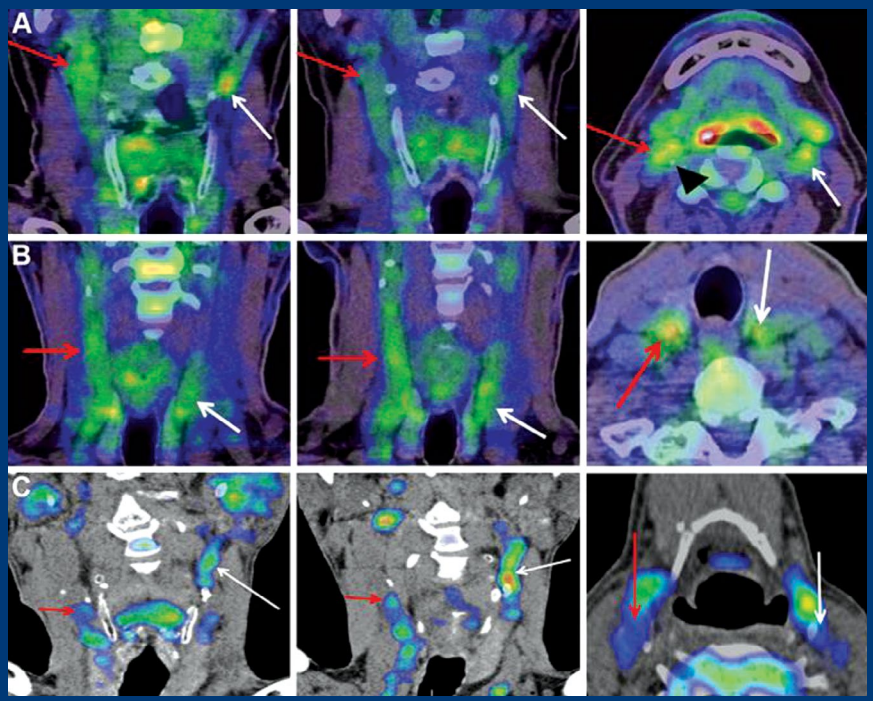
CARDIOLOGY JOURNAL

Impact Factor: 1.669

November 2020, Vol. 27, No. 6, pp. 661–908 www.cardiologyjournal.org



Chan Joon Kim et al., see figure legend on page 767

ISSN 1897–5593

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) 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 (169.43 points), MEDLINE, Scopus, SJR, Ulrich's Periodicals Directory, Web of Science CC and WorldCat database, Ministry of Science and Higher Education score (40 points). Current Impact Factor of "Cardiology Journal" (2019) is 1.669.

Advertising: For details on media opportunities within this journal please contact the advertising sales department ul. Swietokrzyska 73, 80–180 Gdansk, tel: (+48 58) 320 94 94, e-mail: viamedica@viamedica.pl
The Editors take no responsibility for the published advertisements.

Editorial policies and author guidelines are published on journal website: www.cardiologyjournal.org

Legal note: https://journals.viamedica.pl/cardiology_journal/about/legalNote

19-0181.006.001

CARDIOLOGY JOURNAL

www.cardiologyjournal.org

November 2020, Vol. 27, No. 6

Table of Contents

LETTERS TO THE EDITOR

COVID-19

Clinical cardiology

VIA MEDICA

EXPERTS' VIEWPOINT

Cardiology Journal
2020, Vol. 27, No. 6, 661–676
DOI: 10.5603/CJ.a2020.0132

ISSN 1897–5593
eISSN 1898–018X

Prolonged antithrombotic therapy in patients after acute coronary syndrome: A critical appraisal of current European Society of Cardiology guidelines

Jacek Kubica[1], Piotr Adamski[1], Piotr Niezgoda[1], Dimitrios Alexopoulos[2], Jolita Badarienė[3], Andrzej Budaj[4], Katarzyna Buszko[5], Dariusz Dudek[6, 7], Tomasz Fabiszak[1], Mariusz Gąsior[8], Robert Gil[9], Diana A. Gorog[10], Stefan Grajek[11], Paul A. Gurbel[12], Marcin Gruchała[13], Miłosz J. Jaguszewski[13], Stefan James[14], Young-Hoon Jeong[15], Bernd Jilma[16], Jarosław D. Kasprzak[17], Andrzej Kleinrok[18, 19], Aldona Kubica[20], Wiktor Kuliczkowski[21], Jacek Legutko[22], Maciej Lesiak[11], Jolanta M. Siller-Matula[23, 24], Klaudiusz Nadolny[25, 26], Krzysztof Pstrągowski[1], Salvatore Di Somma[27], Giuseppe Specchia[28], Janina Stępińska[29], Udaya S. Tantry[12], Agnieszka Tycińska[30], Monica Verdoia[31], Wojciech Wojakowski[32], Eliano P. Navarese[1]

[1]Department of Cardiology and Internal Medicine, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland; [2]National and Kapodistrian University of Athens Medical School, Attikon University Hospital, Athens, Greece; [3]Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania; [4]Department of Cardiology, Center of Postgraduate Medical Education, Grochowski Hospital, Warsaw, Poland; [5]Department of Theoretical Foundations of Bio-Medical Science and Medical Informatics, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland; [6]Institute of Cardiology, Jagiellonian University Medical College, Krakow, Poland; [7]Maria Cecilia Hospital, GVM Care and Research, Cotignola (RA), Ravenna, Italy; [8]3rd Department of Cardiology, Silesian Center for Heart Diseases, Faculty of Medicine in Zabrze, Medical University of Silesia, Zabrze, Poland; [9]Department of Invasive Cardiology, Center of Postgraduate Medical Education, Central Hospital of the Internal Affairs and Administration Ministry, Warsaw, Poland; [10]Postgraduate Medicine, University of Hertfordshire, United Kingdom and Faculty of Medicine, National Heart and Lung Institute, Imperial College, London, United Kingdom; [11]Department of Cardiology, Poznan University of Medical Sciences, Poznan, Poland; [12]Sinai Center for Thrombosis Research and Drug Development, Sinai Hospital of Baltimore, MD, USA; [13]1st Department of Cardiology, Medical University of Gdansk, Poland; [14]Department of Medical Sciences and Uppsala Clinical Research Center, Uppsala University Hospital, Uppsala, Sweden; [15]Department of Internal Medicine, Gyeongsang National University School of Medicine and Cardiovascular Center, Gyeongsang National University Changwon Hospital, Changwon, South Korea; [16]Department of Clinical Pharmacology, Medical University of Vienna, Austria; [17]1st Department and Chair of Cardiology, Medical University of Lodz, Bieganski Hospital, Lodz, Poland; [18]University of Information Technology and Management in Rzeszow, Poland; [19]Department of Cardiology, The Pope John Paul II Hospital in Zamosc, Poland; [20]Department of Health Promotion, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland; [21]Department of Cardiology, Medical University of Wrocław, Poland; [22]Department of Interventional Cardiology, Institute of Cardiology, Jagiellonian University Medical College, John Paul II Hospital in Krakow, Poland; [23]Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, Poland; [24]Department of Cardiology, Medical University of Vienna, Austria; [25]Department of Emergency Medical Service, Strategic Planning University of Dabrowa Gornicza, Poland; [26]Faculty of Medicine, Katowice School of Technology, Katowice, Poland; [27]Department of Medical-Surgery Sciences and Translational Medicine, University La Sapienza, Rome, Italy; [28]Pavia, Italy; [29]Department of Intensive Cardiac Therapy, National Institute of Cardiology, Warsaw, Poland; [30]Department of Cardiology, Medical University of Bialystok, Poland; [31]Division of Cardiology, Ospedale degli Infermi ASL Biella, Università del Piemonte Orientale, Italy; [32]Division of Cardiology and Structural Heart Diseases, Medical University of Silesia, Katowice, Poland

Address for correspondence: Prof. Jacek Kubica, Department of Cardiology and Internal Medicine, Collegium Medicum, Nicolaus Copernicus University, ul. M. Skłodowskiej-Curie 9, 85–094 Bydgoszcz, Poland, tel: +48 52 5854023, fax: +48 52 5854024, e-mail: jkubica@cm.umk.pl

Received: 22.09.2020 Accepted: 12.10.2020

This article has been co-published in the 'Medical Research Journal' 2020, vol. 5, no. 3, pages: 177–190, doi: 10.5603/MRJ.a2020.0035 with permission of both Editorial Boards and the Publisher.

Abstract

The increased risk of non-cardiovascular death in patients receiving clopidogrel or prasugrel in comparison with the placebo group in the Dual Antiplatelet Therapy (DAPT) trial in contrast to the decreased risk of cardiovascular death and all-cause death seen in patients treated with low-dose ticagrelor in the EU label population of the PEGASUS-TIMI 54 trial, resulted in inclusion in the 2020 ESC NSTE-ACS guidelines the recommendation for use of clopidogrel or prasugrel only if the patient is not eligible for treatment with ticagrelor.

The prevalence of the primary outcome composed of cardiovascular death, stroke, or myocardial infarction was lower in the low-dose rivaroxaban and acetylsalicylic acid (ASA) group than in the ASA-alone group in the COMPASS trial. Moreover, all-cause mortality and cardiovascular mortality rates were lower in the rivaroxaban-plus-ASA group.

Comparison of the PEGASUS-TIMI 54 and COMPASS trial patient characteristics clearly shows that each of these treatment strategies should be addressed at different groups of patients. A greater benefit in post-acute coronary syndrome (ACS) patients with a high risk of ischemic events and without high bleeding risk may be expected with ASA and ticagrelor 60 mg b.i.d. when the therapy is continued without interruption or with short interruption only after ACS. On the other hand, ASA and rivaroxaban 2.5 mg b.i.d. seems to be a better option when indications for dual antithrombotic therapy (DATT) appear after a longer time from ACS (more than 2 years) and/or from cessation of DAPT (more than 1 year) and in patients with multiple vascular bed atherosclerosis. Thus, both options of DATTs complement each other rather than compete, as can be presumed from the recommendations. However, a direct comparison between these strategies should be tested in future clinical trials. (Cardiol J 2020; 27, 6: 661–676)

Key words: prolonged antithrombotic therapy, chronic coronary syndrome, acute coronary syndrome, rivaroxaban, ticagrelor, clopidogrel, prasugrel

Introduction

Conventional antithrombotic therapy following myocardial revascularization in acute coronary syndrome (ACS) patients comprises low-dose acetylsalicylic acid (ASA) and a P2Y12 receptor inhibitor — a combination referred to as dual antiplatelet therapy (DAPT) — for up to 12 months after ACS [1–5]. However, increased risk of ischemic events persists in a substantial proportion of stable patients who have completed this period of DAPT after ACS [6–9].

According to the 2019 European Society of Cardiology (ESC) guidelines for the diagnosis and management of chronic coronary syndromes (CCS), "adding a second antithrombotic drug to ASA for long-term secondary prevention should be considered in patients with a high risk of ischemic events and without high bleeding risk" (class of recommendation IIa, level of evidence A) — as a dual antithrombotic therapy (DATT). This strategy "may be also considered in patients with at least a moderately increased risk of ischemic events and without high bleeding risk" (class of recommendation IIb, level of evidence A) [10].

The same document specifies risk factors defining high and moderate risk of ischemic complications as well as high bleeding risk in patients with CCS, remaining in sinus rhythm (Table 1) [10].

The 2020 ESC guidelines for the management of ACSs in patients presenting without persistent ST-segment elevation modified the ischemic risk assessment (Table 2) and introduced a definition of a high risk of bleeding according to the Academic Research Consortium for High Bleeding Risk (Table 3) [11].

It is also expressed in the guidelines that prolonged antithrombotic therapy with a combination of ASA and either a second antiplatelet agent or rivaroxaban at the "vascular dose" of 2.5 mg b.i.d can be considered an option for patients with increased ischemic risk, who completed the standard 12-month DAPT following myocardial revascularization due to acute myocardial infarction (MI). The pivotal question that arises at this point is: which treatment should be applied to

Table 1. Risk factors of high/moderate ischemic and high bleeding risk in patients with chronic coronary syndromes in sinus rhythm according to the 2019 ESC CCS guidelines [10].

High ischemic risk*	High bleeding risk
Diffuse multivessel CAD with at least one of the following: • Diabetes mellitus requiring medication • Recurrent MI • PAD • CKD with eGFR 15–59 mL/min/1.73 m^2	• Prior history of intracerebral hemorrhage or ischemic stroke • History of other intracranial pathology • Recent gastrointestinal bleeding or anemia due to possible gastrointestinal blood loss • Other gastrointestinal pathology associated with increased bleeding risk • Liver failure • Bleeding diathesis or coagulopathy • Extreme old age or frailty • Renal failure requiring dialysis or with eGFR < 15 mL/min/1.73 m^2

*Moderate risk if any single factor, including HF, is present; CAD — coronary artery disease; CKD — chronic kidney disease; GFR — estimated glomerular filtration rate; HF — heart failure; MI — myocardial infarction; PAD — peripheral artery disease

Table 2. Risk factors of ischemic events — criteria for extended treatment with a second antithrombotic agent according to the 2020 ESC NSTE-ACS guidelines [11].

High thrombotic risk	Moderate thrombotic risk
Complex CAD and at least 1 criterion Risk enhancers: • DM requiring medication • Recurrent MI • Multivessel CAD • Polyvascular disease (CAD plus PAD) • Premature (< 45 years) or accelerated (new lesion within a 2-year time frame) CAD • Concomitant systemic inflammatory disease (e.g. human immunodeficiency virus, systemic lupus erythematosus, chronic arthritis) • CKD with eGFR 15–59 mL/min/1.73 m^2 Technical aspects: • ≥ 3 stents implanted • ≥ 3 lesions treated • Total stent length > 60 mm • Previous complex revascularization (left main, bifurcation stenting with ≥ 2 stents implanted, chronic total occlusion, stenting of last patent vessel) • Previous stent thrombosis on antiplatelet treatment	**Non-complex CAD and at least 1 criterion** • DM requiring medication • Recurrent MI • Polyvascular disease (CAD plus PAD) • CKD with eGFR 15-59 mL/min/1.73 m^2

CAD — coronary artery disease; CKD — chronic kidney disease; DM — diabetes mellitus; eGFR — estimated glomerular filtration rate; MI — myocardial infarction; PAD — peripheral artery disease

which patient? Unfortunately, the indications and cautions mentioned in the guidelines are too vague and too limited to assist practicing physicians in making this choice in the real-world scenario (Table 4) [10, 11]. Thus, according to the authors of this position paper, the essential practical implications of these recommendations are still missing. Therefore, while designing the ELECTRA-SIRIO 2 randomized clinical trial, aiming to assess strategies of treatment in stable patients after MI, we decided to analyze ESC recommendations as well as available evidence regarding this issue [12, 13].

Trials supporting recommendation for DATT in CCS patients after MI

The ESC recommendations [10, 11] are based on several large randomized clinical trials con-

Table 3. Criteria for high bleeding risk according to the Academic Research Consortium for High Bleeding Risk at the time of percutaneous coronary intervention (bleeding risk is high if at least one major or two minor criteria are met) [11].

Major	Minor
Anticipated use of long-term OAC	Age ≥ 75 years
Severe or end-stage CKD (eGFR <30 mL/min)	Moderate CKD (eGFR 30-59 mL/min)
Hemoglobin < 11 g/dL	Hemoglobin 11–12.9 g/dL for men or 11–11.9 g/dL for women
Spontaneous bleeding requiring hospitalization and/ortransfusion in the past 6 months or at any time, if recurrent	Spontaneous bleeding requiring hospitalization and/or transfusion within the past 12 months, not meeting the major criterion
Baseline thrombocytopenia (platelet count < 100 -10^9/L)	Chronic use of oral non-steroidal anti-inflammatory drugs or steroids
Chronic bleeding diathesis	Ischemic stroke not meeting the major criterion
Liver cirrhosis with portal hypertension	
Active malignancy (excluding non-melanoma skin cancer) within the past 12 months	
Previous spontaneous intracranial hemorrhage	
Previous traumatic intracranial hemorrhage within the past 12 months	
Presence of a brain arteriovenous malformation	
Moderate or severe ischemic stroke within the past 6 months	
Recent major surgery or major trauma within 30 days prior to PCI	
Non-deferrable major surgery on DAPT	

CKD — chronic kidney disease; DAPT — dual antiplatelet therapy; eGFR — estimated glomerular filtration rate; PCI — percutaneous coronary intervention; OAC — oral anticoagulant

Table 4. Treatment options for dual antithrombotic therapy in combination with acetylsalicylic acid (75–100 mg daily) in patients with a high or moderate risk of ischemic events and without high bleeding risk [10, 11].

Drug option	Dose	Indication	Additional cautions	Supporting trial
Clopidogrel	75 mg o.d.	Post-MI in patients who have tolerated DAPT for 1 year		DAPT
Prasugrel	10 mg o.d. or 5 mg o.d.; if body weight < 60 kg or age > 75 years	Post-PCI for MI in patients who have tolerated DAPT for 1 year	Age > 75 years	DAPT TL-PAS
Ticagrelor	60 mg b.i.d.	Post-MI in patients who have tolerated DAPT for 1 year		PEGASUS-TIMI 54
Rivaroxaban	2.5 mg b.i.d.	Post-MI > 1 year or multivessel CAD [10] or Patients with CAD or symptomatic PAD at high risk of ischemic events [11]	CrCl 15–29 mL/min	COMPASS

CAD — coronary artery disease; CrCl — creatinine clearance; DAPT — dual antiplatelet therapy; MI — myocardial infarction; PAD — peripheral artery disease; PCI — percutaneous coronary intervention

Table 5. Clinical trials supporting the 2019 European Society of Cardiology (ESC) guidelines for the diagnosis and management of chronic coronary syndromes (according to citations) [14–22].

Study ClinicalTrials.gov	Publication	Patients	Study treatment	Outcome
DAPT NCT00977938	Mauri et al. NEJM 2014 [14]	N = 9961 pts 12 m after DES implantation	clo 1 × 75 mg or pra 1 × 10 mg or 1 × 5 mg in pts who weighed < 60 kg and ASA vs. placebo and ASA up to 30 m	DAPT beyond 1 year after DES placement reduced the risks of ST and MACCE, but was associated with an increased risk of bleeding
	Yeh et al. JACC 2015 [15]	N = 11,648 pts MI (n = 3576) No-MI (n = 8072) 12 m after stent implantation DES (n = 9961) BMS (n = 1687)	clo 1 × 75 mg or pra 1 × 10 mg or 1 × 5 mg in pts who weighed < 60 kg and ASA vs. placebo and ASA up to 30 m	30 m of DAPT after stent placement reduced risk of ST and MI in pts with and without MI and increased bleeding
DAPT/TL-PAS NCT00997503 Sub-population of the DAPT trial	Garratt et al. Circulation 2015 [16]	N = 2191 pts 12 m after TAXUS implantation	pra 1 × 10 mg or 1 × 5 mg in pts who weighed < 60 kg and ASA vs. placebo and ASA up to 30 m	DAPT continued for 30 m after stent placement reduced ischemic events through reduction in MI and ST. Withdrawal of prasugrel was followed by increase in MI after 12 and 30 m therapy
PEGASUS-TIMI 54 NCT01225562	Bonaca et al. NEJM 2015 [17]	21,162 pts 1 to 3 years after MI	tic 2 × 90 mg and ASA vs. tic 2 × 60 mg and ASA vs. placebo and ASA up to 36 m	DAPT reduced risk of CV death, MI, or stroke and increased risk of major bleeding
	Bhatt et al. JACC 2016 [18]	21,162 pts DM (n = 6806) No-DM (n = 14,355) 1 to 3 years after MI		In pts with DM DAPT reduced risk of recurrent ischemic events including CV death and CHD death
	Bonaca et al. JACC 2016 [19]	21,162 pts PAD (n = 1143) No-PAD (n = 20,017) 1 to 3 years after MI		DAPT reduced MACE and MALE in PAD patients
	Bonaca et al. EHJ 2016 [20]	18,761 pts 1 to 3 years after MI DAPT cessation prior to randomization: ≤ 30 days (n = 7181) > 30 days to 1 year (n = 6501) > 1 year (n = 5079)		The benefit of DAPT was higher in pts continuing on or re-starting early after interruption of P2Y12 inhibition when compared with pts stable > 2 years from MI and off P2Y12 inhibitor > 1 year. The increase in bleeding events with ticagrelor was similar regardless of this time interval
	Bansilal et al. JACC 2018 [21]	21,162 pts MVD (n = 12,558 pts) No-MVD (n = 8600 pts) 1 to 3 years after MI		In pts with MVD DAPT reduced risk of MACE and CE, and increased the risk of major bleeding, but not ICH or fatal bleeding

ASA — acetylsalicylic acid; BMS — bare-metal stent; CE — coronary events (coronary death, MI, or stent thrombosis); CHD — coronary heart disease; clo — clopidogrel; CV — cardiovascular; DAPT — dual antiplatelet therapy; DES — drug-eluting stent; DM — diabetes mellitus; ICH — intracranial hemorrhage; MACCE — major adverse CV and cerebrovascular events (death, MI, or stroke); MACE — major adverse CV events (CV death, MI, or stroke); MALE — major adverse limb events (acute limb ischemia or peripheral revascularization for ischemia); MI — myocardial infarction; MVD — multivessel disease; PAD — peripheral artery disease; pra — prasugrel; pts — patients; riv — rivaroxaban; ST — stent thrombosis; TAXUS — paclitaxel-eluting stent; tic — ticagrelor

ducted in various populations (Table 5) [14–22]. Inclusion and exclusion criteria as well as the profile of patients enrolled in these trials should be used to determine indications for particular agents.

Table 5 (cont.). Clinical trials supporting the 2019 European Society of Cardiology (ESC) guidelines for the diagnosis and management of chronic coronary syndromes (according to citations) [14–22].

Study ClinicalTrials.gov	Publication	Patients	Study treatment	Outcome
COMPASS NCT01776424	Eikelboom et al. NEJM 2017 [22]	27,395 pts with stable atherosclerotic vascular disease	riv 2 × 2.5 mg and ASA vs. riv 2 × 5 mg and placebo vs. placebo and ASA	Pts assigned to riv plus ASA had better CV outcomes and more major bleeding events than those assigned to ASA alone. Riv alone did not result in better CV outcomes than ASA alone and resulted in more major bleeding events

ASA — acetylsalicylic acid; BMS — bare-metal stent; CE — coronary events (coronary death, MI, or stent thrombosis); CHD — coronary heart disease; clo — clopidogrel; CV — cardiovascular; DAPT — dual antiplatelet therapy; DES — drug-eluting stent; DM — diabetes mellitus; ICH — intracranial hemorrhage; MACCE — major adverse CV and cerebrovascular events (death, MI, or stroke); MACE — major adverse CV events (CV death, MI, or stroke); MALE — major adverse limb events (acute limb ischemia or peripheral revascularization for ischemia); MI — myocardial infarction; MVD — multivessel disease; PAD — peripheral artery disease; pra — prasugrel; pts — patients; riv — rivaroxaban; ST — stent thrombosis; TAXUS — paclitaxel-eluting stent; tic — ticagrelor

Dual antiplatelet therapy with ASA and a P2Y12 receptor inhibitor

Tolerability of DAPT during the recommended 12-month therapy period and reduction of the risk of ischemic events outweighing the elevated bleeding risk is a premise for prolonged therapy with a P2Y12 receptor inhibitor and ASA [23–25]. According to the citations in the ESC guidelines [10, 11], indications to use clopidogrel, prasugrel, or ticagrelor in combination with ASA in patients with CCS after ACS are based on the data coming from the DAPT [14, 15, 26], TL-PAS [16], and PEGASUS-TIMI 54 trials [17–21].

The Dual Antiplatelet Therapy (DAPT) trial assessed the benefits and risks of 30 vs. 12 months of DAPT with a thienopyridine derivate (clopidogrel or prasugrel) and ASA in patients with ischemic heart disease due to stenotic or occlusive lesions in either native coronary arteries or coronary artery bypass grafting treated with stent implantation [14, 15, 26]. The choice of thienopyridine and its dose followed the local standard of practice in the study sites. Out of the 11,648 randomized patients (9961 treated with drug-eluting stents [DES], 1687 with bare-metal stents [BMS]), 30.7% presented with MI. After 12 months of DAPT, patients were randomly assigned to continue treatment with thienopyridine or placebo for another 18 months; all patients continued receiving ASA. Continuation of DAPT beyond 1 year after DES implantation, as compared with ASA therapy alone, significantly reduced the risk of stent thrombosis (0.4% vs. 1.4%; hazard ratio [HR] 0.29; $p < 0.001$), MI (2.1% vs. 4.1%; HR 0.47; $p < 0.001$), MI not related to stent thrombosis (1.8% vs. 2.9%; HR 0.59; $p < 0.001$), and major adverse cardiovascular and cerebrovascular events (4.3% vs. 5.9%; HR 0.71 (95% confidence interval [CI] 0.59–0.85; $p < 0.001$), but was associated with an increased risk of moderate or severe bleeding (2.5% vs. 1.6%, $p = 0.001$). An elevated risk of stent thrombosis and MI was observed in both groups during the first 3 months after discontinuation of thienopyridine treatment [14]. The risk of death from any cause was higher in the group that continued to receive thienopyridine as compared with the placebo group (2.0% vs. 1.5%; HR 1.36; $p = 0.05$). During the secondary-analysis period (month 12 to month 33) the rate of all-cause mortality was higher in the thienopyridine group: 2.3% vs. 1.8%, respectively (HR 1.36; $p = 0.04$). The difference was driven by an increase in the number of non-cardiovascular deaths (mainly related to bleeding, fatal trauma, and cancer) in the thienopyridine group. It is not clear what proportion of these deaths was related to evaluated treatment, as some of the deaths not defined as bleeding-related were mediated by bleeding [14].

The TAXUS Liberté Post Approval Study (TL-PAS) — a subpopulation of DAPT — included patients who were treated with a TAXUS Liberté paclitaxel-eluting stent and prasugrel [16]. The TL-PAS patients represented the largest group of patients implanted with a paclitaxel-eluting coronary stent, and the largest cohort receiving prasugrel, enrolled into the DAPT study. The occurrence of the DAPT study co-primary composite end point (death, MI, or stroke) was lower in patients receiving the combination of prasugrel and ASA for 30 months compared with 12 months (3.7% vs. 8.8%; HR 0.407; $p < 0.001$) solely through the

reduction in MI rate (1.9% vs. 7.1%; HR 0.255; $p < 0.001$). The incidence of stent thrombosis was also lower with longer dual antiplatelet therapy (0.2% vs. 2.9%; HR 0.063; $p < 0.001$). Rates of death and stroke were similar in both groups. Withdrawal of prasugrel was followed by an increase in the rate of MI after both 12 and 30 months of therapy. The optimal duration of DAPT with prasugrel after implantation of a TAXUS Liberté paclitaxel-eluting stent remains unknown, but it appears to be longer than 30 months [16].

The results of this study are of limited relevance because paclitaxel-eluting stents are no longer used due to the increased risk of major adverse cardiac events mainly driven by a higher rate of MI, target-vessel revascularization, and stent thrombosis, especially a very late one [27, 28].

The PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54) trial was designed to test the hypothesis that long-term therapy with ticagrelor added to low-dose ASA reduces the risk of major adverse cardiovascular events (MACE) in stable patients with a history of MI [17]. Patients were randomized in a 1:1:1 ratio to receive ticagrelor 90 mg b.i.d., 60 mg b.i.d., or placebo. Reduction in the primary end point (MACE: composite of cardiovascular death, MI, or stroke) in both ticagrelor-treated study arms (7.85% and 7.77%, respectively) vs. placebo (9.04%) at 3 years of follow-up was observed (HR for ticagrelor 90 mg b.i.d. vs. placebo, 0.85; $p = 0.008$; HR for ticagrelor 60 mg b.i.d. vs. placebo, 0.84; $p = 0.004$). Differences promoting therapy with a combination of ticagrelor and ASA over ASA alone were shown in the rate of MI (HR for ticagrelor 90 mg b.i.d. vs. placebo, 0.81; $p = 0.01$; HR for ticagrelor 60 mg b.i.d. vs. placebo, 0.84; $p = 0.03$) and in the rate of stroke; however, in the latter case, only for ticagrelor 60 mg b.i.d. vs. placebo (1.47% vs. 1.94%; HR 0.75; $p = 0.03$). As far as safety of the treatment is concerned, major bleedings were more frequent in individuals receiving ticagrelor, either 90 mg b.i.d. or 60 mg b.i.d., compared with those in whom placebo was administered, 2.6% and 2.3% vs. 1.06%, respectively (HR for ticagrelor 90 mg b.i.d., 2.69; $p < 0.001$; HR for ticagrelor 60 mg, 2.32; $p < 0.001$); however, no differences were found in the rates of fatal or non-fatal intracranial bleeding episodes in the ticagrelor-treated arms as compared with placebo (0.63% and 0.71%, vs. 0.60%, respectively) [17].

Out of the 21,162 patients enrolled in the PEGASUS-TIMI 54 trial, 6806 had diabetes [18]. Because patients with diabetes have a higher risk of MACE, the absolute risk reduction tended to be greater in patients with vs. without diabetes (1.5% vs. 1.1%, respectively). Moreover, in patients with diabetes, ticagrelor reduced the rate of cardiovascular mortality by 22% ($p < 0.05$) and coronary heart disease deaths by 34% ($p = 0.01$) [18].

In a subset of patients with peripheral artery disease (PAD), the greater absolute risk reduction in MACE (4.1%) was due to their higher absolute ischemic risk [19]. The 60 mg b.i.d. dose of ticagrelor showed a particularly favorable impact on cardiovascular as well as all-cause mortality in comparison with placebo (4.2% vs. 9.6%; HR 0.47; $p = 0.014$ and 8.2% vs. 14.0%; HR 0.52; $p = 0.0074$) [19]. In patients with multi-vessel disease, ticagrelor reduced the risk of MACE (7.94% vs. 9.37%; HR 0.82; $p = 0.004$), including reduction in coronary death (HR 0.64; $p = 0.002$) [21].

The analysis of results according to the time between randomization to the PEGASUS-TIMI 54 trial and previous cessation of DAPT with P2Y12 inhibitor and ASA after MI revealed better outcomes in patients who had stopped DAPT more recently [20]. Patients were categorized by time from the last P2Y12 receptor inhibitor dose (days: ≤ 30, 30–360, > 360). The benefit of ticagrelor (reduction in MACE rate) depended on the time from the last dose, and was more pronounced in patients continuing on or re-starting after only a brief interruption of P2Y12 inhibition than in patients who had proven themselves stable more than 2 years from MI and off P2Y12 inhibitor therapy for more than a year with hazard ratios for ticagrelor (pooled doses) vs. placebo of 0.73; $p < 0.001$, 0.86; $p = 0.11$, and 1.01; $p = 0.96$, respectively, by category (P-trend for interaction < 0.001). The benefit within 30 days of stopping DAPT was similar regardless of time from MI. On the other hand, the increase in bleeding events with ticagrelor was similar regardless of this time interval [20]. According to these results, the European Medicines Agency approved European (EU) label recommends that treatment with ticagrelor 60 mg b.i.d. may be a continuation of the initial one-year treatment with ticagrelor 90 mg b.i.d. (or other P2Y12 receptor inhibitor) in high-risk patients with MI [29]. Treatment with ticagrelor 60 mg b.i.d. can also be initiated up to 2 years from the MI, or within 1 year after stopping previous P2Y12 receptor inhibitor treatment. Therefore, an analysis evaluating the efficacy and safety of treatment in a PEGASUS-TIMI 54

subpopulation receiving low-dose ticagrelor recommended for treatment in the EU label (n = 10,779: 5388 in the ticagrelor 60 mg b.i.d. and 5391 in the placebo group) was performed [30]. DATT with ticagrelor 60 mg b.i.d. in the EU label population reduced the composite of cardiovascular death, MI, or stroke (7.9% vs. 9.6%; HR 0.80; p = 0.001). Moreover, in the EU label population this DATT strategy was associated with lower hazard ratios for cardiovascular death (0.71; p = 0.0041), MI (0.83; p = 0.041), and all-cause death (0.80; p = 0.018). Better efficacy was associated with a higher risk of Thrombolysis in Myocardial Infarction (TIMI) major bleeding occurrence (2.5% vs. 1.1%; HR 2.36; p < 0.001), without an increase in fatal or intracranial bleedings, confirming a favorable benefit-risk balance for long-term ticagrelor 60 mg b.i.d. in this population [30, 31].

Ticagrelor proved to be similarly effective in patients with and without a history of coronary stenting, suggesting also a benefit in the prevention of spontaneous atherothrombotic events not related to stent thrombosis [32].

The increased risk of non-cardiovascular death in patients receiving clopidogrel or prasugrel in comparison with the placebo group in the DAPT trial [14], in contrast to the decreased risk of cardiovascular death and all-cause death seen in patients treated with low-dose ticagrelor in the EU label population of the PEGASUS-TIMI 54 trial [30], resulted in inclusion in the 2020 ESC NSTE-ACS guidelines the recommendation for use of clopidogrel or prasugrel only if the patient is not eligible for treatment with ticagrelor [11].

Dual antithrombotic therapy with ASA and rivaroxaban

Continued occurrence of recurrent ischemic events despite treatment with potent P2Y12 receptor inhibitors (prasugrel and ticagrelor) and ASA stimulated interest in exploring the efficacy and safety of direct oral anticoagulants in patients with ACS [33].

Reduction in ischemic event risk with rivaroxaban (2.5 mg or 5 mg b.i.d.) added to standard DAPT with ASA and a P2Y12 inhibitor has been shown to be superior to placebo in patients with ACS in the ATLAS ACS 2-TIMI 51 trial. However, only the 2.5 mg b.i.d. dose of rivaroxaban was associated with a survival benefit. Moreover, the increase in risk of major bleeding was lower with the 2.5 mg b.i.d. rivaroxaban dose [34]. These results provided a promising basis for low-dose rivaroxaban in addition to ASA in patients with CCS.

According to the citations in the ESC guidelines [10, 11], the indications for use of rivaroxaban in combination with ASA in patients with CCS after ACS are based on the results of the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial [22, 35–37].

The COMPASS trial was aimed to test the hypothesis that rivaroxaban in combination with ASA or given alone is more effective than ASA alone in preventing recurrent cardiovascular events, with acceptable safety, in patients with stable atherosclerotic vascular disease [22]. Patients with stable atherosclerotic vascular disease were randomly assigned to receive rivaroxaban (2.5 mg b.i.d.) plus ASA (100 mg q.d.), rivaroxaban (5 mg b.i.d.), or ASA (100 mg q.d.) in a 1:1:1 ratio. The prevalence of the primary outcome composed of cardiovascular death, stroke, or MI was lower in the rivaroxaban-plus-ASA group than in the ASA--alone group (4.1% vs. 5.4%; HR 0.76; p < 0.001). Moreover, all-cause mortality and cardiovascular mortality rates were lower in the rivaroxaban-plus--ASA group as compared with the ASA-alone group (for all-cause mortality: 3.4% vs. 4.1%; HR 0.82; p = 0.01; for cardiovascular mortality: 1.7% vs. 2.2%; HR 0.78; p = 0.02). Superiority of DATT with low rivaroxaban dose and ASA over ASA alone was observed also for the risk of stroke (0.9% vs. 1.6%; HR 0.58; p < 0.001). This benefit was achieved at the cost of a higher major bleeding rate in the rivaroxaban-plus-ASA group (3.1% vs. 1.9%; HR 1.70; p < 0.001), but with no significant difference in fatal bleeding (0.2% vs. 0.1%; HR 1.49; p = 0.32). A substantial reduction in ischemic strokes and embolic/uncertain strokes with low-dose rivaroxaban and ASA was also confirmed in an additional analysis of this trial [38], suggesting a potential for this new antithrombotic option in primary and secondary stroke prevention. Favorable clinical outcome with DATT was also confirmed by an analysis of net clinical benefit [37].

No clinical benefit with regard to the primary outcome was observed in the 5 mg b.i.d. rivaroxaban-alone group as compared with the ASA-alone group, but major bleeding events occurred more frequently in the rivaroxaban-alone group. The study was prematurely terminated due to the superiority of the rivaroxaban-plus-ASA therapy after a mean follow-up of 23 months [22]. In patients with stable coronary artery disease (CAD) (n = 24,824), addition of rivaroxaban to ASA resulted in a similar

impact on the efficacy and safety of the treatment. DATT with rivaroxaban and ASA compared with ASA alone reduced the primary outcome (4% vs. 6%; HR 0.74; $p < 0.0001$) and mortality (3% vs. 4%; HR 0.77; $p = 0.0012$), but increased the rate of major bleeding (3% vs. 2%; HR 1.66; $p < 0.0001$) [35]. There were 17,028 patients (69%) with a history of previous MI; however, patients who gained the most in the PEGASUS-TIMI 54 trial (EU label population), i.e. those between the first and second year after MI (72.9% of the total population), in the COMPASS trial accounted for only 9.3% of all patients with CAD. Together with patients within the first year after MI, this subpopulation of CAD patients in the COMPASS trial accounted for 14.3%, and according to a subgroup analysis the clinical benefit in terms of the primary outcome was not significant, in contrast to patients over 5 years after MI [35].

Of the 16,560 patients with CCS in the COMPASS trial, 9862 (59.6%) patients had a history of previous percutaneous coronary intervention (PCI). The average time from PCI to randomization was 5.4 years. DATT with rivaroxaban compared with ASA alone in patients with or without previous PCI resulted in consistent MACE reduction (PCI: 4.0% vs. 5.5%; HR 0.74; no PCI: 4.4% vs. 5.7%; HR 0.76; P-interaction = 0.85) and mortality reduction (PCI: 2.5% vs. 3.5%; HR 0.73; no PCI: 4.1% vs. 5.0%; HR 0.80; P-interaction = 0.59), but was associated with an increased rate of major bleeding (PCI: 3.3% vs. 2.0%; HR 1.72; no PCI: 2.9% vs. 1.8%; HR 1.58, P-interaction = 0.68) [38]. Among those with previous PCI 1 year and beyond, the effects on MACE and mortality were consistent irrespective of time since last PCI and irrespective of a history of previous MI (P-interaction = 0.64) [39].

The combination of ASA plus rivaroxaban provided a similar relative degree of clinical benefit in patients with and without diabetes mellitus. However, due to a higher baseline risk, the absolute benefits appeared larger in patients with diabetes mellitus, including a 3-fold greater reduction in all-cause mortality [36].

Patient characteristics in trials supporting recommendation for DATT in CCS patients after MI

Different inclusion and exclusion criteria in trials supporting the ESC guidelines [10] displayed in Table 6 lead to several pivotal differences in the characteristics of patients enrolled to these trials (Table 7). Patients after ischemic stroke were included into the DAPT, TL-PAS, and COMPASS trials, but not into the PEGASUS-TIMI 54 trial. Only 36% of subjects in the COMPASS trial had a history of previous PCI, while in the PEGASUS-TIMI 54, DAPT, and TL-PAS trials this percentage was 83%, 100%, and 100%, respectively. All patients in the PEGASUS-TIMI 54, 62.6% in COMPASS, and only 21.6% in the DAPT trial had a history of MI before enrolment into the trial. Finally, a huge difference regarding the interval between MI and randomization in the PEGASUS-TIMI 54 (1.7 year) and COMPASS trial (7.1 years) should be highlighted. Several minor differences between the investigated populations should also be noted [17–22, 34–36] (Table 7).

In the DAPT trial, an increased all-cause mortality risk was observed in patients on prolonged treatment with clopidogrel or prasugrel and ASA. Moreover, the reported clinical benefit of this therapeutic strategy (DAPT trial and TL-PAS) was mainly dependent on reduction of the risk of MI and stent thrombosis in patients in whom a paclitaxel-eluting coronary stent was implanted, while this type of stent is no longer in use due to increased risk of MI, target-vessel revascularization, and stent thrombosis, especially very late one. Furthermore, the results of separate analyses for clopidogrel and prasugrel failed to demonstrate any significant impact on the clinical outcome [14–16, 26–28]. When considering treatment with clopidogrel, its volatile pharmacodynamic effects related to variable efficiency of conversion to its active metabolite, partly associated with loss-of-function variants in the CYP2C19 gene, leading to a lack of efficacy in some patients, should be taken into account [40–43].

Thus, the rationale to recommend prolonged DAPT with any of these drugs, in our opinion, is limited.

In contrast to the DAPT trial and TL-PAS, the messages provided by the PEGASUS-TIMI 54 and COMPASS trials seem to be clear and unambiguously positive for DATT with ticagrelor 60 mg mg b.i.d. and rivaroxaban 2.5 mg b.i.d., respectively. However, the indications for DATT including ticagrelor or rivaroxaban need to be clarified because the overlapping of eligibility between PEGASUS-TIMI 54 and COMPASS criteria (Fig. 1) is not reflected by overlapping of evaluated populations according to patient characteristics of both trials (Table 6, 7).

PEGASUS-TIMI 54 versus COMPASS approach

In an attempt to answer the question: "Who could benefit most from the PEGASUS-TIMI 54

Table 6. Inclusion and exclusion criteria of clinical trials supporting the 2019 European Society of Cardiology (ESC) guidelines.

Study Clinical Trials.gov	DAPT TL-PAS NCT00977938 TL-PAS NCT00997503	PEGASUS-TIMI 54 NCT01225562	COMPASS NCT01776424
Key inclusion criteria	> 18 years of age PCI with stent 12 months free from MI, stroke, repeat coronary revascularization, ST, and moderate or severe bleeding, and compliant	> 50 years of age MI occurring 1 to 3 years prior to randomization and at least 1 of the following risk factors: — age ≥ 65 years of age — diabetes mellitus — second prior MI (> 1 year ago) — multivessel CAD — chronic renal dysfunction CrCl < 60 mL/min — on treatment and tolerating ASA 75–150 mg once daily	CAD defined as 1 of the following: — MI within the last 20 years — multivessel CAD with symptoms or with history of stable or unstable angina — multivessel PCI or CABG surgery Subjects with CAD must also meet at least 1 of the following criteria: — age ≥ 65, or — age < 65 Documented atherosclerosis or revascularization involving at least 2 vascular beds or at least 2 additional risk factors: — current smoker — diabetes mellitus — renal dysfunction with eGFR < 60 mL/min — heart failure — ischemic stroke ≥ 1 month ago PAD defined as one of the following: — previous revascularization for PAD — previous limb or foot amputation for arterial vascular disease — history of intermittent claudication and at least 1 of the following Previous carotid revascularization or asymptomatic carotid artery stenosis ≥ 50% as diagnosed by duplex ultrasound or angiography
Key exclusion criteria	Stent diameter < 2.2 or > 4.0 mm Pregnant women Planned surgery necessitating discontinuation of antiplatelet therapy Life expectancy < 3 years Concurrent enrolment in another study Subjects on oral anticoagulants Hypersensitivity or allergies to one of the drugs Subjects unable to give informed consent Subject treated with both DES and BMS during the index procedure Switched thienopyridine type or dose within 6 months before randomization PCI or cardiac surgery between 6 weeks post index procedure and randomization	Planned use of ADP receptor blockers, dipyridamole, or cilostazol Planned coronary, cerebrovascular, or peripheral arterial revascularization Need for chronic anticoagulation Known bleeding diathesis or coagulation disorder Patients with: — a history of intracranial bleeding — central nervous system tumor or intracranial vascular abnormality — intracranial or spinal cord surgery within 5 years — gastrointestinal bleeding within the past 6 months, or major surgery within 30 days History of ischemic stroke Patients considered to be at risk of bradycardic events CABG in the past 5 years Known severe liver disease Renal failure requiring dialysis or anticipated need for dialysis during the course of the study Pregnancy or lactation Life expectancy < 1 year	High risk of bleeding Need for dual antiplatelet therapy, other non-ASA antiplatelet therapy, or oral anticoagulant therapy Stroke within 1 month or any history of hemorrhagic or lacunar stroke Severe heart failure with known ejection fraction < 30% or New York Heart Association class III or IV symptoms eGFR < 15 mL/min Any known hepatic disease associated with coagulopathy Known non-cardiovascular disease that is associated with poor prognosis (e.g. metastatic cancer) or that increases the risk of an adverse reaction to study interventions History of hypersensitivity or known contraindication for rivaroxaban, ASA, pantoprazole, or excipients

ASA — acetylsalicylic acid; BMS — bare-metal stent; CABG — coronary artery bypass grafting; CAD — coronary artery disease; CrCl — creatinine clearance; DES — drug-eluting stent; eGFR — estimated glomerular filtration rate; MI — myocardial infarction; PAD — peripheral artery disease; PCI — percutaneous coronary intervention; ST — stent thrombosis

Table 7. Study population characteristics of trials supporting the 2019 European Society of Cardiology (ESC) guidelines.

Study ClinicalTrials.gov	DAPT NCT00977938 TL-PAS NCT00997503	PEGASUS-TIMI 54 NCT01225562	COMPASS NCT01776424
Number of patients	11,648	21,162	27,395
Number of CAD patients	11,648	21,162	24,824
CAD patients [%]	100	100	90.6
Age [years]	61.7 ± 10.2	65.3 ± 8.4	68.2 ± 7.9
Female sex [%]	25.4	23.9	22.0
Diabetes mellitus [%]	30.6	32.2	37.8
Hypertension [%]	74.9	77.5	75.3
Tobacco use [%]	24.6	16.7	21.4
Previous stroke [%]	3.3	0	3.8
Heart failure [%]	4.7	20.0	21.5
Peripheral arterial disease [%]	5.8	5.4	27.3
Chronic kidney disease (GFR < 60 mL/min) [%]	4.23	23,2	23.1
Previous PCI [%]	100	83.0	36
Previous MI [%]	21.6	100	62.2
Previous STEMI [%]	10.5	53.6	NA
Years since MI [median]	1	1.7	7.1
Patients with previous MI within 1–2 years [%] *based on DAPT cessation **out of CAD subpopulation	NA	72.9*	9.3**
Duration of study treatment [months]	30	33	23
Discontinuation rate in the study arm [%] *ticagrelor 60 mg b.i.d. **rivaroxaban 2.5 mg b.i.d. + ASA	21.4	28.7*	16.5**

ASA — acetylsalicylic acid; CAD — coronary artery disease; DAPT — dual antiplatelet therapy; GFR — glomerular filtration rate; MI — myocardial infarction; NA — non available; PCI — percutaneous coronary intervention; STEMI — ST-segment elevation myocardial infarction

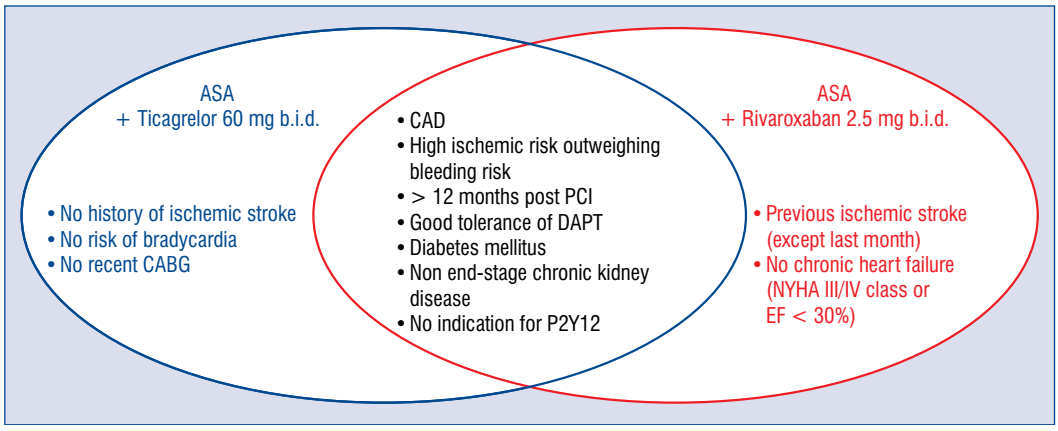


Figure 1. Overlapping of PEGASUS-TIMI 54 and COMPASS trials inclusion criteria; DAPT — dual antiplatelet therapy; CAD — coronary artery disease; CABG — coronary artery bypass grafting; EF — ejection fraction; NYHA — New York Heart Association; PCI — percutaneous coronary intervention.

rather than from the COMPASS approach among CAD patients?", Brunetti et al. [44] proposed a flow-chart for identification of the optimal treatment, based solely on the PEGASUS-TIMI 54 and COMPASS trial inclusion and exclusion criteria. According to the authors, the choice between rivaroxaban and ticagrelor should be based on the presence of severe renal failure (defined as estimated glomerular filtration rate < 15 mL/min), severe heart failure (ejection fraction < 30% or New York Heart Association [NYHA] class III or IV symptoms), or strong interaction with CYP3A4 or P-glycoprotein, the presence of which indicates the PEGASUS-TIMI 54 approach [44]. The proposed strategy may be helpful in some, but probably few subjects, leaving the dilemma of choosing between ticagrelor and rivaroxaban unresolved in a majority of post-MI patients with a high risk of ischemic events and without high bleeding risk.

A similar algorithm was developed by Capodanno et al. [45]; however, in this case previous ischemic stroke was the only differentiating factor between the recommended DATT strategies. There is no doubt that this factor should be taken into account due to the differences in the PEGASUS-TIMI 54 and COMPASS inclusion and exclusion criteria. Nevertheless, considering that none of the patients included in the PEGASUS-TIMI 54 trial and only 3.8% of patients in the COMPASS trial experienced ischemic stroke previously (Table 7), the evidence to support this recommendation is weak, and the vast majority of post-MI subjects requiring DATT will remain without clear indications, with both strategies deemed by the authors equally acceptable in patients without a prior stroke [45]. The statement that candidates for the PEGASUS-TIMI 54 trial strategy might mostly benefit from uninterrupted DAPT after the recommended 12-month course of DAPT after MI [45] is indeed supported by the analysis of the trial results [21], showing the highest benefit of DATT with ticagrelor in patients continuing on or re-starting after only a brief interruption of P2Y12 inhibition. On the other hand, according to the subgroup analysis of the COMPASS trial, the clinical benefit in terms of primary outcome, despite a clear trend, was not significant in patients enrolled within 2 years of MI. Unquestionable superiority of treatment with low rivaroxaban dose in combination with ASA over ASA alone was seen in subjects over 5 years after MI [35].

The superiority of DATT with low-dose rivaroxaban over ASA alone in patients with CAD and PAD was pointed out by Ramacciotti et al. [46]. The 18% mortality reduction with rivaroxaban added to ASA is a unique finding; however, it is difficult to accept the statement that this strategy simply represents a paradigm shift for all patients requiring secondary prevention, because the COMPASS trial population is very different from the PEGASUS--TIMI 54 trial population (Table 7).

According to González-Juanatey et al. [47], during the first year after ACS, DAPT should be recommended, but after 12 months the ischemic and bleeding risk should be re-evaluated and among patients with high-risk features, and switching from DAPT to the COMPASS regimen should be strongly considered. This interesting concept, however, before being taken under consideration, should first be assessed in a clinical trial, because cessation of DAPT is associated with an increased risk of thrombotic events [14, 20], and evidence regarding the efficacy and safety of switching from a P2Y12 receptor inhibitor to rivaroxaban is lacking.

Besides antithrombotic therapy in a setting of low bleeding risk, multifactorial interventions including lipid-lowering treatment in high-risk CAD patients might be a promising option to significantly improve the prognosis [48].

In order to apply a proper strategy of treatment to a post-ACS patient remaining in sinus rhythm, several factors need to be considered (Fig. 2):

- risk of cardiovascular ischemic events;
- risk of bleeding events;
- current antiplatelet treatment;
- time since last ACS;
- time since DAPT termination;
- type of implanted stent;
- known hypersensitivity to treatment with rivaroxaban and ticagrelor, prasugrel, or clopidogrel;
- comorbidities: history of ischemic stroke, recent coronary artery bypass grafting, risk of bradycardia, renal insufficiency with estimated glomerular filtration rate < 15 mL/min, heart failure with ejection fraction < 30% or NYHA class III or IV, PAD or other atherothrombotic multiple vascular bed involvement (AMVBI).

For patients who discontinued their DAPT before 12 months after ACS due to intolerance of P2Y12 receptor inhibitor or ASA, treatment with one antiplatelet agent or a switch to another antithrombotic agent should be considered.

Regardless of the treatment strategy chosen, the basis of effectiveness is patient adherence to medication. Therefore, health education aimed at explaining the purpose of therapy should be applied [49–54].

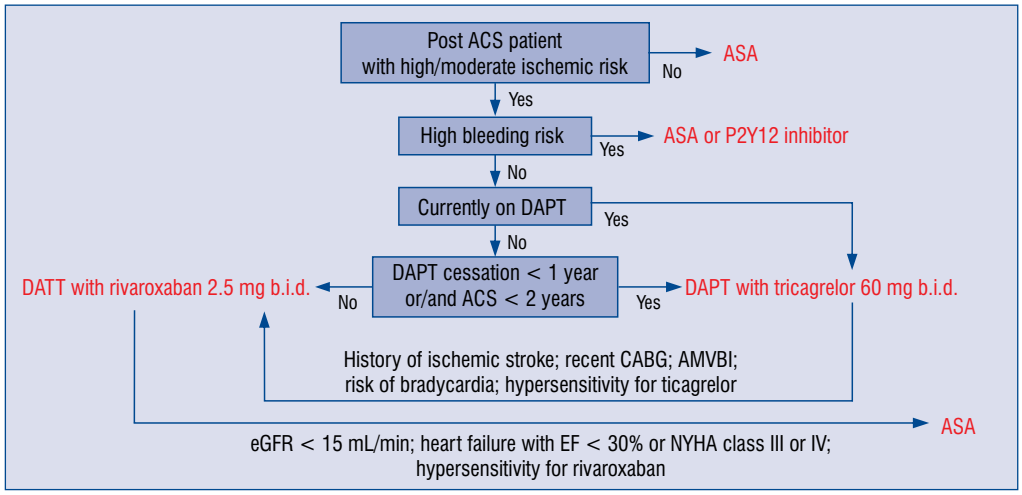


Figure 2. A schematic algorithm for drug assignment for prolonged antithrombotic treatment in patients > 12 months after acute coronary syndrome (ACS) in sinus rhythm; ASA — acetylsalicylic acid; AMVBI — atherothrombotic multiple vascular bed involvement; CABG — coronary artery bypass grafting; DAPT — dual antiplatelet therapy; eGFR — estimated glomerular filtration rate; EF — ejection fraction; NYHA — New York Heart Association.

Thus, implementation of a multidisciplinary approach involving a proper selection of patients with high risk for thrombosis and low risk for bleeding may help to achieve long-term anti-ischemic benefits with low bleeding risk. The latter approach should be based on the assessment of individual patient's propensity for thrombosis and bleeding in conjunction with demographic and clinical variables. Finally, stratification of patients for continued DAPT with ASA and low dose of ticagrelor vs. switching to combination therapy with ASA plus very low dose of rivaroxaban and finding the correct timing for this transition still poses a challenge. There is urgent need for a study investigating this issue. Potential utility of biomarkers or assays for platelet function and thrombin pathway function assessment remains an unexplored area in the stratification of patients for long-term therapy [55].

Summary

The comparison of the PEGASUS-TIMI 54 and COMPASS trial patient characteristics clearly shows that each of these treatment strategies should be addressed at different groups of patients. A greater benefit in post-ACS patients with a high risk of ischemic events and without high bleeding risk may be expected with ASA and ticagrelor 60 mg b.i.d. when the therapy is continued without interruption or with short interruption only after ACS. On the other hand, ASA and rivaroxaban 2.5 mg b.i.d. seems to be a better option when indications for DATT appear after a longer time from ACS (more than 2 years) and/or from cessation of DAPT (more than 1 year) and in patients with multiple vascular bed atherosclerosis. Thus, both options of DATTs complement each other rather than compete, as can be presumed from the recommendations. However, a direct comparison between these strategies should be probably tested in future clinical trials.

Conflict of interest: Jacek Kubica — speaker and consultancy honoraria from: AstraZeneca, Bayer, Boehringer Ingelheim, Orion Pharma; Piotr Adamski — speaker honoraria from: AstraZeneca; Piotr Niezgoda — none; Dimitrios Alexopoulos — speaker and consultancy honoraria from: AstraZeneca, Bayer, Pfizer, Boehringer Ingelheim, Medtronic, Biotronik; Jolita Badarienė — speaker honoraria from: Boehringer Ingelheim, Servier, Bayer; grants from: Amgen, AstraZeneca; Andrzej Budaj — grants and personal fees from AstraZeneca; grants from Sanofi; grants and personal fees from Bristol-Myers Squibb/Pfizer; grants from Boehringer-Ingelheim and Novartis; grants and personal fees from GlaxoSmithKline; and grants from Eisai outside the submitted work; Katarzyna Buszko — none; Dariusz Dudek — none; Tomasz Fabiszak — none; Mariusz Gąsior — speaker honoraria from: AstraZeneca; Robert Gil — speaker honoraria from: AstraZeneca; Diana A. Gorog — speaker honoraria from: AstraZeneca, Bayer, Boehringer Ingelheim; Institutional grant from Bayer; Stefan Grajek — speaker

honoraria from: AstraZeneca, Bayer, Servier; Paul A. Gurbel — grants and personal fees from: Bayer HealthCare LLC, Otitopic Inc., Amgen, Janssen, and US WorldMeds LLC; grants from: Instrumentation Laboratory, Haemonetics, Medicure Inc., Idorsia Pharmaceuticals, and Hikari Dx; personal fees from: UpToDate; relator and expert witness in litigation involving clopidogrel; two patents: Detection of restenosis risk in patients issued and Assessment of cardiac health and thrombotic risk in a patient; Marcin Gruchała — none; Miłosz J. Jaguszewski — speaking fees and travel grants from: Boheringer Ingelheim, Bayer, AstraZeneca, and Pfizer outside the submitted work; Stefan James — institutional research grants from: AstraZeneca, Bayer, Jansen, The Medicines Company, Abbot Vascular and Boston Scientific; honoraria from: AstraZeneca, Bayer, and Medtronic; Young-Hoon Jeong — speaker honoraria from: AstraZeneca, Daiichi Sankyo, Sanofi-Aventis, Han-mi Pharmaceuticals and Yuhan Pharmaceuticals; and research grants or support from: Yuhan Pharmaceuticals and U&I Corporation; Bernd Jilma — none; Jarosław D. Kasprzak — speaker honoraria from: AstraZeneca, Bayer; Andrzej Kleinrok — none; Aldona Kubica — speaker honoraria from: AstraZeneca; Wiktor Kuliczkowski — none; Jacek Legutko — speaker and consultancy honoraria from: AstraZeneca, Bayer; Maciej Lesiak — speaker and consultancy honoraria from: AstraZeneca, Bayer; Jolanta M. Siller-Matula — speaker honoraria from: Chiesi, Bayer, Medtronic, Daiichi Sankyo, BMS; Klaudiusz Nadolny — speaker honoraria from: AstraZeneca; Krzysztof Pstrągowski — none; Salvatore Di Somma — none; Giuseppe Specchia — none; Janina Stępińska — speaker and consultancy honoraria from: AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, Pfizer, Sanofi; Udaya S. Tantry — honoraria from: UptoDate; Agnieszka Tycińska — speaker honoraria from: Bayer, AstraZeneca, Servier, Krka, Orion Pharma, Fresenius, Fisher & Paykel; Monica Verdoia — none; Wojciech Wojakowski — speaker honoraria from: AstraZeneca, Pfizer, Boehringer Inhelheim; Eliano P. Navarese — speaker and consultancy honoraria from: AstraZeneca, Abbott, Bayer, Sanofi-Regeneron, Amgen, Pfizer, outside the submitter work; grants from Amgen, Abbott.

References

1. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019; 40(2): 87–165, doi: 10.1093/eurheartj/ehy394, indexed in Pubmed: 30165437.
2. Myat A, Tantry US, Kubica J, et al. Current controversies in the use of aspirin and ticagrelor for the treatment of thrombotic events. Expert Rev Cardiovasc Ther. 2016; 14(12): 1361–1370, doi: 10.1080/14779072.2016.1247693, indexed in Pubmed: 27740874.
3. Navarese EP, Khan SU, Kołodziejczak M, et al. Comparative Efficacy and Safety of Oral P2Y Inhibitors in Acute Coronary Syndrome: Network Meta-Analysis of 52 816 Patients From 12 Randomized Trials. Circulation. 2020; 142(2): 150–160, doi: 10.1161/CIRCULATIONAHA.120.046786, indexed in Pubmed: 32468837.
4. Kubica J, Adamski P, Paciorek P, et al. Treatment of patients with acute coronary syndrome: Recommendations for medical emergency teams: Focus on antiplatelet therapies. Updated experts' standpoint. Cardiol J. 2018; 25(3): 291–300, doi: 10.5603/CJ.a2018.0042, indexed in Pubmed: 29671864.
5. Kubica J, Jaguszewski M. ISAR-REACT 5 — What have we learned? Cardiol J. 2019; 26(5): 427–428, doi: 10.5603/CJ.a2019.0090, indexed in Pubmed: 31536136.
6. Ostrowska M, Kubica J, Adamski P, et al. Stratified Approaches to Antiplatelet Therapies Based on Platelet Reactivity Testing. Front Cardiovasc Med. 2019; 6: 176, doi: 10.3389/fcvm.2019.00176, indexed in Pubmed: 31850373.
7. Fox KAA, Carruthers KF, Dunbar DR, et al. Underestimated and under-recognized: the late consequences of acute coronary syndrome (GRACE UK-Belgian Study). Eur Heart J. 2010; 31(22): 2755–2764, doi: 10.1093/eurheartj/ehq326, indexed in Pubmed: 20805110.
8. Jernberg T, Hasvold P, Henriksson M, et al. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. Eur Heart J. 2015; 36(19): 1163–1170, doi: 10.1093/eurheartj/ehu505, indexed in Pubmed: 25586123.
9. Rapsomaniki E, Thuresson M, Yang E, et al. Using big data from health records from four countries to evaluate chronic disease outcomes: a study in 114 364 survivors of myocardial infarction. Eur Heart J Qual Care Clin Outcomes. 2016; 2(3): 172–183, doi: 10.1093/ehjqcco/qcw004, indexed in Pubmed: 29474617.
10. Knuuti J, Wijns W, Saraste A, et al. ESC Scientific Document Group. 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.
11. Collet JP, Thiele H, Barbato E, et al. ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2020 [Epub ahead of print], doi: 10.1093/eurheartj/ehaa575, indexed in Pubmed: 32860058.
12. Kubica J, Adamski P, Buszko K, et al. Platelet inhibition with standard vs. lower maintenance dose of ticagrelor early after myocardial infarction (ELECTRA): a randomized, open-label, active-controlled pharmacodynamic and pharmacokinetic study. Eur Heart J Cardiovasc Pharmacother. 2019; 5(3): 139–148, doi: 10.1093/ehjcvp/pvz004, indexed in Pubmed: 30689800.
13. Kubica J, Adamski P, Buszko K, et al. Rationale and Design of the Effectiveness of LowEr maintenanCe dose of TicagRelor early After myocardial infarction (ELECTRA) pilot study. Eur Heart J Cardiovasc Pharmacother. 2018; 4(3): 152–157, doi: 10.1093/ehjcvp/pvx032, indexed in Pubmed: 29040445.
14. Mauri L, Kereiakes DJ, Yeh RW, et al. DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after

drug-eluting stents. N Engl J Med. 2014; 371(23): 2155–2166, doi: 10.1056/NEJMoa1409312, indexed in Pubmed: 25399658.
15. Yeh RW, Kereiakes DJ, Steg PG, et al. DAPT Study Investigators. Benefits and risks of extended duration dual antiplatelet therapy after PCI in patients with and without acute myocardial infarction. J Am Coll Cardiol. 2015; 65(20): 2211–2221, doi: 10.1016/j.jacc.2015.03.003, indexed in Pubmed: 25787199.
16. Garratt KN, Weaver WD, Jenkins RG, et al. Prasugrel plus aspirin beyond 12 months is associated with improved outcomes after TAXUS Liberté paclitaxel-eluting coronary stent placement. Circulation. 2015; 131(1): 62–73, doi: 10.1161/CIRCULATIONAHA.114.013570, indexed in Pubmed: 25400062.
17. Bonaca MP, Bhatt DL, Cohen M, et al. PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med. 2015; 372(19): 1791–1800, doi: 10.1056/NEJMoa1500857, indexed in Pubmed: 25773268.
18. Bhatt DL, Bonaca MP, Bansilal S, et al. Reduction in ischemic events with ticagrelor in diabetic patients with prior myocardial infarction in PEGASUS-TIMI 54. J Am Coll Cardiol. 2016; 67(23): 2732–2740, doi: 10.1016/j.jacc.2016.03.529, indexed in Pubmed: 27046160.
19. Bonaca MP, Bhatt DL, Storey RF, et al. Ticagrelor for prevention of ischemic events after myocardial infarction in patients with peripheral artery disease. J Am Coll Cardiol. 2016; 67(23): 2719–2728, doi: 10.1016/j.jacc.2016.03.524, indexed in Pubmed: 27046162.
20. Bonaca MP, Bhatt DL, Steg PG, et al. Ischaemic risk and efficacy of ticagrelor in relation to time from P2Y12 inhibitor withdrawal in patients with prior myocardial infarction: insights from PEGASUS-TIMI 54. Eur Heart J. 2016; 37(14): 1133–1142, doi: 10.1093/eurheartj/ehv531, indexed in Pubmed: 26491109.
21. Bansilal S, Bonaca MP, Cornel JH, et al. Ticagrelor for secondary prevention of atherothrombotic events in patients with multivessel coronary disease. J Am Coll Cardiol. 2018; 71(5): 489–496, doi: 10.1016/j.jacc.2017.11.050, indexed in Pubmed: 29406853.
22. Eikelboom J, Connolly S, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med. 2017; 377(14): 1319–1330, doi: 10.1056/nejmoa1709118.
23. Adamski P, Adamska U, Ostrowska M, et al. Evaluating current and emerging antithrombotic therapy currently available for the treatment of acute coronary syndrome in geriatric populations. Expert Opin Pharmacother. 2018; 19(13): 1415–1425, doi: 10.1080/14656566.2018.1510487, indexed in Pubmed: 30132731.
24. Boinska J, Koziński M, Kasprzak M, et al. Diurnal variations in tissue factor and tissue factor pathway inhibitor concentrations in relation to on-treatment platelet reactivity: an analysis of patients with acute myocardial infarction. Platelets. 2020; 31(7): 877–883, doi: 10.1080/09537104.2019.1693037, indexed in Pubmed: 31744370.
25. Adamski P, Buszko K, Sikora J, et al. Determinants of high platelet reactivity in patients with acute coronary syndromes treated with ticagrelor. Sci Rep. 2019; 9(1): 3924, doi: 10.1038/s41598-019-40628-0, indexed in Pubmed: 30850677.
26. Mauri L, Kereiakes DJ, Normand SLT, et al. Rationale and design of the dual antiplatelet therapy study, a prospective, multicenter, randomized, double-blind trial to assess the effectiveness and safety of 12 versus 30 months of dual antiplatelet therapy in subjects undergoing percutaneous coronary intervention with either drug-eluting stent or bare metal stent placement for the treatment of coronary artery lesions. Am Heart J. 2010; 160(6): 1035–41, 1041.e1, doi: 10.1016/j.ahj.2010.07.038, indexed in Pubmed: 21146655.
27. Li P, Liu JP. Long-term risk of late and very late stent thrombosis in patients treated with everolimus against paclitaxel-eluting stents: an updated meta-analysis. Coron Artery Dis. 2014; 25(5): 369–377, doi: 10.1097/MCA.0000000000000109, indexed in Pubmed: 24818639.
28. Dangas GD, Serruys PW, Kereiakes DJ, et al. Meta-analysis of everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease: final 3-year results of the SPIRIT clinical trials program (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions). JACC Cardiovasc Interv. 2013; 6(9): 914–922, doi: 10.1016/j.jcin.2013.05.005, indexed in Pubmed: 24050859.
29. EMA/CHMP/18297/2016. 17 December 2015. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/001241/WC500203874.pdf (17 June 2019).
30. Dellborg M, Bonaca MP, Storey RF, et al. Efficacy and safety with ticagrelor in patients with prior myocardial infarction in the approved European label: insights from PEGASUS-TIMI 54. Eur Heart J Cardiovasc Pharmacother. 2019; 5(4): 200–206, doi: 10.1093/ehjcvp/pvz020, indexed in Pubmed: 31218354.
31. Verdoia M, Kedhi E, Suryapranata H, et al. Ticagrelor in the prevention of coronary and non-coronary atherothrombotic events: A comprehensive meta-analysis of 10 randomized trials. Atherosclerosis. 2019; 284: 136–147, doi: 10.1016/j.atherosclerosis.2019.02.011, indexed in Pubmed: 30884417.
32. Furtado RHM, Nicolau JC, Magnani G, et al. Long-term ticagrelor for secondary prevention in patients with prior myocardial infarction and no history of coronary stenting: insights from PEGASUS-TIMI 54. Eur Heart J. 2020; 41(17): 1625–1632, doi: 10.1093/eurheartj/ehz821, indexed in Pubmed: 31811715.
33. Gurbel PA, Fox KAA, Tantry US, et al. Combination Antiplatelet and Oral Anticoagulant Therapy in Patients With Coronary and Peripheral Artery Disease. Circulation. 2019; 139(18): 2170–2185, doi: 10.1161/CIRCULATIONAHA.118.033580, indexed in Pubmed: 31034291.
34. Mega JL, Braunwald E, Wiviott SD, et al. ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2012; 366(1): 9–19, doi: 10.1056/NEJMoa1112277, indexed in Pubmed: 22077192.
35. Connolly S, Eikelboom J, Bosch J, et al. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. The Lancet. 2018; 391(10117): 205–218, doi: 10.1016/s0140-6736(17)32458-3.
36. Bhatt DL, Eikelboom JW, Connolly SJ, et al. COMPASS Steering Committee and Investigators. Role of Combination Antiplatelet and Anticoagulation Therapy in Diabetes Mellitus and Cardiovascular Disease: Insights From the COMPASS Trial. Circulation. 2020; 141(23): 1841–1854, doi: 10.1161/CIRCULATIONAHA.120.046448, indexed in Pubmed: 32223318.
37. Steffel J, Eikelboom JW, Anand SS, et al. The COMPASS Trial: Net Clinical Benefit of Low-Dose Rivaroxaban Plus Aspirin as Compared With Aspirin in Patients With Chronic Vascular Disease. Circulation. 2020; 142(1): 40–48, doi: 10.1161/CIRCULATIONAHA.120.046048, indexed in Pubmed: 32436455.

38. Sharma M, Hart RG, Connolly SJ, et al. Stroke Outcomes in the COMPASS Trial. Circulation. 2019; 139(9): 1134–1145, doi: 10.1161/CIRCULATIONAHA.118.035864, indexed in Pubmed: 30667279.
39. Bainey KR, Welsh RC, Connolly SJ, et al. COMPASS Investigators. Rivaroxaban Plus Aspirin Versus Aspirin Alone in Patients With Prior Percutaneous Coronary Intervention (COMPASS--PCI). Circulation. 2020; 141(14): 1141–1151, doi: 10.1161/CIRCULATIONAHA.119.044598, indexed in Pubmed: 32178526.
40. Kozinski M, Bielis L, Wisniewska-Szmyt J, et al. Diurnal variation in platelet inhibition by clopidogrel. Platelets. 2011; 22(8): 579–587, doi: 10.3109/09537104.2011.582900, indexed in Pubmed: 21627410.
41. Kubica A, Kozinski M, Grzesk G, et al. Genetic determinants of platelet response to clopidogrel. J Thromb Thrombolysis. 2011; 32(4): 459–466, doi: 10.1007/s11239-011-0611-8, indexed in Pubmed: 21706290.
42. Kubica A, Kasprzak M, Siller-Matula J, et al. Time-related changes in determinants of antiplatelet effect of clopidogrel in patients after myocardial infarction. Eur J Pharmacol. 2014; 742: 47–54, doi: 10.1016/j.ejphar.2014.08.009, indexed in Pubmed: 25199965.
43. Gurbel PA, Tantry US. Do platelet function testing and genotyping improve outcome in patients treated with antithrombotic agents?: platelet function testing and genotyping improve outcome in patients treated with antithrombotic agents. Circulation. 2012; 125(10): 1276–87; discussion 1287, doi: 10.1161/CIRCULATIONAHA.111.031195, indexed in Pubmed: 22412089.
44. Brunetti ND, De Gennaro L, Di Biase M, et al. Prolonged double antiplatelet therapy vs association of antiplatelet and low dose of anticoagulant therapy: PEGASUS or COMPASS? Int J Cardiol Heart Vasc. 2019; 24: 100401, doi: 10.1016/j.ijcha.2019.100401, indexed in Pubmed: 31763434.
45. Capodanno D, Bhatt DL, Eikelboom JW, et al. Dual-pathway inhibition for secondary and tertiary antithrombotic prevention in cardiovascular disease. Nat Rev Cardiol. 2020; 17(4): 242–257, doi: 10.1038/s41569-019-0314-y, indexed in Pubmed: 31953535.
46. Ramacciotti E, Weitz JI. Rivaroxaban plus aspirin for cardiovascular protection: Rationale for the vascular dose and dual pathway inhibition. Thromb Res. 2019; 184: 44–49, doi: 10.1016/j.thromres.2019.09.033, indexed in Pubmed: 31706067.
47. González-Juanatey JR, Almendro-Delia M, Cosín-Sales J, et al. Residual risk reduction opportunities in patients with chronic coronary syndrome. Role of dual pathway inhibition. Expert Rev Clin Pharmacol. 2020; 13(7): 695–706, doi: 10.1080/17512433.2020.1772056, indexed in Pubmed: 32434452.
48. Kalbacher D, Waldeyer C, Blankenberg S, et al. Beyond conventional secondary prevention in coronary artery disease-what to choose in the era of CANTOS, COMPASS, FOURIER, ODYSSEY and PEGASUS-TIMI 54? A review on contemporary literature. Ann Transl Med. 2018; 6(16): 323, doi: 10.21037/atm.2018.08.03, indexed in Pubmed: 30364059.
49. Kubica A, Kasprzak M, Obońska K, et al. Discrepancies in assessment of adherence to antiplatelet treatment after myocardial infarction. Pharmacology. 2015; 95(1-2): 50–58, doi: 10.1159/000371392, indexed in Pubmed: 25592409.
50. 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.
51. Kubica A, Obońska K, Fabiszak T, et al. Adherence to antiplatelet treatment with P2Y12 receptor inhibitors. Is there anything we can do to improve it? A systematic review of randomized trials. Curr Med Res Opin. 2016; 32(8): 1441––1451, doi: 10.1080/03007995.2016.1182901, indexed in Pubmed: 27112628.
52. Kosobucka A, Michalski P, Pietrzykowski Ł, et al. The impact of readiness to discharge from hospital on adherence to treatment in patients after myocardial infarction. Cardiol J. 2020 [Epub ahead of print], doi: 10.5603/CJ.a2020.0005, indexed in Pubmed: 32037501.
53. Pietrzykowski Ł, Michalski P, Kosobucka A, et al. Medication adherence and its determinants in patients after myocardial infarction. Sci Rep. 2020; 10(1): 12028, doi: 10.1038/s41598-020-68915-1, indexed in Pubmed: 32694522.
54. Kubica A, Bączkowska A. Rationale for motivational interventions as pivotal element of multilevel educational and motivational project (MEDMOTION). Folia Cardiologica. 2020; 15(1): 6–10, doi: 10.5603/FC.2020.0003.
55. Gurbel PA, Tantry US. Deciding about prolonged ticagrelor therapy in coronary clot formers: an ongoing dilemma. Eur Heart J. 2016; 37(14): 1143–1144, doi: 10.1093/eurheartj/ehv573, indexed in Pubmed: 26530109.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2020, Vol. 27, No. 6, 677–684
DOI: 10.5603/CJ.a2019.0018

ISSN 1897–5593
eISSN 1898–018X

Long-term clinical results of biodegradable vascular scaffold ABSORB BVS™ using the PSP-technique in patients with acute coronary syndrome

Jarosław Hiczkiewicz[1], Sylwia Iwańczyk[2], Aleksander Araszkiewicz[2], Magdalena Łanocha[2], Dariusz Hiczkiewicz[1], Stefan Grajek[2], Maciej Lesiak[2]

[1]Department of Cardiology, Multidisciplinary District's Hospital, Nowa Sol, University of Zielona Gora, Poland
[2]1st Department of Cardiology, University of Medical Sciences, Poznan, Poland

Abstract

Background: *The PSP (predilatation, sizing, post-dilatation)-technique was developed to improve the prognosis of patients after bioresorbable vascular scaffold (BVS) implantation. In acute coronary syndrome (ACS) the use of BVS is particularly demanding and carries some potential risk regarding aggressive lesion preparation, proper vessel sizing due to spasm and thrombus inside the artery. The aim herein, was to determine the long-term results of BVS stenting in ACS patients depending on the scaffold implantation technique.*

Methods: *The present study is a prospective, two-center study, which consisted of 182 patients who underwent percutaneous coronary intervention (PCI) with BVS (Absorb, Abbott Vascular, Santa Clara, California, USA) implantation for the ACS. All patients were divided into two groups. The first consisted of 52 patients treated with the PSP-technique (PSP group). The second group enrolled 130 patients treated with a non-PSP procedure (non-PSP group).*

Results: *The procedure was successful in all patients. The mean observation time was 28.8 ± 16.5 months (median 28.3 months, interquartile range 24.0 [17.0–41.0] months). It was found that target vessel failure (TVF) was consistently reduced in patients using the PSP-technique as compared with the non-PSP group (5.8% vs. 17.7%, $p = 0.03$). Moreover, PSP-technique was superior to non-PSP-technique concerning major adverse cardiac events (MACE) (3.7% vs. 22.3%, $p = 0.02$). Logistic regression analysis revealed that the use of PSP technique significantly decreased the risk of target vessel revascularization (odds ratio [OR] 0.11, $p = 0.01$), TVF (OR 0.28, $p = 0.03$) and MACE (OR 0.29, $p = 0.02$).*

Conclusions: *The PSP-technique for BVS implantation improves long-term results and should also be recommended for newer generations of the bioresorbable scaffold.* (Cardiol J 2020; 27, 6: 677–684)

Key words: acute coronary syndrome, acute myocardial infarction, STEMI, NSTEMI, angiography, coronary, bioresorbable devices/polymers

Introduction

Bioresorbable vascular scaffolds (BVSs) are a first-generation technology introduced to overcome the limitations of metallic stents [1, 2]. Unfortunately, recent reports of randomized trials revealed several negative results compared with drug eluting stents (DESs) [3–5], especially a higher rate of target-vessel myocardial infarction (MI) and scaffold thrombosis [6]. Thick struts of

Address for correspondence: Sylwia Iwańczyk, MD, 1st Department of Cardiology, University of Medical Sciences, ul. Długa 1/2, 61–848 Poznań, Poland, tel: +48 61 854 92 93, fax: +48 61 854 90 94, e-mail: syl.iwanczyk@gmail.com

Received: 5.07.2018 Accepted: 16.09.2018

BVS delay endothelialization, correlate with flow disturbance and, in consequence, increase the risk of scaffold thrombosis [7]. Different constructions and mechanical properties make the proper choice of scaffold diameter and its implantation crucial to the results of the procedure. The recent studies have focused on optimal pre-dilatation, sizing of the vessel and post-dilatation to improve treatment results. Ortega-Paz et al. [8] presented the predictive value of PSP (predilatation, sizing, post-dilatation) scores on clinical outcomes. It was an independent predictor of a 1-year device-oriented composite endpoint composed of cardiac death, target vessel MI, and clinically driven target lesion revascularization (TLR). However, the use of BVS and its implantation using PSP-technique in acute coronary syndrome (ACS), the most prothrombotic form of atherosclerosis, is demanding and carries some potential risk regarding aggressive lesion preparation, proper vessel sizing due to spasm and thrombus inside the artery. Moreover, BVS has raised concerns regarding over-expansion, disruption, and the effect of post-dilatation following implantation [9, 10].

Evidence regarding optimal BVS implantation technique in ACS remains limited. These data would be useful in subsequent generations of bioresorbable scaffolds. The aim of the study is to determine results of BVS stenting in ACS depending on scaffold implantation technique.

Methods

Study design

In this prospective, two-center study, a total of 182 patients were consecutively selected who underwent percutaneous coronary intervention (PCI) with BVS (Absorb, Abbott Vascular, Santa Clara, California, USA) implantation for ACS between December 2012 and October 2015. Eligible patients were hemodynamically stable with left ventricular ejection fraction > 30% and had a life expectancy of at least 5 years. In angiography, they had at least one significant coronary artery stenosis, with no restrictions as to the number, severity or lesion location. Patients were divided into two groups, depending on implantation technique. The first consisted of 52 patients treated with the PSP-technique (PSP group). The second group enrolled 130 patients treated with a non-PSP procedure (non-PSP group). In this group, predilatation was performed in 120 (92.3%) and 17 (13.1%) in post-dilatation patients, respectively.

Table 1. Exclusion criteria.

Known intolerance to acetylsalicylic acid, heparin, Poly L-lactic acid, everolimus, contrast material
Active bleeding or coagulopathy or patients on chronic anticoagulation therapy
Poor compliance
Severe tortuous, calcified or angulated coronary anatomy of the study vessel
Fibrinolysis prior to percutaneous coronary intervention

Patients excluded from the study were with: cardiogenic shock, the life expectancy of less than 1 year. The use of metallic stents during the index procedure and the target vessel reference diameter were < 2.3 mm and > 3.7 mm by visual estimate. Detailed exclusion criteria are presented in Table 1.

Ethics approval was obtained from the Institutional Review Committees in each institution. The study was performed following ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Implantation technique

The PCI procedure was performed according to current PCI guidelines. PSP technique is the recommended optimal implantation method of ABSORB BVS. The definition was derived from the GHOST registry and included three steps: predilatation, proper vessel sizing, and post-dilatation. In PSP group, these implantation criteria were met in all patients. Predilatation was performed using non-compliant (NC) balloon 1:1 ratio with reference vessel diameter (RVD) to obtain optimal lesion preparation. The alternative balloons (scoring or cutting) were considered if NC balloon was not completely expanded. Proper scaffold sizing was based on angiography guidance and online quantitative coronary angiography (QCA) according to RVD. During implantation, the balloon was inflated slowly with 2 atmospheres every 5 s, maintaining the final pressure for 20 s in the scaffold. Post-dilatation was carried out with an NC balloon > 1:1 ratio with RVD up to 0.5 mm at ≥ 16 atmospheres to confirm the full expansion of the scaffold and optimize overlap zone. In non-PSP group pre- and post-dilatation were at the discretion of the operator, however, were performed according to the principles of PSP technique.

Peri- and post-procedural pharmacotherapy

Each patient naive to antiplatelet therapy, received a loading dose of 300 mg acetylsalicylic acid followed by the maintenance daily dose of 75 mg and one of the following: clopidogrel 600 mg (n = 97; 53.3%), prasugrel 60 mg (n = 1; 0.5%), or ticagrelor 180 mg (n = 84; 46.2%) in loading doses before or immediately after PCI, followed by a maintenance dose of clopidogrel (75 mg *o.d.*), prasugrel (10 mg *o.d.*), or ticagrelor (90 mg twice daily) for a minimum of 12 months. The decision about the continuation of dual antiplatelet therapy (DAPT) after 12 months was made individually for the patient depending on risk of thrombosis. A bolus of unfractionated heparin, 100 U/kg was administered intravenously during the procedure. The remaining pharmacotherapy was applied according to contemporary guidelines.

Data collection

All data were collected in an electronic database. Clinical follow-up was obtained 30 days, 6 months, 1 year and every following year after the procedure by direct contact with patients or telephone interview, and additionally a review of medical reports if the patient had been hospitalized.

Patients were monitored the for the following endpoints: death, MI, scaffold thrombosis, TLR, target vessel revascularization (TVR) and target vessel failure (TVF), defined as cardiac death, target vessel MI, and TVR. Additionally, cumulative major adverse cardiac events (MACE) rate, composed of cardiac death, non-fatal infarction or reintervention were analyzed.

Definitions

ST-segment elevation myocardial infarction (STEMI) was defined as an electrocardiographic ST-segment elevation concomitant with characteristic symptoms of myocardial ischemia and subsequent release of biomarkers of myocardial necrosis [11]. New or presumed new left bundle branch block has been considered a STEMI equivalent. Non-ST-segment elevation myocardial infarction (NSTEMI) definition involved the presence of angina chest pain with a marked elevation of myocardial necrosis biomarkers and no evidence of ST-segment elevation in the electrocardiogram (ECG). Unstable angina was diagnosed in patients with symptoms of myocardial ischemia and no troponin elevation, with or without ECG changes indicative of ischemia (e.g., ST-segment depression or transient elevation or new T wave inversion) [12]. Death was defined as all-cause mortality during the follow-up. Scaffold thrombosis was determined according to the Academic Research Consortium definition [13, 14]. TLR was set as a target segment reintervention including 5 mm proximal and distal to the scaffold.

Revascularization was indicated if symptoms of myocardial ischemia occurred, and positive stress test, electrocardiographic evidence of ischemia at rest, and/or > 70% diameter in-lesion stenosis on angiography were observed. A procedure was angiographically successful with residual diameter stenosis of less than 30% after scaffold implantation in combination with Thrombolysis in Myocardial Infarction (TIMI) III coronary flow. Procedure success was defined as angiographic success in the absence of in-hospital MACE.

Table 2. Baseline clinical characteristics.

Characteristics	PSP--technique	Non-PSP--technique
N	52	130
Male	34 (65.4%)	94 (72.3%)
Age [years]	60 ± 11	58 ± 11
STEMI	7 (13.5%)	22 (16.9%)
NSTEMI	11 (21.2%)	37 (28.5%)
Unstable angina	24 (46.2%)	24 (53.8%)
Cardiovascular risk factors:		
Hypertension	34 (65.4%)	114 (87.7%)
Diabetes mellitus	9 (17.3%)	32 (24.6%)
IDDM	4 (7.7%)	12 (9.2%)
Cardiovascular history:		
Prior MI	14 (26.9%)	24 (18.5%)*
Prior CABG	2 (3.8%)	7 (5.4%)
Prior PCI	13 (25.0%)	35 (26.9%)
Chronic kidney disease	4 (7.7%)	12 (9.2%)

*p < 0.05, Mann-Whitney test or t-student test, as appropriate; CABG — coronary artery bypass grafting; IDDM - insulin-dependent diabetes mellitus; MI — myocardial infarction; NSTEMI — non-ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention; STEMI — ST-segment elevation myocardial infarction

Results

The baseline characteristics of the study groups are presented in Table 2. According to these data, clinical presentation and prevalence of cardiovascular risk factors did not differ between groups (for all, p > 0.05). In both, middle aged men with hypertension predominated. About one-third of patients suffered from diabetes mellitus. It was noticed that previous MI was significantly more often in the non-PSP group. In turn, the PSP group had more complex lesions, such as higher rate of left main

Table 3. Baseline angiography characteristics.

Characteristics	PSP-technique	Non-PSP-technique
Multivessel disease	16 (30.8%)	71 (55.0%)
Target vessel location:		
LM	4 (7.7%)	0 (0.0%)*
LAD	26 (50.0%)	62 (47.7%)
RCA	10 (19.2%)	30 (23.1%)
LCX	8 (15.4%)	22 (16.9%)
Other	4 (7.7%)	16 (12.3%)
Lesion type B2/C	32 (61.5%)	128 (98.5%)*
Calcification	5 (9.6%)	1 (0.8%)*
Bifurcation lesion	14 (26.9%)	14 (10.8%)*
Thrombus	3 (5.8%)	5 (3.8%)
RVD [mm]	3.1 ± 0.4	2.91 ± 0.4
MLD [mm]	0.4 ± 0.2	0.31 ± 0.2
Diameter stenosis [%]	87.3 ± 8.2	88.01 ± 6.7
Quantitative coronary analysis	34 (65.4%)	9 (6.8%)
Visual estimate	18 (34.6%)	121 (93.2%)
Total number of scaffolds	61	149
Mean scaffolds per lesion	1.17	1.15
Mean scaffold length per lesion	27.2 ± 10.7	22.5 ± 11.1
Mean scaffold diameter per lesion	3.0 ± 0.4	3.0 ± 0.4
Radial approach	50 (96.1%)	125 (96.1%)
Pre-dilatation	52 (100%)	120 (92.3%)
Mean pre-dilatation balloon diameter [mm]	2.9 ± 0.5	2.7 ± 0.5
Maximum pre-dilatation pressure [atm]	13.1 ± 2.3	13.5 ± 1.2
Post-dilatation	52 (100%)	2 (0.5%)*
Mean post-dilatation balloon diameter [mm]	3.1 ± 0.8	3.5 ± 0.0
Max post-dilatation pressure [atm]	17.8 ± 2.4	16.0 ± 2.3
Complications occurring any time during the procedure:		
MACE	0 (0.0%)	0 (0.0%)
Dissection	2 (1.5%)	1 (1.9%)
Distal embolism	0 (0.0%)	0 (0.0%)
No-reflow	0 (0.0%)	0 (0.0%)
Angiographic success	52 (100%)	130 (100%)
Procedure success	52 (100%)	130 (100%)

*$p < 0.05$, Mann-Whitney test or t-student test, as appropriate; LAD — left artery descending; LCx — left circumflex artery; LM — left main; MACE — major adverse cardiac events; MLD — minimal lumen diameter; RCA — right coronary artery; RVD — reference vessel diameter

disease, target bifurcation lesion, and significant calcification. There was a significantly higher rate of lesions of type B2/C in the non-PSP group (Table 3).

Total length of the implanted scaffold was significantly higher in the PSP group compared with the non-PSP group (26.8 ± 12.5 mm vs. 22.5 ± 10.3 mm, $p = 0.02$). Quantitative coronary analysis demonstrated a significant more upper reference vessel diameter and lower post-procedural diameter stenosis in patients treated with PSP technique.

Procedural success was obtained in all patients. In 3 cases coronary dissection occurred and was successfully covered with an additional scaffold. No peri-procedural MACE were reported. Detailed angiographic characteristics are presented in Table 3.

Complete follow-up was available in 88.5% after 12 months, 83.5% after 24 months, and 63.2% after 36 months. The mean observation time was 28.8 ± 16.5 months (median 28.3 months, inter-

Table 4. Results.

Characteristics	PSP--technique	Non-PSP--technique
All cause death	3 (5.8%)	4 (3.1%)
Cardiac death	2 (3.8%)	2 (1.5%)
Any MI	1 (1.9%)	10 (7.7%)
Target vessel MI	1 (1.9%)	6 (4.6%)
Scaffold thrombosis	0 (0%)	1 (0.8%)
Target lesion revascularization	0 (0%)	7 (5.4%)
Target vessel revascularization	1 (1.9%)	19 (14.6%)*
Target vessel failure	3 (5.8%)	23 (17.7%)*
MACE	4 (3.7%)	29 (22.3%)*

*p < 0.05, Mann-Whitney test, as appropriate; MACE — major adverse cardiac events; MI — myocardial infarction

quartile range 24.0 [17.0–41.0] months). The rate of all-cause death and cardiac death was similar in both groups. There was a trend to a higher incidence of MI and TLR in the non-PSP-technique group, however, it was not statistically significant. Scaffold thrombosis occurred only in 1 patient during hospitalization (definite sub-acute thrombosis). No further scaffold thrombosis occurred at follow-up. TVF was consistently reduced in patients using the PSP technique as compared with non-PSP-technique group (5.8% vs. 17.7%, p = 0.03). Moreover, PSP-technique was superior to non-PSP-technique concerning MACE (3.7% vs. 22.3%, p = 0.02) (Table 4).

The logistic regression analysis revealed that use of the PSP technique significantly decreased the risk of TVR (odds ratio [OR] = 0.11, p = 0.01), TVF (OR = 0.28, p = 0.03) and MACE (OR = 0.29, p = 0.02).

Discussion

In this study, it was found that pre-dilatation, proper sizing, and post-dilatation, cold PSP-technique, improve long-term clinical results of bioresorbable absorb scaffolds in patients with ACS. PSP-technique reduces the risk of TVR, TVF, and MACEs by almost 8-fold.

Recently, preliminary results for BVS are not very encouraging. The main concerns regard thrombosis and restoration of vessel functionality at long-term follow-up. Data from the randomized ABSORB Japan (2 years), ABSORB III (2 years), ABSORB II (3 years), and AIDA (2-year mean follow-up) trials demonstrated a higher rate of very late scaffold thrombosis with BVS compared to CoCr-EES [3, 4, 15]. Increased strut thickness delays endothelialization and correlates with flow disturbance, increased risk of strut fracture and disruption because of overexpansion [16]. Additionally, BVSs are not as stretchable as metallic stents and cannot be expanded beyond specified limits. Due to these specific properties, implantation of BVS should be performed particularly carefully. PSP technique (precise pre-dilatation and vessel sizing before BVS implantation and post-dilation following implantation) was associated with lower risk of thrombotic events in context with a non-PSP technique [17]. Predilatation and proper vessel sizing increases the rate of successful device delivery and correct expansion. The data showed that a correct size of the vessel is the most critical determinant of event-free rate during the year subsequent to implantation [18, 19]. The MICAT authors suggested that very-late events could also be associated with a suboptimal sizing of the vessel [20]. In turn, an optimal post-dilation prevents adverse events by maximizing scaffold dimensions, embed struts into plaque, avoid acute malapposition, and reduce shear stress [19].

The PSP technique has been investigated for ABSORB BVS technology [21]. Firstly, it was considered as the five golden "P"s: prepare the lesion, properly size, pay attention to expansion limits, post-dilate with non-compliant balloon as well as pay attention to DAPT [22]. This concept was supported by a group of European experts in a consensus document regarding optimal implantation technique [16] and by results from the MICAT registry (The Coronary Slow-flow and Microvascular Diseases Registry) [20]. In this study, optimal implantation technique significantly reduced the rate of scaffold thrombosis. The post-hoc analysis of the GHOST-EU registry showed a reduction of device-oriented composite endpoint at 1-year follow-up when all three steps of the PSP technique were performed correctly [18].

Moreover, a pooled analysis of the ABSORB trials (ABSORB II, III, CHINA, JAPAN, and EXTEND) revealed that an optimal PSP-technique was strongly associated with clinical outcomes during long-term follow-up [19]. The rationale for the use of BVS in the setting of the ACS are data suggesting that implantation of a temporary scaffold is associated with stabilization of atherosclerotic plaque without a permanent metallic cage. According to recent data, the safety and clinical outcomes of BVS in ACS patients are comparable

to that of modern DESs [23]. From a retrospective study, it is also known that scaffold thrombosis can be reduced, when appropriate BVS size, pre- and post-dilatation were employed [24]. In the present study, the rate of scaffold thrombosis was not negligible and occurred in only 1 patient in the non-PSP group who did not have post-dilatation.

Although aggressive lesion preparation improves the rate of successful device delivery, pre-dilatation potentially increases the risk of plaque disruption, thrombus mobilization, and distal embolism [25]. Usually, it is recommended to use semi- or non-compliant balloons with a diameter 0.5 mm smaller or equal to the size of the planned device and characteristics [24]. In the present study, all lesions were pre-dilated in PSP group and 92.3% lesions in non-PSP groups without complications. In all these cases, manual thrombus aspiration was applied before pre-dilatation. The overall procedural success rate was 100%, including all cases with evident thrombus.

Due to the limited expansion and BVS sizes available, vessel sizing is crucial in performing accurate scaffold implantation, especially in patients with ACS. In this group, proper vessel sizing can be limited due to spasm and thrombus inside the artery [26, 27]. Scaffold diameter should be selected according to the reference vessel diameter. The gold standard of correct RVD estimation after proper pre-dilation, and excluded under expansion or malapposition is intravascular imaging [21]. Tanaka et al. [28] reported that patients treated with intravascular imaging guidance, post-dilation balloon/scaffold ratio was higher and final residual percentage stenosis was lower compared with those treated with an angio-guided approach. However, despite the angio- and QCA guided PSP technique has several limitations, such as limited information of the atherosclerotic plaque composition, limited visibility of the scaffold in the angiography, difficulties in the estimation of RVD, and uncertainty of possible scaffold under expansion or malapposition, these techniques are used in the 3 steps of implantation in most patients. This results from the still limited availability of optical coherence tomography and intravascular ultrasound due to high cost. In the current study the QCA guided approach dominated in the PSP group (65.4%), and angiography-guided approach in non-PSP group (93.2%).

According to the recommended PSP technique, all scaffolds should be post-dilated with NC balloon. However, ACS patients have a potentially increased risk of over-expansion, disruption, and the effect of post-dilatation following its implantation [9, 10]. The ASSURE Registry (21.3% unstable angina) showed that a slight systematic oversizing of BVS, followed by high pressure post-dilatation, is safe and effective [29]. In turn, short-term results of the RAI registry (1,505 patients, 59% ACS) confirmed that high post-dilation rate (96.8%) might mitigate BVS-related events [30]. In a pooled analysis of the BVS Expand and BVS STEMI registries (351 patients, 72.6% ACS), post-dilation in ACS group was only 41.3% [31].

A comparison of BVS vs. everolimus eluting stent (EES) in STEMI patients with a high rate of post-dilation showed favorable mid-term results [32]. In the BVS STEMI first propensity score matching comparisons between 151 BVS patients and 151 EES patients, the MACE rate was higher in the BVS group (9.8% vs. 3.6%, $p = 0.02$, and TLR was 5.7% vs. 1.3%, $p = 0.05$) [33]. Interestingly, the 30-day MACE rate in BVS patients without post-dilatation was 6.8% and 3.6% in patients with post-dilatation. Of note, all BVS cases with acute scaffold thrombosis had no post-dilatation at the index procedure suggesting that optimization of the implantation technique is of paramount importance even in the acute setting. Imori et al. [17] also confirmed the importance of BVS post-dilation in the ACS setting. At 24 month follow-up, a higher rate of MACE was observed in BVS compared to EES in consecutive ACS patients before and after propensity score matching. However, after sensitivity analysis, MACE rates in BRS patients with post-dilation were significantly lower than in those without post-dilation and were comparable to EES patients (6.0% vs. 12.6% vs. 4.7%, $p < 0.001$). scaffold thrombosis rates were only slightly lower in the BVS group with post-dilatation, but were higher in both BVS groups than in EES patients (2.0% vs. 2.6% vs. 1.2%, $p = 0.09$).

Contrarily to the ABSORB III 2-year results, the investigators did not find any relation between clinical outcomes with either the implantation technique (74% BVS post-dilation rate) or the diameter of the treated vessels or the presenting symptoms. However, among the patients in the scaffold group who had definite or probable device thrombosis, 19% had a residual diameter stenosis of 30% or greater; among the patients who did not have device thrombosis, 9% had a residual percent diameter stenosis of 30% or greater ($p = 0.05$) highlighting the importance to obtain maximal BVS expansion at the end of the procedure. In the present study, post-dilatation was applied in all

patients in the PSP group without complications and only in 2 (1.5%) patients in the non-PSP group.

Conclusions

The implantation of BVSs according to the PSP-technique reduced rates of TVR, TVF, as well as MACE, compared with non-PSP-technique implantation during long-term observation. The PSP-technique for BVS implantation improves long-term results and should also be recommended for newer generations of bioresorbable scaffold.

Conflict of interest: Maciej Lesiak has received payments as an individual for the advisory board and speaker honoraria from Abbott Vascular, Astra-Zeneca, Biotronik, Boston Scientific and Tryton Medical. Stefan Grajek has received payments as an individual on the advisory board and speaker honoraria from Astra-Zeneca, Servier, Pfizer, Sandoz, Adamed, Polpharma. Aleksander Araszkiewicz has received payments as an individual for the advisory board and speaker honoraria from Abbott Vascular. None of the other authors have relationships with Industry to declare.

References

1. Giacchi G, Ortega-Paz L, Brugaletta S, et al. Bioresorbable vascular scaffold implantation in acute coronary syndromes: clinical evidence, tips and tricks. Post Kardiol Interw. 2015; 11(3): 161–169, doi: 10.5114/pwki.2015.54006, indexed in Pubmed: 26677353.
2. Gomez-Lara J, Brugaletta S, Jacobi F, et al. Five-Year optical coherence tomography in patients with ST-segment-elevation myocardial infarction treated with bare-metal versus everolimus-eluting stents. Circ Cardiovasc Interv. 2016; 9(10), doi: 10.1161/CIRCINTERVENTIONS.116.003670, indexed in Pubmed: 27702766.
3. Serruys PW, Chevalier B, Sotomi Y, et al. Comparison of an everolimus-eluting bioresorbable scaffold with an everolimus-eluting metallic stent for the treatment of coronary artery stenosis (ABSORB II): a 3 year, randomised, controlled, single-blind, multicentre clinical trial. Lancet. 2016; 388(10059): 2479–2491, doi: 10.1016/S0140-6736(16)32050-5, indexed in Pubmed: 27806897.
4. Wykrzykowska JJ, Kraak RP, Hofma SH, et al. Bioresorbable Scaffolds versus Metallic Stents in Routine PCI. N Engl J Med. 2017; 376(24): 2319–2328, doi: 10.1056/NEJMoa1614954, indexed in Pubmed: 28402237.
5. Kereiakes DJ, Ellis SG, Metzger C, et al. 3-year clinical outcomes with everolimus-eluting bioresorbable coronary scaffolds: the absorb III trial. J Am Coll Cardiol. 2017; 70(23): 2852–2862, doi: 10.1016/j.jacc.2017.10.010, indexed in Pubmed: 29100702.
6. Ali ZA, Serruys PW, Kimura T, et al. 2-year outcomes with the Absorb bioresorbable scaffold for treatment of coronary artery disease: a systematic review and meta-analysis of seven randomised trials with an individual patient data substudy. Lancet. 2017; 390(10096): 760–772, doi: 10.1016/S0140-6736(17)31470-8, indexed in Pubmed: 28732815.
7. Kolandaivelu K, Swaminathan R, Gibson WJ, et al. Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. Circulation. 2011; 123(13): 1400–1409, doi: 10.1161/CIRCULATIONAHA.110.003210, indexed in Pubmed: 21422389.
8. Ortega-Paz L, Brugaletta S, Sabaté M. Impact of PSP technique on clinical outcomes following bioresorbable scaffolds implantation. J Clin Med. 2018; 7(2), doi: 10.3390/jcm7020027, indexed in Pubmed: 29415486.
9. De Ribamar Costa J, Abizaid A, Bartorelli AL, et al. Impact of post-dilation on the acute and one-year clinical outcomes of a large cohort of patients treated solely with the Absorb Bioresorbable Vascular Scaffold. EuroIntervention. 2015; 11(2): 141–148, doi: 10.4244/EIJY15M05_06, indexed in Pubmed: 25982921.
10. Ormiston JA, Serruys PW, Regar E, et al. A bioabsorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSORB): a prospective open-label trial. Lancet. 2008; 371(9616): 899–907, doi: 10.1016/S0140-6736(08)60415-8, indexed in Pubmed: 18342684.
11. Onuma Y, Serruys PW, Perkins LEL, et al. Intracoronary optical coherence tomography and histology at 1 month and 2, 3, and 4 years after implantation of everolimus-eluting bioresorbable vascular scaffolds in a porcine coronary artery model: an attempt to decipher the human optical coherence tomography images in the ABSORB trial. Circulation. 2010; 122(22): 2288––2300, doi: 10.1161/CIRCULATIONAHA.109.921528, indexed in Pubmed: 20975003.
12. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation. 2012; 126(16): 2020–2035, doi: 10.1161/CIR.0b013e31826e1058, indexed in Pubmed: 22923432.
13. Laskey WK, Yancy CW, Maisel WH. Thrombosis in coronary drug-eluting stents: report from the meeting of the Circulatory System Medical Devices Advisory Panel of the Food and Drug Administration Center for Devices and Radiologic Health, December 7-8, 2006. Circulation. 2007; 115(17): 2352–2357, doi: 10.1161/CIRCULATIONAHA.107.688416, indexed in Pubmed: 17470710.
14. Cutlip DE, Windecker S, Mehran R, et al. 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.
15. Onuma Y, Sotomi Y, Shiomi H, et al. Two-year clinical, angiographic, and serial optical coherence tomographic follow-up after implantation of an everolimus-eluting bioresorbable scaffold and an everolimus-eluting metallic stent: insights from the randomised ABSORB Japan trial. EuroIntervention. 2016; 12(9): 1090–1101, doi: 10.4244/EIJY16M09_01, indexed in Pubmed: 27597270.
16. Tamburino C, Latib A, van Geuns RJ, et al. Contemporary practice and technical aspects in coronary intervention with bioresorbable scaffolds: a European perspective. EuroIntervention. 2015; 11(1): 45–52, doi: 10.4244/EIJY15M01_05, indexed in Pubmed: 25599676.
17. Imori Y, D'Ascenzo F, Gori T, et al. Impact of postdilatation on performance of bioresorbable vascular scaffolds in patients with acute coronary syndrome compared with everolimus-eluting stents: A propensity score-matched analysis from a multicenter "real-world" registry. Cardiol J. 2016; 23(4): 374–383, doi: 10.5603/CJ.a2016.0052, indexed in Pubmed: 27515481.

18. Ortega-Paz L, Capodanno D, Gori T, et al. Predilation, sizing and post-dilation scoring in patients undergoing everolimus-eluting bioresorbable scaffold implantation for prediction of cardiac adverse events: development and internal validation of the PSP score. EuroIntervention. 2017; 12(17): 2110–2117, doi: 10.4244/EIJ-D-16-00974, indexed in Pubmed: 28246060.
19. Stone GW, Abizaid A, Onuma Y, et al. Effect of technique on outcomes following bioresorbable vascular scaffold implantation: analysis from the ABSORB trials. J Am Coll Cardiol. 2017; 70(23): 2863–2874, doi: 10.1016/j.jacc.2017.09.1106, indexed in Pubmed: 29100704.
20. Puricel S, Cuculi F, Weissner M, et al. Bioresorbable Coronary Scaffold Thrombosis: Multicenter Comprehensive Analysis of Clinical Presentation, Mechanisms, and Predictors. J Am Coll Cardiol. 2016; 67(8): 921–931, doi: 10.1016/j.jacc.2015.12.019, indexed in Pubmed: 26916481.
21. Absorb Bioresorbable Vascular Scaffold System [Internet]. https://www.vascular.abbott:80/us/products/coronary-intervention/absorb-bioresorbable-scaffold-dissolving-stent.html (cited 2018 Jun 12).
22. Everaert B, Felix C, Koolen J, et al. Appropriate use of bioresorbable vascular scaffolds in percutaneous coronary interventions: a recommendation from experienced users : A position statement on the use of bioresorbable vascular scaffolds in the Netherlands. Neth Heart J. 2015; 23(3): 161–165, doi: 10.1007/s12471-015-0651-3, indexed in Pubmed: 25626696.
23. Iwańczyk S, Hiczkiewicz J, Araszkiewicz A, et al. Evaluation of bioresorbable vascular scaffolds in acute coronary syndrome: A two-center, one-year follow-up analysis. Cardiol J. 2018; 25(4): 479–486, doi: 10.5603/CJ.a2017.0131, indexed in Pubmed: 29168541.
24. Ellis SG, Steffenino G, Kereiakes DJ, et al. Clinical, angiographic, and procedural correlates of acute, subacute, and late absorb scaffold thrombosis. JACC Cardiovasc Interv. 2017; 10(18): 1809–1815, doi: 10.1016/j.jcin.2017.06.067, indexed in Pubmed: 28935071.
25. Pan M, Romero M, Ojeda S, et al. Fracture of bioresorbable vascular scaffold after side-branch balloon dilation in bifurcation coronary narrowings. Am J Cardiol. 2015; 116(7): 1045–1049, doi: 10.1016/j.amjcard.2015.07.015, indexed in Pubmed: 26243578.
26. Spaulding C, Henry P, Teiger E, et al. Sirolimus-eluting versus uncoated stents in acute myocardial infarction. N Engl J Med. 2006; 355(11): 1093–1104, doi: 10.1056/NEJMoa062006, indexed in Pubmed: 16971716.
27. Stone GW, Lansky AJ, Pocock SJ, et al. Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. N Engl J Med. 2009; 360(19): 1946–1959, doi: 10.1056/NEJMoa0810116, indexed in Pubmed: 19420364.
28. Tanaka A, Latib A, Kawamoto H, et al. Clinical outcomes of a real-world cohort following bioresorbable vascular scaffold implantation utilising an optimised implantation strategy. EuroIntervention. 2017; 12(14): 1730–1737, doi: 10.4244/EIJ-D-16-00247, indexed in Pubmed: 27746400.
29. Wöhrle J, Naber C, Schmitz T, et al. Beyond the early stages: insights from the ASSURE registry on bioresorbable vascular scaffolds. EuroIntervention. 2015; 11(2): 149–156, doi: 10.4244/EIJY14M12_10, indexed in Pubmed: 25499836.
30. Cortese B, Ielasi A, Moscarella E, et al. Thirty-Day outcomes after unrestricted implantation of bioresorbable vascular scaffold (from the prospective RAI registry). Am J Cardiol. 2017; 119(12): 1924–1930, doi: 10.1016/j.amjcard.2017.03.017, indexed in Pubmed: 28438304.
31. Felix CM, Onuma Y, Fam JM, et al. Are BVS suitable for ACS patients? Support from a large single center real live registry. Int J Cardiol. 2016; 218: 89–97, doi: 10.1016/j.ijcard.2016.05.037, indexed in Pubmed: 27232918.
32. Farag M, Spinthakis N, Gorog DA, et al. Use of bioresorbable vascular scaffold: a meta-analysis of patients with coronary artery disease. Open Heart. 2016; 3(2): e000462, doi: 10.1136/openhrt-2016-000462, indexed in Pubmed: 27621831.
33. Fam JM, Felix C, van Geuns RJ, et al. Initial experience with everolimus-eluting bioresorbable vascular scaffolds for treatment of patients presenting with acute myocardial infarction: a propensity-matched comparison to metallic drug eluting stents 18-month follow-up of the BVS STEMI first study. Eurointervention. 2016; 12(1): 30–37, doi: 10.4244/EIJV12I1A6., indexed in Pubmed: 27173859.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2020, Vol. 27, No. 6, 685–692
DOI: 10.5603/CJ.a2019.0113

ISSN 1897–5593
eISSN 1898–018X

Quantitative flow ratio-guided surgical intervention in symptomatic myocardial bridging

Quan Qi[1,*], Gang Liu[2,*], Zhize Yuan[3,*], Lili Liu[4], Shengxian Tu[4], Qiang Zhao[3]

[1]Department of Cardiac Surgery, First Hospital of Lanzhou University, Lanzhou, Gansu, China
[2]Department of Cardiology, Yuyao People's Hospital, Yuyao, Zhejiang, China
[3]Department of Cardiac Surgery, RuiJin Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai, China
[4]Biomedical Instrument Institute, School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai, China

Abstract

Background: *Patients with myocardial bridging (MB) are associated with adverse cardiovascular events, but a decision to perform surgical intervention, especially for patients with systolic intermediate stenosis, is a difficult clinical issue. Fractional flow reserve (FFR) represents a novel method for the functional evaluation of coronary stenosis, but the relationship between FFR and MB remains controversial because of the cyclic dynamic stenosis of MB. Quantitative flow ratio (QFR) is a novel index allowing fast assessment of FFR from a diagnostic coronary angiography. This study aimed to investigate the relationship between QFR and MB patients and to further develop a prediction model of QFR-guided surgical intervention for these patients.*

Methods: *Forty-five symptomatic lone MB patients who had undergone coronary angiography were consecutively enrolled in this study. MB was located in the middle of left anterior descending artery with intermediate stenosis during systole. The patients were retrospectively divided into a medical therapy group or a surgical therapy group. Systolic geometry based QFR (SG-QFR) and diastolic geometry based QFR (DG-QFR) were calculated based on three-dimensional quantitative coronary angiography and patient-specific flow velocity. Subsequently, time-averaged QFR (TA-QFR) is defined as the average of SG-QFR and DG-QFR.*

Results: *Receiver operating characteristic curve analysis revealed that TA-QFR (AUC = 0.91; 95% CI: 0.79–0.98) was found to be the best pre-operative index for surgical intervention to MB, when compared with DG-QFR (AUC = 0.69; 95% CI: 0.53–0.82; difference: 0.22; 95% CI: 0.04–0.41; p = 0.02) and SG-QFR (AUC = 0.87; 95% CI: 0.74–0.95; difference: 0.04; 95% CI: 0.00–0.08; p = 0.03).*

Conclusions: *TA-QFR improved the performance of functional evaluation in MB patients with intermediate stenosis during systole and is useful for guiding surgical intervention.* (Cardiol J 2020; 27, 6: 685–692)

Key words: quantitative flow ratio, surgical intervention, myocardial bridging

Introduction

Myocardial bridging (MB) is a band of myocardial tissue, under which a segment of the coronary artery running in the epicardial tissue. The characteristic angiographic appearance of MB shows systolic narrowing of the artery with relatively normal vessel diameter during diastole. MB has once been

Address for correspondence: Qiang Zhao, MD, PhD, Department of Cardiac Surgery, Rui jin Hospital, Shanghai Jiaotong University School of Medicine, No. 197, Rui jin Er Road, Shanghai 200025, China, tel: +86 34186000, fax: +86 21 64333548, e-mail: zq11607@rjh.com.cn

Shengxian Tu, PhD, Room123, Med-X Research Institute, Shanghai Jiao Tong University, No. 1954, Hua Shan Road, Shanghai 200030, China, tel: +86 21 62932631, fax: +86 21 62932156, e-mail: sxtu@sjtu.edu.cn

**These authors contributed equally to this work.*

Received: 3.06.2019 Accepted: 30.11.2019

considered as a benign condition. However, recent studies have suggested that MB was associated with myocardial ischemia, atrioventricular block, arrhythmias, and even sudden cardiac death [1–3]. Therefore, an effective assessment model is desirable for clinical decision making in patients with MB, especially when coupled with intermediate stenosis during systole.

The concept of the fractional flow reserve (FFR) was developed by Pijls in 1995 [4]. The measurement of FFR is increasingly used to evaluate the functional significance of coronary stenosis and it was demonstrated to be a good performance [5]. However, because of potential limitations of conventional FFR, like time-consuming, high expense, and other factors, utilization of FFR worldwide make it a poor choice, in general, with a few exceptions [6]. Quantitative flow ratio (QFR) is a novel index allowing a quick assessment of FFR from a diagnostic coronary angiography, which has the potential to resolve the limitations of FFR, as mentioned above [7–9]. Due to the cyclical, dynamic nature of stenosis in MB patients (dynamic compression of the coronary artery extending from the systole into the diastole), using the conventional QFR computation is not adequate in evaluating MB [10]. On the other hand, QFR can be computed from specific stenotic geometry during cardiac cycle. The objective of this study was to demonstrate that a combination of QFR computations at different cardiac phases could be used to predict patients with MB who require surgical intervention.

Methods

Study design

This was a retrospective and observational study. Symptomatic lone MB patients who had undergone coronary angiography were included. All patients were given optimal doses of beta-blockers (BB) and calcium channel blockers (CCB). During follow-up, if medical therapy was not adequate to relieve symptoms of patients with MB, then coronary artery bypass grafting or surgical myotomy was performed. The other patients were continued on medical therapy. So, the patients were divided into two groups: the medical therapy group or the surgical therapy group. An overview of the study design is demonstrated in Figure 1. It was hypothesized that a combination of QFR computations at different cardiac phases can be used to predict patients with MB who require surgical intervention. The study protocol was approved by the ethics committee of the documented hospital.

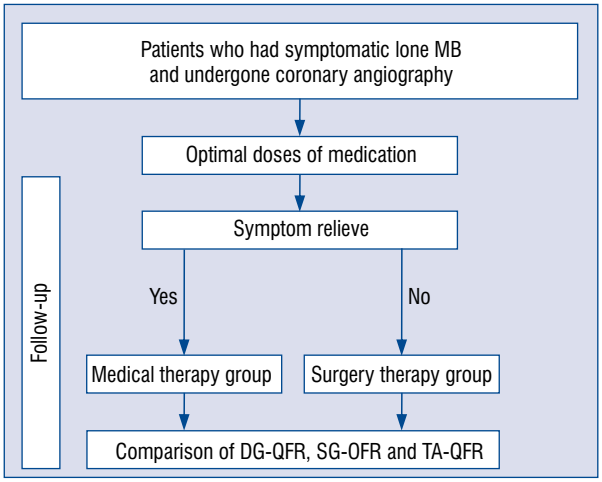


Figure 1. Overview of the study design; MB — myocardial bridging; SG-QFR — systolic geometry based quantitative flow ratio; DG-QFR — diastolic geometry based quantitative flow ratio; TA-QFR — time-averaged quantitative flow ratio.

Study population

A total of 45 symptomatic lone MB patients who underwent invasive coronary angiography at Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, from September 2016 to January 2019, were consecutively enrolled in this study. Inclusion criteria were: 1) age > 18 years; 2) all patients were diagnosed with MB in a catheterization laboratory. The characteristic angiographic appearance of MB includes systolic narrowing or the so called "milking effect" of the artery with a relatively normal vessel diameter during the diastolic period; 3) MB patients who were identified as having systolic stenosis in mid-left anterior descending coronary artery segment; 4) the MB in all patients had intermediate stenosis during systole (defined by a percent diameter stenosis 50% to 90% during systole by visual estimation); 5) all patients were given optimal doses of BB and CCB with the objective of relieving symptoms and signs of myocardial ischemia; 6) two angiographic projections > 25° apart were recorded by flat-panel X-ray systems; 7) nitroglycerine was given prior to the angiographic acquisitions. Exclusion criteria were: 1) overlap or foreshortening (> 90%) between nearby vessels in invasive coronary angiography (ICA) images; 2) poor ICA image quality.

Invasive coronary angiography image acquisition, geometrical reconstruction and QFR computation

Angiographic images were recorded at 15 frames/s by monoplane X-ray systems (Innova 2100, GE). ICA images were analyzed by an experienced analyst who had been trained in three-dimensional quantitative coronary angiography (3D QCA) and QFR. Angiographic projections with minimal overlap and foreshortening were selected, then 3D geometrical reconstruction was performed and QFR was computed, using a prototype software package (QAngio XA 3D prototype, Medis special bv, Leiden, the Netherlands) [8]. Angiographic views at end-systolic and end-diastolic phases were selected and the interrogated vessel was reconstructed at both end-systolic and end-diastolic phases. Subsequently, the systolic geometry based QFR (SG-QFR) and diastolic geometry based QFR (DG-QFR) were derived using patient-specific flow velocity and a recently developed QFR computational algorithm [8, 11]. Vessel QFR at the most distal position of the reconstructed vessel was used. The time-averaged QFR (TA-QFR) is defined as the average of SG-QFR and DG-QFR.

Statistical analysis

Normally distributed continuous variables are expressed as mean ± standard deviation or as median if abnormally distributed, whereas categorical variables are expressed as percentages. Clinical characteristics data were collected per-patient and remaining calculations were on a per-vessel basis. The performance of TA-QFR, SG-QFR and DG--QFR in predicting lesions was assessed by using accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) together with their 95% confidence intervals (CIs), then by making a comparison between prognostic performance of TA-QFR, SG-QFR and DG-QFR. Receiver-operating characteristic (ROC) curves were generated and the area under the curve (AUC) was calculated. The Youden index was used as a criterion to identify the optimal cutoff value for TA-QFR, SG-QFR and DG-QFR in predicting surgical intervention. Paired comparisons in ROC curves were performed by the DeLong method using MedCalc (version 13.0, MedCalc Software BVBA, Ostend, Belgium). Comparisons between the two groups were performed using the Student t-test with IBM SPSS (version 19.0, Armonk, New York). $p < 0.05$ was considered to be statistically significant.

Results

Patient baseline clinical and stenosis characteristics

A total of 45 symptomatic MB patients with intermediate stenosis during systole were consecutively included. Twenty (44.4%) patients remained symptomatic despite optimal doses of BB or CCB. No major cardiac events were observed and all patients were asymptomatic during follow-up in both groups. Patient baseline clinical characteristics are listed in Table 1. There were no statistically significant differences between the two groups regarding patient clinical characteristics. Stenosis characteristics are listed in Table 2. At the end-diastolic phase, interrogated vessels had an average percent diameter stenosis (DS%), minimum lumen diameter (MLD), reference vessel diameter and minimum lumen area (MLA) of 26.1 ± 6.7% vs. 33.2 ± 11.5% ($p = 0.02$), 1.57 ± ± 0.29 mm vs. 1.55 ± 0.29 mm ($p = 0.80$), 2.20 ± ± 0.40 mm vs. 2.36 ± 0.27 mm ($p = 0.12$), 2.07 ± ± 0.81 mm^2 vs. 2.22 ± 0.79 mm^2 ($p = 0.52$) for the medical therapy group compared with the surgical therapy group whereas at the end-systolic phase, the same vessels interrogated had an average DS%, MLD, reference vessel diameter and MLA of 41.4 ± ± 9.1% vs. 57.3 ± 9.5% ($p = 0.00$), 1.29 ± 0.30 mm vs. 1.02 ± 0.19 mm ($p = 0.00$), 2.20 ± 0.40 mm vs. 2.41 ± 0.29 mm ($p = 0.05$), 1.52 ± 0.61 mm^2 vs. 1.13 ± 0.40 mm^2 ($p = 0.02$) during systole between two groups, respectively. Representative examples of X-ray angiography, 3D angiographic reconstruction and computation of QFR are shown in Figures 2 and 3.

Computation of QFR

The computed QFR values are listed in Table 3. DG-QFR between the two groups was 0.96 ± 0.02 vs. 0.93 ± 0.06 ($p = 0.03$) and SG-QFR between the two groups was 0.89 ± 0.07 vs. 0.74 ± 0.10 ($p = 0.00$). TA-QFR between the two groups was 0.92 ± 0.03 vs. 0.83 ± 0.06 ($p = 0.00$).

Accuracy of TA-QFR for diagnostic performance

TA-QFR had a greater area under the curve (AUC = 0.91; 95% CI 0.79–0.98), when compared with DG-QFR (AUC = 0.69; 95% CI 0.53–0.82]; difference: 0.22; 95% CI 0.04–0.41; $p = 0.02$) and SG-QFR (AUC = 0.87; 95% CI 0.74–0.95; difference: 0.04; 95% CI 0.00–0.08; $p = 0.03$) (Fig. 4). From the ROC curve, the best cutoff value for

Table 1. Patient baseline clinical characteristics (n = 45).

Risk factors	Medical therapy group (n = 25)	Surgical therapy group (n = 20)	P
Age [years]	59.16 ± 9.67	55.80 ± 7.61	0.21
Female, sex	14 (25%)	6 (20%)	0.08
Body mass index [kg/m^2]	23.35 ± 3.70	24.59 ± 2.87	0.22
History of blood pressure	5 (24%)	3 (21%)	0.86
Diabetes	3 (24%)	5 (21%)	0.55
Hypercholesteremia	3 (24%)	3 (21%)	1.00
Smoking	7 (24%)	5 (21%)	0.69
EuroSCORE	0.64 ± 0.12	0.62 ± 0.16	0.58
Percent of medical therapy:			
Beta-blocker	18 (25%)	14 (20%)	0.88
Dose/day [mg]	36.94 ± 12.14	33.93 ± 12.20	0.49
CCB	7 (25%)	6 (20%)	0.88
Dose/day [mg]	62.50 ± 22.57	67.50 ± 23.35	0.55
Time (follow-up) [months]	22.76 ± 10.30	23.15 ± 8.53	0.89

Variables are in number (%), mean ± standard deviation; CCB — calcium channel blocker

Table 2. Baseline lesion characteristics (n = 45).

Baseline lesion characteristics	Diastole			Systole		
	Medical therapy group	Surgical therapy group	P	Medical therapy group	Surgical therapy group	P
Percent diameter stenosis	26.1 ± 6.7	33.2 ± 11.5	0.02	41.4 ± 9.1	57.3 ± 9.5	0.00
Minimum lumen diameter [mm]	1.57 ± 0.29	1.55 ± 0.29	0.80	1.29 ± 0.30	1.02 ± 0.19	0.00
Reference vessel diameter [mm]	2.20 ± 0.40	2.36 ± 0.27	0.12	2.20 ± 0.40	2.41 ± 0.29	0.06
Minimum lumen area [mm^2]	2.07 ± 0.81	2.22 ± 0.79	0.52	1.52 ± 0.61	1.13 ± 0.40	0.02

Variables are mean ± standard deviation. Anatomical parameters were quantified by three-dimensional quantitative coronary.

TA-QFR in predicting patients requiring surgical therapy was found at 0.88. This resulted in a better diagnostic performance, with an accuracy of 89%, sensitivity of 85%, specificity of 92%, PPV of 90%, and NPV of 89%. Applying a cutoff value of 0.88 to TA-QFR resulted in 23 true positives, 17 true negatives, 2 false positives, and 3 false negatives. The diagnostic performance of TA-QFR vs. DG-QFR, and SG-QFR was listed in Table 4.

Discussion

The main findings of the present study are: 1) TA-QFR is a novel index to assess patients with MB; 2) TA-QFR has a higher value in predicting MB patients who require surgical intervention, when compared with DG-QFR and SG-QFR; 3) The optimal cut-off value of TA-QFR in predicting MB patients who require surgical intervention was 0.88, with an overall accuracy of 89%, sensitivity of 85%, specificity of 92%, PPV of 90%, and NPV of 89%, respectively.

Myocardial bridging is a congenital coronary anomaly, and the incidence of MB is highest in the left anterior descending coronary artery [12]. MB appears as systolic compression by invasive coronary with relatively normal vessel diameter during diastole. It has been acknowledged that MB can influence dynamic nature of coronary arteries. Furthermore, some studies showed that myocardial vessel compression existed not only in systole but was also persistent during diastole [13]. In some

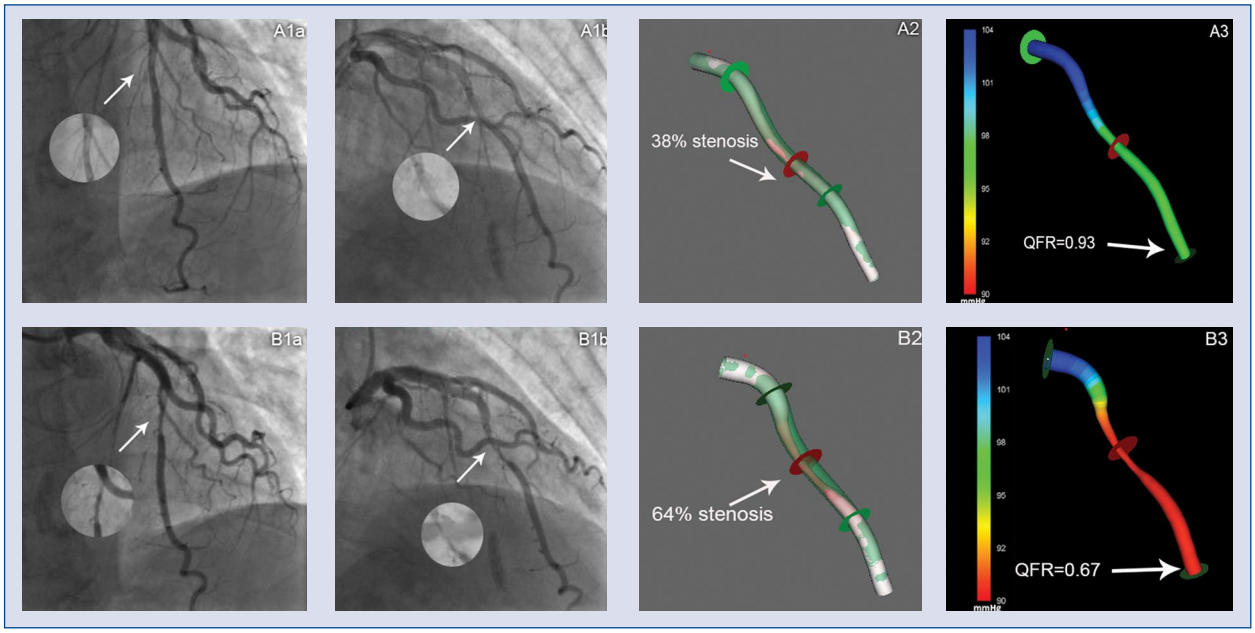


Figure 2. Three-dimensional angiographic reconstruction and computation of quantitative flow ratio (QFR) in the surgical therapy group; **A1a, A1b.** X-ray angiographic projectionsat end-diastolic phase; **B1a, B1b.** X-ray angiographic projectionsat end-systolic phase; **A2.** Diastolic geometry reconstructed from panel 1a and panel 1b; **B2.** Systolic geometry reconstructed from panel B1a and panel B1b; **A3.** DG-QFR computed from the diastolic geometry; **B3.** SG-QFR computed from the systolic geometry.

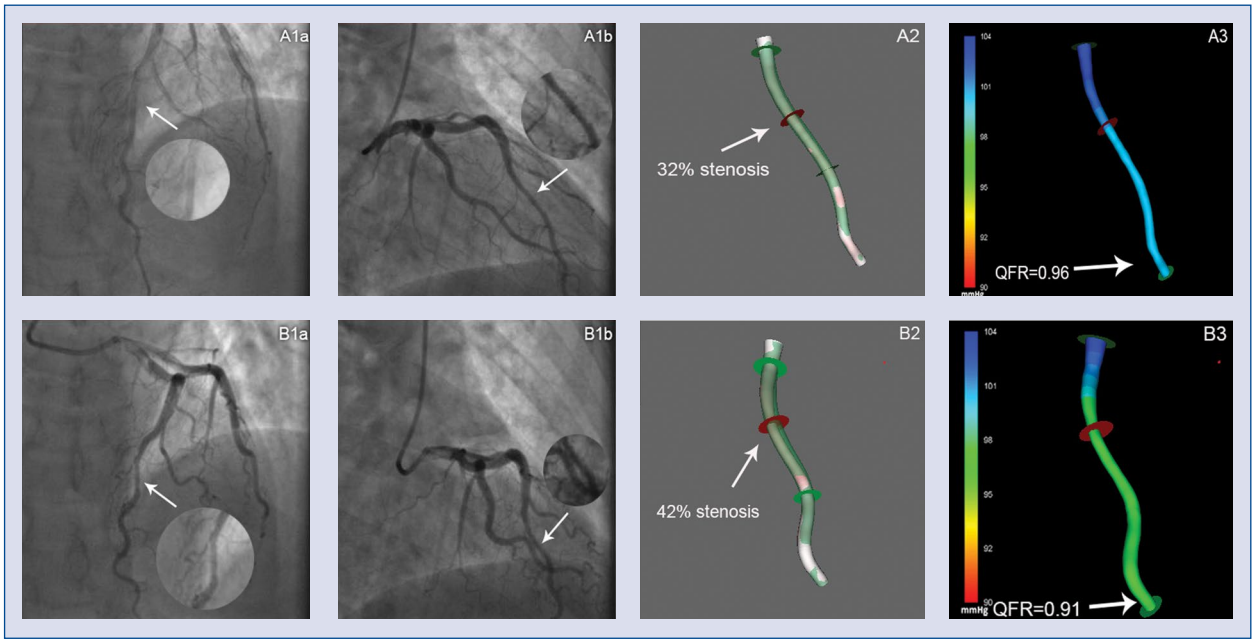


Figure 3. Three-dimensional angiographic reconstruction and computation of quantitative flow ratio (QFR) in the medical therapy group; **A1a, A1b.** X-ray angiographic projectionsat end-diastolic phase; **B1a, B1b.** X-ray angiographic projectionsat end-systolic phase; **A2.** Diastolic geometry reconstructed from panel 1a and panel 1b; **B2.** Systolic geometry reconstructed from panel B1a and panel B1b; **A3.** DG-QFR computed from the diastolic geometry; **B3.** SG-QFR computed from the systolic geometry.

studies, and case reports, it was associated with cardiac ischemia, angina, arrhythmias, or even sudden death [14, 15]. However, the optimal approach to assess MB by coronary angiography as well as by FFR remains unclear, due to the cyclic dynamic stenosis of MB [16]. Therefore, MB of-

Table 3. Quantitative flow ratio (QFR) between the two groups (n = 45).

