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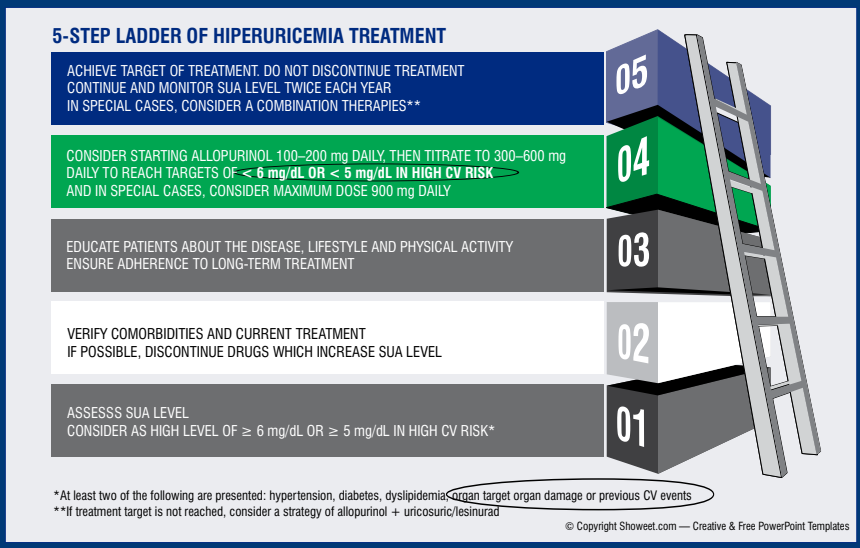

Claudio Borghi et al., see figure legend on page 8

POSITION PAPER

1 **Expert consensus for the diagnosis and treatment of patient with hyperuricemia and high cardiovascular risk: 2021 update** — C. Borghi et al.

ORIGINAL ARTICLES

15 **Out-of-hospital cardiac arrest treated by emergency medical service teams during COVID-19 pandemic: A retrospective cohort study** — M.J. Borkowska et al.

23 **Immersive technologies as a solution for general data protection regulation in Europe and impact on the COVID-19 pandemic** — K. Proniewska et al.

34 **New-onset atrial fibrillation during COVID-19 infection predicts poor prognosis** — A. Pardo Sanz et al.

41 **Coronary artery height differences and their effect on fractional flow reserve** — F. Al-Janabi et al.

49 **Comparison of long-term radial artery occlusion following trans-radial coronary intervention using 6-french versus 7-french sheaths** — Y. Fan et al.

58 **Low dose of ROSuvastatin in combination with EZEtimibe effectively and permanently reduce low density lipoprotein cholesterol concentration independently of timing of administration (ROSEZE): A randomized, crossover study — preliminary results** — K. Obońska et al.

67 **Ischemic and non-ischemic patterns of late gadolinium enhancement in heart failure with reduced ejection fraction** — P.S. Matusik et al.

77 **The non-invasive evaluation of heart function in patients with an acute myocardial infarction: The role of impedance cardiography** — L. Lewicki et al.

86 **Short and long-term results of endoscopic atraumatic coronary artery off-pump bypass grafting in patients with left anterior descending artery stenosis** — R. Abusamra et al.

95 **Predicting survival in out-of-hospital cardiac arrest patients undergoing targeted temperature management: The Polish Hypothermia Registry Risk Score** — Ł. Kołtowski et al.

101 **Usefulness of transesophageal echocardiography before cardioversion in atrial arrhythmias** — K. Kosmalska et al.

110 **Paramedic versus physician-staffed ambulances and prehospital delays in the management of patients with ST-segment elevation myocardial infarction** — A. Borowicz et al.

118 **Pretreatment with antiplatelet drugs improves the cardiac function after myocardial infarction without reperfusion in a mouse model** — K. Zhang et al.

129 **ST2 in patients with severe aortic stenosis and heart failure** — A. Cai et al.

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CARDIOLOGY JOURNAL

www.cardiologyjournal.org

January 2021, Vol. 28, No. 1

Table of Contents

EDITORIAL NOTE

Message from the Editors to our Reviewers — Thank you for your support

POSITION PAPER

Expert consensus for the diagnosis and treatment of patient with hyperuricemia and high cardiovascular risk: 2021 update

Claudio Borghi, Justyna Domienik-Karłowicz, Andrzej Tykarski, Krystyna Widecka, Krzysztof J. Filipiak, Miłosz J. Jaguszewski, Krzysztof Narkiewicz, Giuseppe Mancia 1

ORIGINAL ARTICLES

COVID-19

Out-of-hospital cardiac arrest treated by emergency medical service teams during COVID-19 pandemic: A retrospective cohort study

Magdalena J. Borkowska, Jacek Smereka, Kamil Safiejko, Klaudiusz Nadolny, Maciej Maslanka, Krzysztof J. Filipiak, Milosz J. Jaguszewski, Lukasz Szarpak 15

Immersive technologies as a solution for general data protection regulation in Europe and impact on the COVID-19 pandemic

Klaudia Proniewska, Agnieszka Pręgowska, Damian Dołęga-Dołęgowski, Dariusz Dudek 23

New-onset atrial fibrillation during COVID-19 infection predicts poor prognosis

Ana Pardo Sanz, Luisa Salido Tahoces, Rodrigo Ortega Pérez, Eduardo González Ferrer, Ángel Sanchez Recalde, José Luis Zamorano Gómez 34

Interventional cardiology

Coronary artery height differences and their effect on fractional flow reserve

Firas Al-Janabi, Grigoris Karamasis, Chritopher M. Cook, Alamgir M. Kabir, Rohan O. Jagathesan, Nicholas M. Robinson, Jeremy W. Sayer, Rajesh K. Aggarwal, Gerald J. Clesham, Paul R. Kelly, Reto A. Gamma, Kare H. Tang, Thomas R. Keeble, John R. Davies 41

Comparison of long-term radial artery occlusion following trans-radial coronary intervention using 6-french versus 7-french sheaths

Yanming Fan, Qingmin Wei, Junna Cai, Yanbo Wang, Xianghua Fu 49

Clinical cardiology

Low dose of ROSuvastatin in combination with EZEtimibe effectively and permanently reduce low density lipoprotein cholesterol concentration independently of timing of administration (ROSEZE): A randomized, crossover study — preliminary results

Karolina Obońska, Michał Kasprzak, Kamila Tymosiak, Tomasz Fabiszak, Magdalena Krintus, Jacek Kubica 58

Ischemic and non-ischemic patterns of late gadolinium enhancement in heart failure with reduced ejection fraction

Patrycja S. Matusik, Amira Bryll, Paweł T. Matusik, Tadeusz J. Popiela 67

The non-invasive evaluation of heart function in patients with an acute myocardial infarction: The role of impedance cardiography

Lukasz Lewicki, Marta Fijalkowska, Maciej Karwowski, Konrad Siebert, Grzegorz Redlarski, Aleksander Palkowski, Radoslaw Targonski, Janusz Siebert 77

Short and long-term results of endoscopic atraumatic coronary artery off-pump bypass grafting in patients with left anterior descending artery stenosis

Rafik Abusamra, Marek Król, Krzysztof Milewski, Mateusz Kachel, Loai Abudaqa, Justyna Jankowska-Sanetra, Kamil Derbisz, Krzysztof Sanetra, Anna Sobieszek, Piotr P. Buszman, Wojciech Wojakowski, Paweł E. Buszman, Andrzej Bochenek, Marek Cisowski 86

Predicting survival in out-of-hospital cardiac arrest patients undergoing targeted temperature management: The Polish Hypothermia Registry Risk Score

Łukasz Kołtowski, Beata Średniawa, Agnieszka Tycińska, Magdalena Czajkowska, Magdalena Niedziela, Wiesław Puchalski, Ewa Szczerba, Robert Kowalik, Robert Ryczek, Barbara Zawiślak, Elżbieta Kremis, Konrad Koza, Agnieszka Nazaruk, Joanna Wolska, Michał Ordak, Grzegorz Opolski, Janina Stępińska 95

Usefulness of transesophageal echocardiography before cardioversion in atrial arrhythmias

Katarzyna Kosmalska, Małgorzata Rzyman, Paweł Miękus, Natasza Gilis-Malinowska, Radosław Nowak, Marcin Fijałkowski 101

Paramedic versus physician-staffed ambulances and prehospital delays in the management of patients with ST-segment elevation myocardial infarction

Artur Borowicz, Klaudiusz Nadolny, Kamil Bujak, Daniel Cieśla, Mariusz Gąsior, Bartosz Hudzik 110

Basic science and experimental cardiology

Pretreatment with antiplatelet drugs improves the cardiac function after myocardial infarction without reperfusion in a mouse model

Kandi Zhang, Wenlong Yang, Mingliang Zhang, Yaping Sun, Tiantian Zhang, Junling Liu, Junfeng Zhang 118

ST2 in patients with severe aortic stenosis and heart failure

Andrew Cai, Alejandra Miyazawa, Nicholas Sunderland, Susan E. Piper, Thomas G.J. Gibbs, Duolao Wang, Sadie Redding, George Amin-Youseff, Olaf Wendler, Jonathan Byrne, Philip A. MacCarthy, Ajay M. Shah, Theresa A. McDonagh, Rafał Dworakowski 129

REVIEW ARTICLES

Interventional cardiology

Drug-coated balloon treatment in coronary artery disease: Recommendations from an Asia-Pacific Consensus Group

Ae-Young Her, Eun-Seok Shin, Liew Houng Bang, Amin Ariff Nuruddin, Qiang Tang, I-Chang Hsieh, Jung-Cheng Hsu, Ong Tiong Kiam, ChunGuang Qiu, Jie Qian, Wan Azman Wan Ahmad, Rosli Mohd Ali 136

Clinical cardiology

Multimodality cardiovascular imaging in pulmonary embolism

Hyung Yoon Kim, Kye Hun Kim, Jahae Kim, Jong Chun Park 150

TECHNOLOGY NOTE

Interventional cardiology

First-in-human radiofrequency ablation of ventricular tachycardia performed through an Atrial Flow Regulator device

Mateusz Wilkowski, Łukasz Lewicki, Rafał Olszewski, Adam Priebe, Miłosz J. Jaguszewski, Marek Szołkiewicz 161

RESEARCH LETTERS

Interventional cardiology

Hyperemic contrast velocity assessment improves accuracy of the image-based fractional flow reserve calculation

Balázs Tar, Csaba Jenei, Áron Üveges, Gábor Tamás Szabó, András Ágoston, Csaba András Dézsi, András Komócsi, Dániel Czuriga, Attila Juhász, Zsolt Kőszegi 163

Clinical cardiology

QRS duration and cardiovascular mortality in Asian patients with heart failure and preserved and reduced ejection fraction

Jonathan Yap, Yann Shan Keh, Tong Shen, Carolyn S.P. Lam, Shaw Yang Chia, Fazlur Rehman Jaufeerally, Wilson Ong, David Sim, Chi-Keong Ching 166

Perioperative D-dimer levels after transcatheter aortic valve replacement: Comparison of patients with and without anticoagulant therapy

Akihiro Tobe, Akihito Tanaka, Yoshiyuki Tokuda, Toshihiko Nishi, Yusuke Miki, Kenji Furusawa, Hideki Ishii, Akihiko Usui, Toyoaki Murohara 170

Familial dilated cardiomyopathy associated with a novel heterozygous RYR2 early truncating variant

Sarah Costa, Argelia Medeiros-Domingo, Alessio Gasperetti, Alexander Breitenstein, Jan Steffel, Federica Guidetti, Andreas J. Flammer, Katja E. Odening, Frank Ruschitzka, Firat Duru, Ardan M. Saguner 173

BRIEF COMMUNICATION

Clinical cardiology

Effects of intracoronary antithrombotics on ventricular function: A comparison of tenecteplase versus abciximab during primary percutaneous intervention in myocardial infarction

Francisco J. Morales-Ponce, Pablo González-Pérez, Sara Blasco-Turrión, Juan Antonio Sánchez-Brotons, Carmen Collado-Moreno, Pedro Martínez-Romero, Eduardo Martínez-Morentín, Pilar Caro-Mateo 176

IMAGES IN CARDIOVASCULAR MEDICINE

Interventional cardiology

Left main revascularization with intracoronary lithotripsy guided by optical coherence tomography

Pawel Gasior, Malwina Nicpon-Smolarek, Andrzej Ochala 179

Synergistic application of high-speed rotational atherectomy and intravascular lithotripsy for a severely calcified undilatable proximal left anterior descending coronary artery bifurcation lesion: Case of rotalithoplasty-facilitated DK-CRUSH

Tomasz Pawłowski, Jacek Legutko, Paweł Modzelewski, Robert J. Gil 181

Chimney stent deployment to overcome an acute right coronary occlusion due to a small right coronary sinus during transcatheter aortic valve implantation procedure

Mario García Gómez, Sandra Santos Martínez, Ana Serrador Frutos, Tania Rodríguez Gabella, Ignacio J. Amat Santos 183

Successful percutaneous mechanical thrombectomy of an Impella CP-related femoral artery thrombosis

Sophie Degrauwe, Juan F. Iglesias, Frederic Glauser, Marco Roffi 185

Clinical cardiology

Emergency assessment of proximal left anterior descending coronary stent permeability using transthoracic echocardiography

Georgios Giannakopoulos, José David Arroja, Alexandre Guinand, Hajo Müller 187

Intermittent wide QRS complex sinus bradycardia in a 72-year-old woman

Adrián Jerónimo, Julián Palacios-Rubio, Javier Higueras 189

Multiple heart beats: A unique presentation of cardiac rhabdomyoma

Seigo Okada, Yuji Ohnishi, Takashi Furuta, Hirofumi Inoue, Shunji Hasegawa 190

Silent journey of a late lead pacemaker perforation

Luísa Gonçalves, Inês Pires, João Santos, Joana Correia, Vanda Neto, Davide Moreira, Inês Almeida, António Costa, Costa Cabral 191

OBITUARY

In memoriam Emil Płowiecki

Luis Antonio Íñigo García 193

VIA MEDICA

EDITORIAL NOTE

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The Journal's national and international pool of reviewers has been increasing systematically over recent years. So too are the number of submissions to the Journal which are also growing. So if you are interested in joining, please send us an e-mail with your areas of expertise and interest, and a short bio.

