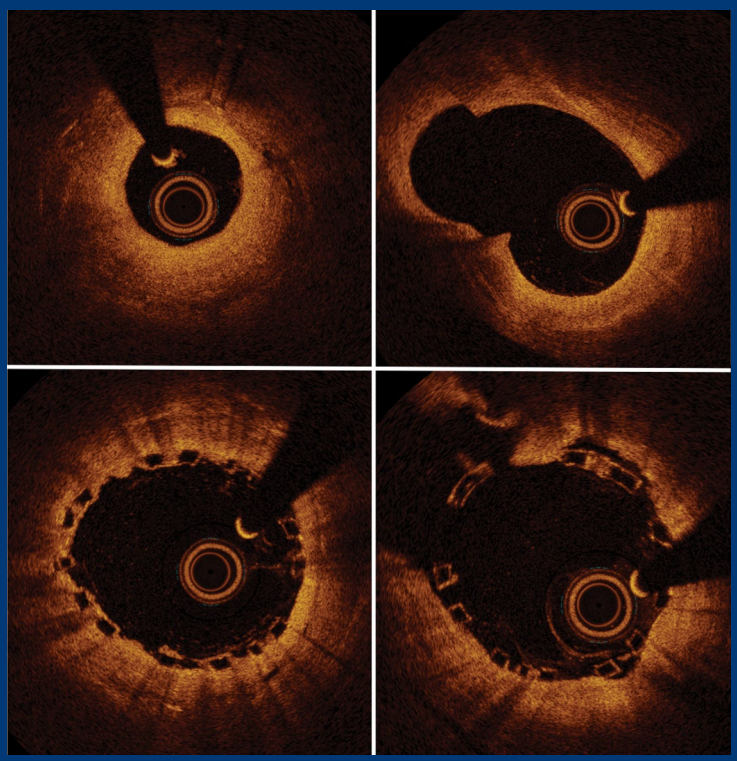
CARDIOLOGY JOURNAL

Impact Factor: 1.743

May 2019, Vol. 26, No. 3, pp. 215–306 www.cardiologyjournal.org



Grzegorz Zuk et al., see figure legend on page 305

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.

This journal is edited under the auspices of the International Society of Holter and Noninvasive Electrocardiology.

Cardiology Journal (ISSN 1897-5593) is published 6 times a year by VM Media sp. z o.o. VM Group sp.k.

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

18-0225.003.001

Journal has an international indexation in CrossRef, EBSCO, EMBASE, FMJ, Google Scholar, Science Citation Index Expanded, Index Copernicus (155.56 points), MEDLINE, Scopus, SJR, Ulrich's Periodicals Directory, Web of Science CC and WorldCat database, Ministry of Science and Higher Education score (20 points). Current Impact Factor of "Cardiology Journal" (2018) is 1.743.

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 57, e-mail: dsk@viamedica.pl
The Editors take no responsibility for the published advertisements.

CARDIOLOGY JOURNAL

www.cardiologyjournal.org

May 2019, Vol. 26, No. 3

Table of Contents

IMAGES IN CARDIOVASCULAR MEDICINE

Interventional cardiology

Clinical cardiology

LETTER TO THE EDITOR

Interventional cardiology

VIA MEDICA

POSITION PAPER

Cardiology Journal
2019, Vol. 26, No. 3, 215–225
DOI: 10.5603/CJ.a2019.0054

ISSN 1897–5593

Consensus document for invasive coronary physiologic assessment in Asia-Pacific countries

Hak Seung Lee[1], Joo Myung Lee[2], Chang-Wook Nam[3], Eun-Seok Shin[4], Joon-Hyung Doh[5], Neng Dai[6], Martin K.C. Ng[7], Andy S.C. Yong[8], Damras Tresukosol[9], Ajit S. Mullasari[10], Rony Mathew[11], Praveen Chandra[12], Kuang-Te Wang[13], Yundai Chen[14], Jiyan Chen[15], Kai-Hang Yiu[16], Nils P. Johnson[17], Bon-Kwon Koo[1]

[1]Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, Seoul, Republic of Korea
[2]Division of Cardiology, Department of Internal Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[3]Department of Medicine, Keimyung University Dongsan Medical Center, Daegu, Republic of Korea
[4]Department of Cardiology, Ulsan University Hospital, University of Ulsan College of Medicine, Korea
[5]Department of Medicine, Inje University Ilsan Paik Hospital, Goyang, Korea
[6]Department of Cardiology, Shanghai Institute of Cardiovascular Disease, Zhongshan Hospital, Fudan University, Shanghai, China
[7]Department of Cardiology, Royal Prince Alfred Hospital, Camperdown, Australia
[8]Department of Cardiology, Concord Hospital, Sydney, Australia
[9]Division of Cardiology, Siriraj Hospital, Mahidol University, Bangkok, Thailand
[10]Institute of Cardiovascular Diseases, The Madras Medical Mission, Chennai, India
[11]Lisie Hospital, Kochi, Kerala, India
[12]Medanta, Gurgaon, India
[13]Division of Cardiology, Department of Internal Medicine, Mackay Memorial Hospital, Taitung Branch, Taiwan
[14]Department of Cardiology, Chinese PLA General Hospital, Beijing, China
[15]Guangdong Provincial Key Laboratory of Coronary Heart Disease Prevention, Guangdong Cardiovascular Institute, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China
[16]Division of Cardiology, Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong, China
[17]McGovern Medical School at UTHealth and Memorial Hermann Hospital, Houston, Texas, United States

Abstract

Background: *Currently, invasive physiologic assessment such as fractional flow reserve is widely used worldwide with different adoption rates around the globe. Patient characteristics and physician preferences often differ in the Asia-Pacific (APAC) region with respect to treatment strategy, techniques, lesion complexity, access to coronary physiology and imaging devices, as well as patient management. Thus, there is a need to construct a consensus document on recommendations for use of physiology-guided percutaneous coronary intervention (PCI) in APAC populations. This document serves as an overview of recommendations describing the best practices for APAC populations to achieve more consistent and optimal clinical outcomes.*

Address for correspondence:

Prof. Bon-Kwon Koo, MD, PhD, Seoul National University College of Medicine, 101 Daehang-ro, Chongno-gu, Seoul, 110-744, Korea, tel: 82-2-2072-2062 (office), 82-2-2072-2677 (cath lab), fax: 82-2-3675-0805, e-mail: bkkoo@snu.ac.kr

Nils P. Johnson, MD, MS, Weatherhead PET Center, McGovern Medical, School at UTHealth, 6431 Fannin Street, Room, MSB 4.256, Houston, Texas 77030, United States, e-mail: nils.johnson@uth.tmc.edu

Received: 15.12.2018 Accepted: 9.06.2019

Methods and Results: *A comprehensive multiple-choice questionnaire was provided to 20 interventional cardiologists from 10 countries in the APAC region. Clinical evidence, tips and techniques, and clinical situations for the use of physiology-guided PCI in APAC were reviewed and used to propose key recommendations. There are suggestions to continue to develop evidence for lesion and patient types that will benefit from physiology, develop directions for future research in health economics and local data, develop appropriate use criteria in different countries, and emphasize the importance of education of all stakeholders. A consensus recommendation to enhance the penetration of invasive physiology-based therapy was to adopt the 5E approach: Evidence, Education, Expand hardware, Economics and Expert consensus.*

Conclusions: *This consensus document and recommendations support interventional fellows and cardiologists, hospital administrators, patients, and medical device companies to build confidence and encourage wider implementation of invasive coronary physiology-guided therapy in the APAC region.*
(Cardiol J 2019; 26, 3: 215–225)

Key words: coronary physiology, invasive physiologic assessment, quality improvement

Introduction

Coronary angiography can no longer be considered a gold standard for determining the functional significance of coronary stenosis given its known limitations including eccentric plaque morphology, frequent lack of a normal reference segment, visual overestimation, and inter-observer variability [1–3]. As a consequence of these limitations, intracoronary physiology assessment and imaging have been developed to provide superior diagnostic information for coronary stenotic lesions [4, 5]. Fractional flow reserve (FFR) was developed to define the functional significance of a coronary stenosis in a cardiac catheterization laboratory. In addition, resting pressure-derived physiologic indices have also been developed and used in daily clinical practice [6]. However, their penetration rate in the Asia-Pacific (APAC) region is highly variable and low in general.

This consensus statement for the APAC region briefly reviews important clinical studies to develop a practical message regarding when and how to use coronary physiology, and aims to promote physician education at different stages of adopting physiologic assessment into clinical practice.

Methods

This paper is based on a meeting sponsored by Abbott Vascular in April 2018 of 20 interventional cardiologists from 10 countries (Australia, China, India, Japan, Korea, Singapore, Taiwan and Thailand) with significant experience in performing physiology-guided percutaneous coronary intervention (PCI). The goal of the meeting was to understand invasive physiology practice across the APAC region and to develop a consensus statement. A pre-meeting survey was followed by an interactive discussion. The participants included high-volume interventional cardiologists with extensive experience:

- at least 300 PCIs performed per year;
- ~2/3rd performing 6–10 physiology procedures per month; 1/3rd performing more than 10 physiology procedures per month;
- 2/3rd administering intravenous hyperemia during physiology-guided PCI;
- 2/3rd considering physiology during ST-segment elevation myocardial infarction (STEMI).

Clinical evidence, tips and techniques, and clinical situations for the use of physiology-guided PCI in APAC were reviewed and used to propose key recommendations. Against the backdrop of the available clinical evidence and the physicians' personal experience, the group discussed multiple issues pertaining to physiology-guided PCI.

- Lesion/patient subsets recommended and not recommended for invasive physiologic assessment;
- Current evidence gaps and areas for further research;
- Trends of differential utilization of coronary physiologic assessment;
- Learning curve and barriers to routine adoption of physiologic assessment;
- Impact of appropriate use criteria on physiologic assessment adoption in APAC countries;
- Resting physiology:
  - clinical evidence about resting flow,
  - benefits and limitations of adopting rest-

ing physiologic assessment into daily practice,
- role of non-hyperaemic resting ratios such as resting full-cycle ratio (RFR) or diastolic pressure ratio (dPR) to drive the adoption of invasive physiologic assessment;

— Technologies to assess microvascular disease:
- current role of coronary flow reserve (CFR) and index of microcirculatory resistance (IMR) in clinical practice, based on evidence,
- evidence gaps for CFR and IMR,
- relevance of CFR and IMR as a mainstream clinical tool,
- role of CFR in clinical practice: current and future.

Results and discussion

Key findings of the pre-meeting survey are as follows:

— FFR was the most common physiology index, followed by IMR and instantaneous wave-free ratio (iFR);

— Common criteria for considering physiology assessment in clinical practice were intermediate or ambiguous lesions and stenosis of bifurcation lesions, in-stent restenosis, left main lesions, multi-vessel disease, and STEMI. However, all agreed that stenosis severity alone should not be the sole gatekeeper for invasive physiologic assessment;

— Adenosine was the hyperaemic agent of choice based on its availability. However, intracoronary nicorandil was also considered as an alternative agent based on equivalent hyperaemic efficacy and significantly lower procedural time and patient discomfort [7, 8];

— Cost and additional time needed to conduct the procedure were identified as the main factors preventing the routine use of physiologic assessment. Multiple factors were identified as potentially being able to increase physiology--guided PCI. These are separately discussed as recommendations of the group;

— Use of post-PCI physiology still remains an emerging area, with a majority of interventional cardiologists using it in < 25% of the total number of physiology procedures;

— Despite the latest evidence including theoretical support of reliability in FFR value and prognostic benefit of an FFR-guided strategy for non-culprit lesions during STEMI presentation, more than 50% of respondents do not use it routinely;

— The use of CFR and IMR as a physiological tool remains modest with only limited operators understanding its potential. Availability of more clinical evidence, better software, and a simplified clinical protocol may support adoption of CFR and IMR;

— iFR, one of several pressure-derived physiologic indices that avoids hyperaemia, has few users in the APAC regions as a routine procedure. Some factors supporting iFR in practice include fewer side effects compared with FFR, faster procedural time and lower cost;

— Education of all stakeholders (consultants, technicians, nursing staff, patients, referring physicians, and insurers) was identified as a key step and is discussed separately in the recommendations section.

Numerous factors influence treatment decision patterns and differ among countries. Physicians will always rely on a combination of their knowledge, experience, and the guidelines to shape a therapeutic strategy. The following are a summary of issues discussed during the meeting.

Current guidelines and clinical evidence

The latest update of the American College of Cardiology/American Heart Association (ACC/AHA) Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease states: "It has been suggested in several studies that a PCI (percutaneous coronary intervention) strategy guided by FFR may be superior to a strategy guided by angiography alone." [9]. In the absence of non-invasive proof of ischemia, FFR performed in a coronary stenosis with a 40–90% diameter reduction was given a "class I recommendation" and "level of evidence A" in the guidelines for coronary revascularization published by the European Society of Cardiology (ESC) in 2019 (Table 1) [10].

Based on the results of several randomized, prospective clinical studies and registries evaluating physiology-guided PCI in many thousands of patients, the clinical relevance of FFR is well established and documented (Fig. 1). Even when non-invasive proof of ischemia is available, FFR measurements often change clinical judgment regarding the need to revascularize a given coronary artery stenosis [11]. Table 2 shows the summary of studies which investigated the changes in

Table 1. Recommendations on functional testing and for lesion assessment — 2018 European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines on myocardial revascularization.

Recommendations	Class of recommendation	Level of evidence
When evidence of ischaemia is not available, FFR or iFR are recommended to assess the hemodynamic relevance of intermediate-grade stenosis	I	A
FFR-guided PCI should be considered in patients with multivessel disease undergoing PCI	IIa	B

FFR — fractional flow reserve; iFR — instantaneous wave free ratio; PCI — percutaneous coronary intervention

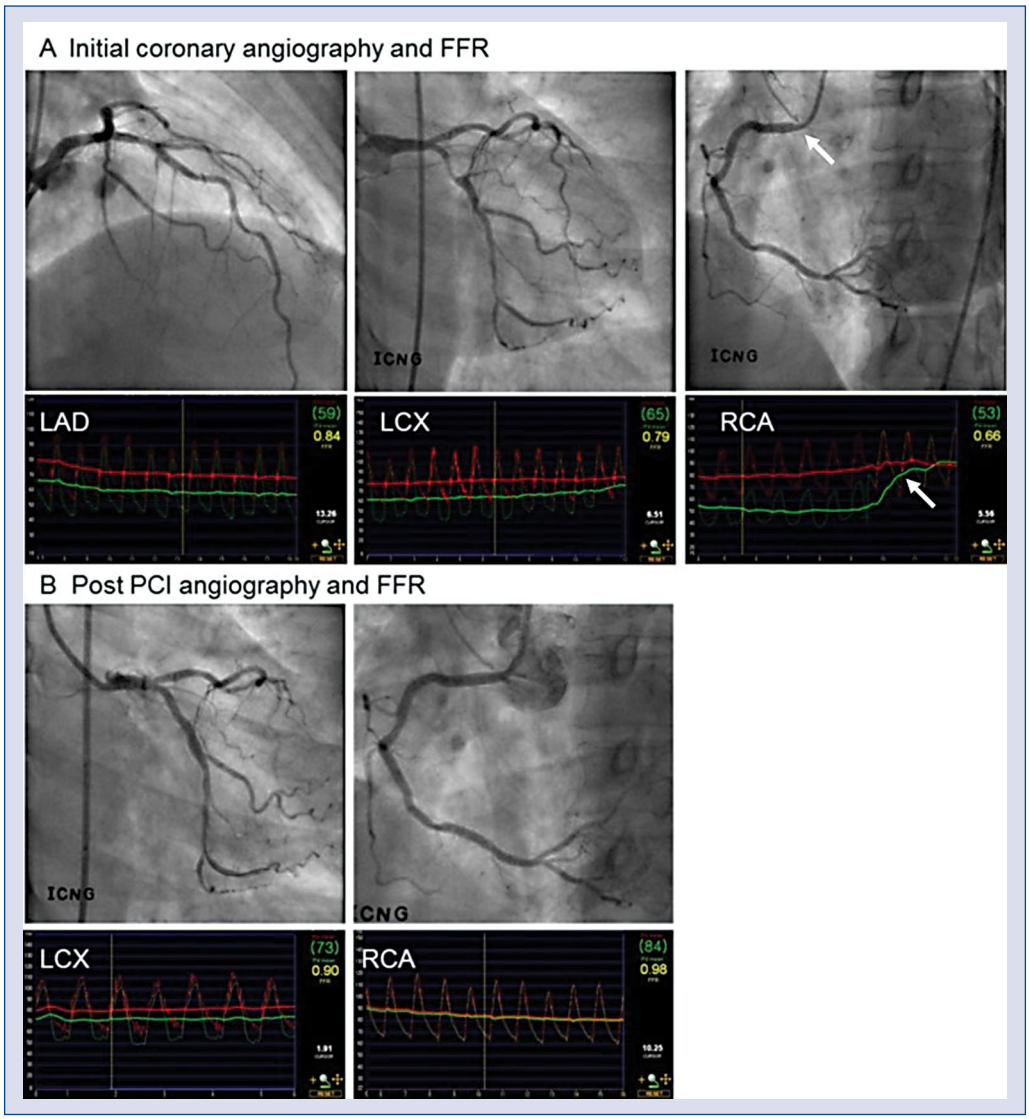


Figure 1. A case of physiology guided percutaneous coronary intervention (PCI). **A.** A patient showed angiographically, two vessel disease with stenosis in left anterior descending artery (LAD) and left circumflex artery (LCX). However, fractional flow reserve (FFR) in LAD, LCX and right coronary artery (RCA) was 0.84, 0.79, and 0.66, respectively. In contrast to angiographic assessment, physiologic assessment showed that the targets of revascularization were LCX and RCA, not LAD. In RCA, significant pressure step-up occurred at the ostium (arrow); **B.** PCI was performed for proximal LCX and RCA lesions and post PCI FFR at LCX and RCA was 0.90 and 0.98, respectively.

Table 2. Changes in management strategy after invasive physiologic assessment.

Trial [year]	Subjects	Pressure wire assessment	Change in management strategy
DEFINE REAL (2018) [12]	Multivessel disease	FFR and/or iFR Intermediate lesions	26.9% (130 of 484 patients)
POST-IT (2016) [13]	FFR in ≥ 1 vessel	FFR Operator's discretion	44.2% (406 of 918 patients)
FAMOUS-NSTEMI (2015) [14]	NSTEMI	FFR All lesions with ≥ 30% stenosis	21.6% (38 of 176 patients)
CVIT-DEFER (2015) [15]	FFR in ≥ 1 vessel	FFR Intermediate lesions	39.0% (1205 of 3093 patients)
R3F (2014) [16]	Ambiguous stenosis +	FFR Angiographically 35% to 65% stenosis	43.2% (464 of 1,075 patients)
RIPCORD (2014) [17]	Stable chest pain	FFR All coronary arteries ≥ 2.25 mm	26.5% (53 of 200 patients)

FFR — fractional flow reserve; iFR — instantaneous wave free ratio; NSTEMI — non-ST-segment elevation myocardial infarction; PW — pressure wire

management strategy after invasive physiologic assessment [12–17].

Key findings from previous pivotal FFR trials can be summarised as follows:

— DEFER trial [18] showed that FFR-based deferral of revascularization for a functionally insignificant stenosis was safe in up to 15 years of follow-up, and revascularization of these lesions could not have improved the prognosis. The DEFER-DES trial [19], which was conducted in the era of drug-eluting stents, also showed similar results to the DEFER trial;

— FAME trial [20] showed that an FFR-guided strategy reduced the risk of major adverse cardiac events compared with an angiography-guided strategy, with less use of stents per patient, contrast media, and medical cost. Recently published 5-year follow-up data showed no late catch-up of events in the FFR-guided group;

— FAME II trial [21] clearly showed that in patients with stable coronary artery disease (CAD), an initial FFR-guided PCI strategy resulted in a sustained clinical benefit compared with medical therapy alone using a composite primary endpoint of death, myocardial infarction, or urgent revascularization at 5 years. Patients without hemodynamically significant stenosis had a favourable long-term outcome with medical therapy alone;

— COMPARE ACUTE [22]: In patients with STEMI and multi-vessel disease who underwent primary PCI of an infarct-related artery, the addition of immediate FFR-guided complete revascularization of non-infarct-related arteries in the acute setting resulted in the risk of a composite cardiovascular outcome that was lower than the risk among those who were treated for the infarct-related artery only. This reduction was mainly driven by the decreased need for subsequent revascularization;

— DANAMI-3-PRIMULTI [23]: In patients with STEMI and multi-vessel disease who underwent primary PCI of an infarct-related artery, the addition of staged FFR-guided complete revascularization of non-infarct-related arteries (median interval 2 days) resulted in the risk of a composite cardiovascular outcome that was lower than the risk among those who were treated for an infarct-related artery only. This reduction was mainly driven by a decreased need for subsequent revascularization [9].

Clinical application of resting physiologic indices

Recently, iFR was introduced as an alternative to FFR that does not require hyperaemia (Fig. 2). Two large randomized trials, the DEFINE-FLAIR [24] and the iFR-SWEDEHEART trial [25], claimed non-inferiority of iFR compared with FFR but did not focus on the 20% of lesions with discordant treatment decisions between iFR and FFR. In studies by Lee et al. [26–28], both iFR and FFR changed significantly according to different anatomical and hemodynamic stenosis severity. However, FFR showed more sensitive changes to the severity of a stenosis than iFR. Currently, European guidelines

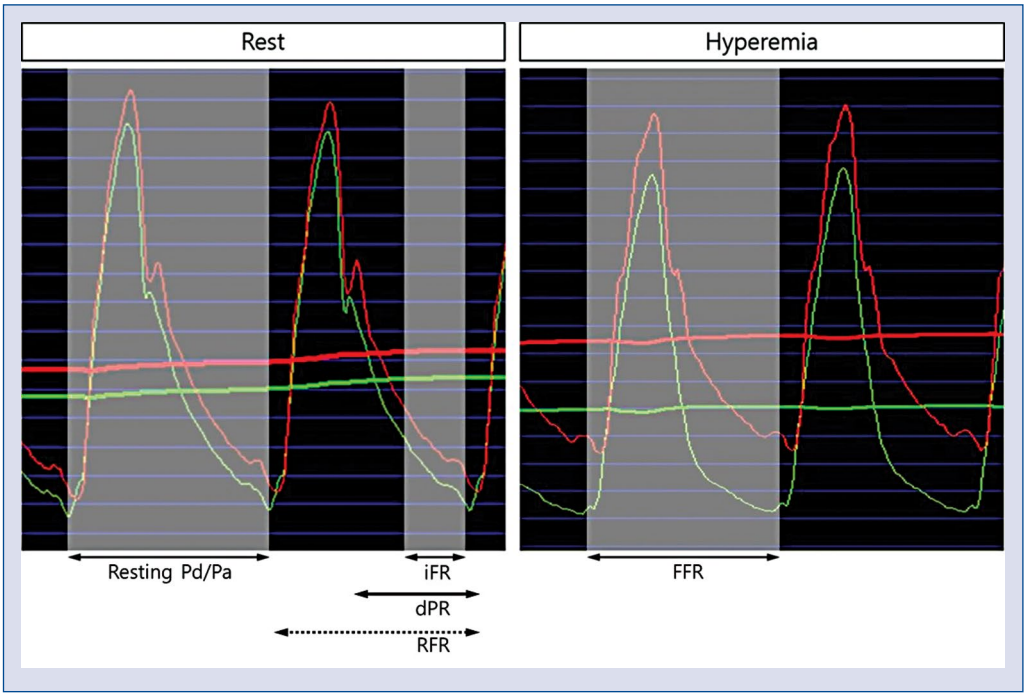


Figure 2. Resting and hyperemic pressure-derived invasive physiologic indices; abbreviations — see text.

consider iFR as largely equivalent to FFR [9]. Integration of both resting and hyperaemic physiologic indices may provide better information for clinical decision-making as recent studies suggested that the discordance between iFR and FFR might have clinical implications [29–31]. In addition to iFR, resting physiologic indices such as dPR or diastolic hyperemia-free ratio and RFR have been introduced and showed equivalent diagnostic performance to iFR [32, 33]. As FFR is the most commonly used invasive physiologic index in the APAC region, further discussion is needed to provide a guide for use of resting indices in daily practice.

Role of microvascular assessment

Since the coronary artery system has three components (epicardial coronary arteries, arterioles, and capillaries), myocardial ischemia can occur within any one of these levels. Although the microvascular system cannot be visualized by invasive coronary angiography, its function can be evaluated by invasive physiologic assessment. It is well-known that the presence of microvascular dysfunction is associated with a poor prognosis in patients who do not have significant epicardial CAD (Fig. 3). IMR is a specific index for microvascular status and can be measured by a thermodilution technique. CFR represents the microvascular status when there is no significant epicardial disease and can be measured using a Doppler wire or a pressure/temperature-sensor guide wire. The international IMR registry with 1,096 Asian and Western patients (1,452 vessels) found that there was no correlation between IMR and FFR values ($r = 0.01$; $p = 0.62$) and between IMR and angiographic percent diameter stenosis ($r = -0.03$; $p = 0.25$) [34]. The optimal cut off value in patients with stable CAD was 25 (arbitrary units). In a Korean study which investigated the prognosis of patients according to CFR and IMR levels, the presence of low CFR in conjunction with high IMR was the most powerful independent predictor for clinical events among patients with high FFR [35]. These results suggest that the use of invasive physiologic assessment for microvascular disease should be encouraged, as it can help identify patients at high risk for future cardiovascular events among those with high FFR. In order for microvascular assessment to be used more, the logistic and reimbursement issues need to be resolved, along with more education about microvascular disease and techniques for its assessment.

Global physiology practice

Invasive coronary physiology is used worldwide now, with the first instance of resting coronary

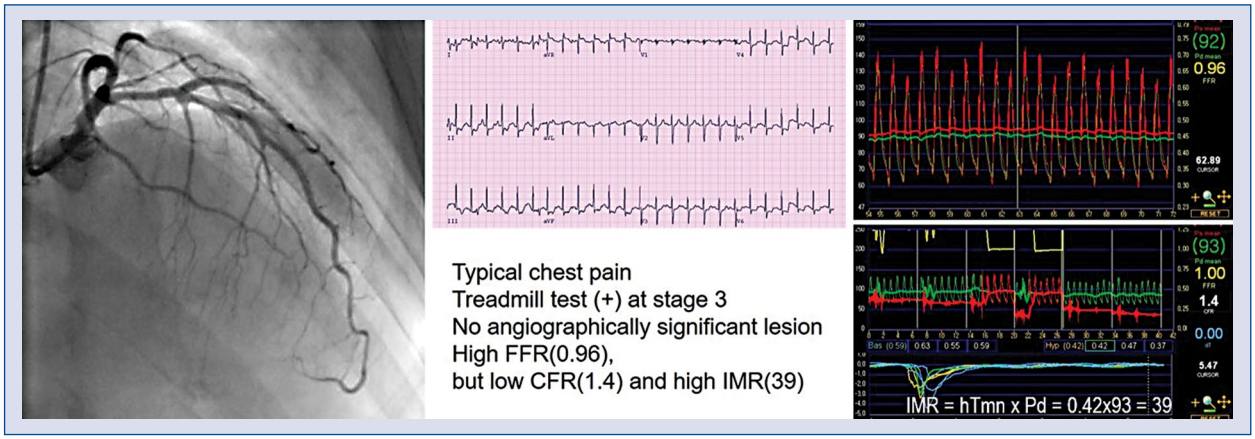


Figure 3. A case of microvascular disease assessed by coronary flow reserve (CFR) and index of microcirculatory resistance (IMR). The patient presented with typical chest pain on exertion and a positive exercise stress test. Coronary angiography showed no obstructive epicardial coronary artery disease and fractional flow reserve (FFR) was insignificant in the left anterior descending artery (LAD). However, CFR was low and IMR was high in LAD, suggesting the presence of microvascular disease; hTmn — hyperemic mean transit time; Pd — mean distal coronary pressure.

Table 3. Public Reporting of Coronary Physiology Uptake [38]

Country	Year	PW	PCI	PW/PCI	Temporal change	Hospital-level reporting?
Sweden [39]	2017	NR	NR	26%	3.1-fold in 10 years	Yes
United Kingdom [40]	2016	18,811	100,483	19%	3.5-fold in 8 years	Yes
Italy [41]	2016	11,000	218,751	5%	1.4-fold in 4 years	Yes
Europe EAPCI [42]	2015	NR	889,957	16%	2-fold in 5 years	Per country
United States [43]	2014	3,465*	NR	31%	3.8-fold in 5 years	No
Australia [44]	2015	NR	3,869	19%	100-fold in 9 years	Per state

*Limited to a subset of the 59,375 patients in the National Cardiovascular Data Registry CathPCI Registry with lesions deemed 40–70% by visual assessment. EAPCI — European Association of Percutaneous Cardiovascular Interventions; NR — not reported; PCI — percutaneous coronary intervention; PW — intracoronary pressure wire

pressure across a stenosis recorded by Gruentzig et al. [36] during his initial PCI. Despite this early introduction, the practical use of coronary physiology in the cardiac catheterization laboratory started only in the late 1990's. FFR was first described by Pijls et al. [37] in 1993 and has been evaluated since then in numerous large randomized trials and real-world registries. Tracking the uptake of coronary physiology by dividing the number of pressure wires by the number of PCI's (albeit an imperfect metric) demonstrates an enormous growth in many parts of the world, including some APAC countries [38], as detailed in Table 3 [39–44].

Barriers for adoption of invasive physiologic assessment in a cardiac catheterization laboratory

Despite clear evidence and guideline recommendations, many interventional cardiologists continue to rely on visual assessment of stenosis severity alone rather than using physiologic assessment in a cardiac catheterization laboratory. Multiple reasons have been attributed to the differential use of physiology-guided PCI. These factors include:

— logistics;
— cost;
— availability of hyperaemic agents;
— extra-time for physiologic assessment;
— concerns regarding potential complications;
— uncertainty about optimal performance of physiology assessment;
— relying on invasive imaging assessment;
— interpretation of FFR measurements, particularly in complex situations, such as multi-vessel disease, left main disease, serial lesions, and patients with coronary artery bypass grafts.

Although intracoronary pressure assessment is not technologically challenging to perform, sev-

eral aspects were suggested to guarantee precise measurements: nitrate administration, proper wire position to avoid artefact, flushing and guide control to avoid damping or ventricularisation, and a post-procedure drift check.

An important issue raised during the meeting was the cost and availability of different hyperaemic agents. Although the intravenous infusion of adenosine/ATP (140 μg/kg/min) is generally regarded as a gold standard hyperemic method, the use and availability of various hyperaemic agents differs among APAC regions. In Korea and Japan, the use of intracoronary nicorandil (2 mg bolus) and papaverine have become popular in clinical practice due to its safety, ease of use, and relatively long-acting effects [7, 8].

Recommendations that can increase coronary physiology uptake in APAC countries (5E Approach)

Evidence

Since most of the large randomized study data has been generated in Western countries, there is a clear need to generate local APAC real-world data. This could be either in the form of decision-making strategy trials like RIPCORD, or in-country large registries like SCAAR (Sweden). Several groups of APAC countries recently published the results of important physiologic studies and those study results from APAC need to be highlighted [19, 26, 45–50]. The group also felt that in-country registry data can provide good scientific evidence to respective health authorities to incorporate invasive physiology in guidelines and reimbursement. Cost effectiveness and clinical outcomes should be an integral part of such a platform. There may also be the potential of conducting 'recovery audits' of catheterization laboratories, just like those done in the United States.

Education

Education will play a significant role in establishing physiology-guided PCI as a standard practice. There was unanimous agreement to focus on younger interventional cardiologists and fellows and ensure that they are aware of the benefits of physiologic assessment. While this may be a challenge given the lack of learning opportunities in an individual hospital or center, academic societies and industry can play an important role in imparting education at an early stage in their careers. This can be achieved through scientific agenda at important conferences, demonstration through live cases, expert tours etc. Involvement of cardiac catheterization laboratory technicians and nurses will also be crucial to the success of any physiology education program. They are important stakeholders in the entire process and need to be included in the education strategy. The group also felt that it is extremely important to establish patient awareness of physiology-guided PCI. In different healthcare systems in APAC, given the varying reimbursement structures, patient awareness efforts will play a key role in driving benefits of physiologic assessment. The group recommended a dedicated patient-centric approach that can address the potential harm of 'over-stenting'.

Expand capital penetration

Though a limited role exists for interventional cardiologists in improving product availability, the group recommended developing the infrastructure at small/medium centers, rather than just focusing on high volume centers. Sometimes large volume PCI centres may not fully understand the implications of such a technology and would be resistant to bring about any change in the existing set-up. Smaller volume hospitals tend to invest more in newer technology to continuously upgrade their infrastructure and quality of outcomes.

Economics

The group strongly felt that health economics would be one of the most important factors to impact the adoption of physiology-guided PCI. There is a strong need to establish the cost effectiveness of the therapy through local registries as the bulk of the evidence has been generated in Western healthcare systems which are structured very differently than APAC healthcare. Positive health economy data will support reimbursement and, in turn, the utility of the therapy.

Expert consensus

There is growing clinical evidence for the value of coronary physiologic assessment and its beneficial effect on outcomes of coronary interventional procedures for patients. However, a common misconception among interventional cardiologists is that physiology may have a negative impact on the advancements of PCI procedures. Some interventional cardiologists believe that with increasing physiology-guided PCI, the number of overall PCI procedures will come down and this will discourage the value of the PCI procedures, and, as such, prefer stenting over physiologic assessment. There is also a perception that the ad-

dition of physiological measurements would lead to more time spent in the cardiac catheterization laboratory. In the absence of in-country guidelines or appropriate use criteria in most APAC countries, interventional cardiologists have been inconsistent in their approach to physiologic assessment. Lack of equipment for physiologic assessment and reimbursement in most APAC countries limits such procedures. Though health authorities in some countries have already started to develop guidelines around invasive physiologic assessment and considering reimbursement, there is still a long way to go before it becomes a part of the routine treatment protocol.

Conclusions

This consensus document and recommendations supports interventional fellows and cardiologists, hospital administrators, patients, and medical device companies to build confidence and encourage wider implementation of the invasive coronary physiology-guided therapy in the APAC region. More consensus meetings and targeted education are needed to guide the proper use of invasive physiologic assessment in the APAC region.

Conflict of interest: None declared

References

1. Topol EJ, Nissen SE. Our preoccupation with coronary luminology. The dissociation between clinical and angiographic findings in ischemic heart disease. Circulation. 1995; 92(8): 2333–2342, indexed in Pubmed: 7554219.
2. Yamagishi M, Hosokawa H, Saito S, et al. Coronary disease morphology and distribution determined by quantitative angiography and intravascular ultrasound--re-evaluation in a cooperative multicenter intravascular ultrasound study (COMIUS). Circ J. 2002; 66(8): 735–740, indexed in Pubmed: 12197597.
3. Toth G, Hamilos M, Pyxaras S, et al. Evolving concepts of angiogram: fractional flow reserve discordances in 4000 coronary stenoses. Eur Heart J. 2014; 35(40): 2831–2838, doi: 10.1093/eurheartj/ehu094, indexed in Pubmed: 24644308.
4. Pijls NH, Van Gelder B, Van der Voort P, et al. Fractional flow reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. Circulation. 1995; 92(11): 3183–3193, indexed in Pubmed: 7586302.
5. Toth GG, Toth B, De Vroey F, et al. Revascularization decisions in patients with stable angina and intermediate lesions: results of the international survey on interventional strategy. Circ Cardiovasc Interv. 2014; 7(6): 751–759, doi: 10.1161/CIRCINTERVENTIONS.114.001608, indexed in Pubmed: 25336468.
6. Zaleska M, Kołtowski Ł, Maksym J, et al. Alternative methods for functional assessment of intermediate coronary lesions. Cardiol J. 2019 [Epub ahead of print], doi: 10.5603/CJ.a2019.0027, indexed in Pubmed: 30912574.
7. Lee JM, Kato D, Oi M, et al. Safety and efficacy of intracoronary nicorandil as hyperaemic agent for invasive physiological assessment: a patient-level pooled analysis. EuroIntervention. 2016; 12(2): e208–e215, doi: 10.4244/EIJV12I2A34, indexed in Pubmed: 27290680.
8. Jang HJ, Koo BK, Lee HS, et al. Safety and efficacy of a novel hyperaemic agent, intracoronary nicorandil, for invasive physiological assessments in the cardiac catheterization laboratory. Eur Heart J. 2013; 34(27): 2055–2062, doi: 10.1093/eurheartj/eht040, indexed in Pubmed: 23396491.
9. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. Considerations for the choice between coronary artery bypass grafting and percutaneous coronary intervention as revascularization strategies in major categories of patients with stable multivessel coronary artery disease: an accompanying article of the task force of the 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J. 2019; 40(2): 204–212, doi: 10.1093/eurheartj/ehy532, indexed in Pubmed: 30165435.
10. Fihn SD, Blankenship JC, Alexander KP, et al. American College of Cardiology/Americal Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Thorac Cardiovasc Surg. 2015; 149(3): e5–23, doi: 10.1016/j.jtcvs.2014.11.002, indexed in Pubmed: 25827388.
11. Lachance P, Déry JP, Rodés-Cabau J, et al. Impact of fractional flow reserve measurement on the clinical management of patients with coronary artery disease evaluated with noninvasive stress tests prior to cardiac catheterization. Cardiovasc Revasc Med. 2008; 9(4): 229–234, doi: 10.1016/j.carrev.2008.02.002, indexed in Pubmed: 18928947.
12. Van Belle E, Gil R, Klauss V, et al. Impact of routine invasive physiology at Time of angiography in patients with multivessel coronary artery disease on reclassification of revascularization strategy: results from the DEFINE REAL study. JACC Cardiovasc Interv. 2018; 11(4): 354–365, doi: 10.1016/j.jcin.2017.11.030, indexed in Pubmed: 29471949.
13. Van Belle E, Baptista SB, Raposo L, et al. Impact of Routine Fractional Flow Reserve on Management Decision and 1-Year Clinical Outcome of Patients With Acute Coronary Syndromes: PRIME-FFR (Insights From the POST-IT [Portuguese Study on the Evaluation of FFR-Guided Treatment of Coronary Disease] and R3F [French FFR Registry] Integrated Multicenter Registries — Implementation of FFR [Fractional Flow Reserve] in Routine Practice). Circ Cardiovasc Interv. 2017; 10(6), doi: 10.1161/CIRCINTERVENTIONS.116.004296, indexed in Pubmed: 28615234.
14. Layland J, Oldroyd KG, Curzen N, et al. Fractional flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction: the British Heart Foundation FAMOUS-NSTEMI randomized trial. Eur Heart J. 2015; 36(2): 100–111, doi: 10.1093/eurheartj/ehu338, indexed in Pubmed: 25179764.

15. Nakamura M, Yamagishi M, Ueno T, et al. Modification of treatment strategy after FFR measurement: CVIT-DEFER registry. Cardiovasc Interv Ther. 2015; 30(1): 12–21, doi: 10.1007/s12928-014-0266-4, indexed in Pubmed: 24816634.
16. Van Belle E, Rioufol G, Pouillot C, et al. Outcome impact of coronary revascularization strategy reclassification with fractional flow reserve at time of diagnostic angiography: insights from a large French multicenter fractional flow reserve registry. Circulation. 2014; 129(2): 173–185, doi: 10.1161/CIRCULATIONAHA.113.006646, indexed in Pubmed: 24255062.
17. 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.
18. Zimmermann FM, Ferrara A, Johnson NP, et al. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. Eur Heart J. 2015; 36(45): 3182–3188, doi: 10.1093/eurheartj/ehv452, indexed in Pubmed: 26400825.
19. Park SH, Jeon KH, Lee JM, et al. Long-Term Clinical Outcomes of Fractional Flow Reserve-Guided Versus Routine Drug-Eluting Stent Implantation in Patients With Intermediate Coronary Stenosis: Five-Year Clinical Outcomes of DEFER-DES Trial. Circ Cardiovasc Interv. 2015; 8(12): e002442, doi: 10.1161/CIRCINTERVENTIONS.115.002442, indexed in Pubmed: 26643736.
20. van Nunen LX, Zimmermann FM, Tonino PAL, et al. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. Lancet. 2015; 386(10006): 1853–1860, doi: 10.1016/S0140-6736(15)00057-4, indexed in Pubmed: 26333474.
21. Xaplanteris P, Fournier S, Pijls NHJ, et al. Five-Year Outcomes with PCI Guided by Fractional Flow Reserve. N Engl J Med. 2018; 379(3): 250–259, doi: 10.1056/NEJMoa1803538, indexed in Pubmed: 29785878.
22. Smits PC, Abdel-Wahab M, Neumann FJ, et al. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction. N Engl J Med. 2017; 376(13): 1234–1244, doi: 10.1056/NEJMoa1701067, indexed in Pubmed: 28317428.
23. Engstrøm T, Kelbæk H, Helqvist S, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomised controlled trial. Lancet. 2015; 386(9994): 665–671, indexed in Pubmed: 26347918.
24. 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: 1824–1834.
25. 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.
26. Lee JM, Hwang D, Park J, et al. Exploring coronary circulatory response to stenosis and its association with invasive physiologic indexes using absolute myocardial blood flow and coronary pressure. Circulation. 2017; 136(19): 1798–1808, doi: 10.1161/CIRCULATIONAHA.117.029911, indexed in Pubmed: 28851731.
27. 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.
28. Lee JM, Doh JH, Nam CW, et al. Functional approach for coronary artery disease: filling the gap between evidence and practice. Korean Circ J. 2018; 48(3): 179–190, doi: 10.4070/kcj.2017.0393, indexed in Pubmed: 29557104.
29. Lee J, Shin ES, Nam CW, et al. Clinical outcomes according to fractional flow reserve or instantaneous wave-free ratio in deferred lesions. JACC: Cardiovasc Interv. 2017; 10(24): 2502–2510, doi: 10.1016/j.jcin.2017.07.019.
30. Lee JM, Shin ES, Nam CW, et al. Discrepancy between fractional flow reserve and instantaneous wave-free ratio: Clinical and angiographic characteristics. Int J Cardiol. 2017; 245: 63–68, doi: 10.1016/j.ijcard.2017.07.099, indexed in Pubmed: 28789845.
31. Lee JM, Hwang D, Park J, et al. Physiologic mechanism of discordance between instantaneous wave-free ratio and fractional flow reserve: Insight from N-ammonium positron emission tomography. Int J Cardiol. 2017; 243: 91–94, doi: 10.1016/j.ijcard.2017.05.114, indexed in Pubmed: 28600102.
32. 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.
33. Svanerud J, Ahn JM, Jeremias A, et al. Validation of a novel non-hyperaemic index of coronary artery stenosis severity: the Resting Full-cycle Ratio (VALIDATE RFR) study. EuroIntervention. 2018; 14(7): 806–814, doi: 10.4244/EIJ-D-18-00342, indexed in Pubmed: 29790478.
34. Lee JM, Layland J, Jung JH, et al. Integrated physiologic assessment of ischemic heart disease in real-world practice using index of microcirculatory resistance and fractional flow reserve: insights from the International Index of Microcirculatory Resistance Registry. Circ Cardiovasc Interv. 2015; 8(11): e002857, doi: 10.1161/CIRCINTERVENTIONS.115.002857, indexed in Pubmed: 26499500.
35. Lee JM, Jung JH, Hwang D, et al. Coronary flow reserve and microcirculatory resistance in patients with intermediate coronary stenosis. J Am Coll Cardiol. 2016; 67(10): 1158–1169, doi: 10.1016/j.jacc.2015.12.053, indexed in Pubmed: 26965536.
36. Grüntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. N Engl J Med. 1979; 301(2): 61–68, doi: 10.1056/NEJM197907123010201, indexed in Pubmed: 449946.
37. Pijls NH, van Son JA, Kirkeeide RL, et al. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. Circulation. 1993; 87(4): 1354–1367, indexed in Pubmed: 8462157.
38. Johnson NP, Koo BK. Coronary psychology: do you believe? JACC Cardiovasc Interv. 2018; 11(15): 1492–1494, doi: 10.1016/j.jcin.2018.05.021, indexed in Pubmed: 30093054.
39. SWEDEHEART Annual Report. 2017.
40. BCIS Audit Slide Deck. 2016.
41. Dati di attività dei Laboratori di Emodinamica. 2016.
42. Barbato E, Dudek D, Baumbach A, et al. Current trends in coronary interventions: an overview from the EAPCI registries. EuroIntervention. 2017; 13(Z): Z8–Z10, doi: 10.4244/eijv13iza2.
43. Desai NR, Bradley SM, Parzynski CS, et al. Appropriate Use Criteria for Coronary Revascularization and Trends in Utilization, Patient Selection, and Appropriateness of Percutaneous Coronary Intervention. JAMA. 2015; 314(19): 2045–2053, doi: 10.1001/jama.2015.13764, indexed in Pubmed: 26551163.