QFR	Medical therapy group	Surgical therapy group	P
DG-QFR	0.96 ± 0.02	0.93 ± 0.06	0.03
SG-QFR	0.89 ± 0.07	0.74 ± 0.10	0.00
TA-QFR	0.92 ± 0.03	0.83 ± 0.06	0.00

Variables are mean ± standard deviation. SG-QFR — systolic geometry based QFR; DG-QFR — diastolic geometry based QFR; TA-QFR — time-averaged QFR

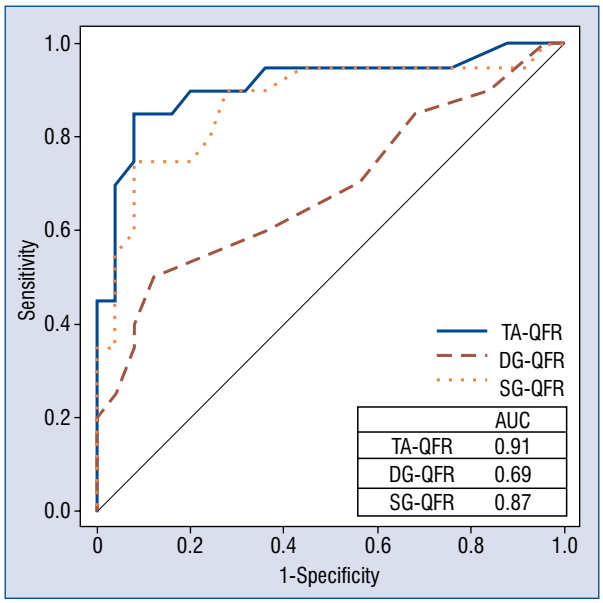


Figure 4. Receiver operating characteristic (ROC) curves for the discrimination of functionally significant stenosis. ROC curves compare sensitivity and specificity of TA-QFR versus DG-QFR (p = 0.02) and SG-QFR (p = 0.03) for the prediction of surgical intervention for myocardial bridging patients; SG-QFR — systolic geometry based quantitative flow ratio; DG-QFR — diastolic geometry based quantitative flow ratio; TA-QFR — time-averaged quantitative flow ratio.

ten causes clinical dilemmas, which widely raise concerns [17].

Fractional flow reserve has been recommended as class IA evidence for identifying hemodynamically significant coronary lesions when evidence of myocardial ischemia is unavailable according to the European Society of Cardiology guidelines and is increasingly applied in clinical settings for the time being [18, 19]. However, the adoption of conventional FFR is limited due to aforementioned practical drawbacks. QFR emerges as a novel, fast,

Table 4. Diagnostic performance of quantitative flow ratio (QFR) and three-dimensional quantitative coronary angiography anatomical indices.

	TA-QFR ≤ 0.88	DG-QFR ≤ 0.93	SG-QFR ≤ 0.78
Accuracy	89 (80–98)	71 (58–84)	84 (73–96)
Sensitivity	85 (62–97)	50 (27–73)	75 (51–91)
Specificity	92 (74–99)	88 (69–98)	92 (74–99)
PPV	90 (69–97)	77 (51–91)	88 (66–97)
NPV	89 (73–96)	69 (58–78)	82 (68–91)

Values are number (95% confidence interval). SG-QFR — systolic geometry based QFR; DG-QFR — diastolic geometry based QFR; TA-QFR — time-averaged QFR; PPV — positive predictive value; NPV — negative predictive value

non-invasive method for the assessment of FFR, which based on patient-specific flow velocity and a coronary geometric model, shows good correlation and agreement with pressure-derived FFR, with a diagnostic accuracy of 86% (95% CI 78% to 93%) [8, 20].

Fractional flow reserve assessment of MB has caused longstanding concerns. It has been reported that diagnostic functional severity of MB was facilitated after inotropic stimulation, which can increase vessel compression in MB [21]. Escaned demonstrated that a combination of diastolic FFR with dobutamine being chosen as an inotropic challenge among patients with MB, improved the assessment of myocardial ischemia. However, the significance of dobutamine testing for clinical decision-making remained unclear and the acquisition of diastolic FFR was a sophisticated procedure with measuring errors [10, 22]. Moreover, limited application of conventional FFR was found among patients with MB, as time-consuming, side effects associated with vasodilator administration, higher expense, etc. Conventional FFR is inadequate for MB assessment since cyclic dynamic stenosis during cardiac cycle, results in an underestimation of functional stenosis severity of MB [10, 23]. Therefore, a reasonable FFR-guided assessment model is demanded for guiding therapeutic strategies of patients with symptomatic lone MB.

In the present study, SG-QFR, DG-QFR was calculated for each patient and geometric models were reconstructed at the end-systolic phase and at the end-diastolic phase, respectively. As the existence of cyclic dynamic stenosis, that is, systolic compression and diastolic are relatively normal, hemodynamic significance might be overestimated or underestimated in the systolic phase or dias-

tolic phase. FFR measurement during the diastolic phase seems inadequate for MB assessment [10]. However, QFR computation was not done during the whole systolic phase nor the diastolic phase. Thus, computational deviation cannot be neglected. TA-QFR, unlike conventional FFR which is measured during the whole cardiac cycle, and is defined as the average of SG-QFR and DG-QFR, can both consider the systolic phase and the diastolic phase and then compensate for the downsides of SG-QFR, DG-QFR. As shown in Figure 4, AUC was significantly higher for TA-QFR (AUC = 0.91; 95% CI 0.79–0.98) compared with DG-QFR (AUC = 0.69; 95% CI 0.53–0.82) and SG-QFR (AUC = 0.87; 95% CI 0.74–0.95]. So TA-QFR can improve the performance of a functional evaluation in MB patients with intermediate stenosis during systole, with an accuracy of 89% (SG-QFR ≤ 0.88) and shows the superiority of TA-QFR over other conventional methods for the assessment of patients with MB who require surgical intervention with an optimal cut-off value of 0.88.

Conclusions

The time-averaged QFR improved the performance of functional evaluation in MB patients with intermediate stenosis during systole and is useful for guiding surgical intervention.

Acknowledgements

We acknowledge support of the Science and Technology Commission of Shanghai Municipality (Grant No. 18440731700), the Program of Shanghai Technology Research Leader, the Medical Engineering Interdisciplinary Program of Shanghai Jiao Tong University (Grant YG2016ZD09), the Health Industry Scientific Research Project of Gansu Province (GSWSKY2018-49) and the Natural Science Foundation of Gansu Province (18JR3RA349).

Conflict of interest: Doctor Shengxian Tu received a research grant from Medis Medical Imaging and Pulse Medical Imaging Technology. Other authors report no conflict of interest regarding this manuscript.

References

1. Corban MT, Hung OY, Eshtehardi P, et al. Myocardial bridging: contemporary understanding of pathophysiology with implications for diagnostic and therapeutic strategies. J Am Coll Cardiol. 2014; 63(22): 2346–2355, doi: 10.1016/j.jacc.2014.01.049, indexed in Pubmed: 24583304.
2. Tarantini G, Migliore F, Cademartiri F, et al. Left anterior descending artery myocardial bridging: a clinical approach. J Am Coll Cardiol. 2016; 68(25): 2887–2899, doi: 10.1016/j.jacc.2016.09.973, indexed in Pubmed: 28007148.
3. Ryan N, Escaned J. Myocardial bridge as a cause of persistent post percutaneous coronary intervention angina identified with exercise intracoronary physiology. Eur Heart J. 2017; 38(13): 1001, doi: 10.1093/eurheartj/ehw501, indexed in Pubmed: 27807054.
4. Pijls NHJ, Klauss V, Siebert U, et al. Coronary pressure measurement after stenting predicts adverse events at follow-up: a multicenter registry. Circulation. 2002; 105(25): 2950–2954, doi: 10.1161/01.cir.0000020547.92091.76, indexed in Pubmed: 12081986.
5. Luu JM, Friedrich MG, Harker J, et al. Relationship of vasodilator-induced changes in myocardial oxygenation with the severity of coronary artery stenosis: a study using oxygenation-sensitive cardiovascular magnetic resonance. Eur Heart J Cardiovasc Imaging. 2014; 15(12): 1358–1367, doi: 10.1093/ehjci/jeu138, indexed in Pubmed: 25104812.
6. Neglia D, Rovai D, Caselli C, et al. Detection of significant coronary artery disease by noninvasive anatomical and functional imaging. Circ Cardiovasc Imaging. 2015; 8(3), doi: 10.1161/CIRCIMAGING.114.002179, indexed in Pubmed: 25711274.
7. Xu Bo, Tu S, Qiao S, et al. Diagnostic accuracy of angiography-based quantitative flow ratio measurements for online assessment of coronary stenosis. J Am Coll Cardiol. 2017; 70(25): 3077–3087, doi: 10.1016/j.jacc.2017.10.035, indexed in Pubmed: 29101020.
8. Tu S, Westra J, Yang J, et al. Diagnostic accuracy of fast computational approaches to derive fractional flow reserve from diagnostic coronary angiography. JACC: Cardiovascular Interventions. 2016; 9(19): 2024–2035, doi: 10.1016/j.jcin.2016.07.013.
9. Westra J, Tu S, Campo G, et al. Diagnostic performance of quantitative flow ratio in prospectively enrolled patients: An individual patient-data meta-analysis. Catheter Cardiovasc Interv. 2019; 94(5): 693–701, doi: 10.1002/ccd.28283, indexed in Pubmed: 30963676.
10. Escaned J, Cortés J, Flores A, et al. Importance of diastolic fractional flow reserve and dobutamine challenge in physiologic assessment of myocardial bridging. J Am Coll Cardiol. 2003; 42(2): 226–233, doi: 10.1016/s0735-1097(03)00588-6, indexed in Pubmed: 12875756.
11. Tu S, Barbato E, Köszegi Z, et al. Fractional flow reserve calculation from 3-dimensional quantitative coronary angiography and TIMI frame count: a fast computer model to quantify the functional significance of moderately obstructed coronary arteries. JACC Cardiovasc Interv. 2014; 7(7): 768–777, doi: 10.1016/j.jcin.2014.03.004, indexed in Pubmed: 25060020.
12. Gupta MD, Girish MP, Trehan V, et al. Myocardial bridging in all major epicardial vessels. JACC Cardiovasc Interv. 2014; 7(10): e129–e131, doi: 10.1016/j.jcin.2014.02.020, indexed in Pubmed: 25341715.
13. Xu Z, Wu Q, Li H, et al. Myotomy after previous coronary artery bypass grafting for treatment of myocardial bridging. Circulation. 2011; 123(10): 1136–1137, doi: 10.1161/CIRCULATIONAHA.110.989129, indexed in Pubmed: 21403124.
14. Ding H, Yang Q, Shang K, et al. Estimation of shear stress by using a myocardial bridge-mural coronary artery simulating device. Cardiol J. 2017; 24(5): 530–538, doi: 10.5603/CJ.a2016.0084, indexed in Pubmed: 27714723.

15. Azzalini L, Ancona MB, Mitomo S, et al. Self-apposing stent fracture in the context of myocardial bridging leading to in-stent chronic total occlusion: When the muscle trumps the metal. Cardiol J. 2018; 25(1): 144–145, doi: 10.5603/CJ.2018.0011, indexed in Pubmed: 29512100.
16. Tremmel J, Schnittger I. Myocardial bridging. J Am Coll Cardiol. 2014; 64(20): 2178–2179, doi: 10.1016/j.jacc.2014.07.993.
17. Okutucu S, Aparci M, Sabanoglu C, et al. Assessment of cardiac autonomic functions by heart rate recovery indices in patients with myocardial bridge. Cardiol J. 2016; 23(5): 524–531, doi: 10.5603/CJ.a2016.0046, indexed in Pubmed: 27387063.
18. Honda K, Okamura Y, Nishimura Y, et al. Graft flow assessment using a transit time flow meter in fractional flow reserve-guided coronary artery bypass surgery. J Thorac Cardiovasc Surg. 2015; 149(6): 1622––1628, doi: 10.1016/j.jtcvs.2015.02.050, indexed in Pubmed: 25840755.
19. Montalescot G, Sechtem U, et al. 2013 ESC Guidelines on the management of stable coronary artery disease. Eur Heart J. 2013; 34(38): 2949–3003, doi: 10.1093/eurheartj/eht296, indexed in Pubmed: 23996286.
20. Westra J, Andersen B, Campo G, et al. Diagnostic performance of in procedure angiography derived quantitative flow reserve compared to pressure derived fractional flow reserve: the FAVOR II Europe Japan study. J Am Heart Assoc. 2018; 7(14), doi: 10.1161/jaha.118.009603, indexed in Pubmed: 29980523.
21. Yoshino S, Cassar A, Matsuo Y, et al. Fractional flow reserve with dobutamine challenge and coronary microvascular endothelial dysfunction in symptomatic myocardial bridging. Circulation. 2014; 78(3): 685–692, doi: 10.1253/circj.cj-13-0846.
22. Kunamneni PB, Rajdev S, Krishnan P, et al. Outcome of intracoronary stenting after failed maximal medical therapy in patients with symptomatic myocardial bridge. Catheter Cardiovasc Interv. 2008; 71(2): 185–190, doi: 10.1002/ccd.21358, indexed in Pubmed: 18327835.
23. Farag A, Al-najjar Y, Eichhöfer J. Adenosine-induced vasospasticity in a myocardial bridge…endothelial dysfunction? JACC: Cardiovascular Interventions. 2015; 8(2): e21–e22, doi: 10.1016/j.jcin.2014.09.017, indexed in Pubmed: 25700764.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2020, Vol. 27, No. 6, 693–704
DOI: 10.5603/CJ.a2020.0148

ISSN 1897–5593
eISSN 1898–018X

Heart failure in Poland: Left ventricular assist device destination therapy and other challenges of interventional cardiology and cardiac surgery

Mariusz Kuśmierczyk[1], Jacek Różański[1], Michał Zembala[2], Dariusz Dudek[3, 4], Wojciech Braksator[5], Tomasz Grodzicki[6], Piotr Hoffman[7], Jerzy Sadowski[3, 8], Marcin Gruchała[9], Jacek Legutko[3, 10], Piotr Siondalski[11], Karol Wierzbicki[3, 8], Bogusław Kapelak[3, 8], Grzegorz Opolski[12], Andrzej Juraszek[1], Katarzyna Bondaryk[13], Jacek Walczak[14], Izabela Pieniążek[14], Maciej Grys[14], Piotr Przygodzki[15]

[1]Department of Cardiac Surgery and Transplantology, National Institute of Cardiology, Warsaw, Poland; [2]Department of Cardiac Surgery Heart and Lung Transplantation and Mechanical Circulatory Support Silesian Center for Heart Diseases, Zabrze, Poland; [3]Institute of Cardiology, Jagiellonian University Medical College, Krakow, Poland; [4]Maria Cecilia Hospital, GVM Care and Research, Cotignola (RA), Ravenna, Italy; [5]Department of Sports Cardiology and Non-invasive Cardiac Imaging, 2nd Medical Faculty, Medical University of Warsaw, Poland; [6]Department of Internal Medicine and Gerontology, Medical College, Jagiellonian University, Krakow, Poland; [7]Department of Congenital Heart Disease, National Institute of Cardiology, Warsaw, Poland; [8]Department of Cardiovascular Surgery and Transplantology, The John Paul II Hospital, Krakow, Poland; [9]1st Department of Cardiology, Medical University of Gdansk, Poland; [10]Department of Interventional Cardiology, The John Paul II Hospital, Krakow, Poland; [11]Cardiac and Vascular Surgery Department, Medical University of Gdansk, Poland; [12]1st Chair and Department of Cardiology, Medical University of Warsaw, Poland; [13]Law Office Bondaryk, Warsaw, Poland; [14]Arcana Institute a Certara Company, Krakow, Poland; [15]Abbott Health Economics and Reimbursement, Warsaw, Poland

Abstract

Patients with severe heart failure (HF), who are not eligible for cardiac transplantation and receive optimal medical management, based mainly on the use of pharmacological treatment and devices such as resynchronization therapy (implantable cardioverter-defibrillator), achieve poor clinical outcomes and constitute a group with extremely poor prognosis. Currently, the technology used in the latest generation left ventricular assist devices (LVADs), such as the HeartMate 3, makes it possible to achieve patient survival at the level obtained by patients after heart transplantation, and they can be used not only in patients eligible for heart transplantation as a bridge to transplant, but also in those with significantly worse prognosis, who are ineligible for heart transplantation as destination therapy.

The objective of this publication is to present recommendations from experts in cardiology and cardiac surgery, supported by clinical trial results, on the use of LVADs as a destination therapy in HF patients who are not eligible for cardiac transplantation. The paper also presents the issue of cardiac transplantation and extracorporeal membrane oxygenation therapy in Poland, as well as current challenges faced by interventional cardiology and cardiac surgery in Poland. (Cardiol J 2020; 27, 6: 693–704)

Key words: heart failure, left ventricular assist device, destination therapy, extracorporeal membrane oxygenation, dilated cardiomyopathy

Address for correspondence: Dr. Izabela Pieniążek, Instytut Arcana, ul. Kuklińskiego 17, 30–720 Kraków, Poland, tel: +48 519 116 861, e-mail: izabela.pieniazek@certara.com

Received: 24.08.2020 Accepted: 12.10.2020

Introduction

The following recommendations are based on presentations and discussions that took place during the Advisory Committee meeting organized in collaboration with the 'Quo Vadis Cardiologia?' initiative. The goal was to gather the opinions of leading experts (16 experts in total) in the fields of conservative cardiology, interventional cardiology, electrophysiology, and cardiac surgery regarding aspects of the use of left ventricular assist devices (LVADs) as a destination therapy (DT) among Polish patients. In addition, the situation of transplantation procedures and the most important challenges of interventional cardiology and cardiac surgery in Poland were discussed [1].

LVADs as destination therapy

In a selected group of patients with heart failure (HF), mechanical circulatory support (MCS) may help to achieve sustained improvements in quality of life and life expectancy. While for many patients the use of MCS is still a bridge to transplant or to recovery, for those with irreversible permanent lesions, MCS is a DT due to the insufficient number of donors and increasingly improved technical solutions [2–4]. This applies primarily to patients with severe HF:

— with accompanying renal failure — high risk of dialysis after orthotopic heart transplantation;
— who are significantly overweight (over 100 kg) — difficulty in obtaining a donor;
— with persistent pulmonary hypertension high risk of primary graft failure after transplantation.

Continuous-flow left ventricular assist devices (CF-LVADs) revolutionized the management of HF patients. These compact, fully implantable cardiac pumps are able to provide a significant increase in survival and improve the function and quality of life in a selected group of patients. For such a large group of people facing a high risk of short-term mortality and a small chance of heart transplantation, implantation of CF-LVADs gives the greatest hope. In patients with a CF-LVAD the annual survival rate is 82%, while in patients with pulsatile flow devices it is 61% [5, 6].

INTERMACS is an American registry of patients in which data on MCS are collected from mandatory submissions regarding LVAD implantations in the United States (US) and, on a voluntary basis, from some other countries or centers. The latest INTERMACS report, published in 2017, states that over 22,000 implantations of different MCS systems have been recorded in the last decade, of which 90% are CF-LVADs. On the basis of the available data, we know today that:

— 25% of the MCS devices are implanted as a bridge to transplant;
— 24% of the MCS devices are implanted to improve the patients' clinical status to be considered as a bridge to candidacy;
— 51% of the MCS devices are implanted under DT (compared to 3.9% in 2009) [7].

Over several decades, technical development of LVADs designed for long-term support has been observed. New solutions in the field of pump drive construction, miniaturization, and materials, as well as battery life and performance were implemented. This is directly related to a significant reduction in thromboembolic complications, bleedings, and infections, which makes these devices safe for permanent use and reduces hospital admissions. We can now distinguish three LVAD generations. First-generation LVADs include HeartMate I, LionHeart, and Novacor. Second-generation devices are DeBakey VAD, Incor, Jarvik 2000, and HeartMate II. The third and most recent LVAD generation includes devices such as HeartWare or HeartMate 3 [8].

The two US Food and Drug Administration-approved and CE-marked LVADs predominantly used in long-term treatment are HeartWare and HeartMate 3. HeartMate 3 replaced the previous HeartMate II (a continuous-flow line pump) [9].

Implantation of the ventricular support system is a procedure performed in patients with severe and reversible (or irreversible) heart damage, who have exhausted all alternative treatment options, i.e. no other cardiac surgery can be performed, and pharmacological treatment cannot be expected to stop further disease progression. The LVAD is implanted through a sternotomy or using a minimally invasive technique (through left-sided mini-thoracotomy combined with right-sided upper mini-thoracotomy or mini-sternotomy) and involves the implantation of a device that ensures blood circulation by pumping it out of the left ventricle and into the aorta. The procedure is performed with extracorporeal circulation or, in selected cases, without its use. Long-term LVADs are used for longer than a month. Depending on the type of device, the drive system is pneumatic or electrical.

The LVAD that will ensure the best effectiveness as a DT in patients not eligible for a heart transplant should have, above all, a very good hemocompatibility profile:

— achieving long survival times;
— which will be free from hemocompatibility-related events such as a stroke, pump thrombosis, hemolysis, or other thromboembolic events (Table 1).

At the same time, this translates into a significant improvement in the functional status and quality of life in this group of patients.

Advances in the management of heart disease, in particular in the area of LVAD implantation, has led to the development of pulse and then continuous flow devices. The latest-generation LVADs — centrifugal with continuous flow — are fully implanted into the pericardial sac. In these devices, the rotors are magnetically levitated, which eliminates the spaces not washed by blood, which used to be the main source of thromboembolic complications. Miniaturization of the devices has improved patient quality of life and functioning outside hospital. In some groups of patients with end-stage HF, who are not candidates for orthotopic heart transplantation, but whose expected survival is > 1 year in good functional condition, left ventricular support can be considered as a DT to reduce clinical signs indicative of the risk of rehospitalization and premature death (European Society of Cardiology [ESC] class IIa, level B recommendation). This safe, reliable, durable, and implantable mechanism supporting the function of the left ventricle is considered an effective device for DT [10]. Using LVADs is beneficial in terms of the improvement of hemodynamic parameters (consisting of an increase of ejection fraction and of cardiac index, reduction of pulmonary wedge pressure and left ventricular end-diastolic dimension) and, consequently, improvement also of clinical parameters (improvement in functional class — New York Heart Association [NYHA], quality of life, prolonged life expectancy) [6].

The 2016 ESC guidelines for diagnosis and treatment of acute and chronic HF contain a list of indications for which MCS devices are implanted (Table 2) and recommendations for the use of MSC in patients with refractory HF (Table 3).

The selection of an appropriate device depends on many factors, including the expected duration of treatment, the need for correct ventricular support, and the patient's body surface area. It is very important to exclude absolute contraindications to ventricular assist device (VAD) implantation. However, each case is assessed individually, and the listed criteria are drawn up solely for reference. At times, VADs are implanted in patients who do not yet meet the above criteria [3].

Table 1. Key parameters of long-term mechanical circulatory support (LT-MCS) devices [7].

LT-MCS characteristic
Ability to generate adequate blood flow and pressure
Easy replacement of components that may fail
Easy system removal during heart transplantation or explantation after the failing heart's function is restored
Small size
Fully implantable and easily renewable power source
Durability
No immunogenicity
Low degree of hemolysis
Low risk of infectious complications

Hemodynamic criteria for the use of VADs include:
— cardiac index < 2 L/min/m^2;
— systolic blood pressure (SBP) < 90 mmHg;
— pulmonary capillary wedge pressure (PCWP > 20 mmHg;
— diuresis < 20 mL/h [11].

Patients with severe symptoms persisting for more than 2 months, despite optimal medical and implantable device therapy, and more than one of the following, are candidates for LVAD implantation:
— left ventricular ejection fraction (LVEF) < 25% and, if measured, peak oxygen VO_2 < 12 mL/kg/min;
— ≥ 3 hospitalizations for HF within the last 12 months without an obvious precipitating cause;
— dependence on IV inotropic therapy;
— progressive end-organ dysfunction (worsening renal and/or liver function) due to reduced perfusion rather than inadequate ventricular filling pressure (PCWP ≥ 20 mmHg and SBP ≤ 80–90 mmHg or cardiac index ≤ 2 L/min/m^2);
— absence of severe right ventricular dysfunction, including severe tricuspid regurgitation [11].

The reference candidate for an LVAD is a patient with chronic, congestive left ventricular failure, with a history of frequent decompensation, requiring intravenous inotropic therapy (INTERMACS 3: dependent stability) at the time of qualification or in the past, with normal or slightly impaired right ventricular function. In patients with HF exacerbation, who require escalation of drug therapy or the use of other MCS devices (IABP or

Table 2. Indications for mechanical circulatory support (2016 ESC Guidelines for the Diagnosis and Management of Acute and Chronic Heart Failure) [11].

Indication	Rationale
Bridge to decision (BTD)/ /bridge to bridge (BTB)	Use of short-term MCS (e.g. ECLS or ECMO) in patients with cardiogenic shock until stabilization of hemodynamics and organ perfusion, exclusion of contraindications to long-term MCS (brain damage after resuscitation), and evaluation of additional therapeutic options including long-term ventricular assist device therapy and heart transplant
Bridge to candidacy (BTC)	Use of MCS (usually LVAD) to improve end-organ function to make an ineligible patient eligible for a heart transplant
Bridge to transplant (BTT)	Use of MCS (LVAD or BiVAD) to keep patients who are at high risk of death alive until a donor organ is available
Bridge to recovery (BTR)	Use of MCS (typically LVAD) to keep patients alive until cardiac function recovers sufficiently and removal of MCS is possible
Destination therapy (DT)	Long-term use of MCS (LVAD) as an alternative to heart transplantation in patients with end-stage heart failure ineligible for transplantation or for long-term waiting for heart transplantation

BiVAD — biventricular assist device; ECLS — extracorporeal life support; ECMO — extracorporeal membrane oxygenation; LVAD — left ventricular assist device; MCS — mechanical circulatory support

Table 3. Recommendations for the implantation of mechanical circulatory support in patients with refractory heart failure (2016 ESC Guidelines for the Diagnosis and Management of Acute and Chronic Heart Failure) [11].

Class	Level	Recommendation
IIa	C	LVADs should be considered in patients with end-stage HFrEF, despite optimal medical therapy and device therapy, who are eligible for cardiac transplantation in order to improve symptoms, and reduce the risk of heart failure hospitalization and the risk of premature death (BTT).
IIa	B	LVADs should be considered in patients with end-stage HFrEF, despite optimal medical (mainly ACEI or sacubitril/valsartan, beta-blockers, and MRA) and device therapy (e.g. implantable cardioverter defibrillator and/or cardiac resynchronization therapy), who are not eligible for cardiac transplantation, to reduce the risk of premature death (destination therapy)

ACEI — angiotensin converting enzyme inhibitor; BTT — bridge to transplant; HFrEF — heart failure with reduced ejection fraction; LVADs — left ventricular assist devices; MRA — mineralocorticoid receptor antagonist

ECMO; INTERMACS class 2), LVAD implantation is a life-saving method with proven efficacy and a good safety profile.

In patients with milder disease — defined by INTERMACS as groups 4–5 — LVAD implantation may be considered as a prevention of frequent hospitalizations due to HF to improve prognosis and quality of life, especially in the population of patients with contraindications for transplantation or whose expected waiting time for the organ (e.g. obese patients) is very long [12].

Contraindications for VAD implantation include:

— irreversible advanced hepatic or renal failure;
— active systemic infection;
— chronic obstructive pulmonary disease;
— disseminated cancer;
— clinically significant purpura;
— cerebrovascular disease [3].

Unfortunately, despite the use of advanced technology, LVADs are not free of defects, and their implantation may result in early and late complications.

The main complications in patients with an implanted LVAD are driveline infections occurring in about 30% of patients and, less commonly, generalized device-related infections. There may be a risk of infection at any time after implantation, but it usually occurs between week 2 and month 12 after the procedure. The infections are usually caused by Gram-positive (*Staphylococcus aureus, epidermidis*) or, less frequently, Gram-negative bacteria (*Pseudomonas aeruginosa, Enterobacter*, and *Klebsiella sp.*) and fungi. In individual cases

infection may lead to the development of bacteremia, sepsis, or endocarditis. Sepsis developing in patients with MCS promotes the formation of embolisms in the central nervous system or multiple organ failure, and it is the major cause of death. Therefore, the driveline exit site requires particular care. Dressings should be changed in fully aseptic conditions (masks, sterile gloves), washed with mild antibacterial soap and sterile saline, then covered with a sterile dressing. In addition, the driveline itself should be protected from excessive movement to minimize the risk of mechanical trauma [13]. Currently, in the event of failure of antibiotic therapy, surgical driveline repositioning is effectively used to treat infection in the exit site area. Heart transplantation is the ultimate treatment option in this situation [1].

Another significant complication is gastrointestinal bleeding or bleeding into the central nervous system, which is usually more severe. On the one hand, it is associated with the use of anticoagulants (warfarin and acetylsalicylic acid), and on the other hand, with changes in the circulatory system likely caused by less physiological continuous flow in the majority of modern circulatory support systems. The incidence of this bleeding can be reduced up to two-fold through telemonitoring. Daily international normalized ratio measurement can eliminate the risk of bleeding [1].

Moreover, the risk of device dysfunction caused by the formation of blood clots, damage to the driveline, or other electromechanical causes cannot be ignored [14]. The negative effects of thrombosis and its incidence may be limited by daily monitoring of the LVAD patient via telehealth technology [1].

An example of a telehealth system is Remedizer, which is an application used to monitor patients' health with LVADs after hospitalization [15], developed in cooperation with the National Institute of Cardiology of the Primate of the Millennium Cardinal Stefan Wyszynski in Warsaw. Patients use mobile devices to independently monitor pump parameters and vital signs such as blood pressure, weight, and body temperature, as well as blood coagulability, and to control the medications intake. The data are automatically sent to the monitoring center, where the coordinating person conducts a thorough assessment of the treatment and makes decisions on medical interventions if the patient's health state causes any concern [15].

According to data from the 2017 INTERMACS report, only about 20% of patients receiving MCS did not experience serious adverse events, such as infections, bleeding, stroke, device dysfunction, or death in the 3 years of follow-up. However, the patients' quality of life significantly improved in the first 3 months. This improvement without serious adverse events is later maintained at a similar level. Paradoxically, patients receiving long-term LVAD treatment often do not agree to the proposed heart transplant, fully approving their assisted functioning. In some patients the improvement is so spectacular that the conversion from NYHA class IV to class I/II is achieved, enabling outpatient treatment with supportive care and even removal of the device [7].

HeartMate 3 — third-generation LVAD

The HeartMate (HM) 3 LVAD is the most recent third-generation pump used for long-term cardiac support in patients with severe HF, which is usually irreversible. The device is used as a bridge to transplant, which enables the patient to survive until a heart transplant is performed. It can also be used as a DT in patients with contraindications for cardiac transplantation. The HM 3 LVAD, which replaced the previous HM II axial flow pump, is smaller than the earlier pneumatic pumps and therefore easier for the surgeon to implant. It is implanted into the left ventricle of the heart and helps to support the patient's heart for a period of several weeks up to many years [5]. The HM 3 LVAD partially mimics the pulse rate, periodically increasing rotations. This is important because the natural blood flow has a pulsating character and as such determines the proper function of the endothelium of the blood vessels. Implantable circulatory support models usually provide continuous flow. This flow is thought to be responsible for distant VAD complications (e.g. hemorrhagic, thromboembolic events). That is why such high hopes are associated with the latest third-generation pumps, such as HM 3, in which the flow rate changes every 2 s, creating a 'pulsation' that mimics the natural blood flow in the human body. This solution contributes to the reduction of the number of complications related to the implantation or use of the device [5, 6].

LVAD HeartMate 3 as DT in clinical trials

The randomized clinical trial MOMENTUM 3 compared the clinical efficacy and safety of HM 3 LVAD with HM 2 LVAD in patients with severe HF. Participants were enrolled regardless of the indication for the device implantation; however, in the results analysis the data were stratified by the indication for implantation. Finally, approximately 60% of the patients who enrolled in the

Table 4. Distribution of patients according to the indication for use of the HeartMate 3 (HM3) or the HeartMate 2 (HM2) pump in the MOMENTUM 3 study [6].

Indication for LVAD implantation	HM3 (n = 515)	HM2 (n = 505)	Total (n = 1020)
BTT (bridge to transplant)	112 (22%)	120 (24%)	232 (23%)
BTC (bridge to candidacy)	86 (17%)	78 (15%)	164 (16%)
1. Likely to be candidates for a heart transplant	45 (8%)	43 (9%)	88 (9%)
2. Moderately likely to be candidates for a heart transplant	32 (6%)	33 (7%)	65 (6%)
3. Unlikely to be candidates for a heart transplant	9 (2%)	2 (0.3%)	11 (0.8%)
DT (destination therapy): patients who are ineligible for a heart transplant	317 (62%)	307 (60%)	624 (61%)

LVAD — left ventricular assist device

Table 5. Comparison of the clinical effectiveness of the HeartMate 3 left ventricular assist device implanted in the destination therapy (DT) or bridge to transplant/bridge to candidacy (BTT/BTC) indication in the MOMENTUM 3 study.

Endpoint	DT (n = 624)	BTT/BTC (n = 396)
2-year event-free survival	73.2%	76.8%
2-year overall survival	76.7%	82.7%
Survival at 2 years free of stroke	88.1%	89.2%
Survival at 2 years free of pump thrombosis	97.5%	99.4%

MOMENTUM 3 trial had an LVAD implanted as a DT. These participants were not eligible for heart transplantation (Table 4) [6].

The primary endpoint of the MOMENTUM 3 study was a 2-year event-free experience (a disabling stroke or reoperation to replace or remove a malfunctioning device). A disabling stroke was defined as a modified Rankin score > 3.

Patients not eligible for a transplant, who received the HM 3 device as a DT, achieved a 2-year event-free survival of 73.2%, which was significantly higher compared to 58.7% in patients with an HM 2 device. The likelihood of an event occurrence (a disabling stroke or reoperation to replace or remove a malfunctioning device) was almost two times lower for patients implanted with an HM 3 pump than for patients implanted with an HM 2 (hazard ratio [HR] = 0.61; 95% confidence interval [CI] 0.46–0.81; p = 0.0006).

The use of the HM 3 device lowered the risk of adverse events in the form of a disabling stroke or reoperation, in order to replace/remove a malfunctioning device in the population of patients not eligible for heart transplantation, who received the LVAD as a DT at a level comparable to that in the population of patients who received the device as a bridge to transplant/bridge to candidacy (BTT/BTC) (HR = 0.61 and HR = 0.62, respectively; 95% CI 0.40–0.94; p = = 0.02). Similar effectiveness of the HM 3 LVAD was demonstrated in the DT and BTT/BTC populations in terms of the 2-year event-free survival, 2-year overall survival, survival at 2 years free of stroke, and survival at 2 years free of pump thrombosis (Table 5).

Although no patient included in the MOMENTUM 3 study was NYHA class I or II, as early as at 3 months post implantation of the HM 3, the functional status of 70% of patients improved and they were classified as NYHA class I or II. During the 2 years of follow-up, the percentage of patients with NYHA class I or II increased gradually and reached 80% at 2 years post implantation of the HM 3 LVAD, regardless of the indication, DT, or BTT/BTC (vs. baseline [p < 0.0001]).

In patients with the HM3 LVAD, an improvement from baseline in the 6-minute walking test was observed, irrespective of the intended goal of LVAD use: DT or BTT/BTC (p < 0.0001).

The quality of life based on EQ-5D-5L VAS form improved significantly at 3 months post implantation of the HM3 LVAD (from the baseline value of 50 to 72) and was sustained for 2 years after pump implantation, achieving a score of 76 after implantation of the HM3 pump and at the end of the follow-up, irrespective of the intended

goal of LVAD use: DT or BTT/BTC (vs. baseline [$p < 0.0001$]).

Currently, the technology used in the HM 3 pump allows patient survival at the same level of patients after heart transplantation and enables its use not only in patients eligible for heart transplantation as a BTT, but also in patients with considerably worse prognosis, i.e. not eligible for a heart transplantation as a DT. An important point is that patients with an implanted HM 3 LVAD as DT can achieve high clinical outcomes comparable to those in the group of patients receiving such treatment as a BTT/BTC.

Funding

Obtaining public financing of DT depends on creating a separate guaranteed health service, introducing uniform criteria for qualifying the patient to obtain this benefit, and making the procedure independent of the currently financed heart transplantation service. While under the ordinance of the Minister of Health of November 12, 2015, there were no restrictions on the use of LVAD therapy as DT, and the qualification for obtaining this service by the patient still remains associated with the transplantation procedure. Therefore, it is not clear from a legal point of view whether it is necessary to evaluate the clinical condition of the patients in terms of their suitability for cardiac transplantation during the process of qualification for an LVAD implantation. The ambiguity of these legal regulations in practice discourages healthcare providers from making decisions about LVAD implantation regardless of their patients' compliance with eligibility criteria for a heart transplant.

It is necessary to separate the LVAD implantation procedure as DT from the item currently described as highly specialized services. A change in the description of this service can be performed either by changing the description of the current highly able 4 service or by creating a new, separate basket of services including only the implantation of LVADs as DT. Taking into account the available clinical data and the premises for financing public health services, the creation of a new basket of services including exclusively the implantation of LVADs as a DT is an optimal solution for the system.

Polish guidelines for MCS

In Poland, the management procedures relating to HF patients are developed by the College of Family Physicians and the Working Group on Heart Failure of the Polish Cardiac Society. The current treatment protocol is described in the 2017 guidelines. The guidelines were developed based on the 2016 ESC recommendations, which were also adopted by the Polish Cardiac Society. The 2017 guidelines developed by the College of Family Physicians and the Polish Cardiac Society recommend the use of LVADs in treatment-resistant patients who are classified with American College of Cardiology/American Heart Association (ACC/AHA) stage D HF [16].

In order to change the negative statistics for HF patients in Poland, the KONS ('Comprehensive care for patients with heart failure') system has been developed. Its introduction is expected to result in improved life expectancy, a reduced number of hospitalizations, decreased sickness absence, improved quality of life, and reduced indirect costs resulting from incapacity for work and sickness absenteeism (Social Insurance Institution [ZUS]). The main goal of the undertaking is to limit the effects of HF in Poland. The scope of the intervention includes the identification of HF symptoms, then diagnostics, therapy, rehabilitation, and long-term and palliative care [17, 18].

Eligibility criteria for patients and centers for the use of LVAD DT

According to clinical experts, all LVADs should be implanted as DT, which means that patients with an LVAD should not undergo a heart transplant unless specific indications exist. A heart transplantation in an LVAD patient is indicated when the individual presents with right ventricular failure and device- or driveline-related infection that cannot be treated surgically and/or with antibiotics. Hearts should be reserved for patients in a younger age group [1].

Clinical experts believe that pulmonary hypertension is not an absolute contraindication to LVAD implantation (it is sometimes indicative of a good condition of the right ventricle) but is a classic contraindication for a heart transplant. In addition, the age of patients should not be a factor determining their access to an LVAD. However, increasing the age of patients qualifying to receive an LVAD without setting an age limit will result in an increasing risk of complications. The best outcomes following an LVAD pump implantation are achieved in patients in INTERMACS 3 or 4 profiles — for instance, considerable quality of life improvement is achieved. Patients with cardiomyopathy and a history of cancer are usually not eligible for cardiac transplantation. In these patients, an LVAD is the optimal solution [1].

LVAD therapy should be contraindicated in patients with addiction to alcohol (alcoholic cardiomyopathy) or other psychoactive substances, if they were used at least a year prior to the planned intervention. In addition, a patient with an LVAD should have support of a family member, who should be trained in using the device and advised about possible adverse events.

Experts have agreed that it is necessary to create a roadmap describing measures needed to introduce LVADs as DT in Poland, from establishing the patient eligibility criteria (eligibility algorithm), through conducting healthcare personnel training on LVAD patient care (e.g. paramedics, primary care physicians in the patient's region of residence), to preparing society and hospital wards for the increasing number of LVAD patients.

An important element of postoperative care for patients with LVADs is the treatment of device-related complications, which should be managed in dedicated, specialized or initial centers depending on the complication, its extent, and prognosis. Many LVAD complications (e.g. gastrointestinal bleeding, stroke) do not require treatment at an implantation center. The main complication requiring treatment at the initial center is driveline infection.

It is recommended that LVAD pump implantations be performed at a small number of experienced heart transplantation centers where all remaining cardiological technologies are also available, because this will lead to more effective patient monitoring and adverse-effect management. In Poland, these should be 5 centers participating in the heart transplant program. Increasing the number of such sites is not necessary. In Germany, even though approximately 1000 LVADs are implanted each year, the mortality rate is high (about 33%). This is due to the fact that LVADs are implanted in over 40 centers, the majority of which do not run a heart transplant program. These centers do not perform such strict monitoring and management of adverse effects [1].

Estimation of the population of patients potentially eligible for LVAD DT

According to the 2018 map of health needs (*Mapa potrzeb zdrowotnych*), the incidence of HF in Poland is 364.1/100,000, which translates into 140,000 new HF cases each year. The paper published in 2018 entitled "Comprehensive care for patients with heart failure in Poland: suggested organizational solutions" reported the number of HF patients in Poland to be 750,000 [18].

According to clinical experts, in Poland, around 200–300 LVADs should be implanted annually. This number should increase with improved LVAD availability. The newly created health service for LVAD implantation could be provided in 5 transplantation centers that would meet the criteria defined in the service description. Assuming that about 40 LVAD implantation procedures are performed per year per center, the initial annual number of LVAD implantations can be estimated at 200 (with a gradual increase in the following years). Given the eligibility criteria for LVAD DT, it can be expected that the number of implantations with this indication will be around 100 per year in the initial period [1].

The use of LVADs and the reduction of lost patient productivity

In the group of working-age patients with LVADs, lost productivity due to the disease will be significantly reduced. Not only does LVAD implantation extend patients' lives compared to optimal medical care, but it also enables them to return to work, which is consistent with the improvement in health status demonstrated in clinical trials and expressed by the transition to lower NYHA functional classes (from NYHA III/IV to NYHA I/II). The MOMENTUM study results regarding centrifugal and axial pumps demonstrated that 12 months after LVAD implantation, the clinical status of 81% of patients indicated they were in NYHA class I or II, while the baseline percentage of these patients was 0% [6, 19]. The use of LVADs will have an additional positive impact on the quality of life and productivity of patients' close relatives and careers.

The heart transplant procedure situation in Poland

For many people, heart transplantation is the only effective treatment for end-stage HF. Patients can be qualified for transplantation if all treatment methods available to them have been exhausted, including pharmacological and surgical ones, and if no significant contraindications for the procedure are identified. The most common cause of severe HF, which is an indication for a heart transplantation, is coronary heart disease and dilated cardiomyopathy, resulting from an inflammatory process or another cause, which is often impossible to determine. Less frequently identified HF is associated with valvular, congenital, or acquired malformations and other heart diseases [20].

The final decision to qualify the patient for heart transplantation is made by the Heart Failure Heart Team (HFHT), which includes the following: an experienced cardiac surgeon, a transplantologist, a cardiologist, an anesthesiologist, a psychologist, a transplant coordinator, an LVAD coordinator, and a physiotherapist in the transplantation center. On the basis of the health status of the sick recipient, the qualification procedure is determined as:

— elective — patients with stable cardiovascular and respiratory status who receive conservative treatment for HF;
— emergency — patients presenting with symptoms of severe HF despite specialist inpatient treatment; indications for inclusion in this list include intravenous therapy with drugs affecting heart activity (e.g. catecholamines), MCS (IABP, LVADs/BiVADs), as well as refractory arrhythmias [20].

The rules for including patients on the POLTRANSPLANT National Waiting List are as follows: The recipient's candidacy is reported to the National Waiting List kept by the POLTRANSPLANT Organization and Coordination Center for Transplantation Issues in Warsaw, which coordinates, supervises, and manages the register of all cell, tissue, and organ transplantations in Poland. The entry is made by the Transplant Coordinator, who begins to monitor the recipient's health on an ongoing basis from the moment the recipient is added to the list with particular attention to the following:

— patient's well-being and general health;
— patient's body weight;
— patient's international normalized ratio;
— the procedure mode (elective/emergency) — if necessary, the Coordinator reports a change of the qualification mode to the POLTRANSPLANT National Waiting List and monitors the change of the qualification decision.

The recipient entered in the National Waiting List is notified in writing of the entry into the Registers of Transplantations of the Ministry of Health by the POLTRANSPLANT Organization and Coordination Center for Transplantation Issues [20].

In Poland, the number of patients awaiting a heart transplant is increasing year by year. Even though the number of heart transplants is also increasing, it is still too low in relation to the demand. In 2018, 147 heart transplants were performed, and of these, only 23 procedures were scheduled, and the remaining ones were performed as an emergency. At the same time, experts indicate that existing transplant centers have the means to perform three times as many heart transplant procedures. The number of transplant centers should not be increased because the existing ones fully satisfy the country's needs. It is estimated that a transplant center should perform at least one heart transplant per month to ensure optimal treatment outcomes. In 2018, 326 new patients were registered for a heart transplant; however, in 2018 alone, 100 patients from the list died while awaiting a new heart. At the end of 2018, the number of patients waiting for a heart transplant was 453. Poland boasts (after the US) the highest number of hypoplastic left heart syndrome surgeries in the world. This defect results in a single ventricular heart and a possible heart transplant in the future. In total, 40% of patients with severe HF die within a year or require hospital readmission. This is a group with unmet needs for which just the use of an LVAD offers not only a chance for survival but also for a significant improvement in quality of life [1].

Major challenges of interventional cardiology: cardiogenic shock and high--risk percutaneous coronary intervention

Poland is among Europe's leading countries when it comes to the equipment in its interventional cardiology centers. However, it is necessary to invest in the use of percutaneous circulatory support pumps (e.g. Impella) for patients with cardiogenic shock and as hemodynamic support in high-risk percutaneous coronary intervention (protected percutaneous coronary intervention).

Cardiogenic shock, despite early coronary intervention, correction of mechanical defects, and the use of inotropic agents, is still a life-threatening complication of heart disease. Impaired end-organ perfusion caused by low cardiac output, if not reversed, leads to multiple organ dysfunction and death. One of the methods of treating cardiogenic shock is the use of MCS devices [21].

There are currently several types of these devices in use. They differ in their effectiveness and mechanism of operation, and can be divided into the following:

— short-term MCS devices i.e. Impella and intra-aortic balloon pump (IABP);
— extracorporeal membrane oxygenation (ECMO);
— implantable LVADs (e.g. HM3 LVAD) or biventricular assist devices,
— total artificial heart [22].

They differ, among other things, in the technique of insertion (percutaneous or surgical), the influence on individual heart structures (support of the left, right, or both ventricles), and in terms of the possibility of combined use with ECMO [22].

The 2018 ESC/EACTS guidelines on myocardial revascularization list the following short-term MCS devices:

— percutaneous LVAD;
— veno-arterial ECMO;
— IABP, which may have a beneficial effect on some hemodynamic parameters, but does not improve survival; therefore, the routine use of IABPs in patients with cardiogenic shock complicating acute myocardial infarction is not recommended [23].

ECMO

Interventions performed to decrease left ventricular workload include the following:

— percutaneous — Impella (possible vascular complications due to access route);
— surgical — ECMO:
  • intermediate-term cardiac and respiratory support or respiratory support alone,
  • can be used in a broad range of patients,
  • percutaneous and direct implantation [1].

ECMO involves the use of extracorporeal circulation based on a modern centrifugal pump to oxygenate blood and eliminate carbon dioxide in the oxygenator. Extracorporeal circulation makes it possible to adjust the blood flow rate and accurately control its temperature. Blood is transported to and from the ECMO machine using a plastic cannula system. To reduce the risk of blood clot formation during ECMO, adequate anticoagulation is required with unfractionated heparin and activated partial thromboplastin time kept between 45 and 60 seconds [24].

Depending on the underlying disease and the expected effect, two main ECMO circuit configurations are used:

— veno-venous (VV), in which a cannula is placed into the jugular and/or femoral vein, or a special dual-lumen cannula is inserted into the jugular vein. This set-up is used in cases of severe respiratory failure without circulatory dysfunction when the option of mechanical ventilation has been exhausted. The primary goal of this therapy is to provide the body with oxygen and eliminate carbon dioxide. Oxygenated blood from the oxygenator is transported back to the venous system and then through the right ventricular myocardium to the lungs, left atrium, left ventricle, and aorta;
— veno-arterial (VA), which involves placing a venous cannula in the jugular and/or femoral vein and an arterial cannula in the femoral artery, ascending aorta, or subclavian artery. This type of vascular cannulation is used in cases of circulatory failure or concomitant cardiopulmonary dysfunction. If the decision to use ECMO during cardiac surgery is made, the cannulation can be performed directly through the chest (most often with cannulae placed in the right atrium and ascending aorta) — this is called central cannulation. The inflow of oxygenated blood to the arterial system with adequate kinetic energy generated by the ECMO pump supports the blood flow that the myocardium cannot provide [24].

In cases of respiratory failure, VV ECMO is used primarily in patients with severe pneumonia and acute respiratory distress syndrome. Indications for VA ECMO include the following:

— post cardiotomy;
— shock in post-coronary artery bypass grafting patients;
— post-myocardial infarction VSD;
— *de novo* cardiogenic shock;
— HF exacerbation;
— primary graft dysfunction;
— heart transplant rejection [1].

Experience with ECMO at the Institute of Cardiology in Warsaw:

— from 2013 to the end of 2019, mainly VA ECMO: n = 300 implantations (2013, n = 25 → 2018, n = 63);
— N = 133 deaths on ECMO (55.6%) (2013: 15 deaths [60%] → 2018: 21 deaths [33.34%]).

ECMO in interventional cardiology is a universal tool because it can provide support during percutaneous coronary intervention and in cases of cardiogenic shock; in addition, it can be used simultaneously with IABP. Moreover, ECMO is an effective strategy for stabilizing critically ill patients as a bridge to long-term MCS. A 2019 retrospective study demonstrated that in patients on ECMO support as a bridge to HM3 LVAD, survival to discharge was 81% [25]. The combined use of ECMO and Impella is also promising. When this system is used, Impella ensures additional left ventricle unloading, optimizing ECMO operation [26].

Conclusions

Patients with severe HF, especially those in NYHA class III/IV, who present with concomitant diseases that preclude their qualification for a heart transplant, are a group with unmet needs in terms of survival, and they have poor functional status, various mobility limitations, and associated significantly reduced quality of life. Current optimal medical care provided with the use of pharmacological agents and medical devices such as implantable cardioverter-defibrillator and IABP is not enough to fulfil these needs. MCS based on LVAD DT is an alternative option for this patient population. The LVAD that will achieve the best clinical effectiveness as DT in this group of patients should be characterized above all by a very good hemocompatibility profile that will allow for long survival, free of events related to hemocompatibility, such as stroke, pump thrombosis, hemolysis, or other thromboembolic events. At the same time, this translates into a significant improvement in functional status and quality of life.

LVAD HM3 has all of the above-mentioned features of optimal DT in patients with severe HF, who do not qualify for a heart transplant. Its use enables patients to achieve significantly longer survival than with optimal medical management. In addition, the device meets the patients' needs in terms of significantly improved functional status and quality of life. Positive outcomes achieved in patients not qualified for heart transplantation, who received the HM3 LVAD, are comparable with those in individuals qualifying for a heart transplant, who underwent HM3 implantation as a BTT/BTC. Technological progress and innovative technological solutions applied in the HM3 LVAD allow for a 2-year overall survival comparable to that achieved in patients with a heart transplant.

In a paper published in 2019, leading Polish experts in the field of cardiology and cardiac surgery indicated that the use of the HM3 LVAD would contribute to the improvement of patient survival, health-related quality of life, reduction of treatment costs, and limitation of the number of adverse cardiovascular events. They also indicated that in Poland, pump implantation and heart transplantation are included in the same healthcare service. Therefore, there is no procedure available that would cover the costs of hospitalization following a ventricular assist device implantation. It was emphasized that one of the measures that should be developed in order to increase patient access to HM3 technology is a public funding system appropriate for this purpose [5].

Moreover, experts have indicated that currently the number of LVAD procedures, especially LVAD DT, is very limited. One of the reasons for this is excessively restrictive inclusion criteria and the lack of a separate service dedicated to LVAD DT. Experts recommend that the implantation of LVADs should be carried out in several Polish centers experienced in heart transplantations, because this will lead to more effective patient monitoring and adverse effect management.

Conflict of interest: None declared

References

1. Advisory Board Meeting 'Quo Vadis Cardiologia': Innovation & Health Economics Poland (HF/CMD).
2. Sobieszczańska-Małek M. Mechaniczne wspomaganie: czy tylko pomost do przeszczepu serca? Kardiol Pol. 2012; 70(11): 1182–1186.
3. Bielecka A. Urządzenia wspomagające pracę komór: leczenie pomostowe do momentu uzyskania ponownej wydolności komory lub do czasu przeszczepu oraz leczenie docelowe. Folia Cardiologica Excerpta. 2007; 2(2): 54–64.
4. Michalak M. Inwazyjne leczenie niewydolności serca. Choroby Serca i Naczyń. 2014; 11(1): 47–50.
5. Dudek D, Banasiak W, Braksator W, et al. Recommendations on the use of innovative medical technologies in cardiology and cardiac surgery and solutions leading to increased availability for Polish patients. Cardiol J. 2019; 26(2): 114–129, doi: 10.5603/CJ.a2019.0007, indexed in Pubmed: 30761517.
6. Mehra MR, Uriel N, Naka Y, et al. MOMENTUM 3 Investigators. A fully magnetically levitated left ventricular assist device — final report. N Engl J Med. 2019; 380(17): 1618–1627, doi: 10.1056/NEJMoa1900486, indexed in Pubmed: 30883052.
7. Pinney SP. Left ventricular assist devices for lifelong support. J Am Coll Cardiol. 2017; 69(23): 2845–2861.
8. Starska A. Nowości w mechanicznym wspomaganiu krążenia. Kardiologia Inwazyjna. 2013; 8(4).
9. Zieliński T. Wspomaganie lewokomorowe – metoda o rosnącym znaczeniu w leczeniu zaawansowanej niewydolności serca. Kardiologia po Dyplomie. 2018: 03.
10. Mehra MR. Evolving disruption in left ventricular assist systems: forgiving but not yet forgettable. Eur J Heart Fail. 2019; 21(1): 98–100, doi: 10.1002/ejhf.1340, indexed in Pubmed: 30508266.
11. Ponikowski P, Voors AA, Anker SD. Wytyczne ESC dotyczące diagnostyki i leczenia ostrej i przewlekłej niewydolności serca w 2016 roku, Grupa Robocza Europejskiego Towarzystwa Kardiologicznego (ESC) do spraw diagnostyki i leczenia ostrej i przewlekłej niewydolności serca. Kardiol Pol. 2016; 74(10): 1037–1147, doi: 10.5603/KP.2016.0141.
12. Rubiś P. U których pacjentów z niewydolnością serca należy rozważyć wszczepienie urządzenia wspomagającego czynność lewej komory? Medycyna Praktyczna Kardiologia. 2018.

13. Han J, Trumble DR. Cardiac assist devices: early concepts, current technologies, and future innovations. Bioengineering (Basel). 2019; 6(1), doi: 10.3390/bioengineering6010018, indexed in Pubmed: 30781387.
14. Sterczyński R. Mechaniczne wspomaganie krążenia oddala przeszczep serca. Medical Tribune. 2016.
15. Szymanski J, Juraszek A, Jasińska M, et al. REMEDIZER- An Innovative Program of Remote Home Care for Patients with Implanted Mechanical Heart Support. Single Centre Experience. J Heart Lung Transplantation. 2019; 38(4): S461–S462, doi: 10.1016/j.healun.2019.01.1176.
16. Nessler J. Projekt programu kompleksowej opieki nad chorymi z niewydolnością serca (KONS). Kardiologia Inwazyjna. 2018; 13(6): 10–17.
17. Gierczyński J, Priorytety zdrowotne w kontekście demograficznego i gospodarczego rozwoju Polski. Wnioski i rekomendacje na przykładzie niewydolności serca. Raport Warsaw Enterprise Institute. Warsaw, 2018.
18. Nessler J. Kompleksowa opieka nad chorymi z niewydolnością serca w Polsce: propozycje rozwiązań organizacyjnych. Kardiol Pol. 2018; 76(2): 479.
19. Goldstein D, Naka Y, Horstmanshof D, et al. Association of clinical outcomes with left ventricular assist device use by bridge to transplant or destination therapy intent. JAMA Cardiology. 2020; 5(4): 411, doi: 10.1001/jamacardio.2019.5323.
20. W oczekiwaniu na przeszczep serca. Poradnik informacyjno — edukacyjny dla Pacjenta i jego Bliskich. Fundacja Śląskiego Centrum Chorób Serca. 2013.
21. Lamarche Y, Cheung A, Ignaszewski A, et al. Comparative outcomes in cardiogenic shock patients managed with Impella microaxial pump or extracorporeal life support. J Thorac Cardiovasc Surg. 2011; 142(1): 60–65, doi: 10.1016/j.jtcvs.2010.07.075, indexed in Pubmed: 20880553.
22. Drabik A. Mechaniczne wspomaganie rzutu serca. Przegląd metod i urządzeń. Inżynier i Fizyk Medyczny. 2017; 6: 57–60.
23. Neumann FJ, Sousa-Uva M, Alfonso F, et al. Wytyczne ESC/EACTS dotyczące rewaskularyzacji mięśnia sercowego. Kardiol Pol. 2018; 76(12): 1585–1664, doi: 10.5603/KP.2018.0228.
24. Arendarczyk A, Wilimski R, Michniewicz M, et al. Zasady kwalifikacji do ECMO u osób dorosłych. Folia Cardiologica. 2017; 12(1): 113–117, doi: 10.5603/fc.2017.0016.
25. Ayers BC, Sagebin F, Wood K, et al. Extracorporeal Membrane Oxygenation is an Effective Bridge to Left Ventricular Assist Device Implantation. J Heart Lung Transplantation. 2019; 38(4): S436–S437, doi: 10.1016/j.healun.2019.01.1113.
26. Tschöpe C, Van Linthout S, Klein O, et al. Mechanical Unloading by Fulminant Myocarditis: LV-IMPELLA, ECMELLA, BI-PELLA, and PROPELLA Concepts. J Cardiovasc Transl Res. 2019; 12(2): 116–123, doi: 10.1007/s12265-018-9820-2, indexed in Pubmed: 30084076.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2020, Vol. 27, No. 6, 705–714
DOI: 10.5603/CJ.a2018.0159

ISSN 1897–5593
eISSN 1898–018X

Elective lung resection increases spatial QRS-T angle and QTc interval

Szymon Bialka[1], Andrzej Jaroszynski[2], Todd T. Schlegel[3, 4], Hanna Misiolek[1], Damian Czyzewski[5], Marek Sawicki[6], Piotr Skoczylas[6], Magdalena Bielacz[7], Mateusz Bialy[8], Lukasz Szarpak[9], Wojciech Dabrowski[8]

[1]Department of Anaesthesiology and Intensive Therapy, School of Medicine with Division of Dentistry in Zabrze, Medical University of Silesia, Katowice, Poland
[2]Department of Nephrology, Institute of Medical Science, Jan Kochanowski University of Kielce, Poland
[3]Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden
[4]Nicollier-Schlegel SARL, Trélex, Switzerland
[5]Department of Thoracic Surgery, School of Medicine with Division of Dentistry in Zabrze, Medical University of Silesia, Katowice
[6]Department of Thoracic Surgery, Medical University of Lublin, Poland
[7]Institute of Tourism and Recreation, State Vocational College of Szymon Szymonowicz, Zamosc, Poland
[8]Department of Anaesthesiology and Intensive Therapy, Medical University of Lublin, Poland
[9]Lazarski University, Warsaw, Poland

Abstract

Background: *Lung resection changes intra-thoracic anatomy, which may affect electrocardiographic results. While postoperative cardiac arrhythmias have been recognized after lung resection, no study has documented changes in vectorcardiographic variables in patients undergoing this surgery. The purpose of this study was to analyse changes in spatial QRS-T angle (spQRS-T) and corrected QT interval (QTc) after lung resection.*

Methods: *Adult patients undergoing elective lung resection under general anaesthesia were studied. The patients were allocated into four groups: those undergoing (1) left lobectomy (LL); (2) left pneumonectomy (LP); (3) right lobectomy (RL); and (4) right pneumonectomy (RP). The spQRS-T angle and QTc interval were measured one day before surgery (baseline) and 24, 48 and 72 h after surgery.*

Results: *Seventy-one adult patients (47 men and 24 women) aged 47–80 (65 ± 7) years were studied. In the study group as a whole, lung resection was associated with significant increases in spQRS-T ($p < 0.001$) and QTc ($p < 0.05$ at 24 and 48 h and $p < 0.01$ at 72 h). The greatest changes were noted in patients undergoing LP. Postoperative atrial fibrillation (AF) was noted in 6.4% of patients studied, in whom the widest spQRS-T angle and the most prolonged QTc intervals were also noted.*

Conclusions: *Lung resection widens the spQRS-T angle and prolongs the QTc interval, especially in patients undergoing LP. While postoperative AF was a relatively rare complication after lung resection in this study, it was associated with the widest spQRS-T angles and most prolonged QTc intervals.*
(Cardiol J 2020; 27, 6: 705–714)

Key words: vectorcardiography, spatial QRS-T angle, corrected QT interval, atrial fibrillation, general anaesthesia

Address for correspondence: Wojciech Dabrowski, MD, PhD, Department of Anaesthesiology and Intensive Therapy, Medical University of Lublin, ul. Jaczewskiego 8, 20–954 Lublin, Poland, tel: +48 81 724 43 32, e-mail: w.dabrowski5@yahoo.com

Received: 28.09.2018 Accepted: 28.11.2018

Introduction

Cardiac arrhythmias, including atrial fibrillation (AF), have been recognized as frequent complications after thoracic surgery [1–4]. Different kinds of cardiac arrhythmias have been noted in one-fifth of patients after lung resection, AF being the most common [4, 5]. Many studies have documented an increased risk of morbidity and mortality in thoracic surgical patients with postoperative cardiac arrhythmias [5–11]; however, only some have proposed risk factors for predicting postoperative cardiac disorders [9–11]. A history of ischemic heart disease, cardiovascular disorders and electrocardiographic Q waves are known predisposing factors for postoperative cardiac arrhythmias [10, 11].

Postoperative cardiopulmonary complications occur within 30 days after pulmonary resection and include pulmonary edema, ventricular fibrillation, complete heart block, various cardiac arrhythmias and sudden cardiac death [10, 11]. Changes in intra-thoracic anatomy following lung resection may affect heart function, leading to hemodynamic and electrocardiographic disorders. Experimental studies have documented supraventricular tachycardia (sinus tachycardia and AF) occurring within 2 weeks after lobectomy or pneumonectomy [12]. Other electrocardiographic changes following pneumonectomy or lobectomy have included increases in P duration, ST-depression, delayed precordial R-wave transition and displacement of the QRS vector. The most striking changes were noted in patients who underwent left pneumonectomy or left upper segmentectomy and left lower lobectomy [7]. However, according to available research, no study has documented changes in spatial QRS-T angle (spQRS-T) or corrected QT interval (QTc) after lung resection.

Vectorcardiography (VCG) is a spatial method of electrocardiography (ECG) that enables visualizing, through the cardiac cycle, the continuous moments of the cardiac vector as loops. Vectorcardiograms and associated parameters such as the spQRS-T, i.e., the spatial angle between cardiac depolarization and repolarization, can also now be easily derived from standard 12-lead ECGs [13, 14]. While normal ranges for spQRS-T vary by method and by study, most studies have suggested that normal values lie below 100–110° for men and below 90° for women [14–17]. Of note, a widened spQRS-T is an independent predictor of cardiac arrhythmias and sudden cardiac death [14–17]. In healthy patients without apparent ECG pathology, cardiovascular mortality has been found to be 0.8% for spQRS-T between 0 and 50°, increasing to 2.3% for borderline spQRS-T (50–100°) and to 5.1% for spQRS-T angle between 100° and 180° [15, 17]. Additionally, spQRS-T wider than 100° can identify cardiomyopathic patients at a high risk of life-threatening ventricular arrhythmias for whom cardioverter-defibrillator devices might be most appropriate [18].

The corrected QT interval is an electrocardiographic parameter providing information on both cardiac depolarization and repolarization, especially the latter. Its prolongation has been observed in patients with electrolyte disorders and coronary diseases who are treated with antiarrhythmics or subjected to general anaesthesia with a volatile anesthetic [19–21]. A prolonged QTc interval has been well recognized as a parameter indicating an increased risk of malignant ventricular arrhythmias [22, 23]. Although a prolonged QTc has been noted in patients undergoing surgery with pneumoperitoneum [24, 25] and cardiac surgery [26], changes in QTc have not been recognised in patients undergoing lobectomy or pneumonectomy. It should be noted that severe right and/or left ventricular dysfunction has been documented echographically following lobectomy or pneumonectomy [27]. The purpose of this study was to analyze changes in spQRS-T and QTc in patients undergoing lung resection.

Methods

Ethical considerations

This prospective observational study was conducted in adult patients undergoing elective thoracic surgery under general anesthesia. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board and the Bioethical Committee for Human Studies of the Medical University at Lublin, Poland (KE-0254/220/2016). Written informed consent was obtained from all participants. One day before surgery all patients were examined and a 12-lead ECG without overt clinical abnormality was the main criterion for patient inclusion. The exclusion criteria were: congenital heart defects, myocardial infarct and myocarditis history, cerebral stroke history, endocrine and metabolic diseases. Patients who required re-thoracotomy due to postoperative bleeding were also excluded.

Patient description

Anaesthesia. One day before surgery, routine blood examination was performed to assess

complete blood count, blood glucose and urea, creatinine, serum electrolytes and blood type. All patients received the same premedication composed of a single oral dose (2 mg) of estazolam (Polfa, Warsaw, Poland). Just before anaesthesia induction, all patients were routinely monitored with continuous ECG for heart rate, intermittent and non-invasive arterial blood pressure measurements and continuous pulse oximetry (SpO_2). The urinary bladder was catheterized in all patients before anaesthesia induction.

General anesthesia was induced intravenously with a single dose of fentanyl (Polfa, Warsaw, Poland) and propofol (AstraZeneca, United Kingdom). A single bolus of rocuronium (0.6 mg/kg body weight) (Rocuronium B. Braun, Germany) was administered to each patient before tracheal intubation with a double-lumen tracheal tube, the placement of which was controlled with bronchoscopy. All participants were ventilated using intermittent positive pressure ventilation, and anaesthesia was maintained throughout the procedure using 100% oxygen and inhaled sevoflurane (AbbVie, UK) at a dose of 0.8–1.2 minimal alveolar concentration and fractionated doses of fentanyl. Intra-operative ventilation was performed with an expiratory/inspiratory ratio of 1:2, a tidal volume of 5–6 mL//kg body weight, a respiration rate of 9–12/min and positive end-respiratory pressure (PEEP) + 5 cm H_2O. Ventilation was controlled by $EtCO_2$ and SpO_2, which were maintained between 35–40 mmHg and 92–100% saturation during surgery with both double and single lung ventilation monitored via SpaceLabs monitor (SpaceLabs Healthcare, OSI systems, USA). During surgery, all patients received a continuous infusion of balanced crystalloids (Sterofundin ISO, B. Braun Melsungen, Germany). In patients not responding adequately to the crystalloid infusion, a single dose of ephedrine (Ephedrini hydrochlorici, Polfa Warsaw, Poland) was administered. Anaesthesia was used to maintain mean arterial pressure above 70 mmHg. After completion of the surgery, sevoflurane was discontinued. The neuromuscular blockade was reversed using a single dose of atropine (0.5 mg) and neostigmine (2.5 mg). Patients were extubated upon satisfactory emergence from general anesthesia and admitted to the Postoperative Intensive Care Unit. Postoperative pain was treated with fractionated doses of paracetamol (Bristol Myers Squibb, Warsaw, Poland). During the first and second postoperative days, all patients received intravenous mixture of potassium and magnesium at doses that depended on blood concentrations.

Surgery. After induction of anesthesia, pulmonectomy or lobectomy was performed with thoracotomy through the 4^{th} or 5^{th} intercostal space. Then, pleuraecotomy was performed through the 6^{th} intercostal space. The chest was closed in layers, including muscle, subcutaneous tissue, and the subcuticular layer, using resorbable sutures. Skin staples were used for the final cutaneous suture (Johnson and Johnson, New Jersey, USA).

Measurements

ECG, derived VCG. The method used for VCG measurement was presented previously [23]. Surface 12-lead resting ECG was recorded using a Cardiax device (IMED Co., Ltd., Budapest, Hungary). The recordings in each time period were automatically averaged to a single beat and transformed into three orthogonal leads, X, Y and Z, according to the inverse Dower method [14, 28]. The projections of maximum vectors of QRS and T-waves in frontal, transverse, and left sagittal planes and on x, y, and z axes were then obtained. Next, the value for the spatial QRS-T angle automatically calculated from the maximum spatial QRS and T vectors, as well as the values for the QTc interval, were obtained directly from Cardiax software. For detection of the QT interval and calculation of QTc, Cardiax software utilizes a median-beats related "global QT interval" algorithm similar to that described by Xue [29].

Study protocol and patient division. Electrocardiography was performed at four time points: 1 day before surgery (baseline value) and 24, 48 and 72 h after surgery. All measurements were performed in the horizontal position. Patients were allocated into four groups: patients undergoing left pneumonectomy (LP), left lobectomy (LL), right pneumonectomy (RP) or right lobectomy (RL), respectively.

Statistical analysis

A statistical analysis was performed using Statistica 12 software (StatSoft). Demographic data were summarized as frequencies and percentages. Categorical variables were compared using the χ^2 and Fisher exact test or χ^2 with the Yates correction where applicable. For variables with a normal distribution, means and standard deviations (SD) were calculated, and the Student unpaired *t*-test was used for variables with a normal distribution as confirmed by the Shapiro-Wilk test. For variables with a non-normal distribution, the Wilcoxon signed-rank, Mann-Whitney-U, Kruskal-Wallis ANOVA and post hoc Dunnett's multiple compari-

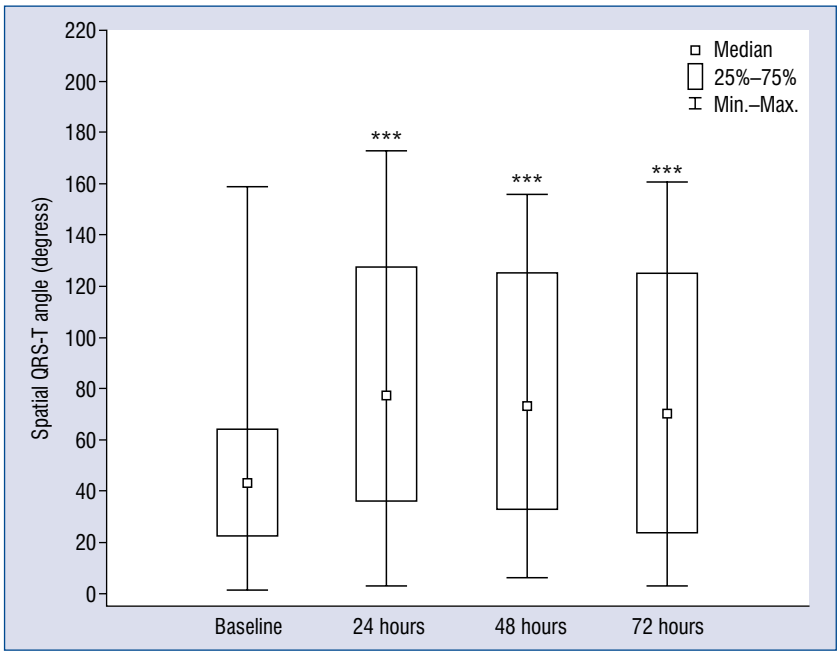


Figure 1. Changes in spatial QRS-T angle in the studied population. Time points: baseline — 1 day before surgery, and 24, 48 and 72 hours after surgery; ***p < 0.001 in comparison with baseline.

son tests were used. A $p < 0.05$ was considered significant. The power of the statistical tests was assessed by the G*Power test.

Results

Seventy-one adult patients (47 men and 24 women) aged 65 ± 7 years (range 47–80), undergoing general anaesthesia and elective lung surgery for pulmonary neoplasm were included. In the studied group: 32 patients underwent left lobectomy (group LL: 14 patients — upper lobectomy and 18 patients — lower lobectomy), 9 — left pneumonectomy (group LP), 23 — right lobectomy (group RL: 10 patients — upper lobectomy and 13 patients — lower lobectomy) and 7 — right pneumonectomy (group RP). Forty-nine patients were treated for concomitant arterial hypertension (I° or II° according to the World Health Organization classification) with beta-blockers (38 patients), Ca^{+2} blockers (9 patients), angiotensin converting enzyme inhibitors (44 patients) and diuretic drugs. Twenty-six patients were prescribed magnesium and 10 both magnesium and potassium for more than 1 month prior to surgery. Among all participants, the mean time of anaesthesia was 161 ± 45 min, and the surgical time was 115 ± 30.7 min. The mean body mass index was 26.6 ± 5.2 kg/m^2. The mean arterial pressure and SpO_2 were 68–100 mmHg and 92–100%, respectively, during anaesthesia and surgery. None of the patients required intensive fluid therapy during surgery or the early postoperative period, and a possible insufficiency of intravascular fluids was supplemented with crystalloid infusion (Sterofundin ISO, B. Braun Melsungen, Germany). Immediately after anaesthesia completion, all patients were transferred to the Postoperative Intensive Care Unit. A sinus rhythm was noted in all participants with mean heart rates of 76.4 ± 15.7/min, 78.5 ± 14.8/min and 81.5 ± 14.1/min at postoperative days 1, 2 and 3, respectively.

Atrial fibrillation was noted in 9 (6.4%) patients at 5–10 postoperative days — 7 after left lung surgery and 2 after right lung surgery ($\chi^2 = 1.69$, $p = 0.19$, χ^2 with Yates correction = 0.89 for $p = 0.35$). Additionally, postoperative AF was noted in 6 patients after pneumonectomy (LP) and 3 after lobectomy (1 after LL and 2 after RL) ($\chi^2 = 11.5$, $p = 0.001$, χ^2 with Yates correction = 8.79 for $p = 0.01$). None of the other patients required treatment for postoperative cardiac arrhythmias, and the 12-lead ECG showed a sinus rhythm throughout the study period.

In the patient group as a whole, spQRS-T increased at 24, 48 and 72 h after surgery (Fig. 1). Changes in spQRS-T were similar in patients undergoing left and right lung surgery; however, a significantly wider spQRS-T was noted in patients after pneumonectomy than lobectomy (Table 1).

Table 1. Comparison of changes in spatial QRS-T angle and QTc intervals in patients undergoing left lobectomy (group LL) pneumonectomy (group LP), right lobectomy (group RL) and right pneumonectomy (group RP).

	Baseline	24 hours	48 hours	72 hours
Spatial QRS-T angle				
LL	38.5 [31; 56]	80** [63.25; 93.5]	70.5* [48; 87]	67.5 [21.25; 115.5]
LP	56‡ [50.25; 84.25]	129*†‡ [128; 133.5]	147*††‡ [130.5; 149.25]	145*††‡‡ [134.5; 154]
RL	47.5†† [24.75; 97.75]	47 [31.25; 135]	72* [38.25; 137]	65* [30.5; 120.75]
RP	20 [6; 27]	33 [10.5; 47]	42* [9.5; 99.5]	43* [15; 109.5]
Corrected QT interval				
LL	425.5 [420; 442.2]	439.5 [429.5; 452.75]	435 [420.5; 558]	446** [430.5; 455.75]
LP	443.5‡ [59.25; 85]	462.5‡‡ [98; 147]	464.5 [111.5; 156.3]	462* [93.6; 174.5]
RL	428 [418.5; 478]	434 [421; 465.25]	431.5 [407.5; 480]	444.5 [427.75; 480.75]
RP	411 [406; 414]	421 [412; 423]	414 [409; 443]	406 [403; 423]

Values shown are medians [quartile 1 and 3]. LL (n = 32), LP (n = 9), RL (n = 23), RP (n = 7). The small number of patients with pneumonectomy limits statistical power ($1 - \beta \geq 0.8$).
*p < 0.05 versus Baseline; †p < 0.05 and ††p < 0.01 — pneumonectomy versus lobectomy (LP vs. LL and RP vs. RL, respectively); ‡p < 0.05 and ‡‡p < 0.01 — left versus right pneumonectomy or left versus right lobectomy (LP vs. RP and LL vs. RL, respectively).

Table 2. Comparison of changes in spatial QRS-T angle and QTc intervals in patients with atrial fibrillation (AF) in the late postoperative period and patients with an uncomplicated postoperative period (n-AF).

	Baseline	24 hours	48 hours	72 hours
Spatial QRS-T angle				
AF	50 [47; 56]	129*† [88; 135.5]	143* [75; 147]	102 [59; 145]
n-AF	33.5 [20.25; 68.75]	69** [32.25; 116.75]	71.5** [26.25; 120.75]	66** [24.; 123.5]
Corrected QT interval				
AF	439 [427.5; 445.5]	453 [439; 462.75]	469† [455; 470.5]	462* [451.5; 467]
n-AF	425 [414; 445.5]	434 [421.25; 455.5]	434.5 [412.5; 458.75]	435 [423; 455.75]

Values shown are medians [quartile 1 and 3]. AF (n = 9), n-AF (n = 62). The small number of patients with postoperative AF limits statistical power ($1 - \beta \geq 0.8$).
*p < 0.05 and **p < 0.001 versus Baseline; †p < 0.05 — complicated postoperative period by AF versus uncomplicated postoperative period

Additionally, a wider spQRS-T was noted after LP than RP at all time points whereas this angle was comparable in patients undergoing LL and RL (Table 1). In patients with, compared to those without postoperative AF, the spatial QRS-T angle was significantly wider only at 24 h postoperatively (Table 2). Representative serial 12-lead ECGs from a patient who underwent LP are presented in Figure 2.

In the patient group as a whole, QTc intervals were also prolonged after lung resection (Fig. 3). Although prolongation of the QTc was similar in patients undergoing left and right lung surgery independent of the type of surgery, LP prolonged the QTc significantly more than RP (Table 1). The corrected QT interval was also significantly longer at 48 and 72 h in patients with versus those without postoperative AF (Table 2).

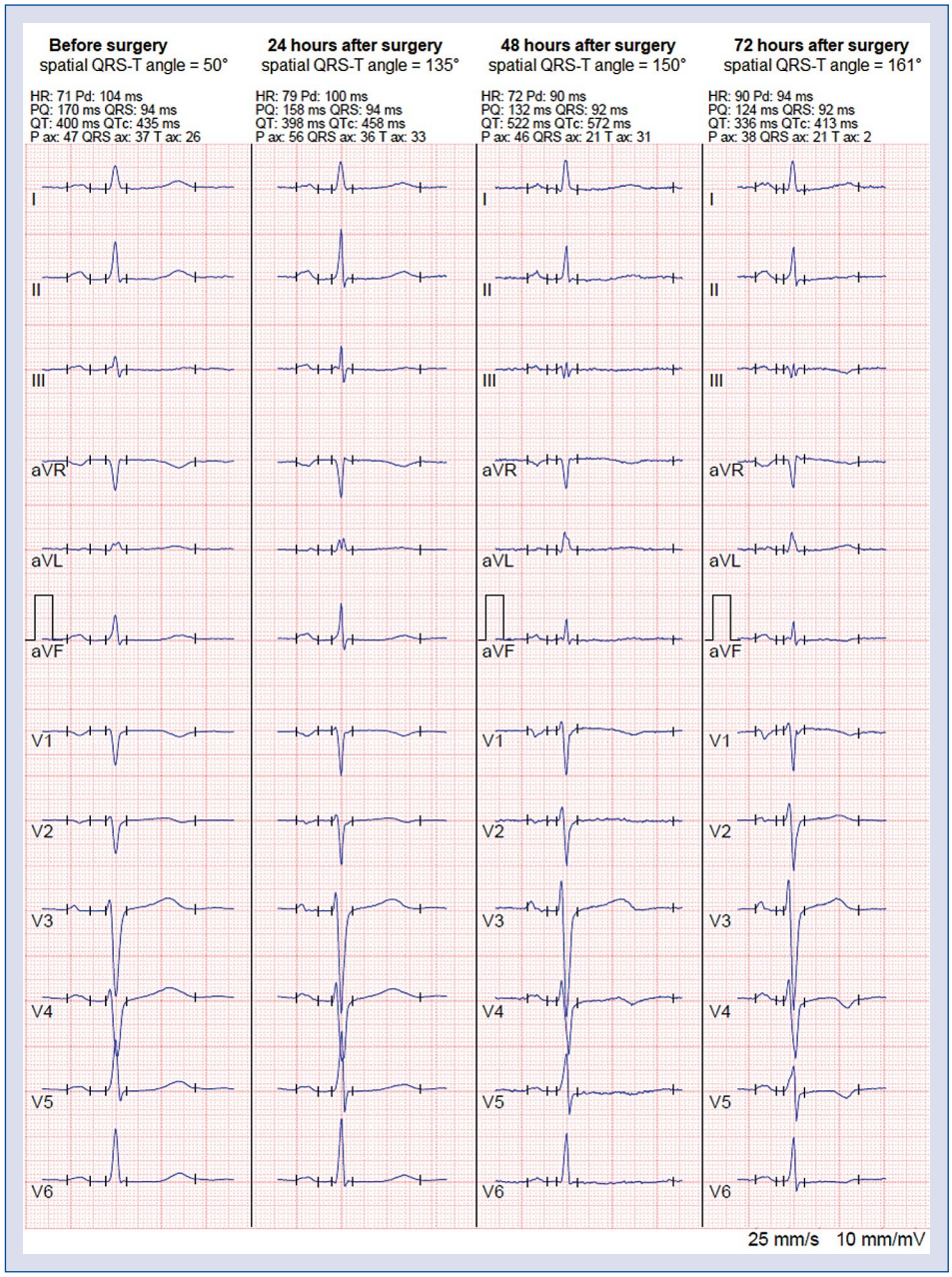


Figure 2. Representative changes in the spatial QRS-T angle and 12-lead electrocardiogram of a patient who underwent left pneumonectomy.

Discu/ssion

According to available research, this is the first study documenting effects of lung resection on spQRS-T and QTc. Pneumonectomy and lobectomy affected spQRS-T and QTc; however, the most striking changes were noted in patients undergoing left rather than right lung surgery, especially LP. Additionally, patients with postoperative AF had wider spQRS-T and longer QTc in the early postoperative period.

The spQRS-T angle presents the directional differences between the ventricular repolarization and depolarization [30]. It has been suggested to be a strong predictor for all-cause and cardiac mortality in middle-aged and elderly patients [15, 17, 30]. Additionally, a wide spQRS-T has been shown to predict life-threatening ventricular arrhythmias [15–18] and silent myocardial ischemia/ /infarction [31, 32]. Several factors affect spQRS-T. The spQRS-T angle evolves with age and depends

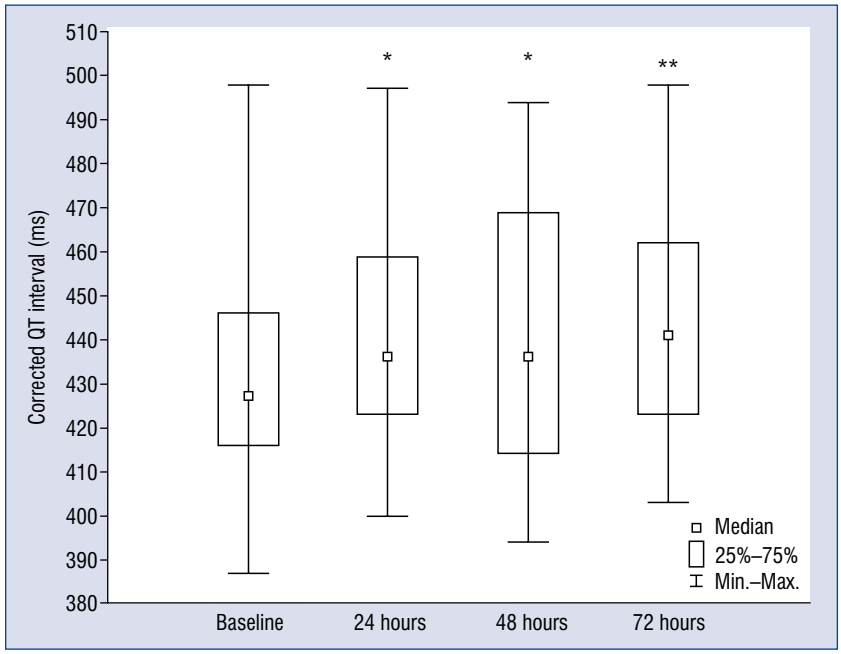


Figure 3. Changes in the corrected QT interval of the studied population. Time points: baseline — 1 day before surgery, and 24, 48 and 72 hours after surgery; *p < 0.05 and **p < 0.01 in comparison with baseline.

on sex and physical condition [13–17, 33, 34]. Changes in body position as well as in intra-thoracic volume following diaphragm elevation due to increases in intra-abdominal pressure, which may also disturb ventricular repolarization, thus widening the spQRS-T [25, 35, 36]. Gul and colleagues documented a completely altered QRS complex in patients with changes in intra-thoracic anatomy following eventration of the diaphragm and displacement of the bowels into the thoracic cavity [37].

In the present study, an increase in spQRS-T in patients after lung resection was observed, the most substantive changes occurring in patients after LP. A lack of or significant reduction in heart compression during respiration probably disturbs the QRS loop configuration and affects the heart's hemodynamic function. In people with normal pulmonary function, the amplitude of the maximum leftward force affects the QRS vector, decreasing significantly during inspiration, whereas the amplitude of the maximum posterior force increases. The QRS vector displaces posteriorly and inferiorly with a decrease in spatial magnitude of approximately 10%, leading to an increase in the spQRS-T angle [37]. Previous studies have shown that right-lung resection causes a right-sided QRS vector shift in 100% of patients after RP and in 75%, 58.3% and 50% after right upper segmentectomy, lower left lobectomy and right upper segmentectomy, respectively [7]. On the other hand, left-lung resection results in a left-sided QRS vector shift in 100% of patients after LP and in 87%, 66.7%, 57.9% and 55.6% of patients after left upper lobectomy, left upper segmentectomy, right lower lobectomy and right middle lobectomy, respectively [7]. The present study was not focused on, and thus did not fully confirm these disturbances. However, LP spectacularly increased spQRS-T in the patient group as a whole, with disturbances in spQRS-T being significantly lower in patients after RP. It should be noted that the small number of patients with pneumonectomy limited the power of the analysis, and may have impacted results.

A 6.4% incidence of postoperative AF was lower than that in other reports [1–6]. A significantly wider spQRS-T angle was noted in all of these patients. Several studies have confirmed a strong relationship between a wider spQRS-T and the occurrence of potentially lethal arrhythmias in patients with left ventricular systolic dysfunction [15–17, 30, 38]. The risk of cardiac arrhythmia significantly increases with spQRS-T wider than 100° [15, 16, 30]. It should be noted that spQRS-T increased above 100° in relatively more patients with postoperative AF and that the higher angle was observed 48 h after surgery.

Postoperative AF might result from postoperative electrolyte disorders; however, all affected

patients received potassium and magnesium supplementation, and their blood potassium concentration was higher than 4.0 mmol/L (data not shown). The incidence of AF was significantly higher in patients after pneumonectomy, in agreement with other studies [4–6]. Although none of the patients presented with myocardial ischemia, it can also be speculated that postoperative AF might be a result of silent myocardial ischemia. Many patients had a history of smoking and chronic obstructive pulmonary disease, which are often associated with atherosclerosis and coronary diseases. Indeed, silent myocardial ischemia/infarct has been shown to be associated with a widened spQRS-T angle [32]; however, this speculation would require further dedicated confirmation.

In the present study, QTc was prolonged after left-side resection and was significantly longer than after right-side resection. Additionally, QTc was longer in patients with postoperative AF. The QTc interval represents myocardial depolarization and repolarization. Its normal value is below 460 ms for women and below 440 ms for men, with borderline values ranging 461–479 ms and 441–459 ms for women and men, respectively; a prolonged value is defined as a value higher than 480 ms and 460 ms for women and men, respectively [23].

A prolonged QTc interval is also associated with an increased risk of life-threatening arrhythmias, including polymorphic ventricular tachycardia (torsade de points), and a significant increase in the risk for such pathology increases markedly in patients with QTc intervals longer than 500 ms. However, the risk of cardiac arrhythmia also increases when QTc lengthens more than 60 ms compared with the baseline value [39].

Female sex and older age predisposes QTc interval prolongation. Pathologically prolonged QTc has been noted in patients with electrolyte disturbances such as hypokalemia, hypomagnesemia and/or hypocalcemia, myocardial ischemia, heart failure and severe bradycardia [19, 20, 31]. Many medications can also result in asymptomatic or symptomatic QTc interval prolongation, their administration sometimes being associated with an increased risk for cardiac arrhythmias [22].

It should be noted that volatile anaesthetics and some opioids, including fentanyl, significantly prolong QTc. However, there is controversy as to whether propofol has an effect [22, 40–42]. Chang et al. [41] documented a prolongation of QTc following propofol anesthesia. Oji et al. [40] noted the shortening of QTc after target-controlled infusion of propofol. In contrast, Kleinsasser et al. [42] did not observe an effect of propofol on QTc interval. Additionally, some local anaesthetics used for epidural anaesthesia during lung surgery can also affect QTc [9]. In the present study, a prolonged QTc only in patients undergoing left-lung resection was observed, but all participants received the same kind of anesthesia. Unfortunately for reasons of logistics, it was not possible to study changes in QTc more immediately after surgery.

Limitations of the study

An important limitation of the present study was the small number of patients undergoing elective pneumonectomy, which notably limits study-related statistical power. Generally, the available screening examinations enable cancer diagnosis in its early stages and have a fundamental role in the possible kinds of treatment. The lack of an analysis of spQRS-T and QTc as a function of blood electrolyte concentration or preoperative or postoperative spirometric features or pharmacological treatment was also considered a limitation.

Conclusions

In the present study, an effect of lung resection on spQRS-T and the QTc interval was documented. Generally, lung resection induced spQRS-T widening and QTc prolongation; however, the most striking widening and prolongation were noted in patients undergoing LP. Additionally, AF episodes were primarily noted in patients after left-lung resection who had prolonged QTc interval.

Conflict of interest: None declared

References

1. Giambrone GP, Wu X, Gaber-Baylis LK, et al. Incidence and implications of postoperative supraventricular tachycardia after pulmonary lobectomy. J Thorac Cardiovasc Surg. 2016; 151(4): 982–988, doi: 10.1016/j.jtcvs.2015.11.057, indexed in Pubmed: 26778376.
2. Sanecka A, Biernacka EK, Szperl M, et al. QTc prolongation in patients with hearing loss: Electrocardiographic and genetic study. Cardiol J. 2016; 23(1): 34–41, doi: 10.5603/CJ.a2015.0062, indexed in Pubmed: 26412604.
3. Lee JH, Lim C, Kim JS, et al. Early and mid-term results of coronary endarterectomy: Influence of cardiopulmonary bypass and surgical techniques. Cardiol J. 2017; 24(3): 242–249, doi: 10.5603/CJ.a2017.0027, indexed in Pubmed: 28281737.
4. Elrakhawy HM, Alassal MA, Elsadeck N, et al. Predictive factors of supraventricular arrhythmias after noncardiac thoracic surgery: a multicenter study. Heart Surg Forum. 2014; 17(6): E308–E312, doi: 10.1532/HSF98.2014412, indexed in Pubmed: 25586281.

5. Iwata T, Nagato K, Nakajima T, et al. Risk factors predictive of atrial fibrillation after lung cancer surgery. Surg Today. 2016; 46(8): 877–886, doi: 10.1007/s00595-015-1258-4, indexed in Pubmed: 26471506.
6. Rena O, Papalia E, Oliaro A, et al. Supraventricular arrhythmias after resection surgery of the lung. Eur J Cardiothorac Surg. 2001; 20(4): 688–693, indexed in Pubmed: 11574209.
7. Chhabra L, Bajaj R, Chaubey VK, et al. Electrocardiographic impacts of lung resection. J Electrocardiol. 2013; 46(6): 697.e1–697.e8, doi: 10.1016/j.jelectrocard.2013.05.140, indexed in Pubmed: 23830322.
8. Ivanovic J, Maziak DE, Ramzan S, et al. Incidence, severity and perioperative risk factors for atrial fibrillation following pulmonary resection. Interact Cardiovasc Thorac Surg. 2014; 18(3): 340–346, doi: 10.1093/icvts/ivt520, indexed in Pubmed: 24336699.
9. Güven O, Sazak H, Alagöz A, et al. The effects of local anaesthetics on QT parameters during thoracic epidural anaesthesia combined with general anaesthesia: ropivacaine versus bupivacaine. Balkan Med J. 2013; 30(4): 410–414, doi: 10.5152/balkanmedj.2013.9275, indexed in Pubmed: 25207150.
10. Brunelli A, Cassivi SD, Fibla J, et al. External validation of the recalibrated thoracic revised cardiac risk index for predicting the risk of major cardiac complications after lung resection. Ann Thorac Surg. 2011; 92(2): 445–448, doi: 10.1016/j.athoracsur.2011.03.095, indexed in Pubmed: 21704295.
11. Miura N, Kohno M, Ito K, et al. Lung cancer surgery in patients aged 80 years or older: an analysis of risk factors, morbidity, and mortality. Gen Thorac Cardiovasc Surg. 2015; 63(7): 401–405, doi: 10.1007/s11748-015-0546-7, indexed in Pubmed: 25868520.
12. Kocatürk M, Salci H, Yilmaz Z, et al. Pre- and post-operative cardiac evaluation of dogs undergoing lobectomy and pneumonectomy. J Vet Sci. 2010; 11(3): 257–264, indexed in Pubmed: 20706034.
13. Draisma HHM, Schalij MJ, van der Wall EE, et al. Elucidation of the spatial ventricular gradient and its link with dispersion of repolarization. Heart Rhythm. 2006; 3(9): 1092–1099, doi: 10.1016/j.hrthm.2006.05.025, indexed in Pubmed: 16945809.
14. Cortez DL, Schlegel TT. When deriving the spatial QRS-T angle from the 12-lead electrocardiogram, which transform is more Frank: regression or inverse Dower? J Electrocardiol. 2010; 43(4): 302–309, doi: 10.1016/j.jelectrocard.2010.03.010, indexed in Pubmed: 20466388.
15. Yamazaki T, Froelicher VF, Myers J, et al. Spatial QRS-T angle predicts cardiac death in a clinical population. Heart Rhythm. 2005; 2(1): 73–78, doi: 10.1016/j.hrthm.2004.10.040, indexed in Pubmed: 15851268.
16. Borleffs CJ, Scherptong RWC, Man SC, et al. Predicting ventricular arrhythmias in patients with ischemic heart disease: clinical application of the ECG-derived QRS-T angle. Circ Arrhythm Electrophysiol. 2009; 2(5): 548–554, doi: 10.1161/CIRCEP.109.859108, indexed in Pubmed: 19843923.
17. Voulgari C, Pagoni S, Tesfaye S, et al. The spatial QRS-T angle: implications in clinical practice. Curr Cardiol Rev. 2013; 9(3): 197–210, indexed in Pubmed: 23909632.
18. Borleffs CJ, Scherptong RWC, Man SC, et al. Predicting ventricular arrhythmias in patients with ischemic heart disease: clinical application of the ECG-derived QRS-T angle. Circ Arrhythm Electrophysiol. 2009; 2(5): 548–554, doi: 10.1161/CIRCEP.109.859108, indexed in Pubmed: 19843923.
19. Michishita R, Ishikawa-Takata K, Yoshimura E, et al. Influence of dietary sodium and potassium intake on the heart rate corrected-QT interval in elderly subjects. J Nutr Sci Vitaminol. 2015; 61(2): 138–146, doi: 10.3177/jnsv.61.138, indexed in Pubmed: 26052144.
20. Thomas SHL, Behr ER. Pharmacological treatment of acquired QT prolongation and torsades de pointes. Br J Clin Pharmacol. 2016; 81(3): 420–427, doi: 10.1111/bcp.12726, indexed in Pubmed: 26183037.
21. Paventi S, Santevecchi A, Ranieri R. Effects of sevoflurane versus propofol on QT interval. Minerva Anestesiol. 2001; 67(9): 637–640, indexed in Pubmed: 11731753.
22. De Vecchis R, Ariano C, Di Biase G, et al. Malignant ventricular arrhythmias resulting from drug-induced QTc prolongation: a retrospective study. J Clin Med Res. 2018; 10(7): 593–600, doi: 10.14740/jocmr3470w, indexed in Pubmed: 29904445.
23. Steinberg C. Diagnosis and clinical management of long-QT syndrome. Curr Opin Cardiol. 2018; 33(1): 31–41, doi: 10.1097/hco.0000000000000465.
24. Ekici Y, Bozbas H, Karakayali F, et al. Effect of different intra-abdominal pressure levels on QT dispersion in patients undergoing laparoscopic cholecystectomy. Surg Endosc. 2009; 23(11): 2543–2549, doi: 10.1007/s00464-009-0388-4.
25. Dabrowski W, Jaroszynski A, Jaroszynska A, et al. Intra-abdominal hypertension increases spatial QRS-T angle and elevates ST-segment J-point in healthy women undergoing laparoscopic surgery. J Electrocardiol. 2017; 50(2): 214–222, doi: 10.1016/j.jelectrocard.2016.10.002, indexed in Pubmed: 28029353.
26. Mirbolouk F, Arami S, Salari A, et al. Corrected QT-interval and dispersion after revascularization by percutaneous coronary intervention and coronary artery bypass graft surgery in chronic ischemia. J Invasive Cardiol. 2014; 26(9): 444–450, indexed in Pubmed: 25198488.
27. Wang Z, Yuan J, Chu W, et al. Evaluation of left and right ventricular myocardial function after lung resection using speckle tracking echocardiography. Medicine. 2016; 95(31): e4290, doi: 10.1097/MD.0000000000004290, indexed in Pubmed: 27495031.
28. Edenbrandt L, Pahlm O. Vectorcardiogram synthesized from a 12-lead ECG: superiority of the inverse Dower matrix. J Electrocardiol. 1988; 21(4): 361–367, indexed in Pubmed: 3241148.
29. Xue QT. Interval Measurement: What Can We Really Expect? Computers in Cardiology. 2006; 33(385): 388.
30. Kück K, Isaksen JL, Graff C, et al. Spatial QRS-T angle variants for prediction of all-cause mortality. J Electrocardiol. 2018; 51(5): 768–775, doi: 10.1016/j.jelectrocard.2018.05.011, indexed in Pubmed: 30177310.
31. Zhang ZM, Rautaharju PM, Prineas RJ, et al. Electrocardiographic QRS-T angle and the risk of incident silent myocardial infarction in the Atherosclerosis Risk in Communities study. J Electrocardiol. 2017; 50(5): 661–666, doi: 10.1016/j.jelectrocard.2017.05.001, indexed in Pubmed: 28515002.
32. Kamphuis V, Blom N, Zwet Ev, et al. Normal values of the ventricular gradient and QRS-T angle, derived from the pediatric electrocardiogram. J Electrocardiol. 2018; 51(3): 490–495, doi: 10.1016/j.jelectrocard.2018.01.002.
33. Kenttä T, Karsikas M, Kiviniemi A, et al. Dynamics and rate-dependence of the spatial angle between ventricular depolarization and repolarization wave fronts during exercise ECG. Ann Noninvasive Electrocardiol. 2010; 15(3): 264–275, doi: 10.1111/j.1542-474X.2010.00374.x, indexed in Pubmed: 20645970.
34. Obata Y, Ruzankin P, Ong QiJ, et al. The impact of posture on the cardiac depolarization and repolarization phases of the QT interval in healthy subjects. J Electrocardiol. 2017; 50(5):

640–645, doi: 10.1016/j.jelectrocard.2017.03.001, indexed in Pubmed: 28330682.
35. Dabrowski W, Schlegel TT, Wosko J, et al. Changes in spatial QRS-T angle and QTc interval in patients with traumatic brain injury with or without intra-abdominal hypertension. J Electrocardiol. 2018; 51(3): 499–507, doi: 10.1016/j.jelectrocard.2017.12.038, indexed in Pubmed: 29310923.
36. Gul EE, Can I, Ozbek O. Displacement of the heart by diaphragm: is this heart alternating? J Electrocardiol. 2011; 44(4): 465–466, doi: 10.1016/j.jelectrocard.2010.09.002, indexed in Pubmed: 21093872.
37. Yamada N. Effects of respiration on the vectorcardiogram obtained with the Frank lead system. Acta Med Okayama. 1985; 39(4): 297–313, doi: 10.18926/AMO/31492, indexed in Pubmed: 4050536.
38. Pratt CM, Al-Khalidi HR, Brum JM, et al. Cumulative experience of azimilide-associated torsades de pointes ventricular tachycardia in the 19 clinical studies comprising the azimilide database. J Am Coll Cardiol. 2006; 48(3): 471–477, doi: 10.1016/j.jacc.2006.04.075, indexed in Pubmed: 16875971.
39. Muensterman ET, Tisdale JE. Predictive analytics for identification of patients at risk for QT interval prolongation: a systematic review. Pharmacotherapy. 2018; 38(8): 813–821, doi: 10.1002/phar.2146, indexed in Pubmed: 29882591.
40. Oji M, Terao Y, Toyoda T, et al. Differential effects of propofol and sevoflurane on QT interval during anesthetic induction. J Clin Monit Comput. 2013; 27(3): 243–248, doi: 10.1007/s10877-012-9420-7, indexed in Pubmed: 23242843.
41. Chang DJ, Kweon TD, Nam SB, et al. Effects of fentanyl pretreatment on the QTc interval during propofol induction. Anaesthesia. 2008; 63(10): 1056–1060, doi: 10.1111/j.1365-2044.2008.05559.x, indexed in Pubmed: 18616522.
42. Kuenszberg E, Loeckinger A, Kleinsasser A, et al. Sevoflurane, but not propofol, significantly prolongs the Q-T interval. Anesth Analg. 2000; 90(1): 25–27, indexed in Pubmed: 10624970.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2020, Vol. 27, No. 6, 715–725
DOI: 10.5603/CJ.a2018.0158

ISSN 1897–5593
eISSN 1898–018X

Risk factor paradox: No prognostic impact of arterial hypertension and smoking in patients with ventricular tachyarrhythmias

Kathrin Weidner[1]*, Michael Behnes[1]*, Jonas Rusnak[1], Gabriel Taton[1], Tobias Schupp[1], Linda Reiser[1], Armin Bollow[1], Thomas Reichelt[1], Dominik Ellguth[1], Niko Engelke[1], Philipp Kuche[1], Jorge Hoppner[2], Ibrahim El-Battrawy[1], Siegfried Lang[1], Christoph A. Nienaber[3], Kambis Mashayekhi[4], Dennis Ferdinand[5], Christel Weiss[5], Martin Borggrefe[1], Ibrahim Akin[1]

[1]First Department of Medicine, University Medical Center Mannheim (UMM), Faculty of Medicine Mannheim, University of Heidelberg, European Center for AngioScience (ECAS), and German Center for Cardiovascular Research (DZHK) partner site Heidelberg/Mannheim, Mannheim, Germany
[2]Clinic for Diagnostic and Interventional Radiology Heidelberg, University of Heidelberg, Germany
[3]Royal Brompton and Harefield Hospitals, NHS, London, United Kingdom
[4]Department of Cardiology and Angiology II, University Heart Center Freiburg, Bad Krozingen, Germany
[5]Institute of Biomathematics and Medical Statistics, University Medical Center Mannheim (UMM), Faculty of Medicine Mannheim, University of Heidelberg, Mannheim, Germany

Abstract

Background: *Data regarding the outcome of patients with ventricular tachyarrhythmias related to arterial hypertension (AHT) and smoking is limited. The study sought to assess the prognostic impact of AHT and smoking on survival in patients presenting with ventricular tachyarrhythmias.*

Methods: *All consecutive patients surviving ventricular tachycardia (VT) and ventricular fibrillation (VF) upon admission to the University Medical Center Mannheim (UMM), Germany from 2002 to 2016 were included and stratified according to AHT and smoking by propensity score matching. The primary prognostic endpoint was all-cause mortality at 30 months.*

Results: *A total of 988 AHT-matched patients (494 each, with and without AHT) and a total of 872 smoking-matched patients (436 each, with and without smoking) were included. The rates of VT and VF were similar in both groups (VT: AHT 60% vs. no AHT 60%; smokers 61% vs. non-smokers 62%; VF: AHT 35% vs. no AHT 38%; smokers 39% vs. non-smokers 38%). Neither AHT nor smoking were associated with the primary endpoint of long-term all-cause mortality at 30 months (long-term mortality rates: AHT/no AHT, 26% vs. 28%; log-rank $p = 0.525$; smoking/non-smoking, 22% vs. 25%; log-rank $p = 0.683$).*

Conclusions: *Paradoxically, neither AHT nor smoking were associated with differences of long-term all-cause mortality in patients presenting with ventricular tachyarrhythmias.* (Cardiol J 2020; 27, 6: 715–725)

Key words: ventricular tachyarrhythmias, arterial hypertension, smoking, long-term all-cause mortality

Address for correspondence: PD Dr. med. Michael Behnes, First Department of Medicine, University Medical Center Mannheim (UMM), Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany, tel: +49 621 383 6239, fax: +49 621 383 2012, e-mail: michael.behnes@umm.de

Received: 30.07.2018 Accepted: 7.11.2018

**Kathrin Weidner and Michael Behnes contributed equally to this study.*

Introduction

Sudden cardiac death (SCD) related to ventricular tachyarrhythmias accounts for 15–20% of all deaths in the Western world and remains associated with poor clinical outcomes [1]. Therefore, it is important to stratify high-risk patients presenting with ventricular tachyarrhythmias according to their individual risk for future outcomes.

Arterial hypertension (AHT) and nicotine, a major component of cigarettes inhaled during smoking, are common cardiovascular risk factors for coronary artery disease (CAD) and heart failure (HF) [2–4]. Patients suffering from CAD and HF are at risk of developing life-threatening ventricular tachyarrhythmias [2, 5]. Ventricular tachyarrhythmias are also associated with left ventricular hypertrophy (LVH) due to long-standing AHT [4, 6]. The pathogenesis of ventricular tachyarrhythmias in patients suffering from AHT is multifactorial, including hemodynamic and electrophysiological changes such as QT-prolongation [2, 7]. Likewise, it could be speculated if an antihypertensive medication including thiazide diuretics might induce electrolyte shifts such as hypokalemia alleviating the onset of ventricular tachyarrhythmias [2, 8]. The influence of AHT on the development of ventricular tachyarrhythmias is well described, whereas the prognostic impact of AHT in these high-risk patients is unclear.

Smoking of cigarettes is the most important modifiable risk factor for CAD [9]. The effect of smoking on progression of CAD is well established [3]. Nicotine by itself might induce acute vascular events due to induction of hypercoagulable states, induction of endothelial dysfunction, catecholamine release, and several toxic effects of increased carbon monoxide blood levels [10]. The role of smoking itself on ventricular tachyarrhythmias is still debated [2, 3]. Nicotine has been proven to induce arrhythmogenesis in animals, whereas these findings have not yet been approved in humans [3]. However, there is no data available as to whether smoking has an impact on long-term mortality in patients presenting with ventricular tachyarrhythmias [3].

Therefore, the present study evaluates the prognostic impact of AHT and smoking on long-term all-cause mortality in patients presenting with ventricular tachyarrhythmias upon admission.

Methods

Study patients, design and data collection

The present study retrospectively included all consecutive patients with ventricular tachyarrhythmias from 2002 until 2016 at one institution. All relevant clinical data related to the index event was documented using patient files, daily records, documentation from diagnostic examinations and laboratory values, electrocardiograms (ECG), device recordings, and all further information derived from the electronic hospital information system.

Ventricular tachyarrhythmias are comprised of ventricular tachycardia (VT) and ventricular fibrillation (VF), as defined by current international guidelines [11]. Sustained VT was defined by VT with a duration of more than 30 s or causing hemodynamic collapse within 30 s. Non-sustained VTs were defined as less than 30 s. VTs were comprised of wide QRS complexes (≥ 120 ms) at a rate greater than 100 bpm [11]. Ventricular tachyarrhythmias were documented by 12-lead ECG, ECG tele-monitoring and implantable cardioverter-defibrillators (ICD). In cases of unstable course or during cardiopulmonary resuscitation (CPR) documentation was performed by external defibrillator monitoring. Documented VF was treated by external defibrillation and in cases of prolonged instability with additional intravenous anti-arrhythmic drugs during CPR. Further documented data contained baseline characteristics, prior medical history, prior medical treatment, length of index stay, detailed findings of laboratory values at baseline, data derived from all non-invasive or invasive cardiac diagnostics and device therapies. These included coronary angiography, electrophysiological examination, prior or newly implanted ICDs, pacemakers or cardiac contractility modulators, which had already been implanted at index or at follow-up. Imaging modalities comprised echocardiography or cardiac magnetic resonance imaging (cMRI). The overall presence of an activated ICD summarizes the total sum of all patients with either a prior implanted ICD before admission, those undergoing new ICD implantation at index stay, as well as those with ICD implantation at the complete follow-up period after index hospitalization, referring to sole ICD, subcutaneous-ICD (s-ICD) and cardiac resynchronization therapy with defibrillator function (CRT-D). Pharmacological treatment was documented according to the discharge medication of patients surviving index hospitalization. Rates of overall

ICDs and of pharmacological therapies refer to the number of surviving patients being discharged from index hospitalization.

The documentation period lasted from the index event until 2016. Documentation of all medical data was performed by independent cardiologists at the patients' individual period of hospitalization and were blinded to the final data analyses.

The present study is derived from an analysis of the "Registry of Malignant Arrhythmias and Sudden Cardiac Death-Influence of Diagnostics and Interventions (RACE-IT)" and represents a single-center registry including retrospectively consecutive patients presenting with ventricular tachyarrhythmias and SCD being acutely admitted to the University Medical Center Mannheim (UMM), Germany (clinicaltrials.gov identifier: NCT02982473) from 2002 until 2016. The registry was carried out according to the principles of the Declaration of Helsinki and was approved by the Medical Ethics Committee II of the Faculty of Medicine Mannheim, University of Heidelberg, Germany.

The medical center covers a general emergency department for emergency admission of traumatic, surgical, neurological and cardiovascular conditions. Interdisciplinary consultation is an in-built feature of this 24/7 service, and is connected to a stroke unit, four intensive care units with extracorporeal life support and a chest pain unit to alleviate rapid triage of patients. The cardiology department itself includes 24 h catheterization and electrophysiologic laboratories, a hybrid operating room and telemetry units.

Definition of study groups, inclusion and exclusion criteria

For the present analysis risk stratification was performed according to AHT and smoking. AHT was defined by international guidelines as systolic blood pressure levels ≥ 140 mmHg and/or diastolic blood pressure levels ≥ 90 mmHg, at which the benefits of treatment overweighed the risks of treatment, i.e. lifestyle modification or antihypertensive drugs [12]. Smoking was defined by daily nicotine use [13]. Overall exclusion criteria comprised patients with early cardiac death. Early cardiac death was defined as cardiac death occurring < 24 h after onset of ventricular tachyarrhythmias or an assumed unstable cardiac condition on index admission [11]. No further exclusion criteria were present.

Each patient was counted only once for inclusion when presenting with the first episode of ventricular tachyarrhythmias.

Study endpoints

The primary prognostic endpoint was all-cause mortality at long-term follow-up of 30 months. Overall follow-up lasted until 2016. All-cause mortality was documented using our electronic hospital information system and by directly contacting state resident registration offices ("bureau of mortality statistics") across Germany. Identification of patients was verified by place of name, surname, day of birth and registered living address. Lost to follow-up rate was 1.7% (n = 48) regarding survival until the end of the follow-up period.

Statistical methods

Quantitative data are presented as mean ± standard error of mean (SEM), median and interquartile range (IQR), and ranges depending on the distribution of the data and were compared using the Student t test for normally distributed data or the Mann-Whitney U test for nonparametric data. Deviations from a Gaussian distribution were tested by the Kolmogorov-Smirnov test. The Spearman rank correlation for nonparametric data was used to test univariate correlations. Qualitative data are presented as absolute and relative frequencies and were compared using the χ^2 test or the Fisher exact test, as appropriate.

Uni-variable stratification was performed using the Kaplan-Meier method with comparisons between groups using uni-variable hazard ratios (HR) given together with 95% confidence intervals applied in the propensity-matched cohorts.

Follow-up periods for evaluation of all-cause mortality was in accordance with the median survival of diseased patients to guarantee complete survival of at least 50% of patients. Patients not meeting long-term follow-up were censored.

The result of a statistical test was considered significant for $p < 0.05$, p values ≤ 0.01 were defined as a statistical trend. SAS, release 9.4 (SAS Institute Inc., Cary, NC, USA) and SPSS (Version 25, IBM Armonk, New York, USA) were used for statistics.

Propensity score matching

Propensity matching was applied in advance (see study flow chart) and all statistical calculations as outlined above were performed in the propensity matched cohort afterwards.

In randomized controlled trials patients with or without a specific treatment would have a 50% chance of being treated and balanced measured and unmeasured baseline characteristics would be expected. However, patients cannot be rand-

omized in real-life according to AHT and smoke. An observational study usually recruits consecutive real-life patients without randomization resulting in varying chances between 0% and 100% to receive imbalances in baseline characteristics and treatments. Therefore, differences inoutcomes of specific groups might be explained by heterogeneous distribution of baseline characteristics and applied therapies. To further reduce this selection bias, a 1:1 propensity-scores were used for AHT vs. no AHT and smokers vs. non-smokers, to assemble matched cohorts, in which patients were well-balanced regarding all measured baseline characteristics. 1:1 propensity score matching was performed and included the entire study cohort [14, 15].

Propensity scores were created according to the presence of the following independent variables: age, gender, diabetes, chronic kidney disease (CKD) (glomerular filtration rate < 60 mL/min/1.73 m^2), CAD, left ventricular dysfunction, CPR, acute myocardial infarction (AMI), cardiogenic shock, presence of an ICD and index ventricular tachyarrhythmias (VT vs. VF).

Based on propensity score values counted by logistic regression, for each AHT a non-AHT patient and for each smoking patient, a non-smoking patient with a similar propensity score value was found (accepted difference of propensity score value < 5%).

Results

Study population

Propensity-matched cohorts of consecutive patients presenting with ventricular tachyarrhythmias on admission at our institution consisted of a total of 988 patients in AHT and 872 patients in smoking cohorts (Fig. 1).

In the AHT cohort (494 patients in each group), the rate of VT and VF was similar in both groups (VT: AHT 60% vs. no AHT 60%; VF: AHT 40% vs. no AHT 40%) (Table 1). No further differences were observed for prognosis-relevant factors at index including CKD, CAD, AMI, cardiogenic shock, cardiomyopathy as well as discharge medication with beta-blockers, angiotensin-converting enzyme inhibitors (ACEI) and aldosterone antagonists in between AHT and no AHT patients (Table 1).

In the smoking cohort (436 patients in each group), the rate of VT and VF was similar in both groups (VT: smokers 61% vs. non-smokers 62%; VF: smokers 39% vs. non-smokers 38%) (Table 2). Despite matching for prognosis-relevant factors

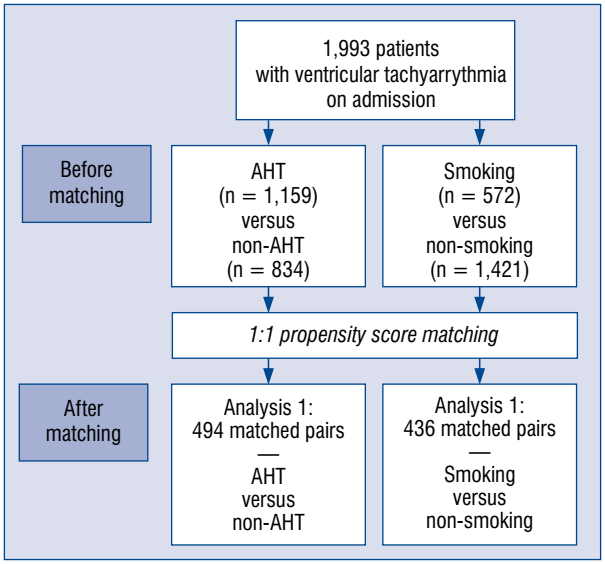


Figure 1. Flow chart of study population; AHT — arterial hypertension.

at index including CKD, CAD, AMI, cardiogenic shock, cardiomyopathies and atrial fibrillation, smokers were still more likely to have a prior history of AHT, hyperlipidemia, cardiac family history and ACEI at discharge (Table 2).

The AHT cohort and the smoker's cohort were well matched for left ventricular function, cardiac therapies at index including CPR, diagnostics including coronary angiography and CAD status and device therapies (Tables 1, 2). Smokers underwent coronary angiography more often and revealed a higher rate of overall CAD.

All-cause mortality and survival data

Paradoxically, at long-term follow-up high-risk AHT patients presenting with ventricular tachyarrhythmias were not associated with the primary endpoint of long-term all-cause mortality at 30 months (IQR 96 days – 5.5 years) compared to no AHT patients (mortality rates: AHT, 26% vs. no AHT: 28%; log-rank p = 0.525) (Fig. 2).

Arterial hypertension was not associated with the primary endpoint of long-term all-cause mortality in CRT (HR 0.511 [0.132–1.976]; p = 0.330) and no-CRT patients (HR 0.942 [0.736–1.205]; p = 0.942) as well as in patients with left ventricular ejection fraction (LVEF) > 35% and LVEF < 35% (LVEF > 35%, log-rank p = 0.497; LVEF < 35%, log-rank p = 0.753) (data not shown).

Accordingly, smokers presenting with ventricular tachyarrhythmias on admission were not associated with the primary endpoint of all-cause

Table 1. Characteristics of matched patients with or without arterial hypertension.

Characteristic	Non-AHT (n = 494; 50%)		AHT (n = 494; 50%)		P
Gender: male	376	(76%)	378	(77%)	0.881
Age, median (range)	65 (21–89)		65 (30–94)		0.396
Ventricular tachyarrhythmias:					
VT	296	(60%)	298	(60%)	0.897
VF	198	(40%)	196	(40%)	
Cardiovascular risk factors:					
Diabetes mellitus	90	(18%)	115	(23%)	0.050
Hyperlipidemia	74	(15%)	211	(43%)	**0.001**
Smoking	140	(28%)	160	(32%)	0.166
Cardiac family history	52	(11%)	63	(13%)	0.275
Comorbidities at index stay:					
Acute myocardial infarction	161	(33%)	145	(29%)	0.271
Cardiogenic shock	58	(12%)	59	(12%)	0.922
Cardiopulmonary resuscitation	187	(38%)	177	(36%)	0.510
Cardiomyopathy	78	(16%)	60	(12%)	0.099
Valvular heart disease	44	(9%)	42	(9%)	0.821
Atrial fibrillation	137	(28%)	173	(35%)	**0.014**
Cardiac surgery	7	(1%)	7	(1%)	1.000
Hyperkalemia	7	(1%)	8	(2%)	0.795
Hypokalemia	28	(6%)	34	(7%)	0.431
Stroke	15	(3%)	19	(4%)	0.485
Clinically significant bleeding	18	(4%)	16	(3%)	0.727
Anemia	24	(5%)	31	(6%)	0.331
Septic shock	13	(3%)	13	(3%)	1.000
Chronic kidney disease	217	(44%)	219	(44%)	0.898
Liver cirrhosis	7	(1%)	4	(0.8%)	0.363
Coronary angiography:					
Coronary angiography, overall	337	(68%)	368	(75%)	0.029
Coronary artery disease	243	(72%)	254	(69%)	0.130
No evidence of CAD:	94	(28%)	114	(31%)	0.163
1-vessel	78	(23%)	100	(27%)	0.069
2-vessel	88	(26%)	70	(19%)	0.118
3-vessel	77	(23%)	84	(23%)	0.547
Presence of CABG	37	(11%)	44	(12%)	0.684
Presence of CTO	71	(21%)	60	(16%)	0.085
PCI	157	(47%)	138	(38%)	**0.015**
Left ventricular function:					0.786
LVEF > 55%	143	(29%)	150	(30%)	
LVEF 54–35%	176	(36%)	162	(33%)	
LVEF < 35%	175	(35%)	182	(37%)	
Patients at discharge	426	(86%)	442	(89%)	0.119
Overall ICDs	131	(31%)	132	(30%)	0.911
Medication at discharge:					
Beta-blocker	358	(84%)	379	(86%)	0.482
ACEI	290	(68%)	314	(71%)	0.342
Alosterone antagonist	48	(11%)	58	(13%)	0.404

→

Table 1. (cont.). Characteristics of matched patients with or without arterial hypertension.

Characteristic	Non-AHT (n = 494; 50%)		AHT (n = 494; 50%)		P
Hospitalization time [days], median (IQR):					
Total hospitalization time	13 (8–22)		14 (8–23)		0.991
ICU time	4 (0–8)		3 (0–8)		0.278
Follow-up time [days], mean; median (range)	1719;1539 (3–5095)		1809;1595 (3–5106)		0.331
All-cause mortality at 30 months:					
At index	68	(14%)	52	(11%)	0.119
At follow up	68	(14%)	76	(15%)	0.471
Overall	136	(28%)	128	(26%)	0.377

ACEI — angiotensin converting enzyme inhibitor; AHT — arterial hypertension; AMI — acute myocardial infarction; CABG — coronary artery bypass grafting; CAD — coronary artery disease; CTO — coronary chronic total occlusion; ICD — implantable cardioverter-defibrillator; ICU — intensive care unit; IQR — interquartile range; LVEF — left ventricular ejection function; PCI — percutaneous coronary intervention; VF — ventricular fibrillation; VT — ventricular tachycardia

Table 2. Baseline characteristics according to smoking status.

Characteristic	Non-smoking (n = 436; 50%)		Smoking (n = 436; 50%)		P
Gender: male	362	(83%)	365	(84%)	0.785
Age, median (range)	65 (16–92)		63 (21–88)		**0.001**
Ventricular tachyarrhythmias:					
VT	269	(62%)	266	(61%)	0.835
VF	167	(38%)	170	(39%)	
Cardiovascular risk factors:					
Arterial hypertension	252	(58%)	293	(67%)	**0.004**
Diabetes mellitus	113	(26%)	110	(25%)	0.816
Hyperlipidemia	135	(31%)	180	(41%)	**0.002**
Cardiac family history	33	(8%)	85	(20%)	**0.001**
Comorbidities at index:					
Acute myocardial infarction	132	(30%)	155	(36%)	0.097
Cardiogenic shock	39	(9%)	56	(13%)	0.065
Cardiomyopathy	47	(11%)	36	(8%)	0.204
Cardiopulmonary resuscitation	156	(36%)	156	(36%)	1.000
Valvular heart disease	30	(7%)	26	(6%)	0.581
Atrial fibrillation	120	(28%)	123	(28%)	0.821
Cardiac surgery	4	(0.9%)	15	(3%)	**0.011**
Hyperkalemia	3	(0.7%)	6	(1%)	0.315
Hypokalemia	31	(7%)	16	(4%)	**0.024**
Stroke	8	(2%)	19	(4%)	**0.032**
Clinically significant bleeding	6	(1%)	15	(3%)	**0.047**
Anemia	19	(4%)	21	(5%)	0.746
Septic shock	5	(1%)	13	(3%)	0.057
Chronic kidney disease	175	(40%)	173	(40%)	0.890
Liver cirrhosis	3	(0.7%)	6	(1%)	0.315
Coronary angiography:					
Coronary angiography, overall	297	(68%)	328	(75%)	**0.020**
Coronary artery disease	234	(54%)	263	(60%)	**0.047**

→

Table 2 (cont.). Baseline characteristics according to smoking status.

Characteristic	Non-smoking (n = 436; 50%)		Smoking (n = 436; 50%)		P
No evidence of CAD:	63	(21%)	65	(20%)	0.837
1-vessel	73	(25%)	97	(30%)	**0.040**
2-vessel	81	(27%)	71	(22%)	0.797
3-vessel	80	(27%)	95	(29%)	0.205
Presence of CABG	45	(15%)	44	(13%)	0.535
Presence of CTO	69	(23%)	68	(21%)	0.450
PCI	123	(41%)	157	(48%)	0.105
Left ventricular function:					0.679
LVEF > 55%	126	(29%)	125	(29%)	
LVEF 54–35%	153	(35%)	152	(35%)	
LVEF < 35%	157	(36%)	159	(37%)	
Patients at discharge	399	(91%)	389	(89%)	0.181
Overall ICDs	115	(29%)	124	(32%)	0.467
Medication at discharge:					
Beta-blocker	338	(85%)	341	(88%)	0.231
ACEI	257	(64%)	286	(74%)	**0.006**
Aldosterone antagonist	32	(8%)	47	(12%)	0.058
Hospitalization time [days], median (IQR):					
Total hospitalization time	12 (4–23)		13 (8–23)		0.261
ICU time	3 (0–8)		3 (0-8)		0.383
Follow-up time [days], mean; median (range)	1954; 1930 (3–5095)		1693; 1527 (3–5089)		**0.006**
All-cause mortality at 30 months:					
At index	37	(9%)	47	(11%)	0.191
At follow up	71	(16%)	51	(12%)	0.051
Overall	108	(25%)	98	(22%)	0.425

ACEI — angiotensin converting enzyme inhibitor; AHT — arterial hypertension; AMI — acute myocardial infarction; CABG — coronary artery bypass grafting; CAD — coronary artery disease; CTO — coronary chronic total occlusion; ICD — implantable cardioverter-defibrillator; ICU — intensive care unit; IQR — interquartile range; LVEF — left ventricular ejection function; PCI — percutaneous coronary intervention; VF — ventricular fibrillation; VT — ventricular tachycardia

mortality at 30 months compared to non-smokers (mortality rate smokers: 22% vs. non-smokers: 25%; log-rank p = 0.683) (Fig. 3). Even in patients with LVEF > 35% smoking was not associated with any mortality difference (LVEF > 35%, log-rank p = 0.649; LVEF < 35%, log-rank p = 0.239) (data not shown).

Discussion

The present study evaluates the prognostic impact of AHT and smoking on long-term all-cause mortality in high-risk patients presenting consecutively with ventricular tachyarrhythmias on admission. Paradoxically, this well-matched analysis suggests that neither AHT nor smoking were associated with increased secondary long-term all-cause mortality at 30 months in patients presenting consecutively with ventricular tachyarrhythmias straight from the admission scenario.

Previous studies showed that LVH due to AHT is a risk factor for ventricular tachyarrhythmias [16]. Data from the Framingham cohort demonstrated in 1985, that AHT may increase the risk of sustained or non-sustained VT in the presence of LVH [17]. Depending on the grade of LVH, the authors showed an increasing risk of cardiovascular and death of any cause. However, this study did not report on a long-term follow up of patients presenting on admission with ventricular tachyarrhythmias according to the presence of AHT. The present study did not prove any prognostic impact of AHT on long-term prognosis in patients presenting with ventricular tachyarrhythmias. Notably, no prog-

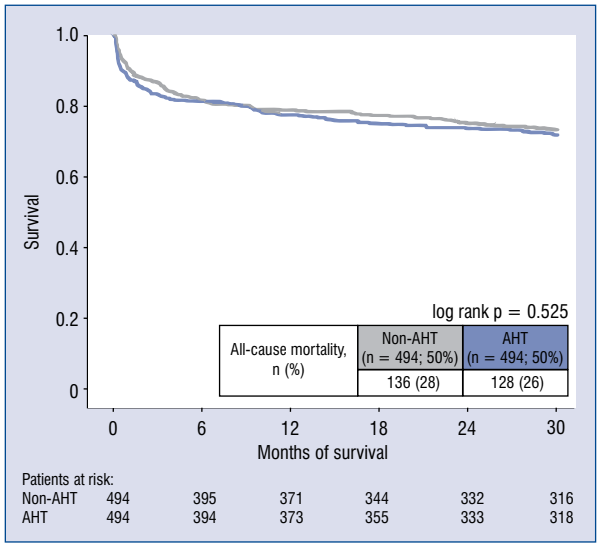


Figure 2. Long-term all-cause mortality of patients presenting with ventricular tachyarrhythmias stratified according to the presence and absence of arterial hypertension (AHT).

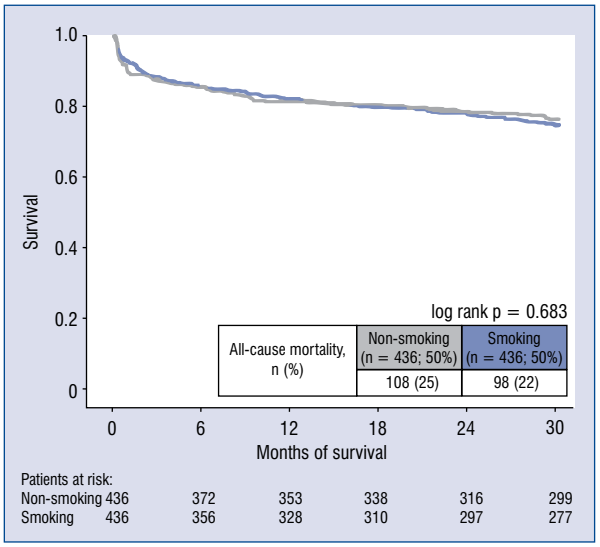


Figure 3. Long-term all-cause mortality of patients presenting with ventricular tachyarrhythmias stratified according to the presence and absence of smoking.

nostic impact of AHT was additionally observed in patients with or without CRT devices.

McLenachan et al. [18] compared patients with and without LVH and AHT assessed by 12-lead ECG (each n = 50) including matching for age, sex, smoking and blood-pressure levels. It was demonstrated that AHT/LVH patients had a significant higher rate of ventricular tachyarrhythmias and SCD compared to patients without LVH [18]. Furthermore, effective control of blood pressure was shown to prevent ventricular tachyarrhythmias and SCD [16]. Especially, antihypertensive drugs, such as thiazide diuretics, were associated with ventricular tachyarrhythmias due to electrolyte shifts. Although, the exact mechanism is not fully understood, hypokalemia might play an important role [19]. In the double-blind and randomized HOPE-study the ACEI ramipril was associated with a reduced rate of death, myocardial infarction, stroke and cardiac arrest compared to placebo [20]. Since their market approval in the early 1980s, ACEI became the international gold standard in the therapy of AHT. ACEI are known to attenuate adverse structural myocardial remodeling and progression of LVH [21–23]. Data from Framingham and MCLenachan were collected until 1985/1987, whereas data about ACEI treatment were not reported sufficiently. It might be speculated as to whether the lack of prognostic impact of AHT itself may be attributed to modern therapies including ACEI within 2002 and 2016. In this study 26% of AHT patients had been already treated with ACEI.

