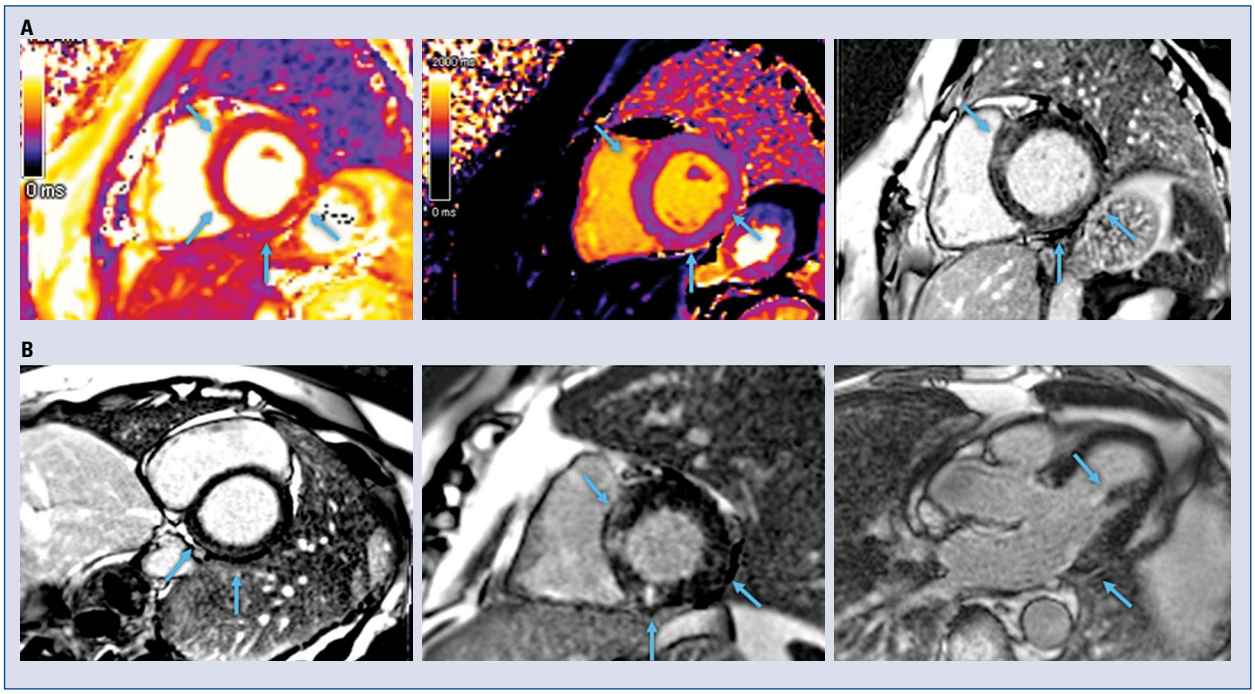


Figure 1. Typical lesions found in cardiac magnetic resonance examination in patients with a history of recent COVID-19 pneumonia and symptoms suggesting cardiac involvement. **A.** Locally (blue arrows) increased T2 (**left**) and T1 (**middle**) relaxation times pointing out areas of acute injury/ongoing inflammation, paralleled by subtle intramyocardial areas of irreversible damage (inflammatory necrosis/fibrosis) as shown by late gadolinium enhancement (LGE) (**right**) in a 63-year-old patient about 6 weeks post COVID-19 pneumonia. Global T2 relaxation time was 46 ms (the institutional reference range: 39–49 ms) with local (arrows) increase (segmental ROI average values T2 = 52 ms in the basal septal, T2 = 52 ms in the basal inferior, and 53 ms in the basal inferolateral segments). Global T1 value was 994 ms (the institutional reference range: 951–1035 ms) with local increase in the septum (1065 ms) as well as inferior (1050 ms) and inferolateral segments (1056 ms); **B.** Examples of LGE patterns in the study group (blue arrows); **Left**: Subtle subepicardial LGE in the basal inferior and/or inferolateral segment, representing the most common LGE pattern in our post-COVID cohort; **Middle**: Intramyocardial areas of LGE in the basal septal, inferior, and inferolateral segments; **Right**: Long-axis 3-chamber plane in the same patient, showing involvement of the basal inferolateral segment and the posterior papillary muscle.

motion-corrected [PSIR MOCO] sequence) for tissue characterization [2].

Fifty consecutive patients experiencing persistent cardiac symptoms after recovery from COVID-19 were included in the study. The mean age of patients was 47.3 ± 10.1 (range 27–69) years, and 40% (n = 20) were men. Most of the patients reported dyspnea (50%; n = 25) or fatigue (36%; n = 18) as the predominant complaint. Nearly one-third of the study participants (30%; n = 15) had a previous history of hypertension, and 14 (28%) individuals were obese. The mean time from the diagnosis of COVID-19 infection to the CMR examination was 51.5 ± 28.0 (range 11–113) days. Twenty-one (42%) study participants required hospitalization during the acute phase of COVID-19 infection. Among them, 15 (71%) required supplemental oxygen therapy, 5 (24%) received remdesivir, 15 (71%) steroids, and 3 (14%) were treated with convalescent plasma. Thirty-four (68%) patients were qualified as moderately ill and 16 (32%) as severely ill.

Cardiac involvement was confirmed by CMR in 30 (60%) patients. Reduced left ventricular (LV) systolic function according to institutional thresholds based on the literature [3] (i.e., LV ejection fraction < 57%) was found in 4 (8%) patients. None of the patients had reduced right ventricular (RV) systolic function (i.e., RV ejection fraction < 52% in men and < 51% in women) [3].

Late gadolinium enhancement was present in 30 (60%) patients. In this sub-group, 60% (n = 18) had at least 2-segment involvement. Three-segment involvement was seen in 4 (13%) cases and 3 (10%) patients had 4-segment involvement. Most LGE lesions were located at inferolateral (76%, n = 23) and inferior (43%, n = 13) segments at base. Additionally, among patients with LGE, in

2 cases markedly elevated native T1 and T2 values were shown, suggestive of ongoing myocardial inflammation. Small pericardial effusion was found in 1 patient. Figure 1 illustrates typical CMR findings noted in our patients.

Importantly, our study demonstrated abnormal CMR findings in the majority of symptomatic patients with recent COVID-19 pneumonia. The most common finding was LGE, predominantly located in the basal inferolateral or inferior segments. A relatively low prevalence of active myocardial inflammation with T1 and T2 myocardial mapping was revealed.

Our findings correspond with a previously reported high incidence of myocardial injury secondary to COVID-19 infection [1, 4]. Puntmann et al. [5], in their study of 100 unselected patients after recent COVID-19 pneumonia using CMR imaging, showed cardiac involvement in 78% of participants and ongoing myocardial inflammation in 60% of cases. These findings were independent of preexisting conditions, severity and overall course of acute illness, and time from the original diagnosis. Positive LGE with patterns typically occurring in myocarditis was described in prior case reports and observational studies in post-COVID-19 patients [5, 6]. It is worth emphasizing that the presence of LGE is considered a strong predictor of adverse clinical outcome [7]. Additionally, recent CMR mapping techniques enable quantitative detection of myocardial edema, inflammation, or diffuse fibrosis. In our study group, increased native T1 and T2 values suggestive of ongoing myocarditis were observed in 2 (4%) cases, similar to a previous report by Brito et al. [8] and in contrast with the aforementioned study by Puntmann et al. [5]. These apparent discrepancies in the literature should be analyzed with all due consideration regarding cohort characteristics (e.g., age, co-morbidities, disease severity, time from diagnosis). This also underlines the role of the parametric mapping sequences because they quantitatively assess ongoing inflammation and can shed light on the evolution of COVID-19-related myocardial injury. It should be emphasized, however, that mapping techniques are intrinsically complex and can be methodologically challenging. Therefore, to provide reliable insight, they must be utilized according to the guidelines, and institution-specific reference ranges should be established [9]. A prior study indicated that native T1 and myocardial extracellular volume values are independent risk factors of adverse clinical outcomes in dilated cardiomyopathy [10].

The results of this pilot study indicate the necessity of continued cardiological evaluation of patients with persistent symptoms of possible cardiac origin after recovery from COVID-19 pneumonia. Our findings confirm that persistence of cardiac symptoms after COVID-19 recovery may be related to the heart involvement. Future research is needed to determine the potential clinical significance of CMR findings observed in post-COVID-19 patients.

Conflict of interest: None declared

References

1. Shi S, Qin Mu, Shen Bo, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in wuhan, china. JAMA Cardiol. 2020; 5(7): 802–810, doi: 10.1001/jamacardio.2020.0950, indexed in Pubmed: 32211816.
2. Kellman P, Arai AE. Cardiac imaging techniques for physicians: late enhancement. J Magn Reson Imaging. 2012; 36(3): 529–542, doi: 10.1002/jmri.23605, indexed in Pubmed: 22903654.
3. Kawel-Boehm N, Maceira A, Valsangiacomo-Buechel ER, et al. Normal values for cardiovascular magnetic resonance in adults and children. J Cardiovasc Magn Reson. 2015; 17: 29, doi: 10.1186/s12968-015-0111-7, indexed in Pubmed: 25928314.
4. Inciardi RM, Lupi L, Zaccone G, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020; 5(7): 819–824, doi: 10.1001/jamacardio.2020.1096, indexed in Pubmed: 32219357.
5. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020; 5(11): 1265–1273, doi: 10.1001/jamacardio.2020.3557, indexed in Pubmed: 32730619.
6. Gravinay P, Issa N, Girard D, et al. CMR and serology to diagnose COVID-19 infection with primary cardiac involvement. Eur Heart J Cardiovasc Imaging. 2021; 22(1): 133, doi: 10.1093/ehjci/jeaa169, indexed in Pubmed: 32556106.
7. Becker MAJ, Cornel JH, van de Ven PM, et al. The prognostic value of late gadolinium-enhanced cardiac magnetic resonance imaging in Nonischemic dilated cardiomyopathy: a review and meta-analysis. JACC Cardiovasc Imaging. 2018; 11(9): 1274–1284, doi: 10.1016/j.jcmg.2018.03.006, indexed in Pubmed: 29680351.
8. Brito D, Meester S, Yanamala N, et al. High prevalence of pericardial involvement in college student athletes recovering from COVID-19. JACC Cardiovasc Imaging. 2021; 14(3): 541–555, doi: 10.1016/j.jcmg.2020.10.023, indexed in Pubmed: 33223496.
9. Messroghli DR, Moon JC, Ferreira VM, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). J Cardiovasc Magn Reson. 2017; 19(1): 75, doi: 10.1186/s12968-017-0389-8, indexed in Pubmed: 28992817.
10. Barison A, Del Torto A, Chiappino S, et al. Prognostic significance of myocardial extracellular volume fraction in nonischaemic dilated cardiomyopathy. J Cardiovasc Med (Hagerstown). 2015; 16(10): 681–687, doi: 10.2459/JCM.0000000000000275, indexed in Pubmed: 26090916.

VIA MEDICA

RESEARCH LETTER

Cardiology Journal
2021, Vol. 28, No. 6, 979–982
DOI: 10.5603/CJ.a2021.0138

ISSN 1897–5593
eISSN 1898–018X

Successful treatment of severe COVID-19 pneumonia with tocilizumab: A series of three cases

Joanna Chochoł-Labun[1], Renata Wachnicka-Truty[1], Małgorzata Sinica-Latecka[1], Katarzyna Sikorska[2], Marek Koziński[1]

[1]Department of Cardiology and Internal Diseases, Institute of Maritime and Tropical Medicine, Medical University of Gdansk, Gdynia, Poland

[2]Department of Tropical and Parasitic Diseases, Institute of Maritime and Tropical Medicine, Medical University of Gdansk, Gdynia, Poland

Severe coronavirus disease 2019 (COVID-19) pneumonia associated with cytokine storm remains a challenge for clinicians. It is usually complicated by multiple organ dysfunction and despite optimal contemporary therapy leads to high mortality.

In this research letter, we present 3 consecutive patients with severe COVID-19 pneumonia who between January and March 2021 were successfully treated with tocilizumab (a humanized antibody to the soluble interleukin-6 [IL-6] receptor) added to the standard therapy. This treatment was approved by the local ethics committee and subsequently all patients provided an informed written consent. On admission, all patients were moderately/severely ill with predominant respiratory failure and markedly elevated C-reactive protein (CRP) concentration (Table 1). Therapy with tocilizumab was initiated on day 1 in 2 patients and on day 6 in the 3rd one when he developed respiratory collapse requiring high flow oxygen therapy. All patients received two doses of tocilizumab and then their CRP concentration dropped on average by 71%. Following administration of tocilizumab combined with best known therapy, all patients were slowly and continuously improving. They all were discharged home in a relatively good condition and at a short-term follow-up are mildly symptomatic or asymptomatic.

The decision to use tocilizumab was based on the promising results of randomized clinical trials (RCTs) published since March 2020 [1–10]. The largest and most recent study with the most spectacular outcomes is the RECOVERY trial [1]. When we treated our patients its results have only been published as a preprint. This trial included 4,116 participants receiving invasive ventilation (14%), non-invasive ventilation (41%) or usual oxygen therapy (45%). All enrolled patients had oxygen saturation < 92% and CRP concentration > 75 mg/dL. Median CRP in the RECOVERY trial was 143 [interquartile range 107–204] mg/L which is similar to our patients. Additionally, 82% of patients in the REVOVERY trial received systemic corticosteroids at randomization. The primary endpoint (all-cause 28-day mortality) was substantially reduced in the tocilizumab on top of standard care vs. standard care alone group (29% vs. 33%, p = 0.007), with consistent results in all predefined subgroups. Significant reductions in terms of secondary endpoints were also achieved in tocilizumab-treated patients (discharge from hospital alive within 28 days [54% vs. 47%], composite outcome of invasive mechanical ventilation or death [33% vs. 38%] and use of hemodialysis or hemofiltration [5% vs 7%]). Tocilizumab benefits were observed regardless of the level of respiratory support and were additional to the benefits of systemic corticosteroids, another class of anti-inflammatory agents. Also, the results of two moderate size RCTs indicated clinical benefits of tocilizumab. In the REMAP-CAP trial conducted in critically ill patients with COVID-19 pneumonia receiving organ support in

Address for correspondence: Prof. Marek Koziński, MD, PhD, FESC, Department of Cardiology and Internal Diseases, Institute of Maritime and Tropical Medicine, Medical University of Gdansk, ul. Powstania Styczniowego 9B, 81–519 Gdynia, Poland, tel: +48 58 699 84 06, e-mail: marek.kozinski@gumed.edu.pl

Received: 6.04.2021 Accepted: 10.10.2021 Early publication date: 27.10.2021

Table 1. Characteristics of patients with severe COVID-19 pneumonia and respiratory failure treated with tocilizumab.