44. May AN, Kull A, Gunalingam B, et al. The uptake of coronary fractional flow reserve in Australia in the past decade. Med J Aust. 2016; 205(3): 127, indexed in Pubmed: 27465768.
45. Koo BK, Kang HJ, Youn TJ, et al. Physiologic assessment of jailed side branch lesions using fractional flow reserve. J Am Coll Cardiol. 2005; 46(4): 633–637, doi: 10.1016/j.jacc.2005.04.054, indexed in Pubmed: 16098427.
46. Koo BK, Park KW, Kang HJ, et al. Physiological evaluation of the provisional side-branch intervention strategy for bifurcation lesions using fractional flow reserve. Eur Heart J. 2008; 29(6): 726–732, doi: 10.1093/eurheartj/ehn045, indexed in Pubmed: 18308689.
47. Ahn JM, Park DW, Shin ES, et al. Fractional flow reserve and cardiac events in coronary artery disease: data from a prospective IRIS-FFR registry (interventional cardiology research incooperation society fractional flow reserve). Circulation. 2017; 135(23): 2241–2251, doi: 10.1161/CIRCULATIONAHA.116.024433, indexed in Pubmed: 28356440.
48. Lee JM, Koo BK, Shin ES, et al. Clinical implications of three-vessel fractional flow reserve measurement in patients with coronary artery disease. Eur Heart J. 2018; 39(11): 945–951, doi: 10.1093/eurheartj/ehx458, indexed in Pubmed: 29020260.
49. Chen SL, Zhang JJ, Han Y, et al. Double Kissing Crush Versus Provisional Stenting for Left Main Distal Bifurcation Lesions: DKCRUSH-V Randomized Trial. J Am Coll Cardiol. 2017; 70(21): 2605–2617, doi: 10.1016/j.jacc.2017.09.1066, indexed in Pubmed: 29096915.
50. Li SJ, Ge Z, Kan J, et al. Cutoff value and long-term prediction of Clinical events by FFR measured immediately after implantation of a drug-eluting stent in patients with coronary artery disease: 1- to 3-year results from the DKCRUSH VII registry study. JACC Cardiovasc Interv. 2017; 10(10): 986–995, doi: 10.1016/j.jcin.2017.02.012, indexed in Pubmed: 28456699.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2019, Vol. 26, No. 3, 226–232
DOI: 10.5603/CJ.a2018.0029

ISSN 1897–5593

Feasibility of zero or near zero fluoroscopy during catheter ablation procedures

Laurent M. Haegeli[1, 2, *], Linda Stutz[1, *], Mohammed Mohsen[1], Thomas Wolber[1], Corinna Brunckhorst[1], Chol-Jun On[1], Firat Duru[1]

[1]Arrhythmia and Electrophysiology, Department of Cardiology, University Heart Center, University Hospital Zurich, Switzerland
[2]Division of Cardiology, Medical University Department, Kantonsspital Aarau, Switzerland

Abstract

Background: *Awareness of risks associated with radiation exposure to patients and medical staff has significantly increased. It has been reported before that the use of advanced three-dimensional electroanatomical mapping (EAM) system significantly reduces fluoroscopy time, however this study aimed for zero or near zero fluoroscopy ablation to assess its feasibility and safety in ablation of atrial fibrillation (AF) and other tachyarrhythmias in a "real world" experience of a single tertiary care center.*

Methods: *This was a single-center study where ablation procedures were attempted without fluoroscopy in 34 consecutive patients with different tachyarrhythmias under the support of EAM system. When transseptal puncture (TSP) was needed, it was attempted under the guidance of intracardiac echocardiography (ICE).*

Results: *Among 34 patients consecutively enrolled in this study, 28 (82.4%) patients were referred for radiofrequency ablation (RFA) of AF, 3 (8.8%) patients for ablation of right ventricular outflow tract (RVOT) ventricular extrasystole (VES), 1 (2.9%) patient for ablation of atrioventricular nodal reentry tachycardia (AVNRT), 2 (5.9%) patients for typical atrial flutter ablation. In 21 (62%) patients the entire procedure was carried out without the use of fluoroscopy. Among 28 AF patients, 15 (54%) patients underwent ablation without the use of fluoroscopy and among these 15 patients, 10 (67%) patients required TSP under ICE guidance while 5 (33%) patients the catheters were introduced to left atrium through a patent foramen ovale. In 13 AF patients, fluoroscopy was only required for double TSP. The total procedure time of AF ablation was 130 ± 50 min. All patients referred for atrial flutter, AVNRT, and VES of the RVOT ablation did not require any fluoroscopy.*

Conclusions: *This study demonstrates the feasibility of zero or near zero fluoroscopy procedure including TSP with the support of EAM and ICE guidance in a "real world" experience of a single tertiary care center. When fluoroscopy was required, it was limited to TSP hence keeping the radiation dose very low.* (Cardiol J 2019; 26, 3: 226–232)

Key words: catheter ablation, fluoroscopy, atrial fibrillation, arrhythmia, three-dimensional electroanatomical mapping

Introduction

Recently, the awareness of risks associated with radiation exposure to patients and medical staff has significantly increased. The risks of injury hazard by medical radiation exposure are caused by deterministic (dose-dependent) effects such as radiation injury to the skin secondary to high peak skin doses and by stochastic (non dose-dependent) effects such as increased radiation-induced cancer

Address for correspondence: Laurent M. Haegeli, MD, Arrhythmia and Electrophysiology, Department of Cardiology, University Heart Center, University Hospital Zurich, Zurich, Switzerland, tel: +41 44 255 87 62, fax: +41 44 255 44 01, e-mail: laurent.haegeli@usz.ch

Received: 22.07.2017 Accepted: 22.01.2018

**Laurent M. Haegeli and Linda Stutz share first authorship.*

risk and genetic effects [1, 2]. These risks are of particular concern for young or obese patients and for patients who undergo long, repeated or complex procedures [3, 4]. Moreover, operators, nurses and technical staff are exposed to significant and potentially hazardous doses of ionizing radiation on a daily basis resulting in life-time risk for malignancy, cataract and congenital defects [5, 6]. Since the beginning of interventional electrophysiology for diagnosis and therapy of cardiac arrhythmias, fluoroscopy techniques have been widely used to navigate catheters within the heart and the vessels and to monitor their position. In recent years, technical developments have led to the routine and wide-spread use of non-fluoroscopic three-dimensional (3D) electro-anatomical navigation and mapping systems for radiofrequency ablation (RFA) of tachyarrhythmias including atrial fibrillation (AF) resulting in a significant reduction of radiation dose during mapping and ablation of complex arrhythmias [7–13]. Minimizing the exposure to radiation is recommended by the American College of Cardiology teaching the ALARA principle — keeping the radiation "as low as reasonably achievable" [14, 15]. It has been reported before that the use of 3D electro-anatomical mapping (EAM) system significantly reduces fluoroscopy time and radiation dose however the aim of this study was to assess the feasibility and the safety of zero or near zero fluoroscopy mapping and ablation of AF and other tachyarrhythmias in a "real world" experience of a single tertiary care center.

Methods

Among patients referred to the Division of Arrhythmia and Electrophysiology at the University Heart Center in Zurich, Switzerland, 34 patients were enrolled consecutively in the study. Majority of patients in the study group were referred for RFA of AF (28 patients). Few patients with other tachyarrhythmias were also enrolled: 2 with typical atrial flutter (AFL), 3 with idiopathic ventricular extrasystole (VES) from the right ventricular outflow tract (RVOT) and 1 with atrioventricular nodal reentry tachycardia (AVNRT). Percutaneous access for all catheters was via the right femoral vein. Written informed consent was obtained from all patients. All clinical cardiac characteristics as well as important comorbidities were recorded according to the regulations of the local Institutional Committee on Human Research. This was a single-center study.

Procedural safety

Pre-procedure and post-procedure patient management, as well as intra-procedure anticoagulation policy were in accordance with practice guidelines and our hospital policies.

All operators performing the ablation procedures were senior staff with experience in catheter navigation under 3D EAM system. Different imaging modalities were used including intracardiac echocardiography (ICE), transesophageal echocardiography (TEE) and magnetic resonance imaging (MRI) as needed. Although the intention was to perform zero fluoroscopy procedure, all operators were allowed to use fluoroscopy if required for patient safety and that is why fluoroscopy was used in 13 patients.

Catheter ablation of AF

Patients scheduled for AF ablation underwent MRI of the pulmonary veins (PV) and left atrium (LA) before the procedure to identify anatomical variants, to assess the exact anatomical position and size of PV ostia and to merge with CARTO 3 system (Biosense Webster, Diamond Bar, CA, USA) (Fig. 1). TEE was also done before the procedure to rule out thrombi in the LA and to document the presence of a patent foramen ovale (PFO). For mapping and ablation, a 3D EAM system, CARTO 3 system (Biosense Webster, Diamond Bar, CA, USA) was used. All procedures were performed under conscious sedation using midazolam and fentanyl.

A 6 F steerable decapolar Dynamic XT catheter (Boston Scientific, Marlborough, MA, USA) was positioned in the coronary sinus for mapping and pacing purposes. For ablation an 8 F Thermocool bi-directional (D-F curve) catheter was used (Biosense Webster, Diamond Bar, CA, USA). A steerable 7 F multipolar Lasso catheter (Biosense Webster, Diamond Bar, CA, USA) was used for mapping of the PVs and to confirm procedural endpoint of electrical isolation. The transseptal punctures (TSP) were performed using Brockenborough (BRK-1) needle (St. Jude Medical, St. Paul, MN, USA) through 8 F Preface guiding sheath (Biosense Webster, Diamond Bar, CA, USA) and was attempted under the guidance of Acuson Acuna ultrasound catheter (Siemens Healthcare, Erlangen, Germany).

Catheter positioning into and within the cardiac chamber of interest as well as mapping and ablation were attempted without fluoroscopy with the support of EMA. A fast anatomical map was created

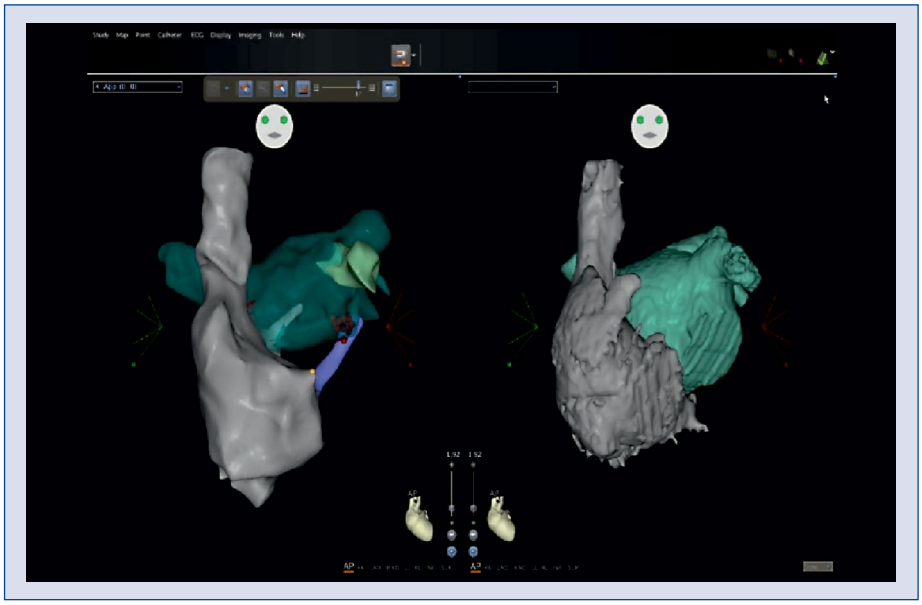


Figure 1. Left panel showing the three-dimensional electroanatomical CARTO maps (Biosense Webster, Diamond Bar, CA, USA) of right (gray) and left (green) atria with coronary sinus (blue) and right panel with three-dimensional reconstruction from magnetic resonance imaging. Both panels show the images from the anteroposterior view.

using the Lasso catheter to create a 3D geometry of LA and PV without fluoroscopy. PV isolation was performed by wide-area circumferential point-by-point RFA around the ostia of the ipsilateral PVs. The procedural endpoint was electrical isolation (entrance and exit block) documented using the Lasso mapping catheter. Power was limited to 30 Watts and flow was adjusted from 2 mL/min up to 30 mL/min to achieve this power. In patients with a history of typical AFL (5 patients in our group) a cavotricuspid isthmus ablation line was added. If sinus rhythm was not restored following ablation, the patient was cardioverted with a direct current shock.

In 5 patients the catheters were introduced to LA through a PFO without the need of TSP. In 3 patients with PFO, ICE was used to allocate the site of PFO that was crossed by the ablation catheter along with its Preface guiding sheath. In 2 patients with PFO, the ablation catheter (through the Preface guiding sheath) was brought to the superior vena cava and dragged caudally till the typical jump to the foramen ovale region was detected with 3D EAM. Then the ablation catheter along with its guiding sheath were advanced into the LA.

In 1 patient, TSP was done without the use of fluoroscopy or ICE as following: first a fast anatomical map was created using the ablation catheter (through Preface guiding sheath) to create a 3D right atrium and vena cava geometry. The His bundle region was marked. Then the Preface guiding sheath (with only the tip of ablation catheter exposed out of the sheath) was brought to the superior vena cava and dragged caudally till the typical jump to the foramen ovale region was detected and marked with 3D EAM. The ablation catheter was pulled out of the guiding sheath and the sheath was kept in same place of the foramen ovale region. The dilator of the guiding sheath and the Brockenbrough (BRK-1) needle (with metal arrow on needle hub and sheath sidearm pointing at 4 o'clock) were inserted within the sheath and TSP was done successfully.

Catheter ablation of RVOT VES

Thermocool bi-directional (D-F curve) catheter was used (Biosense Webster, Diamond Bar, CA, USA) to create RVOT geometry. Earliest electrical activation region was mapped in 3D EAM system and VES was successfully ablated.

Catheter ablation of typical AFL

A 6 F steerable decapolar Dynamic XT catheter (Boston Scientific, Marlborough, MA, USA) was positioned in the coronary sinus. Thermocool bi-directional (D-F curve) catheter was used (Biosense Webster, Diamond Bar, CA, USA) to create right atrium geometry with the tricuspid annulus and both vena cava superior and inferior. The His

bundle region was marked. An ablation line was performed in the region of cavotricuspid isthmus creating a bi-directional block.

Catheter ablation of AVNRT

A Navistar 4 mm (D Curve) ablation catheter (Biosense Webster, Diamond Bar, CA, USA) was used to create right atrium geometry. The His bundle region was marked and the anatomical and characteristical electrical slow pathway region was identified and successfully ablated.

Results

Thirty four patients were consecutively enrolled in the study. The baseline clinical characteristics are summarized in Table 1. All patients had a structurally normal heart with preserved left ventricular systolic function and without valvular heart disease. Twenty eight (82.4%) patients were referred for catheter ablation of AF (22 with paroxysmal and 6 with persistent AF). The remaining 6 patients were referred either for ablation of typical AFL, VES from the RVOT or AVNRT (Table 2). Among AF patients, 5 patients had additional typical AFL. 39% of AF patients had anatomical variants of the PVs and 18% had a PFO (Table 3).

In 21 (62%) patients the entire procedure was carried out without the use of fluoroscopy. Among the 28 AF patients, the procedure was performed with zero fluoroscopy in 15 (54%) patients. Ten (67%) AF patients required TSP under ICE guidance to access the LA while in 5 (33%) patients the catheters were introduced into the LA through a PFO (in 3 patients with the help of ICE and in 2 without as previously described). All patients in the series referred for atrial AFL, AVNRT, and VES of the RVOT ablation did not require fluoroscopy (Fig. 2).

Procedure time and fluoroscopy use

The total procedure time for ablation of AF was 130 ± 50 min. Most of the time (59.9 ± 20 min) was required for the ablation of PVs (Table 4). Fluoroscopy was required in 13 AF patients solely for double TSP in order to safely access the LA despite the availability of ICE. In our patient series fluoroscopy was only used for the TSPs. The median total fluoroscopy time was 2.6 ± 2.2 min and the dose area product 13 ± 27 gray × cm^2. Mapping of the LA and wide-area circumferential ablation around the PVs did not require the use of fluoroscopy.

Table 1. Patient characteristics.

Number of patients	34 (100%)
Age [years]	56 ± 12.4
Male	24 (71%)
Left atrium diameter [mm]	41.7 ± 0.6
Hypertension	15 (44.1%)
Coronary artery disease	6 (17.7%)
Diabetes mellitus	1 (2.9%)
CVA/TIA	5 (14.7%)
Heart failure	2 (5.9%)

CVA — cerebrovascular attack; TIA — transient ischemic attack

Table 2. Types of arrhythmias.

Atrial fibrillation:	28 (82.4%)
Paroxysmal AF	22
Persistent AF	6
Atrial flutter:	
Atrial flutter alone	2 (5.9%)
In combination with paroxysmal AF	4 (11.8%)
In combination with persistent AF	1 (2.9%)
VES RVOT	3 (8.8%)
AVNRT	1 (2.9%)

AF — atrial fibrillation; VES — ventricular extrasystole; RVOT — right ventricular outflow tract; AVNRT — atrioventricular reentrant tachycardia

Table 3. Pulmonary vein anatomy.

Normal anatomy (2 right, 2 left pulmonary veins)	17 (61.0%)
Common left ostium	6 (21.4%)
Three right pulmonary veins	5 (17.9%)
Patent foramen ovale	5 (17.9%)

Table 4. Procedural and fluoroscopy times.

Total procedure time [min]	130 ± 50
Catheter placement [min]	20 ± 5
Left atrial mapping [min]	15 ± 8
Left atrial ablation [min]	59.9 ± 20
Total X-ray time [min]	2.6 ± 2.2
Dose area product [Gray × cm^2]	13 ± 27

Procedural endpoint and outcome

All procedures were successfully carried out. In AF patients, isolation of all PVs was validated using the Lasso catheter placed at each ostium

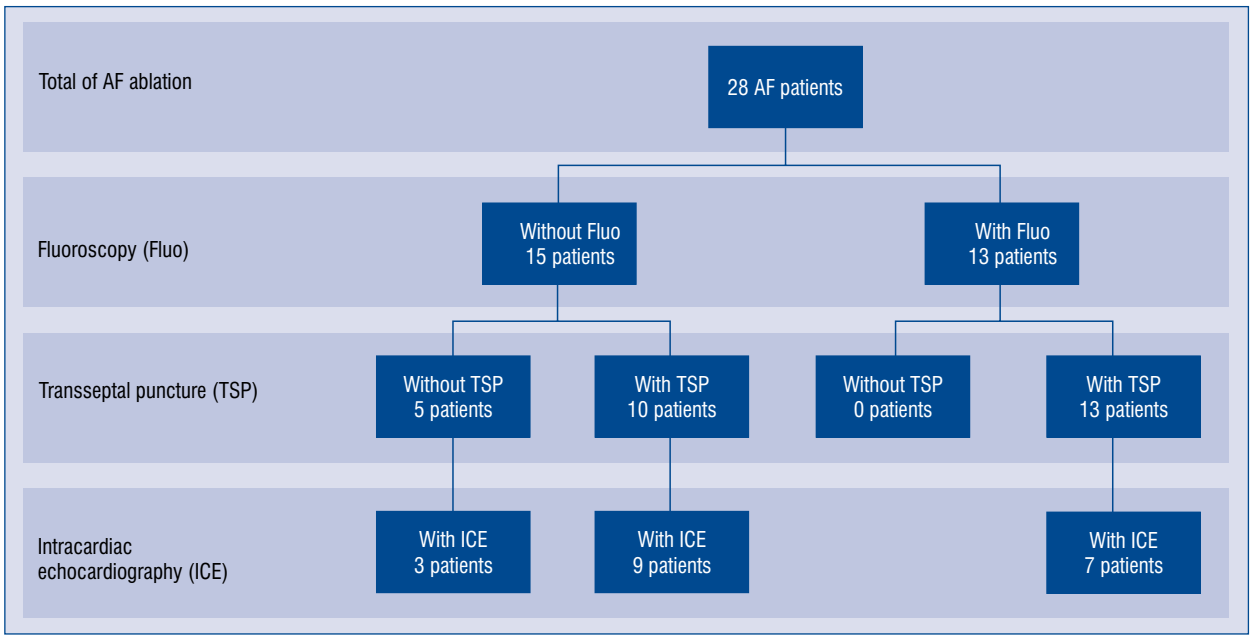


Figure 2. Atrial fibrillation (AF) ablation and fluoroscopy use.

which realized confirmation of isolation of all PVs by documentation of entrance and exit block. For typical AFL ablation, the cavotricuspid isthmus was checked for bidirectional block. VES of the RVOT was ablated successfully with complete abolition of VES. After slow pathway ablation, there was no AVNRT inducible at rest or under adrenergic stimulation with isoprenalin.

One patient in whom AF ablation was performed without fluoroscopy and after uncomplicated TSP guided by ICE had a post-procedural pericardial tamponade which was resolved by immediate percutaneous drainage. No other complications occurred in this study group.

Discussion

Over the last years, the awareness of radiation hazards to patients and professional staff has significantly increased. Reduction of radiation exposure in electrophysiological procedures, such as AF ablation, should always be considered. 3D EAM systems with their constant updating technologies that allows precise location visualization of diagnostic and ablation catheters and allows fast anatomical mapping of cardiac chambers have shown to contribute to significant reduction of fluoroscopy time and radiation dose. Lee et al. [16] have shown that the use of contact force-sensing catheter during AF ablation significantly reduces fluoroscopy times by 77%, radiation dose by 71%, and procedural time by 19%. However the median fluoroscopy time in the force-sensing catheter group was 9.5 min and median radiation dose was 1043.5 mGy × cm^2. This study showed that zero or near zero fluoroscopy was feasible in patients referred for catheter ablation of AF and other tachyarrhythmias with the support of EAM and ICE guidance. Fluoroscopy was only used if required and limited to assist in difficult TSP hence keeping the radiation time and dose very low (2.6 ± 2.2 min and 13 ± 2.7 gray × cm^2, respectively). Catheter placement, navigation, mapping and ablation can be done with the support of EAM. TSP can be done safely under the guidance of ICE imaging. The LA can be accessed safely in the presence of PFO under ICE guidance without the need of TSP.

Other groups have shown feasibility of fluoroscopy-free PV isolation in 26 out of 30 consecutive patients with a documented PFO [17]. Bulava et al. [18] demonstrated the feasibility of zero fluoroscopy ablation in 40 patients with paroxysmal AF using ICE imaging and 3D EAM mapping with contact force measurements. Reddy et al. [19] showed complete fluoroless catheter ablation of paroxysmal AF in 20 patients using combination of ICE and 3D EAM system.

In a series of 19 out of 21 patients, Ferguson et al. [20] demonstrated that AF ablation was feasible without fluoroscopic guidance. Double TSP were performed with ICE guidance and facilitated by electrocautery. In 2 cases fluoroscopy was used to assist TSP.

Kerst et al. [21] showed in a group of 30 patients that contact force-controlled zero fluoroscopy catheter ablation is generally feasible in right-sided and left atrial cardiac arrhythmias.

Hindricks et al. [22] compared the results of catheter ablation to cure typical AFL using conventional ablation strategy and electro-anatomically guided mapping and ablation. They found that cavotricuspid isthmus ablation to cure typical AFL was highly effective and safe, both in conventional and electro-anatomically guided ablation group. The use of EAM system significantly reduced fluoroscopy exposure time by almost 50%, however this was at the expense of an increased cost of the procedure.

Limitations of the study

Because of the small number of patients in the resent study group, it was difficult to make conclusions about safety. A much larger multi-center study would be needed to determine any true increase in the rate of catheter-related complications as a result of using this technique given that the incidence of cardiac tamponade and catheter perforation during AF ablation is low.

Conclusions

This study demonstrates the feasibility of an entire zero or near zero fluoroscopy procedure including transseptal puncture for patients with AF and other tachyarrhythmias under the support of 3D EAM systems and ICE imaging in a "real world" experience of a single tertiary care center. When fluoroscopy was required, it was limited to transseptal puncture and hence keeping the radiation dose very low.

Conflict of interest: Laurent M. Haegeli reports compensation for participation on a speaker bureau from St. Jude Medical and Biosense Webster. Other authors have no disclosures.

References

1. Lickfett L, Mahesh M, Vasamreddy C, et al. Radiation exposure during catheter ablation of atrial fibrillation. Circulation. 2004; 110(19): 3003–3010, doi: 10.1161/01.CIR.0000146952.49223.11, indexed in Pubmed: 15505084.
2. Rosenthal LS, Beck TJ, Williams J, et al. Acute radiation dermatitis following radiofrequency catheter ablation of atrioventricular nodal reentrant tachycardia. Pacing Clin Electrophysiol. 1997; 20(7): 1834–1839, indexed in Pubmed: 9249839.
3. Ector J, Dragusin O, Adriaenssens B, et al. Obesity is a major determinant of radiation dose in patients undergoing pulmonary vein isolation for atrial fibrillation. J Am Coll Cardiol. 2007; 50(3): 234–242, doi: 10.1016/j.jacc.2007.03.040, indexed in Pubmed: 17631216.
4. Kidouchi T, Suzuki S, Furui S, et al. Entrance skin dose during radiofrequency catheter ablation for tachyarrhythmia: a multicenter study. Pacing Clin Electrophysiol. 2011; 34(5): 563–570, doi: 10.1111/j.1540-8159.2010.03016.x, indexed in Pubmed: 21609338.
5. Calkins H, Niklason L, Sousa J, et al. Radiation exposure during radiofrequency catheter ablation of accessory atrioventricular connections. Circulation. 1991; 84(6): 2376–2382, indexed in Pubmed: 1959193.
6. Perisinakis K, Damilakis J, Theocharopoulos N, et al. Accurate assessment of patient effective radiation dose and associated detriment risk from radiofrequency catheter ablation procedures. Circulation. 2001; 104(1): 58–62, indexed in Pubmed: 11435338.
7. Scaglione M, Biasco L, Caponi D, et al. Visualization of multiple catheters with electroanatomical mapping reduces X-ray exposure during atrial fibrillation ablation. Europace. 2011; 13(7): 955–962, doi: 10.1093/europace/eur062, indexed in Pubmed: 21421574.
8. Stabile G, Scaglione M, del Greco M, et al. Reduced fluoroscopy exposure during ablation of atrial fibrillation using a novel electroanatomical navigation system: a multicentre experience. Europace. 2012; 14(1): 60–65, doi: 10.1093/europace/eur271, indexed in Pubmed: 21893511.
9. Huo Y, Christoph M, Forkmann M, et al. Reduction of radiation exposure during atrial fibrillation ablation using a novel fluoroscopy image integrated 3-dimensional electroanatomic mapping system: A prospective, randomized, single-blind, and controlled study. Heart Rhythm. 2015; 12(9): 1945–1955, doi: 10.1016/j.hrthm.2015.05.018, indexed in Pubmed: 26001508.
10. Steven D, Servatius H, Rostock T, et al. Reduced fluoroscopy during atrial fibrillation ablation: benefits of robotic guided navigation. J Cardiovasc Electrophysiol. 2010; 21(1): 6–12, doi: 10.1111/j.1540-8167.2009.01592.x, indexed in Pubmed: 19793149.
11. Raju H, Whitaker J, Taylor C, et al. Electroanatomic mapping and transoesophageal echocardiography for near zero fluoroscopy during complex left atrial ablation. Heart Lung Circ. 2016; 25(7): 652–660, doi: 10.1016/j.hlc.2016.01.018, indexed in Pubmed: 26979468.
12. Khaykin Y, Oosthuizen R, Zarnett L, et al. CARTO-guided vs. NavX-guided pulmonary vein antrum isolation and pulmonary vein antrum isolation performed without 3-D mapping: effect of the 3-D mapping system on procedure duration and fluoroscopy time. J Interv Card Electrophysiol. 2011; 30(3): 233–240, doi: 10.1007/s10840-010-9538-9, indexed in Pubmed: 21253840.
13. Kozluk E, Rodkiewicz D, Piątkowska A, et al. Safety and efficacy of cryoablation without the use of fluoroscopy. Cardiol J. 2018; 25(3): 327–332, doi: 10.5603/CJ.a2017.0065, indexed in Pubmed: 28612907.
14. Limacher MC, Douglas PS, Germano G, et al. ACC expert consensus document. Radiation safety in the practice of cardiology. American College of Cardiology. J Am Coll Cardiol. 1998; 31(4): 892–913, indexed in Pubmed: 9525565.
15. Haegeli LM, Calkins H. Catheter ablation of atrial fibrillation: an update. Eur Heart J. 2014; 35(36): 2454–2459, doi: 10.1093/eurheartj/ehu291, indexed in Pubmed: 25053659.
16. Lee G, Hunter RJ, Lovell MJ, et al. Use of a contact force-sensing ablation catheter with advanced catheter location significantly re-

duces fluoroscopy time and radiation dose in catheter ablation of atrial fibrillation. Europace. 2016; 18(2): 211–218, doi: 10.1093/europace/euv186, indexed in Pubmed: 26318548.
17. Kühne M, Knecht S, Mühl A, et al. Fluoroscopy-Free pulmonary vein isolation in patients with atrial fibrillation and a patent foramen ovale using solely an electroanatomic mapping system. PLoS One. 2016; 11(1): e0148059, doi: 10.1371/journal.pone.0148059, indexed in Pubmed: 26820309.
18. Bulava A, Hanis J, Eisenberger M. Catheter ablation of atrial fibrillation using zero-fluoroscopy technique: a randomized trial. Pacing Clin Electrophysiol. 2015; 38(7): 797–806, doi: 10.1111/pace.12634, indexed in Pubmed: 25790320.
19. Reddy VY, Morales G, Ahmed H, et al. Catheter ablation of atrial fibrillation without the use of fluoroscopy. Heart Rhythm. 2010; 7(11): 1644–1653, doi: 10.1016/j.hrthm.2010.07.011, indexed in Pubmed: 20637313.
20. Ferguson JD, Helms A, Mangrum JM, et al. Catheter ablation of atrial fibrillation without fluoroscopy using intracardiac echocardiography and electroanatomic mapping. Circ Arrhythm Electrophysiol. 2009; 2(6): 611–619, doi: 10.1161/CIRCEP.109.872093, indexed in Pubmed: 20009075.
21. Kerst G, Weig HJ, Weretka S, et al. Contact force-controlled zero-fluoroscopy catheter ablation of right-sided and left atrial arrhythmia substrates. Heart Rhythm. 2012; 9(5): 709–714, doi: 10.1016/j.hrthm.2011.12.025, indexed in Pubmed: 22222276.
22. Hindricks G, Willems S, Kautzner J, et al. EuroFlutter Investigators. Effect of electroanatomically guided versus conventional catheter ablation of typical atrial flutter on the fluoroscopy time and resource use: a prospective randomized multicenter study. J Cardiovasc Electrophysiol. 2009; 20(7): 734–740, doi: 10.1111/j.1540-8167.2009.01439.x, indexed in Pubmed: 19298568.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2019, Vol. 26, No. 3, 233–240
DOI: 10.5603/CJ.a2018.0035

ISSN 1897–5593

Thermic sealing in femoral catheterization: First experience with the Secure Device

Michael Sacherer[1], Ewald Kolesnik[1], Friederike von Lewinski[1], Nicolas Verheyen[1], Karin Brandner[1], Markus Wallner[1, 2], Deborah M. Eaton[2], Olev Luha[1], Robert Zweiker[1], Dirk von Lewinski[1]

[1]Division of Cardiology, Medical University Graz, Austria
[2]Temple University Lewis Katz School of Medicine, Cardiovascular Research Center, Philadelphia, PA, Unites States

Abstract

Background: *Devices currently used to achieve hemostasis of the femoral artery following percutaneous cardiac catheterization are associated with vascular complications and remnants of artificial materials are retained at the puncture site. The Secure arterial closure Device induces hemostasis by utilizing thermal energy, which causes collagen shrinking and swelling. In comparison to established devices, it has the advantage of leaving no foreign material in the body following closing. This study was designed to evaluate the efficacy and safety of the Secure Device to close the puncture site following percutaneous cardiac catheterization.*

Methods: *The Secure Device was evaluated in a prospective non-randomized single-center trial with patients undergoing 6 F invasive cardiac procedures. A total of 67 patients were enrolled and the device was utilized in 63 patients. Fifty diagnostic and 13 interventional cases were evaluated. Femoral artery puncture closure was performed immediately after completion of the procedure. Time to hemostasis (TTH), time to ambulation (TTA) and data regarding short-term and 30-day clinical follow-up were recorded.*

Results: *Mean TTH was 4:30 ± 2:15 min in the overall observational group. A subpopulation of patients receiving anticoagulants had a TTH of 4:53 ± 1:43 min. There were two access site complications (hematoma > 5 cm). No major adverse events were identified during hospitalization or at the 30 day follow-up.*

Conclusions: *The new Secure Device demonstrates that it is feasible in diagnostic and interventional cardiac catheterization. With respect to safety, the Secure Device was non-inferior to other closure devices as tested in the ISAR closure trial.* (Cardiol J 2019; 26, 3: 233–240)

Key words: catheterization, vascular closure device, thermal vascular occlusion, Secure Device System, femoral vascular access

Introduction

Interventional cardiology has become a leader in both diagnosing and treating coronary artery disease. Although radial access seems to be favoured in acute coronary syndrome, femoral access is commonly used worldwide in both acute and chronic settings.

Following catheterization, the standard procedure for closing the common arteria femoralis is mechanic compression to achieve hemostasis. Applying pressure to the puncture site and prolonging

Address for correspondence: Assoc. Prof. Dirk von Lewinski, MD, PhD, Department of Cardiology, Medical University of Graz, Auenbruggerplatz 15, 8036 Graz, Austria, tel: +43 316 385 80684, fax: +43 316 385 13733, e-mail: dirk.von-lewinski@medunigraz.at

Received: 6.02.2018 Accepted: 19.03.2018

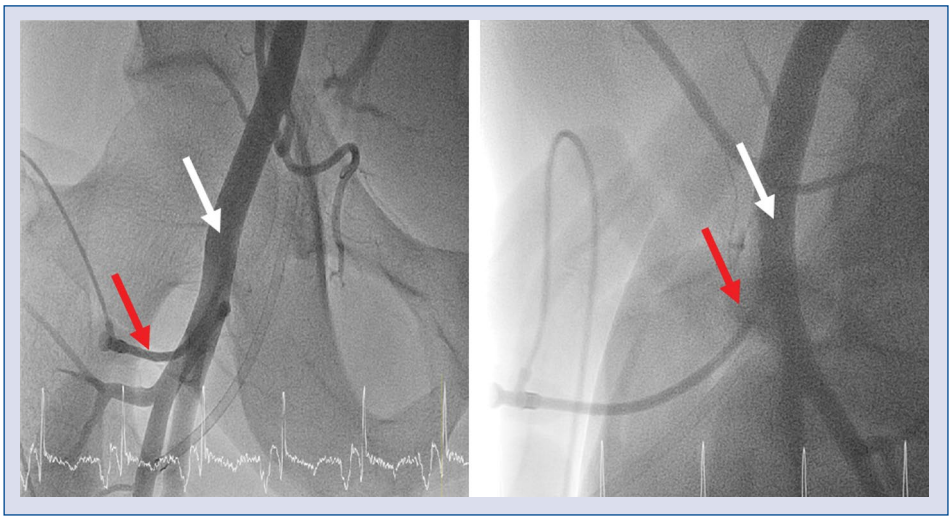


Figure 1. X-ray examination of patient prior to Secure arterial closure Device implantation; puncture site location control; red arrow — 6 F sheath; white arrow — common femoral artery.

the time to mobilization leads to discomfort for the patient and promotes side effects of immobilization. Furthermore, manual compression in combination with compression devices usage is associated with increased personnel requirements and considerable financial burden for health care institutions [1].

Hemostatic devices are categorized as being pressure devices, hemostatic pads or active vascular closure devices. Currently available active closure devices are divided into three groups: collagen plugs, suture based devices and plugs/clips. Clips are most frequently made of bio-resorbable materials or metal applied to both the inner and/ /or outer layer of the arterial wall [2, 3].

Generally, the majority of closure devices leave foreign materials either inside or outside the blood vessel, which are either permanently left in place or gradually dissolve over time. Objects that are left inside the body could potentially lead to the development of limb ischemia, occlude an artery, be a source of infection or disable re-puncture at the same site for months. Taking these potential adverse effects into consideration, a vascular closure device that achieves hemostasis without requiring any components to be left in the patient's body would be desirable. The principle of thermal vessel occlusion is currently under investigation [4].

The secure arterial closure device was developed to enable hemostasis using thermal energy to achieve vessel occlusion without leaving any foreign materials inside the patient. A clinical study was conducted in Georgia on 42 patients, using an earlier version of the device. The earlier version of the device was Conformité Européenne approved and used in Germany on 50 patients. Clinical data regarding performance and safety have not yet been published.

The hypothesis was that the Secure Device System is non-inferior in terms of vascular access site complication to other vascular closure devices [5].

Methods

The study was a prospective single center single group study designed to evaluate the safety and performance of the Secure Device (Model: SE-HE-A2) powered by an external power supply. The study was performed from September 2016 to January 2017 after receiving approval from the Austrian Federal Office of Safety and Health Care (BASG). All procedures and investigations were accomplished in accordance to the Declaration of Helsinki and approved by the local ethics committee (ref. no: 28-364 ex15/16). Written informed consent was obtained from every individual participating.

The patients included were undergoing either coronary angiography and/or coronary intervention procedures using 6 French sheaths. Detailed inclusion and exclusion criteria are shown in the **Supplementary materials**. An angiogram was performed at the access site to evaluate puncture location and artery morphology. Puncture locations above the femoral bifurcation were defined as feasible for the Secure Device occlusion (Fig. 1) and only arteries with a diameter above 6 mm and

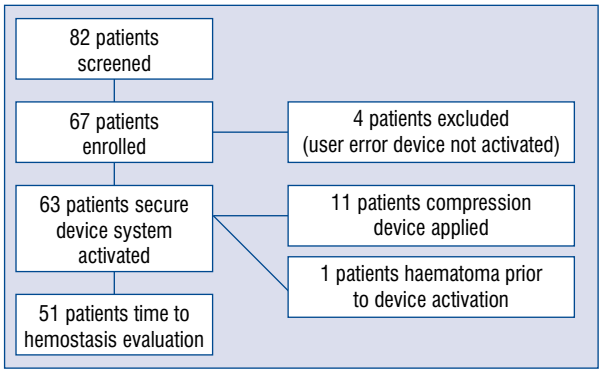


Figure 2. Flowchart of patients included in the trial.

an artery depth greater than 10 mm to the surface of the skin were accepted for inclusion. Exclusion criteria included heavy calcification visualized at the angiogram or a medical history of obstructive peripheral artery disease.

Eighty-two individuals were screened during the study procedures and 67 subjects were enrolled in the clinical trial after final intra-procedural inclusion (Fig. 2).

The system included an artery locator, a dilator and the Secure Device itself (Fig. 3). After finishing the procedure, the artery locator was introduced via the sheath with the help of the deployer at the proximal end. After successful introduction, the deployer was disconnected and removed. The sheath can be withdrawn while the deployed artery locator remains within the artery. To enlarge the tissue canal, the dilator was "screwed" in until the green mark was visible behind the dilator at the artery locator shaft. After removing the dilator, the Secure Device was inserted and advanced until the green indicator was visible on the same level as the alignment mark on the device to ensure optimal positioning of the heating dome (Fig. 4). Gentle permanent tension at the artery locator seals the hole in the artery during closing procedure. A stabilization slider at the base of the Secure Device ensured the correct pressure was applied.

The heating process was activated manually by pressing the activation button on the handle. A built-in test monitored the device while it was being activated. While the heating process was occurring, the artery locater was automatically un-deployed and retracted into the Secure Device handle. The heating process was regularly terminated within 5 to 7 s. Arterial closure LED light and vibration signal indicated the end of the procedure. After being rotated 90 degrees', the Secure Device and the artery locater were easily removed from the patient. Minimal oozing from subcutaneous vessels may have occurred. Light compression was performed to prevent local subcutaneous bleeding on an as needed basis.

Time to hemostasis (TTH) was determined as the time between Secure Device removal and observed hemostasis in minutes and seconds. Device malfunctions were recorded and analysed regarding their relation to safety. Device malfunction included device related malfunction due to indicated inactivity or premature stopping of the heating process as well as mechanical obstacles and user errors using the device. The primary readout for this study was vascular access site complications. These complications included palpable hematoma measuring at least 5 cm in size, pseudo aneurysms, arteriovenous fistula formation, major bleeding related to the access site, acute leg ischemia, the need for vascular surgical or interventional treatment and local infections at 30 days after the procedure. Adverse events not previously described were investigated. Time to ambulation (TTA) was measured as the time from the Secure Device being removed from the patient to the subjects being able to walk at least 10 m.

Follow up of the patients took place at 4 time points: 2–4 h after Secure Device use, at ambulation, prior to discharge and a final examination 30 days after the procedure.

Statistical analysis

All parameters are expressed as mean ±standard deviation of the mean, as number of patient counts or percentage. TTH (primary endpoint) and TTA are expressed as mean ± standard deviation of the mean, as minutes (TTH) or hours (TTA). The statistical analysis of the complication rate was designed to reject the null hypothesis that the Secure Device is inferior in terms of vascular access-site complications to vascular closure devices (FemoSeal and Exoseal) as described in the ISAR-CLOSURE trial [5].

The ISAR-CLOSURE trial reported a complication rate of 6.9% in patients that were treated with a vascular closure devices. This was considered to be the null-hypothesis proportion for this trial. As in the ISAR-CLOSURE trial, considering that the majority of expected complications are not severe in nature, a non-inferiority margin that represents 140% of the null-hypothesis proportion was chosen, which results in a 3% margin of non-inferiority. The expected complication rate for the

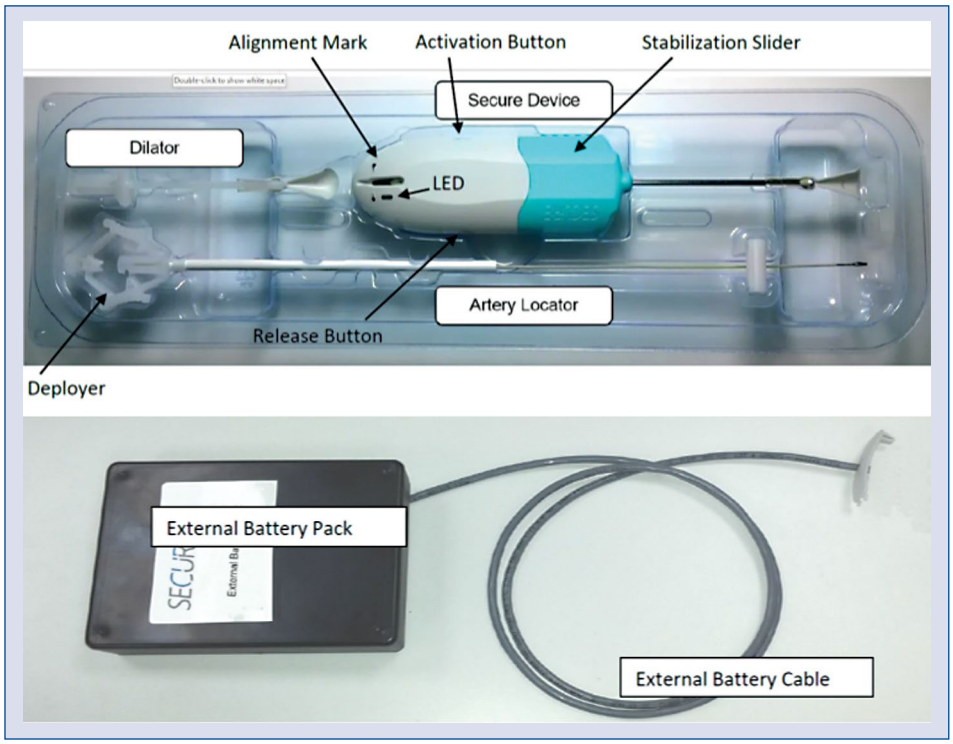


Figure 3. Secure Device including artery locator, dilator and the Secure artery closure Device. The external battery pack is not sterile and reusable. The tip of the artery locator with the deploying unit is made of nitinol and is covered by an elastic membrane made by PolyBlend (Advan Source biomaterials, Wilmington, MA). The shaft of the artery locator, made of Polyether Ether Ketone, served as a guide for the secure device. The dilator is made of a high-density plastic and should be inserted at an angle of approximately 45° to the artery. The tip of the Secure Device is 4.5 mm in diameter and made of silicone coated silver plated copper. A plastic wire protruded 1–2 mm from the stainless-steel tube at the end of the locator, indicating a fully deployed artery locator tip.

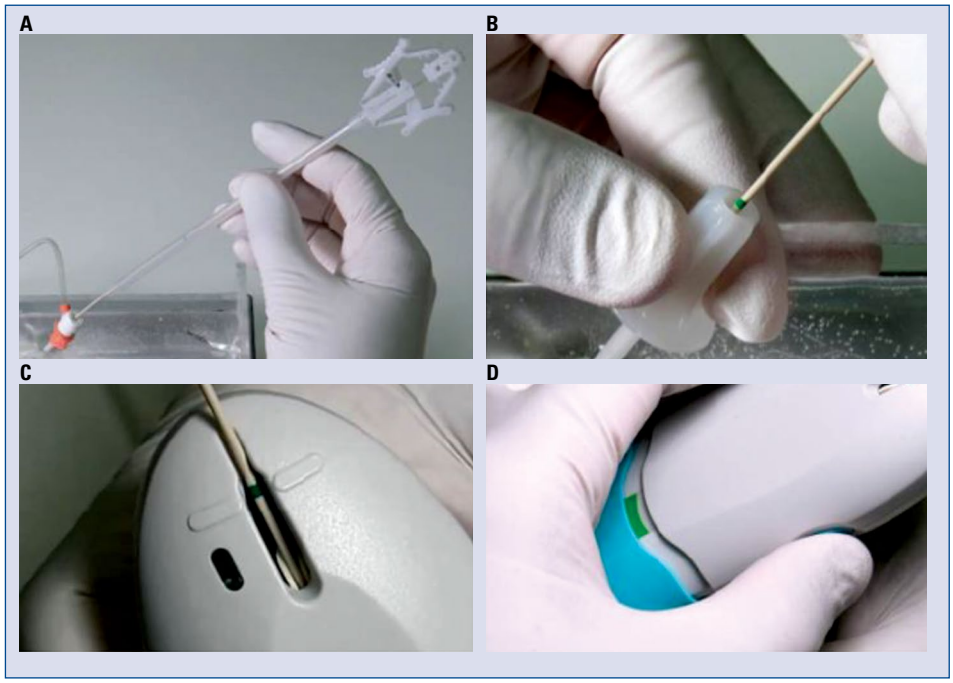


Figure 4. A. Artery locator insertion and deploying the artery locator in the vessel; removing the sheath over the artery locator shaft; **B.** Pre-dilating the tissue tract; **C.** Inserting the Secure arterial closure Device to the alignment mark; **D.** Activate the Secure arterial closure Device to close the vessel.

Secure Device was estimated to be at most 5%. Given a type I error rate of $\alpha = 5\%$, a power of 80%, a null-hypothesis proportion of 6.9%, an expected true proportion of 5%, and a non-inferiority margin of 3%, the necessary sample size was determined to be 123 subjects.

However, the study was terminated early as the manufacturers board decided to discontinue the investment in Secure Device on December, 13 2016. Until then 67 patients were enrolled into the trial and all follow-up visits were performed.

Results

The average age of enrolled patients was 64.8 ± 15.6 years with an average body mass index of 28. Final activation of the Secure Device was performed in 63 cases. In 4 cases the device was installed but due to user error it was not activated. In these cases, manual compression was applied with no clinical disadvantage. Patient characteristics are listed in Table 1.

Table 1. Clinical characteristics of patients included in the study.

Basic characteristics	
Patients enrolled	67
Mean age	64.8 ± 15.6
Body mass index	28.2 ± 4.2
Female	19.4%
Intervention	13
Blood pressure [mmHg]	136.5 ± 25.6 / 73.7 ± 11.7
Heart rate [/min]	78.5 ± 11.7
Concommitend medication	
ACE-I	10.4%
Beta-blocker	58.2%
Statin	56.7%
Aspirin	64.2%
Anticoagulant	29.9%
$P2Y_{12}$ inhibitor	23.9%
Heparin	17.9%
Baseline und follow-up lab	
Hemoglobin [g/dL]	14.0 ± 1.6
Platelet count [10^9/L]	207.5 ± 71.2
INR	1.1 (0.85–1.46)
PTT [s]	33.3 ± 4.9
FU hemoglobin [g/dL]	13.3 ± 1.8
FU PLTC [10^9/L]	234.6 ± 88.1

ACE-I — angiotensin converting enzyme inhibitor; FU — follow-up; INR — international normalized ratio; PTT — partial thromboplastin time

Time to hemostasis

Time to haemostasis (primary performance endpoint) was statistically evaluated in 51 subjects. The mean TTH was 4:30 ± 2:15 min in the overall observational group with a maximum time of 13:00 min and a minimum time of 2:00 min. Eleven of the subjects undergoing statistical analysis regarding TTH received anticoagulation medications (all unfractionated heparin; 70 IU/kg). In this subpopulation, TTH was 4:53 ± 1:43 min. TTH was not documented in 12 patients in which a Cathofix® compression system was applied if TTH was not achieved after > 5 min. One of these patients had a haematoma prior to the closing procedure. In 11 patients hemostasis was not primarily reached within 3–5 min and the physician decided to apply a compression assist system (Femostop®). In these cases TTH was not acquired.