A majority of patients included in the present study suffered from systolic HF (LVEF < 55%) in almost two thirds of cases. Heart failure, especially in advanced stages (LVEF < 35%) is accompanied by progressive AHT in terms of low-output failure [24]. This might additionally support the hypothesis of risk-factor paradox in patients presenting with ventricular tachyarrhythmias related to AHT. Here, the implantation of CRT-devices represents an established treatment option in patients with wide QRS complexes and LVEF < 35% [25, 26], and aims to improve left ventricular dysfunction by an effective biventricular stimulation rate of > 98%, which in turn, may increase systolic blood pressure. However, there are known predictors of ineffective CRT response, such as permanent atrial fibrillation, massively dilated left ventricles, severe mitral regurgitation, and large ischemic anteroseptal or posterior scars of the left ventricle [26]. In order to test for potential bias, the present study demonstrates that AHT had no effect on prognosis and neither in CRT, non-CRT and LVEF < 35% patients. However, the outlined circumstances might additionally support the hypothesis of the entitled risk-factor paradox in patients presenting with ventricular tachyarrhythmias related to AHT.

The only and most modifiable cardiovascular risk factor represents the smoking of cigarettes, however smoking is still the leading preventable

cause of death in the United States [3]. Smoking is directly associated with atherosclerosis, whereas its influence in patients with ventricular tachyarrhythmias is still unclear [3]. Several experimental studies investigated the toxicity of nicotine in animals and cell cultures. Mehta et al. [27] investigated the effect of intravenous application of nicotine in healthy dogs. In their dose-response study, increased rates of arrhythmias were observed at a dosage of 50 μg/kg (equivalent in humans of 2 smoked cigarettes), including supraventricular, atrioventricular junctional and ventricular arrhythmias [27]. An intravenous dosage of nicotine at 100 μg/kg was shown to induce fatal ventricular flutter and fibrillation. The arrhythmogenic side effect of nicotine was explained by increased carbon monoxide and oxidative stress [27]. Unfortunately, these experimental results are not directly comparable to humans, due to long-term use of smoking in humans [3, 27].

In a case-control study including 95 CAD patients undergoing bypass surgery smoking was an independent predictor of atrial fibrosis [28]. Goette et al. [28] demonstrated increased levels of collagen type III within an organo-typical atrial tissue culture model of smokers. This pro-fibrotic status (i.e. increase of extracellular matrix turnover and subsequent adverse structural myocardial remodeling) as a consequence of nicotine was also shown in an experimental study in dogs by Shan et al. [29], where a dose-dependent increase of atrial remodeling after intravenous administration of nicotine over 30 days was documented. Atrial tissue was preserved during open-heart surgery of the dogs and the fibrous tissue was finally quantified microscopically [3]. Furthermore, arrhythmogenesis might be related to tissue hypoxemia, oxidative stress and increased carbon monoxide by binding hemoglobin during smoking [30, 31].

Plank et al. [32] investigated in a sub-study of the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT-trial) the risk of first and recurrent ventricular tachyarrhythmias in patients with mild HF and ICD therapy according to smoking [32]. The study compared 465 non-smokers, 780 past smokers and 197 current smokers with ischemic and non-ischemic cardiomyopathy [32]. Current smokers with mild HF were shown to be associated with higher risk of ventricular tachyarrhythmias compared to past- and non-smokers [32]. The MADIT-II trial showed that the risk of ventricular tachyarrhythmias in patients with CAD-related HF is higher in current smokers compared to past- and non-smokers. They also showed that smokers had a significantly higher risk for inadequate ICD-shocks [33]). MADIT-II and MADIT-CRT were primary preventive studies, whereas the present study included patients who already survived an episode of ventricular tachyarrhythmias on admission. Unfortunately, sub-analyses of MADIT did not undergo propensity matching which questions the results due to cofounding of heterogeneous sub-groups regarding comorbidities.

Data about the effect of nicotine and cardiac arrhythmia are limited in humans. Pharmacodynamics of nicotine is complex including the biphasic dose-response curve and additional development of nicotine tolerance. Therefore, more studies in humans are necessary to prove potential acute toxic and long-term prognostic effects of nicotine in patients presenting with ventricular tachyarrhythmias [3, 34–36]. Consistently, smoking does represent a risk factor for development of CAD and chronic obstructive pulmonary disease (COPD). Both diseases might promote ventricular tachyarrhythmias by themselves [37]. No evidence is yet available whether smoking may affect prognosis in the absence of CAD and COPD, even in high-risk patients with ventricular tachyarrhythmias.

In conclusion, this study demonstrates a paradox that neither AHT nor smoking reveal any impact on long-term prognosis in terms of all-cause mortality in high-risk patients presenting with ventricular tachyarrhythmias on admission.

Limitations of the study

This observational and retrospective registry-based analysis reflects a realistic picture of consecutive health-care supply of high-risk patients presenting with ventricular tachyarrhythmias right upon hospital admission. Lost to follow-up rate regarding the evaluated endpoint of all-cause mortality was minimal. Additionally, heterogeneity within the study population was controlled by 1:1 propensity-matched analyses. The potential influence of optimal treatment of hypertensive patients as well as investigation of smoking cessation programmes being offered at the documented institution might still have influenced the present results to a minor extent. Despite retrospective propensity-score matching with similar rates of cardioprotective drugs in both AHT and no AHT patients and no differences after stratification into left ventricular dysfunction, a certain bias may still be present especially in hypotensive patients associated with progressive HF usually receiving minor dosages and numbers of cardioprotective

drugs. Also, a CRT-treatment might improve the blood pressure and consecutive the survival in hypotensive patients. The prognostic impact of AHT and smoking in patients with ventricular tachyarrhythmias has to be re-evaluated in further studies.

Conclusions

Paradoxically, AHT and smoking were not associated with increased long-term all-cause mortality at 30 months in patients presenting with ventricular tachyarrhythmias on admission.

Funding: Supported by the DZHK (Deutsches Zentrum fuer Herz-Kreislauf-Forschung — German Centre for Cardiovascular Research).

Conflict of interest: None declared

References

1. Green D, Roberts P, New D, et al. Sudden cardiac death in hemodialysis patients: an in-depth review. Am J Kidney Dis. 2011; 57(6): 921–929, doi: 10.1053/j.ajkd.2011.02.376.
2. Lip G, Coca A, Kahan T, et al. Hypertension and cardiac arrhythmias: a consensus document from the European Heart Rhythm Association (EHRA) and ESC Council on Hypertension, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). EP Europace. 2017; 19(6): 891–911, doi: 10.1093/europace/eux091.
3. D'Alessandro A, Boeckelmann I, Hammwhöner M, et al. Nicotine, cigarette smoking and cardiac arrhythmia: an overview. Eur J Prev Cardiol. 2012; 19(3): 297–305, doi: 10.1177/1741826711411738, indexed in Pubmed: 22779085.
4. Lip GYH, Coca A, Kahan T, et al. Hypertension and cardiac arrhythmias: executive summary of a consensus document from the European Heart Rhythm Association (EHRA) and ESC Council on Hypertension, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). Eur Heart J Cardiovasc Pharmacother. 2017; 3(4): 235–250, doi: 10.1093/ehjcvp/pvx019, indexed in Pubmed: 28541499.
5. Aronow WS, Epstein S, Koenigsberg M, et al. Usefulness of echocardiographic abnormal left ventricular ejection fraction, paroxysmal ventricular tachycardia and complex ventricular arrhythmias in predicting new coronary events in patients over 62 years of age. Am J Cardiol. 1988; 61(15): 1349–1351, indexed in Pubmed: 3376895.
6. Levy D, Anderson KM, Savage DD, et al. Risk of ventricular arrhythmias in left ventricular hypertrophy: the Framingham Heart Study. Am J Cardiol. 1987; 60(7): 560–565, indexed in Pubmed: 2957907.
7. Sultana R, Sultana N, Rashid A, et al. Cardiac arrhythmias and left ventricular hypertrophy in systemic hypertension. J Ayub Med Coll Abbottabad. 2010; 22(4): 155–158, indexed in Pubmed: 22455286.
8. Roush GC, Sica DA. Diuretics for hypertension: a review and update. Am J Hypertens. 2016; 29(10): 1130–1137, doi: 10.1093/ajh/hpw030, indexed in Pubmed: 27048970.
9. Services UDoHaH. The 2004 United States Surgeon General's Report: The Health Consequences of Smoking. N S W Public Health Bull. 2004;15(5-6). 107.
10. Benowitz NL, Hansson A, Jacob P. Cardiovascular effects of nasal and transdermal nicotine and cigarette smoking. Hypertension. 2002; 39(6): 1107–1112, indexed in Pubmed: 12052850.
11. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015; 36(41): 2793–867.
12. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018; 39(33): 3021–3104, doi: 10.1093/eurheartj/ehy339, indexed in Pubmed: 30165516.
13. Wienbergen H, Hambrecht R. [ESC-Guidelines 2016 - Prevention of Cardiovascular Diseases in Clinical Practice]. Dtsch Med Wochenschr. 2017; 142(3): 189–192, doi: 10.1055/s-0042-113928, indexed in Pubmed: 28187483.
14. Ferdinand D, Otto M, Weiss C. Get the most from your data: a propensity score model comparison on real-life data. Int J Gen Med. 2016; 9: 123–131, doi: 10.2147/IJGM.S104313, indexed in Pubmed: 27274306.
15. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res. 2011; 46(3): 399–424, doi: 10.1080/00273171.2011.568786, indexed in Pubmed: 21818162.
16. Kannel WB, McGee DL. Epidemiology of sudden death: insights from the Framingham Study. Cardiovasc Clin. 1985; 15(3): 93–105, indexed in Pubmed: 3833369.
17. Levy D, Garrison R, Savage D, et al. Prognostic Implications of Echocardiographically Determined Left Ventricular Mass in the Framingham Heart Study. N Engl J Med. 1990; 322(22): 1561–1566, doi: 10.1056/nejm199005313222203.
18. McLenachan JM, Henderson E, Morris KI, et al. Ventricular arrhythmias in patients with hypertensive left ventricular hypertrophy. N Engl J Med. 1987; 317(13): 787–792, doi: 10.1056/NEJM198709243171302, indexed in Pubmed: 2957590.
19. Siscovick DS, Raghunathan TE, Psaty BM, et al. Diuretic therapy for hypertension and the risk of primary cardiac arrest. N Engl J Med. 1994; 330(26): 1852–1857, doi: 10.1056/NEJM199406303302603, indexed in Pubmed: 8196728.
20. Correction: Effects of An Angiotensin-Converting-Enzyme Inhibitor, Ramipril, on Cardiovascular Events in High-Risk Patients. N Engl J Med. 2000; 342(18): 1376, indexed in Pubmed: 10706908.
21. Mancia G, Fagard R, Narkiewicz K, et al. Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2013; 31(7): 1281–1357, doi: 10.1097/01.hjh.0000431740.32696.cc, indexed in Pubmed: 23817082.
22. Captopril--a decade of discovery. Proceedings of a symposium. London, 24-25 October 1985. Postgrad Med J. 1986; 62 Suppl 1: 1–191, indexed in Pubmed: 3534844.

23. Smith CG, Vane JR, Smith CG, et al. The discovery of captopril. FASEB J. 2003; 17(8): 788–789, doi: 10.1096/fj.03-0093life, indexed in Pubmed: 12724335.
24. Dickstein K, Vardas PE, Auricchio A, et al. 2010 Focused Update of ESC Guidelines on device therapy in heart failure: an update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC Guidelines for cardiac and resynchronization therapy. Developed with the special contribution of the Heart Failure Association and the European Heart Rhythm Association. Europace. 2010; 12(11): 1526–36.
25. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail. 2008; 10(10): 933–989, doi: 10.1016/j.ejheart.2008.08.005, indexed in Pubmed: 18826876.
26. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: The Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Europace. 2013; 15(8): 1070–1118, doi: 10.1093/europace/eut206.
27. Mehta M, Jain A, Mehta A, et al. Cardiac arrhythmias following intravenous nicotine: experimental study in dogs. J Cardiovasc Pharmacol Ther. 2016; 2(4): 291–297, doi: 10.1177/107424849700200407.
28. Goette A, Lendeckel U, Kuchenbecker A, et al. Cigarette smoking induces atrial fibrosis in humans via nicotine. Heart. 2007; 93(9): 1056–1063, doi: 10.1136/hrt.2005.087171, indexed in Pubmed: 17395670.
29. Shan H, Zhang Y, Lu Y, et al. Downregulation of miR-133 and miR-590 contributes to nicotine-induced atrial remodelling in canines. Cardiovasc Res. 2009; 83(3): 465–472, doi: 10.1093/cvr/cvp130, indexed in Pubmed: 19398468.
30. Leone A. Biochemical markers of cardiovascular damage from tobacco smoke. Curr Pharm Des. 2005; 11(17): 2199–2208, indexed in Pubmed: 16026289.
31. Andre L, Boissière J, Reboul C, et al. Carbon monoxide pollution promotes cardiac remodeling and ventricular arrhythmia in healthy rats. Am J Respir Crit Care Med. 2010; 181(6): 587–595, doi: 10.1164/rccm.200905-0794OC, indexed in Pubmed: 20019346.
32. Plank B, Kutyifa V, Moss AJ, et al. Smoking is associated with an increased risk of first and recurrent ventricular tachyarrhythmias in ischemic and nonischemic patients with mild heart failure: a MADIT-CRT substudy. Heart Rhythm. 2014; 11(5): 822–827, doi: 10.1016/j.hrthm.2014.02.007, indexed in Pubmed: 24509214.
33. Goldenberg I, Moss AJ, McNitt S, et al. Cigarette smoking and the risk of supraventricular and ventricular tachyarrhythmias in high-risk cardiac patients with implantable cardioverter defibrillators. J Cardiovasc Electrophysiol. 2006; 17(9): 931–936, doi: 10.1111/j.1540-8167.2006.00526.x, indexed in Pubmed: 16759297.
34. Benowitz N. Pharmacology of Nicotine: Addiction, Smoking-Induced Disease, and Therapeutics. Annu Rev Pharmacol Toxicol. 2009; 49(1): 57–71, doi: 10.1146/annurev.pharmtox.48.113006.094742.
35. Benowitz NL. Clinical pharmacology of nicotine. Annu Rev Med. 1986; 37(1): 21–32, doi: 10.1146/annurev.me.37.020186.000321.
36. Fattinger K, Verotta D, Benowitz NL. Pharmacodynamics of acute tolerance to multiple nicotinic effects in humans. J Pharmacol Exp Ther. 1997; 281(3): 1238–1246, indexed in Pubmed: 9190859.
37. Falk JA, Kadiev S, Criner GJ, et al. Cardiac disease in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2008; 5(4): 543–548, doi: 10.1513/pats.200708-142ET, indexed in Pubmed: 18453369.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2020, Vol. 27, No. 6, 726–734
DOI: 10.5603/CJ.a2018.0143

ISSN 1897–5593
eISSN 1898–018X

Kinetics of selected serum markers of fibrosis in patients with dilated cardiomyopathy and different grades of diastolic dysfunction of the left ventricle

Sylwia Wiśniowska-Śmiałek[1], Ewa Dziewięcka[1], Katarzyna Holcman[1], Ewa Wypasek[2], Lusine Khachatryan[3], Aleksandra Karabinowska[3], Maria Szymonowicz[3], Agata Leśniak-Sobelga[1], Marta Hlawaty[1], Magdalena Kostkiewicz[1], Piotr Podolec[1], Paweł Rubiś[1]

[1]Department of Cardiac and Vascular Diseases, John Paul II Hospital, Krakow, Poland
[2]Department of Molecular Biology, John Paul II Hospital, Krakow, Poland
[3]Jagiellonian University, Medical Collage, Krakow, Poland

Abstract

Background: *Fibrosis of the extracellular matrix (ECM) in dilated cardiomyopathy (DCM) is common and compromises both systolic and diastolic function. The aim of this study was to investigate the kinetics of ECM fibrosis markers over a 12 month follow-up in patients with DCM based on the severity of diastolic dysfunction (DD).*

Methods: *Seventy consecutive DCM patients (48 ± 12.1 years, ejection fraction 24.4 ± 7.4%) were included in the study. The grade of DD was determined using the ASE/EACVI algorithm. Markers of ECM fibrosis were measured at baseline and at 3 and 12 month follow-ups: collagen type I and III (PICP, PINP, PIIICP, PIIINP), transforming growth factor beta-1 (TGF1-β), connective tissue growth factor (CTGF) and galectin-3 were measured.*

Results: *Patients were divided into three groups according to DD severity: 30 patients with grade I, 18 with grade II and 22 with grade III of DD. Levels of PICP, PINP were increased over a 12-month period, while PIIINP decreased and PIIICP unchanged. Levels of TGF1-β decreased from the 3 to the 12-month points in grade I and II DD, and in grade III they remained unchanged. Levels of CTGF decreased over 12 months in grade III DD but were unchanged in grades I and II. Galectin-3 levels remained the same over all observation periods, irrespective of DD grade.*

Conclusions: *Regardless of the DD grade, markers of collagen type I synthesis increased, markers of collagen type III decreased. Levels of TGF and CTGF had a tendency to decrease. Galectin-3 was revealed not to be a marker discriminating the severity of DD.* (Cardiol J 2020; 27, 6: 726–734)

Key words: dilated cardiomyopathy, diastolic dysfunction, markers of fibrosis

Introduction

The prevalence of heart failure (HF) is 1–2% of the adult population in developed countries [1]. According to the current classification of diastolic dysfunction (DD), virtually all patients with HF with reduced ejection fraction (HFrEF) have at least a mild degree of DD [2]. Irrespective of HF etiology, e.g. ischemic or non-ischemic, progressive abnormalities in the extracellular matrix (ECM) result in a gradual worsening of both systolic and diastolic function. Reactive fibrosis of ECM typi-

Address for correspondence: Dr. Sylwia Wiśniowska-Śmiałek, Collegium Medicum of Jagiellonian University, Department of Cardiac and Vascular Diseases, John Paul II Hospital, ul. Prądnicka 80, 31–202 Kraków, Poland, tel: +48 12 614 22 87, fax: +48 12 614 33 32, e-mail: swisniowskasmialek@gmail.com

Received: 13.07.2018 Accepted: 8.11.2018

cally is observed in dilated cardiomyopathy (DCM) and importantly contributes to HF progression. Altered components of ECM, e.g. relative increase of collagen type I over III, leads to the stiffening of the myocardium and further worsening DD. Thus, ECM fibrosis and DD seems to be interrelated.

Extracellular matrix fibrosis can be studied directly by means of endomyocardial biopsy or non-invasively with magnetic resonance. Furthermore, measurement of serum markers of fibrosis may provide insight into myocardial pathology. The dynamics of collagen turnover may be studied via circulating markers of collagen synthesis which are released into the bloodstream during conversion into the mature collagens [3–5]. In addition, levels of fibrosis controlling factors, including transforming growth factor beta-1 (TGF1-β), connective tissue growth factor (CTGF) or galectin-3 may also indicate ongoing ECM fibrosis [6]. Numerous studies have explored the role of serum markers of fibrosis in various cardiac disorders, including HF, DCM and hypertension. In the majority of these studies only single measurements of markers of interests were performed and, based on those baseline values, associations were investigated. Conversely, a minority of studies examined for the kinetics of those markers, which may be equally important as patterns of biomarkers over time may be more relevant than single measures.

Under a previous investigation, 12-month kinetics of serum markers of collagen synthesis, TGF and CTGF, in DCM patients were stratified according to duration of disease and fibrosis status [7]. Different patterns of these markers were observed over time in patients with and without ECM fibrosis. Despite an extensive literature search, no studies were found exploring the relationship between the kinetics of serum markers and DD in patients with DCM. Therefore, in this study, the aim was to investigate changes over time in selected markers of fibrosis in DCM patients stratified on the basis of DD over a 12-month observation period.

Methods

Study groups

From July 2014 to October 2015, 70 consecutive patients with DCM were included. DCM was diagnosed according to the current European Society of Cardiology 2007 guidelines after exclusion of significant coronary artery disease, primary heart valve disease, congenital heart disease and arterial hypertension [8]. All patients were in the New York Heart Association (NYHA) class I–III for at least 2 preceding weeks. An assessment of patient status, echocardiographic examinations and blood sampling were repeated at 3 and 12 months. The study protocol was approved by the relevant institutional committees and ethics committees. All patients gave written informed consent prior to inclusion in the study. During the study, 4 (5.7%) patients died within the first 3 months and another 2 (3%) within 12 months. Thus, there were 64 (94.3%) patients which comprised follow-up data.

Echocardiography

All measurements, including DD assessment, were performed according to the recommendations of the European Associations of Cardiovascular Imaging (EACVI) [2]. Based on the EACVI algorithm, DCM patients were divided into three groups; grade I, II or III DD.

Laboratory measurements

Venous blood samples and laboratory testing of serum markers of fibrosis were conducted using methods described in recent papers [9]. The concentrations of collagen synthesis markers and fibrosis controlling markers were determined in plasma using a commercially available ELISA tests as follows: collagen type 1 (manufacture reference values 46.7–178.9 pg/mL), procollagen I N-terminal propeptide (PINP 30.2–55.1 pg/mL), procollagen III N-terminal propeptide (PIIINP 2.69–63.56 ng/mL), procollagen I C-terminal propeptide (PICP 64–186 pg/mL = 0.064–0.186 ng/mL), procollagen III C-terminal propeptide (PIIICP 5.2–35.5 ng/mL), connective tissue growth factor (CTGF 2.3–42.5 ng/mL) (all from Cloud Clone Corp. Houston, TX, USA); TGF1-β (4.639–14.757 pg/mL = 4.639–14.757 ng/mL) (Diaclone SAS, Besancon Cedex, France), galectin-3 (4–114 ng/mL) (Abbott Diagnostics, Vienna, Austria). All measurements were performed by technicians blinded to the sample status. Intra-assay and inter-assay coefficients of variation were < 7%.

Statistical analysis

The normality of distribution of variables was assessed with the Shapiro-Wilk test. Comparisons of clinical parameters in the three groups were conducted with the Kruskal-Wallis ANOVA nonparametric analysis of variance, with repeated measurements since differences between the time-points were not distributed normally. A post-hoc analysis was conducted with the Dunnett test which is designed for heterogeneous covariance. All results were considered statistically significant

Table 1. Baseline characteristics of the study population divided according to diastolic dysfunction grade.

Parameter	Diastolic dysfunction			P
	Grade I	Grade II	Grade III	
Number	30	18	22	
Age [years]	48.4 (42–53)	47.61 (39–56)	47.96 (36–61)	0.99
Sex (male/female)	27/3	18/0	18/4	0.16
BMI [kg/m^2]	28.166 (24.5–31.2)	25.3 (21–30)	27.6 (22.3–30.9)	0.16
NYHA class (I–IV)	2.37 ± 0.76	2.57 ± 0.73	2.77 ± 0.61	0.08
LVESD/BSA [mm/m^2]	27.6 (24.4–30.5)***	34.10 (26–39)	31.43 (29.3–35.5)	**0.01**
LVEDD/BSA [mm/m^2]	33.9 (29.5–36)	39.7 (33–43.5)	35.99 (32.2–40.5)	0.06
E-wave [m/s]	0.6 (0.48–0.7)***	0.79 (0.62–0.9)	0.94 (0.77–1.04)*	**0.00**
A-wave [m/s]	0.7 (0.6–0.76)***	0.44 (0.34–0.59)	0.34 (0.25–0.4)*	**0.00**
E/A ratio	0.86*	1.43	2.9**	**0.00**
LVEF [%]	26.4 (20–33)	23.39 (17–30)	22.46 (17–25)	0.14
ECG rhythm sinus/AFL/ /cardiac stimulator	26/4/0	11/5/2	19/2/1	0.06
QRS complex [ms]	103.67(80–120)	115.56(80–140)	22.46 (17–25)	0.14
Hemoglobin [g/dL]	15.10 (14.6–16.0)***	13.76 (12.6–15.2)	14.1 (13.2–15)	**0.004**
Creatinine [μmol/L]	83.43 (68–96)	92.11 (72–112)	114.41 (13.2–15)	0.07
eGFR [mL/min]	94.07 (81–107)	82.19 (65.5–102)	76.3 (57–104)	**0.04**
NT-proBNP [pg/mL]	1917 (296–1898)***	5627.8 (1736–5060)	6802 (1211–4924)*	**0.00**
Beta-blocker	29 (96.7%)	18 (100%)	22 (100%)	0.51
ACEI/ARB	28 (93.3%)/1 (6.7%)	16 (88.9%)/1 (1.1%)	22 (100%)/0 (0%)	0.31/0.57
MRA	28 (93.3%)	18 (100%)	20 (90.9%)	0.45
Furosemidum	9 (30%)***	15 (83.3%)	17 (77.3%)*	**0.00**
Vitamin K antagonist	1 (6.7%)	0 (0%)	1 (4.5%)	0.68
NOAC	3 (10%)	3 (16.7%)	1 (4.5)	0.45
ICD/CRT-D	7 (23.3%)	10 (55.6%)	9 (40.9%)	0.13

*p-values for comparison between grades I, II, and III diastolic dysfunction (DD): $p < 0.05$ (grade I DD vs. grade III DD); **p-values for comparison between grades I, II, and III diastolic dysfunction (DD): $p < 0.05$ (grade II DD vs. grade III DD); ***p-values for comparison between grade I, II, and III diastolic dysfunction (DD): $p < 0.05$ (grade I DD vs. grade II DD); ACEI — angiotensin converting enzyme inhibitor; AFL — atrial flutter; ARB — angiotensin receptor type 1 blocker; A-wave — late mitral inflow velocity; BMI — body mass index; CRT-D — cardiac resynchronization therapy with cardioverter-defibrillator; E/A — ratio of early mitral inflow E-wave and late mitral inflow A-wave velocity; ECG — electrocardiogram; eGFR — estimated glomerular filtration rate; E-wave — early mitral inflow velocity, ICD— implantable cardioverter-defibrillator; LVEDD/BSA — indexed to body surface area left ventricular end-diastolic diameter; LVEF — left ventricular ejection fraction; LVESD/BSA — indexed to body surface area left ventricular end-systolic diameter; MRA — mineralocorticoid receptor antagonist; NOAC — non-vitamin K antagonist oral anticoagulants; NT-proBNP — amino-terminal pro B-type natriuretic peptide; NYHA — New York Heart Association class

when p value was < 0.05. Statistical analysis was conducted with Statistica version 13.1 software.

Results

Baseline characteristics

Table 1 shows the baseline characteristics of patients in the three groups of patients stratified according to DD grade. Patients with grade II DD had significantly larger left ventricular end-systolic diameter as assessed by body surface area (34.1 mm/m^2), while there were no differences in patients with grade I and III DD. E-wave and A-wave had significantly higher values in grade II and grade III DD in comparison to grade I DD while E/A ratio was highest in patients with grade III DD [2, 9]. There were no differences in age, gender, NYHA classification or body mass index between the groups. Patients with grade I DD had the highest concentration of hemoglobin (15.1 g/ /dL), while patients with grade II and grade III DD had significantly higher level of amino-terminal pro B-type natriuretic peptide (5627.8 pg/mL and 6802 pg/mL, respectively). No differences were observed in the frequency of sinus rhythm, atrial fibrillation or duration of QRS between the groups. All patients were receiving optimal HF pharmacotherapy but patients with grade III DD

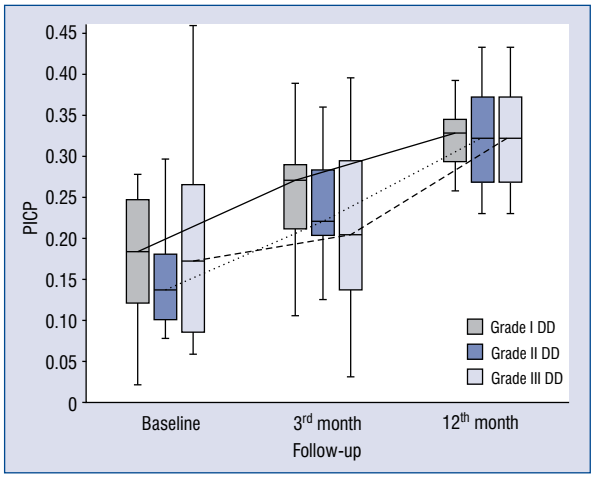


Figure 1. Comparison of baseline, 3- and 12-month serum levels of procollagen type I carboxy-terminal peptide (PICP) in patients with different diastolic dysfunction (DD) grades.

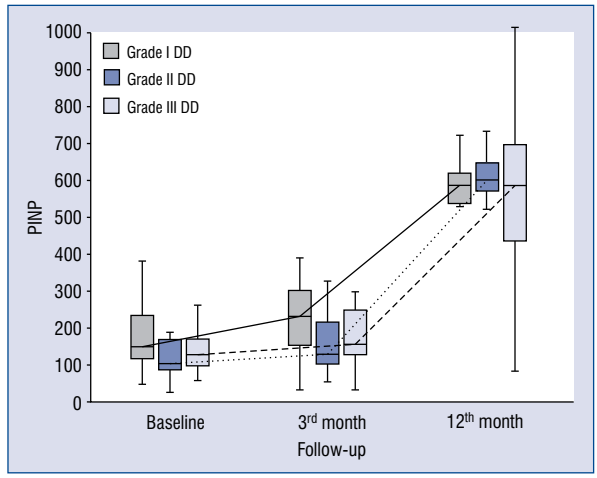


Figure 2. Comparison of baseline, 3- and 12-month serum levels of procollagen type I amino-terminal peptide (PINP) in patients with different diastolic dysfunction (DD) grades.

required a loop diuretic more often. There were also no differences in implantable cardioverter-defibrillator or cardiac resynchronization therapy with cardioverter-defibrillator implantations between groups.

Kinetics of the serum markers of fibrosis in patients with grade I diastolic dysfunction

Baseline, 3 and 12-month levels of serum markers of collagen synthesis, TGF1-β, CTGF and galectin-3 in patients with DD grade I are presented in the Figure 1. Blood levels of markers of collagen type I synthesis (PICP and PINP) consistently increased from baseline to the 3- and 12-month observation points. In contrast, dynamics of markers of collagen type III synthesis behaved in the opposite manner. Changes in markers of collagen type III synthesis (PIIICP) were not significant, whereas PIIINP levels decreased during the observation period. TGF1-β values were unchanged from baseline to the 3-month time-point but decreased significantly between the 3- and 12-month time-point. Finally, levels of CTGF and galectin-3 did not change over the observational period.

Kinetics of the serum markers of fibrosis in patients with grade II diastolic dysfunction

Baseline, 3- and 12-month levels of serum markers of collagen synthesis, TGF1-β, CTGF and galectin-3 in patients with DD grade I are presented in Figure 2. Blood levels of collagen type I synthesis marker — PICP consistently increased from baseline to the 3- and 12-month time-points, whereas PINP increased from the 3- to 12-month time-point. Markers of collagen type III synthesis, PIIICP and PIIINP, behaved differently. PIIICP increased significantly over the period of observation but PIIINP decreased over a longer observation period between 3 to 12 months. TGF1-β blood levels did not differ between baseline and 3-month follow-up, however it decreased between 3- and 12-month time-points. Levels of CTGF and galectin-3 remained unchanged over 12-months of observation.

Kinetics of the serum markers of fibrosis in patients with grade III diastolic dysfunction

Baseline, 3- and 12-month levels of serum markers of collagen synthesis, TGF1-β, CTGF and galectin-3 in patients with DD grade I are presented in the Figure 3. Levels of markers of collagen type I synthesis PICP and PINP remained unchanged from baseline to 3-month time-point but both increased between 3- and 12-month time-points. Changes in PIIICP were not significant, whereas values of PIIINP significantly decreased over a longer period of observation from baseline to 12 months and from 3 to 12 months. TGF1-β blood levels remained unchanged over 12 months of observation, whereas CTGF levels decreased between baseline and 12 months. Finally, levels of galectin-3 did not differ between baseline, 3- and 12-month time-points.

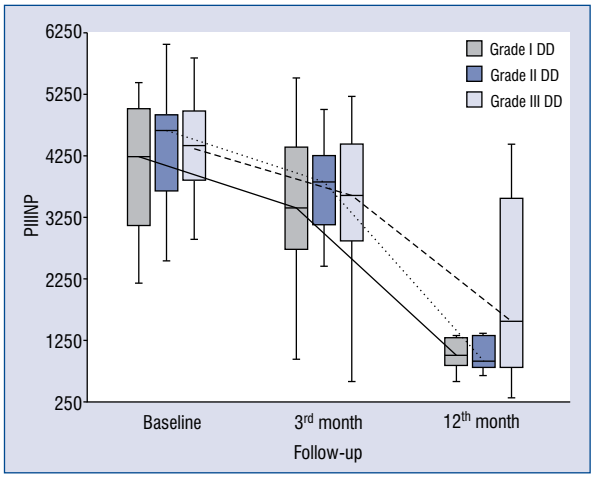


Figure 3. Comparison of baseline, 3- and 12-month serum levels of procollagen type III amino-terminal peptide (PIIINP) in patients with different diastolic dysfunction (DD) grades.

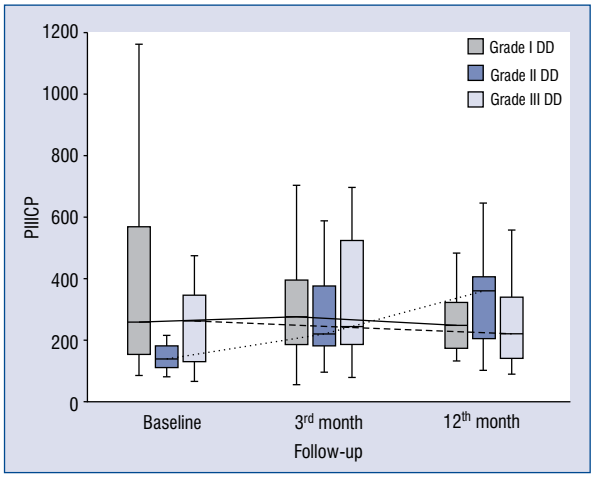


Figure 4. Comparison of baseline, 3- and 12-month serum levels of procollagen type III carboxy-terminal peptide (PIIICP) in patients with different diastolic dysfunction (DD) grades.

Comparison of kinetics of serum markers of fibrosis between patients with various grades of diastolic dysfunction

In general, the kinetics of markers of collagen type I and III synthesis did not differ between patients with different DD grades, e.g. markers of collagen type I synthesis (PICP, PINP) increased (Figs. 1, 2), whereas markers of collagen type III synthesis (PIIINP) decreased over the 12-month period of observation regardless of DD grade (Fig. 3). However, it should be noted that the baseline values of PIIICP were higher and similar in grade I and grade III DD in comparison to patients with grade II DD (Fig. 4). Conversely, levels of PINP at the 3 months were significantly higher in grade I compared to grade II and III DD. Blood levels of TGF1-β and CTGF did not differ at baseline, at 3- and 12-months of observation, regardless of DD grade. The kinetics of TGF1-β were initially unchanged (during the first 3 months) of observation and then decreased (between 3 to 12 months) in patients with grade I and II DD, but the kinetics did not change during the observation period in patients with grade III DD (Fig. 5). The kinetics of CTGF were similar in patients with different DD grades and, while levels had a tendency to decrease, significant changes could only be observed in patients with grade III DD (Fig. 6). Finally, galectin-3 levels did not differ between patients with different DD grades either at baseline nor at 3- and 12-month observational points (Fig. 7).

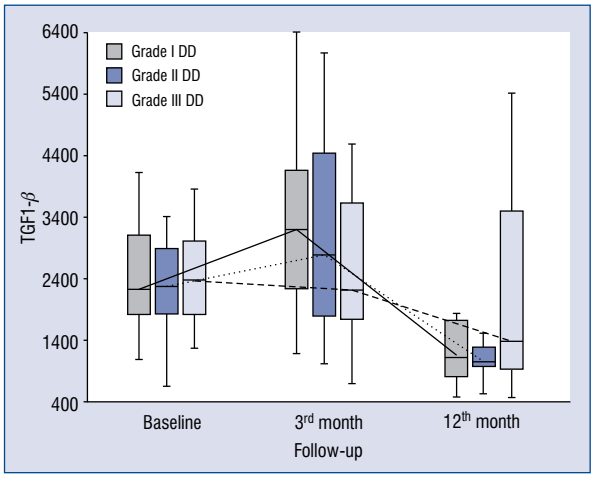


Figure 5. Comparison of baseline, 3- and 12-month serum levels of transforming growth factor beta-1 (TGF1-β) in patients with different diastolic dysfunction (DD) grades.

Correlations between serum markers of fibrosis and diastolic function parameters

A weak negative correlation was observed between baseline serum levels of PINP and baseline left atrial volume index (LAVI) ($r = -0.3$; $p < 0.05$) and between baseline PINP and LAVI at 3 months ($r = -0.29$; $p < 0.05$). At 12 months, there was a moderate correlation between PINP and E/A ratio ($r = 0.46$; $p < 0.05$). As markers of collagen type III synthesis, PIIINP nega-

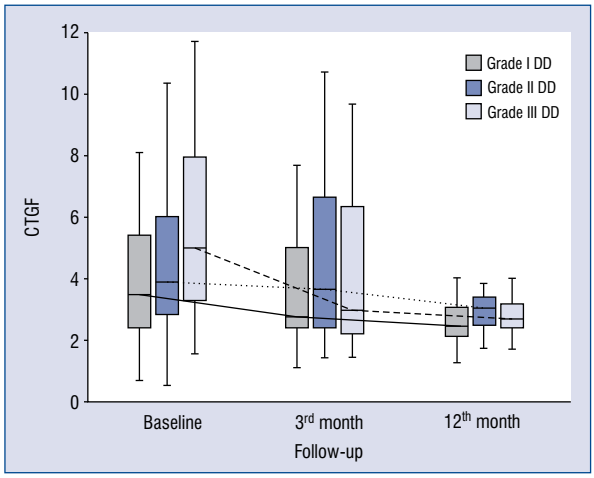


Figure 6. Comparison of baseline, 3- and 12-month serum levels of connective tissue growth factor (CTGF) in patients with different diastolic dysfunction (DD) grades.

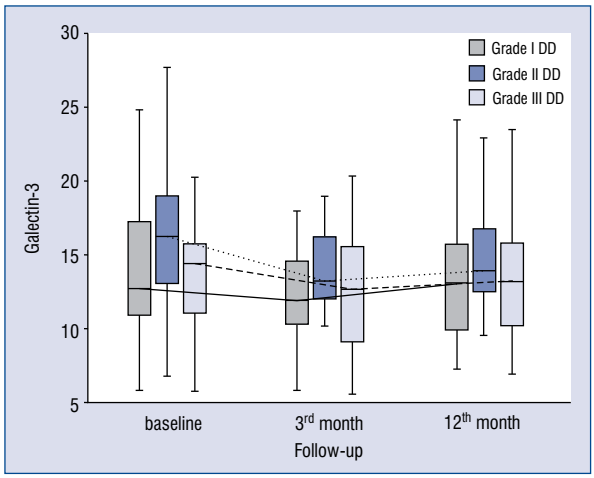


Figure 7. Comparison of baseline, 3- and 12-month serum levels of galectin-3 in patients with different diastolic dysfunction (DD) grades.

tively correlated with E/E' ratio and E' ($r = –0.4$ and $r = –0.34$; $p < 0.05$) at 3 months and with E' at 12 months ($r = –0.31$; $p < 0.05$), whereas PIIICP at 12 months correlated with E/E' and LAVI ($r = 0.34$; $r = 0.36$; $p < 0.05$, respectively). TGF1-β at baseline correlated with LAVI ($r = –0.33$; $p < 0.05$). CTGF at 3 months correlated with E/E' at 12 months ($r = 0.3$; $p < 0.05$) and CTGF at 12 months correlated with E/E' at 12 months ($r = 0.31$; $p < 0.05$). Galectin-3 at baseline correlated with tricuspid regurgitation velocity and E-wave ($r = 0.3$ and $r = 0.26$; $p < 0.05$, respectively). Galectin-3 at 3 months correlated with 3-month E' velocity ($r = 0.42$; $p < 0.05$) and between 3-month and baseline E/A ratio and tricuspid regurgitation velocity ($r = 0.28$; $p < 0.05$ and $r = 0.27$; $p < 0.05$, respectively).

Discussion

Kinetics of collagen synthesis markers in patients with various grades of diastolic dysfunction

The process of ECM fibrosis in DCM has been extensively studied. However, the kinetics of collagen synthesis markers and its relationship to DD are poorly understood. While several papers discussed selected markers of fibrosis and the development of DD, few refer to DD in DCM. The present study is the first to report that long term (12^{th}-month period) synthesis of collagen type I is enhanced, whereas synthesis of collagen type III is diminished in DCM patients, regardless of diastolic dysfunction degree. Intuitively, it may be thought that patients with more advanced DD (restrictive filling) have higher collagen synthesis but in fact collagen type I synthesis is uniformly increased in all DD groups. Collagens types I and III have different physical properties, e.g. collagen type I has a higher tensile strength and collagen type III is more elastic and complaint [10, 11]. Thus, an increase in collagen type I may contribute to further worsening of DD. Consequently, collagen I and III ratios remained the same in patients with various DD grades. Of note, among markers of collagen type III synthesis (PIIICP and PIIINP), only PIIINP levels significantly decreased during the whole period, while PIIICP behaved differently, with a tendency to decrease and only increase in grade II DD. This observation cannot be easily explained, but it should be emphasized that only PIIINP is a truly proven marker of collagen synthesis, while the role of PIIICP is less clear [12].

Few studies have demonstrated the relationship between markers of collagen synthesis and DD under differing cardiac conditions. The most frequently described marker, which exhibited an association with DD was PICP. Demir et al. [13] has shown that hypertensive patients with DD had a significantly higher serum level of PICP compared to those without DD. Another group reported that the serum level of PICP was related to DD in patients with early stage type 2 diabetes mellitus [14]. Roongsritong and colleagues also described the relationship between PICP and DD in elderly patients [15]. It should be emphasized that those studies reported associations between

particular markers of fibrosis and DD but no relationships were found between those markers and degree of DD. Only a few researchers have discussed this issue. Roongsritong et al. [16] has shown that PICP was related to the severity of DD in patients with HFrEF. They observed that the PICP level was significantly higher among patients with a more severe degree of DD compared to those with less severe DD. In the present study, no correlation was observed between PICP and DD grade. However, it should be noted that the authors used a currently outdated approach to DD classification and consequently compared only two groups of patients with non-severe (mild to moderate) and severe DD [16]. Therefore, from a methodological point of view it is impossible to compare the results of the present study to those observed by Roongsritong et al. [16]. The current observations showed that PINP correlated with the E/A ratio, a crucial parameter in the DD algorithm. This may suggest that patients with advanced DD and a higher E/A ratio had a higher level of PINP. Further, Rossi et al. [17] compared serum levels of PIIINP between three groups with DD with non-restrictive, reversible restrictive and irreversible restrictive filling patterns. The authors observed that PIIINP was significantly higher in patients with a restrictive mitral inflow pattern [17]. However, the classification of patients according to mitral inflow pattern, described in the cited study, varies from the current grading of DD. In addition to the fact that this classification of DD is no longer used, the authors compared unmatched patient groups, with 9 patients having restrictive versus 88 patients having a non-restrictive filling pattern. In the present study, a negative correlation between PIIINP and E/E' ratio was demonstrated. This may suggest that patients with grade I DD and a lower E/E' ratio had higher serum levels of PIIINP. This observation seems accurate, since a heart muscle rich in collagen III is characterized by greater flexibility and elasticity and therefore has an improved diastolic function.

Kinetics of TGF, CTGF and galectin-3 in patients with various diastolic dysfunction grades

Levels of TGF1-β were similar regardless of the DD grade and the kinetics of TGF1-β did not differ between the subgroups. Numerous studies have confirmed that TGF and its downstream mediator — CTGF are crucial molecules stimulating cardiac fibrosis [18]. Thus, one may speculate that TGF1-β would be highest in patients with grade III DD. However, observed herein was that TGF levels were similar in all three DD groups. One possible explanation is that serum levels of TGF are not equivalent to the expression of TGF in the myocardium [19]. Additionally, not all of TGF1-β but only its active forms are involved in biological processes, and, as confirmed earlier, levels of TGF1-β and its active metabolites may not be correlated [20]. Conversely, the pro-fibrotic mechanisms of TGF1-β includes not only differentiation of cardiac fibroblasts to myofibroblasts, which have higher activity for collagen production, but also a differentiation throughout its effector cytokine — CTGF [21, 22]. In the present study, serum levels of CTGF did not differ significantly between the subgroups but a positive correlation was observed between CTGF and E/E' ratio. This may suggest that patients with more advanced DD (higher E/E' ratio) had higher levels of CTGF. Wu et al. [23] reached similar conclusions and demonstrated that serum levels of CTGF were the highest among patients with severe DD. With respect to the 12-month kinetics of CTGF levels were found to decrease homogenously in all patients regardless of DD severity but significant changes were only observed in grade III of DD.

Galectin-3 plays an important role in the pathogenesis of left ventricular remodeling [24]. Only a few studies have examined the relationship between galectin-3 and DD in HF. Wu et al. [25] reported correlations between plasma galectin-3 and E/E' in advanced HFpEF. Gurel et al. [26] demonstrated that galectin-3 was an independent predictor of DD in patients with end-stage renal failure undergoing dialyses. Another study compared serum levels of galectin-3 in patients with HFrEF and HFpEF and demonstrated that it was higher in patients with HFrEF and correlated with E/E' ratio [27]. Observed herein, was that galectin-3 levels were similar regardless of DD grade and remained stable over 12 months. However, a positive correlation between galectin-3 and E'-wave which reflects the rate of myocardial relaxation [28] was also observed. Nevertheless, based on the analysis, serum levels of galectin-3 seemed not to be a good marker of DD severity in DCM. One possible explanation could be that circulating galectin-3 does not correlate with its myocardial expression as has been recently reported by Besler et al. [29].

In summary, 12-month kinetics of fibrosis controlling molecules (TGF, CTGF, and galectin-3) were similar in three DD groups. Furthermore, the pattern of TGF and CTGF was the same and decreasing, and as such is probably not a good

target for eventual anti-TGF or anti-CTGF agents, provided that blood expression of those molecules have any relations with their myocardial counterparts or fibrosis progression, which at present is uncertain. What is more, it should be reiterated that the fact that none of the seven markers of fibrosis under study turned out to have a different pattern in all three DD groups and thus, none can serve as a marker of DD degree.

Limitations of the study

There are several potential limitations to this study. The division of DCM patients was based on the current DD classification, resulting in relatively small subgroups, which may have impacted statistical relevance. As reported in previous studies, serum levels of ECM fibrosis markers might not reflect their myocardial expression and thereby may only be weakly correlated with myocardial function.

Conclusions

Twelve-month kinetics of serum markers of fibrosis in DCM patients with various grades of DD is characterized with similar patterns. Regardless of the DD grade, markers of collagen type I synthesis increased and markers of collagen type III decreased (mainly PIIINP). Levels of TGF and CTGF had a tendency to decrease over the observation period, whereas kinetics of galectin-3 was stable. This observation may indicate that the presence of myocardial fibrosis is just one component, among others, that affects DD.

Acknowledgements

This work was funded through the National Science Center, Poland (Grant 2013/09/D/NZ5/00252) and the Department of Scientific Research and Structural Funds of Medical College, Jagiellonian University (Grant K/ZDS/004596).

Conflict of interest: None declared

References

1. Ponikowski P, Voorse AA, Anker SD, et al. 2016 Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur J Heart Fail. 2016; 18: 891–975.
2. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016; 29(4): 277–314, doi: 10.1016/j.echo.2016.01.011, indexed in Pubmed: 27037982.
3. Rubiś P, Totoń-Żurańska J, Wiśniowska-Śmiałek S, et al. Right ventricular morphology and function is not related with microRNAs and fibrosis markers in dilated cardiomyopathy. Cardiol J. 2017 [Epub ahead of print], doi: 10.5603/CJ.a2017.0099, indexed in Pubmed: 28840590.
4. Querejeta R, López B, González A, et al. Increased collagen type I synthesis in patients with heart failure of hypertensive origin: relation to myocardial fibrosis. Circulation. 2004; 110(10): 1263–1268, doi: 10.1161/01.CIR.0000140973.60992.9A, indexed in Pubmed: 15313958.
5. Klappacher G, Franzen P, Haab D, et al. Measuring extracellular matrix turnover in the serum of patients with idiopathic or ischemic dilated cardiomyopathy and impact on diagnosis and prognosis. Am J Cardiol. 1995; 75(14): 913–918, doi: 10.1016/s0002-9149(99)80686-9.
6. Dobaczewski M, Chen W, Frangogiannis NG. Transforming growth factor (TGF)-β signaling in cardiac remodeling. J Mol Cell Cardiol. 2011; 51(4): 600–606, doi: 10.1016/j.yjmcc.2010.10.033, indexed in Pubmed: 21059352.
7. Rubiś P, Wiśniowska-Smiałek S, Wypasek E, et al. 12-month patterns of serum markers of collagen synthesis, transforming growth factor and connective tissue growth factor are similar in new-onset and chronic dilated cardiomyopathy in patients both with and without cardiac fibrosis. Cytokine. 2017; 96: 217–227, doi: 10.1016/j.cyto.2017.04.021, indexed in Pubmed: 28460256.
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. Rubiś P, Wiśniowska-Śmialek S, Wypasek E, et al. Fibrosis of extracellular matrix is related to the duration of the disease but is unrelated to the dynamics of collagen metabolism in dilated cardiomyopathy. Inflamm Res. 2016; 65(12): 941–949, doi: 10.1007/s00011-016-0977-3, indexed in Pubmed: 27516211.
10. Marijianowski MM, Teeling P, Mann J, et al. Dilated cardiomyopathy is associated with an increase in the type I/type III collagen ratio: a quantitative assessment. J Am Coll Cardiol. 1995; 25(6): 1263–1272, doi: 10.1016/0735-1097(94)00557-7, indexed in Pubmed: 7722119.
11. Pauschinger M, Knopf D, Petschauer S, et al. Dilated cardiomyopathy is associated with significant changes in collagen type I/III ratio. Circulation. 1999; 99(21): 2750–2756, indexed in Pubmed: 10351968.
12. Izawa H, Murohara T, Nagata K, et al. Mineralocorticoid receptor antagonism ameliorates left ventricular diastolic dysfunction and myocardial fibrosis in mildly symptomatic patients with idiopathic dilated cardiomyopathy: a pilot study. Circulation. 2005; 112(19): 2940–2945, doi:10.1161/CIRCULATIONAHA.105.571653, indexed in Pubmed: 16275882.
13. Demir M, Acartürk E, Inal T, et al. Procollagen type I carboxy-terminal peptide shows left ventricular hypertrophy and diastolic dysfunction in hypertensive patients. Cardiovasc Pathol. 2007; 16(2): 69–74, doi: 10.1016/j.carpath.2006.09.010, indexed in Pubmed: 17317538.
14. Ihm SH, Youn HJ, Shin DI, et al. Serum carboxy-terminal propeptide of type I procollagen (PIP) is a marker of diastolic dysfunction in patients with early type 2 diabetes mellitus. Int J Cardiol. 2007; 122(3): e36–e38, doi: 10.1016/j.ijcard.2007.07.057, indexed in Pubmed: 17920710.

15. Roongsritong C, Bradley J, Sutthiwan P, et al. Elevated carboxy-terminal peptide of procollagen type I in elderly patients with diastolic dysfunction. Am J Med Sci. 2006; 331(3): 131–133, indexed in Pubmed: 16538073.
16. Roongsritong C, Sadhu A, Pierce M, et al. Plasma carboxy-terminal peptide of procollagen type I is an independent predictor of diastolic function in patients with advanced systolic heart failure. Congest Heart Fail. 2008; 14(6): 302–306, doi: 10.1111/j.1751--7133.2008.00014.x, indexed in Pubmed:19076852.
17. Rossi A, Cicoira M, Golia G, et al. Amino-terminal propeptide of type III procollagen is associated with restrictive mitral filling pattern in patients with dilated cardiomyopathy: a possible link between diastolic dysfunction and prognosis. Heart. 2004; 90(6): 650–654, indexed in Pubmed: 15145870.
18. Glazer NL, Macy EM, Lumley T, et al. Transforming growth factor beta-1 and incidence of heart failure in older adults: the Cardiovascular Health Study. Cytokine. 2012; 60(2): 341–345, doi: 10.1016/j.cyto.2012.07.013, indexed in Pubmed: 22878343.
19. Hein S, Arnon E, Kostin S, et al. Progression from compensated hypertrophy to failure in the pressure-overloaded human heart: structural deterioration and compensatory mechanisms. Circulation. 2003; 107(7): 984–991, indexed in Pubmed: 12600911.
20. Khan SA, Joyce J, Tsuda T. Quantification of active and total transforming growth factor-β levels in serum and solid organ tissues by bioassay. BMC Res Notes. 2012; 5: 636, doi: 10.1186/1756-0500-5-636, indexed in Pubmed: 23151377.
21. Petrov VV, Fagard RH, Lijnen PJ. Stimulation of collagen production by transforming growth factor-beta1 during differentiation of cardiac fibroblasts to myofibroblasts. Hypertension. 2002; 39(2): 258–263, indexed in Pubmed: 11847194.
22. Accornero F, van Berlo JH, Correll RN, et al. Genetic analysis of connective tissue growth factor as an effector of transforming growth factor β signaling and cardiac remodeling. Mol Cell Biol. 2015; 35(12): 2154–2164, doi: 10.1128/MCB.00199-15, indexed in Pubmed: 25870108.
23. Wu CK, Wang YC, Lee JK, et al. Connective tissue growth factor and cardiac diastolic dysfunction: human data from the Taiwan diastolic heart failure registry and molecular basis by cellular and animal models. Eur J Heart Fail. 2014; 16(2): 163–172, doi: 10.1002/ejhf.33, indexed in Pubmed:24464932.
24. de Boer RA, Yu L, van Veldhuisen DJ. Galectin-3 in cardiac remodeling and heart failure. Curr Heart Fail Rep. 2010; 7(1): 1–8, doi: 10.1007/s11897-010-0004-x, indexed in Pubmed: 20425490.
25. Wu CK, Su MY, Lee JK, et al. Galectin-3 level and the severity of cardiac diastolic dysfunction using cellular and animal models and clinical indices. Sci Rep. 2015; 5: 17007, doi: 10.1038/srep17007, indexed in Pubmed: 26582585.
26. Gurel OM, Yilmaz H, Celik TH, et al. Galectin-3 as a new biomarker of diastolic dysfunction in hemodialysis patients. Herz. 2015; 40(5): 788––794, doi:10.1007/s00059-015-4303-6, indexed in Pubmed: 25990624.
27. Michalski B, Trzciński P, Kupczyńska K, et al. The differences in the relationship between diastolic dysfunction, selected biomarkers and collagen turn-over in heart failure patients with preserved and reduced ejection fraction. Cardiol J. 2017; 24(1): 35–42, doi: 10.5603/CJ.a2016.0098, indexed in Pubmed: 27748500.
28. Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. Circulation. 2000; 102(15): 1788–1794, indexed in Pubmed:11023933.
29. Besler C, Lang D, Urban D, et al. Plasma and cardiac galectin-3 in patients with heart failure reflects both inflammation and fibrosis: implications for its use as a biomarker. Circ Heart Fail. 2017; 10(3), doi: 10.1161/CIRCHEARTFAILURE.116.003804, indexed in Pubmed: 28288987.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2020, Vol. 27, No. 6, 735–741
DOI: 10.5603/CJ.a2018.0115

ISSN 1897–5593
eISSN 1898–018X

Comparison of temperature measurements in esophagus and urinary bladder in comatose patients after cardiac arrest undergoing mild therapeutic hypothermia

Julia M. Umińska[1], Katarzyna Buszko[1], Jakub Ratajczak[1], Piotr Łach[1], Krzysztof Pstrągowski[1], Anita Dąbrowska[1], Piotr Adamski[1], Grzegorz Skonieczny[2], Jacek Manitius[1], Jacek Kubica[1]

[1]Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland
[2]Ludwik Rydygier Voivodship Polyclinical Hospital, Torun, Poland

Abstract

Background: *Mild therapeutic hypothermia (MTH) is a recommended method of treatment for comatose out-of-hospital cardiac arrest (OHCA) survivors. However, the proper site of temperature measurement in MTH is still not defined. The aim of this study was to compare temperature measurements in the esophagus and urinary bladder in comatose post-OHCA patients treated with MTH.*

Methods: *This temperature comparison protocol was a part of a prospective, observational, multicenter cohort study. The study population included 36 unconscious patients after resuscitation for OHCA. The patient's core temperature was independently measured every hour during MTH in the urinary bladder and in the esophagus.*

Results: *The mean temperature was lower in the esophagus (differences during induction phase: 1.04 ± 0.92°C, $p < 0.0001$; stabilization phase: 0.54 ± 0.39°C, $p < 0.0001$; rewarming phase: 0.40 ± 0.47°C, $p < 0.0001$). Nevertheless, a strong correlation between both sites was found ($R^2 = 0.83$, $p < 0.001$). The decrease in temperature observed in the esophagus during the induction phase was faster when compared with the urinary bladder (1.09 ± 0.71°C/h vs. 0.83 ± 0.41°C/h; $p = 0.002$). As a consequence, time to reach temperature < 34.0°C was longer when temperature was measured in the urinary bladder (the difference between medians of the time 1.0 [0–1.5] h, $p < 0.001$).*

Conclusions: *Urinary bladder temperature measurements may lag behind temperature changes measured in the esophagus. Monitoring temperature simultaneously in the esophagus and in the urinary bladder is an accessible and reliable combination, although esophageal measurements seem to better reflect the dynamics of temperature changes, thus it seems to be more appropriate for MTH control. ClinicalTrials.gov Identifier: NCT02611934* (Cardiol J 2020; 27, 6: 735–741)

Key words: cardiac arrest, mild therapeutic hypothermia, temperature measurement

Introduction

Several relatively small randomized studies involving unconscious cardiac arrest survivors showed a significant improvement in neurologic function and survival rate with mild therapeutic hypothermia (MTH) of a target temperature between 32°C and 34°C [1–3]. A favorable effect of MTH on survival and neurological outcome was confirmed in meta-analysis pooling data from non-randomized studies [4]. However, results of the largest available randomized trial published

Address for correspondence: Julia M. Umińska, MD, Department of Cardiology and Internal Medicine, Collegium Medicum, Nicolaus Copernicus University, ul. M. Skłodowskiej-Curie 9, 85–094 Bydgoszcz, Poland, tel: +48 52 585 4023, fax: +48 52 585 49 4024, e-mail: julia@uminska.net

Received: 9.07.2018 Accepted: 21.07.2018

by Nielsen et al. [5] did not show superiority of MTH at the targeted temperature of 33°C above fever prevention at a targeted temperature of 36°C. Therefore, in the current European Society of Cardiology (ESC) guidelines for both strategies are proposed as equivalent for comatose cardiac arrest survivors [6].

Regardless of the target temperature, an accurate temperature control during MTH is required [7]. Measurement of central circulation temperature or brain tissue temperature is difficult to apply in an emergency setting, therefore surrogate sites such as urinary bladder, rectum, tympanic membrane, or esophagus, are often used [8–11]. However, the current guidelines do not define the proper site of temperature measurement for MTH control. It is recommended that patients undergoing hypothermia body core temperature should be measured at two different sites [12], band yet for feedback-controlled devices with endovascular cooling catheters or surface cooling, only one temperature measurement site for automatic guidance of MTH is required [13]. Esophagus and urinary bladder are currently the most commonly used sites.

Based on the available data from studies with a low number of patients enrolled it was hypothesized that the temperature measured in the urinary bladder is not accurate when compared to the esophageal temperature at the induction phase of MTH. As expected herein, lagging of measurements in urinary bladder is behind the core temperature change measured in esophagus.

The aim of this study was to perform a 24-h, complete (covering three MTH phases: induction, stabilization and warming) comparison of temperature measurements in the esophagus and urinary bladder in comatose patients after cardiac arrest treated with MTH.

Methods

Study design

This temperature comparison protocol was a part of a prospective, observational, multicenter cohort study entitled Mild Therapeutic Hypothermia for Patients with Acute Coronary Syndrome and Cardiac Arrest Treated with Percutaneous Coronary Intervention (the UNICORN trial) [14]. The study was conducted in accordance with the principles contained in the Declaration of Helsinki and Good Clinical Practice guidelines. The study was approved by the Ethics Committee of Nicolaus Copernicus University in Torun, Collegium Medicum in Bydgoszcz (study approval reference number KB 615/2015).

Study population

The study population included 36 unconscious patients after resuscitation for out-of-hospital cardiac arrest (OHCA) with shockable rhythm presenting with acute coronary syndrome (ACS). Initially 42 patients were enrolled in the study, however 6 of them were eventually excluded from analysis due to a lack of complete data. Baseline characteristics of study participants are presented in Table 1.

After admission to the study center and confirmation of initial diagnosis, patients were screened for eligibility to the trial. All enrolled subjects were treated with MTH in addition to standard therapy baccording to the previously described protocol [14]. Inclusion criteria were defined as:

— age ≥ 18 years;
— OHCA survivor;
— sustained return of spontaneous circulation (ROSC) for more than 20 min after resuscitation;
— unconsciousness with a score of ≤ 8 on the Glasgow Coma Scale after ROSC;
— shockable initial rhythm;
— diagnosis or suspicion of ACS.

The exclusion criteria included:

— unwitnessed OHCA;
— obvious or suspected pregnancy;
— known serious infection before OHCA;
— known bleeding diathesis;
— confirmed or suspected internal bleeding;
— confirmed or suspected acute stroke;
— confirmed or suspected cerebral injury;
— known serious neurological dysfunction before OHCA (Cerebral Performance Category ≤ 4);
— known serious disease making 180 days of survival unlikely;
— hemodynamic instability with systolic blood pressure < 65 mmHg despite the treatment;
— time delay from ROSC to MTH induction > 240 min;
— asystole or pulseless electrical activity as the initial rhythm [14].

Treatment and temperature measurement

Mild therapeutic hypothermia was induced and maintained for 24 h at a target temperature of 33°C using Intravascular Temperature Management™, CoolGard 3000® (Zoll Circulation Inc., USA) and a MTH-dedicated catheter (Mon-a-Therm™ Foley Catheter with Temperature Sensor 400TM, Covidi-

Table 1. Baseline characteristics of patients.

Variable	Patients undergoing MTH procedure (n = 36)
Demographic characteristics	
Age [years]	62.3 ± 12.9
Female	6 (16.7%)
Medical history	
Diabetes mellitus	13 (36.1%)
Arterial hypertension	17 (47.2%)
Prior stroke	2 (5.6%)
Prior myocardial infarction	11 (30.5%)
Patient status on admission and in-hospital management	
GCS on hospital admission:	
3–4 points	25 (69.5%)
5–6 points	11 (30.6%)
7–8 points	0 (0.0%)
Shock on hospital admission	22 (61.1%)
LVEF on hospital admission [%]	32.6 ± 8.8
Underlying cause of OHCA:	
STEMI	22 (61.2%)
NSTEMI	6 (16.7%)
Other	8 (22.2%)
Presence of CAD:	
Single-vessel	10 (27.8%)
Multi-vessel	20 (55.6%)
Without significant coronary lesions	6 (16.7%)
Treatment with PCI	30 (83.3%)
Use of IABC	4 (11.1%)
Patient status on discharge	
Survival rate	24 (66.6%)
CPC at discharge:	
1	9 (25%)
2	6 (16.6%)
3	7 (19.4%)
4	2 (5.6%)
5	12 (33.3%)

Data are presented as mean ± standard deviation or number (percentages). CAD — coronary artery disease; CPC — Cerebral Performance Category; GCS — Glasgow Coma Score; IABC — intra-aortic balloon counterpulsation; LVEF — left ventricular ejection fraction; MTH — mild therapeutic hypothermia; NSTEMI — non-ST-segment elevation myocardial infarction; OHCA — out-of-hospital cardiac arrest; PCI — percutaneous coronary intervention; STEMI — ST-segment elevation myocardial infarction

ent Company, Ireland) introduced into the inferior vena cava through a femoral vein. The induction phase was supported by infusion of cold saline (0.9% solution of sodium chloride at the temperature of 4°C) and use of ice packs. The rewarming phase was conducted in an actively controlled manner (0.3°C per hour). The cooling device used urinary bladder temperature as feedback to guide changes in patient temperature.

Each patient's core temperature was independently measured every hour during the MTH procedure (including induction of hypothermia and rewarming phase) in the urinary bladder and in the lower one third of the esophagus using a dedicated monitor (Monitor Philips IntelliVue MP-60, temperature module M1029A, Philips Medical Systems, UK) and catheter (ER 400-9 Level® Esophageal Temperature Probe Thermistor, Smiths Medical ASD Inc., USA). Before every clinical application both probes were calibrated ex-vivo and checked for measurement concordance.

All patients were mechanically ventilated with a concomitant continuous intravenous infusion of propofol and fentanyl for sedation and analgesia, and treated according to current ESC guidelines.

Sample size calculation

Based on a sample size calculation and data published by Lefrant et al. [15] and assuming a two-sided alpha value of 0.05, it was calculated that enrolment of 18 patients would provide a 95% power to detect significant differences between temperatures measured in the urinary bladder and the esophagus. To provide more reliable data, it was decided to double the minimum number of patients to be enrolled (n = 36).

Statistical analysis

Statistical calculations were performed using the Statistica 12.5 package (StatSoft, Tulsa, OK, USA). Due to the absence of normal distribution of data (as assessed by the Shapiro-Wilk test) all analyses were performed using nonparametric tests. The differences between paired medians were compared with the Wilcoxon signed rank test. The differences between medians together with lower and upper quartiles were quoted. In all cases, two-sided p-values < 0.05 were considered significant.

Results

The temperature was measured in all patients every hour during three phases of MTH (induction, stabilization and rewarming). In total 3286 temperature measurements were analyzed (1643 for each site — esophagus and urinary bladder).

The mean temperature measured in the esophagus was lower when compared with temperature in the urinary bladder during all three phases of MTH procedure (Figs. 1, 2). The greatest difference in temperature assessed at these sites was observed during the induction phase (difference of 1.04 ± 0.92°C, $p < 0.0001$). Temperature differences between measurement sites at stabilization and rewarming phases were smaller than during induction, however these differences were also statistically significant (stabilization: difference of 0.54 ± 0.39°C, $p < 0.0001$; rewarming: difference of 0.40 ± 0.47°C, $p < 0.0001$). Nevertheless, a strong correlation between temperature measurement sites was found ($R^2 = 0.8348$, $p < 0.001$).

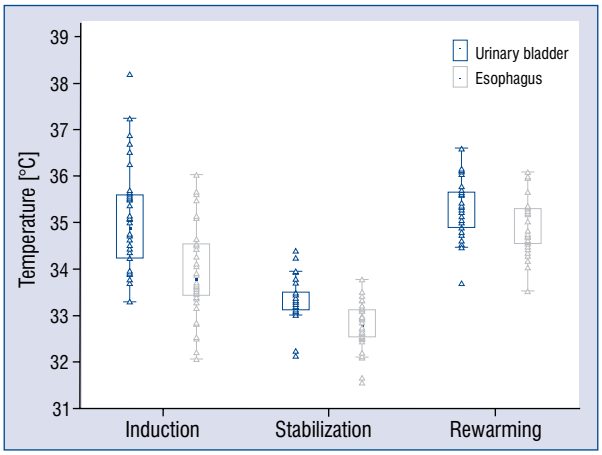


Figure 1. Mean temperatures at the induction, stabilization and rewarming phase of mild therapeutic hypothermia.

The temperature measured in the esophagus decreased faster than in the urinary bladder during the induction phase (1.09 ± 0.71°C/h vs. 0.83 ± ± 0.41°C/h; $p = 0.002$). As a consequence, time to reach hypothermia (< 34.0°C) was longer when temperature was measured in the urinary bladder than in the esophagus. The difference between medians of time to the target temperature at each site was 1.0 (0.5–1.5) hour with $p < 0.001$.

During the second phase of MTH, well managed temperature stabilization was reached. The vast majority of measurements, regardless of measurement site, remained within target limits (32–34°C) (Figs. 1, 2).

Temporary velocities of temperature changes were greatest during the induction phase, smaller in the rewarming phase, while in the stabilization phase they remained close to zero.

The Bland-Altman plot of temperatures measured in the esophagus vs. temperatures measured in the urinary bladder confirmed substantial differences between both methods (Fig. 3).

Discussion

Although temperature of blood perfusing the hypothalamus is a reference of core body temperature, pulmonary artery temperature is considered the gold standard in critical care, because it has been shown to be closest to the temperature in the high internal jugular vein and core body temperature [16]. Nevertheless, pulmonary artery catheterization is not routinely performed in intensive care patients. When evaluating possible surrogates for pulmonary artery temperature, it

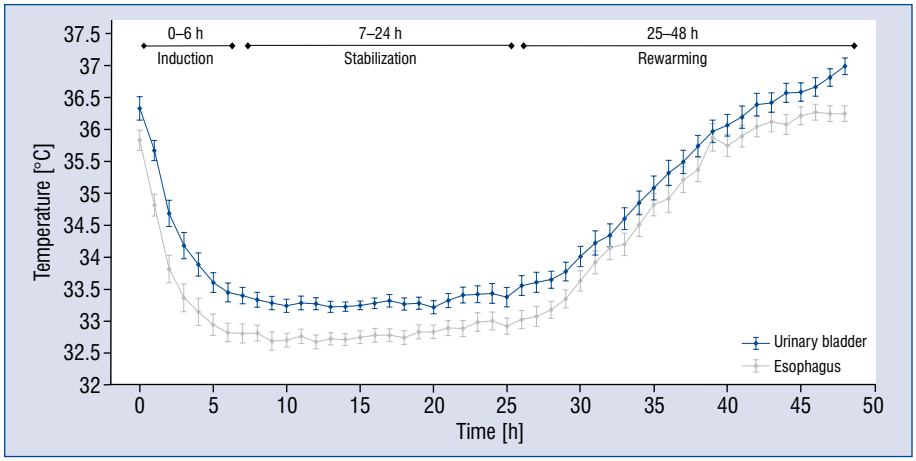


Figure 2. Temperatures measured in the esophagus and urinary bladder in patients undergoing mild therapeutic hypothermia.

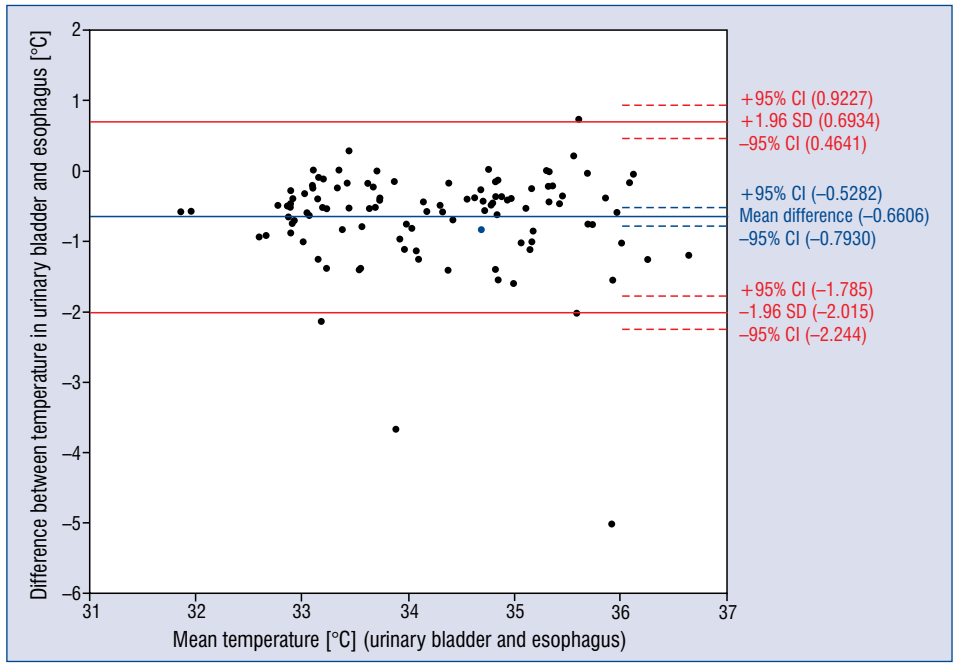


Figure 3. Bland-Altman Plot analysis of temperature difference as measured in the esophagus and urinary bladder; CI — confidence interval; SD — standard deviation.

was generally agreed that it would be desirable to have an accurate, easy-to-use monitoring. Yet, from a literature review it was evident that there is still much conflicting data regarding the best surrogate for measuring core temperature [11, 12, 16–18].

The main findings of this study were significant differences in temperature measurements performed in the esophagus and urinary bladder during MTH procedure. The temperature in the esophagus was lower during hypothermia with the greatest differences observed during the induction phase. As a result, time to reach the target temperature was approximately 1 h longer when the temperature was assessed in the urinary bladder compared with the esophagus.

Very few, low subject number and fragmentary studies comparing different methods of temperature monitoring during MTH are available [13, 17, 19, 20]. Some reports suggest that urinary bladder site does not reflect real-time temperature changes when hypothermia is induced, and temperature changes at this location lag behind body core temperature changes [17, 19]. This observation however, was not confirmed in other studies [15, 20].

Maintenance of the core temperature within 32–34°C is one of the most important issues during MTH. Lefrant et al. [15] showed that mean differences in blood temperature in the pulmonary artery vs. esophageal and urinary bladder temperatures were 0.11 ± 0.30°C and –0.21 ± 0.20°C, respectively, in patients with temperatures which ranged from 33.7°C to 40.2°C. According to this study, urinary bladder measurement site is preferable because its accuracy reaches ± 0.4°C in the most critically ill patients, while the esophageal temperature could be an alternative when urinary bladder temperature cannot be used as an esophageal probe can easily be inserted in intubated and sedated patients. However, according to Shin et al. [13] the accuracy of urinary bladder temperature measurement during the induction phase was lower than at maintenance and rewarming phases. Erickson and Kirklin [18] found that when patients were normothermic, bladder temperature was slightly higher than pulmonary artery temperature, but this was reversed when patients became hypothermic.

Data originating from another study suggested that during rapid temperature change in patients undergoing cardiopulmonary bypass in deep hypothermia, nasopharyngeal, esophageal, and pulmonary nartery temperatures corresponded with brain temperature with smaller mean differences than temperatures measured at the tympanic membrane, urinary bladder, rectum, axilla, and sole of the foot [8]. Nevertheless, the differences reported for deep hypothermia may not reflect the situation present in MTH.

Markota et al. [19] compared temperature changes measured in the esophagus and urinary

bladder in 8 survivors of cardiac arrest at the induction phase of MTH with cold saline infusion. Target temperature was achieved significantly earlier in the esophagus as compared with the urinary bladder (33 ± 15 min vs. 63 ± 15 min; p = 0.006). The decrease in temperature measured in the esophagus was much faster (3.27 ± 1.27°C/h vs. 1.6 ± ± 0.89°C/h; p = 0.008) with the greatest differences after 30–35 min [19]. On the other hand, a study by Knapik et al. [20] comparing pulmonary artery, nasopharyngeal, and urinary bladder temperatures in 12 OHCA survivors undergoing MTH found no differences between these sites. In that study, however, the induction of hypothermia was much longer (time to target temperature in esophagus was 4.2 ± 3.6 h). The mean cooling rate was 0.89 ± 0.96°C/h. The major limitation of both aforementioned studies was a low number of patients enrolled [19, 20]. Of note, the rate of temperature decrease observed in urinary bladder in the present study was similar to the rate reported by Markota et al. [19] and by Knapik et al. [20].

According to results obtained by Krizanac et al. [17] in 20 patients undergoing MTH, the temperature difference between pulmonary artery and esophagus was 0.1 ± 0.1°C during the overall procedure of hypothermia and 0.2 ± 0.2°C during the induction phase. The respective differences between pulmonary artery and urinary bladder were 0.1 ± 0.2°C and 0.4 ± 0.3°C (p < 0.01 for all differences). These dissimilarities may result in serious differences of cooling duration and actual core temperature magnitude, when different temperature assessment sites are applied [17]. The current results confirmed this presumption, however showed much higher differences between temperatures measured in the esophagus and urinary bladder, especially during induction of MTH. Thus, a cautious approach is warranted in order not to induce over-cooling when using urinary bladder temperature for hypothermia guidance.

According to available research, the present study has the highest number of systematic, complete (covering three MTH phases: induction, stabilization and warming) comparison of temperature measurements in the esophagus and urinary bladder in comatose patients after cardiac arrest treated with MTH.

Limitations of the study

The main limitation of this study was a lack of other temperature measurement sites, especially the pulmonary artery, which seems to be the most reliable site for core body temperature measurement.

Conclusions

The temperature measured in the esophagus remains lower during all three phases of MTH procedure compared with temperature evaluated in the urinary bladder. However, during the stabilization phase most measurements remain within target limits (32–34°C) regardless of the applied method.

Urinary bladder temperature measurements may lag behind temperature changes measured in the esophagus and time to reach target temperature may be longer when assessing temperature in the urinary bladder.

Monitoring temperature simultaneously in the esophagus and in the urinary bladder is an accessible and reliable combination, although esophageal measurements seem to better reflect the dynamics of temperature changes, thus it seems to be more appropriate for MTH control.

Funding: This study has been developed as part of the "Diamentowy Grant" project financed by the Ministry of Science and Higher Education of the Republic of Poland from research funds for the years 2015–2018 (DI2014 009144).

Conflict of interest: None declared

References

1. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med. 2002; 346(8): 557–563, doi: 10.1056/NEJMoa003289, indexed in Pubmed: 11856794.
2. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med. 2002; 346(8): 549–556, doi: 10.1056/NEJMoa012689, indexed in Pubmed: 11856793.
3. Dumas F, White L, Stubbs BA, et al. Long-term prognosis following resuscitation from out of hospital cardiac arrest: role of percutaneous coronary intervention and therapeutic hypothermia. J Am Coll Cardiol. 2012; 60(1): 21–27, doi: 10.1016/j.jacc.2012.03.036, indexed in Pubmed: 22742398.
4. Kim YM, Yim HW, Jeong SH, et al. Does therapeutic hypothermia benefit adult cardiac arrest patients presenting with nonshockable initial rhythms?: A systematic review and meta-analysis of randomized and non-randomized studies. Resuscitation. 2012; 83(2): 188–196, doi: 10.1016/j.resuscitation.2011.07.031, indexed in Pubmed: 21835145.
5. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med. 2013; 369(23): 2197–2206, doi: 10.1056/nejmoa1310519.

6. 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, doi: 10.1093/eurheartj/ehx393, indexed in Pubmed: 28886621.
7. Coppler PJ, Marill KA, Okonkwo DO, et al. Concordance of brain and core temperature in comatose patients after cardiac arrest. Ther Hypothermia Temp Manag. 2016; 6(4): 194–197, doi: 10.1089/ther.2016.0010, indexed in Pubmed: 27249337.
8. Stone JG, Young WL, Smith CR, et al. Do standard monitoring sites reflect true brain temperature when profound hypothermia is rapidly induced and reversed? Anesthesiology. 1995; 82(2): 344–351, indexed in Pubmed: 7856892.
9. Deakin CD, Nolan JP, Soar J, et al. European Resuscitation Council Guidelines for Resuscitation 2010 Section 4. Adult advanced life support. Resuscitation. 2010; 81(10): 1305–1352, doi: 10.1016/j.resuscitation.2010.08.017, indexed in Pubmed: 20956049.
10. Soar J, Nolan JP, Böttiger BW, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 3. Adult advanced nlife support. Resuscitation. 2015; 95: 100–147, doi: 10.1016/j.resuscitation.2015.07.016, indexed in Pubmed: 26477701.
11. Eshel GM, Safar P. Do standard monitoring sites affect true brain temperature when hyperthermia is rapidly induced and reversed. Aviat Space Environ Med. 1999; 70(12): 1193–1196, indexed in Pubmed: 10596773.
12. Camboni D, Philipp A, Schebesch KM, et al. Accuracy of core temperature measurement in deep hypothermic circulatory arrest. Interact Cardiovasc Thorac Surg. 2008; 7(5): 922–924, doi: 10.1510/icvts.2008.181974, indexed in Pubmed: 18658167.
13. Shin J, Kim J, Song K, et al. Core temperature measurement in therapeutic hypothermia according to different phases: comparison of bladder, rectal, and tympanic versus pulmonary artery methods. Resuscitation. 2013; 84(6): 810–817, doi: 10.1016/j.resuscitation.2012.12.023, indexed in Pubmed: 23306812.
14. Kubica J, Pstrągowski K, Adamski P, et al. Mild therapeutic hypothermia for patients with acute coronary syndrome and cardiac arrest treated with percutaneous coronary intervention (UNICORN). The design and rationale for the prospective, observational, multicenter study. Med Res J. 2016; 1(1): 23–27, doi: 10.5603/mrj.2016.0004.
15. Lefrant JY, Muller L, de La Coussaye JE, et al. Temperature measurement in intensive care patients: comparison of urinary bladder, oesophageal, rectal, axillary, and inguinal methods versus pulmonary artery core method. Intensive Care Med. 2003; 29(3): 414–418, doi: 10.1007/s00134-002-1619-5, indexed in Pubmed: 12577157.
16. Schmitz T, Bair N, Falk M, et al. A comparison of five methods of temperature measurement in febrile intensive care patients. Am J Crit Care. 1995; 4(4): 286–292, indexed in Pubmed: 7663592.
17. Krizanac D, Stratil P, Hoerburger D, et al. Femoro-iliacal artery versus pulmonary artery core temperature measurement during therapeutic hypothermia: an observational study. Resuscitation. 2013; 84(6): 805–809, doi: 10.1016/j.resuscitation.2012.11.022, indexed in Pubmed: 23200998.
18. Erickson RS, Kirklin SK. Comparison of ear-based, bladder, oral, and axillary methods for core temperature measurement. Crit Care Med. 1993; 21(10): 1528–1534, indexed in Pubmed: 8403963.
19. Markota A, Palfy M, Stožer A, et al. Difference between bladder and esophageal temperatures in mild induced hypothermia. J Emerg Med. 2015; 49(1): 98–103, doi: 10.1016/j.jemermed.2014.12.059, indexed in Pubmed: 25881889.
20. Knapik P, Rychlik W, Duda D, et al. Relationship between blood, nasopharyngeal and urinary bladder temperature during intravascular cooling for therapeutic hypothermia after cardiac arrest. Resuscitation. 2012; 83(2): 208–212, doi: 10.1016/j.resuscitation.2011.09.001, indexed in Pubmed: 21906572.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2020, Vol. 27, No. 6, 742–748
DOI: 10.5603/CJ.a2018.0109

ISSN 1897–5593
eISSN 1898–018X

Increased systemic arterial stiffness in patients with chronic thromboembolic pulmonary hypertension

Monika Sznajder, Olga Dzikowska-Diduch, Katarzyna Kurnicka, Marek Roik, Dominik Wretowski, Piotr Pruszczyk, Maciej Kostrubiec

Department of Internal Medicine and Cardiology with Venous Thromboembolism Center, Medical University of Warsaw, Poland

Abstract

Background: *Chronic thromboembolic pulmonary hypertension (CTEPH) is a complication of venous thromboembolism (VTE) resulting from non-dissolving thromboemboli in the pulmonary arteries. Previous observations indicate a higher prevalence of atherosclerosis and cardiovascular risk factors in patients with VTE and CTEPH. The purpose of the present study was to evaluate the arterial stiffening assessed by pulse wave velocity (PWV), a marker of arterial stiffness, in CTEPH patients in comparison with a matched control group (CG).*

Methods: *The study group consisted of 26 CTEPH patients (9 male and 17 female, age 69 ± 10 years) and 22 CG (10 male, 12 female, age 67 ± 8 years). In all subjects a physical examination, carotid-femoral PWV and transthoracic echocardiography were performed. Right heart catheterization was done in all CTEPH.*

Results: *Chronic tromboembolic pulmonary hypertension patients had significantly higher PWV than CG (10.3 ± 2.5 m/s vs. 9 ± 1.3 m/s, $p < 0.05$), even though systolic blood pressure was higher in CG (120 ± 11 vs. 132 ± 14 mmHg, $p = 0.002$). PWV correlated only with age and pulmonary vascular resistance (PVR) in CTEPH ($r = 0.45$, $p = 0.03$ and $r = 0.43$, $p = 0.03$, respectively). Arterial stiffening defined as PWV > 10 m/s was found in 11 (42%) CTEPH patients and in 5 (23%) cases from CG ($p = 0.13$). CTEPH patients with PWV > 10 m/s were older (74 ± 8 vs. 66 ± 10 years, $p < 0.05$), had decreased oxygen saturation (SaO_2 89 [73–96]% vs. 96 [85–98]%, $p < 0.01$) and tended to have higher PVR (8.1 [3.1–14.0] vs. 5.2 [3.1–12.7] HRU, $p = 0.10$).*

Conclusions: *Arterial stiffness, assessed with PWV, is increased in CTEPH. The elevated PWV is associated with older age, lower SaO_2 and higher PVR in CTEPH.* (Cardiol J 2020; 27, 6: 742–748)

Key words: arterial stiffness, pulse wave velocity, chronic thromboembolic pulmonary hypertension, atherosclerosis

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare but severe complication of pulmonary embolism (PE) caused by the persistent obstruction of the pulmonary arteries. CTEPH was observed in 3.8% of patients within 2 years after acute PE [1].

Recently, the growing number of studies suggested that atherosclerosis and venous thromboembolism (VTE) can have a common etiology involving inflammatory processes [2].

"Classic" risk factors for cardiovascular disease (like smoking, hypertension, diabetes, dyslipidemia, and an unhealthy lifestyle) have an impact on VTE risk [3]. Patients with symptomatic athero-

Address for correspondence: Maciej Kostrubiec, MD, PhD, FESC, Department of Internal Medicine and Cardiology, Medical University of Warsaw, ul. Lindleya 4, 02–005 Warszawa, Poland, tel: +48 22 502 1112, e-mail: maciej.kostrubiec@wum.edu.pl

Received: 7.11.2017 Accepted: 18.03.2018

sclerosis were reported to have an increased risk of VTE, whereas patients with clinical symptoms of VTE more often developed atherosclerosis [2].

The unfavourable structural and functional changes in the peripheral arteries caused by atherosclerosis leads to a reduction in their elastic properties and finally results in their increased stiffness. Aortic stiffening is one of the earliest detectable markers of vascular remodeling [4] and a predictor of cardiovascular events [5]. The predictive value of aortic stiffening measured as carotid-femoral pulse wave velocity (PWV) is considered the gold standard for assessment of the regional arterial stiffening. PWV allows for the prediction of cardiovascular mortality regardless of SCORE stratification [5, 6].

Risk factors associated with an increase of arterial stiffness include age [5, 7], hypertension [8] and, to a lesser extent, gender and other classic risk factors of cardiovascular diseases [5]. A recent study has indicated a higher incidence of coronary artery disease in patients with CTEPH when compared to survivors of acute pulmonary embolism with excluded CTEPH [9]. The suggested mechanisms promoting coronary artery disease in patients with persistent, non-resolved organized pulmonary artery thrombi included inflammation, systemic and local hypercoagulability, and endothelial injury. All these factors also play an integral mechanistic role in the pathophysiology of artery stiffening. The aim of the present study was to evaluate systemic arterial stiffening assessed with PWV in CTEPH patients in comparison with a matched control group (CG).

Methods

Patients with CTEPH diagnosis established in accordance with European Society of Cardiology/ /European Respiratory Society (ESC/ERS) guidelines were included in the study [1]. Completing at least 3 months of effective anticoagulant therapy, a mean pulmonary artery pressure ≥ 25 mmHg, and wedge pressure in the pulmonary artery < 15 mmHg in right heart catheterization (RHC) present in patients with pulmonary arterial perfusion defects on imaging examinations confirmed the diagnosis of CTEPH. Patients matched by age, gender, and concomitant diseases associated with atherosclerosis were included in CG. Patients with severe diabetes mellitus, chronic kidney disease, ischemic heart disease, peripheral vascular disease, previous stroke or systemic rheumatic diseases were excluded from the study.

A physical examination, carotid-femoral PWV, transthoracic echocardiography and six-minute walk test were conducted on the same day, while RHC in CTEPH patients performed within 48 h after PWV. Systemic pulse pressure (PP) was calculated as the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP).

The study was conducted in accordance with the guidelines of Good Clinical Practice and with the approval of the local Ethics Committee. All patients received detailed information about the study and provided voluntary written consent to participate.

Pulse wave velocity assessment

Carotid-femoral PWV measurement was performed after a night's rest in a horizontal position with the camera Complior SR (Artech Medical Company, Paris, France) equipped with two TY-306 tonometric sensors recording changes in pressure in the range 0.01–100 Hz, which comprises harmonic frequencies of pressure waves generated at various heart rates. Sensors were placed at the right common carotid artery and right femoral artery [5]. After the detection, registration, and computer processing the impulses were enhanced to draw out a curve of the pulse wave of the carotid artery and the femoral artery. Then, the time delay between the onset of the two pulse waves was automatically assessed and the pulse wave velocity was calculated (the distance between sites of measurements, divided by the delay time). The mean of three distance measurements was included in the analysis.

The value of the PWV indicating *a* healthy artery is still debatable, however, the ESH/ESC 2013 guidelines proposed PWV > 10 m/s to be considered abnormal [6].

Echocardiography

Transthoracic echocardiography examination was performed in all patients according to the recommendations of the European Association of Cardiovascular Imaging and the guidelines of the Echocardiography Working Group of Polish Cardiac Society [10, 11]. Phillips iE 33 (Andover, Md., USA) with a 2.5–3.5 MHz transducer was used. The size of both ventricles, ejection fraction (LVEF) and diastolic function of left ventricle, tricuspid annular plane systolic excursion (TAPSE), pulmonary velocity value and pattern, tricuspid regurgitation peak gradient, and the dimensions of the inferior vena cava were assessed.

Laboratory tests

Kidney function was estimated according to the results of the glomerular filtration rate (eGFR) calculated from the Modification of Diet in Renal Disease formula from serum creatinine concentration.

Six-minute walk test

The distance an individual was able to walk over a total of 6 min was measured. Heart rate (HR), blood pressure (BP), oxygen saturation (SaO_2) and dyspnoea (Borg Dyspnoea Score) were also recorded before and after exertion [1]. Desaturation was defined as the difference between the baseline arterial blood saturation and SaO_2 measured immediately after the test.

Right heart catheterization

An experienced interventional cardiologist performed RHC in patients with CTEPH to confirm the diagnosis. The right atrial, right ventricular, pulmonary artery and wedge pressures were measured. The thermodilution method was used to determine stroke volume (SV), cardiac index (CI), and indexed pulmonary vascular resistance (PVR) [12].

Statistical analysis

Variables with normal distribution are presented as mean with standard deviation (SD), while variables without such distribution are described as median and range (min–max). The Student t-test or Mann-Whitney test was used for comparisons between the two groups. The Fisher or χ^2 tests were used to compare discrete variables, as appropriate. The Spearman or Pearson correlation coefficients were calculated, respectively. A stepforward multivariable analysis was performed to indicate the predictors associated with PWV > 10 m/s. All tests were two-sided. Data were considered significant at $p < 0.05$. STATISTICA (StatSoft 13.1, Inc. 2016, Tulsa, OK, USA) software was used for statistical calculations.

Results

The study group consisted of 26 patients with CTEPH (9 men and 17 women, age 69 ± 10 years), while 22 patients (10 men, 12 women, age 67 ± 8 years) were qualified to CG. Patients with CTEPH presented II–III World Health Organization (WHO) functional class. Dyslipidemia and hypertension were present in 8 (30.8%) and 18 (69.2%) patients with CTEPH and in 10 (45.5%) and 13 (59.1%) of CG, respectively. Total and low-density lipoprotein (LDL) plasma cholesterol concentrations were higher, while high density lipoprotein (HDL) cholesterol was lower in CTEPH patients than in controls. The prevalence of smoking history and diabetes did not differ significantly between groups. The clinical characteristics of studied subjects are presented in Table 1. CTEPH patients presented lower LVEF, decreased TAPSE and increased RV to LV dimensions ratio. Moreover, patients with CTEPH presented lower GFR than CG. The six-minute walk distance was remarkably longer in CG than in CTEPH patients (Table 1). CTEPH patients had significantly higher PWV than controls (PWV 10.3 ± 2.5 m/s vs. 9 ± 1.3 m/s, $p < 0.05$) (Fig. 1), even though SBP and PP were higher in the control group (Table 1).

Pulse wave velocity correlated only with age and PVR in patients with CTEPH ($r = 0.45$, $p = 0.03$ and $r = 0.43$, $p = 0.03$, respectively), while in controls PWV correlated with age and inversely with body mass index ($r = 0.54$, $p = 0.01$ and $r = –0.43$, $p < 0.05$, respectively). Interestingly, there was no correlation between PWV and SBP nor DBP in any group.

There was a borderline correlation between PWV and pulmonary compliance (ratio of SV to PP) ($r = 0.37$, $p = 0.07$), while the association between PWV and systemic arterial compliance was nonsignificant ($r = 0.29$, $p = 0.16$).

Arterial stiffening defined as PWV > 10 m/s was found in 11 (42%) patients with CTEPH and in 5 (23%) cases from CG. CTEPH patients with PWV > 10 m/s compared to CTEPH patients with PWV ≤ 10 m/s were older (74 ± 8 vs. 66 ± 10 years, $p < 0.05$), had decreased oxygen saturation (SaO_2 89 [73–96]% vs. 96 [85–98]%, $p < 0.01$) and tended to have higher PVR (8.1 [3.1–14.0] vs. 5.2 [3.1–12.7] HRU, $p \leq 0.10$) (Fig. 2). PWV > 10 m/s was not associated with lower SaO_2 in controls. Multivariable analysis revealed the only significant predictor of PWV > 10 m/s was SaO_2 (odds ratio [OR] 0.90; 95% confidence interval [CI] 0.68–0.95, $p < 0.01$).

Discussion

The artery stiffening, associated with increased morbidity and mortality, is an important sign of systemic vascular disease. PWV is an independent predictor of adverse cardiovascular events and all-cause mortality. A 1 m/s rise of its value increases cardiovascular risk by more than 10% [13].

The decreased arterial compliance results in an increase of central SBP, limits cardiac output and

Table 1. Characteristics of the study groups.

Parameters	CTEPH (n = 26)	CG (n = 22)	P
Clinical characteristics			
Gender (male/female)	9/17	10/12	0.32
Age [years]	69 ± 10	67 ± 8	0.36
BMI [kg/m^2]	28 ± 5	29 ± 4	0.23
Heart rate [bpm]	66 ± 11	68 ± 12	0.52
Systolic BP [mmHg]	120 ± 11	132 ± 14	0.002
Diastolic BP [mmHg]	76 ± 11	79 ± 8	0.43
Pulse pressure [mmHg]	43 ± 11	53 ± 12	0.005
eGFR [mL/min]	62 ± 13	89 ± 15	0.0001
SaO_2 [%]	91 ± 7	98 ± 1	0.002
6MWD [m]	348 ± 136	599 ± 107	< 0.0001
Total cholesterol [mg/dL]	183 ± 56	144 ± 37	< 0.01
LDL cholesterol [mg/dL]	113 ± 51	79 ± 33	0.01
HDL cholesterol [mg/dL]	55 ± 15	42 ± 14	< 0.01
Triglycerides [mg/dL]	98 ± 46	128 ± 57	0.06
Fasting glucose [mg/dL]	100 ± 39	96 ± 12	0.60
History of smoking	9 (35%)	3 (14%)	0.09
Diabetes mellitus	5 (19%)	1 (5%)	0.15
Echocardiographic parameters			
LVEF [%]	55 ± 4	62 ± 4	< 0.0001
TAPSE [mm]	18 ± 5	24 ± 3	< 0.0001
TRPG [mmHg]	74 ± 22	22 ± 10	< 0.0001
RV/LV	1.3 ± 0.3	0.8 ± 0.1	< 0.0001
Right heart catheterization results of CTEPH			
mPAP [mmHg]	43 ± 9		
PVR [HRU]	6.9 ± 2.9		
Cardiac index [L/min/m^2]	2.7 ± 0.6		

Data are shown as mean ± standard deviation or number (percentage). 6MWD — six minute walk distance; BMI — body mass index; BP — blood pressure; CG — control group; CTEPH — chronic thromboembolic pulmonary hypertension; eGFR — glomerular filtration rate; HDL — high density lipoprotein; HRU — hybrid reference units (Wood units); LDL — low density lipoprotein; LVEF — left ventricular ejection fraction; mPAP — mean pulmonary artery pressure; PVR — pulmonary vascular resistance; RV/LV — right ventricle/left ventricle; SaO_2 — arterial oxygen saturation; TAPSE — tricuspid annular plane systolic excursion; TRPG — tricuspid regurgitation peak gradient

augments the LV overload. Consequently, coronary blood flow is reduced and cardiac ischemia can develop [4]. The elevation of the PWV in CTEPH patients, compared with the age-matched and adjusted for the presence of comorbidity controls, indicates an increased arterial stiffness in the former. Moreover, the increased arterial stiffness in patients with CTEPH may suggest a greater risk of developing diseases associated with atherosclerosis.

Interestingly, the distinct nature of venous thrombosis and arterial thrombosis is being frequently questioned in recent studies. There is a high number of common risk factors for these diseases [2, 3]. Furthermore, patients with clinical symptoms of VTE, particularly idiopathic, have an increased risk of symptomatic atherosclerosis [2]. Additionally, patients with unprovoked VTE have a higher risk of acute cardiovascular events including acute myocardial infarction and ischemic stroke, than patients with provoked VTE [14].

The value of PWV depends on the thickness of the vascular wall and its elastic properties. It is inversely related to the inner radius of the vessels and blood viscosity. Increased stiffness limits systolic expandability, while a loss of flexibility and cushioning mechanism leads to an increased SBP and a relative reduction of DBP, with a subsequent

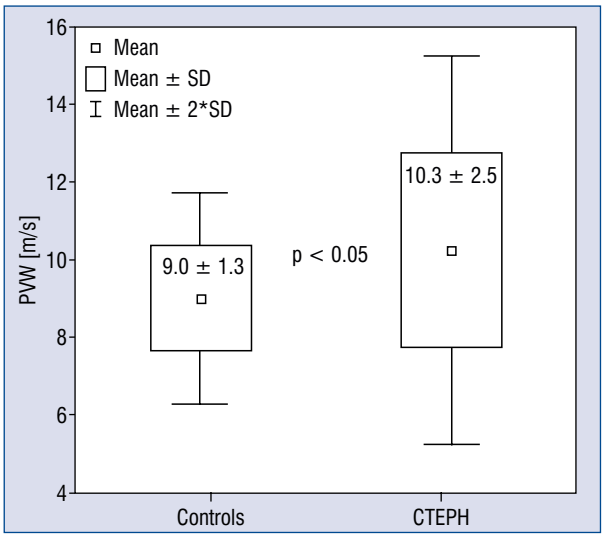


Figure 1. Pulse wave velocity (PWV) value in control group and chronic thromboembolic pulmonary hypertension (CTEPH) patients; SD — standard deviation.

elevation of PP and cardiac afterload [15]. Interestingly, in the current study CTEPH patients were found to have higher PWV despite of lower SBP and PP. Low SBP is common in CTEPH due to low SV.

Vascular stiffening develops from a complex interaction between stable and dynamic changes involving structural and cellular elements of the vessel wall, including the role of scaffolding proteins, extracellular matrix, inflammatory molecules, endothelial cell function, reactive oxidant species and genetics [16].

In CTEPH the pathological lesions are formed by organized thrombi tightly attached to the pulmonary arterial medial layer, replacing the normal intima [17]. The pathophysiology of distal disease may involve predominant obstructions of subsegmental elastic pulmonary arteries, arteriopathy of small muscular arteries and arterioles distal to non-obstructed vessels and pulmonary arteriopathy of small muscular arteries and arterioles distal to totally or partially obstructed vessels [18]. Distal pulmonary vasculopathy in both the occluded and nonoccluded pulmonary vascular bed is characterized by lesions considered typical for idiopathic pulmonary arterial hypertension. The pathogenesis of these vascular lesions may involve the endothelium, platelet production, release of mediators and altered pulmonary blood flow. Medial hypertrophy, intimal proliferative, and fibrotic changes can be found in CTEPH [19, 20]. However, the down regulation of angiogenic gene expression and the dysfunction of endothelial cells, which may also impair thrombus resolution, were reported as well [21]. Moreover, systemic inflammation seems to be involved in the development of CTEPH [22].

Many patients with CTEPH develop hypoxemic respiratory insufficiency. In the present study PWV correlated with PVR, age and SaO_2, however, in multivariable analysis decreased SaO_2 was the only significant predictor of PWV > 10 m/s. The association of vascular stiffening with age was previously well described [5, 7]. The decreased SaO_2 can deteriorate endothelium function and increase BP leading to arterial stiffening. Moreover, the low oxygen concentration can cause a rise of PVR and pulmonary arterial pressure [23]. The PVR is related to the geometry of small distal resistive pulmonary arterioles and is considered to reflect the functional status of pulmonary vascular endothelium/smooth muscle cell coupled system. PVR is also positively related to blood viscosity and may be influenced by changes in the perivascular alveolar and pleural pressure [24]. Jujo et al. [20] suggested that a close relationship

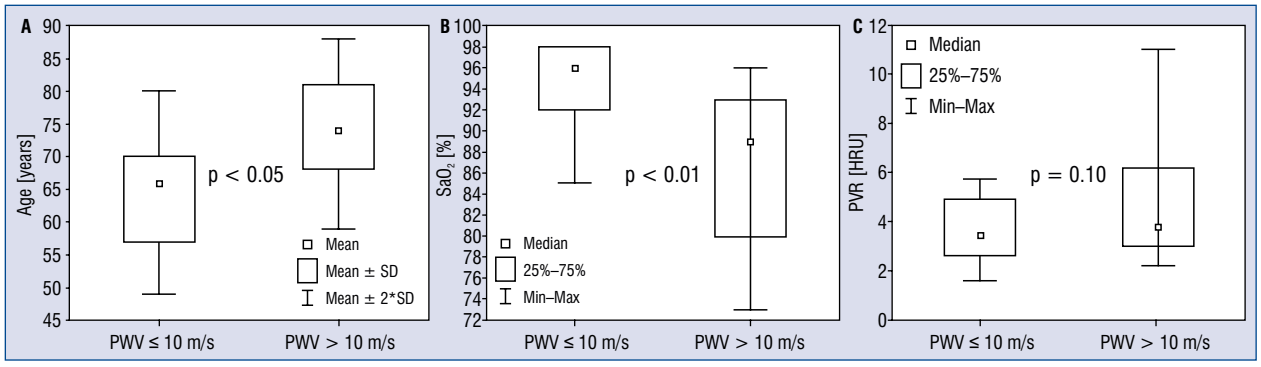


Figure 2. The comparison of age (**A**), arterial oxygen saturation (SaO_2) (**B**), and pulmonary vascular resistance (PVR) (**C**) between chronic thromboembolic pulmonary hypertension (CTEPH) patients with pulse wave velocity (PWV) above and below/equal to 10 m/s; SD — standard deviation.

between severe pulmonary arterial remodeling and elevated PVR could be the result of luminal narrowing of pulmonary muscular arteries. The pathomechanisms underlying CTEPH-related atherosclerotic arterial alternations are not clear. There are no studies available regarding whether thromboembolic pulmonary hypertension triggers mechanisms that may affect systemic arteries such as the aorta. Hou et al. [25] assessed the carotid artery in pulmonary hypertension and revealed that its stiffening might be related to the release of endothelium dependent vasoconstrictors and a decreased concentration of vasodilators. Additionally, in a meta-analysis by Wang et al. [26] which included 3198 patients with chronic obstructive pulmonary disease, markers of subclinical atherosclerosis and cardiovascular risk assessed inter alia with PWV were significantly elevated. The results of the present study point to a significant correlation between arterial stiffening, assessed by PWV, and low SaO_2, older age, and increased PVR. They also suggest an association between increased stiffness of the systemic arteries with the occlusion of pulmonary arteries and decreased blood oxygenation in patients with CTEPH.

Limitations of the study

This is a single center study on a relatively small group of patients with a very rare disease. The observations were not blinded, however, due to a semi-automatic measurement methodology, the influence of the investigator seems negligible. Based on the results of the current study it is impossible to conclude the pathogenesis of arterial stiffening in CTEPH, however, the indicated associations suggest possible mechanisms and directions for further studies.

Conclusions

Arterial stiffness, a marker of atherosclerosis assessed as pulse wave velocity, is increased in patients with chronic thromboembolic pulmonary hypertension compared to matched controls. The elevated PWV is associated with older age, higher pulmonary vascular resistance and especially with lower oxygen saturation in chronic thromboembolic pulmonary hypertension.

Conflict of interest: None declared

References

1. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016; 37(1): 67–119.
2. Franchini M, Mannucci PM. Association between venous and arterial thrombosis: clinical implications. Eur J Intern Med. 2012; 23(4): 333–337, doi: 10.1016/j.ejim.2012.02.008, indexed in Pubmed: 22560380.
3. Riva N, Donadini MP, Ageno W. Epidemiology and pathophysiology of venous thromboembolism: similarities with atherothrombosis and the role of inflammation. Thromb Haemost. 2015; 113(6): 1176–1183, doi: 10.1160/TH14-06-0563, indexed in Pubmed: 25472800.
4. Cavalcante JL, Lima JAC, Redheuil A, et al. Aortic stiffness: current understanding and future directions. J Am Coll Cardiol. 2011; 57(14): 1511–1522, doi: 10.1016/j.jacc.2010.12.017, indexed in Pubmed: 21453829.
5. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J. 2006; 27(21): 2588–2605, doi: 10.1093/eurheartj/ehl254, indexed in Pubmed: 17000623.
6. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Practice Guidelines for the Management of Arterial Hypertension. Blood Pressure. 2014; 23(1): 3–16, doi: 10.3109/08037051.2014.868629.
7. McEniery CM, Hall IR, Qasem A, et al. ACCT Investigators. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). J Am Coll Cardiol. 2005; 46(9): 1753–1760, doi: 10.1016/j.jacc.2005.07.037, indexed in Pubmed: 16256881.
8. Simon AC, Levenson J, Bouthier J, et al. Evidence of early degenerative changes in large arteries in human essential hypertension. Hypertension. 1985; 7(5): 675–680, indexed in Pubmed: 4030039.
9. Roik M, Wretowski D, Kostrubiec M, et al. High prevalence of severe coronary artery disease in elderly patients with non-operable chronic thromboembolic pulmonary hypertension referred for balloon pulmonary angioplasty. Postepy Kardiol Interwencyjnej. 2016; 12(4): 355–359, doi: 10.5114/aic.2016.63637, indexed in Pubmed: 27980550.
10. 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.
11. Kasprzak JD, Płońska E, Szyszka A, et al. Echokardiografia w praktyce klinicznej–Standardy Sekcji Echokardiografii Polskiego Towarzystwa Kardiologicznego 2007. Kardiol Pol. 2007; 65(9): 1142–62.
12. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary em-

bolism. Eur Heart J. 2014; 35(43): 3033–69, 3069a, doi: 10.1093/eurheartj/ehu283, indexed in Pubmed: 25173341.
13. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol. 2010; 55(13): 1318–1327, doi: 10.1016/j.jacc.2009.10.061, indexed in Pubmed: 20338492.
14. Becattini C, Vedovati MC, Ageno W, et al. Incidence of arterial cardiovascular events after venous thromboembolism: a systematic review and a meta-analysis. J Thromb Haemost. 2010; 8(5): 891–897, doi: 10.1111/j.1538-7836.2010.03777.x, indexed in Pubmed: 20095999.
15. Safar M. Tętnice w nadciśnieniu tętniczym. Lippincott-Raven, Philadelphia, 1997.
16. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. Arterioscler Thromb Vasc Biol. 2005; 25(5): 932–943, doi: 10.1161/01.ATV.0000160548.78317.29, indexed in Pubmed: 15731494.
17. Fedullo PF, Auger WR, Kerr KM, et al. Chronic thromboembolic pulmonary hypertension. N Engl J Med. 2001; 345(20): 1465–1472, doi: 10.1056/NEJMra010902, indexed in Pubmed: 11794196.
18. Galiè N, Kim NHS. Pulmonary microvascular disease in chronic thromboembolic pulmonary hypertension. Proc Am Thorac Soc. 2006; 3(7): 571–576, doi: 10.1513/pats.200605-113LR, indexed in Pubmed: 16963536.
19. O'Connell C, Montani D, Savale L, et al. Chronic thromboembolic pulmonary hypertension. Presse Med. 2015; 44(12 Pt 2): e409–e416, doi: 10.1016/j.lpm.2015.10.010, indexed in Pubmed: 26585271.
20. Jujo T, Sakao S, Ishibashi-Ueda H, et al. Evaluation of the Microcirculation in Chronic Thromboembolic Pulmonary Hypertension Patients: The Impact of Pulmonary Arterial Remodeling on Postoperative and Follow-Up Pulmonary Arterial Pressure and Vascular Resistance. PLoS One. 2015; 10(8): e0133167, doi: 10.1371/journal.pone.0133167, indexed in Pubmed: 26252755.
21. Lang I. Chronic thromboembolic pulmonary hypertension: a distinct disease entity. Eur Respir Rev. 2015; 24(136): 246–252, doi: 10.1183/16000617.00001115, indexed in Pubmed: 26028636.
22. Quarck R, Wynants M, Verbeken E, et al. Contribution of inflammation and impaired angiogenesis to the pathobiology of chronic thromboembolic pulmonary hypertension. Eur Respir J. 2015; 46(2): 431–443, doi: 10.1183/09031936.00009914, indexed in Pubmed: 26113681.
23. Hunter KS, Lammers SR, Shandas R. Pulmonary vascular stiffness: measurement, modeling, and implications in normal and hypertensive pulmonary circulations. Compr Physiol. 2011; 1(3): 1413–1435, doi: 10.1002/cphy.c100005, indexed in Pubmed: 23733649.
24. Chemla D, Castelain V, Hervé P, et al. Haemodynamic evaluation of pulmonary hypertension. Eur Respir J. 2002; 20(5): 1314–1331, indexed in Pubmed: 12449189.
25. Hou Y, Yuan LJ, Xing CY, et al. Carotid arterial stiffness in patients with congenital heart disease-related pulmonary hypertension assesed with rediofrequency data technique. Echocardiography 2015; 32(11): 1676–1680. doi: 10.1111/echo.12925, indexed in Pubmed: 25732062.
26. Wang LY, Zhu YN, Cui JJ, et al. Subclinical atherosclerosis risk markers in patients with chronic obstructive pulmonary disease: A systematic review and meta-analysis. Respir Med. 2017; 123: 18–27, doi: 10.1016/j.rmed.2016.12.004, indexed in Pubmed: 28137492.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2020, Vol. 27, No. 6, 749–755
DOI: 10.5603/CJ.a2018.0107

ISSN 1897–5593
eISSN 1898–018X

Predictors of syncope in patients with severe aortic stenosis: The role of orthostatic unload test

Paweł Kleczyński, Paweł Petkow Dimitrow, Artur Dziewierz, Agata Wiktorowicz, Tomasz Rakowski, Andrzej Surdacki, Dariusz Dudek

2nd Department of Cardiology, Jagiellonian University, Krakow, Poland

Abstract

Background: *There is a paucity of data regarding response of cerebral blood flow to the postural unloading maneuver and its impact on the risk of syncope in patients with aortic stenosis (AS). The aim of the present study was to assess effects of orthostatic stress test on changes in carotid and vertebral artery blood flow and its association with syncope in patients with severe AS.*

Methods: *108 patients were enrolled (72 with and 36 patients without syncope) with severe isolated severe AS. Peak systolic blood-flow velocity (PSV) and end-diastolic velocity in the carotid arteries and vertebral arteries were measured by duplex ultrasound in the supine position and at 1–2 min after the assumption of the standing position.*

Results: *The orthostatic stress test induced a significant decrease in carotid and vertebral arterial flow velocities in all examined arteries ($p < 0.001$). The median (interquartile range) of mean change in PSV for carotid arteries was higher for patients with syncope (syncope [–] vs. syncope [+]: –0.6 cm/s [–1.8, 1.0] vs. –7.3 cm/s [–9.5, –2.0]; $p < 0.001$) and similarly for vertebral arteries (–0.5 cm/s [–2.0, 0.5] vs. –4.8 cm/s [–6.5, –1.3]; $p < 0.001$, respectively). Age, aortic valve area, and mean change in PSV for carotid arteries were independently associated with syncope.*

Conclusions: *In patients with AS, a decrease in carotid and vertebral arterial flow velocities in the standing position was observed and was associated with syncope. The present findings may support the value of an orthostatic test in identifying patients with severe AS and a high risk of syncope.* (Cardiol J 2020; 27, 6: 749–755)

Key words: aortic stenosis, syncope, orthostatic stress, Doppler ultrasound, cerebral blood flow

Introduction

Aortic stenosis (AS) with its primarily calcific form has an increasing prevalence in adults of advanced age and therefore requires a comprehensive diagnostic approach and treatment [1]. Syncope is a common symptom in patients with severe AS, and worsens prognosis, however, there remains scarce data regarding its predictors. Patients with severe AS should undergo a Doppler ultrasound examination of carotid and vertebral arteries as a part of a complex assessment before surgical valve replacement or transcatheter aortic valve implantation (TAVI). However, evaluation of valve disorder only at resting conditions may undervalue the real status of the defect and its clinical effects. Orthostatic-induced changes in Doppler echocardiographic evaluation of transaortic gradient in patients with AS have been shown previously [2]. Several studies have reported the importance of an upright position during exercise or in a passive way to determine left ventricular outflow tract gradients in hypertrophic cardiomyopathy and other conditions [3–5]. Moreover, in a recent study a significant blood velocity drop in carotid and vertebral arteries in patients with AS compared to healthy subjects was found but with no relation to syncope, probably due to low sample size [6].

Address for correspondence: Paweł Kleczyński, MD, PhD, 2nd Department of Cardiology, Jagiellonian University, ul. Kopernika 17, 31–501 Kraków, Poland, tel: +48 12 424 71 81, fax: +48 12 424 71 84, e-mail: kleczu@interia.pl

Received: 11.06.2018 Accepted: 1.09.2018

In this study, the aim was to assess effects of an orthostatic stress test on changes in carotid and vertebral artery blood flow and its association with syncope in patients with severe AS.

Methods

One hundred and eight patients who underwent comprehensive echocardiography were included and carotid duplex ultrasound in the documented department from those who fulfilled the following inclusion criteria: severe, "isolated" AS, defined as an aortic valve area < 1.0 cm^2; preserved left ventricular ejection fraction (> 50%); and sinus rhythm. Exclusion criteria were: detected significant atherosclerosis in carotid/vertebral arteries, more than mild concomitant mitral valve dysfunction, or atrial flutter/fibrillation, suboptimal Doppler signal during orthostatic stress. Patients were divided into two groups, patients presenting with (syncope [+]) and without syncope (syncope [–]). Standard echocardiography was done using Vivid 7 (General Electric, Fairfield, USA). M-mode and two-dimensional echocardiograms were obtained for each patient, which was followed by a pulsed and continuous-wave Doppler ultrasound. Conventional techniques were used to measure the echocardiographic parameters. During the orthostatic test the patient stood for 1–2 min with their left hand on their head and the gradient assessment from the apical window was assessed. The ultrasound transducer (4–10 MHz linear-array transducer) was used to perform carotid duplex ultrasound routinely in the supine position with peak systolic velocity (PSV) and end diastolic velocity (EDV) assessment in common carotid artery, internal carotid artery (ICA) and vertebral artery (VA). In the second part of the examination, during an orthostatic test the patient stood for 1–2 min and carotid duplex ultrasound was performed, again with velocity measurements, respectively. Heart rate was assessed at baseline and after 1–2 min of orthostatic stress. Additionally, spectral analysis of flow pattern with time-averaged maximum velocity was assessed (TAMAX [cm/s]), time-averaged mean velocity (TAMEAN [cm/s]) and flow volume [mL/min] at baseline and in an upright position. Each echocardiographic and Doppler ultrasound parameter was assessed repeatedly 3 times and mean value was taken into the analysis. Change (delta) in PSV and EDV was calculated as a difference between values obtained in the standing and lying position. Mean change of PSV and EDV in carotid arteries was calculated as a mean of measurements from left and right common carotid artery, and left and right ICA. Similarly, mean change of PSV and EDV in vertebral arteries was calculated as a mean of measurements from left and right VA. The study protocol was approved by the institutional ethical board. All patients gave their written consent.

Statistical analysis

Continuous variables were presented as medians (interquartile ranges). Categorical variables were expressed as percentages. Differences between patients with and without syncope were tested using the χ^2 test and the Fisher exact test for dichotomous variables and the Mann-Whitney U-test for continuous variables. Differences between echocardiographic/duplex ultrasound parameters assessed in supine and upright position were assessed using the Wilcoxon signed-rank test. Independent predictors of syncope were identified using multivariate logistic regression analysis. Forward selection in logistic regression with the probability value for covariates to enter the model was set at 0.05 level. All reported clinical, echocardiographic and duplex ultrasound data were tested as possible covariates. Relative risks of syncope were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). In addition, receiver operating characteristic (ROC) curve analysis was used to assess the ability of selected parameters to detect patients with syncope. Area under ROC curves were compared using DeLong's method. All tests were 2-tailed, and a p value of < 0.05 was considered statistically significant. All statistical analysis was performed using SPSS software, version 15.0 (SPSS Inc., Chicago, Illinois).

Results

A total of 108 patients with severe AS were enrolled. Of these, 72 patients were with and 36 without syncope. Patients with syncope were older and more likely to present with a higher New York Heart Association class and had lower aortic valve area (AVA) as compared with patients without syncope (Table 1). Table 2 depicts Doppler ultrasound data. Median heart rate in patients with syncope was 78.0 (65.0–82.0) at baseline and 79.0 (64.0–83.0) in upright position ($p = 0.93$) and 70.0 (60.0–78.0) at baseline and 70.0 (62.0–79.0) while standing in patients without syncope ($p = 0.75$). The orthostatic stress test induced significant decreases in carotid and vertebral arterial flow velocities ($p < 0.001$ for all). Importantly, change (delta) in PSV and EDV was higher in patients with than without syncope (Table 2).

Table 1. Demographic, clinical and echocardiographic data.

Variable	Syncope (–) (n = 36)	Syncope (+) (n = 72)	P
Age [years]	69.0 (64.5, 72.0)	79.0 (73.5, 83.0)	< 0.001
Male gender	41.7%	33.3%	0.40
Diabetes mellitus	25.0%	36.1%	0.59
NYHA class:			< 0.001
I	47.2%	15.3%	
II	47.2%	44.4%	
III	5.6%	37.5%	
IV	0.0%	2.8%	
GFR [mL/min/1.73 m^2]	53.0 (45.0, 54.0)	58.5 (43.8, 82.1)	0.56
HR supine [bpm]	77.0 (69.0, 80.0)	76.0 (65.0, 78.5)	0.27
TG max supine [mmHg]	95.0 (91.0, 100.0)	97.0 (75.0, 107.0)	0.79
TG max upright [mmHg]	88.0 (84.0, 90.5)	91.0 (70.0, 100.0)	0.68
TG max delta [mmHg]	–7.0 (–9.5, –4.0)	–6.0 (–9.0, –3.1)	0.29
TG mean supine [mmHg]	47.5 (44.0, 51.0)	50.0 (45.0, 58.0)	0.11
TG mean upright [mmHg]	42.0 (40.0, 44.0)	47.0 (41.0, 54.0)	0.002
TG mean delta [mmHg]	–4.0 (–6.5, –2.0)	–3.0 (–4.0, –1.0)	0.049
AVA [cm^2]	0.9 (0.8, 1.0)	0.7 (0.6, 0.8)	< 0.001
LVEF [%]	62.5 (60.0, 65.0)	62.0 (55.0, 65.0)	0.54

AVA — aortic valve area; GFR — glomerular filtration rate; HR — heart rate; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; TG — transaortic gradient

Table 2. Doppler ultrasound data.

Variable	Syncope (–) (n = 36)	Syncope (+) (n = 72)	P
PSV LCCA [cm/s]			
Supine	123.5 (117.0, 131.5)	100.0 (95.0, 117.5)	< 0.001
Upright	124.0 (117.0, 132.0)	92.0 (90.0, 116.5)	< 0.001
Delta	–1.0 (–2.5, 1.0)	–7.0 (–8.0, –2.0)	< 0.001
EDV LCCA [cm/s]			
Supine	22.5 (17.0, 25.0)	25.0 (23.0, 27.0)	< 0.001
Upright	21.0 (17.5, 22.5)	22.0 (20.0, 24.0)	0.015
Delta	–1.0 (–2.5, 0.0)	–4.0 (–5.0, –1.0)	0.014
LCCA TAMAX [cm/s]			
Supine	48.2 (44.2, 49.7)	46.8 (43.3, 49.6)	0.55
Upright	45.1 (42.2, 46.7)	37.8 (35.9, 44.7)	0.017
Delta	–1.8 (–3.9, –1.7)	–6.8 (–7.0, –1.2)	0.016
LCCA TAMEAN [cm/s]			
Supine	23.5 (22.7, 24.8)	23.7 (22.1, 25.1)	0.78
Upright	21.2 (20.8, 22.3)	18.4 (17.4, 22.8)	0.029
Delta	–2.1 (–2.6, –1.2)	–4.1 (–5.0, –0.7)	0.024
LCCA Flow volume [mL/min]			
Supine	699.9 (636.0, 728.1)	699.9 (643.1, 723.5)	0.76
Upright	699.1 (629.1, 704.2)	674.7 (609.2, 690.2)	0.06
Delta	–25.1 (–27.7, –20.7)	–32.3 (–42.0, –6.5)	< 0.001

→

Table 2 (cont.). Doppler ultrasound data.

Variable	Syncope (–) (n = 36)	Syncope (+) (n = 72)	P
PSV LICA [cm/s]			
Supine	120.0 (113.0, 126.5)	96.0 (91.0, 115.0)	< 0.001
Upright	122.0 (114.5, 130.0)	91.0 (85.5, 115.0)	< 0.001
Delta	0.0 (–2.0, 1.5)	–6.0 (–9.0, –1.0)	< 0.001
EDV LICA [cm/s]			
Supine	20.0 (15.0, 21.5)	22.0 (20.5, 23.0)	0.003
Upright	19.5 (15.5, 21.0)	20.0 (19.0, 21.0)	0.049
Delta	–1.0 (–1.0, 0.0)	–5.0 (–6.0, –1.0)	< 0.001
PSV LVA [cm/s]			
Supine	45.0 (43.0, 47.5)	45.0 (43.0, 49.0)	0.44
Upright	44.0 (42.0, 46.0)	40.0 (37.5, 46.0)	0.01
Delta	–1.0 (–2.0, 1.0)	–6.0 (–7.0, –1.0)	< 0.001
EDV LVA [cm/s]			
Supine	9.0 (8.0, 10.0)	13.0 (10.0, 15.0)	< 0.001
Upright	9.0 (8.0, 10.0)	11.0 (10.0, 12.0)	< 0.001
Delta	0.0 (–1.0, 0.0)	–4.0 (–6.0, 0.0)	0.001
PSV RCCA [cm/s]			
Supine	124.0 (117.5, 132.0)	100.0 (93.5, 117.5)	< 0.001
Upright	124.0 (117.0, 132.0)	94.5 (89.5, 116.5)	< 0.001
Delta	–1.0 (–3.0, 1.0)	–7.0 (–9.0, –1.5)	0.001
EDV RCCA [cm/s]			
Supine	22.5 (17.0, 25.0)	24.0 (22.0, 26.0)	0.006
Upright	21.0 (17.5, 22.5)	19.0 (18.0, 23.0)	0.039
Delta	–1.0 (–2.5, 0.0)	–4.5 (–6.0, –1.0)	0.001
RCCA TAMAX [cm/s]			
Supine	47.4 (44.2, 49.7)	46.8 (43.3, 49.6)	0.72
Upright	45.0 (41.3, 47.7)	37.9 (36.1, 47.5)	0.07
Delta	–2.1 (–3.6, –1.3)	–6.9 (–7.1, –1.2)	0.014
RCCA TAMEAN [cm/s]			
Supine	23.5 (22.7, 24.7)	23.6 (22.2, 25.1)	0.64
Upright	21.3 (20.5, 22.5)	18.1 (17.4, 22.3)	0.028
Delta	–1.8 (–2.2, –1.5)	–4.4 (–5.2, –0.7)	0.015
RCCA Flow volume [mL/min]			
Supine	699.9 (637.0, 728.1)	699.1 (641.2, 723.7)	0.72
Upright	687.6 (620.8, 700.5)	673.5 (610.5, 710.6)	0.08
Delta	–20.4 (–27.6, –20.9)	–26.8 (–28.3, –6.7)	< 0.001
PSV RICA [cm/s]			
Supine	120.0 (113.0, 126.5)	95.0 (90.5, 115.0)	< 0.001
Upright	122.5 (114.5, 130.0)	91.5 (85.0, 115.5)	< 0.001
Delta	0.0 (–2.0, 1.5)	–5.8 (–7.0, –1.5)	< 0.001
EDV RICA [cm/s]			
Supine	20.0 (14.5, 21.0)	21.5 (20.0, 23.0)	0.001
Upright	21.5 (16.5, 22.0)	18.5 (18.5, 21.0)	0.03
Delta	0.0 (–1.0, 1.0)	–4.5 (–6.0, –1.0)	< 0.001
PSV RVA [cm/s]			
Supine	44.5 (43.0, 46.5)	45.0 (43.0, 47.0)	0.52
Upright	44.0 (43.0, 46.0)	42.0 (40.0, 44.5)	0.001
Delta	0.0 (–2.0, 1.0)	–5.0 (–6.0, –1.0)	< 0.001
EDV RVA [cm/s]			
Supine	9.0 (8.0, 10.0)	13.0 (11.0, 14.0)	< 0.001
Upright	9.0 (7.5, 11.0)	12.0 (10.5, 12.0)	< 0.001
Delta	0.0 (–1.5, 0.0)	–4.0 (–6.0, 0.0)	0.001

EDV — end diastolic velocity; LCCA — left common carotid artery; LICA — left internal carotid artery; LVA — left vertebral artery; PSV — peak systolic velocity; RCCA — right common carotid artery; RICA — right internal carotid artery; RVA — right vertebral artery; TAMAX — time-averaged maximum velocity; TAMEAN — time-averaged mean velocity

Table 3. Receiver-operating characteristic curve analysis for the prediction of syncope.

Variable	AUC	P	Optimal cut off value	Sensitivity	Specificity
Age [years]	0.80	< 0.001	> 75	70.8%	86.1%
Aortic valve area [cm^2]	0.75 (0.66–0.83)	< 0.001	≤ 0.8	76.5%	63.9%
Change in PSV carotid [cm/s]	0.78 (0.68–0.85)	< 0.001	≤ –6.0	77.8%	77.8%
Change in PSV vertebral [cm/s]	0.71 (0.62–0.79)	< 0.001	≤ –3.5	75.0%	72.2%
Change in EDV carotid [cm/s]	0.74 (0.65–0.82)	< 0.001	≤ –3.3	75.0%	72.2%
Change in EDV vertebral [cm/s]	0.67 (0.58–0.76)	0.003	≤ –1.5	76.4%	52.8%

AUC — area under curve; EDV — end diastolic velocity; PSV — peak systolic velocity

The median (IQR) of mean change in PSV for carotid arteries was higher for patients with syncope (syncope [–] vs. syncope [+]: –0.6 cm/s (–1.8, 1.0) vs. –7.3 cm/s (–9.5, –2.0); p < 0.001) and similarly for VAs: (–0.5 cm/s [–2.0, 0.5] vs. –4.8 cm/s [–6.5, –1.3]; p < 0.001, respectively).

In the multivariate logistic regression analysis age (OR 1.101 per 1 year, 95% CI 1.026–1.183; p = 0.008), AVA (OR 0.071 per 1 cm^2, 95% CI 0.005–1.033; p = 0.05), mean change in PSV in carotid arteries (OR 0.818 per 1 cm/s, 95% CI 0.673–0.995; p = 0.044) were identified as independent predictors of syncope. In ROC analysis, age, AVA, change in PSV and EDV for both carotid and vertebral arteries were good predictors of syncope (Table 3). However, predictive ability of PSV or EDV derived from carotid arteries was better than what was derived from vertebral arteries.

Discussion

One hundred and eight patients with severe AS by echocardiography and Doppler ultrasound of blood flow in extracranial arteries in either the supine position or after orthostatic stress were evaluated. Moreover, an assessment to find optimal predictors of syncope in those patients and the ability to identify the following factors predicting syncope: age, AVA and decreased blood flow velocities in carotid and vertebral arteries after an orthostatic unload test. Aortic valve stenosis in its calcific form and with an increasing prevalence in the population of 65 year-olds and over requires a comprehensive clinical and echocardiographic assessment before any treatment [1]. Additionally, patients with severe AS should undergo a Doppler ultrasound examination of carotid and vertebral arteries as a part of a comprehensive assessment before surgical valve replacement or TAVI to reveal any severe stenosis or occlusion. In patients scheduled for TAVI there are concerns linked to the presence of significant stenosis or occlusion of ICA and rapid ventricular pacing during balloon aortic valvuloplasty and prosthesis deployment. In patients undergoing surgery, major concerns are related to intraprocedural hypotonia resulting in hypoperfusion in cerebral blood flow. The common symptom of AS is syncope, which initially may develop only during exercise or with changes in the body position. It may be caused by decreased cerebral blood flow, also as a result of arrhythmias [1, 7–10]. Several studies assessed the increased incidence of syncope in patients with severe AS but failed to show a link between any parameter apart from aortic valve stenosis severity and possible ventricular arrhythmias [9–11]. Left ventricular hypertrophy which occurs in patients with AS and reduced ejection fraction are well-known predictors of higher incidence of arrhythmias [12–15]. Conduction disturbances, resulting with syncope, caused by calcifications are also possible. The evaluation of valve disorder only at resting conditions may underestimate the real state of the defect and its clinical impact. Orthostatic-induced changes in Doppler echocardiographic measures of transaortic gradient in patients with AS have been described before [2]. Standing is an incremental activity of everyday life and may induce a fall in patients predisposed to syncope recognized as important problem in patients with cardiac disease. Performing Doppler ultrasound for screening purposes may not be enough and, in a considered opinion, should also be extended to an orthostatic unload test in AS patients. In a previous study, emphasis of the role of the orthostatic stress test in patients with severe AS, in whom was found a significant decrease in carotid and vertebral arterial flow velocities and flow volume in the upright position [6]. Sato et al. [16] showed that blood flow in the internal carotid artery and medial cerebral artery were reduced

during the head-up tilt test. Furthermore, Ogoh et al. [17] recently provided data that the effect of graded orthostatic stress on vertebral artery blood flow may be associated with hemodynamic changes in posterior rather than anterior cerebral blood flow. In the present study, however, mean PSV in carotid arteries were highly associated with syncope among all Doppler ultrasound parameters. Moreover, citing another study, the aim was to assess the effects of the orthostatic stress test on carotid and vertebral artery blood flow in patients with severe AS undergoing TAVI [18]. All duplex ultrasound parameters assessed in supine position have significantly improved in patients after TAVI as compared to baseline. The orthostatic stress test induced a decrease in carotid and vertebral arterial flow velocities in AS patients before and after TAVI. However, the drop in velocities and flow volume was numerically lower after TAVI. Therefore, TAVI may have some beneficial effect on extracranial artery blood flow by minimalization of its decrease as a response to orthostatic stress when assessed in long-term follow-up. In another study by Cammalleri et al. [19] monitoring of carotid Doppler measurements may be a useful and noninvasive method for acute assessment of the improvement of hemodynamic flow after TAVI for the cerebral region. A significant improvement of blood flow was found as the systolic peak velocity and the time average mean velocity increased at the end of the procedure.