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POSITION PAPER

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Expert consensus for the diagnosis and treatment of patient with hyperuricemia and high cardiovascular risk: 2021 update

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While fundamental concepts outlined in the 2018 consensus [1] will be revisited, emphasis will be placed on the more recent developments.

Definition and epidemiology: Constantly increasing burden and importance of hyperuricemia

Uric acid (UA) is the end product of purine metabolism, and its concentration in blood can increase in humans, great apes, and dalmatian dogs as a consequence of a genetic mutation that occurred millions of years ago and contribute to human evolution from less evolved species [2]. These elevated plasma levels of UA are the final result of almost three different mechanisms under genetic control and involve UA production, renal excretion, and gut absorption [3]. Under physiological conditions, UA synthesis and excretion are balanced in the body. Once this balance is disturbed, it leads to hyperuricemia (HU). Typically, male UA levels greater than 7 mg/dL (420 μmol/L) and female UA levels greater than 6 mg/dL (360 μmol/L) are considered hyperuricemia.

The latest scientific data published after our first consensus [4, 5] indicates that mean serum uric acid (sUA) has increased constantly according to the prevalence of concomitant diseases in many populations, while the prevalence of HU increases with age and is higher in men than premenopausal women due to estrogen's positive influence on urate excretion by the kidneys [4]. The United States National Health and Nutrition Examination Survey (NHANES 2007–2016) estimated the HU prevalence to be 20.2% for men (22.8 million) and 20.0% for women (24.4 million). In simple terms, 1 in 5 men and 1 in 5 women suffer from HU. The prevalence of sUA levels > 6.0 mg/dL was 32.3% overall (75.8 million), 49.5% among men (55.8 million), and 16.4% among women (20.0 million).

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**Equal contribution*

The overall mean sUA level was 5.39 mg/dL (95% confidence interval [CI] 5.34–5.45), with mean sUA levels of 6.04 mg/dL and 4.79 mg/dL among men and women, respectively. Moreover, the prevalence rates of HU remained stable between 2007 and 2016 (p for trend > 0.05) [5]. Of note, the prevalence of HU increased with age, with the highest being 27.8% (3.1 million) among individuals aged 80 years or older. Among patients aged 65 years or older, the prevalence of HU was 27.2% (12.6 million) [5]. Recently published data by the Irish health system indicate that from 2006 to 2014, the prevalence of HU increased from 19.7% to 25.0% in men and from 20.5% to 24.1% in women (p < 0.001). Moreover, age-specific prevalence increased in all groups from 2006 to 2014, and the magnitudes of the increases were similar for each age category [6].

The prevalence of HU increased significantly with worsening renal function, from 12.2% in patients with estimated glomerular filtration rate (eGFR) > 90 mL/min to 63.9% in patients with eGFR < 15 mL/min [6].

The adoption of a Western lifestyle by natives of other countries and cultures and a change in the socioeconomic background through immigration to Western countries and movement from rural to urban communities have influenced sUA levels [7, 8].

The pathophysiological effect of hyperuricemia on cardiovascular disease: What matters more? Overproduction or underexcretion?

First and foremost, an increased sUA level is the result of a purine/fructose-rich diet, genetic or environmental factors, metabolic disorders, as well as either: (1) its endogenous overproduction (due to, e.g., purine-rich diet, an error of purine metabolism affected by phoribosyl-pyrophosphate synthetase or purine salvage pathway influenced by hypoxanthine-xanthine phosphoribosyl transferase; cell breakdown or excessive purine turnover: lymphoproliferative diseases, myeloproliferative disease, polycythemia vera, Paget disease [9], psoriasis, tumor lysis, hemolysis, rhabdomyolysis, and exercise; [10] or — in most cases — by (2) insufficient excretion (caused by acute or chronic kidney disease [CKD], acidosis: lactic acidosis, ketoacidosis; hypovolemia, medication/ /toxin: diuretic, niacin, pyrazinamide, ethambutol, cyclosporin, beryllium, salicylates, lead, alcohol; sarcoidosis, hyperparathyroidism, hypothyroidism, Bartter syndrome, and Down syndrome [11–13].

It should be emphasized that due to the limitations of the current knowledge on what is more important for unfavorable cardiovascular effect of HU — overproduction of UA (increased activity of xanthine oxidase with reactive oxygen species formation) or limited excretion (effects of UA per se), the topic has become one of the hottest in the field of cardiovascular research and hyperuricemia. However, the mechanism of impaired oxidative mechanism which was widely described in a previous version of this document seems to be more consistent.

Genetics: Possibilities for individualized diagnoses and care strategies?

There is growing evidence that genetics and environmental factors play a key role in HU's development [14]. Considering HU's pathophysiological aspects, it can be divided into overproduction (liver) and underexcretion types (gut, kidney). Indeed, genome-wide association studies identified the genetic basis of HU as dominated by loci containing urate transporters and interacting proteins involved in the excretion of urate; among them SLC2A9 (GLUT9), ABCG2, SLC22A11, SLC17A1–SLC17A4, and PDZK1; and proteins associated with metabolic pathways (e.g., GCKR, A1CF, IGF1R) [15]. Among these, GLUT9 and ABCG2 were recognized as the most significant [16]. Indeed, SLC2A9 (GLUT9) has a key role in urate transport and reabsorption. GLUT9-encoded protein is useful in urate excretion into urine and the reabsorption of urate into the blood. Differences among variants of GLUT9 also influence the excretion of UA in urine and its reabsorption to blood [17]. Systematic analysis of GLUT9's variants confirms its key role in the treatment of HU. Moreover, the ABCG2 gene (BCRP) is engaged in intestinal excretion and UA transport in proximal tubule epithelial cells [18]. Mutations in ABCG2 impede proper sUA regulation and lead to HU. Of note, in hemochromatosis patients, iron/ /heme overload enhances the activity of xanthine oxidase and — through p53 — causes the reduction of ABCG2 expression. This leads to a reduction in UA intestinal excretion and subsequent accumulation in tissue and serum, causing hereditary hemochromatosis-associated arthritis [19].

Among many others, one should acknowledge organic anion transporters 10 (OAT10, SLC22A13), acting as a key part of urate transport from urine to the blood; lactate dehydrogenase D (LDHD), decreasing excretion of UA [20];

hypoxanthine-guanine phosphoribosyltransferase (HGPRT) whose deficiency caused by an HPRT1 mutation leads to elevated UA levels in the blood, which are associated with Kelley-Seegmiller syndrome, Lesch-Nyhan syndrome, and HU [21]; mitochondrial seryl-tRNA synthetase precursor, a member of the class II tRNA synthetase family, which is involved in the ligation of serine to tRNA (Ser) and is involved in selenocysteinyl-tRNA (sec) biosynthesis in mitochondria [22]; xanthine dehydrogenase (XDH), influencing the oxidation of hypoxanthine to xanthine and the oxidation of xanthine to UA [23], therefore reducing the levels of xanthine oxidoreductase. Drabkin et al. [20] confirmed that a mutation could cause HU in LDHD within the putative catalytic site of the encoded d-lactate dehydrogenase, which results in increased blood levels of d-lactate — typically present in blood in miniscule amounts. As a consequence, excessive renal secretion of d-lactate in exchange for UA reabsorption culminates in HU. In line with the human phenotype, injection of d-lactate into naive mice resulted in HU [20].

These advances lead to a clear-cut approach to individualized patient care; genetic data can be informative about the prognosis in patients suffering from HU and help clinicians select dosage of urate-lowering therapy (ULT) and offer the correct advice on lifestyle changes.

Recent studies linking hyperuricemia to cardiovascular disease

Hyperuricemia and ischemic heart disease

We look forward to the results of the ALL-HEART study, which is a multicenter, controlled, prospective, randomized trial, examining the effects of allopurinol (up to 600 mg daily) vs. no treatment on cardiovascular outcome (non-fatal myocardial infarction, non-fatal stroke or cardiovascular death) in patients with coronary artery disease. The secondary goals are to determine the cost-effectiveness of adding allopurinol to usual therapy, determine whether allopurinol improves the quality of life, and to determine the safety and tolerability of giving allopurinol to patients with ischemic heart disease (without a history of gout). The main inclusion criteria were patients of 60 years of age and over and ischemic heart disease. The main exclusion criteria were history of gout, eGFR < 30 mL/min, and moderate-to-severe heart failure and significant hepatic disease [24].

Hyperuricemia and hypertension

An ample body of evidence widely acknowledges that the association between an increase in relative risk of hypertension and high levels of sUA remains independent of traditional risk factors [25–33]. A substantial meta-analysis of 18 studies confirmed an increase of 13% in the incidence of new-onset hypertension for every 1% increase in sUA levels [25]. The PAMELA (Pressioni Arteriose Monitorate e Loro Associazioni) study confirmed that a rise in sUA by 1 mg/dL was associated with a significant increase in the risk of developing the new-onset home and ambulatory hypertension (odds ratio [OR] 1.34, 95% CI 1.06–1.7, p = 0.015; OR 1.29, 95% CI 1.05–1.57, p = 0.014; respectively) [26]. Finally, the Saku study confirmed that HU predicted the risk of developing hypertension was independent of alcohol drinking status [34].

Hyperuricemia and stroke

Serum uric acid plays a key and influential role in the physiopathology of stroke [35]. Kim et al. [36] reported that HU was associated with a significantly higher risk of both stroke incidence (relative risk [RR] 1.41) and mortality (RR 1.36) in their meta-analyses of unadjusted study estimates. Accordingly, Zhong et al. [37] in their meta-analysis confirmed similar results; elevated sUA levels were significantly associated with an increased risk of stroke in both men (RR 1.10 per 1 mg/dL increase in sUA) and women (RR 1.11 [1.09–1.13]). In the newest study to date; CIRCS investigators presented that elevated sUA level is an independent predictor of total stroke in women but not in men. The positive association present in women was mostly attributable to ischemic stroke and was more pronounced among nonusers of antihypertensive medication [38].

Hyperuricemia and metabolic syndrome

As mentioned above, several studies demonstrated that sUA level is associated with metabolic syndrome, high body mass index (BMI), waist circumference, high fasting blood glucose levels, and dyslipidemia [39]. Shirasawa et al. [40] analyzed data derived from 96,863 participants and confirmed that the adjusted OR for HU was considerably increased in obesity (with central obesity) compared with normal weight, regardless of sex (men: OR 2.12, 95% CI 2.03–2.21; women: OR 3.54, 95% CI 3.21–3.90) and was statistically increased in normal weight with central obesity

compared to normal weight (men: OR 1.44, 95% CI 1.36–1.52; women: OR 1.41, 95% CI 1.27–1.57). They concluded that middle-aged Japanese adults with normal weight but having central obesity should be screened using a combination of BMI and waist to height ratio and be educated about how to prevent HU [40].

Hyperuricemia and atrial fibrillation

Currently, evidence on serum urate with the risk of atrial fibrillation (AF) is mainly from cross sectional studies, based on prevalent AF cases, and were limited by only a 1-time measurement of serum urate. However, in a large prospective cohort study with 123,238 participants conducted from 2006 to 2012, both an increased cumulative average and elevations in serum urate over time were associated with increased risk of incident AF (adjusted hazard ratio [HR] 1.91, 95% CI 1.32–2.76, p = 0.001 for trend). The combination of high sUA and high-sensitivity C-reactive protein levels was associated with a significantly increased risk of incident AF (adjusted HR 2.63, 95% CI 1.63–4.23). Li et al. [41] provided evidence of an association between a relatively common treatable metabolic alteration (higher serum urate) and a common cardiac rhythm disorder (AF) with substantial morbidity and mortality. Moreover, Hong et al. [42] confirmed that the association between sUA and AF was significant (p = 0.001) after adjusting for potential confounding factors.

Hyperuricemia and liver diseases

The relationship between HU and liver disease has not been clearly described. Undoubtedly, the increased level of sUA is the result of a diet rich in purine and fructose, genetic and environmental factors, metabolic disorders, as well as endogenous overproduction or — in most cases — impaired excretion of UA [43–46]. Uric acid synthesis is mainly influenced by phosphoribosyl pyrophosphate synthetase and the purine pathway [46]. Some publications indicate the association of increased levels of sUA with non-alcoholic fatty liver disease, which is a part of metabolic syndrome, and chronic hepatitis. In experimental studies, the UA-stimulated expression of aldose reductase in both cultured hepatocytes (HepG2 cells) and hyperuricemic rat livers were associated with endogenous fructose production triglyceride accumulation through UA-induced oxidative stress and stimulation of the nuclear transcription factor activated T5 cells (NFAT5). Uric acid also potentiated the effects of elevated glucose levels to stimulate the accumulation of triglycerides in the liver. Hyperuricemic rats exhibited elevated hepatic aldose reductase expression, endogenous fructose accumulation, and fat accumulation was significantly reduced by allopurinol co-administration. Thus, HU is correlated with the occurrence of hypertriglyceridemia and non-alcoholic fatty liver disease, which secondarily induces the development of non-alcoholic steatohepatitis [47, 48].