Access site complication rate

Two out of 63 (3.2%) individuals experienced access site associated complications (primary safety endpoint). A palpable haematoma of > 5 cm was the only complication in these 2 subjects. In terms of severity, both hematomas were categorized as mild since they were only superficial but were neither indurated nor visibly swollen. By the 30 day follow-up, both hematomas had completely resolved. Since there were only 63 patients actively treated with the device, instead of the 123 subjects originally planned for according to the statistical sample size calculation, the confidence interval of the results was larger than expected.

Device malfunction rate

Sixty-nine devices were used in 63 patients. Two devices had malfunctions (secondary endpoint) that hindered activation of the Secure Device itself. In 14 devices there was either major (activation of the device) or minor (artery locator protruding) problems during the vascular closing procedure, representing a 20.3% malfunction rate. Additionally, another 8.7% of the Secure Device applications failed due to user errors and device misuse. In these cases, either parts of the closing procedure or the whole procedure failed. In 1 case the missing fixation of the artery locator during insertion of the device did not work, and made it necessary to also change the system with the deployed artery locator. In some cases an incomplete artery locator retraction at the end of the closing procedure hindered complete vascular occlusion, at which point manual compression was applied.

Adverse events and severe adverse events

In addition to main access site complication rate, additional adverse events as secondary endpoint were analyzed. The most frequent adverse events observed were small hematomas. All small hematomas were totally resolved within a short time and not detected 30 days after the procedure. One patient experienced a decrease in blood pressure, local infection (elevated C-reactive protein, inconspicuous access site, normal chest X-ray and unremarkable urine test) and developed bruising. An acute allergic reaction to the contrast agent used was investigated in 2 patients and an initial manifestation of diabetes was detected in another patient. The only reported severe adverse event was an unexpected ST-segment elevation myocardial infarction with stent thrombosis after percutaneous coronary intervention (PCI), 10 min after the closing procedure was completed, which was then followed by a second PCI.

Time to ambulation

The time between Secure Device System activation and patient ambulation was assessed. Mean time to ambulation was 8:04 ± 6:32 h. In the subgroup of patients who received anticoagulants, the mean time to ambulation was 12:45 ± 8:54 h.

Discussion

This study was initiated to investigate the safety and efficacy performance of the Secure Device System in clinical routine. While manual compression is still the gold standard following femoral access vascular intervention, vascular closure devices have been found to be safe and associated with less complications in femoral access after coronary angiography [6]. Nevertheless, the incidence of complications such as hematomas and pseudoaneurysms are often discussed with controversy [7]. Relevant complications include groin hematomas, bleeding, arteriovenous fistulas and pseudoaneurysms developing at the puncture site as shown at meta-analysis level. In a PCI setting the rate of complications were higher compared to diagnostic catheters [8]. More recent data on a large cohort of patients investigated intravascular and extravascular devices compared to manual compression. Vascular closure devices showed non-inferiority to manual compression in terms of vascular access site complications [5]. Comparable results were found with the polymer disc based device FemoSeal®, which accomplished faster haemostasis with less hematoma formation [6]. Suture based closure device and plug based devices, regardless of whether they use metal or collagen, ultimately leave foreign materials either directly in the arterial wall or within the surrounding tissue [5, 9].

Foreign materials may be a problem for a patient in long-term if re-puncture is necessary or potentially a source for local reactions in the arterial wall or the adventitial surrounding. In a small number of patients, the presence of a foreign material could lead to limb ischemia. Although interventional treatment of limb ischemia seems feasible [10], these are major adverse events. In clinical practice, repetitive use of devices at the same puncture site is avoided. Since there is no human data regarding fibrosis at the site of puncture, investigating the local effects of collagen based devices has been limited to animal models. In tissue samples and histological analysis of the collagen plug vessel narrowing and peri-adventitial inflammation inducing extravascular scarring was found in a dog model [11]. A recent trial in minipigs also described vessel stenosis influencing blood flow and histological alterations following closure using collagen plugs [12].

Research into active vascular closure devices that do not leave foreign materials at the puncture site is a growing field. The idea of using thermal energy to achieve arterial access occlusion is becoming a focus. The pathophysiological mechanism of thermal occlusion is the result of the local collagen shrinkage outside the vessel and local swelling to achieve hemostasis [4]. In this small trial, TTH was accomplished after 3 min for diagnostic procedures and 4 min for interventional catheterization, and no severe adverse events were reported.

In one fifth of the device applications, either device activation issues or intra-procedural obstacles resulted in changing the device or switching to manual compression. Although malfunctions are a common problem in vascular closure devices, malfunction rates are highly variable depending on the device. The StarClose System, a clip based device, has a malfunction rate around 1.1%. AngioSeal, a well-established collagen plug induced vascular closure device, has been found to have malfunction rates up to 10% [13, 14]. The majority of the device malfunctions occurred at the beginning of the Secure Device activation, so the device was able to be changed and did not influence the study procedure. None of the device malfunctions were related to patient safety.

The average time to hemostasis in the 54 assessed individuals was slightly above 4 min (2 to 13 min). The complication rate was low for the

Secure Device. Clinical follow-up included physical examination focussing on the access site. No duplex was performed unless auscultation or palpation were suspicious for an access site complication. Although physical examinations were all performed by experienced clinicians it cannot be ruled out that a vascular complication only detectable by duplex might have been present. However, there was no case of an access site related problem within the 30 day follow-up, supporting the idea that no additional complications developed. The only access site associated complication was the occurrence of a hematoma larger than 5 cm. In 2 cases, a relevant hematoma was detected. The device was successfully applied in both cases and time to hemostasis was obtained in 5 and 6 min after device activation, respectively.

Although the study was terminated after only 63 patients with active use of the Secure Device, since the measured proportion of access site complications was 3.2%, lower than the expected proportion of up to 5%, the data from the 63 patients was sufficient to reject the predefined null-hypothesis. However, it should be noted that baseline characteristics between this trial and the ISAR-CLOSURE trial revealed some differences. The percentage of female participants as well as average age was higher in the ISAR CLOSURE trial increasing the risk for bleeding whereas body mass index was higher in the present study. With respect to anticoagulation and antithrombotic medication there was comparable use of acetylsalicylic acid in both trials (~2/3 of all patients) but $P2Y_{12}$ inhibitors were used more often in the ISAR-CLOSURE trial whereas anticoagulation was more frequent in the present trial. An important difference regarding the follow-up of the patients is the systematic duplex-sonographic follow-up in ISAR-CLOSURE. Although it cannot be ruled out that routine duplex was more sensitive to detect access site complications (predefined complications were the composite of hematoma ≥ 5 cm, pseudoaneurysm, arterio-venous fistula, access-site-related major bleeding, acute ipsilateral leg ischemia, need for vascular surgical/interventional treatment or local infection) these should have been detected with this two step approach.

It is known that minor vascular events have been found to occur frequently with different devices [15]. Besides the two primary safety endpoint events of groin hematomas > 5 cm, 9 small local hematomas were reported as adverse events. Three other anticipated adverse events were reported. Either blood pressure decrease, infection or bruising was observed in 3 different patients. All of the investigated events might be potentially device related, although they were evaluated only descriptively in this trial.

In the subgroup of patients that received manual compression after Secure Device activation, as decided by the physician, the time to hemostasis was not evaluated.

The present study investigated a moderate rate of user failure, although extensive training had been performed. In prior clinical experience with the application system, especially the artery locator and the handling of the Secure Device itself, it requires additional practice in order to become adept. Compared to other vascular closure devices, further development of the device might increase user friendly application.

Conclusions

Vascular occlusion devices are commonly used for femoral access catheterization.

The new Secure Device uses thermal energy and has been found to be feasible in both diagnostic and interventional cardiac catheterization in this small and prematurely concluded trial. In comparison to established devices, it has the advantage of leaving no foreign material in the body following closure.

Based on the limited data available it seems to be non-inferior to other closure devices in terms of safety.

However, the rate of malfunctions was still significant and requests further development of the technique.

Further clinical investigation will be needed regarding the Secure Device thermal vascular closure technique in larger patient populations.

Funding: The study was funded by Calore Medical Ltd., 14 HaIlan st., Or Akiva, Israel, 30600.

Conflict of interest: Michael Sacherer, Olev Luha and Robert Zweiker were sub-investigators, Karin Brandner was study nurse and Dirk von Lewinski was principle investigator in this funded trial.

References

1. Walter J, Vogl M, Holderried M, et al. Manual Compression versus Vascular Closing Device for Closing Access Puncture Site in Femoral Left-Heart Catheterization and Percutaneous Coronary Interventions: A Retrospective Cross-Sectional Comparison of Costs and Effects in Inpatient Care. Value Health. 2017; 20(6): 769–776, doi: 10.1016/j.jval.2016.05.004, indexed in Pubmed: 28577694.

2. Hon LQ, Ganeshan A, Thomas SM, et al. An overview of vascular closure devices: what every radiologist should know. Eur J Radiol. 2010; 73(1): 181–190, doi: 10.1016/j.ejrad.2008.09.023, indexed in Pubmed: 19041208.
3. Krishnasamy VP, Hagar MJ, Scher DJ, et al. Vascular closure devices: technical tips, complications, and management. Tech Vasc Interv Radiol. 2015; 18(2): 100–112, doi: 10.1053/j.tvir.2015.04.008, indexed in Pubmed: 26070622.
4. Davidson LJ, Luna J, Virmani R, et al. First human experience of thermal arterial closure. Catheter Cardiovasc Interv. 2014; 84(1): 30–36, doi: 10.1002/ccd.25152, indexed in Pubmed: 23934606.
5. Schulz-Schüpke S, Helde S, Gewalt S, et al. Comparison of vascular closure devices vs manual compression after femoral artery puncture: the ISAR-CLOSURE randomized clinical trial. JAMA. 2014; 312(19): 1981–1987, doi: 10.1001/jama.2014.15305, indexed in Pubmed: 25399273.
6. Holm NR, Sindberg B, Schou M, et al. Randomised comparison of manual compression and FemoSeal™ vascular closure device for closure after femoral artery access coronary angiography: the CLOSure dEvices Used in everyday Practice (CLOSE-UP) study. EuroIntervention. 2014; 10(2): 183–190, doi: 10.4244/EIJV10I2A31, indexed in Pubmed: 24603054.
7. Koreny M, Riedmüller E, Nikfardjam M, et al. Arterial puncture closing devices compared with standard manual compression after cardiac catheterization: systematic review and meta-analysis. JAMA. 2004; 291(3): 350–357, doi: 10.1001/jama.291.3.350, indexed in Pubmed: 14734598.
8. Nikolsky E, Mehran R, Halkin A, et al. Vascular complications associated with arteriotomy closure devices in patients undergoing percutaneous coronary procedures: a meta-analysis. J Am Coll Cardiol. 2004; 44(6): 1200–1209, doi: 10.1016/j.jacc.2004.06.048, indexed in Pubmed: 15364320.
9. Martin JL, Pratsos A, Magargee E, et al. A randomized trial comparing compression, Perclose Proglide and Angio-Seal VIP for arterial closure following percutaneous coronary intervention: the CAP trial. Catheter Cardiovasc Interv. 2008; 71(1): 1–5, doi: 10.1002/ccd.21333, indexed in Pubmed: 18098171.
10. Dong H, Peng M, Jiang X, et al. Endovascular therapy for Angio-seal-related acute limb ischemia: Perioperative and long-term results. Catheter Cardiovasc Interv. 2017; 89(S1): 609–615, doi: 10.1002/ccd.26936, indexed in Pubmed: 28191744.
11. Gargiulo NJ, Veith FJ, Ohki T, et al. Histologic and duplex comparison of the perclose and angio-seal percutaneous closure devices. Vascular. 2007; 15(1): 24–29, doi: 10.2310/6670.2007.00004, indexed in Pubmed: 17382051.
12. Kabelitz L, Nonn A, Nolte KW, et al. Long term outcome after application of the angio-seal vascular closure device in minipigs. PLoS One. 2016; 11(9): e0163878, doi: 10.1371/journal.pone.0163878, indexed in Pubmed: 27682594.
13. Spiliopoulos S, Katsanos K, Karnabatidis D, et al. Safety and efficacy of the StarClose vascular closure device in more than 1000 consecutive peripheral angioplasty procedures. J Endovasc Ther. 2011; 18(3): 435–443, doi: 10.1583/10-3277.1, indexed in Pubmed: 21679086.
14. Minko P, Katoh M, Gräber S, et al. Obesity: an independent risk factor for insufficient hemostasis using the AngioSeal vascular closure device after antegrade puncture. Cardiovasc Intervent Radiol. 2012; 35(4): 775–778, doi: 10.1007/s00270-011-0230-y, indexed in Pubmed: 21792734.
15. Schmelter C, Liebl A, Poullos N, et al. Suitability of Exoseal vascular closure device for antegrade femoral artery puncture site closure. Cardiovasc Intervent Radiol. 2013; 36(3): 659–668, doi: 10.1007/s00270-012-0501-2, indexed in Pubmed: 23070109.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2019, Vol. 26, No. 3, 241–252
DOI: 10.5603/CJ.a2019.0034

ISSN 1897–5593

Study of epidemiological aspects of hyperuricemia in Poland

Katarzyna Kostka-Jeziorny[1], Krystyna Widecka[2], Andrzej Tykarski[1]

[1]Department of Hypertensiology, Angiology and Internal Diseases, Poznan University of Medical Sciences, Poznan, Poland
[2]Department of Hypertensiology and Internal Diseases, Pomeranian Medical University, Szczecin, Poland

This article appeared parallel to the journal *Nadciśnienie Tętnicze w Praktyce 2019; 5(1): 1–12* in the Polish language.

Abstract

Background: *The results of the latest epidemiological studies show that the problem of hyperuricemia affects many millions of people. The main purpose of the study was to assess the knowledge of physicians with regard to the epidemiology and treatment of hyperuricemia in Poland.*

Methods: *CAPI (computer assisted personal interview) interviews were conducted using short questionnaires among primary health care physicians, cardiologists and diabetologists. The entire questionnaire included 11 questions. Questions were asked to physicians at 5 different periods in time. The number of physicians surveyed, depended on the time period, and ranged from 8663 to 9980.*

Results: *Only every 1 in 7 physicians (14%) considered that hyperuricemia in patients with cardiovascular risk factors begins when the uric acid level is 5 mg/dL, thus in line with the expert recommendations. 72% of respondents asked to indicate the uric acid levels they consider to be indicative of hyperuricemia in patients in the cardiovascular risk group, gave values ranging from 6 to 7 mg/dL, namely the values justified in cases of a patient without such a risk, i.e. in the general population. 86% of doctors surveyed gave values different from that recommended by experts.*

Conclusions: *The findings of the questionnaire in this survey suggests that doctors often underestimate the problem of hyperuricemia in patients with a high risk of cardiovascular disease. An important step towards more effective therapy of hyperuricemia in routine clinical practice is to raise the awareness of hyperuricemia and its comorbidities both among doctors and patients and encourage monitoring and treatment.* (Cardiol J 2019; 26, 3: 241–252)

Key words: hyperuricemia, arterial hypertension

Introduction

The results of recent epidemiological studies show that hyperuricemia affects many millions of people [1]. In the coming years, and in connection with an epidemic of obesity, metabolic disorders and an aging population among others factors, a further gradual increase in the incidence of hyperuricemia should be expected [2, 3].

Already on the basis of earlier studies, a conclusion was drawn that the relative risk of cardiovascular complications in patients, including

Address for correspondence: Katarzyna Kostka-Jeziorny, MD, PhD, Department of Hypertensiology, Angiology and Internal Diseases, Poznan University of Medical Sciences, ul. Długa 1/2, 61–848 Poznań, Poland, tel: +48 61 854 91 82, fax: +48 61 854 90 86, e-mail: kostkajeziorny@gmail.com

Received: 20.02.2019 Accepted: 18.04.2019

Table 1. Questions at 5 periods in time with the following number of participating physicians.

	1st period	2nd period	3rd period	4th period	5th period
Duration of the period	September – – November 2017	December 2017 – – January 2018	February – – March 2018	April – May 2018	June 2018
Number of surveyed physicians	9980	9740	9525	8663–9470	6910

patients with hypertension, increases with a growing level of uric acid in blood serum [4]. However, there was no evidence that hyperuricemia is a factor contributing to the development of cardiovascular disorders, because after considering the other risk factors in statistical analysis, the effect of hyperuricemia seemed to be insignificant [5]. In the recent years, there has been a revival of an interest in uric acid as a prognostic and causative factor in cardiovascular disease (CVD). The analysis of large clinical trials on the relationship between hyperuricemia and the risk of cardiovascular complications in hypertensive patients clearly points to uric acid as an independent predicative factor.

According to the Guidelines of the Polish Society of Arterial Hypertension in 2015, the determination of uric acid concentration is a basic test in patients with hypertension together with a morphology test, glycemia test, determination of sodium and potassium, lipid profile, creatinine, estimated glomerular filtration rate, albuminuria assessment and urinalysis [6]. Also, the latest 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) Guidelines for the management of arterial hypertension not only mentions the uric acid test as a basic test, but also considers it to be a factor affecting cardiovascular risk [7].

The definition of hyperuricemia varies widely between publications, which means that epidemiological studies are inconsistent. However, based on the recent studies, analyses and recommendations, physicians should seek to reach and maintain lifelong uric acid levels of < 6 mg/dL in the general population, and in patients with high cardiovascular risk, the target uric acid level of 5 mg/dL should be considered [8]. According to the latest Expert Consensus on the diagnosis and treatment of patients with hyperuricemia and high cardiovascular risk, the target uric acid levels of < 5 mg/dL should be considered in patients with high cardiovascular risk, presenting at least two of the following risk factors: hypertension, diabetes, dyslipidemia, recent stroke or myocardial infarction and chronic kidney disease (CKD) [9].

The main purpose of the study was to assess the knowledge of physicians with regard to the epidemiology and treatment of hyperuricemia in Poland. Research objectives were divided into three groups. The aim of the first group was to assess physician awareness with regard to the incidence of hyperuricemia, and in particular the frequency of ordering appropriate tests and application of therapeutic solutions. The aim of the second group was to identify the actual risk of CVD and metabolic syndrome due to hyperuricemia according to primary health care physicians, cardiologists and diabetologists. An assessment of physician attitudes to the reference values of uric acid concentration levels, screening tests and hyperuricemia therapies available on the market, as well as identification of treatment-related barriers was the goal of the third study group.

Methods

CAPI (computer assisted personal interview) interviews were conducted using short questionnaires among primary health care physicians, cardiologists and diabetologists. The entire questionnaire included 11 questions. Questions were asked to physicians at 5 different periods (Table 1). The number of physicians surveyed, depending on the time period, and ranged from 8663 to 9980. The doctors were asked the following questions:

— Question 1. What concentration of uric acid do you consider to be hyperuricemia in patients at risk of cardiovascular disease?
— Question 2. What diseases are, in your opinion, are most often accompanied by hyperuricemia?
— Question 3. What is the average age of your patients with hyperuricemia > 5 mg/dL (298 μmol/L) in the cardiovascular risk group?
— Question 4. How often do you order tests to measure uric acid concentration in blood serum for patients with hyperuricemia > 5 mg/dL (298 μmol/L) in the cardiovascular risk group?
— Question 5. What is the average uric acid concentration of your hyperuricemia patients from the cardiovascular risk group?

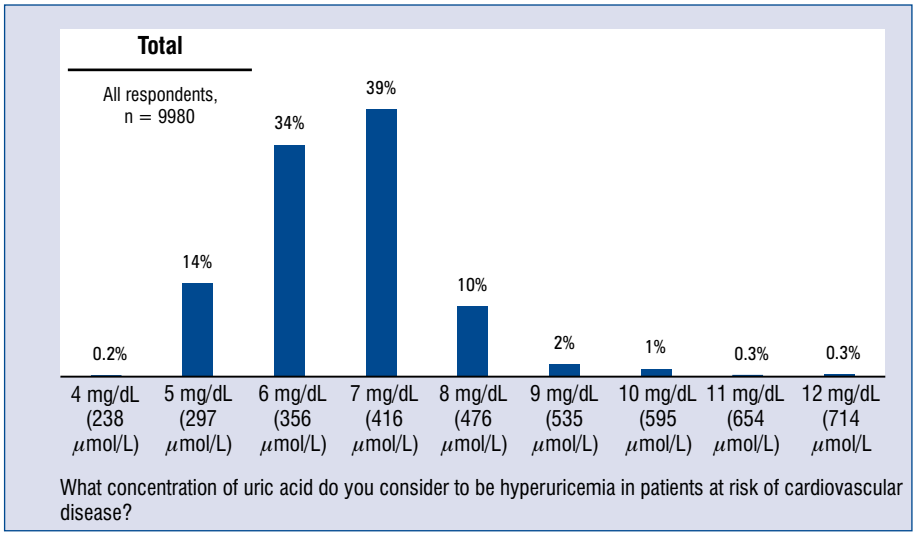


Figure 1. Uric acid reference concentration value considered by physicians as hyperuricaemia at the patients of cardiovascular risk group — distribution of all the responses.

— Question 6. At what concentration of uric acid in a patient at risk of cardiovascular disease do you administer pharmacological treatment of hyperuricemia?
— Question 7. In what percentage of patients from the cardiovascular risk group (> 5 mg/dL, 298 μmol/L) taking medicines to reduce uric acid levels have you decreased the dose of the medicine in the last 3–4 months?
— Question 8. In what percentage of patients from the cardiovascular risk group (> 5 mg/dl, 298 μmol/L) taking medicines aimed to reduce uric acid levels have you increased the dose of the medicine in the last 3–4 months?
— Question 9. In your opinion, how long should be the pharmacological treatment of hyperuricaemia last in patients with cardiovascular risk (> 5 mg/dL, 298 μmol/L)?
— Question 10. From your observations, what are the effects on hyperuricemia on cardiovascular risk (> 5 mg/dL, 298 μmol/L)?
— Question 11. Have you noticed an increase in the incidence of hyperuricemia in patients with cardiovascular risk (> 5 mg/dL, 298 μmol/L) over the past 2 years?

The study was performed over a period from September 2017 to June 2018. Questions were asked at 5 periods with the following number of participating physicians (Table 1).

Results

Only every 1 in 7 physicians (14%) considers that hyperuricemia in patients with cardiovascular risk factors begins when the uric acid level is 5 mg/dL, thus in line with the expert recommendations [8, 9]. 72% of respondents asked to indicate the uric acid levels they consider to be indicative of hyperuricemia in patients in the cardiovascular risk group gave values ranging from 6 to 7 mg/dL, namely the values justified in cases of patients without such a risk, i.e. in the general population. 86% of doctors surveyed gave values different from that recommended by experts, namely other than 5 mg/dL, as the reference value of hyperuricemia in patients presenting with cardiovascular risk factors (Fig. 1).

In answer to the question of what diseases, according to them, most often accompany hyperuricemia, physicians indicated the most often hypertension (91%), metabolic syndrome (89%) and diabetes (84%) (Fig. 2).

According to the doctors surveyed, the average age of patients with hyperuricemia > 5 mg/dL (298 μmol/L) in the cardiovascular risk group was 55 years. Nearly 1/3 doctors had declared that the average age of their patients with hyperuricemia > 5 mg/dL (298 μmol/L) in the cardiovascular risk group was 50 years or less, and the next one third of doctors indicated that the age was 60 years or more (Fig. 3).

Almost half of the doctors (48%) order a test of uric acid concentration in blood serum once a year in patients with hyperuricemia > 5 mg/dL (298 μmol/L) in the cardiovascular risk group, and more than 1/3 of physicians (38%) order the test twice a year (Fig. 4).

Average concentration levels of uric acid in patients with hyperuricemia > 5 mg/dL

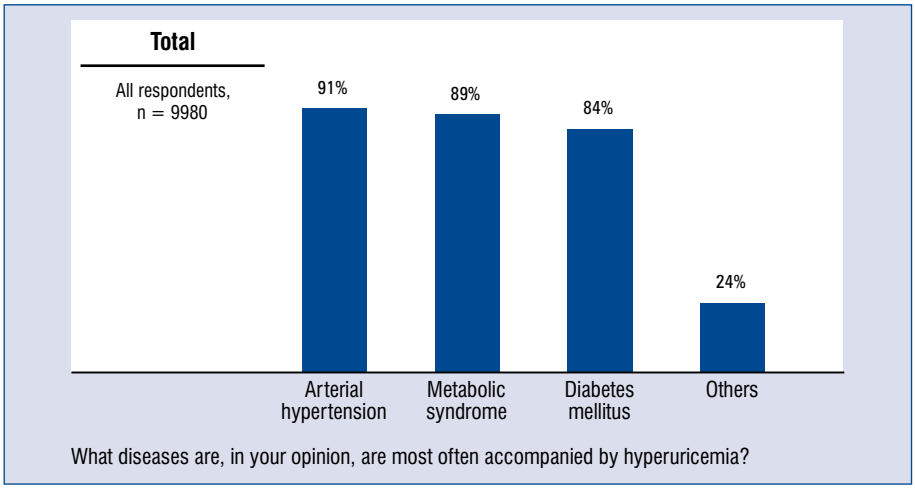


Figure 2. Diseases usually accompanied by hyperuricaemia — distribution of responses.

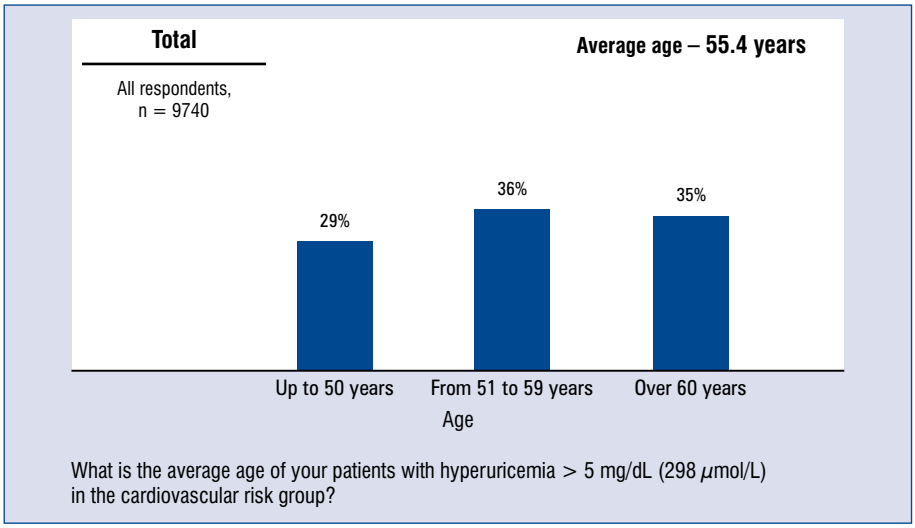


Figure 3. Average age of patients with hyperuricaemia > 5 mg/dL (298 μmol/L) of the cardiovascular risk group — distribution of responses and average.

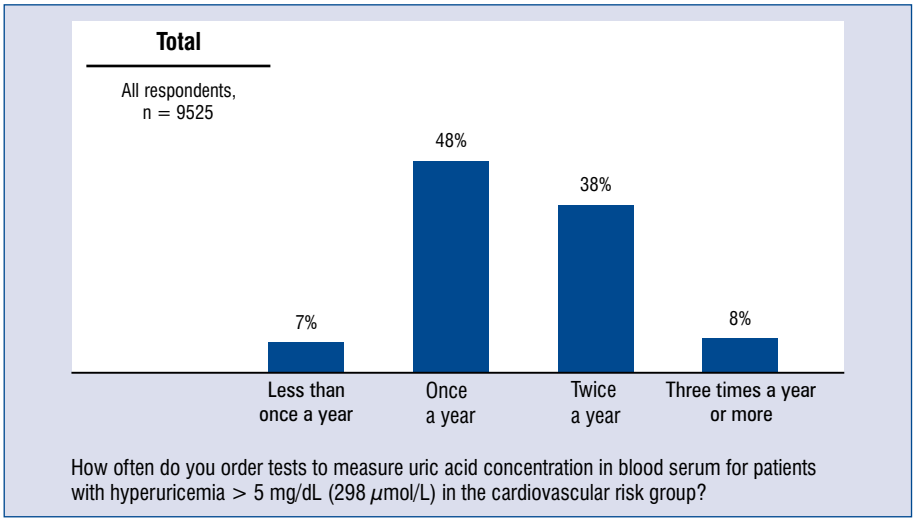


Figure 4. Frequency of ordering urea acid tests in serum at patients with hyperuricaemia > 5 mg/dL (298 μmol/L) of the cardiovascular risk group — distribution of responses.

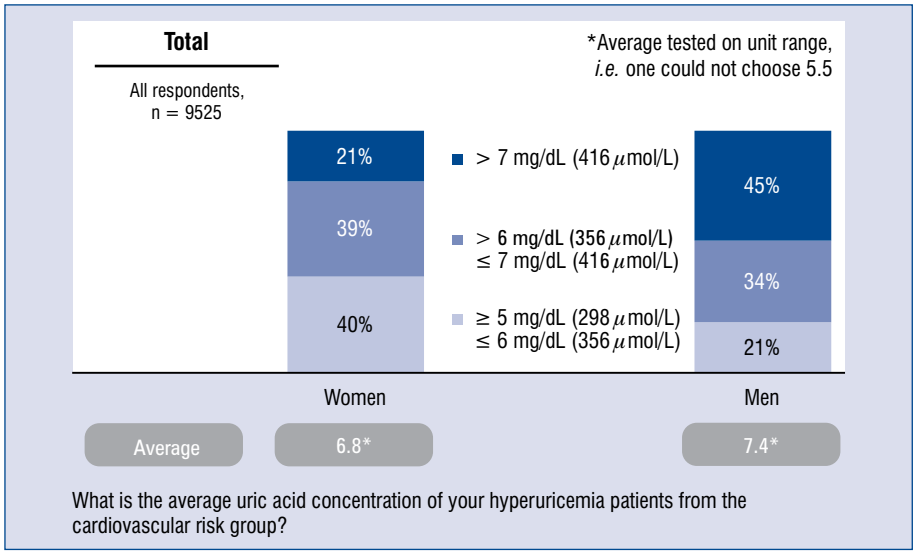


Figure 5. Average concentration of uric acid at patients with hyperuricemia > 5 mg/dL (298 μmol/L) of the cardiovascular risk group — distribution of responses and average.

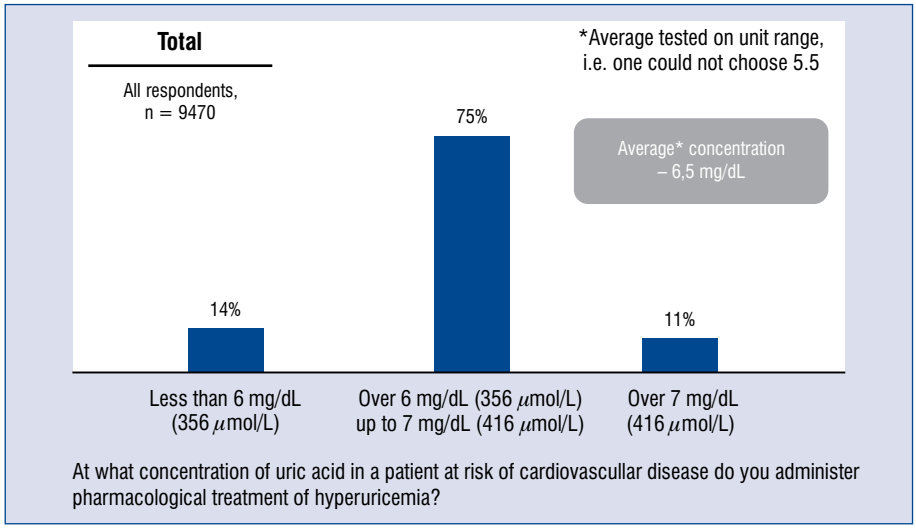


Figure 6. Uric acid concentration value at which the physician includes pharmacologic treatment of hyperuricemia for patients of the cardiovascular risk group — aggregated distribution of responses and average.

(298 μmol/L) in the cardiovascular risk group is higher among men than among women. It is on average 6.8 mg/dL in female patients and 7.4 mg/dL in male patients (Fig. 5).

The vast majority of doctors, namely 75% of respondents commence pharmacological treatment of hyperuricemia in a patient at risk of CVD, when the concentration of uric acid is between 6 and 7 mg/dL, 14% — when this concentration is lower than 6 mg/dL, and another 11% — when it is above 7 mg/dL (Fig. 6).

Physicians generally do not reduce the dose of medicine that lowers uric acid concentration in patients with hyperuricemia in the cardiovascular risk group. 72% of physicians had not reduced the dose of medicines in their patients in the prior 3–4 months. The average percentage of patients with hyperuricemia in the cardiovascular risk group, from doctors who had reduced the dose of medicine which reduces uric acid concentration was 14% (taking into account only doctors had reduced dosage). Almost all doctors increased the doses of medicine reducing uric acid concentration in patients with hyperuricemia in the cardiovascular risk group — only 2% of physicians over the prior 3–4 months did not have this type of patient.

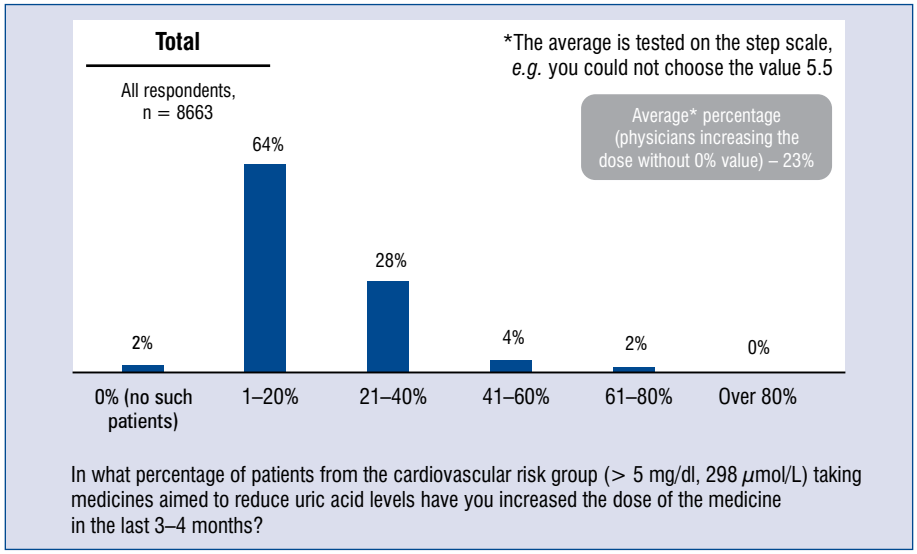


Figure 7. Percentage of patients with hyperuricemia > 5 mg/dL (298 μmol/L) in the cardiovascular risk group taking medicines lowering uric acid concentration, whose doctor had increased the dose in the prior 3–4 months — aggregated distribution of responses and the average.

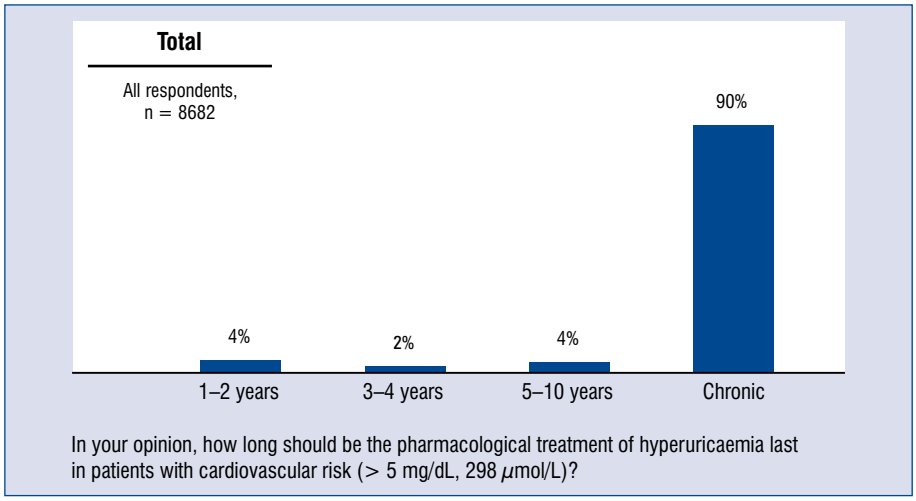


Figure 8. The assumed length of pharmacological treatment of hyperuricemia for patients in the cardiovascular risk group (> 5 mg/dL; 298 μmol/l) — distribution of responses.

The average percentage of patients with hyperuricemia in the cardiovascular risk group, in cases of doctors who had increased the dose of drugs that lower medicines reducing uric acid concentration is 23% (includes only dose-increasing doctors) (Fig. 7).

90% of doctors believe that pharmacological treatment of hyperuricemia in patients in the cardiovascular risk group should be included permanently (Fig. 8).

Nearly 80% of respondents believe that hyperuricemia (> 5 mg/dL; 298 μmol/L) has a high impact on cardiovascular risk. The remaining 20% of doctors believed that the effect of hyperuricemia on cardiovascular risk is moderate (Fig. 9). Moreover, 91% doctors have observed an increase in the occurrence of hyperuricemia over the prior 2 years in patients from the cardiovascular risk group (Fig. 10).

Discussion

Based on available research and recommendations, the target uric acid concentration of < 5 mg/dL

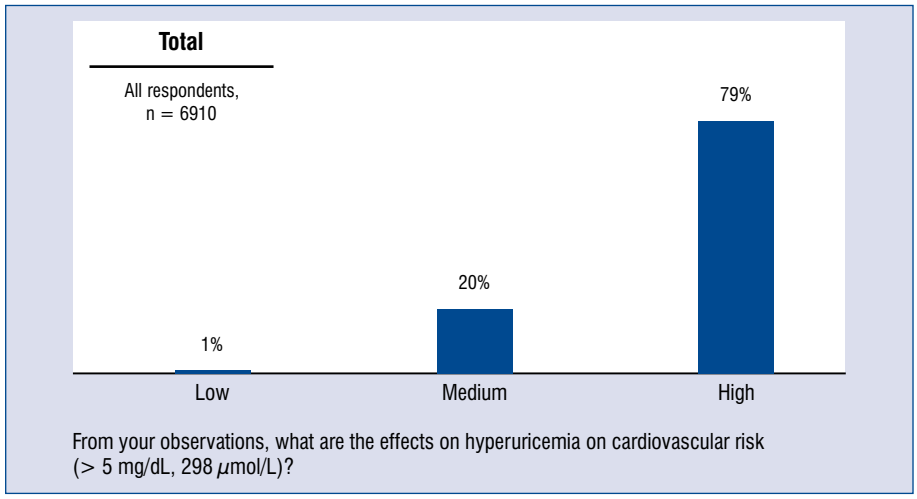


Figure 9. Assessment of the impact of hyperuricemia (> 5 mg/dL, 298 μmol/L) on cardiovascular risk — distribution of responses.

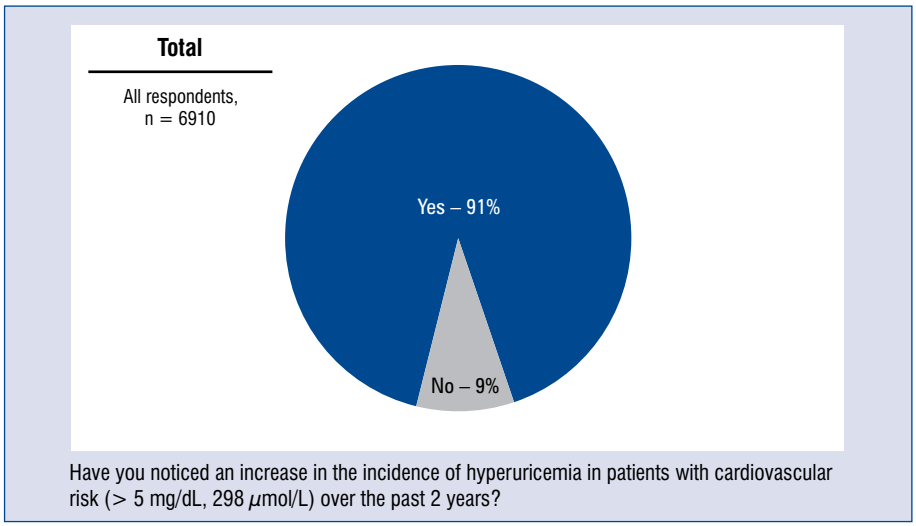


Figure 10. Frequency of hyperuricemia for patients in the cardiovascular risk group (> 5 mg/dL; 298 μmol/L) within the prior 2 years — distribution of responses.

should be considered in patients with high cardiovascular risk. High cardiovascular risk patients are considered to be those persons with hypertension, diabetes, metabolic syndrome, diagnosed atherosclerosis of any vascular bed (including patients with coronary artery disease [CAD] or atherosclerotic cerebrovascular disease) [8]. According to the position of international experts, the target uric acid concentration of < 5 mg/dL should be considered in patients with high cardiovascular risk, presenting with at least two of the following factors: hypertension, diabetes, dyslipidaemia, recent stroke or myocardial infarction, CKD [9].

It should be noted that the PAMELA study confirmed the benefits of maintaining a level of approximately 5 mg/dL in patients with high cardiovascular risk [10]. In the present study, patients were randomly recruited from the general population and subjected to a detailed assessment of the cardiovascular risk profile. Echocardiography and blood pressure measurements were also performed other than at the doctor's office. Data analysis suggests the limit value of uric acid concentration of 5.4 mg/dL, providing the best sensitivity ratio to the specificity of the study in predicting the risk of cardiovascular mortality and 4.9 mg/dL for total mortality.

The findings of the current study show that relatively few doctors are aware of the recommendations related to the treatment of hyperuricemia in patients with high cardiovascular risk. Only 14% of doctors (1 in 7 respondents) indicate the value recommended by experts, and 3/4 (72%) of respondents asked to indicate uric acid levels they considered to be hyperuricemia in patients from the cardiovascular risk group, indicate values ranging from 6 to 7 mg/dL, i.e. the value justified in patients without such a risk. Yet, it should not be surprising that doctor responses may have been influenced by the many years of definitions of hyperuricemia, which have differed significantly between publications, i.e. epidemiological studies were inconsistent. Hyperuricemia used to be considered present when uric acid concentration in blood serum exceeded 7 mg/dL in male patients and 6 mg/dL in female patients. According to another definition hyperuricemia was defined as values above 6.4–6.8 mg/dL, at 37°C, being the total saturation of the plasma with sodium urate takes place [11]. Therefore, it still seems necessary to educate the medical community with regards to the definition of the value of hyperuricemia in patients with high cardiovascular risk.

Uric acid is recognized as an independent risk factor in the development of many macrovascular and microvascular disorders, including arterial hypertension [12], metabolic syndrome [13, 14], CAD [15], diabetes [16], cerebrovascular disease [17, 18], CKD [19] or other CVD [20, 21]. When asked what diseases, in their opinion, are most often associated with hyperuricemia, the respondents listed the following: hypertension (91%), metabolic syndrome (89%) and diabetes (84%). An increased concentration of uric acid impairs oxygen metabolism, stimulates the renin–angiotensin system and inhibits the secretion of endothelial nitric oxide. Therefore, it contributes to the development of microvascular complications in arterioles vasoconstriction, renal vasoconstriction, and persistent sodium chloride hypertension [22, 23]. As evidenced, most physicians are aware of the relationship between the increase in a relative risk of hypertension and high levels of uric acid [24, 25]. Most also know the relationship between hyperuricemia and metabolic syndrome. Diabetes as a disease often accompanying hyperuricemia is also indicated much less frequently — by 8 out of 10 doctors. It seems that respondents have the knowledge that elevated uric acid is the result of a diet which is rich in purine/fructose, genetic and environmental factors, metabolic disorders as well as endogenous overproduction or, in most cases, impaired excretion of uric acid. Pre-clinical test results suggest that endothelial dysfunction, inflammatory reaction and oxidative stress in fat cells play a key role in the development of metabolic syndrome [26]. Some studies describe the relationship between uricemia and obesity, between uricemia and obesity and insulin resistance. Therefore, uric acid was suggested as a component of the metabolic syndrome [27].

Yet, what was surprising was the lack of awareness of the doctors surveyed, of the relationship between hyperuricaemia and ischemic heart disease, and thus a growing cardiovascular risk. Oxidative stress caused by increased xanthine oxidase activity has a very negative effect on the endothelium vascular system, including coronary arteries [28, 29]. Based on data from the NHANES I study (First National Health and Nutrition Examination Study), Freedman et al. [1] proved that any increase in the value of uric acid concentration by 60 μmol/L is linked with a 48% increase in the risk of ischemic heart disease in women. In patients demonstrating cardiovascular complications (with angiographically diagnosed CAD, after ischemic stroke, with chronic heart failure) it has been shown that uric acid concentration is an independent prognostic factor for general and cardiovascular mortality of patients [30–32].

Moreover, the surveyed doctors do not mention the correlation of hyperuricemia with CKD, and high levels of uric acid, which indeed play a key role in the development and progression of CKD. It also remains an independent factor in the progression of CKD, even after adjustment for all classical co-existing diseases, such as hypertension, proteinuria and dyslipidaemia. This relationship was confirmed in patients with IgA nephropathy, diabetic nephropathy, after organ transplantation and in autosomal dominant polycystic kidney disease.

Almost 1/3 of physicians declared that the average age of their patients with hyperuricemia $>$ 5 mg/dL (298 μmol/L) in the cardiovascular risk group was 50 years or less, and another 1/3 declared that their age was 60 years or more. The prevalence hyperuricemia depends on the sex, age and race and reaches its peak in people at around the age of 70. In young and healthy people, before puberty, it is low and usually does not exceed 3.6 mg/dL. In men, it is on average 5 $\pm$ 2 mg/dL, and in women at childbearing age it is on average 1 mg/dL lower, and increases after menopause (the role of oestrogen). Yet, it should be remembered that the elevated concentration of uric acid is observed in almost 90% of adolescents with primary hypertension [33].

Almost half of physicians in the present study check serum uric acid concentration once a year in patients with hyperuricemia > 5 mg/dL (298 μmol/L) in the cardiovascular risk group and 38% of physicians will order the test for their patients twice a year. In patients in whom are introduced a hyperendemic agent, urine acid concentration should be controlled every 4 weeks after each increase of the dose until a therapeutic goal is achieved. According to the recommendations, after a therapeutic goal is achieved the dose of a drug reducing uric acid concentration (in practice, allopurinol) should be maintained, and uric acid concentration should be monitored periodically, twice a year.

The vast majority of doctors, namely 3/4 of respondents start pharmacological treatment of hyperuricemia in patients at risk of CVD only when the concentration of uric acid is between 6 and 7 mg/dL, 14% — when the concentration is lower than 6 mg/dL, and another 11% — when it is above 7 mg/dL. Once again one should be reminded that based on the current knowledge of physicians, they consider treatment with allopurinol when the level of uric acid is above 5 mg/dL in patients with high cardiovascular risk, presenting at least two of the following conditions: hypertension, diabetes, dyslipidaemia, recent stroke or myocardial infarction or CKD.

The international consensus on hyperuricemia in patients with high cardiovascular risk suggests that physicians should consider administering an initial dose of allopurinol of 100 mg daily, and gradually increase it to 300–600 mg per day, until the target concentration of uric acid is reached [9, 34]. A slow increase in the dose of allopurinol has resulted from the need to minimize the likelihood of an incidence of side effects, especially in patients with hypersensitivity to allopurinol or severe cutaneous allergic reactions (SCARs), which usually occurs after 8 weeks of the treatment [35–37]. There are several factors that especially contributed to the development of this syndrome, such as high initial doses, CKD, parallel use of diuretics or the presence of HLA-B*5801 [38, 39]. Almost all doctors surveyed in the study declared that they increased doses of uric acid-lowering drugs in patients with hyperuricemia in the cardiovascular risk group — only 2% of physicians over the prior 3–4 months did not have such patients. The average percentage of patients with hyperuricemia from the cardiovascular risk groups in which doctors increase the dose of medicine lowering uric acid levels is 23% (taking into account only doctors who increase the dose).