Orthostatic unload is a very fast, safe and easy stress test without cost. It can be performed without additional equipment in terms of echocardiographic and carotid and vertebral Doppler ultrasound assessment. As shown, the estimation of the changes in cerebral blood flow in response to the orthostatic stress test in patients with AS may be linked to syncope and therefore for prognosis. Moreover, decreased blood flow in carotid and vertebral arteries in the supine position may play a role in asymptomatic patients with AS and may facilitate the time point of a decision about the final treatment — surgical valve replacement or TAVI.

Limitations of the study

The exclusion criteria of the study significantly constrained patient recruitment and resulted in relatively small sample size. Quality of acoustic window for Doppler assessment may also limit the use of the method.

Conclusions

In patients with AS, a decrease in carotid and vertebral arterial flow velocities in the standing position was observed and was associated with syncope. The present findings may support the value of the orthostatic test in identifying patients with severe AS and a higher risk of syncope.

Conflict of interest: None declared

References

1. Falk V, Baumgartner H, Bax JJ, et al. ESC Scientific Document Group, ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017; 38(36): 2739–2791, doi: 10.1093/eurheartj/ehx391, indexed in Pubmed: 28886619.
2. Dimitrow PP, Sorysz D. Orthostatic stress echocardiography as a useful test to measure variability of transvalvular pressure gradients in aortic stenosis. Cardiovasc Ultrasound. 2013; 11: 15, doi: 10.1186/1476-7120-11-15, indexed in Pubmed: 23706028.
3. Dimitrow PP, Bober M, Michałowska J, et al. Left ventricular outflow tract gradient provoked by upright position or exercise in treated patients with hypertrophic cardiomyopathy without obstruction at rest. Echocardiography. 2009; 26(5): 513–520, indexed in Pubmed: 19452607.
4. Dimitrow PP, Cheng TO. Standing position alone or in combination with exercise as a stress test to provoke left ventricular outflow tract gradient in hypertrophic cardiomyopathy and other conditions. Int J Cardiol. 2010; 143(3): 219–222, doi: 10.1016/j.ijcard.2010.04.026, indexed in Pubmed:20442001.
5. Mason DT, Braunwald E, Ross J. Effects of changes in body position on the severity of obstruction to left ventricular outflow in idiopathic hypertrophic subaortic stenosis. Circulation. 1966; 33(3): 374–382, indexed in Pubmed: 5904414.
6. Kleczyński P, Petkow Dimitrow P, Dziewierz A, et al. Decreased carotid and vertebral arterial blood-flow velocity in response to orthostatic unload in patients with severe aortic stenosis. Cardiol J. 2016; 23(4): 393–401, doi: 10.5603/CJ.a2016.0043, indexed in Pubmed: 27367481.
7. Ross J. Jr, Braunwald E. Aortic stenosis Circulation. 1968; 38: 61–67.
8. Schwartz LS, Goldfischer J, Sprague GJ, et al. Syncope and sudden death in aortic stenosis. Am J Cardiol. 1969; 23(5): 647–658, indexed in Pubmed:5771033.
9. Satoh M, Saeki M, Yamazoe M, et al. Syncope in aortic stenosis during continuous electrocardiographic monitoring. A case report. Jpn Circ J. 1988; 52(12): 1415–1418, doi: 10.1253/jcj.52.1415.
10. Omran H, Fehske W, Rabahieh R, et al. Valvular aortic stenosis: risk of syncope. J Heart Valve Dis. 1996; 5(1): 31–34, indexed in Pubmed: 8834722.
11. Orłowska-Baranowska E, Baranowski R, Hryniewiecki T. Incidence of syncope and cardiac arrest in patients with severe aortic stenosis. Pol Arch Med Wewn. 2014; 124(6): 306–312, indexed in Pubmed: 24781653.
12. Sorgato A, Faggiano P, Aurigemma GP, et al. Ventricular arrhythmias in adult aortic stenosis: prevalence, mechanisms,

and clinical relevance. Chest. 1998; 113(2): 482–491, indexed in Pubmed: 9498969.
13. Batur MK, Açil T, Onalan O, et al. Is ventricular repolarization heterogeneity a cause of serious ventricular tachyarrhythmias in aortic valve stenosis? Clin Cardiol. 2000; 23(6): 449–452, indexed in Pubmed: 10875037.
14. Koşar F, Tandoğan I, Hisar I, et al. QTc dispersion measurement for risk of syncope in patients with aortic stenosis. Angiology. 2001; 52(4): 259–265, doi: 10.1177/000331970105200405, indexed in Pubmed: 11330508.
15. Tsai JP, Lee PY, Wang KT, et al. Torsade de pointes in severe aortic stenosis: case report. J Heart Valve Dis. 2007; 16(5): 504–507, indexed in Pubmed:17944122.
16. Sato K, Fisher J, Seifert T, et al. Blood flow in internal carotid and vertebral arteries during orthostatic stress. Exp Physiol. 2012; 97(12): 1272–1280, doi:10.1113/expphysiol.2012.064774.
17. Ogoh S, Sato K, Okazaki K, et al. Blood flow in internal carotid and vertebral arteries during graded lower body negative pressure in humans. Exp Physiol. 2015; 100(3): 259–266, doi: 10.1113/expphysiol.2014.083964, indexed in Pubmed: 25641216.
18. Kleczyński P, Petkow Dimitrow P, Dziewierz A, et al. Transcatheter aortic valve implantation improves carotid and vertebral arterial blood flow in patients with severe aortic stenosis: practical role of orthostatic stress test. Clin Cardiol. 2017; 40(7): 492–497, doi: 10.1002/clc.22684, indexed in Pubmed: 28273361.
19. Cammalleri V, Romeo F, Marchei M, et al. Carotid Doppler sonography: additional tool to assess hemodynamic improvement after transcatheter aortic valve implantation. J Cardiovasc Med (Hagerstown). 2018; 19(3): 113–119, doi: 10.2459/JCM.0000000000000622, indexed in Pubmed: 29351134.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2020, Vol. 27, No. 6, 756–761
DOI: 10.5603/CJ.a2018.0064

ISSN 1897–5593
eISSN 1898–018X

The atherogenic index of plasma and its impact on recanalization of chronic total occlusion

Jan-Erik Guelker[1, 2, 3]*, Alexander Bufe[1, 2, 3]*, Christian Blockhaus[1, 2], Knut Kroeger[4], Thomas Rock[1, 2], Ibrahim Akin[5], Michael Behnes[5], Kambis Mashayekhi[6]

[1]Department of Cardiology, Heart Centre Niederrhein, Helios Clinic Krefeld, Germany
[2]Institute for Heart and Circulation Research, University Cologne, Germany
[3]University Witten/Herdecke, Witten, Germany
[4]Department of Angiology, Helios Clinic Krefeld, Germany
[5]First Department of Medicine, University Medical Centre Mannheim (UMM), Faculty of Medicine Mannheim, University of Heidelberg, Germany
[6]Division of Cardiology and Angiology II, University Heart Center Freiburg, Bad Krozingen, Germany

Abstract

Background: *The plasma-derived atherogenic index (AIP) is associated with an increasing risk for cardiovascular diseases. Whether an increased AIP may predict the complexity of percutaneous coronary intervention (PCI) of chronic total occlusion (CTO), according to available research, has never been investigated before.*

Methods: *Three hundred seventeen patients were included prospectively and treated with PCI for at least one CTO between 2012 and 2017. High-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) plasma levels were measured 24 h before PCI. All patients were stratified into tertiles of AIP (defined as 0.11, 0.11–0.21, > 0.21) based on their TG/HDL-C (AIP) levels.*

Results: *Mean AIP of all patients undergoing CTO-PCI was 0.53 ± 0.29. The majority of patients were male (82.6%), and mean age was 61 ± 10.4 years. Increased AIP > 0.21 was associated with longer occlusion length (statistical trend p = 0.082) and stent routes (p = 0.022) and with a higher number of implanted stents (n > 4) (statistical trend p = 0.072). Success rates were similar in all AIP categories (p = 0.461). In-hospital PCI-related complications were rare and not statistically different (p = 0.852).*

Conclusions: *This study demonstrates for the first time that an increased AIP may predict the complexity of CTO-PCI and additionally may help to improve planning and quality of CTO-PCI.* (Cardiol J 2020; 27, 6: 756–761)

Key words: atherogenic index, chronic total occlusion, coronary artery disease, percutaneous coronary intervention

Introduction

Recanalization of chronic total occlusion (CTO) still remains a challenging procedure in interventional cardiology. A CTO of a coronary artery can be identified in up to 18% among patients with a clinical indication for coronary angiography. With the advent of novel recanalization techniques and emerging devices, percutaneous coronary intervention (PCI) has become promising leading treatment option for these patients [1–5].

Address for correspondence: Jan-Erik Guelker, MD, Heartcentre Niederrhein, Department of Cardiology, Helios Clinic Krefeld, Lutherplatz 40, 47805 Krefeld, Germany, Institute for Heart and Circulation Research, University Cologne, Germany, tel: 0049-2151-32-4366, fax: 0049-2151-32-2026, e-mail: jan-erik.guelker@helios-gesundheit.de

Received: 14.03.2018 Accepted: 4.05.2018

*Contributed equally

The atherogenic index of plasma (AIP), the logarithm of molar ratio of triglyceridemia (TG) to high-density lipoprotein cholesterol (HDL-C) has been established as one marker to predict plasma atherogenicity and coronary artery disease (CAD) [6, 7]. Although some lipid variables were associated with the extent of CAD, the specific ratio of TG to HDL-C ratio showed the strongest association respectively. Variation of TG/HDL-C ratio may also be more associated with substantial alterations in metabolic indices predictive for increasing risk of ischemic heart disease compared to variation of low-density lipoprotein cholesterol (LDL-C)/HDL-C ratio [6, 7]. Is has been shown recently that AIP may reveal highest sensitivity for predicting acute coronary events [8].

Within this context, this study assessed the association between AIP, as a major risk factor of CAD, and CTO and CTO-PCI, as a complex coronary intervention.

Methods

Between 2012 and 2017, a total of 317 patients undergoing CTO-PCI in a German high volume CTO center. All patients had a clinical indication for CTO-PCI and/or positive functional ischemia test assessed by magnetic resonance imaging (MRI) or stress-echocardiography in the territory of the occluded coronary artery.

All procedures were performed via femoral access using 7-french guiding catheters; in the majority of patients contralateral injections of contrast were performed to determine the length of the lesion and the existence and extent of collateral connections. Decisions to treat patients either by antegrade or retrograde CTO-PCI techniques was based on operator discretion. To prevent thrombembolic complications heparin was administered intravenously during CTO-PCI, guided by activated clotting time (> 300 s).

The J-CTO score, combining several parameters of CTO including the degree of calcification of lesion, bending > 45° in CTO segment, blunt proximal cap, length of occluded segment (> 20 mm) and a previously failed recanalization attempt, was calculated for all patients [9].

After PCI a dual antiplatelet therapy consisting of 100 mg of acetylsalicylic acid once daily indefinitely and 75 mg of clopidogrel once daily for at least 6 months was continued. Procedural success was defined as successful recanalization of CTO with a residual stenosis < 30% and restoration of Thrombolysis in Myocardial Infarction (TIMI)-flow grade 3.

A composite safety endpoint summarizing severe complications such as all-cause mortality, vessel perforation, myocardial infarction (MI) and thrombembolic events was evaluated for all patients.

Triglycerides and HDL-C levels were measured after taking venous blood samples in EDTA tubes 24 h before the procedure. Analysis of plasma or serum total cholesterol (TC) and HDL was measured directly in serum while TG were measured enzymatically in serum or plasma [10]. TG/HDL-C was calculated as TG (mmol/L) divided by HDL-C (mmol/L). The patients were separately grouped into tertiles based on TG/HDL-C levels. It has been demonstrated before that an AIP value of under 0.11 is associated with low risk of cardiovascular disease (CVD); the values between 0.11 to 0.21 and upper than 0.21 are associated with intermediate and increased risks, respectively [6, 7].

Statistical analysis

The distribution of continuous variables is characterized by mean ± standard deviation, or median and minimum–maximum, the distribution of categorical variables by absolute and relative frequencies.

The Shapiro-Wilk test was used to test for normality of data. The differences of distributions of continuous variables between three AIP categories were tested with the Kruskal–Wallis test (rejected normality) or F test. Differences in distributions of categorical variables were tested using the Fisher exact test.

According to the exploratory character of analysis all p values were interpreted as descriptive measures rather than as definitive inferential measures.

Results

The overall procedural success rate was 86% which is in accordance with actual trials. The majority of the patients were male (82.6%), and the mean age was 61 ± 10.4 years. The mean AIP of all patients was 0.53 ± 0.29; male patients were younger than women (60.3 ± 10.2 years vs. 64.6 ± ± 10.7 years; $p < 0.005$). 92% of patients were already under medication with cholesterol synthesis enzyme (CSE) inhibitors. No differences were found between patients with CSE inhibitor to those without CSE in this study population.

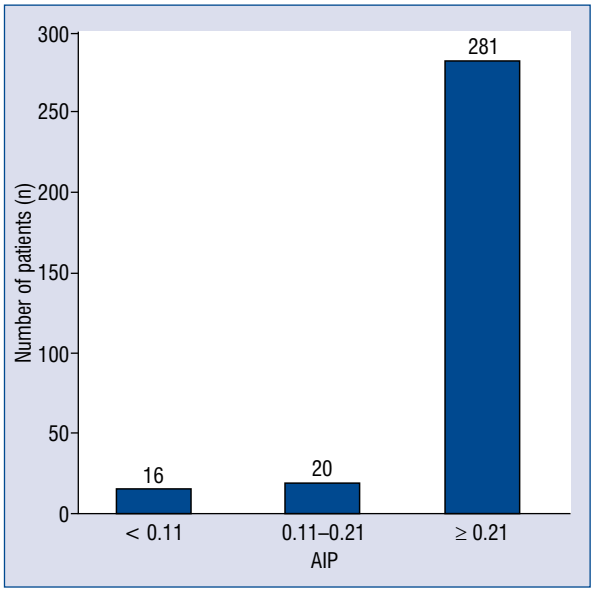


Figure 1. Distribution of atherogenic index of plasma (AIP) categories.

Figure 1 shows a disproportionate distribution of AIP categories in the present cohort. Only 5% of patients (n = 16) had a normal AIP level of < 0.11. Table 1 presents baseline characteristics of the patients studied, and are classified by AIP categories.

Patients with an AIP > 0.21 were more frequent male (p = 0.075) and had a higher body mass index (BMI) (p = 0.023). They also had a higher LDL-C (p = 0.043) and suffered more frequently from arterial hypertension (p = 0.084). There was an increase of frequency of diabetes mellitus (DM), BMI, smoking and family history of CAD alongside an increase in AIP. In summary, these cardiovascular risk factors were associated with a high AIP.

This increase was also seen for some periprocedural characteristics as shown in Table 2.

A high AIP > 0.21 was associated with longest occlusions (statistical trend p = 0.082), the longest stent routes (p = 0.022; Table 1) and highest number of the implanted stents (n > 4) after successful recanalization (statistical trend p = 0.072) (Table 2). Although the J-CTO score — representing the complexity of the CTO lesion — was related to a high AIP (p = 0.015; Fig. 2), procedural variables such as amount of contrast medium, examination time and fluoroscopy time were independent of the extent of AIP.

Table 1. Baseline and periprocedural characteristics of the study patients, classified by atherogenic index of plasma (AIP) categories.

Variable	AIP			
	< 0.11	0.11–0.21	> 0.21	P
Number	16	20	281	
Age [years]*	62 (37–86)	61 (39–81)	61 (33–87)	0.870
Male gender	68.8% (11)	70.0% (14)	84.3% (237)	0.075
BMI [kg/m²]*	26.0 (21–39)	27.0 (19–35)	27.4 (17–45)	0.023
Diabetes mellitus	18.8% (3)	30.0% (6)	24.6% (69)	0.742
Smoking	25.0% (4)	30.0% (6)	46.6% (131)	0.101
COPD	6.3% (1)	15.0% (3)	7.1% (20)	0.377
LDL-C > 100 mg/dL	18.8% (3)	50.0% (10)	50.5% (142)	0.043
Hypertension	56.3% (9)	75.0% (15)	79.4% (223)	0.084
Family history of CAD	12.5% (2)	25.0% (5)	27.4% (77)	0.446
Prior MI	6.3% (1)	30.0% (6)	28.8% (81)	0.139
Prior CABG	12.5% (2)	0.0% (0)	13.2% (37)	0.245
Prior CTO-PCI attempt	37.5% (6)	35.0% (7)	49.8% (140)	0.325
Prior PCI	37.5% (6)	30.0% (6)	40.2% (113)	0.706
LVEF ≥ 40%	93.8% (15)	100% (20)	97.5% (274)	0.403
Amount of contrast medium [mL]*	220.9 (90–500)	226.8 (90–600)	228.2 (70–600)	0.736
Examination time [min]*	108.4 (45–180)	95.3 (30–220)	110.9 (15–300)	0.110
Fluoroscopy time [min]*	37.4 (11–76)	34.9 (4–94)	37.6 (7–104)	0.476
Lenght of occlusion [mm]*	32.8 (15–70)	29.5 (15–70)	37.6 (10–100)	0.082
Stent diameter [mm]*	3.0 (2.5–3.5)	2.9 (2.5–3.5)	3.1 (2.25–4.0)	0.122
Lenght of stent [mm]	61.0 (23–119)	52.2 (18–104)	69.1 (12–157)	0.022

*Median (min–max); BMI — body mass index; CABG — coronary artery bypass graft surgery; CAD — coronary artery disease; COPD — chronic obstructive pulmonary disease; CTO — chronic total occlusion; LDL-C — low density lipoprotein cholesterol; LVEF — left ventricular ejection fraction; MI — myocardial infarction; PCI — percutaneous coronary intervention

Table 2. Angiographic characetristics and procedural outcome, classified by median atherogenic index of plasma (AIP).

Variable	N	Mean AIP	P
CTO in:			0.862
LAD	87	0.511	
LCX	32	0.564	
RCA	197	0.528	
Coronary vessel disease:			0.535
1	93	0.522	
2	123	0.513	
3	102	0.556	
Blunt stump/no stump	215	0.536	0.483
Tortuosity > 90°	226	0.538	0.315
Severe calcification	248	0.538	0.208
J-CTO score:			0.015
0	9	0.358	
1	28	0.366	
2	56	0.587	
3	77	0.539	
4	108	0.558	
5	39	0.502	
Retrograde approach	80	0.596	0.015
Drug eluting stents	270	0.525	0.662
Number of stents:			0.072
0	36	0.545	
1	53	0.424	
2	117	0.553	
3	25	0.531	
≥ 4			
Success	272	0.524	0.461
Complications	20	0.531	0.852

CTO — chronic total occlusion; J–CTO — Japansese chronic total occlusion; LAD — left anterior descending; LCX — left circumflex; RCA — right coronary artery

A majority of patients suffered from a multivessel coronary disease; 38.8% had coronary 2-vessel disease and 32.2% coronary 3-vessel disease.

No differences in procedural success rates in different AIP categories was shown (p = 0.461). In-hospital, acute procedural complications were rare and showed no statistically significant difference (p = 0.852). They included mostly vascular complications such as a local hematoma at puncture site (n = 19) and one cardiac tamponade which could be treated with a pericardiocentesis without further consequences. No severe complications such as peri-procedural death or ST-segment elevation myocardial infarction occurred.

Discussion

Dyslipidemia is an established risk factor for CVD in the general population.

The AIP, which was first described by Dobiášová and Frohlich in 2001 [11], is a comprehensive lipid index, and a strong marker for predicting risk of CAD [8]. In this retrospective study, we examined the association between AIP and patients with CTO and CTO recanalization, respectively. According to available research, no data are available in the current literature about this issue.

The present data emphasizes several important aspects. First, we did show that AIP may predict complexity of a CTO, evaluated by J-CTO score, including severe calcification, tortuosity, stump morphology and lesion length. Second, it could demonstrated that AIP is associated with peri-procedural characteristics such as number and length of stents after a successful recanalization. Third, it was confirmed that AIP is closely related to several cardiovascular risk factors including male gender.

These findings are in accordance with previous trials, showing a strong association between AIP, cardiovascular risk factors and severity of CAD [7, 12]. Therefore Niroumand et al. [12] has suggested that AIP could be used as a regular monitoring index of CAD in every day practice, while Wan et al. [13] proved that an elevated AIP is a powerful independent predictor of all-cause mortality and for subsequent CVD after coronary revascularization [13]. Lee et al. [14] confirmed prognostic relevance of AIP within a nationwide prospective cohort including more than 1,000 patients with a terminal renal failure. Furthermore Shimizu et al. [15] found a significant positive correlation between DM and AIP and as well as with carotid intima-media thickness, progression and arterial stiffness.

An explanation may be the association of AIP with LDL-C particle size, insulin resistance and metabolic syndrome [11, 16–18]. Hermans et al. [19] demonstrated a relationship between AIP and vascular damage and an association with residual vascular risk, beta-cell function loss and microangiopathy in diabetic patients.

The present study observes that patients with a higher BMI revealed an increased AIP (p = 0.023). These findings are in agreement

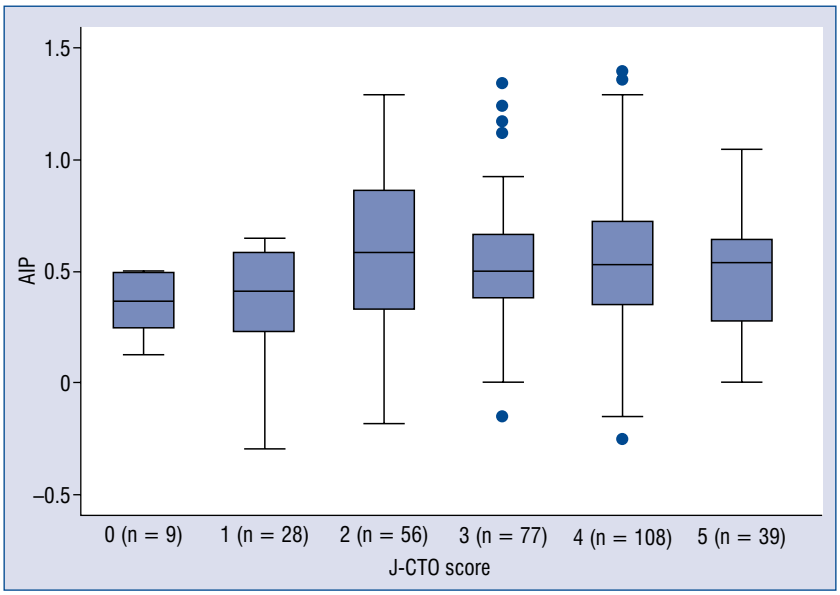


Figure 2. Atherogenic index of plasma (AIP) in Japanese chronic total occlusion (J-CTO) score categories.

with previous data that proved close association between abnormalities of blood lipoproteins and habits of people, such as life style and eating habits [12, 20, 21].

Higher AIP correlates with a higher J-CTO Score, but failed to shown as a predictor for procedural success in CTO recanalization. Lemieux et al. [6] proved that in predicting CAD the AIP is superior to other indices like TC/HDL-C ratio and LDL-C/HDL-C ratio [6]. Furthermore Yildiz et al. [22] suggested that AIP might be a method which can be used for both diagnosis of subclinical atherosclerosis and in deceleration processes of its progression.

The fact that the AIP is associated with male gender in this study ($p = 0.075$) is in accordance with a large chinese cohort with over 430 patients which showed increased AIP being independently associated with coronary heart disease in Chinese males [23].

The AIP may be helpful to estimate the complexity of the procedure in advance and to make a decision on this basis. It is also easy to calculate and may be included in daily clinical practice. Unfortunately it could not demonstrated that this index can predict possible complications related to the complex coronary intervention of CTO-PCI. Gritzenko et al. [24] pointed out that AIP may be necessary to risk assessment before PCI and CABG. In a trial of 186 patients it was shown that this index can significantly predict re-stenosis after CABG and PCI.

Limitations of the study

The present study is a retrospective analysis and all data are collected from a single-center. The results of this study may have been influenced by selection criteria, operator experience, and varying techniques used by operators. Furthermore, there was no data about the impact of long term follow-up of AIP in CTO patients. Another limitation may be that the matched and un-matched data used in this study were already collected. Thus, the analysis represents an observational character only.

Conclusions

The TG/HDL-C ratio may be an independent predictor for complexity of a CTO. Prospective evaluation of AIP as a determinant of the lesion may add adjunctive information for procedural planning of intervention.

Conflict of interest: Dr. Kambis Mashayekhi received consulting/speaker honoraria from Abbott Vascular, Asahi Intecc, Biotronik, Boston Scientific, Daiichi Sankyo, Nitiloop, Vascular Solution, Termuo. Other authors declare no conflict of interest.

References

1. Fefer P, Knudtson ML, Cheema AN, et al. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. J Am Coll Cardiol. 2012; 59(11): 991–997, doi: 10.1016/j.jacc.2011.12.007, indexed in Pubmed: 22402070.
2. Tomasello SD, Boukhris M, Giubilato S, et al. Management strategies in patients affected by chronic total occlusions: results from the Italian Registry of Chronic Total Occlusions. Eur Heart J. 2015; 36(45): 3189–3198, doi: 10.1093/eurheartj/ehv450, indexed in Pubmed: 26333367.
3. Bufe A, Haltern G, Dinh W, et al. Recanalisation of coronary chronic total occlusions with new techniques including the retrograde approach via collaterals. Neth Heart J. 2011; 19(4): 162–167, doi: 10.1007/s12471-011-0091-7, indexed in Pubmed: 22020996.
4. Galassi AR, Tomasello SD, Reifart N, et al. In-hospital outcomes of percutaneous coronary intervention in patients with chronic total occlusion: insights from the ERCTO (European Registry of Chronic Total Occlusion) registry. EuroIntervention. 2011; 7(4): 472–479, doi: 10.4244/EIJV7I4A77, indexed in Pubmed: 21764666.
5. Stähli BE, Gebhard C, Gick M, et al. Impact of body mass index on long-term mortality in women and men undergoing percutaneous coronary intervention for chronic total occlusion. Int J Cardiol. 2016; 224: 305–309, doi: 10.1016/j.ijcard.2016.09.057, indexed in Pubmed: 27665402.
6. Lemieux I, Lamarche B, Couillard C, et al. Total cholesterol/HDL cholesterol ratio vs LDL cholesterol/HDL cholesterol ratio as indices of ischemic heart disease risk in men: the Quebec Cardiovascular Study. Arch Intern Med. 2001; 161(22): 2685–2692, indexed in Pubmed: 11732933.
7. Lemos da Luz P, Favarato D, Faria-Neto Junior JR, et al. High ratio of triglycerides to hdl-cholesterol predicts extensive coronary disease. Clinics. 2008; 63(4), doi: 10.1590/s1807-59322008000400003.
8. Khazaál MS. Atherogenic Index of Plasma (AIP) as a parameter in predicting cardiovascular risk in males compared to the conventional dyslipidemic indices (cholesterol ratios). Karbala J Med. 2013; 6(1): 1506–11.
9. Morino Y, Abe M, Morimoto T, et al. J-CTO Registry Investigators. Predicting successful guidewire crossing through chronic total occlusion of native coronary lesions within 30 minutes: the J-CTO (Multicenter CTO Registry in Japan) score as a difficulty grading and time assessment tool. JACC Cardiovasc Interv. 2011; 4(2): 213–221, doi: 10.1016/j.jcin.2010.09.024, indexed in Pubmed: 21349461.
10. Cox RA, García-Palmieri MR. Cholesterol, Triglycerides, and Associated Lipoproteins. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd.
11. Dobiášová M, Frohlich J. The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate inapob-lipoprotein-depleted plasma (FERHDL). Clin Biochem. 2001; 34(7): 583–588, doi: 10.1016/s0009-9120(01)00263-6.
12. Niroumand S, Khajedaluee M, Khadem-Rezaiyan M, et al. Atherogenic Index of Plasma (AIP): A marker of cardiovascular disease. Med J Islam Repub Iran. 2015; 29: 240, indexed in Pubmed: 26793631.
13. Wan Ke, Zhao J, Huang H, et al. The association between triglyceride/high-density lipoprotein cholesterol ratio and all-cause mortality in acute coronary syndrome after coronary revascularization. PLoS One. 2015; 10(4): e0123521, doi: 10.1371/journal.pone.0123521, indexed in Pubmed: 25880982.
14. Lee MiJ, Park JT, Han SH, et al. The atherogenic index of plasma and the risk of mortality in incident dialysis patients: Results from a nationwide prospective cohort in Korea. PLoS One. 2017; 12(5): e0177499, doi: 10.1371/journal.pone.0177499, indexed in Pubmed: 28549070.
15. Shimizu Y, Nakazato M, Sekita T, et al. Association of arterial stiffness and diabetes with triglycerides-to-HDL cholesterol ratio for Japanese men: the Nagasaki Islands Study. Atherosclerosis. 2013; 228(2): 491–495, doi: 10.1016/j.atherosclerosis.2013.03.021, indexed in Pubmed: 23601500.
16. McLaughlin T, Reaven G, Abbasi F, et al. Is there a simple way to identify insulin-resistant individuals at increased risk of cardiovascular disease? Am J Cardiol. 2005; 96(3): 399–404, doi: 10.1016/j.amjcard.2005.03.085, indexed in Pubmed: 16054467.
17. Hermans MP, Ahn SA, Rousseau MF. log(TG)/HDL-C is related to both residual cardiometabolic risk and β-cell function loss in type 2 diabetes males. Cardiovasc Diabetol. 2010; 9: 88, doi: 10.1186/1475-2840-9-88, indexed in Pubmed: 21156040.
18. Onat A, Can G, Kaya H, et al. "Atherogenic index of plasma" (log10 triglyceride/high-density lipoprotein-cholesterol) predicts high blood pressure, diabetes, and vascular events. J Clin Lipidol. 2010; 4(2): 89–98, doi: 10.1016/j.jacl.2010.02.005, indexed in Pubmed: 21122635.
19. Hermans MP, Ahn SA, Rousseau MF. The atherogenic dyslipidemia ratio [log(TG)/HDL-C] is associated with residual vascular risk, beta-cell function loss and microangiopathy in type 2 diabetes females. Lipids Health Dis. 2012; 11: 132, doi: 10.1186/1476-511X-11-132, indexed in Pubmed: 23046637.
20. Kanthe PS, Patil BS, Bagali Sh, et al. Atherogenic Index as a Predictor of Cardiovascular Risk among Women with Different Grades of Obesity. IJCRIMPH. 2012; 4(10): 1767–1774.
21. Flier JS. Biology of Obesity. In: Kasper DL, Fauci AS, Longo DL, Braunwald E, Hauser SL, Jameson JL. eds. Harrison's Principles of Internal Medicine.17th ed. New York, NY : 462–464.
22. Yildiz G, Duman A, Aydin H, et al. Evaluation of association between atherogenic index of plasma and intima-media thickness of the carotid artery for subclinic atherosclerosis in patients on maintenance hemodialysis. Hemodial Int. 2013; 17(3): 397–405, doi: 10.1111/hdi.12041, indexed in Pubmed: 23551383.
23. Ni W, Zhou Z, Liu T, et al. Gender-and lesion number-dependent difference in "atherogenic index of plasma" in Chinese people with coronary heart disease. Sci Rep. 2017; 7(1): 13207, doi: 10.1038/s41598-017-13267-6, indexed in Pubmed: 29038593.
24. Gritzenko O, Chumakova G, Veselovskaya N. Atherogenic indexes as predictors of stenotic complication after percutaneous coronary interventions or coronary artery bypass graft. Atherosclerosis. 2015; 241(1): e212, doi: 10.1016/j.atherosclerosis.2015.04.1005.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2020, Vol. 27, No. 6, 762–771
DOI: 10.5603/CJ.a2018.0069

ISSN 1897–5593
eISSN 1898–018X

Effect of moderate-intensity statin therapy on plaque inflammation in patients with acute coronary syndrome: A prospective interventional study evaluated by 18F-FDG PET/CT of the carotid artery

Chan Joon Kim[1], Eun Ji Han[2], Eun-Ho Chu[1], Byung-Hee Hwang[3], Jin-Jin Kim[3], Ki-Bae Seung[4], Sung Hoon Kim[5], Joo Hyun O[5], Kiyuk Chang[4]

[1]Department of Cardiology, College of Medicine, Uijoengbu St. Mary's Hospital, The Catholic University of Korea, Uijoenbu-si, Gyeonggi-do, Republic of Korea
[2]Department of Radiology, College of Medicine, Daejeon St. Mary's Hospital, The Catholic University of Korea
[3]Department of Cardiology, College of Medicine, St. Paul's Hospital, The Catholic University of Korea, Seoul, Republic of Korea
[4]Department of Cardiology, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea
[5]Department of Radiology, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea

Abstract

Background: *Asian patients with acute coronary syndrome (ACS) are frequently prescribed moderate--intensity statin in real practice, even during the early stage of ACS. Under assessment herein was the effect of moderate-intensity statin therapy on the resolution of plaque inflammation during the first month after ACS, a period with highest recurrent ischemic events, using dual time point ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT).*

Methods: *This prospective study included statin-naïve patients with ACS and non-calcified carotid plaques (≥ 3 mm on ultrasound images). Baseline FDG PET/CT images of the carotid arteries of the patients were obtained. Then, all patients received atorvastatin (20 mg/day); follow-up FDG PET/ /CT images of the carotid arteries were then obtained after 1 month of therapy. The primary endpoint measurement was the change in the target-to-background ratio (TBR) of the carotid artery between the initial and follow-up FDG PET/CT scans.*

Results: *Thirteen ACS patients completed the initial and follow-up FDG PET/CT scans. Moderate-intensity statin therapy failed to reduce plaque inflammation at 1 month after ACS (TBR 1.60 ± 0.20 at baseline vs. 1.50 ± 0.40 after therapy; $p = 0.422$) but significantly reduced serum low-density lipoprotein cholesterol (LDL-C) levels (mean LDL-C 101.2 ± 21.1 mg/dL at baseline vs. 70.7 ± 12.4 mg/dL after therapy; $p < 0.001$). Changes in the TBR and serum LDL-C levels were not correlated ($r = –0.27$, $p = 0.243$).*

Conclusions: *Dual time point FDG PET/CT imaging demonstrates that moderate-intensity statin therapy was insufficient in suppressed plaque inflammation within the first month after ACS in Asian patients, even though achieving target LDL levels.* (Cardiol J 2020; 27, 6: 762–771)

Key words: statin, ^{18}F-FDG PET/CT, low-density lipoprotein cholesterol, acute coronary syndromes

Address for correspondence: Kiyuk Chang, MD, PhD, Department of Cardiology, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Banpo-daero 222, Seocho-gu, Seoul 137-701, Republic of Korea, tel: +82-2-2258-6032, fax: +82-2-2258-1138, e-mail: kiyuk@catholic.ac.kr

Received: 13.09.2017 Accepted: 11.06.2018

Introduction

High-intensity statin therapy has significantly improved the clinical outcomes of patients with acute coronary syndrome (ACS). Because the greatest risk for recurrent cardiovascular (CV) events occurs during the first month after ACS [1, 2], the early initiation of high-intensity statin therapy in ACS patients at the time of intense vascular inflammation improves their CV prognosis by systematically stabilizing highly inflamed plaques. Indeed, a previous study demonstrated the benefits of early statin therapy in reducing ischemic events within 30 days subsequent to ACS [3].

Statins are prescribed at lower starting doses to patients at risk of developing side effects: Asian, female, those with smaller body frame, age exceeding 65 years, kidney or liver disease, or excessive alcohol consumption. Asian patients especially, receive lower doses of statin in most clinical settings compared with their Western counterparts [4]. In clinical practice, only 14.2% of Korean ACS patients received high-intensity statin therapy even after percutaneous coronary intervention (PCI) [5]. Moreover, in the 2013 ACC/AHA guidelines, Asian ancestry is considered as a characteristic that might modify a decision to use high-intensity statin therapy [6]. However, no evidence exists that moderate-intensity statin therapy is sufficient to resolve plaque inflammation in earlier stages of ACS in Asians.

To address this issue, dual time point ^{18}F--fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) imaging of carotid arteries was used. FDG PET/CT provides a noninvasive measure of carotid plaque inflammation in patients [7] and successfully monitors alterations in plaque inflammation following therapy with simvastatin [8, 9] and antioxidant probucol [10]. Under investigation in this study was the effect of moderate-intensity statin therapy on plaque inflammation in early-stage non-ST-segment elevation (NSTE)-ACS patients by performing a longitudinal spatial assessment of statin-modulated alterations of carotid FDG uptake. An assessment was also made as to whether changes in plasma low-density lipoprotein cholesterol (LDL-C) levels, a clinical marker of statin efficacy, correlated with changes in carotid FDG uptake.

Methods

Design and subjects

This study was a prospective observational study involving statin treatment and imaging assessment of atherosclerotic plaque inflammation using dual time point FDG PET/CT scans of carotid arteries. The study protocol was approved by the institutional review board of Seoul St. Mary's Hospital, Seoul, Korea (KC09MISV0195). All subjects provided written informed consent. Patients were eligible for this study if they presented with NSTE-ACS, underwent PCI and had non-calcified atherosclerotic plaques ≥ 3 mm in carotid arteries, as identified using cervical ultrasound (US) examination (Fig. 1). Patients with any of the following conditions were excluded: statin or thiazolinedione therapy within the prior 4 weeks; elevated liver enzyme levels (≥ 2.5 times the normal upper limit); congestive heart failure of New York Heart Association (NYHA) classification class 2 to 4; age < 18 years; and pregnancy. All patients first underwent initial FDG PET/CT scans of their carotid arteries within 7 days after index PCI, followed by statin treatment. One month later, follow-up FDG PET/CT scans of the carotid arteries were performed.

Statin therapy

All study subjects received 20 mg atorvastatin immediately after baseline FDG PET/CT scanning. All medications, including antidiabetic medications, antiplatelet agents and antihypertensive medications, taken by patients prior to baseline FDG PET/CT scanning were continued.

^{18}F-FDG PET/CT imaging

After a minimum of 6 h of fasting, patients with blood sugar levels of less than 130 mg/dL were intravenously administered approximately 10 mCi of ^{18}F-FDG. Diabetic patients were instructed not to take oral anti-hyperglycemic agents or to inject insulins during fasting time. The patients were then encouraged to drink water and urinate often and had bed rest prior to image acquisition. 90 min after the FDG injection, PET/CT images of the neck region were obtained using a dedicated PET/CT scanner (High Definition Biograph Truepoint; Siemens, Germany). For carotid imaging, non-contrast-enhanced CT images were obtained from the skull base to the lower margin of the neck and were used for attenuation correction (40-section helical, 5 mm section slice). PET images were acquired at 10 min per bed position, from approximately 2 to 4 beds. Contrast enhancement was not performed throughout PET/CT imaging. One month after atorvastatin therapy, follow-up PET/CT images of carotid arteries of 13 of the 20 patients were obtained using the same imaging protocol.

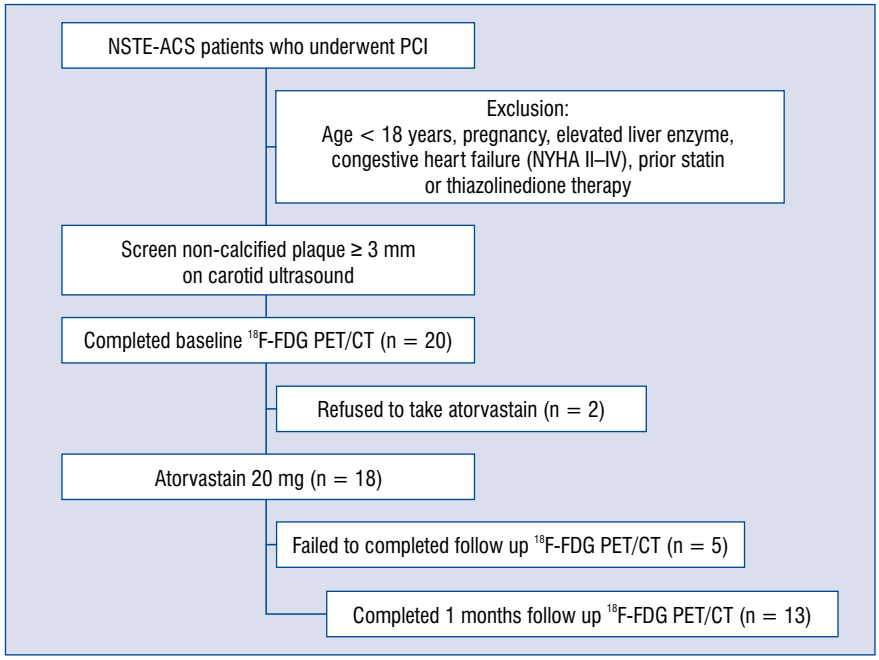


Figure 1. Study design — flow chart of the patient enrollment process and study schema; abbreviations — see text.

^{18}F-FDG PET/CT analysis

The FDG-PET/CT images were visually evaluated for the presence of abnormal FDG uptake in the bilateral carotid arteries. FDG uptake in the arterial plaques was then quantified by measuring the standardized uptake value (SUV) corrected for body weight. The SUV was calculated usinga pixel activity value within the region of interest (ROI) placed on the entire vasculature obtained from consecutive, co-registered transaxial FDG--PET and non-contrast-enhanced CT images. The SUV_{max} was recorded as the highest pixel activity value within the ROI for every slice of the vessel. The SUV_{max} was measured along carotid arteries at 5-mm intervals in an axial orientation. The mean SUV_{max} was calculated by averaging SUV_{max} values for all slices within arterial territories. The arterial target-to-background ratio (TBR) was calculated by dividing maximal arterial SUV by blood (jugular vein) FDG uptake to produce a blood-corrected arterial SUV ($SUV_{carotid/jugular}$). Additionally, metabolic lesion volumes (MLV) were computed for each patient's carotid artery lesions by adding all pixels with SUVs greater than the designated cut-off values (SUV cutoff was set at 1.0, or SUV_{max} of neck muscle was used) in manually defined ROIs. Two nuclear medicine physicians who were blinded to patient clinical information performed FDG uptake measurements, which were then averaged. When the difference in measurements between the two readers was greater than 20%, a third nuclear medicine physician helped to reach a consensus. The change in TBR (ΔTBR) was defined as the difference in TBR between baseline and follow-up PET/CT images of the neck.

The primary endpoint value was the absolute change in TBR within an index vessel after 1 month of atorvastatin therapy. The index vessel was defined as the carotid artery in which plaque buildup was detected using cervical ultrasound before treatment. In cases where both carotid arteries had detectable plaque buildup, the artery with the higher FDG uptake was chosen as the index vessel.

^{18}F-FDG PET/CT reproducibility test

FDG PET/CT reproducibility tests were performed at the participating institution using phantoms asa requisite condition for enrollment in unrelated international drug trials. The various PET/CT system parameters were also assessed for quality control on a daily and bimonthly basis as part of a routine clinical practice.

Measurement of blood metabolic, lipid, and inflammatory parameters

Blood was collected before and 1 month after atorvastatin therapy for the measurement of serum metabolic, lipid, and inflammatory parameters. Fasting serum glucose, total cholesterol, triglyceride, direct LDL-C and direct high-density

lipoprotein cholesterol (HDL-C) levels were measured using a Hitachi 7600 automatic chemistry analyzer (Hitachi Co., Tokyo, Japan) with reagents obtained from Sekisui Medical (Tokyo, Japan). High-sensitivity C-reactive protein (hsCRP) levels were measured using an immunoturbidimetric assay with reagents obtained from Wako Pure Chemical Industries (Osaka, Japan) and a Hitachi 7600 automatic chemistry analyzer. Serum insulin levels were measured according to the radioimmunoassay method using an immunoradiometric assay kit obtained from Dinabot Co. (Tokyo, Japan). Plasma matrix metalloproteinase-9 (MMP-9), monocyte chemoattractant protein-1 (MCP-1) and plasminogen activator inhibitor-1 (PAI-1) levels were measured using enzyme-linked immunosorbent assay (ELISA) kits (R&D systems, MN, USA). The homeostatic model assessment (HOMA) index was calculated based on serum glucose and insulin levels.

Statistical analysis

Assuming that 20% of patients would not be available for dual time point PET/CT, it was estimated that 18 patients would provide 80% power to detect an absolute decrease of 0.15 or greater in TBR, with a standard deviation of 0.2 and $\alpha = 0.05$ using 20 mg atorvastatin, based on the findings of a previous study [8].

Statistical analyses were performed using SPSS (v18.0; San Diego, CA). Data are expressed as the mean ± standard error of the mean (SEM). Paired Student t-test was used to assess differences in FDG uptake and blood parameters before and after therapy. Unpaired Student t-tests were used to test differences in the FDG uptake and blood parameters according to statin response. Spearman's correlation coefficients (r-values) were calculated for correlations. A p-value of less than 0.05 was considered statistically significant.

Results

Characteristics of the study population

Twenty statin-naïve patients who underwent PCI and were found to have non-calcified plaques in their carotid arteries consented to undergo dual time point FDG PET/CT studies of their carotid arteries, and 13 patients completed both pre- and post-statin FDG PET/CT scans and laboratory exams (Fig. 1). 11 male and 2 female patients were included, with a mean age of 67.3 years (52–78 years). 9 patients presented with unstable angina, and 4 patients presented with NSTE myocardial infarction (NSTEMI). All patients received acetylsalicylic acid and clopidogrel. 7 patients had diabetes mellitus and all of them were using oral hypoglycemic agents. The clinical profile and PCI data are summarized in Table 1.

Table 1 Baseline characteristics of patients in the study (n = 13).

Age [years] (range)	67.3 (52–78)
Male	11 (84.6%)
Diagnosis at presentation:	
Unstable angina	9 (69.2%)
NSTEMI	4 (30.8%)
Hypertension	9 (69.2%)
Diabetes mellitus	7 (53.8%)
Current smoker	3 (23.1%)
BMI [kg/m^2]	24.7 ± 2.5
Atorvastatin dose: 20 mg	13 (100%)
Other medications:	
ASA	13 (100%)
Clopidogrel	13 (100%)
ARB/ACEI	12 (92.3%)
β-blocker	10 (76.9%)
PCI data:	
Three vessel disease	3 (23.0%)
Two vessel disease	3 (23.0%)
One vessel disease	7 (53.8%)
Mean stent diameter [mm]	3.08 ± 0.29
Total stent length [mm]	39.4 ± 20.4
Total number of stent	1.69 ± 0.85
Number of B2 or C	0.77 ± 0.83
Peak CK-MB [ng/mL]	159.2 ± 165.3
Peak troponin I [ng/mL]	132.2 ± 143.9

ARB/ACEI — angiotensin receptor blocker/angiotensin-converting enzyme inhibitor; ASA — acetylsalicylic acid; BMI — body mass index; CK — creatinine kinase; NSTEMI — non-ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention

Treatment effects of moderate-intensity atorvastatin on plasma lipid, metabolic and inflammatory parameters

Statin therapy significantly reduced serum total cholesterol ($p < 0.001$) and triglyceride ($p = 0.033$) levels. Serum LDL-C levels markedly decreased from 101.2 ± 21.1 mg/dL to 70.7 ± ± 12.4 mg/dL ($p < 0.001$) following 1 month of statin therapy (Table 2). However, no change in serum HDL-C levels was observed. After statin therapy, 5 patients had follow-up serum LDL-C levels greater than 70 mg/dL but less than 90 mg/dL. In contrast to these improved lipid profiles, plasma inflammatory markers such as hsCRP, MMP-9

Table 2 Baseline and post-statin therapy values of serum lipid, metabolic and inflammatory markers as well as fluorodeoxyglucose (FDG) uptake parameters.

	Baseline	Post-statin	P
Total cholesterol [mg/dL]	163.9 ± 18.5	129.0 ± 18.6	< 0.001
Triglycerides [mg/dL]	131 ± 81.9	99.5 ± 51.8	0.033
LDL cholesterol [mg/dL]	101.2 ± 21.1	70.7 ± 12.4	< 0.001
HDL cholesterol [mg/dL]	36.5 ± 8.1	38.4 ± 9.3	0.373
Glucose [mg/dL]	126.5 ± 32.9	107.0 ± 14.2	0.029
hsCRP [mg/dL]	0.60 ± 0.82	0.21 ± 0.24	0.073
MMP-9 [ng/mL]	3.6 ± 2.8	3.7 ± 3.0	0.935
PAI-1 [ng/mL]	40.4 ± 23.6	21.6 ± 11.0	0.003
MCP-1 [pg/mL]	32.7 ± 21.1	33.0 ± 9.0	0.965
Mean SUV_{max}	2.2 ± 0.5	2.0 ± 0.3	0.174
TBR	1.6 ± 0.2	1.5 ± 0.4	0.422
$MLV_{1.0}$ [mm^3]	705.4 ± 724.2	733.1 ± 1213.1	0.926
MLV_{SCM} [mm^3]	1683.8 ± 1612.5	1149.2 ± 872.6	0.349

HDL — high-density lipoprotein; hsCRP — high-sensitivity C-reactive protein; LDL — low-density lipoprotein; MCP-1 — monocyte chemoattractant protein-1; $MLV_{1.0}$ — metabolic lesion volume computed using an SUV cutoff of 1.0; MLV_{SCM} — metabolic lesion volume computed using an SUV cutoff of sternocleidomastoid muscle; MMP-9 — matrix metalloproteinase-9; PAI-1 — plasminogen activator inhibitor-1; SUV_{max} — maximum standardized uptake value; TBR — ratio of the maximum standardized uptake value of the carotid plaque over the maximum standardized uptake value of the jugular vein

and MCP-1 were not significantly reduced despite statin therapy. Only PAI-1 responded to one-month statin therapy (p = 0.003).

Dual time point FDG PET/CT of carotid arteries

As assessed by 90-min post-FDG PET/CT images, no significant difference was noted in FDG uptake parameters before and after statin therapy (Table 2). Baseline and follow-up TBR values (1.60 ± 0.2 vs. 1.50 ± 0.40, respectively) were not significantly different (p = 0.422). Additionally, statin therapy did not alter any other FDG uptake parameter: (1) SUV_{max} (baseline 2.2 ± 0.5 vs. post-statin 2.0 ± 0.3, p = 0.174); (2) the MLV of carotid lesions with a fixed SUV cutoff of 1.0 ($MLV_{1.0}$; baseline 705.4 ± 724.2 mm^3 vs. post-statin 733.1 ± 1,213.1 mm^3, p = 0.926); (3) MLV with each patient's sternocleidomastoid (SCM) muscle SUV_{max} as the cutoff (MLV_{SCM}; baseline 1,683.8 ± ± 1,612.5 mm^3 vs. 1,149.2 ± 872.6 mm^3, p = 0.349). When individually analyzed, nine patients had decreased TBR values at follow-up ("statin-responder by PET" group; Fig. 2A), and 4 patients showed similar or paradoxically increased TBR despite adequate statin therapy ("statin-non-responder by PET" group; Fig. 2B, C). The mean follow-up plasma LDL-C levels were 69.8 ± 13.7 mg/dL in the "statin-responder by PET" group and 72.9 ± ± 9.9 mg/dL in the "statin-nonresponder by PET" group, and no significant difference was found between the two groups (p = 0.691).

Comparison of changes in the blood inflammatory markers and FDG uptake parameters between patients with post-statin LDL levels of less than and greater than 70 mg/dL

No differences in blood inflammatory parameters, including hsCRP, MMP-9, MCP-1 and PAI-1, or in FDG PET/CT parameters, including the mean SUV_{max}, TBR, $MLV_{1.0}$ and MLV_{SCM} were observed between the two groups (Table 3).

Comparison of changes in the blood inflammatory marker between statin responder by PET and non-responder

The inflammatory markers and FDG uptake markers were compared between PET-CT responder and non-responder. There were significant differences in MMP-9 change (ΔMMP-9) (baseline–follow-up) (responder –1.99 ± 3.02 vs. 3.04 ± 2.31, p = 0.042), however no significant differences were noted in other inflammatory markers (Table 4).

Correlation between plasma LDL-C levels and carotid FDG uptake

No correlation was observed between baseline serum LDL-C levels and the TBR (r = –0.57, p = 0.54) and between ΔLDL-C and ΔTBR (r = –0.35, p = 0.264). Additionally, no significant correlations were found between ΔLDL-C and

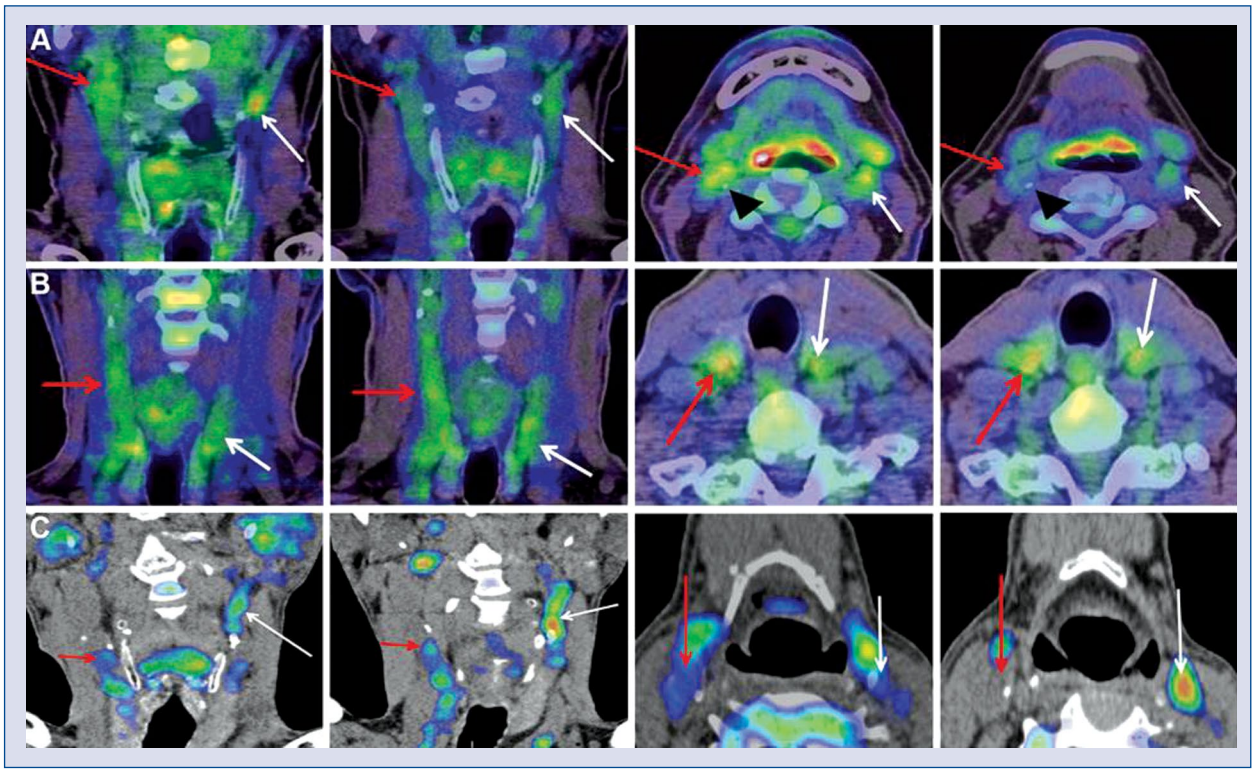


Figure 2. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) images — representative dual time point FDG PET/CT images of carotid arteries according to the response to statin therapy. **A.** "Responder by FDG PET/CT". Ill-defined FDG activity is noted in the bilateral carotid arteries of a 64-year-old male. Coronal and axial images were obtained before (left column) and after (right column) statin therapy. The PET image acquisition time was set at 10 min per bed to improve sensitivity. The red arrows point to the right carotid artery, and white arrows point to the left carotid artery. Focal FDG uptake in the periphery of the carotid arteries reveals a decreased intensity and extent after statin therapy, despite a post-statin low density lipoprotein cholesterol (LDL-C) level of 86 mg/dL (above the target LDL-C level). The ratio of the maximum standardized uptake value of carotid plaque over the maximum standardized uptake value of the jugular vein (TBR) changed from 1.59 to 1.15, with baseline carotid maximum standardized uptake value (SUV_{max}) of 2.24 and jugular vein SUV_{max} of 1.41, and follow-up carotid 1.70 and jugular 1.48. Black arrowheads point to focal calcifications in the right carotid artery wall, which does not correspond to the highest FDG uptake focus as previously reported [18] but rather functions as a landmark for analyzing dual time point images in this study. **B.** "Nonresponder by FDG PET/CT." Multi-focal FDG uptake areas are noted along the bilateral carotid arteries of a 56-year-old male. Coronal and axial images were obtained before (left column) and after (right column) statin therapy. The red arrows point to the right carotid artery, and the white arrows point to the left carotid artery. Post-statin images show a similar focal FDG uptake intensity and extent in the periphery of carotid arteries compared with pre-statin images, despite a low post-therapy LDL-C level of 50.6 mg/dL. TBR was essentially unchanged from 1.48 to 1.47, with baseline carotid SUV_{max} of 1.85 and jugular vein SUV_{max} of 1.25, and follow-up carotid 2.01 and jugular 1.37. **C.** "Nonresponder by PET/CT." Ill-defined focal FDG uptake areas are present in the bilateral carotid arteries of a 78-year-old male. Coronal and axial images were obtained before (left column) and after (right column) statin therapy. Red arrows point to the right carotid artery, and white arrows to the left carotid artery. The FDG uptake in the periphery of carotid arteries shows a similar or increased intensity and extent after therapy, suggesting a lack of improvement in plaque inflammation despite a low post-therapy LDL-C level of 61 mg/dL. TBR was increased from 1.69 to 2.18, with baseline carotid SUV_{max} of 2.67 and jugular vein SUV_{max} of 1.58, and follow-up carotid 2.62 and jugular 1.20.

changes in three other FDG uptake parameters were ΔSUV_{max}, $\Delta MLV_{1.0}$ and ΔMLV_{SCM} ($r = -0.15$, $p = 0.623$; $r = 0.268$, $p = 0.377$; and $r = 0.600$, $p = 0.067$, respectively). In the analysis between FDG uptake parameters and inflammatory markers, no correlation was observed between ΔTBR and changes in inflammatory markers ΔCRP, ΔMMP-9, ΔPAI-1 and ΔMCP-1 ($r = -0.086$, $p = 0.872$; $r = -0.667$, $p = 0.071$; $r = -0.591$, $p = 0.056$; $r = -0.471$, $p = 0.265$).

Table 3. Comparison of the changes in plasma inflammatory markers and fluorodeoxyglucose (FDG) uptake parameters between statin responders and statin non-responders.

Δ parameters (baseline–follow up)	Post-statin LDL-C ≤ 70 mg/dL (n = 8)	Post-statin LDL-C > 70 mg/dL (n = 5)	P
ΔhsCRP [mg/dL]	0.34 ± 0.74	0.44 ± 0.58	0.814
ΔMMP-9 [ng/mL]	0.18 ± 2.4	-0.40 ± 5.08	0.843
ΔPAI-1 [ng/mL]	16.8 ± 21.3	21.7 ± 10.6	0.349
ΔMCP-1 [pg/mL]	–10.7 ± 7.8	7.9 ± 28.1	0.246
Mean ΔSUV_{max}	0.1 ± 0.5	0.4 ± 0.5	0.356
ΔTBR	0.1 ± 0.5	0.1 ± 0.3	0.926
$\Delta MLV_{1.0}$ [mm^3]	–283.8 ± 1206.0	382.0 ± 649.2	0.825
ΔMLV_{SCM} [mm^3]	113.8 ± 991.9	1208.0 ± 3013.4	0.354

Δ — change; hsCRP — high-sensitivity C-reactive protein; MCP-1 — monocyte chemoattractant protein-1; $MLV_{1.0}$ — metabolic lesion volume computed using SUV cutoff of 1.0; MLV_{SCM} — metabolic lesion volume computed using an SUV cutoff of sternocleidomastoid muscle; MMP-9 — matrix metalloproteinase-9; PAI-1 — plasminogen activator inhibitor-1; SUV_{max} — maximum standardized uptake value; TBR — ratio of maximum standardized uptake value of carotid plaque over maximum standardized uptake value of the jugular vein

Table 4. Comparison of changes in plasma inflammatory markers and fluorodeoxyglucose (FDG) uptake parameters between positron emission tomography/computed tomography (PET/CT) responders and non-responders.

Δparameters (baseline–follow up)	PET-CT responders (n = 9)	PET-CT non-responders (n = 4)	P
ΔTBR	0.59 ± 0.71	–0.64 ± 1.01	0.026
ΔhsCRP [mg/dL]	0.44 ± 0.78	1.39 ± 1.46	0.332
ΔMMP-9 [ng/mL]	–1.99 ± 3.02	3.04 ± 2.31	0.042
ΔPAI-1 [ng/mL]	18.5 ± 14.6	28.30 ± 20.15	0.501
ΔMCP-1 [pg/mL]	4.63 ± 27.0	–10.29 ± 2.13	0.246

Δ — change; hsCRP — high-sensitivity C-reactive protein; MCP-1 — monocyte chemoattractant protein-1; MMP-9 — matrix metalloproteinase-9; PAI-1 — plasminogen activator inhibitor-1; TBR — ratio of the maximum standardized uptake value of carotid plaque over the maximum standardized uptake value of the jugular vein

Discussion

In this prospective dual time point study of carotid FDG uptake, moderate-intensity statin therapy occasionally failed to suppress plaque inflammation in ACS patients. Although moderate-intensity statin therapy successfully achieved target plasma LDL-C levels of approximately 70 mg/dL in all patients with ACS, about 31% (4 out of 13) patients failed to lower the levels of plasma and imaging biomarkers of plaque inflammation during the early stage following ACS, whereas 69% (9 out of 13) succeeded.

The early initiation of high-intensity statin therapy significantly improved early and late clinical outcomes in ACS patients compared with standard-dose statin therapy [11, 12]. Observational studies have also supported the early use of high-intensity statin therapy in ACS patients [13]. However, many practitioners believe that Asians require lower statin doses [4], and the recommended doses of most statins approved in Japan are indeed much lower than those in the US [14]. A JAPAN-ACS study further demonstrated that 20 mg/day of atorvastatin led to the significant regression of coronary atherosclerosis after 8–12 months of therapy [15]. However, no studies have validated the hypothesis that moderate-intensity statin therapy is sufficient to reduce plaque inflammation within 30 days after ACS in Asian patients.

FDG PET/CT was employed in this study, which can precisely map, quantify, and track alterations in statin-induced plaque inflammation, to image carotid arteries [8]. Additionally, all patients selected who presented with NSTE-ACS and were treated with drug-eluting stent implantation and dual antiplatelet therapy; thus, the anti-inflammatory effect of statins on atherosclerotic

plaques could be observed exclusively. Although the systemic inflammatory state in ACS can affect carotid plaque inflammation, the choice to include ACS patients in this study was made. Although statins exert both systemic and local effects during this critical period after ACS, and the degree of statin efficacy differs when acting systemically versus locally, statin therapy should nevertheless suppress the inflammatory burden in carotid plaques. With this unique study design, it was observed that moderate-intensity statin therapy during the first month after ACS often succeeds but sometimes fails to resolve plaque inflammation in Asian patients.

Notably, poor correlations were observed both between changes in carotid FDG uptake parameters and those in LDL-C levels and between changes in carotid FDG uptake parameters and other plasma inflammatory markers following statin therapy during the acute period of ACS. In contrast, previous studies have shown associations between reduced carotid FDG uptake and decreased LDL-C levels [9] and between decreased MMP-1 and hsCRP levels [16, 17]. The following factors might have contributed to this discrepancy between FDG uptake and blood metabolic and inflammatory markers: (1) Inadequacy of serum LDL-C levels as a barometer of plaque inflammation, especially in the highly vulnerable period followed by plaque rupture; (2) Shortcomings of the clinical FDG PET/CT system currently used to quantify the inflammatory state in atherosclerotic lesions; and/or (3) Insufficiency of the duration of medication to clarify a mutual correlation; (4) Change in FDG uptake contributable to factors other than that of statin [18]. Atherosclerotic plaques are often dynamic in vivo and the FDG uptake is often transient throughout longitudinal clinical course with or without specific treatments [19, 20].

Using FDG uptake to measure the number and metabolic activity of macrophages in a given plaque and measuring serum LDL concentrations may be incongruent because these measures represent two closely related but distinct aspects of complex activities in a vulnerable plaque. Indeed, LDL-C might not mark all of the benefits of statin therapy, and there is insufficient evidence to state that achieving target LDL-C levels (< 70 mg/dL) will decrease CV events in the critical period after ACS [21]. In terms of FDG uptake, although the change in vascular inflammation independent of statin was not excluded, it is reasonable to expect statin does contribute to antinflammatory effect on vasculature in proportion to dose.

Limitations of the study

This study has several limitations. First, the duration of moderate-intensity statin therapy only lasted for 1 month; this period may be insufficient to draw a firm conclusion regarding whether moderate-intensity statin therapy can reduce plaque inflammation in Asian ACS patients. Most similar studies demonstrating the anti-inflammatory action of statins on plaques used treatments lasting 3 months [8, 22]. However, the objective of this study was to investigate whether moderate-intensity statin therapy was sufficient to resolve plaque inflammation within the first month after ACS, which represents the period of highest risk for recurrent CV events. A previous study showed that the effect of statins on reducing FDG uptake can be observed within as early as 4 weeks and that this reduction was in turn correlated with a further reduction after 12 weeks [22]. Additionally, a small, randomized study in Asian ACS patients showed that fluvastatin exerted a significant dose-dependent anti-inflammatory effect in as early as 1 week [23]. Consequently, the authors hypothesized that the anti-inflammatory effect of moderate-intensity statin therapy might be observed and measured using PET/CT within as early as 4 weeks after therapy if the statin is to be effective. If statin therapy is as effective as currently believed, the intensity of statin therapy rather than the 4-week time frame likely dictates the outcome. This needs to be studied separately in a similar patient population.

Second, the present study lacks a control group. The results of a single group "before–after" study such as the present one should be interpreted with caution. The result of the present study should not be considered conclusive on thequestion as to whether moderate-intensity statin is justified in treating Asian NSTE-ACS patients. Although not conclusive, the results presented suggest that because moderate-intensity statin therapy inconsistently "cool down" inflammatory status in atherosclerotic plaques in this study population, high-dose statin therapy might be more beneficial for patients with certain ACSs, even in patients at risk of developing statin side effects.

Third, the conclusion of this study is based on a small number of patients who underwent initial and follow-up FDG PET/CT scans. Regrettably, there were difficulties in recruiting patients who met our strict inclusion criteria consenting to undergo two FDG PET/CT exams. Thus, there was an inability to draw definitive conclusions. Although the sample was small, it showed that

30% of ACS patients exhibited significant carotid plaque inflammation despite good statin compliance and the achievement of target LDL goals and that moderate-intensity statin therapy is insufficient during an early stage after ACS.

Fourth, in the analysis of FDG PET/CT imaging, plaques 3 mm or greater on carotid artery US were selected and this criterion may have been an insufficient predictor of true plaque inflammation. The measured TBR as well as LDL levels were relatively low and the present patient group may not represent patients with a heavy inflammatory burden of plaques.

Additionally, the non-enhance CT used in the present FDG PET/CT imaging may have limited the resolution of atherosclerotic plaques.

Conclusions

In summary, by using dual time point FDG PET/CT images of carotid arteries in ACS patients, this study demonstrates that early moderate-intensity statin therapy does not guarantee resolution of atherosclerotic plaque inflammation after 1 month of statin therapy and the present data indicate it may fail in 30% of patients. Furthermore, plasma LDL-C levels do not reflect the status of local plaque inflammation.

Funding: This study was supported by a grant from the Korea Healthcare Technology R&D Project, Ministry for Health & Welfare, Republic of Korea (A070001).

Conflict of interest: None declared

References

1. Wright RS, Anderson JL, Adams CD, et al. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST--Elevation Myocardial Infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the American Academy of Family Physicians, Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. J Am Coll Cardiol. 2011; 57: e215–e367.
2. Timmis AD. Plaque stabilisation in acute coronary syndromes: clinical considerations. Heart. 2003; 89(10): 1268–1272, indexed in Pubmed: 12975445.
3. Ray KK, Cannon CP, McCabe CH, et al. PROVE IT-TIMI 22 Investigators. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT-TIMI 22 trial. J Am Coll Cardiol. 2005; 46(8): 1405–1410, doi: 10.1016/j.jacc.2005.03.077, indexed in Pubmed:16226162.
4. Wang P. Statin dose in Asians: is pharmacogenetics relevant? Pharmacogenomics. 2011; 12(11): 1605–1615, doi: 10.2217/pgs.11.98, indexed in Pubmed: 22044416.
5. Kim MJ, Jeon DS, Gwon HC, et al. Current statin usage for patients with acute coronary syndrome undergoing percutaneous coronary intervention: multicenter survey in Korea. Clin Cardiol. 2012; 35(11): 700–706, doi: 10.1002/clc.22038, indexed in Pubmed: 22825844.
6. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014; 63(25 Pt B): 2889–2934, doi: 10.1016/j.jacc.2013.11.002, indexed in Pubmed: 24239923.
7. Tawakol A, Migrino RQ, Bashian GG, et al. In vivo 18F-fluorodeoxyglucose positron emission tomography imaging provides a noninvasive measure of carotid plaque inflammation in patients. J Am Coll Cardiol. 2006; 48(9): 1818–1824, doi: 10.1016/j.jacc.2006.05.076, indexed in Pubmed: 17084256.
8. Tahara N, Kai H, Ishibashi M, et al. Simvastatin attenuates plaque inflammation: evaluation by fluorodeoxyglucose positron emission tomography. J Am Coll Cardiol. 2006; 48(9): 1825–1831, doi: 10.1016/j.jacc.2006.03.069, indexed in Pubmed: 17084257.
9. Rudd JHF, Machac J, Fayad ZA. Simvastatin and plaque inflammation. J Am Coll Cardiol. 2007; 49(19): 1991–1992, doi: 10.1016/j.jacc.2007.03.003, indexed in Pubmed: 17498586.
10. Ogawa M, Magata Y, Kato T, et al. Application of 18F-FDG PET for monitoring the therapeutic effect of antiinflammatory drugs on stabilization of vulnerable atherosclerotic plaques. J Nucl Med. 2006; 47(11): 1845–1850, indexed in Pubmed: 17079818.
11. Cannon C, Braunwald E, McCabe C, et al. Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes. N Engl J Med. 2004; 350(15): 1495–1504, doi: 10.1056/nejmoa040583.
12. Navarese EP, Kowalewski M, Andreotti F, et al. Meta-analysis of time-related benefits of statin therapy in patients with acute coronary syndrome undergoing percutaneous coronary intervention. Am J Cardiol. 2014; 113(10): 1753–1764, doi: 10.1016/j.amjcard.2014.02.034, indexed in Pubmed: 24792742.
13. Stenestrand U, Wallentin L. Early statin treatment following acute myocardial infarction and 1-year survival. JAMA. 2001; 285(4): 430–436, indexed in Pubmed: 11242427.
14. Saito M, Hirata-Koizumi M, Urano T, et al. A literature search on pharmacokinetic drug interactions of statins and analysis of how such interactions are reflected in package inserts in Japan. J Clin Pharm Ther. 2005; 30(1): 21–37, doi: 10.1111/j.1365-2710.2004.00605.x, indexed in Pubmed: 15659001.
15. Hiro T, Kimura T, Morimoto T, et al. Effect of intensive statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome: a multicenter randomized trial evaluated by volumetric intravascular ultrasound using pitavastatin versus atorvastatin (JAPAN-ACS [Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome] study). J Am Coll Cardiol. 2009; 54(4): 293–302, doi: 10.1016/j.jacc.2009.04.033, indexed in Pubmed: 19608026.
16. Wu YW, Kao HL, Chen MF, et al. Characterization of plaques using 18F-FDG PET/CT in patients with carotid atherosclerosis and correlation with matrix metalloproteinase-1. J Nucl Med. 2007; 48(2): 227–233, indexed in Pubmed: 17268019.

17. Tahara N, Kai H, Yamagishi Si, et al. Vascular inflammation evaluated by [18F]-fluorodeoxyglucose positron emission tomography is associated with the metabolic syndrome. J Am Coll Cardiol. 2007; 49(14): 1533–1539, doi: 10.1016/j.jacc.2006.11.046, indexed in Pubmed: 17418291.
18. Ben-Haim S, Kupzov E, Tamir A, et al. Evaluation of 18F-FDG uptake and arterial wall calcifications using 18F-FDG PET/CT. J Nucl Med. 2004; 45(11): 1816–1821, indexed in Pubmed: 15534049.
19. Ben-Haim S, Kupzov E, Tamir A, et al. Changing patterns of abnormal vascular wall F-18 fluorodeoxyglucose uptake on follow-up PET/CT studies. J Nucl Cardiol. 2006; 13(6): 791–800, doi: 10.1016/j.nuclcard.2006.07.008, indexed in Pubmed: 17174810.
20. Menezes LJ, Kayani I, Ben-Haim S, et al. What is the natural history of 18F-FDG uptake in arterial atheroma on PET/CT? Implications for imaging the vulnerable plaque. Atherosclerosis. 2010; 211(1): 136–140, doi: 10.1016/j.atherosclerosis.2010.01.012, indexed in Pubmed: 20202634.
21. Schwartz G, Olsson A. The Case for Intensive Statin Therapy After Acute Coronary Syndromes. Am J Cardiol. 2005; 96(5): 45–53, doi: 10.1016/j.amjcard.2005.06.026.
22. Tawakol A, Fayad ZA, Mogg R, et al. Intensification of statin therapy results in a rapid reduction in atherosclerotic inflammation: results of a multicenter fluorodeoxyglucose-positron emission tomography/computed tomography feasibility study. J Am Coll Cardiol. 2013; 62(10): 909–917, doi: 10.1016/j.jacc.2013.04.066, indexed in Pubmed: 23727083.
23. Yang J, Li XP, Zhao SP, et al. The effect of different doses of fluvastatin on inflammatory markers in the early phase of acute coronary syndrome. Clin Chim Acta. 2006; 368(1-2): 183–187, doi: 10.1016/j.cca.2005.12.029, indexed in Pubmed: 16472797.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2020, Vol. 27, No. 6, 772–779
DOI: 10.5603/CJ.a2019.0002

ISSN 1897–5593
eISSN 1898–018X

Slow breathing improves cardiovascular reactivity to mental stress and health-related quality of life in heart failure patients with reduced ejection fraction

Kamila Lachowska[1], Jerzy Bellwon[1], Joanna Moryś[2], Marcin Gruchała[1], Dagmara Hering[1, 3]

[1]1st Department of Cardiology, Medical University of Gdansk, Poland
[2]Department of Clinical Psychology, Medical University of Gdansk, Poland
[3]Department of Hypertension and Diabetology, Medical University of Gdansk, Poland

Abstract

Background: *Previous studies have demonstrated therapeutic benefits of slow breathing (SLOWB) in chronic heart failure (HF) but its impact on cardiovascular reactivity in response to laboratory stressors remains unknown.*

Methods: *Using device-guided breathing this study explored the acute and long-term effects of SLOWB on hemodynamic responses to handgrip, mental and cold pressor tests, and health-related quality of life (QoL) in stable HF patients with reduced ejection fraction (HFrEF) who had received all available optimal drug and device therapies. Blood pressure (BP) and heart rate (HR) were measured in 21 patients with HFrEF (23.9 ± 5.9%) at rest, during laboratory stressors, before and after acute SLOWB, and 12 weeks after SLOWB home training (30 min daily). Health-related QoL (MacNew questionaries) was assessed before and 12 weeks after SLOWB home training.*

Results: *Resting BP significantly increased in response to three laboratory stressors. Pressor and cardiac changes during mental stress were greater than responses to the handgrip test ($p < 0.05$). Mental stress also produced a greater HR change than cold pressor test ($p < 0.05$). Both acute and long-term SLOWB significantly reduced BP and HR responses to mental stress ($p < 0.05$), but not to isometric and cold pressor tests. SLOWB improved scores of all domains of QoL ($p < 0.05$) at 12 weeks follow-up.*

Conclusions: *These findings demonstrate that SLOWB reduces acute and chronic effects of cardiovascular reactivity to mental stress and improves various aspects of health-related QoL in patients with severe HFrEF. Whether stress reduction and psychological changes achieved with SLOWB may translate to improved outcomes in HFrEF warrants further exploration.* (Cardiol J 2020; 27, 6: 772–779)

Key words: heart failure with reduced ejection fraction, slow breathing, hemodynamics, laboratory stressors, health-related quality of life

Introduction

Chronic heart failure (HF) is considered a global pandemic with survival outcomes as malignant as some common cancers [1]. The progression of HF, worsening of symptoms and increasingly frequent hospitalizations negatively influence patient functional ability and health-related quality of life (QoL) [2–5]. Depression is one of the most important factors determining QoL in HF patients, this also contributes to social isolation [6, 7]. Depressed mood and vital exhaustion are strong predictors of

Address for correspondence: Prof. Dagmara Hering, MD, PhD, Department of Hypertension and Diabetology, Medical University of Gdansk, ul. Dębinki 7c, 80–952 Gdańsk, Poland, tel: +48 58 349 2065, fax: +48 58 349 2601, e-mail: hering@gumed.edu.pl

Received: 22.11.2018 Accepted: 3.01.2019

low life expectancy, all-cause and cardiovascular (CV) mortality, independent of classical risk factors [8–12]. Acute emotional stress has been linked to a high incidence of acute CV events, arrhythmias and sudden cardiac death [13]. Mental stress *per se* is a potent trigger for myocardial ischemia. Chronic effects of mental stress and psychological states have been reported as important independent predictors of coronary heart disease, atherosclerosis, hypertension and other adverse consequences [13, 14]. CV responses to mental stress independently predicted fatal and non-fatal cardiac and vascular events in patients with coronary artery disease (CAD) [15, 16]. Furthermore, altered CV reactivity to acute mental stress were independently associated with an increased risk of earlier mortality in HF [17].

Despite the disease burden, there are a limited number of clinical studies in patients with very severe HF. Given the importance of psychological distress and poor QoL to the severity of HF, associated morbidity and mortality, hospital readmission, and duration of hospital stay [2, 4, 18–21], interventions to specifically target potentiated reactivity to mental challenges, physical exertion [22], social aspects and associated QoL are likely to be of substantial clinical benefit. The feasibility and therapeutic effectiveness of the slow breathing (SLOWB) technique has been documented in chronic HF [23–28]. Very recently, it was documented that SLOWB home training improves clinical symptoms, physical and cardiorespiratory capacity, and vagal activity in patients with severe HF with reduced ejection fraction (HFrEF) irrespective of HF etiology [29]. However, health-related QoL in response to SLOWB is less known, demonstrating an overall improvement without a clear trend toward a reduction of any specific component [25] or a non-significant tendency toward improved QoL [27]. The impact of SLOWB on CV responses to laboratory stressors remain unknown in HF. Therefore, this study investigated CV reactivity to laboratory-induced stressors and whether, and to what extent home paced SLOWB may restrain hemodynamic responses to challenge stressors and improve QoL in patients with severe HFrEF.

Methods

Subjects

The study was approved by the Institutional Ethics Committee and written informed consent was obtained from all patients. This prospective study was previously described in detail [29] and included a total of 21 non-smoking patients (16 males, 5 females) with stable chronic HFrEF diagnosed as per European Society of Cardiology (ESC) guidelines [4, 30]. Patients were recruited from a larger cohort of HF patients following the CONSORT guidelines. Only patients who received all available treatment options including optimal medical drug and device therapies were enrolled. All patients were receiving stable doses of optimal multi-drug therapy which had been kept unchanged for at least 6 weeks prior to study enrolment and was maintained (including drugs and dosage) over the 3-month study period.

Study protocol

Patients were studied at baseline before and after acute performance of SLOWB exercise, and then at 3 months follow-up of monitored SLOWB home training according to the same protocol. Measurements of continuous beat-to-beat finger blood pressure (BP), heart rate (HR), respiration and saturation (ADInstruments, Dual Bio Amp; ADInstruments, Ltd., Oxford, UK) were recorded in a supine position at rest over a 20-min duration followed by an application of two laboratory stressors (i.e. sustained handgrip, mental arithmetic) under carefully standardized conditions. Then patients performed a SLOWB exercise with the use of device-guided breathing (RESPeRATE®) for 15 min. Following SLOWB and a 20-min recovery period, application of sustained handgrip and mental arithmetic tests were repeated. A cold pressor test was performed once at the end of the study protocol, due to its sustained hemodynamic effects. The protocol investigating the impact of SLOWB on CV responses to laboratory stressors is consistent with a previous study in patients with untreated essential hypertension [31].

In line with our established protocol [31–33], an isometric handgrip test was conducted by asking patients to sustain a handgrip of 30% of patient maximum voluntary contraction using a dynamometer. Mental stress was performed by asking the subject to do serial subtractions as fast as possible. Each stress test lasted 3 min with a 10-min rest period between tests. Following a 10-min recovery period, a cold pressor test was performed by immersing the hand into an ice water container for 2 min.

MacNew Health-related Quality of Life questionnaire

The MacNew is a self-administered heart disease-specific health-related QoL instrument and

addresses three major QoL domains: the Emotional, Physical, and Social domains. This instrument consists of 27 items, each with a 7-point Likert response scale, measuring the 3 inter-related domains of physical activities (13-item), emotional (14-item) and social functioning (13-item). There are 5 items related to patient symptoms including angina, shortness of breath, fatigue, dizziness and aching legs. The maximum possible score in any domain is 7 and the minimum is 1 with the minimal important difference of 0.50 points on the 7-point MacNew global scale and each subscale. Domain scores are calculated by taking the average of the responses to the items in each domain and by averaging all 27 items providing a global health-related QoL score. Amongst other conditions, the MacNew questionnaire has been validated in HF patients [34, 35]. As part of the international HeartQOL Study, the MacNew form was translated into Polish demonstrating its reliability and validity in patients with CAD, myocardial infarction and HF [36, 37].

The MacNew questionnaire was completed by all patients at baseline and by 16 (76%) participants 3 months after SLOWB home training.

Serum biochemistry

Routine blood tests were performed in all patients at each study visit at the associated Clinical Laboratory Centre.

Slow-breathing technique

A device-guided SLOWB pacing (goal below 10 breaths per minute) was performed twice daily with each session lasting 15 min, through use of an ad hoc device RESPeRATE® (Intercure Ltd., Northern Industrial Area, Israel) as described previously [31]. At the first visit, patients were instructed on how to synchronize their breathing with guiding tones generated by the RESPeRATE® in response to their breathing pattern. Following the completion of all tests at baseline, all patients received the device and a translated training manual on its use in a home setting. Performance of SLOWB exercise was scheduled for two 15-min daily sessions (in total 30 min per day) over the 3 months. Patients were asked to breathe effortlessly and gradually at home, irrespective of the time of the day, in a quiet room and in a comfortable position as recommended in the RESPeRATE® manual. Patients were called by an investigator (K.L.) weekly through the duration of the study to obtain information stored on the device regarding the SLOWB exercise (i.e. number of sessions, therapeutic minutes, initial breathing, final breathing rate, the ability to synchronize respiratory rate with guiding tones, breath detection). Patients were asked to repeat all tests after 3 months of SLOWB home exercise.

Table 1. Heart failure (HF) etiology and associated co-morbidities of the entire study cohort.

Parameter	Number (n = 21)
Ischemic HF	9 (43%)
Non-ischemic HF	12 (57%)
Myocardial infarction	8 (38%)
Paroxysmal AF	3 (14%)
Persistent AF	2 (10%)
Arterial hypertension	8 (38%)
Diabetes	5 (24%)
CKD (eGFR < 60 mL/min/1.73 m^2)	6 (29%)
PCI	6 (29%)
CABG	3 (14%)
ICD	9 (43%)
CRT-D	7 (33%)

Data expressed as numbers or percentage (%). AF — atrial fibrillation; CKD — chronic kidney disease; PCI — percutaneous coronary intervention; CABG — coronary artery bypass graft; ICD — implantable cardioverter-defibrillator; CRT-D — cardiac resynchronization therapy defibrillator

Statistical analysis

Results are expressed as means ± standard deviation (SD) or percentage (%). Changes in variables between baseline and 3 month follow-up were analyzed using a paired t-test. Analysis was performed on ranks for non-Gaussian data. Statistical analysis was performed using SigmaPlot Version 13.0.0.83 (Systat Software, Inc. Leadtools, Dundas Software LTD. Reg. No. 775201235). The sample size and power calculation for this patient cohort had been published previously [29]. An additional analysis revealed that 10 patients would have 80% power for a paired t-test in detecting an increase in systolic BP (SBP) in response to mental stress of 3.4 mmHg at the level of significance 0.05 and an estimated SD of 3.4. The present study revealed that 21 patients with a SD of 3.4 and an increase in SBP of 3.4 mmHg had a power of 99.2%. A value of $p < 0.05$ was considered statistically significant.

Results

Patient demographic characteristics are shown in Table 1. Twenty-one patients with HFrEF in New York Heart Association classes I (n = 5), II (n = 13) and III (n = 3) had a mean left ventricular ejection fraction (LVEF) of 23.9 ± 5.9%, at the

Table 2. Acute cardiovascular reactivity to mental stress, handgrip and cold pressor tests in heart failure with reduced ejection fraction patients at baseline.

Measurements	Before test	After test	Δ changes	P
Handgrip test				
SBP [mmHg]	113 ± 7	116 ± 9	3.4 ± 3.4	< 0.001
DBP [mmHg]	88 ± 5	90 ± 6	2.1 ± 2.4	< 0.001
HR [bpm]	64 ± 8	66 ± 6	2.5 ± 4.1	< 0.05
Mental stress				
SBP [mmHg]	114 ± 9	119 ± 9	5.7 ± 5.0	< 0.0001
DBP [mmHg]	88 ± 5	92 ± 6	3.2 ± 2.4	< 0.0001
HR [bpm]	65 ± 6	69 ± 8	4.8 ± 6.0	< 0.01
Cold pressor test				
SBP [mmHg]	118 ± 10	121 ± 13	3.5 ± 6.7	< 0.01
DBP [mmHg]	90 ± 5	92 ± 7	1.5 ± 2.9	< 0.05
HR [bpm]	64 ± 7	65 ± 7	0.9 ± 4.4	0.39

Data are means ± standard deviation. SBP — systolic blood pressure; DBP — diastolic blood pressure; HR — heart rate

age of 52 ± 17 years and a body mass index (BMI) of 28 ± 4 kg/m^2.

Patients were on optimal drug therapy including beta-blockers (carvedilol, bisoprolol or metoprolol), aldosterone antagonists (spironolactone or eplerenone), angiotensin-converting enzyme inhibitors (ACEI, quinapril, ramipril, enalapril or perindopril). Three patients were receiving angiotensin II receptor blockers (valsartan or telmisartan) due to intolerance of ACEI. Other drugs included amiodarone (n = 5), ivabradine (n = 4), trimetazidine (n = 3), furosemide (n = 11), torasemide (n = 9), statins (n = 14) (atorvastatin, rosuvastatin or simvastatin), acetylsalicylic acid (n = 5) and anticoagulants (n = 12) including warfarin, dabigatran or rivaroxaban. No patients were receiving Entresto (sacubitril/valsartan).

Systolic BP and diastolic BP (DBP) significantly increased in response to acute exposure to handgrip, mental and cold pressor tests at baseline visit (Table 2). However, pressor (5.7 ± 4.5 vs. 3.4 ± 3.4, $p < 0.05$) and cardiac (4.8 ± 6.0 vs. 2.5 ± 4.1, $p < 0.05$) responses to mental stress were significantly greater than the handgrip test. Mental stress also produced a greater HR change than cold pressor test (4.8 ± 6.0 vs. 0.9 ± 4.4, $p < 0.05$) but not in BP (5.7 ± 4.5 vs. 3.5 ± 6.7, $p = 0.13$). A significant rise in HR was observed following isometric and arithmetic tests but not cold pressor test (Table 2).

Acute effects of SLOWB on SBP, DBP and HR responses to mental and handgrip stress tests are demonstrated in Table 3. BP and HR responses to isometric handgrip tests were similar before and after acute SLOWB (Table 3).

Acute SLOWB significantly reduced BP and HR responses to mental stress (Table 3).

Long-term SLOWB home training resulted in further significant attenuation of BP and HR responses to mental tests but had no significant impact on hemodynamic responses to handgrip and cold pressor tests (Table 3).

SLOWB home training significantly improved physical, mental and social components, and a global score in HFrEF (Fig. 1).

Discussion

The novel finding of the present study is that both acute and long-term SLOWB significantly diminishes CV effects of mental stress but not physical stressors in patients with severe HFrEF. This report also documents that, in these HFrEF patients, a 3-month SLOWB home training improves subjective health-related QoL in all domains including physical, mental, social components and a global score.

Recent reports documenting the effectiveness of SLOWB home training in improving oxygen saturation, cardiorespiratory capacity, functional performance, vagal activity, LVEF and reducing pulmonary pressure and breathlessness highlight the important role of breathing frequency in HF patients [23, 25, 26, 28, 29, 38–40].

High sympathetic excitation is a hallmark of HF and independent predictor of CV mortality in

Table 3. Changes in systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) in responses to handgrip and mental stress tests before and after acute effects of slow breathing (SLOWB) at baseline, and at 3 month follow-up (3MFU) of SLOWB home training in heart failure with reduced ejection fraction patients.

Measurement	Before SLOWB — baseline	After SLOWB	P	Before SLOWB — 3MFU	After SLOWB	P	P: baseline vs. 3MFU
Handgrip test							
Δ SBP [mmHg]	3.4 ± 3.4	3.0 ± 3.2	0.49	2.5 ± 3.4	2.6 ± 3.1	0.91	0.25
Δ DBP [mmHg]	2.1 ± 2.4	2.1 ± 2.2	0.38	1.8 ± 2.8	2.7 ± 2.9	0.57	0.52
Δ HR [bpm]	2.5 ± 4.1	1.8 ± 3.3	0.70	1.0 ± 7.6	4.0 ± 5.4	0.14	0.97
Mental stress							
Δ SBP [mmHg]	5.7 ± 4.5	3.7 ± 3.1	< 0.05	3.4 ± 4.1	1.3 ± 3.4	< 0.05	< 0.05
Δ DBP [mmHg]	3.2 ± 2.4	2.1 ± 2.1	< 0.01	2.2 ± 2.4	1.5 ± 1.9	0.17	< 0.05
Δ HR [bpm]	4.8 ± 6.0	2.8 ± 5.9	< 0.05	2.7 ± 5.0	2.2 ± 4.5	0.19	< 0.05
Cold pressor test							
Δ SBP [mmHg]	–	3.5 ± 6.7	–	–	3.3 ± 5.8	–	0.93
Δ DBP [mmHg]	–	1.5 ± 2.9	–	–	1.5 ± 3.1	–	0.95
Δ HR [bpm]	–	0.9 ± 4.4	–	–	–0.01 ± 3.5	–	0.29

Data are means ± standard deviation.

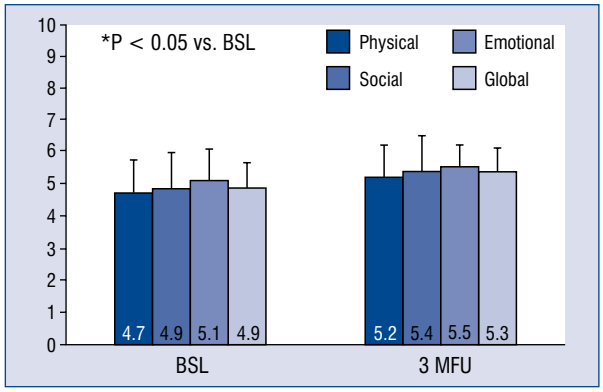


Figure 1. Effects of slow breathing (SLOWB) home training on health-related quality of life changes in physical, mental and social domains, and a global score in heart failure with reduced ejection fraction (HFrEF) patients at 3 month follow-up (3 MFU) compared to baseline (BSL).

chronic HF [41–43]. The magnitude of sympathetic activation has been directly linked to the severity of HF and reduced left ventricle (LV) function [44]. LV dysfunction results in several neurohumoral compensatory mechanisms including increases in HR, myocardial oxygen demand, ischemia, myocardial contractility, peripheral vasoconstriction and blood volume to maintain cardiac output and peripheral tissue perfusion [45]. However, with further LV impairment and HF progression, the compensatory regulatory alterations in autonomic control may be counter effective, contributing to a depletion of myocardial noradrenaline (NA) store and decreased myocardial adrenoreceptor density, subsequently potentiating stress to cardiac muscle, impairment of reactivity to exogenous challenges (i.e. physical exertion, fatigue, dyspnoea) and CV responses, thereby worsening prognosis. While pharmacological blockade of neurohumoral hyperactivation provides a biological rationale for HF management, the increasing number of hospitalizations for HF decompensation and associated death suggests the necessity for additional treatment options. In this context, our recent findings and others of beneficial effects of SLOWB home training are likely to be associated with breaking or weakening the vicious cycle in patients with severe HFrEF [29].

Previous studies have demonstrated that both exaggerated (likely occurring at an earlier stage of disease) and blunted (likely occurring in an advanced stage of disease) CV and hormonal reactivity to psychological stress bear negative prognostic health outcomes [46, 47]. In chronic HF (mean LVEF 31.8 ± 6.9%), low DBP and HR responses to acute mental stress were independently associated with a higher mortality risk [17]. In the present study, patients with severe HFrEF (mean LVEF 23.9 ± 5.9%) had diminished BP and HR reactivity to laboratory stressors compared to patients with untreated essential hypertension [31]. In patients with severe HFrEF, the magnitude

of pressor and cardiac responses to mental stress were markedly reduced and reached one-fourth and one-third of the values obtained in patients with untreated essential hypertension [31]. Similarly, CV reactivity to hand-grip and cold pressor tests were substantially attenuated in HFrEF compared to hypertensive patients likely as a result of higher sympathetic drive in the failing heart compared to essential hypertension.

Notably, mental arithmetic stress *per se* has been shown to induce threefold increases in NA release from sympathetic nerves to the heart in essential hypertension [48] and to cause silent myocardial ischemia in patients with CAD [49]. This observation indicates that repetitive exposure to psychological factors is likely to cause silent damage to the heart, adversely affecting the CV system (i.e. alterations in myocardial oxygen demand and supply), thereby predisposing acute adverse events. The present study found significant increases in BP and HR responses to all laboratory stressors with a greater CV reactivity to mental stress than isometric and cold pressor tests. Moreover, in this study acute SLOWB significantly reduced BP and HR responses to acute mental stress, whereas a 3-month therapy with SLOWB led to a further and pronounced reduction in CV responses to mental stress in patients with severe HFrEF that is beyond improvements in oxygen saturation, functional performance levels, cardiorespiratory capacity and HR variability [29]. Whether the incremental benefit on stress reduction achieved with SLOWB is likely to translate to improved outcomes in HFrEF needs to be investigated in larger clinical trials.

A further important finding observed after 3 months of SLOWB was an improvement in health-related QoL including mental, physical, social and global domains. This could be of clinical relevance given the high incidence of depression in HF and its adverse contribution to the long-term prognosis. The current management of HF predominantly aims at reducing symptoms of hypervolemia and arrhythmia with the subsequent reduction in hospitalization rates [4], whereas the mental health component is often ignored in clinical practise, mostly due to the lack of the validity and significance of QoL assessment methods. Recently, it has been highlighted that data documenting effects of therapeutic and behavioural interventions on prognostic parameters, exercise performance, functional capacity and psychological status in advance HF are scarce [3]. Of note, the psychological care is not available for the vast majority of HF patients and is rather limited to antidepressant therapy [4], indicating an unmet need for patient participation in behavioral therapy to regain control of the disease and manage breathing rate. In this context, the present findings support the notion that the assessment of QoL using MacNew questionnaires can be easily implemented in clinical practice for HF management, particularly in the absence of a professional psychotherapist. Certainly, SLOWB therapy is easy to use in home settings and a cost-effective approach to be offered to HF patients to improve patient engagement in health care and associated QoL.

It is noteworthy to mention that a substantial proportion of HF patients on optimal pharmacological and HF device therapies report subjective perceptions of dyspnoea in the absence of objective indications of hypervolemia. In this clinical scenario, SLOWB home training exerts beneficial effects in treating breathlessness. The present findings are supported by objective evidence documenting long-term effectiveness of SLOWB home training in improving oxygen saturation, functional performance levels, cardiorespiratory function and slowing progression of the disease in patients with severe HFrEF [29].

Strengths of the present study include precise evaluations of acute and long-term effects of SLOWB on hemodynamic responses to laboratory stressors in patients with severe HFrEF who received available treatment options as per ESC guidelines. Secondly, medication remained unchanged during the 3-month therapy of SLOWB home training, thereby eliminating potential confounding effects of drug therapy. Thirdly, all patients reached final breathing rate of 6 ± 1 breaths/min at the end of the RESPeRATE® session and significantly reduced a spontaneous breathing rate at 3 months follow-up [29]. Fourthly, no patient presented with active stimulation during exposure to laboratory tests and response dependent stimulation which might have affected results of the HR change under the stressors. Finally, no patient experienced worsening of HF or other events over the duration of the study indicating clinical benefits achieved with SLOWB therapy.

Limitations of the study

The limitations of the present study include a modest number of patients and the lack of a control group. However, this study was a logical continuation of previous clinical experience in patients with essential hypertension who underwent a similar study protocol and could thereby

serve as controls. Moreover, the present study included patients with severe HFrEF who received evidence-based therapy for HF and still remain at high risk for HF decompensation, hospital readmission and HF-related mortality. While the possible occurrence of a potential "learning effect", with repetition of applied stressor tests over time could be viewed as a limitation, it was previously shown that no changes in hemodynamics were observed in response to repeated mental or isometric tests without SLOWB therapy [31].

Conclusions

The present results indicate that even in the absence of other available treatment options, behavioural intervention such as SLOWB home training appears to have substantial impact on distress and health-related QoL in severe HFrEF on top of evidence-based HF management. These favourable benefits of SLOWB occurred in addition to improvements in cardiorespiratory capacity, functional performance levels, vagal activity and attenuation of HF progression. While this study involves patients with very severe HFrEF, it seems that SLOWB as an add-on therapy may provide beneficial effects on mental, social, physical and global components in all HF patients independent of HF etiology. Ideally these benefits could be tested in further clinical studies.

Acknowledgements

The authors would like to thank to Mrs Wiesława Kucharska for her support with patient and data management.

Funding: This study was supported by Research Fellowship Grant from the European Society of Hypertension (01/2007) and the Statutory Grant (ST-85/2015) of the Medical University of Gdansk, Poland.

Conflict of interest: None declared

References

1. Mamas MA, Sperrin M, Watson MC, et al. Do patients have worse outcomes in heart failure than in cancer? A primary care-based cohort study with 10-year follow-up in Scotland. Eur J Heart Fail. 2017; 19(9): 1095–1104, doi: 10.1002/ejhf.822, indexed in Pubmed: 28470962.
2. O'Loughlin C, Murphy NF, Conlon C, et al. Quality of life predicts outcome in a heart failure disease management program. Int J Cardiol. 2010; 139(1): 60–67, doi: 10.1016/j.ijcard.2008.09.003, indexed in Pubmed: 18851887.
3. Nieminen MS, Dickstein K, Fonseca C, et al. The patient perspective: Quality of life in advanced heart failure with frequent hospitalisations. Int J Cardiol. 2015; 191: 256–264, doi: 10.1016/j.ijcard.2015.04.235, indexed in Pubmed: 25981363.
4. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016; 37(27): 2129–2200, doi: 10.1093/eurheartj/ehw128, indexed in Pubmed: 27206819.
5. Kutyifa V, Rice J, Jones R, et al. Impact of non-cardiovascular disease burden on thirty-day hospital readmission in heart failure patients. Cardiol J. 2018; 25(6): 691–700, doi: 10.5603/CJ.2018.0147, indexed in Pubmed: 30600831.
6. Freedland KE, Carney RM, Rich MW, et al. Effect of depression on prognosis in heart failure. Heart Fail Clin. 2011; 7(1): 11–21, doi: 10.1016/j.hfc.2010.08.003, indexed in Pubmed: 21109204.
7. Mbakwem A, Aina F, Amadi C. -Depression in Patients with Heart Failure: Is Enough Being Done? Card Fail Rev. 2016; 2(2): 110––112, doi: 10.15420/cfr.2016:21:1, indexed in Pubmed: 28785463.
8. Ladwig KH, Baumert J, Marten-Mittag B, et al. Room for depressed and exhausted mood as a risk predictor for all-cause and cardiovascular mortality beyond the contribution of the classical somatic risk factors in men. Atherosclerosis. 2017; 257: 224–231, doi: 10.1016/j.atherosclerosis.2016.12.003, indexed in Pubmed: 28110940.
9. Chen LH, Li CY, Shieh SM, et al. Predictors of fatigue in patients with heart failure. J Clin Nurs. 2010; 19(11-12): 1588–1596, doi: 10.1111/j.1365-2702.2010.03218.x, indexed in Pubmed: 20579199.
10. Perez-Moreno AC, Jhund PS, Macdonald MR, et al. Fatigue as a predictor of outcome in patients with heart failure: analysis of CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure). JACC Heart Fail. 2014; 2(2): 187–197, doi: 10.1016/j.jchf.2014.01.001, indexed in Pubmed: 24720928.
11. Hwang SL, Liao WC, Huang TY. Predictors of quality of life in patients with heart failure. Jpn J Nurs Sci. 2014; 11(4): 290–298, doi: 10.1111/jjns.12034, indexed in Pubmed: 24238344.
12. Kowalczys A, Bohdan M, Gruchała M. Prognostic value of daytime heart rate, blood pressure, their products and quotients in chronic heart failure. Cardiol J. 2017 [Epub ahead of print], doi: 10.5603/CJ.a2017.0130, indexed in Pubmed: 29131282.
13. Hering D, Lachowska K, Schlaich M. Role of the sympathetic nervous system in stress-mediated cardiovascular disease. Curr Hypertens Rep. 2015; 17(10): 80, doi: 10.1007/s11906-015-0594-5, indexed in Pubmed: 26318888.
14. Niklas AA, Flotyńska A, Zdrojewski T, et al. Trends in hypertension prevalence, awareness, treatment, and control among Polish adults 75 years and older during 2007-2014. Cardiol J. 2018; 25(3): 333–344, doi: 10.5603/CJ.a2018.0043, indexed in Pubmed: 29671863.
15. Jiang W, Babyak M, Krantz DS, et al. Mental stress--induced myocardial ischemia and cardiac events. JAMA. 1996; 275(21): 1651–1656, indexed in Pubmed: 8637138.
16. Wei J, Rooks C, Ramadan R, et al. Meta-analysis of mental stress-induced myocardial ischemia and subsequent cardiac events in patients with coronary artery disease. Am J Cardiol. 2014; 114(2): 187–192, doi: 10.1016/j.amjcard.2014.04.022, indexed in Pubmed: 24856319.
17. Kupper N, Denollet J, Widdershoven J, et al. Cardiovascular Reactivity to Mental Stress and Mortality in Patients With Heart Failure. JACC: Heart Fail. 2015; 3(5): 373–382, doi: 10.1016/j.jchf.2014.12.016.
18. Faller H, Störk S, Schowalter M, et al. Is health-related quality of life an independent predictor of survival in patients with

chronic heart failure? J Psychosom Res. 2007; 63(5): 533–538, doi: 10.1016/j.jpsychores.2007.06.026, indexed in Pubmed: 17980227.
19. Lewis EF, Lamas GA, O'Meara E, et al. CHARM Investigators. Characterization of health-related quality of life in heart failure patients with preserved versus low ejection fraction in CHARM. Eur J Heart Fail. 2007; 9(1): 83–91, doi: 10.1016/j.ejheart.2006.10.012, indexed in Pubmed: 17188020.
20. Kato N, Kinugawa K, Seki S, et al. Quality of life as an independent predictor for cardiac events and death in patients with heart failure. Circ J. 2011; 75(7): 1661–1669, indexed in Pubmed: 21532181.
21. Ramos S, Prata J, Rocha-Gonçalves F, et al. Quality of life predicts survival and hospitalisation in a heart failure portuguese population. Appl Res Qual Life. 2016; 12(1): 35–48, doi: 10.1007/s11482-016-9449-8.
22. Czubaszewski Ł, Straburzyńska-Lupa A, Migaj J, et al. Comparison of prognostic values of cardiopulmonary and heart rate parameters in exercise testing in men with heart failure. Cardiol J. 2018; 25(6): 701–708, doi: 10.5603/CJ.a2017.0070, indexed in Pubmed: 28612902.
23. Bernardi L, Spadacini G, Bellwon J, et al. Effect of breathing rate on oxygen saturation and exercise performance in chronic heart failure. Lancet. 1998; 351(9112): 1308–1311, doi: 10.1016/S0140-6736(97)10341-5, indexed in Pubmed: 9643792.
24. Boarin S, Malfatto G, Caldara G, et al. Device-guided home-based slow breathing training in patients with congestive heart failure. Effects on exercise capacity, ventilation and ventricular function. Eur Heart J. 2006; 27: 332–332.
25. Parati G, Malfatto G, Boarin S, et al. Device-guided paced breathing in the home setting: effects on exercise capacity, pulmonary and ventricular function in patients with chronic heart failure: a pilot study. Circ Heart Fail. 2008; 1(3): 178–183, doi: 10.1161/CIRCHEARTFAILURE.108.772640, indexed in Pubmed: 19808287.
26. Ekman I, Kjellström B, Falk K, et al. Impact of device-guided slow breathing on symptoms of chronic heart failure: a randomized, controlled feasibility study. Eur J Heart Fail. 2011; 13(9): 1000–1005, doi: 10.1093/eurjhf/hfr090, indexed in Pubmed: 21803755.
27. Drozdz T, Bilo G, Debicka-Dabrowska D, et al. Blood pressure changes in patients with chronic heart failure undergoing slow breathing training. Blood Press. 2016; 25(1): 4–10, doi: 10.3109/08037051.2016.1099800, indexed in Pubmed: 26513698.
28. Kawecka-Jaszcz K, Bilo G, Drożdż T, et al. Effects of deviceguided slow breathing training on exercise capacity, cardiac function, and respiratory patterns during sleep in male and female patients with chronic heart failure. Pol Arch Intern Med. 2017; 127(1): 8–15, doi: 10.20452/pamw.3890, indexed in Pubmed: 28075423.
29. Lachowska K, Bellwon J, Narkiewicz K, et al. Long-term effects of device-guided slow breathing in stable heart failure patients with reduced ejection fraction. Clin Res Cardiol. 2019; 108(1): 48–60, doi: 10.1007/s00392-018-1310-7, indexed in Pubmed: 29943271.
30. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure]. Kardiol Pol. 2016; 74(10): 1037–1147.
31. Hering D, Kucharska W, Kara T, et al. Effects of acute and long-term slow breathing exercise on muscle sympathetic nerve activity in untreated male patients with hypertension. J Hypertens. 2013; 31(4): 739–746, doi: 10.1097/HJH.0b013e32835eb2cf, indexed in Pubmed: 23385649.
32. Hering D, Kara T, Kucharska W, et al. High-normal blood pressure is associated with increased resting sympathetic activity but normal responses to stress tests. Blood Press. 2013; 22(3): 183–187, doi: 10.3109/08037051.2012.759689, indexed in Pubmed: 23356493.
33. Hering D, Kara T, Kucharska W, et al. Longitudinal tracking of muscle sympathetic nerve activity and its relationship with blood pressure in subjects with prehypertension. Blood Press. 2016; 25(3): 184–192, doi: 10.3109/08037051.2015.1121708, indexed in Pubmed: 26654200.
34. Dixon T, Lim LLY, Oldridge NB. The MacNew heart disease health-related quality of life instrument: reference data for users. Qual Life Res. 2002; 11(2): 173–183, indexed in Pubmed: 12018740.
35. Höfer S, Schmid JP, Frick M, et al. Psychometric properties of the MacNew heart disease health-related quality of life instrument in patients with heart failure. J Eval Clin Pract. 2008; 14(4): 500–506, doi: 10.1111/j.1365-2753.2007.00905.x, indexed in Pubmed: 18462292.
36. Oldridge N, Saner H, McGee HM. The Euro Cardio-QoL Project. An international study to develop a core heart disease health-related quality of life questionnaire, the HeartQoL. Eur J Cardiovasc Prev Rehabil. 2005; 12(2): 87–94, indexed in Pubmed: 15785293.
37. Moryś JM, Höfer S, Rynkiewicz A, et al. The Polish MacNew heart disease heath-related quality of life questionnaire: a validation study. Cardiol J. 2015; 22(5): 541–550, doi: 10.5603/CJ.a2015.0027, indexed in Pubmed: 26004936.
38. Bernardi L, Porta C, Spicuzza L, et al. Slow breathing increases arterial baroreflex sensitivity in patients with chronic heart failure. Circulation. 2002; 105(2): 143–145, indexed in Pubmed: 11790690.
39. Kawauchi TS, Umeda II, Braga LM, et al. Is there any benefit using low-intensity inspiratory and peripheral muscle training in heart failure? A randomized clinical trial. Clin Res Cardiol. 2017; 106(9): 676–685, doi: 10.1007/s00392-017-1089-y, indexed in Pubmed: 28255812.
40. Drozdz T, Bilo G, Debicka-Dabrowska D, et al. Blood pressure changes in patients with chronic heart failure undergoing slow breathing training. Blood Press. 2016; 25(1): 4–10, doi: 10.3109/08037051.2016.1099800, indexed in Pubmed: 26513698.
41. Cohn JN, Levine TB, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med. 1984; 311(13): 819–823, doi: 10.1056/NEJM198409273111303, indexed in Pubmed: 6382011.
42. Kaye DM, Lefkovits J, Jennings GL, et al. Adverse consequences of high sympathetic nervous activity in the failing human heart. J Am Coll Cardiol. 1995; 26(5): 1257–1263, doi: 10.1016/0735-1097(95)00332-0, indexed in Pubmed: 7594040.
43. Petersson M, Friberg P, Eisenhofer G, et al. Long-term outcome in relation to renal sympathetic activity in patients with chronic heart failure. Eur Heart J. 2005; 26(9): 906–913, doi: 10.1093/eurheartj/ehi184, indexed in Pubmed: 15764611.
44. Grassi G, Seravalle G, Cattaneo BM, et al. Sympathetic activation and loss of reflex sympathetic control in mild congestive heart failure. Circulation. 1995; 92(11): 3206–3211, indexed in Pubmed: 7586305.
45. Lucia Cde, Femminella G, Gambino G, et al. Adrenal adrenoceptors in heart failure. Frontiers Physiol. 2014; 5: 246, doi: 10.3389/fphys.2014.00246.
46. Phillips A. Blunted as well as exaggerated cardiovascular reactivity to stress is associated with negative health outcomes. Jpn Psychol Res. 2011; 53(2): 177–192, doi: 10.1111/j.1468-5884.2011.00464.x.
47. Phillips AC, Ginty AT, Hughes BM. The other side of the coin: blunted cardiovascular and cortisol reactivity are associated with negative health outcomes. Int J Psychophysiol. 2013; 90(1): 1–7, doi: 10.1016/j.ijpsycho.2013.02.002, indexed in Pubmed: 23454029.
48. Esler M, Jennings G, Lambert G. Measurement of overall and cardiac norepinephrine release into plasma during cognitive challenge. Psychoneuroendocrinology. 1989; 14(6): 477–481, indexed in Pubmed: 2623135.
49. Deanfield JE, Kensett M, Wilson RA, et al. Silent myocardial ischaemia due to mental stress. Lancet. 1984; 2(8410): 1001–1005, indexed in Pubmed: 6149394.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2020, Vol. 27, No. 6, 780–788
DOI: 10.5603/CJ.a2019.0024

ISSN 1897–5593
eISSN 1898–018X

Impact of mild therapeutic hypothermia on bioavailability of ticagrelor in patients with acute myocardial infarction after out-of-hospital cardiac arrest

Julia M. Umińska[1], Jakub Ratajczak[2], Katarzyna Buszko[3], Przemysław Sobczak[2], Wiktor Sroka[4], Michał P. Marszałł[4], Piotr Adamski[2], Klemen Steblovnik[5], Marko Noč[5], Jacek Kubica[2]

[1]Department of Geriatrics, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland
[2]Department of Cardiology and Internal Medicine, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland
[3]Department of Theoretical Foundations of Biomedical Science and Medical Informatics, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland
[4]Department of Medicinal Chemistry, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland
[5]Center for Intensive Internal Medicine, University Medical Center Ljubljana, Slovenia

Abstract

Background: *Out-of-hospital cardiac arrest (OHCA) frequently occurs in the early phase of acute myocardial infarction (MI). Survivors require percutaneous coronary intervention (PCI) with concomitant dual antiplatelet therapy. Target temperature management, including mild therapeutic hypothermia (MTH), should be applied in comatose patients after resuscitation. However, an increased risk of stent thrombosis in patients undergoing hypothermia is observed. The aim of this study was to assess the impact of MTH on pharmacokinetics of ticagrelor in cardiac arrest survivors with MI treated with MTH and PCI.*

Methods: *In a prospective, observational, single-center study pharmacokinetics of ticagrelor were evaluated in 41 MI patients, including 11 patients after OHCA undergoing MTH (MTH group) and 30 MI patients without OHCA and MTH (no-MTH group). Blood samples were drawn before administration of a 180 mg ticagrelor loading dose, and 30 min, 1, 2, 4, 6, 12, and 24 h after the loading dose.*

Results: *In patients treated with MTH total exposure to ticagrelor during the first 12 h after the loading dose and maximal plasma concentration of ticagrelor were significantly lower than in the no-MTH group ($AUC_{(0–12)}$: 3403 ± 2879 vs. 8746 ± 5596 ng·h/mL, difference: 61%, p = 0.01; C_{max}: 475 ± 353 vs. 1568 ± 784 ng/mL, p = 0.0002). Time to achieve maximal ticagrelor plasma concentration was also delayed in the MTH group (t_{max} for ticagrelor: 12 [6–24] vs. 4 [2–12] h, p = 0.01).*

Conclusions: *Bioavailability of ticagrelor was substantially decreased and delayed in MI patients treated with MTH after OHCA.*

Trial registration: ClinicalTrials.gov Identifier: NCT02611934 (Cardiol J 2020; 27, 6: 780–788)

Key words: cardiac arrest, myocardial infarction, hypothermia, ticagrelor, platelets, pharmacokinetics

Address for correspondence: Julia M. Umińska, MD, Department of Geriatrics, Collegium Medicum, Nicolaus Copernicus University, ul. M. Skłodowskiej-Curie 9, 85–094 Bydgoszcz, Poland, tel: +48 52 585 49 00, fax: +48 52 585 49 21, e-mail: julia.m.kubica@gmail.com

Received: 18.02.2019 Accepted: 20.02.2019

Introduction

Out-of-hospital cardiac arrest (OHCA) frequently occurs in the early phase of acute myocardial infarction (MI). OHCA survivors presenting symptoms of acute MI require primary percutaneous coronary intervention (PCI) with concomitant dual antiplatelet therapy (DAPT), including acetylsalicylic acid (ASA) and a $P2Y_{12}$ receptor inhibitor [1–4]. Early administration of antiplatelet agents is necessary as the highest risk of stent thrombosis was reported within the early phase after stent implantation [5]. Ticagrelor and prasugrel are the preferred $P2Y_{12}$ inhibitors in this clinical setting [6–11]. In patients remaining in a coma after resuscitation targeted temperature management should be applied with a constant core temperature between 32°C and 36°C [12].

It has been shown that plasma concentrations of ticagrelor and its active metabolite (AR-C124910XX) are diminished in patients with ST-segment elevation MI. This effect is even more pronounced with concomitant morphine administration [13–19]. In survivors of OHCA due to MI additional factors including mild therapeutic hypothermia (MTH) may further impede ticagrelor's bioavailability [20–22]. The decreased antiplatelet effect of ticagrelor caused by hindered pharmacokinetics might be responsible for an increased risk of stent thrombosis in resuscitated patients undergoing MTH despite DAPT [23, 24].

Thus, the present study was designed [21] and performed using a prospective observational approach to assess pharmacokinetics of ticagrelor in MI patients after OHCA treated with primary PCI and MTH.

Methods

The study was designed and performed as a phase IV, single-center, investigator-initiated, prospective, observational trial aimed to compare pharmacokinetics of ticagrelor between MI patients after OHCA treated with primary PCI and MTH (MTH group) and MI patients without OHCA treated with primary PCI (no-MTH group). The inclusion as well as exclusion criteria for both groups have been previously published [21].

Mild therapeutic hypothermia was defined as a body core temperature below 34°C, with a target temperature of 33°C. In order to reach the target temperature and maintain it over subsequent 24 h, intravascular cooling supported by cold saline (4°C) infusion and external cooling at the induction phase of MTH were used. The MTH procedure applied in this study has also been previously described [21].

All study participants received treatment according to the European Society of Cardiology guidelines. All patients included in the trial received a 300 mg loading dose (LD) of plain ASA and a 180 mg LD of ticagrelor in integral tablets administered through a nasogastric tube in the MTH group, and orally in the no-MTH group.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the Ethics Committee of The Nicolaus Copernicus University in Torun, Collegium Medicum in Bydgoszcz (approval number KB 339/2015). All MI patients without MTH provided written, informed consent to participate in the study before enrollment, as additional blood sampling was required. In patients treated with MTH due to OHCA it was not possible to obtain informed consent, however these patients did not require additional sampling outside the standard protocol of MTH monitoring. This is a sub-study of the Mild Therapeutic Hypothermia for Patients with Acute Coronary Syndrome and Cardiac Arrest Treated with Percutaneous Coronary Intervention (UNICORN) study (ClinicalTrials.gov Identifier: NCT02611934).

Endpoints

The primary endpoint of this study was the area under the plasma concentration-time curve ($AUC_{(0–12)}$) for ticagrelor during the first 12 h after administration of LD. Secondary endpoints included $AUC_{(0–12)}$ for AR-C124910XX, $AUC_{(0-6)}$ for ticagrelor and AR-C124910XX, maximum concentration of ticagrelor and AR-C124910XX for 12 h (C_{max12}), and time to C_{max} (t_{max}) for ticagrelor and AR-C124910XX, plasma concentrations of ticagrelor and AR-C124910XX at baseline, and 30 min, 1, 2, 4, 6, 12, and 24 h after ticagrelor LD.

Evaluation of pharmacokinetics

Blood samples for pharmacokinetic evaluation were drawn before administration of a 180 mg ticagrelor LD, and 30 min, 1, 2, 4, 6, 12, and 24 h after LD. Ticagrelor and AR-C124910XX plasma concentrations were analyzed using liquid chromatography coupled with tandem mass spectrometry. Analysis was performed using Shimadzu UPLC Nexera X2 system consisting of LC-30AD pumps, SIL-30AC Autosampler, CTO-20AC column oven, FCV-20-AH2 valve unit, and DGU-20A5R degasser coupled with Shimadzu 8030 ESI-QqQ mass spec-

Table 1. Characteristics of patients enrolled in the study group — mild therapeutic hypothermia (MTH) and control group (no-MTH).

	MTH group (n = 11)	No-MTH group (n = 30)	P
Gender, male	73% (8)	80% (24)	NS
Age [years]	62.0 ± 11.9	64.4 ± 10.3	NS
History of:			
Coronary artery disease	27% (3)	20% (6)	NS
Acute myocardial infarction	27% (3)	13% (4)	NS
PCI	27% (3)	20% (6)	NS
CABG	0% (0)	0% (0)	NS
Heart failure	9% (1)	0% (0)	NS
Arterial hypertension	54.5% (6)	47% (14)	NS
Stroke	9% (1)	0% (0)	NS
Smoking	45.5% (5)	60% (18)	NS
Acute myocardial infarction:			
STEMI	54.5% (6)	60% (18)	NS
NSTEMI	45.5% (5)	40% (12)	
Number of vessels diseased:			
1	36.4% (4)	27 % (8)	NS
2	18.2% (2)	43% (13)	
3	45.5% (5)	30% (9)	
TIMI before PCI:			
0	45.5% (5)	40% (12)	NS
1	27% (3)	6.6% (2)	
2	9% (1)	6.6% (2)	
3	18.2% (2)	47% (14)	
TIMI after PCI:			
0	0% (0)	0% (0)	NS
1	0% (0)	3.3% (1)	
2	0% (0)	0% (0)	
3	100% (11)	96.7% (29)	
Number of used stents:			
0	0% (0)	3.3% (1)	NS
1	54.5% (6)	70% (21)	
2	36.4% (4)	20% (6)	
3 or more	9% (1)	6.6% (2)	
Echocardiography:			
LVEF [%]	34.0 ± 11.6	45.5 ± 7.9	0.003

CABG — coronary artery bypass grafting; LVEF — left ventricular ejection fraction; NS — non significant; NSTEMI — non-ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention; STEMI — ST-segment elevation myocardial infarction; TIMI — Thrombolysis in Myocardial Infarction

trometer. Lower limits of quantification were 4.69 ng/mL for both ticagrelor and AR-C124910XX [25].

Statistical analysis

All calculations were performed using Statistica 13.0 package (StatSoft, Tulsa, OK, USA). Continuous variables are presented as means ± standard deviation and median with quartiles. For categorical variables, counts with percentages have been used. Due to non-normal data distribution (as verified with the Shapiro-Wilk test), comparisons between both groups at each measurement point were performed with the Mann-Whitney test. For comparison of categorical variables, the χ^2 test or the Fisher exact test was applied as appropriate. In all cases p values ≤ 0.05 were considered significant.

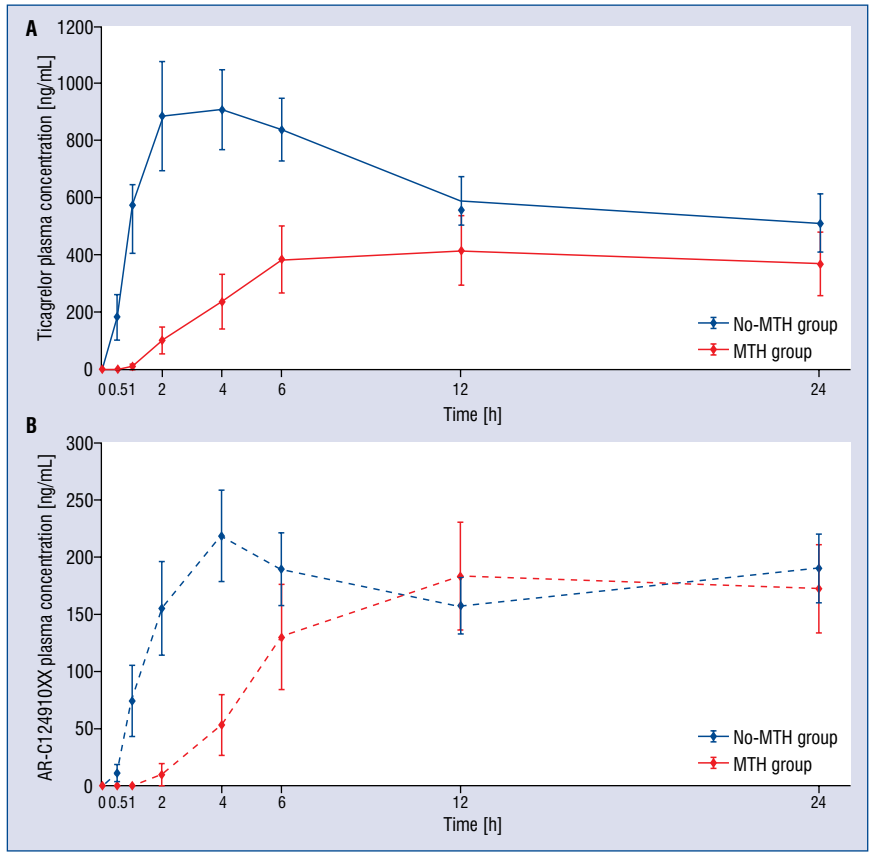


Figure 1. The exposures to ticagrelor (**A**) and AR-C124910XX (**B**) within 24 h after the administration of ticagrelor loading dose (180 mg). Only patients with complete data were included; MTH — mild therapeutic hypothermia.

Results

Overall 43 MI patients were included in the study. There were no significant differences in baseline characteristics between both groups, except higher left ventricular ejection fraction in the no-MTH group (Table 1). Initially, 13 patients were enrolled into the MTH group, however complete data (results from all study time-points) were available for only 7 patients, as 4 of them had died before 24 h from the beginning of the MTH procedure. Additionally, 2 patients from MTH group were excluded from the analysis of the primary end point due to hemolysis in blood samples that precluded complete pharmacokinetic evaluation. Ventricular fibrillation was the first recorded rhythm during cardiac arrest in all 13 patients. The no-MTH group consisted of 30 MI patients without OHCA treated with primary PCI.

Analysis of bioavailability of ticagrelor and AR-C124910XX revealed pronounced differences between compared groups (Fig. 1). Total exposures to both ticagrelor and AR-C124910XX within the first 12 h after LD administration, as measured by the $AUC_{(0–12)}$ was significantly lower in MTH group vs. no-MTH group for ticagrelor ($AUC_{(0–12)}$: 3403 ± 2879 vs. 8746 ± 5596 ng·h/mL, corresponding to a difference of 61%, p = 0.01), while no difference for AR-C124910XX was present ($AUC_{(0–12)}$: 1195 ± 1022 vs. 1963 ± 1726 ng·h/mL, difference: 40%, p = 0.3). The observed differences were more pronounced during the first 6 h after ticagrelor LD ($AUC_{(0–6)}$ for ticagrelor: 1012 ± ± 981 vs. 4487 ± 3608 ng·h/mL, difference: 77%, p = 0.01; $AUC_{(0–6)}$ for AR-C124910XX: 253 ± 281 vs. 922 ± 980 ng·h/mL, difference: 73%, p = 0.06). The maximal plasma concentration of ticagrelor was lower in MTH group vs. no-MTH group (C_{max} for ticagrelor: 475 ± 353 vs. 1568 ± 784 ng/mL, p = 0.0002), whereas there were no differences in maximal concentration of the metabolite between the groups (C_{max} for AR-C124910XX: 203 ± 121 vs. 337 ± 186 ng/mL; p = 0.1). Time to achieve maximal plasma concentrations was delayed for both ticagrelor and AR-C124910XX in MTH group vs. no-MTH group (t_{max} for ticagrelor: 12 [6–24] vs. 4 [2–12] h, p = 0.01; t_{max} for AR-C124910XX: 18 [12–24] vs. 4 [4–12] h, p = 0.01) (Fig. 1).

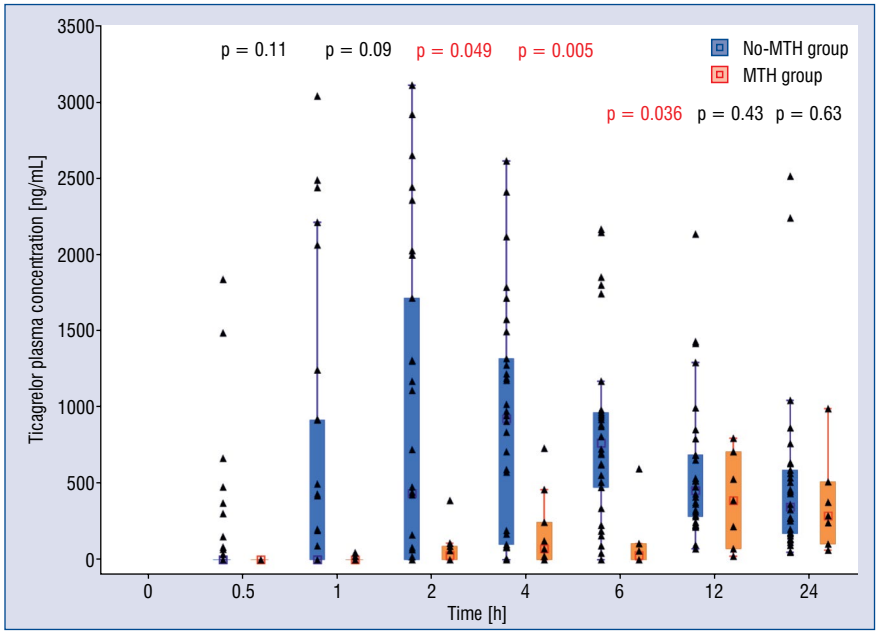


Figure 2. Plasma concentrations of ticagrelor over in mild therapeutic hypothermia (MTH) group (n = 11) vs. no-MTH group (n = 30). All available data presented.

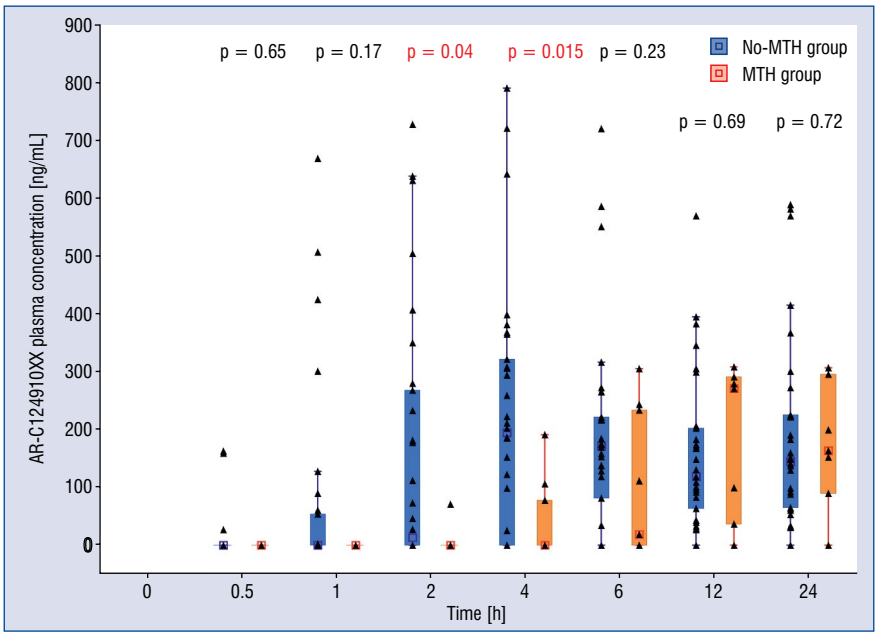


Figure 3. Plasma concentrations of AR-C124910XX over in mild therapeutic hypothermia (MTH) group (n = 11) vs. no-MTH group (n = 30). All available data presented.

Comparison of plasma concentrations of ticagrelor in consecutive time-points showed significant discrepancy between the groups with higher drug concentrations seen in no-MTH group, starting from the first hour after administration of ticagrelor LD (Fig. 2). The difference reached level of statistical significance at 2, 4 and 6 h post-LD (no-MTH group vs. MTH group, respectively: 882.45 ± 1041.77 vs. 70.36 ± 118.70 ng/mL, p = 0.049; 904.43 ± 758.31 vs. 183.41 ± 255.35 ng/mL, p = 0.005; 834.58 ± 595.51 vs. 382.09 ± ± 329.72 ng/mL, p = 0.036). Higher concentrations of AR-C124910XX in no-MTH group were present up to 6 h (Fig. 3), and this difference was significant

at 2 and 4 h (no-MTH group vs. MTH group, respectively: 155.25 ± 223.16 vs. 7.10 ± 22.46 ng/mL, p = 0.04; 218.82 ± 219.14 vs. 41.67 ± 69.12 ng/mL, p = 0.015).