Jang et al. [49] investigated UA levels and their relationship to disease progression in 373 patients with biopsy-confirmed chronic hepatitis C (CHC) enrolled in interferon-based antiviral therapy. In this study HU was defined as UA levels > 7 mg/dL in men and > 6.0 mg/dL in women. Hyperuricemia was found in 15.8% of CHC patients, but UA levels did not differ between CHC patients and the control group of healthy subjects matched for sex and age (5.54 ± 1.20 mg/dL vs. 5.45 ± 1.45 mg/dL, p = 0.3). Logistic regression analysis showed that factors related to HU in men included BMI (OR/CI 1.12/1.05–1.30, p = 0.006) and advanced fibrosis (F3–4) (OR/CI 0.27/0.09–0.83, p = 0.02), while factors associated with HU in women included eGFR (OR/CI 0.97/0.95–0.99, p = 0.02) and diabetes (OR/CI 3.03/1.11–8.25, p = 0.03). There was a significant downward trend in sUA levels with the progression of fibrosis in men (6.21 ± 1.03 mg/dL, 5.82 ± 1.16 mg/dL, and 5.44 ± 1.28 mg/dL in stages F0–2, F3 and F4, respectively, trend p = 0.01), indicating that HU was inversely related to the severity of liver disease in men with CHC [49]. Petta et al. [50] do not share this opinion; in a study of 496 patients with biopsy-confirmed CHC treated with pegylated interferon and ribavirin, there was no independent association between UA levels and necroinflammatory activity, fibrosis, nor sustained virologic response. However, the association of HU with the severity of steatosis was confirmed (OR 3.176, 95% CI 1.828–5.517, p <0.001), which could potentially be a therapeutic target in the treatment of CHC [50]. Moreover, Jang et al. [51], in a group of 213 patients, where HU was defined as UA levels > 7.0 mg/dL in men and > 6.0 mg/dL in women, showed that sUA levels decreased significantly after eradication of hepatitis C virus by the use of direct antiviral drugs. Improvement was only observed in patients with fibrosis-4 ratio (FIB-4) < 6.5 (37.1% vs. 25.7%, p = 0.001). The multivariate analysis showed that factors associated with significantly reduced sUA levels were FIB-4 < 6.5 (OR/95% CI 3.22/1.04–9.95, p = 0.04) and eGFR < 60 mL/min/1.73 m^2 (OR/95% CI 4.34/1.94–9.73, p < 0.001 [51].

Hyperuricemia and COPD

Identification of prognostic biomarkers for chronic obstructive pulmonary disease (COPD) may help improve therapy for patients at high risk. In univariate analysis, HU was associated with a higher risk of mortality in patients with COPD (HR 2.29, 95% CI 1.07–4.88, p = 0.032). Further analysis confirmed that HU was independently associated with a higher risk of mortality in patients with COPD (HR 2.68, 95% CI 1.18–6.09, p = 0.019) [52]. Moreover, it was recently published that sUA could activate the nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, leading to interleukin (IL)-1β secretion. In COPD patients, UA and uric ratio with creatinine (UCR) were positively associated with white blood cells, C-reactive protein, and IL-1β. COPD smokers had lower UA and UCR values. Standard COPD therapy did not affect UA or UCR, while patients with cardiovascular diseases (CVD) had higher UA, but not UCR, levels. Multiparameter models of UA and UCR that included IL-1β were able to correctly classify 86% and 90% of cases, respectively [53].

Current uric acid thresholds predicting cardiovascular events: Including improved cardiovascular risk estimation

As described in a previous document [1], sUA is considered an independent factor in the development of a wide variety of vascular disorders: hypertension [54], metabolic syndrome [55, 56], coronary artery disease [57], diabetes [58], cerebrovascular disease [59, 60], CKD [61], as well as other CVD [62, 63] and — conversely — these comorbidities increase the incidence of HU [64]. It is worth paying attention to other conditions, both those from the genre of metabolic syndrome (e.g., non-alcoholic fatty liver, non-alcoholic steatohepatitis) and those whose presence may affect the clinical course of disorders in the cardiovascular system (e.g., COPD [65] or incident asthma in men [66]).

What we know so far, is that some studies have found a robust association between sUA level and CVD not only in patients with clearly diagnosed HU but also in those with values considered normal to high > 5.2–5.5 mg/dL [67–69]. Moreover, this relationship concerned both subclinical and clinical manifestations of diseases [64], and remained highly significant even after renal function adjustment.

Of note, the Working Group on sUA and cardiovascular risk within the Italian Society of Hypertension designed the URRAH (Uric Acid Right for Heart Health) study, whose aim was to assess — in a group of 22,714 subjects — the level of UA above which the independent risk of CVD may increase in a significant manner in the general population [70]. Virdis et al. [71] confirmed that the threshold UA levels were **4.7 mg/dL** (95% CI 1.21–1.93 mg/dL) for increasing all-cause mortality, **5.6 mg/dL** (95% CI 4.99–6.21 mg/dL) for increasing cardiovascular mortality, and were significantly lower than levels referenced in clinical diagnostic criteria [71]. Considering the sex of the patients, the threshold for sUA for all-cause mortality was 5.4 mg/dL (95% CI 4.80–6.57) in men and 4.7 mg/dL (95% CI 4.40–5.10) in women. Most importantly for clinical practice is that the novel sUA thresholds allow for a significant net reclassification of — and improvement in — the Heart Score risk chart's present values for all-cause and cardiovascular mortality, 0.26 and 0.27, respectively.

In summation, this large-sample study led to a significant improvement in risk classification of the well-validated and guideline-recommended scale, the Heart Score. Further analysis for factors not included in the Heart Score such as hematocrit, diuretics, alcohol consumption, BMI, and eGFR did not significantly affect results [71]. The results reported by Virdis et al. [71] are largely superimposable over those obtained in several different populations of subjects enrolled in observational studies and show an increase in the relative risk of major cardiovascular events in the presence of sUA levels ranging between 4.5 and 5.5 mg/dL [72–75]. Previously reported investigations in smaller groups gave partially corroborative results specifically in the following contexts: in comparison to the Framingham Risk Score [72], in later life only [73], in patients undergoing percutaneous coronary interventions due to acute coronary syndrome [74], and in hypertensive patients; conflicting results were yielded in NHANES III [75]. The lower threshold level reported for CVD compared with gout can be explained by the causative role of the oxidative stress associated with the production of sUA by xanthine-oxidase that occurs with lower concentrations of serum urate and is largely independent of the inflammatory role of UA deposition.

A large body of evidence confirms the contribution of HU to the worsening of cardiovascular, diabetic, lipid, and renal diseases [76–78]; thereby supporting the conclusion that increased sUA levels correlate with elevated cardiovascular risk [79, 80] and further stressing the importance of a redefinition of threshold levels referred to during

identification of patients at risk of CVD in the presence of hyperuricemia.

URRAH researchers identified the prognostic cut-off values of sUA in predicting fatal and morbid heart failure; sUA more than 5.34 mg/dL (CI 4.37––5.6, sensitivity 52.32, specificity 63.96, $p < 0.0001$) was the univariate prognostic cut-off value for all heart failure, whereas sUA more than 4.89 mg/dL (CI 4.78–5.78, sensitivity 68.29, specificity 49.11, $p < 0.0001$) was the prognostic cut-off value for fatal heart failure [81]. Moreover, Huang et al. [82] analyzed ten studies involving 12,854 acute heart failure patients and confirmed that acute heart failure patients with the highest sUA levels had an increased risk of all-cause mortality (risk ratio [RR] 1.43, 95% CI 1.31–1.56) and a combined endpoint of death or readmission (RR 1.68, 95% CI 1.33–2.13), after adjusting for potential variables. Therefore, elevation in sUA levels significantly increased risks of all-cause mortality and combined endpoint of death or readmission by 11% and 12%, respectively, for every 1 mg/mL, they were elevated [82]. Also, URRAH researchers adjusted for such confounders as age, arterial hypertension, diabetes, CKD, smoking habits, ethanol intake, BMI, hematocrit, low-density lipoprotein cholesterol, and use of diuretics in multivariate Cox regression analyses and identified an independent association between sUA and fatal myocardial infarction across the whole database (HR 1.381, 95% CI 1.096–1.758, $p = 0.006$) and in women, specifically (HR 1.514, 95% CI 1.105–2.075, $p < 0.01$), but not in men [83].

Hyperuricemia and cardiovascular events: A high serum uric acid level and its influence on cardiovascular outcome

As we mentioned earlier, several studies have confirmed the relationship between sUA and CVD mortality [26, 84]. However, Rahimi-Sakak et al. [85] performed a meta-analysis of 44 prospective cohort studies with dose-response analysis published between 2000 and 2018 to determine the relationship between sUA and CVD mortality. Pooled results confirmed a significant positive association between sUA levels and risk of CVD mortality (HR 1.45, 95% CI 1.33–1.58, $I^2 = 79\%$). Sub-group analysis yielded that this association was stronger in women compared to men. Also, there was a significant non-linear association between sUA levels and CVD mortality risk ($r = 0.0709$, $p = 0.001$) [85]. In a cross-sectional study, Lee et al. [86] investigated the relationship of sUA with CVD risk in the Korean adult general population (8781 participants from first and second years of the Seventh Korea National Health and Nutrition Examination Survey 2016–2017). There was a significant association of sUA with 10-year CVD risk scores after adjusting for physical activity, BMI, serum creatinine, and alcohol consumption in both sexes ($p < 0.001$); at sUA levels of 6.9 mg/dL, the CVD risk was lowest [86].

Hyperuricemia treatment and cardiovascular outcomes: Allopurinol remains first-line urate-lowering therapy

In a systematic review of 24 guidance documents, 19 of them provided target levels for long-term sUA control, most of which recommended 6.0 mg/dL (or 360 μmol/L), except the South African guidelines, which recommended 5.0 mg/dL (300 μmol/L) [87]. Also, the Polish Society of Hypertension Guidelines 2019 recommend 5.0 mg/dL level for long-term sUA control [88]. Still, the definition of HU varies greatly across clinical trials, making epidemiological reports somewhat inconsistent and difficult to compare.

Xanthine-oxidase inhibitors (XOI), especially allopurinol, are still recommended by almost all guidelines as a **first-line ULT**. The results on febuxostat have recently been implemented after publication of the FAST trial (long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout: a multicenter, prospective, randomized, open-label, non-inferiority trial) [89, 90] that reported divergent results from those described by the CARES (Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities) study [91].

Febuxostat: Further clinical trials needed?

Febuxostat, a nonpurine XOI, is recommended in patients refractory or intolerant to allopurinol and requires no dose limitation in CKD stages 1–3. Febuxostat induces potent inhibition of XO and greater hypouricemic activity than the commonly used allopurinol doses [92]. However, preliminary results from a safety trial with febuxostat versus allopurinol, mainly based on a large-scale, randomized study design has suggested a modestly higher rate of cardiovascular events with febuxostat [93]. Based on the preceding study's findings, treatment with febuxostat in patients at high cardiovascular risk has not been recommended. Another safety oriented randomized controlled trial reporting results of a 32-month follow-up (n = 6190), demonstrated the compa-

rable effects of febuxostat and allopurinol on the primary cardiovascular end-point with a higher rate in the secondary objectives of all-cause and cardiovascular mortality in the febuxostat group than in the allopurinol group (HR for death from any cause 1.22, 95% CI 1.01–1.47; HR for cardiovascular death 1.34, 95% CI 1.03–1.73) [91]. In the meantime, a meta-analysis of 35 studies did not show a significant difference between febuxostat and allopurinol in cardiovascular events (RR 1.69, 95% CI 0.54–5.34, p = 0.37) [94]. Moreover, in the FREED study of over 1000 elderly patients with HU, 25% relative risk reduction in composite with death to any cause, cerebrovascular disease, non-fatal coronary artery disease, heart failure requiring hospitalization, an arteriosclerotic disease requiring treatment, renal impairment, and AF was observed in the febuxostat group compared to the non-febuxostat group. There was no difference in cardiovascular clinical outcomes examined separately with febuxostat versus control treatment.

In contrast, the European Medicines Agency (EMA)-required Febuxostat versus Allopurinol Streamlined Trial (FAST), published in the Lancet, does not support the finding of an increased cardiovascular risk of febuxostat, despite using higher (EMA-approved) dosages compared to the CARES trial [90]. In 6128 patients (with previous CVD), for the incidence of the primary endpoint (a composite of hospitalization for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome, non-fatal stroke, or cardiovascular death), on-treatment, febuxostat (172 patients [1.72 events per 100 patient-years]) was non-inferior to allopurinol (241 patients [2.05 events per 100 patient-years]; adjusted HR 0.85 [95% CI 0.70–1.03], p < 0.0001) [90]. In editorial comments, Bardin and Richette [89] underlined that patients in the CARES study had more severe gout than those in the FAST study and that all patients in CARES had a history of CVD in contrast to 2046 (33.4%) of 6128 in FAST. No excess of deaths was observed in this subgroup of patients in FAST. Still, their group size might be insufficient to fully assess febuxostat risk in patients with severe CVD [89]. Thus, further clinical trials are needed to clarify this issue and provide clear evidence for the withdrawal of the Food and Drug Administration alert in this issue.