Allopurinol therapy in patients with high cardiovascular risk is a chronic treatment. 90% of the respondents gave such a response. Nearly 80% of physicians believe that hyperuricemia (> 5 mg/dL, 298 μmol/L) considerably affects cardiovascular risk. The remaining 20% of doctors believe that the impact of hyperuricemia on cardiovascular risk is moderate. Hyperuricemia plays an important pathophysiological role in the development of hypertension, type 2 diabetes and is an independent cardiovascular risk factor.

Important data confirming the predictive value of uric acid concentrations were obtained based from observations of the original Framingham heart study cohort. Thus, the study showed an increased risk of ischemic disease and myocardial infarction in patients with high levels of uric acid in serum. Krishnan et al. [40] confirmed the independent effect of uric acid on the risk of acute myocardial infarction. In the Rotterdam Study (n = 4385) in patients without a history of myocardial infarction or stroke at the beginning of the study, high uric acid concentrations were associated with a distant risk of myocardial infarction and stroke [41]. In a study by Ndrepepa et al. [42] the total of 5124 patients with acute coronary syndromes (1629 myocardial infarction with ST segment elevation, 1332 myocardial infarction without ST segment elevation and 2163 with unstable angina) were divided into quartiles according to uric acid concentration levels as follows: quartile 1: 1.3–5.3 mg/dL (77–315 μmol/L); quartile 2: 5.3–6.3 mg/dL (315–375 μmol/L); quartile 3: 6.3–7.5 mg/dL (375–446 μmol/L); quartile 4: 7.5–18.4 mg/dL (446–1094 μmol/L). After 1 year of observations there were 80 deaths in quartile 1, 77 deaths in quartile 2, 72 deaths in quartile 3, and 221 deaths in the quartile 4 of uric acid concentrations. The unadjusted mortality risk ratio was 3.05 (95% confidence interval 2.54–3.67, $p < 0.001$) for the quartile 4 vs. quartile 1 of these concentrations. It should be noted that after taking into account the traditional cardiovascular risk factors, renal functions and inflammation, the relationship between uric acid concentration and mortality remained significant.

91% of the physicians surveyed had seen an increase in the incidence of hyperuricemia in patients at risk of CVD over the prior 2 years. The trend observed by doctors is correct. In the coming years, due to the epidemic of obesity, metabolic disorders and an aging population, the incidence of hyperuricemia will continue to be observed. It is also related to rapid economic development and a changing lifestyle of societies which enjoy a higher social and economic status. Rising uric acid levels also result from the adoption of a Western

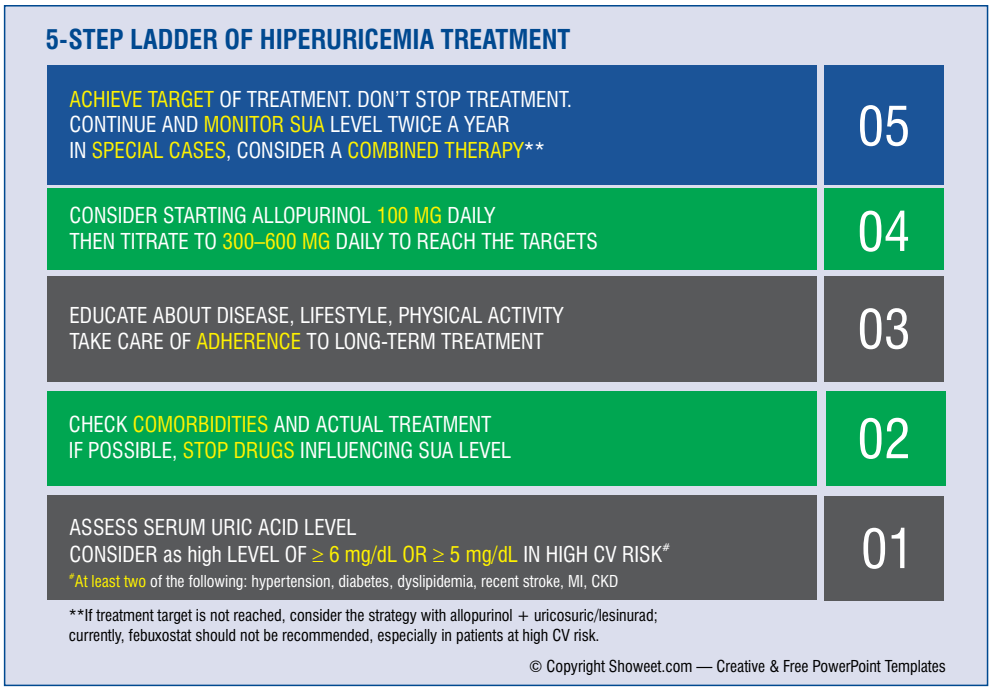


Figure 11. Management strategy for patients suffering from hyperuricemia [9]; CV — cardiovascular; CKD — chronic kidney disease; MI — myocardial infarction; SUA — serum uric acid.

lifestyle and changing economic status. Increased morbidity from hyperuricemia is also favoured by such commonly adopted habits as excessive consumption of products rich in purines (meat, offal), fructose, glucose and fructose syrup or alcohol.

Conclusions

The findings of the questionnaire in the present survey suggest that doctors often underestimate the problem of hyperuricemia in patients with high risk of CVD. An important step towards more effective therapy of hyperuricemia in routine clinical practice will be to raise the awareness of hyperuricemia and comorbidities both among doctors and patients and encourage their monitoring and treatment. Patients should be educated on the impact some foods on the development of uricemia: high consumption red meat and seafood, alcohol, fructose and sweetened beverages. Research has also confirmed that weight loss and regular physical activity should be highly recommended.

The dissemination of information about the new norm for uricemia in high-risk cardiovascular patients was largely supported by the introduction of an appropriate legend containing information about standards for different patient populations in the results of tests conducted by the majority of large medical laboratories. Introduction of explanatory information, as was previously the case in the lipid profile (different purpose of therapy depending on cardiovascular risk), will certainly help to raise awareness of hyperuricemia in cardiac patients and achieving therapeutic goals.

Allopurinol should be the first-line treatment of hyperuricemia. An initial dose of 100 mg of allopurinol daily should be considered. The dose should gradually be increased to 300–600 mg per day until reaching the goal conforming to the target uric acid concentration. In cases where a therapeutic goal cannot be achieved; the treatment should be changed to a more complex therapy.

The international consensus on the treatment of patients with hyperuricemia and high cardiovascular risk, suggests a simple 5-step scheme (Fig. 11 [9]). This scheme should considered a sort of road map for doctors in the treatment of patients with high cardiovascular risk with co-occurring hyperuricemia.

Conflict of interest: None declared

References

1. Freedman DS, Williamson DF, Gunter EW, et al. Relation of serum uric acid to mortality and ischemic heart disease. The NHANES I Epidemiologic Follow-up Study. Am J Epidemiol. 1995; 141(7): 637–644, indexed in Pubmed: 7702038.

2. Smith E, Hoy D, Cross M, et al. The global burden of gout: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis. 2014; 73(8): 1470–1476, doi: 10.1136/annrheumdis-2013-204647, indexed in Pubmed: 24590182.
3. Roddy E, Choi HK. Epidemiology of gout. Rheum Dis Clin North Am. 2014; 40(2): 155–175, doi: 10.1016/j.rdc.2014.01.001, indexed in Pubmed: 24703341.
4. Culleton B, Larson M, Kannel W, et al. Serum Uric Acid and Risk for Cardiovascular Disease and Death: The Framingham Heart Study. Ann Intern Med. 1999; 131(1): 7–13, doi: 10.7326/0003-4819-131-1-199907060-00003.
5. Ostrander LD, Lamphiear DE. Coronary risk factors in a community. Findings in Tecumseh, Michigan. Circulation. 1976; 53(1): 152–156, doi: 10.1161/01.cir.53.1.152, indexed in Pubmed: 1244237.
6. Tykarski A, Narkiewicz K, Gaciong Z, et al. 2015 guidelines for the management of hypertension. Recommendations of the Polish Society of Hypertension — short version. Kardiol Pol. 2015; 73(8): 676–700, doi: 10.5603/KP.2015.0157, indexed in Pubmed: 26304155.
7. 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.
8. Widecka K, Szymański FM, Filipiak KJ, et al. Stanowisko ekspertów dotyczące hiperurykemii i jej leczenia u pacjentów z wysokim ryzykiem sercowo-naczyniowym. Arterial Hypertens. 2017; 21(1): 1–9, doi: 10.5603/AH.2017.0001, indexed in Pubmed: 30394510.
9. Borghi C, Tykarski A, Widecka K, et al. Expert consensus for the diagnosis and treatment of patient with hyperuricemia and high cardiovascular risk. Cardiol J. 2018; 25(5): 545–563, doi: 10.5603/CJ.2018.0116, indexed in Pubmed: 30394510.
10. Bombelli M, Toso E, Peronio M, et al. The Pamela study: main findings and perspectives. Curr Hypertens Rep. 2013; 15(3): 238–243, doi: 10.1007/s11906-013-0348-1, indexed in Pubmed: 23609611.
11. Beck L. Clinical disorders of uric acid metabolism. Med Clin North Am. 1981; 65(2): 401–411, doi: 10.1016/s0025-7125(16)31531-0, indexed in Pubmed: 6894473.
12. Cannon PJ, Stason WB, Demartini FE, et al. Hyperuricemia in primary and renal hypertension. N Engl J Med. 1966; 275(9): 457–464, doi: 10.1056/NEJM196609012750902, indexed in Pubmed: 5917940.
13. Ford ES, Li C, Cook S, et al. Serum concentrations of uric acid and the metabolic syndrome among US children and adolescents. Circulation. 2007; 115(19): 2526–2532, doi: 10.1161/CIRCULATIONAHA.106.657627, indexed in Pubmed: 17470699.
14. Puig JG, Martínez MA. Hyperuricemia, gout and the metabolic syndrome. Curr Opin Rheumatol. 2008; 20(2): 187–191, doi: 10.1097/BOR.0b013e3282f4b1ed, indexed in Pubmed: 18349749.
15. Tuttle KR, Short RA, Johnson RJ. Sex differences in uric acid and risk factors for coronary artery disease. Am J Cardiol. 2001; 87(12): 1411–1414, indexed in Pubmed: 11397367.
16. Dehghan A, van Hoek M, Sijbrands EJG, et al. High serum uric acid as a novel risk factor for type 2 diabetes. Diabetes Care. 2008; 31(2): 361–362, doi: 10.2337/dc07-1276, indexed in Pubmed: 17977935.
17. Schretlen DJ, Inscore AB, Vannorsdall TD, et al. Serum uric acid and brain ischemia in normal elderly adults. Neurology. 2007; 69(14): 1418–1423, doi: 10.1212/01.wnl.0000277468.10236.f1, indexed in Pubmed: 17909154.
18. Lehto S, Niskanen L, Rönnemaa T, et al. Serum uric acid is a strong predictor of stroke in patients with non-insulin-dependent diabetes mellitus. Stroke. 1998; 29(3): 635–639, indexed in Pubmed: 9506605.
19. Yu KH, Kuo CF, Luo SF, et al. Risk of end-stage renal disease associated with gout: a nationwide population study. Arthritis Res Ther. 2012; 14(2): R83, doi: 10.1186/ar3806, indexed in Pubmed: 22513212.
20. Abbott RD, Brand FN, Kannel WB, et al. Gout and coronary heart disease: the Framingham Study. J Clin Epidemiol. 1988; 41(3): 237–242, indexed in Pubmed: 3339376.
21. De Vera MA, Rahman MM, Bhole V, et al. Independent impact of gout on the risk of acute myocardial infarction among elderly women: a population-based study. Ann Rheum Dis. 2010; 69(6): 1162–1164, doi: 10.1136/ard.2009.122770, indexed in Pubmed: 20124358.
22. Watanabe S, Kang DH, Feng L, et al. Uric acid, hominoid evolution, and the pathogenesis of salt-sensitivity. Hypertension. 2002; 40(3): 355–360, indexed in Pubmed: 12215479.
23. Lin C, Zhang Pu, Xue Y, et al. Link of renal microcirculatory dysfunction to increased coronary microcirculatory resistance in hypertensive patients. Cardiol J. 2017; 24(6): 623–632, doi: 10.5603/CJ.a2017.0074, indexed in Pubmed: 28653312.
24. Krishnan E, Kwoh CK, Schumacher HR, et al. Hyperuricemia and incidence of hypertension among men without metabolic syndrome. Hypertension. 2007; 49(2): 298–303, doi: 10.1161/01.HYP.0000254480.64564.b6, indexed in Pubmed: 17190877.
25. Mellen PB, Bleyer AJ, Erlinger TP, et al. Serum uric acid predicts incident hypertension in a biethnic cohort: the atherosclerosis risk in communities study. Hypertension. 2006; 48(6): 1037–1042, doi: 10.1161/01.HYP.0000249768.26560.66, indexed in Pubmed: 17060502.
26. Furukawa S, Fujita T, Shimabukuro M, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. J Clin Invest. 2004; 114(12): 1752–1761, doi: 10.1172/JCI21625, indexed in Pubmed: 15599400.
27. Fabbrini E, Serafini M, Colic Baric I, et al. Effect of plasma uric acid on antioxidant capacity, oxidative stress, and insulin sensitivity in obese subjects. Diabetes. 2014; 63(3): 976–981, doi: 10.2337/db13-1396, indexed in Pubmed: 24353177.
28. Prasad M, Matteson EL, Herrmann J, et al. Uric acid is associated with inflammation, coronary microvascular dysfunction, and adverse outcomes in postmenopausal women. Hypertension. 2017; 69(2): 236–242, doi: 10.1161/HYPERTENSIONAHA.116.08436, indexed in Pubmed: 27993955.
29. Farquharson C, Butler R, Hill A, et al. Allopurinol improves endothelial dysfunction in chronic heart failure. Circulation. 2002; 106(2): 221–226, doi: 10.1161/01.cir.0000022140.61460.1d, indexed in Pubmed: 12105162.
30. Bickel C, Rupprecht H, Blankenberg S, et al. Serum uric acid as an independent predictor of mortality in patients with angiographically proven coronary artery disease. Am J Cardiol. 2002; 89(1): 12–17, doi: 10.1016/s0002-9149(01)02155-5, indexed in Pubmed: 11779515.
31. Wong KYK, MacWalter RS, Fraser HW, et al. Urate predicts subsequent cardiac death in stroke survivors. Eur Heart J. 2002; 23(10): 788–793, doi: 10.1053/euhj.2001.2970, indexed in Pubmed: 12009718.

32. Hare J, Johnson R. Uric acid predicts clinical outcomes in heart failure. Circulation. 2003; 107(15): 1951–1953, doi: 10.1161/01.cir.0000066420.36123.35, indexed in Pubmed: 12707249.
33. Feig DI, Johnson RJ. Hyperuricemia in childhood primary hypertension. Hypertension. 2003; 42(3): 247–252, doi: 10.1161/01.HYP.0000085858.66548.59, indexed in Pubmed: 12900431.
34. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis. 2017; 76(1): 29–42, doi: 10.1136/annrheumdis-2016-209707, indexed in Pubmed: 27457514.
35. Stamp LK, O'Donnell JL, Zhang M, et al. Using allopurinol above the dose based on creatinine clearance is effective and safe in patients with chronic gout, including those with renal impairment. Arthritis Rheum. 2011; 63(2): 412–421, doi: 10.1002/art.30119, indexed in Pubmed: 21279998.
36. Rees F, Jenkins W, Doherty M. Patients with gout adhere to curative treatment if informed appropriately: proof-of-concept observational study. Ann Rheum Dis. 2013; 72(6): 826–830, doi: 10.1136/annrheumdis-2012-201676, indexed in Pubmed: 22679303.
37. Ramasamy SN, Korb-Wells CS, Kannangara DRW, et al. Allopurinol hypersensitivity: a systematic review of all published cases, 1950-2012. Drug Saf. 2013; 36(10): 953–980, doi: 10.1007/s40264-013-0084-0, indexed in Pubmed: 23873481.
38. Hershfield MS, Callaghan JT, Tassaneeyakul W, et al. Clinical pharmacogenetics implementation consortium guidelines for human leukocyte antigen-B genotype and allopurinol dosing. Clin Pharmacol Ther. 2013; 93(2): 153–158, doi: 10.1038/clpt.2012.209, indexed in Pubmed: 23232549.
39. Hande KR, Noone RM, Stone WJ. Severe allopurinol toxicity. Description and guidelines for prevention in patients with renal insufficiency. Am J Med. 1984; 76(1): 47–56, indexed in Pubmed: 6691361.
40. Krishnan E, Pandya BJ, Lingala B, et al. Hyperuricemia and untreated gout are poor prognostic markers among those with a recent acute myocardial infarction. Arthritis Res Ther. 2012; 14(1): R10, doi: 10.1186/ar3684, indexed in Pubmed: 22251426.
41. Bos MJ, Koudstaal PJ, Hofman A, et al. Uric acid is a risk factor for myocardial infarction and stroke: the Rotterdam study. Stroke. 2006; 37(6): 1503–1507, doi: 10.1161/01.STR.0000221716.55088.d4, indexed in Pubmed: 16675740.
42. Ndrepepa G, Braun S, Haase HU, et al. Prognostic value of uric acid in patients with acute coronary syndromes. Am J Cardiol. 2012; 109(9): 1260–1265, doi: 10.1016/j.amjcard.2011.12.018, indexed in Pubmed: 22325088.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2019, Vol. 26, No. 3, 253–259
DOI: 10.5603/CJ.a2017.0085

ISSN 1897–5593

Simple platelet markers: Mean platelet volume and congestive heart failure coexistent with periodontal disease. Pilot studies

Maciej R. Czerniuk[1], Zbigniew Bartoszewicz[2], Iwona Dudzik-Niewiadomska[3], Tomasz Pilecki[4], Renata Górska[1], Krzysztof J. Filipiak[5]

[1]Department of Oral Medicine and Periodontal Disease, Medical University of Warsaw, Poland
[2]Endocrinology Laboratory, Department of Internal Diseases and Endocrinology, Medical University of Warsaw, Poland
[3]Department of Internal Medicine and Cardiology with the Center of Management of Thromboembolic Disease, Medical University of Warsaw, Poland
[4]Department of Immunology, Transplantology and Internal Diseases, Medical University of Warsaw, Poland
[5]First Chair and Department of Cardiology, Medical University of Warsaw, Poland

Abstract

Background: *Conducted pilot study concerning mean platelet volume (MPV) parameter among patients suffering from congestive heart failure and periodontal disease.*

Methods: *Examination of dynamic changes of platelet and periodontal markers in group of 50 patients before and an average of 6 months subsequent to professional periodontal treatment.*

Results: *Both platelet and periodontal parameters decreased after periodontal treatment, what is more, the decrease of MPV value due to periodontal disease/mm improvement was shown to be statistically significant ($p = 0.05$).*

Conclusions: *Improvement of periodontal status may influence decrease of MPV value and increase of congestive heart failure treatment efficacy and effect patient comfort. It is a new, not frequently used pattern of chronic disease treatment optimalization.* (Cardiol J 2019; 26, 3: 253–259)

Key words: mean platelet volume, platelets, congestive heart failure, periodontal disease, inflammatory response

Introduction

Numerous papers have documented prognostic value of mean platelet volume (MPV) in cardiovascular pathology [1–7], including published research on correlation between MPV and periodontal disease (PDe) in coronary patients [8]. A thorough search on correlation between MPV and exacerbated heart failure revealed only 2 publications in this area [9, 10]. MPV has not yet been studied in patients with congestive heart failure (CHF), including those with coexistent PDe.

The aim of this study was to assess the dynamics of changes of MPV in CHF patients with diagnosis of PDe. The authors made an attempt to design a clinical pilot study that will verify the following hypotheses: (A) Is MPV an appropriate marker of periodontal parameters change the dynamics? Analyzed BEFORE periodontal intervention; (B) Is MPV an appropriate marker of periodontal parameters change the dynamics? Whether a clinical decrease of some periodontal parameters (CAL/mm, PI, and PD/mm) may result in MPV? Analyzed AFTER periodontal intervention.

Address for correspondence: Maciej R. Czerniuk, DMD, MSc, PhD, Department of Oral Medicine and Periodontal Disease, Medical University of Warsaw, ul. Miodowa 18, 00–246 Warszawa, Poland, tel/fax: +48 22 502 20 99, e-mail: mczerniuk@o2.pl

Received: 12.03.2017 Accepted: 8.07.2017

There is a correlation between the decrease of inflammatory process presented by plasma concentration of the following parameters: tumor necrosis factor-alpha (TNF-α), N-terminal pro-B--type natriuretic peptide (NT-proBNP), C-reactive protein (CRP) and improvement of CHF patient status, including better prognosis [11–17]. Numerous researchers have shown that elimination of inflammation in PDe results in a significant reduction of chronic inflammatory process and may lead to additional benefits including improvement of vascular endothelium [18–22].

Methods

A pilot group of 50 patients aged 36–92 years including 15 women and 35 men (average age 64 years), admitted to the Department of Cardiology of the Medical University of Warsaw with a diagnosis of CHF. Those patients were also diagnosed with PDe that required periodontal treatment.

This pilot study was conducted in accordance with 1964 Declaration of Helsinki and was approved by the Ethics Committee of the Medical University of Warsaw (KB/54/A/2013). All patients have read and signed informed consent forms.

After obtaining their consent, all patients enrolled in the study underwent the following diagnostic assessment:

— Biochemical blood tests on admission day and on average 6 months after periodontal treatment: blood count, iodine and potassium concentration, lipid profile, CRP and TNF-α levels, NT-proBNP and fibrinogen concentration.
— Examination of oral hygiene: approximal plaque index (API) inspected on approximal spaces of the first and third quadrants from the oral aspect and of the second and fourth quadrant from the buccal aspect and bleeding on probing (BOP) probed on 4 surfaces of each tooth (mesial, distal, platal/lingual, buccal) during initial standard periodontal therapeutic assessment (scaling, root-planing, sanitation of oral cavity as well as treatment of oral mucosa pathologies). Number and status of teeth, number and status of impacted teeth, gangrenous roots, currently used prosthetic restorations, as well as surgical and prosthetic treatment indications were assessed [23].
— Periodontal examination of clinical attachment loss (CAL/mm) and probing depth (PD/ /mm) in oral cavity with the use of periodontal probe WHO 621 in 6 measurement points around each tooth (mesial buccal, distal buccal, middle of buccal surface, mesial palatal/ /lingual, distal palatal/lingual, middle of palatal/ /lingual surface) and dental orthopantomogram radiograph (OPG) in CHF patients following conventional periodontal therapy assessment: removal of bacterial biofilm from tooth surface (scaling) and smoothing (root-planing) to prevent re-accumulation of bacteria, sanitation of oral cavity as well as periodontal reassessment on average 6 months (3–9 months) after treatment.

Study patients were treated in accordance with current CHF treatment guidelines, without need of modifications of pharmacological therapy, and their clinical status was stable throughout the study. Based upon results of initial examination, pilot specialist periodontal treatment was commenced in patients with coexistent CHF and PDe in a reference clinical center.

This paper presents statistical analysis of a relationship between dynamic MPV changes in relation to PDe and oral hygiene status.

Blood samples were collected from all 50 study patients on admission day (examination-1), and then 3–9 months (on average 6 months) after periodontal treatment was completed (examination-2). Blood samples were centrifuged and serum was tested for blood count including diagnostic parameters of platelet count and volume, which were the subject of the study and were further analyzed. A standard blood work-up kit (R&D Systems, Inc., Minneapolis, USA) was used in accordance with manufacturer instructions in the Central Laboratory Department of Hematology, Oncology and Internal Diseases of the Medical University of Warsaw.

The status of CHF was examined before and after periodontal therapy by two experienced cardiologists blinded to the periodontal therapy outcomes and indices.

The periodontal study was conducted at the Department of Oral Medicine and Periodontal Disease of the Medical University of Warsaw, with the use of periodontal probe WHO 621. During the examination antibiotics were administered prophylactically. All patients received Augmentin® (amoxicillinum, acidum clavulanicum) 1.0 g (1 d/every 12 h), and for those with penicillin intolerance Dalacin C® (clindamycinum) 0.3 g (1 d/every 8 h) was prescribed. For periodontal examination, patients received single, prophylactic dose (Augmentin® — 2 g; Dalacin C® — 0.6 g) according to guidelines concerning examination of such patients issued by the Polish Society of Periodontology. API/% and

BOP/% were assessed, scaling, root-planing and orthopantomogram radiograph were performed. Detailed instructions for daily oral hygiene were provided. The above described activities were termed as periodontal intervention.

Following periodontal assessment, also with antibiotic administration, examination of clinical attachment loss (CAL/mm) as well as probing depth (PD/mm — probing depth), degree of furcation involvement, and 3-stage Hall's tooth mobility scale, where stage 1 represents lingual or buccal/palatal mobility, no more than 1 mm; stage 2 — lingual or buccal/palatal mobility between 1 and 2 mm; stage 3 — vertical and horizontal mobility that interrupts proper articulation was performed [24, 25]. Each tooth was examined and mean parameters values were calculated for individual patients.

All patients received standard periodontal therapy: scaling and root planing with sanitation of oral cavity including extraction of gangrenous roots under antibiotic prophylaxis regimen. For periodontal treatment full antibiotic therapy was administered (Augmentin® — 14 doses/7 days; Dalacin C® — 15 doses/5 days) according to the same guidelines. Recommended oral hygiene at home includedbrushing teeth twice a day, in the morning and in the evening, as well as antiseptic mouth rinsing. Patients were encouraged to stay in touch with researchers in case of any doubts regarding their oral cavity status and hygiene routine.

Statistical analysis

Obtained results underwent statistical analysis in order to assess the influence of treatment on MPV with reference to selected periodontal parameters. Following statistical tests were performed to verify stated hypotheses.

Statistical analysis was performed with Mann-Whitney test for dependent groups to verify differences between observations and Wilcoxon test to assess differences between selected study groups (H.B. Mann, D.R. Whitney [1947] "On a test of whether one of two random variables is stochastically larger than the other". Annals of Mathematical Statistics, 18, 50–60).

Results

All patients were diagnosed with severe chronic generalized periodontitis (CAL > 5 mm and PD > 7 mm) according to American Academy of Periodontology 2000 classification [26].

Pilot study of 50 CHF patients with coexistent PDe on admission day has shown that mean API and BOP values were very high, respectively: API: 74% in women and 81% in men; BOP: 100% in women and 90% in men. Mean PD/mm values both for women and men were 5.7 mm. Mean CAL/mm values were 5.2 mm for women and 5.3 mm for men. Among women the average number of teeth in the upper arch was 12 and in lower arch — 11. In the group of men the average number of teeth in maxilla was 11 and in mandible — 10.

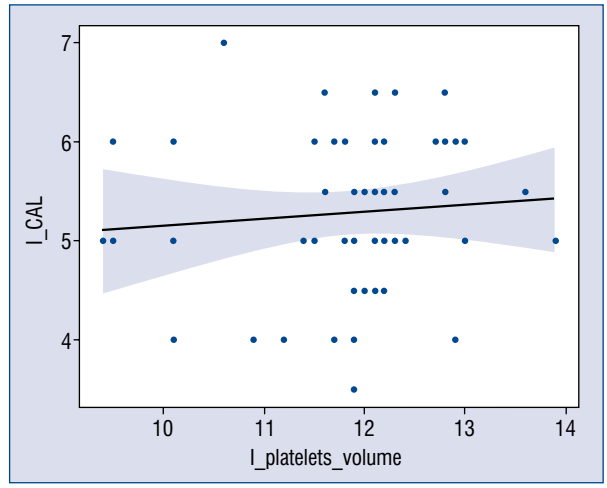


Figure 1. The values of mean platelet volume (MPV) vs. clinical attachment loss (CAL/mm) before periodontal intervention (MPV ± SD 0.91; CAL/mm ± SD 0.39); SD — standard deviation.

A. Study results show that as far as first hypothesis is concerned, patients before periodontal intervention, high values of MPV parameter have shown correlation with high values of the following parameters: CAL/mm, plaque index (PI) and PD/mm obtained during the first assessment (examination-1).

A.I. MPV vs. CAL/mm (examination-1)

Statistical analysis has shown that higher MPV value is associated with higher CAL/mm value. Presented model did not show statistically significant relationship. The numerical relationship was positive. The following results were obtained: statistical value W: 0.3694; p: 0.5462 (Fig. 1).

A.II. MPV vs. PD/mm (examination-1)

Statistical analysis has shown that PD/mm values are subtle. In addition: although there is no clear trend in relationship between these parameters a positive trend is present, the highest MPV values are for patients with PD/mm 7 mm (the highest) value obtained (Fig. 2).

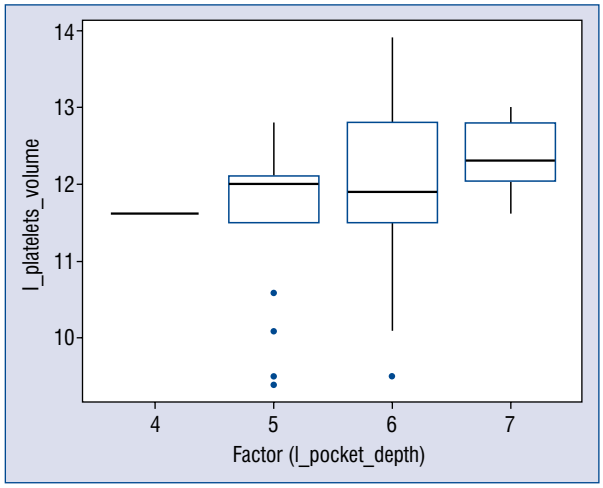


Figure 2. The values of mean platelet volume (MPV) vs. probing depth (PD/mm) before periodontal intervention (MPV ± SD 0.91; PD/mm ± SD 0.60); SD — standard deviation.

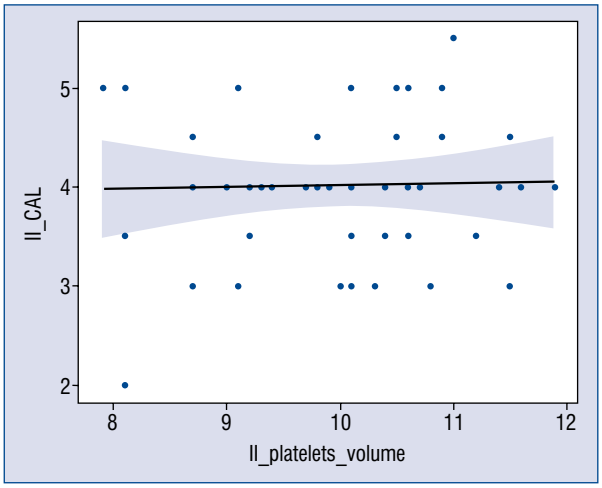


Figure 3. The values of mean platelet volume (MPV) vs. clinical attachment loss (CAL/mm) after periodontal intervention (MPV ± SD 0.98; CAL/mm ± SD 0.80); SD — standard deviation.

B. Study results show that as far as second hypothesis is concerned in patients after periodontal intervention high values of MPV parameter have shown correlation with high values of the following parameters: CAL/mm, PI and PD/mm, obtained during the second assessment (examination-2).

B.I. MPV vs. CAL/mm (examination-2)

Statistical analysis has shown that there is virtually no relationship between CAL/mm and MPV value after periodontal intervention. The presented model did not show any statistically significant relationship. The following results were obtained: statistical value W: 0.03385; p: 0.8548 (Fig. 3).

B.II. MPV vs. PD/mm (examination-2)

Statistical analysis has shown that PD/mm values are subtle. In addition: there is a positive trend (higher PD/mm is associated with higher MPV value), and the highest MPV values are for PD/mm 5 mm (the highest) (Fig. 4).

B.III. MPV change vs. CAL/mm change

Assessment whether CAL/mm parameters change observed before and after periodontal intervention is associated with MPV. For CAL/mm change at 1.5 mm MPV is higher and characterized with grater variability. Following results were obtained: statistical value W: 306.5; p: 0.3076 (Fig. 5).

Results show that this difference is not significant. It should be noted that for greater CAL/mm change MPV distribution towards higher values

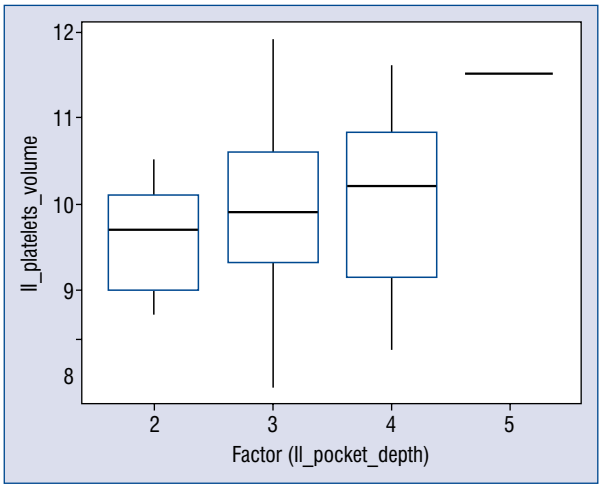


Figure 4. The values of mean platelet volume (MPV) vs. probing depth (PD/mm) after periodontal intervention (MPV ± SD 0.98; PD/mm ± SD 0.74); SD — standard deviation.

was observed. It is therefore justified that the change of CAL value has influenced an increased MPV distribution.

B.IV. MPV change vs. PD/mm change

Correlation between PD/mm parameter change before and after periodontal intervention and MPV was tested. PD/mm value changes are subtle, and importantly values 1 and 4 are scarce and will not be further analyzed. The following results were obtained: statistical value W: 0.3694; p: 0.5462 (Fig. 6).

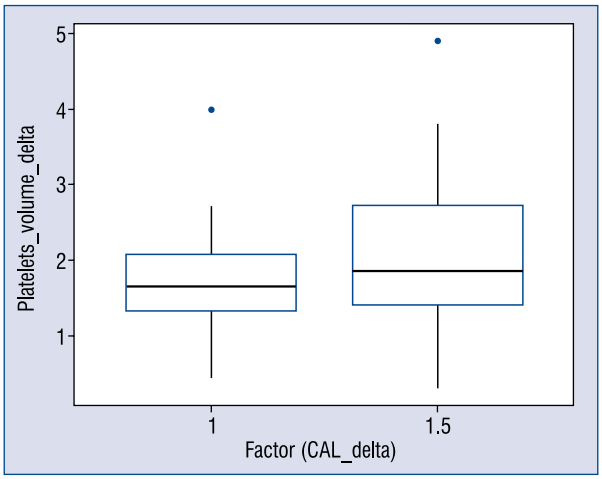


Figure 5. The values of Δ mean platelet volume (ΔMPV) vs. Δ clinical attachment loss (ΔCAL/mm) during experiment observation (ΔMPV ± SD 14.58; ΔCAL/mm ± SD 53.51); SD — standard deviation.

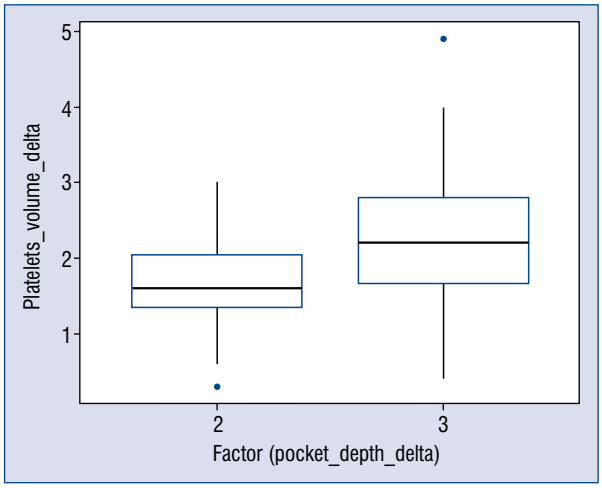


Figure 6. The values of Δ mean platelet volume (ΔMPV) change vs. Δ probing depth (ΔPD/mm) during experiment observation (ΔMPV ± SD 14.58; ΔPD/mm ± SD 7.42); SD — standard deviation.

There is positive relationship between PD/mm change and MPV change. PD/mm value change after value 1 and 4 were deleted is shown on the box plot. For larger PD/mm value changes increased MPV value change occurred. The test has shown a statistically significant difference of 5%.

Periodontal assessment was performed after PDe treatment (the so called periodontal intervention) was completed. The number of patients remained constant during whole study. API values decreased to 28% among women and 30% among men. BOP also significantly decreased to 36% in women group and 41% in men. Both gender groups resulted in CAL/mm value 4.0 mm and PD/mm 3.3 mm. After oral cavity sanitation, the average number of remaining teeth in women was 10 for maxilla and 9 for mandible, among men 9 and 8, respectively.

Discussion

Fifty patients ≤ 92 years (age: 36–92; mean age: 64 years) with CHF and PD diagnosis were enrolled into this pilot study. It was found that MPV measurements on admission day as well as clinical periodontal assessment (examination-1) are different from results obtained after standard periodontal treatment (examination-2). S A statistically significant decrease of PD value over a of mean of a 6 month observation period (3–9 months) was noted.

In addition to a decrease of BOP and PI values in all study patients, mean increase in CAL/mm values of 1.5 mm was noted showing advantage of restoration over destruction processes within alveolar bone of maxilla and mandible. It should be noted that no highly specialized Guided Bone Regeneration (GBR) and/or Guided Tissue Regeneration (GTR) procedures were performed, justifying potential likelihood of including this type of therapy into CHF treatment standard.

Significant correlation between a decrease of clinical PD/mm values and increased MPV value change and decrease should be noted. Statistical analysis has shown that the decrease in PD/mm value which is much easier to obtain by basic dental care, has resulted in better effects in study group patients than CAL/mm decrease that can be mainly obtained only by highly specialized, expensive periodontal procedures.

In this pilot study group during a 6-month observation no signs of heart failure exacerbation were observed, and pharmacological therapy that was in accordance with current CHF treatment guidelines, required no modifications of each medicament dose and type (Tables 1 and 2).

Authors of this paper have focused their research on the relationship between PDe and heart disease. Current studies and observations as well as published results referred patients who were hospitalized due to acute coronary syndromes [11–15, 27]. Results of this pilot study have shown that proper and complex oral hygiene may influence blood serum levels of CRP, NT-proBNP and TNF-α which are all markers of inflammation [18, 28–32]. Individualized patterns of CHF patient

Table 1. Clinical characteristics of study population.

Gender	Age (av.)	NYHA class/ /mean EF	Myocardial infarction	Hypertension	CAD	Dislipidemia	Diabetes
Women (n = 15)	64	II–III/38 ± 9%	8 (53%)	13 (87%)	8 (53%)	7 (47%)	2
Men (n = 35)	63	II–IV/38 ± 11%	21 (60%)	32 (91%)	27 (77%)	18 (51%)	4

CAD — coronary artery disease; EF — ejection fraction; NYHA — New York Heart Association

Table 2. Pharmacological treatment.

Gender	ACEI, sartans	Beta-antagonists	Aldosterone antagonists	ICD/CRT	Statins
Women (n = 15)	100%	100%	93%	13%	80%
Men (n = 35)	100%	100%	94%	11%	80%

ACEI — angiotensyn convering enzyme inhibitors; CRT — cardiac resynchronization therapy; ICD — implantable cardioverter-defibrillator

care, seems obvious and also results in prognosis improvement, increased treatment efficacy and patient comfort [33–35].

Limitations of the study

The main limitation of the study was the small group of patients included. Secondly, was the absence of a control group. However, it is very difficult to create such a control group for two reasons. One — patients could not be found with CHF and a healthy peridontium in among the general population. Secondly, it would be ethically controversial to treat PDe only in a subgroup of patients. Therefore, after taking into consideration the Ethics Committee opinion on this study, we have decided to perform it in this form and call it a pilot study.

Conclusions

Results of this pilot study should be verified in a larger patient cohort. The results of this study show that:

— decreases of PD/mm results in significantly better results of MPV (p = 0.05) than reduction of CAL/mm value;
— specialist periodontal treatment may result in decreased MPV value in patients with coexistent CHF and PDe;
— examed platelet parameter may have prognostic value in CHF, periodontal treatment of CHF and PDe patients might improve their long-term prognosis, but it ought to be verified in a prospective study;
— the above conclusions are, to the authors' best knowledge, first published conclusions in this area and require verification on a larger patient population.

Funding: This research study was funded by the National Science Center (N N403 218139).

Conflict of interest: None declared

References

1. Karataş MB, Çanga Y, İpek G, et al. Association of admission serum laboratory parameters with new-onset atrial fibrillation after a primary percutaneous coronary intervention. Coron Artery Dis. 2016; 27(2): 128–134, doi: 10.1097/MCA.0000000000000333, indexed in Pubmed: 26693808.
2. Bolat I, Akgul O, Cakmak HA, et al. The prognostic value of admission mean platelet volume to platelet count ratio in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Kardiol Pol. 2016; 74(4): 346–355, doi:10.5603/KP.a2015.0179, indexed in Pubmed: 26365942.
3. Sansanayudh N, Numthavaj P, Muntham D, et al. Prognostic effect of mean platelet volume in patients with coronary artery disease. A systematic review and meta-analysis. Thromb Haemost. 2015; 114(6): 1299–1309, doi: 10.1160/TH15-04-0280, indexed in Pubmed: 26245769.
4. Yılmaz F, Köklü E, Kizilirmak Yilmaz F, et al. Evaluation of mean platelet volume and platelet distribution width in patients with asymptomatic intermediate carotid artery plaque. Kardiol Pol. 2017; 75(1): 35–41, doi: 10.5603/KP.a2016.0129, indexed in Pubmed: 27714714.
5. İleri M, Kanat S, Gürsoy HT, et al. Increased mean platelet volume in rheumatic mitral stenosis: assessment of clinical and echocardiographic determinants. Kardiol Pol. 2015; 73(1): 46–53, doi: 10.5603/KP.a2014.0115, indexed in Pubmed: 24846369.