	Patient 1	Patient 2	Patient 3
Demographic data			
Age [years]	61	61	70
Gender	Male	Female	Male
Clinical characteristics and course, including respiratory status and support			
Body mass index [kg/m^2]	25	34	27
Comorbidities	Bronchial asthma, acute kidney injury (stage 1 according to KDIGO)	Hypertension, paroxysmal atrial fibrillation, history of pulmonary embolism, bronchial asthma, status post colon cancer surgery	Type 2 diabetes mellitus, diabetic neuropathy
Duration of symptom onset to hospital admission [days]	7	7	12
Clinical status on 7 level ordinal scale on hospital admission	4	4	4
Extent of the involved lung tissue on CT [%]	27*	78	75
Oxygen saturation on admission [%]	90 then deterioration to 75 on day 3	80	70
Minimal arterial pO_2 [mmHg]	49.5	45.1	50.3
Respiratory support	High flow oxygen through a nasal cannula [up to 60 L/min through 16 days]	Supplemental oxygen through a face mask [up to 17 L/min through 11 days]	Supplemental oxygen through a face mask [up to 17 L/min through 10 days]
Blood culture	All negative (obtained twice in all patients)		
Laboratory measurements on hospital admission			
Lymphocyte count [G/L]	0.35	0.75	0.95
CRP concentration [mg/L]	137.1	209.7	169
Procalcitonin concentration [ng/mL]	0.28	0.2	0.22
D-dimer concentration [ng/mL]	35200	768	Not available
Creatinine concentration [mg/dL]	1.44 (after patient hydration a decrease to 0.83)	0.94	0.94
Lactate dehydrogenase activity [U/L]	720	454	Not available
Cardiac troponin T	Negative	Mildly elevated (0.055 ng/L)	Negative
Pharmacotherapy during hospitalization			
Treatment with dexamethasone	Yes (6 mg IV once daily)	Yes (6 mg IV once daily)	Yes (6 mg IV once daily)
Treatment with remdesivir	Yes (initiated on day 3)	Yes (initiated on day 3)	Yes (initiated on day 1)
Anticoagulation	Prophylactic dose of enoxaparin	Rivaroxaban 20 mg/day	Prophylactic dose of enoxaparin
Treatment with tocilizumab	Initiated on day 6 at the dose of 600 mg IV which was repeated on day 7	Initiated on day 1 at the dose of 720 mg IV which was repeated on day 2	Initiated on day 2 at the dose of 640 mg IV which was repeated on day 3
Effect of tocilizumab administration on CRP concentration	After 2nd dose a decrease from 137 to 56 mg/L on the 2nd day	After 2nd dose a decrease from 209 to 40 mg/L on the 3rd day	After 2nd dose a decrease from 169 to 58 mg/L on the 3rd day

→

Table 1 (cont.). Characteristics of patients with severe COVID-19 pneumonia and respiratory failure treated with tocilizumab.

	Patient 1	Patient 2	Patient 3
Antibiotic therapy	Ceftriaxone initiated on admission then on day 2 changed for piperacillin/ /tazobactam then on day 8 changed for meropenem for 7 days	Ceftriaxone initiated on admission and continued for 10 days	Ceftriaxone initiated on admission and continued for 10 days
Hospital discharge and follow-up			
Length of hospitalization [days]	28	13	14
Clinical status at the end of hospitalization	Discharged in a relatively good condition with the need of temporal low flow oxygen supplementation at home		
Length of follow-up [days]	53	26	31
Clinical status at the end of follow-up	Fully recovered without any respiratory failure	The need of temporary low flow oxygen supplementation at home	

*No control CT was performed after deterioration of the respiratory status as the patients was treated with high flow oxygen therapy and we were not able to transport him safely without tracheal intubation; CRP — C-reactive protein; CT — computed tomography; KDIGO — Kidney Disease: Improving Outcomes; pO_2 — partial pressure of oxygen; SpO_2 — oxygen saturation

intensive care units, treatment with the IL-6 receptor antagonist (tocilizumab [n = 353] or sarilumab [n = 48]) when compared with the control group (n = 402) improved clinical outcomes, including 90-day survival [2]. Similarly, the EMPACTA trial demonstrated superiority of tocilizumab (n = 249) over placebo (n = 128) on the primary composite endpoint of mechanical ventilation or death by day 28, but without any improvement in mortality [3]. This study included only patients who did not require mechanical ventilation at randomization. Importantly, several small/moderate size (all largely underpowered for assessment of hard clinical endpoints) RCTs indicated a neutral effect of tocilizumab on clinical outcomes [4–7], with some minor benefits seen in the CORIMUNO-19 study [5]. On the other hand, the TOCIBRAS trial was stopped early after inclusion of 129 participants due to a signal of increased mortality at 15 days related to tocilizumab therapy (11/65 [17%] vs. 2/64 [3%]) [8]. This finding may be simply due to chance, considering the very low mortality in the standard care alone group. In all of the RCTs discussed above, adverse events were not more frequent in the tocilizumab vs. placebo/standard care group [1–8]. Finally, an updated meta-analysis of all available RCTs performed by the ROCOVERY investigators shows all-cause mortality benefit in patients hospitalized for COVID-19 pneumonia and treated with tocilizumab added to usual care when compared with the usual care alone group (relative risk 0.87; 95% confidence interval 0.79–0.96; p = 0.005), with a substantial heterogeneity among the included trials [1]. Furthermore, it is suggested that tocilizumab may exert an additive beneficial effect in remdesivir-treated patients [9], as was used in the present case series.

Based on the totality of the research evidence [10] and our clinical experience, we believe that tocilizumab is well tolerated and may be beneficial on top of standard therapy if early initiated in patients with COVID-19 pneumonia and both enhanced inflammatory response and a large extent of the involved lung tissue. However, further RCTs are necessary to define best tocilizumab responders.

Conflict of interest: None declared

References

1. Abani O, Abbas A, Abbas F, et al. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021; 397(10285): 1637–1645, doi: 10.1016/s0140-6736(21)00676-0, indexed in Pubmed: 33933206.
2. Gordon AC, Mouncey PR, Al-Beidh F, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. N Engl J Med. 2021; 384(16): 1491–1502, doi: 10.1056/NEJMoa2100433, indexed in Pubmed: 33631065.
3. Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with Covid-19 pneumonia. N Engl J Med. 2021; 384(1): 20–30, doi: 10.1056/NEJMoa2030340, indexed in Pubmed: 33332779.
4. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. N Engl J Med. 2020; 383(24): 2333–2344, doi: 10.1056/NEJMoa2028836, indexed in Pubmed: 33085857.

5. Hermine O, Mariette X, Tharaux PL, et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. JAMA Intern Med. 2021; 181(1): 32–40, doi: 10.1001/jamainternmed.2020.6820, indexed in Pubmed: 33080017.
6. Rosas IO, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with severe Covid-19 pneumonia. N Engl J Med. 2021; 384(16): 1503––1516, doi: 10.1056/NEJMoa2028700, indexed in Pubmed: 33631066.
7. Salvarani C, Dolci G, Massari M, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. JAMA Intern Med. 2021; 181(1): 24–31, doi: 10.1001/jamainternmed.2020.6615, indexed in Pubmed: 33080005.
8. Veiga VC, Prats JA, Farias DLC, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ. 2021; 372: n84, doi: 10.1136/bmj.n84, indexed in Pubmed: 33472855.
9. Akinosoglou K, Velissaris D, Ziazias D, et al. Remdesivir and tocilizumab: Mix or match. J Med Virol. 2021; 93(1): 56–58, doi: 10.1002/jmv.26117, indexed in Pubmed: 32492200.
10. Ghosn L, Chaimani A, Evrenoglou T, et al. Interleukin-6 blocking agents for treating COVID-19: a living systematic review. Cochrane Database Syst Rev. 2021; 3: CD013881, doi: 10.1002/14651858.CD013881, indexed in Pubmed: 33734435.

VIA MEDICA

RESEARCH LETTER

Cardiology Journal
2021, Vol. 28, No. 6, 983–985
DOI: 10.5603/CJ.a2021.0062

ISSN 1897–5593
eISSN 1898–018X

Left atrial and left atrial appendage remodeling after transcatheter aortic valve replacement: Preliminary results

Tian-Yuan Xiong[1, 2], Fei Chen[1], Yi-Jian Li[1], Yuan Feng[1], Mao Chen[1]

[1]Department of Cardiology, West China Hospital, Sichuan University, Chengdu, PR China
[2]State Key Lab of Hydraulics and Mountain River Engineering, Sichuan University, Chengdu, PR China

Atrial fibrillation (AF) is a common comorbidity in transcatheter aortic valve replacement (TAVR) recipients. The reported incidence of pre-existing AF in this patient population ranges from 34% to 49%, while new-onset AF after TAVR is also not rare (6.8–8.6%). Both carries with an increased risk of mortality and stroke [1]. It is recognized that the assessment of the left atrial (LA) and left atrial appendage (LAA) anatomy and function has important prognostic implications in AF and the risk of stroke [2]. The relief from pressure overload by TAVR might help in reverse remodeling of LA and LAA, but no study to date has evaluated the sequential change of these structures post-TAVR. Such information should be of interest as bias exists when diagnosing new-onset AF by ambulatory electrocardiogram or the ICD-9 code during any re-hospitalization. Thus, the present study sought to report our preliminary results on the 1-year volume changes of LA and LAA post-TAVR.

The volume of LA and LAA were retrospectively assessed, LAA morphology and take-off position in 43 consecutive TAVR recipients due to symptomatic severe aortic stenosis from multislice computed tomography (MSCT) performed pre-procedurally (referred to as pre-TAVR), post-procedurally before discharge (referred to as in-hospital) and 1-year post-TAVR. This study was approved by the institutional review board. Written informed consent were obtained from all patients.

Acquisition and reconstruction of MSCT scans in the documented center have been described previously [3]. Mimics 21.0 (Materialise NV, Leuven, Belgium) was used to perform three-dimensional reconstruction, segmentation and volume calculation of LA and LAA in systole as previously described [4]. LAA morphology was classified into chicken-wing (CW) and non-CW type [5]. LAA positions were classified based on the superior aspect of the LAA orifice with that of the left superior pulmonary vein orifice as high, middle, or low [5]. Reverse remodeling was defined as an absolute change in volume, while discordant remodeling was defined as an increase in LAA volume but a decrease in LA volume or vice versa. Baseline characteristics and follow-up data were extracted from a dedicated database.

Continuous variables were presented as mean ± standard deviation or median (interquartile range) as appropriate. Comparisons of volume change at the three points in time were carried by the Friedman M test and followed by post-hoc pairwise multiple comparisons. Intra- and inter-observer reliability in measuring LA and LAA volume were assessed in 10 randomly selected patients from the cohort with intraclass correlation coefficient (ICC). All computations relied on commercially available software (SPSS IBMS v21; SPPS Inc., Chicago, USA), with statistical significance set at two-tailed 0.05.

The mean age of this cohort was 73.9 ± 6.4 years. Female patients accounted for 41.9% of this cohort. Procedural success was achieved in all patients. A total of 7 (16.3%) patients were documented with pre-existing AF. CW-type LAA was identified in 37 (86.0%) patients. There were 4.6%, 51.2% and 44.2% of patients with a high, mid and low take-off of LAA, respectively. The volume of LA decreased continuously during 1-year follow-up (pre-TAVR vs. in-hospital vs. 1 year: 122.0

Address for correspondence: Prof. Mao Chen, Department of Cardiology, West China Hospital, Sichuan University, #37 Guoxue Alley, Chengdu, 610041, PR China, tel: 86-28-85423362, fax: 86-28-85423170, e-mail: hmaochen@vip.sina.com

Received: 16.12.2020 Accepted: 6.06.2021 Early publication date: 16.06.2021

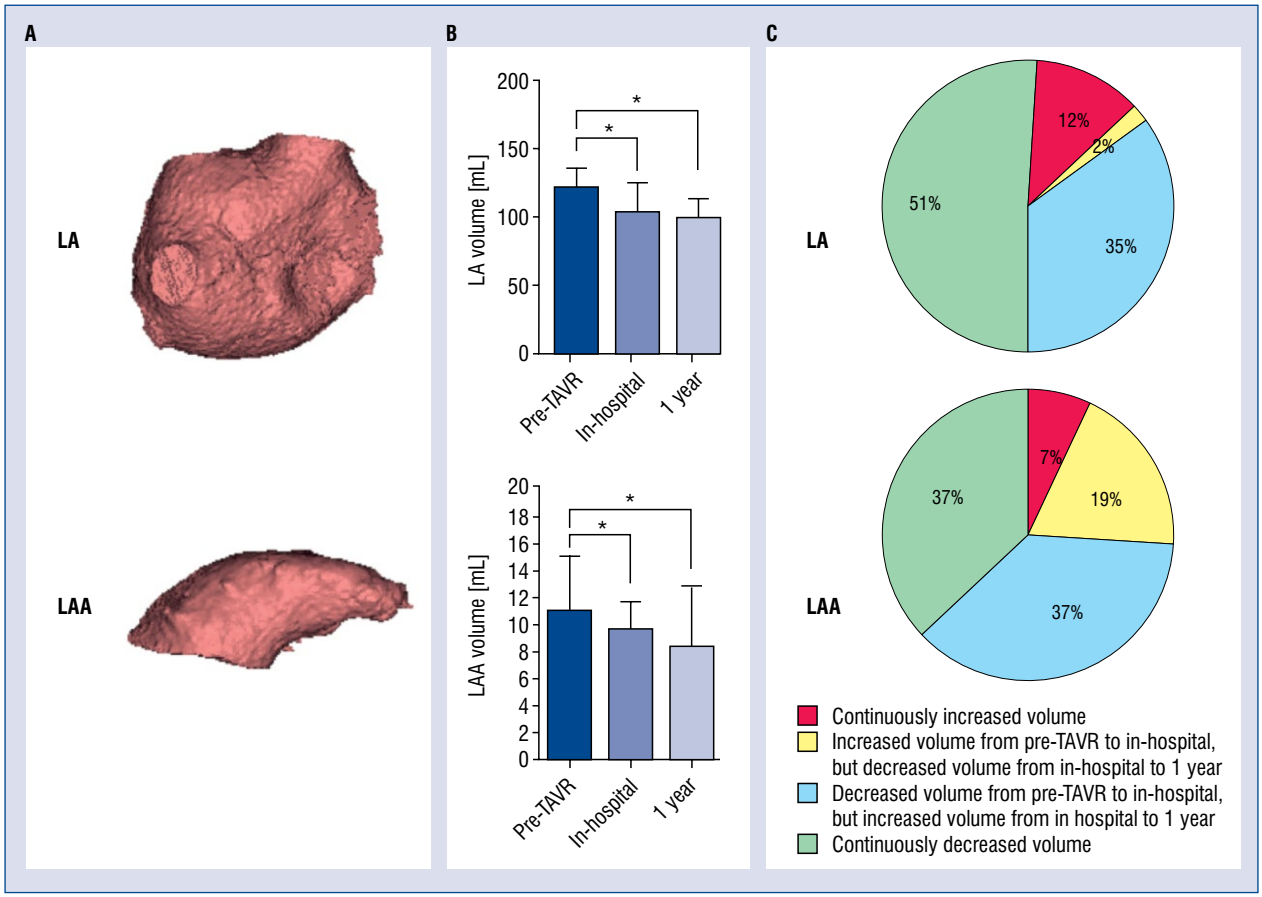


Figure 1. Left atrium (LA) and left atrial appendage (LAA) remodeling pattern post-transcatheter aortic valve replacement (TAVR); **A.** Three-dimensional segmentation of LA and LAA; **B.** Serial changes of volumes of LA and LAA during 1-year follow-up post-TAVR;*Stands for reaching statistical significance in post-hoc multiple comparisons; **C.** The distribution of different patterns of volume change in the LA and LAA post-TAVR.