Uric acid and COVID-19

There are not many studies on the relationship between sUA and coronavirus disease 2019 (COVID-19). However, of note that favipiravir, a purine nucleic acid analog and antiviral agent studied in Japan to treat COVID-19, has frequent side effects [95]. Favipiravir's action causes it as a moderate inhibitor of organic anion transporters 1 and 3 (OAT1 and OAT3), which are involved in UA excretion in the kidney, as well as by its influence on UA reuptake via urate transporter 1 (URAT1) in the proximal renal tubules. Elevated UA levels were found to return to normal after discontinuation of favipiravir, and favipiravir is not recommended for long periods to treat viral infection [96, 97]. Moreover, in a Japanese, prospective, randomized, open-label trial of early versus late favipiravir treatment in hospitalized patients with COVID-19, 84.1% developed transient HU [98].

Management strategies: Updated five-step recommendations for the treatment of patients with increased serum uric acid levels (Fig. 1)

STEP 1: Assess serum uric acid level

The measurement of sUA concentration is recommended as a part of screening in cardiac/ /hypertensive patients by experts of both the European Society of Cardiology and the European Society of Hypertension [99].

Our recommendation remains unchanged: the optimal target of sUA levels should be 6 mg/dL (360 μmol/L). Serum uric acid levels should be monitored regularly and maintained at < 6 mg/dL. Still, despite the lack of randomized controlled trials, one should consider an sUA target of < 5 mg/dL in patients with high cardiovascular risk comprised of at least two of the following: hypertension, diabetes, dyslipidemia, organ target organ damage or previous cardiovascular events.

STEP 2: Check comorbidities and active treatments and stop the administration of drugs that influence serum uric acid

Appropriate strategies should be defined and implemented in patients with HU, regarding more aggressive control of concomitant risk factors and the use of drugs indirectly affecting UA levels. Efficient management of concomitant diseases that influence sUA levels, such as hypertension, type 2 diabetes, metabolic syndrome, CKD, and CVD [56, 61–64] should be the procedure of choice. In clinical scenarios, feasible changes should be considered if the potential benefits exceed the potential harms, particularly:

— Diuretics, among them hydrochlorothiazide — switching from hydrochlorothiazide to alternative antihypertensive agents, if possible;

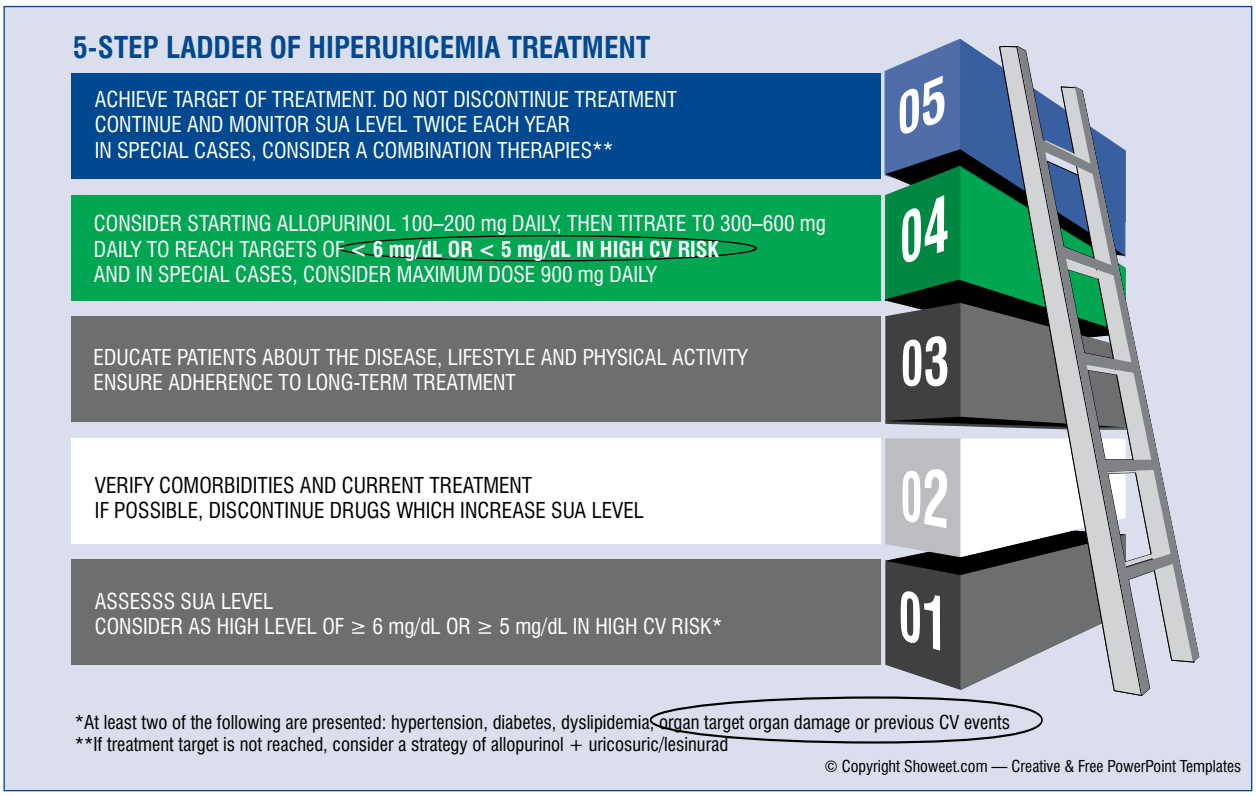

Figure 1. Management strategy for patients suffering from hiperuricemia; CV — cardiovascular; SUA — serum uric acid.

— Angiotensin II receptor blockers (ARBs) — although losartan is the only antihypertensive drug that lowers sUA level [100], switching from other ARBs to losartan is NOT recommended;
— Low-dose acetylsalicylic acid (ASA) — cessation of low-dose ASA in primary cardiovascular prevention patients or switching to alternatives, if possible; cessation of low-dose ASA in secondary cardiovascular prevention patients is NOT recommended;
— Cholesterol-lowering agents — switching from cholesterol-lowering drugs to fenofibrate is NOT recommended.

Building multidisciplinary teams for optimal diagnostics and management strategies, with an appropriate estimation of HU's significance, is necessary. It is essential to improve adherence to clinical practice guidelines, raise awareness of HU and associated comorbidities, and prompt their more diligent and specific monitoring.

STEP 3: Recommended life-style changes

Among the most significant lifestyle changes are:

— Limiting intake of purines, including red meat and seafood;
— Limiting intake of high-fructose corn syrup. Based on the Third National Health and Nutrition Examination Survey, sUA levels increase with increasing sugar-sweetened soft drink intake. After adjusting for covariates, sUA levels associated with sugar-sweetened soft drink consumption categories (< 0.5, 0.5–0.9, 1–3.9, and ≥ 4 servings/day) were greater than those associated with no intake (by 0.08, 0.15, 0.33, and 0.42 mg/dL, respectively) (95% CI 0.11–0.73, $p < 0.001$ for trend) [101];
— Limiting alcohol. Limiting or abstaining from alcohol leads to decreased UA levels by 1.6 mg/dL compared to the control group [102];
— Weight loss and regular physical activity for patients who are overweight or obese [103, 104];
— Adding coffee, dairy products, cherries [100, 105], and ascorbic acid [106].

STEP 4: Give xanthine oxidase inhibitors as first-line therapy, titrated to achieve serum uric acid target

As mentioned earlier, allopurinol, XOI, is recommended as a first-line ULT in agreement with most of the guidelines. According to the summary of product characteristics of allopurinol, the rec-

ommended initial allopurinol dosage is 100 to 200 mg daily in mild conditions, 300 to 600 mg daily in moderate conditions, 700 to 900 mg daily in severe conditions. **The dosage should be titrated up to achieve the desired sUA target level** [107].

Importantly — due to its renal excretion — in patients with CKD, impaired renal function may lead to retention of the drug and/or its metabolites (oxypurinol) with subsequent prolongation of plasma half-lives. For this reason, in severe CKD, it may be appropriate to use less than 100 mg per day or to use single doses of 100 mg at longer intervals than 1 day. In special situations and the presence of appropriate equipment, the dose should be adjusted to maintain plasma oxypurinol levels below 100 μmol/L (15.2 mg/L). If allopurinol is used in dialysis patients, it should be administered at a 300–400 mg dose immediately after dialysis, but without additional doses on other days [107].

STEP 5: Achieve targeted serum uric acid levels, do not stop treatment, continue monitoring serum uric acid levels twice per year; in special cases, consider combined therapy

Only 2 in 5 patients with HU reached the target of sUA with this therapy [108]. Suppose that the sUA target cannot be achieved. In this case, the dose should be escalated with supervision up to 900 mg of allopurinol, or the patient should be switched to benzbromarone or combined therapy of benzbromarone and allopurinol (**STEP 5**), except in patients with eGFR of < 30 mL/min [109]. However, escalations should be performed carefully to achieve optimal treatment goals, mainly due to allopurinol hypersensitivity syndrome and severe cutaneous allergic reactions, usually after 8 weeks of therapy [110–112]. Factors that are known to contribute to the development of this syndrome include initial doses that are too high, CKD, accompanying use of diuretics, and the presence of HLA-B*5801 [113, 114].

Although high-dose allopurinol (≥ 300 mg/dL) is associated with a reduced risk of all-cause mortality [7, 115], consideration of an optimal dose seems to be a major factor design of future research.

Lesinurad is an oral selective inhibitor of URAT1 and OAT4 renal transporters, which increase renal UA excretion and lower sUA levels by inhibiting UA reabsorption. A dose of 200 mg daily is recommended in combination with XOIs in patients who do not achieve treatment targets. Adding lesinurad can increase the efficiency of XOIs (compared to monotherapy) and help avoid maximal XOI dosages [116]. In a CLEAR study, lesinurad of 200 mg or 400 mg together with allopurinol significantly increased the proportion of patients who achieved the sUA target levels compared to allopurinol (54.2%, 59.2%, and 27.9%, respectively, $p < 0.0001$) [117]. The approval of lesinurad was based on data from three pivotal phase III studies (CLEAR 1, CLEAR 2, and CRYSTAL), which assessed lesinurad 200 mg and 400 mg doses. The target sUA level was achieved by significantly more patients on lesinurad 200 mg plus allopurinol group (CLEAR 1 and CLEAR 2 trials) or lesinurad 200 mg plus febuxostat group (CRYSTAL study) compared to patients who received either XOI alone. The safety profile of lesinurad 200 mg plus an XOI was comparable to allopurinol or febuxostat alone. To summarize, lesinurad, in combination with allopurinol, is a novel option for the treatment of HU in adults with gout who have not achieved their target sUA levels with allopurinol alone (STEP 5) [118, 119]. Once the sUA target is achieved continuously, ULT's dose should be maintained indefinitely with ongoing monitoring of sUA levels twice a year (**STEP 5**) [117, 120].

Many unresolved questions still remain: Areas in need of further study

First and foremost, UA's treatment target may still need to be reconsidered, especially since data from the URRAH study identified new cardiovascular thresholds and improved algorithms for assessing total cardiovascular risk. Still, there is a clear need for further evidence to support the treatment of asymptomatic HU, although a large body of evidence does show the beneficial effect of ULT on cardiovascular results.

Most relevant recommendations: The take home message for the clinical practitioners

In conclusion, we would like to summarize our opinions that should be helpful to clinicians treating patients suffering from hyperuricemia and at high cardiovascular risk:

— 1 in 5 patients suffers from HU. The prevalence of HU is continuously increasing;
— All patients with HU should be effectively informed about environmental and pharmacological factors influencing HU, comorbidities, and cardiovascular risk factors; be advised about the immediately required lifestyle and

diet modifications and weight loss, if necessary; and strict adherence to recommended treatments;
— Both patients and physicians of all specialties (especially primary care physicians, cardiologists, and pulmonologists) should strive to obtain and maintain lifelong sUA levels lower than 6 mg/dL; for patients at high cardiovascular risk, the target level should be 5 mg/dL;
— As mentioned earlier, allopurinol — a XOI — is recommended as a first-line ULT. According to the summary of product characteristics of allopurinol, the recommended initial allopurinol dosage is 100 mg to 200 mg daily in mild conditions, 300 mg to 600 mg daily in moderate conditions, and 700 mg to 900 mg daily in severe conditions;
— The dosage of XOIs should be titrated up to achieve the desired sUA target level and monitored twice a year thereafter to establish the correct level of sUA;
— If the sUA target levels are not reached, combined therapy of allopurinol + lesinurad might be considered.

Conflict of interest: Claudio Borghi has received honoraria for participation in national or international meetings from: Servier, Menarini Corporate, Daiichi Sankyo, Sanofi, Alfasigma, Gilead, Novartis; Justyna Domienik-Karłowicz has received speaker honoraria from Egis; Andrzej Tykarski has received honoraria for participation in national meetings from: Biopharm, Egis, Gedeon-Richter, Krka, Medtronic, Menarini, Servier; Krystyna Widecka has received speaking fees from: Servier, Krka, Egis, Berlin-Chemie/Menarini, Gedeon-Richter, Merck; Krzysztof J. Filipiak has received speaker honoraria from: Egis, Berlin-Chemie/Menarini; Miłosz J. Jaguszewski has speaker honoraria from: Egis, Servier; Krzysztof Narkiewicz has received speaker honoraria from: Egis, Berlin-Chemie/ /Menarini; Giuseppe Mancia has received honoraria for participation in national or international meetings from: AstraZeneca, Böhringer Ingelheim, Daiichi Sankyo, Medtronic, Menarini, Merck, Novartis, Recordati, Sandoz, Sanofi, Servier.