6. Łysek R, Szafraniec K, Polak M, et al. Relationship between past myocardial infarction, periodontal disease and Porphyromonas gingivalis serum antibodies: A case-control study. Cardiol J. 2018; 25(3): 386–392, doi: 10.5603/cj.a2017.0015.
7. Wożakowska-Kapłon B, Włosowicz M, Gorczyca-Michta I, et al. Oral health status and the occurrence and clinical course of myocardial infarction in hospital phase: a case-control study. Cardiol J. 2013; 20(4): 370–377, doi: 10.5603/CJ.2013.0095, indexed in Pubmed: 23913455.
8. Androsz-Kowalska O, Jankowski K, Rymarczyk Z, et al. Correlation between clinical parameters of periodontal disease and mean platelet volume in patients with coronary artery disease: a pilot study. Kardiol Pol. 2013; 71(6): 600–605, doi: 10.5603/KP.2013.0124, indexed in Pubmed: 23797433.
9. Kandis H, Ozhan H, Ordu S, et al. The prognostic value of mean platelet volume in decompensated heart failure. Emerg Med J. 2011; 28(7): 575–578, doi: 10.1136/emj.2009.088401, indexed in Pubmed: 20660896.
10. Budak YU, Huysal K, Demirci H. Correlation between mean platelet volume and B-type natriuretic peptide concentration in emergency patients with heart failure. Biochem Med (Zagreb). 2015; 25(1): 97–102, doi: 10.11613/BM.2015.012, indexed in Pubmed: 25672473.
11. Czerniuk M, Filipiak KJ, Górska R, et al. [Periodontal state and cardiovascular diseases]. Pol Arch Med Wewn. 1999; 101(5): 433–436, indexed in Pubmed: 10740424.
12. Czerniuk MR, Górska R, Filipiak KJ, et al. Inflammatory response to acute coronary syndrome in patients with coexistent periodontal disease. J Periodontol. 2004; 75(7): 1020–1026, doi: 10.1902/jop.2004.75.7.1020, indexed in Pubmed: 15341362.
13. Czerniuk MR, Górska R, Filipiak KJ, et al. C-reactive protein in patients with coexistent periodontal disease and acute coronary syndromes. J Clin Periodontol. 2006; 33(6): 415–420, doi: 10.1111/j.1600-051X.2006.00931.x, indexed in Pubmed: 16677330.
14. Zaremba M, Górska R, Suwalski P, et al. Periodontitis as a risk factor of coronary heart diseases? Adv Med Sci. 2006; 51 Suppl 1: 34–39, indexed in Pubmed: 17458056.
15. Czerniuk MR, Gorska R, Filipiak KJ, et al. The influence of periodontal diseases on intensivity and dynamice of inflammation response in patients with acute coronary syndromes. Dent Med Probl. 2002; 39(1): 31–37.
16. Czerniuk MR, Eickholz P, Grötz KA. Oral cavity infections: why should cardiologists care about them? Kardiol Pol. 2015; 73(10): 901–908, doi:10.5603/KP.2015.0188, indexed in Pubmed: 26521837.
17. Czerniuk M, Bartoszewicz Z, Filipiak K, et al. Osoczowe stężenia NT-proBNP u pacjentów z niewydolnością serca i współistniejącą chorobą przyzębia: badania pilotażowe. Kardiol Pol. 2017; 75(2): 135–142, doi: 10.5603/kp.a2016.0148.
18. Saffi MA, Furtado MV, Polanczyk CA, et al. Relationship between vascular endothelium and periodontal disease in atherosclerotic lesions: Review article. World J Cardiol. 2015; 7(1): 26–30, doi: 10.4330/wjc.v7.i1.26, indexed in Pubmed: 25632316.
19. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003; 107(3): 499–511, indexed in Pubmed: 12551878.
20. D'Aiuto F, Parkar M, Andreou G, et al. Periodontitis and systemic inflammation: control of the local infection is associated with a reduction in serum inflammatory markers. J Dent Res. 2004; 83(2): 156–160, doi: 10.1177/154405910408300214, indexed in Pubmed: 14742655.
21. Higashi Y, Noma K, Yoshizumi M, et al. Endothelial function and oxidative stress in cardiovascular diseases. Circ J. 2009; 73(3): 411–418, indexed in Pubmed: 19194043.
22. de Araújo Júnior RF, Souza TO, de Medeiros CA, et al. Carvedilol decrease IL-1β and TNF-α, inhibits MMP-2, MMP-9, COX-2, and RANKL expression, and up-regulates OPG in a rat model of periodontitis. PLoS One. 2013; 8(7): e66391, doi: 10.1371/journal.pone.0066391, indexed in Pubmed:23843954.
23. Lange DE, Plagman HC, Eenboom A, et al. Klinische Bewertungsverfaren zur Obiekitiverung der Mundhygiene. Dtsch Zahnarztl Z. 1977; 32: 44–47.
24. Hall WB. Critical Decisions in Periodontology. Fourth Edition, BC Decker Inc, Hamilton, London 2003: 30–31.
25. Hall WB. Clinical Practice. In: Steele PF (ed). Dimensions of Dental Hygiene. Third Edition. Lea&Febiger, Philiadelphia 1982: 153.
26. Dibart S, Dietrich T. Practical periodontal diagnostic and treatment planning. Chapter 2. Wiley-Blackwell, Iowa 2010.
27. Kaisare S, Rao J, Dubashi N. Periodontal disease as a risk factor for acute myocardial infarction. A case-control study in Goans highlighting a review of the literature. Br Dent J. 2007; 203(3): 144–145, doi: 10.1038/bdj.2007.690, indexed in Pubmed: 17694042.
28. Ximénez-Fyvie LA, Haffajee AD, Socransky SS. Comparison of the microbiota of supra- and subgingival plaque in health and periodontitis. J Clin Periodontol. 2000; 27(9): 648–657, indexed in Pubmed: 10983598.
29. Dorn JM, Genco RJ, Grossi SG, et al. Periodontal disease and recurrent cardiovascular events in survivors of myocardial infarction (MI): the Western New York Acute MI Study. J Periodontol. 2010; 81(4): 502–511, doi: 10.1902/jop.2009.090499, indexed in Pubmed: 20367093.
30. Blair FM, Chapple ILC. Prescribing for periodontal disease. Prim Dent J. 2014; 3(4): 38–43, doi: 10.1308/205016814813877234, indexed in Pubmed:25668374.
31. Chukkapalli SS, Velsko IM, Rivera-Kweh MF, et al. Polymicrobial oral infection with four periodontal bacteria orchestrates a distinct inflammatory response and atherosclerosis in apoe null mice. PLoS One. 2015; 10(11): e0143291, doi: 10.1371/journal.pone.0143291, indexed in Pubmed:26619277.
32. Beck JD, Eke P, Heiss G, et al. Periodontal disease and coronary heart disease: a reappraisal of the exposure. Circulation. 2005; 112(1): 19–24, doi:10.1161/CIRCULATIONAHA.104.511998, indexed in Pubmed: 15983248.
33. Tonetti MS, Eickholz P, Loos BG, et al. Principles in prevention of periodontal diseases: Consensus report of group 1 of the 11(th) European Workshop on Periodontology on effective prevention of periodontal and peri-implant diseases. J Clin Periodontol. 2015; 42(Suppl 16): 5–11.
34. Seymour RA. Is gum disease killing your patient? Br Dent J. 2009; 206(10): 551–552, doi: 10.1038/sj.bdj.2009.472, indexed in Pubmed: 19461642.
35. Meyer-Bäumer A, Eick S, Mertens C, et al. Periodontal pathogens and associated factors in aggressive periodontitis: results 5-17 years after active periodontal therapy. J Clin Periodontol. 2014; 41(7): 662–672, doi: 10.1111/jcpe.12255, indexed in Pubmed: 24708362.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2019, Vol. 26, No. 3, 260–264
DOI: 10.5603/CJ.a2017.0154

ISSN 1897–5593

OCULUS study: Virtual reality-based education in daily clinical practice

Paweł Balsam, Sonia Borodzicz, Karolina Malesa, Dominika Puchta, Agata Tymińska, Krzysztof Ozierański, Łukasz Kołtowski, Michał Peller, Marcin Grabowski, Krzysztof J. Filipiak, Grzegorz Opolski

First Chair and Department of Cardiology, Medical University of Warsaw, Poland

Abstract

Background: *Atrial fibrillation (AF) is associated with high risk of stroke and other thromboembolic complications. The OCULUS study aimed to evaluate the effectiveness of the three-dimensional (3D) movie in teaching patients about the consequences of AF and pharmacological stroke prevention.*

Methods: *The study was based on a questionnaire and included 100 consecutive patients (38% women, 62% with AF history). Using the oculus glasses and a smartphone, a 3D movie describing the risk of stroke in AF was shown. Similar questions were asked immediately after, 1 week and 1 year after the projection.*

Results: *Before the projection 22/100 (22.0%) declared stroke a consequence of AF, while immediately after 83/100 (83.0%) ($p < 0.0001$) patients declared this consequence. Seven days after, stroke as AF consequence was chosen by 74/94 (78.7%) vs. 22/94 (23.4%) when compared to the baseline knowledge; $p < 0.0001$, a similar trend was also observed in 1-year follow-up (64/90 [71.1%] vs. 21/90 [23.3%]; $p < 0.0001$). Before the projection 88.3% (83/94) patients responded, that drugs may reduce the risk of stroke, and after 1 week the number of patients increased to (94/94 [100%]; $p = 0.001$). After 1 year 87/90 (96.7%) answered that drugs may diminish the risk of stroke ($p = 0.02$ in comparison to the baseline survey 78/90 [86.7%]). Use of oral anticoagulation to reduce the risk of stroke was initially chosen by 66/94 (70.2%), by 90/94 (95.7%; $p < 0.0001$) 7 days after and by 83/90 (92.2%; $p < 0.0001$) 1 year after.*

Conclusions: *3D movie is an effective tool in transferring knowledge about the consequences of AF and the pivotal role of oral anticoagulation in stroke prevention.* (Cardiol J 2019; 26, 3: 260–264)

Trial registration: *ClinicalTrials.gov, NCT03104231. Registered on 28 March 2017.*

Key words: atrial fibrillation, stroke, education, virtual reality, three-dimensional movie

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in adults, with a significant risk of morbidity and mortality, mainly due to increased risk of stroke and systemic embolism. AF is independently correlated with a 2-fold increased risk of all-cause mortality in women and a 1.5-fold in men [1]. The prevalence of AF is approximately 3% in adults aged 20 years or older and increases with age and presence of hypertension, heart failure, coronary artery disease, valvular heart disease, obesity, diabetes mellitus and chronic kidney disease [1].

Nowadays, identification and prevention of AF risk factors, as well as prevention of thromboembolic events constitute the fundamentals of comprehensive care in AF [1]. Most thromboembolic events may be prevented by oral anticoagulation (OAC), which is suggested to be prescribed to the majority of patients with AF basing on CHA_2DS_2-

Address for correspondence: Sonia Borodzicz, 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 5991958, fax: +48 22 5991957, e-mail: sonia.borodzicz@onet.pl

Received: 13.11.2017 Accepted: 14.12.2017

-VASc score [1]. The current guidelines for the management of AF patients highlight the important role of education in treatment [1, 2]. Therefore, one of the most important factors leading to the achievement of clinical benefit from OAC therapy is an effective cooperation of patients with physicians. Thus, physicians should introduce novel e-solutions to the communication process with patients to increase compliance [3]. Three-dimensional (3D) and virtual reality (VR) models are helpful in every day medical practice [4, 5] but could be also used as educational tools.

The OCULUS study aimed to evaluate whether the VR-3D movie-based education is effective in improving patient knowledge about the consequences of AF and pharmacological possibilities in reducing the risk of stroke. An additional objective of the analysis was to assess factors contributing to OAC usage in the prevention of stroke.

Methods

Study design and population

The OCULUS was a prospective, single center study. The study included hospitalized patients, who were over 18 years old. Only patients with previously diagnosed dementia were excluded from the study. The recruitment phase of the OCULUS study lasted from April 2016 to August 2016. Local ethics committees approved the study. All patients were provided with detailed information and signed informed written consent.

The study was based on a questionnaire (**Suppl. material**), designed by the authors of the study. The questionnaire was composed of questions about sex, age, education, current job, AF history, as well as knowledge about consequences of AF and the importance of OAC therapy in stroke prevention. Consequently, the brief VR-3D movie which is available on Google Play and Appstore was shown using oculus glasses and a smartphone (a version prepared for men is available at the address: https://www.youtube.com/watch?v=5WFxq_m88ds, whereas a version for women is available at the address: https://www.youtube.com/watch?v=S8i7LxBBv0g). The Pfizer Company allowed the authors of the study to use the movie. The movie's plot to inform patients about the risk of stroke and possibilities of its prevention by using OAC. Subsequently, patients were asked a few questions, including what the movie was about, whether AF can affect a patient's life in a negative way, whether it is possible to reduce the risk of stroke and if or by what types of drugs also reduce the risk of stroke. Similar questions were asked to the patients immediately after the movie, 1 week and 1 year later (via telephone follow-up).

Statistical analysis

Categorical variables are presented as a percentage of total for the group. Comparisons of results before and after watching the movie was made using the McNemar test. Bonferroni correction was used for multiple comparisons. Logistic regression was performed to assess factors contributing to OAC usage as a prevention of stroke. A value of $p < 0.05$ was considered significant. The calculations were performed using SAS software 9.4.

Results

The current analysis included 100 patients (38% women). Mean age of the study group was 63 ± 15 years. Data on 7-day follow-up were available for 94 patients (6 patients were lost to telephone follow-up), whereas the 1-year follow-up data were collected from 90 patients (10 patients had not completed the telephone follow-up). Previous history of AF was reported in 62/100 (62.0%) of the patients examined. Before projection of the movie 22/100 (22.0%) of patients answered that stroke is a dangerous consequence of AF, while immediately after the projection the number of patients significantly increased (83/100 [83.0%]; $p < 0.0001$). One week after the number of patients choosing stroke as a consequence of AF was still significantly higher in comparison to the knowledge before the projection (74/94 [78.7%] vs. 22/94 [23.4%]; $p < 0.0001$), similar trend was observed also in the 1-year follow-up (64/90 [71.1%] vs. 21/90 [23.3%]; $p < 0.0001$) (Fig. 1). High number of patients (83/94; 88.3%) asked prior to the projection and all patients (94/94; 100%) who were asked after 7 days responded that the risk of stroke may be reduced by using a specific pharmacological therapy ($p = 0.001$). Moreover, in 1-year follow-up 87/90 (96.67%) of patients confirmed that specific drugs may serve as a possibility to diminish stroke risk ($p = 0.023$ in comparison to the survey before the projection 78/90 [(86.7%]). As for drugs reducing the risk of stroke, OAC chosen by 66/94 (70.2%) of patients prior to the projection and by 90/94 (95.7%) of patients a week after watching the movie ($p < 0.0001$). Importantly, 1 year following the projection the knowledge of OAC as a pharmacologic possibility of stroke risk reduction was significantly improved in comparison to the knowledge prior watching the movie (83/90 [92.2%] vs.

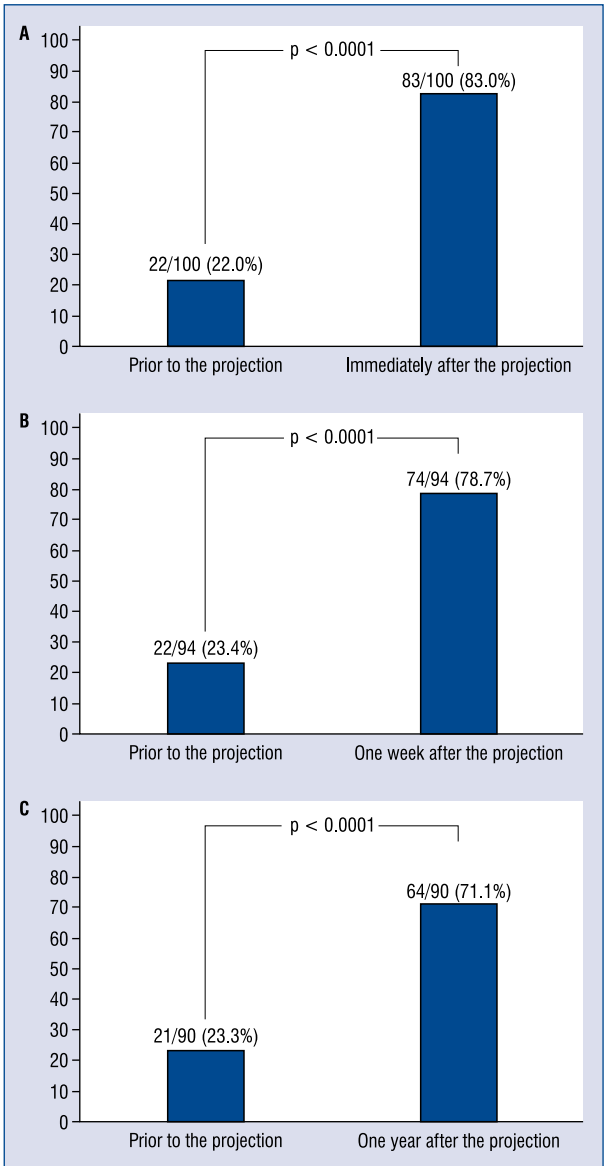


Figure 1. Percentages of patients declaring stroke a dangerous consequence of atrial fibrillation; **A.** Immediately after the projection; **B.** One week after the projection; **C.** One year after the projection.

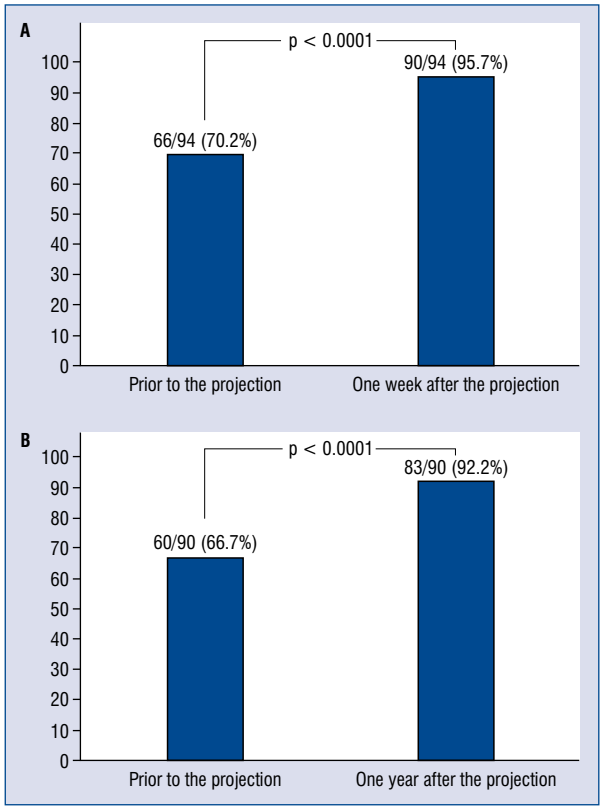


Figure 2. Percentages of patients choosing oral anticoagulants as drugs which reduce the risk of stroke; **A.** One week after projection; **B.** One year after projection.

60/90 [66.7%]; $p < 0.0001$) (Fig. 2). Before the projection 54/94 (57.5%) of patients confirmed previous treatment with OAC, whereas 7 days after the projection the usage of OAC was declared by 66/94 (70.2%) of the patients asked ($p = 0.004$). Also, 1 year after the projection significantly higher number of patients confirmed use of OAC therapy when compared to the baseline survey (65/90 [72.2%] vs. 50/90 [55.6%]; $p = 0.006$) (Fig. 3). The VR-3D movie was acknowledged as a useful tool to spread awareness of consequences of AF by 99/100 (99.0%) of the study participants. Approximately all of the patients (99/100; 99.0%) confirmed that they would enjoy watching similar movies about other diseases. One week after watching the movie 91/93 (97.9%) of patients declared using prescribed OAC therapy in the future, due to the gained knowledge through watching the movie about the consequences associated with AF. The univariate analysis did not reveal any statistically significant relations between age or gender, and the frequency of marking stroke as a consequence of AF or choosing OAC as a possibility of reducing the risk of stroke.

Discussion

The results obtained clearly show that knowledge about the consequences of AF results in an improved declared adherence to treatment with OAC. The vast majority of patients acknowledged that the VR-3D movie technology is an interesting and useful tool to spread the awareness about AF, as well as other diseases.

Results from the European Heart Rhythm Association (EHRA) Survey conducted in 53

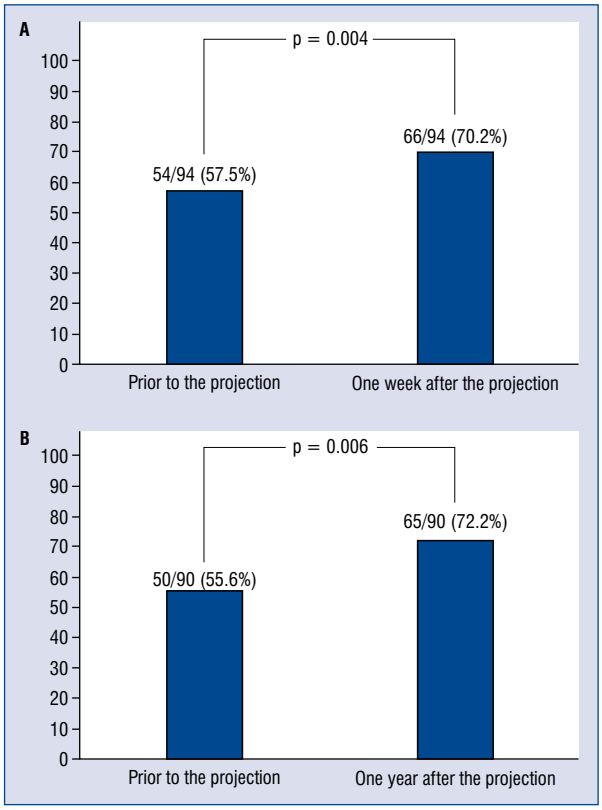


Figure 3. Percentages of patients who declare taking oral anticoagulants previously; **A.** One week after projection; **B.** One year after projection.

European centres revealed, that stroke and bleeding risk management had the highest priority in discussion with AF patients in majority of centres (80.2%) [6]. However, none of the centres used the mobile phone applications to explain the risk of stroke, as a consequence of AF. The majority of centres (92.3%) included in this survey provided discussion with patients to describe the risk of stroke in AF. In addition to the conversation, some of the centres provided illustrative materials from pharmaceutical companies (23.1%), other printed materials (17.3%), links to websites (17.3%), specialized nurse (11.5%) or health psychologist (1 center). Moreover, there was estimated that the percentages of patients who would desist OAC despite the knowledge of advantages and risks of the therapy were: 0.0% in 13.7% of the centers, ≤ 10% in 58.8%, 11–20% in 21.6% and 21–30% in 5.9% of the centers. Interestingly, the prevailing reasons for OAC withdrawal were patient fear of bleeding (41.2% of the centers), underestimation of stroke risk despite having the proper knowledge (21.6%), deficient patient information about the risk of stroke (15.7%), unknown or other reasons (21.6%) [6]. Another EHRA Survey evaluating the level of education about the OAC, conducted in 8 European centres reported, that 90% of patients with AF give the proper explanation for the OAC therapy (which was said as "to thin the blood") [7].

It is known that management of OAC is challenging because of the need for an appropriate balance between hemorrhagic and thromboembolic risks, as well as due to different phenotypes of patients using this therapy. Interestingly, results from the EHRA Survey show that patients without schooling had the highest percentage of bleeding on OAC and previous strokes and the lowest use of OAC for stroke prevention [2]. The OCULUS study did not show any statistically significant correlations between age or gender, and the frequency of marking stroke as a consequence of AF or choosing OAC as a possibility in reducing the risk of stroke.

In 2014 Cleeren et al. [8] conducted a randomized controlled trial which evaluated gaining and recall of knowledge on periodontitis by patients suffering from periodontitis. The authors revealed, that patients who were shown 3D animations had significantly higher scores in knowledge immediately after the projection and in the following 2 weeks in comparison to a narration and drawing group. Therefore, authors of the study agreed, that 3D animations may be a useful tool in the education of patients. VR is also suggested to be effective as a diagnostic application in detecting mild cognitive impairment [9]. Moreover, VR is concerned to be a useful additional tool in rehabilitation after ischemic stroke and cerebral palsy [10, 11]. It has been proven, that patients using VR applications experience less pain and distress, furthermore they also declare awillingness to use VR during the medical procedures related with pain [12]. Also other educational tools, such as an iPad-based application (iBook), is suggested to be beneficial in otologic diseases in improving patient knowledge and satisfaction [13].

Limitations of the study

Some important limitations of the OCULUS study have to be acknowledged. First of all, the analyzed group of patients is relatively small. Secondly, a longer follow-up is required to assess the effectiveness of the 3D movie on patient knowledge and attitude towards compliance. Moreover, the OCULUS study enrolled only hospitalized patients. However, it could be hypothesized that, those patients may have a higher level of knowledge about AF and anticoagulation treatment and what may have had a significant influence on the obtained

results. Thus, there is a need to conduct such a study in the general population.

Conclusions

The OCULUS study shows, that a 3D movie is an effective tool in teaching patients about the consequences of AF and the important role of OAC in stroke prevention. Due to the interesting results of the current study, there is a need to create educational VR-3D movies, which may contribute to the improvement in patient compliance and better treatment outcomes for other diseases. Further multicentre studies would be helpful to evaluate the role of VR-3D-movie-based knowledge transfer for several diseases, not only in AF.

Trial registration

The study has been registered in the ClinicalTrials.gov, NCT03104231. Registered on 28 March 2017.

Conflict of interest: None declared

References

1. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Rev Esp Cardiol. 2017; 70(1): 50, doi: 10.1016/j.rec.2016.11.033, indexed in Pubmed: 28038729.
2. Hernández Madrid A, Potpara TS, Dagres N, et al. Differences in attitude, education, and knowledge about oral anticoagulation therapy among patients with atrial fibrillation in Europe: result of a self-assessment patient survey conducted by the European Heart Rhythm Association. Europace. 2016; 18(3): 463–467, doi: 10.1093/europace/euv448, indexed in Pubmed: 26899998.
3. Milewski K, Małecki A, Orszulik-Baron D, et al. The use of modern telemedicine technologies in an innovative optimal cardiac rehabilitation program for patients after myocardial revascularization: Concept and design of RESTORE, a randomized clinical trial. Cardiol J. 2018 [Epub ahead of print], doi: 10.5603/CJ.a2018.0157, indexed in Pubmed: 30566211.
4. Rymuza B, Grodecki K, Kamiński J, et al. Wykorzystanie hologramu podczas przezcewnikowego wszczepienia zastawki aortalnej u pacjenta ze stenozą dwupłatkowej zastawki aortalnej. Kardiol Pol. 2017; 75(10): 1056–1056, doi: 10.5603/kp.2017.0195, indexed in Pubmed: 29057443.
5. Olejník P, Nosal M, Havran T, et al. Utilisation of three-dimensional printed heart models for operative planning of complex congenital heart defects. Kardiol Pol. 2017; 75(5): 495–501, doi: 10.5603/KP.a2017.0033, indexed in Pubmed: 28281732.
6. Pison L, Potpara TS, Chen J, et al. Scientific Initiative Committee, European Heart Rhythm Association, Scientific Initiatives Committee, and European Heart Rhythm Association. How are patients with atrial fibrillation approached and informed about their risk profile and available therapies in Europe? Results of the European Heart Rhythm Association Survey. Europace. 2015; 17(3): 468–472, doi: 10.1093/europace/euv025, indexed in Pubmed: 25722478.
7. Amara W, Larsen TB, Sciaraffia E, et al. Patients' attitude and knowledge about oral anticoagulation therapy: results of a self-assessment survey in patients with atrial fibrillation conducted by the European Heart Rhythm Association. Europace. 2016; 18(1): 151–155, doi: 10.1093/europace/euv317, indexed in Pubmed: 26462697.
8. Cleeren G, Quirynen M, Ozcelik O, et al. Role of 3D animation in periodontal patient education: a randomized controlled trial. J Clin Periodontol. 2014; 41(1): 38–45, doi: 10.1111/jcpe.12170, indexed in Pubmed: 24111854.
9. Zygouris S, Ntovas K, Giakoumis D, et al. A Preliminary Study on the Feasibility of Using a Virtual Reality Cognitive Training Application for Remote Detection of Mild Cognitive Impairment. J Alzheimers Dis. 2017; 56(2): 619–627, doi: 10.3233/JAD-160518, indexed in Pubmed: 28035922.
10. Schmid L, Glässel A, Schuster-Amft C. Therapists' Perspective on Virtual Reality Training in Patients after Stroke: A Qualitative Study Reporting Focus Group Results from Three Hospitals. Stroke Res Treat. 2016; 2016: 6210508, doi: 10.1155/2016/6210508, indexed in Pubmed: 28058130.
11. Ravi DK, Kumar N, Singhi P. Effectiveness of virtual reality rehabilitation for children and adolescents with cerebral palsy: an updated evidence-based systematic review. Physiotherapy. 2017; 103(3): 245–258, doi: 10.1016/j.physio.2016.08.004, indexed in Pubmed: 28109566.
12. Li A, Montaño Z, Chen VJ, et al. Virtual reality and pain management: current trends and future directions. Pain Manag. 2011; 1(2): 147–157, doi: 10.2217/pmt.10.15, indexed in Pubmed: 21779307.
13. Moshtaghi O, Haidar YM, Sahyouni R, et al. Use of interactive iBooks for patient education in otology. Am J Otolaryngol. 2017; 38(2): 174–178, doi: 10.1016/j.amjoto.2016.12.004, indexed in Pubmed: 28089173.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2019, Vol. 26, No. 3, 265–274
DOI: 10.5603/CJ.a2018.0006

ISSN 1897–5593

Long-term outcomes of mitral valve annuloplasty versus subvalvular sparing replacement for severe ischemic mitral regurgitation

Baotong Li, Hengchao Wu, Hansong Sun, Jianping Xu, Yunhu Song, Wei Wang, Shuiyun Wang

State Key Laboratory of Cardiovascular Disease, Department of Adult Cardiac Surgery, Fuwai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Science, Peking Union Medical College, Beijing, China

Abstract

Background: *Although practice guidelines recommend surgery for patients with severe chronic ischemic mitral regurgitation (CIMR), they do not specify whether to repair or replace the mitral valve. The purpose of this study was to evaluate the long-term outcomes in patients with severe CIMR undergoing mitral valve annuloplasty (MVA) versus subvalvular sparing mitral valve replacement (MVR).*

Methods: *392 consecutive patients who underwent MVA or subvalvular sparing MVR for treatment of severe CIMR were retrospectively reviewed.*

Results: *After adjustment for baseline differences with multivariable regression analysis at 53 months follow-up (interquartile range, 34–81 months), there was no significant difference between the two groups for risk of major adverse cardiac or cerebrovascular events (MACCE), cardiac death, or all-cause death. Propensity score matching extracted 77 pairs. During the follow-up, compared with the MVR group, both the left atrium and left ventricle end-diastolic diameter were markedly larger ($p = 0.013$ and $p = 0.033$, respectively), and the incidence of mitral regurgitation recurrence was significantly higher in the MVA group ($p < 0.001$). No significant difference was observed between the two propensity score-matched groups in composite in-hospital outcomes, overall survival, freedom from cardiac death or MACCE, except subvalvular sparing MVR was associated with a lower incidence of hospitalization for heart failure than MVA ($p = 0.015$).*

Conclusions: *Subvalvular sparing MVR is a suitable management of patients with severe CIMR, it is more favorable to ventricular remodeling and is associated with a lower incidence of hospitalization for heart failure than MVA.* (Cardiol J 2019; 26, 3: 265–274)

Key words: chronic ischemic mitral regurgitation, mitral valve annuloplast, subvalvular sparing mitral valve replacement, coronary artery bypass grafting

Introduction

Chronic ischemic mitral regurgitation (CIMR) is common and is associated with worse long-term survival and functional status [1]. It is generally agreed that severe mitral regurgitation (MR) requires mitral valve intervention, but the optimal management of patients with severe CIMR, specifically the choice between mitral valve annuloplasty (MVA) and mitral valve replacement (MVR), has long been debated [2–5]. To date, there are no prospective randomized trials evaluating

Address for correspondence: Hansong Sun, MD, PhD, State Key Laboratory of Cardiovascular Disease, Department of Adult Cardiac Surgery, Fuwai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Science, Peking Union Medical College, Beijing, China, tel: +86 010 88322351, fax: +86 010 88322351, e-mail: drsunhs@sina.com

Received: 10.06.2017 Accepted: 1.11.2017

the long-term outcomes of MVA versus MVR for severe CIMR, while published series have provided a wide range of results for long-term outcomes. Considering the different conclusions which might have been derived from heterogeneity of patient cohorts and methods of treatment, the present study is a long-term design and propensity score (PS) matched analysis to evaluate the effectiveness of MVA versus sub-valvular sparing MVR for severe CIMR.

Methods

Patients and study design

This study was approved by the Human Research Ethics Committee of the Fuwai Hospital and was performed in accordance with the Declaration of Helsinki and approved guidelines. CIMR was defined by coronary angiographic and echocardiographic findings according to accepted criteria, i.e., 1) MR occurring more than 16 days after myocardial infarction; 2) type I/IIIb leaflet dysfunction following Carpentier's classification; and 3) 70% or greater stenosis of at least one coronary artery, with wall motion abnormalities of the corresponding left ventricular (LV) segment [3].

Between January 2003 and December 2014, a total of 1040 patients with CIMR were hospitalized to undergo coronary artery bypass grafting (CABG) combined with MVA or MVR. From the initial cohort, 642 patients were excluded for various reasons [3], i.e., 1) Preoperative MR ≤ 2+, congenital valvular heart disease, rheumatic or degenerative valvular disease, infective endocarditis, presence of aortic valve regurgitation or stenosis, emergency surgery, repeat operation; or 2) Performance of other procedures, such as LV reconstruction/reshaping, partial band/pericardial annuloplasty, or procedures other than mitral ring annuloplasty for treatment. Moreover, the patients who underwent MVR without preserving the subvalvular apparatus were excluded. In addition, 6 were lost to follow-up. Thus, the final study cohort comprised 392 patients: 306 (78.1%) patients underwent MVA whereas 86 (21.9%) underwent subvalvular sparing MVR.

Baseline patient characteristics, echocardiography data, operative data, and surgical techniques were collected from the division of cardiovascular surgery database and individual medical records. Patients were followed up through the internet or by telephone interview and outpatient department records.

Surgical technique

All surgical procedures were performed with standard bypass techniques through median sternotomy by senior surgeons with a special interest in mitral valve surgery. The decision to perform MVA or subvalvular sparing MVR was at the surgeon's discretion. Downsizing ring annuloplasty (2 sizes) was used in all patients subjected to MVA. The ring size was determined by measurements of the intertrigonal distance and anterior leaflet height. Intraoperative transesophageal echocardiography was routinely used. A successful MVA was defined as a leaflet coaptation of ≥ 0.8 cm and MR ≤ 1 at transesophageal echocardiography performed at the end of cardiopulmonary bypass [3, 6]. Subvalvular apparatus were preserved when performing MVR, including posterior leaflet preservation, posterior and partial anterior leaflet preservation and both leaflet preservation. The decision to perform which kind of procedure was at the surgeon's discretion according to situational conditions. The posterior mitral valve leaflet was left intact in all patients undergoing MVR. In 8 of patients undergoing MVR, the middle portion of the anterior leaflet was resected and the remaining leaflet tissue was plicated with individual valve sutures. In 23 patients undergoing MVR, the anterior leaflet of the valve was partly or completely detached from the mitral annulus and divided in the middle at the 12 o'clock position, and the leftward portion of the anterior leaftlet was plicated to the anterolateral commissure with a pledgetted 4–0 polypropylene suture. The rightward a portion of the anterior mitral leaflet was similarly plicated to the posteromedial commissure. Complete revascularization was achieved in all patients with arterial conduits or saphenous vein grafts. All patients received the same perioperative care and medical therapy according to guidelines.

Echocardiography

Two-dimensional and Doppler transthoracic echocardiography examinations were performed before operations and at pre-discharge for all patients. MR was classified as mild (grade 1+), moderate (grade 2+), or severe (grades 3+ and 4+) [7]. LV inferior basal wall motion abnormality (BWMA) includes hypokinesia, dyskinesis and aneurysm. Echocardiographic criteria for aneurysm were evidence of thinning and localized LV dilation or distortion. Dyskinesis was the presence of outward displacement of the LV wall during systole [8, 9].

Statistical analysis

All statistical analyses were performed by SPSS version 20 (IBM SPSS Inc., Chicago, IL), SAS software version 9.2 (SAS Institute) and Graph Pad Prism release 5 (Graph Pad Software Inc., La Jolla, Calif) statistical packages. All reported p values are two sided, and values of $p < 0.05$ were considered to indicate statistical significance. Continuous data are shown as mean ± standard deviation. The Student t test was used to measure the differences for variables with a normal distribution and equal variances. The Wilcoxon rank sum test was used for non-normally distributed variables. Categorical data are displayed as frequencies and percentages and comparisons were made with χ^2 tests (Fisher exact tests if appropriate). A stepwise multivariable Cox proportional hazards model was developed to determine the independent risk factors. Variables with a p value less than 0.10 in the univariate analyses were entered into multivariable models. Differences in risk-adjusted, long-term rates of study outcomes among patients who underwent different surgical procedures were assessed by the use of multivariable Cox proportional hazards regression with adjustment for all patient-level variables in Table 1. Cumulative event rates were calculated using a Kaplan-Meier method, and different event curves of outcomes were compared using a log-rank test.

To reduce the impact of treatment selection bias and potential confounding in the observational study, rigorous adjustment for baseline differences by use of propensity score matching was performed [10]. A PS representing the probability of having subvalvular sparing MVR as opposed to MVA was calculated for each patient by using a non-parsimonious multivariable logistic regression model. Variables used in the model are shown in Table 1. Pairs of patients with MVA and sub-valvular sparing MVR were matched using calipers of width 0.2 standard deviations of logit of the PS [11]. Model discrimination was assessed with C statistics, and model calibration was assessed with Hosmer-Lemeshow statistics. Finally, 77 pairs of patients were matched to obtain risk-adjusted outcome comparisons between the two groups.

Results

Patient characteristics

The demographic, clinical and procedural data of patients who underwent MVA and subvalvular sparing MVR before and after PS matching are illustrated in Table 1. Before matching, patients who underwent subvalvular sparing MVR were older, with a worse mitral regurgitation grade and better left ventricular ejection fraction (EF).

Three kinds of complete symmetric rings were used in the present study, with the median size of 28 mm (interquartile range, 28–29 mm): Duran Ancore (Medtronic, Santa Ana, CA), Carpentier-Edwards Physio ring I (Edwards Lifesciences, Irvine, CA), Carpentier-Edwards Physio ring II (Edwards Lifesciences, Irvine, CA). There were seven types of prosthetic valves, with a median size of 27 mm (interquartile range, 27–29 mm). The rate of bioprosthesis was 46.5% (40/86). Three types of bioprostheses were used (n = 40): Mosaic (Medtronic, Santa Ana, CA), Carpentier-Edwards Perimount (Edwards Lifesciences, Irvine, CA) and Hancock II (Medtronic, Santa Ana, CA). Four types of mechanical valves were used (n = 46): Medtronic Open Pivot (Medtronic, Minneapolis, MN), On-X valve (On-X Life Technology, Austin, TX), CarboMedics Mechanical (Sorin-CarboMedics Inc, Italia, S.r.l) and St. Jude valve (St. Jude Medical, Minneapolis, MN). Subvalvular apparatus were preserved when performing MVR, with posterior leaflet preservation in 55 (64.0%) patients, posterior and partial anterior leaflet preservation in 8 (9.3%) patients, and both leaflets preservation in 23 (26.7%) patients.

Follow-up and outcomes

The clinical follow-up was closed on January 1, 2017. The median follow-up was 53 months (interquartile range, 34–81 months) with a completion rate of 98.5% (392/398) in the overall cohort. During follow-up, 62 (15.8%) patients died, of whom 53 (13.5%) died of a cardiac cause. The overall survival rates at 5 and 10 years were 86.6% and 52.9%, respectively. Freedom from cardiac death at 5 and 10 years were 88.1% and 63.9%, respectively.

After adjustment for baseline differences with Cox proportional hazard model analysis, there was no significant difference between MVA and subvalvular sparing MVR in risks of major adverse cardiac or cerebrovascular events (MACCE: cardiac death, repeat revascularization and myocardial infarction, stroke, subsequent mitral valve surgery, or hospitalization for heart failure), cardiac death, or overall death (for MACCE: $p = 0.063$; for cardiac death: $p = 0.549$; and for overall death: $p = 0.759$) (Table 2).

Risk factor analysis

Multivariable analysis showed that age and preoperative EF were independent predictors of overall death (for age: hazard ratio [HR], 1.03; 95%

Table 1. Baseline demographic and clinical characteristics of patients depending on surgical proced ure.

	Overall patient			Pairs matched by PS			Standardized difference
	MVA (n = 306)	MVR (n = 86)	P	MVA (n = 77)	MVR (n = 77)	P	
Age [years]	59.27 ± 8.46	62.05 ± 9.18	0.009	61.81 ± 7.64	61.64 ± 9.05	0.901	–0.018
Sex (male)*	248 (81.0%)	65 (75.6%)	0.264	64 (83.1%)	61 (79.2%)	0.536	–0.028
Body surface area [m^2]*	1.79 ± 0.18	1.75 ± 0.17	0.079	1.79 ± 0.16	1.76 ± 0.17	0.316	–0.166
Diabetes*	73 (23.9%)	16 (18.6%)	0.304	19 (24.7%)	15 (19.5%)	0.437	–0.133
Hypertension*	159 (52.0%)	45 (52.3%)	0.952	45 (58.4%)	40 (51.9%)	0.418	–0.129
Hyperlipidemia*	124 (40.5%)	36 (41.9%)	0.824	29 (37.7%)	32 (41.6%)	0.621	0.025
COPD*	21 (6.9%)	6 (7.0%)	0.971	6 (7.8%)	3 (3.9%)	0.298	–0.142
History of PCI*	39 (12.7%)	11 (12.8%)	0.991	6 (7.8%)	10 (13.0%)	0.291	0.155
History of heart failure*	162 (52.9%)	46 (53.5%)	0.928	45 (58.4%)	41 (53.2%)	0.516	–0.144
History of stroke*	28 (9.2%)	10 (11.6%)	0.493	8 (10.4%)	10 (13.0%)	0.616	0.015
Ventricular arrhythmia*	17 (5.6%)	4 (4.7%)	0.742	5 (6.5%)	4 (5.2%)	0.731	–
Atrial fibrillation*	38 (12.4%)	7 (8.1%)	0.271	13 (16.9%)	6 (7.8%)	0.086	–0.190
LV aneurysm*	33 (10.8%)	3 (3.5%)	0.038	4 (5.2%)	3 (3.9%)	0.698	–0.034
Unstable angina*	58 (19.0%)	13 (15.1%)	0.414	16 (20.8%)	12 (15.6%)	0.403	–0.144
NYHA functional class (I–IV)*	2.59 ± 0.60	2.60 ± 0.64	0.824	2.60 ± 0.54	2.60 ± 0.63	> 0.999	–0.001
Left main CAD*	60 (19.6%)	12 (14.0%)	0.232	17 (22.1%)	10 (13.0%)	0.138	–0.177
EF [%]*	51.45 ± 11.96	55.87 ± 10.13	0.001	54.42 ± 11.42	55.22 ± 9.87	0.640	0.080
LVEDD [mm]*	58.82 ± 6.57	58.38 ± 6.24	0.580	59.30 ± 6.25	58.51 ± 6.11	0.427	–0.127
LA [mm]*	43.24 ± 6.01	43.95 ± 7.46	0.359	44.48 ± 6.54	43.68 ± 7.53	0.480	–0.108
Grade of MR:*			< 0.001			0.684	–0.059
3+	279 (91.2%)	64 (74.4%)		61 (79.2%)	63 (81.8%)		
4+	27 (8.8%%)	22 (25.6%)		16 (20.8%%)	14 (18.2%%)		
Pulmonary hypertension*	29 (9.5%)	18 (20.9%)	0.004	9 (11.7%)	15 (19.5%)	0.183	–
BWMA*	176 (57.5%)	49 (57.0%)	0.929	42 (54.5%)	44 (57.1%)	0.746	0.052
CABG:							
LIMA*	261 (85.3%)	70 (81.4%)	0.378	65 (84.4%)	62 (80.5%)	0.525	–0.095
Radial artery*	2 (0.7%)	2 (2.3%)	0.216	0 (0.0%)	2 (2.6%)		
Grafts/patient*	2.63 ± 0.84	2.57 ± 0.68	0.464	2.69 ± 0.89	2.57 ± 0.68	0.361	–0.172
Distal anastomoses/patient*	3.12 ± 1.12	2.93 ± 1.00	0.146	3.01 ± 1.12	2.95 ± 1.01	0.706	–0.065

→

Table 1. (cont.). Baseline demographic and clinical characteristics of patients depending on surgical proced ure.

	Overall patient			Pairs matched by PS			Standardized difference
	MVA (n = 306)	MVR (n = 86)	P	MVA (n = 77)	MVR (n = 77)	P	
Distal anastomoses:			0.381			0.987	
LAD	283 (92.5%)	71 (82.6%)		70 (90.9%)	65 (84.4%)		
Diagonal	143 (46.7%)	29 (33.7%)		33 (42.9%)	28 (36.4%)		
LCx system	270 (88.2%)	72 (83.7%)		62 (80.5%)	64 (83.1%)		
Intermediate	26 (8.5%)	12 (14.0%)		8 (10.4%)	9 (11.7%)		
RCA	53 (17.3%)	14 (16.3%)		12 (15.6%)	12 (15.6%)		
PDA	167 (54.6%)	51 (59.3%)		48 (62.3%)	49 (63.6%)		
Concomitant procedure:							
Tricuspid annuloplasty*	24 (7.8%)	19 (22.1%)	< 0.001	13 (16.9%)	17 (22.1%)	0.416	0.124
Modified maze procedure	2 (0.6%)	0 (0.0%)	–	0 (0.0%)	0 (0.0%)	–	
ACC time	103 (85–125%)	113 (88–134%)	0.041	106 (85–123%)	115 (87–135%)	0.111	–
CPB time	146 (123–181%)	166 (126–187%)	0.063	144 (124–182%	167 (129–187%)	0.227	–
Postoperative IABP	18 (5.9%)	4 (4.7%)	0.654	3 (3.9%)	3 (3.9%)	> 0.999	–
Duration of intubation [h]; median (IQR)	21 (15–30)	22 (16–38)	0.119	19 (15–30)	21 (16–37%)	0.190	–
Duration of ICU [h]; median (IQR)	70 (41–93)	84 (43–114)	0.081	69 (41–90)	83 (43–112%)	0.159	–

*Indicates variables entered into logistic regression for propensity score matching; PS — propensity score; MVA — mitral valve annuloplasty; MVR — mitral valve replacement; COPD — chronic obstructive pulmonary disease; PCI — percutaneous coronary intervention; LV — left ventricular; NYHA — New York Heart Association functional class; CAD — coronary artery disease; EF — left ventricular ejection fraction; LVEDD — left ventricular end-diastolic dimension; LA — left atrial dimension; MR — mitral regurgitation; BWMA — left ventricular inferior basal wall motion abnormality; CABG — coronary artery bypass graft; LIMA — left internal mammary artery; LAD — left anterior descending coronary artery; LCx — left circumflex coronary artery; RCA — right coronary artery; PDA — posterior descending artery; ACC — aortic cross-clamp; CPB — cardiopulmonary bypass; IABP — intra-aortic balloon pump; IQR — interquartile range; ICU — intensive care unit

Table 2. Long-term outcomes according to different surgical procedures in the overall population.

	MVA	MVR	Adjusted HR[#] (95% CI)	P
All patients	306	86		
Cardiac death	41 (13.4%)	12 (14.0%)	1.25 (0.60–2.62)	0.549
Overall death	50 (16.3%)	12 (14.0%)	0.90 (0.44–1.82)	0.759
MACCE	82 (26.8%)	14 (16.3%)	0.55 (0.29–1.03)	0.063

[#]Multivariable Cox proportional hazard analysis was used with adjustment for all patient-level variables (Indicated by*) in Table 1. The HRs were reported for MVA with MVR as reference; HR — hazard ratio; CI — confidence interval; MACCE — major adverse cardiac and cerebrovascular event; MVA — mitral valve annuloplasty; MVR — mitral valve replacement.

Table 3. Cox proportional hazard analysis for overall death and major adverse cardiac and cerebrovascular event (MACCE) at long-term follow-up.

Predictors	Univariable		Multivariable	
	P	HR (95% CI)	P	HR (95% CI)
Predictors of overall death:				
Surgical procedures*	0.895	0.96 (0.51–1.80)	0.997	
Age	0.032	1.03 (1.01–1.07)	0.030	1.03 (1.01–1.07)
EF	< 0.001	0.96 (0.94–0.98)	< 0.001	0.96 (0.94–0.98)
Grafts/patient	0.045	1.41 (1.01–1.96)	0.243	
Anastomoses/patient	0.083	1.24 (0.97–1.57)	0.351	
Predictors of MACCE:				
Surgical procedures*	0.119	0.64 (0.36–1.12)	0.260	
Age	0.031	1.03 (1.00–1.05)	0.055	
History of heart failure	0.010	1.72 (1.14–2.60)	0.337	
Ventricular arrhythmia	0.028	2.17 (1.09–4.31)	0.064	
EF	< 0.001	0.95 (0.94–0.97)	< 0.001	0.96 (0.94–0.97)
BWMA	0.004	1.88 (1.23–2.87)	0.357	
Left ventricular aneurysm	0.066	1.77 (0.96–3.25)	0.823	
Grafts/patient	<0.001	1.66 (1.25–2.20)	0.012	1.48 (1.11–1.97)
Anastomoses/patient	0.004	1.33 (1.10–1.61)	0.875	

*Indicates mitral valve annuloplasty or replacement; HR — hazard ratio; CI — confdence interval; EF — left ventricular ejection fraction; BWMA — left ventricular inferior basal wall motion abnormality

confidence interval [CI] 1.01–1.07, p = 0.030; and for EF: HR 0.96; 95% CI 0.94–0.98, p < 0.001), while the number of grafts and preoperative EF were independent predictors of MACCE (for the number of grafts: HR 1.48; 95% CI 1.11–1.97, p = 0.012; and for EF: HR 0.96; 95% CI 0.94–0.97, p < 0.001). Of note, the choice of MVA or subvalvular sparing MVR was not a significant predictor of late overall death or MACCE (p = 0.997 and p = 0.260, respectively) (Table 3).

Results of propensity score matching analysis

After PS matching, 77 pairs were extracted by 1:1 manner using nearest neighbor matching without replacement. Late deaths occurred in 29 patients, including 26 cardiac deaths. The 5- and 10-year overall survival rates were 80.9% and 55.8%, respectively. The 5- and 10-year freedom from cardiac death rates were 82.5% and 62.1%, respectively. There were no differences in preoperative and operative characteristics between the PS-matched patients (Table 1). The incidences of composite in-hospital outcomes (stroke, reoperation for bleeding, application of intra-aortic balloon pump and acute renal failure) were similar between the two PS-matched groups (Table 4). During follow-up, compared with the MVR group, both the left atrium and left ventricle end-diastolic diameter were markedly larger (p = 0.013 and p = 0.033, respectively), and the incidence of MR

Table 4. Early clinical outcomes of propensity score-matched patients.

Variables	MVA (n = 77)	MVR (n = 77)	P
Composite in-hospital outcome	9	15	0.183
In-hospital mortality	1 (1.3%)	2 (2.6%)	0.556
Complications:	8 (10.4%)	13 (16.9%)	0.240
Stroke	0 (0%)	0 (0%)	–
Reoperation for bleeding	1 (1.3%)	3 (3.9%)	0.300
Postoperative IABP	3 (3.9%)	3 (3.9%)	> 0.999
Respiratory complication	3 (2.5%)	5 (7.4%)	0.138
Acute renal failure	1 (1.3%)	2 (2.6%)	0.556

MVA — mitral valve annuloplasty; MVR — mitral valve replacement; IABP — intra-aortic balloon pump

Table 5. Perioperative and follow-up echocardiographic results of propensity score-matched patients.