[44.1] mL vs. 104.5 [43.1] mL vs. 100.7 [33.6] mL, $p < 0.001$), so did the volume of LAA (pre-TAVR vs. in-hospital vs. 1 year: 11.0 [6.8] mL vs. 9.7 [4.6] mL vs. 8.4 [6.3] mL, $p = 0.001$; Fig. 1). In post-hoc multiple comparisons, statistically significant differences in volume was detected between pre-TAVR and in-hospital, but not between in-hospital and 1 year (Fig. 1). On an individual level, the proportion of patients who experienced a continuous decrease in LAA volume was numerically smaller than that for LA volume (37.2% vs. 51.2%, $p = 0.19$; Fig. 1, illustrating the distribution of 4 different patterns of volume change). A total of 10 (23.3%) patients showed discordant remodeling between LA and LAA from pre-TAVR to in-hospital, while the number was 17 (39.5%) from in-hospital to 1 year. At 1 year, a reverse remodeling from pre-TAVR was achieved in 70% and 72% of patients for LA and LAA, respectively.

Intra-observer reliability was excellent for both LAA and LA volume (ICC 0.98, 95% confidence interval [CI] 0.93–0.99; ICC 0.99, 95% CI 0.97–0.99). Inter-observer reliability was good to excellent for LAA volume (ICC 0.94, 95% CI 0.78–0.99) and excellent for LA volume (ICC 0.99, 95% CI 0.91–0.99).

The major finding of this study was that TAVR in general brought reverse remodeling of LA and LAA. A more pronounced decrease was seen in a short period before discharge than during the post-discharge 1-year follow-up. This is consistent with a previous study with echocardiography in patients receiving surgical aortic valve replacement (SAVR) for aortic stenosis [6]. However, a volume increase of LA and LAA was observed at either in-hospital from pre-TAVR or 1 year from in-hospital in roughly more than half of the patients, suggesting a dynamic but not constant change of LA and LAA remodeling post-TAVR. Moreover, patients may have discordant volume change between LA and LAA.

Atrial fibrillation is a comorbidity or complication of outcome implications in the TAVR

population, but the true burden of which is likely underestimated during routine clinical care post-procedurally. In a study involving patients who received permanent pacemaker post-TAVR, a much higher incidence of new-onset AF was detected with data from device checks and 85% subclinical new-onset AF was identified 4 weeks beyond TAVR [7]. This finding illustrated current suboptimal surveillance of subclinical AF and a consequent underuse of anticoagulation therapy, which might translate to a devastating stroke event. Given the structural change of LA and LAA is involved in the onset of AF and its subsequent stroke risk, a follow-up on LA and LAA with readily available MSCT might provide another perspective to this problem. As demonstrated in our study, not all patients benefited from the relief of pressure overload by TAVR and the process of reverse remodeling was sometimes dynamic and discordant. LA volume index actually increased 1-year post-SAVR in patients with a baseline index ≥ 40 mL/$/m^2$ [8]. Around 23% of SAVR recipients remained with left ventricular hypertrophy and LA dilatation 1 year after the procedure, which was associated with a significantly lower survival rate at 3 years [9]. Structural changes in LA and LAA may also precede the development of AF and thrombus formation. Thus, an early identification of patients who would experience volume increase of LA and LAA might contribute to patient management post-TAVR. Further studies to correlate the imaging findings with clinical characteristics and outcomes are needed.

Funding

This work was supported by West China Hospital "1·3·5" Discipline of Excellence Project — Mechanisms of aortic stenosis and the clinical applications; the fellowship of China Postdoctoral Science Foundation (2020M683327); Open Fund Research from State Key Laboratory of Hydraulics and Mountain River Engineering (SKHL1920).

Conflict of interest: None declared

References

1. Mentias A, Saad M, Girotra S, et al. Impact of pre-existing and new-onset atrial fibrillation on outcomes after transcatheter aortic valve replacement. JACC Cardiovasc Interv. 2019; 12(21): 2119–2129, doi: 10.1016/j.jcin.2019.06.019, indexed in Pubmed: 31629743.
2. Delgado V, Di Biase L, Leung M, et al. Structure and function of the left atrium and left atrial appendage: AF and stroke implications. J Am Coll Cardiol. 2017; 70(25): 3157–3172, doi: 10.1016/j.jacc.2017.10.063, indexed in Pubmed: 29268928.
3. Guo Yk, Yang Zg, Shao H, et al. Right ventricular dysfunction and dilatation in patients with mitral regurgitation: analysis using ECG-gated multidetector row computed tomography. Int J Cardiol. 2013; 167(4): 1585–1590, doi: 10.1016/j.ijcard.2012.04.104, indexed in Pubmed: 22578735.
4. Li YG, Gong CQ, Zhao MZ, et al. Cardiac EP Study Group. Determinants of postoperative left atrial structural reverse remodeling in patients undergoing combined catheter ablation of atrial fibrillation and left atrial appendage closure procedure. J Cardiovasc Electrophysiol. 2019; 30(10): 1868–1876, doi: 10.1111/jce.14094, indexed in Pubmed: 31353748.
5. Kishima H, Mine T, Takahashi S, et al. Morphologic remodeling of left atrial appendage in patients with atrial fibrillation. Heart Rhythm. 2016; 13(9): 1823–1828, doi: 10.1016/j.hrthm.2016.06.009, indexed in Pubmed: 27291510.
6. Lisi M, Henein MY, Cameli M, et al. Severity of aortic stenosis predicts early post-operative normalization of left atrial size and function detected by myocardial strain. Int J Cardiol. 2013; 167(4): 1450–1455, doi: 10.1016/j.ijcard.2012.04.057, indexed in Pubmed: 22560912.
7. Megaly M, Garcia S, Anzia LE, et al. Detection of atrial fibrillation and atrial flutter by pacemaker device interrogation after transcatheter aortic valve replacement (TAVR): implications for management. J Invasive Cardiol. 2019; 31(7): E177–E183, indexed in Pubmed: 31257211.
8. Dahl JS, Videbæk L, Poulsen MK, et al. Noninvasive assessment of filling pressure and left atrial pressure overload in severe aortic valve stenosis: relation to ventricular remodeling and clinical outcome after aortic valve replacement. J Thorac Cardiovasc Surg. 2011; 142(3): e77–e83, doi: 10.1016/j.jtcvs.2011.01.032, indexed in Pubmed: 21353251.
9. Hatani T, Kitai T, Murai R, et al. Associations of residual left ventricular and left atrial remodeling with clinical outcomes in patients after aortic valve replacement for severe aortic stenosis. J Cardiol. 2016; 68(3): 241–247, doi: 10.1016/j.jjcc.2015.09.017, indexed in Pubmed: 26527112.

VIA MEDICA

RESEARCH LETTER

Cardiology Journal
2021, Vol. 28, No. 6, 986–988
DOI: 10.5603/CJ.a2021.0103

ISSN 1897–5593
eISSN 1898–018X

Intracardiac ultrasound two-dimensional and three-dimensional reconstruction for navigating percutaneous left atrial appendage occlusion

Witold Streb[1, 2], Katarzyna Mitręga[1], Tomasz Podolecki[1], Stanisław Morawski[1], Wiktoria Kowalska[1], Wirginia Michlicka[1], Zbigniew Kalarus[1, 2]

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

A growing portfolio of transcatheter procedures for structural heart disease poses new challenges in imaging techniques. Left atrial appendage closure (LAAC) represents a group of transcatheter procedures in which imaging is essential, both for guiding the procedure and as a tool for choosing the right occluder size [1–3]. Transesophageal echocardiography (TEE) has been the primary method of peri-procedural imaging, but new solutions are being sought to overcome its limitations. Evaluation is subject to intracardiac echocardiography (ICE) and methods that allow the fusion of images [4]. Only the use of ICE probes offering two-dimensional (2D) images during LAAC procedures has been evaluated so far. The current study compares the effectiveness of guiding the LAAC procedures employing the ICE 2D and ICE enabling three-dimensional reconstruction (ICE 3D).

The single-center prospective registry of LAAC procedures, included 330 consecutive patients with atrial fibrillation and contraindications for oral anticoagulant drugs, were analyzed. The preliminary selection included only LAAC procedures guided by both ICE 2D or ICE 3D. In the population of 31 patients separated in this way, LAAC procedures were performed using Amplatzer Amulet occluder. In 24 patients, LAAC was guided by the AccuNav 8 F probe enabling only 2D images, and in the remaining 7 cases, by the SoundStar 10 F probe, which enables 3D reconstruction. The left atrial appendage (LAA) was imaged by placing the AccuNav probe into the left atrium; for SoundStar probes, LAA images were captured from both the right and the left atrium in different atrial sections. Then the CartoSaund system was used for spatial reconstruction of LAA. All patients fulfilled the Amulet stability criteria before the device's release, as assessed by both ICE and fluoroscopy.

After 6 weeks, TEE was performed to exclude the leakage around the occluder and to assess if the implantation effect was optimal (the entire entrance to LAA covered with a disk without leaving any pouch, occluder axis parallel to LAA neck, separation between the device disk and lobe, optimal compression of the device). Whether ICE 2D or ICE 3D guided the treatment was blinded for the echocardiographer performing TEE.

Considering that the course and effects of LAAC procedures are influenced mainly by conditions related to the LAA anatomy and location of LAA orifice, the assessment of the results obtained with ICE 2D and ICE 3D was made based on cases with similar features. For this purpose, the propensity matching score technique was used. The following variables likely to impact the LAAC procedure were considered: the maximal dimension of the landing zone, the depth of LAA, the morphological type of LAA and the position of the LAA orifice in relation to the pulmonary veins. The matching was based on the optimal algorithm method using Euclidean distances and was carried

Address for correspondence: Dr. Witold Streb, Silesian Center for Heart Diseases in Zabrze, ul. Curie-Skłodowskiej 9, 41–800 Zabrze, Poland, tel: +48 32 271 34 14, e-mail: w.streb@sccs.pl

Received: 30.05.2021 Accepted: 28.08.2021 Early publication date: 10.09.2021

Table 1. Summary of matched intracardiac echocardiography (ICE) two-dimensional (ICE 2D) and ICE three-dimensional (ICE 3D) group characteristics.

Variable	Total	3D ICE	2D ICE	P level
LA [mm]	41.64 ± 3.93	40.29 ± 3.99	43.00 ± 3.65	0.118
LVEDD [mm]	49.6 ± 7.967	46.71 ± 9.32	52.57 ± 5.53	0.159
LVESD [mm]	37.36 ± 9.68	34.29 ± 10.83	40.43 ± 8.00	0.300
LVEF [%]	48.86 ± 14.00	52.29 ± 16.32	45.43 ± 11.34	0.245
LZ min. dimension [mm]	16.86 ± 2.96	15.71 ± 2.87	18.00 ± 2.7	0.235
LZ max. dimension [mm]	19.43 ± 3.20	19.14 ± 4.02	19.71 ± 2.43	0.645
Ostium min. dimension [mm]	20.93 ± 4.78	19.14 ± 3.13	22.71 ± 5.68	0.176
Ostium max. dimesnion [mm]	24.36 ± 3.52	23.29 ± 3.50	25.43 ± 3.46	0.270
LAA orifice area [cm^2]	4.15 ± 1.19	3.94 ± 1.20	4.36 ± 1.24	0.565
MV-LAA distance [mm]	12.64 ± 3.27	12.00 ± 3.42	13.29 ± 3.25	0.515
LA depth [mm]	20.07 ± 7.84	22.14 ± 6.12	18.00 ± 9.26	0.553
LAA morphology:				0.580
Cauliflower	1 (7.14%)	0 (0.00%)	1 (14.29%)	
Chickenwing	11 (78.57%)	6 (85.71%)	5 (71.43%)	
Windsock	2 (14.29%)	1 (14.29%)	1 (14.29%)	
LAA orifice position:				0.565
Low	1 (7.14%)	0 (0.00%)	1 (14.29%)	
Intermediate	7 (50.00%)	4 (57.14%)	3 (42.86%)	
High	6 (42.86%)	3 (42.86%)	3 (42.86%)	

LA — left atrium; LAA — left atrial appendage; LAAC — left atrial appendage closure; LVEDD — left ventricular end-diastolic dimension; LVESD — left ventricular end-systolic dimension; LVEF — left ventricular ejection fraction; max. — maximum; min. — minimum; MV — mitral valve; LZ — landing zone

out in a 1:1 ratio. The logistic regression model was then examined to assess the quality of propensity scores. A goodness-of-fit test (Hosmer-Lemeshow) suggested good model fit $\chi^2 = 4.031$ ($p = 0.909$). Statistical significance was verified by the χ^2 test for qualitative variables and the Mann-Whitney test for quantitative variables. A p-value < 0.05 was considered statistically significant. The calculations were made in the XLSTAT 2021 program.