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Out-of-hospital cardiac arrest treated by emergency medical service teams during COVID-19 pandemic: A retrospective cohort study

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Abstract

Background: *Out-of-hospital cardiac arrest (OHCA) is a challenge for medical personnel, especially in the current COVID-19 pandemic, where medical personnel should perform resuscitation wearing full personal protective equipment. This study aims were to assess the characteristics and outcomes of adults who suffered an OHCA in the COVID-19 pandemic treated by emergency medical service (EMS) teams.*

Methods: *All EMS-attended OHCA adults over than 18 years in the Polish EMS registry were analyzed. The retrospective EMS database was conducted. EMS interventions performed between March 1, and April 30, 2020 were retrospectively screened.*

Results: *In the study period EMS operated 527 times for OHCA cases. The average age of patients with OHCA was 67.8 years. Statistically significantly more frequently men were involved (64.3%). 298 (56.6%) of all OHCA patients had resuscitation attempted by EMS providers. Among resuscitated patients, 73.8% were cardiac etiology. 9.4% of patients had return of spontaneous circulation, 27.2% of patients were admitted to hospital with ongoing chest compression. In the case of 63.4% cardiopulmonary resuscitation was ineffective and death was determined.*

Conclusions: *The present study found that OHCA incidence rate in the Masovian population (central region of Poland) in March–April 2020 period was 12.2/100,000 adult inhabitants. Return of spontaneous circulation in EMS was observed only in 9.4% of resuscitated patients. The presence of shockable rhythms was associated with better prognosis. The prehospital mortality, even though it was high, did not differ from those reported by other studies.* (Cardiol J 2021; 28, 1: 15–22)

Key words: out-of-hospital cardiac arrest, cardiopulmonary resuscitation, return of spontaneous circulation, outcome, COVID-19

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Introduction

Out-of-hospital cardiac arrest (OHCA) remains a major public health problem [1], especially in the emergency medical service (EMS) teams, where staff, due to limited personnel, are often forced to choose which procedure to follow first [2]. As Gräsner et al. [3] indicates, the prevalence of OHCA is 40 cases per 100,000 adults. For the United States and Canada, this is close to 400,000 OHCA cases per year, respectively [4]. The higher prevalence of OHCA of 170/100,000 is indicated by Gach et al. in their study [5]. Majority of OHCAs occur in adults, with a small proportion occurring in pediatric and young adult populations [6].

The challenges faced by medical staff in terms of OHCA are further hampered by the current COVID-19 pandemic, as every pre-hospital patient should be treated as potentially infected with SARS-CoV-2 until this is ruled out [7, 8]. Therefore, following the recommendations of the World Health Organization (WHO), medical personnel providing medical assistance to patients with suspected/confirmed COVID-19 should be equipped with full personal protective equipment. This applies in particular to aerosol generating procedures, such as airway management or cardiopulmonary resuscitation (CPR) [9, 10]. In Polish settings, EMS personnel are usually equipped with a full protective suit, a mask with FFP2 or FFP3 class filter, protective glasses, visor and double gloves. This garment reduces the risk of infection but, as numerous studies have shown, makes it difficult to perform medical procedures, including those so important for CPR, such as chest compressions [10], airway management [11, 12], obtaining vascular access [13, 14], or the administration of drugs and fluids during resuscitation [15, 16].

This study aims were to assess the characteristics and outcomes of adults who suffered an OHCA in the COVID-19 pandemic treated by EMS teams.

Methods

The study was performed following the ethical standards of the Declaration of Helsinki and approved by the institutional review board of the Polish Society of Disaster Medicine (approval no. 01.06.20.IRB).

Study design

Emergency medical service teams' medical records were analyzed. The data were obtained concerning the largest voivodeship in Poland — Masovia Voivodeship. Masovia Voivodeship is the largest voivodeship in Poland both in terms of area and population. It also includes the capital of Poland — Warsaw. The region covers an area of 35,558,47 km^2. As of 31 December 2019, there were about 5.4 million inhabitants, including 4.3 million adults (over than 18 years of age). There are 200 ground-based medical rescue teams located in 128 locations in the voivodeship.

The study population consisted of 527 adult OHCA patients for whom EMS teams intervened from March 1, 2020 to April 30, 2020. Data from adult patients aged 18 years or older with OHCA were analyzed (Fig. 1). Clinical diagnosis was based on the International Statistical Classification of Diseases and Related Health Problems classification in revision 10 [17]. All patients included an intention to treatment analysis. Patients were de-identified after data were collected from digital records.

The study cohort were comprised of adult OHCA patients treated by EMS teams during the above specified periods. Demographic data gathered from electronic medical records included gender, age, medical diagnosis and medical procedure.

Outcomes

Primary outcome of this study was the return of spontaneous circulation (ROSC) in the prehospital period, defined as the steady return of circulation and/or breathing. The etiology of OHCA was categorized as cardiac or noncardiac. Noncardiac causes were subdivided into respiratory disease, stroke, malignant tumor, external causes (e.g., trauma, drowning, burn, asphyxia, or intoxication), or other noncardiac causes. The etiology of OHCA was presumed to be cardiac unless evidence suggested a noncardiac cause [18]. Therefore, the cardiac etiology included confirmed and presumed cases.

Statistical analysis

Data were analyzed by means of the statistical package STATISTICA 13.3EN (Tibco Inc, Tulusa, OK, USA). Categorical variables were expressed as number and percent. Continuous variables were reported as mean and standard deviation (SD) or median and interquartile range (IQR), depending on the normal distribution of the data. Binary data were compared between the treatment groups using by the χ^2 test. Continuous data were compared between groups using the t test. Group differences were calculated, along with their 95% confidence intervals (CI). The authors focused on compar-

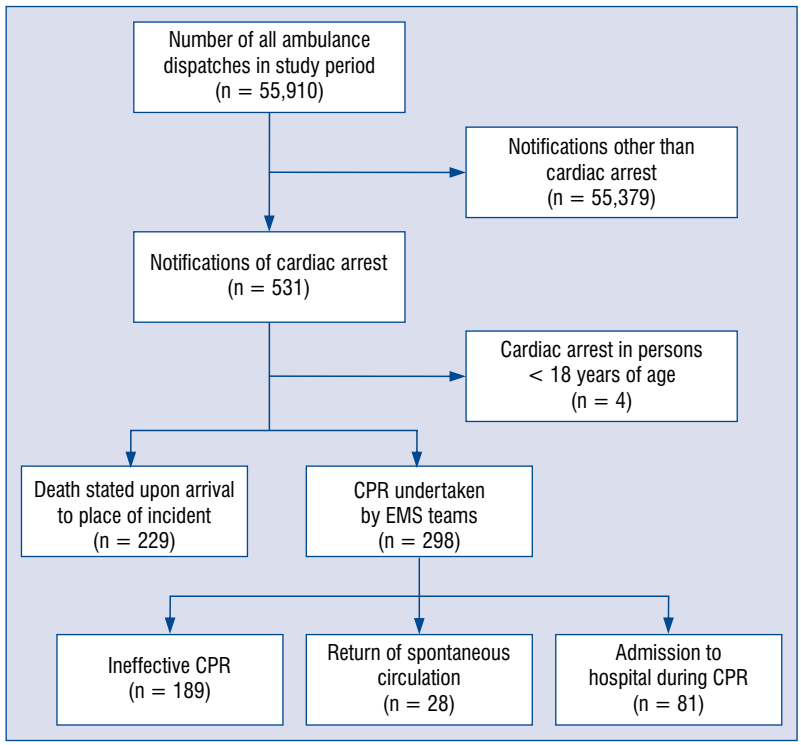

Figure 1. Patients' flow chart; CPR — cardiopulmonary resuscitation; EMS — emergency medical service.

ing means rather than medians, because it was intended to include extreme values in analysis. Thus, the t-test for group comparisons of means was used. A p-value ≤ 0.05 was considered to indicate statistical significance.

Results

In the period from March to April 2020, medical emergency teams from the Mazovian region performed 55,910 interventions, of which 527 interventions were carried out on patients with cardiac arrest, which constituted 0.9% of all intentions in the examined period. CPR was initiated in 298 cases, while in the remaining 229 cases, death before the EMS team had arrived was diagnosed and no resuscitation activities were undertaken (Table 1).

Patients without resuscitation activities where death was diagnosed were statistically significantly older than those in whom CPR activities were undertaken (70.8 vs. 65.4 years, respectively; p = 0.001).

The analysis showed that the time from the call to contact was on average 2 min longer in the case of patients who were found dead without resuscitation (12 vs. 10 min; p = 0.026, respectively). On the other hand, there were no significant differences between the groups in terms of etiology of cardiac arrest, the reason reported during the call or rate of resuscitation provided by bystanders (Table 1).

Return of spontaneous circulation analysis

A detailed distribution of patients in whom CPR was implemented is presented in Table 2. Due to the resuscitation status, patients were divided into three groups. In 189 cases CPR was ineffective, was discontinued, and the patient was found dead. In 28 cases there were 28 cases of pre-hospital ROSC, while 81 patients were transferred to hospital during CPR. The group of patients with unsuccessful CPR or were found dead had the highest age — 67.9 years, compared to those with ROSC — 58.3 years, and those transported to hospital with ongoing CPR — 62.0 years (Fig. 2).

Resuscitation was usually provided in the morning and the time of day did not significantly affect the effectiveness of resuscitation; similarly, there was no significant correlation between the effectiveness of resuscitation and the institution of resuscitation by witnesses or the presence of medical personnel during cardiac arrest.

Table 1. Number and Incidence rate of out-of-hospital cardiac arrests in study period.

Parameter	Total (n = 527)	Resuscitation has been initiated (n = 298)	No resuscitation was undertaken (n = 229)	P
Age, mean (SD)	67.8 (16.2)	65.4 (170.2)	70.8 (14.4)	**0.001**
Age of men	65.0 (15.9)	62.4 (17.4)	68.3 (13.2)	**< 0.001**
Age of women	72.7 (15.5)	70.7 (15.5)	75.3 (15.3)	**< 0.001**
Sex:				
Male (%)	339 (64.3)	192 (64.4)	147 (64.2)	1.0
Female (%)	188 (25.7)	106 (35.6)	82 (35.8)	
Weekday (Monday to Friday)	381 (72.3)	217 (72.8)	164 (71.6)	1.0
Weekend (Saturday and Sunday)	146 (27.7)	81 (27.2)	65 (28.4)	
Morning (8 am to 4 pm)	206 (39.1)	120 (40.3)	86 (37.5)	0.768
Evening (4 pm to 11 pm)	176 (33.4)	95 (31.9)	81 (35.4)	
Night (11 pm to 8 am)	145 (27.5)	83 (27.8)	62 (27.1)	
Time from call to contact with patient, min	11.1 (7.0)	10.0 (5.9)	12.0 (8.2)	**0.026**
Time from call to hospital arrival, min	46.0 (27.3)	45.4 (27.8)		
Time from contact with patient to hospital arrival	57.5 (28.6)	57.3 (29.2)		
Cardiac arrest etiology:				
Cardiac	379 (71.9)	220 (73.8)	159 (69.4)	0.387
Non-cardiac	148 (28.1)	78 (26.2)	70 (30.6)	
Bystander CPR	53 (10.1)	37 (12.4)	16 (10.0)	1.0
SCA in the presence of EMS	25 (4.7)	20 (6.7)	5 (2.2)	1.0
The reason for the call EMS				
Sudden cardiac arrest	134 (25.4)	81 (27.2)	53 (23.1)	0.091
Unconscious	154 (29.2)	89 (29.9)	65 (28.4)	
Syncope	68 (12.9)	37 (12.4)	31 (13.5)	
Chest pain	9 (1.7)	9 (3.0)	0 (0.0)	
Dyspnoea	67 (12.7)	33 (11.1)	34 (14.8)	
Convulsions	13 (2.5)	9 (3.0)	4 (1.7)	
Choking	5 (0.9)	2 (0.7)	3 (1.3)	
Hemorrhage, bleeding	3 (0.6)	2 (0.7)	7 (0.4)	
Injury	3 (0.6)	3 (1.0)	0 (0.0)	
Others	71 (13.7)	33 (11.1)	38 (16.6)	
Initial heart rhythm				
Asystole	400 (75.9)	171 (57.4)	229 (100.0)	< 0.001
PEA	62 (11.8)	62 (20.8)	0 (0.0)	
VF/pVT	65 (12.3)	65 (21.8)	0 (0.0)	

CPR — cardiopulmonary resuscitation; EMS — emergency medical service; NS — not statistically significant; PEA — pulseless electrical activity; pVT — pulseless ventricular tachycardia; SCA — sudden cardiac arrest; SD — standard deviation; VF — ventricular fibrillation

Statistical analysis showed that the first electrocardiogram rhythm observed by medical personnel was significant in terms of CPR effectiveness and follow-up (p = 0.026; Table 2).

Discussion

The aim of this study was perform an epidemiological analysis of OHCA during the imple-

Table 2. Demographic findings according to the relationship between the effectiveness of resuscitation.