Moreover, additional analysis revealed that the proportion of plasma concentration of AR-C124910XX to concentration of ticagrelor changed during observation according to different patterns in MTH group vs. no-MTH group. This proportion was lower in MTH group in comparison to no-MTH group during the first 2 h. The similar ratios were observed 4 h after administration of ticagrelor LD (22.7% vs. 24.2%), and later this proportion was higher in MTH group up to the end of observation, achieving the highest difference at 6 h (80.1% vs. 22.7%). Of note, none of 4 patients who died (all from MTH group) during the study observation period (24 h) had detectable plasma ticagrelor or AR-C124910XX.

Discussion

According to available research, this is the first study assessing the impact of OHCA treated with MTH on pharmacokinetics of ticagrelor in MI patients undergoing primary PCI.

Impaired bioavailability of ticagrelor expressed by lower total exposure, lower maximal plasma concentration and delayed maximal plasma concentration of the drug in patients undergoing MTH and PCI due to OHCA in the course of MI in comparison with patients treated with primary PCI for uncomplicated MI, advocates impaired gastrointestinal absorption of ticagrelor in critically ill patients undergoing therapeutic hypothermia. Moreover, presence of different AR-C124910XX formation rates between compared groups suggests potential diversity in drug metabolism and/or elimination. Recently, it has been reported that the presence of STEMI and diabetes are connected with impaired metabolism of ticagrelor during the first 6 h after ticagrelor LD for acute coronary syndrome [26]. In the current trial clear differences were observed in ticagrelor's active metabolite formation between patients with and without OHCA treated with MTH, however small the size of cardiac arrest, the survivor group did not allow formal conclusions to be drawn. This important issue requires clarification in further research.

Straub et al. [27] showed that adenosine diphosphate (ADP) plays a central role in hypothermia-induced platelet activation during hypothermia, suggesting that inhibition of ADP receptor binding has the potential to protect platelets against hypothermia-induced activation. However, in previously published studies insufficient efficacy of clopidogrel in patients undergoing MTH after OHCA was reported [28–32]. It was mostly explained by accelerated platelet turnover, increased platelet activation as well as by decreased bioavailability of clopidogrel due to its impaired absorption and diminished active metabolite generation [1, 28, 33, 34]. The effect of ticagrelor and prasugrel in this clinical setting is not clear [35].

The high rate of stent thrombosis observed in some studies in resuscitated MI patients treated with MTH and primary PCI may be caused by insufficient inhibition of $P2Y_{12}$ platelet receptors [23, 24, 36–40]. In an observational study published by Gouffran et al. [24], 10.9% of OHCA survivors treated with MTH had stent thrombosis (the latter occurred in 4.2% of patients on clopidogrel, 18.2% on prasugrel, and 16.7% on ticagrelor). Jiménez-Brítez et al. [37] reported in-hospital stent thrombosis in 7.1% of patients, exclusively those treated with clopidogrel (11.4%), while no stent thrombosis occurred in patients on ticagrelor or prasugrel. Joffre et al. [23] found cardiac arrest treated with MTH to be an independent risk factor for confirmed stent thrombosis (odds ratio = 12.9; 95% confidence interval 1.3–124.6, p = 0.027) regardless of the type of $P2Y_{12}$ antagonist. Penela et al. [36] reported clinical resistance to clopidogrel with an extremely high incidence of acute stent thrombosis. In a small group of 11 MTH patients enrolled in the study, stent thrombosis occurred in 5 (31.2%) cases, while 2 other patients experienced other thrombotic complications. Of note, most of the thrombotic complications occurred long after rewarming [36].

It is not clear if hypothermia itself or rather centralization of circulation in critically ill patients is responsible for impairment of ticagrelor absorption. The results of the ISAR-SHOCK registry demonstrated a weaker antiplatelet effect in shock patients receiving either clopidogrel or prasugrel without hypothermia [41]. This observation may suggest that the impaired effect of oral $P2Y_{12}$ inhibitors in OHCA is related not only to hypothermia, but rather multifactorial [41, 42]. Regardless of what the exact mechanisms of ineffectiveness of these drugs are, intravenous infusion of a short-acting $P2Y_{12}$ receptor antagonist — cangrelor — is capable of inhibiting life-threatening platelet-mediated prothrombotic events in the setting of MTH. This innovative pharmacological strategy could significantly improve the safety of MTH [43–45]. Infusion of glycoprotein IIb/IIIa inhibitors

is another therapeutic option allowing patients to overcome shortcomings of oral antiaggregatory agents, it is however, associated with markedly increased risk of bleedings [46–49]

Limitations of the study

The main limitation of the present study, which is similar to all previously published reports, is the low number of enrolled OHCA survivors treated with MTH and primary PCI. This did not permit the evaluation of clinical end points. Moreover, it was not possible herein, to differentiate the impact of MTH from consequences of local circulatory disorders. Also, the current trial did not evaluate pharmacodynamics of ticagrelor.

Nevertheless, careful monitoring of plasma concentrations of ticagrelor and AR-C124910XX at multiple time-points allowed us to demonstrate extensive differences in drug bioavailability between OHCA patients treated with MTH and primary PCI and patients with uncomplicated MI treated with primary PCI. Observations in the present research provide important evidence which may help to elucidate causes of the higher prevalence of stent thrombosis and other thrombotic events in patients undergoing MTH.

Conclusions

Bioavailability of ticagrelor is substantially decreased and delayed in MI patients treated with MTH after OHCA compared with patients with uncomplicated MI and without OHCA requiring MTH.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. The study protocol was published in Medical Research Journal: Umińska MJ, et al. Platelet reactivity during mild therapeutic hypothermia in patients with acute myocardial infarction treated with ticagrelor: study protocol of a single-centre study. Med Res J. 2016; 1(4): 115–119, doi: 10.5603/MRJ.2016.0021.

Funding: This study has been developed as part of the 'Diamentowy Grant' project financed by the Ministry of Science and Higher Education of the Republic of Poland from research funds for the years 2015–2018 (DI2014009144). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest: J.M. Umińska: Beneficient of the "Diamentory Grant" financed by the Ministry of Science and Higher Education of the Republic of Poland from research funds for the years 2015––2018 (DI2014009144); K. Steblovnik and M. Noc: Beneficient of research grant from AstraZeneca; J. Kubica: Consulting fee from AstraZeneca.

References

1. Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015: Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015. Resuscitation. 2015; 95: 202–222, doi: 10.1016/j.resuscitation.2015.07.018, indexed in Pubmed: 26477702.
2. Kubica J, Pstrągowski K, Adamski P, et al. Mild therapeutic hypothermia for patients with acute coronary syndrome and cardiac arrest treated with percutaneous coronary intervention (UNICORN). The design and rationale for the prospective, observational, multicenter study. Med Res J. 2016; 1(1): 23–27, doi: 10.5603/mrj.2016.0004.
3. Adamski P, Adamska U, Ostrowska M, et al. New directions for pharmacotherapy in the treatment of acute coronary syndrome. Expert Opin Pharmacother. 2016; 17(17): 2291–2306, doi: 10.1080/14656566.2016.1241234, indexed in Pubmed: 27677394.
4. Kubica J. The optimal antiplatelet treatment in an emergency setting. Folia Med Copernicana. 2014; 2(3): 73–76.
5. Gurbel PA, Myat A, Kubica J, et al. State of the art: Oral antiplatelet therapy. JRSM Cardiovasc Dis. 2016; 5: 1–10, doi: 10.1177/2048004016652514, indexed in Pubmed: 27298725.
6. Dumas F, Rea TD. Long-term prognosis following resuscitation from out-of-hospital cardiac arrest: role of aetiology and presenting arrest rhythm. Resuscitation. 2012; 83(8): 1001–1005, doi: 10.1016/j.resuscitation.2012.01.029, indexed in Pubmed: 22306255.
7. Ibanez B, James S, Agewall S, et al. ESC Scientific Document Group. 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, doi: 10.1093/eurheartj/ehx393, indexed in Pubmed: 28886621.
8. Kubica J, Adamski P, Paciorek P, et al. Treatment of patients with acute coronary syndrome: Recommendations for medical emergency teams: Focus on antiplatelet therapies. Updated experts' standpoint. Cardiol J. 2018; 25(3): 291–300, doi: 10.5603/CJ.a2018.0042, indexed in Pubmed: 29671864.
9. Kubica J, Adamski P, Paciorek P, et al. Anti-aggregation therapy in patients with acute coronary syndrome - recommendations for medical emergency teams. Experts' standpoint. Kardiol Pol. 2017; 75(4): 399–408, doi: 10.5603/KP.a2017.0057, indexed in Pubmed: 28421594.
10. Navarese EP, Verdoia M, Schaffer A, et al. Ischaemic and bleeding complications with new, compared to standard, ADP-antagonist regimens in acute coronary syndromes: a meta-analysis of randomized trials. QJM. 2011; 104(7): 561–569, doi: 10.1093/qjmed/hcr069, indexed in Pubmed: 21572108.
11. Navarese EP, Buffon A, Kozinski M, et al. A critical overview on ticagrelor in acute coronary syndromes. QJM. 2013; 106(2): 105––115, doi: 10.1093/qjmed/hcs187, indexed in Pubmed: 23097390.

12. Kozinski M, Pstragowski K, Kubica JM, et al. ACS network-based implementation of therapeutic hypothermia for the treatment of comatose out-of-hospital cardiac arrest survivors improves clinical outcomes: the first European experience. Scand J Trauma Resusc Emerg Med. 2013; 21: 22, doi: 10.1186/1757-7241-21-22, indexed in Pubmed: 23531402.
13. Adamski P, Sikora J, Laskowska E, et al. Comparison of bioavailability and antiplatelet action of ticagrelor in patients with ST-elevation myocardial infarction and non-ST-elevation myocardial infarction: A prospective, observational, single-centre study. PLoS One. 2017; 12(10): e0186013, doi: 10.1371/journal.pone.0186013, indexed in Pubmed: 29023473.
14. Adamski P, Ostrowska M, Sikora J, et al. Comparison of Ticagrelor Pharmacokinetics and Pharmacodynamics in STEMI and NSTEMI Patients (PINPOINT): protocol for a prospective, observational, single-centre study. BMJ Open. 2017; 7(4): e013218, doi: 10.1136/bmjopen-2016-013218, indexed in Pubmed: 28446521.
15. Kubica J, Kubica A, Jilma B, et al. Impact of morphine on antiplatelet effects of oral P2Y12 receptor inhibitors. Int J Cardiol. 2016; 215: 201–208, doi: 10.1016/j.ijcard.2016.04.077, indexed in Pubmed: 27128531.
16. Kubica J, Adamski P, Ostrowska M, et al. Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial. Eur Heart J. 2016; 37(3): 245–252, doi: 10.1093/eurheartj/ehv547, indexed in Pubmed: 26491112.
17. Niezgoda P, Sikora J, Barańska M, et al. Crushed sublingual versus oral ticagrelor administration strategies in patients with unstable angina. A pharmacokinetic/pharmacodynamic study. Thromb Haemost. 2017; 117(4): 718–726, doi: 10.1160/TH16-08-0670, indexed in Pubmed: 28203684.
18. Adamski P, Koziński M, Ostrowska M, et al. Overview of pleiotropic effects of platelet P2Y12 receptor inhibitors. Thromb Haemost. 2014; 112(2): 224–242, doi: 10.1160/TH13-11-0915, indexed in Pubmed: 24763899.
19. Kubica J, Adamski P, Ostrowska M, et al. Influence of Morphine on Pharmacokinetics and Pharmacodynamics of Ticagrelor in Patients with Acute Myocardial Infarction (IMPRESSION): study protocol for a randomized controlled trial. Trials. 2015; 16: 198, doi: 10.1186/s13063-015-0724-z, indexed in Pubmed: 25925591.
20. Tilemann LM, Stiepak J, Zelniker T, et al. Efficacy of enteral ticagrelor in hypothermic patients after out-of-hospital cardiac arrest. Clin Res Cardiol. 2016; 105(4): 332–340, doi: 10.1007/s00392-015-0925-1, indexed in Pubmed: 26508414.
21. Umińska J, Koziński M, Pstrągowski K, et al. Platelet reactivity during mild therapeutic hypothermia in patients with acute myocardial infarction treated with ticagrelor: study protocol of a single-centre study. Med Res J. 2017; 1(4): 115–119, doi: 10.5603/mrj.2016.0021.
22. Kubica A, Kasprzak M, Siller-Matula J, et al. Time-related changes in determinants of antiplatelet effect of clopidogrel in patients after myocardial infarction. Eur J Pharmacol. 2014; 742: 47–54, doi: 10.1016/j.ejphar.2014.08.009, indexed in Pubmed: 25199965.
23. Joffre J, Varenne O, Bougouin W, et al. Stent thrombosis: an increased adverse event after angioplasty following resuscitated cardiac arrest. Resuscitation. 2014; 85(6): 769–773, doi: 10.1016/j.resuscitation.2014.02.013, indexed in Pubmed: 24572484.
24. Gouffran G, Rosencher J, Bougouin W, et al. Stent thrombosis after primary percutaneous coronary intervention in comatose survivors of out-of-hospital cardiac arrest: Are the new P2Y12 inhibitors really more effective than clopidogrel? Resuscitation. 2016; 98: 73–78, doi: 10.1016/j.resuscitation.2015.11.006, indexed in Pubmed: 26610376.
25. Tantry US, Bonello L, Aradi D, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. J Am Coll Cardiol. 2013; 62(24): 2261–2273, doi: 10.1016/j.jacc.2013.07.101, indexed in Pubmed: 24076493.
26. Adamski P, Buszko K, Sikora J, et al. Metabolism of ticagrelor in patients with acute coronary syndromes. Sci Rep. 2018; 8(1): 11746, doi: 10.1038/s41598-018-29619-9, indexed in Pubmed: 30082687.
27. Straub A, Breuer M, Wendel HP, et al. Critical temperature ranges of hypothermia-induced platelet activation: possible implications for cooling patients in cardiac surgery. Thromb Haemost. 2007; 97(4): 608–616, indexed in Pubmed: 17393024.
28. Prüller F, Milke OL, Bis L, et al. Impaired aspirin-mediated platelet function inhibition in resuscitated patients with acute myocardial infarction treated with therapeutic hypothermia: a prospective, observational, non-randomized single-centre study. Ann Intensive Care. 2018; 8(1): 28, doi: 10.1186/s13613-018-0366-x, indexed in Pubmed: 29468430.
29. Moudgil R, Al-Turbak H, Osborne C, et al. CAPITAL Investigators. Superiority of ticagrelor over clopidogrel in patients after cardiac arrest undergoing therapeutic hypothermia. Can J Cardiol. 2014; 30(11): 1396–1399, doi: 10.1016/j.cjca.2014.07.745, indexed in Pubmed: 25442437.
30. Ferreiro J, Sánchez-Salado J, Gracida M, et al. Impact of Mild Hypothermia on Platelet Responsiveness to Aspirin and Clopidogrel: an In Vitro Pharmacodynamic Investigation. J Cardiovasc Transl Res. 2014; 7(1): 39–46, doi: 10.1007/s12265-013-9533-5.
31. Rosencher J, Gouffran G, Bougouin W, et al. Optimal antiplatelet therapy in out-hospital cardiac arrest patients treated by primary percutaneous coronary intervention. Resuscitation. 2015; 90: e7–e8, doi: 10.1016/j.resuscitation.2015.02.030, indexed in Pubmed: 25758639.
32. Bednar F, Kroupa J, Ondrakova M, et al. Antiplatelet efficacy of P2Y12 inhibitors (prasugrel, ticagrelor, clopidogrel) in patients treated with mild therapeutic hypothermia after cardiac arrest due to acute myocardial infarction. J Thromb Thrombolysis. 2016; 41(4): 549–555, doi: 10.1007/s11239-015-1274-7, indexed in Pubmed: 26340851.
33. Ibrahim K, Christoph M, Schmeinck S, et al. High rates of prasugrel and ticagrelor non-responder in patients treated with therapeutic hypothermia after cardiac arrest. Resuscitation. 2014; 85(5): 649–656, doi: 10.1016/j.resuscitation.2014.02.004, indexed in Pubmed: 24555950.
34. Kander T, Dankiewicz J, Friberg H, et al. Platelet aggregation and clot formation in comatose survivors of cardiac arrest treated with induced hypothermia and dual platelet inhibition with aspirin and ticagrelor; a prospective observational study. Crit Care. 2014; 18(5): 495, doi: 10.1186/s13054-014-0495-z, indexed in Pubmed: 25292183.
35. Schoergenhofer C, Hobl EL, Staudinger T, et al. Prasugrel in critically ill patients. Thromb Haemost. 2017; 117(8): 1582–1587, doi: 10.1160/TH17-03-0154, indexed in Pubmed: 28692105.
36. Penela D, Magaldi M, Fontanals J, et al. Hypothermia in acute coronary syndrome: brain salvage versus stent thrombosis? J Am Coll Cardiol. 2013; 61(6): 686–687, doi: 10.1016/j.jacc.2012.10.029, indexed in Pubmed: 23265329.
37. Jiménez-Brítez G, Freixa X, Flores-Umanzor E, et al. Out-of-hospital cardiac arrest and stent thrombosis: Ticagrelor versus

clopidogrel in patients with primary percutaneous coronary intervention under mild therapeutic hypothermia. Resuscitation. 2017; 114: 141–145, doi: 10.1016/j.resuscitation.2017.02.015, indexed in Pubmed: 28242212.
38. Bjelland TW, Hjertner Ø, Klepstad P, et al. Antiplatelet effect of clopidogrel is reduced in patients treated with therapeutic hypothermia after cardiac arrest. Resuscitation. 2010; 81(12): 1627–1631, doi: 10.1016/j.resuscitation.2010.07.002, indexed in Pubmed: 20727659.
39. Ibrahim K, Christoph M, Schmeinck S, et al. Clopidogrel and prasugrel non-responder in therapeutic hypothermia after cardiac arrest. Eur Heart J . 2012; 33: 315.
40. Steblovnik K, Blinc A, Mijovski MB, et al. Ticagrelor Versus Clopidogrel in Comatose Survivors of Out-of-Hospital Cardiac Arrest Undergoing Percutaneous Coronary Intervention and Hypothermia: A Randomized Study. Circulation. 2016; 134(25): 2128–2130, doi: 10.1161/CIRCULATIONAHA.116.024872, indexed in Pubmed: 27994027.
41. Orban M, Mayer K, Morath T, et al. The impact of therapeutic hypothermia on on-treatment platelet reactivity and clinical outcome in cardiogenic shock patients undergoing primary PCI for acute myocardial infarction: Results from the ISAR-SHOCK registry. Thromb Res. 2015; 136(1): 87–93, doi: 10.1016/j.thromres.2015.04.029, indexed in Pubmed: 25976448.
42. Ratcovich H, Sadjadieh G, Andersson HB, et al. The effect of TIcagrelor administered through a nasogastric tube to COMAtose patients undergoing acute percutaneous coronary intervention: the TICOMA study. EuroIntervention. 2017; 12(14): 1782–1788, doi: 10.4244/EIJ-D-16-00398, indexed in Pubmed: 28216475.
43. Droppa M, Borst O, Rath D, et al. Impact of Intravenous P2Y12-Receptor Inhibition with Cangrelor in Patients Presenting with Acute Coronary Syndrome and Cardiogenic Shock — a Case Series. Cell Physiol Biochem. 2017; 42(4): 1336–1341, doi: 10.1159/000478962, indexed in Pubmed: 28700987.
44. Krajewski S, Kurz J, Neumann B, et al. Short-acting P2Y12 blockade to reduce platelet dysfunction and coagulopathy during experimental extracorporeal circulation and hypothermia. Br J Anaesth. 2012; 108(6): 912–921, doi: 10.1093/bja/aer518, indexed in Pubmed: 22369765.
45. Kubica J, Kozinski M, Navarese EP, et al. Cangrelor: an emerging therapeutic option for patients with coronary artery disease. Curr Med Res Opin. 2014; 30(5): 813–828, doi: 10.1185/03007995.2014.880050, indexed in Pubmed: 24393016.
46. Kubica A, Kozinski M, Navarese EP, et al. Intracoronary versus intravenous abciximab administration in STEMI patients: overview of current status and open questions. Curr Med Res Opin. 2011; 27(11): 2133–2144, doi: 10.1185/03007995.2011.621417, indexed in Pubmed: 21942506.
47. Kubica J, Koziński M, Navarese EP, et al. Updated evidence on intracoronary abciximab in ST-elevation myocardial infarction: a systematic review and meta-analysis of randomized clinical trials. Cardiol J. 2012; 19(3): 230–242, indexed in Pubmed: 22641541.
48. Navarese EP, Kozinski M, Obonska K, et al. Clinical efficacy and safety of intracoronary vs. intravenous abciximab administration in STEMI patients undergoing primary percutaneous coronary intervention: a meta-analysis of randomized trials. Platelets. 2012; 23(4): 274–281, doi: 10.3109/09537104.2011.619602, indexed in Pubmed: 21988317.
49. Siller-Matula JM, Specht S, Kubica J, et al. Abciximab as a bridging strategy to overcome morphine-prasugrel interaction in STEMI patients. Br J Clin Pharmacol. 2016; 82(5): 1343–1350, doi: 10.1111/bcp.13053, indexed in Pubmed: 27366874.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2020, Vol. 27, No. 6, 789–796
DOI: 10.5603/CJ.a2019.0049

ISSN 1897–5593
eISSN 1898–018X

Valve hemodynamic performance and myocardial strain after implantation of a third-generation, balloon-expandable, transcatheter aortic valve

Sara Fernández-Santos[1], Alexis Théron[2], Philippe Pibarot[3], Frédéric Collart[2], Martine Gilard[4], Marina Urena[5], Tomas Hovorka[6], Philipp Kahlert[7], José Luis Zamorano Gomez[1]

[1]Cardiology Department, University Hospital Ramon y Cajal, Madrid, Spain
[2]Department of Cardiac Surgery, La Timone Public Hospital, Marseille, France
[3]Québec Heart and Lung Institute, Québec, Canada
[4]Cardiology Department, La Cavalle Blanche University Hospital, Brest, France
[5]Cardiology Department, Bichat Claude Bernard Hospital, Paris, France
[6]Biostatistics Department, Edwards Lifesciences, Prague, Czech Republic
[7]West German Heart and Vascular Center, Department of Cardiology and Vascular Medicine, Essen University Hospital, University Duisburg-Essen, Essen, Germany

Abstract

Background: *Left ventricular (LV) mechanics are impaired in patients with severe aortic stenosis (AS); however, transcatheter aortic valve implantation (TAVI) may positively affect LV mechanics. Assessed herein is the performance of the SAPIEN 3 transcatheter heart valve (THV) and the effect of TAVI on LV function recovery, as assessed by global longitudinal strain (GLS).*

Methods: *A subset of patients from the SOURCE 3 registry (n = 276) from 16 European centers received SAPIEN 3 balloon-expandable THV. Echocardiography was performed at baseline, post-procedure, and at 1 year, including assessment of GLS using standard two-dimensional images, and was analyzed in a core laboratory. Paired analyses between baseline and discharge, baseline and at 1 year were conducted.*

Results: *Hemodynamic parameters were improved after TAVI and sustained to 1 year. At 1 year, the rate of moderate to severe paravalvular leaks (PVL), and moderate to severe mitral and tricuspid regurgitations were 1.8%, 1.7%, and 8.0%, respectively. The discharge GLS (–15.6 ± 5.1; p = 0.004; n = 149) improved significantly from baseline (–15.1 ± 4.8) following TAVI. This improvement was sustained at 1 year compared with baseline (–17.0 ± 4.6, p < 0.001; n = 100). Conversely, LV ejection fraction (LVEF) did not significantly change following TAVI (p = 0.47).*

Conclusions: *Following TAVI with a third-generation THV, valve performances were good at 1 year with low PVL rate. The LV mechanics improved immediately after the procedure and were maintained at 1 year. These findings demonstrate the benefit of TAVI on LV mechanics, and suggests that GLS may be superior to LVEF in assessing this benefit.*

Clinicaltrial.gov number: NCT02698956 (Cardiol J 2020; 27, 6: 789–796)

Key words: strain, left ventricular mechanics, echocardiography, aortic stenosis, transcatheter aortic valve implantation

Address for correspondence: Dr. Sara Fernandez Santos, Cardiology Department, University Hospital Ramon y Cajal, Carreta de Colmenar Viejo, 28034 Madrid, Spain, tel: +34 660 463 557, fax: +34 913368515, e-mail: sarafernandezsantos@hotmail.com

Received: 25.01.2019 Accepted: 20.04.2019

Introduction

Degenerative aortic stenosis (AS) is one of the most prevalent cardiovascular diseases in developed countries. Over the past decade, transcatheter aortic valve implantation (TAVI) has emerged as the therapy of choice for patients with AS considered inoperable or at high surgical risk [1, 2]. TAVI has improved the prognosis of these patients. And, as transcatheter heart valves (THV) have evolved, patients who had received TAVI suffered fewer complications.

Aortic stenosis induces a series of adaptive responses. It generates a pressure overload that alters left ventricular (LV) geometry and performance; although, LV volume and LV ejection fraction (LVEF) may be preserved, even in advanced stages of the disease [3]. The most important changes caused by the pressure overload include hypertrophic remodeling [4], diastolic dysfunction [5, 6], and impaired contractility [7].

Patients with AS who are treated with TAVI can experience relief from this pressure overload that is reflected in changes in LV strain [4]. The immediate result of TAVI is often an acute decrease in transvalvular gradient, leading to an improvement of LV mechanics. This could be a precursor to, or a reverse in, remodeling, possibly leading to a reduction in LV mass and an improvement in long-term diastolic function.

Studies have demonstrated that strain (global longitudinal strain [GLS]) imaging is the most appropriate method to evaluate subtle changes in myocardial function that occur in patients with AS [8, 9]. Additionally, GLS is independently predictive of mortality [10]. In a recently published study of 92 patients treated in Europe with either the self-expanding CoreValve (Medtronic, Minneapolis, MN, USA) or the mechanically expanded Lotus valve (Boston Scientific, Natick, MA, USA), TAVI was associated with an immediate improvement in LV mechanics, as demonstrated by GLS increase; although LV systolic function remained unaltered [4].

The literature on post implantation LV mechanics is limited. The impact of TAVI on LV mechanics using GLS in patients who received the SAPIEN 3 (Edwards Lifesciences; Irvine, CA, USA) balloon-expandable, transcatheter valve at 1 year follow-up were analyzed.

Methods

Study population

Patients with symptomatic, severe AS were implanted with the third-generation, balloon-expandable SAPIEN THV (SAPIEN 3). The selection of patients was based on a clinical consensus of the Heart Team. A subset of patients from the SOURCE 3 registry had planned, per protocol, to have their echocardiograms reviewed by an independent central echocardiography core laboratory (ECL; Ramon y Cajal, Madrid). Patients had echocardiograms at baseline, discharge, and at 1 year after implantation.

Intervention and purpose

The SAPIEN 3 Aortic Bioprosthesis European Outcome (SOURCE 3) is a European, post-approval multicenter, observational registry, aimed to evaluate the safety and performance of the SAPIEN 3 THV under real-world conditions. The full cohort of 30-day and 1-year results had been published previously [11, 12]. A protocol was developed for this echocardiographic sub-study. It was approved by the local ethics committees and the respective health authorities in participating countries (France, Germany, United Kingdom, and Italy). All patients provided written, informed consent before the study commenced.

Clinical outcomes (cardiac death and disabling stroke to 1 year and life-threatening bleedings to 30 days) were adjudicated by a clinical event committee.

Patients had two-dimensional (2D) transthoracic echocardiograms according to the protocol. The sites sent the echocardiograms to the core laboratory for comprehensive evaluation of hemodynamic performance of valve and LV function. The protocol stipulated multiple echocardiographic measurements before and after prosthesis implantation, as well as quantification of LV mechanics, measuring LV strain with standard 2D imaging (Image Arena and CPA package, TomTec Imaging System). The assessment of GLS was done using averages of measures taken from images on three views: apical 4-, 3- and 2-chamber views in an 18-segment LV model. To obtain LV strain measurements, endocardial contour needed to be manually outlined, after which the system generated the myocardial perimeter on the end systolic

Table 1. Baseline characteristics of the SOURCE 3 cohort.

	Patients with AS who received SAPIEN 3 THV (n = 276)	Patients with AS who received SAPIEN 3 THV, with no ECL assessment (n = 1670)	P
Demographics and clinical variables			
Age [years], mean ± SD	80.8 ± 7.47	81.7 ± 6.49	0.124
Age ≥ 80 years	184 (66.7%)	1136 (68.0%)	0.677
Female	126 (45.7%)	809 (48.4%)	0.399
Logistic EuroScore, mean ± SD	15.6 ± 10.60, N = 226	18.7 ± 13.46, N = 1558	0.002
EuroScore II, mean ± SD	4.6 ± 3.98, N = 204	5.7 ± 5.71, N = 1295	0.007
NYHA class IV	19 (7.0%), N = 272	150 (9.3%), N = 1607	< 0.001
Hypertension	199 (72.1%)	1392 (83.4%)	0.090
Dyslipidaemia	136 (49.3%)	918 (55.0%)	0.103
History of smoking	95 (34.4%)	490 (29.4%), N = 1669	0.117
Diabetes	70 (25.4%)	504 (30.2%)	0.194
Coronary artery disease	132 (47.8%)	870 (52.1%)	0.546
Myocardial infarction	29 (10.5%)	199 (11.9%)	0.414
Coronary bypass grafting	27 (9.8%)	194 (11.6%), N = 1669	0.001
Congestive heart failure	129 (46.7%)	577 (34.6%)	0.561
Renal insufficiency	80 (29.0%)	455 (27.2%)	0.039
Percutaneous coronary intervention	78 (28.3%)	580 (34.8%), N = 1669	0.124
Aortic valve severity			
Mitral regurgitation (degree moderate to severe)	24 (9.2), N = 260	224 (14.8), N = 1513	0.015
Tricuspid regurgitation (moderate to severe)	18 (7.3), N = 245	162 (11.5), N = 1404	0.059

P values are from the Wilcoxon sum rank test for the continuous variables and the Fisher exact test for categorical variables. AS — aortic stenosis; ECL — echocardiology core laboratory; LV — left ventricle; NYHA — New York Heart Association; SD — standard deviation; THV — transcatheter heart valve

frame. Images of measures in a patient with baseline, discharge, and 1-year measures are displayed in supplementary files (**Suppl. Images 1 and 2**).

Two experienced cardiologists examined all echocardiographic data. Intraoperatory aortograms were also performed during valve implantation by many participating sites. A hemodynamic cardiologist from the core laboratory, who was blinded to the echocardiographic results, evaluated these studies.

The aim of the study was to evaluate the impact of TAVI on myocardial longitudinal LV systolic strain in patients with severe, degenerative AS. Additionally, the ECL evaluated hemodynamic parameters.

Statistical analysis

Study staff at participating centers entered echocardiographic data into an electronic capture system. The Sponsor monitored it before it was sent to the ECL. Comparisons of baseline and procedural characteristics between the subset of patients analyzed and the rest of the SOURCE 3 cohort were conducted using the Wilcoxon sum rank test for the continuous variables and the Fisher exact test for categorical variables.

Echocardiographic parameters were compared between discharge and at 1 year, using paired analysis with the Wilcoxon sum rank test. Mean gradient, effective orifice area (EOA), and GLS were compared (baseline vs. discharge and baseline vs. 1 year), using a paired analysis with the t test.

Results

Baseline and procedural data

A total of 276 patients were enrolled in the echocardiographic analysis between July 2014 and October 2015 in 16 European centers. In summary, patient baseline characteristics were a mean age of 80.8 years and a mean EuroSCORE II of 4.6 ± 3.98 (Table 1). The latter was statistically lower than the mean EuroSCORE II of the SOURCE 3 patients not included in this sub-analysis ($p = 0.002$), as more echo patients had a logistic EuroSCORE of < 10%,

compared with other patients of the SOURCE 3 cohort (35.0% vs. 28.2%; p = 0.041), and fewer echo patients had a logistic EuroSCORE of > 30% compared with other patients of the cohort (10.2% vs. 16.6%; p = 0.011). Most other baseline clinical characteristics and comorbidities were comparable between the subset of patients analyzed and the rest of the SOURCE 3 cohort, except for hypertension (72.1% in the echo patients vs. 83.4% in other SOURCE 3 patients; p < 0.001), congestive heart failure (46.7% vs. 34.6%; p < 0.001), and mitral regurgitation of moderate or severe grade (9.2% vs. 14.8%; p = 0.015).

Most TAVI procedures were performed using a transfemoral approach (87.3%), with the SAPIEN 3 THV 23 mm (40.6%), 26 mm (36.2%), and 29 mm (23.2%).

An intraprocedural angiography was retrieved in 103 patients; most were adjudicated as grade 1, but a small percentage were considered grade 2 (Table 2).

In terms of clinical outcomes, the cohort had a 30-day and 1-year mortality rate of 1.5% and 5.4%, respectively. The cardiac mortality rate was 0.7% and 3.1%, at 30 days and 1 year, respectively. The disabling stroke rate was 0.7% and 1.1%, at 30 days and 1 year, respectively. The life-threatening bleeding rate was 5.4% at 30 days.

Echocardiographic parameters

Aortic regurgitation severity was predominantly grade 1, using both the Seller and Valve Academic Research Consortium-2 criteria (93.2% each; Table 3). Other echocardiographic parameters are presented in Table 4.

Effective orifice area and mean gradient

The TAVI treatment significantly improved the mean EOA from 0.8 ± 0.3 cm^2 at baseline to 1.6 ± 0.6 cm^2 at discharge (Fig. 1, Table 4). This improvement was sustained at 1 year (1.5 ± 0.5 cm^2; p < 0.001 compared with baseline). Similarly, the mean gradient was decreased following the THV treatment from 41.2 ± 14.6 mmHg at baseline to 12.2 ± 5.3 mmHg at discharge (p < 0.001), and was maintained at 1 year (12.7 ± 5.8 mmHg; p < 0.001 compared with baseline).

Total aortic regurgitation and PVL

Few patients had total aortic regurgitation (TAR) at discharge; it was moderate severity in 5 (2.1%) patients and severe in 2 (0.8%) patients (Fig. 2). At 1 year, 3 (1.7%) patients had moderate TAR; no severe TAR was observed (Fig. 2).

Table 2. Procedural characteristics.

Procedural characteristics	Patients who received echocardiograms (n = 276)
Total procedure time [min]	72.1 ± 52.23 (n = 204)
Total anaesthesia time [min]	127.0 ± 84.71 (n = 127)
Access approach:	
Transfemoral	241 (87.3%)
Transapical	26 (9.4%)
Transaortic	7 (2.5%)
Implanted valve size [mm]:	
23 mm	112 (40.6%)
26 mm	100 (36.2%)
29 mm	64 (23.2%)

Table 3. Aortic regurgitation severity.

Criteria	Patients who received intraprocedural angiography (n = 103)
Evaluation with Seller's criteria:	
Grade 1	96 (93.2%)
Grade 2	7 (6.8%)
Grade 3	0 (0%)
Grade 4	0 (0%)
Evaluation with VARC 2 criteria:	
Grade 1	96 (93.2%)
Grade 2	7 (6.8%)
Grade 3	0 (0%)
Grade 4	0 (0%)

VARC — Valve Academic Research Consortium

Similarly, few severe to moderate paravalvular leak (PVLs) were present at discharge (2.9%) and 1 year (1.8%; Fig. 2).

Mitral and tricuspid regurgitation

At discharge, 2 patients had moderate severity mitral regurgitation and 2 had severe mitral regurgitation (Fig. 3). At 1 year, 3 patients had moderate mitral regurgitation. The percentage of mild mitral regurgitation was significantly lower at 1 year compared with discharge (20.3% vs. 28.3%, respectively; p = 0.011).

Table 4. Echocardiographic parameters.

Parameter	Baseline Mean ± SD (n)	Discharge Mean ± SD (n)	1 year Mean ± SD (n)	P* (n) Baseline vs. discharge	P* (n) Discharge vs. 1 year
LVEDV [mL]	81.3 ± 36.0 (211)	76.0 ± 36.1 (183)	80.0 ± 33.7 (130)	0.013 (151)	0.316 (85)
LVESV [mL]	36.3 ± 26.5 (211)	34.8 ± 26.0 (183)	35.5 ± 26.2 (129)	0.028 (151)	0.760 (85)
LVEDD [cm]	4.8 ± 0.8 (221)	4.7 ± 0.8 (187)	4.7 ± 0.8 (123)	0.109 (162)	0.160 (92)
LVESD [cm]	3.2 ± 1.0 (210)	3.2 ± 1.00 (183)	3.1 ± 0.9 (119)	0.036 (152)	0.325 (88)
LVEF [%]	58.6 ± 15.6 (211)	57.5 ± 14.9 (183)	58.8 ± 13.2 (129)	0.471 (151)	0.712 (85)
LV posterior wall diastolic	1.1 ± 0.2 (219)	1.2 ± 0.2 (187)	1.1 ± 0.2 (120)	0.123 (162)	0.025 (90)
Interventricular septum diastolic	1.3 ± 0.3 (221)	1.4 ± 0.3 (192)	1.3 ± 0.2 (120)	0.235 (166)	0.210 (93)
Left atrial volume [mL]	75.6 ± 35.5 (237)	77.4 ± 32.2 (212)	74.9 ± 29.6 (163)	0.754 (186)	0.380 (124)
AV mean gradient [mmHg]	41.2 ± 14.6 (251)	12.2 ± 5.3 (242)	12.7 ± 5.8 (178)	< 0.001 (223)	0.025 (155)
AV area (EOA) [cm^2]	0.8 ± 0.3 (227)	1.6 ± 0.6 (202)	1.5 ± 0.5 (159)	< 0.001 (173)	0.007 (120)
AV velocity time integral	96.7 ± 22.6 (251)	44.0 ± 11.4 (240)	49.6 ± 13.8 (178)	< 0.001 (221)	< 0.001 (153)
Mitral annulus velocity [cm/s]	6.1 ± 1.9 (99)	6.2 ± 2.0 (89)	6.5 ± 2.4 (85)	0.911 (47)	0.167 (44)
E/e' ratio (filling pressures) [mmHg]	17.9 ± 7.9 (96)	17.2 ± 8.1 (86)	17.8 ± 8.1 (80)	0.920 (44)	0.917 (41)
Systolic pulmonary pressure [mmHg]	302.2 ± 52.0 (47)	273.2 ± 42.25 (59)	282.2 ± 45.8 (65)	0.843 (14)	–

*P values are from the Wilcoxon sum rank (paired) test. Mean ± standard deviation (SD) presented in the 3 first columns were calculated on all values available. AV — atrio-ventricular; EOA — effective orifice area; LVEDD — left ventricular end diastolic diameter; LVEF — left ventricular ejection fraction; LVEDV — left ventricular end-diastolic volume; LVESD — left ventricular end-systolic diameter; LVESV — left ventricular end-systolic volume

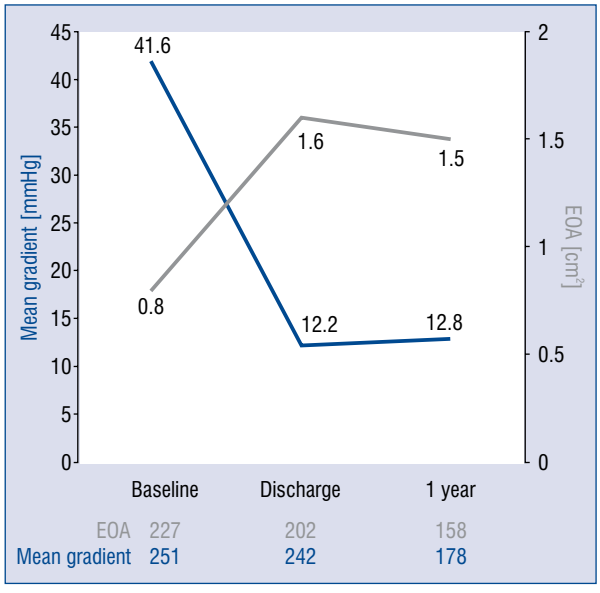


Figure 1. Effective orifice area and mean gradient — paired analyses.

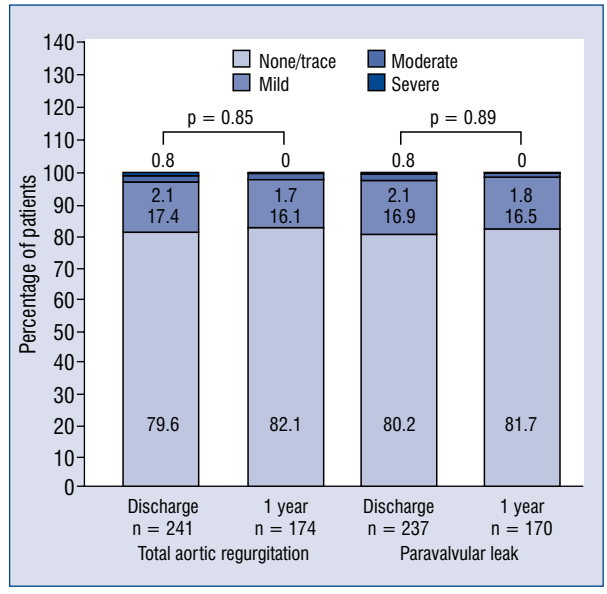


Figure 2. Total aortic regurgitation and paravalvular leak — paired analyses.

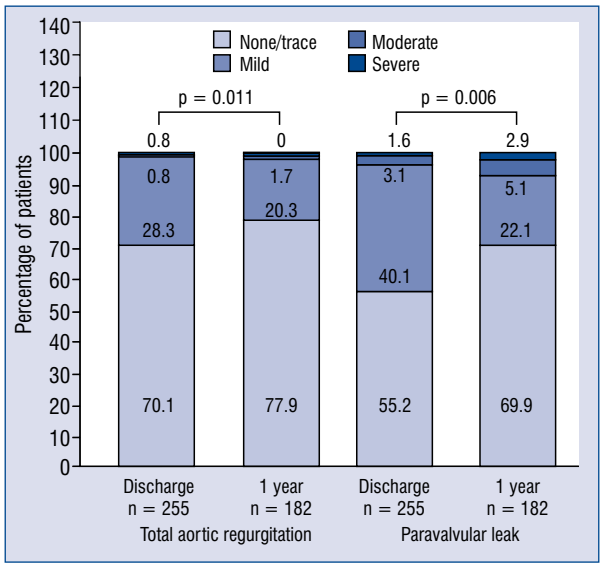


Figure 3. Mitral regurgitation and tricuspid regurgitation — paired analyses.

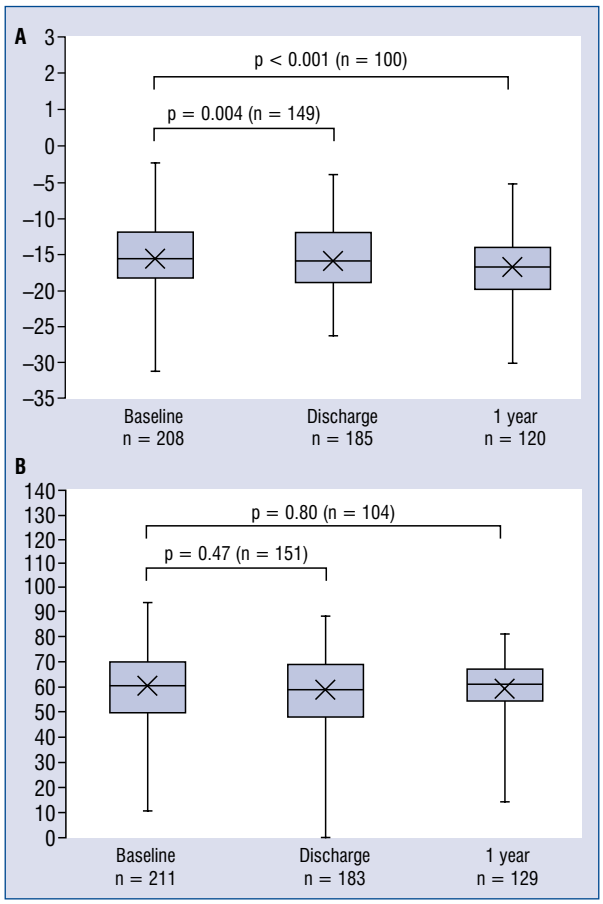


Figure 4. A. Global longitudinal strain analysis; **B.** Left ventricular ejection fraction; the box plot represents the mean ± standard deviation, median, minimum and maximum (whiskers) of the global longitudinal strain. P values compare baseline with discharge, and baseline with 1-year data using the paired t-test.

Similarly, 6 patients suffered from tricuspid regurgitation of moderate severity at discharge and 3 others presented with severe tricuspid regurgitation (Fig. 3). At 1 year, 7 patients presented with moderate tricuspid regurgitation and 4 patients with severe tricuspid regurgitation. The percentage of mild mitral tricuspid regurgitation was significantly lower at 1 year compared with discharge (22.1% vs. 40.1%, respectively; p = 0.006).

Global longitudinal strain analysis

The LV peak systolic longitudinal strain significantly improved after TAVI (Fig. 4A), and significantly increased at 1 year compared with baseline (–17.0 ± 4.6; p = 0.001). No change was observed on the LVEF (Fig. 4B).

Discussion

This echocardiographic evaluation performed in a real-world setting in European patients with severe AS who received a transcatheter SAPIEN 3 demonstrated good valve performance, low PVL of moderate to severe grade at 1 year, and statistically significant improvement in LV function as assessed by GLS. No change in LVEF was observed.

Population studied

It was thought that the population analyzed in the present study was representative of patients with severe AS and were usually referred for the TAVI procedure. Demographic and clinical parameters at baseline were comparable with those of the entire SOURCE 3 cohort, except for a slightly lower surgical risk score in the SOURCE 3 cohort.

Echocardiographic parameters

A comprehensive echocardiographic assessment from randomized trials, including the PARTNER 2 SAPIEN 3 registry, presented comparable mean gradient and EOA at discharge or at 30 days (mean gradient of 11.18 ± 4.35 mmHg and EOA of 1.66 ± 0.38 cm^2; n = 1470) as assessed by the ECL [13].

One potential disadvantage of TAVI is an increased incidence of post-procedural aortic regurgitation, which is an independent predictor of short- and long-term mortality, and which may have a negative impact on LV myocardial recovery [14, 15]. The presence of post-procedural PVL appears to limit LV structural and functional recovery [16]. Post-procedural PVL was rare at 1 year and no patients presented with severe PVL.

Left ventricular strain analysis

The first signs of reverse LV remodeling at discharge were observed, and were sustained for 1 year. A significant increase in GLS was numerically modest, but statistically significant, observed at discharge and not only sustained, but also improved at 1 year. This result represents signs of reverse remodeling, as previously reported in TAVI [4, 17] or surgical aortic valve replacement studies [7]. Several studies have demonstrated an amelioration in LV mass [18], some diastolic filling parameters [18, 19], and left atrial function in patients after TAVI [16, 19]. The LVEF is confounded by the positive remodeling of the left ventricle, i.e., regression of LV concentric hypertrophy; LVEF is not a good marker of LV intrinsic myocardial function.

Limitations of the study

A few patients were not evaluable, mainly because their echocardiographs were of poor quality, so there may have been selection bias.

One of the limitations of the study is loss to follow-up of some patients. The reason for this was due to the multicenter recruitment: many patients travelled far to have the TAVI procedure and could not return for the 12-month echo. However, updates were received from the sites and local phone calls related to the absence of mortality in non-returning patients. In addition, some studies were excluded from analysis due to the poor quality of examinations.

This SOURCE 3 sub-study was designed as a purely echocardiographic study. Consequently, no clinical parameters were collected in follow-up, including those affecting quality of life data. Further studies are required to seek correlation between echocardiographic improvement in LV mechanics and clinical response.

Conclusions

A subset of patients from the SOURCE 3 registry who received the SAPIEN 3 balloon-expandable THV had improved LV mechanics immediately following the procedure that were sustained for 1 year, as determined by standard 2D imaging. The valve performance was good at 1 year, with a low PVL rate.

Acknowledgements

Frederique Maneval of Edwards Lifesciences provided medical writing services, and Tracey Fine of Edwards Lifesciences provided medical editing services.

Funding: Edwards Lifesciences funded this study.

Conflict of interest: Philipp Kahlert has received honoraria as a clinical proctor for Edwards Lifesciences Inc. Tomas Hovorka is an employee of Edwards Lifesciences. Other authors did not declare any conflicts.

References

1. Leon MB, Smith CR, Mack M, et al. PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010; 363(17): 1597–1607, doi: 10.1056/NEJMoa1008232, indexed in Pubmed: 20961243.
2. Smith C, Leon M, Mack M, et al. Transcatheter versus Surgical Aortic-Valve Replacement in High-Risk Patients. N Engl J Med. 2011; 364(23): 2187–2198, doi: 10.1056/nejmoa1103510.
3. Ross J. Afterload mismatch and preload reserve: a conceptual framework for the analysis of ventricular function. Prog Cardiovasc Dis. 1976; 18(4): 255–264, indexed in Pubmed: 128034.
4. Lozano Granero VC, Fernández Santos S, Fernández-Golfín C, et al. Immediate improvement of left ventricular mechanics following transcatheter aortic valve replacement. Cardiol J. 2018; 25(4): 487–494, doi: 10.5603/CJ.a2018.0066, indexed in Pubmed: 29924376.
5. Chang SA, Park PW, Sung K, et al. Noninvasive estimate of left ventricular filling pressure correlated with early and midterm postoperative cardiovascular events after isolated aortic valve replacement in patients with severe aortic stenosis. J Thorac Cardiovasc Surg. 2010; 140(6): 1361–1366, doi: 10.1016/j.jtcvs.2010.02.022, indexed in Pubmed: 20381086.
6. 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.
7. Delgado V, Tops LF, van Bommel RJ, et al. Strain analysis in patients with severe aortic stenosis and preserved left ventricular ejection fraction undergoing surgical valve replacement. Eur Heart J. 2009; 30(24): 3037–3047, doi: 10.1093/eurheartj/ehp351, indexed in Pubmed: 19726436.
8. Weidemann F, Jamal F, Sutherland GR, et al. Myocardial function defined by strain rate and strain during alterations in inotropic states and heart rate. Am J Physiol Heart Circ Physiol. 2002; 283(2): H792–H799, doi: 10.1152/ajpheart.00025.2002, indexed in Pubmed: 12124229.
9. Weidemann F, Jamal F, Kowalski M, et al. Can strain rate and strain quantify changes in regional systolic function during dobutamine infusion, B-blockade, and atrial pacing--implications for quantitative stress echocardiography. J Am Soc Echocardiogr. 2002; 15(5): 416–424, indexed in Pubmed: 12019424.
10. Kusunose K, Goodman A, Parikh R, et al. Incremental prognostic value of left ventricular global longitudinal strain in patients with aortic stenosis and preserved ejection fraction. Circ: Cardiovasc Imaging. 2014; 7(6): 938–945, doi: 10.1161/circimaging.114.002041.

11. Wendler O, Schymik G, Treede H, et al. SOURCE 3 Registry: Design and 30-Day Results of the European Postapproval Registry of the Latest Generation of the SAPIEN 3 Transcatheter Heart Valve. Circulation. 2017; 135(12): 1123–1132, doi: 10.1161/CIRCULATIONAHA.116.025103, indexed in Pubmed: 28104716.
12. Wendler O, Schymik G, Treede H, et al. SOURCE 3: 1-year outcomes post-transcatheter aortic valve implantation using the latest generation of the balloon-expandable transcatheter heart valve. Eur Heart J. 2017; 38(36): 2717–2726, doi: 10.1093/eurheartj/ehx294, indexed in Pubmed: 28605423.
13. Hahn RT, Leipsic J, Douglas PS, et al. Comprehensive echocardiographic assessment of normal transcatheter valve function. JACC Cardiovasc Imaging. 2019; 12(1): 25–34, doi: 10.1016/j.jcmg.2018.04.010, indexed in Pubmed: 29909110.
14. Généreux P, Head SJ, Hahn R, et al. Paravalvular leak after transcatheter aortic valve replacement: the new Achilles' heel? A comprehensive review of the literature. J Am Coll Cardiol. 2013; 61(11): 1125–1136, doi: 10.1016/j.jacc.2012.08.1039, indexed in Pubmed: 23375925.
15. Lerakis S, Hayek SS, Douglas PS. Paravalvular aortic leak after transcatheter aortic valve replacement: current knowledge. Circulation. 2013; 127(3): 397–407, doi: 10.1161/CIRCULATIONAHA.112.142000, indexed in Pubmed: 23339094.
16. Poulin F, Carasso S, Horlick EM, et al. Recovery of left ventricular mechanics after transcatheter aortic valve implantation: effects of baseline ventricular function and postprocedural aortic regurgitation. J Am Soc Echocardiogr. 2014; 27(11): 1133–1142, doi: 10.1016/j.echo.2014.07.001, indexed in Pubmed: 25125314.
17. D'Andrea A, Padalino R, Cocchia R, et al. Effects of transcatheter aortic valve implantation on left ventricular and left atrial morphology and function. Echocardiography. 2015; 32(6): 928–936, doi: 10.1111/echo.12808, indexed in Pubmed: 25323699.
18. Vizzardi E, D'Aloia A, Fiorina C, et al. Early regression of left ventricular mass associated with diastolic improvement after transcatheter aortic valve implantation. J Am Soc Echocardiogr. 2012; 25(10): 1091–1098, doi: 10.1016/j.echo.2012.06.010, indexed in Pubmed: 22819229.
19. Spethmann S, Dreger H, Baldenhofer G, et al. Short-term effects of transcatheter aortic valve implantation on left atrial mechanics and left ventricular diastolic function. J Am Soc Echocardiogr. 2013; 26(1): 64–71.e2, doi: 10.1016/j.echo.2012.10.002, indexed in Pubmed: 23140843.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2020, Vol. 27, No. 6, 797–806
DOI: 10.5603/CJ.a2019.0053

ISSN 1897–5593
eISSN 1898–018X

Echocardiographic assessment of tricuspid regurgitation and pericardial effusion after cardiac device implantation

Katarzyna Wiechecka, Bartosz Wiechecki, Agnieszka Kapłon-Cieślicka, Agata Tymińska, Monika Budnik, Dominika Hołowaty, Krzysztof Jakubowski, Marcin Michalak, Elżbieta Świętoń, Przemysław Stolarz, Roman Steckiewicz, Marcin Grabowski, Piotr Scisło, Janusz Kochanowski, Krzysztof J. Filipiak, Grzegorz Opolski

1st Chair and Department of Cardiology, Medical University of Warsaw, Poland

Abstract

Background: *The frequency of cardiac implantable electronic device (CIED) implantations is constantly increasing. Pericardial effusion (PE) and tricuspid regurgitation (TR) may occur after CIED implantation. The aim of the present study is to evaluate the prevalence and risk factors for new occurrences or progression of TR and PE early after CIED implantation.*

Methods: *This is an on-going, single-center, observational study of patients after their first CIED implantation, with an echocardiographic evaluation within 60 days before and 7 days after the procedure. Data are presented for first 110 consecutive patients who underwent CIED implantation from August 2015 to July 2016.*

Results: *Median age was 75 years, and 44% were women. In total, 87 (79%) pacemakers, 21 (19%) implantable cardioverter-defibrillators and 2 cardiac resynchronization therapy devices were implanted. After CIED implantation, there was TR progression in 17 (16%) patients: 5 patients developed moderate TR, none developed severe TR. An increase in TR was more often observed after implantations performed by operators in training than by certified operators (35% vs. 12%, $p = 0.02$). New PE after the procedure was observed in 8 (7%) patients and was trivial (< 5 mm) in all cases. Patients with new PE after implantation had lower baseline hemoglobin levels and tended to be women.*

Conclusions: *New PE and an increase in TR severity are rare complications early after CIED implantation. Operator experience might be related to TR progression. Increasing the number of patients in the current on-going study will allow a more reliable assessment of the prevalence and risk factors of these complications.* (Cardiol J 2020; 27, 6: 797–806)

Key words: cardiac implantable electronic device, pacemaker, implantable cardioverter-defibrillator, complications

Introduction

Since the first pacemaker implantation in 1958, the number of cardiac implantable electronic devices (CIEDs): permanent pacemakers (PPMs), implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT) has been constantly rising [1]. According to a report from the European Heart Rhythm Association, 500,411 PPMs, 85,289 ICDs and 51,274 CRTs were implanted in European Society of Cardiology (ESC) countries in 2013 [2]. Although CIED implanta-

Address for correspondence: Agnieszka Kapłon-Cieślicka, MD, PhD, 1st Chair and Department of Cardiology, Medical University of Warsaw, Public Central Teaching Hospital in Warsaw, ul. Banacha 1a, 02–097 Warszawa, Poland, tel: +48 22 599 29 58, fax: +48 22 599 19 57, e-mail: agnieszka.kaplon-cieslicka@wum.edu.pl

Received: 28.10.2018 Accepted: 31.03.2019

tion is considered a relatively low-risk procedure, especially if performed in specialized centers, it can lead to some early and late complications [3].

Discovering tricuspid valve leaflet perforation at an autopsy in 1974 was the first described case of right ventricle (RV) lead-associated tricuspid regurgitation (TR) [4]. In general, in most cases, TR is secondary to increased pulmonary and RV pressure resulting in RV and tricuspid annular dilatation; less often it is the result of primary leaflet pathology [5]. In the Framingham Heart Study, the prevalence of moderate to severe TR increased with age, reaching up to 1.5% and 5.6%, respectively, in men and women aged 70 years and more [6]. Due to a lack of prospective studies, the incidence of hemodynamically significant TR after CIED implantation is difficult to estimate, however, in a retrospective, case-control study conducted by Paniagua et al. [7] in a large echocardiography database, the prevalence of moderate to severe TR in patients with transvenous PPM leads was twice as high as in the control group. Depending on time after RV lead implantation, TR can be caused by mechanical interference or lead-related leaflet fibrosis. Mechanical mechanism occurs earlier and includes adherence, impingement of electrodes to tricuspid leaflets or laceration and rarely perforation of valve apparatus, while lead-related fibrosis appears over time after implantation [8, 9]. The relation between tricuspid leaflets and pacing lead might also be crucial in cases of future transvenous lead extraction, which is a complex surgical procedure itself and might cause or increase TR [10]. TR may also occur as a result of atrioventricular dyssynchrony, specifically in ventricular pacing [11]. To avoid future TR after lead implantation some authors suggest only left ventricular lead stimulation especially in patients with either prosthetic tricuspid valve, annulus or baseline severe TR [12]. Regardless of the mechanism, implantation-induced TR is associated with worse prognosis [13, 14]. However, the exact incidence of implantation-induced TR in a modern series is to be determined, as previous studies usually only included small numbers of patients or were limited by lack of baseline echocardiographic assessment [15–17].

Rarely, CIED implantation procedures may be complicated by pericardial effusion (PE) and tamponade, with a prevalence of approximately 2% and 0.6%, respectively [18]. These complications can lead to prolonged hospital stay and higher costs [3, 18].

The aim of the present study is to evaluate the prevalence and progression of TR and PE early after CIED implantation, and to determine risk factors for the development of these complications. This article presents the design of the current study, as well as preliminary results based on data from the first 110 patients.

Methods

Study population

In this single-center, observational, retrospective study, analyses data are presented from 400 consecutive patients after first CIED implantation (PPM, ICD or CRT), who had echocardiographic assessment of TR and PE before and after the procedure. Only patients with echocardiogram performed less than 60 days before and up to 7 days after implantation are included in the study. So far, 110 patients, who underwent device implantation from August 2015 to July 2016, were included in the study.

Data collection

In the study, data on baseline clinical characteristics, results of diagnostic tests performed, and pharmacotherapy (including antithrombotic treatment) are collected retrospectively from medical records. Data on CIED implantation include: type of device, number of leads, localization of leads, device manufacturer, operator, and information on complications (occurrence or progression of TR, occurrence of PE, pneumothorax, or other complications). Five different physician operators performed the CIEDs implantation: operators 1, 3 and 5 are certified operators with more than 10 years experience in CIED implantation, while operators 2 and 4 were, at the time of the procedure performed, operators in training with experience of less than or equal to 5 years.

Echocardiographic assessment

All patients included in this study had two-dimensional transthoracic echocardiogram performed, before and after the procedure. In the documented department, echocardiographic assessment following CIED implantation is routinely performed within 7 days in all patients, as a standard of care, usually on the first day after the procedure, regardless of the patient's clinical condition. Only patients with available pre- and post-implantation transthoracic echocardiography results with assessment of both PE and TR were included in the study. Echocardiograms are performed in the Department's Echocardiography Laboratory (certified with grade C accreditation of the Section of Echocardiography of the Polish

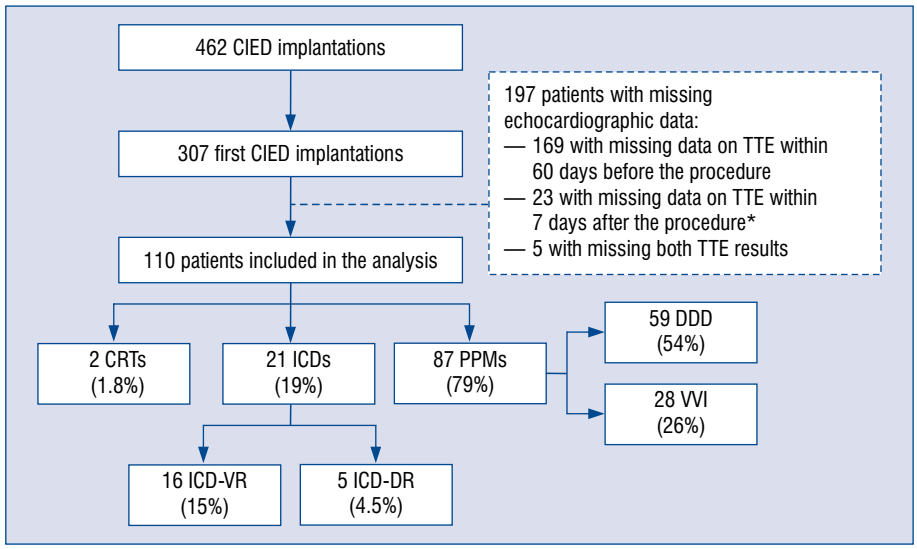


Figure 1. Flow-chart of patient inclusion in the study and types of devices implanted from August 2015 to July 2016; *missing data on tricuspid regurgitation after cardiac implantable electronic device (CIED) implantation; CRT — cardiac resynchronization therapy; ICD — implantable cardioverter-defibrillator; ICD-VR — single-chamber cardioverter-defibrillator; ICD-DR — dual-chamber cardioverter-defibrillator; PPM — permanent pacemaker; DDD — dual-chamber pacemaker; VVI — ventricular single-chamber pacemaker; TTE — transthoracic echocardiography.

Cardiac Society), using Philips iE33 or Philips EPIQ 7 Ultrasound Machines (Philips Medical Systems, Andover, Massachusetts, USA) by qualified echocardiographers. Presence of PE and TR severity are analyzed using all standard views, including parasternal, apical and subcostal views. TR is graded as trivial/mild, moderate and severe according to the current European Association of Cardiovascular Imaging (EACVI) guidelines [19]. PE is graded as trivial (< 5 mm), mild (≥ 5 and < 10 mm), moderate (10–20 mm) and large (> 20 mm) according to ESC guidelines [20].

In the study, TR is described either as newly developed (if no TR was present before the procedure) or as TR progression 1) from trivial/mild to moderate, 2) from moderate to severe, 3) from trivial/mild to severe, or as a decrease in TR severity. Similarly, PE is reported as newly developed or as an increase in the amount of fluid after the procedure.

Clinical endpoints

Primary endpoints include: 1) occurrence or progression of TR, and 2) occurrence or progression of PE after first CIED implantation.

Statistical analysis

Statistical analyses were performed using SPSS software, version 22 (IBM SPSS Statistics 22, New York, USA). Normally distributed continuous variables were presented as mean values and standard deviations, while ordinal variables and non-normally distributed continuous variables as median values and interquartile ranges (IQR). Categorical data were presented as percentages. The significance of differences between groups was determined by the Fisher exact test for categorical variables and the Mann-Whitney U test for continuous and ordinal variables respectively. P-value of ≤ 0.05 was considered significant. All tests were two-tailed.

Results

From August 2015 to July 2016, 110 patients after their first CIED implantation were included in the study. Figure 1 shows flow-chart of patient inclusion in the study and types of devices implanted. Median age of the study group was 75.1 years and 44% were female. Hypertension was present in 77% of patients, coronary artery disease — in 37%, heart failure — in 45%, and atrial fibrillation — in 56%. Table 1 presents baseline clinical characteristics of the study group.

Pre- and post-interventional TR prevalence is shown in Figure 2. Change in TR severity after the procedure was observed in 34 (31%) patients, including 17 (16%) patients with TR worsening and 17 (16%) patients with TR improvement, as

Table 1. Baseline characteristics of the study population and comparison of patients with and without an increase in tricuspid regurgitation (TR) after cardiac device implantation.

Variable	Study population (n = 110)	With an increase in TR (n = 17)	Without an increase in TR (n = 93)	P
Age [years]	75.1 (69.0–84.0)	70.0 (65.0–84.5)	79.0 (69.0–84.0)	0.46
Female gender	44%	59%	41%	0.19
BMI [kg/m^2]	27.9 (24.1–30.7); n = 91	28.1 (23.4–29.8); n = 11	27.7 (24.1–30.8); n = 80	0.97
Comorbidities				
Hypertension	77%	76%	77%	1.00
Coronary artery disease	37%	35%	38%	1.00
Previous MI	18%	12%	19%	0.73
Prior PCI	19%	12%	20%	0.52
Prior CABG	7.3%	0%	8.6%	0.35
Heart failure	45%	47%	44%	1.00
Atrial fibrillation:	56%	41%	58%	0.29
Paroxysmal	29%	24%	30%	0.77
Persistent	5.5%	5.9%	5.4%	1.00
Permanent	21%	12%	23%	0.52
Diabetes	26%	18%	27%	0.55
Obesity	32%	27%	33%	0.56
Hyperlipidemia	67%	82%	65%	0.26
Current or former smoking	33%	29%	33%	1.00
Pharmacotherapy				
Anticoagulation:	67%	53%	70%	0.17
Rivaroxaban	20%	30%	18%	0.50
Dabigatran	6.4%	0%	7.5%	0.59
Vitamin K antagonist	19%	12%	20%	0.50
LMWH as bridging therapy	31%	24%	33%	0.38
Single antiplatelet therapy	26%	18%	27%	0.55
Dual antiplatelet therapy	3.6%	5.9%	3.2%	0.49
Diuretics	73%	65%	75%	0.38
Laboratory findings				
Hemoglobin [g/dL]	13.0 (12.0–14.0)	13.0 (12.0–14.4)	13.0 (12.0–14.0)	0.97
WBC count [10^3/mm^3]	7.1 (5.9–8.5)	6.5 (5.7–8.6)	7.2 (5.9–8.6)	0.60
Platelets [10^3/mm^3]	205 (156–243)	223 (193–243)	202 (149–245)	0.14
Serum creatinine [mg/dL]	1.12 (0.91–1.36)	0.96 (0.87–1.20)	1.17 (0.92–1.39)	0.21
eGFR [mL/min/1.73 m^2]	56 (45–60)	60 (44–60)	55 (45–60)	0.32
CRP [mg/L]	2.35 (1.3–7.0); n = 100	3.1 (1.3–7.2); n = 15	2.2 (1.2–5.6); n = 85	0.50
NT-proBNP [pg/mL]	1123 (482–2313); n = 78	1464 (523–2646); n = 13	991 (464–2238); n = 65	0.62
INR	1.1 (1.0–1.2); n = 104	1.1 (1.0–1.1); n = 15	1.1 (1.0–1.2); n = 89	0.72
APTT [s]	30.9 (27.4–35.8); n = 98	31.5 (28.0–36.8); n = 14	30.9 (27.2–35.6); n = 84	0.68

APTT — activated partial thromboplastin time; BMI — body mass index; CABG — coronary artery bypass grafting; CRP — C-reactive protein; eGFR — estimated glomerular filtration rate; INR — international normalized ratio; LMWH — low-molecular weight heparin; MI — myocardial infarction; NT-proBNP — N-terminal pro-B-type natriuretic peptide; PCI — percutaneous coronary intervention; PT — prothrombin time; WBC — white blood cell

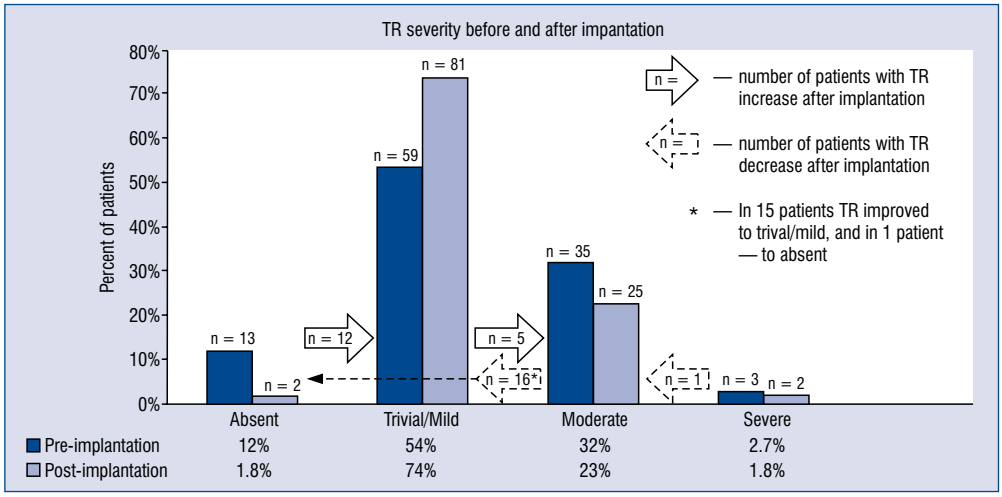


Figure 2. Pre- and post-interventional prevalence of tricuspid regurgitation (TR) in the study group.

presented in Figure 2. Comparison of patients with and without an increase in TR after the procedure is presented in Tables 1 and 2. In the present study, newly developed TR and/or TR progression was more often observed after implantations performed by operators in training than after procedures executed by certified operators (35% vs. 12%, p = 0.02), as shown in Table 3.

None of the patients had any PE before the procedure. PE after the procedure was observed in 8 of 110 patients (7.3%) and only trivial (< 5 mm) amounts were found. Comparisons of patients with and without PE after the procedure is shown in Tables 4 and 5. Patients who developed PE after CIED implantation had lower baseline hemoglobin concentration. There was a tendency for women to develop PE more often.

No cases of pneumothorax nor other severe complications were observed early after CIED implantation in the study group.

Discussion

The preliminary results of the current study suggest that newly developed TR or worsening of TR early after CIED implantation was not very common (16% of patients) and was, in most cases, not hemodynamically significant (at least initially), as none of the patients developed severe TR and only 5 (4.5%) patients developed moderate TR. However, these observations were made early after CIED implantation, and it is difficult to predict further TR progression and its implications in long-term follow-up in these patients. Previous studies did not yield consistent results, mostly because they were retrospective analyses conducted in small patient cohorts, allowing only a rough estimation of post-implantation TR incidence. The present findings are similar to the results of a study by Rothschild et al. [15] on small population (n = 36), where 6 (17%) patients developed an immediate increase in TR grade post-implantation, nevertheless, there was no progression to moderate or severe TR in any of the patients. However, after a median of 113 days, Klutstein et al. [21] reported worsening of TR by more than 2 grades in 18% of patients with pre-procedural TR described as less than moderate. On the contrary, Webster et al. [22] studied a population of 123 patients at a median age of 16 years at the time of RV-lead placement, and reported no TR worsening 8 months after implantation and only modest TR increase (from 1.54 to 1.69 on a scale from 0 to 4) after over 2 years. The discrepancy in results between studies may be partially explained by different time frames of post-procedure TR evaluation, as mechanical component of lead-related TR worsening appears earlier than fibrosis and scarring of valve apparatus. In the present study, prevalence of new TR development/TR progression in patients after procedure differed between the operators and was higher after implantation performed by those less experienced. These findings suggest that the experience of the operator may have significant impact on developing TR regurgitation after the procedure.

Another risk factor for CIED-related TR might be the number of implanted leads. Postaci

Table 2. Comparison of patients with and without an increase in tricuspid regurgitation (TR) after cardiac device implantation — procedure-related variables.

Variable	With an increase in TR (n = 17)	Without an increase in TR (n = 93)	P
Cardiac device type			
DDD	71%; 12/17	51%; 47/93	0.19
VVI	12%; 2/17	28%; 26/93	0.23
ICD	18%; 3/17	19%; 18/93	1.00
CRT	0%; 0/17	2.2%; 2/93	1.00
Number of leads			
1	29%; 5/17	42%; 39/93	0.42
2	71%; 12/17	56%; 52/93	0.30
3	0%; 0/17	2.2%; 2/93	1.00
Type/localization of lead			
Atrial	71%; 12/17	58%; 54/93	0.42
Ventricular for stimulation	82%; 14/17	79%; 73/93	1.00
Ventricular for defibrillation	18%; 3/17	22%; 20/93	1.00
Manufacturer			
Biotronik	65%; 11/17	51%; 47/93	0.50
Medtronic	35%; 6/17	32%; 30/93	0.80
St. Jude Medical	0%; 0/17	17%; 16/93	0.13
Operator			0.051
Operator no. 1	0%; 0/13*	100%; 13/13*	
Operator no. 2	27%; 3/11*	73%; 8/11*	
Operator no. 3	11%; 3/27*	89%; 24/27*	
Operator no. 4	50%; 3/6*	50%; 3/6*	
Operator no. 5	15%; 8/53*	85%; 45/53*	

*Refers to the number of procedures performed by the given operator; DDD — dual-chamber pacemaker; CRT — cardiac resynchronization therapy; ICD — implantable cardioverter defibrillator; VVI — ventricular single-chamber pacemaker

Table 3. Changes in tricuspid regurgitation (TR) severity after procedures performed by certified operators and operators in training.

Post-procedural changes in TR	Certified operators* (93 procedures)	Operators in training** (17 procedures)	P
Increase in TR	12%; 11/93	35%; 6/17	**0.02**
No change in TR	70%; 65/93	65%; 11/17	0.78
Decrease in TR	18%; 17/93	0%; 0/17	0.07

*Operators 1, 3, and 5; **operators 2 and 4

et al. [23] observed that 9% of 32 patients with one ventricular lead and 56% of 18 patients with two ventricular leads developed severe TR. In the current study, only the first CIED implantations are analyzed, and thus the study does not include patients with previously implanted ventricular leads in whom a second ventricular lead (e.g. defibrillation lead) is placed. Al-Bawardy et al. [24] studied a group of 1596 patients who underwent CIED implantation, with a median follow-up of 10 months. Most patients (61%) had 2 leads implanted, 20% had 3 leads implanted. The authors concluded that the type of cardiac device is not related to TR worsening. In contrast, Kim et al. [25] reported that TR worsening was more common after ICD than PPM implantation (32% vs. 21%, p = 0.048). In the present study, ICD implantation was not associated with elevated risk for TR worsening. Increasing the number of patients in the current study would have al-

Table 4. Comparison of patients with and without pericardial effusion after cardiac device implantation — clinical and laboratory variables.

Variable	With pericardial effusion (n = 8)	Without pericardial effusion (n = 102)	P
Age [years]	77.5 (68.0–83.0)	78.5 (68.8–84.0)	0.96
Female gender	75%	41%	**0.08**
BMI [kg/m^2]	26.1 (24.8–34.1); n = 7	28.0 (24.0–30.8); n = 84	0.94
Comorbidities			
Hypertension	75%	78%	1.00
Coronary artery disease	63%	35%	0.12
Previous MI	25%	18%	0.64
Prior PCI	25%	19%	0.65
Prior CABG	13%	6.9%	0.47
Heart failure	25%	46%	0.30
Atrial fibrillation:	50%	56%	1.00
Paroxysmal	38%	28%	0.69
Persistent	13%	4.9%	0.37
Permanent	0%	23%	0.20
Diabetes	13%	27%	0.68
Obesity	13%	33%	0.42
Hyperlipidemia	75%	67%	1.00
Current or former smoking	25%	33%	1.00
Pharmacotherapy			
Anticoagulation:	63%	68%	1.00
Rivaroxaban	25%	20%	0.60
Dabigatran	13%	5.9%	0.36
Vitamin K antagonist	13%	20%	1.00
LMWH as bridging therapy	13%	33%	0.64
Single antiplatelet therapy	25%	26%	1.00
Dual antiplatelet therapy	13%	2.9%	0.26
Diuretics	75%	73%	1.00
Laboratory findings			
Hemoglobin [g/dL]	12.0 (11.7–12.8)	13.0 (12.1–14.1)	**0.04**
WBC count [10^3/mm^3]	8.3 (6.3–10.1)	7.0 (5.9–8.3)	0.13
Platelets [10^3/mm^3]	219 (169–272)	204 (151–243)	0.38
Serum creatinine [mg/dL]	1.17 (0.74–1.28)	1.10 (0.91–1.38)	0.53
eGFR [mL/min/1.73 m^2]	52 (45–60)	57 (44–60)	0.80
CRP [mg/L]	5.6 (1.2–12.5)	2.3 (1.3–5.5); n = 92	0.34
NT-proBNP [pg/mL]	774 (430–5104); n = 7	1187 (559–2240); n = 71	0.97
INR	1.0 (0.99–1.1)	1.1 (1.0–1.2); n = 96	0.36
APTT [s]	30.4 (27.3–35.3); n = 7	31.0 (27.4–35.9); n = 90	0.86

APTT — activated partial thromboplastin time; BMI - body mass index; CABG — coronary artery bypass grafting; CRP — C-reactive protein; eGFR — estimated glomerular filtration rate; INR — international normalized ratio LMWH — low-molecular weight heparin; MI — myocardial infarction; NT-proBNP — N-terminal pro-B-type natriuretic peptide; PCI — percutaneous coronary intervention; PT — prothrombin time; WBC — white blood cell

lowed establishing whether the number and type of implanted leads is related to the risk of TR development or worsening.

Some data suggest that the technique of echocardiographic evaluation of post-procedural TR may also affect the results. In one retrospective

Table 5. Comparison of patients with and without pericardial effusion after cardiac device implantation — procedure-related variables.

Variable	With pericardial effusion (n = 8)	Without pericardial effusion (n = 102)	P
Cardiac device type			
DDD	63%; 5/8	53%; 54/102	0.72
VVI	25%; 2/8	26%; 26/102	1.00
ICD	13%; 1/8	20%; 20/102	1.00
CRT	0%; 0/8	2.0%; 2/102	1.00
Number of leads			
1	25%; 2/8	42%; 42/102	0.47
2	75%; 6/8	57%; 58/102	0.46
3	0%; 0/8	2.0%; 2/102	1.00
Type/localization of lead			
Atrial	75%; 6/8	59%; 60/102	0.47
Ventricular for stimulation	88%; 7/8	78%; 80/102	0.70
Ventricular for defibrillation	13%; 1/8	22%; 22/102	0.70
Manufacturer			
Biotronik	63%; 5/8	52%; 53/102	0.70
Medtronic	13%; 1/8	34%; 35/102	0.27
St. Jude Medical	25%; 2/8	14%; 14/102	0.35
Operator			0.52
Operator no. 1	0%; 0/13*	100%; 13/13*	
Operator no. 2	0%; 0/11*	100%; 11/11*	
Operator no. 3	11%; 3/27*	89%; 24/27*	
Operator no. 4	17%; 1/6*	83%; 5/6*	
Operator no. 5	7.5%; 4/53*	93%; 49/53*	

*Refers to the number of procedures performed by the given operator; DDD — dual-chamber pacemaker; CRT — cardiac resynchronization therapy; ICD — implantable cardioverter defibrillator; VVI — ventricular single-chamber pacemaker

study, transthoracic compared to transesophageal echocardiography detected fewer lead-related TRs in patients after CIED implantation (22% vs. 45%) [26]. The importance of reliable TR diagnosis is related to unfavorable impact of hemodynamically significant TR on prognosis, which results predominantly from its deleterious effects on RV dimensions and function. Other important clinical implications of significant TR include occurrence of rhythm disturbances such as atrial fibrillation and the need for chronic anticoagulation [27, 28].

In the present study, there was also a proportion of patients with a decrease in TR severity after CIED implantation. This might be related to possible volume depletion in these patients (fasting before the procedure, possibly more intensive diuretic treatment), as functional TR is a dynamic disease, changing in response to variation in preload and afterload. Another possible explanation might be that echocardiographic visualization is usually impaired for a few days after CIED implantation due to edema of the subcutaneous tissue in left subclavicular region and the diminished range of left upper limb movement, which might result in an underestimation of the actual TR volume. Furthermore, lead-induced artifacts might have impaired proper assessment of TR.

Herein, consistent with previous publications, new post-implantation PE was a rare complication [18]. A trend towards higher risk of post-procedural PE in women was observed, which is in line with a study by Ohlow et al. [18], in which female gender was associated with a higher incidence of any PE. The authors suggested this may be due to a thinner RV wall in women, related to a reduced extension of ventricular hypotrophy and lower RV pressure in women, as shown in population-based studies [21, 27]. Thinner RV walls could increase the risk of ventricular perforation in women [18]. In the same study by Ohlow et al. [18], patients

developing PE after CIED implantation were more often on antiplatelet therapy than patients without PE after intervention. Tompkins et al. [29] demonstrated that bleeding risk is significantly higher for patients on dual antiplatelet therapy undergoing PPM or ICD implantation and slightly higher for patients receiving acetylsalicylic acid alone. In the present study, patients with post-procedural PE more often received dual antiplatelet therapy than patients without this complication, although this difference did not reach statistical significance. There was no significant difference in the prevalence of post-procedural PE between patients with and without single antiplatelet or anticoagulant treatment, however, this might be related to a relatively small sample size. Still, patients with PE had lower hemoglobin concentration at baseline. In several previous studies, low hemoglobin concentration proved an independent predictor of bleeding, including bleeding complications after cardiac procedures [30, 31]. Importantly, in patients who did develop PE after implantation, only a trivial amount of fluid was observed, with no clinical consequences.

Limitations of the study

The present study has several limitations. First, it is a single-center study, including (thus far) a relatively small cohort of patients. However, the final number of patients in the study will exceed 400. Secondly, as presented in Figure 1, a large number of patients after first CIED implantation were not eligible for inclusion, mainly due to missing data on pre-implantation echocardiogram. Thirdly, echocardiographic assessment is limited to the early post-implantation period, without long-term follow-up. Lastly, this study is a retrospective analysis of medical records, and thus, allows only an approximate estimation of new post-implantation TR and PE incidence.

Conclusions

Preliminary data suggests that CIED implantation may lead to early development or progression of TR in approximately 16% of patients, however, in most of them TR was not hemodynamically significant. It seems that operator experience might be an important risk factor for TR development. PE occurred rarely after CIED implantation, and was, in all cases, trivial and lead to no clinical sequel. Increasing the number of patients in the on-going study will enable a more reliable assessment of the prevalence and the risk factors of those CIED implantation-related complications. Still, the most appropriate method to evaluate the true incidence of those complications would be to conduct a prospective study.

Conflict of interest: Marcin Michalak received educational grants from Biotronik, Medtronic, St. Jude Medical, and speaking fee from Biotronik — outside the submitted work. Marcin Grabowski received speaking/consulting fees from Abbott/St. Jude Medical, Biotronik, Medtronic — outside the submitted work. Other authors report no conflicts of interest.

References

1. Aquilina O. A brief history of cardiac pacing. Images Paediatr Cardiol. 2006; 8(2): 17–81, indexed in Pubmed: 22368662.
2. Raatikainen MJ, Arnar DO, Zeppenfeld K, et al. Statistics on the use of cardiac electronic devices and electrophysiological procedures in the European Society of Cardiology countries: 2014 report from the European Heart Rhythm Association. Europace. 2015; 17 Suppl 1: i1–75, doi: 10.1093/europace/euu300, indexed in Pubmed: 25616426.
3. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Europace. 2013; 15(8): 1070–1118, doi: 10.1093/europace/eut206, indexed in Pubmed: 23801827.
4. Gould L, Reddy CV, Yacob U, et al. Perforation of the tricuspid valve by a transvenous pacemaker. JAMA. 1974; 230(1): 86–87, indexed in Pubmed: 4479257.
5. Agarwal S, Tuzcu EM, Rodriguez ER, et al. Interventional cardiology perspective of functional tricuspid regurgitation. Circ Cardiovasc Interv. 2009; 2(6): 565–573, doi: 10.1161/CIRCINTERVENTIONS.109.878983, indexed in Pubmed: 20031775.
6. Singh JP, Evans JC, Levy D, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). Am J Cardiol. 1999; 83(6): 897–902, indexed in Pubmed: 10190406.
7. Paniagua D, Aldrich HR, Lieberman EH, et al. Increased prevalence of significant tricuspid regurgitation in patients with transvenous pacemakers leads. Am J Cardiol. 1998; 82(9): 1130–2, A9, indexed in Pubmed: 9817497.
8. Al-Bawardy R, Krishnaswamy A, Bhargava M, et al. Tricuspid regurgitation in patients with pacemakers and implantable cardiac defibrillators: a comprehensive review. Clin Cardiol. 2013; 36(5): 249–254, doi: 10.1002/clc.22104, indexed in Pubmed: 23529935.
9. Champagne J, Poirier P, Dumesnil JG, et al. Permanent pacemaker lead entrapment: role of the transesophageal echocardiography. Pacing Clin Electrophysiol. 2002; 25(7): 1131–1134, indexed in Pubmed: 12164456.
10. Gawalko M, Kołodzińska A, Grabowski M, et al. Transvenous lead removal with a fragment of a papillary muscle — a silent complication. Heart Beat J. 2017; 1: 41–42, doi: 10.24255/hbj/68144.
11. Roeffel S, Bracke F, Meijer A, et al. Transesophageal echocardiographic evaluation of tricuspid valve regurgitation during pace-

maker and implantable cardioverter defibrillator lead extraction. Pacing Clin Electrophysiol. 2002; 25(11): 1583–1586, indexed in Pubmed: 12494615.
12. Zawadzki J, Januszkiewicz Ł, Cacko A, et al. Left Ventricular Pacing via Coronary Sinus in a Patient With a Mechanical Tricuspid Valve. Heart Beat J. 2017; 2: 36–37, doi: 10.24255/hbj/81266.
13. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. J Am Coll Cardiol. 2004; 43(3): 405–409, doi: 10.1016/j.jacc.2003.09.036, indexed in Pubmed: 15013122.
14. Höke U, Auger D, Thijssen J, et al. Significant lead-induced tricuspid regurgitation is associated with poor prognosis at long-term follow-up. Heart. 2014; 100(12): 960–968, doi: 10.1136/heartjnl-2013-304673, indexed in Pubmed: 24449717.
15. Rothschild DP, Goldstein JA, Kerner N, et al. Pacemaker-induced tricuspid regurgitation is uncommon immediately post-implantation. J Interv Card Electrophysiol. 2017; 49(3): 281–287, doi: 10.1007/s10840-017-0266-2, indexed in Pubmed: 28685199.
16. Arabi P, Özer N, Ateş AH, et al. Effects of pacemaker and implantable cardioverter defibrillator electrodes on tricuspid regurgitation and right sided heart functions. Cardiol J. 2015; 22(6): 637–644, doi: 10.5603/CJ.a2015.0060, indexed in Pubmed: 26412607.
17. Fanari Z, Hammami S, Hammami MB, et al. The effects of right ventricular apical pacing frequency on left ventricle function and pulmonary artery pressure. Del Med J. 2015; 87(8): 244–247, indexed in Pubmed: 26402927.
18. Ohlow MA, Lauer B, Brunelli M, et al. Incidence and predictors of pericardial effusion after permanent heart rhythm device implantation: prospective evaluation of 968 consecutive patients. Circ J. 2013; 77(4): 975–981, indexed in Pubmed: 23269085.
19. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2013; 14(7): 611–644, doi: 10.1093/ehjci/jet105, indexed in Pubmed: 23733442.
20. Adler Y, Charron P, Imazio M, et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2015; 36(42): 2921–2964, doi: 10.1093/eurheartj/ehv318, indexed in Pubmed: 26320112.
21. Klutstein M, Balkin J, Butnaru A, et al. Tricuspid incompetence following permanent pacemaker implantation. Pacing Clin Electrophysiol. 2009; 32 Suppl 1: S135–S137, doi: 10.1111/j.1540-8159.2008.02269.x, indexed in Pubmed: 19250077.
22. Webster G, Margossian R, Alexander ME, et al. Impact of transvenous ventricular pacing leads on tricuspid regurgitation in pediatric and congenital heart disease patients. J Interv Card Electrophysiol. 2008; 21(1): 65–68, doi: 10.1007/s10840-007-9183-0, indexed in Pubmed: 18040765.
23. Postaci N, Ekşi K, Bayata S, et al. Effect of the number of ventricular leads on right ventricular hemodynamics in patients with permanent pacemaker. Angiology. 1995; 46(5): 421–424, doi: 10.1177/000331979504600509, indexed in Pubmed: 7741326.
24. Al-Bawardy R, Krishnaswamy A, Rajeswaran J, et al. Tricuspid regurgitation and implantable devices. Pacing Clin Electrophysiol. 2015; 38(2): 259–266, doi: 10.1111/pace.12530, indexed in Pubmed: 25377489.
25. Kim JB, Spevack DM, Tunick PA, et al. The effect of transvenous pacemaker and implantable cardioverter defibrillator lead placement on tricuspid valve function: an observational study. J Am Soc Echocardiogr. 2008; 21(3): 284–287, doi: 10.1016/j.echo.2007.05.022, indexed in Pubmed: 17604958.
26. Lin G, Nishimura RA, Connolly HM, et al. Severe symptomatic tricuspid valve regurgitation due to permanent pacemaker or implantable cardioverter-defibrillator leads. J Am Coll Cardiol. 2005; 45(10): 1672–1675, doi: 10.1016/j.jacc.2005.02.037, indexed in Pubmed: 15893186.
27. Michniewicz E, Mlodawska E, Lopatowska P, et al. Patients with atrial fibrillation and coronary artery disease — Double trouble. Adv Med Sci. 2018; 63(1): 30–35, doi: 10.1016/j.advms.2017.06.005, indexed in Pubmed: 28818746.
28. Tomaszuk-Kazberuk A, Kołtowski L, Balsam P, et al. Use of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with atrial fibrillation - Messages from the 2018 EHRA. Cardiol J. 2018; 25(4): 423–440, doi: 10.5603/CJ.2018.0080, indexed in Pubmed: 30211927.
29. Tompkins C, Cheng A, Dalal D, et al. Dual antiplatelet therapy and heparin "bridging" significantly increase the risk of bleeding complications after pacemaker or implantable cardioverter-defibrillator device implantation. J Am Coll Cardiol. 2010; 55(21): 2376–2382, doi: 10.1016/j.jacc.2009.12.056, indexed in Pubmed: 20488310.
30. Tettey M, Aniteye E, Sereboe L, et al. Predictors of post operative bleeding and blood transfusion in cardiac surgery. Ghana Med J. 2009; 43(2): 71–76, indexed in Pubmed: 21326845.
31. Kalra PR, Greenlaw N, Ferrari R, et al. Hemoglobin and change in hemoglobin status predict mortality, cardiovascular events, and bleeding in stable coronary artery disease. Am J Med. 2017; 130(6): 720–730, doi: 10.1016/j.amjmed.2017.01.002, indexed in Pubmed: 28109968.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2020, Vol. 27, No. 6, 807–816
DOI: 10.5603/CJ.a2018.0113

ISSN 1897–5593
eISSN 1898–018X

Identification of biomarkers and mechanisms of diabetic cardiomyopathy using microarray data

Hui Li*, Xiaoyan Li*, Jian Guo, Guifu Wu, Chunping Dong, Yaling Pang, Shan Gao, Yangwei Wang

Department of Endocrinology, Shaanxi Provincial People's Hospital, Xi'an, China

Abstract

Background: *The study aimed to uncover the regulation mechanisms of diabetic cardiomyopathy (DCM) and provide novel prognostic biomarkers.*

Methods: *The dataset GSE62203 downloaded from the Gene Expression Omnibus database was utilized in the present study. After pretreatment using the Affy package, differentially expressed genes (DEGs) were identified by the limma package, followed by functional enrichment analysis and protein–protein interaction (PPI) network analysis. Furthermore, module analysis was conducted using MCODE plug-in of Cytoscape, and functional enrichment analysis was also performed for genes in the modules.*

Results: *A set of 560 DEGs were screened, mainly enriched in the metabolic process and cell cycle related process. Hub nodes in the PPI network were LDHA (lactate dehydrogenase A), ALDOC (aldolase C, fructose-bisphosphate) and ABCE1 (ATP Binding Cassette Subfamily E Member 1), which were also highlighted in Module 1 or Module 2 and predominantly enriched in the processes of glycolysis and ribosome biogenesis. Additionally, LDHA were linked with ALDOC in the PPI network. Besides, activating transcription factor 4 (ATF4) was prominent in Module 3; while myosin heavy chain 6 (MYH6) was highlighted in Module 4 and was mainly involved in muscle cells related biological processes.*

Conclusions: *Five potential biomarkers including LDHA, ALDOC, ABCE1, ATF4 and MYH6 were identified for DCM prognosis.* (Cardiol J 2020; 27, 6: 807–816)

Key words: diabetic cardiomyopathy, expression profile, differential analysis, module analysis, glycolysis, ribosome biogenesis

Introduction

Type 2 diabetes mellitus (T2DM) remains a life-threatening disease worldwide with increasing incidence [1, 2]. The predominant cause of death for T2DM patients was cardiovascular disease [3]. The diabetic cardiomyopathy (DCM) has been recognized as ventricular dysfunction in the absence of hypertension and coronary artery disease, may increase the risk of developing heart failure [4]. Moreover, DCM has been defined as a primary disease progressing into a metabolic disturbance that was mainly due to the elevation of free fatty acid (FFA) and the alteration of glucose metabolism, and would change the myocardial structure and function [5, 6]. It was reported that the mortality of patients with DCM was 42%, and the ST-segment elevation myocardial infarction (STEMI) and non-STEMI mortality in diabetic patients were 72% and 67%, respectively [7]. Currently, there were no specific therapeutic interventions for this predominant complication, except a paucity of proposed drugs such as eplerenone [8]. The understanding of mechanisms on DCM progression would facilitate finding novel targets for treatment of this disease. Several mechanisms in

Address for correspondence: Yangwei Wang, MM, Department of Endocrinology, Shaanxi Provincial People's Hospital, No. 256 Youyi West Road, Xi'an, 710068, China, tel: +86-029-85251331, fax: +86-029-85236987, e-mail: yangweiwang15@hotmail.com

Received: 10.01.2017 Accepted: 3.05.2017

*Co-first authors

charge of DCM were proposed. For instance, it was confirmed that FFA-mediated apoptosis, hypertrophy, and contractile dysfunction were the causative factors for DCM [6]. Oxidative stress was another major cause for the pathogenesis of DCM [9]. The overexpression of insulin like growth factor 1 was reported to act as an inhibitor in DCM development [10]. A more recent study elaborated molecular mechanisms that contributed to functional alterations in the diabetic heart and consequently identified several crucial advanced glycation end products (AGEs), fibrosis related genes including poly (ADP-Ribose) polymerase 1 (PARP-1), Otsuka Long Evans Tokushima fatty (OLETF) and matrix metalloproteinases 2 (MMP-2), inflammatory cytokines such as interleukin-1beta (IL-1β), IL-6, tumor necrosis factor-alpha (TNF-α) and transforming growth factor beta1 (TGF-β1) and altered pathways like mitogen-activated protein kinase (MAPK signaling) and TGF-β signaling, as well as critical miRNAs (miR-143, miR-181, miR-103, miR-107 and miR-802) [11]. However, previous informative findings only partially elucidated the molecular mechanism involved in DCM, and future study for comprehensive illustrating the primary genes and the pathways for the prevention of DCM was needed.

So far, the patient-specific induced pluripotent stem cells (iPSCs) model has been applied to mimic the DCM condition and dilated cardiomyopathy, to investigate therapeutic strategies or epigenetic regulations in these diseases [12–14]. Among them, Drawnel et al. [13] used a patient-specific induced iPSC model to exhibit metabolic disorders during the progression of DCM and finally screened several remarkable molecular drugs such as W7 (calmodulin), penitrem A (sodium and potassium channel blocker) and MCBQ (PDE5 inhibitors) for the prevention of DCM. Although several gene alterations such as the elevated *MYL2*, *MYL4* and *PLN*; and the decreased *NPPA*, *NPPB* and *ACTA1* were validated, the interactions among them and their functions were not interpreted, and thus lacked evidence for the prediction of potent therapeutic targets. Therefore, the expression profile GSE62203 deposited by Drawnel et al. [13] was re-analyzed to identify critical genes by extensive bioinformatical methods including differential analysis, protein–protein interaction (PPI) network and module analysis. Based on the above analyses, the aim herein was to uncover the interrelated regulation mechanisms of DCM and provide novel biomarkers for detection and prevention of DCM.

Methods

Gene expression data

A data set of the gene expression profile GSE62203 containing 4 treated samples (human iPS-derived CMs exposed to glucose, endothelin-1 and cortisol for 2 days *in vitro*) and 4 untreated samples (vehicle-control treated) was utilized in this study, which was deposited by Drawnel et al. [13] in the public Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo) database. In the Drawnel study, CMs were derived from CDI-MRB iPSCs (cellular dynamics international [CDI]). After being cultured for 2 days with conditions of 37°C and 7% CO^2, the plating medium for the CMs was changed for maturation medium (MM) for 3 days. After 3 days, the MM was exchanged for DM (MM+ glucose, endothelin and cortisol) for treated samples or MM+ vehicle control for untreated samples for another 2 days. Thus, the DCM condition was established. The platform for the expression profile was Affymetrix Human Genome U133 Plus 2.0 Array (Affymetrix Inc., Santa Clara, California, USA).

Data preprocessing and differential analysis

The Affy package in Bioconductor (http://www.bioconductor.org/packages/release/bioc/html/affy.html) [15] was employed to perform the pretreatment. The raw data were subjected to background correction, quantile data normalization and probe summarization recruiting the robust multi-array average (RMA) algorithm [16]. After obtaining the gene expression matrix, differentially expressed genes (DEGs) between the 2 kinds of samples were selected based on a t-test using linear models for microarray data (limma, http://www.bioconductor.org/packages//release/bioc/html/limma.html) package of Bioconductor R [17]. The cut-off values for the DEGs identification were $p < 0.05$ and $|\log_2 \text{fold change}| > 0.5$.

Functional enrichment analysis for the DEGs

To explore the altered biological process (BP) and pathways, the DEGs were mapped into gene ontology ([GO], http://www.geneontology. org/) and Kyoto Encyclopedia of Genes and Genomes ([KEGG], http://www.genome.jp/kegg/pathway.html) databases, using Database for Annotation, Visualization and Integration Discovery ([DAVID], http://david.abcc.Ncifcrf.gov/) online tool [18] with the Modified Fisher Exact test [19]. The p-value < 0.05 and the count (number of the genes) > 2 were set as the threshold for significant BP terms and pathways.

Construction of PPI network

To further explore potential correlations from the protein level, which facilitated to illustrate the underlying molecular mechanisms, identified DEGs were mapped into the Search Tool for the Retrieval of Interacting Genes/Proteins ([STRING], http://string-db.org/) database [20]. The PPI network of protein products of the genes was established, containing pairwise interactions with required confidence (combined score) > 0.4. A protein in the network was considered as a 'node' and the 'degree' of a node referred to the interaction pair numbers of a protein. The degree was calculated for each node using connectivity degree analysis. The 'hub' node in the network was deemed as the node with high degrees.

Module analysis of the PPI network

Functional modules of the network was extracted using the MCODE [21] plug-in of Cytoscape software with default parameters (Degree Cutoff: 2, Node Score Cutoff: 0.2, K-Core: 2, Max. Depth: 100) for selection. Subsequently, high scored modules with substantial nodes were further screened out for enrichment analysis, as described above.

Results

DEGs between treated and untreated samples

Based on the aforementioned criteria, a cohort of 560 DEGs was identified between the treated and untreated samples, consisting of 264 up-regulated genes and 296 down-regulated genes (**Supplementary material 1**).

BPs and pathways altered in the treated sample

After GO and KEGG enrichment analysis, the up-regulated DEGs were mainly enriched in metabolic BP terms such as generation of precursor metabolites and energy (GO: 0006091), hexose metabolic process (GO: 0019318), monosaccharide metabolic process (GO: 0005996) and glucose metabolic process (GO: 0006006); and besides response to wounding (GO: 0009611); response to organic substance (GO: 0010033), regulation of cell proliferation (GO: 0042127); while the down-regulated DEGs were significantly enriched in the processes including positive regulation of macromolecule metabolic process (GO: 0010604), cellular response to stress (GO: 0033554), and the cell control related functions such as regulation of apoptosis (GO: 0042981), regulation of programmed cell death (GO:0043067), regulation of cell death (GO:0010941), cell cycle (GO:0007049) and positive regulation of cellular biosynthetic process (GO:0031328) (Table 1).

The over-represented pathways for the up-regulated DEGs were glycometabolism and proteometabolism related pathways including glycolysis/gluconeogenesis (hsa00010), fructose and mannose metabolism (hsa00051), pentose phosphate pathway (hsa00030), starch and sucrose metabolism (hsa00500), arginine and proline metabolism (hsa00330), cysteine and methionine metabolism (hsa00270); by contrast, the prominent ones for down-regulated DEGs were aminoacyl-tRNA biosynthesis (hsa00970) and arginine, and proline metabolism (hsa00330) (Table 2).

The PPI network of the DEGs

By mapping the DEGs into the STRING database, a PPI network was established, comprising of 317 nodes and 929 interactions. As revealed in Figure 1, the remarkable nodes with high degree (> 20) were GAPDH (degree = 49), FN1 (degree = = 30), LDHA (degree = 28), ENO1 (degree= 27), PGK1 (degree = 26), ABCE1 (degree = 25), SOD2 (degree = 23), PKM (degree = 23), GOT1 (degree = 22), HK1 (degree = 22), TPI1 (degree = 21), GPI (degree = 21) and ALDOA (degree = 21).

Functional module network and the enrichment analysis for genes in the modules

According to module analysis of the PPI network, four modules with a high score (> 3) were extracted from the PPI network. There were 14 up-regulated nodes such as ALDOC, LDHA, PGK1 and TPI1 in Module 1 with a final score of 12.923; and 10 nodes including ABCE1, GAR1 and FBL in Module 2 with a final score of 8.222. The Module 3 contained five down-regulated nodes as DDIF3, ATF4, CEBPG, CEBPB and HERPUD1 and achieved a score of 4, while Module 4 consisted of 15 nodes such as CASQ2, CKMT2, IARS, CCT5, ACTA1, CKMT2 and MYH6 and had a score of 3.857 (Fig. 2).

The BP functions of the genes (which encode proteins in the modules) in the four modules were further analyzed. As presented in Table 3, the over-represented BPs for genes in Module 1 were predominantly correlated with the catabolic process of various carbohydrates such as glycolysis (GO:0006096), glucose catabolic process (GO:0006007), monosaccharide catabolic process (GO:0046365) and alcohol catabolic process (GO:0046164); while that for genes in Module 2 were mainly related to ribosome biogenesis and

Table 1. Biological processes significantly affected by the DEGs in treated samples. (Top ten, ranked by gene numbers enriched in a specific process).

Category	Term	Description	Count	P
Up-regulated DEGs				
BP	GO:0006091	Generation of precursor metabolites and energy	28	1.37E-13
BP	GO:0055114	Oxidation reduction	25	2.72E-05
BP	GO:0009611	Response to wounding	24	3.98E-06
BP	GO:0010033	Response to organic substance	23	1.07E-03
BP	GO:0019318	Hexose metabolic process	22	8.75E-13
BP	GO:0005996	Monosaccharide metabolic process	22	1.47E-11
BP	GO:0042592	Homeostatic process	22	3.95E-03
BP	GO:0006006	Glucose metabolic process	21	1.05E-13
BP	GO:0042127	Regulation of cell proliferation	19	4.54E-02
BP	GO:0044057	Regulation of system process	16	5.92E-05
Down-regulated DEGs				
BP	GO:0010604	Positive regulation of macromolecule metabolic process	22	1.20E-02
BP	GO:0033554	Cellular response to stress	21	1.97E-04
BP	GO:0042981	Regulation of apoptosis	20	2.32E-02
BP	GO:0043067	Regulation of programmed cell death	20	2.54E-02
BP	GO:0010941	Regulation of cell death	20	2.62E-02
BP	GO:0009891	Positive regulation of biosynthetic process	19	1.17E-02
BP	GO:0007049	Cell cycle	19	3.14E-02
BP	GO:0006412	Translation	18	6.09E-06
BP	GO:0006396	RNA processing	18	2.41E-03
BP	GO:0031328	Positive regulation of cellular biosynthetic process	18	2.05E-02

DEG — differentially expressed genes; BP — biological process; GO — gene oncology; Count — gene numbers enriched in a specific BP term.

Table 2. Pathways significantly altered by the DEGs in treated samples.

Category	Term	Description	Count	P
Up-regulated DEGs				
KEGG	hsa00010	Glycolysis / Gluconeogenesis	15	3.66E-12
KEGG	hsa00051	Fructose and mannose metabolism	6	4.49E-04
KEGG	hsa00330	Arginine and proline metabolism	7	5.12E-04
KEGG	hsa00500	Starch and sucrose metabolism	6	1.21E-03
KEGG	hsa00030	Pentose phosphate pathway	5	1.25E-03
KEGG	hsa04810	Regulation of actin cytoskeleton	12	2.84E-03
KEGG	hsa04510	Focal adhesion	10	1.57E-02
KEGG	hsa00270	Cysteine and methionine metabolism	4	2.77E-02
KEGG	hsa05012	Parkinson's disease	7	3.78E-02
KEGG	hsa04610	Complement and coagulation cascades	5	4.46E-02
KEGG	hsa05211	Renal cell carcinoma	5	4.67E-02
Down-regulated DEGs				
KEGG	hsa00970	Aminoacyl-tRNA biosynthesis	7	2.92E-05
KEGG	hsa00330	Arginine and proline metabolism	4	4.56E-02

DEG — differentially expressed genes; KEGG — Kyoto Encyclopedia of Genes and Genomes; Count — gene numbers enriched in a specific biological process term

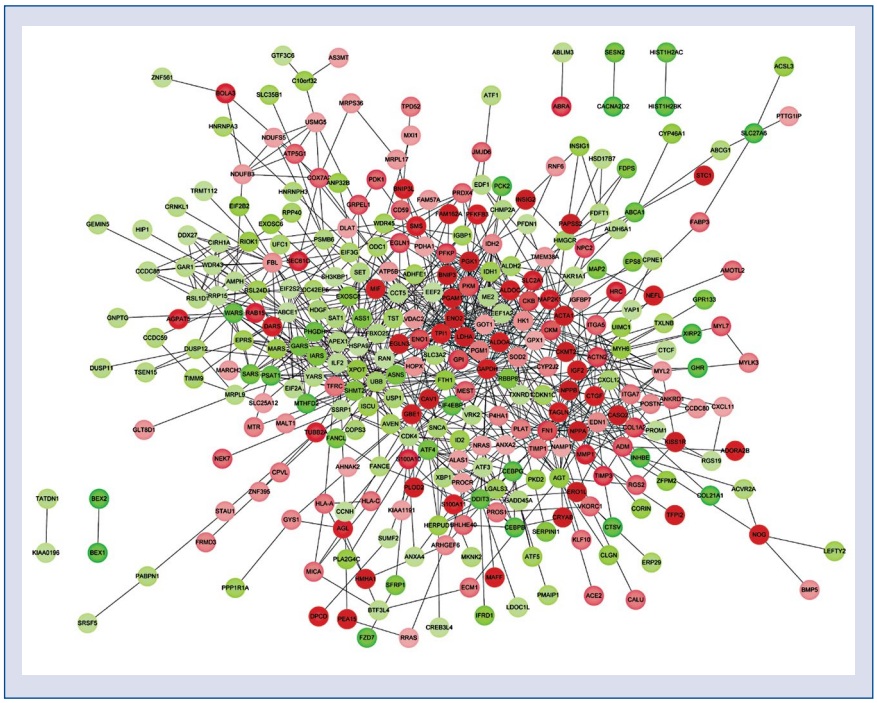


Figure 1. Protein–protein interaction network of differentially expressed genes in iPS-derived cardiomyocytes treated by glucose, endothelin-1 and cortisol. Circles represent protein products of differentially expressed genes, and red denotes up-regulated, green denotes down-regulated; color depth indicates the significance of differential expressed genes.

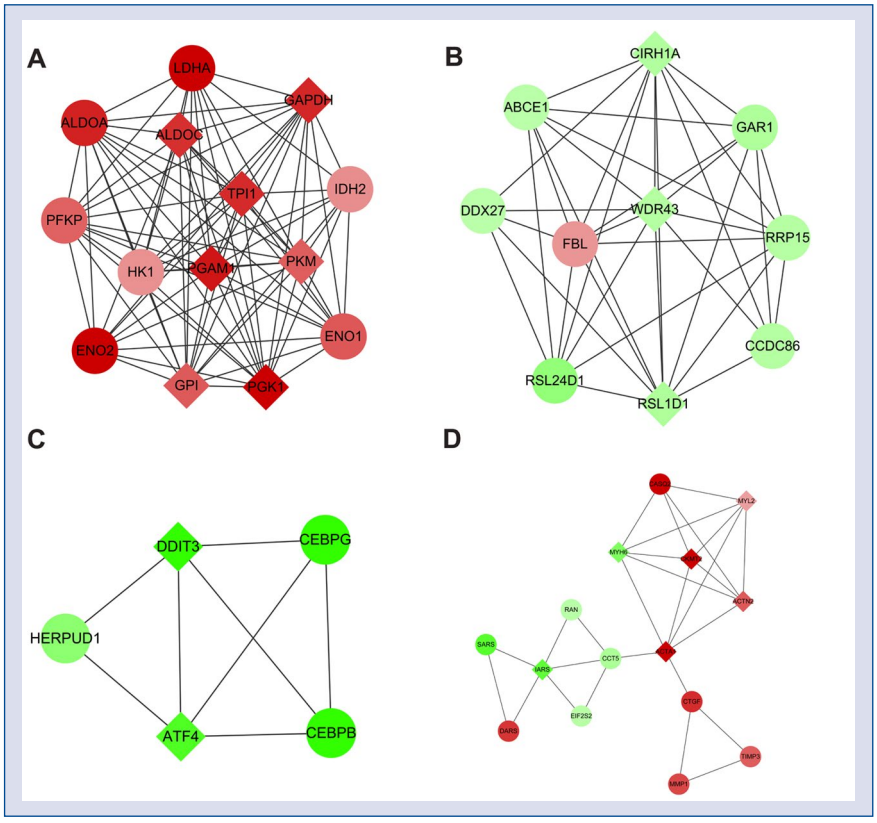


Figure 2. Modules of the protein–protein interaction network. **A.** Module 1; **B.** Module 2; **C.** Module 3; **D.** Module 4. Circles represent protein products of differentially expressed genes, and red denotes up-regulated genes, green denotes down-regulated genes, as well as diamonds stand for hub nodes; color depth indicates the significance of differentially expressed genes.

Table 3. Significantly enriched processes of genes in the module network.

Category	Term	Description	Count	P
Module 1				
BP	GO:0006096	Glycolysis	13	8.68E-30
BP	GO:0006007	Glucose catabolic process	13	1.48E-28
BP	GO:0019320	Hexose catabolic process	13	1.46E-27
BP	GO:0046365	Monosaccharide catabolic process	13	2.12E-27
BP	GO:0046164	Alcohol catabolic process	13	1.17E-26
BP	GO:0044275	Cellular carbohydrate catabolic process	13	2.18E-26
BP	GO:0016052	Carbohydrate catabolic process	13	5.18E-25
BP	GO:0006006	Glucose metabolic process	13	3.64E-23
BP	GO:0006091	Generation of precursor metabolites and energy	14	4.25E-22
BP	GO:0019318	Hexose metabolic process	13	6.06E-22
Module 2				
BP	GO:0042254	Ribosome biogenesis	3	4.78E-04
BP	GO:0022613	Ribonucleoprotein complex biogenesis	3	1.04E-03
BP	GO:0006396	RNA processing	3	9.27E-03
BP	GO:0006364	rRNA processing	2	2.69E-02
BP	GO:0016072	rRNA metabolic process	2	2.81E-02
Module 3				
BP	GO:0034976	Response to endoplasmic reticulum stress	3	3.67E-05
BP	GO:0045935	Positive regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolic process	4	3.77E-04
BP	GO:0051173	Positive regulation of nitrogen compound metabolic process	4	4.14E-04
BP	GO:0010557	Positive regulation of macromolecule biosynthetic process	4	4.34E-04
BP	GO:0031328	Positive regulation of cellular biosynthetic process	4	4.98E-04
BP	GO:0009891	Positive regulation of biosynthetic process	4	5.19E-04
BP	GO:0042981	Regulation of apoptosis	4	8.00E-04
BP	GO:0043067	Regulation of programmed cell death	4	8.23E-04
BP	GO:0010941	Regulation of cell death	4	8.32E-04
BP	GO:0010604	Positive regulation of macromolecule metabolic process	4	9.66E-04
Module 4				
BP	GO:0006936	Muscle contraction	5	1.44E-05
BP	GO:0003012	Muscle system process	5	2.08E-05
BP	GO:0030239	Myofibril assembly	3	2.07E-04
BP	GO:0031032	Actomyosin structure organization	3	3.70E-04
BP	GO:0010927	Cellular component assembly involved in morphogenesis	3	6.14E-04
BP	GO:0006418	tRNA aminoacylation for protein translation	3	1.00E-03
BP	GO:0043039	tRNA aminoacylation	3	1.00E-03
BP	GO:0043038	Amino acid activation	3	1.00E-03
BP	GO:0055002	Striated muscle cell development	3	1.28E-03
BP	GO:0055001	Muscle cell development	3	1.48E-03

BP — biological process; GO — gene oncology; Count — gene numbers enriched in a specific BP term

processing functions including ribosome biogenesis (GO:0042254), RNA processing (GO:0006396) and rRNA metabolic process (GO:0016072). Genes in the Module 3 were significantly correlated with the metabolic process involved in the cellular biosynthesis such as positive regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolic process (GO:0045935), positive

regulation of nitrogen compound metabolic process (GO:0051173), positive regulation of cellular biosynthetic process (GO:0031328); and besides the cell control related BPs including regulation of apoptosis (GO:0042981) and regulation of programmed cell death (GO:0043067); whereas the prominent BPs for the genes in the Module 4 were involved in the processes relating to muscle cells such as muscle contraction (GO:0006936), muscle system process (GO:0003012) and muscle cell development (GO:0055001).

Discussion

The DCM is defined as ventricular dysfunction that occurs in diabetic patients [22] and the iPSC model was applied to detect the metabolic alterations and screen potential genes and molecular drugs [13, 23]. In the present study, the expression profile GSE62203 was utilized to conduct a series of bioinformatic analyses and as a result, identify a cohort of 560 DEGs between treated and untreated samples. The hub nodes in the PPI network were LDHA, ALDOC and ABCE1, which were also highlighted in Module 1 or Module 2 and predominantly enriched in the glycolysis and ribosome biogenesis. Besides, ATF4 was prominent in Module 3; while MYH6 was highlighted in Module 4 which was mainly involved in muscle cells related BPs.

The LDHA (lactate dehydrogenase A) is one of the subunits of LDH which play significant roles in the final step of anaerobic glycolysis by interconversion of pyruvate and lactate using NADH/NAD+ as a co-substrate to allow continuous energy production [24]. It was reported that overexpression of LDHA activity may influence normal glucose metabolism and insulin secretion in the islet beta-cell type, and also result in insulin secretory defects in some forms of T2DM [25, 26]. In addition, the overexpression of LDHA activity might increase the lactate level and lactate–pyruvate interconversion rates in diabetes patients [27]. Similarly, the increased level of LDH was observed in the diabetic group, while luteolin exerted a protective effect against DCM by reducing the content of LDH in serum [28]. Hypoxia-inducible factor (HIF)-1, was a crucial transcription factor in brain ischemic pre-conditioning [29] and the expression of *HIF-1α* was decreased by a diabetic environment [30]. Partial deficiency of HIF-1*α* was proposed to increase the risk of DCM, and interestingly, *LDHA* was one of the target genes of HIF-1 that is involved in glucose metabolism and was upregulated in the HIF-1*α* heterozygous-null mutants [31]. In the present study, LDHA was the striking node in both PPI network and Module 1, and significantly enriched in glycolysis, giving potent evidence that *LDHA* might emerge as a central regulator in the progression of DCM via disturbing the glycolysis process.

ALDOC (aldolase C, fructose-bisphosphate) encodes a member of the class I fructose-biphosphate aldolase family gene, which acts as a catalyst that catalyzes the reversible aldol cleavage of fructose-1,6-biphosphate and fructose 1-phosphate to dihydroxyacetone phosphate and either glyceraldehyde-3-phosphate or glyceraldehyde, respectively in the glycolysis process [32]. Increased glucose was one hallmark of diabetes mellitus (DM) and *ALDOC* was one of the enzymes that promoted glycolysis and was induced by the elevated glucose [33]. Then, the up-regulated *ALDOC* was a positive correlation with the increase of FFA in plasma which might impair insulin secretion to develop T2DM [34, 35]. Additionally, *ALDOC* was up-regulated in the heart tissue in a rodent model of myocardial I/R injury [36]. Though no direct evidence existed that *ALDOC* and *LDHA* were interplayed with regard to diabetes or cardiomyopathy, it was indicated that *ALDOC* and *LDHA* were both up-regulated in a cervical cancer cell line of paclitaxel-resistant HeLa sublines [37]. On the other hand, DM was tightly related to the risk of various cancers including cervical cancer [38]. Notably, *ALDOC* and *LDHA* were both linked to HIF-1, which was associated with the risk of DCM as mentioned above [31]. These findings collectively suggested that the interacted *ALDOC* and *LDHA* might be involved in the regulation of the glycolysis process during DCM progression, as predicted by the current module analysis and enrichment analysis. However, more validations are needed to confirm the regulatory relationship between the two genes.

The *ABCE1* encoded ATP Binding Cassette Subfamily E Member 1 which belongs to a family member of the ATP-binding cassette (ABC) transporters and is primarily known as RNase L inhibitor (RLI) [39]. Zeng et al. [40] had indicated that RNase L activation was responsible for type I diabetes, and it was also suggested that the increased expression of RNase L or down-regulated of its inhibitor (RLI) might enhance the insulin response in muscle cells of obese people [41]. Additionally, further studies demonstrated that the mutation of *ABCB* and gene polymorphisms of *ABCG8* and *ABCG5* have been linked to T2DM

[42, 43]. Moreover, ABC transporters are energy-dependent when transporting various molecules across the biological membranes, while HF is the consequence of insufficient energy supplement of the cardiac pump. Therefore, it was hypothesized that the expression alterations of ABC transporters occurred during human HF [44, 45]. Due to *ABCE1* is a member of ABC transporters, and the present results indicated that the ABCE1 was a prominent down-regulated node in Module 2. Thus, it was predicted that the defective *ABCE1* might have a significant influence on the progression of DCM. However, there is no direct evidence to prove that *ABCE1* had interplayed with DCM, and it still needs further validation to confirm the relationship between the *ABCE1* and DCM.

The endoplasmic reticulum (ER) is a cell system consisting of the lipid synthesis, calcium homeostasis, protein folding, and maturation. The ER stress has been reported in the development of DCM [47, 48]. Moreover, it has been confirmed that ER-triggered apoptosis would contribute to the pathology of DCM [49]. Activating transcription factor 4 (ATF4) is a DNA binding protein. The glucagon-like peptide-1 analog liraglutide (LIRA) was confirmed to protect against DCM by inactivating the ER stress pathway, meanwhile the expression of *ATF4* was decreased with the treatment of LIRA [50], implying that *ATF4* might play significant roles in the progression of DCM, as predicted in the present result that ATF4 was a prominent node in Module 3.

The cardiac muscle myosin MYH6 was decreased in type 2 Zucker diabetic fatty rats [51]. Strikingly, *MYH6* was diminished under the hypertrophic stress (DM-treated with CMs) [13] and was considered a cardiac marker by fluorescent immunostaining [52]. The current results indicated that MYH6 was highlighted in Module 4 and correlated with muscle cells related BPs, suggesting that *MYH6* might also be used as a biomarker for the prognosis of DCM.

Conclusions

In conclusion, five potential biomarkers including *LDHA*, *ALDOC*, *ABCE1*, *ATF4* and *MYH6* were identified for DCM prognosis. During DCM progression, *LDHA* and *ALDOC* might have interplayed and play significant roles via regulation of the glycolysis process. However, these findings need to be further confirmed via extensive validation.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No.81100208).

Conflict of interest: None declared

References

1. Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. BMJ Open. 2016; 6(1): e010210, doi: 10.1136/bmjopen-2015-010210, indexed in Pubmed: 26769791.
2. Heather LC, Clarke K. Metabolism, hypoxia and the diabetic heart. J Mol Cell Cardiol. 2011; 50(4): 598–605, doi: 10.1016/j.yjmcc.2011.01.007, indexed in Pubmed: 21262230.
3. Scirica B, Bhatt D, Braunwald E, et al. Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus. N Engl J Med. 2013; 369(14): 1317–1326, doi: 10.1056/nejmoa1307684.
4. Acar E, Ural D, Bildirici U, et al. Diabetic cardiomyopathy. Anadolu Kardiyol Derg. 2011; 11(8): 732–737, doi: 10.5152/akd.2011.196, indexed in Pubmed: 22137942.
5. Asghar O, Al-Sunni A, Khavandi K, et al. Diabetic cardiomyopathy. Clin Sci (Lond). 2009; 116(10): 741–760, doi: 10.1042/CS20080500, indexed in Pubmed: 19364331.
6. Chavali V, Tyagi SC, Mishra PK. Predictors and prevention of diabetic cardiomyopathy. Diabetes Metab Syndr Obes. 2013; 6: 151–160, doi: 10.2147/DMSO.S30968, indexed in Pubmed: 23610527.
7. Alabas OA, Hall M, Dondo TB, et al. Long-term excess mortality associated with diabetes following acute myocardial infarction: a population-based cohort study. J Epidemiol Community Health. 2017; 71(1): 25–32, doi: 10.1136/jech-2016-207402, indexed in Pubmed: 27307468.
8. Leung M, Wong VW, Heritier S, et al. Rationale and design of a randomized trial on the impact of aldosterone antagonism on cardiac structure and function in diabetic cardiomyopathy. Cardiovasc Diabetol. 2013; 12: 139, doi: 10.1186/1475-2840-12-139, indexed in Pubmed: 24083804.
9. Liu Q, Wang S, Cai Lu. Diabetic cardiomyopathy and its mechanisms: Role of oxidative stress and damage. J Diabetes Investig. 2014; 5(6): 623–634, doi: 10.1111/jdi.12250, indexed in Pubmed: 25422760.
10. Kajstura J, Fiordaliso F, Andreoli AM, et al. IGF-1 overexpression inhibits the development of diabetic cardiomyopathy and angiotensin II-mediated oxidative stress. Diabetes. 2001; 50(6): 1414–1424, indexed in Pubmed: 11375343.
11. Bugger H, Abel E. Molecular mechanisms of diabetic cardiomyopathy. Diabetologia. 2014; 57(4): 660–671, doi: 10.1007/s00125-014-3171-6.
12. Wu H, Lee J, Vincent LG, et al. Epigenetic regulation of phosphodiesterases 2A and 3A underlies compromised β-adrenergic signaling in an iPSC model of dilated cardiomyopathy. Cell Stem Cell. 2015; 17(1): 89–100, doi: 10.1016/j.stem.2015.04.020, indexed in Pubmed: 26095046.
13. Drawnel FM, Boccardo S, Prummer M, et al. Disease modeling and phenotypic drug screening for diabetic cardiomyopathy using human induced pluripotent stem cells. Cell Rep. 2014; 9(3): 810–821, doi: 10.1016/j.celrep.2014.09.055, indexed in Pubmed: 25437537.

14. Churko JM, Sallam KI, Matsa E, et al. Epigenetic regulation of phosphodiesterases 2a and3aunderliescompromisedb-adrenergicsignaling in an ipsc model of dilated cardiomyopathy. Cell Stem Cell. 2015; 17: 1–12.
15. Gautier L, Cope L, Bolstad BM, et al. Affy-analysis of Affymetrix GeneChip data at the probe level. Bioinformatics. 2004; 20(3): 307–315, doi: 10.1093/bioinformatics/btg405, indexed in Pubmed: 14960456.
16. Horiuchi Y, Kano SI, Ishizuka K, et al. Olfactory cells via nasal biopsy reflect the developing brain in gene expression profiles: utility and limitation of the surrogate tissues in research for brain disorders. Neurosci Res. 2013; 77(4): 247–250, doi: 10.1016/j.neures.2013.09.010, indexed in Pubmed: 24120685.
17. Smyth GK. Limma: Linear models for microarray data; Bioinformatics and computational biology solutions using r and bioconductor. Springer. 2005: 397, doi: 420.
18. Huang DaW, Sherman BT, Lempicki RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nat Protoc. 2009; 4(1): 44–57, doi: 10.1038/nprot.2008.211, indexed in Pubmed: 19131956.
19. Grossmann S, Bauer S, Robinson PN, et al. Improved detection of overrepresentation of Gene-Ontology annotations with parent child analysis. Bioinformatics. 2007; 23(22): 3024–3031, doi: 10.1093/bioinformatics/btm440, indexed in Pubmed: 17848398.
20. Szklarczyk D, Franceschini A, Kuhn M, et al. The STRING database in 2011: functional interaction networks of proteins, globally integrated and scored. Nucleic Acids Res. 2011; 39(Database issue): D561–D568, doi: 10.1093/nar/gkq973, indexed in Pubmed: 21045058.
21. Rhrissorrakrai K, Gunsalus KC, Rhrissorrakrai K, et al. MINE: Module Identification in Networks. BMC Bioinformatics. 2011; 12: 192, doi: 10.1186/1471-2105-12-192, indexed in Pubmed: 21605434.
22. Falcão-Pires I, Leite-Moreira AF. Diabetic cardiomyopathy: understanding the molecular and cellular basis to progress in diagnosis and treatment. Heart Fail Rev. 2012; 17(3): 325–344, doi: 10.1007/s10741-011-9257-z, indexed in Pubmed: 21626163.
23. Choi SuMi, Kim Y, Shim JS, et al. Efficient drug screening and gene correction for treating liver disease using patient-specific stem cells. Hepatology. 2013; 57(6): 2458–2468, doi: 10.1002/hep.26237, indexed in Pubmed: 23325555.
24. Kolappan S, Shen DL, Mosi R, et al. Structures of lactate dehydrogenase A (LDHA) in apo, ternary and inhibitor-bound forms. Acta Crystallogr D Biol Crystallogr. 2015; 71(Pt 2): 185–195, doi: 10.1107/S1399004714024791, indexed in Pubmed: 25664730.
25. Ainscow EK, Zhao C, Rutter GA. Acute overexpression of lactate dehydrogenase-A perturbs beta-cell mitochondrial metabolism and insulin secretion. Diabetes. 2000; 49(7): 1149–1155, indexed in Pubmed: 10909972.
26. Chen Y, Wang X, Shao X. A combination of human embryonic stem cell-derived pancreatic endoderm transplant with ldha-repressing miRNA can attenuate high-fat diet induced type II diabetes in mice. J Diabetes Res. 2015; 2015: 796912, doi: 10.1155/2015/796912, indexed in Pubmed: 26770982.
27. Avogaro A, Toffolo G, Miola M, et al. Intracellular lactate- and pyruvate-interconversion rates are increased in muscle tissue of non-insulin-dependent diabetic individuals. J Clin Invest. 1996; 98(1): 108–115, doi: 10.1172/JCI118754, indexed in Pubmed: 8690781.
28. Wang G, Li W, Lu X, et al. Luteolin ameliorates cardiac failure in type I diabetic cardiomyopathy. J Diabetes Complications. 2012; 26(4): 259–265, doi: 10.1016/j.jdiacomp.2012.04.007, indexed in Pubmed: 22626874.
29. Scornavacca G, Gesuete R, Orsini F, et al. Proteomic analysis of mouse brain cortex identifies metabolic down-regulation as a general feature of ischemic pre-conditioning. J Neurochem. 2012; 122(6): 1219–1229, doi: 10.1111/j.1471-4159.2012.07874.x, indexed in Pubmed: 22804628.
30. Thangarajah H, Yao D, Chang EI, et al. The molecular basis for impaired hypoxia-induced VEGF expression in diabetic tissues. Proc Natl Acad Sci U S A. 2009; 106(32): 13505–13510, doi: 10.1073/pnas.0906670106, indexed in Pubmed: 19666581.
31. Bohuslavova R, Kolar F, Sedmera D, et al. Partial deficiency of HIF-1α stimulates pathological cardiac changes in streptozotocin-induced diabetic mice. BMC Endocr Disord. 2014; 14: 11, doi: 10.1186/1472-6823-14-11, indexed in Pubmed: 24502509.
32. Wang CF, Yuan CZ, Wang SH, et al. Differential gene expression of aldolase C (ALDOC) and hypoxic adaptation in chickens. Anim Genet. 2007; 38(3): 203–210, doi: 10.1111/j.1365-2052.2007.01605.x, indexed in Pubmed: 17539972.
33. Kim ES, Isoda F, Kurland I, et al. Glucose-induced metabolic memory in Schwann cells: prevention by PPAR agonists. Endocrinology. 2013; 154(9): 3054–3066, doi: 10.1210/en.2013-1097, indexed in Pubmed: 23709088.
34. Camps SG, Verhoef SPM, Roumans N, et al. Weight loss-induced changes in adipose tissue proteins associated with fatty acid and glucose metabolism correlate with adaptations in energy expenditure. Nutr Metab (Lond). 2015; 12: 37, doi: 10.1186/s12986-015-0034-1, indexed in Pubmed: 26500687.
35. Kashyap S, Belfort R, Gastaldelli A, et al. A sustained increase in plasma free fatty acids impairs insulin secretion in nondiabetic subjects genetically predisposed to develop type 2 diabetes. Diabetes. 2003; 52(10): 2461–2474, indexed in Pubmed: 14514628.
36. Bao W, Aravindhan K, Alsaid H, et al. Albiglutide, a long lasting glucagon-like peptide-1 analog, protects the rat heart against ischemia/reperfusion injury: evidence for improving cardiac metabolic efficiency. PLoS One. 2011; 6(8): e23570, doi: 10.1371/journal.pone.0023570, indexed in Pubmed: 21887274.
37. Peng X, Gong F, Chen Y, et al. Autophagy promotes paclitaxel resistance of cervical cancer cells: involvement of Warburg effect activated hypoxia-induced factor 1-α-mediated signaling. Cell Death Dis. 2014; 5: e1367, doi: 10.1038/cddis.2014.297, indexed in Pubmed: 25118927.
38. Szablewski L. Diabetes mellitus: influences on cancer risk. Diabetes Metab Res Rev. 2014; 30(7): 543–553, doi: 10.1002/dmrr.2573, indexed in Pubmed: 25044584.
39. Chen ZQ, Dong J, Ishimura A, et al. The essential vertebrate ABCE1 protein interacts with eukaryotic initiation factors. J Biol Chem. 2006; 281(11): 7452–7457, doi: 10.1074/jbc.M510603200, indexed in Pubmed: 16421098.
40. Zeng C, Yi X, Zipris D, et al. RNase L contributes to experimentally induced type 1 diabetes onset in mice. J Endocrinol. 2014; 223(3): 277–287, doi: 10.1530/JOE-14-0509, indexed in Pubmed: 25287058.
41. Fabre O, Breuker C, Amouzou C, et al. Defects in TLR3 expression and RNase L activation lead to decreased MnSOD expression and insulin resistance in muscle cells of obese people. Cell Death Dis. 2014; 5: e1136, doi: 10.1038/cddis.2014.104, indexed in Pubmed: 24651439.