Among all patients who underwent LAAC under ICE guidance, the maximal landing zone diameter was 21.36 ± 4.0 mm, and the LAA depth was 24.10 ± 7.9 mm. The most common morphological LAA type was the chickenwing (n = 17, 54.84%), followed by windsock (n = 10, 32.26%), cactus (n = 3, 9.68%) and cauliflower (n = 1, 3.23%). Considering the position of LAA orifice, the intermediate origin was dominant (n = 15, 48.39%). The high location of orifice was also often diagnosed (n = 12, 38.71%), while the low type was sporadic (n = 4, 12.9%).

The characteristics of the left atrium and the LAA in subgroups selected based on the propensity matching score are presented in Table 1.

In the ICE 3D group, the procedure duration was significantly shorter (65.21 ± 26.76 vs. 84.57 ± ± 24.13 min; p = 0.005), and the radiation dose was significantly lower (vs. 126.15 ± 82.28 vs. 133.57 ± ± 1 17.36 mGy; p = 0.038), but the fluoroscopy time was only insignificantly shorter (10.78 ± 4.49 vs. 12.86 ± 8.71 min; p = 0.136). There were no severe complications during the procedures, and they led to the effective elimination of LAA in both groups. In short-term follow-up, all patients survived, no strokes or bleeding complications were found.

The occluder position was considered optimal in 4 (57.14%) cases in the ICE 3D group and 6 (85.71%) in the ICE 2D group (p = 0.237). Moreover, a peridevice leak was more frequent in the ICE 3D group (4 [57.14%] vs. 1 [14.29%]). There were no incidents of device-related thrombus. Despite the SoundStar probe's larger diameter, its use was not associated with more frequent iatrogenic atrial septal defect; 3 (42.86%) cases in ICE 3D vs. 5 (71.43%) cases in the ICE 2D group (p = 0.28).

To date, results of only a few studies evaluating ICE used for imaging during LAAC have been pub-

lished, all of them concerning guiding procedures with probes which allow obtaining 2D images. It was demonstrated that LAAC under ICE guidance is possible and has high technical and procedural effectiveness [5, 6]. Nevertheless, one of the limitations of this method was the lack of 3D imaging. A new solution has recently emerged that enables 3D reconstructions based on the signal from the ICE probe.

The present study confirmed the high efficiency of LAAC performed under ICE guidance with AccuNav or SoundStar probes. The use of ICE and also 3D probes is not associated with a higher risk of peri-procedural complications. However, the reconstruction of 3D images with Soundstar is time-consuming, which contributes to the more frequent acceptance of suboptimal occluder positioning during the procedure. The study results conclude that while ICE 3D and 2D imaging allow for equally effective and safe monitoring of LAAC treatments, the use of spatial reconstructions obtained with the SoundStar transducer does not bring additional benefits. Shorter procedure times were often paid for by a suboptimal implantation effect and more frequent leakage around the occluder.

The main limitation of the presented work is the small group size in which ICE was used. Despite the validation of the propensity matching score for the very small sample size, a bias error in such cases increases and can also affect the comparison results between the two groups [7]. Also, Soundstar probes allowed only for 3D reconstruction, while real-time 3D imaging would probably impact this imaging technique's more favourable assessment.

Conflict of interest: Witold Streb, Katarzyna Mitręga and Zbigniew Kalarus are proctors of Abbott Medical.

References

1. Chow DHf, Bieliauskas G, Sawaya FJ, et al. A comparative study of different imaging modalities for successful percutaneous left atrial appendage closure. Open Heart. 2017; 4(2): e000627, doi: 10.1136/openhrt-2017-000627, indexed in Pubmed: 28761682.
2. Gafoor S, Schulz P, Heuer L, et al. Use of EchoNavigator, a novel echocardiography-fluoroscopy overlay system, for transseptal puncture and left atrial appendage occlusion. J Interv Cardiol. 2015; 28(2): 215–217, doi: 10.1111/joic.12170, indexed in Pubmed: 25676602.
3. Clemente A, Avogliero F, Berti S, et al. Multimodality imaging in preoperative assessment of left atrial appendage transcatheter occlusion with the Amplatzer Cardiac Plug. Eur Heart J Cardiovasc Imaging. 2015; 16(11): 1276–1287, doi: 10.1093/ehjci/jev097, indexed in Pubmed: 25916628.
4. Ribeiro JM, Teixeira R, Puga L, et al. Comparison of intracardiac and transoesophageal echocardiography for guidance of percutaneous left atrial appendage occlusion: A meta-analysis. Echocardiography. 2019; 36(7): 1330–1337, doi: 10.1111/echo.14415, indexed in Pubmed: 31215709.
5. Berti S, Paradossi U, Meucci F, et al. Peri-procedural intracardiac echocardiography for left atrial appendage closure: a dual-center experience. J Am Coll Cardiol Intv. 2014; 7: 1036–1044.
6. Matsuo Y, Neuzil P, Petru J, et al. Left atrial appendage closure under intracardiac echocardiographic guidance: feasibility and comparison with transesophageal echocardiography. J Am Heart Assoc. 2016; 5(10), doi: 10.1161/JAHA.116.003695, indexed in Pubmed: 27680664.
7. Pirracchio R, Resche-Rigon M, Chevret S. Evaluation of the propensity score methods for estimating marginal odds ratios in case of small sample size. BMC Med Res Methodol. 2012; 12: 70, doi: 10.1186/1471-2288-12-70, indexed in Pubmed: 22646911.

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

Cardiology Journal
2021, Vol. 28, No. 6, 989–990
DOI: 10.5603/CJ.2021.0142

ISSN 1897–5593
eISSN 1898–018X

ST-segment elevation myocardial infarction after COVID-19 reinfection: The disseminated thrombotic process

Tomasz A. Michalski*, Tomasz Figatowski*, Milosz J. Jaguszewski

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

This paper was guest edited by Prof. Marek Koziński

A 64-year-old man with no medical history of coronary events was admitted due to a diagnosis of myocardial infarction with prominent ST-segment elevation. He suffered from coronavirus disease 2019 (COVID-19) 7 weeks prior (with a subsequent negative test) as well as arterial hypertension, type 2 diabetes, and obesity. Upon admission, the PCR SARS-CoV-2 screening test was positive anew. Coronary angiography showed a thrombus in the left main (LM) coronary artery with 90% stenosis (Fig. 1A–D). Distal segments of the left anterior descending (LAD) artery and diagonal branch (Dg) were occluded by thromboembolic material. After an intracoronary bolus of eptifibatide, thrombectomy, and balloon angioplasty in LAD, the operator decided to proceed with drug-eluting stent implantation (Fig. 1E, F). In LM, an intervention was completed without residual stenosis with Thrombolysis in Myocardial Infarction (TIMI) 3. The distal segment of LAD and Dg remained TIMI 1 and 0, respectively. Thoracic computed tomography demonstrated specific pulmonary changes (Fig. 1G). An echocardiogram showed a left ventricle (LV) ejection fraction of 44% and a thrombus in the LV apex (Fig. 1H, I; **Suppl. Video 1**). Notably, there was no atrial fibrillation in the past. On discharge, the patient was prescribed warfarin (international normalized ratio 2.0–2.5) with acetylsalicylic acid, and ticagrelor for 3 and 12 months, respectively. A 3-month follow-up revealed no recurrence of COVID-19 and cardiovascular events. The control echocardiography showed dissolution of the LV thrombus; therefore, warfarin therapy was discontinued.

Herein, we present an elegant case reflecting the potential need for an aggressive antithrombotic treatment during and after COVID-19.

Conflict of interest: None declared

Address for correspondence: Tomasz A. Michalski, MD, 1st Department of Cardiology, Medical University of Gdansk, ul. Dębinki 7, 80–952 Gdańsk, Poland, tel: +48 500359592, e-mail: tomasz.michalski190@gmail.com

Received: 17.06.2021 Accepted: 9.08.2021

**Contributed equally*

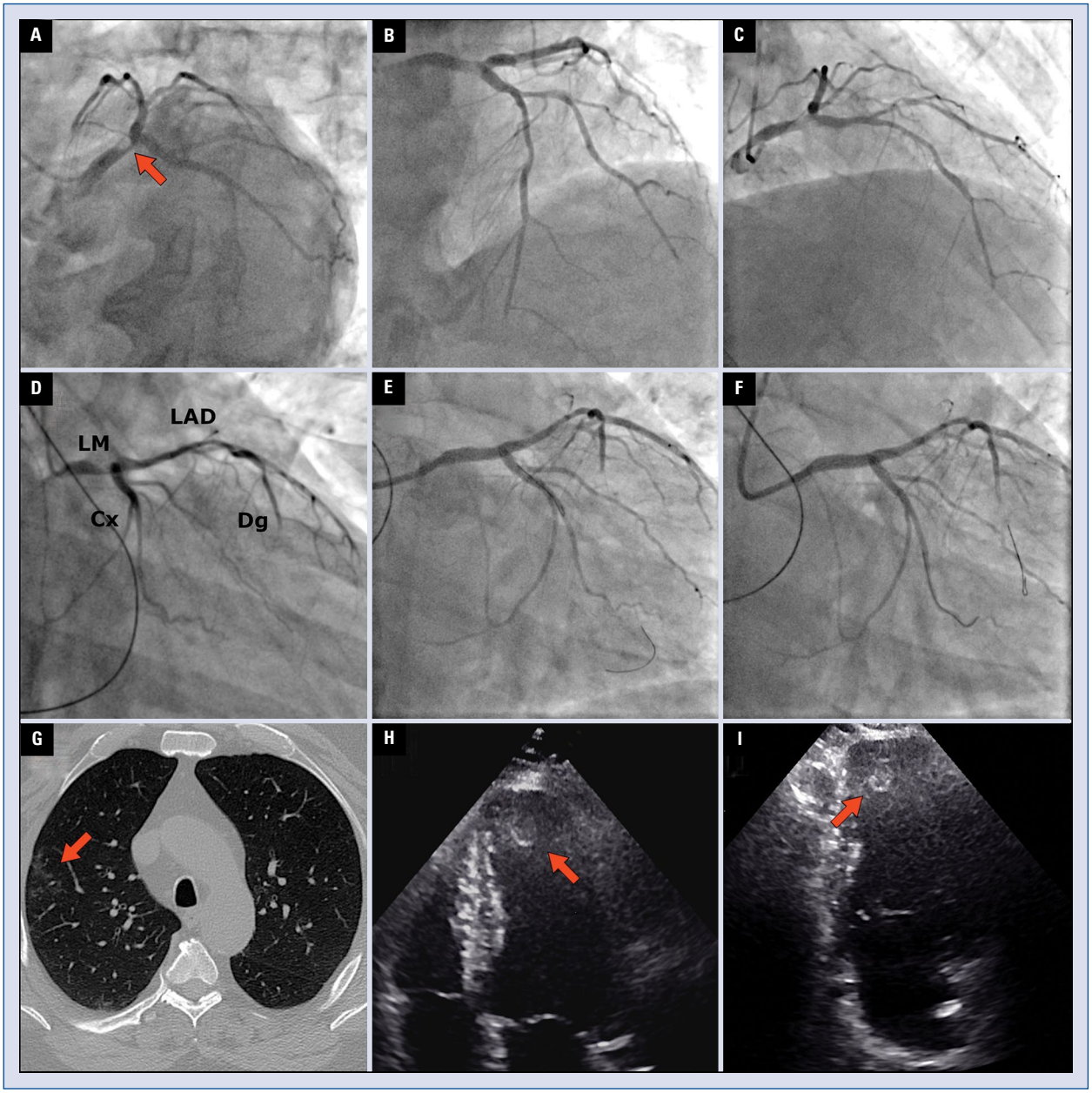


Figure 1. A–D. Thrombus in the left main coronary artery (LM; arrow) and occlusion of the distal left anterior descending artery (LAD) and diagonal branch (Dg); **E.** Direct stenting technique in the LM; **F.** Proximal optimization of the stent in the LM; **G.** Specific for COVID-19 interstitial post-inflammatory changes (arrow) in the lungs; **H, I.** Thrombus (17 mm × 10 mm; arrow) in the apex of the left ventricle visualized in both apical 4- and 2-chamber view of transthoracic echocardiography; Cx — circumflex artery.

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

Cardiology Journal
2021, Vol. 28, No. 6, 991–992
DOI: 10.5603/CJ.2021.0143

ISSN 1897–5593
eISSN 1898–018X

Recanalization of in-stent chronic total occlusion using intravascular lithotripsy and Firehawk® rapamycin target eluting coronary stents: A case report

Alexandru Patrascu, Jonathan Michel, Christian Templin

Department of Cardiology, University Heart Center,
University Hospital Zurich, Switzerland

A 73-year-old patient, who had undergone several stent implantations of the right coronary artery (RCA) after bypass graft failure, was referred for coronary angiography (CAG) based on stable angina and positive imaging stress test for inferior wall ischemia. CAG showed in-stent restenosis of the proximal RCA and chronic total occlusion (CTO) of the mid RCA due to stent underexpansion (Fig. 1A, B).

After vessel intubation and tedious guidewire advancement, pre-dilatations were performed restoring a Thrombolysis in Myocardial Infarction 2 flow. As expansion of a 3.5 mm non-compliant balloon was suboptimal but the lesion could be crossed, intravascular lithotripsy was used instead of rotational atherectomy, facilitating stent deployment (Fig. 1C, D). Furthermore, the stents implanted in the past were at least 6 months old, so endothelialization was presumed, thus not jeopardizing stent architecture. Therefore, 80 impulses were administered to the proximal and mid RCA upon inflation of the 3.5 × 12 mm Shockwave balloon, followed by implantation of 3 Firehawk® rapamycin target eluting coronary stents, ranging in diameter from 2.75 mm to 3.5 mm, as previously everolimus and zotarolimus eluting stents were used (Fig. 1E, F).