Parameter	(A) Died on scene (n = 189)	(B) ROSC (n = 28)	(C) Admission under CPR (n = 81)	P-value	P
Age, mena (SD)	67.9 (16.7)	58.3 (20.7)	62.0 (15.9)	A vs. B = 0.028 A vs. C = 0.007 Other = NS	0.002
Age of men	65.5 (16.7)	54.6 (20.2)	56.3 (18.5)	A vs. B = 0.007 A vs. C = 0.016 Other = NS	< 0.001
Age of women	72.1 (72.3)	66.1 (20.4)	70.2 (17.4)	A vs. B = 0.001 A vs. C = 0.023 Other = NS	< 0.001
Sex:					
Male (%)	120 (63.5)	19 (67.9)	53 (65.4)	NS	1.0
Female (%)	69 (36.5)	9 (32.1)	28 (24.6)		
Weekday (Monday to Friday)	138 (73.0)	18 (64.3)	61 (75.3)	NS	1.0
Weekend (Saturday and Sunday)	51 (27.0)	10 (35.7)	20 (24.7)	NS	
Morning (8 am to 4 pm)	77 (40.7)	9 (32.1)	34 (42.0)	NS	0.460
Evening (4 am to 11 pm)	57 (30.2)	14 (50.0)	24 (29.6)	NS	
Night (11 pm to 8 am)	55 (29.1)	5 (17.9)	23 (28.4)	NS	
Time from call to contact with patient, min	10.8 (5.9)	10.0 (5.9)	9.4 (5.8)	NS	0.427
Time from call to hospital arrival, min		43.6 (18.9)	42.5 (24.0)	NS	0.347
Time from contact with patient to hospital arrival		54.6 (21.4)	53.4 (24.1)	NS	0.249
Cardiac arrest etiology					
Cardiac	142 (75.1)	18 (64.3)	60 (74.1)	NS	1.0
Non-cardiac	47 (24.9)	10 (35.7)	21 (25.9)		
Bystander CPR	23 (12.2)	7 (25.0)	7 (8.6)	NS	1.0
SCA in the presence of EMS	12 (6.3)	2 (7.1)	6 (7.4)	NS	1.0
The reason for the call EMS					
Sudden cardiac arrest	57 (30.2)	6 (21.4)	18 (22.2)	NS	0.650
Unconscious	54 (28.6)	8 (28.6)	27 (33.3)		
Syncope	23 (12.2)	3 (10.7)	11 (13.6)		
Chest pain	6 (3.2)	0 (0.0)	3 (3.7)		
Dyspnoea	21 (11.1)	4 (14.3)	8 (10.0)		
Convulsions	4 (2.1)	3 (10.7)	2 (2.5)		
Choking	2 (1.1)	0 (0.0)	1 (1.2)		
Hemorrhage, bleeding	1 (0.5)	0 (0.0)	0 (0.0)		
Injury	3 (1.6)	0 (0.0)	0 (0.0)		
Others	18 (9.5)	4 (14.3)	11 (13.6)		
Initial heart rhythm					
Asystole	119 (63.0)	15 (53.6)	37 (45.7)	A vs. C = 0.031 Other= NS	**0.026**
PEA	39 (20.6)	4 (14.3)	19 (23.4)	A vs. B = 0.034 B vs. C = 0.019 Other = NS	
VF/pVT	31 (16.4)	9 (32.1)	25 (30.9)	A vs. B = 0.003 A vs. C = 0.005 Other = NS	

CPR — cardiopulmonary resuscitation; EMS — emergency medical service; NS — not statistically significant; PEA — pulseless electrical activity; pVT — pulseless ventricular tachycardia; SCA — sudden cardiac arrest; VF — ventricular fibrillation

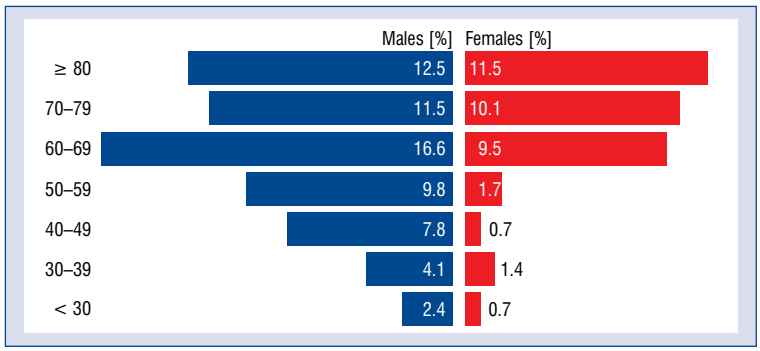

Figure 2. Patient status according to the age.

mentation of restrictions related to the COVID-19 pandemic. According to available research, this is one of the first studies of this type showing the effectiveness of pre-hospital resuscitation during a pandemic, where medical personnel should be dressed in full personal protective equipment and perform all resuscitation activities.

The analysis of the study material showed that 527 patients had OHCA, with only 298 (56.5%) cases of CPR. The remaining patients showed obvious signs of death and died without CPR. Baldi et al. [19] indicates that in the case of Italy, resuscitation was undertaken in 63.5% of patients, while in the same period of 2019 — the percentage of resuscitation undertaken was less than 6% higher.

The mean age of patients with OHCA in the study material was 67.8 years (and 65.4 years for patients on whom CPR was initiated). The age of patients with OHCA in other studies referring to OHCA in COVID-19 outbreak was higher, ranging from 69.7 (17) to 76.3 (2.8) years [19–21]. In the present study, it was also found that men with OHCA were significantly younger than women.

As shown by Baldi et al. [19] the cumulative incidence of OHCA in 2020 was strongly associated with the cumulative incidence of COVID-19 [19, 21]. Baldi et al. [19] compared OHCA that occurred in the provinces of Lodi, Cremona, Pavia, and Mantua during the first 40 days of the COVID-19 outbreak (February 21 through March 31, 2020) with those that occurred during the same period in 2019 and indicate a 58% increase in the rate of OHCA in 2020.

In the current study, cardiac arrest was much more common in men, who accounted for 64.4% of all OHCAs, and 64.4% of cases where resuscitation was undertaken. The higher incidence of OHCA in men is also confirmed by other studies [19]. Besides, a study by Baldi et al. [19] which showed an over 5% increase in OHCA prevalence in 2020 compared to 2019 (respectively: 65.5% vs. 60.3%). Baldi et al. [19] also indicates that only 7.8% of patients were transported with ROSC and 10% with ongoing CPR. In the present study, ROSC was obtained in 9.4% of cases where resuscitation was undertaken and in 27.2% of patients who were transported to hospital with ongoing CPR. In the corresponding period of 2019, it was 19.5% for ROSC and 13.2% for transport with ongoing CPR respectively. Pranata et al. [22] suggest that the COVID-19 pandemic was associated with higher OHCA-related mortality. The numbers might be even higher in developing countries due to poor healthcare and emergency medical service systems [22]. In turn Bhatla et al. [23] indicated that cardiac arrests and arrhythmias are likely the consequence of systemic illness and not solely the direct effects of COVID-19 infection.

An important parameter affecting the effectiveness of CPR is the type of the initially observed rhythm. The study showed that the greatest influence on the ROSC concerning ineffective resuscitation was observed when ventricular fibrillation or pulseless ventricular tachycardia was observed as the first monitored cardiac arrest rhythm (odds ratio = 0.43; 95% CI 0.18–1.04). This is also confirmed by numerous studies [24, 25].

The CPR literature lacks consensus among the authors on the impact of witnessed CPR on the outcomes of OHCA. Shimamoto et al. [26] indicated that in nursing homes, bystander CPR was not associated with improved outcomes of OHCA. This is also confirmed by Lukić et al. [27]. In turn Goto et al. [28] show that dispatcher-assisted bystander child CPR was associated with improved 1-month favorable neurological outcomes. Analysis herein, shows that the bystander CPR

was implemented in 10.1% of all OHCAs, and in 12.4% of OHCA cases where the EMS team undertook resuscitation, but in none of these cases did it show a significant correlation with ROSC. However, having said this, it should be noted that this data was derived from medical records and a description of the dispatcher's call and does not always take this aspect of previous CPR into account, hence it should be assumed that this result is underestimated.

Limitations of the study

This recent study has potential limitations. The first limitation is the fact that the study concerned only patients with OHCA from the Masovia Voivodeship in March and April 2020. This period was chosen deliberately, because then restrictions related to COVID-19 started to be introduced and according to WHO medical personnel should use full personal protective equipment during CPR. Another limitation is the outcome was monitored only at the pre-hospital stage; however, such knowledge also allows a determination the effectiveness of CPR and to indicate the problem of emergency calls coming too late for medical rescue teams.

Conclusions

The present study found that OHCA incidence rate in the Masovian population (central region of Poland) during the March–April 2020 period was 12.2/100,000 adult inhabitants. ROSC in EMS was observed only in 9.4% of resuscitated patients. The presence of shockable rhythms was associated with better prognosis. The prehospital mortality, even though it was high, did not differ from those reported by other studies.

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Conflict of interest: None declared

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Immersive technologies as a solution for general data protection regulation in Europe and impact on the COVID-19 pandemic

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Abstract

Background: *General data protection regulation (GDPR) provides rules according to which data should be managed and processed in a secure and appropriate way for patient requirements and security. Currently, everyone in Europe is covered by GDPR. Thus, the medical practice also requires access to patient data in a safe and secure way.*

Methods: *Holographic technology allows users to see everything visible on a computer screen in a new and less restricted way, i.e. without the limitations of traditional computers and screens.*

Results: *In this study, a three-dimensional holographic doctors' assistant is designed and implemented in a way that meets the GDPR requirements. The HoloView application, which is tailored to run on Microsoft HoloLens, is proposed toallow display and access to personal data and so-called sensitive information of all individual patients without the risk that it will be presented to unauthorized persons.*

Conclusions: *To enhance the user experience and remain consistent with GSPR, a holographic desk is proposed that allows displaying patient data and sensitive information only in front of the doctor's eyes using mixed reality glasses. Last but not least, it boasts of a reduction in infection risk for the staff during the COVID-19 pandemic, affording medical care to be carried out by as few doctors as possible.*
(Cardiol J 2021; 28, 1: 23–33)

Key words: augmented reality, mixed reality, pandemic

Introduction

The general data protection regulation (GDPR), formally called Data Protection Directive 95/46/EC, entered into force in May 2016, and European Union (EU) countries had to transpose it into their national law by 25 May 2018 [EU, 2018]. This legislation consists of 99 articles and deals with the protection of the personal data and so-called sensitive information of all individual EU citizens, and those of the European economic area inside and outside the EU community. It also protects a person and access to European or non-European businesses [1]. What is personal data? According to the European Commission, personal data is any information connected with a citizens private, professional, and/or public life [2]. These are, among others, data like names, surnames, photos, home address or social media activities [Article 2, Article 4(1) and (5) and Recitals (14), (15), (26), (27), (29) and (30)] [3] The second type of information, i.e., sensitive data are related to racial or ethnic origin, political opinions, religious or philosophical beliefs, genetic data, biometric data, health-related data as well as sexual orientation of individuals [Article 4(13), (14) and (15) and Article 9

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and Recitals (51) to (56)] [4]. GDPR is similar to United States (US) privacy law and Federal Trade Commission settlements with companies, but is more restrictive. The impact of GDPR on health services and clinical research on a human subject is, therefore, essential in all aspects [5]. Doctors are obliged to comply with its procedures from information to patients to data sharing requirements. The general principles that should be applied to patients' data are described in Article 5. All personal data of subjects should be available only for a chosen doctor. This is a huge technological challenge. Still, in doctor practices, one can find desks and files full of different types of documentation, books, patient data, and other information. Digitalization is an evolving field and progresses continually, but there is still much to do. An increasing number of doctors have been using this data in their exam rooms, on their tablets, PC's and laptops. All of those devices have the same limitation, a finite amount of information that can be displayed at the same time. Besides that, in most of the cases, a screen with restricted details can be viewed by anyone in the examination room.

Immersive technologies such a virtual reality (VR), augmented reality (AR), and mixed reality (MR) join the real world with a computer-generated one providing a composite view [6]. AR is an enhanced version of the physical world through the use of different stimuli like audio or vision. Applying additional elements to three-dimensional (3D) virtual images should be happening in real-time, be interactive, and enable users, who usually wear a head-mounted display, free movement in 3D displays [7, 8]. Mixed reality is a hybrid of both augmented and virtual realities. AR/VR/MR devices offer a new quality for art and entertainment [9, 10], maintenance [11, 12], architecture [13], industry [14] healthcare delivery and education in medicine [15]. Recently, the number of applications in the healthcare sector have systematically increased. In Tepper et al.'s study [16], augmented reality was used in the operating room to improve the decision-making process and improve the surgeon workflow. It is also increasingly applied in the education sector, like anatomy [17], nursing [18, 19], and neurology [20] courses. AR-based clinical experience allows visually assessing both the external form and an internal organ structure. To introduce this new technique, it is necessary to use specific devices, i.e., head-mounted displays, and various sensors, which will be applied in the diagnosis process [21, 22]. Thus, according to GDPR provisions, holograms and mixed reality devices like Microsoft HoloLens [23] or HTC VIVE Pro [24] can be the right solution. These technologies create an opportunity to remove everything from the doctor's desk except for MR glasses. All personal data are made available only to be seen by said doctor.

This paper aims to find a solution, which follows the 95/46/EC EU directive in the field of medicine. Here, a proposed holographic application (HoloView), that is tailored to run on Microsoft HoloLens [23]. The HoloView application unables users (doctors) to display all information needed about their subjects' health status. Moreover, it gives users a wide range of views. The users felt like they were working on three normal LCD curved screens connected by edges. The biggest plus is that all pieces of information are visible only to the doctor and no one else. The device is secured with built-in monitor whichchecks if the device is taken off of the doctor's head — which results in blocking access to the application. Thus, the proposed approach contributes to personal data security and so-called sensitive information protection.