Variables	MVA (n = 77)			MVR (n = 77)		
	Preoperative	Postoperative	Follow-up	Preoperative	Postoperative	Follow-up
EF [%]	54.42 ± 11.42	52.81 ± 8.68	52.29 ± 8.23	55.22 ± 9.87	52.62 ± 8.62	51.95 ± 9.58
LVEDD mid-ventricle [mm]	59.30 ± 6.25	51.02 ± 6.61	55.91 ± 5.23	58.51 ± 6.11	51.32 ± 8.25	53.75 ± 6.99*
LA [mm]	44.48 ± 6.54	38.32 ± 4.76	45.34 ± 5.82	43.68 ± 7.53	39.34 ± 7.66	42.76 ± 6.25*
Mitral regurgitation:	–	–	41 (53.25%)	–		2 (2.60%)*
Moderate	–	–	32 (41.56%)	–		2 (2.60%)
Severe	–	–	9 (11.69%)	–		0 (0%)
Periprosthetic leak	–	–	–	–		1 (1.30%)

*p < 0.05 vs. MVA; MVA — mitral valve annuloplasty; MVR — mitral valve replacement; EF — left ventricular ejection fraction; LVEDD — left ventricular end-diastolic dimension; LA — left atrial dimension

recurrence was significantly higher in the MVA group ($p < 0.001$) (Table 5). There were no significant differences in overall survival, freedom from cardiac death or MACCE between the two groups (all $p > 0.05$), except for a higher incidence of hospitalization for heart failure in the PS-matched MVA group than in the subvalvular sparing MVR group ($p = 0.015$) (Fig. 1).

Discussion

According to practice guidelines, both MVA and MVR are recommended treatments for correction of severe ischemic MR [12]. However, an optimal surgical approach to treatment of severe ischemic MR remains controversial. Clinical studies have suggested that repair is associated with lower perioperative morbidity and mortality but has a higher risk of recurrence, which confers with a predisposition to atrial fibrillation, heart failure, and readmission, whereas replacement provides higher perioperative mortality but better long-term correction with a lower risk of recurrence [13–15]. When MVR is required, chordal sparing is the preferred technique. Okita et al. [16] and David et al. [17] reported that the subvalvular apparatus preservation results in improved LV function and enhanced survival. Preservation of the mitral subvalvular apparatus led to better postoperative LV function and survival than those after apparatus removal.

In the present study, no difference was observed in the incidences of early mortality or postoperative complications between the two PS-matched groups. Published literature provides a wide range of results in terms of early outcomes. Several recent experiences found no significant difference between the two surgical managements, this is in accordance with the present observations [2, 18], whereas several studies showed that mitral valve repair is associated with lower operative mortality and postoperative complications [19, 20].

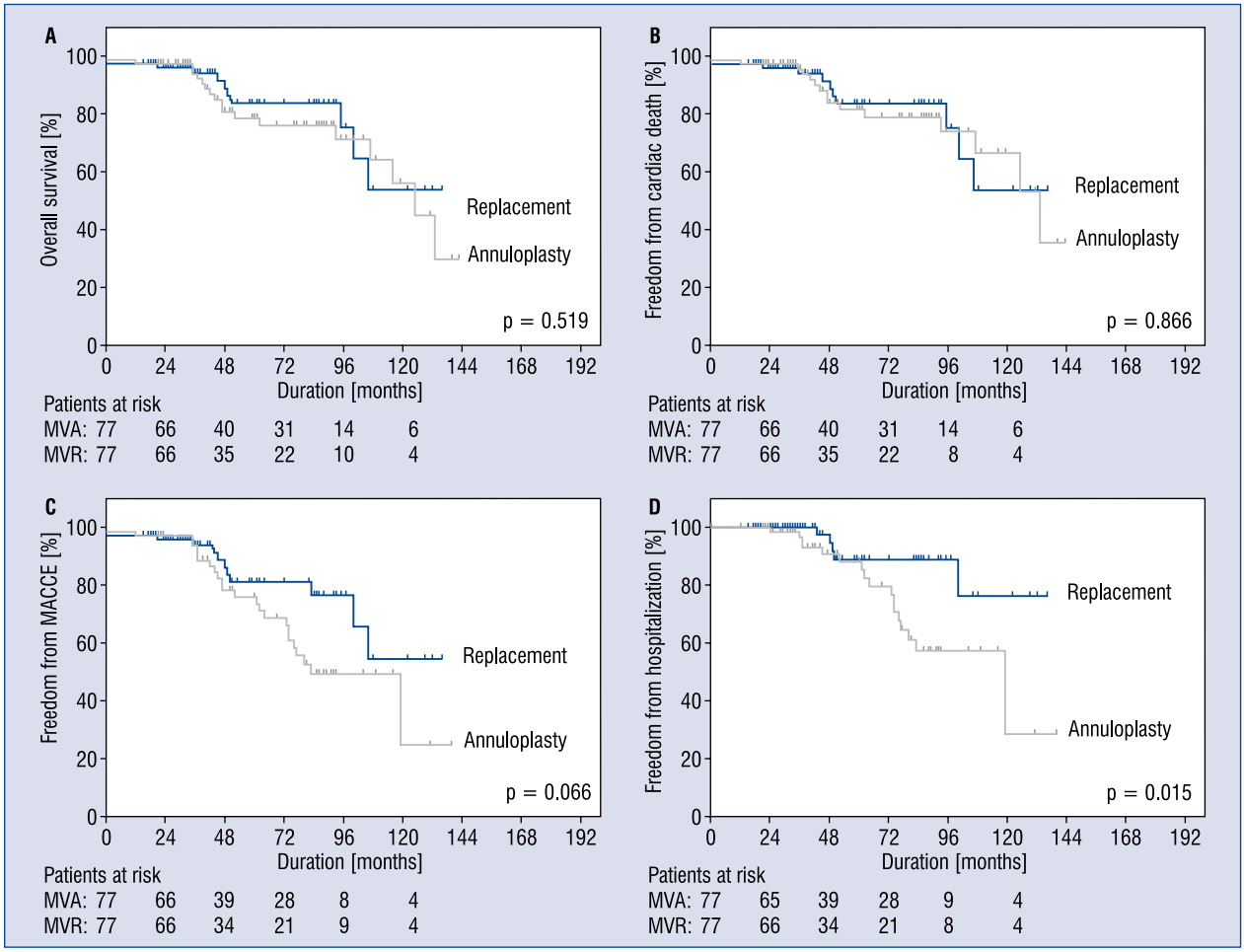


Figure 1. Kaplan-Meier curves for (**A**) overall survival (**B**) freedom from cardiac death (**C**) freedom from MACCE and (**D**) freedom from hospitalization for heart failure in 1:1 propensity score-matched mitral valve annuloplasty group (gray lines) and mitral valve replacement group (black lines); MACCE — major adverse cardiac and cerebrovascular event (cardiac death, repeat revascularization and myocardial infarction, stroke, subsequent mitral valve surgery, or hospitalization for heart failure); MVA — mitral valve annuloplasty; MVR — mitral valve replacement.

After adjustment for baseline differences with Cox proportional hazard model analysis, the present long-term observational study showed no substantial difference between the two managements of risk for MACCE, cardiac death, or overall death. Moreover, PS matching analysis also showed similar results. Follow-up echocardiographic results of PS-matched patients showed that, compared with the MVR group, both the left atrium and left ventricle end-diastolic diameter were markedly larger, and the incidence of MR recurrence was significantly higher in the MVA group. MVR provides a considerably more durable correction of MR than MVA [2, 19], which may have a beneficial effect on long-term outcomes. However, this effect must be weighed against any potential adverse consequences of a prosthetic valve, such as long-term thromboembolism, endocarditis, and structural valve deterioration [2]. The trial conducted by Goldstein et al. [2] showed that, at 2 years after either MVA or MVR for severe ischemic MR, there were no significant between-group differences with respect to LV reverse remodeling, however, the rates of MR recurrence were significantly higher in the MVA group than in the subvalvular sparing MVR group (58.8% vs. 3.8%, $p < 0.001$), related to heart failure and cardiovascular admissions [2]. Another important study carried out by Lorusso et al. [3] showed that 8-year survival was 81.6% ± 2.8% vs. 79.6% ± ± 4.8% in MVA and MVR, respectively ($p = 0.42$). Cohn et al. [21] reported a 5-year survival of 56% and 91.5% in MVA and MVR, respectively, whereas a meta-analysis showed that the relative long-term

risk of death was 35% higher in the MVR group than in the repair group [22].

Such differing conclusions might have been derived from the heterogeneity of patient cohorts. Therefore, in the present study, only patients undergoing MVA or MVR with complete myocardial revascularization were included, without congenital valvular heart disease, rheumatic valvular disease, infective endocarditis, presence of aortic valve regurgitation or stenosis, or having received other procedures. Moreover, the patients who underwent MVR without preserving the subvalvular apparatus were excluded. In addition, a propensity score model was constructed to minimize effects Limitation of confounding variables which ensured the reliability of study results.

Limitations of the study

First, this study reports retrospective data from a single center and is subject to all the limitations inherent to this design. The small study sample might have led to type II statistical errors. An appropriately powered, randomized, controlled trial evaluating the optimal management of CIMR would be useful inconfirming these results. Second, pre-, intra-, and postoperative information about the exact mechanisms and characteristics of MR were not available for all patients. For this reason, the objectives of this study were early and late outcomes. Third, selection bias should be introduced at the time of decision to perform surgical approaches because the decision to perform MVR or MVA may be related to the complexity of the patient and experience of the surgeon. To minimize the effects of selection bias, a propensity score model was constructed. Fourth, because of the 12 year inclusion time, there were three types of rings and seven types of prosthetic valves which could affect heterogeneity of the study. Another limitation is that, although this study assesses surgical approaches to the mitral valve, no detailed information was available regarding medical therapy at follow-up. However, with guideline-directed medical therapy by cardiologists, who had received systematic and standardized clinical training, the potential bias of therapy between groups is expected to be minimized.

Conclusions

The present study indicates that subvalvular sparing MVR was more favorable to ventricular remodeling and associated with a lower incidence of hospitalization for heart failure than MVA at follow-up. Therefore, subvalvular sparing MVR appears to be a suitable management for patients with CIMR undergoing mitral valve surgery and CABG. An appropriately powered, randomized, controlled trial evaluating the optimal management of CIMR would be useful in confirming the present results.

Acknowledgements

The authors thank Shanglin Chen (MD) for the assistance provided in the statistical analysis.

Conflict of interest: None declared

References

1. Bursi F, Enriquez-Sarano M, Nkomo VT, et al. Heart failure and death after myocardial infarction in the community: the emerging role of mitral regurgitation. Circulation. 2005; 111(3): 295–301, doi: 10.1161/01.CIR.0000151097.30779.04, indexed in Pubmed: 15655133.
2. Goldstein D, Moskowitz AJ, Gelijns AC, et al. CTSN. Two-Year Outcomes of Surgical Treatment of Severe Ischemic Mitral Regurgitation. N Engl J Med. 2016; 374(4): 344–353, doi: 10.1056/NEJMoa1512913, indexed in Pubmed: 26550689.
3. Lorusso R, Gelsomino S, Vizzardi E, et al. Mitral valve repair or replacement for ischemic mitral regurgitation? The Italian Study on the Treatment of Ischemic Mitral Regurgitation (ISTIMIR). J Thorac Cardiovasc Surg. 2013; 145(1): 128–139, indexed in Pubmed: 23127376.
4. Di Salvo TG, Acker MA, Dec GW, et al. Mitral valve surgery in advanced heart failure. J Am Coll Cardiol. 2010; 55(4): 271–282, doi: 10.1016/j.jacc.2009.08.059, indexed in Pubmed: 20117430.
5. Perrault LP, Moskowitz AJ, Kron IL, et al. Optimal surgical management of severe ischemic mitral regurgitation: to repair or to replace? J Thorac Cardiovasc Surg. 2012; 143(6): 1396–1403, doi: 10.1016/j.jtcvs.2011.05.030, indexed in Pubmed: 22054660.
6. Vahanian A, Alfieri O, Andreotti F, et al. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS), ESC Committee for Practice Guidelines (CPG), Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC), European Association for Cardio-Thoracic Surgery (EACTS). Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg. 2012; 42(4): S1–44, doi: 10.1093/ejcts/ezs455, indexed in Pubmed: 22922698.
7. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr. 2003; 16(7): 777–802, doi: 10.1016/S0894-7317(03)00335-3, indexed in Pubmed: 12835667.
8. Weyman AE, Peskoe SM, Williams ES, et al. Detection of left ventricular aneurysms by cross-sectional echocardiography. Circulation. 1976; 54(6): 936–944, indexed in Pubmed: 991409.
9. Lebeau R, Di Lorenzo M, Amyot R, et al. A new tool for estimating left ventricular ejection fraction derived from wall motion

score index. Can J Cardiol. 2003; 19(4): 397–404, indexed in Pubmed: 12704486.
10. Li F, Zaslavsky AM, Landrum MB. Propensity score weighting with multilevel data. Stat Med. 2013; 32(19): 3373–3387, doi: 10.1002/sim.5786, indexed in Pubmed: 23526267.
11. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat. 2011; 10(2): 150–161, doi: 10.1002/pst.433, indexed in Pubmed: 20925139.
12. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017; 135(25): e1159–e1195, indexed in Pubmed: 28298458.
13. Al-Radi OO, Austin PC, Tu JV, et al. Mitral repair versus replacement for ischemic mitral regurgitation. Ann Thorac Surg. 2005; 79(4): 1260–1267. discussion -7., doi: 10.1016/j.athoracsur.2004.09.044, indexed in Pubmed: 15797060.
14. Grossi EA, Goldberg JD, LaPietra A, et al. Ischemic mitral valve reconstruction and replacement: comparison of long-term survival and complications. J Thorac Cardiovasc Surg. 2001; 122(6): 1107–1124, doi: 10.1067/mtc.2001.116945, indexed in Pubmed: 11726886.
15. Gillinov AM, Wierup PN, Blackstone EH, et al. Is repair preferable to replacement for ischemic mitral regurgitation? J Thorac Cardiovasc Surg. 2001; 122(6): 1125–1141, doi: 10.1067/mtc.2001.116557, indexed in Pubmed: 11726887.
16. Okita Y, Miki S, Ueda Y, et al. Mitral valve replacement with maintenance of mitral annulopapillary muscle continuity in patients with mitral stenosis. J Thorac Cardiovasc Surg. 1994; 108(1): 42–51, indexed in Pubmed: 8028378.
17. David TE, Ho WC. The effect of preservation of chordae tendineae on mitral valve replacement for postinfarction mitral regurgitation. Circulation. 1986; 74(3 Pt 2): I116–I120, indexed in Pubmed: 3742768.
18. Maltais S, Schaff HV, Daly RC, et al. Mitral regurgitation surgery in patients with ischemic cardiomyopathy and ischemic mitral regurgitation: factors that influence survival. J Thorac Cardiovasc Surg. 2011; 142(5): 995–1001, doi: 10.1016/j.jtcvs.2011.07.044, indexed in Pubmed: 21855899.
19. Dayan V, Soca G, Cura L, et al. Similar survival after mitral valve replacement or repair for ischemic mitral regurgitation: a meta-analysis. Ann Thorac Surg. 2014; 97(3): 758–765, doi: 10.1016/j.athoracsur.2013.10.044, indexed in Pubmed: 24370200.
20. Wang J, Gu C, Gao M, et al. Mitral valve replacement therapy causes higher 30-day postoperative mortality than mitral valvuloplasty in patients with severe ischemic mitral regurgitation: A meta-analysis of 12 studies. Int J Cardiol. 2015; 185: 304–307, doi: 10.1016/j.ijcard.2015.03.170, indexed in Pubmed: 25828670.
21. Cohn LH, Rizzo RJ, Adams DH, et al. The effect of pathophysiology on the surgical treatment of ischemic mitral regurgitation: operative and late risks of repair versus replacement. Eur J Cardiothorac Surg. 1995; 9(10): 568–574, indexed in Pubmed: 8562102.
22. Vassileva CM, Boley T, Markwell S, et al. Meta-analysis of short-term and long-term survival following repair versus replacement for ischemic mitral regurgitation. Eur J Cardiothorac Surg. 2011; 39(3): 295–303, doi: 10.1016/j.ejcts.2010.06.034, indexed in Pubmed: 20727782.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2019, Vol. 26, No. 3, 275–282
DOI: 10.5603/CJ.a2018.0022

ISSN 1897–5593

Hyperuricemia and severity of coronary artery disease: An observational study in adults 35 years of age and younger with acute coronary syndrome

Sai Lv[1, *], Wei Liu[1, *], Yujie Zhou[1], Yuyang Liu[1], Dongmei Shi[1], Yingxin Zhao[1], Xiaoli Liu[1], Jumana W. Alhelal[2], K.S. Shakeenah Ravuru[2]

[1]Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart Lung and Blood Vessel Disease, Beijing, China
[2]International School of Capital Medical University, Beijing, China

Abstract

Background: *Coronary artery disease (CAD) in adults ≤ 35 years of age is rare, but the incidence is on the rise and the risk factors for this age group are largely uncertain. Previous studies have shown that hyperuricemia (HUA) is an independent risk factor for CAD in the general population, whereas the role in adults ≤ 35 years of age with acute coronary syndrome (ACS) is unclear.*

Methods: *Patients, 18–35 years of age, diagnosed with ACS for the first time at the documented institution between January 2005 and December 2015, were enrolled in the current study. The severity of CAD was assessed by the Gensini score. Patients were divided into two groups according to the definition of HUA. The relationship between HUA and CAD severity was assessed based on multi-variate analysis.*

Results: *Seven hundred seventy-one participants fulfilling the criteria were included in this study (mean age, 31.6 years; 94.4% male). HUA, which was defined as a serum uric acid level ≥ 7.0 mg/dL (420μmol/L) in males and ≥ 6.0 mg/dL (357 μmol/L) in females, accounted for 37% of the participants. Multivariate analysis identified that HUA is an independent risk factor of CAD severity, as assessed by the Gensini score, in very young adults with ACS (OR 8.28; 95% CI 1.96–14.59; p = 0.01), and the effect of HUA on CAD severity was second only to diabetes mellitus.*

Conclusions: *Hyperuricemia was shown to be an independent risk factor for CAD severity in young adults with ACS (18–35 years of age).* (Cardiol J 2019; 26, 3: 275–282)

Key words: coronary artery disease, hyperuricemia, Gensini score, severity, young adults

Introduction

Young populations, especially the population ≤ 35 years of age, are often overlooked with respect to the diagnoses of acute coronary syndrome (ACS), even in individuals with multiple risk factors; however, studies have demonstrated that the incidence of coronary artery disease (CAD) in young adults is following an ascending trend [1, 2]. Common risk factors for CAD, such as cigarette smoking, elevated body mass index (BMI), and diabetes mellitus (DM), are known to be associated with young patients; however, recent studies have shown that non-traditional risk factors, such as hyperuricemia (HUA), may also play a role in the development of CAD. Considering the increasing incidence of HUA in a young population, this study was conducted to determine the relationship

Address for correspondence: Dr. Yujie Zhou, MD, PhD, FACC, Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart Lung and Blood Vessel Disease, Anzhen Ave #2, Chaoyang District, Beijing 100029, China, tel: +86 01064456767, e-mail: azzyj12@163.com

Received: 15.10.2017 Accepted: 17.01.2018

**Both authors contributed equally to the article as the first authors.*

between HUA and CAD severity in very young adults with ACS.

Methods

Study population

In this single center, observational study, young adults, 18–35 years of age, diagnosed with ACS for the first time at Anzhen Hospital between 1 January 2005 and 31 December 2015, were enrolled. The study exclusion criteria were as follows: missing uric acid data; gout, inflammatory diseases, autoimmune diseases, heart failure, and renal impairment (an estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2); history of diuretic or anti-hypertension drug use (losartan potassium and hydrochlorothiazide tablets, compound amiloride hydrochloride tablets, and irbesartan and hydrochlorothiazide tablets), which affect the level of uric acid, before admission; and previous percutaneous coronary intervention or coronary artery bypass grafting, congenital heart disease, cardiomyopathy and valvular heart disease. The study was approved by the Institutional Ethics Committee of Beijing Anzhen Hospital. Written informed consent was obtained from each participant.

Laboratory data collection

Blood samples were obtained from all study subjects by vein puncture after at least 12 h of fasting in the morning on the first day of admission and were analyzed using an automated biochemical analyzer to determine the levels of serum uric acid (SUA) and other laboratory indicators such as total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C).

Acute coronary syndromes refers to a group of clinical conditions generated by myocardial ischemia, including unstable angina, non-ST--segment elevation myocardial infarction and ST--segment elevation myocardial infarction [3]. ACS was diagnosed based on elevated cardiac biomarkers with classic symptoms of acute myocardial ischemia and new onset ischemic electrocardiographic abnormalities. Patients without elevated cardiac biomarkers were qualified to participate if symptoms of acute myocardial ischemia were accompanied by a new onset electrocardiographic changes [4]. Hypertension (HTN) was defined as a blood pressure ≥ 140/90 mmHg or using anti-HTN medications according to the 2010 Hypertension Prevention and Treatment Guideline [5]. DM was defined according to the 1999 World Health Organization diabetes diagnostic criteria [6]. A LDL-C level ≥ 130 mg/dL (3.4 mmol/L) was considered elevated, hypertriglyceridemia was defined as a TG ≥ 150 mg/dL (1.7 mmol/L), a HDL-C < 40 mg/dL (1.0 mmol/L) was considered low, and hypercholesterolemia was defined as a TC ≥ 200 mg/dL (5.2 mmol/L). All of the above values were defined according to the 2016 Guidelines for the Prevention and Treatment of Dyslipidemia in Chinese Adults [7]. The National Cholesterol Education Program Adult Treatment Panel III criteria [8] for the metabolic syndrome were used to diagnose study participants with metabolic syndrome. Based on published clinical guidelines, SUA levels ≥ 7.0 mg/dL (420 μmol/L) in males and ≥ 6.0 mg/dL (357 μmol/L) in females were defined as HUA [9]. A personal history of HTN and DM, a family history of CAD, cigarette smoking, and alcohol consumption were collected from electronic medical records.

Gensini score and angiographic analysis

Coronary angiography (CAG) was performed using a standard technique. Coronary angiograms were analyzed by two experienced interventional cardiologists blinded to patient clinical information. CAD was defined as a luminal diameter stenosis ≥ 50% in any of the major epicardial coronary arteries, including the left main, left anterior descending, left circumflex, and right coronary arteries and the main branches of these arteries. Patients with acute myocardial infarction were also considered to have CAD. The severity of CAD was evaluated by the Gensini score. Based on the baseline diagnostic angiogram, the Gensini score was computed by assigning a severity score to each coronary stenosis according to the degree of luminal narrowing. This number was then multiplied by a factor that took into account the geographic importance of the lesion location in the coronary arteries. The Gensini score was then expressed as the sum of scores of all coronary arteries [10].

Statistical analyses

Continuous variables are presented as the mean ± standard deviation (normal distribution) or as the median with interquartile range (non-normal distribution). Categorical variables are presented as frequencies or percentages. Comparisons of normal distribution variables between two groups were achieved using unpaired t-tests. Comparisons of non-normal distribution variables between two groups were performed using the Mann-Whitney U test. For comparisons of categorical variables, χ^2 tests were used. The significant variables in the

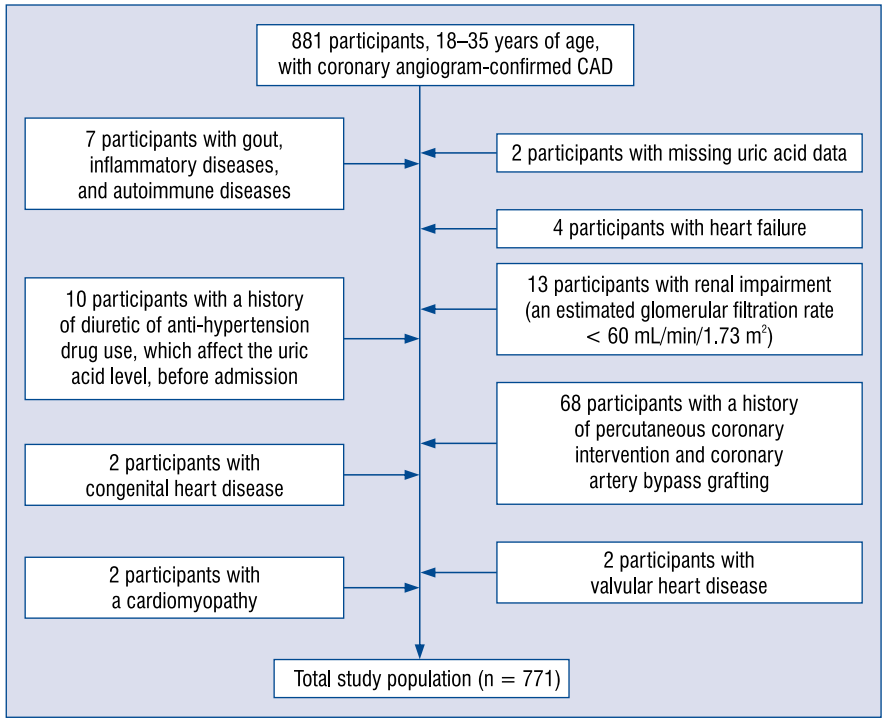


Figure 1. Flow chart of the study shows participant selection based on the inclusion and exclusion criteria among young adults 18–35 years of age with the diagnosis of acute coronary syndrome for the first time at this institution. A total of 771 participants were included in the analysis; CAD — coronary artery disease.

univariate analysis were brought into a multivariate linear regression model to identify predictors of CAD. The relationship between HUA and the severity of CAD was assessed with multi-variate linear regression analysis. A p value ≤ 0.05 (two--sided) was considered statistically significant. All analyses were performed with the statistical software package R and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA) [11].

Results

Patient demographics

A total of 771 participants fulfilling the criteria were included in this observational study (mean age, 31.6 years; 94.4% males). Figure 1 shows the study flow chart. Two hundred eighty-five participants were included in the HUA group, and the remaining 486 participants were included in the normouricemia group. The baseline characteristics are shown in Table 1. Male gender, HTN, and metabolic syndrome were more prevalent in the HUA group than the normouricemic group ($p < 0.05$). The HUA group also had a decreased HDL-C level ($p < 0.001$). Moreover, the serum creatinine and TG levels, and BMI were increased in the HUA group ($p < 0.001$). The other factors which were analyzed (LDL-C, DM, family history of CAD, and alcohol consumption) were not associated with HUA.

Analysis of CAG

Analysis of the coronary angiographic findings demonstrated that multi-vessel disease was more prevalent in the HUA group (47.5% vs. 38.1%; $p = 0.01$). Moreover, the single-vessel disease rate was decreased and the triple-vessel disease rate was increased in the HUA group ($p = 0.036$). Five hundred four (54.1%) patients underwent coronary stent implantation in the current study. In addition, patients undergoing stenting whose number of stents were between 4 and 7 were more common in the HUA group ($p = 0.026$; Table 2).

Univariate analysis of traditional CAD risk factors

Univariate analysis showed that the traditional CAD risk factors, such as DM, LDL-C and BUN levels, were significantly associated with the severity of CAD ($p < 0.05$). Univariate analysis also showed that HUA plays a prominent role in

Table 1. Baseline clinical characteristics in normouricemic and hyperuricemic patients.

	Normouricemic patient group (n = 486)	Hyperuricemic patient group (n = 285)	P
Baseline characteristics			
Age [years]	31.6 ± 3.4	31.7 ± 3.5	0.973
Male	452 (93.0%)	276 (96.8%)	0.025
Alcohol consumption	115 (23.7%)	79 (27.7%)	0.210
BUN [mg/dL]	12.12 ± 4.85	12.75 ± 4.71	0.080
Serum creatinine [mg/dL]	0.86 ± 0.17	0.93 ± 0.19	< 0.001
Triglycerides [mg/dL]	156.82 (110.75–220.61%)	200.24 (140.87–300.35%)	< 0.001
HDL-C [mg/dL]	35.71 ± 8.15	33.87 ± 7.72	0.002
LDL-C [mg/dL]	113.96 ± 46.35	115.87 ± 47.75	0.587
Total cholesterol [mg/dL]	176.60 ± 53.79	183.68 ± 58.10	0.089
Fasting glucose [mg/dL]	104.88 ± 34.24	103.29 ± 30.84	0.519
BMI [kg/m^2]	27.31 ± 3.97	28.86 ± 4.20	< 0.001
Traditional coronary risk factors			
Current smokers	323 (66.5%)	203 (71.2%)	0.170
Family history of CAD	70 (14.4%)	43 (15.1%)	0.795
Hypertension	186 (38.3%)	136 (47.7%)	0.010
Diabetes mellitus	81 (16.7%)	43 (15.1%)	0.565
Metabolic syndrome	257 (53.1%)	193 (68.9%)	< 0.001

Values are given as the mean ± standard deviation, median with interquartile range, or number (%). BUN — blood urea nitrogen; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; BMI — body mass index; CAD — coronary artery disease

the severity of CAD (odds ratio [OR] 6.85; 95% confidence interval [CI] 1.00–12.72; p = 0.022). In contrast, risk factors, such as current smokers, a family history of CAD, TG, HTN and metabolic syndrome were not significantly related to the severity of CAD (Table 3).

Multi-variate linear regression analysis model of different CAD risk factors

A multi-variate linear regression analysis model further showed that traditional CAD risk factors (DM [OR 19.21; 95% CI 10.68–27.75; p < < 0.001] and LDL-C [OR 0.14; 95% CI 0.07–0.20; p < 0.001]) and a non-traditional CAD risk factor (HUA [OR 8.28; 95% CI 1.96–14.59; p = 0.01]) were significant risk factors for the severity of CAD after adjusting for confounding factors (Fig. 2).

Discussion

This is the largest study to date investigating the relationship between HUA and severity of CAD in adults ≤ 35 years of age. The most relevant finding of the current study was that HUA is an independent risk factor for CAD severity. Furthermore, the effect of HUA was shown to be only second to DM on CAD severity in this specific population of young adults.

Previous studies [12, 13] have investigated the relationship between HUA and the severity of CAD; however, the current study is the only study investigating HUA in a young ACS population. Duran et al. [14] studied 246 middle-aged and elderly non-diabetic and non-hypertensive patients with ACS and reported a positive association between HUA and angiographic severity of ischemic heart disease (Gensini score). The results of the Duran et al. study [14] are in agreement with our data; however, the Duran et al. [14] study had a smaller sample size and the participants were older. In young adults, the relationship between HUA and the progression of CAD has also been reported. A study published in 2011 [15] involving a non-CAD population 40 ± 4 years of age (CARDIA database) suggested that SUA levels are directly related to the occurrence and severity of coronary calcifications (subclinical coronary atherosclerosis indicators) independent of traditional risk factors. The study showed that a strong correlation exists between high uric acid levels and atherosclerosis, which in turn suggested that HUA may also be associated with the formation and severity of CAD in

Table 2. Clinical features, angiographic findings, and medical treatment based on the definition of hyperuricemia in coronary artery disease patients.

Baseline characteristics	Normouricemic patients (n = 486)	Hyperuricemic patients (n = 285)	P
Clinical characteristics			
Unstable angina	184 (37.9%)	132 (46.3%)	0.021
NSTEMI	75 (15.4%)	34 (11.9%)	0.178
STEMI	227 (46.7%)	119 (41.7%)	0.182
Angiographic findings of vessel involvement			0.036
None	41 (8.7%)	16 (5.6%)	
Single vessel	252 (53.3%)	133 (46.8%)	
Double vessel	93(19.7%)	62 (21.8%)	
Triple vessel	87 (18.4%)	73 (25.7%)	
Left main disease	29 (6.0%)	23(8.1%)	0.261
Multi-vessel	180 (38.1%)	135 (47.5%)	0.01
Treatment			0.421
Drug	111 (22.8%)	56 (19.6%)	
Intervention	324 (66.7%)	203 (71.2%)	
Coronary artery bypass grafting	51 (10.5%)	26 (9.1%)	
Number of stents per patient:			0.026
0	111 (26.4%)	56 (22.5%)	
1	184 (43.7%)	109 (43.8%)	
2	80 (19.0%)	44 (17.7%)	
3	33 (7.8%)	18 (7.2%)	
4~7	13 (3.1%)	22 (8.8%)	

Values are given as the number (%). NSTEMI — non-ST-segment elevation myocardial infarction; STEMI — ST-segment elevation myocardial infarction

young adults; however, this conclusion was derived from non-CAD participants. An observational study [16], which included 607 premenopausal women, showed that patients with higher levels of SUA had an increased rate of multi-vessel disease. Another study involving SUA levels and premature CAD (< 45 years of age) in 2015 [17] showed that SUA levels > 8 mg/dL are predictive of an increased risk of three-vessel disease (OR 2.345; 95% CI 1.335–4.119) independent of traditional cardiovascular risk factors. The definition of HUA in this study [17] was the same as the current study and the findings are consistent with the present study regarding the relationship between HUA and the number of diseased vessels, the participants, however, were older than the participants in the current study. Moreover, we concluded that the correlation between HUA and the Gensini score was more clinically meaningful than the number of diseased vessels in describing the angiographic severity of CAD. Thus, the current study has great value compared with previous studies [17] confirming the significance of HUA with CAD in a very young population.

The current study showed that HUA may be related to patients with HTN, metabolic syndrome and an increased TG level, however, after multivariate regression analysis to eliminate the impact of other CAD risk factors, HUA still plays an independent role in the development of CAD. Current studies have drawn many different conclusions on the pathologic mechanism of uric acid in the development of CAD [12, 13, 18–21]. Uric acid can crystallize into the formation of monosodium urate crystals, which can result in tissue damage through an inflammatory response process, and thus participate in the occurrence of CAD [22]. In addition to the effect of monosodium urate crystals, there is agreement on the notion that even asymptomatic HUA can induce tissue injury, particularly at the level of coronary vessels [23, 24]. Studies have shown that HUA can lead to CAD through a number of mechanisms, such as stimulating vasoconstriction involving an inflammatory process,

Table 3. Univariate analysis of coronary artery disease risk factors.

Variables	Statistics	Crude HR (95% CI)	P
Age	31.64 ± 3.43	0.67 (–0.17, 1.50)	0.117
Gender:			
Female	43 (5.56)	2.41 (–10.02, 14.84)	0.7039
Male	730 (94.44)	1.0	
Hyperuricemia	285 (36.96)	6.85 (1.00, 12.72)	0.022
	486 (63.04)	1.0	
BUN	12.35 ± 4.81	0.78 (0.19, 1.37)	0.0098
Serum creatinine	0.89 ± 0.18	–7.92 (–23.65, 7.81)	0.324
BMI	27.9 ± 4.12	0.07 (–0.65, 0.80)	0.841
Alcohol consumption:			
Yes	194 (25.1)	–5.54 (–12.11, 1.02)	0.0983
No	579 (74.9)	1.0	
Current smokers:			
Yes	527 (68.18)	4.37 (–1.74, 10.48)	0.162
No	246 (31.82)	1.0	
Family history of CAD:			
Yes	113 (14.62)	5.17 (–2.82, 13.15)	0.205
No	660 (85.38)	1.0	
Hypertension:			
Yes	324 (41.91)	–4.11 (–9.85, 1.63)	0.161
No	449 (58.09)	1.0	
Diabetes mellitus:			
Yes	124 (16.04)	15.48 (7.77, 23.19)	< 0.001
No	649 (83.96)	1.0	
Metabolic syndrome:			
Yes	450 (58.9)	3.25 (–2.57, 9.07)	0.274
No	314 (41.1)	1.0	
Total cholesterol	179.2 ± 55.48	0.12 (0.07, 0.17)	< 0.0001
Triglycerides	214.54 ±174.49	0.02 (0.00, 0.03)	0.0532
LDL-C	114.66 ± 46.84	0.13 (0.07, 0.19)	< 0.0001
HDL-C	35.04 ± 8.04	–0.37 (–0.73, –0.01)	0.0427

Values are given as mean ± standard deviation or number (%). BUN — blood urea nitrogen; CI — confidence interval; HDL-C — high-density lipoprotein cholesterol; HR — hazard ratio; LDL-C — low-density lipoprotein cholesterol; BMI — body mass index; CAD — coronary artery disease

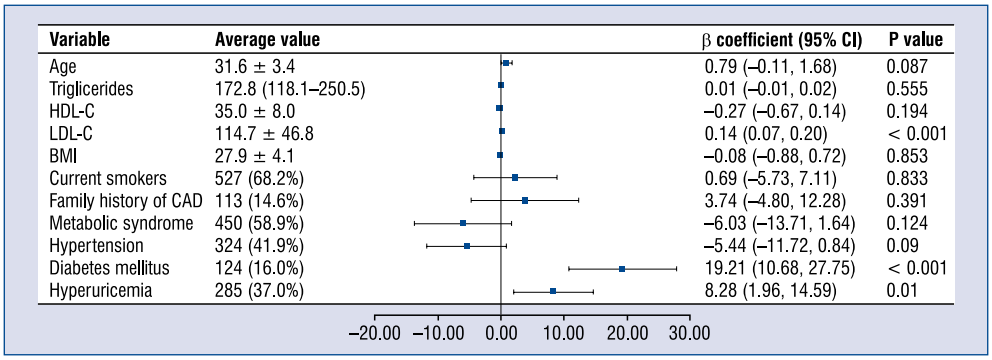


Figure 2. Forest plot of multi-variate linear regression analysis model of different coronary artery disease (CAD) risk factors. HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; BMI — body mass index; CI — confidence interval.

causing oxidative stress and impairing endothelial function [25–28]. These mechanisms are probably related to the incidence and progression of CAD in young adults.

Patient groups < 35 years of age are identified as very young in the literature [29, 30]. In the current study, the age range of participants was narrowed to 18–35 years in an effort to determine the correlation between HUA and the severity of CAD (a predictor of adverse outcomes in CAD) in a specific group (very young adults). Although traditional factors are vital for the prognosis of CAD, HUA was also shown to be an independent risk factor for CAD severity in the current study. Thus, the clinical significance of the current study involves increasing awareness of the importance of the uric acid level in patients ≤ 35 years of age. Clinicians should further instruct patients with asymptomatic HUA to pay more attention to eating habits, including a low purine diet and consuming less alcohol to control uric acid levels to within the normal range. More importantly, HUA was shown to be associated with the prognosis of CAD in young patients in the current study, as evidenced by an increased number of implanted stents associated with poor prognosis of CAD in the HUA group. Thus, the intention was to carry out an in-depth study in the future to determine whether or not HUA is correlated with the prognosis of young patients after percutaneous coronary intervention and whether or not reducing HUA can decrease the severity of CAD.

Limitations of the study

There were several limitations to this study. First, this was not a randomized trial, but an observational study. Second, to define a risk factor with certainty, one has to demonstrate that reducing the factor can improve prognosis. Large randomized trials should be carried out to determine whether or not urate-lowering therapy has beneficial effects for reducing CAD mortality, thus potentially providing new therapeutic methods for the prevention and treatment of CAD. Third, in this study the Gensini score was used rather than the Syntax score to assess CAD severity. Because some patients were treated 10 years ago, and severity was assessed by CAG reports instead of reading the coronary angiogram, the Syntax score was not calculated, however, previous studies have verified the relevance and equivalence, with none inferior to the other [31].

Conclusions

In young adults with ACS (≤ 35 years of age), HUA is an independent risk factor for the severity of CAD after adjusting for potential confounding variables.

Acknowledgements

This work was supported by the Beijing Municipal Administration of Hospitals Clinical Medicine Development of special funding support (code: ZYLX201303 grant number: ¥5000), the National Key Clinical Specialty Construction Project (2013–2014 grant number: ¥5000), and the Beijing Municipal Administration of Hospitals ascent plan (code: DFL20150601 grant number: ¥5000).

Conflict of interest: None declared

References

1. Maroszyńska-Dmoch EM, Wożakowska-Kapłon B. Clinical and angiographic characteristics of coronary artery disease in young adults: a single centre study. Kardiol Pol. 2016; 74(4): 314–321, doi: 10.5603/KP.a2015.0178, indexed in Pubmed: 26365941.
2. Bhardwaj R, Kandoria A, Sharma R. Myocardial infarction in young adults-risk factors and pattern of coronary artery involvement. Niger Med J. 2014; 55(1): 44–47, doi: 10.4103/0300-1652.128161, indexed in Pubmed: 24970969.
3. Kalra S, Duggal S, Valdez G, et al. Review of acute coronary syndrome diagnosis and management. Postgrad Med. 2008; 120(1): 18–27, doi: 10.3810/pgm.2008.04.1756, indexed in Pubmed: 18467805.
4. Schwartz GG, Olsson AG, Abt M, et al. dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Engl J Med. 2012; 367(22): 2089–2099, doi: 10.1056/NEJMoa1206797, indexed in Pubmed: 23126252.
5. Liu LS. Writing Group of 2010 Chinese Guidelines for the Management of Hypertension. [2010 Chinese guidelines for the management of hypertension]. Zhonghua Xin Xue Guan Bing Za Zhi. 2011; 39(7): 579–615, indexed in Pubmed: 22088239.
6. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998; 15(7): 539–553, doi: 10.1002/(SICI)1096-9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S, indexed in Pubmed: 9686693.
7. Zhou J, Zhou Q, Wang DP, et al. Joint committee issued Chinese guideline for the management of dyslipidemia in adults. [ST-segment elevation myocardial infarction in the eastern urban China: from 2001 to 2011]. Zhonghua Xin Xue Guan Bing Za Zhi. 2016; 44(4): 303–308, indexed in Pubmed: 27112607.
8. Thomas GN, Ho SY, Janus ED, et al. Hong Kong Cardiovascular Risk Factor Prevalence Study Steering Committee. The US National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) prevalence of the metabolic syndrome in a Chinese population. Diabetes Res Clin Pract. 2005; 67(3):

251–257, doi: 10.1016/j.diabres.2004.07.022, indexed in Pubmed: 15713358.
9. Kanbay M, Solak Y, Dogan E, et al. Uric acid in hypertension and renal disease: the chicken or the egg? Blood Purif. 2010; 30(4): 288–295, doi: 10.1159/000321074, indexed in Pubmed: 21088389.
10. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol. 1983; 51(3): 606, doi: 10.1016/s0002-9149(83)80105-2, indexed in Pubmed: 6823874.
11. Liu J, Zuo SW, Li Y, et al. Hyperhomocysteinaemia is an independent risk factor of abdominal aortic aneurysm in a Chinese Han population. Sci Rep. 2016; 6: 17966, doi: 10.1038/srep17966, indexed in Pubmed: 26865327.
12. Kim SY, Guevara JP, Kim KMi, et al. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. Arthritis Care Res (Hoboken). 2010; 62(2): 170–180, doi: 10.1002/acr.20065, indexed in Pubmed: 20191515.
13. Braga F, Pasqualetti S, Ferraro S, et al. Hyperuricemia as risk factor for coronary heart disease incidence and mortality in the general population: a systematic review and meta-analysis. Clin Chem Lab Med. 2016; 54(1): 7–15, doi: 10.1515/cclm-2015-0523, indexed in Pubmed: 26351943.
14. Duran M, Kalay N, Akpek M, et al. High levels of serum uric acid predict severity of coronary artery disease in patients with acute coronary syndrome. Angiology. 2012; 63(6): 448–452, doi: 10.1177/0003319711426868, indexed in Pubmed: 22096206.
15. Krishnan E, Pandya BJ, Chung L, et al. Hyperuricemia and the risk for subclinical coronary atherosclerosis--data from a prospective observational cohort study. Arthritis Res Ther. 2011; 13(2): R66, doi: 10.1186/ar3322, indexed in Pubmed: 21501486.
16. Zhang Jw, He Lj, Cao Sj, et al. Association of serum uric acid and coronary artery disease in premenopausal women. PLoS One. 2014; 9(9): e106130, doi: 10.1371/journal.pone.0106130, indexed in Pubmed: 25184207.
17. Dai XM, Wei L, Ma LL, et al. Serum uric acid and its relationship with cardiovascular risk profile in Chinese patients with early-onset coronary artery disease. Clin Rheumatol. 2015; 34(9): 1605–1611, doi: 10.1007/s10067-015-2878-1, indexed in Pubmed: 25630308.
18. Kanbay M, Segal M, Afsar B, et al. The role of uric acid in the pathogenesis of human cardiovascular disease. Heart. 2013; 99(11): 759–766, doi: 10.1136/heartjnl-2012-302535, indexed in Pubmed: 23343689.
19. Volterrani M, Iellamo F, Sposato B, et al. Uric acid lowering therapy in cardiovascular diseases. Int J Cardiol. 2016; 213: 20–22, doi: 10.1016/j.ijcard.2015.08.088, indexed in Pubmed: 26386814.
20. Zuo T, Liu X, Jiang Lu, et al. Hyperuricemia and coronary heart disease mortality: a meta-analysis of prospective cohort studies. BMC Cardiovasc Disord. 2016; 16(1): 207, doi: 10.1186/s12872-016-0379-z, indexed in Pubmed: 27793095.
21. Borghi C, Tykarski A, Widecka K, et al. Expert consensus for the diagnosis and treatment of patient with hyperuricemia and high cardiovascular risk. Cardiol J. 2018; 25(5): 545–563, doi: 10.5603/CJ.2018.0116, indexed in Pubmed: 30394510.
22. Grassi D, Ferri L, Desideri G, et al. Chronic hyperuricemia, uric acid deposit and cardiovascular risk. Curr Pharm Des. 2013; 19(13): 2432–2438, doi: 10.2174/1381612811319130011, indexed in Pubmed: 23173592.
23. Klinenberg JR, Kippen I, Bluestone R. Hyperuricemic nephropathy: pathologic features and factors influencing urate deposition. Nephron. 1975; 14(1): 88–98, doi: 10.1159/000180438, indexed in Pubmed: 235747.
24. Wu L, Yang LJ, Meng XY, et al. Association between hyperuricemia and outcomes in patients undergoing percutaneous coronary intervention. Int J Cardiol. 2016; 204: 152–153, doi: 10.1016/j.ijcard.2015.11.184, indexed in Pubmed: 26657612.
25. Biscaglia S, Ceconi C, Malagù M, et al. Uric acid and coronary artery disease: An elusive link deserving further attention. Int J Cardiol. 2016; 213: 28–32, doi: 10.1016/j.ijcard.2015.08.086, indexed in Pubmed: 26318389.
26. Puddu P, Puddu GM, Cravero E, et al. Relationships among hyperuricemia, endothelial dysfunction and cardiovascular disease: molecular mechanisms and clinical implications. J Cardiol. 2012; 59(3): 235–242, doi: 10.1016/j.jjcc.2012.01.013, indexed in Pubmed: 22398104.
27. Li M, Hu X, Fan Y, et al. Hyperuricemia and the risk for coronary heart disease morbidity and mortality a systematic review and dose-response meta-analysis. Sci Rep. 2016; 6: 19520, doi: 10.1038/srep19520, indexed in Pubmed: 26814153.
28. pmhdev. Xanthine oxidase inhibition for the treatment of cardiovascular disease: a systematic review and meta-analysis — National Library of Medicine - PubMed Health. Centre for Reviews & Dissemination; 2012.
29. Wolfe C, Vacek J. Myocardial Infarction in the Young. Chest. 1988; 94(5): 926–930, doi: 10.1378/chest.94.5.926.
30. Christus T, Shukkur AM, Rashdan I, et al. Coronary Artery Disease in Patients Aged 35 or less - A Different Beast? Heart Views. 2011; 12(1): 7–11, doi: 10.4103/1995-705X.81550, indexed in Pubmed: 21731802.
31. Sinning C, Lillpopp L, Appelbaum S, et al. Angiographic score assessment improves cardiovascular risk prediction: the clinical value of SYNTAX and Gensini application. Clin Res Cardiol. 2013; 102(7): 495–503, doi: 10.1007/s00392-013-0555-4, indexed in Pubmed: 23519584.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2019, Vol. 26, No. 3, 283–291
DOI: 10.5603/CJ.a2018.0027

ISSN 1897–5593

Prevention of in-stent restenosis with endothelial progenitor cell (EPC) capture stent placement combined with regional EPC transplantation: An atherosclerotic rabbit model

You-Hua Huang[1], Qiang Xu[1], Tao Shen[1], Jian-Ke Li[1], Jing-Yu Sheng[2], Hong-Jian Shi[1]

[1]Department of Radiology, Wujin Hospital, Jiangsu University, Changzhou, China
[2]Department of Cardiology, Wujin Hospital, Jiangsu University, Changzhou, China

Abstract

Background: *Even with drug-eluting stents, the risk of in-stent restenosis (ISR) remains high. The goal of this study was to investigate the use of an endothelial progenitor cell (EPC) capture stent plus regional EPC transplantation to reduce the ISR rate.*

Methods: *Endothelial progenitor cell capture stents were fabricated using fibrin gel and anti-CD34 plus anti-VEGFR-2 dual antibodies. Twenty male New Zealand white rabbits established as an atherosclerotic model were randomly divided into two groups: group 1 ($n = 10$), in which EPC capture stents were deployed into the right iliac artery; and group 2 ($n = 10$), in which sirolimus-eluting stents were placed. In both groups, EPCs were transplanted into target vessels beyond the stents, with outflow blocked. Radiologic-pathologic correlation outcomes were reviewed after 2 months.*

Results: *The technical success rate of EPC capture stent placement plus EPC transplantation was 100%. The ISR rate in group 1 was lower than in group 2 (1/10 vs. 4/10; $p > 0.05$). Minimal luminal diameters were larger in group 1 than in group 2 (computed tomographic angiography, 1.85 ± 0.15 mm vs. 1.50 ± 0.20 mm; duplex ultrasound, 1.90 ± 0.10 mm vs. 1.70 ± 0.30 mm; $p > 0.05$). Transplanted EPCs were tracked positively only in group 1. Pathologic analysis demonstrated neointimal hyperplasia thickness of 0.21 ± 0.09 mm in group 1 vs. 0.11 ± 0.07 mm in group 2 ($p < 0.05$).*

Conclusion: *Endothelial progenitor cell capture stent placement plus local EPC transplant decreases the ISR rate through thrombosis reduction rather than through neointimal hyperplasia inhibition.* (Cardiol J 2019; 26, 3: 283–291)

Key words: in-stent restenosis, thrombosis, endothelial progenitor cells, transplantation, drug-eluting stent

Introduction

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in the Western world and developing countries. According to the American Heart Association statistics committee, CVD is responsible for higher costs than any other disease process [1].