The Firehawk® stent proved to be non-inferior to an everolimus-eluting stent in the TARGET All comers trial and has a fully biodegradable polymer, the lowest drug dosage on the market, and an excellent radial strength despite ultrathin (86 μg) struts. This case demonstrates the importance of intravascular lithotripsy in treating in-stent restenosis, even in the presence of CTO. It also highlights that the Firehawk® stent can be used for management of complex lesions.

Conflict of interest: Doctor Christian Templin reports receiving consulting fees from Biotronik, Microport and Schnell Medical; lecture fees from Novartis; and serving on advisory boards from Amgen. All other authors declare no conflict of interest.

Address for correspondence: Christian Templin, MD, PhD, Director Andreas-Grüntzig-Heart-Catheter-Laboratories, Zurich, Switzerland, tel: +41 (0)44 255 9585, e-mail: christian.templin@usz.ch

Received: 24.02.2021 Accepted: 6.06.2021

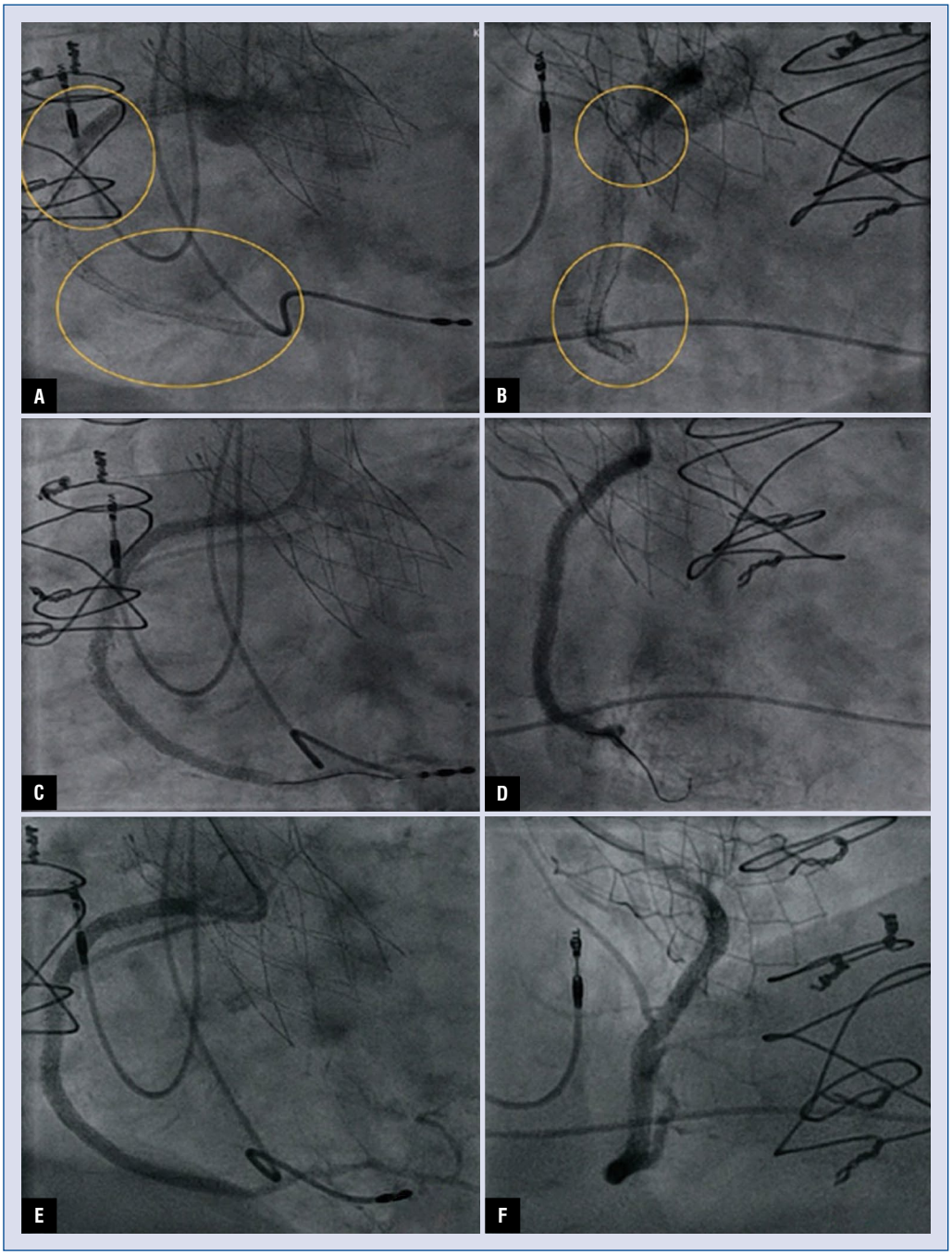


Figure 1. A–F. Left column: Left anterior oblique view of the right coronary artery (RCA); **Right column:** Right anterior oblique view of the RCA; notice long segments of stent under-expansion (yellow circles); **Middle row:** Restoration of Thrombolysis in Myocardial Infarction flow 2 after balloon pre-dilatation and intravascular lithotripsy; **Bottom row:** Final result after implantation of 3 Firehawk® rapamycin target eluting coronary stents.

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

Cardiology Journal
2021, Vol. 28, No. 6, 993–994
DOI: 10.5603/CJ.2021.0144

ISSN 1897–5593
eISSN 1898–018X

Rota-lithotripsy: A combination of rotational atherectomy and intravascular lithotripsy (Shockwaves) as a novel strategy for a rotablation--resistant lesion in a patient with ST-segment elevation myocardial infarction

Adrian Włodarczak[1] *, Piotr Rola[2] *, Mateusz Barycki[2], Barbara Engel[2], Marek Szudrowicz[1], Jan Jakub Kulczycki[1], Maciej Lesiak[3], Adrian Doroszko[4]

[1]Department of Cardiology, The Copper Health Centre (MCZ), Lubin, Poland
[2]Department of Cardiology, Provincial Specialized Hospital, Legnica, Poland
[3]1st Department of Cardiology, University of Medical Sciences, Poznan, Poland
[4]Department of Internal Medicine, Hypertension and Clinical Oncology, Wroclaw Medical University, Wroclaw, Poland

A 71-year-old female was admitted to the documented cath-lab with ST-segment elevation myocardial infarction (STEMI) of the inferior wall. Coronary angiogram revealed acute occlusion of the right coronary artery without other significant lesions (Fig. 1A). Percutaneous coronary intervention (PCI) was performed by the right-radial access, using the JR4.0 (6 F) Guide-Catheter. Initial high-pressure (22 atm.) predilation with a non--compliant balloon (NCB) catheter 2.5 × 20 mm was performed (Fig. 1B). Due to incomplete expansion, the size of NCB was decreased to 2.0 × 15 mm (24 atm.) with unfavourable effect (Fig. 1C). Afterwards, we switched to the 7 F right--radial access (JR 4.0) and despite use of an extra support guidewire, subsequent guide extension and additional anchor-balloon manoeuvre, we were still unable to cross the lesion with the ShockWave Intravascular Lithotripsy (S-IVL) balloon-catheter (3.5 × 12 mm). Therefore, we exchanged a guidewire on the Rotawire-Extra-Support and performed a successful rotational atherectomy (RA) with Rotablator burr size 1.75 mm (Fig. 1D). Subsequently, a high-pressure (22 atm.) inflation of a 3.5 × 15 mm NCB was performed. Despite lesion preparation with the RA, a significant "dogbone effect" was still observed (Fig. 1E). Hence, we performed the S-IVL using a 3.5 × 12 mm catheter. After application of 40 ultrasonic pulses, full expansion was obtained (Fig. 1F). Drug eluting stent 3.5 × × 38 mm (16 atm.) implantation was followed by a 4.0 × 20 mm (20 atm.) NCB post-dilation. Finally, a satisfying angiographic result was obtained, and was confirmed by the optical coherence tomography (minimal lumen area 8.06 cm^2) (Fig. 1G–J).

According to available research, we are the very first to present a well-documented successful application of a complex advanced plaque-modifying method (RA+S-IVL bailout PCI) in a subject with STEMI *via* radial access.

Conflict of interest: None declared

Address for correspondence: Piotr Rola, MD, PhD, Department of Cardiology, Provincial Specialized Hospital Legnica, ul. Iwaszkiewicza 5, 55–220 Legnica, Poland, tel: +48 888 272 007, e-mail: piotr.rola@gmail.com

Received: 25.02.2021 Accepted: 5.05.2021

**Equal authorship*

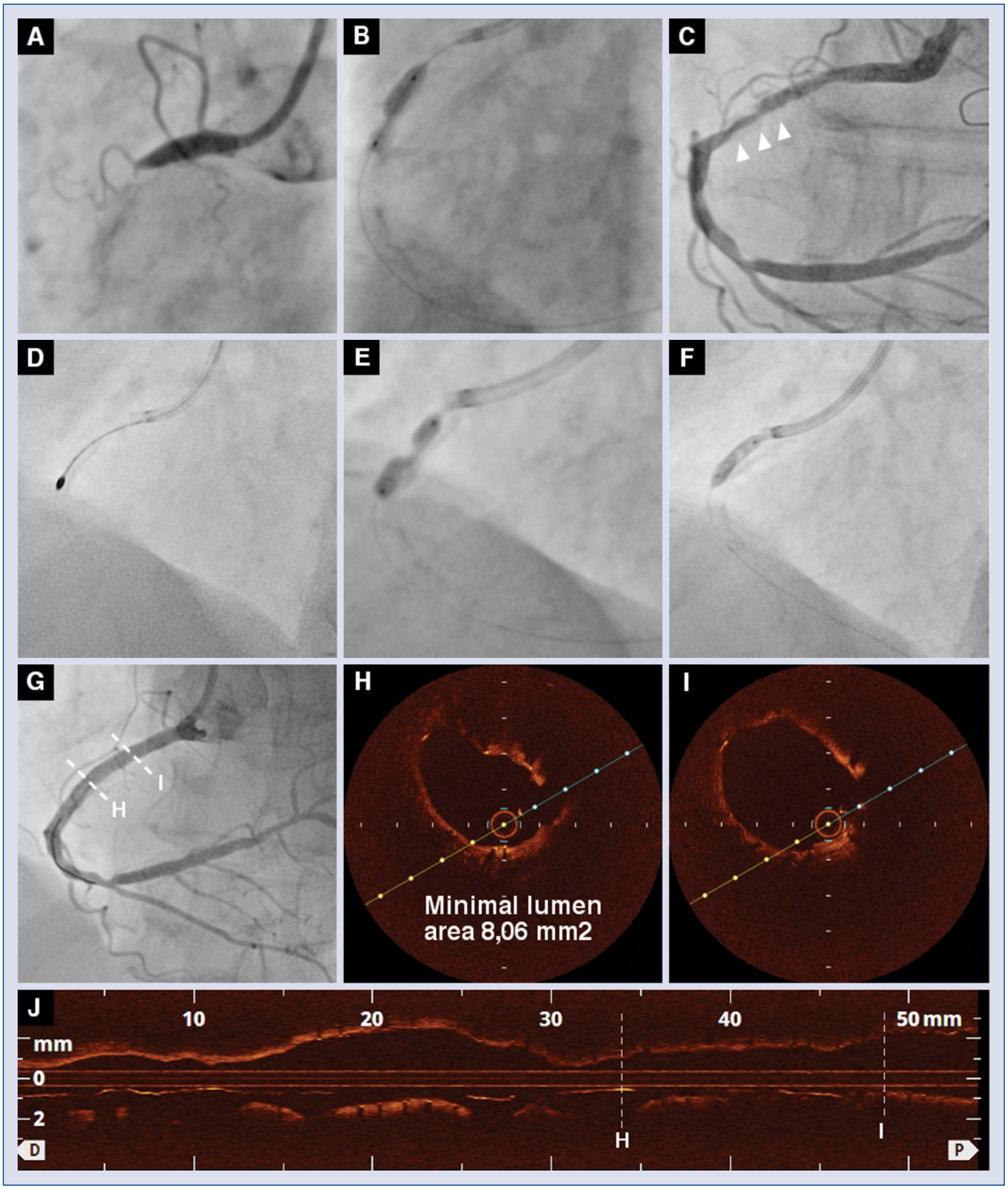


Figure 1. A. initial angiography acute occlusion of right coronary artery (RCA); **B.** Incomplete expansion of 2.5 × 20 mm non-compliant (NC) balloon catheter; **C.** Angiography after restoring flow to RCA-heavily calcified culprit lesions; **D.** Rotational atherectomy (RA) with Rotablator burr size 1.75 mm; **E.** "Dogbone effect" on NC balloon 3.5 × 15 mm after successful RA; **F.** Full expansion of ShockWave Intravascular Lithotripsy catheter after 40 pulses; **G.** Final angiography after drug eluting stent (3.5 × 38 mm) followed by NC 4.0 × 20 mm post-dilation; **H, I, J.** Optical coherence tomography demonstrating satisfying stent expansion and apposition.

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

Cardiology Journal
2021, Vol. 28, No. 6, 995–996
DOI: 10.5603/CJ.2021.0145

ISSN 1897–5593
eISSN 1898–018X

Percutaneous coronary intervention using a mechanical circulatory support system with an Impella centrifugal pump device combined with subsequent cryoablation for atrial fibrillation

Anna Winnicka-Zielińska[1]*, Bogdan Musielak[1, 2]*, Jan Budzianowski[1, 2], Jarosław Hiczkiewicz[1, 2], Paweł Burchardt[3, 4]

[1]Clinical Department of Cardiology, Nowa Sol Multidisciplinary Hospital, Nowa Sol, Poland
[2]Collegium Medicum, University of Zielona Gora, Poland
[3]Department of Hypertensiology, Angiology and Internal Medicine, Poznan University of Medical Sciences, Poznan, Poland
[4]Department of Cardiology, J. Strus Hospital, Poznan, Poland

A 63-year-old man was admitted to an intensive care unit due to non-ST-segment elevation myocardial infarction. He had a history of hypertension, diabetes, coronary artery disease (CAD) and underwent percutaneous coronary intervention of the left circumflex artery and radiofrequency ablation of tricuspid isthmus in 2009 due to a persistent atrial flutter. Transthoracic echocardiography showed a severely reduced left ventricular ejection fraction (LVEF 25%) and severe mitral regurgitation. The patient was qualified for urgent coronarography which revealed advanced multivessel CAD (Fig. 1A, B).