Additionally, the subject of this project is to develop knowledge on the use of HoloView in medical education at all levels during the COVID-19 pandemic. The proposed solution presents new possibilities and enables additional support in the process of clinical (pre-procedural) diagnostics during medical procedures (intraoperative). The simulation of medical procedures through the Mixed Reality HoloView system offers an opportunity to train medical students, paramedics, and doctors across a range of specialists in a safe (risk-free), realistic and repeatable environment. It eliminates harmful consequences to patients and offers repeatable procedures. The system consists of four main components, i.e. central indirect server, an artificial intelligence module based on deep neural networks, a wireless health check sensors platform, and the MR application (HoloView COVID pandemic). The central indirect server is responsible for independent work and all types of communication with external units, digital sensors, and devices. It does an analysis of subject data, classifications, potential diagnoses, and an artificial intelligence-based software pertaining to treatment. The digital diagnostic sensors module allows the performance of health checks on patients.

Methods

Immerse technologies

Augmented reality extends a real environment with computer-generated information using differ-

Figure 1. Microsoft HoloLens.

ent stimuli like audio or vision, rather than replacing the physical world as with VR. It integrates with the users and allows them to manipulate the digital data in real-time and allowing users to manage these data [7, 8]. In 2016, the game called Pokemon Go, which is one of many successful mobile games in the world, was realized using AR technologies and were thus raised to public attention [25, 26]. The number of AR/VR/MR applications in the field of medicine has been increasingly growing since doctors want to give better outcomes for their patients [15]. HoloLens from Microsoft [23] and VIVE Pro from HTC [24] are two commercially available sets for Mixed Reality. First, one is an independent device and does not require a separate operation space or manual controllers. It is fully integrated with Microsoft Enterprise systems; its interface is known to users, which are familiar with using the Windows operating system on other computer platforms. The disadvantage of Microsoft's solution is that the commercial license for HoloLens has a much higher price than VIVE Pro (even taking into account the cost of an additional workstation) [27].

In terms of testing innovative technological solutions, as well as their regular use in the diagnosis, therapy, and rehabilitation of patients, medicine is the leading discipline. In this area, the most practical and promising innovation is exactly the application of Mixed Reality, i.e., the combination of the image of real objects and biological signals with the data obtained, e.g., during the diagnostic process using imaging techniques. It is also predicted that VR, AR, and MR technologies will have a significant impact on the development of telemedicine.

Microsoft HoloLens

During the past few years, thanks to the miniaturization process. In 2016 the Microsoft Corporation released a product called "HoloLens" (Fig. 1) [23]. A device in the form of goggles with a built-in battery, microcomputer, cameras, microphone, speakers, and holographic projectors. A user wears HoloLens, which is in the form of big glasses. Build-in micro projectors generate an image, in fact, a hologram, onto the glasses in front of the user's eyes. HoloLens functionality does not end with only displaying a flat image. The 3D imaging occurs when an active mapping of the environment is used, which fully recognizes the shapes of objects and terrain, in whose area users are moving. Besides that, depth cameras analyze the entire environment around users like tables, chairs, walls, etc. A microcomputer analyzes the shape of the room and decides about a wayto display a hologram in front of the user in a manner compatible with that environment. For example, when placed on a table or displayed on screens on the walls, so the view becomes more natural to the operator using the goggles.

Microsoft HoloLens is the only product that provides interaction: eye-tracking, service using gestures, and voice support. This device is completely autonomous (no connection to a computer or phone to work is needed). It is light, robust and looks very aesthetically pleasing. Depending on the software, the device can display an image in hologram form for both VR and AR.

The first generation of HoloLens glasses were based on a quad-core Intel processor Atom x5-Z8100 clocked at 1.04 GHz. This is a 64-bit

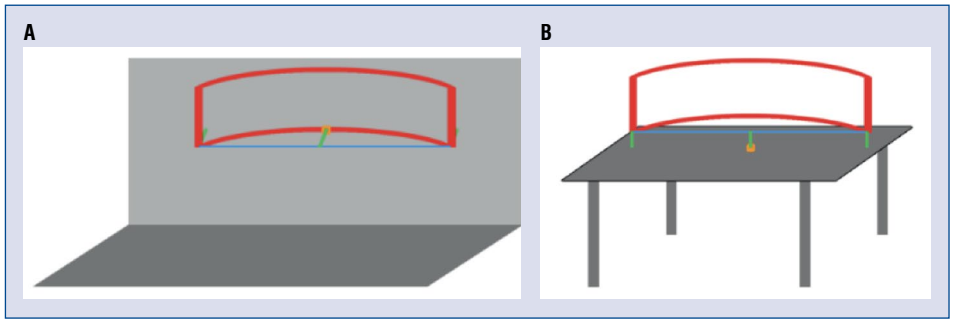

Figure 2. Schemat of the information/images displayed by HoloLens; **A.** On the wall; **B.** On the desk.

unit made in the technological process of 14 nm. It was supported by HoloLens Graphics, which also was prepared by Intel. The first generation was equipped with 2 GB of RAM. HoloLens 2 (second generation) is equipped with a system displaying information in 2K resolution and a 3:2 aspect ratio. Data projection adapts to the operator's eyes, so-called positioning the image relative to eyes-position in 3D. The device has an image sensor (Azure Kinect sensor), an accelerometer, a gyroscope, and a magnetometer. The built-in 8MP camera allows recording movies in 1080 p and 30 fps quality. HoloLens 2 also has five channel microphones and advanced tracking systems for both hands (fully recognizing all hand movements, including individual fingers). The Qualcomm Snapdragon 850 processor performs the whole operation. The device provides 802.11ac wireless connectivity 2×2 a Bluetooth version 5, modules and sensors: inertial measuring unit, four cameras for recognition of the surroundings, one camera for measuring depth, a light sensor and four microphones. For recording video in 30 fps, two photographic cameras are available: the first 2.4 Mpx and the second 1.1 Mpx. The second generation also has bigger storage, a 64 GB data carrier (for the user, just over 54 GB is available). It works under the control of the Windows 10 operating system in a 32-bit version. A 16.5 Wh powers it entirely.

In Figure 2, the display method using HoloLens is presented. The HoloLens area of view is schematically indicated by a red area (red window). Before information/images are displayed, the dedicated application needs to be provided a desired working space. The pointer marked schematically as an orange point, is responsible for this activity (Fig. 3). It knows on which kind of environment the information/images will be displayed on the HoloLens. The whole procedure is done by scanning the environment around the pointer in 3D. The pointer

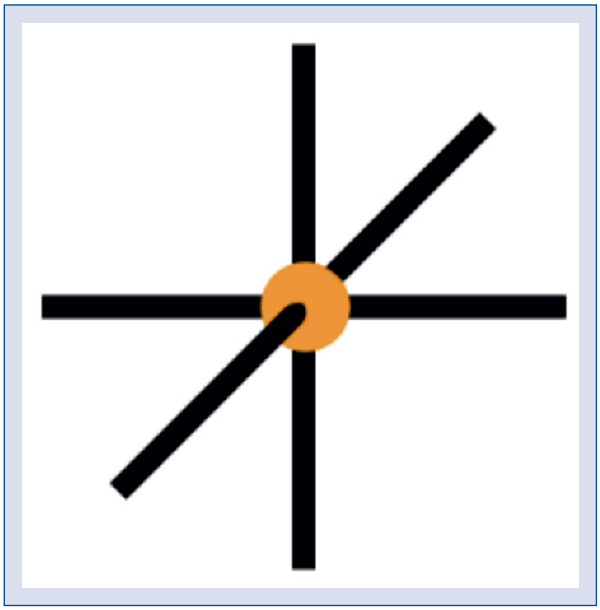

Figure 3. Schematic scan of the environment by the pointer.

performs a two-stage scanning process. In the first step, it scans the mapped environment above and below. If the orange point does not create a vertical line, it means that the user is pointing at a wall (Fig. 2A). The second check is responsible for horizontally checking the mapped area. If checked-point creates a horizontal line, it means that the user is on the table, and the application should be displayed on a horizontal space (Fig. 2B). The main difference between A and B cases is that when the user shows a hologram on the wall, he/she does not want a situation where some of the displayed data will be hidden inside the wall so it will not be visible. Because the proposed application, i.e., HoloView, has a semicircular shaped orange pointer to change the way the hologram projects. If the

pointer is on a wall, it displays HoloView where the middle starts from the pointer schema as presented in Figure 2B. If it is displayed on a desk, the orange pointer is in the middle of the line created by both corners of HoloView shape (Fig. 2A). In the case of holograms on a desk, it displays right away, and can interfere with stuff on the desk, which is also unwanted.

AR/MR application

In recent years, the first devices using holographic technologies have already appeared on the market. Although they differ in image quality, size, weight, and even performance, advances in this technology are visible, and subsequently improved versions or prototype devices show that it is becoming a realistic-looking hologram and will improve over the next few years. The current quality of holograms already allows its effective application in everyday life [28]. In El-Schich et al. [29], the cancer cells using computer-generated holography were analyzed. An interesting application of holographic technology incoherent imaging was presented in Wang et al. [30]. Also, the off-axis digital holography shown in Claus et al. [31] seems to be a promising solution in intraoperative medical imaging. The designing and implementation of AR/MR applications and the flat screens of computers or tablets differ very much. The first one has more control over processes and their design. AR/MR devices in the form of head-mounted display works with the human senses and human preferences which are varied depending on the unit. In the case of HoloLens [23] and application design, it is possible to choose the way of design using voice commands or gestures. Also, the 3D user AR/MR-based interfaces are a huge challenge. Commonly used two-dimensional (2D) interfaces have many buttons, windows, cards, and visual options available in a 2D space. The development of a 3D graphical interface that engages the user visually and has an emotional meaning is an essential part of the design process, in particular to medical aspects. In Aruanno et al. [32], MemHolo, i.e., the prototype of the first HoloLens application designed for a subject suffering from Alzheimer's disease, was presented. Users can practice short-term and spatial memory with it in a controlled virtual environment. In turn, in McDuff et al. [33] system, CardioLens to the physiological measurement of multiple people is shown. CardioLens is a MR application running on Microsoft devices, allows noncontact measurement of the heart rate.

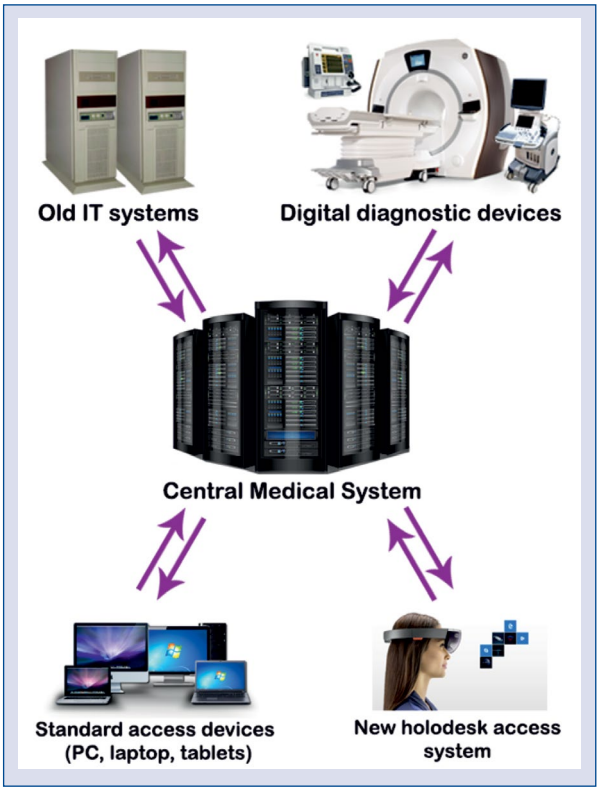

Figure 4. Holographic assistant for doctors (HoloView COVID-19 pandemic assistant for doctors).

Results and Discussion

The general idea of the proposed holographic assistant for a doctor is widely presented in Proniewska et al. [34] and Figure 4. The system consists of four main components, i.e., central indirect server, artificial intelligence module based on deep neural networks, a wireless health check sensors platform, and an MR application (HoloView). The central indirect server is responsible for independent work and all types of communication with external units, digital sensors, and devices. Analysis of a subject's data, classifications, potential diagnoses, and treatment is done by the artificial intelligence-based software. The digital diagnostic sensor module allows for the performance of health checks on patients. HoloView works as a front-end application. The software engineering splits application design into two separate parts: front-end and back-end. The most straightforward example in understanding this can be applied where all data manipulation and storage are placed on the server. This can be called "back end", the entire processing is done behind the user's eyes. There should also

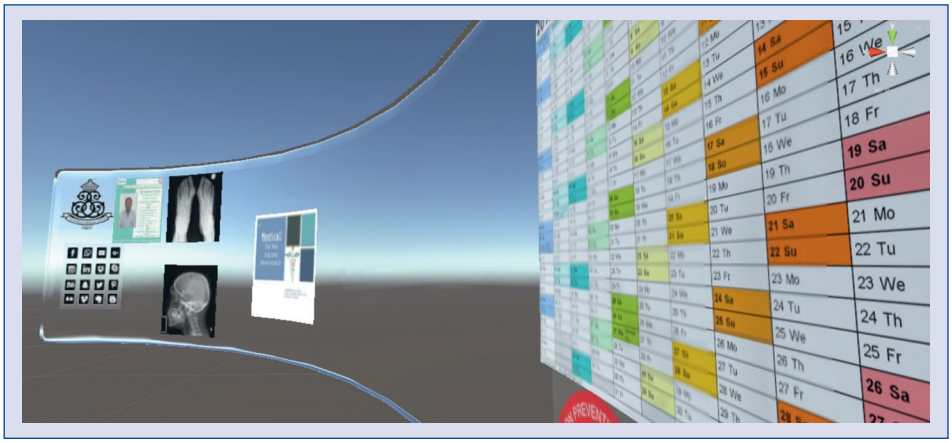

Figure 5. The perspective of the HoloView application as seen through user's eyes.

be an application-client which allows viewing data from a server, sending commands to manipulate it and display everything in a presentation layer ina way that a user will be able to see data most simply and understandably. This is called the front-end.