42. Vasiliou V, Vasiliou K, Nebert DW. Human ATP-binding cassette (ABC) transporter family. Hum Genomics. 2009; 3(3): 281–290, indexed in Pubmed: 19403462.
43. Gok O, Karaali ZE, Acar L, et al. ABCG5 and ABCG8 gene polymorphisms in type 2 diabetes mellitus in the Turkish population. Can J Diabetes. 2015; 39(5): 405–410, doi: 10.1016/j.jcjd.2015.04.004, indexed in Pubmed: 26088706.
44. Ventura-Clapier R, Garnier A, Veksler V. Energy metabolism in heart failure. J Physiology. 2004; 555(1): 1–13, doi: 10.1113/jphysiol.2003.055095.
45. Solbach TF, Paulus B, Weyand M, et al. ATP-binding cassette transporters in human heart failure. Naunyn Schmiedebergs Arch Pharmacol. 2008; 377(3): 231–243, doi: 10.1007/s00210-008-0279-6, indexed in Pubmed: 18392808.
46. Licht A, Schneider E. ATP binding cassette systems: structures, mechanisms, and functions. Open Life Sciences. 2011; 6(5): 785–801, doi: 10.2478/s11535-011-0054-4.
47. Li Z, Zhang T, Dai H, et al. Involvement of endoplasmic reticulum stress in myocardial apoptosis of streptozocin-induced diabetic rats. J Clin Biochem Nutr. 2007; 41(1): 58–67, doi: 10.3164/jcbn.2007008, indexed in Pubmed: 18392099.
48. Li Z, Zhang T, Dai H, et al. Endoplasmic reticulum stress is involved in myocardial apoptosis of streptozocin-induced diabetic rats. J Endocrinology. 2010; 207(1): 123, doi: 10.1677/joe-07-0230r.
49. Xu J, Zhou Qi, Xu W, et al. Endoplasmic reticulum stress and diabetic cardiomyopathy. Exp Diabetes Res. 2012; 2012: 827971, doi: 10.1155/2012/827971, indexed in Pubmed: 22144992.
50. Liu J, Liu Yu, Chen Li, et al. Glucagon-like peptide-1 analog liraglutide protects against diabetic cardiomyopathy by the inhibition of the endoplasmic reticulum stress pathway. J Diabetes Res. 2013; 2013: 630537, doi: 10.1155/2013/630537, indexed in Pubmed: 23671882.
51. Howarth FC, Qureshi MA, Hassan Z, et al. Changing pattern of gene expression is associated with ventricular myocyte dysfunction and altered mechanisms of Ca2+ signalling in young type 2 Zucker diabetic fatty rat heart. Exp Physiol. 2011; 96(3): 325–337, doi: 10.1113/expphysiol.2010.055574, indexed in Pubmed: 21216827.
52. Shinozawa T, Imahashi K, Sawada H, et al. Determination of appropriate stage of human-induced pluripotent stem cell-derived cardiomyocytes for drug screening and pharmacological evaluation in vitro. J Biomol Screen. 2012; 17(9): 1192–1203, doi: 10.1177/1087057112449864, indexed in Pubmed: 22706346.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2020, Vol. 27, No. 6, 817–824
DOI: 10.5603/CJ.a2019.0087

ISSN 1897–5593
eISSN 1898–018X

Infiltration of CD68+ cells correlates positively with matrix metalloproteinase 2 expression in the arteries used as aortocoronary bypass grafts. Possible clinical implications

Bartłomiej Perek[1], Katarzyna Kowalska[2], Bartosz Kempisty[2, 3], Mariusz Nawrocki[3], Michał Nowicki[2], Mateusz Puślecki[1, 4], Danuta Ostalska-Nowicka[5], Łukasz Szarpak[6], Navid Ahmadi[1], Agnieszka Malińska[2]

[1]Department of Cardiac Surgery and Transplantology, Poznan University of Medical Sciences, Poznan, Poland
[2]Department of Histology and Embryology, Poznan University of Medical Sciences, Poznan, Poland
[3]Department of Anatomy, Poznan University of Medical Sciences, Poznan, Poland
[4]Department of Medical Rescue, Poznan University of Medical Sciences, Poznan, Poland
[5]Department of Pediatric Nephrology, Poznan University of Medical Sciences, Poznan, Poland
[6]Lazarski University, Warsaw, Poland

Abstract

Background: *Late failure of arterial aortocoronary conduits may result from abnormal activity of cells found in the vessel wall, including macrophages. The purpose of this study was to assess if there are any associations between the number of macrophages and overexpression of matrix metalloproteinases (MMPs) in the wall of arterial grafts, as well as their clinical significance.*

Methods: *This study involved 128 consecutive patients with a mean age of 64.9 ± 9.7 years who underwent elective surgery for coronary artery disease (CAD). The surplus segments of internal thoracic artery (ITA) and radial arteries (RA) were taken for immunohistochemical analysis of macrophage numbers and MMPs expression. The participants who reached the clinical primary end-point (cardiac-related death, acute coronary syndrome or progression of CAD) had a follow-up angiography.*

Results: *The mean numbers of macrophages were higher on RA (70 [24; 112]) than ITA cross-sections (44 [24; 59]; $p < 0.001$). Median expression of both MMP2 and MMP9 were stronger in the ITA than RA cross-sections ($p < 0.001$). A significant positive correlation of MMP2 expression and a number of macrophages infiltrating the tunica media of arterial segments were noted on both ITA and RA cross-sections. In addition, the arterial segments of the 6 patients who reached clinical end-point had higher numbers of macrophages and stronger MMP2 expression when compared to the rest of the participants.*

Conclusions: *Macrophage infiltration of arterial wall grafts prior to harvesting may be associated with higher risk of late occlusion and MMP2 might be facilitating this process.* (Cardiol J 2020; 27, 6: 817–824)

Key words: coronary artery bypass grafting, arterial aortocoronary grafts, macrophage, matrix metalloproteinase, outcomes

Address for correspondence: Bartłomiej Perek, MD, PhD, Department of Cardiac Surgery and Transplantology, Poznan University of Medical Sciences, ul. Długa 1/2, 61–848 Poznań, Poland, tel: +48 61 854 92 10, e-mail: bperek@ump.edu.pl

Received: 3.12.2018 Accepted: 27.03.2019

Introduction

Coronary artery bypass grafting (CABG) is a method of choice in treating patients with severe coronary artery disease (CAD) [1]. Late adverse outcomes of CABG are determined by durability of aortocoronary conduits as well as progression of atherosclerosis in the native coronary arteries [2, 3]. Due to excellent long-term patency in follow up, the left internal thoracic artery (LITA) implanted in the left anterior descending artery (LAD) has been the gold standard in cardiac surgery for many years [4]. The angiographic and clinical results of the other arteries or veins as a second graft in CABG patients shows a lower efficacy than internal thoracic artery (ITA) [5, 6]. According to the findings of ultrastructural studies, ITA differs from other vessels, not only in morphological terms but also in physiological features, these features make it an exceptional vessel with intrinsic resistance to atherosclerotic degeneration [7].

One of the many theories suggests that, an imbalance in local hemostasis between matrix metalloproteinases (MMPs) and locally released inhibitors, so called tissue inhibitor of metalloproteinases (TIMPs) leads to many pathologies in the vessel wall. In particular, MMP2 and MMP9 known as gelatinase-A and gelatinase-B, respectively, were shown to play an important role in the rupture of atherosclerotic plaques (leading to stroke or acute coronary syndrome), acute aortic dissection and leg venous ulcers [8–11]. Moreover, reduced production of macrophage-derived gelatinases was found to be associated with a significant decrease in plaque area and inhibition of cerebral aneurysm formation in animal experimental models [12, 13]. Although MMPs are expressed in almost all tissues of the human body, their synthesis takes place predominantly in macrophages, endothelial cells and smooth muscle cells [14].

Recent studies have demonstrated that infiltration of the coronary arteries' walls by macrophages is one of the fundamental step in the development of atherosclerosis [15]. Additionally, the presence of CD68+ cells (not yet developed into foam cells) in the intima of the grafted saphenous veins were shown to serve as one of the earliest markers for detection of graft occlusion [16].

In light of the above discussion, it was decided to evaluate the association between macrophage infiltration and overexpression of MMPs in the walls of arteries applied routinely as aortocoronary conduits. The aim will be to eventually determine any potential clinical significance of this phenomenon.

Table 1. Basic preoperative data of examined patients.

Variables	N = 128
Age [years]	64.9 ± 9.7
Obesity (BMI > 30)	52 (40.6%)
Arterial hypertension	83 (64.8%)
Diabetes mellitus treated with insulin	33 (25.8%)
Hyperlipidemia	54 (42.2%)
Neurological events*	11 (8.6%)
Peripheral vascular disease	30 (23.4%)
Chronic obstructive disease	17 (13.3%)
Renal failure**	14 (10.9%)
Active smoking***	63 (49.2%)

Continuous variables are presented as mean ± standard deviation, whereas categorical values are presented as the numbers (percentages). *They refer to both strokes and transient ischemic attacks; **When estimated glomerular filtration rate was below 60 mL/ /min/1.73 m^2; ***The term "active smokers" comprises active smokers and individuals who had given up smoking within 1 year prior to surgery; BMI — body mass index

Methods

This study involved 128 consecutive patients (100 men and 28 women) with a mean age of 64.9 ± ± 9.7 years (ranged 42 through 86) who underwent elective isolated CABG procedures in one cardiac surgical center in the years 2009–2011. Patients were qualified for surgery on the basis of coronary angiography. Basic preoperative data are presented in Table 1.

The study protocol was approved by the Local Bioethical Committee (No. 1201/08) and each patient provided informed written consent for participation in the study.

Biological material obtaining and preparation

During CABG procedures, surplus segments of vessels used as aortocoronary grafts were taken for ultrastructural studies. In all cases, the most distal excess segments of at least one centimeter in length were harvested. Both arteries were dissected free as pedicled grafts. Radial arteries (RA) were obtained from a full skin incision over its entire course. To minimize possible damage to the vessels, surgeons avoided: touching (no-touch technique), excessive manipulation, dilatation, and using high-energy electrocautery. Ultimately 174 segments of vessels, including 128 ITA and 46 RA were saved for histological analysis.

Segments of obtained vessels that passed intraoperative macroscopic inspection for any ab-

normalities were carefully rinsed with 0.9% NaCl at room temperature, slightly dilated, then immersed and fixed in freshly prepared Bouin's solution. The remaining preparatory steps for light microscope examination were described in detail in a previous paper [16]. All immunohistochemical analyses utilized the Dako REAL EnVision Detection System, Peroxidase/DAB, Rabbit/Mouse, K5007 (Dako, Copenhagen, Denmark) and were prepared according to standard procedure [16]. The following mouse monoclonal antibodies: anti-MMP2 (dilution 1:50; NB200-114), anti-MMP9 (dilution 1:250; NB100-78556, both Novus Biologicals, Littleton, United States), and anti-CD68 antibody (dilution 1:100, M0814, Dako) were used. Additionally, an eliminating assay with the following specific antibodies for lymphocyte subpopulations such as anti-CD20cy (1:400 dilution, M0755, Dako), anti-CD3 (1:50 dilution, M7254, Dako), anti-CD8 (1:100 dilution, M7103, Dako) and anti-CD30 (1:40 dilution, M0751, Dako) was carried out [17]. The peroxidase reaction was developed using diaminobenzidine.

Immunohistochemical analysis

Transverse sections of the arteries were observed and analyzed under a brightfield microscope-Olympus BX 50 (OLYMPUS Optical Europe, Germany) equipped with a Mirax-Midi scanner (Carl Zeiss Microimaging GmbH, Germany), coupled with a Panoramic Viewer, version 1.15.4, software (3DHISTECH Ltd., Budapest, Hungary).

The expression of CD68+ cells (a macrophage specific protein) were analyzed throughout the grafted vessel wall, followed by the inspection of specific sections such as; the *tunica intima*, the *tunica media* and the *tunica adventitia*. The intensity of cytoplasmic expression of the MMPs was assessed by applying the semi-quantitative immunoreactive score (IRS) scale according to Remmele and Stegner [18]. This method takes into account the percentage of positive cells (scale from 0 to 4), and intensity of the color reaction (scale from 0 to 3), to produce a final score ranging from 0 to 12, encapsulating points given for individual traits. According to IRS, the expression of the cytoplasmic proteins is classified as negative (IRS 0–1), weak (IRS 2–3), moderate (IRS 4–6) or strong (IRS 8–12).

For every segment analyzed, at least 8 to 10 representative sections were considered in making data more reliable. Immunohistochemical evaluation of protein expression was carried out by two experienced histologists, through blind sample analysis, based on encoded numbers corresponding with the basic rules of positive and negative control. The negative controls were carried out in an identical way to the experimental sample, with the exclusion of primary antibody being replaced with normal mouse serum.

Postoperative outcomes

All patients after discharge were systematically treated in the outpatient clinic. Special attention was paid to control CAD symptoms. If participants reached the clinical study primary endpoint, defined as cardiac-related death, acute coronary syndrome or necessity to carry out coronary angiography due to progression of angina according to Canadian Cardiovascular Society (CCS) scale, a follow-up angiography was performed.

Data management and statistical analysis

The Shapiro-Wilk W test for normality was performed for all continuous variables. These normally distributed data were presented as a mean and standard deviation. Data that did not satisfy the criteria of normal distribution was expressed as a median with the 25^{th} and 75^{th} percentiles, which was compared with the Mann-Whitney U test. Similarly, categorical variables (IRS scale) were presented as medians with the 25^{th} and 75^{th} percentiles. Both types of variables were compared with the non-parametric Mann-Whitney U test. Dychotomic data are presented as numbers (n) and percentages (%). The correlation between the findings of MMPs expression and CD68+ cells on the arterial sections were tested using the Spearman R correlation method. The correlation was defined as 'very strong' when R was between 0.8 and 1.0 (or –0.8 and –1.0), 'strong' between 0.6 and 0.8, or moderate between 0.4 and 0.6.

A p value below 0.05 was considered statistically significant. These statistical analyses were carried out using the Statistica 10.0 Package for Windows (StatSoft, Inc., Tulsa, OK, USA).

Results

CD68+ cells

The mean number of CD68+ cells were higher on RA (70 [24; 112]) than ITA (44 [24; 59]) cross-sections ($p < 0.001$). A detailed analysis to visualize the presence of these cells in both arteries showed a higher number of CD68+ cells in both the tunica media and tunica adventitia, while comparable in the *tunica intima* (Table 2). In both types of arteries, approximately 70% of CD68+ cells were found in the *tunica adventitia* (Fig. 1);

Table 2. CD68+ cell counts and matrix metalloproteinases (MMPs) expressions on arterial cross-sections.

CD68+ cells*	*Tunica intima*	*Tunica media*	*Tunica adventitia*	TN or ME#
ITA (n = 128)	5 (3,12)	4 (2, 10)	28 (17, 44)	44 (24, 59)
RA (n = 46)	4 (2,13)	12 (5, 16)	46 (20, 84)	70 (24, 112)
P**	0.739	< 0.001	< 0.001	< 0.001
MMP2***				
ITA (n = 128)	1 (0, 2)	2 (0, 2)	1 (0, 2)	1 (0, 2)
RA (n = 46)	4 (2, 4)	4 (4, 6)	2 (1, 2)	4 (2, 4)
P	< 0.001	< 0.001	< 0.001	< 0.001
MMP9				
ITA (n = 128)	2 (1, 2)	2 (2, 4)	1 (1, 2)	2 (1, 4)
RA (n = 46)	3 (2, 4)	6 (4, 6)	2 (1, 2)	3 (2, 4)
P	< 0.001	< 0.001	0.010	0.004

*Cell counts are expressed as median (25th percentile, 75th percentile); **ITA vs. RA; ***MMPs expressions are expressed as median (25th percentile, 75th percentile) of IRS points; #Total number (TN) refers to CD68+ cells whereas median expression (ME) to MMPs; ITA — internal thoracic artery; RA — radial artery

Table 3. Correlations between matrix metalloproteinase 2 (MMP2) expression and CD68+ cells on cross-sections of arterial grafts.

Number of CD68+ cells	*Tunica intima*	*Tunica media*	*Tunica adventitia*	Total number
MMP2 (ITA)	NS*	r = 0.409; p = 0.034	NS	r = 0.426; p = 0.029
MMP2 (RA)	NS	r = 0.429; p = 0.001	NS	r = 0.467; p = 0.006

*NS when r index was below 0.400 and p value did not exceed 0.05; ITA — internal thoracic artery; RA — radial artery; NS — non-significant

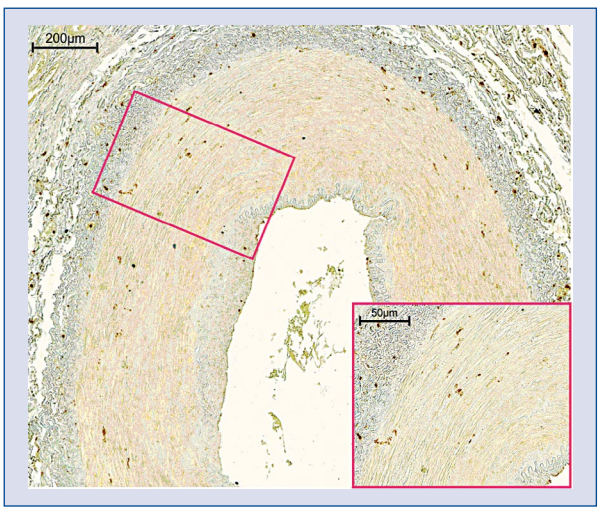


Figure 1. CD68+ cells on the radial artery cross-section. A radial artery segment was harvested from a 55-year-old man with triple-vessel disease. CD68+ cells were found predominantly in the tunica adventitia and outer layers of the tunica media.

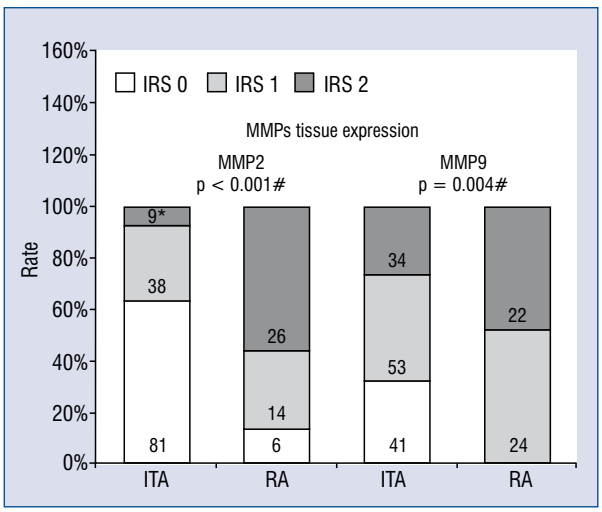


Figure 2. A rate of arterial cross-sections with different immunoreactive score (IRS) of matrix metalloproteinase (MMPs) expressions. More cross-sections of radial artery (RA) as compared to internal thoracic artery (ITA) presented higher IRS for both MMP2 and MMP9 immunostaining; *a number of cross-sections with a given IRS; #ITA vs. RA.

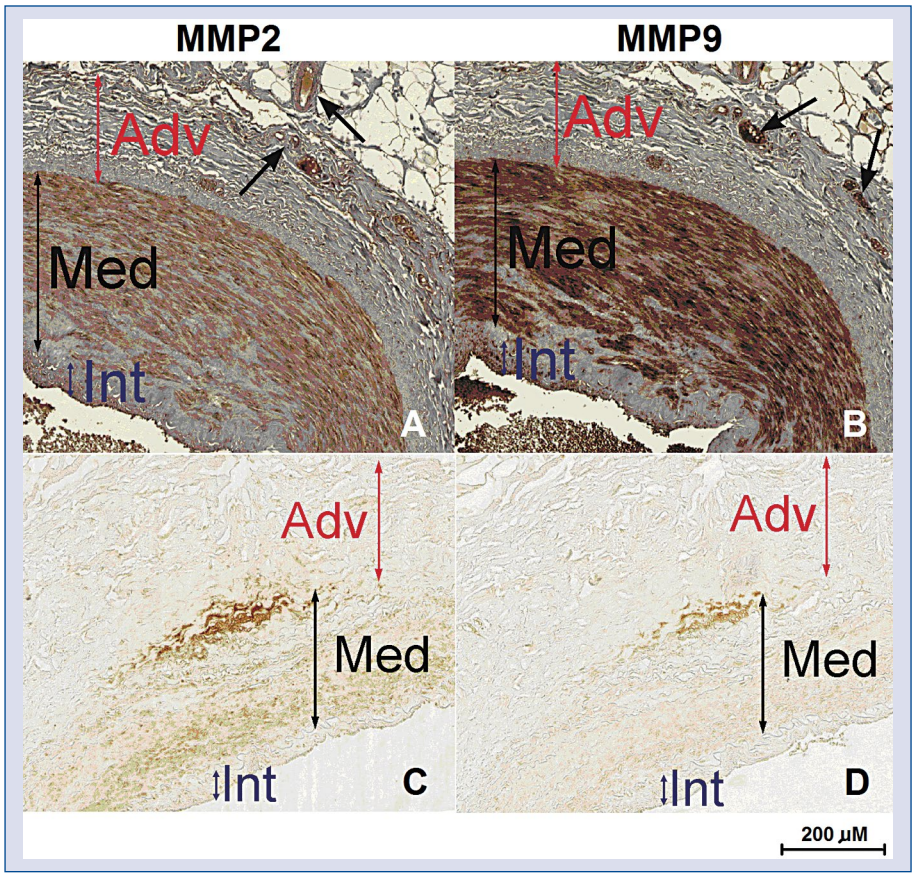


Figure 3. Immunoexpression of matrix metalloproteinase (MMPs) on the arterial cross-sections. The surplus arterial segments were obtained from 72-year-old man with two-vessel disease (severe stenosis in the left anterior descending artery and chronic totally occluded right coronary artery). Tissue expressions of MMP2 (**A**) and MMP9 (**B**) in the tunica media (Med) of radial artery (RA) cross-sections were found to be much stronger than in internal thoracic artery wall; **C.** MMP2; **D.** MMP9. On the RA sections, MMPs-positive cells were also seen in the wall of vasa vasorum (arrows); Adv — tunica adventitia; Int — tunica intima.

of note, these cells were mainly found adjacent to the *vasa vasorum*.

Gelatinases expression

Median expressions of MMP2 using Remmele scale (IRS) for ITA and RA cross-sections were minimal (1 [0, 2]) and moderate (4 [2, 4]), respectively ($p < 0.001$). The same differences were seen in all layers of the arteries (Table 3). No expression of MMP2 (IRS 0–1 points) was noticed in the majority of ITA (81/128) while in less than 15% of RA (6/26) segments (Fig. 2). Similar marked differences were detected for tissue expression of MMP9 (Table 2, Figs. 2 and 3).

Correlation between number of CD68+ cells and gelatinases expression

A significant positive correlation was noted between the total number of CD68+ cells and MMP2 expression in both ITA and RA cross-sections, as well as its presence in the *tunica media* of both arteries (Table 3; Fig. 4). No such correlation was observed between macrophage infiltration and immunostaining for MMP9.

Long-term outcomes and histological findings

Based on the findings of adverse late outcomes of CABG, 25 out of 128 patients reached the primary clinical end-point. From these, coronary angiography of 6 patients revealed an underlying progression of CAD of the native arteries (not addressed during primary surgery), was responsible for their clinical deterioration. The rest of the remaining patients (n = 19), significant occluding lesions were visualized; predominantly in venous grafts (n = 17) followed by RA (n = 4) and in only two cases of ITA segments.

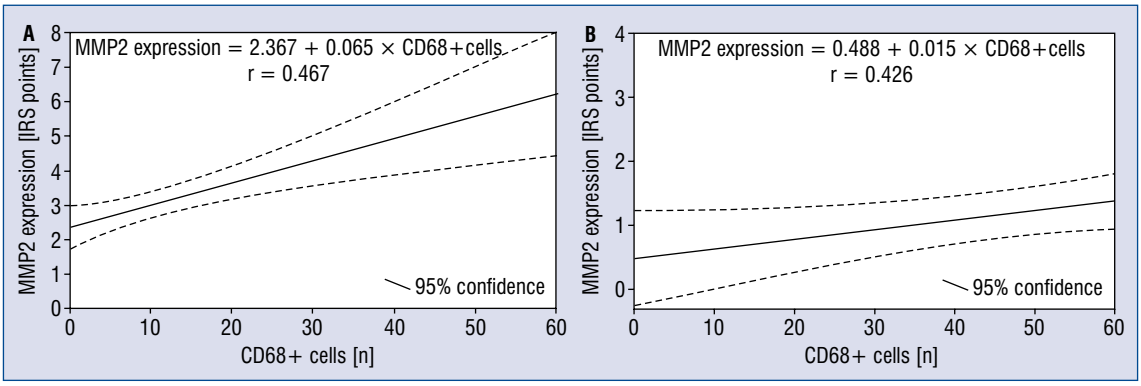


Figure 4. Correlation between matrix metalloproteinase 2 (MMP2) expression and number of CD68+ cells. Moderate correlations were found between median of MMP2 expression and a total number of CD68+ cells. Of note, MMP2 tissue expression was usually higher on the radial artery (**A**) than on the internal thoracic artery (**B**) sections.

Table 4. Number of CD68+ cells and matrix metalloproteinase (MMPs) expression in patients with occluded aortocoronary grafts.

	CD68+ Total [n]	CD68+ Int [n]	CD68+ Med [n]	CD68+ Adv [n]	MMP2 [IRS]	MMP9 [IRS]
ITA 1	49	11	14	24	4	3
ITA 2	62	12	20	30	6	2
RA 1	74	10	27	37	4	4
RA 2	85	14	22	49	6	6
RA 3	72	12	19	41	6	4
RA 4	115	22	31	51	6	4

Adv — tunica adventitia; Int — tunica intima; IRS — immunoreactive score; ITA — internal thoracic artery; Med — tunica media; RA — radial artery

Due to a small number of arterial conduits with significant lesions, no reliable statistical analysis was possible. However, all detailed results of histological assessment and calculations are summarized in Table 4. In all cases reaching the study clinical end-point, arterial segments before their implantation had more CD68+ cells infiltrating the wall accompanied by higher MMPs expressions than median values for a whole group. Additionally, CD68+ cells were localized closer to inner layers of the vessels since their rate in *tunica adventitia* (44.3% to 56.7%) was lower than in the rest of arterial cross-sections (approximately 70%).

Discussion

The first finding of the present study showed that the total number of CD68+ cells was higher in RA than ITA walls. It is highly likely that these cells were macrophages since an eliminating assay was applied. Previous research has found that macrophages participate actively in early stages of vessel wall degeneration, including trans-differentiation, proliferation, microcalcification and migration of vascular smooth muscle cells [18, 19]. Consequently, it is thought that RA conduits composed of a larger percentage of macrophages in the wall prior to their implantation into the coronary arteries are more prone to atherosclerotic degeneration and eventually graft failure. It has been shown in the past, arterial grafts have better long-term prognosis than saphenous vein grafts used for CABG [3, 4]. However, the current study confirmed that even arterial aortocoronary conduits, with pre-existing infiltration by CD68+ should be considered a risk factor of failure in a late follow-up period. It should be stressed again, all conduits which were closed or severely stenotic in the follow-up examination had a higher mean number of macrophages than the mean number in the whole group of examined conduits. However, due to a relatively small number of failed grafts, reliable statistical analysis was not possible. Impressively, the rate of medial and intimal macrophages in these grafts did increase

from about 30% to approximately 50%. Currently, this study is unable to explain if this phenomenon has any significance, nonetheless it was convincing that this finding warrants further research by applying more sophisticated scientific tools such as transmission electron microscopy.

Macrophages may infiltrate the vessel wall from the lumen or from the adventitial *vasa vasorum*. Current evidence suggests that the latter microvessels do not penetrate arterial walls, thus making it a preferred vessel compared to veins [20]. Concurrently, contrary to RA, internal elastic lamina is a tight structure in ITA, physiologically making it non-permeable [21]. This fact could be a possible explanation for differences seen in macrophage representation in the *tunica media* of both arteries. The harvested ITA conduits, which failed within post-discharge period could be due to pre-existing negative microstructural changes such as disruption of internal elastic lamina, which allowed a high number of CD68+ cells to penetrate through this layer. Once again, a more detailed, higher resolution histological study should be carried out to confirm such a brave hypothesis.

The next finding of possible clinical significance was a marked higher expression of MMP2 and MMP9 in the RA than ITA segments. Both MMPs produced by macrophages, with unique abilities to degrade elastin and collagen (the main components of extracellular matrix), are of paramount importance in many pathological processes, including atherosclerosis development and negative remodeling of venous graft applied extensively in CABG procedures [22]. Turner et al. [23] showed selective gene silencing of either MMP2 or MMP9 markedly reduced the invasive capacity of cultured human saphenous vein-smooth muscle cells (SMC), indicating that these MMPs played distinct non-overlapping roles in venous SMC invasion in vitro. Although on a very limited number of vessels, it was shown that some patients developed significant stenosis in graft within the follow-up period. This might be due to abnormally increased tissue activity of MMPs, which may also impact the outcome of arterial aortocoronary grafts. Stronger immunoreactivity for MMPs on the RA than ITA cross-sections should be considered as the next scientific proof that the latter is less prone to negative remodeling, leading to graft failure.

A positive correlation between a number of CD68+ cells in the whole wall (also in the *tunica media*) and tissue MMP2 expression was found. However, comparing histological views of CD68+ cells distribution and MMPs immunoreactivity on the vessel cross-sections, it is not possible that MMPs-positive areas were covered exclusively by macrophages. It can be suggested that CD68+ cells did stimulate SMCs to produce and release MMPs.

Limitations of the study

There are limitations in this study. Immunohistological assessment of the protein expression was carried out before implantation into aortocoronary circulation. Ideally, such analysis would be performed on the grafts explanted after a given period of time. It is possible to carry out such studies, but only in experimental animal models. Tissue expression was assessed on a base of immunohistochemistry. Although this method is accepted as a scientific tool to evaluate protein expressions, it is qualitative rather than quantitative one. While the Remmele scale applied improves quality of the analysis, experience of research remains mandatory. Histologists involved in this project may legitimate their expertise with many previous peer-reviewed publications [22, 24].

Conclusions

Infiltration of the walls of arterial aortocoronary conduits by CD68+ cells before their intraoperative application may be associated with higher risk of late graft occlusion. MMP2 might play a mediatory role in this process, with a greater increase seen in RA than ITA. Moreover, measuring of MMP location by immunohistochemistry is not sufficient to accurately estimate protein activity. Although gel zymography was proposed as a method of highly sensitive detection of gelatinases activity that enabled distinguishing between their active and zymogen forms, but getting reliable quantitative data with this technique was still challenging [25, 26].

Acknowledgements

This study was supported by State Committee for Scientific Research (Grant No. 5958/B/ /P01/2010/38). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest: None declared

References

1. Huang F, Lai W, Chan C, et al. Comparison of bypass surgery and drug-eluting stenting in diabetic patients with left main and/or multivessel disease: A systematic review and meta-analysis of randomized and nonrandomized studies. Cardiol J.

2015; 22(2): 123–134, doi: 10.5603/CJ.a2014.0036, indexed in Pubmed: 24846507.
2. Shavadia J, Norris CM, Graham MM, et al. Symptomatic graft failure and impact on clinical outcome after coronary artery bypass grafting surgery: Results from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease registry. Am Heart J. 2015; 169(6): 833–840, doi: 10.1016/j.ahj.2015.02.022, indexed in Pubmed: 26027621.
3. Gaudino M, Benedetto U, Fremes S, et al. Radial-Artery or saphenous-vein grafts in coronary-artery bypass surgery. N Engl J Med. 2018; 378(22): 2069–2077, doi: 10.1056/nejmoa1716026.
4. Gansera B, Schmidtler F, Angelis I, et al. Patency of internal thoracic artery compared to vein grafts - postoperative angiographic findings in 1189 symptomatic patients in 12 years. Thorac Cardiovasc Surg. 2007; 55(7): 412–417, doi: 10.1055/s-2007-965372, indexed in Pubmed: 17902061.
5. Bonacchi M, Prifti E, Maiani M, et al. Perioperative and clinical-angiographic late outcome of total arterial myocardial revascularization according to different composite original graft techniques. Heart Vessels. 2006; 21(2): 69–77, doi: 10.1007/s00380-005-0856-2, indexed in Pubmed: 16550306.
6. Cao C, Manganas C, Horton M, et al. Angiographic outcomes of radial artery versus saphenous vein in coronary artery bypass graft surgery: a meta-analysis of randomized controlled trials. J Thorac Cardiovasc Surg. 2013; 146(2): 255–261, doi: 10.1016/j.jtcvs.2012.07.014, indexed in Pubmed: 22871565.
7. Fonseca DA, Antunes PE, Cotrim MD. Ultrastructural and histomorphologic properties of the internal thoracic artery: implications for coronary revascularization. Coron Artery Dis. 2017; 28(6): 518–527, doi: 10.1097/MCA.0000000000000527, indexed in Pubmed: 28678142.
8. Heo SH, Cho CH, Kim HOk, et al. Plaque rupture is a determinant of vascular events in carotid artery atherosclerotic disease: involvement of matrix metalloproteinases 2 and 9. J Clin Neurol. 2011; 7(2): 69–76, doi: 10.3988/jcn.2011.7.2.69, indexed in Pubmed: 21779294.
9. Zhang L, Liao Mf, Tian L, et al. Overexpression of interleukin-1$\beta$and interferon-γ in type I thoracic aortic dissections and ascending thoracic aortic aneurysms: possible correlation with matrix metalloproteinase-9 expression and apoptosis of aortic media cells. Eur J Cardiothorac Surg. 2011; 40(1): 17–22, doi: 10.1016/j.ejcts.2010.09.019, indexed in Pubmed: 21349736.
10. Li Ya. Correlation analysis of levels of adiponectin and matrix metalloproteinase-9 with stability of coronary heart disease. Technol Health Care. 2015; 23 Suppl 1: S95–S98, doi: 10.3233/thc-150937, indexed in Pubmed: 26410336.
11. Grzela T, Niderla-Bielinska J, Litwiniuk M, et al. The direct inhibition of MMP-2 and MMP-9 by an enzyme alginogel: a possible mechanism of healing support for venous leg ulcers. J Wound Care. 2014; 23(5): 278–285, doi: 10.12968/jowc.2014.23.5.278, indexed in Pubmed: 24810313.
12. Li TT, Xie Yi, Guo Y, et al. Effect of probucol on vascular remodeling due to atherosclerosis in rabbits: an intravascular ultrasound study. Chin Med J (Engl). 2011; 124(12): 1840–1847, indexed in Pubmed: 21740843.
13. Aoki T, Kataoka H, Morimoto M, et al. Macrophage-derived matrix metalloproteinase-2 and -9 promote the progression of cerebral aneurysms in rats. Stroke. 2007; 38(1): 162–169, doi: 10.1161/01.STR.0000252129.18605.c8, indexed in Pubmed: 17122420.
14. Ghosh A, Pechota LV, Upchurch GR, et al. Cross-talk between macrophages, smooth muscle cells, and endothelial cells in response to cigarette smoke: the effects on MMP2 and 9. Mol Cell Biochem. 2015; 410(1-2): 75–84, doi: 10.1007/s11010-015-2539-3, indexed in Pubmed: 26318311.
15. Otsuka F, Kramer MCA, Woudstra P, et al. Natural progression of atherosclerosis from pathologic intimal thickening to late fibroatheroma in human coronary arteries: A pathology study. Atherosclerosis. 2015; 241(2): 772–782, doi: 10.1016/j.atherosclerosis.2015.05.011, indexed in Pubmed: 26058741.
16. Malinska A, Perek B, Buczkowski P, et al. CD68 expression in aortocoronary saphenous vein bypass grafts. Histochem Cell Biol. 2013; 140(2): 183–188, doi: 10.1007/s00418-012-1069-2, indexed in Pubmed: 23275124.
17. Perek B, Kowalska K, Kempisty B, et al. Gender and age-related variability of macrophage representation in the internal thoracic artery wall: does it matter? J Biol Regul Homeost Agents. 2018; 32(4): 791–802, indexed in Pubmed: 30043561.
18. Chung JiH, Jeon HJu, Hong SY, et al. Palmitate promotes the paracrine effects of macrophages on vascular smooth muscle cells: the role of bone morphogenetic proteins. PLoS One. 2012; 7(2): e29100, doi: 10.1371/journal.pone.0029100, indexed in Pubmed: 22363399.
19. Chatrou MLL, Cleutjens JP, van der Vusse GJ, et al. Intra-Section analysis of human coronary arteries reveals a potential role for micro-calcifications in macrophage recruitment in the early stage of atherosclerosis. PLoS One. 2015; 10(11): e0142335, doi: 10.1371/journal.pone.0142335, indexed in Pubmed: 26555788.
20. Hinojosa-Amaya JM, Villarreal-Silva EE, Elizondo-Omana RE, et al. Conduits for myocardial revascularization grafts: The importance of morphology and imaging. Med Univ. 2010; 47(12): 115–119.
21. Ruengsakulrach P, Sinclair R, Komeda M, et al. Comparative histopathology of radial artery versus internal thoracic artery and risk factors for development of intimal hyperplasia and atherosclerosis. Circulation. 1999; 100(19 Suppl): II139–II144, doi: 10.1161/01.cir.100.suppl_2.ii-139, indexed in Pubmed: 10567293.
22. Perek B, Malinska A, Misterski M, et al. Preexisting high expression of matrix metalloproteinase-2 in tunica media of saphenous vein conduits is associated with unfavorable long-term outcomes after coronary artery bypass grafting. Biomed Res Int. 2013; 2013: 730721, doi: 10.1155/2013/730721, indexed in Pubmed: 24151618.
23. Turner NA, Hall KT, Ball SG, et al. Selective gene silencing of either MMP-2 or MMP-9 inhibits invasion of human saphenous vein smooth muscle cells. Atherosclerosis. 2007; 193(1): 36–43, doi: 10.1016/j.atherosclerosis.2006.08.017, indexed in Pubmed: 16979647.
24. Perek B, Malińska A, Ostalska-Nowicka D, et al. Cytokeratin 8 in venous grafts: a factor of unfavorable long-term prognosis in coronary artery bypass grafting patients. Cardiol J. 2013; 20(6): 583–591, doi: 10.5603/CJ.2013.0142, indexed in Pubmed: 24338534.
25. Toth M, Sohail A, Fridman R. Assessment of gelatinases (MMP-2 and MMP-9) by gelatin zymography. Methods Mol Biol. 2012; 878: 121–135, doi: 10.1007/978-1-61779-854-2_8, indexed in Pubmed: 22674130.
26. Leber TM, Balkwill FR. Zymography: a single-step staining method for quantitation of proteolytic activity on substrate gels. Anal Biochem. 1997; 249(1): 24–28, doi: 10.1006/abio.1997.2170, indexed in Pubmed: 9193704.

VIA MEDICA

REVIEW ARTICLE

Cardiology Journal
2020, Vol. 26, No. 6, 825–835
DOI: 10.5603/CJ.a2019.0027

ISSN 1897–5593
eISSN 1898–018X

Alternative methods for functional assessment of intermediate coronary lesions

Martyna Zaleska[1], Łukasz Kołtowski[1], Jakub Maksym[1], Mariusz Tomaniak[1], Maksymilian Opolski[2], Janusz Kochman[1]

[1]1st Chair and Department of Cardiology, Warsaw Medical University, Warsaw, Poland
[2]Department of Interventional Cardiology and Angiology, Cardinal Wyszynski National Institute of Cardiology, Warsaw, Poland

Abstract

Wire-based fractional flow reserve (FFR) is a diagnostic tool used to evaluate the ischemic burden of coronary lesions. Large-scale studies have shown that FFR-guided revascularization is associated with better clinical outcomes. However, wide adoption of this technology is limited due to the considerable cost, additional time needed for set-up and performance of the measurement as well as the invasiveness of the procedure which requires pressure wire placement across the lesion into the distal segment of the coronary artery. To overcome these limitations new, promising, and less-/non-invasive methods were developed. These methods are based on computational fluid dynamics analysis and three-dimensional lumen reconstruction. The aim of this paper is to review scientific evidence supporting the clinical safety and efficacy of these techniques, such as instantaneous wave-free ratio, quantitative flow ratio and FFR calculated from computed tomographic angiography. (Cardiol J 2020; 27, 6: 825–835)

Key words: coronary angiography, quantitative flow ratio, computational fluid dynamics, fractional flow reserve

Introduction

Coronary artery disease (CAD) is one of the main causes of morbidity and mortality in developed countries [1, 2]. Coronary angiography remains the gold standard for the diagnosis of CAD, however, its ability to differentiate ischemic from non-ischemic lesions is limited. In this respect, fractional flow reserve (FFR), which takes into consideration the functional severity of coronary stenosis, outperforms the traditional diagnostic approach, based solely on morphometric assessment [3, 4]. Unfortunately, the adoption of FFR in everyday clinical practice is slow and is utilized in only a minority of centers [5, 6]. Härle et al. [7] found that FFR was used in 3.2% of all diagnostic procedures performed in Germany. In Poland penetration rate of FFR was even lower and did not exceed 2% in 2014 [8]. The main limiting factors include: 1) considerable time need for set-up and conduction of the examination; 2) high cost of diagnostic probe and adenosine infusion; 3) invasiveness, as it requires insertion of a pressure wire across the lesion into the distal part of the vessel, which is associated with increased risk of serious complications, e.g. ventricular arrhythmias and coronary vessel dissection (occurring in 0.5% of procedures), and 4) patient-related contraindications (hypotension, asthma, second-degree atrioventricular blocks) [9–11]. To overcome these limitations, less invasive techniques based on computational fluid dynamics (CFD) and three-dimensional (3D) lumen reconstruction have been proposed [12–16].

Address for correspondence: Łukasz Kołtowski, MD, PhD, First Chair and Department of Cardiology, Medical University of Warsaw, ul. Banacha 1a, 02–097 Warszawa, Poland, tel: +48 501 418 951, e-mail: lukasz@koltowski.com

Received: 8.11.2018 Accepted: 21.01.2019

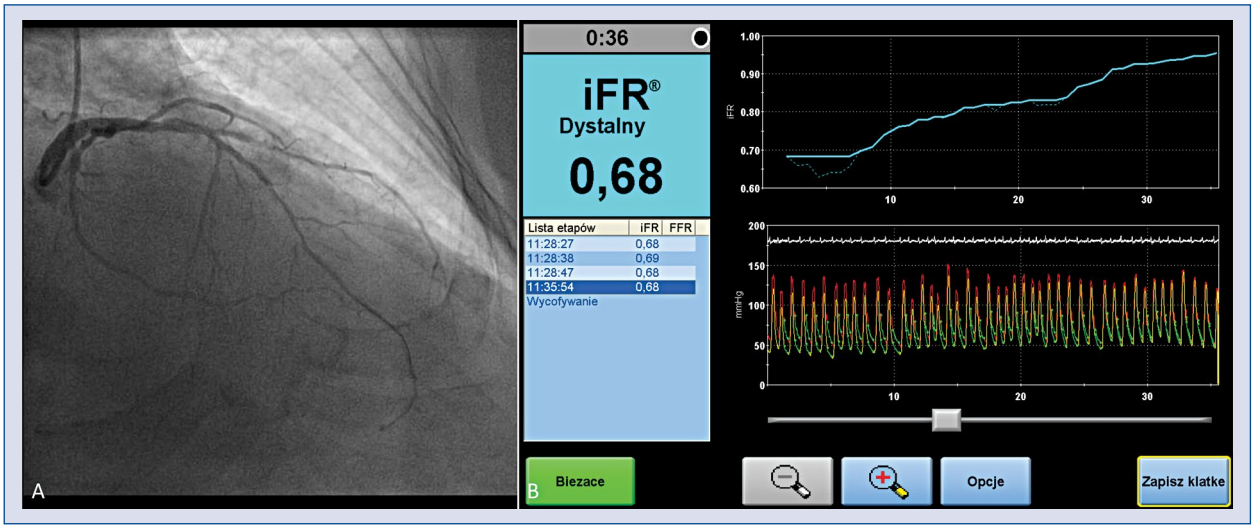


Figure 1. Vessel evaluation with instantaneous wave-free ratio (iFR) method indicates significant lesion in left anterior descending (LAD) artery (iFR = 0.68); **A.** Coronary angiogram with wire position in distal LAD; **B.** The iFR with pullback recording using ScoutTM software.

Pressure wire methods

Instantaneous wave-free ratio

Instantaneous wave-free ratio (iFR) is one alternative method that does not require adenosine infusion (Fig. 1). Although vessel wiring is still necessary, iFR measurements are quicker to perform and are cheaper than FFR. The scientific basis came from findings by Sen et al. [17] who demonstrated that functional assessment of coronary lesions comparable to FFR is possible without drug induced hyperemia, during the so-called "wave-free period". This period is seen in diastole and characterized by minimal and stable coronary resistance (similar to "hyperemic-like" conditions), which makes the trans-stenotic pressure gradient corresponding directly to flow and lesion severity [17].

The first published clinical study evaluating the correlation between iFR and FFR (ADenosine Vasodilator Independent Stenosis Evaluation [ADVISE]) demonstrated a close correlation between values obtained with these two methods ($r = 0.9$; $p < 0.001$) [17]. The possibility of iFR real-time measurement was proven by ADVISE in-practice study. The authors assessed 392 angiographically intermediate lesions and demonstrated that the best cutoff value of iFR corresponding to FFR ≤ 0.80 was an iFR ≤ 0.90 and resulted in classification agreement in 80% of cases, specificity of 79%, sensitivity of 81%, positive predictive value (PPV) of 71% and negative predictive value (NPV) of 87% [18]. What is more, it was shown that iFR correlates more closely than FFR with coronary flow velocity reserve, which suggests that iFR may be a more physiological parameter of disease severity [19].

In 2017, two pivotal trials evaluating iFR in clinical practice were published. The Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization (DEFINE-FLAIR) trial consisting of almost 2500 patients with stable CAD, proved that iFR-guided is noninferior to FFR-guided coronary revascularization with respect to composite risk of death from any cause, nonfatal myocardial infarction (MI) or unplanned revascularization during 1-year follow-up. Additionally, study results showed that in iFR group median procedural time was significantly shorter (40.5 vs. 45 min; $p = 0.001$; iFR vs. FFR, respectively) and fewer patients had adverse procedural symptoms (3.1% vs. 30.8%; $p < 0.001$; iFR vs. FFR, respectively) [20]. The Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome (iFR-SWEDE-HEART) trial consisting of over 2000 patients with stable CAD or acute coronary syndrome (17.5% patients) showed similar results. The primary composite end-point (defined as composite of death from any cause, nonfatal MI or unplanned revascularization) occurred in 6.7% of the patients in the iFR group and in 6.1% of the patients in the FFR group in 1-year follow-up ($p = 0.007$ for noninferiority).

Authors, just as in the previously described study, reported that chest discomfort occurred less often during the iFR-guided procedure (3.0% vs. 68.3%; $p < 0.001$) [21]. Results of these two trials were reflected in European and in American guidelines, in which iFR was regarded as equivalent to FFR in hemodynamic assessment of intermediate-grade stenosis [22, 23].

Alternative pressure wire methods

Over the years other adenosine-free methods based on assessment of diastolic resting indices have been proposed. Recently published data proved a high correlation between iFR and resting distal coronary to aortic pressure (P_d/P_a). Both were associated with lesion anatomic and hemodynamic severity, showing excellent agreement between them [24, 25]. It seems that the adoption of P_d/P_a could be easier, in comparison to iFR, it was analyzable in a significantly higher number of cases [25]. Other diastolic resting indexes included resting P_d/P_a during the complete duration of diastole, in 25% to 75% of diastole, at midpoint of diastole (Fig. 2). All the above-mentioned parameters were proven to be identical to iFR, not only numerically, but also with respect to their agreement to FFR [26]. Though, they are all very promising, further studies are needed to evaluate their clinical value.

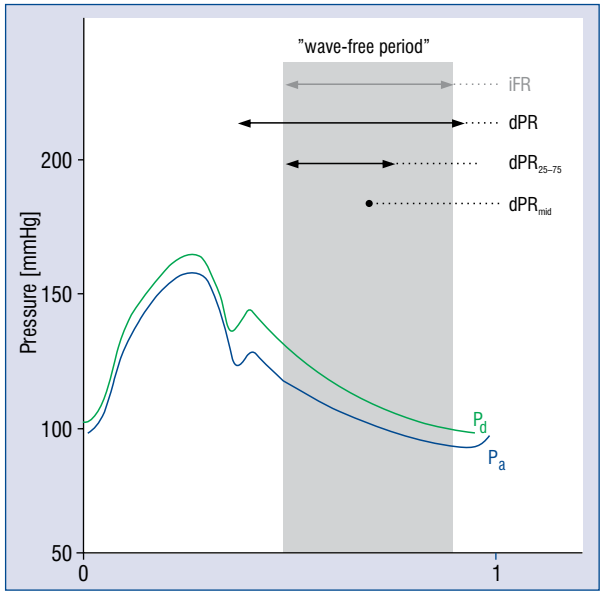


Figure 2. Resting Pd/Pa ratios over different periods of diastole. Based on [26]. Pd — resting distal coronary pressure; Pa — aortic pressure; Pd/Pa — resting distal coronary to aortic pressure; iFR — instantaneous wave-free ratio; dPR — Pd/Pa during the complete duration of diastole; $dPR_{25–75}$ — Pd/Pa in 25% to 75% of diastole; dPR_{mid} — Pd/Pa in midpoint of diastole.

Computational-based methods

Quantitative flow ratio

In 2013 Morris et al. [13] published results from the VIRTUal FFR From Coronary Angiography (VIRTU-1) study, designed to demonstrate the feasibility of FFR computations based solely on two-dimensional (2D) coronary angiography images (virtual FFR [vFFR]). The study population consisted of 19 patients. Compared to FFR, vFFR had an accuracy of 97%, sensitivity of 86%, specificity of 100%, PPV of 100%, and NPV of 97%. Although, there was a strong correlation between vFFR and wire-based FFR ($r = 0.84$), the image analysis was labor- and time-consuming, requiring 24 h to process the above-mentioned data. Of note, authors used a "one-size fits all" approach, which assumed constant coronary vessel resistance. Such an assumption carries the risk of stenosis misclassification due to possible changes in downstream microcirculatory resistance [13].

Papafakis et al. [27] proposed virtual functional assessment index (vFAI) — a quick method of functional assessment of intermediate coronary lesions, which took only 15 min to analyze one vessel. This approach computes distal to proximal pressure ratio over the lesion based on 3D quantitative coronary angiography (QCA) reconstruction and steady-flow CFD. The method was compared to FFR in 120 patients showing accuracy of 88%, sensitivity of 90% and specificity of 86% for the optimal vFAI cut-off point (≤ 0.82). Additionally, the vFAI was superior to 3D QCA in predicting hemodynamic significance of coronary stenosis and demonstrated close correlation and good agreement with wire-based FFR values. The main limitation of vFAI, which is based solely on lesion geometry, is the fact that it does not take into account microvascular resistance and size of myocardial territory subtended by the vessel [27].

To overcome these limitations, the computed FFR (FFR_{QCA}) based on mean volumetric flow rate at hyperemia derived from 3D vessel invasive coronary angiography (ICA) reconstruction, Thrombolysis in Myocardial Infarction (TIMI) frame count and CFD utilization was proposed (Fig. 3). The analysis of 77 vessels provided an 88% overall accuracy of FFR_{QCA} for diagnosis of ischemia (defined as FFR ≤ 0.8). There was a strong correla-

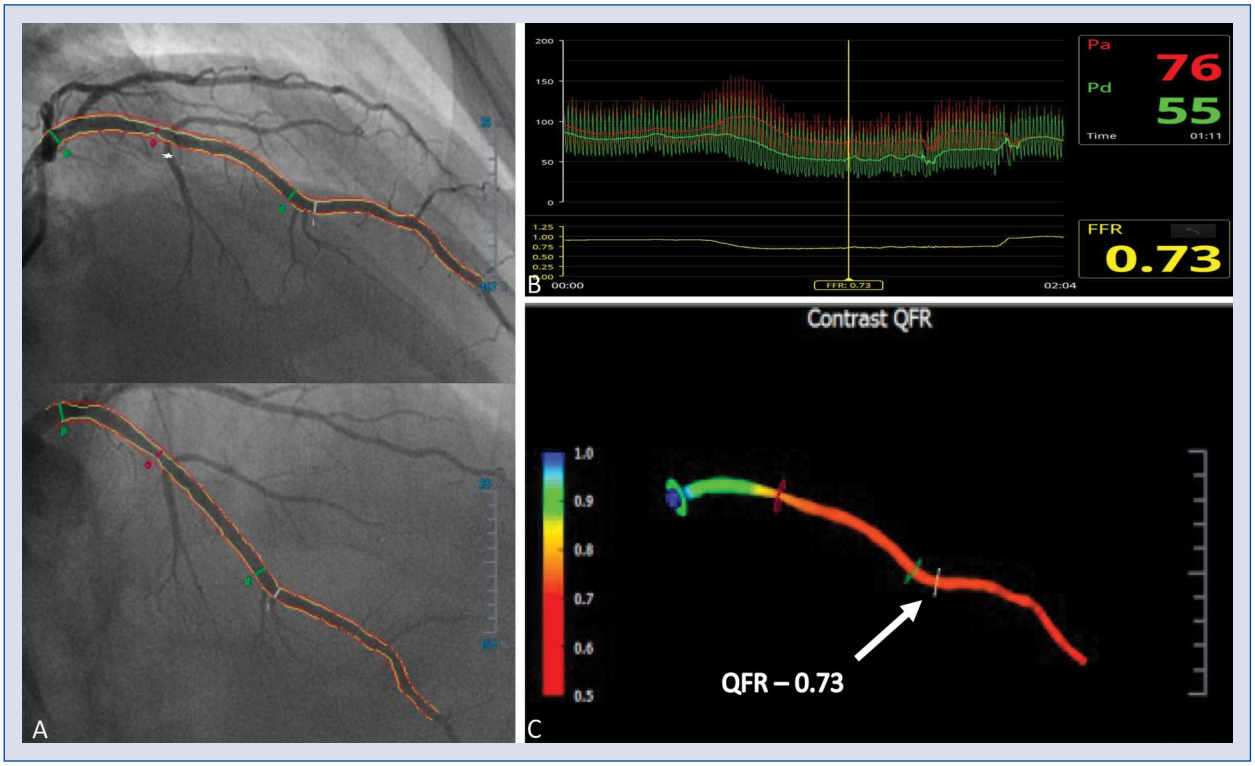


Figure 3. Computation of quantitative flow ratio (QFR) from coronary angiography; **A.** Angiographic projections of the left anterior descending (LAD) artery at > 25° apart; **B.** Fractional flow reserve (FFR) measured during intravenous adenosine infusion was 0.73; **C.** Computed QFR value indicates ischemia (QFR = 0.73). Arrow indicates original location of pressure transducer.

tion between FFR_{QCA} and FFR values (r = 0.81, p < 0.001) with a mean difference of ± 0.06 (p = 0.054) [12].

One of the main advantages of this method is short computation time, which did not exceed 10 min in total processing. Additionally, this method provides an evaluation of the entire coronary tree, whereas in wire-based FFR, only those lesions in which a pressure wire is inserted can be assessed [28].

Further confirmation of diagnostic accuracy of fast computational approaches came from prospective, observational, multicenter Functional Assessment by Various Flow Reconstruction (FAVOR) pilot study, in which 3 different quantitative flow ratio (QFR) computations were compared with standard wire-based FFR measurements. These included: 1) fixed-flow QFR (fQFR) that assumed a universal hyperemic flow velocity of 0.35 m/s); 2) contrast-flow QFR (cQFR) based on individual virtual flow derived from the frame count during contrast injection; 3) adenosine-flow (aQFR) based on individual virtual flow derived from the frame count during maximal adenosine-induced hyperemia. Authors confirmed good agreement between wire-based FFR and each QFR computation. The diagnostic accuracy was comparable for cQFR (86%) and aQFR (87%) and was significantly higher compared to fQFR (80%) indicating that the use of adenosine is not needed in this method [29]. Recently QFR received Conformité Européenne (CE) certificate, allows for wider adoption to everyday clinical practice.

In 2017, results from The FAVOR II China (Functional Diagnostic Accuracy of Quantitative Flow Ratio in Online Assessment of Coronary Stenosis) study were also published. They prospectively enrolled 308 consecutive patients at 5 centers in China. The primary endpoint was to assess if QFR would improve diagnostic accuracy of coronary angiography. Authors met the prespecified performance goal for level of diagnostic accuracy of QFR in identifying hemodynamically significant stenosis. Additionally, they confirmed QFR to have 94.6% sensitivity, 91.7% specificity, 85.5% PPV, and 97.1% NPV and diagnostic accuracy of 92.4% in patient-level analysis, and 92.7% in vessel-level analysis [30].

A recently published study demonstrated retrospectively analyzed results of 306 intermediate lesions, which had been previously evaluated using FFR. In contradiction to previous studies, which utilized core-lab assessment, in this particular study used an on-site QFR calculation in all cases. It showed that the Pearson correlation was strong for QFR ($r = 0.85$). Additionally, optimal QFR decision value of 0.79 was identified, this corresponded to FFR = 0.80 (AUC = 0.94). After introduction of the cut-off value of ≤ 0.74 and > 0.83, an excellent diagnostic performance of QFR was achieved, with sensitivity and specificity > 95%. Additionally, it was confirmed that the time for QFR analysis was relatively short and substantially decreased with the number of analyzed cases. The first 50 QFR analysis took an average of 5 min 59 s, whereas in the final 50 cases the mean time was 2 min 7 s [31].

Westra et al. [32] prospectively evaluated QFR in 240 lesions and correctly classified 83% of the lesions when an FFR cut off value of 0.8 was used. They also achieved a sensitivity of 77%, specificity of 86%, PPV of 87%, and NPV of 75%.

In 2018 the results from The FAVOR II Europe-Japan Study were published. In this international, multicenter trial 329 patients were enrolled. QFR values were calculated online in catherization laboratories during the procedure. Sensitivity and specificity were > 86% for QFR, which was significantly higher than for 2D QCA (sensitivity 44.2%; $p < 0.001$ and specificity 76.5%; $p = 0.002$) [33].

The most recently published study demonstrated that QFR may also be utilized in acute coronary syndrome settings, particularly in guiding non-culprit lesion revascularization in patients presenting with ST-segment elevation MI [34]. Additionally, the QFR good inter-core laboratory reproducibility had already been proven [35].

Although QFR is a very promising method, there are some technical limitations that should be taken into account. At present, the degree of flow-limiting stenosis of the ostial left main and ostial right coronary artery lesions cannot be reliably measured. Supraventricular tachyarrhythmia leading to an altered filling pattern of coronary arteries remains an exclusion criterion for FFR_{QCA} calculation. Additionally, patients with coronary artery bypass grafting supplying evaluated vessels or with collateral circulation have not been adequately studied [12]. Last, the timing of contrast injection may also affect the FFR_{QCA} values.

Additionally, data on clinical outcomes i.e. patient quality of life and cost-effectiveness remains lacking. This gap may will hopefully be addressed by the upcoming FAVOR III trial, which is designed as a prospective, randomized, multicenter clinical outcome study. With a planned enrollment of approximately 2000 patients, it is powered to establish the role of this method in the diagnostic process of CAD patients.

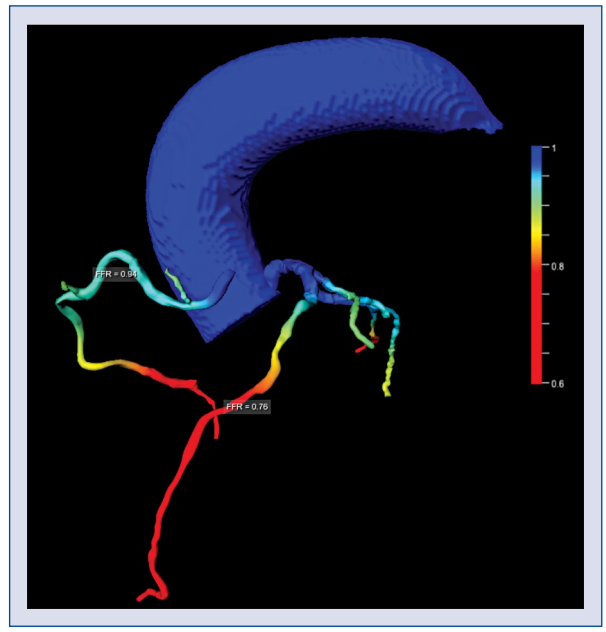


Figure 4. Coronary computed tomography angiography-derived fractional flow reserve indicates no ischemia in right coronary artery with computed value of 0.94, and hemodynamically significant lesion in left anterior descending artery with measured value of 0.76 [Image by courtesy of Drs. Christian Tesche and Maksymilian P. Opolski].

Computed tomographic angiography

Computed tomographic angiography (CTA) of the coronary vessels was the first non-invasive diagnostic imaging method providing data for CFD analysis to derive FFR-equivalent measurements (Fig. 4). Koo et al. [14] analyzed 103 patients, who underwent coronary CTA, QCA and FFR measurement. They performed the computation of FFR from coronary CTA (FFR_{CT}) using a powerful supercomputer to calculate the above-mentioned values. The proposed method utilized semi-automated segmentation of coronary arteries and approximation of the left ventricular mass. Despite the high computing power, a single analysis took approximately 5 h. The FFR_{CT} had an accuracy of 84.3%, sensitivity of 87.9%, specificity of 82.2%, PPV of 73.9%, and NPV of 92.2% for the diagnosis of ischemia-inducing lesions on a per-vessel basis. Additionally, there was a good

Table 1. Summary of studies evaluating methods used to compute fractional flow reserve.

Method	Author	Year	Sample size	Primary endpoint	Major findings	Cutoff values
iFR	Sen et al. [17]	2012	157 stenoses	To determine time period when intracoronary resistance is minimal and stable and there is a possibility to assess stenosis severity without adenosine administration	During "wave-free period" the intracoronary resistance is minimal and stable There is good correlation between iFR and FFR ($r = 0.9$; $p < 0.001$)	Ischemia: FFR < 0.80
iFR	Petraco et al. [18]	2014	392 lesions	To evaluate iFR and FFR diagnostic agreement in "real-world" conditions	the best cutoff to discriminate stenosis with FFR ≤ 0.80 was an iFR ≤ 0.90; sensitivity — 81%; specificity — 79%; PPV — 71%; NPV — 87%	Ischemia: FFR < 0.80
iFR	Petraco et al. [19]	2014	182 patients 216 stenoses	To assess the diagnostic relationship between iFR, FFR coronary flow velocity reserve	iFR has stronger correlation with coronary flow velocity reserve than FFR	Ischemia: FFR ≤ 0.75
iFR	Davies et al. [20]	2017	2492 patients	To determine the efficacy and safety of an iFR-guided vs. an FFR-guided strategy for coronary revascularization	iFR-guided revascularization was noninferior to FFR-guided procedure Less adverse procedural symptoms and clinical signs (including chest pain and dyspnea) in iFR group Median procedural time is shorter in iFR group	Ischemia: FFR ≤ 0.8 iFR ≤ 0.89
iFR	Götberg et al. [21]	2017	2037 patients	To determine if iFR is noninferior to FFR with respect to the rate of subsequent major adverse cardiac events	iFR-guided revascularization was noninferior to FFR-guided procedure More chest discomfort in FFR group	Ischemia: FFR ≤ 0.8 iFR ≤ 0.89
vFFR	Morris et al. [13]	2013	19 patients	To compare vFFR and FFR values	Accuracy — 97%; sensitivity — 86%; specificity — 100%; PPV — 100%; NPV — 97%; strong correlation between vFFR and FFR	Ischemia: FFR < 0.80 Anatomically obstructive CAD: ICA with stenosis > 50%
vFAI	Papafaklis et al. [27]	2014	120 patients 139 vessels	To test the diagnostic performance of the derived vFAI in a real-world patient population with intermediate lesions and compare with FFR values	Accuracy — 88%; sensitivity — 90%; specificity — 86% (for the optimal vFAI cut-off point (≤ 0.82) vFAI was superior to 3D QCA in predicting hemodynamic significance of coronary stenosis; close correlation and good agreement with wire-based FFR values	Ischemia: FFR ≤ 0.80
FFR_{QCA}	Tu et al. [12]	2014	68 patients 77 vessels	To assess FFR_{QCA} predictive value to diagnose ischemia	Overall accuracy — 88%; strong correlation between FFR_{QCA} and FFR; total processing time of around 10 min	Ischemia: FFR ≤ 0.80
QFR	Tu et al. [29]	2016	73 patients 84 vessels	To assess diagnostic accuracy of fast computational approaches to derive FFR from diagnostic coronary angiography	High diagnostic accuracy: fQFR = 80%, cQFR = 86%, aQFR = 87%	Ischemia: FFR ≤ 0.80

→

Table 1 (cont.). Summary of studies evaluating methods used to compute fractional flow reserve.

Method	Author	Year	Sample size	Primary endpoint	Major findings	Cutoff values
QFR	Xu et al. [30]	2017	308 patients 332 vessels	To assess the diagnostic performance of QFR for the diagnosis of hemodynamically significant coronary stenosis	Diagnostic accuracy: patient-level — 92.4%, vessel-level — 92.7%; sensitivity — 94.6%; specificity — 91.7%; PPV — 85.5%; NPV — 97.1%	Ischemia: FFR ≤ 0.80
QFR	Westra et al. [32]	2018	172 patients 240 lesions	To evaluate the feasibility and diagnostic performance of QFR in unselected consecutive patients	QFR correctly classified 83% of the lesions; area under the receiver operating characteristic curve — 0.86; sensitivity — 77%; specificity — 86%; PPV — 87%; NPV — 75%	Ischemia: FFR ≤ 0.80
QFR	Westra et al. [33]	2018	272 patients	To evaluate the value of online QFR during routine ICA for procedural feasibility, diagnostic performance, and agreement with FFR	QFR analysis is superior to angiographic assessment; sensitivity — 86.5%; specificity — 86.9%; median time to QFR — 5 min	Ischemia: FFR ≤ 0.80
QFR	Kołtowski et al. [31]	2018	268 patients 306 lesions	To assess diagnostic accuracy of QFR	Strong Pearson correlation for iQFR (r = 0.85), fQFR (r = 0.73), vQFR (r = 0.78) and IQFR (r = 0.70) Sensitivity and specificity > 95% for iQFR ≤ 0.74 (n = 89, 29%) and > 0.83 (n = 116, 38%), respectively	Ischemia: FFR ≤ 0.80
FFRCT	Koo et al. [14]	2011	103 patients 159 vessels	Diagnostic performance of FFR_{CT} and CCTA stenosis, compared with invasive FFR (as the reference standard)	Accuracy — 84.3%; sensitivity — 87.9%; specificity — 82.2%; PPV — 73.9%; NPV — 92.2% (for diagnosis of ischemia-inducing lesions on per-vessel basis); good correlation between FFR_{CT} and FFR values	Ischemia: FFR_{CT} and FFR ≤ 0.80 Anatomically obstructive CAD: CCTA with stenosis ≥ 50%
FFRCT	Min et al. [15]	2012	252 patients	Whether FFR_{CT} plus CT could improve the per-patient diagnostic accuracy such that the lower boundary of the 1-sided 95% confidence interval of this estimate exceeded 70%	Accuracy — 73%; sensitivity — 90%; specificity — 54%; PPV — 67%; NPV — 84% (for diagnosis of ischemia-inducing lesions on per-patient basis); high NPV; high sensitivity; authors did not achieve the prespecified level of per-patient diagnostic accuracy	Ischemia: FFR_{CT} and FFR ≤ 0.80 Anatomically obstructive CAD: CT and ICA with stenosis ≥ 50%
FFRCT	Nørgaard et al. [16]	2014	254 patients	Per-patient diagnostic performance as assessed by the area under the receiver-operating characteristic curve of FFR_{CT} (≤ 0.80) vs. CCTA (stenosis > 50%) for the diagnosis of hemodynamically significant stenosis (FFR ≤ 0.80) in patients with CCTA stenosis of 30% to 90%	Accuracy — 86%; sensitivity — 84%; specificity — 86%; PPV — 61%; NPV — 95% (for diagnosis of ischemia-inducing lesions on per-vessel basis) FFR_{CT} under 0.8 correlated well with FFR values under 0.8	Ischemia: FFR_{CT} and FFR ≤ 0.80 Anatomically obstructive CAD: CT and ICA with stenosis > 50%

→

Table 1 (cont.). Summary of studies evaluating methods used to compute fractional flow reserve.

Method	Author	Year	Sample size	Primary endpoint	Major findings	Cutoff values
FFR_{CT}	Douglas et al. [36]	2015	584 patients	Percentage of those with planned ICA in whom no significant obstructive CAD was found at ICA within 90 days	CTA/FFR_{CT} testing allowed to reduce number of ICA in patients without obstructive CAD No major adverse cardiac events over 90-day follow-up period in any patient in whom ICA was cancelled based on negative results of CTA/FFR_{CT}	Ischemia: FFR_{CT} and FFR < 0.80 Anatomically obstructive CAD: CT and ICA with stenosis ≥ 50%
FFR_{CT}	Nørgaard et al. [37]	2018	677 patients	To assess real-life clinical outcomes of introduction of strategy including CTA and selective FFR_{CT} in patients with stable CAD	FFR_{CT} is an effective tool to differentiate patients with intermediate-grade coronary lesions who may need further invasive testing	Ischemia: $FFR_{CT} \leq 0.80$

aQFR — adenosine-flow QFR; CAD — coronary artery disease; CCTA — coronary computed tomography angiography; cQFR — contrast-flow QFR; CT — computed tomography; CTA — computed tomography angiography; FFR — fractional flow reserve; FFR_{CT} — FFR calculated from computed tomography; fQFR — fixed-flow QFR; ICA — invasive coronary angiography; iFR — instantaneous wave-free ratio; iQFR — index QFR; lQFR — lesion QFR; NNV — negative predictive value; PPV — positive predictive value; QCA — quantitative coronary angiography; QFR — quantitative flow ratio; vFAI — virtual functional assessment index; vFFR — virtual FFR; vQFR — vessel QFR;

correlation between FFR_{CT} and FFR values, with a slight underestimation by FFR_{CT} (0.022 ± 0.116; p = 0.016). Authors concluded that the addition of FFR_{CT} to standard coronary CTA measurements might enhance diagnostic accuracy and this method's utility [14].

Min et al. [15] studied 252 stable patients who underwent coronary CTA, QCA and FFR measurements. Patients with a history of coronary artery bypass grafting or with suspected in-stent restenosis on the basis of CT were excluded. The FFR_{CT} calculation was also based on coronary CTA. One analysis took up to 6 hours. Authors reported FFR_{CT}'s accuracy of 73%, sensitivity of 90%, specificity of 54%, PPV of 67%, and NPV of 84% for diagnosis of ischemia-inducing lesions on a per-patient basis. The study did not achieve its pre-specified level of per-patient diagnostic accuracy, however, it showed that adding FFR_{CT} analysis to plain CTA assessment improved diagnostic accuracy. Authors emphasized that FFR_{CT} had high negative predictive value and high sensitivity, indicating that coronary angiogram is not needed when FFR_{CT}'s results are normal, despite significant stenosis in CTA [15].

A refined version of FFR_{CT} calculation was evaluated by Nørgaard et al. [16] who studied 254 patients with coronary CTA, QCA and FFR measurements. The new approach was significantly quicker with a mean time to results of less than 4 h (depending on CT scan quality and CAD burden). On a per-vessel basis, authors found diagnostic accuracy of 86%, sensitivity of 84%, specificity of 86%, PPV of 61%, and NPV of 95% for FFR_{CT} under 0.8, which correlated well with FFR values under 0.8. They concluded that FFR_{CT} has high diagnostic performance compared with standard FFR measurements [16].

The multicenter Prospective Longitudinal Trial of FFR_{CT}: Outcome and Resource Impacts (PLATFORM) trial evaluated FFR_{CT} guided revascularization looking at clinical outcomes, cost/resource utilization and quality of life. Overall 584 patients with new onset of chest pain were included. Patients were randomized to standard evaluation (usual care arm) and CTA/FFR_{CT} testing. In the usual care arm, significantly more patients who underwent coronary angiography had no obstructive CAD when compared to CTA/FFR_{CT} care arm (73.3% vs. 12.4%; p < 0.0001). This observation was further confirmed in a propensity score matching analysis of 148 pairs (72% vs. 12%; p < < 0.0001). Most importantly there were no major adverse cardiac events over the 90-day follow-up

Table 2. Comparison of alternative methods of functional assessment of intermediate stenosis.

Comparator	FFR	iFR	QFR	FFR_{CT}
Invasiveness:				
Contrast	+	+	+	+
Invasive coronary angiography	+	+	+	–
Pressure wire	+	+	–	–
Adenosine	+	–	–	–
Data acquisition and processing time	8–10 min*	5–7 min*	3–5 min*	4–6 h*
Online/offline processing	Online	Online	Online	Offline
Costs	+++	++	+	++++

*Excluding standard invasive coronary angiography time and standard computed tomography angiography time; FFR — fractional flow reserve; FFR_{CT} — FFR calculated from computed tomography; iFR — instantaneous wave-free ratio; QFR — quantitative flow ratio

period for any patient in whom ICA was canceled based on negative results of the CTA/FFR_{CT} [36].

Further confirmation of FFR_{CT} diagnostic value comes from a recently published cohort of almost 700 patients, who underwent FFR_{CT} evaluation. The composite endpoint included all-cause death, MI, hospitalization for unstable angina, and unplanned revascularization. Patients were divided into four groups: 1) patients with coronary stenosis < 30% in CTA, who received optimal medical treatment (OMT); 2) patients with $FFR_{CT} > 0.8$, who also received OMT; 3) patients with $FFR_{CT} \leq 0.80$, who did not undergo any further testing and received OMT; 4) patients with $FFR_{CT} \leq 0.80$, who on the top of OMT were referred to ICA. Risk of MI was higher in group 3 than in group 4 (8% vs. 1.3%; $p < 0.001$), indicating that FFR_{CT} is an effective diagnostic tool to differentiate patients with intermediate coronary lesions who may benefit from invasive treatment [37].

In conclusion, the CTA/FFR_{CT} analysis is a safe diagnostic method characterized however, by moderate diagnostic value. In patients already scheduled for CTA, adding FFR_{CT} does not require additional imaging, radiation or medication [14–16]. Limitations of this method include long post-processing time, precluding online analysis and high cost. Additionally, the CTA dataset must be sent to a core laboratory to calculate FFR values. This is expensive and time-consuming. What is more, FFR_{CT} is feasible only in CTA eligible patients, precluding a significant share of the CAD population, such as patients with massive calcifications, atrial fibrillation, previous stent implantation and others [38]. Moreover, vessel size may affect FFR_{CT} values as well. Recently Gaur et al. [39] proved that volume-to-mass ratio, defined as total coronary vessel lumen volume relative to left ventricular mass, has a statistically significant influence on FFR_{CT}'s accuracy and specificity.

Conclusions

Functional assessment of coronary arteries remains a gold standard in the diagnosis of patients with intermediate coronary artery stenosis. In current clinical practice, the adoption of traditional wire-based FFR technology is slow and limited by clinical safety and economic constraints. QFR and FFR_{CT} are the new, less-/non-invasive computational methods that have recently emerged as promising diagnostic tools. The currently available body of evidence, though limited, provides solid grounds in recognizing these technologies as strong candidates to reduce the number of wire-based FFR examinations (Table 1). Advantages and disadvantages of above-mentioned diagnostic tools are summed up in Table 2.

It is thought herein, that all these methods will find their place in the management of patients with CAD. It seems that QFR and FFR_{CT} should be perceived as more complementary, rather than competitive modalities. While FFR_{CT} may lead to better identification of patients who would not benefit from ICA investigation, QFR may be used on-line to assess the hemodynamic significance of a lesion during ICA and eliminate risks associated with wiring of a coronary artery. It is essential to utilize cut-off values in which QFR has excellent agreement with FFR measurements ("grey-zone" concept). If results of the upcoming clinical validation will be positive, one may foresee a change in the current diagnostic algorithm by incorporating

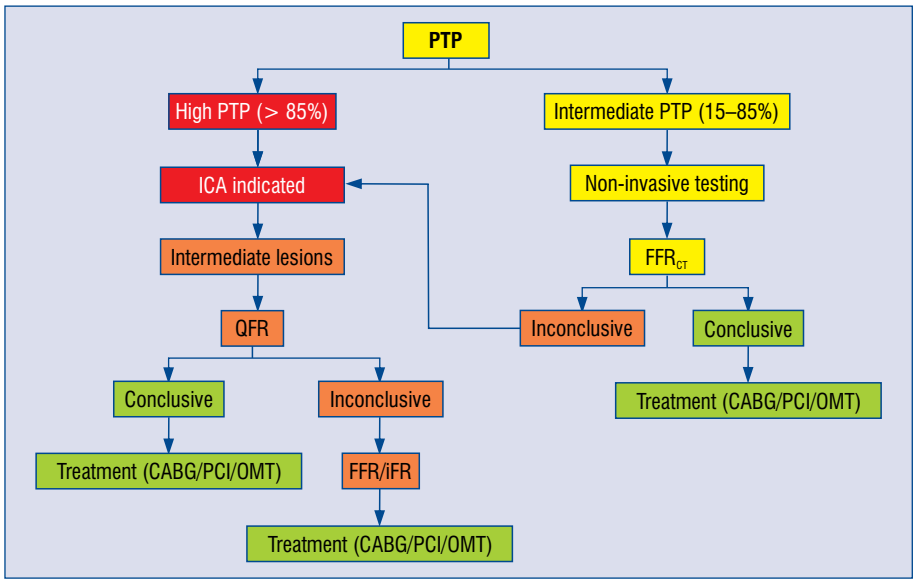


Figure 5. Proposed diagnostic algorithm; PTP — pre-test-probability of coronary artery disease; QFR — quantitative flow ratio; FFR — fractional flow reserve; iFR — instantaneous wave-free ratio; FFR_{CT} — FFR calculated from computed tomography; CABG — coronary artery bypass grafting; PCI — percutaneous coronary intervention; OMT — optimal medical treatment.

alternative methods for functional assessment of intermediate coronary lesions (Fig. 5).

Conflict of interest: None declared

References

1. Mendis S, Davis S, Norrving Bo. Organizational update: the world health organization global status report on noncommunicable diseases 2014; one more landmark step in the combat against stroke and vascular disease. Stroke. 2015; 46(5): e121–e122, doi: 10.1161/STROKEAHA.115.008097, indexed in Pubmed: 25873596.
2. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet. 2015; 385(9963): 117–171, doi: 10.1016/s0140-6736(14)61682-2.
3. Toth G, Toth B, Johnson N, et al. Revascularization decisions in patients with stable angina and intermediate lesions. Circ Cardiovasc Interv. 2014; 7(6): 751–759, doi: 10.1161/circinterventions.114.001608.
4. Biały D, Wawrzyńska M, Arkowski J, et al. Multimodality imaging of intermediate lesions: Data from fractional flow reserve, optical coherence tomography, near-infrared spectroscopy-intravascular ultrasound. Cardiol J. 2018; 25(2): 196–202, doi: 10.5603/CJ.a2017.0082, indexed in Pubmed: 28714527.
5. Dattilo PB, Prasad A, Honeycutt E, et al. Contemporary patterns of fractional flow reserve and intravascular ultrasound use among patients undergoing percutaneous coronary intervention in the United States: insights from the National Cardiovascular Data Registry. J Am Coll Cardiol. 2012; 60(22): 2337–2339, doi: 10.1016/j.jacc.2012.08.990, indexed in Pubmed: 23194945.
6. Dehmer GJ, Weaver D, Roe MT, et al. A contemporary view of diagnostic cardiac catheterization and percutaneous coronary intervention in the United States: a report from the CathPCI Registry of the National Cardiovascular Data Registry, 2010 through June 2011. J Am Coll Cardiol. 2012; 60(20): 2017–2031, doi: 10.1016/j.jacc.2012.08.966, indexed in Pubmed: 23083784.
7. Härle T, Zeymer U, Hochadel M, et al. Real-world use of fractional flow reserve in Germany: results of the prospective ALKK coronary angiography and PCI registry. Clin Res Cardiol. 2017; 106(2): 140–150, doi: 10.1007/s00392-016-1034-5, indexed in Pubmed: 27599974.
8. Ochała A, Siudak Z, Legutko J, et al. Percutaneous interventions in cardiology in Poland in the year 2014. Summary report of the Association of Cardiovascular Interventions of the Polish Cardiac Society AISN PTK. Postepy Kardiol Interwencyjnej. 2015; 11(3): 177–181, doi: 10.5114/pwki.2015.54009, indexed in Pubmed: 26677356.
9. Kumsars I, Narbute I, Thuesen L, et al. Side branch fractional flow reserve measurements after main vessel stenting: a Nordic-Baltic Bifurcation Study III substudy. EuroIntervention. 2012; 7(10): 1155–1161, doi: 10.4244/EIJV7I10A186, indexed in Pubmed: 22334314.
10. Curzen N, Rana O, Nicholas Z, et al. Does routine pressure wire assessment influence management strategy at coronary angiography for diagnosis of chest pain?: the RIPCORD study. Circ Cardiovasc Interv. 2014; 7(2): 248–255, doi: 10.1161/CIRCINTERVENTIONS.113.000978, indexed in Pubmed: 24642999.
11. Park E, Price A, Vidovich MI. Adenosine-induced atrial fibrillation during fractional flow reserve measurement. Cardiol J. 2012; 19(6): 650–651, indexed in Pubmed: 23224932.
12. Tu S, Barbato E, Köszegi Z, et al. Fractional flow reserve calculation from 3-dimensional quantitative coronary angiography and TIMI frame count: a fast computer model to quantify the functional significance of moderately obstructed coronary arteries. JACC Cardiovasc Interv. 2014; 7(7): 768–777, doi: 10.1016/j.jcin.2014.03.004, indexed in Pubmed: 25060020.
13. Morris PD, Ryan D, Morton AC, et al. Virtual fractional flow reserve from coronary angiography: modeling the significance of coronary lesions: results from the VIRTU-1 (VIRTUal Fractional Flow Reserve From Coronary Angiography) study. JACC Cardiovasc Interv. 2013; 6(2): 149–157, doi: 10.1016/j.jcin.2012.08.024, indexed in Pubmed: 23428006.

14. Koo BK, Erglis A, Doh JH, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. J Am Coll Cardiol. 2011; 58(19): 1989–1997, doi: 10.1016/j.jacc.2011.06.066, indexed in Pubmed: 22032711.
15. Min JK, Leipsic J, Pencina MJ, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. JAMA. 2012; 308(12): 1237–1245, doi: 10.1001/2012.jama.11274, indexed in Pubmed: 22922562.
16. Nørgaard BL, Leipsic J, Gaur S, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). J Am Coll Cardiol. 2014; 63(12): 1145–1155, doi: 10.1016/j.jacc.2013.11.043, indexed in Pubmed: 24486266.
17. Sen S, Escaned J, Malik IS, et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. J Am Coll Cardiol. 2012; 59(15): 1392–1402, doi: 10.1016/j.jacc.2011.11.003, indexed in Pubmed: 22154731.
18. Petraco R, Al-Lamee R, Gotberg M, et al. Real-time use of instantaneous wave-free ratio: results of the ADVISE in-practice: an international, multicenter evaluation of instantaneous wave-free ratio in clinical practice. Am Heart J. 2014; 168(5): 739–748, doi: 10.1016/j.ahj.2014.06.022, indexed in Pubmed: 25440803.
19. Petraco R, Hoef Tv, Nijjer S, et al. Baseline instantaneous wave-free ratio as a pressure-only estimation of underlying coronary flow reserve. Circ Cardiovasc Interv. 2014; 7(4): 492–502, doi: 10.1161/circinterventions.113.000926.
20. Davies JE, Sen S, Dehbi HM, et al. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. N Engl J Med. 2017; 376(19): 1824–1834.
21. Götberg M, Christiansen EH, Gudmundsdottir IJ, et al. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. N Engl J Med. 2017; 376(19): 1813–1823, doi: 10.1056/NEJMoa1616540, indexed in Pubmed: 28317438.
22. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2018.
23. Patel M, Calhoon J, Dehmer G, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease. J Nucl Cardiol. 2017; 24(5): 1759–1792, doi: 10.1007/s12350-017-0917-9.
24. Lee JM, Park J, Hwang D, et al. Similarity and difference of resting distal to aortic coronary pressure and Instantaneous wave-free ratio. J Am Coll Cardiol. 2017; 70(17): 2114–2123, doi: 10.1016/j.jacc.2017.09.007, indexed in Pubmed: 29050558.
25. Kobayashi Y, Johnson NP, Zimmermann FM, et al. Agreement of the resting distal to Aortic Coronary pressure with the Instantaneous wave-free ratio. J Am Coll Cardiol. 2017; 70(17): 2105–2113, doi: 10.1016/j.jacc.2017.08.049, indexed in Pubmed: 29050557.
26. Van't Veer M, Pijls NHJ, Hennigan B, et al. Comparison of Different Diastolic Resting Indexes to iFR: Are They All Equal? J Am Coll Cardiol. 2017; 70(25): 3088–3096, doi: 10.1016/j.jacc.2017.10.066, indexed in Pubmed: 29268922.
27. Papafaklis MI, Muramatsu T, Ishibashi Y, et al. Fast virtual functional assessment of intermediate coronary lesions using routine angiographic data and blood flow simulation in humans: comparison with pressure wire - fractional flow reserve. EuroIntervention. 2014; 10(5): 574–583, doi: 10.4244/EIJY14M07_01, indexed in Pubmed: 24988003.
28. Lansky AJ, Pietras C. Fractional flow reserve from 3-dimensional quantitative coronary angiography: fresh light through an old window. JACC Cardiovasc Interv. 2014; 7(7): 778–780, doi: 10.1016/j.jcin.2014.05.002, indexed in Pubmed: 25060021.
29. Tu S, Westra J, Yang J, et al. Diagnostic accuracy of fast computational approaches to derive fractional flow reserve from diagnostic coronary angiography: the international multicenter FAVOR pilot study. JACC Cardiovasc Interv. 2016; 9(19): 2024–2035, doi: 10.1016/j.jcin.2016.07.013, indexed in Pubmed: 27712739.
30. Xu Bo, Tu S, Qiao S, et al. Diagnostic accuracy of angiography-based quantitative flow ratio measurements for online assessment of coronary stenosis. J Am Coll Cardiol. 2017; 70(25): 3077–3087, doi: 10.1016/j.jacc.2017.10.035, indexed in Pubmed: 29101020.
31. Kołtowski Ł, Zaleska M, Maksym J, et al. Quantitative flow ratio derived from diagnostic coronary angiography in assessment of patients with intermediate coronary stenosis: a wire-free fractional flow reserve study. Clin Res Cardiol. 2018; 107(9): 858–867, doi: 10.1007/s00392-018-1258-7, indexed in Pubmed: 30128817.
32. Westra J, Tu S, Winther S, et al. Evaluation of coronary artery stenosis by quantitative flow ratio during invasive coronary angiography: the WIFI II study (wire-free functional imaging II). Circ Cardiovasc Imaging. 2018; 11(3): e007107, doi: 10.1161/CIRCIMAGING.117.007107, indexed in Pubmed: 29555835.
33. Westra J, Andersen BK, Campo G, et al. Diagnostic performance of in-procedure angiography-derived quantitative flow reserve compared to pressure-derived fractional flow reserve: the FAVOR II europe-japan study. J Am Heart Assoc. 2018; 7(14), doi: 10.1161/JAHA.118.009603, indexed in Pubmed: 29980523.
34. Spitaleri G, Tebaldi M, Biscaglia S, et al. Quantitative flow ratio identifies nonculprit coronary lesions requiring revascularization in patients with st-segment-elevation myocardial infarction and multivessel disease. Circ Cardiovasc Interv. 2018; 11(2): e006023, doi: 10.1161/CIRCINTERVENTIONS.117.006023, indexed in Pubmed: 29449325.
35. Chang Y, Chen L, Westra J, et al. Reproducibility of quantitative flow ratio: An inter-core laboratory variability study. Cardiol J. 2020; 27(3): 230–237, doi: 10.5603/CJ.a2018.0105, indexed in Pubmed: 30234896.
36. Douglas PS, Pontone G, Hlatky MA, et al. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFR(CT): outcome and resource impacts study. Eur Heart J. 2015; 36(47): 3359–3367, doi: 10.1093/eurheartj/ehv444, indexed in Pubmed: 26330417.
37. Nørgaard BL, Terkelsen CJ, Mathiassen ON, et al. Coronary CT angiographic and flow reserve-guided management of patients with stable ischemic heart disease. J Am Coll Cardiol. 2018; 72(18): 2123–2134, doi: 10.1016/j.jacc.2018.07.043, indexed in Pubmed: 30153968.
38. Zarins CK, Taylor CA, Min JK. Computed fractional flow reserve (FFTCT) derived from coronary CT angiography. J Cardiovasc Transl Res. 2013; 6(5): 708–714, doi: 10.1007/s12265-013-9498-4, indexed in Pubmed: 23934536.
39. Gaur S, Taylor CA, Jensen JM, et al. FFR derived from coronary CT angiography in Nonculprit Lesions of patients with recent stemi. JACC Cardiovasc Imaging. 2017; 10(4): 424–433, doi: 10.1016/j.jcmg.2016.05.019, indexed in Pubmed: 27743953.

VIA MEDICA

REVIEW ARTICLE

Cardiology Journal
2020, Vol. 27, No. 6, 836–847
DOI: 10.5603/CJ.a2018.0120

ISSN 1897–5593
eISSN 1898–018X

Cardiovascular complications after radiotherapy

Izabela Nabiałek-Trojanowska[1, 2], Ewa Lewicka[2], Anna Wrona[3], Anna M. Kaleta[2], Zuzanna Lewicka-Potocka[1, 2], Grzegorz Raczak[2], Rafał Dziadziuszko[3]

[1]First Department of Cardiology, Medical University of Gdansk, Poland
[2]Department of Cardiology and Electrotherapy, Medical University of Gdansk, Poland
[3]Department of Oncology and Radiotherapy, Medical University of Gdansk, Poland

Abstract

Over the past decades, effective cancer therapies have resulted in a significant improvement in the survival rates for a number of cancers and an increase in the number of cancer survivors. Radiation therapy is widely used in the treatment of cancer, and it can induce various cardiotoxicities that differ considerably from chemotherapy-induced cardiotoxicity. They occur primarily as late radiation-induced complications, several years from the end of anticancer treatment and present as coronary artery disease, heart failure, pericardial disease, valvular heart disease and arrhythmias. Patients who recovered from cancer disease suffer from cardiac complications of anticancer treatment, it affects the quality of their lives and life expectancy, especially if the diagnosis is delayed. These patients may present distinct symptoms of cardiac injury, resulting from radiation-induced neurotoxicity and altered pain perception, which makes diagnosis difficult. This review highlights the need for a screening programme for patients who have undergone radiation therapy and which will subsequently have a potentially profound impact on morbidity and mortality. (Cardiol J 2020; 27, 6: 836–847)

Key words: radiotherapy, ionizing radiation, radiation injuries, cardiotoxicity, neoplasms

Introduction

Radiotherapy, along with surgery and chemotherapy, is a therapeutic technique used for definitive and palliative treatment of cancer. Currently, radiotherapy is a useful tool for the treatment of breast cancer, mediastinal lymphomas, head and neck tumors, and cancers of the lung, oesophagus, thyroid gland, prostate, and the genitals [1]. Cardiovascular complications resulting from radiotherapy were first noted in the 1970s. In 1978, a study in a group of 46 patients who underwent chest radiation revealed that radiotherapy led to cardiac fibrosis (involving the endocardium, myocardium, and pericardium) which mostly manifested clinically with pericarditis [2]. An association between ionizing radiation doses delivered to the heart and cardiac injuries were first noted in 1983. At the same time, a need to reduce the radiation doses applied was emphasized [3]. Studies indicated that the patient survival rate after effective anticancer treatment depended on late complications of the therapy delivered [4]. In patients with Hodgkin lymphoma who underwent radiotherapy, the most common causes of death included a primary or secondary cancer and cardiovascular disease (CVD) [5, 6].

At the present time, established radiation-related cardiovascular complications include coronary artery disease (CAD), valvular heart disease, pericardial disease, heart failure (HF), right ventricular (RV) injury, arrhythmias, peripheral arterial disease, systemic hypertension, pulmonary hypertension, and thromboembolic disease [7]. These findings are the result of long-term follow-up of patients with a history of cancer with a relatively good prognosis for survival, particularly

Address for correspondence: Izabela Nabiałek-Trojanowska, MD, Department of Cardiology, Medical University of Gdansk, ul. Dębinki 7, 80–952 Gdańsk, Poland, tel: +48 781132796, +48 58 349 39 10, fax: +48 58 349 39 20, e-mail: izabela.nabialek@gumed.edu.pl

Received: 14.06.2018 Accepted: 11.10.2018

Hodgkin lymphoma and early-stage breast cancer [8, 9]. A meta-analysis of 25 studies that included patients who received anthracyclines as anticancer treatment in childhood revealed that adding radiotherapy increased the rate of asymptomatic systolic HF [10]. Similarly, an analysis of adult patients who received anthracyclines for the treatment of left-side breast cancer showed that adding radiation therapy increased the risk of HF, which occurred in 0.5% of all patients and in 2.6% of those who received chemotherapy combined with radiation therapy [11].

The mechanism of radiation-related cardiac injury is early acute inflammation of small and medium-sized vessels, with cardiomyocytes necrosis due to hypoxia as a result of microvascular damage and interstitial fibrosis. Reactive oxygen species (ROS) produced in irradiated cells play an important role in cardiac injury, and they may damage cellular membrane proteins and lipids [12–16].

The rate of radiation-related cardiovascular complications depends on several additional risk factors, such as total radiation dose (significantly higher for doses above 30 Gy), fractional radiation doses higher than 2 Gy per day, radiation doses delivered to the heart, the heart volume exposed to radiation, no shielding during radiotherapy, younger age at diagnosis, adjuvant chemotherapy (dependent on the total anthracycline dose), previous CVD, and cardiovascular risk factors [17, 18]. According to the American Society of Clinical Oncology, radiation-related cardiovascular complications develop in 10–30% of patients at 5 to 10 years after treatment [19].

For the last three decades, advances in radiation techniques have led to a reduction in the rates of radiotherapy complications. This was achieved by appropriate treatment planning with the use of three-dimensional (3D) imaging techniques, modern conformal radiation techniques with radiation beam intensity modulation (IMRT), and in the case of Hodgkin lymphoma, with a reduction of irradiated areas by radiation delivery only to involved fields (IFRT) or involved nodes (INRT). These methods allow for a reduction in the heart volume exposed to radiation [19, 20].

Radiation dose to the heart is now strictly controlled in radiotherapy planning systems, and details of radiation exposure are available for treating radiation oncologists in precise dose-volume histogram evaluations. Exact dose to each structure of the heart can also be visualized on each scan of planning computed tomography (CT), allowing for better prediction of early and late toxicity. Due to this progress and an understanding of the association between radiation dose and late cardiac complications of radiotherapy, doses to the heart are now much lower than in the past. In the three largest groups of patients treated with radiotherapy to the chest, typical mean doses to the heart for patients with breast cancer are in the range 1–3 Gy, for patients with lymphomas in the range of 1–10 Gy, and for patients with lung cancer, 1–20 Gy. These doses depend primarily on the anatomical location and stage of the tumor, as well as radiation techniques available in treatment facilities.

Coronary artery disease

Exposing the heart to ionizing radiation during anticancer therapy increases the risk of CAD. Damage to nerve endings caused by neurotoxicity of radiation therapy in the radiated fields is a factor impeding early diagnosis of CAD due to reduction of chest pain sensation in this group of patients. The risk of CAD increases with the radiation dose administered to the heart [21, 22]. The mechanism of radiation-related injury to coronary arteries is multifactorial and includes endothelial damage, atherosclerotic plaque rupture, thrombosis, and vasospasm [7, 12]. Coronary artery lesions associated with radiotherapy are typically located in the ostia and proximal vessel segments. For left- and right-sided breast cancer irradiation they mostly develop in the left anterior descending artery and right coronary artery, respectively, and in the left main coronary artery, the left circumflex artery, and the right coronary artery after mediastinal radiotherapy for Hodgkin lymphoma, corresponding to the areas exposed to radiation [7, 17, 23, 24]. In addition, myocardial perfusion defects are seen regardless of the coronary artery territories, which suggests microvascular damage. This was shown using technetium-99m sestamibi myocardial perfusion scintigraphy in 50% of the observed patients at 1 year following adjuvant radiotherapy for left-sided breast cancer [25].

Modern radiotherapy techniques are still being developed, which creates an opportunity to modify and minimize radiation doses delivered to normal tissue, thus reducing the rates of cardiovascular complications. At the present time, radiotherapy is based on 3D or 4D (accounting for respiratory motion) treatment planning with dose-volume histograms, depicting dose distribution in predefined anatomical areas of the heart. It is possible to delineate the contours of the pericardium and coronary arteries with the available imaging tech-

niques, such as CT or magnetic resonance imaging (MRI). As a result, it is possible to estimate the radiation dose delivered to the whole heart, coronary arteries, atria, ventricles and cardiac conduction system [26, 27].

Progression of CAD in these patients may vary. The disease may occur early, with symptoms of acute coronary syndrome and even sudden cardiac death, but it usually develops slowly and is detected approximately 15 years after treatment. A study based on the observation of 34,825 patients with breast cancer treated with radiotherapy in Sweden and Denmark in 1976–2006 showed that angina and myocardial infarction (MI) occurred with a higher rate in patients irradiated to the left breast compared to those irradiated to the right breast. Furthermore, the radiation dose to the whole heart was on average 6.3 Gy during left-sided radiotherapy and 2.7 Gy during right-sided radiotherapy, showing a relation between the radiation dose delivered to the heart and incident CAD [21]. CAD was found in 10.4% of patients followed for at least 20 years after mediastinal radiotherapy with the radiation dose ranging from 25 to 42 Gy [28].

A study performed on an animal model indicated that radiation therapy accelerated the development of coronary artery atherosclerosis related to hypercholesterolemia [29]. In addition, observation of a large population of patients after treatment for Hodgkin lymphoma revealed that angina, MI, and HF occurred at a higher rate in patients with hypercholesterolemia, diabetes mellitus, and a history of smoking. This analysis also showed that angina and HF occurred more frequently in patients treated at a younger age, below 20 years [6, 30]. A retrospective analysis of patients who underwent radiotherapy for Hodgkin lymphoma revealed that a higher risk of late cardiovascular complications of irradiation showed an association with a younger age, male sex, radiation dose delivered to the whole heart, and dose inhomogeneity [31]. Higher radiation dose homogeneity may be obtained using modern radiotherapy techniques and is associated with a lower risk of cardiac damage for the same radiation dose delivered to the heart. It is an important parameter when planning treatment with ionizing radiation.

In primary prevention of progressive coronary disease each patient after chest radiotherapy should be screened for classic cardiovascular risk factors, with adequate management and correction of modifiable risk factors. A model of screening for CAD depends on the Systemic Coronary Risk Estimation (SCORE) result and accompanying symptoms, and among cancer survivors, it does not differ from the general population [32, 33]. The main issue is the time to start a screening program, because radiotherapy leads to premature onset of CAD mainly in asymptomatic patients. A study on Hodgkin disease survivors, with no symptoms of CAD revealed left ventricular (LV) segment hypokinesis in rest echocardiography in 17% of patients who have had mediastinal radiation therapy with high doses of radiation (more than 35 Gy) [34].

A recent expert consensus statement from European Association of Cardiovascular Imaging and the American Society of Echocardiography [17] recommends echocardiographic evaluation in asymptomatic high-risk patients starting 5 years after radiation exposure and 10 years after exposure in the others, with reassessment every 5 years. According to this document, high-risk patients should also receive a functional non-invasive stress test for CAD detection within 5 to 10 years after completion of chest irradiation. This strategy was adopted in the present center, and as treadmill exercise electrocardiograms (ECGs) may not reflect the burden of CAD, patients who are at least 5 years after radiotherapy are referred for stress echocardiography (including the assessment of changes in LV global longitudinal strain).

Apart from stress echocardiography, either exercise or dobutamine, perfusion single-photon emission CT and MRI may reveal stress-induced LV wall motion abnormality [17]. For younger patients coronary CT angiography is a valuable option because of its high negative predictive value. Exposure to radiation is still an issue, however modern CT scanners allow for dose reduction. Another limitation of coronary CT angiography are advanced calcifications, which if significant may impede detection of coronary arteries stenosis [35]. Cardiac MRI is an excellent method for reliable assessment of cardiac structure and function, but it poses significant logistic and economic challenges.

Pharmacological treatment of CAD does not differ from the general population, it includes acetylsalicylic acid or double antiplatelet therapy after stent implantation, statin, beta-blocker and angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), if not contraindicated. Invasive treatment: percutaneous coronary intervention (PCI) with stent implantation is recommended in patients with acute coronary syndrome or stable CAD refractory to pharmacological therapy. Conservative treatment in these conditions leads to poorer prognosis [33].

In reference to cardiac surgery and coronary artery bypass grafting (CABG), some studies showed increased perioperative risk resulting from mediastinal fibrosis [36, 37], but new research indicates that previous radiotherapy does not increase surgical complications and does not impact long-term survival comparing to cancer-free patients in isolated CABG surgery. The utilization of internal thoracic artery for graft was reduced in the study group, which worsens outcome of CABG in the general population [38]. In patients who have undergone prior chest radiotherapy, CT should be performed before deciding on CABG to evaluate the degree of mediastinal fibrosis and potential calcifications in the ascending aorta and aortic arch, which could impede implantation of aortocoronary grafts. Moreover, regarding potential radiation damage to the internal thoracic artery, angiographic assessment of this artery should be performed. As valvular heart disease could also be a complication of radiotherapy, a detailed valve examination is necessary before CABG in order to avoid repeated sternotomy [38]. In a recent study, patients with prior mediastinal radiotherapy referred for surgical aortic valve replacement have had significantly worse long-term survival compared to a matched control group [37].

Pericardial disease

Currently, pericardial diseases occur less often as a complication of chest radiotherapy. These conditions include acute pericarditis, chronic pericarditis, chronic pericardial effusion, and constrictive pericarditis. They mostly develop in patients treated with a radiation dose of at least 50 Gy [39]. Treatment decisions depend on the type of pericardial disease and the clinical condition of the patient [3, 40].

Common symptoms of acute pericarditis include fever, chest pain related to body position and respiratory movements, pericardial effusion on echocardiography, and ST segment elevation and PR depression in multiple ECG leads. In a patient presenting with acute chest pain or elevated cardiac troponin level, it is necessary to rule out acute coronary syndrome by ECG and echocardiography with LV contractility assessment. Acute exudative pericarditis rarely occurs during radiotherapy, and it is related to inflammation and necrosis of a tumor located near the heart [17]. A study performed on an animal model showed that acute pericarditis developed within 6–48 h after irradiation with a 20–40 Gy dose [40]. Delayed acute pericarditis, either symptomatic or asymptomatic, may develop in 2–5% of patients at 2–145 months after chest radiotherapy. This condition very rarely leads to cardiac tamponade which requires pericardial drainage [7].

Hemodynamically stable patients are usually managed medically, initially with non-steroidal anti-inflammatory drugs and colchicine, followed by glucocorticoids and immunosuppressive drugs if the first-line treatment is ineffective. Spontaneous clearance of pericardial effusion usually takes up to 2 years [17]. Data from patients treated with older radiotherapy techniques indicate that pericardial disease developed in 10–12% of patients at 6 to 18 months after irradiation, with acute pericarditis in 35% of these cases [3, 40].

Patients with impending or actual cardiac tamponade require invasive treatment. Percutaneous pericardiocentesis with extended catheter drainage is considered the safest method to remove excess pericardial fluid in cancer patients, even in those with thrombocytopenia [41, 42]. Surgical drainage is an alternative approach but is associated with a higher perioperative risk.

Chronic pericarditis may occur from 6 months to 15 years after completion of radiotherapy and develops in up to 20% of patients treated with high radiation doses. This process is associated with organization of fibrinous exudates, fibrous adhesions, and collagenous thickening, predominantly of the parietal pericardium. The incidence of pericardial layer thickening following radiation therapy increases with time, affecting 33% of patients after more than 20 years [28, 43]. Its occurrence depends on the radiation dose administered to the whole heart, including both the right and the left atrium [24, 44].

Constrictive pericarditis develops in 4% to 20% of radiotherapy patients, particularly those treated with older techniques, and it usually requires pericardiectomy [17,43, 45, 46]. In suspicion of constrictive pericarditis, constrictive cardiomyopathy should be ruled out by echocardiography, chest X-ray, CT or MRI revealing thickening of pericardium, calcifications, abnormal interventricular septum movement, abnormal mitral valve flow pattern, or by right heart catheterization if these tests are inconclusive [47].

In the case of pericardial effusion, and especially its recurrence, it may be problematic to determine whether it is caused by radiotherapy, tumor progression or infection. Biochemical and microbial blood sample tests, polymerase chain reaction (PCR) are useful, but in some cases

pericardial fluid examination may be required in recognizing pericarditis etiology. According to the newest European Society of Cardiology (ESC) guidelines regarding pericardial disease, diagnosing of etiology should be performed in patients, who present with fever > 38°C, subacute development of symptoms, > 20 mm of fluid in imaging and low response to acetylsalicylic acid/non-steroid anti-inflammatory drug treatment [48].

Imaging and comparing of effusion density in pericardial cavity may be helpful in recognizing etiology: protein-rich fluid, consisting of blood e.g. in aortic aneurysm rupture or aortic dissection; high density fluid in lymph leakage; pericardium thickening in inflammation or thickening with calcification in constrictive pericarditis. Imaging by CT or MRI may reveal direct neoplastic infiltration or metastasis. Positron emission tomography individually or combined with CT (recommended), is helpful in the diagnoses of neoplasmatic etiology of pericarditis if fluodexyglucose uptake in tumor cells is observed.

The most common primary cancer in pericardium is mesothelioma, and benign tumors are lipoma and fibroma. Secondary malignancy comes mostly from lung cancer, breast cancer, melanoma, lymphoma and leukemia. The presence of cancer cells in pericardial fluid is associated with worse outcomes in lung cancer patients but such an association was not found in breast cancer patients [42]. Generally, the utility of the assessment of cancer markers in serum and in pericardial fluid has still not been proven, but a positive result of e.g. *EGFR* mutation test in pericardial effusion in lung cancer influences the decision about targeted anticancer therapy implementation [47]. Pericardium biopsy allows for histological diagnosis of cancer. Among patients with recognized cancer, the spreading of malignancy is a reason of pericarditis in approximately 30% of patients [47].

In cancer etiology of pericarditis, intrapericardial administration of cytostatic or sclerotic agent may decrease a frequency of fluid recurrence. As a palliative treatment, radiotherapy or pleuropericardiotomia alleviates symptoms of recurrent pericarditis.

Valvular heart disease

Valvular heart disease complicating radiotherapy develops in 10% of patients. Radiation-induced valve abnormalities are characteristically distributed, with thickening and calcifications located at the basal and medial parts of the leaflets, while leaflet tips and commissures are spared, allowing distinction from rheumatic disease. Calcification of the mitro-aortic curtain, the junction between the anterior mitral leaflet valve and the aortic root, is also characteristic for post-radiation damage [49]. A retrospective analysis of post-radiotherapy patients with Hodgkin lymphoma showed valvular lesions in 6.2% patients after an average 22 years of observation, with aortic stenosis in more than a half of these patients [22]. However, in another study of patients followed up for at least 20 years after mediastinal radiotherapy with a minimal radiation dose of 35 Gy, aortic stenosis was found in 16%, mitral regurgitation in 60%, and tricuspid regurgitation in 4% of patients in the study group [28]. Valvular lesions are more common on the left side of the heart than on the right side, independently of radiation dose [50]. In cases of severe valvular lesions requiring invasive treatment, transcatheter methods (e.g., transcatheter aortic valve implantation) are considered to be safer compared to conventional valve surgery due to mediastinal fibrosis and aortic calcifications which are common after radiotherapy.

Left ventricular dysfunction

Radiotherapy-induced cardiac damage leads to myocardial fibrosis [39, 51] which mostly results in LV diastolic dysfunction. The main mechanism underlying cardiomyocytes injury is microvascular damage. In addition, combining radiotherapy with cardiotoxic chemotherapy using anthracyclines, especially in young patients and in females with breast cancer, may also lead to LV systolic dysfunction. Advanced myocardial fibrosis may predispose to restrictive cardiomyopathy phenotype observed after radiation therapy, with the presence of severe diastolic dysfunction and symptoms of HF. A differential diagnosis from constrictive pericarditis is recommended by echocardiography, CT, MRI, and right heart catheterization, if required. The principle in diagnosis is reduced myocardial elasticity, that is due to impaired myocardial relaxation in restrictive cardiomyopathy and constricted chambers by pericardium with normal diastolic function in constrictive pericarditis. In restrictive cardiomyopathy transthoracic echocardiography reveals normal or thickened left and right ventricle, normal or reduced LV cavity, enlarged atria, restrictive transmitral filling pattern (E/A ratio > 2), and reduced peak early-diastolic mitral-annular velocities in tissue Doppler (e' < 8 cm/s) independent of respiration. Other imaging modalities, as CT or

MRI may detect structural changes in myocardium e.g. fibrosis and unthickened pericardial layer. Cardiac catheterization reveals increased RV systolic pressure (above 50 mmHg), and LV end-diastolic pressure (LVEDP) by 5 mmHg higher than RV end-diastolic pressure (RVEDP) [47].

Left ventricular systolic function is routinely assessed by LV ejection fraction (LVEF) measurement during echocardiography. The recommended method to evaluate LVEF is 3D echocardiography. If this method is not available, LVEF should be assessed by the 2D biplane Simpson method, based on contouring of the LV cavity during systole and diastole in the apical 4- and 2-chamber views. Disadvantages of this method include its dependence on the appropriate angle of transducer and the fact that it reveals relatively late impairment of LV systolic function.

A new method of an increasing significance is the assessment of LV global longitudinal strain (GLS) by 2D speckle tracking echocardiography (STE). In this technique, a percentage of cardiac muscle shortening in the longitudinal layer is assessed during one or three cardiac cycles. Newer software allows for distinguishing the inner and outer myocardial layers, what is important for diagnosis. Abnormalities within the inner (subendocardial) layer indicate mainly CAD etiology, but can be also present in patients with chemotherapy-induced cardiotoxicity. In turn, abnormalities within the outer (subepicardial) layer indicate myocardial inflammation, rarely cardiotoxicity. Apart from the longitudinal muscle layer, motion in the radial and circumferential myocardial layers may also be tracked by STE. These methods are also used for the assessment of RV function.

An analysis of patients after radiotherapy for chemotherapy-naive early stage of breast cancer showed a decrease in GLS and apical longitudinal strain after radiotherapy for left-sided breast cancer. In this group of patients, a compensatory increase in basal longitudinal strain was also observed. Other conventional echocardiographic parameters were not sensitive enough to show any changes of the LV systolic function. In patients after radiotherapy for right-sided breast cancer, speckle tracking analysis revealed decreased longitudinal strain in basal anterior segments [52]. The observed changes in longitudinal strain corresponded to the irradiated region of the heart. The study showed that assessment of longitudinal strain by STE is a more sensitive method in revealing LV systolic dysfunction compared to LVEF measurements and visual assessment of segmental wall motion abnormalities. A meta-analysis of 16 studies that included patients with HF, acute MI, and valvular heart disease showed a superior predictive value of GLS assessment compared to LVEF for predicting major adverse cardiac events [53].

A study of patients with Hodgkin lymphoma treated with a radiation dose of at least 35 Gy in comparison to the Framingham study population showed a decrease in the LV fractional shortening to less than 30% in 36% of patients in the study group and in 3% of subjects in the Framingham study population [28]. An MRI study showed that late gadolinium enhancement corresponded to the radiation fields within the heart, and that delivery of a radiation dose to the heart had an effect on the occurrence of radiation-induced cardiomyopathy [54]. A study in breast cancer patients revealed that the increase in the serum high-sensitive troponin T level depended on the total radiation dose delivered to the whole heart and the LV. Long-term implications of this finding are unknown and require further studies [55].

In 2011, Polish National Team of Cardiologic and Oncologic Supervision published recommendations regarding care for breast cancer patients [56]. The emphasis was put on prevention, early diagnosis, by highly specific and sensitive methods, and treatment of CVD. The limit of significant LV dysfunction was set on a drop of LVEF of 15%, to value less than 50%.

According to the 2016 ESC guidelines [7], an LVEF decrease by means of echocardiography of more than 10% to a value below the lower limit of normal values (LVEF < 50%) suggests cardiotoxicity. And a relative GLS reduction by more than 15% compared to the baseline may suggest the risk of cardiotoxicity. Both guidelines recommended ACE inhibitor therapy in patients with LVEF lower than 50%. Newer guidelines added monitoring of B-type natriuretic (BNP) peptide or NT-pro-BNP concentration to evaluate cardiac dysfunction and make decisions on starting pharmacological cardiovascular therapy or changing anticancer treatment.

These guidelines refer to complications of chemotherapeutic agents, and it should be noted that specific guidelines regarding radiation-induced heart disease are lacking. According to the 2017 American Society of Clinical Oncology (ASCO) guidelines, patients who were exposed to at least 30 Gy of irradiation containing the heart in the irradiated field, or those who underwent radiotherapy with less than 30 Gy with the heart in the irradiated

field but combined with anthracycline treatment are at increased risk of cardiac dysfunction [57].

If LV systolic dysfunction is detected, it is managed medically similar to other etiologies of HF, mostly with beta-blocker, ACE inhibitors or ARBs [51]. In patients with end-stage HF who underwent radiotherapy, the previous radiation therapy is not a contraindication to cardiac transplantation. Despite technical difficulties in performing the surgery due to severe mediastinal fibrosis in the irradiated regions, the survival rate after cardiac transplantation does not differ significantly from life expectancy after cardiac transplantation in radiotherapy-naive patients [36].

Right ventricular dysfunction

The RV is located immediately behind the anterior chest wall and thus it is most prone to the adverse effects of mediastinal radiotherapy. Although the latest cardiooncological guidelines mostly discuss LV function, it has been recently suggested that cardiovascular morbidity and mortality associated with oncological treatment is also related to the condition of the RV [58].

Radiation-induced RV damage is mainly caused by myocardial fibrosis and remodeling, damage to blood vessels, and accelerated coronary artery atherosclerosis [58]. In addition, radiotherapy--induced pericardial fibrosis may induce RV diastolic dysfunction followed by systolic dysfunction, as the RV is subjected to low afterload under normal conditions [59].

The risk factors for radiotherapy-induced damage to the RV include total and fractional radiation dose, irradiation method, tumor location, and concomitant diseases [58]. In breast cancer patients, the number of individuals with RV systolic dysfunction increases with time following treatment with anthracyclines, trastuzumab and/or radiotherapy [60]. Examination using the novel method of ultrasonic tissue characterization showed an increase in myocardial echogenicity related to the radiation dose. The study was performed in patients with left breast cancer and showed that the RV free wall was exposed to the highest radiation dose during radiotherapy [61]. The increase in RV free wall echogenicity was accompanied by a decreased tricuspid annular plane systolic excursion (TAPSE).

Right ventricular structure and function may be assessed by echocardiography and MRI. Echocardiographic parameters include TAPSE, RV fractional area change, lateral tricuspid annular systolic velocity (RV S'), RV free wall longitudinal strain, and RV wall thickness. The gold standard imaging tool is MRI which allows for precise evaluation of the RV structure and function including end-diastolic volume, end-systolic volume, and RV ejection fraction [62].

Arrhythmias

Electrocardiographic abnormalities and arrhythmias are recognized in 16–36% patients with a history of radiotherapy [7], including bradyarrhythmias, tachyarrhythmias, and various conduction disturbances. These arrhythmias are usually related to fibrosis involving the atria and the conduction system. An association was found between arrhythmic events and the radiation dose in the right atrium, the left atrium and the whole heart in patients treated with high dose radiation therapy for non-small-cell lung cancer [44].

Chemotherapy combined with radiotherapy may increase the arrhythmic risk. Many chemotherapeutic agents lead to the QTc interval prolongation (in particular arsenic trioxide, tyrosine kinase inhibitors, and doxorubicin). Electrolyte disturbances which are common during anticancer treatment (both primary and secondary to vomiting, diarrhoea and skin lesions after radiotherapy) and administration of other drugs that increase the QTc interval (antiemetics, antibiotics, antimycotics, psychotropic agents, and antiarrhythmic drugs) also favour arrhythmic events [7, 28].

Atrial fibrillation (AF) is the most common supraventricular arrhythmia induced by radiotherapy, chemotherapy and/or surgical treatment. Indications for chronic oral anticoagulation have to be considered in patients with AF, which may be problematic due to an elevated risk of both thromboembolic events and bleeding complications in patients with malignancies. Low molecular weight heparins, vitamin K antagonists, and novel oral anticoagulants may be used for anticoagulation [63, 64]. It should be noted that the CHA_2DS_2-VASc and HAS-BLED risk scores to evaluate the risk of thromboembolism and bleeding complications, respectively, have not been validated in cancer patients.

Radiotherapy-induced ventricular arrhythmias are caused by myocardial ischemia and LV dysfunction [7]. Similarly, sinus node dysfunction and atrioventricular conduction disturbances are the result of ischemia, myocardial fibrosis, and direct damage to the cardiac conduction system caused by irradiation [12, 43]. Right bundle branch block is most frequently seen after chest radiotherapy

because the right bundle is situated just under the endocardium and is most susceptible to irradiation-induced damage [16].

In summary, factors favouring the occurrence of arrhythmia such as previous heart disease, QTc prolonging drugs, electrolyte disturbances, kidney function, thyroid hormone level, and impaired hepatic metabolism have to be taken into consideration in patients undergoing radiotherapy. Serious arrhythmias and conduction disturbances need to be treated by either drug therapy or cardiac device implantation.

Peripheral arterial disease

In addition to the effect on the heart, radiotherapy delivered to the neck and mediastinum may also damage blood vessels located in the irradiated area. Mechanisms include direct damage to vessel walls, injury of *vasa vasorum*, fibrosis, and accelerated atherosclerosis [65]. Significant atherosclerotic lesions in either carotid or subclavian arteries were observed in 7.4% of patients at 17 years after radiation therapy. The average patient age at the time these vascular lesions were diagnosed was 34 years, and stroke or a transient ischemic attack occurred at an average age of 51 years [22]. Pathological lesions in femoral arteries developed not earlier than 5 years after radiotherapy of the abdominal and pelvic regions [66, 67]. In addition, irradiation of the abdominal cavity may lead to the development of arterial hypertension mediated by damage to renal vessels.

The severity of arterial damage depends on radiation dose and time since treatment [68]. It was also shown that conventional CAD risk factors including hypertension and hypercholesterolemia have a synergistic effect on the development of radiation-induced arterial disease, and this risk may be minimized with proper treatment [67]. Radiation-induced arterial disease is managed using the same approach as atherosclerotic disease, and the treatment includes use of acetylsalicylic acid, statin, and percutaneous and surgical interventions. Invasive treatment outcomes are similar in patients with or without a history of malignancy [66].

Arterial hypertension and orthostatic hypotension

Irradiation of the head or neck may result in disruption of baroreflex, which in the chronic phase is characterized by severe labile blood pressure (BP), and this condition is commonly referred to as the syndrome of baroreflex failure. The baroreflex normally functions via carotid stretch receptors to maintain heart rate and BP. The mechanism of radiation-induced baroreflex failure is direct damage of carotid sinus receptors and their afferent vagal branches or accelerated atherosclerosis and fibrosis within arterial walls. Decreased baroreflex sensitivity and inefficient inhibitory activity may result in increased sympathetic tone. More rarely, inadequate efferent baroreceptor activity may lead to orthostatic hypotension with syncope, BP drop during sleep and bradycardia.

Baroreflex failure syndrome presents with headache, anxiety, emotional lability, tachycardia, hypertension, orthostatic lightheadedness, and/or hypotensive episodes. There may be severe BP elevation, even exceeding 250 mmHg, which may cause complications such as cerebral hemorrhage or encephalopathy. The onset of increased BP may occur days or weeks from completion of radiotherapy [69]. In differential diagnosis tests to rule out secondary causes of hypertension (e.g., renal artery stenosis or parenchymal disease, pheochromocytoma, other endocrinopathies) should be performed.

Cardiovascular dysfunction in these patients can be detected by ambulatory BP monitoring demonstrating abnormalities in resting BP and increased BP variability. To confirm baroreflex failure, deep breathing, Valsalva maneuver and tests with intravenous administration of phenylephrine or sodium nitroprusside show abnormal BP pattern and a lack of reflex brady- and tachycardia in response to BP changes.

In acute phase primary treatment is antihypertensive therapy and in chronic phase inhibition of central noradrenergic neurotransmission (e.g. clonidine) is recommended. Orthostatic and post-exercise hypotension resulting from baroreflex disorder may be challenging in management of hypertension. Implantation of pacemaker should be considered in patients with malignant bradycardia due to vagotonia, and supplementation of fludrocortisone and dietary salt in case of hypotension [69–75].

Impaired cardio-autonomic functions which were not apparent clinically were shown by Goyal et al. [72] in neck irradiated patients due to cancer disease. The authors evaluated heart rate variability with time domain analysis of 5 min ECG recording. Postural cardiovascular reflexes were studied with changes in BP and heart rate with the lying to standing test. The present study revealed a reduction in overall time domain measures of heart rate variability and weakened postural reflexes in

neck irradiated patients. Whether decreased heart rate variability in neck irradiated patients reflects an independent risk of cardiovascular morbidity requires further investigation. Nevertheless, the dose of radiation delivered to the carotid sinus should be monitored and restricted, as well as radiation oncologists should be aware of baroreflex failure syndrome, as they often could be the first to diagnose it and detect it early.

Summary

Ongoing advances in oncology and treatment of malignant hematological diseases lead to the development of new therapeutic options that increase the proportion of patients with long-term survival chances. This increase in life expectancy of cancer survivors has led to an increased incidence of long-term complications of anticancer therapy, including adverse cardiovascular effects of radiotherapy. The aims of cardiooncology include the prevention, diagnosis, and treatment of CVDs in the population of oncological patients [7, 62, 76]. For patients treated with radiation therapy, there is a need for accurate recommendations regarding the planning and extent of cardiac screening for early diagnosis and effective treatment of cardiovascular complications of radiotherapy [5, 77, 78].

Currently, available data are provided from breast cancer and Hodgkin lymphoma groups, who reach relatively long-term survival. It is necessary to identify groups of patients with higher risk of radiation-induced cardiovascular complications and prepare for them a follow-up plan. It should be taken into consideration that assessment of cardiovascular risk based on the radiation dose delivered to the heart or the volume of the irradiated heart by comparing groups of patients treated with older and newer methods of radiotherapy is difficult, because of relevant differences in radiation techniques. Anyway, according to ASCO guidelines based on meta-analysis of available research, minimizing doses delivered to heart and volume of the irradiated heart is an essential step in the prevention of long-term complications of radiotherapy [57].

In patients who have undergone chest radiation therapy, evaluation based on signs and symptoms and echocardiographic surveillance should be implemented, starting 5 years after treatment in high-risk patients and 10 years in all other patients. Further reassessment should be performed every 5 years. Even if asymptomatic, high-risk patients should also be referred for functional non-invasive stress tests within 5 to 10 years after completing irradiation therapy [17, 42]. Pregnant women and those who are planning pregnancy should be carefully monitored, as gestation may unmask subclinical cardiotoxicity [35].

Another important issue is the treatment of comorbidities and reduction of modifiable cardiovascular risk factors necessary among those patients. According to the ESC guidelines regarding cardiovascular prevention for cancer survivors, recommendations include healthy diet, smoking cessation, reduction of body weight and regular aerobic exercises, which are especially helpful in prevention and treatment of cardiotoxicity [79].

Conflict of interest: None declared

References

1. Gustavsson A, Osterman B, Cavallin-Ståhl E. A systematic overview of radiation therapy effects in non-Hodgkin's lymphoma. Acta Oncol (Madr). 2003; 42(5-6): 605–619, indexed in Pubmed: 14596518.
2. Di Mattéo J, Vacheron A, Heulin A, et al. [Cardiac complications of thoracic radiotherapy]. Arch Mal Coeur Vaiss. 1978; 71(4): 447–452, indexed in Pubmed: 96762.
3. Vacheron A, Heulin A, Baubion N, et al. Cardiac complications of radiotherapy. Ann Cardiol Angeiol (Paris) [Internet. 1983; 32(7): 465–472, indexed in Pubmed: 6660823.
4. Cuzick J, Stewart HJ, Peto R, et al. Overview of randomized trials of postoperative adjuvant radiotherapy in breast cancer. Cancer Clinical Trials. 1987; 71(1): 7–14, indexed in Pubmed: 3539330.
5. Toltz A, Shin N, Mitrou E, et al. Late radiation toxicity in Hodgkin lymphoma patients: proton therapy's potential. J Appl Clin Med Phys. 2015; 16(5): 167–178, doi: 10.1120/jacmp.v16i5.5386, indexed in Pubmed: 26699298.
6. Aleman BMP, van den Belt-Dusebout AW, De Bruin ML, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. Blood. 2007; 109(5): 1878–1886, doi: 10.1182/blood-2006-07-034405, indexed in Pubmed: 17119114.
7. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J. 2016; 37(36): 2768–2801, doi: 10.1093/eurheartj/ehw211, indexed in Pubmed: 27567406.
8. Gaya AM, Ashford R. Cardiac complications of radiation therapy. Clin Oncol. 2005; 17(3): 153–159, doi: 10.1016/j.clon.2004.09.016.
9. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013; 368(11): 987–998, doi: 10.1056/NEJMoa1209825, indexed in Pubmed: 23484825.
10. Kremer L, Pal Hv, Offringa M, et al. Frequency and risk factors of subclinical cardiotoxicity after anthracycline therapy in children: a systematic review. Ann Oncol. 2002; 13(6): 819–829, doi: 10.1093/annonc/mdf167.
11. Valagussa P, Zambetti M, Biasi S, et al. Cardiac effects following adjuvant chemotherapy and breast irradiation in operable breast

cancer. Ann Oncol. 1994; 5(3): 209–216, doi: 10.1093/oxfordjournals.annonc.a058795, indexed in Pubmed: 8186169.
12. Wrona A, Dziadziuszko R, Jassem J. Red.) Szymański F, Filipiak K, Warszawa IP 2017: 137-158. Radioterapia a ryzyko powikłań ze strony układu sercowo-naczyniowego. Nieklasyczne czynniki ryzyka chorób układu sercowo-naczyniowego w gabinecie lekarza praktyka [Internet]. ITEM Publishing 2017: 137-158. Available from: http://bibliografia.gumed.edu.pl/cgi-bin/expertus.exe?KAT=f%3A%5Chidden%5Cexpertus%5Cparametr.02%5C&FST=data.fst&FDT=data.fdt&ekran=ISO&lnkmsk=2&cond=AND&mask=2&F_00=06&V_00=Nieklasyczne+czynniki+ryzyka+chor%F3b+uk%B3adu+sercowo-naczyniowego+w+gabinecie+l.
13. Stewart J, Fajardo L, Gillette S, et al. Radiation injury to the heart. Int J Radiation Oncol *Biology* Physics. 1995; 31(5): 1205–1211, doi: 10.1016/0360-3016(94)00656-6.
14. Rodemann H, Bamberg M. Cellular basis of radiation-induced fibrosis. Radiotherapy Oncol. 1995; 35(2): 83–90, doi: 10.1016/0167-8140(95)01540-w, indexed in Pubmed: 7569029.
15. Hendry JH, Akahoshi M, Wang LiS, et al. Radiation-induced cardiovascular injury. Radiat Environ Biophys. 2008; 47(2): 189–193, doi: 10.1007/s00411-007-0155-7, indexed in Pubmed: 18193445.
16. Bhattacharya S, Asaithamby A. Ionizing radiation and heart risks. Semin Cell Dev Biol. 2016; 58: 14–25, doi: 10.1016/j.semcdb.2016.01.045, indexed in Pubmed: 26849909.
17. Lancellotti P, Nkomo VT, Bergler-Klein J, et al. Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging. 2013; 14(8): 721–740, indexed in Pubmed: 23847385.
18. Marlière S, Vautrin E, Saunier C, et al. Radiation-related heart toxicity: Update in women. Ann Cardiol Angeiol (Paris). 2016; 65(6): 411–419, indexed in Pubmed: 27842711.
19. Carver JR, Shapiro CL, Ng A, et al. American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects. J Clin Oncol. 2007; 25(25): 3991–4008, doi: 10.1200/JCO.2007.10.9777, indexed in Pubmed: 17577017.
20. Kurowicki M, Zaucha R. Zastosowanie radioteraii w chłoniaku Hodgkina. Onkologia w praktyce klinicznej. 2014: 16–23.
21. McGale P, Darby SC, Hall P, et al. Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. Radiother Oncol. 2011; 100(2): 167–175, doi: 10.1016/j.radonc.2011.06.016, indexed in Pubmed: 21752480.
22. Hull MC, Morris CG, Pepine CJ, et al. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of hodgkin lymphoma treated with radiation therapy. JAMA. 2003; 290(21): 2831–2837, doi: 10.1001/jama.290.21.2831, indexed in Pubmed: 14657067.
23. Annest LS, Anderson RP, Li W, et al. Coronary artery disease following mediastinal radiation therapy. J Thorac Cardiovasc Surg. 1983; 85(2): 257–263, indexed in Pubmed: 6823143.
24. Orzan F, Brusca A, Conte MR, et al. Severe coronary artery disease after radiation therapy of the chest and mediastinum: clinical presentation and treatment. Heart. 1993; 69(6): 496–500, doi: 10.1136/hrt.69.6.496.
25. Gyenes G, Fornander T, Carlens P, et al. Detection of radiation-induced myocardial damage by technetium-99m sestamibi scintigraphy. Eur J Nuclear Med. 1997; 24(3): 286–292, doi: 10.1007/bf01728765.
26. Storey MR, Munden R, Strom EA, et al. Coronary artery dosimetry in intact left breast irradiation. Cancer J. 2001; 7(6): 492–497, indexed in Pubmed: 11769861.
27. Duane F, Aznar MC, Bartlett F, et al. A cardiac contouring atlas for radiotherapy. Radiother Oncol. 2017; 122(3): 416–422, doi:10.1016/j.radonc.2017.01.008, indexed in Pubmed: 28233564.
28. Heidenreich PA, Hancock SL, Lee BK, et al. Asymptomatic cardiac disease following mediastinal irradiation. J Am Coll Cardiol. 2003; 42(4): 743–749, indexed in Pubmed: 12932613.
29. Amromin GD, Gildenhorn HL, Solomon RD, et al. The synergism of x-irradiation and cholesterol-fat feeding on the development of coronary artery lesions. J Atheroscl Res. 1964; 4(4): 325–334, doi: 10.1016/s0368-1319(64)80043-0.
30. Glanzmann C, Kaufmann P, Jenni R, et al. Cardiac risk after mediastinal irradiation for Hodgkin's disease. Radiotherapy Oncol. 1998; 46(1): 51–62, doi:10.1016/s0167-8140(97)00125-4.
31. Hahn E, Jiang H, Ng A, et al. Late cardiac toxicity after mediastinal radiation therapy for hodgkin lymphoma: contributions of coronary artery and whole heart dose-volume variables to risk prediction. Int J Radiat Oncol Biol Phys. 2017; 98(5): 1116–1123, doi: 10.1016/j.ijrobp.2017.03.026, indexed in Pubmed: 28721895.
32. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery): Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. Circulation. 2007; 116(17): 1971–1996, doi: 10.1161/CIRCULATIONAHA.107.185700, indexed in Pubmed: 17901356.
33. Iliescu C, Tsitlakidou D, Giza D, et al. Primary Percutaneous Coronary Interventions in Cancer Patients. Cancer Res Front. 2017; 3(1): 64–71, doi:10.17980/2017.64.
34. Heidenreich PA, Kapoor JR. Radiation induced heart disease: systemic disorders in heart disease. Heart. 2009; 95(3): 252–258, doi:10.1136/hrt.2008.149088, indexed in Pubmed: 19144884.
35. Herrmann J, Lerman A, Sandhu NP, et al. Evaluation and management of patients with heart disease and cancer: cardio-oncology. Mayo Clin Proc. 2014; 89(9): 1287–1306, doi: 10.1016/j.mayocp.2014.05.013, indexed in Pubmed: 25192616.
36. Saxena P, Joyce LD, Daly RC, et al. Cardiac transplantation for radiation-induced cardiomyopathy: the Mayo Clinic experience. Ann Thorac Surg. 2014; 98(6): 2115–2121, doi: 10.1016/j.athoracsur.2014.06.056, indexed in Pubmed: 25443015.
37. Donnellan E, Masri A, Johnston DR, et al. Long-term outcomes of patients with mediastinal radiation-associated severe aortic stenosis and subsequent surgical aortic valve replacement: a matched cohort study. J Am Heart Assoc. 2017; 6(5): e005396, doi: 10.1161/JAHA.116.005396, indexed in Pubmed: 28476874.
38. Fender EA, Chandrashekar P, Liang JJ, et al. Coronary artery bypass grafting in patients treated with thoracic radiation: a case-control study. Open Heart. 2018; 5(1): e000766, doi: 10.1136//openhrt-2017-000766, indexed in Pubmed: 29531769.