The Heart Team decided to perform rotablation of the left anterior descending artery with mechanical circulatory support using an Impella centrifugal pump (CP) due to the high risk associated with a surgical procedure. The Impella CP was introduced into the left ventricle through the left femoral artery obtaining 4.0 L/min flow. The procedure was effective and the blood flow marked as grade 3 in the Thrombolysis in Myocardial Infarction (TIMI) system was achieved (Fig. 1C).

Three weeks following his discharge, he experienced an episode of symptomatic paroxysmal atrial fibrillation which led to exacerbation of heart failure (class III according to the New York Heart Association [NYHA] system). The decision was made to urgently perform cryoablation of pulmonary veins (Arctic Front Advance 2nd generation 28 mm) (Fig. 1D). Further hospitalization was carried out without complications or recurring arrhythmia. The patient was discharged in a stable condition (class II of NYHA).

Mechanical circulatory support with an Impella CP device allows for percutaneous procedures in patients with a severely reduced LVEF. It was proven that pulmonary vein isolation in patients with heart failure with reduced ejection fraction was a safe and feasible treatment modality.

Conflict of interest: None declared

Address for correspondence: Jan Budzianowski, MD, PhD, Collegium Medicum, University of Zielona Gora, ul. Zyty 28, 65–046 Zielona Góra, Poland, tel: +48 68 3882 103, e-mail: jbudzianowski@uz.zgora.pl

Received: 21.02.2021 Accepted: 6.06.2021

**Equal contribution*

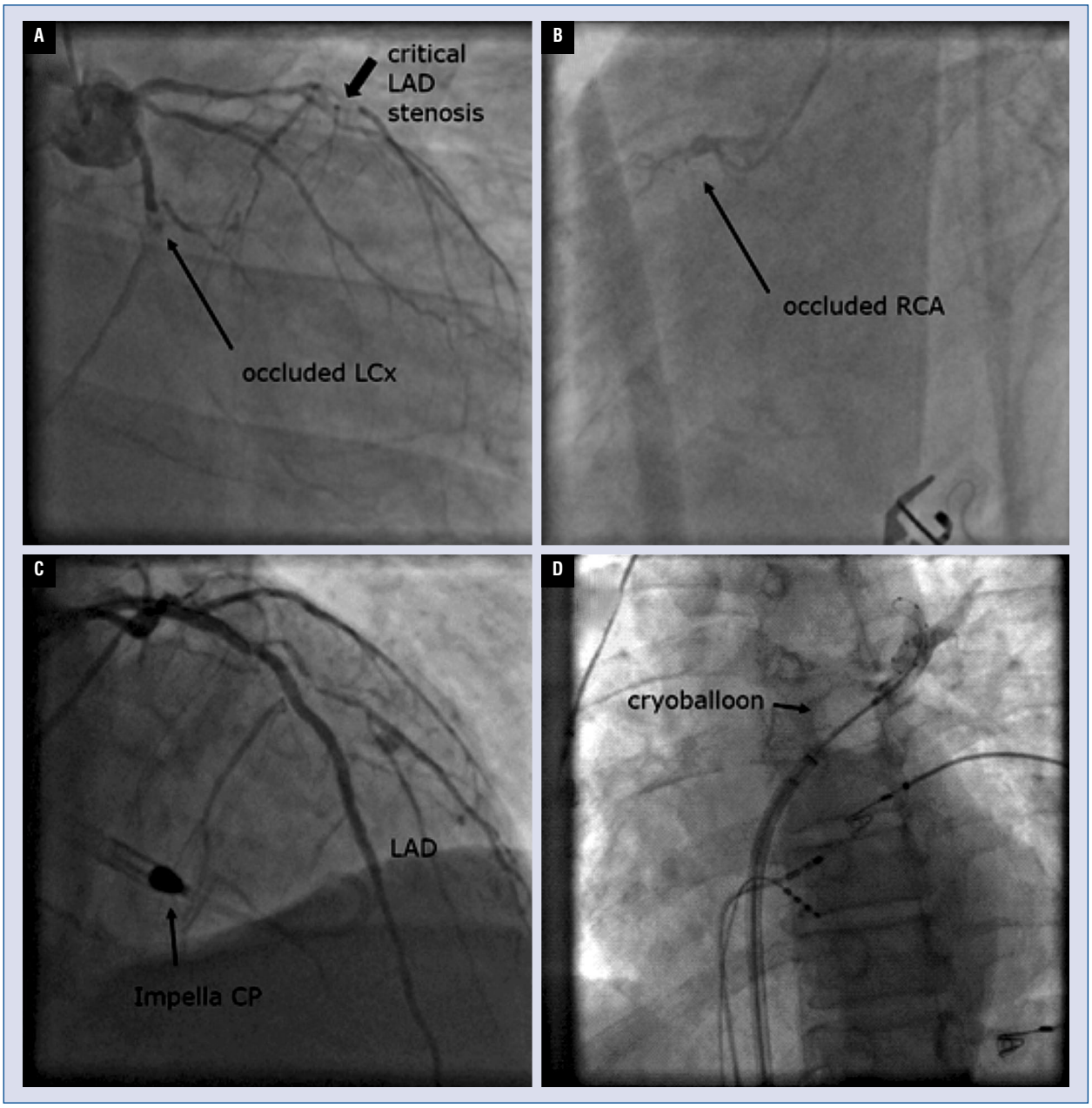


Figure 1. A, B. Initial coronarography: significant stenosis of the 6/7 segment and critical stenosis of the left anterior descending artery (LAD) segment 8, a chronic total occlusion of the left circumflex artery (LCx) in the stent, occlusion of marginal branch 1, a critically stenosed intermediate branch and chronic total occlusion of the right coronary artery (RCA); **C.** The Impella centrifugal pump (CP) in left ventricle. The RCA was intubated through the right femoral access with an EBU 4.0 6FrS guide catheter. The BHW introducer was used for the LAD. Predilatation of critical stenoses was performed by means of 2.0 × 15 mm and 3.0 × 20 mm balloon catheters. Three Orsiro drug eluting stents (2.75 × 30 mm, 3.0 × 40 mm, 3.0 × 22 mm) were implanted without complications; **D.** During the cryoapplication in the upper left pulmonary vein, the sinus rhythm returned.

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

Cardiology Journal
2021, Vol. 28, No. 6, 997–998
DOI: 10.5603/CJ.2021.0146

ISSN 1897–5593
eISSN 1898–018X

Percutaneous removal of a catheter fragment from the right atrium

Arkadiusz Pietrasik, Aleksandra Gąsecka, Adam Juśkiewicz, Piotr Lewandowski, Daria Stelmach, Janusz Kochman

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

A 73-year-old woman treated with chemotherapy was admitted to the surgery department due to the disruption and migration of a fragment of a permanent port-a-cath (Ambix Intraport, Fresenius Kabi, Dublin, Ireland) to the right heart chambers. At admission, the patient was asymptomatic and in good general condition. Chest radiogram confirmed the presence of the disrupted fragment of the catheter within the right heart chambers, in the right atrium and right ventricle (Fig. 1A). Ultrasonography revealed no foreign bodies in the right subclavian vein and within the subcutaneous tissue under the right clavicle.

The patient was consulted within the local Pulmonary Embolism Response Team (PERT) — a multidisciplinary team designed to evaluate the risk of acute pulmonary embolism and determine the optimal therapy. Regarding the stable clinical condition of the patient and the risk of iatrogenic pulmonary embolism, which might result in hemodynamic destabilization, the patient qualified for interventional removal of the disrupted catheter fragment. Percutaneous removal of the catheter was attempted through the right femoral vein, using the Exeter Snare ES 15 loop. The loop was placed at one end of the catheter and tightened (Fig. 1B). The catheter was moved sequentially into the abdominal part of the inferior vena cava (Fig. 1C) and removed through the femoral vein in one piece (Fig. 1D, **Suppl. Video 1**). The disrupted part of the catheter was not further fractured or damaged. There were no complications following the procedure. New port-a-catheter was re-inserted and the patient was able to continue the chemotherapy.

Informed consent was obtained from patient for publication of this case report.

Conflict of interest: None declared

Address for correspondence: Aleksandra Gąsecka, MD, PhD, 1st Chair and Department of Cardiology, Medical University of Warsaw, ul. Banacha 1a, 02–097 Warszawa, Poland, tel: +48 22 599 19 51, e-mail: aleksandra.gasecka@wum.edu.pl

Received: 17.04.2021 Accepted: 5.08.2021

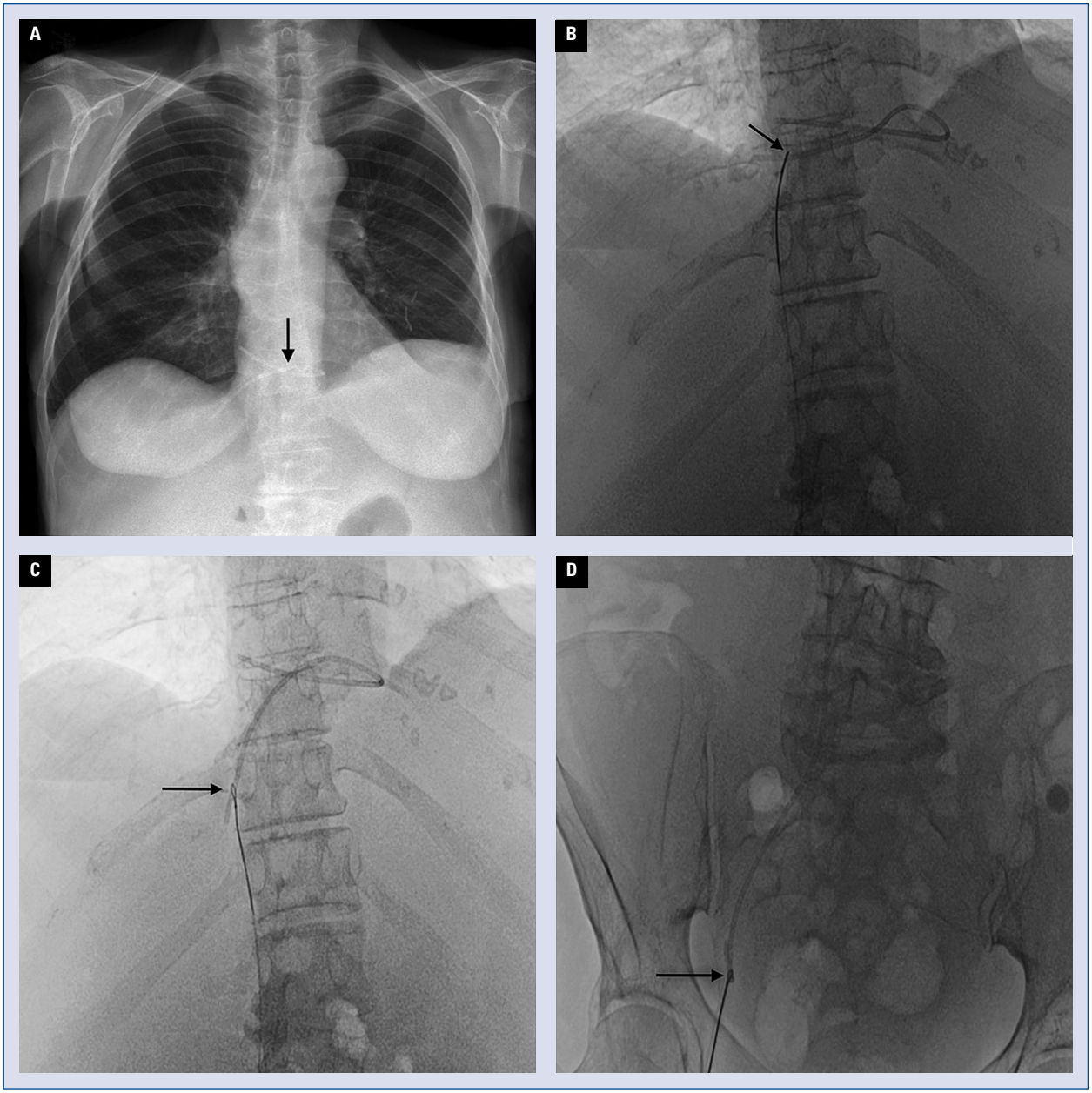


Figure 1. A. Chest radiogram made on admission showing fragment of the catheter within the right heart chambers (arrow); **B.** The Exeter Snare ES 15 loop tightened at one end of the catheter (arrow); **C.** The catheter was moved to the abdominal part of the inferior vena cava (arrow); **D.** Then relocated to the femoral vein and further removed through it (arrow).

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

Cardiology Journal
2021, Vol. 28, No. 6, 999–1000
DOI: 10.5603/CJ.2021.0160

ISSN 1897–5593
eISSN 1898–018X

The short P-wave — Is it really short?

Jakub Mercik[1], Aleksandra Gajek[2], Jadwiga Radziejewska[2], Agnieszka Sławuta[3], Jacek Gajek[4], Dariusz Kozłowski[5]

[1]Department of Emergency Medicine, Wroclaw Medical University, Wroclaw, Poland
[2]Department of Cardiology, Klodzko County Hospital, Klodzko, Poland
[3]Department of Internal and Occupational Diseases, Hypertension and Clinical Oncology, Wroclaw Medical University, Wroclaw, Poland
[4]Department of Emergency Medical Service, Wroclaw Medical University, Wroclaw, Poland
[5]Department of Cardiology and Electrotherapy, Medical University of Gdansk, Poland

An 82 year-old woman with atrial flutter and fibrillation (AF), currently in persistent AF, has undergone radiofrequency-ablation of cavotricuspid isthmus and electrical cardioversion to restore sinus rhythm. Electrocardiogram (ECG) after the procedure showed an unusual morphology of the P-wave, which was examined more closely. The ECGs are presented in the Figure 1.

The complete Bachmann's bundle block cannot be recognized because no negative P-wave deflection in inferior ECG leads is present, thus we assume a fusion of concomitant activation of the left atrium through the simultaneously activated Bachmann's bundle and coronary sinus. A more speculative explanation is that the depletion of left atrial cardiomyocytes is leading to a low amplitude of the terminal P wave deflection [1].