With advances in quality of care, endovascular interventions have improved mortality rates among patients with CVD; however, in-stent restenosis (ISR) remains the greatest obstacle in coronary interventional treatment. Drug-eluting stents (DES) have been shown to dramatically reduce the rates of restenosis and target lesion revascularization when compared with bare-metal stents (BMS) in

Address for correspondence: Hong-Jian Shi, MD, PhD, Department of Radiology, The Affiliated Wujin Hospital, Jiangsu University, Changzhou, China, 213017, tel: +86 519 85579213, +8613776893070, fax: +86 519 85325466, e-mail: shihongjian@sina.com

Received: 8.05.2017 Accepted: 15.01.2018

short- and mid-term studies [2–5]. However, as more complex cases have been included in this research, it has become apparent that the rate of ISR with DES is much higher than initial trials had revealed, with rates as high as 20%; long-term results are especially dismal [6, 7].

In light of this, treatment of DES ISR has become a topic of interest for clinicians. For interventional cardiologists, the greatest dilemma may be how to treat a patient with DES ISR in the absence of any clear-cut guidelines. The modalities available for treatment of DES ISR include routine plain old balloon angioplasty, use of cutting or scoring balloons, use of drug-coated balloons or drug-eluting balloons, use of BMS, use of same DES or different DES, vascular brachytherapy, bypass surgery, use of stent-grafts, or laser atherectomy [8–15]. However, none of these modalities is optimal.

Treating these patients is difficult in part because the mechanisms of ISR and delayed ISR with DES have not been fully investigated. Some studies have suggested that the underlying mechanism of ISR is related to incomplete stent endothelialization [3, 9–11]. If rapid re-endothelialization occurs, the lining of the stent provides a nonthrombogenic surface, interrupting cytokine-driven activation of smooth muscle cells (SMCs) in vascular tissues and accelerating normal wound healing; in this way, late-stage ISR can be alleviated [16]. Thus, cell therapy appears to be an appealing option in these patients. Several studies (mostly experimental animal studies) have evaluated this rapid re-endothelialization strategy by stent strut recruitment of circulation endothelial progenitor cells (EPCs). These studies demonstrated the positive role of enhanced endothelial regeneration in inhibiting acute thrombosis and excessive inflammatory response, facilitating the recovery process, and successfully minimizing severe pseudointimal hyperplasia [17–22]. However, a commercially available EPC capture stent (Genous Bio-engineered R stent, OrbusNeich Medical, Fort Lauderdale, Florida, USA) has not demonstrated the ability to reduce neointimal hyperplasia as the designers had expected. The HEALING trials, which assessed the Genous R stent, demonstrated only slight improvements in rapid re-endothelialized intima formation and the need for short-term dual antiplatelet therapy after stent placement; this stent was also found to be noninferior to DES with respect to target lesion revascularization and rate of major adverse cardiac events [23–26].

This study therefore sought to investigate the feasibility of using a dual antibody-coated EPC capture stent enhanced with regional EPC transplantation to reduce the rate of ISR through rapid re-endothelialization in an atherosclerotic animal model. This study also sought to address the controversy regarding whether rapid re-endothelialization inhibits neointimal hyperplasia in the setting of ISR.

Methods

This study was carried out in accordance with recommendations from the Guide for the Care and Use of Laboratory Animals from the National Institutes of Health. The Institutional Animal Care and Use Committee of Jiangsu University approved the study.

EPC culture

Endothelial progenitor cells were isolated from newly drawn male New Zealand white rabbit (Jingling Farm Center for Animal Experiments, Nanjing, China) peripheral blood via the density gradient centrifuge method. Methods for EPC isolation, culture, and characterization have been described previously [27]. Briefly, second-generation EPCs were harvested on day 12. The phenotypes of CD34, VEGFR-2, and vWF were positively expressed by these cells. The presence of up-taken DiI-Ac-LDL and binding FITC-UEA-1 was confirmed by inverted fluorescence microscopy, indicating that these cells were functional EPCs (Fig. 1).

In vitro dual antibody-coated stent fabrication

Ten nitinol balloon-expandable 3.0 mm × 15 mm 316L stainless steel open-cell design Sun BMS (SINO Medical Sciences Technology Inc, Tianjin, China) were immersed in fibronectin solution (100 μg/mL; Gene Operation, Ann Arbor, USA) and incubated at 37°C in 5% CO_2 for 24 h. Coated rabbit anti-rabbit CD34 (Bioss, Beijing Biosynthesis Biotechnology Co., Ltd, Beijing, China) and anti-rabbit VEGFR-2 (Bioss) stents were constructed in a wet-to-dry lyophilized fashion by bathing the stent in the dual-antibody solution (100 μg/mL) for 1 min and then using a hair dryer to blow dry the stent for 1 min, thus increasing antibody adhesion. This process was repeated 5 times. The scheduled transplant EPCs were labeled with fluorescent cell marker (CM-DiI; Invitrogen,Carlsbad, USA) as previously described [28]. Dual antibody-coated EPC capture stents were then transported from the laboratory to the angiography suite in a sterile fashion.

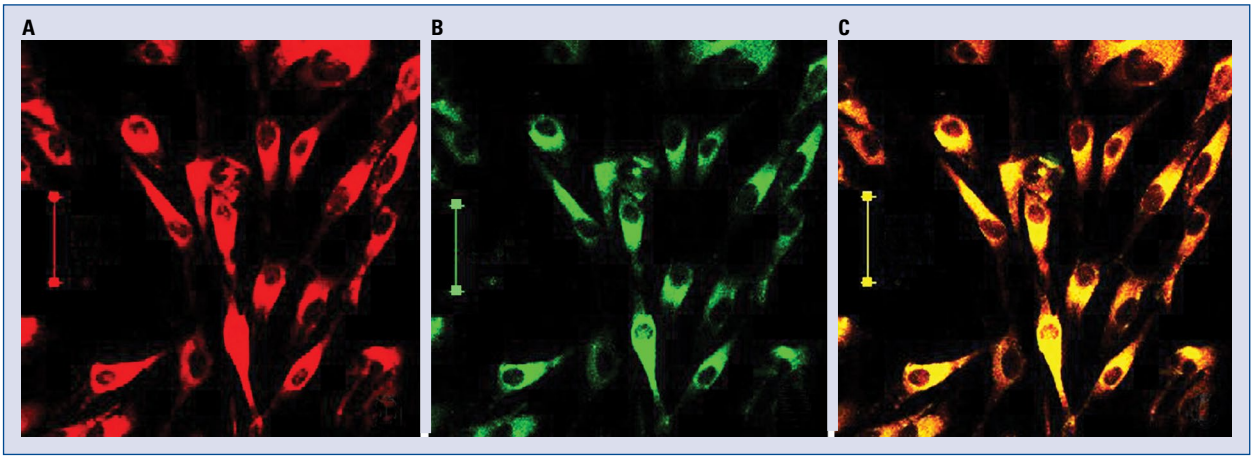


Figure 1. Inverted fluorescent microscopy images of endothelial progenitor cells (EPCs) that endocytosed DiI-Ac-LDL (**A**) and bound FITC-UEA-1 (**B**). The EPCs (overlay of **A** and **B**) are stained yellow (**C**). Scale bar = 50 μm.

In vivo stent placement and cell transplantation

Twenty male New Zealand white rabbits aged 2 months and established as atherosclerotic models were fed a high-lipid diet (normal diet with added 2% cholesterol, 5% fat, 7.5% yolk powder) at Southeast University Experimental Animal Center (Nanjing, China) for at least 1 month before stent deployment. The rabbits were injected intravenously with 10% bovine serum album (Biosharp, Roche, Shanghai, China) 25 mg/kg once daily for 3 consecutive days to induce an immune injury reaction [29]. Serum hypercholesterolemia was demonstrated via laboratory examination. The animals (mean weight, 3.1 ± 0.3 kg) were then randomly divided into one of two study groups: group 1 (n = 10) or group 2 (control group; n = 10).

On the angiography table, the animals were placed under general anesthesia with intravenous phenobarbital (Simcare, Beijing, China) 30 mg/kg; local anesthesia with 2% lidocaine (China Otsuka Pharmaceutical Co., Ltd, Tianjin, China) 4.5 mg/kg was administered via subcutaneous infiltration before surgical incision. For all animals, patent airway and ventilation were maintained throughout the procedure, the circulatory systems were also supported with the administration of intravenous fluids.

Methods for creation of balloon injury and percutaneous stent placement in iliac arteries have been described previously [17]. In this study, a 4-French introducer sheath (Radifocus, Terumo, Japan) was surgically introduced into the right carotid artery and a 2.7 Fr microcatheter (Progreat, Terumo, Japan) was sub-selectively advanced into the lower abdominal aorta under fluoroscopic guidance (Zeego, Siemens, Forchheim, Germany). Post systemically heparinized with 200 IU/kg heparin sodium (Shanghai No.1 Biochemical Pharmacology Co. Ltd,Shanghai, China), maneuvers to create a balloon injury were performed 3 times with a 2.5 mm × 15 mm balloon catheter (Star Progress Medical Ltd., Shanghai, China) at 6 atmospheres of pressure for 30 s in the right common external iliac artery. After the balloon injury was created, ten 3.0 mm × 15 mm dual antibody-coated Sun BMS (group 1) or ten 3.0 mm × 14 mm sirolimus-eluting stents (Excel, JW Medical System, Weihai, China) (group 2) were randomly deployed at the dilated site of the right iliac arteries. Simultaneously, a mean amount of 5×10^6 EPCs labeled with DiI were continuously infused through the microcatheter just above the proximal edge of the stent, with a tourniquet placed on the ipsilateral thigh to block blood runoff for 2 min. After stent deployment, angiography was performed in all animals to exclude any acute thrombus formation.

Postprocedural follow-up

Penicillin 800,000 IU was administered intramuscularly daily for 3 days after the procedure. The animals were fed the high-lipid diet, provided with water ad libitum, and given oral acetylsalicylic acid 12.5 mg once daily during follow-up. One month after the procedure, with the animals under general anesthesia, computed tomography angiography (CTA) was performed using 2.5 mL/kg nonionic iodine medium (Omnipaque, Yangzi Pharmacy Ltd., Taizhou, China) via power injection through an ear edge vein; a dual-source CT SOMATOM

Definition Flash scanner (Siemens AG, Forchheim, Germany) was used for all scans (140 KV and 80 KV; automatically controlled mAs; 10-s delay). CTA data were analyzed using vascular analysis software (Syngo.via, Siemens AG). After CTA was completed, a color Doppler duplex ultrasound examination (Philips HD7 XE, Amsterdam, the Netherlands) was performed to investigate target vessel preparation with the affected limb shaved. CTA and duplex ultrasound examinations were repeated 2 months thereafter before the animals were euthanized. The patency of the target vessel, minimum luminal diameter, and velocity of blood were recorded during these examinations.

Restenosis definition

Binary restenosis is defined as 50% luminal narrowing on follow-up angiography [3]. For this study, ISR was determined by visual estimation and was defined as > 50% luminal narrowing within 5 mm proximal or distal to the stent. According to the current clinical literature, restenosis is identified as "very late" when it occurs 1 year after stent placement in humans [11]. For this animal study, the authors defined ISR as restenosis occurring 2 months after stent placement to account for the differences between rabbits and humans in life expectancies.

Pathologic assessment

The animals were euthanized with 5 mL intravenous 10% KCl administered after 2 months of follow-up. Necropsy was performed immediately. The iliac artery with the stent was evaluated with gross photography and preserved for histologic assessment. Snap frozen slides were prepared in Optimum Cutting Temperature compound (Sakura Finetek Inc., Torrance, California, USA) to test the artery at the proximal and distal ends of the stent for DiI fluorescent stained cells. After tissue fixation in buffered 4% formaldehyde (Guduo Biotechnology, Shanghai, China) for 24 h, the remaining tissue with stent in place was embedded in methyl methacrylate (Hubei Jusheng Bioscience, Wuhan, China) for hard tissue slicing. Tissue segments of proximal, central, and distal regions of the stent were then cut into 6-micron sections with a diamond blade, and these segments were stained with hematoxylin-eosin. Immunohistochemistry staining was performed on separate sections using standard techniques to identify CD34 and VEGFR-2 phenotype expression.

The pseudointimal thickness from the stent struts to the lumen surface was measured at 6 equidistant points around the graft circumference (excluding the thrombus). The pseudointimal area and minimum luminal diameter were measured with microscopy using a LEICA DM LB2 microscope (Leica Microsystems Wetzlar GmbH, Wetzlar, Germany), and the morphometry was analyzed with software (LEICA Qwin v3).

Statistical analysis

Statistical analysis was performed using SPSS Version 19.0 (SPSS, Inc., Chicago, Illinois, USA). Continuous variables were expressed as mean ± standard deviation (SD). An unpaired Student t test was used to compare the EPC capture and DES groups. Categorical data were compared with a χ^2 test or with the Fisher exact test when the expected cell value was < 5. A p value ≤ 0.05 (2-sided) was considered statistically significant.

Results

Stent placement and EPC local transplantation

The technical success rates of stent placement and EPC transplantation were 100% for both groups. Anesthesia accident and cardiac arrest cases (n = 2) that occurred during the preliminary study were excluded from review. No cases of acute thrombosis, stent malposition, or infection occurred during the procedures.

Follow-up data: laboratory and imaging

After consuming a high-lipid diet for 1 month before stent placement, the rabbits had a mean serum cholesterol level of 37.9 ± 1.1 mmol/L, triglyceride level of 3.4 ± 2.3 mmol/L, and low-density lipoprotein cholesterol level of 26.1 ± 2.3 mmol/L, nearly 2- to 8-fold higher than the upper limits of normal values. Fatty liver, arterial atherosclerotic plaque, and foam cells were detected on microscopy examination.

One month after stent placement, CTA demonstrated that all stents were patent in group 1; color Doppler sonography demonstrated 1 case of distal end ISR in group 1, although this case appeared normal on CTA. In Group 2, 1 case of proximal restenosis and 1 case of total occlusion were detected by both CTA and ultrasound, 8 stents were patent. Two months after stent placement, CTA demonstrated that 9 stents were patent in group 1, with 1 distal end ISR; in group 2, there were 3 cases of ISR and 1 case of occlusion (Fig. 2), 6 stents were patent. Therefore, the ISR rate was 1/10 in group 1 and 4/10 in group 2 (p = 0.18).

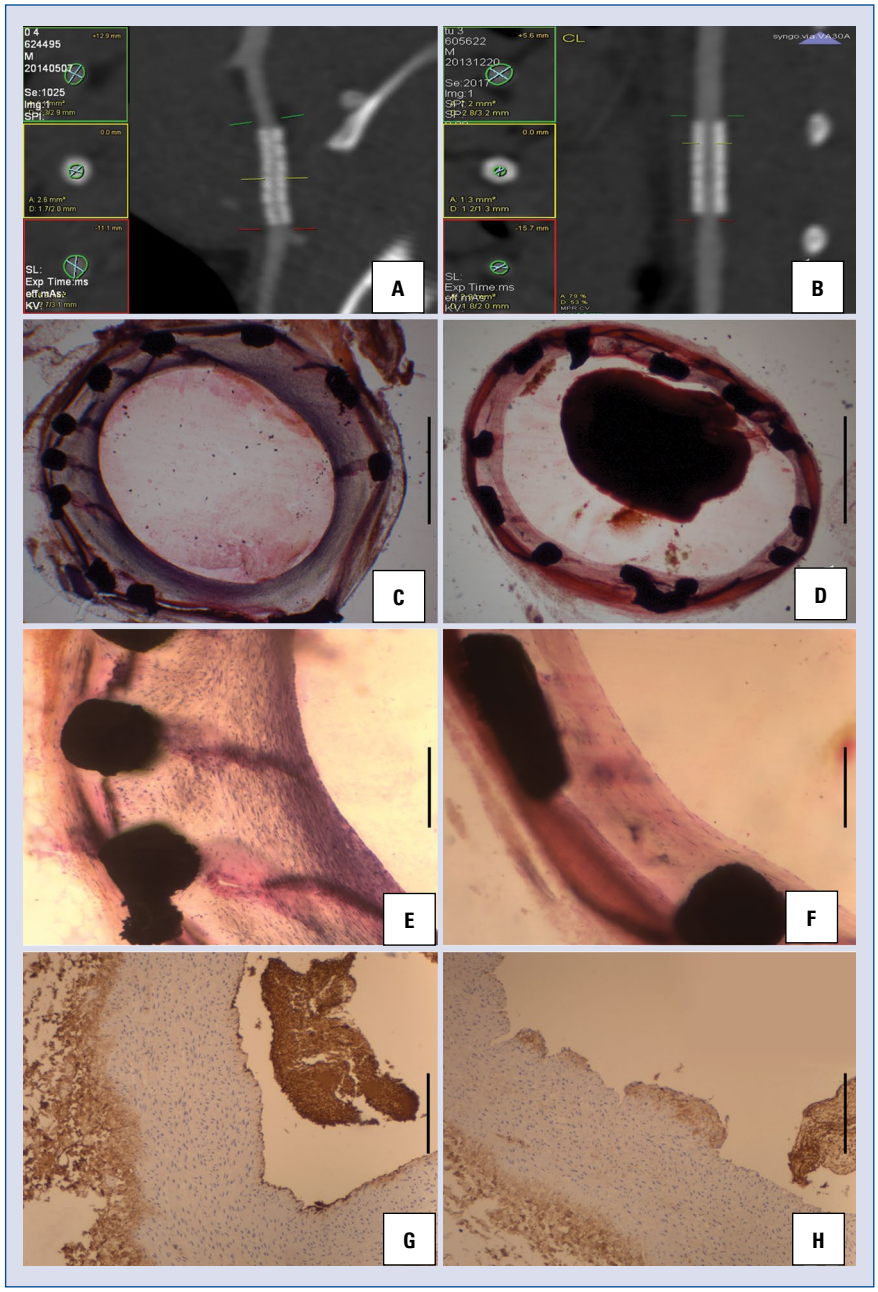


Figure 2. Multiplanar reformatted computed tomography angiography images of endothelial progenitor cells (EPCs) capture stent in group 1 (**A**) and drug-eluting stent in group 2 (**B**) after 2 months of follow-up. Microscopy of hematoxylin-eosin staining in group 1 (**C**, **E**) and group 2 (**D**, **F**) in hard tissue slices. Neointimal hyperplasia was markedly thicker in group 1 than in group 2, and a red thrombus was revealed in the stent lumen in group 2. Immunohistochemical microscopy revealed CD 34+ staining cells (brown) closely lining the endothelium in group 1 (**G**) but loosely lining the endothelium in group 2 (**H**). Scale bar = 1000 μm in images C and D; scale bar = 200 um in images E, F, G, and H.

Although the in-stent minimal diameter and luminal area in group 2 trended somewhat smaller than the in-stent minimal diameter and luminal area in group 1, these differences were not statistically significant ($p > 0.05$; Table 1).

As measured by duplex ultrasound, the velocity of blood in the stent was 61.2 ± 14.4 cm/s in group 1 vs. 74.4 ± 9.0 cm/s in group 2 ($p > 0.05$), and the minimal diameter of the stent was 1.90 ± ± 0.10 mm in group 1 vs. 1.70 ± 0.30 mm in group 2 ($p > 0.05$).

Pathologic analysis of stent segments

DiI-positive cells were extensively detected in samples of the luminal side of the artery from group 1, indicating that the transplanted EPCs

Table 1. Computed tomography angiography data of different site stent luminal diameter and area.

Group	Luminal diameter [cm]			Luminal area [cm^2]		
	Proximal	Minimal	Distal	Proximal	Minimal*	Distal
1	2.38 ± 0.39	1.85 ± 0.15	2.30 ± 0.50	5.10 ± 1.43	3.05 ± 0.45	4.83 ± 1.97
2	2.43 ± 0.49	1.50 ± 0.20	2.23 ± 0.78	5.50 ± 2.13	1.97 ± 0.44	4.80 ± 3.20

*p < 0.05. Group 1 — anti-CD34, anti-VEGFR2 dual antibody coated endothelial progenitor cell capture stent group, Group 2 — sirolimus--eluting stent group

Table 2. Morphometry analysis of samples from group 1 and group 2.

Group	Minimum luminal diameter [mm]	Neo-intimal hyperplasia thickness [mm]*	Intimal hyperplasia area [mm^2]*
1	2.28 ± 0.38	0.21 ± 0.09	1.82 ± 0.52
2	2.68 ± 0.12	0.11 ± 0.07	0.92 ± 0.52

*p < 0.05. Group 1 — anti-CD34, anti-VEGFR2 dual antibody coated endothelial progenitor cell capture stent group, Group 2 — sirolimus--eluting stent group

grew and differentiated to endothelial cells among the pseudointima layer. DiI-positive cells were observed sporadically in samples from group 2.

Microscopy demonstrated integrity of the endothelium layer and exuberant neointimal hyperplasia in group 1. CD34 and VEGFR-2 were positively expressed on the luminal side in group 1. In group 2, almost no intact monolayer endothelium formation was observed, but 3 red thrombi were detected in the stent lumen (Fig. 2). Morphometry demonstrated that the thickness of the neointima in group 1 was significantly greater than in group 2 (0.21 ± 0.09 mm vs. 0.11 ± 0.07 mm; $p < 0.05$). The neointimal area was significantly larger in group 1 (1.82 ± 0.52 mm^2 vs. 0.92 ± 0.52 mm^2, $p < 0.05$), and the minimum luminal diameter was significantly smaller in group 1 (excluding thrombus, 2.28 ± 0.38 mm vs. 2.68 ± 0.12 mm, $p < 0.05$) (Table 2).

Discussion

In this study, transplanted EPCs could be detected on the stent luminal side and were found to have differentiated to functional endothelial cells in vivo in the EPC capture stent group. These results suggest that it is feasible to use a dual antibody-coated EPC capture stent combined with local EPC delivery to achieve rapid re-endothelialization in vivo. A nonsignificant trend toward a reduced rate of late-stage ISR (achieved via inhibition of in-stent thrombosis rather than via reduction of neointimal hyperplasia) in the EPC capture stent group was also noted.

These results differ from those seen in some previous animal studies [17–19]. The authors of these studies concluded that recruiting circulation EPCs on the stent may promote re-endothelialization and inhibit neointimal hyperplasia via the same process. They suggest that the integral endothelium seems not only to prevent neointimal hyperplasia but also to prompt the normal healing process and decrease the rate of acute and chronic thrombosis. Conversely, clinical studies with the Genous R stent and the current study failed to demonstrate this inhibition of neointimal hyperplasia. One possible explanation for this difference is that recruited circulation CD34 EPCs may also transdifferentiate to SMCs under certain conditions (e.g., in the presence of transforming growth factor-beta) [30], suggesting that the specific microenvironment for EPCs determines their fate and the effects of cellular therapy. Therefore, more efforts are needed to improve the EPC microenvironment, which can enhance therapeutic potential [31].

Injury of the endothelium is the first step in atherosclerosis and is the predisposing factor for the occurrence of ISR. Recent studies have suggested that EPCs can treat regional ischemia or injured vessels by prompting angiogenesis [31, 32]. These EPCs, which can be easily harvested from peripheral blood, bone marrow, or the umbilical vein, differentiate into mature endothelial cells in vivo. Previous work demonstrated that

EPCs can be successfully seeded on BMS struts in vitro and in vivo, and this EPC seeding was found to improve patency in transjugular intrahepatic portosystemic shunts in a porcine model [33, 34]. According to available research, in patients with severe atherosclerosis, diabetes, history of heavy smoking, hypercholesterolemia, or older age, there is an extreme paucity of EPCs available in the circulation, and the function of the EPCs that are present is compromised to a certain extent. Local transplantation of allogenous EPCs is a potential option to address this issue [35]. In this study, two different modalities of cell therapy (implanting EPCs and using specific antibody-coated stent-based therapy) were included in an attempt to recruit EPCs. The number of DiI-positive cells from the intima layer was markedly higher in the EPC capture stent group than in the DES group. These results suggest that locally transplanted EPCs are effectively captured by dual antibody-coated stent struts, homing to the wounded site and incorporating into the intima components.

Drug-eluting stent inhibit not only SMC proliferation but also endothelial cell growth, which may explain why no intact endothelium was detected in the DES group in this study. The higher total ISR rate in the DES group was likely due to delayed re-endothelialization, inadequate antibiotic prophylaxis, and invasive surgical protocol [2, 16, 29].

Restenotic and thrombotic processes may occasionally coexist, especially in cases characterized by neointimal hyperplasia plus focal thrombosis inside the stent [3, 36, 37]. The "thromborestenosis" phenomenon is a theory describing how chronic thrombus formation may play an integral role in the development of ISR [38]. Recently, Alfonso et al. suggested that the substrate of ISR encompasses a pathologic spectrum ranging from SMC proliferation to neoatherosclerosis [39, 40]. Among currently available therapeutic modalities for these patients, DES and drug-eluting balloons provide the best clinical and angiographic results in patients with ISR. The investigators suggested that everolimus-eluting stents should be considered the first-line therapy of choice in these challenging scenarios. However, to prevent a primary episode of ISR, combining EPC-capturing technology with drug-eluting technology may be a promising approach for improving clinical outcomes in the future [31]. Further studies are needed to explore this potential approach. Further studies are also needed to determine whether a dual antibody-coated EPC capture stent has a synergistic effect or whether it is more effective than a single antibody- or gene-coated stent.

Limitations of the study

This study had several limitations. First, because the stent was placed in a peripheral rather than a coronary conduit, the rate and mechanism of ISR may not have been identical across cases. Second, the small sample size limited the statistical power of the study. Third, using only male animals may have resulted in sex selection bias, potentially influencing outcomes. Fourth, premature discontinuation of dual antiplatelet therapy (without the use of clopidogrel and cilostazol) varies across clinical settings, which may affect the interpretation of these results. Finally, previous studies have shown that DES is superior to BMS in preventing in-stent stenosis in most clinical settings, and EPC-coated stents have been demonstrated to be more effective than BMS in inhibiting neointima hyperplasia [17–19, 41, 42]. Therefore in this experimental study, the authors directly compared the modified EPC-capture stent with DES; further studies incorporating a larger sample size and with a more robust design (such as including a BMS control arm) are needed.

Conclusions

Use of a dual antibody-coated EPC capture stent concomitant with local EPC transplant decreased the rate of ISR in vivo when compared with DES in an atherosclerotic animal model. This reduced ISR with the use of EPC capture stents may be achieved through a reduction in the in-stent thrombosis rate rather than through inhibition of neointimal hyperplasia.

Acknowledgements

The authors thank Dr. Douglas Coldwell for his kind manuscript preparation, Drs. Yi-Yao Cui and Hui Yu for their technical assistance. The authors also pay great gratitude to Jiangsu Key Laboratory of Molecular Imaging and Functional Imaging, Southeast University for the support of cell culture.

Funding: This study is supported by Natural Science Foundation of Jiangsu Province, China (BK2012589)

Conflict of interest: None declared

References

1. Mozaffarian D, Benjamin EJ, Go AS, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics: 2015 update: a report from the American Heart Association. Circulation. 2015; 131(4): e29–322, doi: 10.1161/CIR.0000000000000152, indexed in Pubmed: 25520374.
2. Serruys PW, Kutryk MJB, Ong ATL. Coronary-artery stents. N Engl J Med. 2006; 354(5): 483–495, doi: 10.1056/NEJMra051091, indexed in Pubmed: 16452560.
3. Dangas GD, Claessen BE, Caixeta A, et al. In-stent restenosis in the drug-eluting stent era. J Am Coll Cardiol. 2010; 56(23): 1897–1907, doi: 10.1016/j.jacc.2010.07.028, indexed in Pubmed: 21109112.
4. Cosgrave J, Agostoni P, Ge L, et al. Clinical outcome following aleatory implantation of paclitaxel-eluting or sirolimus-eluting stents in complex coronary lesions. Am J Cardiol. 2005; 96(12): 1663–1668, doi: 10.1016/j.amjcard.2005.07.082, indexed in Pubmed: 16360354.
5. Stone GW, Ellis SG, Cannon L, et al. TAXUS V Investigators. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. JAMA. 2005; 294(10): 1215–1223, doi: 10.1001/jama.294.10.1215, indexed in Pubmed: 16160130.
6. Cassese S, Byrne RA, Tada T, et al. Incidence and predictors of restenosis after coronary stenting in 10 004 patients with surveillance angiography. Heart. 2014; 100(2): 153–159, doi: 10.1136/heartjnl-2013-304933, indexed in Pubmed: 24270744.
7. Sun Y, Li L, Su Q, et al. Comparative efficacy and safety of drug-eluting stent and conventional therapies in coronary heart disease patients with in-stent restenosis: a meta-analysis. Cell Biochem Biophys. 2014; 68(1): 211–229, doi: 10.1007/s12013-013-9692-7, indexed in Pubmed: 23784750.
8. Unverdorben M, Vallbracht C, Cremers B, et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. Circulation. 2009; 119(23): 2986––2994, doi: 10.1161/CIRCULATIONAHA.108.839282, indexed in Pubmed: 19487593.
9. Holmes DR, Kereiakes DJ, Garg S, et al. Stent thrombosis. J Am Coll Cardiol. 2010; 56(17): 1357–1365, doi: 10.1016/j.jacc.2010.07.016, indexed in Pubmed: 20946992.
10. Tsigkas GG, Karantalis V, Hahalis G, et al. Stent restenosis, pathophysiology and treatment options: a 2010 update. Hellenic J Cardiol. 2011; 52(2): 149–157, indexed in Pubmed: 21478125.
11. Collins MJ, Li X, Lv W, et al. Therapeutic strategies to combat neointimal hyperplasia in vascular grafts. Expert Rev Cardiovasc Ther. 2012; 10(5): 635–647, doi: 10.1586/erc.12.33, indexed in Pubmed: 22651839.
12. Byrne RA, Neumann FJ, Mehilli J, et al. ISAR-DESIRE 3 investigators. Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial. Lancet. 2013; 381(9865): 461–467, doi: 10.1016/S0140-6736(12)61964-3, indexed in Pubmed: 23206837.
13. Razavi MK, Mustapha JA, Miller LE. Contemporary systematic review and meta-analysis of early outcomes with percutaneous treatment for infrapopliteal atherosclerotic disease. J Vasc Interv Radiol. 2014; 25(10): 1489–96, 1496.e1, doi: 10.1016/j.jvir.2014.06.018, indexed in Pubmed: 25130307.
14. Bosiers M, Deloose K, Callaert J, et al. Superiority of stent-grafts for in-stent restenosis in the superficial femoral artery: twelve-month results from a multicenter randomized trial. J Endovasc Ther. 2015; 22(1): 1–10, doi: 10.1177/1526602814564385, indexed in Pubmed: 25775672.
15. Dippel EJ, Makam P, Kovach R, et al. EXCITE ISR Investigators. Randomized controlled study of excimer laser atherectomy for treatment of femoropopliteal in-stent restenosis: initial results from the EXCITE ISR trial (EXCImer Laser Randomized Controlled Study for Treatment of FemoropopliTEal In-Stent Restenosis). JACC Cardiovasc Interv. 2015; 8(1 Pt A): 92–101, doi: 10.1016/j.jcin.2014.09.009, indexed in Pubmed: 25499305.
16. Aoki J, Serruys PW, van Beusekom H, et al. Endothelial progenitor cell capture by stents coated with antibody against CD34: the HEALING-FIM (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth-First In Man) Registry. J Am Coll Cardiol. 2005; 45(10): 1574–1579, doi: 10.1016/j.jacc.2005.01.048, indexed in Pubmed: 15893169.
17. Sharif F, Hynes SO, Cooney R, et al. Gene-eluting stents: adenovirus-mediated delivery of eNOS to the blood vessel wall accelerates re-endothelialization and inhibits restenosis. Mol Ther. 2008; 16(10): 1674–1680, doi: 10.1038/mt.2008.165, indexed in Pubmed: 18714308.
18. Walter DH, Cejna M, Diaz-Sandoval L, et al. Local gene transfer of phVEGF-2 plasmid by gene-eluting stents: an alternative strategy for inhibition of restenosis. Circulation. 2004; 110(1): 36–45, doi: 10.1161/01.CIR.0000133324.38115.0A, indexed in Pubmed: 15210598.
19. Blindt R, Vogt F, Astafieva I, et al. A novel drug-eluting stent coated with an integrin-binding cyclic Arg-Gly-Asp peptide inhibits neointimal hyperplasia by recruiting endothelial progenitor cells. J Am Coll Cardiol. 2006; 47(9): 1786–1795, doi: 10.1016/j.jacc.2005.11.081, indexed in Pubmed: 16682302.
20. Strehlow K, Werner N, Berweiler J, et al. Estrogen increases bone marrow-derived endothelial progenitor cell production and diminishes neointima formation. Circulation. 2003; 107(24): 3059–3065, doi: 10.1161/01.CIR.0000077911.81151.30, indexed in Pubmed: 12810616.
21. Egashira K, Nakano K, Ohtani K, et al. Local delivery of anti-monocyte chemoattractant protein-1 by gene-eluting stents attenuates in-stent stenosis in rabbits and monkeys. Arterioscler Thromb Vasc Biol. 2007; 27(12): 2563–2568, doi: 10.1161/ATVBAHA.107.154609, indexed in Pubmed: 17885211.
22. Garg R, Tellez A, Alviar C, et al. The effect of percutaneous coronary intervention on inflammatory response and endothelial progenitor cell recruitment. Catheter Cardiovasc Interv. 2008; 72(2): 205–209, doi: 10.1002/ccd.21611, indexed in Pubmed: 18651648.
23. Miglionico M, Patti G, D'Ambrosio A, et al. Percutaneous coronary intervention utilizing a new endothelial progenitor cells antibody-coated stent: a prospective single-center registry in high-risk patients. Catheter Cardiovasc Interv. 2008; 71(5): 600–604, doi: 10.1002/ccd.21437, indexed in Pubmed: 18360849.
24. den Dekker WK, Houtgraaf JH, Onuma Y, et al. Final results of the HEALING IIB trial to evaluate a bio-engineered CD34 antibody coated stent (Genous™ Stent) designed to promote vascular healing by capture of circulating endothelial progenitor cells in CAD patients. Atherosclerosis. 2011; 219(1): 245–252, doi: 10.1016/j.atherosclerosis.2011.06.032, indexed in Pubmed: 21763653.

25. Klomp M, Damman P, Beijk MAM, et al. Applying the National Institute for Clinical Excellence criteria to patients treated with the Genous™ Bio-engineered R stent™: a sub-study of the e-HEALING (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth) worldwide registry. Heart Vessels. 2012; 27(4): 360–369, doi: 10.1007/s00380-011-0167-8, indexed in Pubmed: 21725668.
26. Cassese S, Galasso G, Sciahbasi A, et al. Antiplatelet theRapy after Genous EPC-capturing coroNary stenT implantatiOn: the ARGENTO study: a prospective, multicenter registry. Int J Cardiol. 2013; 167(3): 757–761, doi: 10.1016/j.ijcard.2012.03.052, indexed in Pubmed: 22459371.
27. Mai XL, Ma ZL, Sun JH, et al. Assessments of proliferation capacity and viability of New Zealand rabbit peripheral blood endothelial progenitor cells labeled with superparamagnetic particles. Cell Transplant. 2009; 18(2): 171–181, indexed in Pubmed: 19499705.
28. Li Na, Yang H, Lu L, et al. Comparison of the labeling efficiency of BrdU, DiI and FISH labeling techniques in bone marrow stromal cells. Brain Res. 2008; 1215: 11–19, doi: 10.1016/j.brainres.2007.09.095, indexed in Pubmed: 18468584.
29. Falk E. Pathogenesis of Atherosclerosis. J Am Coll Cardiol. 2006; 47(8 Suppl): C7–C12, doi: 10.1016/j.jacc.2005.09.068.
30. Imamura H, Ohta T, Tsunetoshi K, et al. Transdifferentiation of bone marrow-derived endothelial progenitor cells into the smooth muscle cell lineage mediated by tansforming growth factor-beta1. Atherosclerosis. 2010; 211(1): 114–121, doi: 10.1016/j.atherosclerosis.2010.02.040, indexed in Pubmed: 20303084.
31. Xu BY, Xiang MX, Wang Ja. Endothelial Progenitor Cells and In-stent Restenosis. Curr Stem Cell Res Ther. 2015; 10(4): 364–371, indexed in Pubmed: 25654305.
32. Asahara T, Murohara T, Sullivan A, et al. Isolation of putative progenitor endothelial cells for angiogenesis. Science. 1997; 275(5302): 964–967, indexed in Pubmed: 9020076.
33. Shi HJ, Cao AH, Chen J, et al. Transjugular intrahepatic portosystemic shunt with an autologous endothelial progenitor cell seeded stent: a porcine model. Acad Radiol. 2010; 17(3): 358–367, doi: 10.1016/j.acra.2009.10.007, indexed in Pubmed: 19962914.
34. Shi HJ, Cao AH, Teng GJ. Seeding endothelial progenitor cells on a self-expanding metal stent: an in vitro study. J Vasc Interv Radiol. 2010; 21(7): 1061–1065, doi: 10.1016/j.jvir.2010.03.019, indexed in Pubmed: 20610181.
35. Marsboom G, Janssens S. Endothelial progenitor cells: new perspectives and applications in cardiovascular therapies. Expert Rev Cardiovasc Ther. 2008; 6(5): 687–701, doi: 10.1586/14779072.6.5.687, indexed in Pubmed: 18510485.
36. Centemero MP, Stadler JR. Stent thrombosis: an overview. Expert Rev Cardiovasc Ther. 2012; 10(5): 599–615, doi: 10.1586/erc.12.38, indexed in Pubmed: 22651836.
37. Kim MS, Dean LS. In-stent restenosis. Cardiovasc Ther. 2011; 29(3): 190–198, doi: 10.1111/j.1755-5922.2010.00155.x, indexed in Pubmed: 20406239.
38. Farooq V, Gogas BD, Serruys PW. Restenosis: delineating the numerous causes of drug-eluting stent restenosis. Circ Cardiovasc Interv. 2011; 4(2): 195–205, doi: 10.1161/CIRCINTERVENTIONS.110.959882, indexed in Pubmed: 21505166.
39. Fusaro M, Cassese S, Ndrepepa G, et al. Drug-eluting stents for revascularization of infrapopliteal arteries: updated meta-analysis of randomized trials. JACC Cardiovasc Interv. 2013; 6(12): 1284–1293, doi: 10.1016/j.jcin.2013.08.007, indexed in Pubmed: 24355118.
40. Alfonso F, Pérez-Vizcayno M, Cárdenas A, et al. A prospective randomized trial of Drug-Eluting balloons versus everolimus-eluting stents in patients with in-stent restenosis of drug-eluting stents. J Am Coll Cardiol. 2015; 66(1): 23–33, doi: 10.1016/j.jacc.2015.04.063.
41. Spaulding C, Daemen J, Boersma E, et al. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med. 2007; 356(10): 989–997, doi: 10.1056/NEJMoa066633, indexed in Pubmed: 17296825.
42. Kaiser C, Galatius S, Erne P, et al. BASKET–PROVE Study Group. Drug-eluting versus bare-metal stents in large coronary arteries. N Engl J Med. 2010; 363(24): 2310–2319, doi: 10.1056/NEJMoa1009406, indexed in Pubmed: 21080780.

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

Cardiology Journal
2019, Vol. 26, No. 3, 292–293
DOI: 10.5603/CJ.2019.0057

ISSN 1897–5593

Successful percutaneous coronary intervention in patients with recanalized thrombus: Saving a radial artery by snuffbox approach

Yongcheol Kim, Myung Ho Jeong, Min Chul Kim, Doo Sun Sim, Young Joon Hong, Ju Han Kim, Youngkeun Ahn

Department of Cardiology, Chonnam National University Hospital, Gwangju, Korea

A 76-year-old man with chronic kidney disease was referred to the documented clinic suffering from aggravating effort angina. Thus, after treatment with acetylsalicylic acid (300 mg loading dose) and clopidogrel (300 mg loading dose), coronary angiography was tried via left distal radial artery as a preservation of radial artery for arteriovenous fistula creation. This was successfully cannulated by a 5 French sheath (Fig. 1). However, brachial artery anomaly led to a change in the access site using the right snuffbox approach (Fig. 2A). Coronary angiography demonstrated diffuse stenosis with multiple linear filling defects and haziness in the proximal right coronary artery (Fig. 2B). Optical coherence tomography (OCT) showed a honeycomb-like structure with multiple cavities and it was concluded that this represented recanalized thrombus (Fig. 2C, D, **Suppl. Video 1**). OCT assessment led to implantation of a 2.75 × × 38 mm Xience Sierra stent (Abbott Vascular, Santa Clara, CA, USA) and postdilation was achieved with a 3.25 × 12 mm noncompliant at up to 21 atm in the proximal portion of the implanted stent. Repeated OCT assessment demonstrated good stent expansion and strut apposition without edge dissection. Final coronary angiography showed good distal flow without residual stenosis (Fig. 2E).

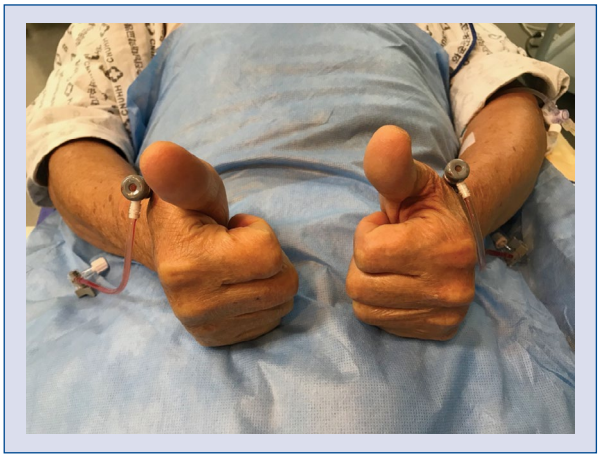


Figure 1. Inserted 5 French sheath via snuffbox approach.

This case highlights that OCT enables confirmation of a rare case of recanalized thrombus and the snuffbox approach can be an alternative access site in patients with renal impairment where the radial artery needs protection for anteriovenous fistula.

Conflict of interest: None declared

Address for correspondence: Myung Ho Jeong, MD, Cardiovascular Convergence Research Center of Chonnam National University Hospital, Gwangju 501-757, Republic of Korea, tel: +82-62-220-6243, fax: +82-62-228-7174, e-mail: myungho@chollian.net

Received: 30.11.2018 Accepted: 21.01.2019

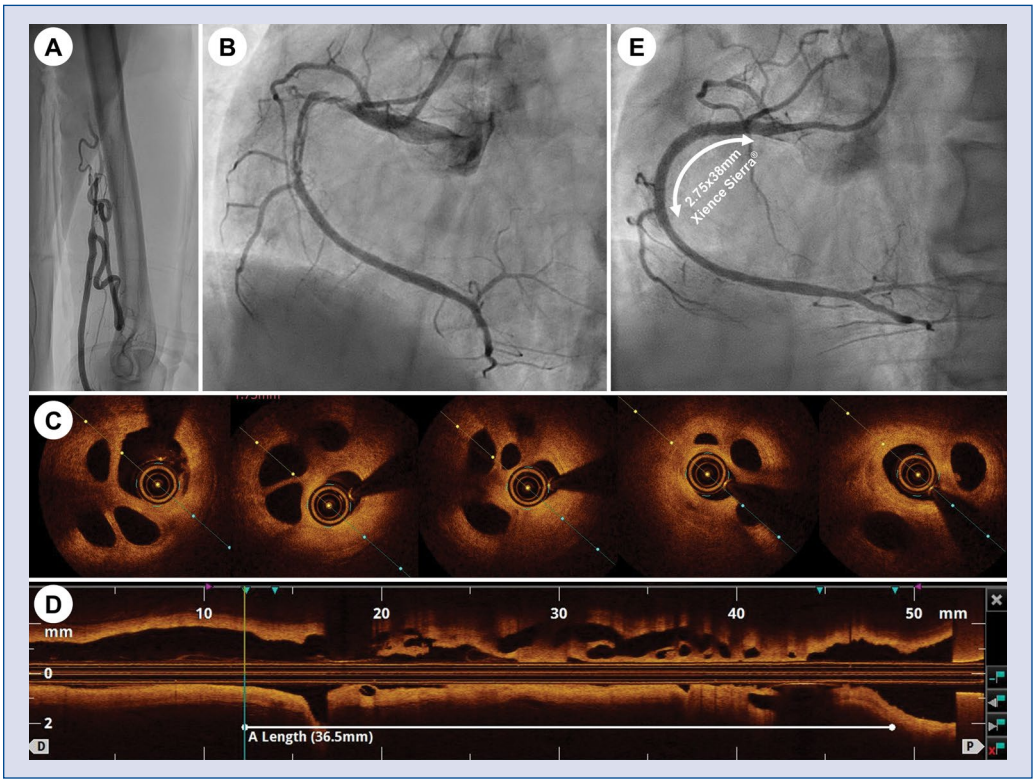


Figure 2. A. Peripheral angiography demonstrating the left brachial artery anomaly; **B.** Angiographic assessment demonstrating multiple linear filling defects and haziness in the proximal coronary artery; **C, D.** Longitudinal and cross-sectional optical coherence tomography imaging demonstrated a honeycomb-like structure with multiple cavities of various sizes; **E.** Final angiogram demonstrated good distal flow without residual stenosis from treatment with 2.75 × 38 mm Xience Sierra® stent.