39. Zhuang XF, Yang YM, Sun XL, et al. Late onset radiation-induced constrictive pericarditis and cardiomyopathy after radiotherapy: A case report. Medicine (Baltimore). 2017; 96(5): e5932, doi: 10.1097/MD.0000000000005932, indexed in Pubmed: 28151876.
40. Fajardo LF, Stewart JR. Experimental radiation-induced heart disease. Light microscopic studies. Am J Pathol. 1970; 59(2): 299–316, indexed in Pubmed: 5443637.
41. Vaitkus P, Herrmann HC, LeWinter MM. Treatment of Malignant Pericardial Effusion. JAMA: J Am Med Assoc. 1994; 272(1): 59, doi:10.1001/jama.1994.03520010071035.
42. El Haddad D, Iliescu C, Yusuf SW, et al. Outcomes of cancer patients undergoing percutaneous pericardiocentesis for pericardial effusion. J Am Coll Cardiol. 2015; 66(10): 1119–1128, doi: 10.1016/j.jacc.2015.06.1332, indexed in Pubmed: 26337990.
43. Nielsen KM, Offersen BV, Nielsen HM, et al. Short and long term radiation induced cardiovascular disease in patients with cancer. Clin Cardiol. 2017; 40(4): 255–261, doi: 10.1002/clc.22634, indexed in Pubmed: 28139844.
44. Wang K, Pearlstein KA, Patchett ND, et al. Heart dosimetric analysis of three types of cardiac toxicity in patients treated on dose-escalation trials for Stage III non-small-cell lung cancer. Radiother Oncol. 2017; 125(2): 293–300, doi: 10.1016/j.radonc.2017.10.001, indexed in Pubmed: 29050957.
45. Orzan F, Brusca A. Radiation-induced constrictive pericarditis. Associated cardiac lesions, therapy and follow-up. G Ital Cardiol. 1994; 24(7): 817–823, indexed in Pubmed: 7926379.
46. Syed FF, Schaff HV, Oh JK. Constrictive pericarditis: a curable diastolic heart failure. Nat Rev Cardiol. 2014; 11(9): 530–544, doi:10.1038/nrcardio.2014.100, indexed in Pubmed: 25072910.
47. Adler Y, Charron P, Imazio M, et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2015; 36(42): 2921–2964, doi: 10.1093/eurheartj/ehv318, indexed in Pubmed: 26320112.
48. Caforio ALP, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2013; 34(33): 2636–2648, doi:10.1093/eurheartj/eht210, indexed in Pubmed: 23824828.
49. Hering D, Faber L, Horstkotte D. Echocardiographic features of Radiation-Associated valvular disease. Am J Cardiol. 2003; 92(2): 226–230, doi:10.1016/s0002-9149(03)00546-0.
50. Adams M, Hardenbergh P, Constine L, et al. Radiation-associated cardiovascular disease. Crit Rev Oncol Hematol. 2003; 45(1): 55–75, doi:10.1016/s1040-8428(01)00227-x.
51. Madan R, Benson R, Sharma DN, et al. Radiation induced heart disease: Pathogenesis, management and review literature. J Egypt Natl Canc Inst. 2015; 27(4): 187–193, doi: 10.1016/j.jnci.2015.07.005, indexed in Pubmed: 26296945.
52. Tuohinen SS, Skyttä T, Poutanen T, et al. Radiotherapy-induced global and regional differences in early-stage left-sided versus right-sided breast cancer patients: speckle tracking echocardiography study. Int J Cardiovasc Imaging. 2017; 33(4): 463–472, doi: 10.1007/s10554-016-1021-y, indexed in Pubmed: 27873127.
53. Kalam K, Otahal P, Marwick TH. Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. Heart. 2014; 100(21): 1673–1680, doi: 10.1136/heartjnl-2014-305538, indexed in Pubmed: 24860005.
54. Umezawa R, Ota H, Takanami K, et al. MRI findings of radiation-induced myocardial damage in patients with oesophageal cancer. Clin Radiol. 2014; 69(12): 1273–1279, doi: 10.1016/j.crad.2014.08.010, indexed in Pubmed: 25246336.
55. Skyttä T, Tuohinen S, Boman E, et al. Troponin T-release associates with cardiac radiation doses during adjuvant left-sided breast cancer radiotherapy. Radiat Oncol. 2015; 10: 141, doi: 10.1186/s13014-015-0436-2, indexed in Pubmed: 26159409.
56. Opolski G, Krzakowski M, Szmit S, et al. Recommendations of National Team of Cardiologic and Oncologic Supervision on cardiologic safety of patients with breast cancer. The prevention and treatment of cardiovascular complications in breast cancer. The Task Force of National Consultants in Cardiology. Kardiol Pol. 2011; 69(5): 520–530, indexed in Pubmed: 21594854.
57. Armenian SH, Lacchetti C, Barac A, et al. Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2017; 35(8): 893–911, doi: 10.1200/JCO.2016.70.5400, indexed in Pubmed: 27918725.
58. Tadic M, Cuspidi C, Hering D, et al. Radiotherapy-induced right ventricular remodelling: the missing piece of the puzzle. Arch Cardiovasc Dis. 2017; 110(2): 116–123, doi: 10.1016/j.acvd.2016.10.003, indexed in Pubmed: 28117246.
59. Groarke JD, Nguyen PL, Nohria A, et al. Cardiovascular complications of radiation therapy for thoracic malignancies: the role for non-invasive imaging for detection of cardiovascular disease. Eur Heart J. 2014; 35(10): 612–623, doi: 10.1093/eurheartj/eht114, indexed in Pubmed: 23666251.
60. Grover S, Leong DP, Chakrabarty A, et al. Left and right ventricular effects of anthracycline and trastuzumab chemotherapy: a prospective study using novel cardiac imaging and biochemical markers. Int J Cardiol. 2013; 168(6): 5465–5467, doi: 10.1016/j.ijcard.2013.07.246, indexed in Pubmed: 24090744.
61. Tuohinen SS, Skyttä T, Virtanen V, et al. Detection of radiotherapy-induced myocardial changes by ultrasound tissue characterisation in patients with breast cancer. Int J Cardiovasc Imaging. 2016; 32(5): 767–776, doi: 10.1007/s10554-016-0837-9, indexed in Pubmed: 26757708.
62. Tadic M, Cuspidi C, Hering D, et al. The influence of chemotherapy on the right ventricle: did we forget something? Clin Cardiol. 2017; 40(7): 437–443, doi: 10.1002/clc.22672, indexed in Pubmed: 28191909.
63. Vedovati MC, Giustozzi M, Verdecchia P, et al. Patients with cancer and atrial fibrillation treated with doacs: A prospective cohort study. Int J Cardiol. 2018; 269: 152–157, doi: 10.1016/j.ijcard.2018.07.138, indexed in Pubmed: 30077526.
64. Laube ES, Yu A, Gupta D, et al. Rivaroxaban for stroke prevention in patients with nonvalvular atrial fibrillation and active cancer. Am J Cardiol. 2017; 120(2): 213–217, doi: 10.1016/j.amjcard.2017.04.009, indexed in Pubmed: 28549819.
65. Kalman PG, Lipton IH, Provan JL, et al. Radiation damage to large arteries. Can J Surg. 1983; 26(1): 88–91, indexed in Pubmed: 6821774.
66. Pherwani AD, Reid JA, Keane PF, et al. Synergism between radiotherapy and vascular risk factors in the accelerated development of atherosclerosis: a report of three cases. Ann Vasc Surg. 2002; 16(5): 671–675, doi: 10.1007/s10016-001-0117-5, indexed in Pubmed: 12183769.

67. Bergqvist D, Jonsson K, Nilsson M, et al. Treatment of arterial lesions after radiation therapy. Surg Gynecol Obstet. 1987; 165(2): 116–1120, indexed in Pubmed: 3603340.
68. Fajardo LF. Berthrong M. Vascular lesions following radiation. Pathol Ann. 1988; 23(1): 297–330, indexed in Pubmed: 3387138.
69. Timmers HULM, Wieling W, Karemaker JM, et al. Baroreflex failure: a neglected type of secondary hypertension. Neth J Med. 2004; 62(5): 151–155, indexed in Pubmed: 15366697.
70. Farach A, Fernando R, Bhattacharjee M, et al. Baroreflex failure following radiotherapy for head and neck cancer: a case study. Pract Radiat Oncol. 2012; 2(3): 226–232, doi: 10.1016/j.prro.2011.06.006, indexed in Pubmed: 24674125.
71. Goldstein DS, Cheshire WP. Beat-to-beat blood pressure and heart rate responses to the Valsalva maneuver. Clin Auton Res. 2017; 27(6): 361–367, doi: 10.1007/s10286-017-0474-y, indexed in Pubmed: 29052077.
72. Goyal M, Shukla P, Gupta D, et al. Cardiovascular sequel of neck irradiation in head and neck cancer patients. Int J Radiat Biol. 2017; 93(7): 711–716, doi: 10.1080/09553002.2017.1303217, indexed in Pubmed: 28376642.
73. Huang CC, Huang TL, Hsu HC, et al. Long-term effects of neck irradiation on cardiovascular autonomic function: a study in nasopharyngeal carcinoma patients after radiotherapy. Muscle Nerve. 2013; 47(3): 344–350, doi: 10.1002/mus.23530, indexed in Pubmed: 23386577.
74. Timmers HJ, Karemaker JM, Lenders JW, et al. Baroreflex failure following radiation therapy for nasopharyngeal carcinoma. Clin Auton Res. 1999; 9(6): 317–324, doi: 10.1007/BF02318378, indexed in Pubmed: 10638805.
75. Goldstein DS. Neurocardiology: therapeutic implications for cardiovascular disease. Cardiovasc Ther. 2012; 30(2): e89–106, doi: 10.1111/j.1755-5922.2010.00244.x, indexed in Pubmed: 21108771.
76. Krupicka J, Marková J, Pohlreich D, et al. Echocardiographic evaluation of acute cardiotoxicity in the treatment of Hodgkin disease according to the German Hodgkin's Lymphoma Study Group. Leuk Lymphoma. 2002; 43(12): 2325–2329, indexed in Pubmed: 12613519.
77. Andratschke N, Maurer J, Molls M, et al. Late radiation-induced heart disease after radiotherapy. Clinical importance, radiobiological mechanisms and strategies of prevention. Radiother Oncol. 2011; 100(2): 160–166, doi: 10.1016/j.radonc.2010.08.010, indexed in Pubmed: 20826032.
78. Senkus-Konefka E, Jassem J. Cardiovascular effects of breast cancer radiotherapy. Cancer Treat Rev. 2007; 33(6): 578–593, doi: 10.1016/j.ctrv.2007.07.011, indexed in Pubmed: 17764850.
79. Guddati AK, Joy PS, Kumar G. Analysis of outcomes of percutaneous coronary intervention in metastatic cancer patients with acute coronary syndrome over a 10-year period. J Cancer Res Clin Oncol. 2016; 142(2): 471–479, doi: 10.1007/s00432-015-2056-5, indexed in Pubmed: 26498773.

VIA MEDICA

REVIEW ARTICLE

Cardiology Journal
2020, Vol. 27, No. 6, 848–856
DOI: 10.5603/CJ.a2018.0067

ISSN 1897–5593
eISSN 1898–018X

Echocardiographic predictors of atrial fibrillation recurrence after catheter ablation: A literature review

Aleksandra Liżewska-Springer, Alicja Dąbrowska-Kugacka, Ewa Lewicka, Łukasz Drelich, Tomasz Królak, Grzegorz Raczak

Department of Cardiology and Electrotherapy, Medical University of Gdansk, Poland

Abstract

Background: *Catheter ablation (CA) is a well-known treatment option for patients with symptomatic drug-resistant atrial fibrillation (AF). Multiple factors have been identified to determine AF recurrence after CA, however their predictive value is rather small. Identification of novel predictors of CA outcome is therefore of primary importance to reduce health costs and improve long-term results of intervention. The recurrence of AF following CA is related to severity of left ventricular (LV) dysfunction, extent of atrial dilatation and fibrosis. The aim of this paper was to present and discuss the latest studies on the utility of echocardiographic parameters in terms of CA effectiveness in patients with paroxysmal and persistent AF.*

Methods: *PubMed, Google Scholar, EBSCO databases were searched for studies reporting echocardiographic preprocedural predictors of AF recurrence after CA. LV systolic and diastolic function, as well as atrial size, strain and dyssynchrony were taken into consideration.*

Results: *Twenty one full-text articles were analyzed, including three meta-analyses. Several echocardiographic parameters have been reported to determine a risk of AF recurrence after CA. There are conventional methods that measure left atrial size and volume, LV ejection fraction, parameters assessing LV diastolic dysfunction, and methods using more innovative technologies based on speckle tracking echocardiography to determine left atrial synchrony and strain. Each of these parameters has its own predictive value.*

Conclusions: *Regarding CA effectiveness, every patient has to be evaluated individually to estimate the risk of AF recurrence, optimally using a combination of several echocardiographic parameters.* (Cardiol J 2020; 27, 6: 848–856)

Key words: atrial fibrillation, catheter ablation, pulmonary vein isolation, echocardiography, predictors, recurrence

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia with a projected prevalence of 14–17 million by the year 2030 in the European Union [1]. AF remains one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity. With large increases in the burden of AF expected in the coming decades, better diagnosis and stratification of treatment selection is of paramount importance.

In recent years catheter ablation (CA) became a common treatment for patients with symptomatic, drug-resistant AF. The success rate of CA, defined as no AF relapse, of up to 70% for patients with paroxysmal AF and around 50% in those with persistent AF [1]. Multiple factors have been identified for AF recurrence after CA, such

Address for correspondence: Dr. Alicja Dąbrowska-Kugacka, Department of Cardiology and Electrotherapy Medical University of Gdansk, ul. Dębinki 7, 80–952 Gdańsk, Poland, e-mail: alicja.dabrowska-kugacka@gumed.edu.pl

Received: 26.03.2018 Accepted: 10.06.2018

as age, AF duration, ventricular and atrial function and comorbidities, however their predictive value is rather small [1, 2]. Therefore, new predictors of procedural outcome are needed for better identification of the most suitable candidates for CA.

Optimal patient selection is crucial to avoid unnecessary risk associated with CA, which can be accompanied by serious complications such as cardiac tamponade, stroke, pulmonary vein stenosis and atrio-esophageal fistula. Finally more accurate prediction can influence a decision for continuation of long-term oral anticoagulant and antiarrhythmic drug therapy.

Much of the information on ventricular and atrial function can be derived from cardiac magnetic resonance and tomography, but for practical reasons echocardiography is mostly used in clinical settings. Active deformation of the heart muscle during the cardiac cycle can be assessed with strain imaging from two-dimentional speckle tracking echocardiography (STE). This technique enables the recognition of subtle cardiac dysfunction and markers myocardial damage. The ultimate goal of these markers is to define different types of AF that are characterized by specific pathophysiology which may warrant early aggressive intervention and will respond favourably to CA. Recurrent AF after CA seems to be higher in patients with signs of atrial cardiomyopathy, also ventricular function plays a major role in the efficacy of this procedure.

The aim of this paper was to present and discuss the latest studies on echocardiographic parameters in terms of CA effectiveness in the treatment of patients with paroxysmal and persistent AF.

PubMed, Google Scholar, EBSCO databases were searched using the key words "echocardiographic predictors of atrial fibrillation after catheter ablation" or "echocardiography atrial fibrillation," "echocardiography pulmonary vein isolation" or "echocardiography catheter ablation." The search returned 104 abstracts, published from 1997 to 2017, all in English. After screening the abstracts, 42 were included for full-text analysis, according to their relevance to the subject. The criteria to include studies were as follows: (A) patients with paroxysmal or persistent AF referred for CA, (B) endpoint analysis taking into account the first recurrence of AF (defined as any documented episode of AF lasting > 30 s). Finally, 21 full-text articles were included in relation to CA in patients with AF. The following echocardiographic criteria were taken into consideration: left (LA) and right atrial (RA) size (diameter, area and volume), left ventricular (LV) ejection fraction (LVEF), parameters assessing LV diastolic dysfunction, atrial strain and dyssynchrony (Table 1).

Methods

Atrial size

It is established that LA size contributes to structural remodeling and therefore to atrial fibrosis [3]. Dilatation of the LA is an independent predictor of new onset AF [4]. It is also a well-known predictor of low success for CA in terms of AF recurrence [5–7].

Zhuang et al. [8] performed a meta-analysis of 22 studies which included over 3700 patients, which showed that an increased antero-posterior diameter of the LA was associated with a higher risk of AF recurrence after CA. The antero-posterior diameter of LA before CA, obtained from the parasternal long-axis view, was 35–50 mm. In patients with arrhythmia recurrences it was 1.87 mm larger than in those with successful pulmonary vein isolation [8]. According to European expert consensus from 2012 the LA diameter over 50–55 mm indicates limited success of CA [6]. In a study performed by Liao et al. [9] on 589 patients with paroxysmal AF, LA diameter over 43 mm and LV systolic diameter over 31 mm were the best cut-off values for predicting AF progression after CA. Their predictive value was highest when both of the above-mentioned diameters were exceeded [9]. LA dilation can be asymmetric and the antero-posterior dimension underestimates and does not truly reflect LA size. Studies focusing on LA area, however, did not confirm its predictive utility. Tomas at al. [10] found that LA area > 24 cm^2 did not predict AF recurrence at 12 month follow up. Njoku et al. [11] in a meta-analysis of 21 observational studies encompassing 3850 patients reported that patients with AF recurrence had larger mean left atrial volume (LAV) and LAV index (LAVi) compared to patients with no arrhythmia relapse. Moreover, they found that increased LAV/LAVi was independently associated with frequent AF recurrences after CA. There was a 3% increase in the odds of AF relapse per unit increase in LAV/LAVi. Shin et al. [12] found that LAVi of 34 mL/m^2 showed a sensitivity of 70% and a specificity of 91% to predict AF recurrence.

Atrial fibrillation is a biatrial disease. RA, with its enlargement and remodeling also involved in AF relapse [13]. Moon et al. [13] reported that increased RA volume index (RAVi) might affect early AF recurrence (within 3 months) after CA and RAVi over 78 mL/m^2 predicted the early recurrence with

Table 1. Studies about the predictive echocardiographic factors of atrial fibrillation recurrence post-catheter ablation.

Total patients (n)	Study type	Paroxysmal AF (n)	Persistent AF (n)	LVEF [%]	Median follow-up [months]	AF recurrences after CA (n)	Prognostic ECHO parameter	Reference
ARIAL SIZE								
3750 (22 studies)	Meta--analysis	2274	1476	NS	6–30 ± 13	NS	LAD was 1.87 mm higher in patients with arrhythmia recurrences	Zhuang et al. 2011
1425 (9 studies)	Meta--analysis	611	544	> 50	17 (mean)	NS	Higher mean LAVi (using ECHO, CT, or MRI)	Njoku et al. 2017
1559 (11 studies)	Meta-analysis	913*	537*	> 50	17 (mean)	NS	Higher mean LAV (using ECHO, CT, or MRI)	
2886 (13 studies)	Meta-analysis	1932	960	> 50	18	NS	Higher mean LAV/LAVi (using ECHO, CT, or MRI)	
470	Retrospective	196	274	> 50	24.3 ± 18	284 (60.6%)	RAD > 35.5 mm (in PAF with LAD > 35 mm)	Nan Wen et al. 2017
LEFT VENTRICULAR SYSTOLIC DYSFUNCTION								
368	Retrospective	170	198	≤ 40 (111 patients), > 50 (157 patients with isolated LVDD), 100 patients with normal LV function	13	NS	LVEF ≤ 40%	Cha et al. 2011
230	Retrospective	80	150	< 50 (97 patients), ≥ 50 (133 patients)	11	NS	LVEF was not a risk factor	Black-Maier et al. 2017
363	Prospective	118	245	≤ 35	37.8	60 (37%)	LVEF ≤ 25%	Marrouche et.al. 2018
LEFT VENTRICULAR DIASTOLIC DYSFUNCTION								
198	Retrospective	173	25	> 50	12	76 (38%)	Average E/e' > 13 (during sinus rhythm)	Hirai et al. 2014
215	Prospective	113	102	> 50	12 ± 6	38 (18%)	Average E/e' > 14	Masuda et al. 2017
22	Retrospective	5	17	> 50	21 ± 12	9 (41%)	E/e' ≥ 15	Okamatsu et al. 2015

→

Table 1 (cont.). Studies about the predictive echocardiographic factors of atrial fibrillation recurrence post-catheter ablation.

Total patients (n)	Study type	Paroxysmal AF (n)	Persistent AF (n)	LVEF (%)	Median follow-up [months]	AF recurrences after CA (n)	Prognostic ECHO parameter	Reference
232	Retrospective	152	80	> 50	36	59 (25%)	LVDD defined as: septal e″< 8 lateral e″ < 10 LAV ≥ 34 mL/m^2 (risk factor of VLR)	Onishi et al. 2017
124	Prospective	70	54	> 50	12	42 (34%, early- during first week after PVI), 26 (27%, late)	E/A ratio (in early recurrence)	Kosiuk et al. 2014
LEFT ATRIAL STRAIN								
686 (8 studies)	Meta-analysis	529	157	> 50	11	232 (94.9%)	LA strain < 22.8% (using QRS or P analysis, using different software packages)	Ma et al. 2016
100	Retrospective	68	32	> 50	12	26 (26%)	Basal LA lateral strain < 25.3%	Yasuda et al. 2015
102	Retrospective Prospective	0	102	> 50	15	57 (56%)	LA strain < 10% (during an episode of persistent AF)	Parwani et al. 2017
42	Prospective	42	0	> 50	14 ± 7	12 (29%)	LA global peak area strain (3D-GASs) < 28.9% (measured in systole, determined by 3D speckle tracking)	Mochizuki et al. 2017
OTHER PARAMETERS								
25	Retrospective	25	0	> 42	20 ± 9	7 (28%)	LA mechanical dyssynchrony (speckle tracking strain analysis)	Loghin et al. 2013
132	Retrospective	132	0	> 50	23 ± 7	38 (28.8%)	FMR ≥ 1 (regurgitation jet area to LA area during sinus rhythm)	Qiao et al. 2016

*1 study not stated; 3D-GASs —left atrial global peak area strain in systole determined by three-dimensional speckle tracking echocardiography; A — late mitral inflow velocity assessed by pulsed wave Doppler; AF — atrial fibrillation; CA — catheter ablation; CT — computed tomography; E — early mitral inflow velocity assessed by pulsed wave Doppler; E/A — mitral early to late diastolic peak ratio assessed by pulsed wave Doppler; e' — early diastolic mitral annular velocity assessed by tissue Doppler; e' — early diastolic mitral annular velocity assessed by tissue Doppler; FMR — functional mitral regurgitation; LA — left atrium; LAD — left atrial diameter; LAV — left atrial volume; LAVi — left atrial volume index; LV — left ventricular; LVDD — left ventricular diastolic dysfunction; LVEF — left ventricular ejection fraction; MRI — magnetic resonance imaging; n — number of patients; PAF — paroxysmal AF; PVI — pulmonary vein isolation; RAD — right atrial diameter assessed in the 4-chamber apical view; VLRs — very late recurrences (> 12 months)

74% sensitivity and 68% specificity [13]. Wen et al. [14] found that RA size predicted successful CA in patients with paroxysmal AF and LA horizontal diameter (determined as the measurement from the middle of mitral isthmus to the LA roof in the 4-chamber apical view) enlargement over 35 mm. RA was measured from the middle of tricuspid isthmus to the RA roof in the 4-chamber apical view, and when this diameter was below 35.5 mm it predicted AF recurrence-free survival at over 2-year follow up. Although a large cohort (over 400 patients) was examined, the results might be applicable only to an Asian population.

Left ventricular systolic function

In previous years several trials comparing amiodarone with CA in AF patients with heart failure (HF) and reduced ejection fraction (HFrEF) showed ablation to be superior at maintaining sinus rhythm [15, 16]. However the efficacy of CA in HFrEF patients with AF is still a matter of debate. Development of AF in HFrEF patients occurs due to eccentric remodeling of the LA. In this group an increase in LA diameter and volume was observed. The underlying electrical substrate driving to AF is likely different than in patients with HF and preserved ejection fraction, where LA stiffness is dominant [17].

In a study performed by Cha et al. [18] three groups of patients with AF undergoing CA were analyzed: 111 with LV systolic dysfunction (LVEF ≤ 40%), 157 with isolated LV diastolic dysfunction (LVEF > 50%) and 100 individuals with normal LV function. The authors reported that AF elimination rate was significantly lower in patients with systolic dysfunction (62%, $p = 0.002$) and non-significantly lower in those with diastolic dysfunction (75%, $p = 0.15$) when compared with the group with normal LV function.

Black-Maier et al. [16] compared two groups of about 100 patients with LVEF of less and over 50% and showed no significant differences in the rates of atrial arrhythmia recurrence between HF patients with preserved and reduced ejection fraction (33.9% vs. 32.6%; $p = 0.8$) at 1-year follow up. The contradictory result may be due to differences in the study population enrolled. Patients in the Black-Maier et al. [16] study were older and were more likely to have hypertension and diabetes mellitus.

The efficacy of CA in patients with HFrEF and AF was uncertain, until the lately published breakthrough CASTLE-AF trial [19]. It was a multicenter, randomized, controlled trial to assess whether CA lowers morbidity and mortality as compared with medical therapy (rate or rhythm control) in patients with coexisting AF and medically managed HF. The study included almost 400 patients with symptomatic paroxysmal or persistent AF and HF in the New York Heart Association class II–IV, LVEF of 35% or less and an implanted defibrillator. Mortality and hospitalization for worsening HF was significantly reduced in patients treated with CA. After 5 year follow-up sinus rhythm was maintained in 63% of patients in the ablation group vs. 22% in the medically treated group ($p < 0.001$). The study also revealed that patients with LVEF of less than 25% were less likely to benefit from ablation than those with LVEF between 25% and 35%. It would be interesting to determine the success rate of CA in patients with advanced HF but preserved ejection fraction.

Left ventricular diastolic dysfunction

Left ventricular diastolic dysfunction may indicate an increase in LV filling pressure, which can influence LA remodeling over the long term [20]. Wall stress due to increased atrial pressure plays an important role in the development of atrial electrical and structural remodeling. Impaired diastolic function has also been reported to be associated with AF recurrences [21]. According to guidelines of the American Society of Echocardiography, LV diastolic dysfunction can be evaluated and graded by mitral inflow assessed by pulsed wave Doppler, tissue Doppler of LV walls, and LA size [22].

In 2014 Hirai et al. [23] reported that elevated LA pressure, as determined by increased average E/e' index (E — early transmitral flow velocity obtained by pulsed wave Doppler; e'— early diastolic mitral velocity measured by tissue Doppler; averaged annular septal and lateral values), was the only echocardiographic parameter that predicted AF recurrence after CA. The E/e' value over 13 indicated increased risk of AF relapse during 12 month follow up.

Three years later Masuda et al. [24] reported that patients with E/e' > 14 before CA more frequently developed recurrent atrial tachyarrhythmias after single and multiple procedures. It was the first study demonstrating that patients with high E/e' ratio, along with age, female sex, low body mass index, and persistent AF more frequently presented low-voltage areas within the LA predisposing to AF, when endocardial voltage mapping was performed during the CA procedure. The relationship between higher E/e' ratio and the presence of low voltage areas in the LA may indicate

that higher E/e' is associated with advanced atrial arrhythmogenic substrate outside the pulmonary veins. This might explain AF recurrences even after a properly performed (without reconnections) pulmonary vein isolation.

Finally Okamatsu et al. [25] who examined 24 patients with hypertrophic cardiomyopathy demonstrated that E/e' ratio was the only predictor of AF recurrence following pulmonary veins isolation (PVI). Patients with E/e' ≥ 15 had a significantly higher risk of AF recurrence than those with E/e' < 15. Thus, patients with AF and mild or moderate LV diastolic dysfunction (E/e' < 15) are better candidates for PVI than those with a restrictive inflow pattern.

In a study performed by Onishi et al. [26] LV diastolic dysfunction at baseline was the only independent risk factor of late AF recurrence, defined as first AF relapse after more than 12 months subsequent to CA. The authors defined LV diastolic dysfunction very strictly and patients had to fulfill all three of the following criteria: early diastolic septal annular velocity e' < 8 cm/s, lateral annular velocity e' < 10 cm/s and LAVi ≥ 34 mL/m^2. After a single CA procedure, reconnections of pulmonary veins could affect recurrence of AF. To minimize the influence of pulmonary vein reconnections, risk factors of late recurrences after multiple CA procedures, not only after a single session were examined. LV diastolic dysfunction appeared to be the only risk factor of late AF relapses.

Kosiuk et al. [27] showed that E/A mitral inflow pattern (early to late mitral inflow velocity ratio, assessed by pulsed-wave Doppler at the level of the mitral valve), which is associated with LV diastolic dysfunction, was the best pre-procedural predictor of short-term AF recurrence during the first week after PVI. An E/A ratio of 1.35 was the cut-off value with the highest sensitivity and specificity for predicting early AF recurrence. In contrast to Onishi et al. [26], the authors reported that none of the parameters evaluating LV diastolic function predicted long-term PVI result (defined as any documented AF episode within a 3–12 month period after ablation). This discrepancy may be due to different definitions of LV diastolic dysfunction applied in both studies. Moreover, Kosiuk et al. [27] analyzed the results of CA after only a single procedure, and it can also explain the contradictory results because, as mentioned above, late AF recurrences are mainly due to pulmonary vein reconnections [28, 29]. Finally, a limited number of patients with severe LV diastolic dysfunction might preclude evaluation of other parameters, like E/e' ratio as predictors of both, short- and long-term AF recurrences after CA.

Left atrial strain

Schneider et al. [30] evaluated results of tissue Doppler imaging (TDI)-based LA strain analysis in patients with AF for the prediction of successful CA. The authors showed that patients with higher atrial strain and strain rate after CA appear to have a greater likelihood of maintaining sinus rhythm. Peak strain and strain rate were measured at each mid-LA segment one day prior to, within 24 hours, and 3 months after CA. A value of 20% for atrial septal systolic strain obtained before the procedure predicted sinus rhythm maintenance after CA, but with rather low sensitivity (57%) and specificity (56%). This method, however, is prone to angulation error and suffers from variable reproducibility. Moreover, it does not allow distinguishing active myocardial contraction from its passive motion.

Two-dimensional STE (2D-STE) is angle independent and thus more useful for LA strain analysis [31]. There are several studies indicating that LA strain has higher predictive value than LA size obtained from conventional echocardiography [31, 32]. The LA strain reflects LA reservoir, conduit and booster pump function. Furthermore, it correlates with the extent of LA fibrosis, especially in patients with persistent AF [7, 33].

A meta-analysis of 8 studies, which included 686 patients with paroxysmal AF showed that global LA strain is useful to identify individuals at high risk of AF recurrence after CA [34]. This analysis included both patients with sinus rhythm or AF at baseline, before PVI. In the group with AF, the beginning of QRS was set as the zero strain point. In patients with sinus rhythm the trigger for strain analysis was put either at the onset of QRS complex or P-wave. LA peak positive strain of less than 22.8% predicted AF recurrence with 78% sensitivity and 75% specificity. These results were independent of the applied method of LA strain analysis: from the beginning of QRS or P-wave, as well as software package used.

Left atrial strain measured on LA lateral wall by 2D-STE might be the most useful parameter for predicting successful AF ablation as it represents pure LA contractile function [35]. Yasuda et al. [35] indicated a significant prognostic value of basal LA lateral total strain, both in patients with sinus rhythm and AF during examination. The authors set the zero strain point at the beginning of QRS complex in the group with AF and at P wave in the group with sinus rhythm. The total strain

was calculated as follows: positive peak strain – negative peak strain. They reported that a value below 25.3% in basal LA lateral strain showed 81% sensitivity and 72% specificity for predicting AF recurrence after CA [35].

Most of the studies included in the mentioned meta-analysis [34] assessed patients with mainly paroxysmal or different types of AF. Parwani et al. [36] reported that low LA peak positive strain (< 10%) during an episode of persistent AF was strongly linked to recurrence of AF after one or even after two CA procedures.

Finally, some results suggest that three--dimensional STE (3D-STE) is potentially more accurate than 2D-STE for assessment of LA dysfunction in patients with AF [37, 38]. Mochizuki et al. [39] assessed patients with paroxysmal AF and found that global LA strain determined by 3D-STE less than 28.9% was a predictor of AF recurrence after the first-time CA Moreover, 3D-STE global LA strain was a better predictor of AF relapse after CA than LA strain obtained by 2D-STE. Three-dimensional strain analysis reflects LA function in many directions: not only longitudinal, but also circumferential and area strains. This can explain its superiority over 2D-STE.

Left atrial mechanical dyssynchrony

The LA mechanical dyssynchrony, which clearly indicates the presence of atrial structural and electrical remodeling, can predict recurrence of AF after CA in patients with paroxysmal AF [40, 41]. It can be determined by different echocardiographic methods.

Den Uijl et al. [41] reported that total atrial conduction time (PA-TDI), reflecting atrial electrical remodeling, was an independent predictor of AF recurrence after PVI. Total atrial conduction time was obtained by measuring the time delay between the onset of the P-wave on the surface electrocardiogram and the peak A'-wave of spectral tissue Doppler tracing on LA lateral wall. The prolonged value of 146 ± 20 ms was associated with AF recurrence after CA (for comparison PA-TDI in healthy subjects was 78 ± 7 ms) [42]. Similarly, Fukushima et al. [43] found that PA-TDI was an independent predictor of AF recurrence in patients with paroxysmal AF. They reported 2.5--fold higher rate of AF relapses in patients with PA-TDI duration > 151.3 ms. Evranos et al. [44] demonstrated a relationship between PA-TDI on LA lateral wall and recurrence of AF in patients treated with cryobaloon ablation. PA-TDI over 125 ms predicted AF recurrence with 80% sensitivity and 90% specificity. Unlike den Uijl et al. [41] they defined PA-TDI as a time interval from the onset of P wave on the surface electrocardiogram to the beginning of the A' wave.

Loghin at al. [40], used an algorithm based on 2D-STE — the vector velocity imaging (VVI) and looked at the timing of peak longitudinal strain obtained on opposing LA walls during atrial contractile phase. They found that maximum opposing walls delay of over 51 ms predicted AF recurrence after CA with 89% sensitivity and 72% specificity. Unfortunately, the study was retrospective and based on a small cohort of 25 patients.

Sarvari et al. [45] measured the dispersion of LA contraction duration, defined as the time difference from the peak of P wave on the surface electrocardiogram during sinus rhythm to maximum LA shortening assessed by 2D-STE strain (peak negative longitudinal strain). The standard deviation of contraction durations measured in 18 LA segments was defined as LA mechanical dispersion. The authors reported that patients with AF relapse and normal (LAV 25 ± 10 mL/m^2) presented with significantly greater LA mechanical dispersion compared with patients after successful CA (38 ± 14 ms vs. 30 ± 12 ms; $p < 0.001$). Therefore LA mechanical dispersion can be a useful tool to predict AF recurrence after CA in patients with structurally normal heart.

Functional mitral regurgitation

Qiao et al. [46] reported that functional mitral regurgitation, defined as regurgitation jet area to LA area ratio ≥ 0.1 in subjects without any primary valvular disease, independently predicted long-term outcomes post ablation in patients with paroxysmal AF. Functional mitral regurgitation was strongly correlated with the presence and extent of low voltage zones within the LA, assessed invasively prior to ablation.

Conclusions

Several echocardiographic parameters have been reported to determine the risk of AF recurrence after CA. These parameters reflect morphology, function and myocardial remodeling in patients with AF. There are conventional methods that measure LA size and volume, LVEF, parameters assessing LV diastolic dysfunction, and methods using more innovative technologies based on STE to determine LA synchrony and strain. Each of these parameters has their own predictive value. Unfortunately, there is no single parameter that

actually enables the prediction of AF relapse after CA. To summarize, the predictors of AF recurrence after CA which were confirmed by several groups were LA diameter > 50–55 mm or LAVi > 34 mL/m^2, E/e' > 13–15, LA strain assessed by STE < 20–25% and total atrial conduction time measured by TDI > 150 ms. The presence of LV systolic dysfunction also lowered CA success rate with a bottom LVEF cut-off value of < 25%. It needs underlining that risk of AF recurrence after CA should be estimated individually, optimally on the basis of several echocardiographic parameters.

Conflict of interest: None declared

References

1. 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.
2. Vizzardi E, Curnis A, Latini MG, et al. Risk factors for atrial fibrillation recurrence: a literature review. J Cardiovasc Med (Hagerstown). 2014; 15(3): 235–253, doi: 10.2459/JCM.0b013e328358554b, indexed in Pubmed: 23114271.
3. Burstein B, Nattel S. Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. J Am Coll Cardiol. 2008; 51(8): 802–809, doi: 10.1016/j.jacc.2007.09.064, indexed in Pubmed: 18294563.
4. Vaziri SM, Larson MG, Benjamin EJ, et al. Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. Circulation. 1994; 89(2): 724–730, indexed in Pubmed: 8313561.
5. Berruezo A, Tamborero D, Mont L, et al. Pre-procedural predictors of atrial fibrillation recurrence after circumferential pulmonary vein ablation. Eur Heart J. 2007; 28(7): 836–841, doi: 10.1093/eurheartj/ehm027, indexed in Pubmed: 17395676.
6. Calkins H, Kuck K, Cappato R, et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-up, Definitions, Endpoints, and Research Trial Design. Heart Rhythm. 2012; 9(4): 632–696.e21, doi: 10.1016/j.hrthm.2011.12.016.
7. Cameli M, Lisi M, Righini FM, et al. Usefulness of atrial deformation analysis to predict left atrial fibrosis and endocardial thickness in patients undergoing mitral valve operations for severe mitral regurgitation secondary to mitral valve prolapse. Am J Cardiol. 2013; 111(4): 595–601, doi: 10.1016/j.amjcard.2012.10.049, indexed in Pubmed: 23211360.
8. Zhuang J, Wang Y, Tang K, et al. Association between left atrial size and atrial fibrillation recurrence after single circumferential pulmonary vein isolation: a systematic review and meta-analysis of observational studies. Europace. 2011; 14(5): 638–645, doi: 10.1093/europace/eur364.
9. Liao YC, Liao JN, Lo LW, et al. Left Atrial Size and Left Ventricular End-Systolic Dimension Predict the Progression of Paroxysmal Atrial Fibrillation After Catheter Ablation. J Cardiovasc Electrophysiol. 2017; 28(1): 23–30, doi: 10.1111/jce.13115, indexed in Pubmed: 27779351.
10. Tomas L, Orosco A, Vergara JM, et al. Predictors of recurrence and outcomes in catheter ablation of paroxysmal atrial fibrillation. Rev Argent Cardiol. 2017; 85(3): 240–246.
11. Njoku A, Kannabhiran M, Arora R, et al. Left atrial volume predicts atrial fibrillation recurrence after radiofrequency ablation: a meta-analysis. Europace. 2018; 20(1): 33–42, doi: 10.1093/europace/eux013, indexed in Pubmed: 28444307.
12. Shin SH, Park MY, Oh WJ, et al. Left atrial volume is a predictor of atrial fibrillation recurrence after catheter ablation. J Am Soc Echocardiogr. 2008; 21(6): 697–702, doi: 10.1016/j.echo.2007.10.022, indexed in Pubmed: 18187293.
13. Moon J, Hong YJ, Shim J, et al. Right atrial anatomical remodeling affects early outcomes of nonvalvular atrial fibrillation after radiofrequency ablation. Circulation . 2012; 76(4): 860–867, doi: 10.1253/circj.cj-11-1232.
14. Wen SN, Liu N, Bai R, et al. Right atrial diameter and outcome of catheter ablation of atrial fibrillation. J Interv Card Electrophysiol. 2017; 49(2): 157–164, doi: 10.1007/s10840-017-0258-2.
15. Di Biase L, Mohanty P, Mohanty S, et al. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial. Circulation. 2016; 133(17): 1637–1644, doi: 10.1161/CIRCULATIONAHA.115.019406, indexed in Pubmed: 27029350.
16. Black-Maier E, Ren X, Steinberg BA, et al. Catheter ablation of atrial fibrillation in patients with heart failure and preserved ejection fraction. Heart Rhythm. 2018; 15(5): 651–657, doi: 10.1016/j.hrthm.2017.12.001, indexed in Pubmed: 29222043.
17. Melenovsky V, Hwang SJ, Redfield MM, et al. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. Circ Heart Fail. 2015; 8(2): 295–303, doi: 10.1161/CIRCHEARTFAILURE.114.001667, indexed in Pubmed: 25593126.
18. Cha YM, Wokhlu A, Asirvatham SJ, et al. Success of ablation for atrial fibrillation in isolated left ventricular diastolic dysfunction: a comparison to systolic dysfunction and normal ventricular function. Circ Arrhythm Electrophysiol. 2011; 4(5): 724––732, doi: 10.1161/CIRCEP.110.960690, indexed in Pubmed: 21747059.
19. Marrouche NF, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med. 2018; 378(5): 417–427, doi: 10.1056/NEJMoa1707855, indexed in Pubmed: 29385358.
20. Hu YF, Hsu TL, Yu WC, et al. The impact of diastolic dysfunction on the atrial substrate properties and outcome of catheter ablation in patients with paroxysmal atrial fibrillation. Circulation. 2010; 74(10): 2074–2078, indexed in Pubmed: 20668352.
21. Park J, Joung B, Uhm JS, et al. High left atrial pressures are associated with advanced electroanatomical remodeling of left atrium and independent predictors for clinical recurrence of atrial fibrillation after catheter ablation. Heart Rhythm. 2014; 11(6): 953–960, doi: 10.1016/j.hrthm.2014.03.009, indexed in Pubmed: 24607916.
22. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016; 29(4): 277–314, doi: 10.1016/j.echo.2016.01.011, indexed in Pubmed: 27037982.

23. Hirai T, Cotseones G, Makki N, et al. Usefulness of left ventricular diastolic function to predict recurrence of atrial fibrillation in patients with preserved left ventricular systolic function. Am J Cardiol. 2014; 114(1): 65–69, doi: 10.1016/j.amjcard.2014.03.061, indexed in Pubmed: 24819904.
24. Masuda M, Fujita M, Iida O, et al. An E/e' ratio on echocardiography predicts the existence of left atrial low-voltage areas and poor outcomes after catheter ablation for atrial fibrillation. Europace. 2018; 20(5): e60–e68, doi: 10.1093/europace/eux119, indexed in Pubmed: 28651348.
25. Okamatsu H, Ohara T, Kanzaki H, et al. Impact of left ventricular diastolic dysfunction on outcome of catheter ablation for atrial fibrillation in patients with hypertrophic cardiomyopathy. Circ J. 2015; 79(2): 419–424, doi: 10.1253/circj.CJ-14-0823, indexed in Pubmed: 25452101.
26. Onishi N, Kaitani K, Amano M, et al. Relationship between left ventricular diastolic dysfunction and very late recurrences after multiple procedures for atrial fibrillation ablation. Heart Vessels. 2018; 33(1): 41–48, doi: 10.1007/s00380-017-1027-y, indexed in Pubmed: 28766046.
27. Kosiuk J, Breithardt OA, Bode K, et al. The predictive value of echocardiographic parameters associated with left ventricular diastolic dysfunction on short- and long-term outcomes of catheter ablation of atrial fibrillation. Europace. 2014; 16(8): 1168–1174, doi: 10.1093/europace/eut415, indexed in Pubmed: 24569573.
28. Ouyang F, Antz M, Ernst S, et al. Recovered pulmonary vein conduction as a dominant factor for recurrent atrial tachyarrhythmias after complete circular isolation of the pulmonary veins: lessons from double Lasso technique. Circulation. 2005; 111(2): 127–135, doi: 10.1161/01.CIR.0000151289.73085.36, indexed in Pubmed: 15623542.
29. Sauer WH, McKernan ML, Lin D, et al. Clinical predictors and outcomes associated with acute return of pulmonary vein conduction during pulmonary vein isolation for treatment of atrial fibrillation. Heart Rhythm. 2006; 3(9): 1024–1028, doi: 10.1016/j.hrthm.2006.05.007, indexed in Pubmed: 16945795.
30. Schneider C, Malisius R, Krause K, et al. Strain rate imaging for functional quantification of the left atrium: atrial deformation predicts the maintenance of sinus rhythm after catheter ablation of atrial fibrillation. Eur Heart J. 2008; 29(11): 1397–1409, doi: 10.1093/eurheartj/ehn168, indexed in Pubmed: 18436560.
31. Hammerstingl C, Schwekendiek M, Momcilovic D, et al. Left atrial deformation imaging with ultrasound based two-dimensional speckle-tracking predicts the rate of recurrence of paroxysmal and persistent atrial fibrillation after successful ablation procedures. J Cardiovasc Electrophysiol. 2012; 23(3): 247–255, doi: 10.1111/j.1540-8167.2011.02177.x, indexed in Pubmed: 21955059.
32. Mirza M, Caracciolo G, Khan U, et al. Left atrial reservoir function predicts atrial fibrillation recurrence after catheter ablation: a two-dimensional speckle strain study. J Interv Card Electrophysiol. 2011; 31(3): 197–206, doi: 10.1007/s10840-011-9560-6, indexed in Pubmed: 21424845.
33. Kuppahally SS, Akoum N, Burgon NS, et al. Left atrial strain and strain rate in patients with paroxysmal and persistent atrial fibrillation: relationship to left atrial structural remodeling detected by delayed-enhancement MRI. Circ Cardiovasc Imaging. 2010; 3(3): 231–239, doi: 10.1161/CIRCIMAGING.109.865683, indexed in Pubmed: 20133512.
34. Ma XX, Boldt LH, Zhang YL, et al. Clinical relevance of left atrial strain to predict recurrence of atrial fibrillation after catheter ablation: a meta-analysis. Echocardiography. 2016; 33(5): 724–733, doi: 10.1111/echo.13184, indexed in Pubmed: 26857344.
35. Yasuda R, Murata M, Roberts R, et al. Left atrial strain is a powerful predictor of atrial fibrillation recurrence after catheter ablation: study of a heterogeneous population with sinus rhythm or atrial fibrillation. Eur Heart J Cardiovasc Imaging. 2015; 16(9): 1008–1014, doi: 10.1093/ehjci/jev028, indexed in Pubmed: 25750193.
36. Parwani AS, Morris DA, Blaschke F, et al. Left atrial strain predicts recurrence of atrial arrhythmias after catheter ablation of persistent atrial fibrillation. Open Heart. 2017; 4(1): e000572, doi: 10.1136/openhrt-2016-000572, indexed in Pubmed: 28674624.
37. Mochizuki A, Yuda S, Oi Y, et al. Assessment of left atrial deformation and synchrony by three-dimensional speckle-tracking echocardiography: comparative studies in healthy subjects and patients with atrial fibrillation. J Am Soc Echocardiogr. 2013; 26(2): 165–174, doi: 10.1016/j.echo.2012.10.003, indexed in Pubmed: 23140846.
38. Kobayashi Y, Okura H, Kobayashi Y, et al. Assessment of atrial synchrony in paroxysmal atrial fibrillation and impact of pulmonary vein isolation for atrial dyssynchrony and global strain by three-dimensional strain echocardiography. J Am Soc Echocardiogr. 2014; 27(11): 1193–1199, doi: 10.1016/j.echo.2014.08.004, indexed in Pubmed: 25240493.
39. Mochizuki A, Yuda S, Fujito T, et al. Left atrial strain assessed by three-dimensional speckle tracking echocardiography predicts atrial fibrillation recurrence after catheter ablation in patients with paroxysmal atrial fibrillation. J Echocardiogr. 2017; 15(2): 79–87, doi: 10.1007/s12574-017-0329-5, indexed in Pubmed: 28155065.
40. Loghin C, Karimzadehnajar K, Ekeruo IA, et al. Outcome of pulmonary vein isolation ablation for paroxysmal atrial fibrillation: predictive role of left atrial mechanical dyssynchrony by speckle tracking echocardiography. J Interv Card Electrophysiol. 2014; 39(1): 7–15, doi: 10.1007/s10840-013-9841-3, indexed in Pubmed: 24310816.
41. den Uijl DW, Gawrysiak M, Tops LF, et al. Prognostic value of total atrial conduction time estimated with tissue Doppler imaging to predict the recurrence of atrial fibrillation after radiofrequency catheter ablation. Europace. 2011; 13(11): 1533–1540, doi: 10.1093/europace/eur186, indexed in Pubmed: 21712264.
42. Erdem FH, Erdem A, Özlü F, et al. Electrophysiological validation of total atrial conduction time measurement by tissue doppler echocardiography according to age and sex in healthy adults. J Arrhythm. 2016; 32(2): 127–132, doi: 10.1016/j.joa.2015.11.006, indexed in Pubmed: 27092194.
43. Fukushima K, Fukushima N, Ejima K, et al. Left atrial appendage flow velocity and time from P-wave onset to tissue Doppler-derived A' predict atrial fibrillation recurrence after radiofrequency catheter ablation. Echocardiography. 2015; 32(7): 1101–1108, doi: 10.1111/echo.12823, indexed in Pubmed: 25362992.
44. Evranos B, Aytemir K, Oto A, et al. Predictors of atrial fibrillation recurrence after atrial fibrillation ablation with cryoballoon. Cardiol J. 2013; 20(3): 294–303, doi: 10.5603/cj.2013.0075.
45. Sarvari SI, Haugaa KH, Stokke TM, et al. Strain echocardiographic assessment of left atrial function predicts recurrence of atrial fibrillation. Eur Heart J Cardiovasc Imaging. 2016; 17(6): 660–667, doi: 10.1093/ehjci/jev185, indexed in Pubmed: 26219297.
46. Qiao Yu, Wu L, Hou B, et al. Functional mitral regurgitation: predictor for atrial substrate remodeling and poor ablation outcome in paroxysmal atrial fibrillation. Medicine (Baltimore). 2016; 95(30): e4333, doi: 10.1097/MD.0000000000004333, indexed in Pubmed: 27472715.

VIA MEDICA

REVIEW ARTICLE

Cardiology Journal
2020, Vol. 27, No. 6, 857–867
DOI: 10.5603/CJ.a2019.0021

ISSN 1897–5593
eISSN 1898–018X

Tachycardia: The hidden cardiovascular risk factor in uncomplicated arterial hypertension

Katarzyna Cierpka-Kmieć, Dagmara Hering

Department of Hypertension and Diabetology, Medical University of Gdansk, Poland

Abstract

Early detection and management of elevated blood pressure is crucial in reducing the burden of cardiovascular disease (CVD). The importance of an absolute risk assessment and patient risk stratification has been highlighted in the European hypertension guidelines since 2003. Amongst numerous risk factors influencing patient prognosis, elevated heart rate (HR) has been indicated as important predictor of future risk of hypertension, coronary heart disease, sudden cardiac death, heart failure, CVD, stroke, total cancer and mortality. Given that resting HR can be easily determined in clinical practice and modified by lifestyle changes as well as beta-blocker therapy, it seems reasonable that lowering resting HR should be a potential target to reduce disease burden and premature mortality. However, there is a lack of outcome studies of HR lowering in tachycardia-related hypertension. This review outlines the underlying mechanisms of early course hypertension pathophysiology with the critical role of the sympathetic nervous system activation, the prognostic significance of fast HR and the mechanistic rationale for the use of non-pharmacological approaches and/or highly long-acting cardioselective beta-blockers with some consideration given to betaxolol properties. (Cardiol J 2020; 27, 6: 857–867)

Key words: essential hypertension, tachycardia, cardiac output, peripheral resistance, muscle sympathetic nerve activity, non-pharmacological approaches, betaxolol

Introduction

Hypertension remains the leading preventable cause of premature deaths worldwide. Despite advances in hypertension prevention, diagnosis and treatment, elevated blood pressure (BP) affects at least one third of the adult global population according to national surveys [1, 2]. Using the recent American College of Cardiology and the American Heart Association guidelines for hypertension definition, the overall burden of the disease is even higher [3], likely to rise further due to the increasing prevalence of obesity worldwide. Notably, the incidence of cardiovascular (CV) disease (CVD) (i.e. myocardial infarction [MI], stroke, heart failure [HF], peripheral artery disease, kidney disease) directly increases from the threshold of 115/75 mmHg in all age groups, in both men and women [4].

Essential hypertension is the most common form of hypertension with no identifiable cause affecting nearly 95% of hypertensive patients. The pathogenesis of primary hypertension is multifactorial and numerous interrelated factors including salt intake, obesity, insulin resistance, genetics, endothelial dysfunction, low birth weight, intrauterine malnutrition and vascular anomalies contribute to raised BP and its relative impact may vary between individuals.

Further emerging risk factor gaining an important recognition is elevated resting heart rate (HR). Tachycardia can reflect a normal body response to various stimuli such as stress, fever, alcohol, smoking, coffee, strenuous exercise or associated

Address for correspondence: Prof. Dagmara Hering, MD, PhD, Department of Hypertension and Diabetology, Medical University of Gdansk, ul. Dębinki 7c, 80–952 Gdańsk, Poland, tel: +48 58 349 2065, fax: +48 58 349 2601, e-mail: hering@gumed.edu.pl

Received: 11.01.2019 Accepted: 4.02.2019

conditions (e.g. anemia, thyroid problems, infection, other). While in clinical practice fast HR can be unnoticed or viewed as a sign of 'nervousness', there is evidence to indicate that the presence of tachycardia and increased cardiac output (CO) are hemodynamic features of early phase of arterial hypertension [5] and important contributors to established hypertension and CVD [6]. Most studies on hypertension have reported that a HR higher than 80–85 bpm confers increased CV and mortality risk [6]. Although the presence of HR of > 80 bpm has been added to patient risk evaluation as per recent European Society of Cardiology and the European Society of Hypertension guidelines [7], the use of beta-blockers in uncomplicated hypertension is still under debate and the therapeutic approach to patients presenting with hypertension-related tachycardia remains empirical. CV outcomes of hypertensive patients treated or non-treated with beta-blockers are inconclusive. Optimal HR levels for hypertensive patients need to be determined.

Hemodynamic pattern of essential hypertension

Hemodynamic characteristics of the initial phase of primary essential hypertension are not unequivocal, either induced by raised CO or increased peripheral resistance [8]. It has been documented that in not less than 30% of children and younger population, fast HR and CO but normal total peripheral resistance precedes the development of high BP. The Tecumseh Blood Pressure Study found that 37% of all patients with untreated borderline and/or mild hypertension demonstrated hyperkinetic state with elevated HR, CO, forearm blood flow and plasma noradrenaline (NA) levels resulting in high sympathetic tone and decreased parasympathetic tone [9]. The hyperkinetic state caused by excessive autonomic drive is likely to be induced by augmented sympathetic activity to the heart and kidney. This selectively elevated NA release from renal and cardiac sympathetic nerves in essential hypertension has been predominantly found in males under the age of 40 [10].

High sympathetic activity is likely to be the underlying mechanism through which HR is associated with high insulin levels, insulin resistance, dyslipidemia, high hematocrit and excess body weight. Indeed, patients with hypertension commonly display other metabolic abnormalities including elevated glucose, insulin and lipid levels which importantly contribute to the HR increase [11, 12]. Weight gain and a lack of physical activity are further independent factors associated with resting tachycardia. Accelerated HR is associated with the magnitude of BP levels [13–16]. Own clinical experience suggests that pre-diabetes and obstructive sleep apnea are not uncommon conditions associated with tachycardia-related hypertension (as summarized in Fig. 1).

With aging and disease progression, CO generally normalized in uncomplicated hypertension, however a shift toward increased vascular resistance potentiates sympathetic activation which is a hallmark of established hypertension. In uncontrolled hypertension, persistent sympathetic activation promotes vascular remodeling, organ damage and adverse CV complications (Fig. 1) [17].

Fast HR in turn not only increases BP and leads to sustained hypertension but also exerts hemodynamically mediated cardiac abnormalities leading to reduced coronary flow reserve and vascular compliance, promoting atherosclerosis, arterial remodeling and plaque instability, endothelium dysfunction and microalbuminuria, importantly contributing to myocardial ischemia, coronary artery disease and HF (Fig. 1). Subsequently, the risk of ischemic heart disease, MI, cardiac arrhythmia and sudden cardiac death have been closely linked to the increased magnitude of HR [18].

Sympathetic activation in essential hypertension

Neurogenic activation underlies no less than 50% of all cases of high BP [19]. With the use of two state of the art methods such as the isotope dilution technique (to estimate the release of NA from the sympathetic nerves innervating internal organ) and the technique of microneurography (to directly assess postganglionic muscle sympathetic nerve activity [MSNA]), it has been documented that hypertension is commonly neurogenic, with the rise in BP being initiated and sustained as a result of potentiated sympathetic activation in the kidney and the heart — the two organs critically involved in neural control of circulation and BP [19, 20]. Increased activity of MSNA has been found in low risk subjects with high-normal BP [21] suggesting that neurogenic excitation may precede overt arterial hypertension [22]. A long-term study documented that in subjects with prehypertension MSNA tracking corresponds with BP changes over time suggesting that tonic activation is likely to influence a time-related increase in resting BP and development of sustained hypertension in prehypertension [23]. In patients with resistant

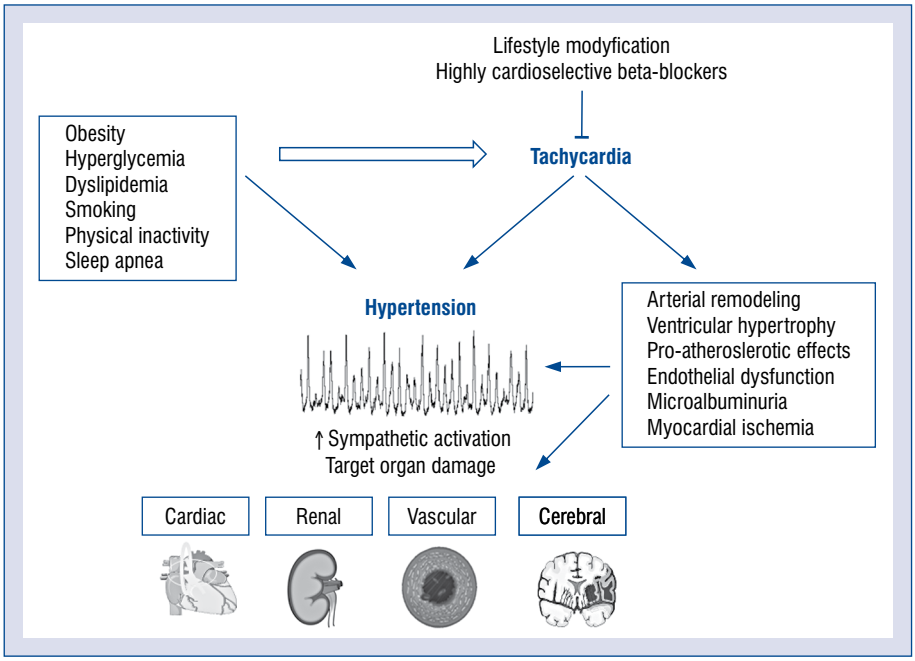


Figure 1. Factors contributing to elevated heart rate and pathophysiological consequences of tachycardia.

hypertension, sympathetic activation is further potentiated, reaching the MSNA levels directly corresponding to HR levels [24, 25]. Furthermore, sympathetic nervous system activation has been documented as the underlying critical cause of hypertension-mediated organ damage [26–28] and independent predictor of mortality and poor CV outcomes [29].

Link between tachycardia and sympathetic activation

Tachycardia and resultant hyperkinetic circulation if sustained over time, leads to an autonomic imbalance and reduced heart rate variability [30]. Microneurographic studies found that sympathetic activity and HR exerts an interactive effect on BP levels [31]. In normotensive subjects (males only, not females) with faster HR, higher levels of MSNA has been linked to higher systolic BP and pulse pressure whereas no similar relationship could be found in subjects with lower HR [31]. On the contrary, the relationship between resting HR and MSNA in hypertension is more complex and not completely understood. It has been documented that HR may be not a reliable indicator of the overall sympathetic activity as no association has been found between supine resting office HR and MSNA in essential hypertension [32]. Notably, ambulatory HR was found to be a superior risk marker to clinic or HR derived from an electrocardiogram (ECG) [33]. Indeed, when 24-h ambulatory BP measurements were applied, MSNA levels have been directly related to ambulatory daytime and night-time HR in a large sample of patients with untreated essential hypertension that were independent of age, body mass index (BMI) and gender [34]. This observation is likely to explain recent findings demonstrating the predictive role of masked (and/or sustained) tachycardia but not office tachycardia in future CV events and mortality [35].

Heart rate as risk factor for cardiovascular disease

Over the past decade elevated HR has gained recognition as an important risk factor for the development of CVD. Numerous epidemiological studies have reported an independent association between tachycardia and CV morbidity and mortality in the general population [18], subjects with prehypertension, patients with hypertension [12], CVD [36], HF [37], total cancer and all-cause mortality [38]. The prognostic value of both home [39] and ambulatory HR [40] has been indicated in the Ohasama Study which included individuals from the Japanese general population with no previous history of CVD including arrhythmia. An increase of 5 bpm in the morning home HR measurement was associated with a 17% increase in risk of CV

mortality which remained statistically significant after adjustment for home BP values. Moreover, even subjects with HR ≥ 70 bpm and home-measured systolic BP within the normal range (< 135 mmHg) had a higher risk of CV mortality compared to those with normal systolic BP and HR values [39]. Further analysis of the Ohasama study revealed that both daytime and nighttime HR predicted all-cause mortality over a 12-year period, however only nighttime HR remains the most important and independent predictor of non-CV mortality [40].

Further proof for the predictive role of HR on CV morbidity primarily in hypertensive men comes from the Framingham study suggesting that HR and BP may act synergistically in the development of CV complications [13]. Supportive evidence for fast HR-related outcomes was also documented in the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial which included patients with high-risk hypertension followed over a 5-year period [41]. It was found that patients in the highest HR quintile had a greater risk for cardiac events when compared to patients in the lowest HR quintile [41]. Notably, the adverse impact of elevated HR on patient prognosis was unrelated to BP control indicating that even patients with reasonably well-controlled hypertension but the presence of tachycardia are at high risk for CV events.

Tachycardia is also a strong predictor of excessive coronary morbidity and CV mortality [42]. A large study of French population found that accelerated resting HR was an independent predictor of non-CV mortality in both genders, and CV mortality in men, independent of age and the presence of hypertension [14]. In this study the HR-related increase in CVD mortality was due to a rise in coronary death but not cerebrovascular mortality. Another long-term study found that individuals with coexisting hypertension and elevated HR had increased risk of both stroke and coronary heart disease [43]. This is likely to occur as a result of plaque disruption due to hemodynamic forces (i.e. hypertension-induced left ventricular hypertrophy and elevated HR) which is a crucial pathophysiological mechanism underlying acute coronary syndrome and the progression of atherosclerosis [44].

There is evidence to indicate that not only masked hypertension is associated with an increased risk for CVD, but also masked tachycardia significantly increased rates of CV events and all-cause mortality [45]. Masked tachycardia has been defined as HR levels values ≤ 85 bpm in the clinic, but an elevated HR out of the clinic (ambulatory mean nighttime > 76 bpm) [45]. Masked tachycardia may occur in as many as 10% of the hypertensive population, and is important because it is not diagnosed by routine medical examinations, but carries an adverse prognosis, both in terms of increased target organ damage and CV events. Possible characteristics of individuals with masked tachycardia are relatively young patients, smokers, sufferers of diabetes or other metabolic disorders, and those who have elevated HR in outpatient settings [45, 46]. The negative association between masked tachycardia and an increased risk for major CV events and all-cause mortality was documented in a study of 7602 patients with newly diagnosed hypertension who were followed over a duration of 5 years [45]. Patients presenting with sustained tachycardia (increased both HR in the office and ambulatory nighttime measurements) had an increased risk of major CV events, but not mortality. After adjustment for additional risk factors including age, gender, BMI, lipid profile and creatinine levels, but not smoking and diabetes, both masked and sustained tachycardia were associated with greater risk of CV events [45]. While the type of beta-blockers used has not been indicated in this study, it is notable that the prognostic significance of tachycardia in predicting future major adverse CV events is independent of beta-blocker use [45].

The prognostic significance of elevated resting HR has been also found in patients with resistant hypertension [33] in whom not only fast (> 75 bpm or > 70 bpm for nighttime HR), but also slow HR (< 60 bpm or < 55 bpm for nighttime HR) predicted CV death. Importantly, approximately 80% of patients from this cohort were treated with beta-blockers which had an impact on HR-related prognosis. Fast HR was a significant risk marker in patients using beta blockers, whereas slow HR was a predictor in those not using beta-blockers suggesting an overall U-shaped phenomenon between the levels of HR and outcomes in patients with resistant hypertension [33]. In view of these findings, it appears that despite achieved BP control, hypertensive patients can remain at high risk for CV and/or non-CV complications.

Beta-blockers in hypertension

Despite the mechanistic rationale for the use of beta-blockers in the treatment of hypertension-related tachycardia, their therapeutic usefulness has been questioned based on the outcomes from meta-analyses of clinical trials. It has been sug-

gested that therapy with beta-blockers may not preclude future CV events and mortality in hypertension. Meta-analysis of a large cohort of patients (n = 94,492) with hypertension found that therapy with beta-blockers led to an increased risk for new-onset diabetes mellitus, occurrence of stroke with no benefit for the hard end-point of death or MI compared to other antihypertensive agents [47]. Further analysis of randomized controlled trials evaluating beta-blockers use in patients with hypertension (n = 34,096) when compared to patients (n = 30,139) taking other antihypertensive agents or patients receiving placebo (n = 3987) indicated that a lower HR (as attained in the beta-blocker group at study end) was associated with greater risk for end points of all-cause mortality, CV mortality, MI, stroke and HF [48]. Notably, nearly 75% of all clinical studies used as reference, atenolol drug in randomized controlled trials of primary hypertension [49], whereas beta-blockers differ in their pharmacokinetic and pharmacodynamic properties which influence their therapeutic impact on patient profiles, and has been discussed elsewhere. The main CV use of beta-blockers is to antagonize cardiac beta1-adrenoceptor responses in the heart and kidneys, whereas some beta-blocking agents possess an affinity for specific beta2, alpha1 or beta3 receptors. The efficacy of beta-blockers depends on their mechanisms of action including the degree of their lipophilicity, hydrophilicity, drug metabolism related to gene polymorphism, intrinsic agonist activity, penetration through the blood–brain barrier, bioavailability, plasma half-life and vasodilation. Smoking status and alterations in central BP have also contributed to the negative impact of beta-blockers on outcomes in managing hypertension. Another meta-analysis reported no major differences in BP lowering between atenolol and other antihypertensive drug class, however, there was a significantly higher mortality, CV mortality and risk of stroke with atenolol treatment than with other active treatments [50, 51]. Further meta-analysis demonstrated the benefits of beta-blocker use in reducing CV endpoints in younger hypertensive subjects, but not in older patients suggesting that age or non-atenolol beta-blocker might be an important determinant of outcomes in response to beta-blockers in hypertension [52]. Most meta-analyses compared the effectiveness of beta-blockers on patient prognosis in hypertension with the use of atenolol, metoprolol, propranolol, and oxprenolol. Despite these findings, clinical trials comparing head-to-head outcomes between various beta-blockers (including beta-blockers with vasodilating effects) in the treatment of hypertension are lacking. Moreover, previous studies on beta-blockers have been primarily designed to treat elevated BP, but not to focus on hypertension-related tachycardia outcomes.

The use of cardio selective beta-blockers is associated with a lower risk of side effects including metabolic disorders [53], while binding beta2 receptors located in lungs, liver, vascular smooth muscle or skeletal muscle result in bronchospasm, peripheral vasoconstriction, alteration of glucose and lipid metabolism [54, 55]. Therapy with a cardioselective nebivolol (causing NO-derived vasodilation) and non-cardioselective carvedilol (causing inhibition of sympathetic alpha-receptors) is associated with less side effects and favorable metabolic profile in addition to pleiotropic action, anti-inflammatory, anticoagulation and antiproliferation properties. Nebivolol also positively affects adipose tissue via acting as an agonist for beta3 adrenoreceptors. Nevertheless, given the different mechanisms of action, the magnitude of HR reduction with either nebivolol or carvedilol will not only take longer in duration but is lower compared to cardio-selective beta-blockers without intrinsic sympathomimetic activity (i.e. atenolol, metoprolol, bisoprolol or betaxolol). Furthermore, increasing doses of metoprolol or bisoprolol caused further decreases in HR (as expected with beta-blockers), whereas increasing doses of carvedilol produced increases in HR, likely as the result of a reflex increase in sympathetic activity secondary to peripheral vasodilation caused by alpha-blocking effects of the drug. In fact, 200 mg of metoprolol and 10 mg of bisoprolol are significantly more effective in reducing HR than 100 mg of carvedilol [56, 57]. However, both metoprolol and bisoprolol have been shown to induce up-regulation of beta-adrenoceptor density and to decrease nocturnal melatonin release [58–60].

Amongst beta-blockers, betaxolol is a long acting highly selective beta1-blocking agent (half-life ~19 h) and has several advantages that are likely to overcome certain limitations of other beta-blockers [61]. Betaxolol provides steady plasma concentration, less fluctuation and intersubject, and intrasubject variability producing a more consistent therapeutic response and more dependable dosage adjustment when compared to atenolol [62]. A further major advantage of betaxolol is the penetration through the blood–brain barrier and the ability to antagonize beta1 receptor that are expressed in several regions and tracts in the central nervous system [61] including the locus coeruleus (LC)

and its projections. Notably, the LC is the major noradrenergic brain nuclei and the largest source of NA production. In this context, it is likely that betaxolol may influence the central nervous system. In fact, betaxolol administration resulted in a rapid reduction of panic anxiety and panic disorder attacks, even in patients with longstanding anxiety, obsessive-compulsive personality disorder and post-traumatic stress [61].

Effects of beta-blockers on sympathetic activation in hypertension

The contribution of increased sympathetic activation to the pathophysiology of hypertension is well established. The question therefore arises, how lowering the HR and BP will affect MSNA levels. Previous studies determining the effects of beta-blockers on sympathetic activity in essential hypertension have shown conflicting results. Atenolol therapy had no effects on plasma NA levels or total body NA spillover in essential hypertension [63]. Microneurography studies have also demonstrated inconsistent results with an increase in MSNA following a short-term therapy with metoprolol in patients with untreated essential hypertension [64] or increase in MSNA after acute administration of atenolol in healthy subjects [65]. Other studies reported no changes in MSNA in response to chronic therapy with metoprolol [66] and atenolol [67].

On the contrary, a recent study found age-related differences in hemodynamic and sympathetic profile in hypertension-related tachycardia and age-dependent autonomic neural responses to betaxolol therapy [68]. An 8-week therapy with betaxolol resulted in HR and systolic BP decreases in all males with untreated essential hypertension and ambulatory tachycardia. However, the magnitude of HR reduction was greater in younger (–29 ± 4 bpm, $p < 0.001$) than older subjects (–17 ± 4 bpm, $p = 0.002$), whereas the degree of BP reduction was greater in older subjects (–27 ± 7 mmHg, $p = 0.007$) compared to younger (–13 ± 4 mmHg, $p = 0.01$) males. In older subjects, despite BP and HR decreases, there was a significant decrease in MSNA (–13 ± 5 bursts/min, $p < 0.05$). No significant changes in MSNA (3 ± 3 bursts/min, $p = 0.47$) were found in younger males at 8 week follow-up. These findings suggest that betaxolol exerts favorable effects on autonomic neural control in hypertension-induced tachycardia irrespective of age. In this context, further longer-term clinical trials on betaxolol are required to determine CV outcomes in hypertension-related tachycardia.

Aside from effective HR, BP and MSNA control in hypertension-related tachycardia, therapy with betaxolol has been found favorable in reducing maternal BP without any deleterious effect on the fetus and the newborn [69]. Furthermore, recently a large case-control study in Taiwan found that patients with chronic obstructive pulmonary disease (COPD) taking selective beta-blockers had a lower risk of severe exacerbations compared to patients with COPD who experienced a higher risk of severe exacerbations during an increased mean daily dose of non-cardioselective beta-blockers [70]. Amongst selective beta-blockers which COPD patients were taking (i.e. acebutolol, atenolol, bisoprolol, betaxolol, metoprolol), in particular one selective beta-blocker betaxolol had a significantly lower risk of severe exacerbations. This study indicates that betaxolol may be the preferred choice of selective beta-blocker for patients with COPD, whereas non-cardioselective beta-blockers should not be prescribed for patients with COPD.

Non-pharmacological treatment of tachycardia

Considering the contribution of elevated HR to the development of arterial hypertension and patient prognosis, interventions aiming at lifestyle changes including physical exercise, weight loss, smoking cessation and stress reduction are considered effective in lowering fast HR (Fig. 1).

Despite mounting evidence linking physical inactivity to the growing and significant burden of chronic disease including CVD, this risk factor continues to be often ignored in prevention programs. Regular physical exercise results in reducing HR, increasing parasympathetic activity and decreasing sympathetic activity in the human heart at rest [71–74]. While these study protocols were different regarding the type of physical activity, duration of exercise and follow-up period, it was found that regular endurance training led to a decrease of resting HR and favorable modulation of autonomic neural control, which in turn may contribute to improved patient prognosis and reduced mortality. The HERITAGE Family Study found a small but statistically significant decrease of resting HR (from a minimum of 2.7 to a maximum of 4.6 bpm) in all healthy participants ($n = 507$) assigned to three age-related groups (17–29 years, 30–49 years and 50–65 years) following a 20-week endurance exercise program [72]. Aerobic physical training has been shown to improve cardiac autonomic modulation in hypertension independently of an-

giotensin converting enzyme inhibitor treatment [75] and reduce CV mortality risk in cohort studies including hypertensive patients [76, 77]. Notably, hypertensive subjects benefit from regular physical exercise in lowering BP and improve CV outcomes [7]. While the magnitude of BP reduction with endurance training is greater than other types of exercise, more research is needed to determine the right dose of exercise [78, 79] and impact of physical activity on HR levels and associated outcomes in hypertension-induced tachycardia.

Given the link between obesity and higher resting BP and HR values and resultant autonomic impairment characterized by reduced parasympathetic activity and relative predominance of sympathetic activity [80], body weight reduction is considered as a crucial non-pharmacological approach in the treatment of tachycardia, metabolic abnormalities and elevated BP. In this context, clinically important are findings of the very recent PREVIEW lifestyle intervention study which followed-up 2,500,000 patients with obesity and pre-diabetes who underwent a low-energy diet for 8 weeks [81]. In this study men and women responded differently in terms of HR reduction (–6.4 ± 1.1 in men vs. 4.9 ± 1.1 bpm in women). In addition to rapid weight loss, an 8-week low energy diet was associated with improvements in numerous parameters including insulin resistance, metabolic syndrome Z-score, C-peptide, fat mass, high density lipoprotein cholesterol, fat-free mass, hip circumference and pulse pressure [81]. Further proof for HR reduction following weight loss 2 years after gastric bypass surgery comes from the Utah Obesity Study [82]. In this study, in severely obese patients weight loss of an average of 100 ± 37 lb was accompanied by a reduction in resting HR by –13 bpm and improved HR recovery after exercise when compared to the non-surgical group (weight loss of 3 ± 22 lb and HR reduction by –6 bpm). Whether, and to what extent lowering of HR may contribute to reduced CV mortality merits further investigation.

Further proof for reducing HR following weight loss has been demonstrated in young normotensive males who were randomized to a low-calorie diet, therapy with moxonidine, combination of both therapies and the control group [83]. Following 6-month follow-up, weight loss of 7.6 ± 1.9 led to a reduction of HR by –11.7 ± 2.7 bpm and MSNA by –10.5 ± 2.3 bursts/min which was comparable to the effects of a combination of both low-calorie diet and moxonidine. Moxonidine alone decreased HR by –4.7 ± 3.0 bmp and MSNA by –11.0 ± 1.2 without an impact on body weight [83]. These findings suggest that weight loss programs are essential in overweight subjects with the potential to reverse sympathetic CV profile prior to development of established hypertension.

Amongst lifestyle habits, hypertensive patients should be counselled to stop smoking. Both acute and chronic smoking has been directly linked to increases in BP, HR and MSNA levels [84, 85] which may play a critical mechanistic role in the development and progression of hypertension, CVD and mortality. Available evidence indicates that smoking cessation almost completely reverses risk of CVD, thereby is considered the single most effective lifestyle intervention. Quitting smoking results in a rapid and persistent drop of HR [86], improvement of HR variability [87] and exerts beneficial effects on CV health by reducing the increased excess risk among former smokers [88].

Stress is another major factor contributing to fast HR, development of hypertension, CVD and arrhythmias as previously reviewed in detail [89]. Non-pharmacological approaches such as transcendental meditation, yoga technique and slow breathing therapy have been shown to alter stress response, modulate cardiac autonomic regulation, increase HR variability and vagal dominance [90–94].

Conclusion and clinical perspectives

Prevention of excess CV events and mortality caused by elevated HR remains a challenging problem. While elevated HR can be triggered by numerous factors, an appropriate assessment of resting HR followed by lifestyle interventions is essential in clinical practice in both patient risk stratification and prevention of tachycardia-related disease. Nearly 1 in 3 hypertensive patients commonly demonstrates hyperkinetic hypertension at the early course of the disease and tachycardia can be an indicator of established hypertension associated with obesity, metabolic abnormalities and obstructive sleep apnea. Undoubtedly, lifestyle modification is the cornerstone for the prevention of hypertension, in particular regular physical activity, weight loss and smoking cessation should be an integral part of treating resting tachycardia in uncomplicated hypertension. While studies on beta-blockers in the treatment of hypertension are inconclusive, notably a therapy with highly cardio-selective beta-blocker such as betaxolol can effectively reduce HR, BP and modulate sympathetic neural control in patients with tachycardia

which is a strong independent risk factor for CV events and associated mortality. Given the lack of studies comparing head-to-head CV outcomes with the use of highly cardio selective beta-blockers (i.e. betaxolol, bisoprolol and nebivolol), there is an unmet need in continuing clinical trials in hypertension in order to determine the optimal HR levels that would preclude tachycardia-mediated organ damage.

Conflict of interest: None declared

References

1. Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. Circulation. 2018; 137(12): e67–e6e492, doi: 10.1161/CIR.0000000000000558, indexed in Pubmed: 29386200.
2. Niklas AA, Flotyńska A, Zdrojewski T, et al. Trends in hypertension prevalence, awareness, treatment, and control among Polish adults 75 years and older during 2007-2014. Cardiol J. 2018; 25(3): 333–344, doi: 10.5603/CJ.a2018.0043, indexed in Pubmed: 29671863.
3. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018; 71(6): 1269–1324.
4. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002; 360(9349): 1903–1913, indexed in Pubmed: 12493255.
5. Julius S. The association of tachycardia with obesity and elevated blood pressure. J Pediatr. 2002; 140(6): 643–645, doi: 10.1067/mpd.2002.125519, indexed in Pubmed: 12072864.
6. Palatini P, Rosei EA, Casiglia E, et al. Management of the hypertensive patient with elevated heart rate: Statement of the Second Consensus Conference endorsed by the European Society of Hypertension. J Hypertens. 2016; 34(5): 813–821, doi: 10.1097/HJH.0000000000000865, indexed in Pubmed: 26982382.
7. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens. 2018; 36(10): 1953–2041, doi: 10.1097/HJH.0000000000001940, indexed in Pubmed: 30234752.
8. Folkow B. Physiological aspects of primary hypertension. Physiol Rev. 1982; 62(2): 347–504, doi: 10.1152/physrev.1982.62.2.347.
9. Julius S, Krause L, Schork N, et al. Hyperkinetic borderline hypertension in Tecumseh, Michigan. J Hypertens. 1991; 9(1): 77–84, doi: 10.1097/00004872-199101000-00012.
10. Esler M, Jennings G, Biviano B, et al. Mechanism of elevated plasma noradrenaline in the course of essential hypertension. J Cardiovasc Pharmacol. 1986; 8 Suppl 5: S39–S43, indexed in Pubmed: 2427882.
11. Palatini P, Casiglia E, Pauletto P, et al. Relationship of tachycardia with high blood pressure and metabolic abnormalities: a study with mixture analysis in three populations. Hypertension. 1997; 30(5): 1267–1273, indexed in Pubmed: 9369286.
12. Palatini P, Julius S. Association of tachycardia with morbidity and mortality: pathophysiological considerations. J Hum Hypertens. 1997; 11 Suppl 1: S19–S27, indexed in Pubmed: 9321736.
13. Gillman MW, Kannel WB, Belanger A, et al. Influence of heart rate on mortality among persons with hypertension: the Framingham Study. Am Heart J. 1993; 125(4): 1148–1154, indexed in Pubmed: 8465742.
14. Benetos A, Rudnichi A, Thomas F, et al. Influence of heart rate on mortality in a French population: role of age, gender, and blood pressure. Hypertension. 1999; 33(1): 44–52, indexed in Pubmed: 9931080.
15. Thomas F, Bean K, Provost JC, et al. Combined effects of heart rate and pulse pressure on cardiovascular mortality according to age. J Hypertens. 2001; 19(5): 863–869, indexed in Pubmed: 11393668.
16. Paul L, Hastie CE, Li WS, et al. Resting heart rate pattern during follow-up and mortality in hypertensive patients. Hypertension. 2010; 55(2): 567–574, doi: 10.1161/HYPERTENSIONAHA.109.144808, indexed in Pubmed: 20038750.
17. Julius S, Nesbitt S. Sympathetic overactivity in hypertension. A moving target. Am J Hypertens. 1996; 9(11): 113S–120S, indexed in Pubmed: 8931844.
18. Kannel WB, Kannel C, Paffenbarger RS, et al. Heart rate and cardiovascular mortality: the Framingham Study. Am Heart J. 1987; 113(6): 1489–1494, indexed in Pubmed: 3591616.
19. Esler M. The 2009 Carl Ludwig Lecture: Pathophysiology of the human sympathetic nervous system in cardiovascular diseases: the transition from mechanisms to medical management. J Appl Physiol (1985). 2010; 108(2): 227–237, doi: 10.1152/japplphysiol.00832.2009, indexed in Pubmed: 19940096.
20. Esler M, Lambert E, Schlaich M. Point: Chronic activation of the sympathetic nervous system is the dominant contributor to systemic hypertension. J Appl Physiol (1985). 2010; 109(6): 1996–8; discussion 2016, doi: 10.1152/japplphysiol.00182.2010, indexed in Pubmed: 20185633.
21. Greenwood JP, Stoker JB, Mary DA. Single-unit sympathetic discharge : quantitative assessment in human hypertensive disease. Circulation. 1999; 100(12): 1305–1310, indexed in Pubmed: 10491375.
22. Hering D, Kara T, Kucharska W, et al. High-normal blood pressure is associated with increased resting sympathetic activity but normal responses to stress tests. Blood Press. 2013; 22(3): 183–187, doi: 10.3109/08037051.2012.759689, indexed in Pubmed: 23356493.
23. Hering D, Kara T, Kucharska W, et al. Longitudinal tracking of muscle sympathetic nerve activity and its relationship with blood pressure in subjects with prehypertension. Blood Press. 2016; 25(3): 184–192, doi: 10.3109/08037051.2015.1121708, indexed in Pubmed: 26654200.
24. Hering D, Lambert EA, Marusic P, et al. Substantial reduction in single sympathetic nerve firing after renal denervation in patients with resistant hypertension. Hypertension. 2013;

61(2): 457–464, doi: 10.1161/HYPERTENSIONAHA.111.00194, indexed in Pubmed: 23172929.
25. Hering D, Marusic P, Walton AS, et al. Sustained sympathetic and blood pressure reduction 1 year after renal denervation in patients with resistant hypertension. Hypertension. 2014; 64(1): 118–124, doi: 10.1161/HYPERTENSIONAHA.113.03098, indexed in Pubmed: 24732891.
26. Mancia G, Grassi G, Giannattasio C, et al. Sympathetic activation in the pathogenesis of hypertension and progression of organ damage. Hypertension. 1999; 34(4): 724–728, doi: 10.1161/01.hyp.34.4.724.
27. Schlaich MP, Kaye DM, Lambert E, et al. Relation between cardiac sympathetic activity and hypertensive left ventricular hypertrophy. Circulation. 2003; 108(5): 560–565, doi: 10.1161/01.CIR.0000081775.72651.B6, indexed in Pubmed: 12847071.
28. Grassi G, Seravalle G, Quarti-Trevano F, et al. Sympathetic and baroreflex cardiovascular control in hypertension-related left ventricular dysfunction. Hypertension. 2009; 53(2): 205–209, doi: 10.1161/HYPERTENSIONAHA.108.121467, indexed in Pubmed: 19124679.
29. Zoccali C, Mallamaci F, Parlongo S, et al. Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. Circulation. 2002; 105(11): 1354––1359, indexed in Pubmed: 11901048.
30. Guzzetti S, Piccaluga E, Casati R, et al. Sympathetic predominance in essential hypertension: a study employing spectral analysis of heart rate variability. J Hypertens. 1988; 6(9): 711–717, indexed in Pubmed: 3183374.
31. Narkiewicz K, Somers VK. Interactive effect of heart rate and muscle sympathetic nerve activity on blood pressure. Circulation. 1999; 100(25): 2514–2518, indexed in Pubmed: 10604889.
32. Grassi G, Vailati S, Bertinieri G, et al. Heart rate as marker of sympathetic activity. J Hypertens. 1998; 16(11): 1635–1639, indexed in Pubmed: 9856364.
33. Salles GF, Cardoso CRL, Fonseca LL, et al. Prognostic significance of baseline heart rate and its interaction with beta-blocker use in resistant hypertension: a cohort study. Am J Hypertens. 2013; 26(2): 218–226, doi: 10.1093/ajh/hps004, indexed in Pubmed: 23382406.
34. Hering D, Kucharska W, Kara T, et al. Resting sympathetic outflow does not predict the morning blood pressure surge in hypertension. J Hypertens. 2011; 29(12): 2381–2386, doi: 10.1097/HJH.0b013e32834c1ecd, indexed in Pubmed: 21986622.
35. Palatini P, Reboldi G, Beilin LJ, et al. Masked tachycardia. A predictor of adverse outcome in hypertension. J Hypertens. 2017; 35(3): 487–492, doi: 10.1097/HJH.0000000000001194, indexed in Pubmed: 27930441.
36. Jouven X, Empana JP, Schwartz PJ, et al. Heart-rate profile during exercise as a predictor of sudden death. N Engl J Med. 2005; 352(19): 1951–1958, doi: 10.1056/NEJMoa043012, indexed in Pubmed: 15888695.
37. Pocock SJ, Wang D, Pfeffer MA, et al. Predictors of mortality and morbidity in patients with chronic heart failure. Eur Heart J. 2006; 27(1): 65–75, doi: 10.1093/eurheartj/ehi555, indexed in Pubmed: 16219658.
38. Aune D, Sen A, ó'Hartaigh B, et al. Resting heart rate and the risk of cardiovascular disease, total cancer, and all-cause mortality: a systematic review and dose-response meta-analysis of prospective studies. Nutr Metab Cardiovasc Dis. 2017; 27(6): 504–517, doi: 10.1016/j.numecd.2017.04.004, indexed in Pubmed: 28552551.
39. Hozawa A, Ohkubo T, Kikuya M, et al. Prognostic value of home heart rate for cardiovascular mortality in the general population: the Ohasama study. Am J Hypertens. 2004; 17(11 Pt 1): 1005–1010, doi: 10.1016/j.amjhyper.2004.06.019, indexed in Pubmed: 15533725.
40. Hozawa A, Inoue R, Ohkubo T, et al. Predictive value of ambulatory heart rate in the Japanese general population: the Ohasama study. J Hypertens. 2008; 26(8): 1571–1576, doi: 10.1097/HJH.0b013e3283041172, indexed in Pubmed: 18622234.
41. Julius S, Palatini P, Kjeldsen SE, et al. Usefulness of heart rate to predict cardiac events in treated patients with high-risk systemic hypertension. Am J Cardiol. 2012; 109(5): 685–692, doi: 10.1016/j.amjcard.2011.10.025, indexed in Pubmed: 22169130.
42. Palatini P, Julius S. Heart rate and the cardiovascular risk. J Hypertens. 1997; 15(1): 3–17, doi: 10.1097/00004872-199715010-00001.
43. Zhong C, Zhong X, Xu T, et al. Combined effects of hypertension and heart rate on the risk of stroke and coronary heart disease: a population-based prospective cohort study among Inner Mongolians in China. Hypertens Res. 2015; 38(12): 883–888, doi: 10.1038/hr.2015.90, indexed in Pubmed: 26289782.
44. Heidland UE, Strauer BE. Left ventricular muscle mass and elevated heart rate are associated with coronary plaque disruption. Circulation. 2001; 104(13): 1477–1482, indexed in Pubmed: 11571239.
45. Palatini P, Reboldi G, Beilin LJ, et al. Masked tachycardia. A predictor of adverse outcome in hypertension. J Hypertens. 2017; 35(3): 487–492, doi: 10.1097/HJH.0000000000001194, indexed in Pubmed: 27930441.
46. Hering D, Grassi G. Prognostic significance of masked tachycardia in hypertension: evidence from a prospective international registry. J Hypertens. 2017; 35(3): 468–470, doi: 10.1097/HJH.0000000000001234, indexed in Pubmed: 28121837.
47. Bangalore S, Parkar S, Grossman E, et al. A meta-analysis of 94,492 patients with hypertension treated with beta blockers to determine the risk of new-onset diabetes mellitus. Am J Cardiol. 2007; 100(8): 1254–1262, doi: 10.1016/j.amjcard.2007.05.057, indexed in Pubmed: 17920367.
48. Bangalore S, Sawhney S, Messerli FH. Relation of beta-blocker-induced heart rate lowering and cardioprotection in hypertension. J Am Coll Cardiol. 2008; 52(18): 1482–1489, doi: 10.1016/j.jacc.2008.06.048, indexed in Pubmed: 19017516.
49. Ripley TL, Saseen JJ. Beta-blockers: a review of their pharmacological and physiological diversity in hypertension. Ann Pharmacother. 2014; 48(6): 723–733, doi: 10.1177/1060028013519591, indexed in Pubmed: 24687542.
50. Carlberg Bo, Samuelsson O, Lindholm LH. Atenolol in hypertension: is it a wise choice? Lancet. 2004; 364(9446): 1684–1689, doi: 10.1016/S0140-6736(04)17355-8, indexed in Pubmed: 15530629.
51. Larochelle P, Tobe SW, Lacourcière Y. β-Blockers in hypertension: studies and meta-analyses over the years. Can J Cardiol. 2014; 30(5 Suppl): S16–S22, doi: 10.1016/j.cjca.2014.02.012, indexed in Pubmed: 24750978.
52. Kuyper LM, Khan NA. Atenolol vs nonatenolol β-blockers for the treatment of hypertension: a meta-analysis. Can J Cardiol. 2014; 30(5 Suppl): S47–S53, doi: 10.1016/j.cjca.2014.01.006, indexed in Pubmed: 24750981.
53. Tucker WD, Theetha Kariyanna P. Selective Beta-1-Blockers. In: StatPearls. Treasure Island, FL. 2018.

54. Sharma AM, Pischon T, Hardt S, et al. Hypothesis: Beta-adrenergic receptor blockers and weight gain: A systematic analysis. Hypertension. 2001; 37(2): 250–254, indexed in Pubmed: 11230280.
55. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. Lancet. 2007; 369(9557): 201–207, doi: 10.1016/S0140-6736(07)60108-1, indexed in Pubmed: 17240286.
56. Stoschitzky K, Koshucharova G, Zweiker R, et al. Differing beta-blocking effects of carvedilol and metoprolol. Eur J Heart Fail. 2001; 3(3): 343–349, indexed in Pubmed: 11378006.
57. Stoschitzky K. Individual beta-blockers for individual patients. An article from the E-Journal of the ESC Council for Cardiology Practice. Vol. 6, N° 19. ; 15: Jan.
58. Brodde OE. Beta 1- and beta 2-adrenoceptors in the human heart: properties, function, and alterations in chronic heart failure. Pharmacol Rev. 1991; 43(2): 203–242, indexed in Pubmed: 1677200.
59. Stoschitzky K, Sakotnik A, Lercher P, et al. Influence of beta-blockers on melatonin release. Eur J Clin Pharmacol. 1999; 55(2): 111–115, indexed in Pubmed: 10335905.
60. Stoschitzky K, Stoschitzky G, Brussee H, et al. Comparing beta-blocking effects of bisoprolol, carvedilol and nebivolol. Cardiology. 2006; 106(4): 199–206, doi: 10.1159/000093060, indexed in Pubmed: 16679760.
61. Swartz CM. Betaxolol in anxiety disorders. Ann Clin Psychiatry. 1998; 10(1): 9–14, indexed in Pubmed: 9622045.
62. Kunka RL, Wong YY, Andersen RL, et al. Steady-state fluctuation and variability of betaxolol and atenolol plasma levels. Ther Drug Monit. 1989; 11(5): 523–527, indexed in Pubmed: 2573178.
63. Jacobs MC, Lenders JW, Smits P, et al. Long-term beta 1-adrenergic blockade restores adrenomedullary activity in primary hypertension. J Cardiovasc Pharmacol. 1997; 30(3): 338–342, indexed in Pubmed: 9300318.
64. Sundlöf G, Wallin BG, Strömgren E, et al. Acute effects of metoprolol on muscle sympathetic activity in hypertensive humans. Hypertension. 1983; 5(5): 749–756, indexed in Pubmed: 6618637.
65. Cogliati C, Colombo S, Ruscone TG, et al. Acute beta-blockade increases muscle sympathetic activity and modifies its frequency distribution. Circulation. 2004; 110(18): 2786–2791, doi: 10.1161/01.CIR.0000146335.69413.F9, indexed in Pubmed: 15505096.
66. Wallin BG, Sundlöf G, Strömgren E, et al. Sympathetic outflow to muscles during treatment of hypertension with metoprolol. Hypertension. 1984; 6(4): 557–562, indexed in Pubmed: 6378790.
67. Burns J, Mary DA, Mackintosh AF, et al. Arterial pressure lowering effect of chronic atenolol therapy in hypertension and vasoconstrictor sympathetic drive. Hypertension. 2004; 44(4): 454–458, doi: 10.1161/01.HYP.0000141411.94596.0f, indexed in Pubmed: 15326085.
68. Hering D, Kucharska W, Chrostowska M, et al. Age-dependent sympathetic neural responses to ß selective beta-blockade in untreated hypertension-related tachycardia. Blood Press. 2018; 27(3): 158–165, doi: 10.1080/08037051.2018.1423543, indexed in Pubmed: 29308931.
69. Boutroy MJ, Morselli PL, Bianchetti G, et al. Betaxolol: a pilot study of its pharmacological and therapeutic properties in pregnancy. Eur J Clin Pharmacol. 1990; 38(6): 535–539, indexed in Pubmed: 1973651.
70. Huang YL, Lai CC, Wang YH, et al. Impact of selective and nonselective beta-blockers on the risk of severe exacerbations in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2017; 12: 2987–2996, doi: 10.2147/COPD.S145913, indexed in Pubmed: 29066880.
71. Levy WC, Cerqueira MD, Harp GD, et al. Effect of endurance exercise training on heart rate variability at rest in healthy young and older men. Am J Cardiol. 1998; 82(10): 1236–1241, indexed in Pubmed: 9832101.
72. Wilmore J, Stanforth P, Gagnon J, et al. Heart rate and blood pressure changes with endurance training: The HERITAGE Family Study. Med Scien Sports Exercise. 2001: 107–116, doi: 10.1097/00005768-200101000-00017.
73. Carter JB, Banister EW, Blaber AP. Effect of endurance exercise on autonomic control of heart rate. Sports Med. 2003; 33(1): 33–46, doi: 10.2165/00007256-200333010-00003, indexed in Pubmed: 12477376.
74. Perini R, Tironi A, Cautero M, et al. Seasonal training and heart rate and blood pressure variabilities in young swimmers. Eur J Appl Physiol. 2006; 97(4): 395–403, doi: 10.1007/s00421-006-0174-0, indexed in Pubmed: 16636862.
75. Cozza IC, Di Sacco THR, Mazon JH, et al. Physical exercise improves cardiac autonomic modulation in hypertensive patients independently of angiotensin-converting enzyme inhibitor treatment. Hypertens Res. 2012; 35(1): 82–87, doi: 10.1038/hr.2011.162, indexed in Pubmed: 21956728.
76. Leitzmann MF, Park Y, Blair A, et al. Physical activity recommendations and decreased risk of mortality. Arch Intern Med. 2007; 167(22): 2453–2460, doi: 10.1001/archinte.167.22.2453, indexed in Pubmed: 18071167.
77. Rossi A, Dikareva A, Bacon SL, et al. The impact of physical activity on mortality in patients with high blood pressure: a systematic review. J Hypertens. 2012; 30(7): 1277–1288, doi: 10.1097/HJH.0b013e3283544669, indexed in Pubmed: 22573122.
78. Leggio M, Bendini MG, D'Emidio S, et al. Exercise dose in clinical practice: Right is better than more. Cardiol J. 2018; 25(2): 287–288, doi: 10.5603/CJ.2018.0040, indexed in Pubmed: 29717780.
79. Kaleta AM, Lewicka E. Exercise dose in clinical practice: Should safety limits be set? Cardiol J. 2018; 25(2): 289–290, doi: 10.5603/CJ.2018.0041, indexed in Pubmed: 29717781.
80. Rossi RC, Vanderlei LC, Gonçalves AC, et al. Impact of obesity on autonomic modulation, heart rate and blood pressure in obese young people. Auton Neurosci. 2015; 193: 138–141, doi: 10.1016/j.autneu.2015.07.424, indexed in Pubmed: 26260435.
81. Christensen P, Meinert Larsen T, Westerterp-Plantenga M, et al. Men and women respond differently to rapid weight loss: Metabolic outcomes of a multi-centre intervention study after a low-energy diet in 2500 overweight, individuals with pre-diabetes (PREVIEW). Diabetes Obes Metab. 2018; 20(12): 2840–2851, doi: 10.1111/dom.13466, indexed in Pubmed: 30088336.
82. Wasmund SL, Owan T, Yanowitz FG, et al. Improved heart rate recovery after marked weight loss induced by gastric bypass surgery: two-year follow up in the Utah Obesity Study. Heart Rhythm. 2011; 8(1): 84–90, doi: 10.1016/j.hrthm.2010.10.023, indexed in Pubmed: 20970524.
83. Lambert EA, Sari CI, Eikelis N, et al. Effects of moxonidine and low-calorie diet: cardiometabolic benefits from combination of both therapies. Obesity (Silver Spring). 2017; 25(11): 1894–1902, doi: 10.1002/oby.21962, indexed in Pubmed: 28865109.
84. Hering D, Somers VK, Kara T, et al. Sympathetic neural responses to smoking are age dependent. J Hypertens. 2006; 24(4): 691–695, doi: 10.1097/01.hjh.0000217851.95583.57, indexed in Pubmed: 16531797.

85. Hering D, Kucharska W, Kara T, et al. Smoking is associated with chronic sympathetic activation in hypertension. Blood Press. 2010; 19(3): 152–155, doi: 10.3109/08037051.2010.484150, indexed in Pubmed: 20429695.
86. Persico AM. Persistent decrease in heart rate after smoking cessation: a 1-year follow-up study. Psychopharmacology (Berl). 1992; 106(3): 397–400, indexed in Pubmed: 1570388.
87. Harte CB, Meston CM. Effects of smoking cessation on heart rate variability among long-term male smokers. Int J Behav Med. 2014; 21(2): 302–309, doi: 10.1007/s12529-013-9295-0, indexed in Pubmed: 23397454.
88. Mons U, Müezzinler A, Gellert C, et al. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. BMJ. 2015; 350: h1551, doi: 10.1136/bmj.h1551, indexed in Pubmed: 25896935.
89. Hering D, Lachowska K, Schlaich M. Role of the Sympathetic Nervous System in Stress-Mediated Cardiovascular Disease. Curr Hypertens Rep. 2015; 17(10): 80, doi: 10.1007/s11906-015-0594-5, indexed in Pubmed: 26318888.
90. Schneider RH, Grim CE, Rainforth MV, et al. Stress reduction in the secondary prevention of cardiovascular disease: randomized, controlled trial of transcendental meditation and health education in Blacks. Circ Cardiovasc Qual Outcomes. 2012; 5(6): 750–758, doi: 10.1161/CIRCOUTCOMES.112.967406, indexed in Pubmed: 23149426.
91. Tyagi A, Cohen M. Yoga and heart rate variability: A comprehensive review of the literature. Int J Yoga. 2016; 9(2): 97–113, doi: 10.4103/0973-6131.183712, indexed in Pubmed: 27512317.
92. Hering D, Kucharska W, Kara T, et al. Effects of acute and long-term slow breathing exercise on muscle sympathetic nerve activity in untreated male patients with hypertension. J Hypertens. 2013; 31(4): 739–746, doi: 10.1097/HJH.0b013e32835eb2cf, indexed in Pubmed: 23385649.
93. Lachowska K, Bellwon J, Narkiewicz K, et al. Long-term effects of device-guided slow breathing in stable heart failure patients with reduced ejection fraction. Clin Res Cardiol. 2019; 108(1): 48–60, doi: 10.1007/s00392-018-1310-7, indexed in Pubmed: 29943271.
94. Lachowska K, Bellwon J, Moryś J, et al. Slow breathing improves cardiovascular reactivity to mental stress and health-related quality of life in heart failure patients with reduced ejection fraction. Cardiol J. 2019 [Epub ahead of print], doi: 10.5603/CJ.a2019.0002, indexed in Pubmed: 30697682.

VIA MEDICA

REVIEW ARTICLE

Cardiology Journal
2020, Vol. 27, No. 6, 868–874
DOI: 10.5603/CJ.a2019.0025

ISSN 1897–5593
eISSN 1898–018X

The use of anticoagulants in chronic kidney disease: Common point of view of cardiologists and nephrologists

Justyna Domienik-Karłowicz[1], Olga Tronina[2], Wojciech Lisik[3], Magdalena Durlik[2], Piotr Pruszczyk[1]

[1]Department of Internal Medicine and Cardiology with the Center for Diagnosis and Treatment of Venous Thromboembolism, Medical University of Warsaw, Poland
[2]Department of Transplantation Medicine and Nephrology, Medical University of Warsaw, Poland
[3]Department of General and Transplantation Surgery, Medical University of Warsaw, Poland

Abstract

In patients diagnosed with chronic kidney disease (CKD), atrial fibrillation (AF) is associated with an increased risk of thromboembolism and stroke. Moreover, patients with CKD — especially those in end-stage renal disease — also present an increased risk of bleeding. Oral anticoagulation is the most effective form of thromboprophylaxis in patients with AF and an increased risk of stroke. However, the underuse of these drugs was observed, mainly due to safety reasons and restricted evidence on efficacy. Much evidence suggests that non-vitamin K-dependent oral anticoagulant agents significantly reduce the risk of stroke, intracranial hemorrhage, and mortality, with lower to similar major bleeding rates compared with vitamin K antagonists, such as warfarin, in normal renal function subjects. Thus, they are currently recommended for that group of patients. However, their metabolism is largely dependent on the kidneys for elimination, and current knowledge in this area is limited due to patients with a decreased glomerular filtration rate are usually excluded from clinical trials. The present review article focuses on currently available data on oral anticoagulants in patients with moderate to advanced chronic kidney disease and those with end stage renal disease. (Cardiol J 2020; 27, 6: 868–874)

Key words: anticoagulation therapy, atrial fibrillation, chronic kidney disease, non-vitamin K-dependent oral anticoagulants, warfarin

Introduction

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for ≥ 3 months, with implications for health. Criteria for CKD (either of the following were present for 3 months): (1) Markers of kidney damage (one or more): (i) Albuminuria (AER ≥ 30 mg/24 h; ACR ≥ 30 mg/g); (ii) Urine sediment abnormalities; (iii) Electrolyte and other abnormalities due to tubular disorders; (iv) Abnormalities detected by histology; (v) Structural abnormalities detected by imaging; (vi) History of kidney transplantation; (2) Or/and decreased glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 (GFR categories G3a–G5) [1, 2]. In accordance to The National Kidney Foundation, CKD is divided into different stages: stage G1 incorporates patients with eGFR > 90 mL/min/1.73 m^2, stage G2 with patients with eGFR 60–90 mL/min/1.73 m^2, stage G3a and G3b with eGFR 45–59 and 30–44 mL/min/1.73 m^2, respectively, stage G4 (4) with eGFR 15–30 mL/min/1.73 m^2, and stage G5 (5) with eGFR < 15 mL/min/1.73 m^2, including hemodialysis patients. Stage G1 or G2 can be diagnosed only when the following abnormalities are presented: structural kidney abnormalities

Address for correspondence: Justyna Domienik-Karłowicz, MD, Department of Internal Medicine and Cardiology with the Center for Diagnosis and Treatment of Venous Thromboembolism, Medical University of Warsaw, ul. Lindley'a 4, 00–005 Warszawa, Poland, tel: +22 502 11 44, fax: +22 502 13 63, e-mail: jdomienik@tlen.pl

Received: 11.11.2018 Accepted: 21.02.2018

or/and proteinuria or/and albuminuria or/and urine sediment abnormalities. Hemorrhagic as well as thrombocytic complications, are common in patients with renal disease [3]. The incidence rate of atrial fibrillation (AF) in patients with CKD stage 5 is about 7–13%, 2–3 times more often than reported for the general population [4, 5].

Kooiman et al. [6] in their multicenter retrospective cohort analyzed the medical charts of AF patients from the Leiden anticoagulation clinic and found CKD (MDRD formula) in 34.2% of AF patients: 30.9% of patients had stage 3 CKD, 2.5% — stage 4, and 0.8% end-stage kidney disease. Moreover, ATRIA investigators confirmed that CKD increases the risk of thromboembolism in AF independently of other risk factors. They observed that an increased risk of stroke is associated with a progressively lower level of eGFR compared to a rate of ≥ 60 mL/min/1.73 m^2: relative risk of 1.16 (95% confidence interval [CI] 0.95–1.40) for eGFR of 45 to 59 mL/min/1.73 m^2 and 1.39 (95% CI 1.13–1.71) for eGFR < 45 mL/min/ 1.73 m^2 (p = 0.0082 for trend) [7, 8].

A different form of anticoagulation

The present study focused on different forms of anticoagulation in a specific group of patients with CKD, due to their universal usage and accumulation risk in impaired renal function [9], usage referring to: heparins, fondaparinux, rivaroxaban, apixaban, edoxaban, dabigatran. Of note, only elimination of unfractionated heparin is independent of renal function. It is important to underline that elimination of low-molecular-weight heparins (LMWH) is cleared by the kidneys and its elimination depends on renal function, therefore higher concentrations can lead to bleeding complications in patients with advanced CKD. Consequently, patients with impaired renal function, increased exposure to enoxaparin is associated with an increased risk of bleeding. Due to a significantly increased concentration of LMWH (enoxaparin, nadroparin, dalteparin, tinzaparin) in blood serum of these patients (G4, G5), a dosage adjustment is required both during the therapeutic and prophylactic use and/or measurement of anti-Xa level is suggested. In hemodialysis patients, the recommended dose of enoxaparin (1 mg/kg) is administered to the arterial line of the extracorporeal circulation at the beginning of dialysis, enough for a 4-h dialysis. If fibrin rings are found, for instance after a longer than usual dialysis, an additional dose of 0.5 mg to 1 mg/kg may be given. In high bleeding risk patients, such as elderly patients, those with CKD, liver disease, cardiovascular diseases, hematological abnormalities (thrombocytopenia, anemia), diabetes mellitus, history of bleeding, vulnerability to drug interactions or due to polypharmacy, the dose should be reduced to 0.5–0.75 mg/kg of body mass [10]. In order to determine the bleeding risk, the following calculators are used: $HEMORR_2HAGES$ score or HAS-BLED score [10]. Moreover, the type of vascular access is also significant for bleeding risk. Damages or infections of central vascular catheters or synthetic arteriovenous grafts, patient-dependent factors, bystander diseases, administered medications, an ability to take care of angioaccess, or finally factors related to the hemodialysis procedure increasing the risk of bleeding complications [11, 12]. Although no dose adjustment is required in patients with moderate CKD, caution is recommended [13, 14].

Fondaparinux is not recommended in patients with GFR < 20 mL/min either [15].

It is excreted mainly (64–77%) by the kidneys as an unchanged compound. Its elimination half-life is about 17 h in healthy young subjects and about 21 h in healthy elderly subjects. It should be noted that patients with eGFR < 50 mL/min are at increased risk of bleeding and venous thromboembolism (VTE). In patients with eGFR > 50 mL/min, no dosage reduction is required. It has been used successfully at a dose of 2.5 mg instilled into the dialysis circuit for anticoagulation during dialysis in patients with heparin-induced thrombocytopenia [15]. According to all recommendations, patients with G3a, G3b, and G4 CKD (eGFR from 20 to 50 mL/min), in order to prevent VTE or in the case of treating superficial venous thrombosis, the dosage needs to be decreased to 1.5 mg one daily. In patients with creatinine clearance (CrCL) > 20 mL/min, treated for unstable angina, non-ST-elevation or ST-elevation myocardial infarction, there is no need to decrease the dosage of the drug, although the data regarding treatment with a dosage of 2.5 mg in the case of CrCL 20–30 mL/min is limited. In the case of treatment of acute deep vein thrombosis and acute pulmonary embolism, depending on body mass, the suggested dosage is from 5 to 10 mg/d (for patients 50–100 kg of body mass the suggested dosage is 7.5 mg once daily s.c. < 50 kg body mass — 5 mg/d, > 100 kg body mass — 10 mg/d). In patients > 100 kg and with CrCL 30–50 mL/min, after administering the initial dose of 10 mg/d it is useful to consider lowering the dosage to 7.5 mg/d. In these cases fondaparinux should not be administered in patients with CrCL

< 30 mL/min. Total fondaparinux clearance is about 40% lower compared to patients with normal renal function. Kalicki et al. a study of 12 patients showed that fondaparinux can anticoagulate the dialysis circuit, although less effective than unfractionated heparin (measured by anti-Xa level and a visual scale of clotting of the circuit) [16, 17].

The therapy with warfarin among patients older than 74 years of age with AF, according to the Alberta Kidney Disease Network, was associated with lower risk of the composite ischemic outcome (all-cause death, ischemic stroke, transient ischemic attack) compared to non-use — adjusted hazard ratio (HR), 95% confidence interval (CI) for eGFR categories ≥ 90, 60–89, 45–59, 30–44, and < 30 mL/min/1.73 m^2: HR 0.59, 95% CI 0.35–1.01, HR 0.61, 95% CI 0.54–0.70, HR 0.55, 95% CI 0.47–0.65, HR 0.54, 95% CI 0.44–0.67, and HR 0.64, 95% CI 0.47–0.87, respectively) [18]. Moreover, in comparison to no therapy, anticoagulation with warfarin was not associated with higher risk of major bleeding, except for those with stage 2 CKD (HR 1.36; 95% CI 1.13–1.64). The therapeutic international normalized ratio recommendation is usually between 2 and 3, but, despite this, patients can have an increased risk of bleeding. This depends on patient age and comorbidities. However, Shah et al. confirmed that routine warfarin use cannot be considered the preferred anticoagulant for reducing the risk of stroke in most patients with AF and CKD [19, 20]. Their study indicated that, in dialysis patients with AF, warfarin use, in comparison with non-use, did not reduce the risk of stroke. Moreover, it is associated with a 44% higher risk of a bleeding event, whereas warfarin use in non-dialysis patients with AF was associated with a 13% lower risk of stroke and a 19% higher risk of a bleeding event [19, 20].

Data from the Danish Registry showed an increased risk of bleeding with warfarin (HR 2.24, 95% CI 2.10–2.38, $p < 0.001$) among all patients who had any renal disease, when compared to those who had no renal disease, and there was an increased risk of bleeding with warfarin (HR 2.70, 95% CI 2.38–2.3.07, $p < 0.001$) among all patients who had CKD requiring renal replacement therapy [21]. The safety and effectiveness of warfarin and direct oral anticoagulants across the range of eGFR in real-world settings was summarized by Shin et al. [22]. The patients with eGFR < 60 mL/min/1.73 m^2 who took direct oral anticoagulants for AF had a slightly higher risk of bleeding compared with those on warfarin, but had similar benefits from the prevention of ischemic stroke [22]. Some researchers focus on other important objections to treatment via warfarin, i.e. the association of warfarin with subcutaneous arteriolar calcification, calciphylaxis [23]. Anticoagulant-related nephropathy (ARN) is a type of acute kidney injury (AKI) that results from severe glomerular hemorrhage in patients receiving supratherapeutic doses of warfarin and mainly in those who already have multiple risk factors for AKI. Usually, ARN appears in the first 3 months after starting warfarin. AKI with unexplained glomerular hemorrhage was also documented in patients who were over-anticoagulated with dabigatran, apixaban and heparin [24–26]. Substantial GFR loss in both the warfarin and dabigatran cohorts is about 2 to 3 mL/min/year. This is 2 to 3 times greater than the expected estimated GFR decline attributable to aging (1 mL/min/year) [27]. The risk may be higher in patients with CKD and is associated with increased mortality (> 25% in the month after the onset of ARN). The risk of ARN at the onset of coagulopathy is about 20% overall and about 37% in patients with CKD [28]. The final diagnosis of ARN can be confirmed after a kidney biopsy is performed. The pathogenesis includes glomerular hemorrhage, predominant lesion of tubular epithelial cell injury and obstruction with red blood cells (RBCs) and RBC casts [29]. Notwithstanding, studies, that have examined the incidence of ARN, have relied upon a presumptive diagnosis of ARN defined as GFR changes from baseline over time according to the level of INR control rather than a histopathological diagnosis [27].

The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with preserved renal function anticoagulated with non-vitamin K antagonist oral anticoagulants due to AF recommends monitoring renal function at least once a year in order to detect deterioration of renal function and for adaptation of dosage [9]. In patients with eGFR < 60 mL/min/1.73 m^2 they recommended evaluation of renal function more frequently [30]. All four non-vitamin K antagonist oral anticoagulants showed better efficacy and safety in patients with stage 1–3 of CKD. Reduced dosages of rivaroxaban, apixaban, and edoxaban are accepted for use in patients with stage 4 CKD; dabigatran should be used only in patients with eGFR > 30 mL/min [30]. There are no studies widely assessing the efficacy and safety of non-vitamin K antagonist oral anticoagulants in patients with stage 5 CKD [30]. However, non-vitamin K anticoagulant treatment in transplanted patients should be used with specific attention due to the risk of

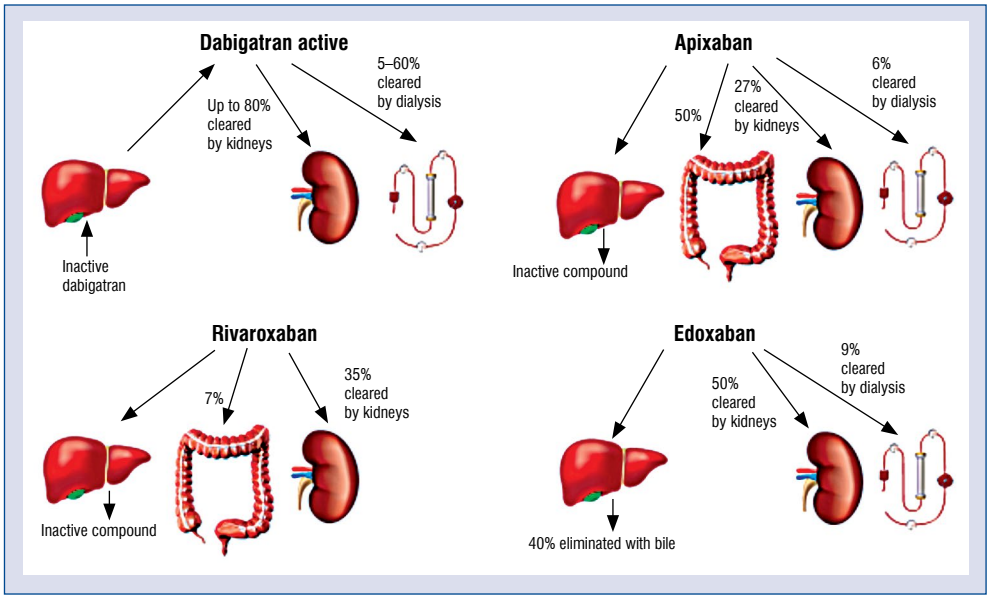


Figure 1. Metabolic aspects or chosen oral anticoagulants.

interactions with calcineurin inhibitors (CNIs). Dabigatran is a substrate of P-gp. CNIs inhibit P-gp. Concurrent CNIs therapy increases bleeding risk. When compared to anti-Xa inhibitors transplant recipients immunosuppressed with CNIs, who were prescribed dabigatran were more likely to require a decrease in tacrolimus dose during therapy and had more major bleeding events. Cyclosporine (CsA) inhibits CYP3A. CsA also led to a substantial inhibition of P-gp activity when compared to tacrolimus or sirolimus. A two-fold increase in rivaroxaban area under curve (AUC) were noted when administered with strong CYP3A4 inhibitors and rivaroxaban-cyclosporine interaction may be clinically more relevant than with tacrolimus [31]. Until more data are available on the interactions between rivaroxaban and CNIs, a rivaroxaban dose should be based on anti-Xa activity, especially in patients receiving CsA [32]. According to the European Summary of Product Characteristics, the dose of edoxaban should be 50% reduced for nonvalvular AF and VTE in patients who concomitantly receive cyclosporine and the recommended dose is 30 mg once daily.

Dabigatran

According to the summary of product characteristics, dabigatran is eliminated up to 80% through the kidneys (Fig. 1). Thus, CKD can easily cause accumulation of the drug. Using dabigatran in patients with eGFR < 30 mL/min/1.73 m^2 is contraindicated in Europe [30]. The mean terminal half-life of dabigatran is approximately 9 h in younger healthy volunteers, is prolonged to 12–16 h in older healthy volunteers, and extended even more — 25–30 h — in individuals with CrCL < 30 mL/min [33]. In patients with G3 CKD, a dose of 75 mg twice daily is recommended, due to confirmation in phase I is that in this group half-time can increase 2.7-fold in comparison to patients without renal impairment. In a small group of volunteers with severe CKD impairment (G4, G5 CKD), the total impact of dabigatran on the body (AUC) was about 6 times higher and the half-life was about two times longer than in a population without renal impairment (Table 1) [30].

Table 1. Half-life of total dabigatran in healthy subjects and subjects with impaired renal function.

GFR CrCL [mL/min]	gMean (gCV%; range) Half-life
≥ 80	13.4 (25.7%; 11.0–21.6)
≥ 50 – < 80	15.3 (42.7%;11.7–34.1)
≥ 30 – < 50	18.4 (18.5%;13.3–23.0)
< 30	27.2(15.3%; 21.6–35.0)

CrCL — creatinine clearance; GFR — glomerular filtration rate

Chan et al. [34] in "Circulation," drew our attention to dabigatran in a population of chronic hemodialysis patients with AF (off label). Dabigatran is partially removed by dialysis, i.e. 62%

of a 50-mg dose in 2 h and 68% of it in 4 h. Most importantly, it increased the risk of bleeding, and did not decrease the stroke risk. The event rate of major bleeding was higher for dabigatran (83.1 events per 100 patient-years) than in comparison to warfarin group (35.9 events per 100 patient-years). The mortality rate from bleeding was higher in patients on dabigatran (19.2 deaths per 100 patient-years) in comparison to warfarin (10.2 deaths per 100 patient-years). It is worth noting that the occurrence of embolic stroke was 9.0/100 patient-years in comparison to warfin (5.8) and the occurrence of arterial embolism was 1.6/100 patient-years in dabigatran group and 0.7 in the warfarin one [34]. Feldberg et al. [35] in their systematic review, which included 10 studies, underlined that for moderate CKD patients (eGFR 30–60 mL/min/1.73 m^2) there was no difference in stroke outcomes between dabigatran 110 mg [HR 0.78, 95% CI 0.51–1.21] and warfarin. However, the risk of stroke or systemic embolism was significantly reduced with dabigatran 150 mg versus warfarin (HR 0.55, 95% CI 0.34–0.89). Either 110 mg or 150 mg dabigatran presented no significant difference in major bleeding when compared to warfarin. In hemodialysis patients, there was no difference in stroke outcomes between dabigatran and warfarin. In this group of patients, dabigatran was associated with an increased major bleeding risk [34, 35].

Rivaroxaban

According to the summary of product characteristics, rivaroxaban is mostly (2/3) metabolized by cytochrome P450 enzymes, half of which is eliminated through the kidneys and the other half being excreted with feces (Fig. 1). Therefore, renal insufficiency resulted in an increase in exposure to rivaroxaban. In individuals with eGFR between 50 and 80 mL/min, G3 CKD and G4 CKD, rivaroxaban plasma concentrations (AUC) were increased 1.4-, 1.5-, and 1.6-fold, respectively. Notably, there are very limited data in patients with end-stage renal disease [36]. However, due to high plasma protein binding, > 90%, rivaroxaban is not expected to be dialyzable [30], even with high flux dialyzers [37]. As aforementioned, Chan et al. [34] in "Circulation," focused on dialyzed patients using oral anticoagulants. The event rate of major bleeding was higher in the rivaroxaban group (68.4 events per 100 patient-years), although lower in the warfarin group (with 35.9 events per 100 patient-years). The mortality rate from bleeding was higher in patients on rivaroxaban (16.2) than on warfarin (10.2). Coleman et al. [38], using US MarketScan claims data, analyzed rivaroxaban and warfarin users with nonvalvular AF and moderate-to-severe CKD. There were no differences in major bleeding or hemorrhagic stroke and an insignificant reduction in systemic embolism and ischemic stroke between cohorts. What is more, in the heart failure group, the hazard of developing stroke, systemic embolism ischemic stroke, or major bleeding was not found to be different between rivaroxaban and warfarin users [38–40]. The ROCKET AF trial included patients with AF and G3 CKD who received a dose of 15 mg/d. In this group, the rates of stroke and systemic embolism were higher when compared to patients with better renal function. Thus, rivaroxaban had no significant benefits in patients with G3 CKD when compared to warfarin [30].

Apixaban

According to the summary of product characteristics, apixaban is eliminated up to 27% via the kidneys (Fig. 1). The fact that this is the lowest value for all non-vitamin K antagonist oral anticoagulants [30] is noteworthy. In the ARISTOTLE trial, patients with AF and mild/moderate renal dysfunction (stage 1–3 CKD) received half a dose of 2 × 2.5 mg/d. Patients with more advanced disease were excluded from the study. Bleeding episodes were less frequent with apixaban in comparison to warfarin in patients with renal dysfunction. Moreover, a more profound analysis of patients with CKD revealed that bleeding episodes and cardiovascular events were more common with impaired renal function [30, 41, 42]. In the retrospective cohort study, which consisted of patients with end-stage kidney disease on dialysis and AF, and compared standard/reduced (5 mg/2.5 mg twice a day) dose of apixaban with warfarin. In matched cohorts, a standard dose of apixaban was associated with lower risk of thromboembolism and mortality compared to reduced-dose apixaban and warfarin. Apixaban use may be also associated with a lower risk of bleeding [43]. However, it should be underlined that special attention is required in solid organ transplant recipients, commonly requiring anticoagulation and being maintained on cyclosporine and tacrolimus. Apixaban exposure probably doubles in this situation and requires dose reduction or avoidance. Kraft et al. (see [44, 45]) examined the drug interactions between cyclosporine (100 mg) and tacrolimus (5 mg) with 10 mg apixaban administered orally in 12 healthy men. Based on this small

study, cyclosporine increased apixaban exposure by 20%, and tacrolimus decreased apixaban exposure by 22% [44, 45].

Edoxaban

According to the summary of product characteristics, edoxaban is eliminated by up to 50% through the kidneys (Fig. 1) [30]. The ENGAGE AF-TIMI 48 Trial evaluated the efficacy and safety of edoxaban versus warfarin for stroke or systemic embolism prevention and bleeding risk across 30–50 mL/min and > 50 mL/min creatinine clearance CKD patients. Bleeding rates were lower at all levels of CrCL with higher dose edoxaban regimen and the risk of stroke or systemic embolism was similar [46]. In the HOKUSAI-VTE trial, edoxaban (30 mg once a day) and warfarin were compared in patients with stage 1–3 CKD. No difference was found between edoxaban and warfarin regarding bleeding events. Moreover, edoxaban (15 mg once a day) and warfarin were compared in patients with stage 4 CKD. No significant difference was revealed between edoxaban and warfarin regarding bleeding events. Notably, in hemodialysis patients, edoxaban was not eliminated and there was no need for an additional dose of edoxaban if a single dose of 15 mg was administered [30]. It is worth noticing that according to product characteristics edoxaban blood levels were lower in patients with better renal function, this means 40% less in patients with eGFR ≥ 95 mL/min when compared to patients with eGFR between 50 and 80 mL/min.

Conclusions

The use of anticoagulants in CKD is common, but for safety reasons it is commonly restricted to patients with stage 1–3 CKD. Dose reductions are necessary for patients with even a moderate reduction of renal function. Further studies are necessary and required.

Conflict of interest: Piotr Pruszczyk — lectures, fees, and advisory boards for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer; Justyna Domienik-Karłowicz, Olga Tronina, Wojciech Lisik — no conflict of interest.