A recent population study of 285,933 individuals assessed the P-wave duration and its clinical importance. In the follow-up the authors observed the development of AF and cases of death were clearly related to a very short P-wave (< 89 ms). The intermediate, long and a very long P-wave also increased the risk of AF and death in comparison to reference duration (90–110 ms) [2].

The standard ECG recording could contribute to such measurement inaccuracies which would be responsible for the category of 'short P-wave' and to the conclusions which are having a clinical impact on many patients. In fact, there are interatrial conduction disturbances and prolonged P-wave duration. It should be suspected, especially in the elderly with a history of atrial arrhythmia. To address the issue, we suggest a paper speed of 50 mm/s and a double gain of 0.5 mV/10 mm.

Conflict of interest: None declared

References

1. Baranchuk A, Bayés de Luna A. The P-wave morphology: what does it tell us? Herzschrittmacherther Elektrophysiol. 2015; 26(3): 192–199, doi: 10.1007/s00399-015-0385-3, indexed in Pubmed: 26264481.
2. Nielsen JB, Kühl JT, Pietersen A, et al. P-wave duration and the risk of atrial fibrillation: Results from the Copenhagen ECG Study. Heart Rhythm. 2015; 12(9): 1887–1895, doi: 10.1016/j.hrthm.2015.04.026, indexed in Pubmed: 25916567.

Address for correspondence: Jakub Mercik, MD, Department of Emergency Medicine, Wroclaw Medical University, ul. Borowska 213, 50–556 Wroclaw, Poland, tel: 793166288, e-mail: jakub.mercik@wp.pl

Received: 23.07.2021 Accepted: 21.10.2021

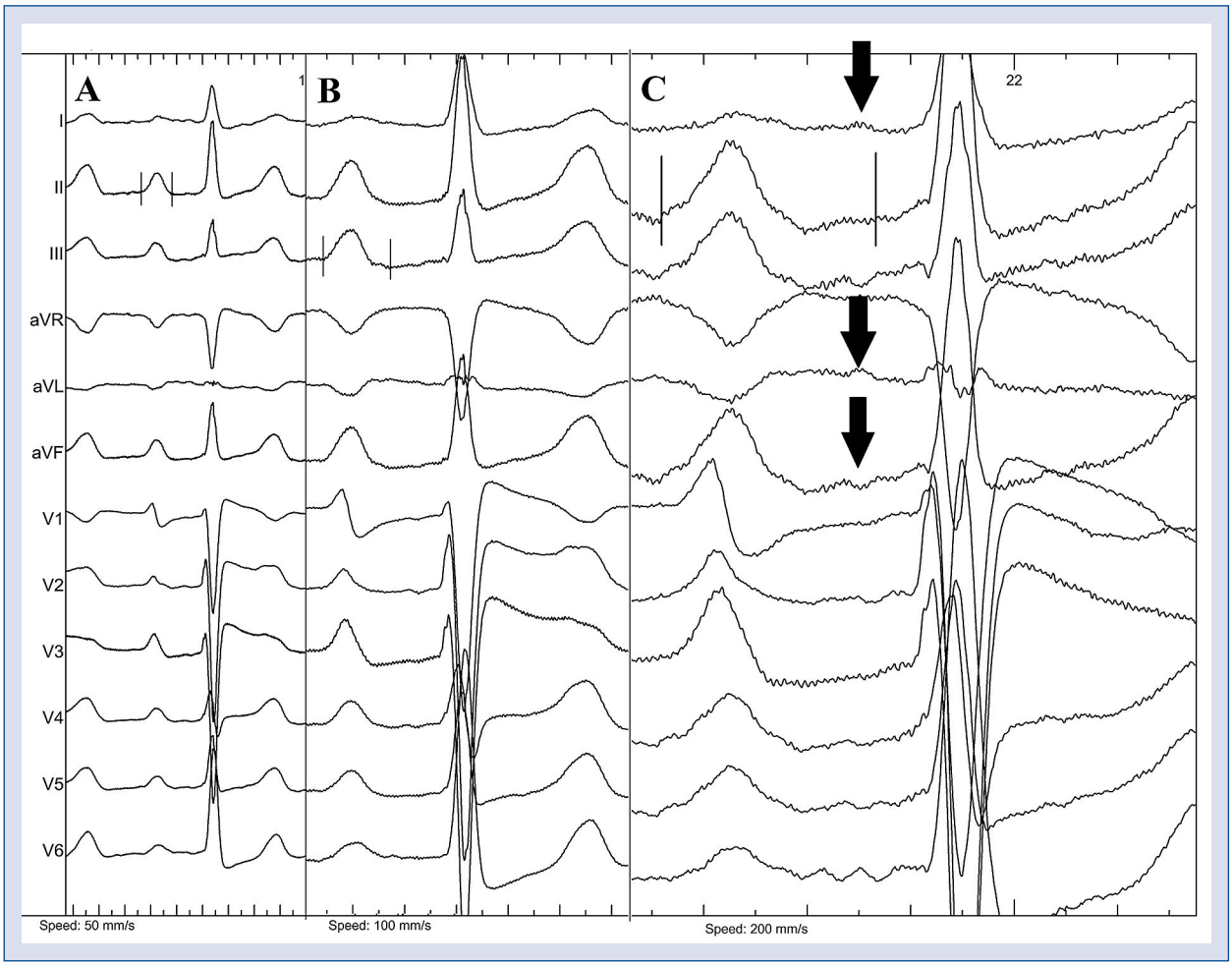


Figure 1. Twelve-lead electrocardiogram tracings; **A.** Paper speed at 50 mm/s and enhancement ×16, the P-wave duration of 112 ms, PR interval 216 ms, QRS complex duration 104 ms; **B.** Paper speed at 100 mm/s and enhancement ×32, the P wave duration of 120 ms, PR interval 228 ms, QRS complex duration 102 ms; **C.** Paper speed at 200 mm/s and enhancement ×64, the P-wave duration of 206 ms, PR interval 229 ms, QRS complex duration 99 ms. The vertical lines mark the beginning and the end of the P wave in each setting. The arrow presents the real end of the P wave.

VIA MEDICA

LETTER TO THE EDITOR

Cardiology Journal
2021, Vol. 28, No. 6, 1001–1002
DOI: 10.5603/CJ.a2021.0161

ISSN 1897–5593
eISSN 1898–018X

Heart inflammation risk after COVID-19 vaccine

Lukasz Szarpak[1, 2, 3], Michal Pruc[3], Mariusz Koda[2], Francesco Chirico[4, 5]

[1]Institute of Research Outcomes, Maria Sklodowska-Curie Medical Academy, Warsaw, Poland
[2]Research Unit, Maria Sklodowska-Curie Bialystok Oncology Center, Bialystok, Poland
[3]Research Unit, Polish Society of Disaster Medicine, Warsaw, Poland
[4]Post-graduate School of Occupational Health, Università Cattolica del Sacro Cuore, Rome, Italy
[5]Health Service Department, Italian State Police, Milan, Italy

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a severe threat to the healthcare system and medical personnel since the beginning of the pandemic [1]. The vaccination program against coronavirus disease 2019 (COVID-19) has been in Europe for a long period. After taking the preparation, some patients have unfavorable post-vaccination responses. The majority of them are minor, but they can be, in individual cases, significant or severe. One of the primary reasons why people do not take COVID-19 vaccinations is because they are afraid of the negative effects. Myocarditis and SARS-CoV-2 infection are linked in a major way [2]. Myocarditis is an uncommon side effect of mRNA immunization, especially in younger and adult males, and occurs most usually after the second dosage with a 7-day gap. Myocarditis accounted for 0.4% of all vaccine-related adverse events, according to an observational analysis of 151.1 million persons who had been vaccinated. The number of instances of post-vaccination myocarditis was 0.95 per 100,000, and 1.05 per 100,000 in younger men under the age of 18, whereas in the whole population it was expected to be 2.12 per 100,000 [3]. Two Israeli studies estimate the risk of myocarditis after receiving the Pfizer–BioNTech injection, with one estimating a two in 100,000 probability of acquiring the illness. A total of 136 persons suffered myocarditis after receiving the Pfizer–BioNTech COVID-19 vaccination in one trial of more than 5,1 million participants. Within 1 month of receiving a Pfizer injection, 136 incidences of myocarditis were detected, according to the study. Ninety-five percent of the cases were mild, but one individual died. After getting their second dosage of the Pfizer–BioNTech vaccine, up to 4 in 100,000 males experienced myocarditis, although the prevalence for women was less than 1 in 100,000. In general, fully vaccinated people were nearly twice as likely as unvaccinated people to be diagnosed with myocarditis after their second dose, however, young males aged 16–19 had a 15 in 100,000 risk of getting myocarditis. The great majority of these incidents were mild and addressed quickly. Myocarditis was also more likely to develop after the second vaccination dosage than after the first, according to the researchers [4]. Only 54 incidences of myocarditis were found in the other trial, which included more than 2.5 million participants who got the vaccine. Also, they discovered that 2 out of every 100,000 persons who had at least one Pfizer injection suffered myocarditis, with the rate rising to almost 11 out of 100,000 in males aged 16–29. Overall, mild symptoms accounted for 76% of the cases, whereas moderate symptoms accounted for 22% [5]. According to the CDC, the risk of myocarditis in hospitalized patients infected with COVID-19 is 15.7 times higher than in individuals who have not been exposed to the virus [6]. Furthermore, men are more likely than women to acquire myocarditis as a result of SARS-CoV-2 infection, with the risk being highest in children under the age of 16 and in the elderly over the age of 50. In adults 16 and older, the danger of getting myocarditis is outweighed by the COVID-19 vaccination. Infection

Address for correspondence: Lukasz Szarpak, Assoc. Prof. PhD, DPH, DBA, MBA, Institute of Research Outcomes, Maria Sklodowska-Curie Medical Academy, Al. Solidarności 12, 03–411 Warszawa, Poland, e-mail: lukasz.szarpak@gmail.com

Received: 28.11.2021 Accepted: 4.12.2021 Early publication date: 7.12.2021

with SARS-CoV-2 was found to be 18 times more likely to cause myocarditis in this age range in previous investigations, a substantially larger risk than that reported after vaccination [7]. We should also be aware of the consequences of LONG-COVID-19 illness, including the possibility of myocarditis [8]. Data from 1/5 of the United States population was also evaluated, revealing that in the first 12 months of the pandemic, men aged 12 to 17 years old were most likely to have myocarditis within 3 months after COVID-19 infection, with an incidence of around 450 per million infections [9]. This is especially essential since immunizations also protect against the LONG-COVID-19 syndrome, COVID-19-induced myocarditis, and consequences such acute renal failure, arrhythmia, and thrombosis. The risk of heart inflammation from the COVID-19 vaccine is extremely low, and given the benefits of vaccination, such as a significantly lower risk of hospitalization and severe course, as well as a significantly higher risk of developing myocarditis during the disease or during the course of LONG-COVID-19, this should not be a deterrent to vaccinate or cause concern among the public and physicians. Failure to vaccinate will result in more damage and a higher risk of myocarditis in the case of infection, which is extremely likely given the current SARS-CoV-2 viral incidence. We should not be scared of this vaccination since it is the only effective form of protection against COVID-19 presently available, especially because it minimizes the chance of the virus mutating and evading immune control [10]. Given the present status of the pandemic, it appears that SARS-CoV-2 exposure is unavoidable.

Acknowledgments

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

Conflict of interest: None declared

References

1. Dzieciatkowski T, Szarpak L, Filipiak KJ, et al. COVID-19 challenge for modern medicine. Cardiol J. 2020; 27(2): 175–183, doi: 10.5603/CJ.a2020.0055, indexed in Pubmed: 32286679.
2. Wańha W, Wybraniec M, Kapłon-Cieślicka A, et al. Myocardial infarction in the shadow of COVID-19. Cardiol J. 2020; 27(5): 478–480, doi: 10.5603/CJ.2020.0152, indexed in Pubmed: 33165896.
3. Urdaneta V, Esposito D, Mansi J, et al. Myocarditis after mRNA-1273 vaccination: a population-based analysis of 151 million vaccine recipients worldwide. MedRev. 2021, doi: 10.1101/2021.11.11.21265536.
4. Mevorach D, Anis E, Cedar N, et al. Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel. N Engl J Med. 2021 [Epub ahead of print], doi: 10.1056/NEJMoa2109730, indexed in Pubmed: 34614328.
5. Witberg G, Barda N, Hoss S, et al. Myocarditis after Covid-19 vaccination in a large health care organization. N Engl J Med. 2021 [Epub ahead of print], doi: 10.1056/NEJMoa2110737, indexed in Pubmed: 34614329.
6. Boehmer TK, Kompaniyets L, Lavery AM, et al. Association between COVID-19 and myocarditis using hospital-based administrative data - united states, march 2020-january 2021. MMWR Morb Mortal Wkly Rep. 2021; 70(35): 1228–1232, doi: 10.15585/mmwr.mm7035e5, indexed in Pubmed: 34473684.
7. Barda N, Dagan N, Ben-Shlomo Y, et al. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. N Engl J Med. 2021; 385(12): 1078–1090, doi: 10.1056/NEJMoa2110475, indexed in Pubmed: 34432976.
8. Lorente-Ros A, Monteagudo Ruiz JM, Rincón LM, et al. Myocardial injury determination improves risk stratification and predicts mortality in COVID-19 patients. Cardiol J. 2020; 27(5): 489–496, doi: 10.5603/CJ.a2020.0089, indexed in Pubmed: 32589258.
9. Singer ME, Taub IB, Kaelber DC. Risk of myocarditis from COVID-19 infection in people under age 20: a population-based analysis. medRxiv. 2021, doi: 10.1101/2021.07.23.21260998, indexed in Pubmed: 34341797.
10. Szarpak L, Savytskyi I, Pruc M, et al. Variant lambda of the severe acute respiratory syndrome coronavirus 2 virus: A serious threat or the beginning of further dangerous mutations. Cardiol J. 2021 [Epub ahead of print], doi: 10.5603/CJ.a2021.0121, indexed in Pubmed: 34642924.