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

Cardiology Journal
2019, Vol. 26, No. 3, 294–295
DOI: 10.5603/CJ.2019.0058

ISSN 1897–5593

A case of a de-novo lesion in the left circumflex artery treated with excimer laser and drug-coated balloon under the guidance of optical frequency domain imaging

Shinichiro Masuda[1], Takashi Shibui[1], Takaaki Tsuchiyama[1], Takashi Ashikaga[2]

[1]Department of Cardiology, Tokyo Metropolitan Hiroo Hospital, Tokyo, Japan
[2]Department of Cardiology, Japanese Red Cross Musashino Hospital, Tokyo, Japan

A 72-year-old man who previously underwent percutaneous coronary intervention with a drug-eluting stent implantation from the left main trunk and extending to proximal left anterior descending artery was admitted to the documented hospital for angina pectoris. Coronary angiography (CAG) revealed 90% stenosis at the ostium of the left circumflex artery (LCX) (Fig. 1A). Excimer laser coronary angioplasty (ELCA) was performed using a 0.9 mm concentric laser catheter at a pulse rate of 25 Hz and energy output of 45 mJ/mm^2, 35 Hz and 55 mJ/mm^2, and 45 Hz and 60 mJ/mm^2 for a total of 5200 pulses and balloon angioplasty using a drug-coated balloon (DCB) under the guidance of optical frequency domain imaging (OFDI), which revealed fibrous plaque and eccentric severe calcification (Fig. 1B). After ELCA, minimum lumen area (MLA) increased from 1.4 mm^2 to 2.6 mm^2 (Fig. 1C) and on final OFDI to 3.9 mm^2 along with minor plaque dissection (Fig. 1D). Final CAG demonstrated optimal result without flow limitation (Fig 1E). After discharge, no significant clinical events were reported. Eight months later, follow-up CAG and OFDI were performed. Follow-up CAG demonstrated no restenosis at the ostium of the LCX (Fig. 1F). OFDI showed that the MLA slightly decreased from 3.9 mm^2 to 3.5 mm^2 and that the minor dissection had clearly improved (Fig. 1G). The DCB is efficacious in de-novo coronary artery lesions [1], which mainly contributed to suppress the restenosis in this case; however, although OFDI after ELCA demonstrated a slight increase in MLA, ELCA might be attributed to the lesion debulking and modification leading to optimal balloon expansion. A similar mechanism was previously reported in the case of in-stent restenosis [2]. For acute myocardial infarction, the combined use of ELCA and DCB for de-novo coronary artery disease works synergistically to reduce restenosis [3]. Stent-less strategy employing ELCA and DCB may be an effective revascularization of large vessel de-novo lesions, when traditional stent deployment is not a viable option.

Informed consent was obtained from the patient in accordance with the Helsinki Declaration.

Acknowledgements

The authors wish to thank Dr. Richard H. Kaszynski for reviewing and revising this manuscript.

Conflict of interest: None declared

References

1. Uskela S, Kärkkäinen JM, Eränen J, et al. Percutaneous coronary intervention with drug-coated balloon-only strategy in stable coronary artery disease and in acute coronary syndromes: An all-comers registry study. Catheter Cardiovasc Interv. 2019; 93(5): 893–900, doi: 10.1002/ccd.27950, indexed in Pubmed: 30380186.
2. Yin Da, Maehara A, Mezzafonte S, et al. Excimer laser angioplasty-facilitated fracturing of napkin-ring peri-stent calcium in a chronically underexpanded stent: documentation by optical coherence tomography. JACC Cardiovasc Interv. 2015; 8(8): e137–e139, doi: 10.1016/j.jcin.2015.02.018, indexed in Pubmed: 26205458.
3. Harima A, Sairaku A, Inoue I, et al. Real-life experience of a stent-less revascularization strategy using a combination of excimer laser and drug-coated balloon for patients with acute coronary syndrome. J Interv Cardiol. 2018; 31(3): 284–292, doi: 10.1111/joic.12495, indexed in Pubmed: 29464846.

Address for correspondence: Shinichiro Masuda, MD, Department of Cardiology, Tokyo Metropolitan Hiroo Hospital, 2-34-10, Ebisu, Shibuya-ku, Tokyo, 150-0013, Japan, tel: +08-3-3444-1181, fax: +08-3-3444-3196, e-mail: giga627@yahoo.co.jp

Received: 24.07.2018 Accepted: 28.01.2019

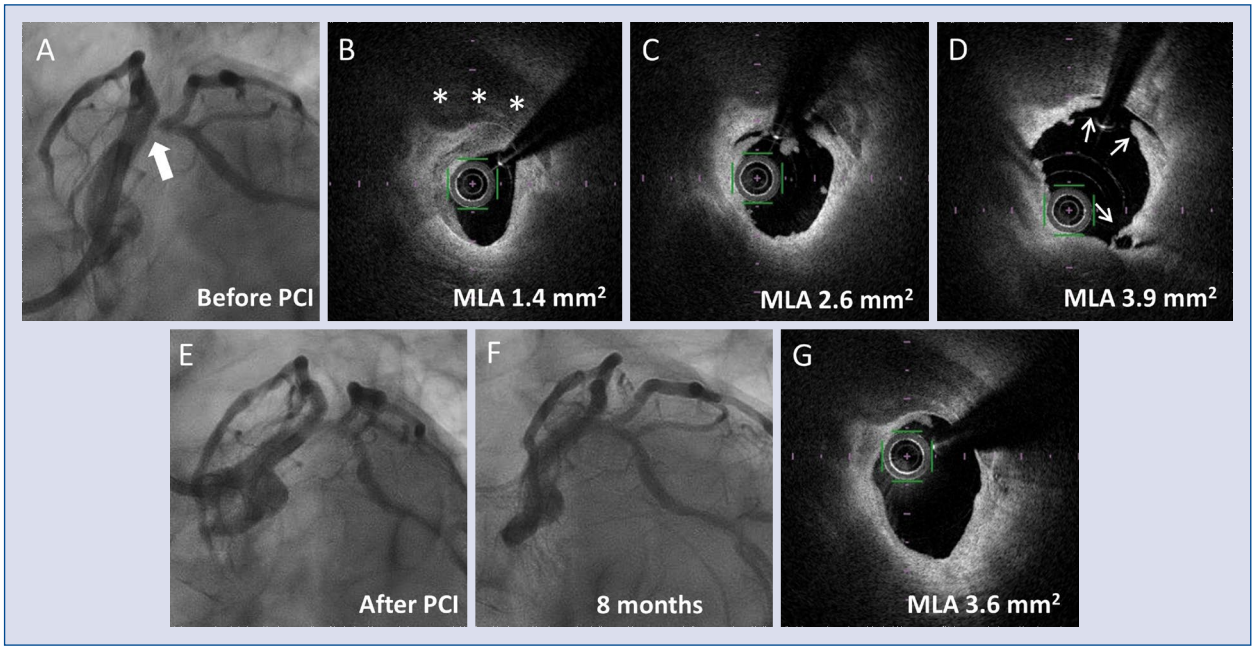


Figure 1. Coronary angiography (CAG) and optical frequency domain imaging (OFDI) findings of the culprit lesion at the time of percutaneous coronary intervention (PCI) and subsequent follow-up CAG. **A.** CAG before PCI showing severe stenosis at the ostium of the left circumflex artery (white arrow); **B.** OFDI image before PCI showing eccentric severe calcification (asterisks), and a minimum lumen area (MLA) of 1.4 mm^2; **C.** OFDI image after excimer laser coronary angioplasty with MLA of 2.6 mm^2; **D.** Final OFDI image at the PCI demonstrates a small plaque dissection (white arrows) and MLA of 3.9 mm^2; **E.** CAG after PCI showing optimal results; **F.** CAG at follow-up shows no restenosis; **G.** OFDI at follow-up CAG showing improvements in plaque dissection and a slight reduction in the MLA from 3.9 mm^2 to 3.6 mm^2.

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

Cardiology Journal
2019, Vol. 26, No. 3, 296–297
DOI: 10.5603/CJ.2019.0059

ISSN 1897–5593

Coronary artery fistula and premature coronary atherosclerosis

Łukasz Turek[1], Anna Polewczyk[1, 2], Marianna Janion[1, 2], Marcin Sadowski[2, 3]

[1]2nd Department of Cardiology, Swietokrzyskie Cardiology Center, Kielce, Poland
[2]Medical Faculty and Health Sciences, The Jan Kochanowski University, Kielce, Poland
[3]Catheterization Laboratory, Swietokrzyskie Cardiology Center, Kielce, Poland

A 48-year-old man with insignificant family history and without cardiovascular risk factors was admitted due to typical retrosternal chest pain of 30 min duration. Physical examination was within normal limits. Transthoracic echocardiography revealed anterior wall basal segments hypokinesis. Signs of ongoing myocardial ischemia in admission electrocardiogram (ST-segment depression in V_1–V_4) together with a significant rise in cardiac troponin T level (from 4.9 to 143.4 ng/L) resulted in a diagnosis of acute coronary syndrome without ST-segment elevation as most probable. Coronary angiography revealed a critical stenosis of a marginal branch (Fig. 1A) and coronary artery fistula (CAF) originating from the left main coronary artery (Fig. 1C, D). A successful percutaneous coronary intervention of the marginal branch with drug-eluting stent implantation was performed (Fig. 1B). The patient's further recovery was uneventful. A repeat careful echocardiographic examination was able to detect flow to the right pulmonary artery (Fig. 1E, F). Moreover, diameter measurements of cardiac chambers, pulmonary and systemic flow ratios (Qp/Qs) and systolic pulmonary artery pressure determined by Doppler echocardiography were normal. Multidetector computed tomography is commonly used to detect and enhance visualization of the complex geometry of coronary fistulas, however, in this case the computed tomography scan was not performed related to an absence of pressure and volume overload on echocardiographic study, the patient was asymptomatic with CAF (unexplained relation of CAFs to incidence of atherosclerotic coronary artery disease) and radiological protection. This patient was recommended conservative management of CAF as the first-line treatment option and further follow-up. CAF is a rare vascular anomaly with an estimated prevalence of 0.002% in the general population and it can reach up to 5% in patients undergoing coronary angiography. In adults, about 30% of CAF cases are associated with coronary atherosclerosis — however, the relationship between CAFs and coronary atherosclerosis has not yet been clarified.

Conflict of interest: None declared

Address for correspondence: Łukasz Turek, 2nd Department of Cardiology, Swietokrzyskie Cardiology Center, ul. Grunwaldzka 45, 25–736 Kielce, Poland, tel: +48 692199654, e-mail: garbit.garbit@interia.pl

Received: 24.11.2018 Accepted: 4.02.2019

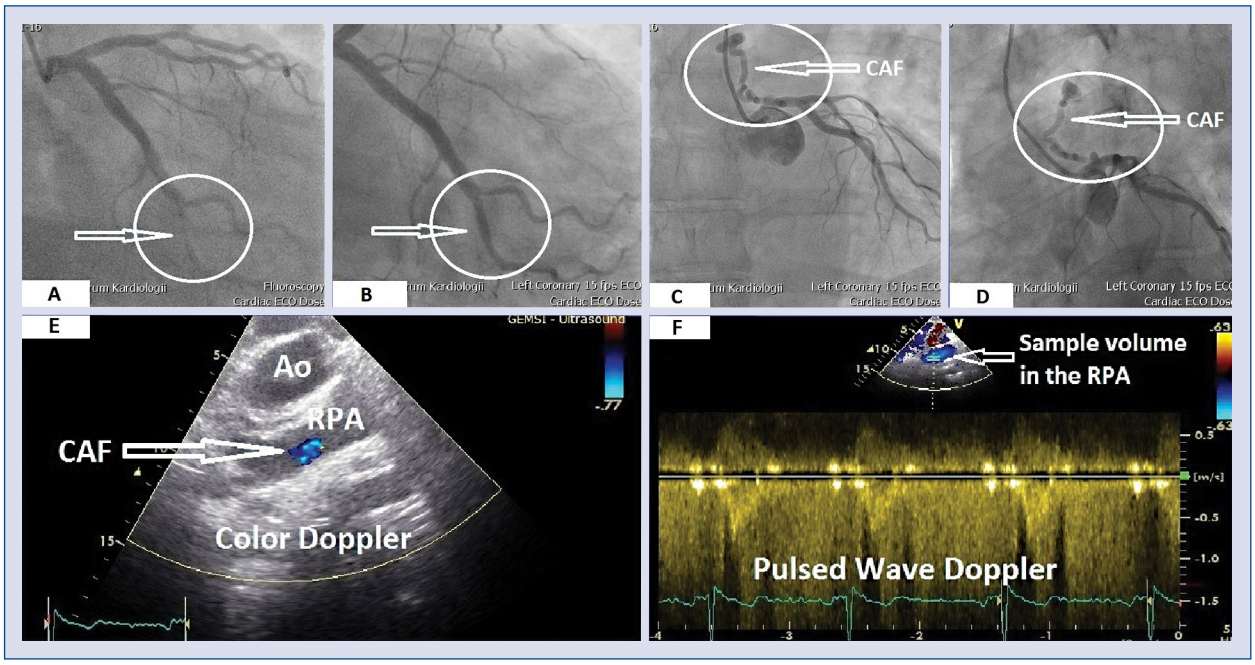


Figure 1. A. Coronary angiography: critical stenosis of the marginal branch (arrow); **B.** Coronary angiography: successful percutaneous coronary intervention of marginal branch (arrow); **C, D.** Coronary angiography: coronary artery fistula (CAF; arrow); **E.** Echocardiography study — suprasternal view of long axis of right pulmonary artery (RPA) — color flow Doppler images: CAF flow (arrow); **F.** Echocardiography study — suprasternal view of long axis of RPA — pulsed-wave Doppler: CAF flow (arrow) — sample volume in the RPA; Ao — aortic arch.

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

Cardiology Journal
2019, Vol. 26, No. 3, 298–299
DOI: 10.5603/CJ.2019.0060

ISSN 1897–5593

Reactive arthritis-associated aortitis followed by Yersinia Enterocolitica infection: Multimodal imaging

Rafał Gałąska[1], Anna Masiak[2], Dorota Kulawiak-Gałąska[3], Zenobia Czuszyńska[2], Karolina Dorniak[4], Marcin Fijałkowski[1]

[1]1st Department of Cardiology, Medical University of Gdansk, Poland
[2]Chair and Department of Internal Diseases, Connective Tissue Diseases and Geriatrics, Medical University of Gdansk, Poland
[3]Department of Radiology, Medical University of Gdansk, Poland
[4]Department of Noninvasive Cardiac Diagnostics, Medical University of Gdansk, Poland

A 51-year-old female was admitted to the Department of Cardiology due to severe aortic insufficiency. Her medical history revealed she had been treated 5 years earlier with naproxen and oral corticosteroids for seronegative arthritis. Echocardiography performed at that time revealed she had mild aortic insufficiency. Four years later when her arthritis recurred, after serological tests (IgA 85.2 U/mL, IgG 88.4 U/mL IgM 36.7 U/mL, positive over 25 U/mL) she was diagnosed with yersiniosis. The patient was treated with ciprofloxacine (5 weeks) and ceftriaxone (another 3 weeks). Despite this treatment she still had active arthritis in her right wrist, nodular erythema and heel enthesopathy. Her C-reactive protein was persistently elevated (21 mg/dL). Echocardiography revealed severe aortic regurgitation with moderately decreased left ventricular ejection fraction and thickening of the wall of the ascendens aorta (Fig. 1A, B). Aortic wall involvement was confirmed by mulitdetector computed tomography, magnetic resonance examinations, and positron emission tomography (Fig. 1C, D, **Suppl. Video 1**). She was then diagnosed with noninfectious aortitis. The patient was treated with corticosteroids and cyclophosphamide which resulted in a complete resolution of her rheumatic symptoms. Control mulitdetector computed tomography and magnetic resonance examinations revealed only partial withdrawal of the primary changes in the aorta (Fig. 1E, F) with regions of delayed enhancement in the wall of her ascendens aorta, aortic arch and its branches (Fig. 1G, H). Due to symptomatic severe aortic insufficiency, the aortic valve was replaced with a St. Jude 23 prothesis which resulted in significant improvement of exercise tolerance as well as left ventricular function.

Reactive arthritis is an immune-mediated seronegative arthritis that belongs to a group of spondyloarthropathies and develops after a gastrointestinal or genitourinary system infection. This patient is unique for several reasons. She presented isolated arthritis without involvement of eyes and sacroiliac joints and her HLA B27 test was negative. The opinion presented herein is that the Yersinia infection led to reactive arthritis as well as to aortitis and severe aortic insufficiency. Reactive arthritis has been considered a self-limited disease, but in fact symptoms can persist for many years and can lead to serious target organ complications.

Conflict of interest: None declared

Address for correspondence: Dr. Rafał Gałąska, 1st Department of Cardiology, Medical University of Gdansk, ul. Dębinki 7, 80–952 Gdańsk, Poland, tel: +48 58 349 25 04, fax: +48 58 346 12 01, e-mail: rgal@gumed.edu.pl
Received: 2.01.2019 Accepted: 22.01.2019

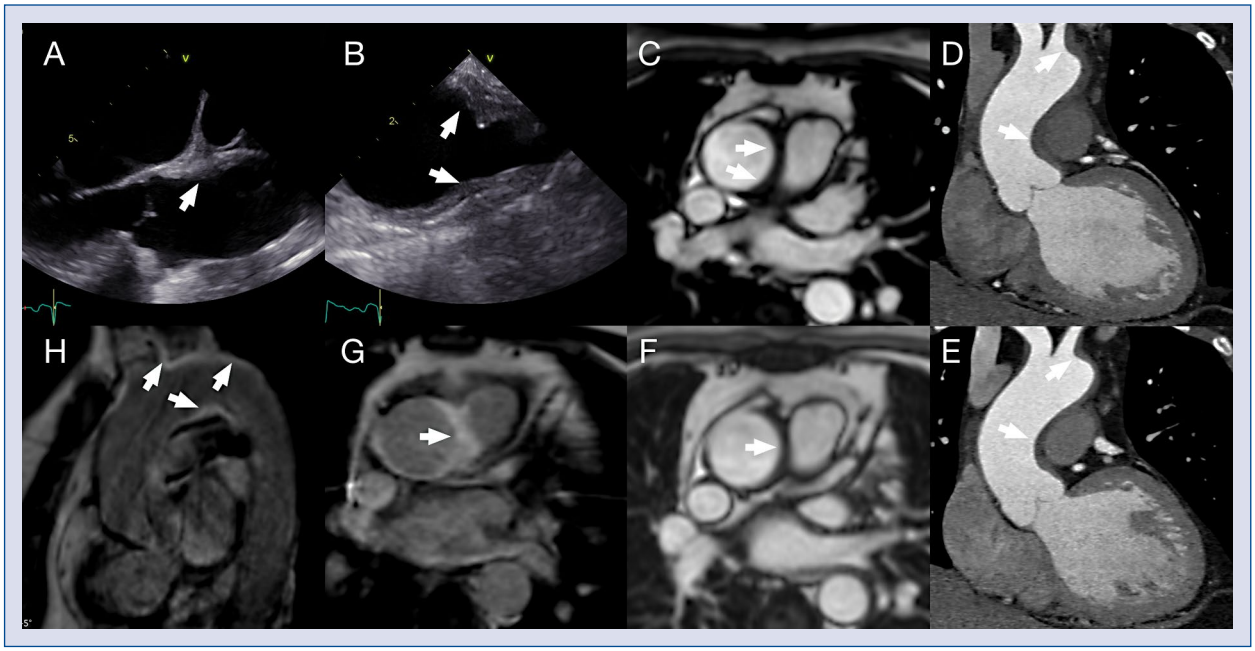


Figure 1. A. Transesophageal echocardiography, focal thickening of the ascendens aorta wall (arrows) before treatment; **B.** Transesophageal echocardiography, thickening of the wall of the aortic arch and proximal parts of its branches (arrows) before treatment; **C.** TrueFisp magnetic resonance examinations imaging of ascending aorta, note a semilunar thickening of the aortic wall before treatment (arrows); **D.** Mulitdetector computed tomography multiplanar reconstruction demonstrating a thickening of the wall of the ascending aorta and aortic arch before treatment; **E.** Mulitdetector computed tomography after treatment; **F.** TrueFisp magnetic resonance examination imaging after treatment; **G.** Delayed enhancement magnetic resonance examination imaging, note regions of the enhancement of the wall of the ascending aorta; **H.** Delayed enhancement magnetic resonance examinations imaging, note regions of the enhancement of the wall of the aortic arch and its branches.

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

Cardiology Journal
2019, Vol. 26, No. 3, 300–301
DOI: 10.5603/CJ.2019.0061

ISSN 1897–5593

Recurrent and life-threatening strokes after pacemaker implantation in a patient affected by concealed superior sinus venosus atrial septal defect

Giusy Sirico[1], Andrea Montisci[2], Domenico Sirico[3], Alfonso Ielasi[4], Michele Criscuolo[5], Mauro Preziosa[5], Maurizio Tespili[4], Massimo Mantica[1]

[1]Department of Cardiac Electrophysiology and Pacing, Istituto Clinico Sant'Ambrogio, Milan, Italy
[2]Department of Anesthesia and Intensive Care, Cardiothoracic Center, Istituto Clinico Sant'Ambrogio, Milan, Italy
[3]Paediatric Cardiology Services, Royal Brompton Hospital and Harefield NHS Foundation Trust, London, United Kingdom
[4]Department of Clinical and Interventional Cardiology, Istituto Clinico Sant'Ambrogio, Milan, Italy
[5]Department of Radiology, Istituto Clinico Sant'Ambrogio, Milan, Italy

A 68-year-old woman was referred to the documented hospital after large and consecutive strokes following pacemaker implantation. Upon arrival she was aphasic, hemiplegic and lethargic. Electrocardiogram showed constant QRS stimulated in right bundle branch block pattern. Transthoracic echocardiography showed leads positioned in left heart with right chambers dilation and estimated pulmonary artery systolic pressure of 35 mmHg. Angiography with a pigtail catheter in the innominate vein showed overriding superior vena cava between right and left atria, with leads ending up inside the left heart (**Suppl. Video 1**, Fig. 1A, left). Lead removal was then performed to prevent further cardio-embolic strokes and new right chamber endocardial leads were implanted. Critical clinical conditions discouraged an epicardial pacing system implantation. Pacemaker dependency compelled positioning the first new active fixation leads in right atrial appendage and right ventricular septum before left side lead removal. At left anterior oblique fluoroscopy four leads were temporarily present in four chambers of the heart (Fig. 1A, right) showing left sided leads posteriorly located. Previous leads were then extracted from left heart without complication. Final electrocardiogram showed stimulated QRS in a left bundle branch block pattern. Contrast chest computed tomography scan at sagittal plane (Fig. 1B, left) and three-dimensional reconstruction (Fig. 1B, right) showed concealed superior sinus venosus atrial septal defect with partial anomalous pulmonary venous return. Images herein highlight an occasional diagnosis of sinus venosus atrial septal defect following an inadvertent lead malposition associated to cerebral embolism.

Conflict of interest: None declared

Address for correspondence: Giusy Sirico, MD, PhD, Istituto Clinico Sant'Ambrogio, Via Giuseppe Faravelli 16, 20149 Milan, Italy, tel: +39-02-33127712, fax: +39-02-33127711, e-mail: giusy.sirico@gmail.com

Received: 31.01.2019 Accepted: 7.02.2019

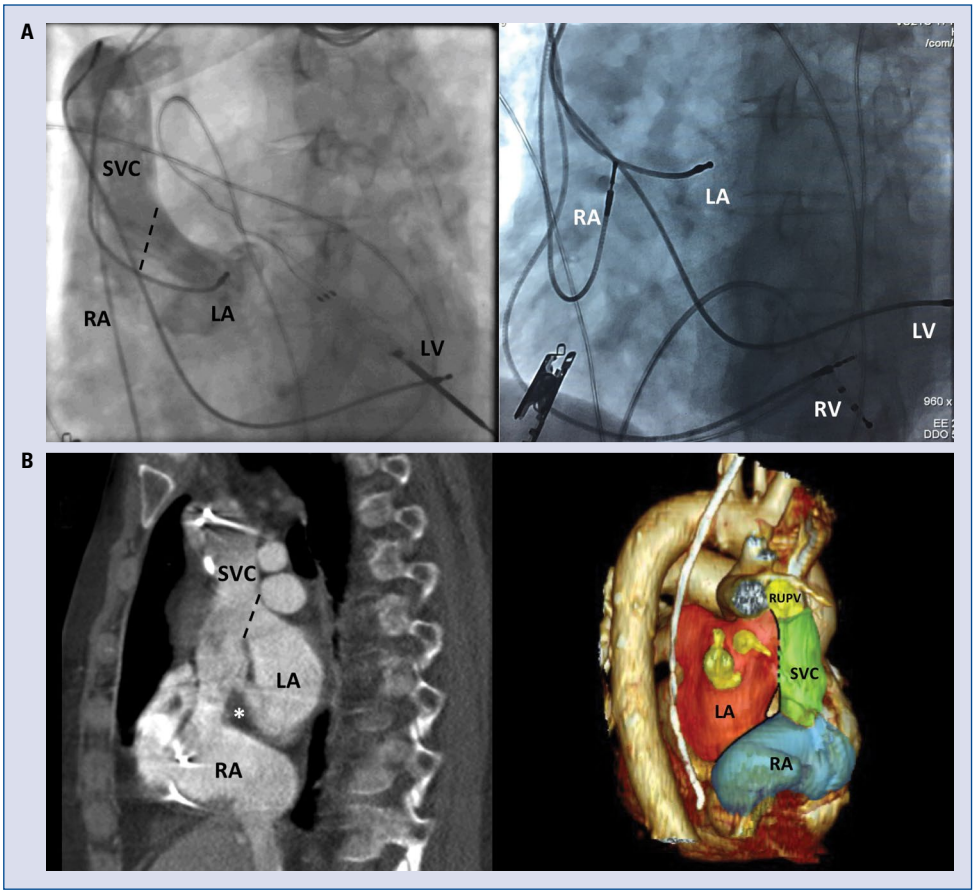


Figure 1. A. Superior vena cava (SVC) selective angiography (left) showing shunt between right and left atria through the sinus venosus atrial septal defect (SVASD) and left anterior oblique fluoroscopy (right) showing four leads temporarily present in four chambers of the heart; **B.** Chest computed tomography scan: sagittal plane (left) showing SVASD (dashed line) at the upper most part of inter atrial septum (asterisk) with SVC overriding the defect and three-dimensional reconstruction (right) showing the position of the superior SVASD (dotted black line) and abnormal drainage of the right upper pulmonary vein (RUPV) to the SVC. Left atrium (LA) in red, right atrium (RA) in blue, SVC in green and RUPVs in yellow; LV — left ventricle; RV — right ventricle.

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

Cardiology Journal
2019, Vol. 26, No. 3, 302–303
DOI: 10.5603/CJ.2019.0062

ISSN 1897–5593

Atrial septal defect type II and upper limb malformation in 40-year-old male as a manifestation of Holt-Oram syndrome

Ewa Szymczyk, Paulina Wejner-Mik, Piotr Lipiec, Błażej Michalski, Jarosław D. Kasprzak

Department of Cardiology, Medical University of Lodz, Poland

The present study is the case of a 40-year-old Caucasian male with bilateral, symmetric malformation of the upper limbs; absence of I metacarpals and thumbs (Fig. 1D, E). He was admitted to the Department of Cardiology because of impaired exercise tolerance (New York Heart Association [NYHA] II/III) and recurrent palpitations. His mother died when he was an infant at the age of 36 years, and two of his brothers died at the age of 3 and 15 years because of untreated congenital heart disease — none of them presented with skeletal abnormalities.

On electrocardiogram sinus rhythm was 70 bpm, first-degree atrioventricular block and incomplete right bundle branch block were found. Transthoracic and transesophageal echocardiography revealed normal left ventricular function and right ventricular overload due to large, an unusually elongated (elliptic, 27 × 13 mm in size) type II atrial septal defect with hemodynamically significant left-to-right shunt (TAPSE 20 mm, S' RV 13 cm/s, RVIT 52 mm, RAA 24 cm^2, Fig. 1A, B). Based on four-dimensional echocardiographic area sizing, an atrial septal defect nitinol occluder (Memopart 26 mm, Lepu Medical) was implanted percutaneously via femoral vein (Fig. 1C) with complete atrial septal defect closure. Control echocardiography after 3 and 6 months showed a good result of occluder implantation with significant clinical improvement (NYHA I).

This case report is an example of Holt-Oram syndrome (heart-hand syndrome) which is an autosomal dominant disorder characterized by upper limb malformations in association with congenital heart lesions and increased risk for cardiac conduction abnormalities. Life expectancy for Holt-Oram syndrome varies among affected individuals and predominantly depends on the severity of the congenital heart defect.

Conflict of interest: None declared

Address for correspondence: Ewa Szymczyk, MD, PhD, Department of Cardiology, Bieganski Hospital, Medical University of Lodz, ul. Kniaziewicza 1/5, 91–347 Łódź, Poland, tel/fax: +48 42 251 60 15, e-mail: eszymczyk@ptkardio.pl

Received: 3.02.2019 Accepted: 9.02.2019

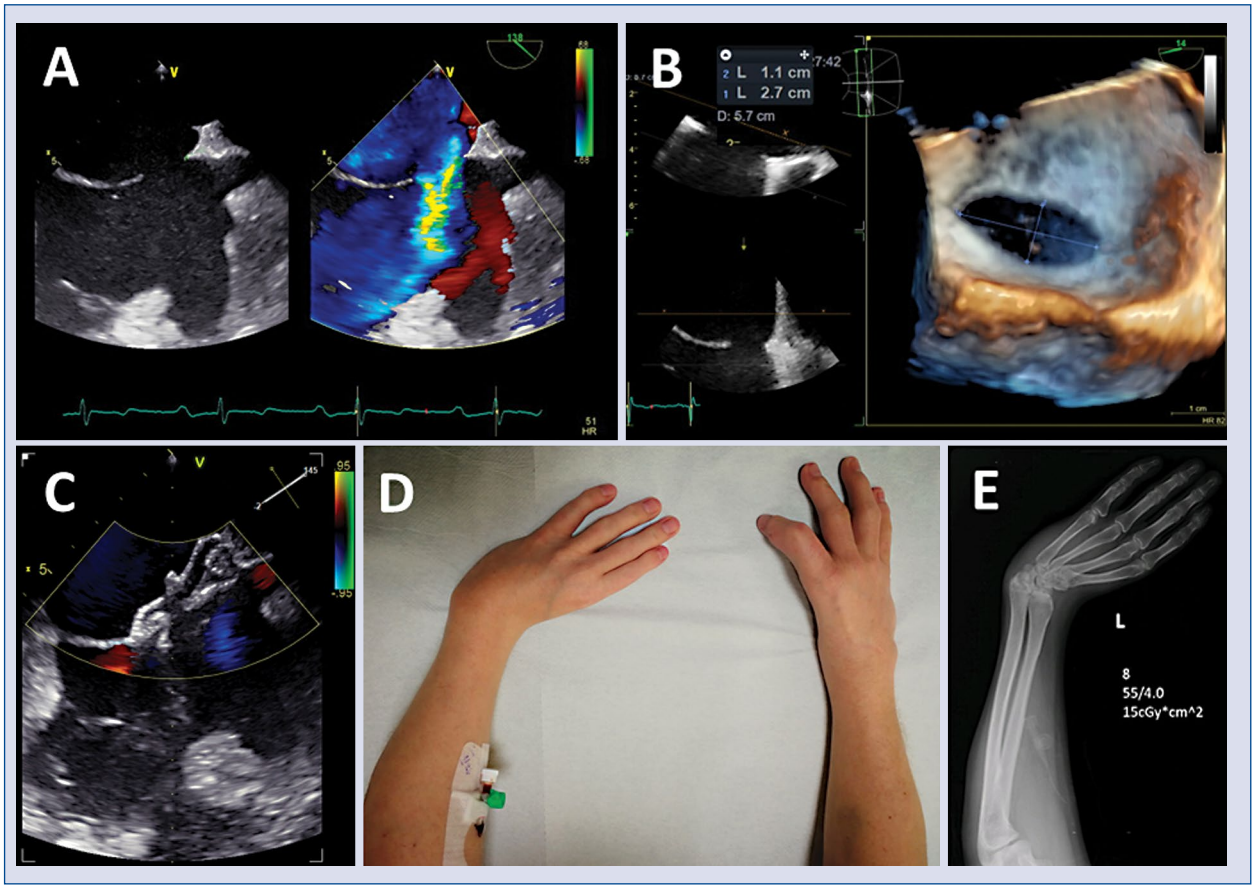


Figure 1. A. Two-dimensional transesophageal echocardiography with color Doppler — type II atrial septal defect with hemodynamically significant left-to-right shunt; **B.** Three-dimensional transesophageal echocardiography — elongated (elliptic, 27 × 13 mm in size) type II atrial septal defect; **C.** Two-dimensional transesophageal echocardiography with color Doppler — good result of Memopart 26 mm occluder implantation; **D, E.** Malformation of upper limbs (real photo and X-ray) — absence of I metacarpals and thumbs.

VIA MEDICA

LETTER TO THE EDITOR

Cardiology Journal
2019, Vol. 26, No. 3, 304–306
DOI: 10.5603/CJ.2019.0063

ISSN 1897–5593

Challenging treatment of in-stent restenosis in a coronary bifurcation by implantation of a bioresorbable scaffold under optical coherence tomography guidance

Grzegorz Zuk[1], Dariusz Ciecwierz[1], Piotr Drewla[1], Marcin Gruchala[1], Juan Luis Gutiérrez-Chico[2, 3], Milosz J. Jaguszewski[1, 3]

[1]Interventional Cardiology, 1st Department of Cardiology, University Clinical Center, Gdansk, Poland
[2]Punta de Europa University Hospital, Algeciras (Cádiz), Spain
[3]Institute of Cadiovascular Translational Research of the Atlantic (ICTRA), Berlin, Germany

This paper was guest edited by Prof. Marek Koziński

A 67-year-old male patient with stable angina, hypertension and hypercholesterolemia who underwent bare metal stent (BMS) implantation in the distal right coronary artery (RCA) (Azule 3 × 9 mm) and everolimus-eluting stent (EES) implantation in the first diagonal branch (D1) (Xience 2.25 × 18 mm) and in the proximal circumflex branch (LCx) (Xience 3 × 28 mm). One year subsequent to the precedure the patient was readmitted for relapse of the angina Canadian Cardiovascular Society scale II, exhibiting a positive exercise test. The coronary angiography showed a distal-edge in-stent restenosis (ISR) in the distal RCA, extending to the posterior descending artery (PDA), Medina 110 bifurcation (Fig. 1A). Optical coherence tomography (OCT) showed predominantly fibrolipidic restenotic tissue, with minimal lumen area (MLA) 1.95 mm^2, minimal lumen diameter (MLD) 1.57 mm, proximal reference vessel diameter (RVD) 3.1 mm, distal RVD 2.75 mm and lesion length 21.2 mm (Fig. 1B, C).

Optical coherence tomography-guided implantation of a bioresorbable scaffold (BRS) to treat the bifurcation ISR was performed through a radial approach, using a 6 french guiding-catheter. Guidewires were placed in the PDA and in the posterolateral artery (PLA), in order to protect the side branch in case of an eventual occlusion. Predilation 1:1 with a non-compliant (NC) balloon 3.0 × 18 mm (16 atm) was performed until the balloon was completely expanded in angiography. A second OCT run verified fragmentation of restenotic tissue and sufficient luminal gain to ensure adequate scaffold expansion. A poly-lactide BRS (ABSORB 3 × 28 mm) was then slowly deployed at 12 atm, holding pressure for 60 s. Proximal-optimalization-technique with an NC-balloon 3.25 × 15 mm (16 atm) was then performed by placing the proximal edge of the distal marker of the balloon at the carina of the PDA-PLA bifurcation, with an optimal angiographic result (Fig. 1D). A final OCT pullback showed optimal apposition and expansion (MLA 5.3 mm^2/MLD 2.6 mm; Fig. 1E), structural integrity of the device and clear access to the PLA side branch through the scaffold struts (Fig. 1F). Three-month follow-up documented an optimal clinical and angiographical result (**Suppl. Video 1**).

Poly-lactide BRS are supposed to resorb completely [1–5], depending on the specific device and on patient/local conditions. The resorption restores vasomotion and eventually normal endothelial

Address for correspondence: Milosz J. Jaguszewski, MD, PhD, FESC, 1st Department of Cardiology, Medical University of Gdansk, ul. Dębinki 7, 80–210 Gdańsk, Poland, tel: +48 58 349 25 00, fax: +48 58 346 12 01, e-mail: mjaguszewski@escardio.com.pl

Received: 24.07.2018 Accepted: 15.02.2019

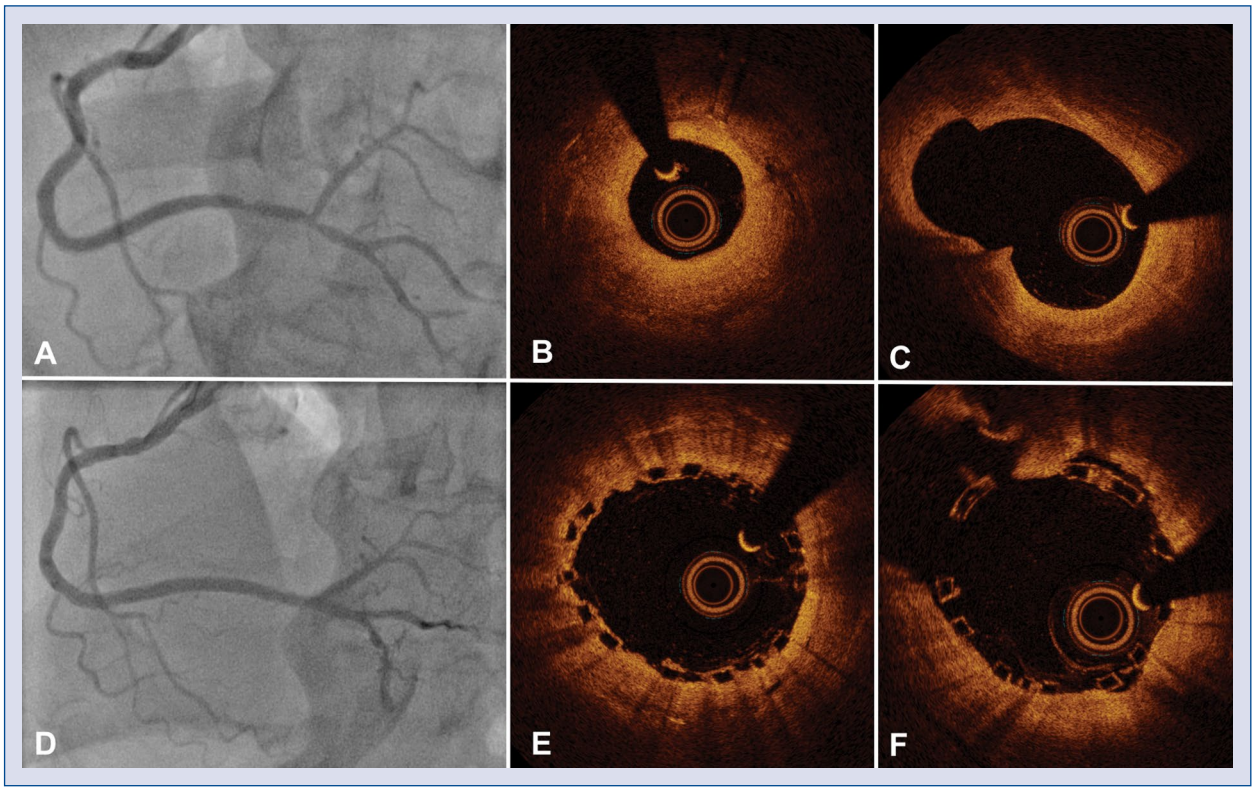


Figure 1. A, D. The coronary angiography shows a distal-edge in-stent restenosis in the distal right coronary artery, extending to the PDA, Medina 110 bifurcation; **B**, **C**. Optical coherence tomography (OCT) shows predominantly fibrolipidic restenotic tissue; **D**. An optimal angiographic result after proximal-optimalization-technique with a non-compliant-balloon 3.25 × 15 mm (16 atm) performed by placing the proximal edge of the distal marker of the balloon at the carina of the PDA-PLA bifurcation; **E**, **F**. Optimal apposition, expansion and structural integrity of the device and clear access to the PLA side branch through the scaffold struts as assessed by OCT; PDA — posterior descending artery; PLA — posterolateral artery.

function [2, 6, 7]. Moreover, the disappearance of a permanent foreign body in the vessel wall is also intended to minimize inflammation and risk of device failure, i.e. very late BRS-thrombosis, neoatherosclerosis, restenosis and catch-up phenomenon. Nonetheless, the suitability of polylactide BRS for bifurcations is currently a matter of debate, with reported higher risks of side branch occlusion [8] and of scaffold rupture following some bifurcation techniques [9, 10]. Some scientific reports however, focus on dedicating interventional techniques to minimize these risks [10, 11]. ISR is also a challenging scenario for BRS, because the expansion of the scaffold is sensibly inferior than in on-label indications [12] and reported clinical outcomes are inconsistent to date [13, 14]. The current case reports the successful treatment of a lesion combining both bifurcation and ISR challenges, by implanting a BRS. OCT-guidance played an instrumental role in achieving an optimal result and it may be considered for all off-label indications of BRS devices.

Conflict of interest: None declared

References

1. Oberhauser JP, Hossainy S, Rapoza RJ. Design principles and performance of bioresorbable polymeric vascular scaffolds. EuroIntervention. 2009; 5 Suppl F: F15–F22, doi: 10.4244/EIJV5IFA3, indexed in Pubmed: 22100671.
2. Serruys PW, Ormiston JA, Onuma Y, et al. A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. Lancet. 2009; 373(9667): 897–910, doi: 10.1016/S0140-6736(09)60325-1, indexed in Pubmed: 19286089.
3. 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.
4. Verheye S, Ormiston JA, Stewart J, et al. A next-generation bioresorbable coronary scaffold system: from bench to first clinical evaluation: 6- and 12-month clinical and multimodality imaging results. JACC Cardiovasc Interv. 2014; 7(1): 89–99, doi: 10.1016/j.jcin.2013.07.007, indexed in Pubmed: 24139932.
5. Campos CM, Muramatsu T, Iqbal J, et al. Bioresorbable drug-eluting magnesium-alloy scaffold for treatment of coronary artery disease. Int J Mol Sci. 2013; 14(12): 24492–24500, doi: 10.3390/ijms141224492, indexed in Pubmed: 24351829.
6. Serruys PW, Onuma Y, Dudek D, et al. Evaluation of the second generation of a bioresorbable everolimus-eluting vascular scaffold for the treatment of de novo coronary artery stenosis: 12-month clinical and imaging outcomes. J Am Coll Cardiol. 2011; 58(15): 1578–1588, doi: 10.1016/j.jacc.2011.05.050, indexed in Pubmed: 21958884.
7. Serruys PW, Chevalier B, Dudek D, et al. A bioresorbable everolimus-eluting scaffold versus a metallic everolimus-eluting stent for ischaemic heart disease caused by de-novo native coronary artery lesions (ABSORB II): an interim 1-year analysis of clinical and procedural secondary outcomes from a randomised controlled trial. Lancet. 2015; 385(9962): 43–54, doi: 10.1016/S0140-6736(14)61455-0, indexed in Pubmed: 25230593.
8. Muramatsu T, Onuma Y, García-García HM, et al. Incidence and short-term clinical outcomes of small side branch occlusion after implantation of an everolimus-eluting bioresorbable vascular scaffold: an interim report of 435 patients in the ABSORB-EXTEND single-arm trial in comparison with an everolimus-eluting metallic stent in the SPIRIT first and II trials. JACC Cardiovasc Interv. 2013; 6(3): 247–257, doi: 10.1016/j.jcin.2012.10.013, indexed in Pubmed: 23517836.
9. Ormiston JA, Webber B, Ubod B, et al. Absorb everolimus-eluting bioresorbable scaffolds in coronary bifurcations: a bench study of deployment, side branch dilatation and post-dilatation strategies. EuroIntervention. 2015; 10(10): 1169–1177, doi: 10.4244/EIJY14M05_08, indexed in Pubmed: 24835848.
10. Ormiston JA, Webber B, Ubod B, et al. An independent bench comparison of two bioresorbable drug-eluting coronary scaffolds (Absorb and DESolve) with a durable metallic drug-eluting stent (ML8/Xpedition). EuroIntervention. 2015; 11(1): 60–67, doi: 10.4244/EIJY15M02_03, indexed in Pubmed: 25680225.
11. Derimay F, Souteyrand G, Motreff P, et al. Sequential proximal optimizing technique in provisional bifurcation stenting with everolimus-eluting bioresorbable vascular scaffold: fractal coronary bifurcation bench for comparative test between absorb and XIENCE xpedition. JACC Cardiovasc Interv. 2016; 9(13): 1397–1406, doi: 10.1016/j.jcin.2016.04.021, indexed in Pubmed: 27388830.
12. Rivero F, Bastante T, Cuesta J, et al. Treatment of in-stent restenosis with bioresorbable vascular scaffolds: optical coherence tomography insights. Can J Cardiol. 2015; 31(3): 255–259, doi: 10.1016/j.cjca.2014.11.017, indexed in Pubmed: 25660152.
13. Moscarella E, Ielasi A, Granata F, et al. Long-Term Clinical Outcomes After Bioresorbable Vascular Scaffold Implantation for the Treatment of Coronary In-Stent Restenosis: A Multicenter Italian Experience. Circ Cardiovasc Interv. 2016; 9(4): e003148, doi: 10.1161/CIRCINTERVENTIONS.115.003148, indexed in Pubmed: 27059683.
14. Jamshidi P, Nyffenegger T, Sabti Z, et al. A novel approach to treat in-stent restenosis: 6- and 12-month results using the everolimus-eluting bioresorbable vascular scaffold. EuroIntervention. 2016; 11(13): 1479–1486, doi: 10.4244/EIJV11I13A287, indexed in Pubmed: 27107313.