References

1. Beto J, Bhatt N, Gerbeling T, et al. Overview of the 2017 KDIGO CKD-MBD Update: Practice Implications for Adult Hemodialysis Patients. J Ren Nutr. 2019; 29(1): 2–15, doi: 10.1053/j.jrn.2018.05.006, indexed in Pubmed: 30150095.
2. Isakova T, Nickolas TL, Denburg M, et al. KDOQI US Commentary on the 2017 KDIGO Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Am J Kidney Dis. 2017; 70(6): 737–751, doi: 10.1053/j.ajkd.2017.07.019, indexed in Pubmed: 28941764.
3. Lutz J, Menke J, Sollinger D, et al. Haemostasis in chronic kidney disease. Nephrol Dial Transplant. 2014; 29(1): 29–40, doi: 10.1093/ndt/gft209, indexed in Pubmed: 24132242.
4. Charytan D, Patrick A, Liu J, et al. Trends in the use and outcomes of implantable cardioverter-defibrillators in patients undergoing dialysis in the united states. Am J Kidney Dis. 2011; 58(3): 409–417, doi: 10.1053/j.ajkd.2011.03.026.
5. Winkelmayer WC, Patrick AR, Liu J, et al. The increasing prevalence of atrial fibrillation among hemodialysis patients. J Am Soc Nephrol. 2011; 22(2): 349–357, doi: 10.1681/asn.2010050459.
6. Kooiman J, van de Peppel WR, van der Meer FJM, et al. Incidence of chronic kidney disease in patients with atrial fibrillation and its relevance for prescribing new oral antithrombotic drugs. J Thromb Haemost. 2011; 9(8): 1652–1653, doi: 10.1111/j.1538-7836.2011.04347.x, indexed in Pubmed: 21585647.
7. Go AS, Fang MC, Udaltsova N, et al. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. Circulation. 2009; 119(10): 1363–1369, doi: 10.1161/CIRCULATIONAHA.108.816082, indexed in Pubmed: 19255343.
8. Li M, Liu T, Luo Di, et al. Systematic review and meta-analysis of chronic kidney disease as predictor of atrial fibrillation recurrence following catheter ablation. Cardiol J. 2014; 21(1): 89–95, doi: 10.5603/CJ.a2013.0116, indexed in Pubmed: 23990188.
9. Tomaszuk-Kazberuk A, Kołtowski L, Balsam P, et al. Use of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with atrial fibrillation - Messages from the 2018 EHRA. Cardiol J. 2018; 25(4): 423–440, doi: 10.5603/CJ.2018.0080, indexed in Pubmed: 30211927.
10. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016; 149(2): 315–352, doi: 10.1016/j.chest.2015.11.026, indexed in Pubmed: 26867832.
11. Brophy DF, Sica DA. Use of enoxaparin in patients with chronic kidney disease: safety considerations. Drug Saf. 2007; 30(11): 991–994, doi: 10.2165/00002018-200730110-00001, indexed in Pubmed: 17973538.
12. Jose MD, Marshall MR, Read G, et al. Fatal dialysis vascular access hemorrhage. Am J Kidney Dis. 2017; 70(4): 570–575, doi: 10.1053/j.ajkd.2017.05.014, indexed in Pubmed: 28673467.
13. Sciascia S, Radin M, Schreiber K, et al. Chronic kidney disease and anticoagulation: from vitamin K antagonists and heparins to direct oral anticoagulant agents. Intern Emerg Med. 2017; 12(8): 1101–1108, doi: 10.1007/s11739-017-1753-2, indexed in Pubmed: 28929298.
14. Cocco G, Jerie P. New concepts in the therapy of atrial fibrillation. Cardiol J. 2016; 23(1): 3–11, doi: 10.5603/CJ.a2015.0053, indexed in Pubmed: 26412599.
15. Haase M, Bellomo R, Rocktaeschel J, et al. Use of fondaparinux (ARIXTRA) in a dialysis patient with symptomatic heparin-induced thrombocytopaenia type II. Nephrol Dial Transplant. 2005; 20(2): 444–446, doi: 10.1093/ndt/gfh544, indexed in Pubmed: 15673695.
16. Fiaccadori E, Maggiore U, Regolisti G. Balancing thromboembolic risk against vitamin K antagonist-related bleeding and accelerated calcification: is fondaparinux the Holy Grail for end-

stage renal disease patients with atrial fibrillation? Nephrol Dial Transplant. 2013; 28(12): 2923–2928, doi: 10.1093/ndt/gft334, indexed in Pubmed: 24026242.
17. Kalicki R, Aregger F, Alberio L, et al. Use of the pentasaccharide fondaparinux as an anticoagulant during haemodialysis. Thromb Haemost. 2017; 98(12): 1200–1207, doi: 10.1160/th07-07-0444.
18. Tonelli M, Wiebe N, Bello A, et al. Concentrations of trace elements and clinical outcomes in hemodialysis patients: a prospective cohort study. Clin J Am Soc Nephrol. 2018; 13(6): 907–915, doi: 10.2215/CJN.11451017, indexed in Pubmed: 29599300.
19. Lee M, Saver JL, Hong KS, et al. Warfarin use and risk of stroke in patients with atrial fibrillation undergoing hemodialysis: a meta-analysis. Medicine (Baltimore). 2016; 95(6): e2741, doi: 10.1097/MD.0000000000002741, indexed in Pubmed: 26871818.
20. Shah M, Avgil Tsadok M, Jackevicius CA, et al. Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing dialysis. Circulation. 2014; 129(11): 1196–1203, doi: 10.1161/CIRCULATIONAHA.113.004777, indexed in Pubmed: 24452752.
21. Lip GYH, Al-Khatib SM, Cosio FG, et al. Contemporary management of atrial fibrillation: what can clinical registries tell us about stroke prevention and current therapeutic approaches? J Am Heart Assoc. 2014; 3(4), doi: 10.1161/JAHA.114.001179, indexed in Pubmed: 25164944.
22. Shin JI, Secora A, Alexander GC, et al. Risks and Benefits of Direct Oral Anticoagulants across the Spectrum of GFR among Incident and Prevalent Patients with Atrial Fibrillation. Clin J Am Soc Nephrol. 2018; 13(8): 1144–1152, doi: 10.2215/CJN.13811217, indexed in Pubmed: 30002224.
23. Han KH, O'Neill WC. Increased peripheral arterial calcification in patients receiving warfarin. J Am Heart Assoc. 2016; 5(1), doi: 10.1161/JAHA.115.002665, indexed in Pubmed: 26811161.
24. Brodsky SV, Hebert LA. Anticoagulant-Related nephropathy: is an AKI elephant hiding in plain view? J Am Coll Cardiol. 2016; 68(21): 2284–2286, doi: 10.1016/j.jacc.2016.09.926, indexed in Pubmed: 27884246.
25. Brodsky SV. Acute kidney injury aggravated by treatment initiation with apixaban: Another twist of anticoagulant-related nephropathy. Kidney Res Clin Pract. 2017; 36(4): 387–392.
26. Ryan M, Ware K, Qamri Z, et al. Warfarin-related nephropathy is the tip of the iceberg: direct thrombin inhibitor dabigatran induces glomerular hemorrhage with acute kidney injury in rats. Nephrol Dial Transplant. 2014; 29(12): 2228–2234, doi: 10.1093/ndt/gft380, indexed in Pubmed: 24009280.
27. Böhm M, Ezekowitz MD, Connolly SJ, et al. Changes in renal function in patients with atrial fibrillation: an analysis from the RE-LY trial. J Am Coll Cardiol. 2015; 65(23): 2481–2493, doi: 10.1016/j.jacc.2015.03.577, indexed in Pubmed: 26065986.
28. Wheeler DS, Giugliano RP, Rangaswami J. Anticoagulation-related nephropathy. J Thromb Haemost. 2016; 14(3): 461–467, doi: 10.1111/jth.13229, indexed in Pubmed: 26670286.
29. Golbin L, Vigneau C, Touchard G, et al. Warfarin-related nephropathy induced by three different vitamin K antagonists: analysis of 13 biopsy-proven cases. Clin Kidney J. 2017; 10(3): 381–388, doi: 10.1093/ckj/sfw133, indexed in Pubmed: 28616216.
30. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018; 39(16): 1330–1393, doi: 10.1093/eurheartj/ehy136, indexed in Pubmed: 29562325.
31. Wannhoff A, Weiss KH, Schemmer P, et al. Increased levels of rivaroxaban in patients after liver transplantation treated with cyclosporine A. Transplantation. 2014; 98(2): e12–e13, doi: 10.1097/TP.0000000000000223, indexed in Pubmed: 25022236.
32. Wannhoff A, Weiss K, Schemmer P, et al. Increased anti-xa activity of rivaroxaban in patients after liver transplantation treated with cyclosporine A. Transplantation. 2014; 98: 712, doi: 10.1097/00007890-201407151-02421.
33. Knauf F, Chaknos CM, Berns JS, et al. Dabigatran and kidney disease: a bad combination. Clin J Am Soc Nephrol. 2013; 8(9): 1591–1597, doi: 10.2215/CJN.01260213, indexed in Pubmed: 23868901.
34. Chan KE, Edelman ER, Wenger JB, et al. Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. Circulation. 2015; 131(11): 972–979, doi: 10.1161/CIRCULATIONAHA.114.014113, indexed in Pubmed: 25595139.
35. Feldberg J, Patel P, Farrell A, et al. A systematic review of direct oral anticoagulant use in chronic kidney disease and dialysis patients with atrial fibrillation. Nephrol Dial Transplant. 2019; 34(2): 265–277, doi: 10.1093/ndt/gfy031, indexed in Pubmed: 29509922.
36. Klil-Drori AJ, Tagalakis V. Direct oral anticoagulants in end-stage renal disease. Semin Thromb Hemost. 2018; 44(4): 353–363, doi: 10.1055/s-0037-1621715, indexed in Pubmed: 29320795.
37. Muster H, Alcorn H. Rivaroxaban in chronic hemodialysis patients. Am J Nephrol. 2016; 43(4): 227–228, doi: 10.1159/000445329, indexed in Pubmed: 27100995.
38. Coleman CJ, Turpie AGG, Bunz TJ, et al. Effectiveness and safety of rivaroxaban versus warfarin in frail patients with venous thromboembolism. Am J Med. 2018; 131(8): 933–938, doi: 10.1016/j.amjmed.2018.02.015, indexed in Pubmed: 29526541.
39. Martinez BK, Bunz TJ, Eriksson D, et al. Effectiveness and safety of rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation and heart failure. ESC Heart Fail. 2019; 6(1): 10–15, doi: 10.1002/ehf2.12365, indexed in Pubmed: 30299591.
40. Coleman CI, Weeda ER, Nguyen E, et al. Effectiveness and safety of rivaroxaban vs. warfarin in patients 80+ years of age with non-valvular atrial fibrillation. Eur Heart J Qual Care Clin Outcomes. 2018; 4(4): 328–329, doi: 10.1093/ehjqcco/qcx044, indexed in Pubmed: 29121212.
41. Lutz J, Jurk K, Schinzel H. Direct oral anticoagulants in patients with chronic kidney disease: patient selection and special considerations. Int J Nephrol Renovasc Dis. 2017; 10: 135–143, doi: 10.2147/ijnrd.s105771.
42. Granger CB, Alexander JH, McMurray JJV, et al. ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011; 365(11): 981–992, doi: 10.1056/NEJMoa1107039, indexed in Pubmed: 21870978.
43. Siontis KC. Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States. Circulation. 2018; 138(15): 1519–1529.
44. Christians U, Jacobsen W, Benet LZ, et al. Mechanisms of clinically relevant drug interactions associated with tacrolimus. Clin Pharmacokinet. 2002; 41(11): 813–851, doi: 10.2165/00003088-200241110-00003, indexed in Pubmed: 12190331.
45. Bashir B, Stickle DF, Chervoneva I, et al. Drug-drug interaction study of apixaban with cyclosporine and tacrolimus in healthy volunteers. Clin Transl Sci. 2018; 11(6): 590–596, doi: 10.1111/cts.12580, indexed in Pubmed: 29972633.
46. Bohula EA, Giugliano RP, Ruff CT, et al. Impact of renal function on outcomes with edoxaban in the ENGAGE AF-TIMI 48 trial. Circulation. 2016; 134(1): 24–36, doi: 10.1161/CIRCULATIONAHA.116.022361, indexed in Pubmed: 27358434.

VIA MEDICA

TECHNOLOGY NOTE

Cardiology Journal
2020, Vol. 27, No. 6, 875–878
DOI: 10.5603/CJ.a2020.0136

ISSN 1897–5593
eISSN 1898–018X

Feasibility of airway segmentation from three-dimensional rotational angiography

Sebastian Goreczny[1, 2], Alexander Haak[2, 3, 4], Gareth John Morgan[2, 3], Jenny Zablah[2, 3]

[1]Polish Mother's Memorial Hospital, Research Institute, Lodz, Poland
[2]Children's Hospital of Colorado, Aurora, Colorado, United States
[3]University of Colorado Hospital, Aurora, Colorado, United States
[4]Philips Healthcare, Andover, Massachusetts, United States

Introduction

Stent implantation for vascular lesions, as with branch pulmonary artery stenosis in patients with congenital heart disease has become a standard procedure with proven long-term efficacy [1]. Compression of an airway by a stent placed in an adjacent branch pulmonary artery is a rare but recognized complication, especially in patients with a complex cardiac anatomy [2]. This potential complication highlights the importance of adequate visualization of the vessel-airway relationship, which may influence an intervention plan in the cardiac catheterization laboratory [3, 4].

Flexible bronchoscopy has been used to guide endovascular stenting decreasing the risk of catastrophic airway compression [5]. Other specialists prefer cross-section imaging such as magnetic resonance imaging or computed tomography (CT) of the chest to better assess the vessel/airway relationship prior to a procedure and interventional planning [6].

Over the last decade three-dimensional rotational angiography (3DRA) has become a useful tool to assess complex cardiac anatomy in the catheterization laboratory [7]. The incremental adoption of 3DRA in clinical practice has demonstrated the advantages in identifying these anatomical spatial relationships in patients with congenital heart disease. The technique described herein, displays this relationship by simultaneous airway and vascular segmentation and reconstruction from 3DRA using commercially available tools.

The limitation

Although 3DRA has been gaining wider acceptance, there are few reports exploring the potential for integrating airway and vascular structures with this imaging modality. Truong et al. [8] showed the feasibility of creating multiplanar reformat images of the airways after 3DRA but were not able to segment them or produce a 3D reconstruction. A few reports describe the use of 3DRA for 3D presentation of topological airway relationships using a vendor specific angiographic software package [4, 9].

The solution

Outside cardiology, tools have been developed to facilitate identification and segmentation of anatomic features using cone beam CT (XperCT, Philips Healthcare) in a multi-slice 3D view, to guide interventional procedures like biopsies and embolization [10]. The present study investigated the use of interventional radiology software tool utilizing 3DRA images to develop a protocol for airway segmentation and reconstruction during cardiac catheterization in patients with congenital heart defects. XperGuide (Philips Healthcare) is a segmentation tool which allows stepwise 3D segmentation of structures with a low contrast ratio and irregular boundaries [10]. We developed a method of using this software package to allow presentation of the airway and the airway-vessel (pulmonary artery) relationship (Fig. 1). On

Address for correspondence: Sebastian Goreczny, MD, PhD, Department of Cardiology, Polish Mother's Memorial Hospital, Research Institute, ul. Rzgowska 281/289, 93–338 Łódź, Poland, tel: +48 42 271 14 78, fax: +48 42 271 14 70, e-mail: sebastiangoreczny@yahoo.pl

Received: 26.10.2020 Accepted: 13.10.2020

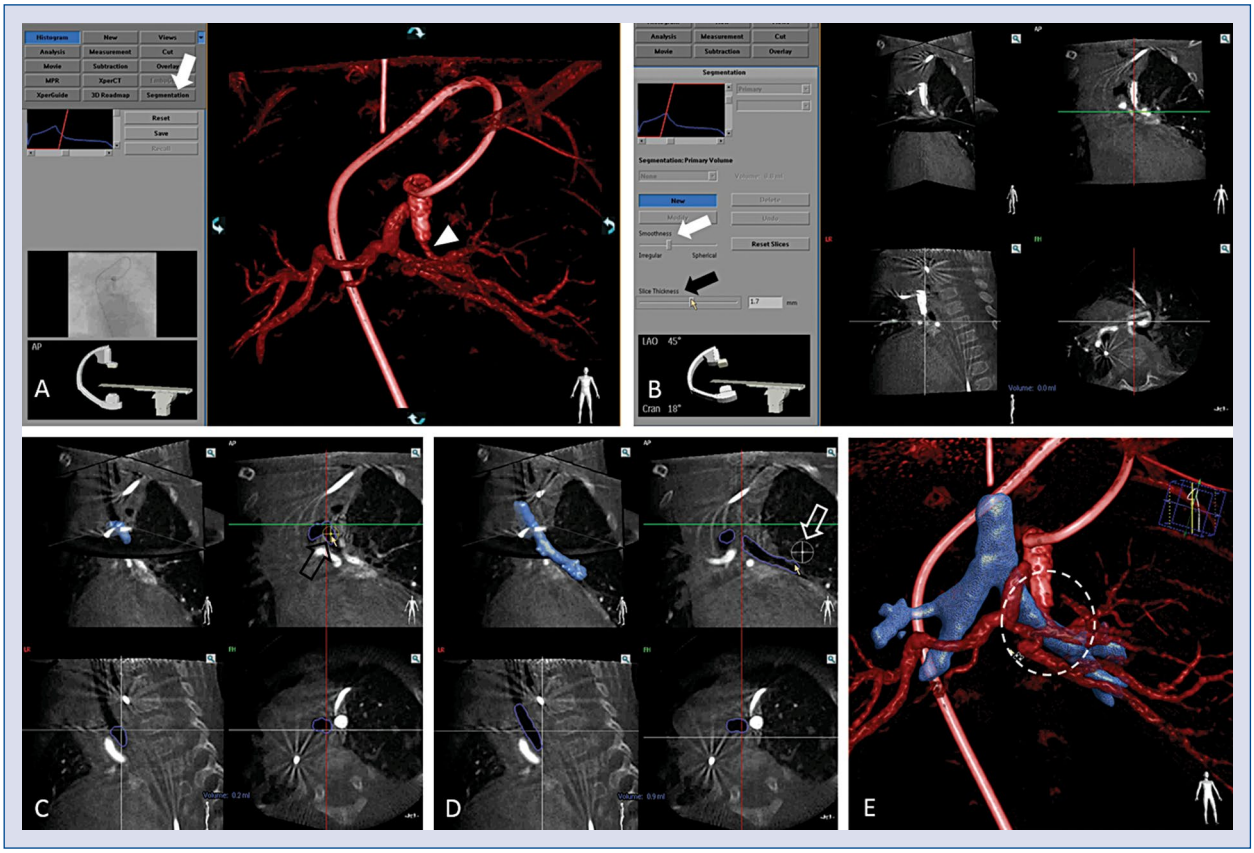


Figure 1. Step by step airway segmentation from three-dimensional rotational angiography (3DRA) in a patient after previous stent implantation to a major aorto-pulmonary collateral artery (MAPCA). A vascular reconstruction from 3DRA shows the narrow segment (white arrowhead) of the MAPCA distal to the previously implanted stent (**A**). Airway segmentation (white arrow) with XperGuide (Philips Healthcare) was performed for better visualization of the mechanism of the narrowing. Segmentation of the airway was conducted on three perpendicular planes of multiplanar reformats (**B**). At the beginning of the segmentation smoothness of the 3D airway and slice thickness of multiplanar reformats was selected according to operator preference. Manual growing of the airway was commenced at the level of the distal trachea and the proximal left main bronchus (black empty arrow) (**C**). Distal left main bronchus was corrected from outside (white empty arrow) (**D**). Finally, the vascular and airway 3D volumes were presented together clearly showing compression of the left main bronchus on distal segment of MAPCA (white dashed circle) (**E**).

a 3DRA data set the airway has a dark contrast (air) and can be manually segmented easily. Contrast filled pulmonary arteries can be automatically segmented and reconstructed with the potential for manual corrections where necessary. Both the vascular and airway structures can then be presented in the same virtual space allowing 3D visualization of the vessel and airway relationship (Fig. 2A–C). This complex can then be projected onto live fluoroscopy to guide cardiac catheterization.

The validation

Three-dimensional rotational angiography was performed in 23 patients for visualization of pulmonary arteries. Seventeen patients had biventricular circulations, whist the remaining 6 had single ventricle cardiac physiology at various stages of palliation. Figure 2D shows patient characteristics and procedural data. Airway segmentation was performed successfully in 21 patients (21/23, 91.3%). In 1 patient the isocenter of the imaging apparatus was set too anteriorly, resulting in only partial inclusion of the airway in the 3D volume. In the other patient, extensive artifacts from multiple, previously implanted vascular occlusion coils did not allow accurate visualization of the airways for segmentation.

The trachea was segmented in all patients (21), the left and right main bronchus in 21 (100%) and 20 (95%) patients, respectively (Fig. 2E).

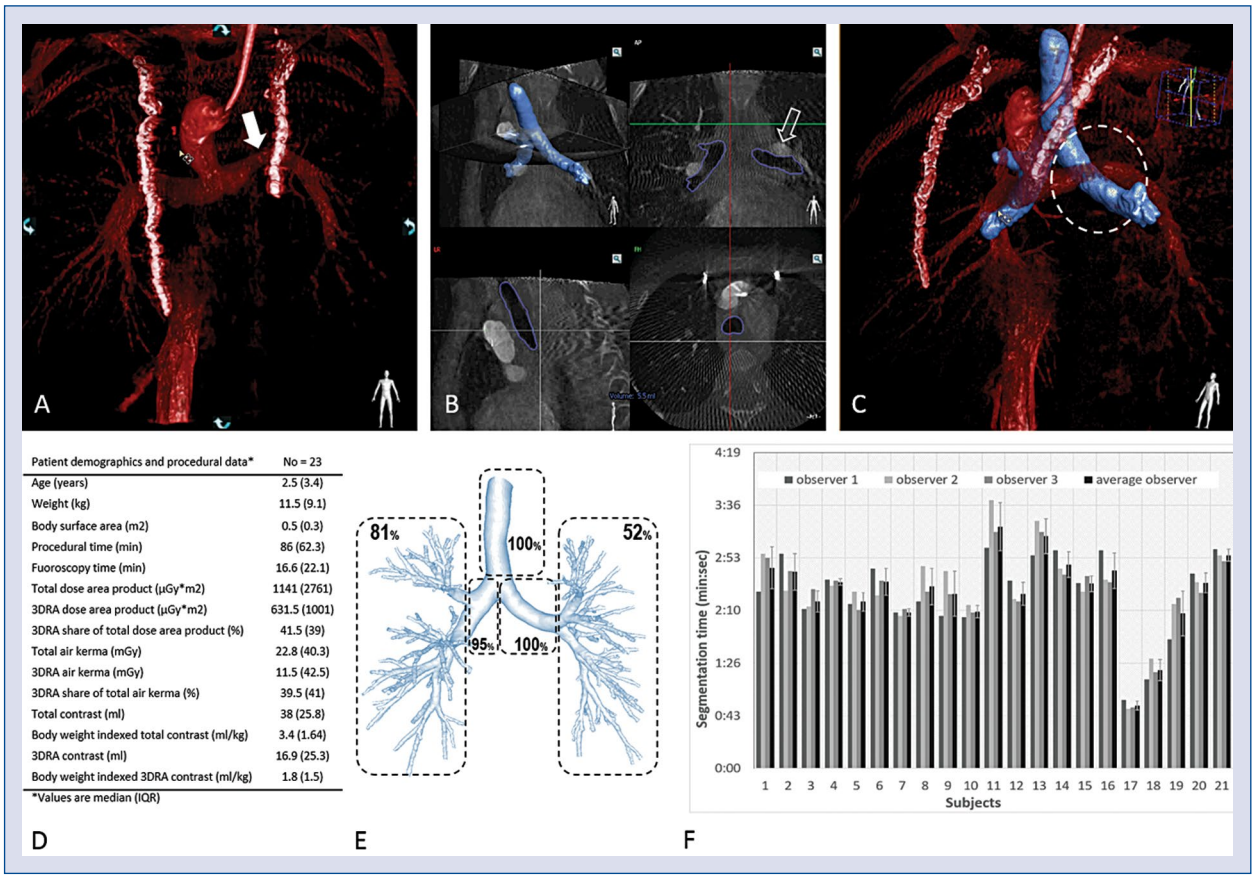


Figure 2. Example of airway segmentation (XperGuide, Philips Healthcare) from three-dimensional rotational angiography (3DRA) in patients after partial cavo-pulmonary connections (**A–C**). A raw reconstruction from 3DRA shows narrowing of the proximal left pulmonary artery (LPA, white arrow) (**A**). Already during airway segmentation on multiplanar reformats close relationship between the LPA (white empty arrow) and the left main bronchus (LMB) was noted (**B**). The vascular and airway 3D volumes, presented together, clearly reveal close relationships between the LPA and the LMB (white dashed circle) (**C**). Patient demographics and procedural data (**D**). Percentage of successful segmentation of particular airway segments (**E**). Comparison of the segmentation times of the three independent observers (observer 1–3) and the average segmentation time (average observer) (**F**). The error bars represent the standard deviation of the segmentation time between the three observers. It can be noted that there was a good agreement in the segmentation times between the observers indicating that segmentation complexity and difficulties were experienced similarly.

Three patients were surreptitiously identified with airway anatomy variants or anomalies including 1 tracheal right upper bronchus, 1 patient diagnosed with right atrial isomerism based on the identification of bilateral morphological right bronchial anatomy, and 1 patient was noted to have major aortopulmonary collateral compression caused by the adjacent airway (Fig. 1). The median time for segmentation and production of an airway and vascular reconstruction was 2.4 (range 0.81–3.81) min with no significant time difference between the three operators ($p = 0.9$; Fig. 2F).

Conclusions

This study shows the feasibility of quick and accurate airway segmentation from 3DRA. Segmentation of proximal airways was possible during a routine 3DRA acquisition of pulmonary arteries without any dedicated airway imaging protocol. As well as providing important incidental diagnoses in 3 patients, this rapid process provided valuable information for decision making and procedural guidance with overlay on live fluoroscopy. Further studies are warranted to explore clinical benefits of this technique of airway segmentation.

Conflict of interest: Alexander Haak is an employee of Philips Healthcare.

References

1. Ing FF, Khan A, Kobayashi D, et al. Pulmonary artery stents in the recent era: Immediate and intermediate follow-up. Catheter Cardiovasc Interv. 2014; 84(7): 1123–1130, doi: 10.1002/ccd.25567, indexed in Pubmed: 24910458.
2. Moszura T, Mazurek-Kula A, Dryzek P, et al. Bronchial compression as adverse effect of left pulmonary artery stenting in a patient with hypoplastic left heart syndrome. Pediatr Cardiol. 2010; 31(4): 530–533, doi: 10.1007/s00246-009-9601-4, indexed in Pubmed: 19937008.
3. Moszura T, Dryzek P, Goreczny S, et al. A 10-year single-centre experience in percutaneous interventions for multi-stage treatment of hypoplastic left heart syndrome. Cardiol Young. 2014; 24(1): 54–63, doi: 10.1017/S104795111200220X, indexed in Pubmed: 23402359.
4. Krings GJ, van der Stelt F, Molenschot MMC, et al. Oval stenting in left pulmonary artery stenosis: a novel double balloon technique to prevent airway compression in single ventricle. EuroIntervention. 2020; 15(13): 1209–1215, doi: 10.4244/EIJ-D-18-01079, indexed in Pubmed: 30834894.
5. Ebrahim M, Hagood J, Moore J, et al. Bronchoscopic guidance of endovascular stenting limits airway compression. Catheter Cardiovasc Interv. 2015; 85(5): 832–836, doi: 10.1002/ccd.25772, indexed in Pubmed: 25504498.
6. Grohmann J, Stiller B, Neumann E, et al. Bronchial compression following pulmonary artery stenting in single ventricle lesions: how to prevent, and how to decompress. Clin Res Cardiol. 2016; 105(4): 323–331, doi: 10.1007/s00392-015-0924-2, indexed in Pubmed: 26415706.
7. Góreczny S, Krings G, Hijazi ZM, et al. Pros, cons and future perspectives - three questions on three dimensional guidance for cardiac catheterization in congenital heart disease. Post Kardiol Interw. 2019; 15(3): 263–273, doi: 10.5114/aic.2019.87688, indexed in Pubmed: 31592250.
8. Truong UT, Fagan TE, Deterding R, et al. Use of rotational angiography in assessing relationship of the airway to vasculature during cardiac catheterization. Catheter Cardiovasc Interv. 2015; 86(6): 1068–1077, doi: 10.1002/ccd.26004, indexed in Pubmed: 26279410.
9. Borik S, Volodina S, Chaturvedi R, et al. Three-dimensional rotational angiography in the assessment of vascular and airway compression in children after a cavopulmonary anastomosis. Pediatr Cardiol. 2015; 36(5): 1083–1089, doi: 10.1007/s00246-015-1130-8, indexed in Pubmed: 25762468.
10. Fu ZY, Feng Yu, Ma C, et al. Endovascular treatment of cavernous sinus dural arteriovenous fistulas via direct transorbital puncture using cone-beam computed tomography image guidance: report of 3 cases. World Neurosurg. 2019; 130: 306–312, doi: 10.1016/j.wneu.2019.07.002, indexed in Pubmed: 31299303.

VIA MEDICA

STUDY PROTOCOL

Cardiology Journal
2020, Vol. 27, No. 6, 879–883
DOI: 10.5603/CJ.a2020.0137

ISSN 1897–5593
eISSN 1898–018X

Pomeranian atRial flOw reguLatOr iN conGestive hEart failuRe (PROLONGER): Study protocol

Łukasz Lewicki[1, 3], Katarzyna Kosmalska[2], Sebastian Liedtke[3], Maciej Karwowski[3], Janusz Siebert[1, 4], Robert Sabiniewicz[5], Jakub Kiedrzyn[3], Adrian Kot[3], Marek Szołkiewicz[3]

[1]University Center for Cardiology, Gdansk, Poland
[2]Department of Cardiology, Pomeranian Hospitals, Gdynia, Poland
[3]Department of Cardiology and Angiology, Kashubian Center for Heart and Vascular Diseases, Pomeranian Hospitals, Wejherowo, Poland
[4]Department of Family Medicine, Medical University of Gdansk, Poland
[5]Department of Pediatric Cardiology and Congenital Heart Disease, Medical University of Gdansk, Poland

Background

Heart failure (HF) remains as important challenge in cardiovascular medicine. The incidence increases with age reaching 10% of the human population after the seventh decade of life [1, 2]. Despite advances in HF therapy, morbidity remains high regardless of HF etiology. Treatment is focused mainly on the reduction of symptoms; however, it has been shown to date that a reduction in mortality was achieved only in heart failure patients with reduced ejection fraction (HFrEF) [3]. On top of that, the group of patients with heart failure with preserved ejection fraction (HFpEF) continues to grow.

The diastolic dysfunction, which is common among HFpEF patients is mainly driven by diminished left ventricle relaxation, increased volume and filling pressures in the left atrium that leads to pulmonary congestion [4, 5]. In these patients, treatment options are limited mainly to diuretics.

A novel conception of therapy based on creating a communication between both atria has been proposed recently. The left to right interatrial shunt enables decompression of the left atrium and thus may improve patient symptoms [6, 7].

There are three different devices available for patients with either HFrEF or HFpEF: interatrial shunt device (IASD, Corvia Medical Inc., Tewksbury, MA, USA); V-Wave shunt (V-Wave Ltd., Caesarea, Israel) and the Atrial Flow Regulator (AFR, Occlutech, Heslingborg, Sweden). The initial safety and efficacy have been proved for the first two devices in small studies [6, 7]. Atrial Flow Regulator is a self-expandable double-disc nitinol wire mesh construction allowing communication across the interatrial septum. The offered fenestration diameter ranges from 4 mm to 10 mm, but for HF patients only the 8 mm and 10 mm have the European CE mark. The device is fully repositionable and retrievable.

There are few data concerning the effectiveness of interatrial shunting. It is reasonable to focus on defining clinical and hemodynamic parameters, thus predicting who would benefit from interatrial shunting. The Pomeranian atRial flOw reguLatOr iN conGestive hEart failuRe (PROLONGER) study was designed for this purpose.

Methods

Study design

The PROLONGER study (ClinicalTrials.gov identifier NCT04334694) is a prospective, open-label clinical trial aimed to define invasive and non-invasive parameters that could predict a positive response for AFR therapy among patients with HF. The observation period will include peri-procedural hospitalization and a 12 month follow-up with four control visits: after 1, 3, 6 and 12 months, respectively.

Address for correspondence: Łukasz Lewicki, MD, PhD, University Center for Cardiology, ul. Dębinki 2, 80–211 Gdańsk, Poland, tel: +48 501 702 885, e-mail: luklewicki@gmail.com

Received: 21.05.2020 Accepted: 13.10.2020

Patients' selection

Around 30 patients will be enrolled. The main inclusion criterion is symptomatic HF, either HFrEF or HFpEF. An elevated left heart filling pressure has to be confirmed in all eligible patients before the AFR procedure. Detailed inclusion and exclusion criteria are presented in Table 1.

Blinding (masking)

As the PROLONGER is an open-label, single--arm study, both the participants and investigators will not be blinded to the allocated intervention.

Interventions

All eligible patients will undergo detailed screening using echocardiography, impedance cardiography (ICG) and right heart catheterization prior to AFR implantation.

Echocardiography. The transthoracic echocardiography (TTE) examinations will be taken as recommended by European Society of Cardiology (ESC) and American Heart Association (AHA). Patients will be imaged in the left lateral decubitus position. Images will be obtained in the parasternal and apical chamber views.

The echocardiography protocol consists of the following elements recorded with three cardiac cycles loop recordings:

— Long axis view (LAX): Dimensions of left and right ventricles, left atrium, morphology and function of aortic and mitral valves;
— Short axis view (SAX): Morphology and function of aortic and pulmonic valves; pulse wave Doppler in right ventricle outflow tract (RVOT) (assessment of acceleration time);
— Apical 4 and 2 C plane:
  - Assessment of right ventricle dimension right ventricle inflow tract (RVIT), right atrium area, left atrium volume index (LAVI),
  - Assessment of left ventricle systolic function (ejection fraction by Simpson method and by speckle tracking imaging),
  - Assessment of left ventricle diastolic function (by using mitral flow, mitral annulus diastolic velocity, left atrial volume, tricuspid regurgitation (TR) velocity,
  - Assessment of right ventricle systolic function by tricuspid annular plane systolic excursion (TAPSE), right ventricle fractional area change and speckle tracking imaging,
  - Morphology and function of mitral valve,
  - Mechanism and quantitative assessment of mitral regurgitation,
  - Morphology and function of aortic valve,

Table 1. The inclusion and exclusion criteria in PROLONGER study.

Inclusion criteria	
1	Age ≥ 18 years
2	Symptomatic HF in NYHA class III or IV ambulatory
3	Optimal medical therapy of HF according to ESC guidelines for last 6 months
4	Hospitalization because of HF decompensation in last 12 months
5	Absence of significant valvular disease requiring cardiac surgery
6	Life expectancy ≥ 1 year
7	Written informed consent obtained from the patient
8	Left ventricular ejection fraction ≥ 15%
9	Elevated left heart filling pressures: • PAWP in rest > 15 mmHg or • PAWP > 25 mmHg during handgrip test
Exclusion criteria	
1	Participation in another clinical trial in last 30 days
2	Acute infection or sepsis
3	Severe coagulation disorder
4	Allergy to nickel or titanium
5	Severe peripheral artery disease disabling 6MWT
6	Allergy to antiplatelet drugs, oral anticoagulation or heparin
7	Contraindications to transesophageal echocardiography
8	Pregnancy
9	ASD or presence of ASD septal occluder
10	Severe PFO with significant left to right shunt in rest
11	Intracardiac thrombus
12	ACS or PCI or CABG in last 6 months
13	Severe pulmonary hypertension: • Right atrial pressure ≥ PAWP • Right atrial pressure ≥ 20 mmHg
14	Planned heart transplantation
15	TIA or stroke within last 6 months
16	CRT therapy within last 6 months

HF — heart failure; NYHA — New York Heart Association; ESC — European Society of Cardiology; PAWP — pulmonary artery wedge pressure; 6MWT — six-minute walk test; ASD — atrial septal defect; PFO — patent foramen ovale; ACS — acute coronary syndrome; PCI — percutaneous coronary intervention; CABG — coronary artery bypass grafting; TIA — transient ischemic attack; CRT — cardiac resynchronization therapy

- Morphology and function of tricuspid valve,
- Quantitative assessment of tricuspid regurgitation;

— Subcostal view:
- Position and flow (color Doppler) in AFR device, flow gradient (continuous wave Doppler).

The TTE examinations will be done before AFR and during each follow up visit.

All patients will also be imaged with transesophageal echocardiography (TEE) in standard views to:

— Exclude intra-cardiac thrombus;
— Exclude presence of patent foramen ovale (PFO) or atrial septal defect (ASD);
— Assess anatomy of interatrial septum.

The TEE examinations will be done prior to AFR procedure and during the first follow up visit.

Impedance cardiography. All patients will be examined using an ICG.

The PhysioFlow® Q-LinkTM is a noninvasive hemodynamic evaluation system to assess patient cardiovascular state using the analysis of transthoracic bio-impedance signals.

PhysioFlow System measures the change in impedance by injecting a high frequency alternating electrical current (66 kHz) of low magnitude (4.5 mA peak to peak) towards the thorax between two electrodes positioned on the neck and another two positioned on xiphoïd process. The use of a high frequency current eliminates the risk of interference with heart and brain bioelectrical activity. In addition, as the impedance of skin-electrodes is very low at high frequency, tissues will not endure any thermal effects and patients feels nothing.

Specific calculations conducted, as part of further analysis will be based on values obtained in the supine position.

The measurement scheme will be as follows: the first ICG will be done 1 day prior to the AFR procedure. Four ICG and two ECG pre-gelled electrodes will be placed: two (Z1, Z2) on the left side of the patient's neck, one (Z3) at the level of the xiphoid and the last one (Z4) just to the right to Z3. The ICG data will be collected continuously (beat by beat) for 30 min. The blood pressure will be taken every 10 min and stored for analysis. The following parameters will be measured continuously: cardiac index (CI [l/min/m^2]), stroke volume index (SVi [mL/m^2]), left cardiac work index (LCWi [kg·m/m^2]), contractility index (CTi), ventricular ejection time (VET [ms]), systemic vascular resistance index (SVRi [dyn·s/cm^5·m^2]), thoracic fluid content index (TFCi [1/kΩ·m^2]) and heart rate (HR [1/min]).

The values of these parameters will be recorded beat-to-beat. Specific calculations conducted, as part of further analysis, will be based on the values obtained in the supine position.

The ICG examinations will be done before AFR and during each follow up visit.

Invasive right heart catheterization. All eligible patients before enrolling to the study will undergo a diagnostic right heart catheterization using a Swan-Ganz catheter (SGC). After ultrasound-guided puncture of internal jugular or subclavian vein, a SGC will be introduced via the right ventricle to a pulmonary artery. The following pressure curves will be obtained in patients at rest:

— Right atrium/upper vena cava pressure;
— Right ventricle pressure;
— Mean pulmonary artery pressure;
— Pulmonary artery wedge pressure (PAWP).

Furthermore, a cardiac output (CO) will be measured using the thermodilution method.

The following hemodynamic parameters will be calculated:

— Cardiac index;
— Systemic vascular resistance;
— Pulmonary vascular resistance.

In the next step, subjects will be asked to perform a handgrip test for a maximal tolerated period of time until fatigued. The measurement of PAWP and CO will then be obtained.

If a resting PAWP will be above 15 mmHg or exercise PAWP above 25 mmHg, patients will be qualified for AFR implantation. A right atrial pressure above 20 mmHg or exceeding PAWP will be the contraindication for the atrial shunting procedure.

Invasive catheterization will be performed before AFR and during the first follow up visit.

The AFR procedure. The procedure will be performed under general anesthesia. A three-dimensional TEE guided trans-septal puncture will be performed followed by insertion of an Amplatzer Stiff wire in a left upper pulmonary vein. Next, a 10–14 mm diameter balloon septostomy to facilitate AFR implantation through a 12–14 F dedicated delivery system. Before releasing the device, an invasive trans atrial gradient will be measured through an 8–10 mm fenestration. The left to right shunt and mean gradient will be confirmed in TEE. After releasing an AFR device, a delivery system will be removed and a puncture site will be sealed with hemostatic suture.

The patients will be discharged during the following couple of days. Subjects with history of atrial fibrillation will continue anticoagulation therapy and those without atrial fibrillation will be treated with double antiplatelet drugs for 3 months.

Outcomes

Primary outcome measures. The primary outcome is clinical improvement within 12 months after AFR implantation defined as at least 10% increase in six-minute walk test (6MWT) compared to baseline.

Secondary outcomes measures. (1) Clinical improvement expressed in reduction of New York Heart Association (NYHA) class; (2) Device related adverse event: device migration, embolization, device related thrombus, shunt occlusion, or need for device removal.

Other outcome measures. (1) Reduction of PAWP at rest 30 days after AFR implantation. (2) Reduction of PAWP during a handgrip test 30 days after AFR implantation. (3) Kansas City Cardiomyopathy Questionnaire (KCCQ-12) within 12 months after AFR implantation. (4) Clinical adverse events within 12 months after AFR implantation: cardiac mortality or rehospitalization for HF decompensation.

Correlation of echocardiographic, invasive and impedance parameters with clinical outcome. All hemodynamic data will be analyzed post-hoc to test any correlation with clinical outcome after AFR procedure.

Data collection and management

All clinical data including demographic information, results of blood laboratory tests performed locally will be stored for further analysis. Digital files containing raw data obtained from echocardiography and fluoroscopy will also be collected.

Statistical methods

Continuous data will be summarized by means of mean value, median, minimum, maximum, standard deviation and number of observations. Categorical data will be expressed as means of absolute and relative frequencies. A series of statistical tests including: the Shapiro-Wilk test, ANOVA, unpaired t-test, the Mann-Whitney U or χ^2 test will be done. Clinical adverse events will be tabulated.

Ethical considerations

A local ethics committee has approved the PROLONGER study protocol.

Discussion

The concept of creating an interatrial shunt leading to decompression of left atrium is an attractive therapy for patients with HF.

Presented herein, is the PROLONGER study protocol. This is a single center, open label clinical study aimed at defining invasive and non-invasive clinical parameters that could predict a positive response for implantation of AFR.

Three available shunt devices have been tested in a series of small studies to date. The initial results are promising; however, the question of which population would benefit most from interatrial shunting has been raised.

In the AFR PRELIEVE study some, but not all patients showed symptoms improvement. The 6MWT distance significantly increased only among HFrEF patients. The interpretation of single statistically significant results such as change in NYHA class or increase in 6MWT distance should be cautious, because the patient numbers were small. Both HFpEF and HFrEF patients presented reduced resting PAWP compared to baseline, however only in HFpEF subjects, the difference reached statistical significance [8].

In the present study we are going to focus on clinical parameters as: 6MWT test and NYHA functional class.

Although the study is not designed to show device related adverse events, these will also be reported.

A hemodynamic profile will be assessed by an invasive right heart catheterization as well as using non-invasive impedance cardiography.

The ICG is a non-invasive diagnostic tool enabling reliable assessment of patients' hemodynamic profile [9–13].

There are data supporting a good correlation between impedance diagnostics and invasive assessment of cardiac output and systemic vascular resistance [14]. Our previous experience with this procedure in patients with acute myocardial infarction was recently published [15].

Unlike previously published studies, the focus will be to perform exercise invasive catheterization using a simple handgrip test instead of standard cyclo-ergometer. Although a handgrip test in not well validated, it allows a patient to perform significant exertion.

The hemodynamic data obtained from SGC and ICG will be analyzed post-hoc in order to seek any correlation of cardiac filling pressures and cardiac performance with clinical improvement after the AFR procedure.

The first patient enrolled to PROLONGER study presented substantial clinical improvement in the 6MWT distance, which almost doubled and a reduction of NYHA class. Diagnostic right heart catheterization revealed a significant reduction in PAWP, mean pulmonary artery and right atrial pressures [16].

A 12 month follow-up is planned with four control visits, which should allow assessment of clinical and hemodynamic responses for AFR.

Conflict of interest: None declared

References

1. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart. 2007; 93(9): 1137–1146, doi: 10.1136/hrt.2003.025270.
2. Redfield MM, Jacobsen SJ, Burnett JC, et al. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA. 2003; 289(2): 194–202, doi: 10.1001/jama.289.2.194, indexed in Pubmed: 12517230.
3. Ponikowski P, Voors A, Anker S, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2016; 37(27): 2129–2200, doi: 10.1093/eurheartj/ehw128.
4. Lam CSP, Voors AA, de Boer RA, et al. Heart failure with preserved ejection fraction: from mechanisms to therapies. Eur Heart J. 2018; 39(30): 2780–2792, doi: 10.1093/eurheartj/ehy301, indexed in Pubmed: 29905796.
5. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. Eur Heart J. 2011; 32(6): 670–679, doi: 10.1093/eurheartj/ehq426, indexed in Pubmed: 21138935.
6. Shah SJ, Feldman T, Ricciardi MJ, et al. One-Year safety and clinical outcomes of a transcatheter interatrial shunt device for the treatment of heart failure with preserved ejection fraction in the reduce elevated left atrial pressure in patients with heart failure (REDUCE LAP-HF I) trial: a randomized clinical trial. JAMA Cardiol. 2018; 3(10): 968–977, doi: 10.1001/jamacardio.2018.2936, indexed in Pubmed: 30167646.
7. Guimarães L, Bergeron S, Bernier M, et al. Interatrial shunt with the second-generation V-Wave system for patients with advanced chronic heart failure. EuroIntervention. 2020; 15(16): 1426–1428, doi: 10.4244/EIJ-D-19-00291, indexed in Pubmed: 31422927.
8. Paitazoglou C, Özdemir R, Pfister R, et al. The AFR-PRELIEVE trial: a prospective, non-randomised, pilot study to assess the Atrial Flow Regulator (AFR) in heart failure patients with either preserved or reduced ejection fraction. EuroIntervention. 2019; 15(5): 403–410, doi: 10.4244/EIJ-D-19-00342, indexed in Pubmed: 31130524.
9. Niu X, Zhang Q, Xiao D, et al. A retrospective study of hemodynamic changes in patients after off-pump coronary artery bypass graft surgery using impedance cardiography. Med Sci Monit. 2019; 25: 3454–3462, doi: 10.12659/MSM.913289, indexed in Pubmed: 31073116.
10. Louvaris Z, Spetsioti S, Andrianopoulos V, et al. Cardiac output measurement during exercise in COPD: A comparison of dye dilution and impedance cardiography. Clin Respir J. 2019; 13(4): 222–231, doi: 10.1111/crj.13002, indexed in Pubmed: 30724023.
11. Małek ŁA, Mróz A, Czajkowska A, et al. Accuracy of impedance cardiography for hemodynamic assessment during rest and exercise in wheelchair rugby players. Res Q Exerc Sport. 2019; 90(3): 336–343, doi: 10.1080/02701367.2019.1600651, indexed in Pubmed: 31082312.
12. Kurpaska M, Krzesiński P, Gielerak G, et al. Exercise impedance cardiography reveals impaired hemodynamic responses to exercise in hypertensives with dyspnea. Hypertens Res. 2019; 42(2): 211–222, doi: 10.1038/s41440-018-0145-y, indexed in Pubmed: 30504821.
13. Woltjer HH, Bogaard HJ, de Vries P. The technique of impedance cardiography. Eur Heart J. 1997; 18(9): 1396–1403, doi: 10.1093/oxfordjournals.eurheartj.a015464.
14. Silver MA, Cianci P, Brennan S, et al. Evaluation of impedance cardiography as an alternative to pulmonary artery catheterization in critically ill patients. Congest Heart Fail. 2004; 10(2 Suppl 2): 17–21, doi: 10.1111/j.1527-5299.2004.03410.x, indexed in Pubmed: 15073481.
15. Lewicki L, Fijalkowska M, Karwowski M, et al. The non-invasive evaluation of heart function in patients with an acute myocardial infarction: The role of impedance cardiography. Cardiol J. 2019 [Epub ahead of print], doi: 10.5603/CJ.a2019.0098, indexed in Pubmed: 31642052.
16. Lewicki Ł, Sabiniewicz R, Siebert J, et al. Atrial flow regulator as a novel therapy for patients with chronic heart failure. Cardiol J. 2020; 27(3): 309–311, doi: 10.5603/CJ.a2020.0077, indexed in Pubmed: 32436584.

VIA MEDICA

RESEARCH LETTER

Cardiology Journal
2020, Vol. 27, No. 6, 884–885
DOI: 10.5603/CJ.2020.a0179

ISSN 1897–5593
eISSN 1898–018X

Impact of COVID-19 on bystander cardiopulmonary resuscitation in out-of-hospital cardiac arrest: Is it as bad as we think?

Mahdi Al-Jeabory[1], Kamil Safiejko[2], Szymon Bialka[3], Michal Pruc[4], Aleksandra Gasecka[5, 6], Lukasz Szarpak[2, 4, 7]

[1]Department of Emergency Medicine, Medical University of Warsaw, Poland
[2]Maria Sklodowska-Curie Bialystok Oncology Center, Bialystok, Poland
[3]Department of Anesthesiology and Critical Care, School of Medicine with Division of Dentistry in Zabrze, Medical University of Silesia, Zabrze, Poland
[4]Polish Society of Disaster Medicine, Warsaw, Poland
[5]1st Chair and Department of Cardiology, Medical University of Warsaw, Poland
[6]Laboratory of Experimental Clinical Chemistry, Amsterdam University Medical Center, Amsterdam, The Netherlands
[7]Maria Sklodowska-Curie Medical Academy in Warsaw, Poland

Scquizzato et al. [1] in their meta-analysis showed out-of-hospital cardiac arrest had worse short-term outcomes during the pandemic than a non-pandemic period, suggesting direct effects of COVID-19 infection and indirect effects from lockdown and disruption of healthcare systems. The American Heart Association (AHA) has issued an interim guideline on basic life support during COVID-19 [2, 3]. Since 2010, the AHA removed rescue breaths guidelines from the basic life support algorithm in favor of a hands-only approach for resuscitation performed by the public for individuals [4, 5]. As show by Rosell Ortiz et al. [6] the frequency of undertaking resuscitation by bystanders before the pandemic was 51.5% and during the pandemic it was 42.6%. Borkowska et al. [7] show the cardiopulmonary resuscitation (CPR) rapidity during the pandemic at the level of 10.1%. The reduction in the frequency of resuscitation by the witnesses of an incident in the Rosell Ortiz study [6] may be because of the increased level of fear of SARS-CoV-2 infection per person with cardiac arrest [8]. One might suppose that limitation of movement or lockdown also influenced such behavior, however, studies by Rosell Ortiz et al. [6] and Chan et al. [9] seem to contradict this thesis. In these studies, the witnessed cardiac arrest was at a comparable level both before the COVID-19 pandemic and during the pandemic. As showed by Jorge-Soto et al. [10] brief hands-on training supported by real-time feedback of CPR quality helps future schoolteachers improve their knowledge, self-confidence and CPR skills and build pro-health attitudes and increase the chances of undertaking CPR.

In order to verify the influence of COVID-19 on the frequency of resuscitation by witnesses of the event, a systematic review and meta-analysis were performed.

This review was performed according to the Cochrane Collaboration methodological guidelines. We conducted a literature search in the EMBASE, PubMed, Web of Science, Scopus and Cochrane Library databases, covering the publication period from databases inception to November 15, 2020. Two investigators (M.P. and S.B.) independently reviewed the articles obtained. Disagreements between the two investigators were resolved by a third reviewer (A.G. or L.S.).

All results are presented with a 95% confidence interval (CI). When the continuous out-

Address for correspondence: Lukasz Szarpak, Assoc Prof., PhD, MBA, Maria Sklodowska-Curie Medical Academy in Warsaw, ul. Solidarnosci 12, 03–411 Warszawa, Poland, tel: +48 500186225, e-mail: lukasz.szarpak@gmail.com

Received: 26.11.2020 Accepted: 9.12.2020

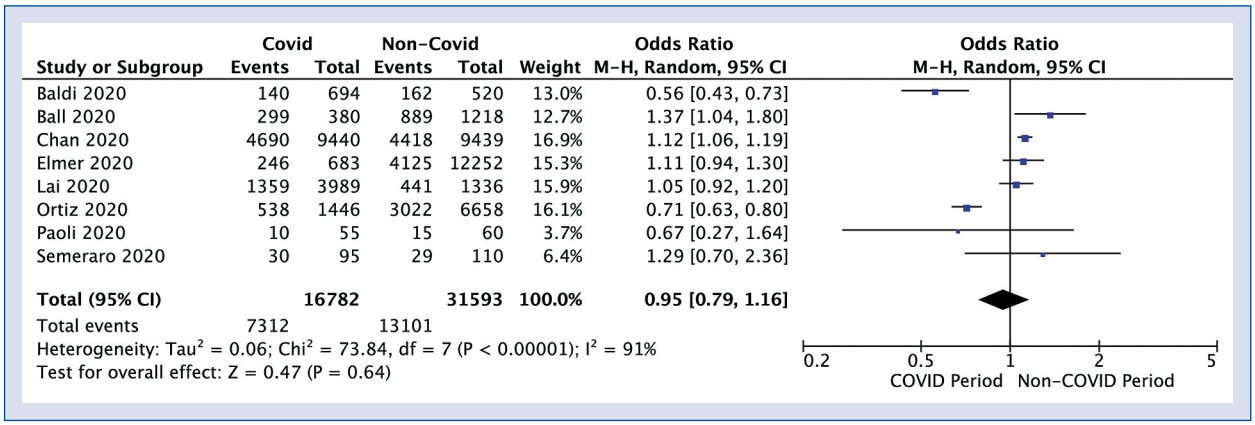


Figure 1. Forest plot of bystander cardiopulmonary resuscitation rate in COVID-19 versus non-COVID-19 period. The center of each square represents the weighted odds ratios for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results.

come was reported in a study as median, range, and interquartile range, estimated means and standard deviations using the formula described by Hozo et al. [11] were used. Heterogeneity of the effect sizes was checked with the I^2 index. If $p > 0.1$ and $I^2 < 50\%$, a fixed effect model was used, otherwise a random effect model was chosen. All statistical analyzes were carried out using RevMan 5.4 software (The Cochrane Collaboration, Oxford, Copenhagen, Denmark).

Eight studies reported bystander CPR ratio in COVID-19 and pre-COVID-19 periods. Bystander CPR rate in COVID-19 period was 43.6% vs. 41.5% for non-COVID-19 period (odds ratio: 0.95; 95% CI: 0.79–1.16; $p = 0.64$; I^2: 91%; Fig. 1). Detailed characteristics of the studies included in the analysis are presented in **Supplementary Table 1**.

In summary, the meta-analysis performed showed a slightly higher frequency of CPR by witnesses during the COVID-19 pandemic compared to the periods preceding the pandemic. However, despite this fact, the effectiveness of resuscitation in out-of-hospital cardiac arrest is significantly lower than in the pre-pandemic period.

Conflict of interest: None declared

References

1. Scquizzato T, Landoni G, Paoli A, et al. Effects of COVID-19 pandemic on out-of-hospital cardiac arrests: A systematic review. Resuscitation. 2020 [Epub ahead of print], doi: 10.1016/j.resuscitation.2020.10.020, indexed in Pubmed: 33130157.
2. Edelson DP, Sasson C, Chan PS, et al. Interim Guidance for Basic and Advanced Life Support in Adults, Children, and Neonates With Suspected or Confirmed COVID-19: From the Emergency Cardiovascular Care Committee and Get With The Guidelines-Resuscitation Adult and Pediatric Task Forces of the American Heart Association. Circulation. 2020; 141(25): e933–e943, doi: 10.1161/CIRCULATIONAHA.120.047463, indexed in Pubmed: 32270695.
3. Smereka J, Iskrzycki Ł, Makomaska-Szaroszyk E, et al. The effect of chest compression frequency on the quality of resuscitation by lifeguards. A prospective randomized crossover multicenter simulation trial. Cardiol J. 2019; 26(6): 769–776, doi: 10.5603/CJ.a2018.0121, indexed in Pubmed: 30338845.
4. Majer J, Jaguszewski MJ, Frass M, et al. Does the use of cardiopulmonary resuscitation feedback devices improve the quality of chest compressions performed by doctors? A prospective, randomized, cross-over simulation study. Cardiol J. 2019; 26(5): 529–535, doi: 10.5603/CJ.a2018.0091, indexed in Pubmed: 30155865.
5. Abelsson A, Lundberg L. Prehospital CPR training performed with visual feedback. Disaster Emerg Med J. 2018; 3(2): 41–45, doi: 10.5603/demj.2018.0010.
6. Rosell Ortiz F, Fernández Del Valle P, Knox EC, et al. Influence of the Covid-19 pandemic on out-of-hospital cardiac arrest. A Spanish nationwide prospective cohort study. Resuscitation. 2020 [Epub ahead of print], doi: 10.1016/j.resuscitation.2020.09.037, indexed in Pubmed: 33049385.
7. 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. 2020 [Epub ahead of print], doi: 10.5603/CJ.a2020.0135, indexed in Pubmed: 33140396.
8. Perman SM. Overcoming fears to save lives: COVID-19 and the threat to bystander CPR in out-of-hospital cardiac arrest. Circulation. 2020; 142(13): 1233–1235, doi: 10.1161/CIRCULATIONAHA.120.048909, indexed in Pubmed: 32795100.
9. Chan PS, Girotra S, Tang Y, et al. Outcomes for out-of-hospital cardiac arrest in the united states during the coronavirus disease 2019 pandemic. JAMA Cardiol. 2020 [Epub ahead of print], doi: 10.1001/jamacardio.2020.6210, indexed in Pubmed: 33188678.
10. Jorge-Soto C, Abilleira-González M, Otero-Agra M, et al. Schoolteachers as candidates to be basic life support trainers: a simulation trial. Cardiol J. 2019; 26(5): 536–542, doi: 10.5603/CJ.a2018.0073, indexed in Pubmed: 30009374.
11. 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.

VIA MEDICA

RESEARCH LETTER

Cardiology Journal
2020, Vol. 27, No. 6, 886–887
DOI: 10.5603/CJ.a2020.0171

ISSN 1897–5593
eISSN 1898–018X

Evidence of diagnostic value of ferritin in patients with COVID-19

Lukasz Szarpak[1, 2, 3], Artur Zaczynski[3], Dariusz Kosior[4, 5], Szymon Bialka[6], Jerzy R. Ladny[7, 8], Natasza Gilis-Malinowska[9], Jacek Smereka[8, 10], Luiza Kanczuga-Koda[2], Aleksandra Gasecka[11], Krzysztof J. Filipiak[11], Milosz J. Jaguszewski[9]

[1]Maria Sklodowska-Curie Medical Academy in Warsaw, Poland
[2]Maria Sklodowska-Curie Bialystok Oncology Center, Bialystok, Poland
[3]Central Clinical Hospital of the Ministry of the Interior and Administration in Warsaw, Poland
[4]Department of Cardiology and Hypertension with Electrophysiological Lab, Central Clinical Hospital of the Ministry of the Interior and Administration in Warsaw, Poland
[5]Faculty of Medicine, Collegium Medicum, Cardinal Stefan Wyszynski University, Warsaw, Poland
[6]Department of Anesthesiology and Intensive Care, Medical University of Silesia, Katowice, Poland
[7]Chair of Emergency Medicine and Disaster, Medical University in Bialystok, Poland
[8]Polish Society of Disaster Medicine, Warsaw, Poland
[9]First Department of Cardiology, Medical University of Gdansk, Poland
[10]Department of Emergency Medical Service, Wroclaw Medical University, Wroclaw, Poland
[11]First Chair and Department of Cardiology, Medical University of Warsaw, Poland

This paper was guest edited by Prof. Togay Evrin

The current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic forces medical personnel to search for alternative early diagnosis methods of the patient's condition [1]. An essential element of the diagnosis of a patient with COVID-19 is to understand the impact of various laboratory tests on the severity of the disease. An example of this research can be determining the level of ferritin, which is considered an indicator of the body's iron supply. As iron levels fall, the blood ferritin levels fall [2]. The concentration of 1 μg/L corresponds to 8 mg of iron in the reserve pool [3]. When healthy, 20% of the body's iron is bound to ferritin. Ferritin bound iron accounts for 95% of the hepatic iron stores. According to World Health Organization, adult women's norm ranges from 15 to 150 μg/L, for men from 15 to 200 μg/L [4]. Moreover, ferritin is considered an acute phase protein, so its concentration also increases inflammation and infections. This limits the possibility of using its determination to assess systemic iron resources, even in terms of the diagnosis of COVID-19 severity [5, 6]. Abbaspour et al. [7] showed that ferritin is a crucial mediator of immune dysregulation via direct immune-suppressive and pro-inflammatory effects, contributing to cytokine storm.

The present study aimed to determine the usefulness of ferritin as a predictor of a patient's severity with COVID-19 in a performer systematic review and meta-analysis. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [8] and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines for reporting systematic reviews and meta-analyses of observational studies [9].

Three authors (L.S., J.S., and S.B) independently searched relevant literature. The current Pubmed, Embase, Cochrane, Web of Science, Scopus (from database inception to November 10, 2020) was explored. The whole search strategy used free words, including "ferritin" AND "COVID-19"

Address for correspondence: Lukasz Szarpak, Assoc. Prof. PhD, MBA, Maria Skłodowska-Curie Medical Acedemy in Warsaw, ul. Solidarności 12, 03–411 Warszawa, Poland, tel: +48 500186225, e-mail: lukasz.szarpak@gmail.com

Received: 14.11.2020 Accepted: 17.11.2020

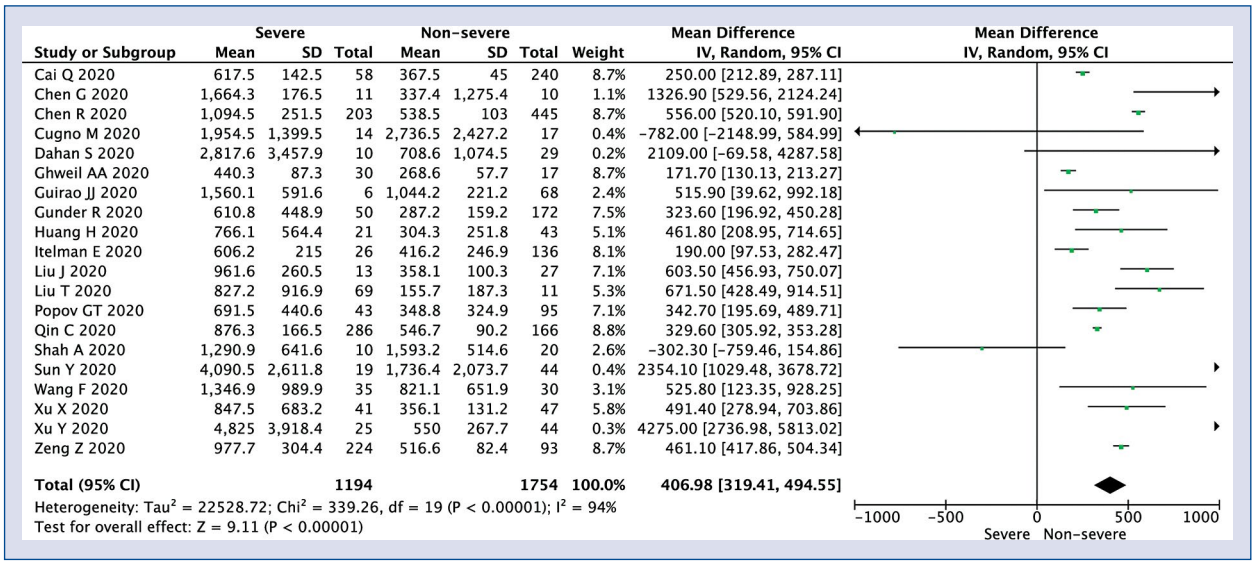


Figure 1. Forest plot of ferritin levels in severe versus non-severe groups. The center of each square represents the odds ratio for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results; SD — standard deviation.

OR "SARS-CoV-2". The reference lists of all eligible trials and reviews were screened for additional citations. Publications were restricted to the English language.

Twenty studies reported ferritin levels in severe and non-severe patient groups. Polled analysis showed that it significantly correlated higher ferritin levels with the more severe condition of the COVID-19 patient (MD: 406.98; 95% CI: 319.41–494.55; $p < 0.001$; I^2: 94%; Fig. 1). Detailed characteristics of the studies included in the meta-analysis are presented in **Supplementary Digital Content**. Higher ferritin levels were also associated with more frequent hospitalization in intensive care unit conditions (MD: 748.96; 95% CI: 444.45–1053.48; $p < 0.001$; I^2: 89%), and higher mortality in COVID-19 patients (MD: 594.43; 95% CI: 345.7–843.17; $p < 0.001$; I^2: 99%; **Supplementary Digital Content**).

In conclusion, this systematic review and meta-analysis show a close correlation between ferritin levels and the state of the COVID-19 patient. Higher ferritin levels were associated with a more severe patient condition, more intensive care unit exposure, and higher mortality.

Acknowledgements

Study supported by the ERC Research NET and 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. Evrin T, Demirel B, Szarpak L, et al. Galectin-3: a novel blood test for the classification of patients with COPD. An observational study. Dis Emerg Med J. 2019; 4(3): 77–82, doi: 10.5603/demj.a2019.0016.
3. Salman Z, Yılmaz T, Mehmetçik G. The relationship between ferritin levels and oxidative stress parameters in serum of β-thalassemia major patients. Arch Biochem Biophys. 2018; 659: 42–46, doi: 10.1016/j.abb.2018.09.020, indexed in Pubmed: 30287235.
4. Dopsaj V, Martinovic J, Dopsaj M, et al. Gender-specific oxidative stress parameters. Int J Sports Med. 2011; 32(1): 14–19, doi: 10.1055/s-0030-1267930, indexed in Pubmed: 21086243.
5. Henry BM, de Oliveira MH, Benoit S, et al. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med. 2020; 58(7): 1021–1028, doi: 10.1515/cclm-2020-0369, indexed in Pubmed: 32286245.
6. Katipoğlu B, Sönmez LÖ, Vatansev H, et al. Can hematological and biochemical parameters fasten the diagnosis of COVID-19 in emergency departments? Dis Emerg Med J. 2020, doi: 10.5603/demj.a2020.0039.
7. Abbaspour N, Hurrell R, Kelishadi R. Review on iron and its importance for human health. J Res Med Sci. 2014; 19(2): 164–174, indexed in Pubmed: 24778671.
8. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015; 350: g7647, doi: 10.1136/bmj.g7647, indexed in Pubmed: 25555855.
9. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000; 283(15): 2008–2012, doi: 10.1001/jama.283.15.2008, indexed in Pubmed: 10789670.

VIA MEDICA

RESEARCH LETTER

Cardiology Journal
2020, Vol. 27, No. 6, 888–890
DOI: 10.5603/CJ.a2020.0163

ISSN 1897–5593
eISSN 1898–018X

Left main coronary artery ostial disease: Prognostic role of the gap-angle ratio

Gianluca Rigatelli[1]*, Marco Zuin[2]*, Pavel Nikolov[3], Dobrin Vassilev[3]

[1]Section of Cardiovascular and Endoluminal Interventions, Rovigo General Hospital, Rovigo, Italy
[2]Department of Internal Medicine, University of Ferrara, School of Medicine, Ferrara, Italy
[3]Department of Cardiology, Alexandrovska University, School of Medicine, Sofia, Bulgaria

Treatment of aorto-ostial coronary artery disease remains a challenge for interventional cardiologists due to the high rate of restenosis and stent misplacement often results in poor cardiovascular outcomes [1, 2]. Its anatomical position and plaque morphology may impact the rigidity of the lesion, possibly complicating the stenting procedure [3]. The gap-angle ratio (GAR) has been recently proposed as a method to describe the right coronary artery ostial stenosis rigidity and its impact on post-stenting outcomes [4]. We evaluated the use of the same parameter to describe isolated left main (LM) coronary artery ostial disease, analysing the prognostic role of GAR in these patients before stenting.

The clinical and instrumental records of 5435 consecutive patients underwent to coronary angiography in the documented institution were retrospectively analysed between January 2011 to January 2018 to identify patients with an isolated ostial LM disease and bypass surgery contraindications and/or refusal as determined by the local Heart Team. The local board approved the study.

A significant ostial LM lesion was defined as a lesion with > 50% diameter stenosis within 3 mm of the aortic ostium by quantitative coronary angiography analysis. Target lesion failure (TLF) was defined as the composite of cardiovascular death, target-vessel myocardial infarction, and clinically driven target lesion revascularization (TLR). For each patient we assessed the angle between the greater curvature of the aortic wall and LM take-off during both the diastolic (i.e. minimum angle) and systolic phases (i.e. maximum angle) in right anterior oblique (30°) position. The LM-GAR was calculated as follows:

$$\frac{\text{Maximum angle–Mimimum angle}}{\text{Mimimum angle}} \quad (1)$$

As evidenced in the formula (1), a high LM-GAR would indicate large motion of the LM ostium, similarly to the observations performed by Ohashi et al. [4]. Two independent cardiologists performed the measurement using the same software with an agreement of 98.3%.

Stent repositioning after the first attempt and misplacement with need of a second stent were also recorded and analysed in each patient.

Information about the in-hospital outcome was obtained from an electronic clinical database for patients maintained at the documented institution and by reviewing hospital records for those discharged to referring hospitals. Post-discharge survival status was obtained from the Municipal Civil Registries.

Sixty-one patients were identified with isolated LM ostial stenosis: 7 were excluded due to a history of aortic valve replacement, 3 had concomitant significant lesions of the mid-left anterior descending or LM bifurcation, 2 had an aortitis and one was admitted due to a ST-segment elevation myocardial infarction. Finally, 47 patients (36 males, mean age 68.2 ± 10.2 years) were analysed (Table 1). During the procedure, patients who experienced stent repositioning or stent displacement

Address for correspondence: Prof. Gianluca Rigatelli, MD, PhD, FACP, FACC, FESC, FSCAI, Section of Adult Congenital Heart Disease Interventions, Cardiovascular Diagnosis and Endoluminal Interventions, Rovigo General Hospital, 45100 Rovigo, Italy, tel: +3903471912016, fax: +390425394513, e-mail: jackyheart71@yahoo.it

Received: 2.05.2020 Accepted: 24.10.2020

Gianluca Rigatelli and Marco Zuin equally contributed to the study.

Table 1. General characteristics of the patients enrolled, also stratified according the left main gap angle ratio (LM-GAR).

	All (n = 47)	LM-GAR < 0.23 (n = 34)	LM-GAR ≥ 0.24 (n = 13)	P
Age [years]	68.2 ± 10.2	66.0 ± 9.8	70.4 ± 11.3	0.19
Males	36 (76.5%)	26 (76.7%)	10 (76.9%)	0.98
Hypertension	24 (51.0%)	18 (52.9%)	6 (46.1%)	0.67
Dyslipidemia	24 (51.0%)	14 (41.1%)	10 (76.9%)	0.03
Diabetes mellitus	20 (42.5%)	11 (32.3%)	9 (69.2%)	0.02
Previous smokers	21 (55.6%)	14 (41.1%)	7 (53.8%)	0.43
Active smokers	6 (12.7%)	4 (11.7%)	2 (15.3%)	0.74
Previous MI	8 (17.0%)	5 (14.7%)	3 (23.0%)	0.50
Heart failure	10 (21.2%)	7 (20.5%)	3 (23.0%)	0.85
CKD°	15 (31.9%)	8 (23.5%)	7 (53.8%)	0.05
COPD	7 (14.8%)	5 (14.7%)	2 (15.3%)	0.97
Stroke	7 (14.8%)	4 (11.7%)	3 (23.0%)	0.33
LVEF [%]	47.1 ± 9.2	46.2 ± 8.7	48.1 ± 9.8	0.55
CCS	2.3 ± 0.5	2.3 ± 0.9	2.4 ± 0.6	0.71
SYNTAX score	9.4 ± 3.9	9.4 ± 3.6	9.5 ± 4.1	0.94
Basal MLD [mm]	1.7 ± 1.1*	1.7 ± 1.3*	1.8 ± 1.0*	0.80
Final MLD [mm]	4.3 ± 0.5	4.3 ± 0.6	4.4 ± 0.3	0.57
Lesion length [mm]	12.1 ± 3.6	11.8 ± 2.5	12.3 ± 3.5	0.58
Orsiro[1]	10 (21.2%)	7 (20.5%)	3 (23.0%)	0.85
Onyx[2]	25 (53.1%)	18 (52.9%)	7 (53.8%)	0.95
Promus Premier[3]	12 (25.3%)	9 (26.4%)	3 (23.0%)	0.81
1-year TLF	7 (14.8%)	2 (5.8%)	5 (38.4%)	0.005
1-year CV mortality	4 (8.5%)	1 (2.9%)	3 (23.0%)	0.03
Maximum angle°	103.6 ± 9.8	101.9 ± 7.8	105.4 ± 13.2	0.26
Minimum angle°	83.3 ± 10.5	82.2 ± 12.1	84.4 ± 8.6	0.55
Angle gap°	20.3 ± 9.2	19.7 ± 9.2	21.0 ± 9.6	0.67
LM-GAR	0.26 ± 0.32	0.11 ± 0.60	0.42 ± 0.17	< 0.0001

°Defined as an estimate glomerular filtration rate, using the CKD-EPI formula, < 60 mL/min/m^2

*p < 0.0001 between basal and final MLD after post dilatation in each group

[1]Biotronik Inc., Bulak, Switzerland; [2]Medtronic Inc., Galway, Ireland; [3]Boston Scientific Corp. Mantik, MA, USA

MI — myocardial infarction; CKD — chronic kidney disease; COPD — chronic obstructive pulmonary disease; LVEF — left ventricular ejection fraction; CCS — Canadian Cardiovascular Score; MLD — minimal lumen diameter; TLF — target lesion failure; CV — cardiovascular

resulting in need for a second stent (15 patients) had a mean LM-GAR angle higher than those without: 0.26 ± 0.02 vs. 0.21 ± 0.03 (p = 0.03).

On receiver operating characteristic analysis the optimal cut-off value for LM-GAR, as a predictor of 1-year TLF was ≥ 0.24 (area under curve of 0.86 ± 0.5; 95% confidence interval [CI] 0.76–0.96, p = 0.002). At a mean follow-up of 11.9 ± 0.6 months, the rate of both TLF (38.4% vs. 5.8%, p = 0.005) and cardiovascular mortality (23.0% vs. 2.9%, p = 0.03) were significantly higher in patients with an LM-GAR ≥ 0.24. Sensitivity, specificity, positive predictive value and negative predictive value of LM-GAR for TLF were 81.8%, 94.1%, 69.2%, and 94.1, respectively. Mantel-Cox analysis revealed that there was a significant statistical difference in the occurrence of TLF after 1 year between patients with a LM-GAR < 0.23 compared with those having a LM-GAR ≥ 0.24 (log rank [Mantel–Cox] χ^2 10.2, p = 0.01]. Moreover, a multivariate Cox regression analysis demonstrated that 1-year TLF (hazard ratio [HR] 3.34, 95% CI 2.29–3.77, p = 0.001) were independently predicted by dyslipidaemia (HR 2.26, 95% CI 1.89–2.46, p < 0.001) and diabetes mellitus (HR 1.86, 95% CI 1.45–2.16, p = 0.03).

The present results suggest that LM-GAR was able to predict the incidence of TLF and cardiovascular mortality at 1 year in patients with isolated LM ostial stenosis treated with percutaneous coronary intervention (PCI). Both the degree of steepness of the LM takeoff angle as well as extensive motion of the LM ostium are independent risk factors of adverse clinical events in the long-term period in these patients [1].

In the current study it was postulated that a high LM-GAR indicate large motion of the LM ostium which potentially can complicate stent placement and deployment resulting in stent malapposition or mild displacement. This hypothesis was confirmed by a statistically significant higher LM-GAR ratio in patients who experienced such problems during PCI.

High LM-GAR ratio seems to correlate with a potential increased challenge during the procedure and with less favourable outcomes at 1 year compared to patients with lower LM-GAR ratios: patients with a LM-GAR ratio ≥ 0.24 require particular attention during PCI in order to overcome the large vessel motion, such as extra-backup guiding catheter and double wiring of the LM bifurcation.

Conflict of interest: None declared

References

1. Dishmon DA, Elhaddi A, Packard K, et al. High incidence of inaccurate stent placement in the treatment of coronary aorto-ostial disease. J Invasive Cardiol. 2011; 23(8): 322–326, indexed in Pubmed: 21828393.
2. Patel Y, Depta JP, Patel JS, et al. Impact of intravascular ultrasound on the long-term clinical outcomes in the treatment of coronary ostial lesions. Catheter Cardiovasc Interv. 2016; 87(2): 232–240, doi: 10.1002/ccd.25034, indexed in Pubmed: 23728924.
3. Gutiérrez-Chico JL, Villanueva-Benito I, Villanueva-Montoto L, et al. Szabo technique versus conventional angiographic placement in bifurcations 010-001 of Medina and in aorto-ostial stenting: angiographic and procedural results. EuroIntervention. 2010; 5(7): 801–808, doi: 10.4244/eijv5i7a134, indexed in Pubmed: 20142194.
4. Ohashi K, Abe D, Kuroki N, et al. Clinical impact of the gap-angle ratio in patients with ostial lesions of the right coronary artery undergoing percutaneous coronary intervention. Heart Vessels. 2019; 34(11): 1717–1727, doi: 10.1007/s00380-019-01417-x, indexed in Pubmed: 31028408.

VIA MEDICA

RESEARCH LETTER

Cardiology Journal
2020, Vol. 27, No. 6, 891–893
DOI: 10.5603/CJ.a2020.0107

ISSN 1897–5593
eISSN 1898–018X

Usability testing and satisfaction of "The Patient Access": A mobile health application for patients with venous thromboembolic disease. A pilot study

Piotr Merks[1, 2, 3, 8], Urszula Religioni[4], Karolina Arciszewska[5, 6], Walentyn Pankiewicz[5], Miłosz Jaguszewski[7, 8], Regis Vaillancourt[9]

[1]Faculty of Medicine, Collegium Medicum, Cardinal Stefan Wyszynski University, Warsaw, Poland
[2]Department of Pharmaceutical Technology, Faculty of Pharmacy, Collegium Medicum in Bydgoszcz, Poland
[3]Scientific Consortium of Cardinal Stefan Wyszynski University with Piktorex Sp. z o.o. in Warsaw, Collegium Medicum, Cardinal Stefan Wyszynski University, Warsaw, Poland
[4]Collegium of Business Administration, Warsaw School of Economics, Warsaw, Poland
[5]Pharmacy "Pod Gryfem", Bialystok, Poland
[6]Faculty of Organic Chemistry, Medical University of Bialystok, Poland
[7]First Department of Cardiology, Medical University of Gdansk, Poland
[8]Polish Pharmaceutical Group SA, Lodz, Poland
[9]Children's Hospital of Eastern Ontario, ON, Canada

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

Venous thromboembolic disease (VTE) is a challenging issue in medicine and for public health [1]. VTE is the third most common cardiovascular disease after ischemic heart disease and ischemic stroke. Approximately half of the patients with symptomatic, untreated venous thrombosis develop pulmonary embolism, and 10% of cases end in sudden death. Death in untreated patients is about 30%. However, after initiating treatment, it decreases to 3–8% [2].

It is particularly challenging to ensure the effectiveness of therapy for patients with VTE. Most patients, due to comorbidities, take many medications, which carries the risk of interactions and other drug-related problems. An additional issue is adherence to therapy. Patients often do not achieve satisfactory health results due to non-adherence. They usually take medicine incompletely, inconsistently, or not at all. Polypharmacy, inappropriate prescription, and drug-related problems increase morbidity and mortality rates and contribute to a large waste of health resources. All these situations require effective action to improve the quality of patient care [3].

A practical solution for patients is the use of various mHealth (mobile health) technologies [4]. mHealth is a sub-segment of eHealth and is defined as the use of mobile computing and communication technologies (e.g., mobile phones, wearable sensors) for health services and information [5]. mHealth includes various methods of interaction with the patient — text messages, reminders, but also phone applications.

Many studies are confirming the impact of mHealth applications on improving patient outcomes in different populations and at varying levels of healthcare. Applications are particularly important for chronically ill patients, including the elderly.

Currently, many mHealth applications are available for patients. They support prevention diagnostics, patient monitoring, correct use of medicines, as well as communication between the patient and healthcare staff [5]. mHealth is used in patients with diabetes, chronic obstructive pulmonary disease, or cardiovascular diseases, including hypertension, atrial fibrillation, or stroke patients.

Address for correspondence: Dr. Piotr Merks, Faculty of Medicine, Collegium Medicum, Cardinal Stefan Wyszynski University, ul. Wóycickiego1/3, 01–938 Warszawa, Poland, tel: +48602101979, e-mail: p.merks@uksw.edu.pl

Received: 20.05.2020 Accepted: 13.08.2020

Table 1. Descriptive statistics of System Usability Scale (SUS) results.

No. of SUS question	M	Median	SD	Min	Max
1. I think that I would like to use this system frequently	2.81	3	1.11	1	4
2. I found the system unnecessarily complex	1.88	1.5	1.11	1	4
3. I thought the system was easy to use	4.35	5	1.11	2	5
4. I think that I would need the support of a technical person to be able to use this system	1.75	1	1.13	1	4
5. I found the various functions in this system were well integrated	4.13	4	0.81	3	5
6. I thought there was too much inconsistency in this system	1.94	2	0.93	1	4
7. I would imagine that most people would learn to use this system very quickly	4.31	5	0.87	3	5
8. I found the system very cumbersome to use	1.69	1	1.01	1	4
9. I felt very confident using the system	3.31	3	1.25	1	5
10. I needed to learn a lot of things before I could get going with this system	2.13	2	1.20	1	5

M — average value; SD — standard deviation; Min — minimum value; Max — maximum value

According to available research, there are no mobile applications dedicated to patients with VTE disease. Given the seriousness of this disease, a decision was made to develop a mobile application for patients with VTE disease. "The Patient Access" is an application that enables the correct and safe use of medicine for people with VTE disease. The application displays all drug information in written and graphic forms. It also has the function of drug reminders and is a compendium of knowledge about VTE disease. The application significantly increases the likelihood that patients will use medications as directed, which is especially important when taking any drug.

To date, the functionality and usability of "The Patient Access" mobile application has been verified and will support safe drug dosing for people with VTE disease.

Testing the application involved assessing the usability of a prototype, allowing users to explore the application in detail and formulate conclusions about both the prototype and the final shape of the product. Testing was performed by a target group of product users [6].

After an application demonstration, each participant was asked to answer the questions included in the System Usability Scale (SUS). SUS contains ten statements related to the subjective assessment of utility. The participant assigns points to each statement (according to the Likert 5-point scale) assessing the extent to which he agrees with the statement. SUS has a good façade validity and high reliability (Cronbach's alpha 0.91) [7, 8].

This study took place at a community pharmacy in Bialystok, Poland. Participants were recruited among persons buying anticoagulants at the pharmacy. Study participants had to regularly use a smartphone or tablet, which ensured that they the basic skills in operating new technologies. The age of study participants (> 18 years) was also an important criterion. Data were collected from March to May 2020.

Sixteen further potential users of the application took part in the study. Sample sizes for testing the usability of a high-fidelity prototype require only 5–10 participants to identify 80% of product problems [9, 10]. For this reason, 16 people participating in the study were a sufficient number. The average age of the subjects was 64.44 (SD = 15.56). The respondents mainly had a higher education (81.25%).

After calculating the score according to the SUS scale key, the overall assessment of usability of "The Patient Access" application was rated at 73.59 points.

Analyzing the average score to each statement in the SUS questionnaire (Table 1), it can be assessed that most patients agreed with the statements regarding the ease of use of the application and proper integration of functions:

— "I thought the system was easy to use" (M = 4.35; SD = 1.11);
— "I would imagine that most people would learn to use this system very quickly" (M = 4.31; SD = 0.87);
— "I found the various functions in this system were well integrated" (M = 4.13; SD = 0.81).

Respondents, disagreed most with statements regarding the inconvenience of use, the need to help another person when using the application, or excessive system complexity:

— "I found the system very cumbersome to use" (M = 1.69; SD = 1.01);
— "I think that I would need the support of a technical person to be able to use this system" (M = 1.75; SD = 1.13);
— "I found the system unnecessarily complex" (M = 1.99; SD = 1.11).

This project is innovative because it was the first to focus on creating an application supporting drug dosage in people with VTE disease. This usability and satisfaction research allowed us to validate this application before the market launch. "The Patient Access" application has been highly rated by potential users. Users also indicated those features that should be developed in the next phase of work on the application.

Funding: This was supported by an education grant from Boehringer Ingelheim, Vienna, Austria.

Conflict of interest: The content outlined herein, represents the individual opinions of the authors and may not necessarily represent the viewpoints of their employers. Piotr Merks is employed as CEO of Piktorex sp. z o.o., is employed at the Cardinal Stefan Wyszynski University in Warsaw, Poland, Department of Pharmacy, Collegium Medicum in Bydgoszcz and as an Advisor of the management board for Research and Innovation at the Polish Pharmaceutical Group S.A. Miłosz Jaguszewski is employed as a University Professor at the First Department of Cardiology, Medical University of Gdansk, Poland and Scientific Officer at Polish Pharmaceutical Group SA and as such, authors must stress that this additional study was done purely for academic interest only and must not be construed in any way as an investment recommendation.

References

1. ISTH Steering Committee for World Thrombosis Day. Thrombosis: a major contributor to the global disease burden. J Thromb Haemost. 2014; 12(10): 1580–1590, doi: 10.1111/jth.12698, indexed in Pubmed: 25302663.
2. Kapitan-Malinowska B, Bogołowska-Stieblich A. Żylna choroba zakrzepowo-zatorowa. Post Nauk Med. 2009; 5: 345–354.
3. Mangin D, Bahat G, Golomb BA, et al. International Group for Reducing Inappropriate Medication Use & Polypharmacy (IGRIMUP): Position Statement and 10 Recommendations for Action. Drugs Aging. 2018; 35(7): 575–587, doi: 10.1007/s40266-018-0554-2, indexed in Pubmed: 30006810.
4. Petrovic M, Somers A, Marien S, Spinewine A. Optimization of drug use in older people: a key factor for a successful ageing. In: The Cambridge Handbook of Successful Aging. Cambridge University Press, Cambridge 2019: 237–262.
5. Burke LE, Ma J, Azar KMJ, et al. Current science on consumer use of mobile health for cardiovascular disease prevention: a scientific statement from the American Heart Association. Circulation. 2015; 132(12): 1157–1213, doi: 10.1161/CIR.0000000000000232, indexed in Pubmed: 26271892.
6. Stinson JN, Jibb LA, Nguyen C, et al. Development and testing of a multidimensional iPhone pain assessment application for adolescents with cancer. J Med Internet Res. 2013; 15(3): e51, doi: 10.2196/jmir.2350, indexed in Pubmed: 23475457.
7. Bangor A, Kortum P, Miller J. Determining what individual SUS scores mean: adding an adjective rating scale. J Usability Studies. 2009; 4(3): 114–123.
8. Brooke J. SUS – A quick and dirty usability scale [online]. Usability Evaluation in Industry. http://hell.meiert.org/core/pdf/sus.pdf (Accessed May 2, 2020).
9. Lewis JR. Sample sizes for usability studies: additional considerations. Hum Factors J Hum Factors Ergon Soc. 1994; 36(2): 368–378, doi: 10.1177/001872089403600215, indexed in Pubmed: 8070799.
10. Sauro J. 10 Things To Know About The System Usability Scale (SUS) [online]. http://www.measuringusability.com/blog/10-things-SUS.php (May 2, 2020).

VIA MEDICA

RESEARCH LETTER

Cardiology Journal
2020, Vol. 27, No. 6, 894–896
DOI: 10.5603/CJ.a2020.0128

ISSN 1897–5593
eISSN 1898–018X

Teaching medical applications and workflow of three-dimensional printing to medical students: Results of a pilot elective course

Jarosław Meyer-Szary, Agastya Patel, Marlon Souza Luis, Robert Sabiniewicz, Joanna Kwiatkowska

Department of Pediatric Cardiology and Congenital Heart Defects, Medical University of Gdansk, Poland

Three-dimensional printing (3Dp) employs a process of placing layers upon layers of material to create a physical object based on a digitally designed model [1]. The process (workflow) of making 3D models involves data acquisition from two-dimensional (2D) images, virtual reconstruction and physical printing [1]. 3Dp models are sought as an effective means for educating not only medical students, but also physicians, residents, nurses and other healthcare providers, as well as an aid in planning and training (simulating) procedures [2–8]. Having had experience in the field and seeing the increasing interest, as depicted by a growing body of literature, in medical 3Dp leads to a question of whether it is worthwhile and possible to teach undergraduate medical students about the basics of 3Dp workflow within a reasonably short timeframe. For this purpose, a pilot hands-on 3Dp elective course was organized to expose medical students to the potential of 3Dp in the hopes of raising their awareness and interest in the concept.

The course was comprised of 15 teaching hours, equally divided into 5 days. The first 3 days of the course included seminars on the following topics — medical applications of 3Dp (with examples from experience and published literature); available software, printing technologies and materials; and overview of the 3Dp workflow. The seminars were given by a pediatric cardiologist with experience in medical 3Dp and representatives of Zortrax and Sinterit, well-known as desktop 3D-printer manufacturing companies. During the seminars, students asked questions and actively participated in discussion. The last 2 days consisted of hands-on workshops, wherein students worked in pairs on four computed tomography (CT) scans to prepare models of scapula, middle aortic syndrome, vascular ring and trachea, and coronary arteries, respectively. On the first day of the workshop, the students were taught how to segment the region of interest from the 2D images, create a digital 3D model and inspect them for artifacts, which were fixed if present. Each pair practiced these steps on all four CT scans using Materialise Mimics Innovation Suite 22.0. The students then prepared a STL file for the vascular ring and trachea model, which was printed overnight for the second workshop day. On the last day, the students were taught how to post-process the printed 3D model (e.g. removing support structures). Each pair worked together on their models to prepare the final product, which they were allowed to take home.

Fourteen 4th and 5th year medical students from the Medical University of Gdansk participated in this pilot course. The enrollment for the course was done through an online system on a "first-come, first-served" basis. Ten students were eligible to take part in the study — three had prior experience in making 3Dp models and one did not consent to take part in the study. To gauge the effectiveness of the course, a questionnaire and a technical test was developed which the students filled out prior to entering and after completing the course. The entry questionnaire consisted of 22 Likert scale items assessing their familiarity with 3Dp, their opinion on its applications and their perception of

Address for correspondence: Agastya Patel, Department of Pediatric Cardiology and Congenital Heart Defects, Medical University of Gdansk, ul. M. Skłodowskiej-Curie 3a, 80–211, Gdańsk, Poland, tel: +48 58 349 28 82, e-mail: agastyap24@gmail.com

Received: 13.03.2020 Accepted: 21.07.2020

Table 1. Results of entry- and exit-subjective questionnaire and objective technical test scores.

	Entry-responses (n = 10) Median (IQR)	Exit-response (n = 10) Median (IQR)	P
3Dp models are accurate and precise representation of patient's anatomy	3 (2.75–4)	4 (3.75–5)	**0.02**
Working through the process of making 3Dp models would improve my understanding of anatomy	4.5 (3–5)	5 (4.75–5)	0.18
3D printing helps in understanding pathologies and planning medical interventions	4 (3.75–4.25)	5 (4.75–5)	**0.01**
3Dp models can be used to plan, prepare and practice surgical procedures	4 (3–5)	5 (4–5)	0.22
3D printing has a role in medical education	4.5 (4–5)	5 (4–5)	0.75
3D printing can be used to make customized prothesis and implants	5 (4–5)	5 (4–5)	0.75
3Dp models can be used to educate patients about their diseases and treatment	4 (3–5)	5 (5–5)	**0.03**
3D printing can be used in pharmaceutical research (e.g. drug dosages, delivery system	3 (2–3)	4 (3–5)	**0.02**
3Dp models can be used in administering doses of radiotherapy in treatment of superficial cancers	3 (2–3)	3.5 (2–4.25)	0.34
3D printing can be currently used to make organs for transplantation	2 (2–3.25)	2.5 (1–5)	0.35
3Dp models can be used to make physical libraries of several pathologies and their variants	4 (3–5)	5 (4.75–5)	0.38
3D printing is a widely researched concept in medicine and healthcare	3 (2–3)	5 (2.75–5)	**0.03**
Senior doctors can benefit from 3Dp models	5 (3.75–5)	5 (4–5)	0.63
Medical residents can benefit from 3Dp models	5 (3–5)	5 (5–5)	0.5
Medical students can benefit from 3Dp models	5 (3–5)	5 (5–5)	0.13
Nurses can benefit from 3Dp models	4 (3–5)	5 (4.75–5)	0.13
Patients can benefit from 3Dp models	4.5 (4–5)	5 (5–5)	0.06
3D printing models is an extremely time consuming	4.5 (3–5)	5 (3.75–5)	0.19
3D printing models is a very costly process	3 (3–5)	4 (2.75–4.25)	> 0.99
The process of printing 3D models is difficult. It requires a lot of skill and experience	3 (3–4.25)	3 (2–4)	0.23
It is possible to customize 3D printed models after they are printed (e.g. adding colors, textures, labels etc.)	4 (2.75–5)	4.5 (3.75–5)	0.19
Technical Test Scores*	6.3 ± 1.34	8.4 ± 1.65	**0.0049**

*Results reported in means ± standard deviation. Analyzed using the Paired T-test; 3Dp — three-dimensional printing; IQR — interquartile range

creating 3Dp models. In the exit questionnaire, the students were asked about which step of the 3Dp workflow was the most challenging for them and to give their opinion on how the course may have influenced their medical education. It included 6 Likert scale items regarding the content and quality of the course. The technical test included 7 true/false and 1 open question along with a question regarding the order of steps in 3Dp workflow. A statistical analysis of the questionnaire responses and test scores was performed using the Wilcoxon test and Paired T-test with GraphPad Prism 8.0. As indicators of significance, two-tailed p-values of < 0.05 was used.

Prior to starting the course, 70% of the students stated that they were "somewhat familiar" with the concept of 3Dp. In comparison, 40% believed that they "have experience" and 60% were "somewhat familiar" at the end of the course (**Suppl. Fig. 1A**). The course was able to positively change the opinion of the students regarding the following medical applications of 3Dp — creating

accurate representations of a specific patient's anatomy (p = 0.02), helpful in understanding pathologies and planning medical interventions (p = 0.01), beneficial for patient education (p = 0.03) and application in pharmaceutical research (p = 0.02) (Table 1). After the course, they also realized the scientific interest in researching the concept of 3Dp in the field of medicine (p = 0.03). In both entry and exit responses, the students unanimously agreed that 3Dp has a role in medical education, making customized protheses, and practicing surgical procedures. At the end of the course, 40% of students disagreed that 3Dp is difficult and requires experience as compared to 0% before the course (**Suppl. Fig. 1B**).

Majority (60%) of the students found segmentation to be the most challenging step in the 3Dp workflow, the rest found analyzing the CT images, inspecting the digital model and preparing the model for printing to be more challenging (**Suppl. Fig. 1C**). All students were pleased with the content and methods of teaching 3Dp used in the course (**Suppl. Fig. 1D**). Every student stated that they would be interested in participating in such courses in the future and would recommend them to fellow students (**Suppl. Fig. 1D**). It was also seen that learning the process of 3Dp and its application had a positive impact on the experience of learning medicine of each student participating in the course (**Suppl. Fig. 1D**). The students scored significantly higher in the technical exit test (mean score = 8.4 vs. 6.3, p = 0.005). Majority (60%) of students were able to correctly arrange the steps of the 3Dp workflow in the exit test as compared to only 30% in the entry test (**Suppl. Fig. 1E**).

Three-dimensional printing is a relatively novel and emerging concept in the field of medicine with widespread applications. It is therefore worthwhile introducing undergraduate medical students to, not only its uses but also the process of creating 3Dp models. The present study demonstrates that the course including hands-on workshops such as these are effective for this purpose. Learning and experiencing 3Dp workflow adds an additional skill to the repertoire of a student while also enhancing their medical education. Courses like these have the potential of raising interest and attracting students to partake and contribute in furthering the practice of medical 3Dp.

Conflict of interest: None declared

References

1. Luo H, Meyer-Szary J, Wang Z, et al. Three-dimensional printing in cardiology: Current applications and future challenges. Cardiol J. 2017; 24(4): 436–444, doi: 10.5603/CJ.a2017.0056, indexed in Pubmed: 28541602.
2. Chen S, Pan Z, Wu Y, et al. The role of three-dimensional printed models of skull in anatomy education: a randomized controlled trail. Sci Rep. 2017; 7(1): 575, doi: 10.1038/s41598-017-00647-1, indexed in Pubmed: 28373643.
3. Wang L, Ye X, Hao Q, et al. Three-dimensional intracranial middle cerebral artery aneurysm models for aneurysm surgery and training. J Clin Neurosci. 2018; 50: 77–82, doi: 10.1016/j.jocn.2018.01.074, indexed in Pubmed: 29439905.
4. Wake N, Rosenkrantz AB, Huang R, et al. Patient-specific 3D printed and augmented reality kidney and prostate cancer models: impact on patient education. 3D Print Med. 2019; 5(1): 4, doi: 10.1186/s41205-019-0041-3, indexed in Pubmed: 30783869.
5. Olivieri LJ, Su L, Hynes CF, et al. „Just-In-Time" Simulation Training Using 3-D Printed Cardiac Models After Congenital Cardiac Surgery. World J Pediatr Congenit Heart Surg. 2016; 7(2): 164–168, doi: 10.1177/2150135115623961, indexed in Pubmed: 26957398.
6. Biglino G, Capelli C, Koniordou D, et al. Use of 3D models of congenital heart disease as an education tool for cardiac nurses. Congenit Heart Dis. 2017; 12(1): 113–118, doi: 10.1111/chd.12414, indexed in Pubmed: 27666734.
7. Meyer-Szary J, Woźniak-Mielczarek L, Sabiniewicz D, et al. Feasibility of in-house rapid prototyping of cardiovascular three-dimensional models for planning and training non-standard interventional procedures. Cardiol J. 2019; 26(6): 790–792, doi: 10.5603/CJ.2019.0115, indexed in Pubmed: 31970736.
8. Sabiniewicz R, Meyer-Szary J, Potaż P, et al. Melody valve implantation pre-procedural planning using custom-made 3D printed model of the region of interest. Adv Interv Cardiol. 2018; 14(2): 210–211, doi: 10.5114/aic.2018.76419, indexed in Pubmed: 30008780.

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

Cardiology Journal
2020, Vol. 27, No. 6, 897–898
DOI: 10.5603/CJ.2020.0173

ISSN 1897–5593
eISSN 1898–018X

Successful optical coherence tomography-guided stent ablation with rotational atherectomy for an underexpanded stent

Yongcheol Kim, Deok-Kyu Cho, Ji Woong Roh, Oh-Hyun Lee, Eui Im, Donghoon Choi

Division of Cardiology, Department of Internal Medicine, Yonsei University College of Medicine and Cardiovascular Center, Yongin Severance Hospital, Yongin, Korea

A 62-year-old man with a history of ischemic heart disease and dyslipidemia presented with aggravating effort angina. He underwent stent implantation with a 3.0 × 40 mm sirolimus-eluting stent at the mid portion of left anterior descending artery 2 years prior, but a heavily calcified lesion led to severe stent underexpansion, which did not resolve despite postdilation with a non-compliant (NC) balloon (**Suppl. Video 1**). Angiography demonstrated aggravated luminal narrowing in the underexpanded stent site (Fig. 1A, **Suppl. Video 2**); therefore, stent ablation with rotational atherectomy was planned. Pre-interventional optical coherence tomography (OCT) demonstrated that the diameter of the underexpanded stent was between 1.24 and 1.66 mm (Fig. 1B, C, **Suppl. Video 3**), which was also confirmed on three-dimensional OCT (Fig. 1D). OCT assessment led to stent ablation using a stepwise increase in burr size, from 1.25 mm to 1.50 mm and finally 1.75 mm. Following stent ablation, OCT showed no visible strut area in the site of the previously underexpanded stent (Fig. 1E, F). However, a minimal lumen area of 2.27 mm^2 led to the performance of drug-coated balloon angioplasty with a 3.0 × 20 mm Pantera Lux (Biotronik, Bülach, Switzerland) after balloon dilation with a 3.0 × 15 mm NC balloon at 24 atm. Final angiography showed good distal flow without residual stenosis (Fig. 1G, **Suppl. Video 4**).

This report highlights the superior resolution of OCT, which can aid in choosing the optimal burr size, and presents OCT images of successful stent ablation.

Acknowledgements

The authors would like to thank all the staff, especially Dae Seok Jang, working in the cardiac catheterization laboratories at Yongin Severance Hospital for their commitment to this study.

Conflict of interest: None declared

Address for correspondence: Deok-Kyu Cho, MD, Cardiovascular Center, Yongin Severance Hospital, 363 Dongbaekjukjeon-daero, Giheung-gu, Yongin 16995, Korea, tel: 82-31-5189-8755, fax: 82-31-5189-8567, e-mail: chodk123@yuhs.ac

Received: 5.06.2020 Accepted: 5.06.2020

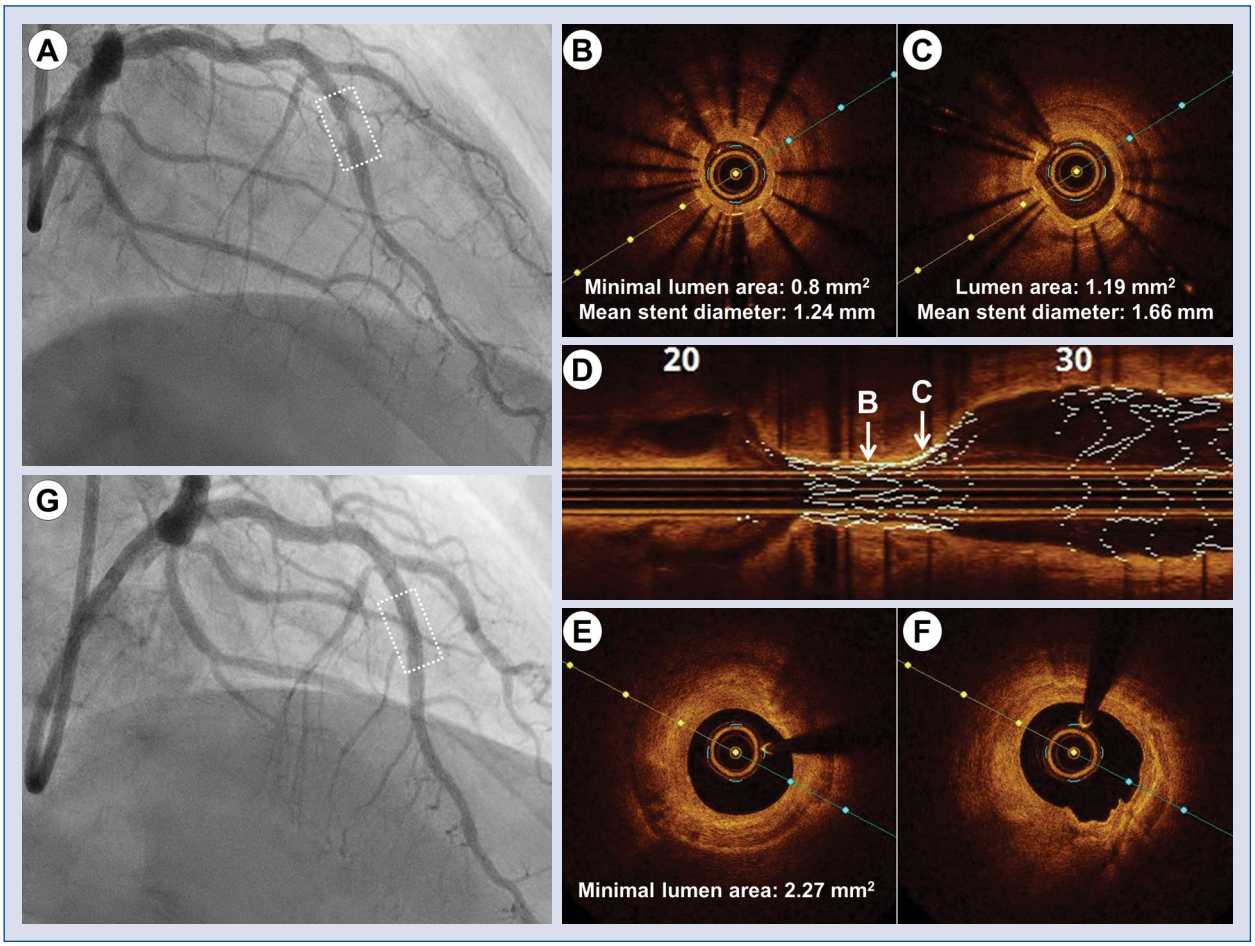


Figure 1. A. Initial angiography demonstrating underexpanded stent (white box); **B, C.** Cross-sectional optical coherence tomography (OCT) imaging of underexpanded stent site; **D.** Three-dimensional OCT reconstructed strut image of underexpanded stent site; **E, F.** OCT demonstrating no visible struts after stent ablation with rotational atherectomy; **G.** Final angiography demonstrating no residual stenosis after treatment with 3.0 × 20 mm drug-coated balloon.

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

Cardiology Journal
2020, Vol. 27, No. 6, 899
DOI: 10.5603/CJ.2020.0174

ISSN 1897–5593
eISSN 1898–018X

Recurrent sinus of Valsalva aneurysm with thrombogenesis after surgical repair

Meng Zhao[1], Jieyu Lu[1], Jingxin Zhou[2], Yanhu Wu[2]

[1]Nanjing Medical University, Nanjing, Jiangsu, China
[2]Department of Cardiovascular Surgery, the First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China

A 36-year-old woman was admitted to hospital experiencing paroxysmal palpitations for 1 month. Surgical repair of a ruptured sinus of a Valsalva aneurysm was done when she was 10 years old. After admission, the transthoracic echocardiography examination showed that the aortic non-coronary sinus was dilated (45 × 36 mm) and a moderately stronger signal could be seen within (45 × 17 mm). Coronary computed tomography angiography indicated an expanded aortic non-coronary sinus (5.3 × 4.9 cm) with low density areas within (Fig. 1). The coagulation function tests revealed D-dimer 0.8 mg/L. After anesthesia, transesophageal ultrasound identified a mass of thrombus in the expanded sinus. During the operation, the right atrium and aorta were cut open, a massive, grey, smelly purulent thrombus out of the aneurysm was then removed (**Suppl. Video 1**). The thrombus was sent to the pathology department for pathological tests. Then, a pericardial patch a was used to fix the opening of the aneurysm through the incision of the aorta and another patch b was used to reinforce it through the rupture in the right atrium. A double helical suture was used to eliminate the sac of the aneurysm. After the operation, transesophageal ultrasound showed that the thrombus had disappeared and that the aneurysm was minimized. Ten days post-surgery, transthoracic echocardiography showed that the expanded non-coronary aneurysm, pre-surgery, was replaced by a hyperechoic mass (20 × 21 mm), in which a blood signal could not be detected. Pathological examination of the thrombus indicated fibrous tissue without structure. The patient recovered well and left the hospital successfully.

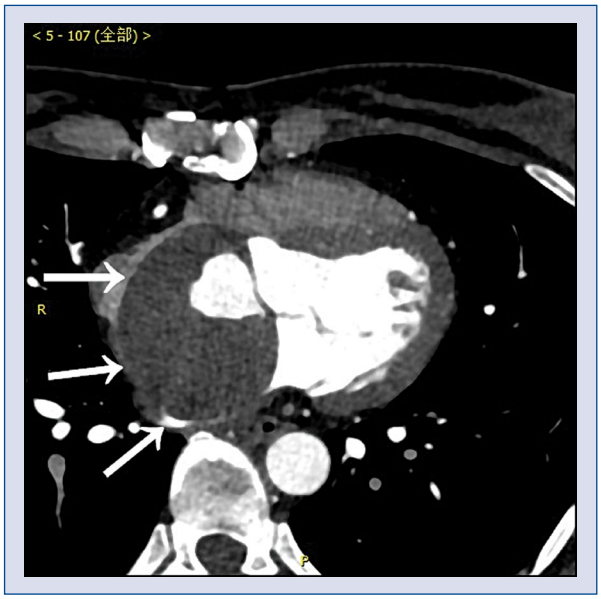


Figure 1. Low density areas can be found in the expanded aortic non-coronary sinus.

Funding: This work was financially supported by projects of the National Scientific Foundation of China (NSFC, grant nos.81700340).

Conflict of interest: None declared

Address for correspondence: Yanhu Wu, MD, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, China, 210029, tel: +86 13951945999, fax: +86 25 83724440, e-mail: wuyanhu@njmu.edu.cn

Received: 13.04.2020 Accepted: 13.04.2020

VIA MEDICA

LETTER TO THE EDITOR

Cardiology Journal
2020, Vol. 27, No. 6, 900–901
DOI: 10.5603/CJ.2020.0175

ISSN 1897–5593
eISSN 1898–018X

Cardiac tamponade as a cause of COVID-19

Oliver Robak[1], Maciej Dudek[2], Jerzy R. Ladny[2, 3], Lukasz Szarpak[2, 4, 5], Natasza Gilis-Malinowska[6], Michael Frass[1]

[1]Department of Medicine I, Medical University of Vienna, Austria
[2]Polish Society of Disaster Medicine, Warsaw, Poland
[3]Chair of Emergency Medicine and Disaster, Medical University Bialystok, Poland
[4]Maria Sklodowska-Curie Medical Academy in Warsaw, Poland
[5]Maria Sklodowska-Curie Bialystok Oncology Center, Bialystok, Poland
[6]First Department of Cardiology, Medical University of Gdansk, Poland

We read with great interest an article by Li et al. [1] which reviewed the cardiovascular complications in COVID-19 patients. The authors discuss many disease entities, including cardiac injury, myocarditis, acute coronary syndrome, heart failure, or sudden cardiac arrest. However, it is worth adding to this catalog cardiac tamponade, which is a pathological condition that directly threatens a patient's life. It consists in filling the pericardial cavity with a fluid that has the nature of an exudate or effusion, thus hindering filling the atria. Tamponade may arise because of infarction, trauma, mediastinal tumors and many other clinical conditions [2, 3].

Since December 2019, the world has been struggling with the pandemic of infections of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19). There is an increased recognition of cardiac involvement in patients with COVID-19 as it confers a worse prognosis. The most common cardiac complications include acute myocardial injury, arrhythmias, acute myocarditis and severe left ventricular dysfunction. However, several authors including Asif et al. [4] present a case of COVID-19-associated acute viral pericarditis complicated by large pericardial effusion and cardiac tamponade. Also, Hakmi et al. [5] showed that cardiac tamponade with concomitant biventricular failure can develop in COVID-19 patients.

As mentioned previously, cardiac tamponade is a life-threatening condition and, in the event of intensification of symptoms, requires urgent intervention in the form of decompression of the pericardial sac. However, in order not to delay the tamponade diagnosis procedure, especially in patients with suspected/confirmed COVID-19, when medical staff wears full personal protective equipment for aerosol generating procedures (PPE AGP), ultrasonography may be helpful [6, 7]. For this purpose, the Focus Assessment Transthoracic in Emergency (FATE) protocol can be used.

The aim of the aforementioned is to perform basic echocardiographic projections — sub-sternal, apical, parasternal and bilateral pleural projections (in the middle axillary lines in the costal arch). The ultrasonographic images acquired in this way allows confirmation or exclusion of cardiac tamponade, and, with its presence under ultrasound control, it is also possible to drain it.

In conclusion, cardiac tamponade, which can also be associated with COVID-19 infection, is a therapeutic challenge requiring immediate confirmation and implementation of invasive treatment.

Acknowledgements

Study supported by the ERC Research NET and Polish Society of Disaster Medicine.

Conflict of interest: None declared

Address for correspondence: Lukasz Szarpak, Assoc. Prof. PhD, MBA, Maria Sklodowska-Curie Medical Academy in Warsaw, ul. Solidarności 12, 03–411 Warszawa, Poland, tel: +48 500186225, e-mail: lukasz.szarpak@gmail.com

Received: 25.11.2020 Accepted: 25.11.2020

References

1. 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.
2. Sabatel-Perez F, Sastre-Perona MA, Alonso MB, et al. Extrapericardial cardiac tamponade due to massive retrosternal hematoma. Cardiol J. 2019; 26(5): 616–617, doi: 10.5603/CJ.2019.0105, indexed in Pubmed: 31701516.
3. Shibutani H, Yutaka K, Mukai Yu, et al. Cardiac tamponade secondary to right ventricular perforation caused by a temporary pacemaker lead in the course of myocardial infarction. Cardiol J. 2018; 25(4): 538–539, doi: 10.5603/CJ.2018.0087, indexed in Pubmed: 30211934.
4. Asif T, Kassab K, Iskander F, et al. Acute pericarditis and cardiac tamponade in a patient with COVID-19: a therapeutic challenge. Eur J Case Rep Intern Med. 2020; 7(6): 001701, doi: 10.12890/2020_001701, indexed in Pubmed: 32523921.
5. Hakmi H, Sohail A, Brathwaite C, et al. Cardiac tamponade in COVID-19 patients: Management and outcomes. J Card Surg. 2020 [Epub ahead of print], doi: 10.1111/jocs.14925, indexed in Pubmed: 32790006.
6. Pérez-Casares A, Cesar S, Brunet-Garcia L, et al. Echocardiographic evaluation of pericardial effusion and cardiac tamponade. Front Pediatr. 2017; 5: 79, doi: 10.3389/fped.2017.00079, indexed in Pubmed: 28484689.
7. Dudek M, Szarpak L, Ruetzler K. Application of interventional ultrasound in emergency medicine conditions. Disaster Emerg Med J. 2018; 3(4): 137–147, doi: 10.5603/demj.2018.0029.

VIA MEDICA

LETTER TO THE EDITOR

Cardiology Journal
2020, Vol. 27, No. 6, 902–903
DOI: 10.5603/CJ.2020.0176

ISSN 1897–5593
eISSN 1898–018X

Cardiac troponin I and T: Exploring popularity with Google Trends

Giuseppe Lippi[1], Fabian Sanchis-Gomar[2]

[1]Section of Clinical Biochemistry, University of Verona, Italy
[2]Department of Physiology, Faculty of Medicine, University of Valencia and INCLIVA Biomedical Research Institute, Valencia, Spain

There is now firm evidence that the measurement of cardiac troponins, either I (cTnI) or T (cTnT) using high-sensitivity immunoassays, is the mainstay for diagnosing both ischemic and non-ischemic myocardial injury, regardless of the cutoff point, as we have read in the article by Bjurman et al. [1]. Recent evidence attests that neither of these two biomarkers seem superior to the other for the purposes of diagnosing myocardial infarction, so that they can be ideally used interchangeably [2]. Since little information is currently available on the worldwide preference of one biomarker over the other, a retrospective analysis was carried out based on Google Trends, to establish which of the two cardiac troponins is more popular than the other.

Google Trends (Google Inc., Mountain View, CA, USA) is one of the most widely accessed tools in digital epidemiology. It is a freely available Google instrument, typically used for analyzing the popularity of top search queries in Google over time, across various geographical regions and using different languages. The search volume (expressed as Google Trends weekly Score) is finally displayed in graphical format, where the top value (i.e., 100) represents the maximum volume of Google searches for one or more given keywords [3]. In the present analysis, we used the keywords "troponin I" and "troponin T" in the field "topic", with no geographical or language restriction (thus including potential local translations), from the oldest searchable period (i.e., year 2004) up to present time (i.e., January 2020). The results of this search were downloaded in comma-separated values, and were imported into an Excel file (Microsoft, Redmond, WA, USA), and analyzed with Analyse-it (Analyse-it Software Ltd, Leeds, UK). Results were expressed as mean ± standard deviation and significance of differences was assessed with the Mann-Whitney test. The study was performed in accordance with the Declaration of Helsinki, under the terms of relevant local legislation.

The primary results of weekly volume of Google searches for cTnI and cTnT from 2004 to the present year are shown in Figure 1. Although the volume of weekly Google searches for cTnI and cTnT was found to be almost identical between the years 2004–2010 (49.3 ± 18.2 vs. 49.4 ± 11.2; $p = 0.478$), the number of weekly searches in Google for cTnT became steadily higher than that for cTnI in the following period, i.e., between 2011 to present year (57.0 ± 12.1 vs. 42.5 ± 8.7; mean difference, 29% and 95% confidence interval [CI] 27–31%; $p < 0.001$). This trend was magnified during the prior 12 months, whereby comparing the weekly volume of Google searches for cTnT (80.7 ± 4.1) and cTnI (58.8 ± 3.8), the mean gap further increased to 31% (95% CI 27–35%; $p < 0.001$). Interestingly, the weekly volume of Google searches for cTnI remained higher in United States, Mexico, Brazil, Portugal, France, Iran, China, and Japan, amongst others, while that for cTnT appeared to be predominant in the remaining countries.

It has recently been demonstrated that assessment of Web-based inclinations, using tools such as Google Trends, reflects human behaviors along with preference to access some specific diagnostic and/or therapeutic resources [4], including the worldwide use of cardiac biomarkers [5]. Therefore, the results of this analysis suggests that, despite the existence of only one fully-automated

Address for correspondence: Prof. Giuseppe Lippi, Section of Clinical Biochemistry, University Hospital of Verona, Piazzale LA Scuro, 37134 Verona, Italy, tel: +39-045-8124308, fax: +39-045-8122970, e-mail: giuseppe.lippi@univr.it

Received: 31.01.2020 Accepted: 22.02.2020

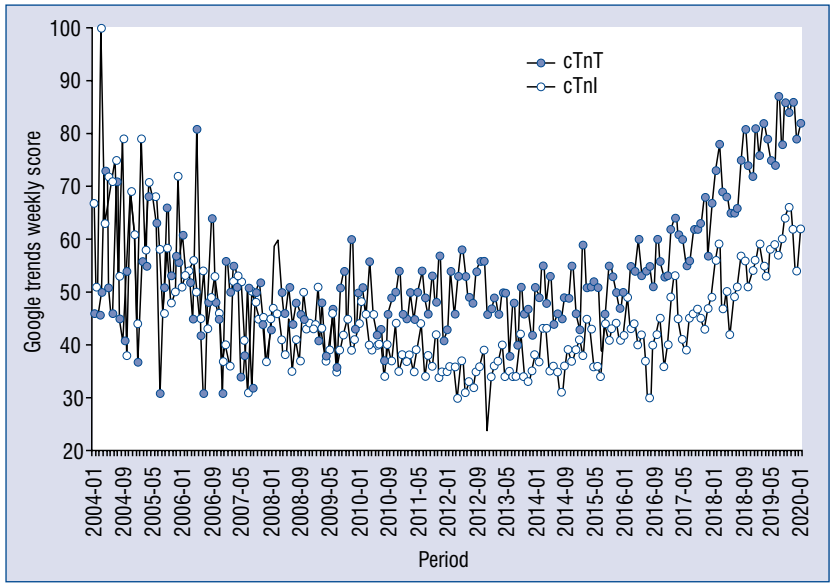


Figure 1. Trend of worldwide weekly Google Trends searches for cardiac troponin I (cTnI) and cardiac troponin T (cTnT) between 2004 and January 2020.

immunoassay for measuring cTnT, the current popularity of cardiac biomarkers seems to favor cTnT. Even in areas traditionally bound to cTnI, such as Canada and northern Europe, the scenario has changed during the past decade, especially during the past 12 months, with a weekly volume of Google searches for cTnT offsetting that for cTnI. The recent clearance of high-sensitivity-cTnT immunoassay in United States is probably linked with the observed change in tendency, which has led to broad diffusion of the test in the country [6]. Interestingly, the gap between the weekly Google searches for cTnI and cTnT in the United States has narrowed from ~50 vs. ~20 in the mid-2010s, to ~50 vs. ~35 in the past 12 months (data not shown).

Conflict of interest: None declared

References

1. Bjurman C, Zywczyk M, Lindahl B, et al. Decreased admissions and hospital costs with a neutral effect on mortality following lowering of the troponin T cutoff point to the 99th percentile. Cardiol J. 2017; 24(6): 612–622, doi: 10.5603/CJ.a2017.0079, indexed in Pubmed: 28695975.
2. Lippi G, Cervellin G. Is one cardiac troponin better than the other? J Lab Precis Med. 2019; 4: 19, doi: 10.21037/jlpm.2019.04.06.
3. Lippi G, Mattiuzzi C, Cervellin G. Is digital epidemiology the future of clinical epidemiology? J Epidemiol Glob Health. 2019; 9(2): 146, doi: 10.2991/jegh.k.190314.003, indexed in Pubmed: 31241874.
4. Mavragani A, Ochoa G, Tsagarakis KP. Assessing the methods, tools, and statistical approaches in google trends research: systematic review. J Med Internet Res. 2018; 20(11): e270, doi: 10.2196/jmir.9366, indexed in Pubmed: 30401664.
5. Lippi G, Mattiuzzi C, Cervellin G. Trends of popularity of cardiac biomarkers: Insights from Google Trends. Emergency Care Journal. 2018; 14(3): 7769, doi: 10.4081/ecj.2018.7769.
6. Rubini Gimenez M, Badertscher P, Twerenbold R, et al. Impact of the US food and drug administration-approved sex-specific cutoff values for high-sensitivity cardiac troponin T to diagnose myocardial infarction. Circulation. 2018; 137(17): 1867–1869, doi: 10.1161/CIRCULATIONAHA.117.031940, indexed in Pubmed: 29685935.

VIA MEDICA

LETTER TO THE EDITOR

Cardiology Journal
2020, Vol. 27, No. 6, 904–905
DOI: 10.5603/CJ.2020.0177

ISSN 1897–5593
eISSN 1898–018X

Golden ratio in congestive heart failure: A promising proportion for prognosis and decompensation

Ertan Yetkin[1], Selcuk Ozturk[2], Bilal Cuglan[3], Hasan Turhan[1]

[1]Istinye University Liv Hospital, Department of Cardiology, Istanbul, Turkey
[2]Ankara Education and Research Hospital, Cardiology Clinic, Ankara, Turkey
[3]Beykent University, Faculty of Medicine, Department of Cardiology, Istanbul, Turkey

The article published by Kowalczys et al. [1] was read with great enthusiasm and interest. Briefly, the prognostic value of daytime heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressure (BP), and their multiplication products and ratios was assessed in congestive heart failure (CHF) patients. Accordingly, it was found that daytime DBP and products including HR × DBP and HR × SBP may be valuable risk stratification factors for predicting death and decompensation in stable patients [1]. Beyond the prognostic implication of HR, BP and their products in patients with stable CHF, attention was paid to the value of SBP and DBP itself, in terms of the golden ratio. In the study population, Kowalczys et al. [1] found mean daytime SBP and DBP of patients with stable CHF as 114 mmHg and 70 mmHg, respectively. The ratio of SBP to DBP gives 1.62, which is very close to the golden ratio as described previously by the famous mathematicians Euclid and Fibonacci [2]. In addition, it is also noteworthy to calculate the ratio of SBP to DBP in patients with decompensated (107.0/60.7 mmHg) and non-decompensated (115.3/72.1 mmHg) status during the follow-up period. SBP/DBP in patients without decompensation is 1.59; whereas it is 1.76 in decompensated patients, which shows a distinct deviation from the golden ratio.

In principle, golden proportion is an observation that the ratio of any two sequential Fibonacci numbers approximates to the value of 1.618, which is named as the Greek letter Phi (φ) [2]. The Fibonacci series or golden ratio represents itself in a variety of natural settings such as the design of patterns in flowers, branching of leaves; and have also been used in the modeling of biological and financial systems as well as in electronics and music [2–4]. By defining the systolic phase interval as the time between the tip of the R wave and the end of the T wave on electrocardiography, the diastole/systole ratio has demonstrated as 1.611 and R-R interval/diastole ratio as 1.618, which is very close to golden ratio [5]. Furthermore, the ratio of the left ventricular end-diastolic to the end-systolic diameters gives a ratio equal to 1.614, which is quite close to the golden ratio [6]. In a similar manner, Henein et al. [7] have demonstrated that vertical and transverse dimensions of the heart are in accordance with the golden ratio in healthy humans. However, in the end-stage HF patients the ratio significantly decreases [7]. Likewise, SBP to DBP ratios have been shown to be very close to the golden ratio both in the systemic and pulmonary vascular system [8–10]. Yetkin et al. [8] observed that night-time proportions of systemic systolic to diastolic pressures are the closest results to the golden ratio; however, during the daytime it is a bit far from the golden ratio which might be explained by the changing balance between sympathetic and parasympathetic activity [8]. In this regard, it is exciting to observe the SBP/DBP ratio as very close to the golden proportions in stable CHF and deviated in decompensated patients. Values of the SBP/DBP rate, which are higher than or show considerable deviation from the golden ratio, might be a useful criterion for predicting decompensation in stable CHF patients with the support of future clinical studies.

Conflict of interest: None declared

Address for correspondence: Dr. Selcuk Ozturk, Ankara Education and Research Hospital, Cardiology Clinic, Ulucanlar Street, 06230, Ankara, Turkey, tel: +905535376613, e-mail: selcukozturk85@hotmail.com

Received: 25.12.2019 Accepted: 25.12.2019

References

1. Kowalczys A, Bohdan M, Gruchała M. Prognostic value of daytime heart rate, blood pressure, their products and quotients in chronic heart failure. Cardiol J. 2019; 26(1): 20–28, doi: 10.5603/CJ.a2017.0130, indexed in Pubmed: 29131282.
2. Persaud-Sharma D. O'Leary J. Fibonacci series, golden proportions, and the human biology. Austin J Surg. 2015; 2(5): 1–7.
3. Yalta K, Ozturk S, Yetkin E. Golden ratio and the heart: A review of divine aesthetics. Int J Cardiol. 2016; 214: 107–112, doi: 10.1016/j.ijcard.2016.03.166, indexed in Pubmed: 27060268.
4. Ozturk S, Yalta K, Yetkin E. Golden ratio: A subtle regulator in our body and cardiovascular system? Int J Cardiol. 2016; 223: 143–145, doi: 10.1016/j.ijcard.2016.08.147, indexed in Pubmed: 27537743.
5. Yetkin G, Sivri N, Yalta K, et al. Golden ratio is beating in our heart. Int J Cardiol. 2013; 168(5): 4926–4927, doi: 10.1016/j.ijcard.2013.07.090, indexed in Pubmed: 23890853.
6. Yetkin E, Çelik T, Arpaci M, et al. Left ventricular diameters as a reflection of „extreme and mean ratio". Int J Cardiol. 2015; 198: 85–86, doi: 10.1016/j.ijcard.2015.06.164, indexed in Pubmed: 26156320.
7. Henein MY, Zhao Y, Nicoll R, et al. The human heart: application of the golden ratio and angle. Int J Cardiol. 2011; 150(3): 239–242, doi: 10.1016/j.ijcard.2011.05.094, indexed in Pubmed: 21703707.
8. Yetkin E, Topbaş U, Yanik A, et al. Does systolic and diastolic blood pressure follow Golden Ratio? Int J Cardiol. 2014; 176(3): 1457–1459, doi: 10.1016/j.ijcard.2014.08.065, indexed in Pubmed: 25150476.
9. Chemla D, Boulate D, Weatherald J, et al. Golden ratio and the proportionality between pulmonary pressure components in pulmonary arterial hypertension. Chest. 2019; 155(5): 991–998, doi: 10.1016/j.chest.2018.12.006, indexed in Pubmed: 30594558.
10. Yetkin E, Çuğlan B, Turhan H, et al. Does golden ratio reside in pulmonary circulation? Chest. 2019; 156(3): 629–630, doi: 10.1016/j.chest.2019.04.112, indexed in Pubmed: 31511152.

VIA MEDICA

LETTER TO THE EDITOR

Cardiology Journal
2020, Vol. 27, No. 6, 906–907
DOI: 10.5603/CJ.2020.0178

ISSN 1897–5593
eISSN 1898–018X

Golden ratio in congestive heart failure: A promising proportion for prognosis and decompensation. Authors' reply

Anna Kowalczys[1, 2], Michał Bohdan[1], Marcin Gruchała[1]

[1]First Department of Cardiology. Medical University of Gdansk, Poland
[2]Department of Pharmacology. Medical University of Gdansk, Poland

We would like to thank Yetkin et al. [1] for interesting and insightful comments regarding our publication. They suggested that systolic blood pressure/diastolic blood pressure (SBP/DBP) ratio is associated with golden ratio and might be useful for stratifying the risk of heart failure (HF) decompensation [1].

Heart failure decompensation is one of the most difficult challenges in the management of patients with HF [2]. It needs to be highlighted that each HF decompensation should be regarded as a life-threatening condition and adversely affects the prognosis in this group of patients [2]. One of the very important research goals in the field of HF is the search for factors that may lead to a reduction in HF decompensations [2]. Early identification of potential risk factors enables the improvement of effectiveness of care in patients with chronic HF. In this context, the prospect of using new tools to identify patients at high risk of HF decompensation is very interesting and requires further attention.

The golden proportion was known already in antiquity and was attributed to exceptional aesthetic values [3, 4]. Golden ratio, estimated as phi = 1.618, has been described not only in mathematics but also in many other fields such as nature, architecture, art and science [3, 4]. Many authors have indicated a possible link of golden ratio with the human cardiovascular system [3–10]. Several data demonstrated the existance of golden proportion particularly in left ventricle dimensions measured in transthoracic echocardiography [3, 5–7]. Moreover, Gibson et al. [9] revealed an association between the Fibonacci sequence and distribution of culpirit lesions in coronary arteries in patients with myocardial infarction with ST-segment elevation. Many researchers have also been interested in the relationship between the golden proportion, SBP/DBP and DBP/pulse pressure ratios [3, 4, 8, 10]. Recently, Papaioannou et al. [8] analyzed the NHANES data from 31,622 individuals and reported that participants with SBP/DBP values that deviate from the 1.618 have a significantly higher risk of death in comparison to those with blood pressure values close to golden ratio.

Yetkin et al. [1] observed that in our study population SBP/DBP ratio is very close to 1.618 in stable patients with HF. Moreover, they estimated that SBP/DBP ratio in patients with recent HF decompensation differs significantly from this value [1]. Indeed, taking into account the above observations, SBP/DBP ratio value may be important in estimating the risk of decompensation in stable patients with HF. However, it should be emphasized that our study had limitations that may have affected the above results. First, the population in our study was small and diverse and included not only patients with HF due to coronary artery disease, but were also caused by other etiological factors. Secondly, most of our patients had various comorbidities and cardiovascular risk factors. Finally, all patients were treated pharmacologically with drugs that affect blood pressure and heart rate, which may have had an impact on the potential prognostic value of the SBP/DBP ratio. Furthermore, the methodology of our study included only daytime multiple blood pressure measurements during hospitalization [11]. Meanwhile, Yetkin et

Address for correspondence: Anna Kowalczys, MD, First Department of Cardiology, Medical University of Gdansk, ul. Dębinki 7, 80–211 Gdańsk, Poland, tel: +48 58 349 25 00, fax: +48 58 346 12 01, e-mail: anna.roz@gumed.edu.pl

Received: 14.12.2020 Accepted: 14.12.2020

al. [10] suggested that particularly the night-time SBP/DBP ratio measurements were close to the golden ratio. Therefore, future research in this area should take into account the application of 24-hour ambulatory blood pressure monitoring.

Currently, there is still little data in the literature on the prognostic significance of SBP/DBP ratio, double product and other ratios involving heart rate and blood pressure in patients with HF. Therefore, large studies are needed to determine their usefulness and applicability in clinical practice.

Conflict of interest: None declared

References

1. Yetkin E, Ozturk S, Cuglan B, et al. Golden ratio in congestive heart failure: A promising proportion for prognosis and decompensation. Cardiol J. 2020; 27(6), 904–905, doi: 10.5603/CJ.2020.0177.
2. Ponikowski P, Voors AA, Anker SD, et al. ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016; 37(27): 2129–2200, doi: 10.1093/eurheartj/ehw128, indexed in Pubmed: 27206819.
3. Yalta K, Ozturk S, Yetkin E. Golden Ratio and the heart: A review of divine aesthetics. Int J Cardiol. 2016; 214: 107–112, doi: 10.1016/j.ijcard.2016.03.166, indexed in Pubmed: 27060268.
4. Ozturk S, Yalta K, Yetkin E. Golden ratio: A subtle regulator in our body and cardiovascular system? Int J Cardiol. 2016; 223: 143–145, doi: 10.1016/j.ijcard.2016.08.147, indexed in Pubmed: 27537743.
5. Henein MY, Zhao Y, Nicoll R, et al. Golden Ratio Collaborators. The human heart: application of the golden ratio and angle. Int J Cardiol. 2011; 150(3): 239–242, doi: 10.1016/j.ijcard.2011.05.094, indexed in Pubmed: 21703707.
6. Çelik M, Gökoğlan Y, Develi S, et al. The golden ratio of the human heart. Gulhane Med J. 2015; 57(1): 1–4, doi: 10.5455/gulhane.43279.
7. Yetkin E, Çelik T, Arpaci M, et al. Left ventricular diameters as a reflection of „extreme and mean ratio". Int J Cardiol. 2015; 198: 85–86, doi: 10.1016/j.ijcard.2015.06.164, indexed in Pubmed: 26156320.
8. Papaioannou TG, Vavuranakis M, Gialafos EJ, et al. Blood pressure deviation from the golden ratio φ and all-cause mortality: a pythagorean view of the arterial pulse. Int J Appl Basic Med Res. 2019; 9: 55–57, doi: 10.4103/ijabmr.IJABMR 103_18.
9. Gibson C, Gibson W, Murphy S, et al. Association of the Fibonacci Cascade with the distribution of coronary artery lesions responsible for ST-segment elevation myocardial infarction. Am J Cardiol. 2003; 92(5): 595–597, doi: 10.1016/s0002-9149(03)00731-8.
10. Yetkin E, Topbaş U, Yanik A, et al. Does systolic and diastolic blood pressure follow Golden Ratio? Int J Cardiol. 2014; 176(3): 1457–1459, doi: 10.1016/j.ijcard.2014.08.065, indexed in Pubmed: 25150476.
11. Kowalczys A, Bohdan M, Gruchała M. Prognostic value of daytime heart rate, blood pressure, their products and quotients in chronic heart failure. Cardiol J. 2019; 26(1): 20–28, doi: 10.5603/CJ.a2017.0130, indexed in Pubmed: 29131282.