VIA MEDICA

LETTER TO THE EDITOR

Cardiology Journal
2021, Vol. 28, No. 6, 1003–1004
DOI: 10.5603/CJ.a2021.0162

ISSN 1897–5593
eISSN 1898–018X

Cardiopulmonary resuscitation in COVID-19

Jacek Smereka[1], Andrzej Raczynski[1], Pawel Wroblewski[1], Jaroslaw Baranski[2]

[1]Department of Emergency Medical Service, Wroclaw Medical University, Wroclaw, Poland
[2]Department of Humanities and Social Sciences, Wroclaw Medical University, Wroclaw, Poland

The coronavirus disease 2019 (COVID-19) pandemic has caused and is still causing enormous medical, social, economic and political problems. New mutations, concerns about transmissibility, vaccine resistance, vaccination rates in particular professional and age groups, areas or countries, as well as the capacity of health care systems and individuals are a source of concern not only for politicians, medical personnel, physicians but for every member of society who is anxious about the future [1–3].

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, among its many risks, also affects the risk of sudden cardiac arrest during the illness, during recovery and thereafter [4]. Avoiding deaths associated with deterioration of patient care due to an ongoing pandemic or the coexistence of COVID-19 with other conditions, including life-threatening conditions, is a significant concern [5]. For medical personnel working in both the in-hospital and prehospital setting, cardiopulmonary resuscitation (CPR) in patients with suspected or confirmed SARS-CoV-2 infection is associated with several technical issues related to the quality of chest compressions (CC) and the performance of advanced resuscitation measures, including airway management. The issue of responder safety is of particular importance: medical personnel should always be expected to be fully professional and to reduce the risk of infection, but rescuers, bystanders, and witnesses should also be considered based on their risk acceptance to vaccination and the relationship between the rescuer and victim. In first aid, it is acceptable to perform CC alone without ventilation, but it should be taken into account that even CC significantly promote aerosol generation and may increase the risk of infection for those providing assistance [6].

Many medical personnel are willing to assist regardless of the risk of infection or danger to the rescuer, treating it as their mission, guided by dedication and responding with compassion for patients. An ethical attitude is essential to help with commitment and reduce patients' fears in a skillful way. However, care must always be taken to ensure that work is well organized and resources are available to minimize the risks to medical staff.

A different issue is the qualification of patients for treatment in the intensive care department/ /settings, including eligibility to attempt CPR and the potential ethical dilemmas associated with qualifying patients for advanced treatment when equipment and medical staff and other resources are limited [2]. Everyone has the right to appropriate treatment, and no one should be denied available treatment — to the extent that medical personnel and the health care system are able. The availability of appropriate procedures for health professionals to deal with the stresses on the health system is a way to protect them from the adverse effects of working in extreme conditions. When considering ethical issues, elements such as safety, accessibility, availability, and ability should be taken into account and the patient's real chances in the context of risk factors, conditions, and expected outcome [7, 8].

The qualification of patients for the initiation of CPR, including its duration and timing of termination of resuscitation, should also be considered in this regard. The use of personal protective equipment may affect the quality and thus the effectiveness of resuscitation actions undertaken [9, 10]. Another problem is the availability of medical

Address for correspondence: Jacek Smereka, Assoc. Prof., PhD, MD, Department of Emergency Medical Service, Wroclaw Medical University, ul. Bartla 6, 52–443 Wrocław, Poland, tel: +48 601967070, e-mail: jacek.smereka@umed.wroc.pl

Received: 4.12.2021 Accepted: 4.12.2021 Early publication date: 7.12.2021

emergency teams, the possibility to reach the scene of an accident in a short period when the health care systems are heavily overloaded, including the emergency medical services system — the availability of ambulances is reduced. In a hospital setting, the time of initiation of resuscitation actions may also be affected by the time of arrival and donning of full personal protective equipment.

It is worth noting that the ERC recommends that medical personnel should be properly protected during CPR, i.e. wear airborne-precaution personal protective equipment (PPE) including gloves, long-sleeved gown, filtering facepiece 3 (FFP3) or N99 mask/respirator (FFP2 or N95 if FFP3 not available) as well as eye and face protection (full-face shield/visor or polycarbonate safety glasses or equivalent) [7]. Note that international societies recommend that during resuscitation in healthcare settings, resuscitation teams should consist only of persons who have been trained in the proper use of PPE and who have access to and are provided with such equipment [7]. During CC, the risk of generating aerosols is very high, and airway management is also considered an aerosol-generating procedure. Particular attention should be paid to the use of high-quality filters connecting the self-inflating bag, the mask and supraglottic airway device or endotracheal tube to minimize the risk of virus spread [7].

Unfortunately, with the observed trend in the number and characteristics of patients with severe COVID-19, consideration should be given to performing CPR in children with SARS-CoV-2 infection, in whom cardiac arrest may be due to respiratory or other causes. In general, similar standards as for adults with SARS-CoV-2 infection apply, but special attention should be paid to the airway, airway management, and rapid recognition of life-threatening conditions in the child.

The COVID-19 pandemic affects resuscitation of both adults and children, organizational and practical issues, particularly demanding the organization and quality of the efforts undertaken. Given the current epidemiological situation, every practitioner must be prepared to perform CPR in the specific circumstances accompanying with individual protective measures and the associated difficulties and limitations before such an event occurs.

Conflict of interest: None declared

References

1. Kowalik MM, Trzonkowski P, Łasińska-Kowara M, et al. COVID-19 — Toward a comprehensive understanding of the disease. Cardiol J. 2020; 27(2): 99–114, doi: 10.5603/CJ.a2020.0065, indexed in Pubmed: 32378729.
2. Dzieciatkowski T, Szarpak L, Filipiak KJ, et al. COVID-19 challenge for modern medicine. Cardiol J. 2020; 27(2): 175–183, doi: 10.5603/CJ.a2020.0055, indexed in Pubmed: 32286679.
3. Smereka J, Szarpak L, Filipiak K. Modern medicine in COVID-19 era. Dis Emerg Med J. 2020, doi: 10.5603/demj.a2020.0012.
4. Li G, Saguner AM, An J, et al. Cardiovascular disease during the COVID-19 pandemic: Think ahead, protect hearts, reduce mortality. Cardiol J. 2020; 27(5): 616–624, doi: 10.5603/CJ.a2020.0101, indexed in Pubmed: 32789839.
5. Wańha W, Wybraniec M, Kapłon-Cieślicka A, et al. Myocardial infarction in the shadow of COVID-19. Cardiol J. 2020; 27(5): 478–480, doi: 10.5603/CJ.2020.0152, indexed in Pubmed: 33165896.
6. Al-Jeabory M, Safiejko K, Bialka S, et al. Impact of COVID-19 on bystander cardiopulmonary resuscitation in out-of-hospital cardiac arrest: Is it as bad as we think? Cardiol J. 2020; 27(6): 884–885, doi: 10.5603/CJ.a2020.0179, indexed in Pubmed: 33346369.
7. Nolan JP, Monsieurs KG, Bossaert L, et al. European Resuscitation Council COVID-Guideline Writing Groups. European Resuscitation Council COVID-19 guidelines executive summary. Resuscitation. 2020; 153: 45–55, doi: 10.1016/j.resuscitation.2020.06.001, indexed in Pubmed: 32525022.
8. Szarpak L, Ruetzler K, Dabrowski M, et al. Dilemmas in resuscitation of COVID-19 patients based on current evidence. Cardiol J. 2020; 27(3): 327–328, doi: 10.5603/CJ.a2020.0066, indexed in Pubmed: 32419130.
9. Malysz M, Dabrowski M, Böttiger BW, et al. Resuscitation of the patient with suspected/confirmed COVID-19 when wearing personal protective equipment: A randomized multicenter crossover simulation trial. Cardiol J. 2020; 27(5): 497–506, doi: 10.5603/CJ.a2020.0068, indexed in Pubmed: 32419128.
10. Malysz M, Jaguszewski M, Szarpak L, et al. Comparison of different chest compression positions for use while wearing CBRN-PPE: a randomized crossover simulation trial. Dis Emerg Med J. 2020, doi: 10.5603/demj.a2020.0034.

VIA MEDICA

LETTER TO THE EDITOR

Cardiology Journal
2021, Vol. 28, No. 6, 1005–1006
DOI: 10.5603/CJ.a2021.0163

ISSN 1897–5593
eISSN 1898–018X

COVID-19 are dangerous to the kidneys in any situation, not only in a pandemic: LONG-COVID-19 and kidney disease

Togay Evrin, Burak Katipoglu

Department of Emergency Medicine, Ufuk University Medical Faculty, Dr Ridvan Ege Education and Research Hospital, Ankara, Turkey

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) posed a major threat to health care and medical staff from the start of the epidemic, but its impact will extend beyond this pandemic and into the future [1]. The kidney is one of the organs that has been infected with SARS-CoV-2. Podocytes, proximal renal tubular cells, and glomerular endothelial cells, as well as perhaps mesangial cells and Bowman's capsule epithelium, exhibit the essential angiotensin converting enzyme type 2 (ACE2) for viral entry. The expression of ACE2 in the kidneys is extremely high, maybe 100 times higher than in the lungs [2]. Infected individuals have much higher levels of angiotensin 2 in their blood, which activates the renin–angiotensin system, causing extensive endothelial dysfunction [3]. Patients who have had coronavirus disease 2019 (COVID-19)-induced acute kidney injury (AKI) are not uncommon these days, and they have a significantly increased risk of developing progressive chronic kidney disease (CKD) as a result of their treatment. Mechanical breathing, continuous renal replacement treatment, and extracorporeal membrane oxygenation are frequently used to help patients with severe and critical COVID-19 [4]. AKI is detected in around 28% of COVID-19 patients who are hospitalized, and 9% of these patients who undergo kidney replacement treatment [5]. However, given the growing body of evidence, it appears that it is not just the survival of AKI associated with COVID-19 that can cause damage to kidney disease associated with COVID-19. COVID-19 increased the risk of CKD, according to United States research that utilized electronic health data from the Veterans Health Administration to conduct a complete evaluation of lengthy COVID-19. This risk was largest among individuals who had severe illness. Even beyond the first 30 days after diagnosis of COVID-19, unfavorable renal symptoms such as urinary tract infections, AKI, and CKD occurred in individuals who required hospitalization [6]. Patients with COVID-19 in China, which indicated that 6 months after COVID-19 hospitalization, 35% of patients had impaired kidney function (estimated glomerular filtration rate [eGFR] < 90 mL/min/1.73 m^2). Surprisingly, during follow-up, 13% of patients who did not develop AKI during hospitalization showed a decrease in eGFR [7]. In a study of more than 1.7 million persons, 90,000 of whom were COVID-19 survivors with symptoms lasting at least 30 days, it was shown that roughly 5% of them had a 30% drop in a vital measure of kidney function (eGFR). This means that those infected with LONG-COVID-19 were 25% more likely than uninfected people to acquire a 30% drop in eGFR, with a larger risk in those who survived the more severe sickness. However, the condition impacted many patients who were not hospitalized [8]. From the perspective of some studies, which indicate that 5% of vaccinated patients develop LONG-COVID-19, and in the unvaccinated group, 11% may pose a serious nephrology challenge during and after the pandemic itself, when we deal with a huge percent-

Address for correspondence: Togay Evrin, PhD, MD, Department of Emergency Medicine, Ufuk University Medical Faculty, Dr Ridvan Ege Education and Research Hospital, Ufuk Ünv. Cd No:1, 06510 Çankaya/Ankara, Turkey, e-mail: togayevrin71@gmail.com

Received: 4.12.2021 Accepted: 4.12.2021 Early publication date: 7.12.2021

age of patients with ailments of the kidneys [9]. Clinicians who must pay close attention to kidney function evaluation will play a critical role, not only in the group of hospitalized patients, but also in the group of seemingly asymptomatic patients, and notably in the group of patients with LONG--COVID-19. Vaccinations also play an important role in reducing the risk of serious illness, hospitalization, and complications such as LONG-COVID-19. In the current epidemiological crisis, it is critical to vaccinate as many people as possible in order to protect them against the long-term impacts of complications from the pandemic. We must also remember that vaccinated people may also become ill, even mildly, and suffer complications even after an asymptomatic form of the disease, so remember to wear masks and social distance [10].

Conflict of interest: None declared

References

1. Dzieciatkowski T, Szarpak L, Filipiak KJ, et al. COVID-19 challenge for modern medicine. Cardiol J. 2020; 27(2): 175–183, doi: 10.5603/CJ.a2020.0055, indexed in Pubmed: 32286679.
2. Huang Z, Jiang Y, Chen J, et al. Inhibitors of the renin-angiotensin system: The potential role in the pathogenesis of COVID-19. Cardiol J. 2020; 27(2): 171–174, doi: 10.5603/CJ.a2020.0056, indexed in Pubmed: 32286678.
3. Smereka J, Szarpak L, Filipiak K. Modern medicine in COVID-19 era. Dis Emerg Med J. 2020, doi: 10.5603/demj.a2020.0012.
4. Yu M, Cheng X. Cardiac injury is independently associated with mortality irrespective of comorbidity in hospitalized patients with coronavirus disease 2019. Cardiol J. 2020; 27(5): 472–473, doi: 10.5603/CJ.2020.0150, indexed in Pubmed: 33165894.
5. Silver SA, Beaubien-Souligny W, Shah PS, et al. The prevalence of acute kidney injury in patients hospitalized with COVID-19 infection: a systematic review and meta-analysis. Kidney Med. 2021; 3(1): 83–98.e1, doi: 10.1016/j.xkme.2020.11.008, indexed in Pubmed: 33319190.
6. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature. 2021; 594(7862): 259–264, doi: 10.1038/s41586-021-03553-9, indexed in Pubmed: 33887749.
7. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021; 397(10270): 220–232, doi: 10.1016/S0140-6736(20)32656-8, indexed in Pubmed: 33428867.
8. Bowe B, Xie Y, Xu E, et al. Kidney outcomes in long COVID. J Am Soc Nephrol. 2021; 32(11): 2851–2862, doi: 10.1681/ASN.2021060734, indexed in Pubmed: 34470828.
9. Antonelli M, Penfold RS, Merino J, et al. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. Lancet Infect Dis. 2021 [Epub ahead of print], doi: 10.1016/S1473-3099(21)00460-6, indexed in Pubmed: 34480857.
10. Szarpak L, Smereka J, Filipiak KJ, et al. Cloth masks versus medical masks for COVID-19 protection. Cardiol J. 2020; 27(2): 218–219, doi: 10.5603/CJ.a2020.0054, indexed in Pubmed: 32285928.