The proposed application is designed according to a rule that a user with a client-server connection over HTTP post/gets commands which automatically download and send data from the server. Here, the data are stored as an XML file. HoloView can adapt to any existing client-server infrastructure. Adaptation of the server has only one requirement, i.e., use of the data in an XML format. The dedicated server location is set up statically on the application. The presentation of the data displayed using the HoloLens device is a big challenge. All information should be given in the most attractive way so users will accept this without the related stress in changing his habits related to using the 3D application instead of 2D applications. HoloView application utilizes multiple curved screens on a user's desk (Fig. 5). The user, wearing HoloLens glasses, feels like he/she is using three normal LCD curved screens connected by edges. But there are crucial differences that make the HoloLens device with it's dedicated application a much better solution. First, the unused working space on the user field of view disappears. It can be compared to taking away everything from the desk and not using an LCD screen. In cases where this space is needed again, it is enabled automatically. Secondly, if someone is using spacial mapping to display information it happens in just a few seconds, goggles scan the environment around them and create the space/room in their memory model. The user then decides in which place they would like to see the information. HoloLens device displays data which looks like they were developed specifically for that user's environment. This is made possible owing to the use of spatial mapping, which helps to show the script. It allows deciding in which form, what way, what size, data should be displayed to fill the entire available space.

To make the hologram "right", it is important to examine a few aspects in developing the application. The main challenge in creating an AR/MR application is to understand so-called spatial mapping, which is a digital representation of the real world. To design a spatial awareness system, the Microsoft Mixed Reality Toolkit (MRTK) was used [35]. This is a cross-platform for building AR, MR, and VR. It offers functions like "ToolTip", which enables creating a user interface annotation with the line that points somewhere on the 3D object. Another interesting function is "Manipulation Handler", which allows one to "take" a 3D object and rotate it as with a hand manipulating a physical object in reality. HoloLens 2 has a new function, i.e., eye-tracking, which allows mapping points where an operator looks. This could be used with an intuitive zoom functionality. The MRTK platform scans the environment around the HoloLens glasses while the users move their heads. During the scanning process, the memory device inside, the HoloLens creates a 3D model of the space. In the next step, this model can be used to generate behaviors and interactions as realized in the real world. For example, when a ball is rolling on a table and reaches the edge of the table, it will fall and change its position to the floor level. Another critical issue with designing and implementing AR/MR applications is hologram placement, i.e., selection

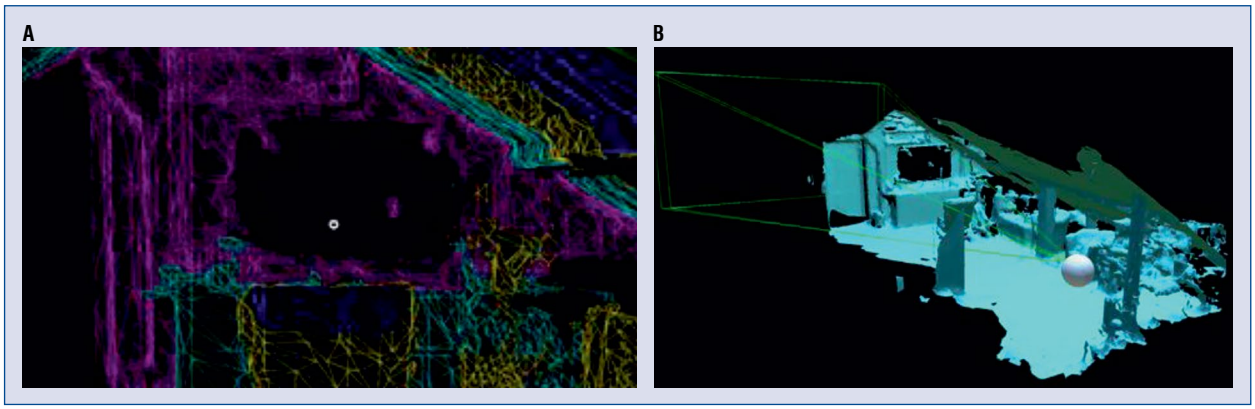

Figure 6. Images of the mapping process; **A.** The mapped environment with HoloLens position; **B.** Operator's perspective view.

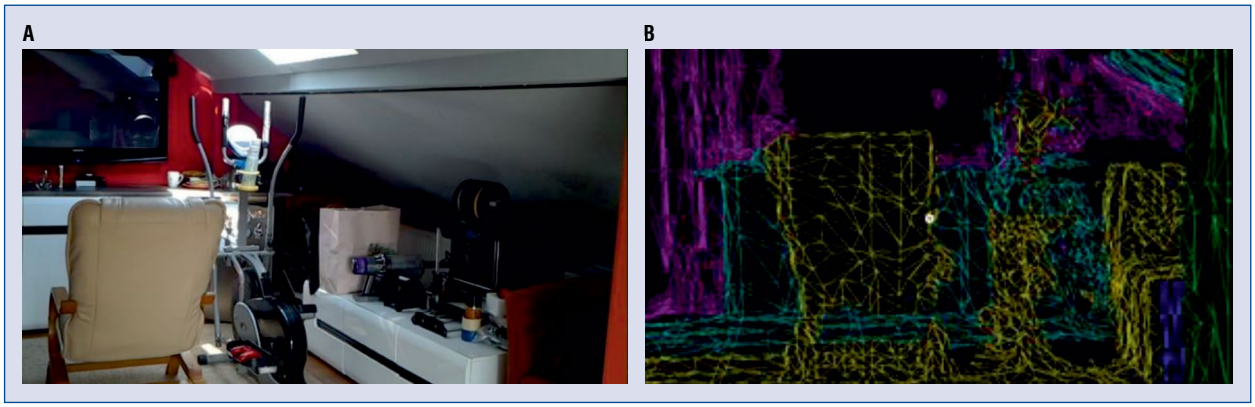

Figure 7. Spatial mapping mesh trough the HoloLens covering a room; **A.** Photo was taken with a camera built into the goggles; **B.** Shot of the scanned space.

of a spatial location. To avoid losing a sense of control by users, a specially mapped model of the environment to place and affix generated holograms in the space required. This is important when wanting to see a 3D model locked in space, which stays in the same place. For example, when the model of a box is generated, which is later placed on a table, this box should stay exactly in one place. Even when we walk around the table, it should remain in the same position on the table. An understanding of occlusion is also required. The application should also react to a specially mapped environment in a certain way, i.e., provide additional visual feedback. A good example can be a virtually displayed LCD screen on a table. When we place it in front of this generated model, for example, a real laptop, the screen of our model should react in the right way. In some cases, the users can interact with the holograms, and occlusion is not necessary. Of course, AR/MR would not be the same without physical reactions. When creating a rubber ball model that fell from the table, it is expected to bounce on the floor. A different reaction is that which is desired from a glass cup, which should break into pieces.

In Figure 6A, the mapped environment (attic room) using HoloView is shown. The location of the HoloLens, i.e., white ball relative to the room and the direction of view, its angle, and area that HoloLens view covers, marked by green lines, are illustrated. It is a model generated inside the HoloLens system that also serves to determine the response of models/holograms relative to the environment. The same scene from an operator's point of view is presented in Figure 6B. This frame is indicated by the green lines, which are visible in Figure 6A. The mesh reflects scene geometry by surface, which can be filtered and textured after the scanning process.

In Figure 7A a real photo of the mapped frame is presented while in Figure 7B corresponding

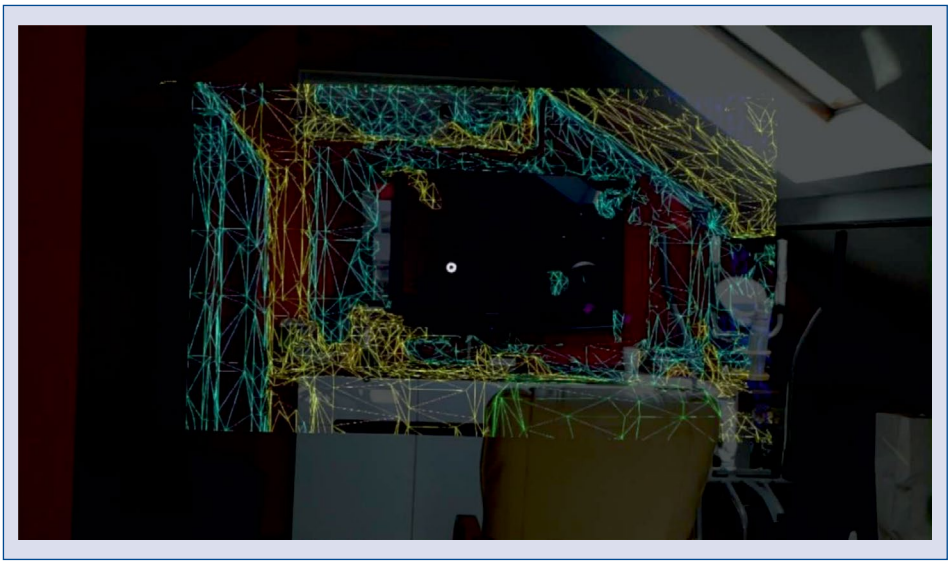

Figure 8. The limited vision range using the first generation of the Microsoft goggles.

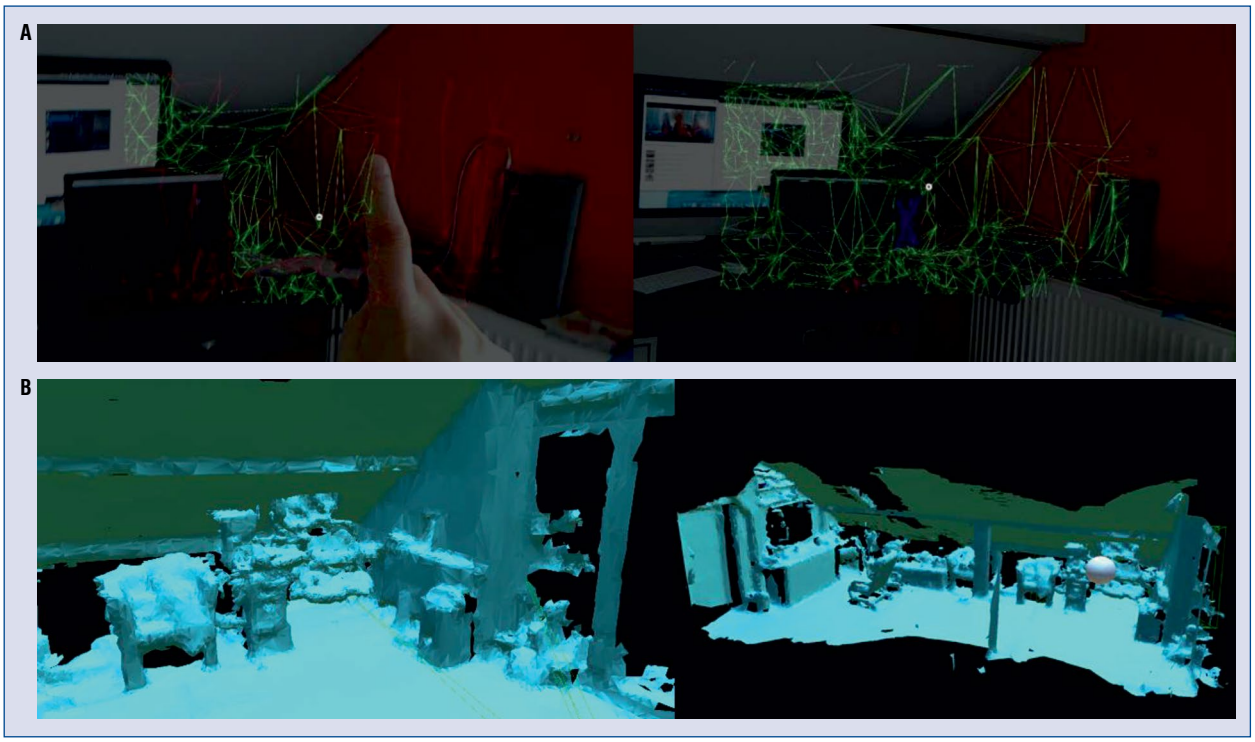

Figure 9. Shot of a corner of the room using HoloLens; **A.** Spatial mapping; **B.** Mapped area.

scanned space is shown. A view of the HoloLens with the spatial map of activity is visualized in Figure 8. The limited range of vision offered by the first generation of the goggles is visible, i.e., only part of the image has an overlaid spatial mapping. The spatial mapping of the room is also shown in Figure 9A, while in Figure 9B a mapped environment marked by the white ball position of the HoloLens is presented.

Thus, the HoloLens changes the way that information can be perceived, i.e., doctors' documentation working space. The proposed solution

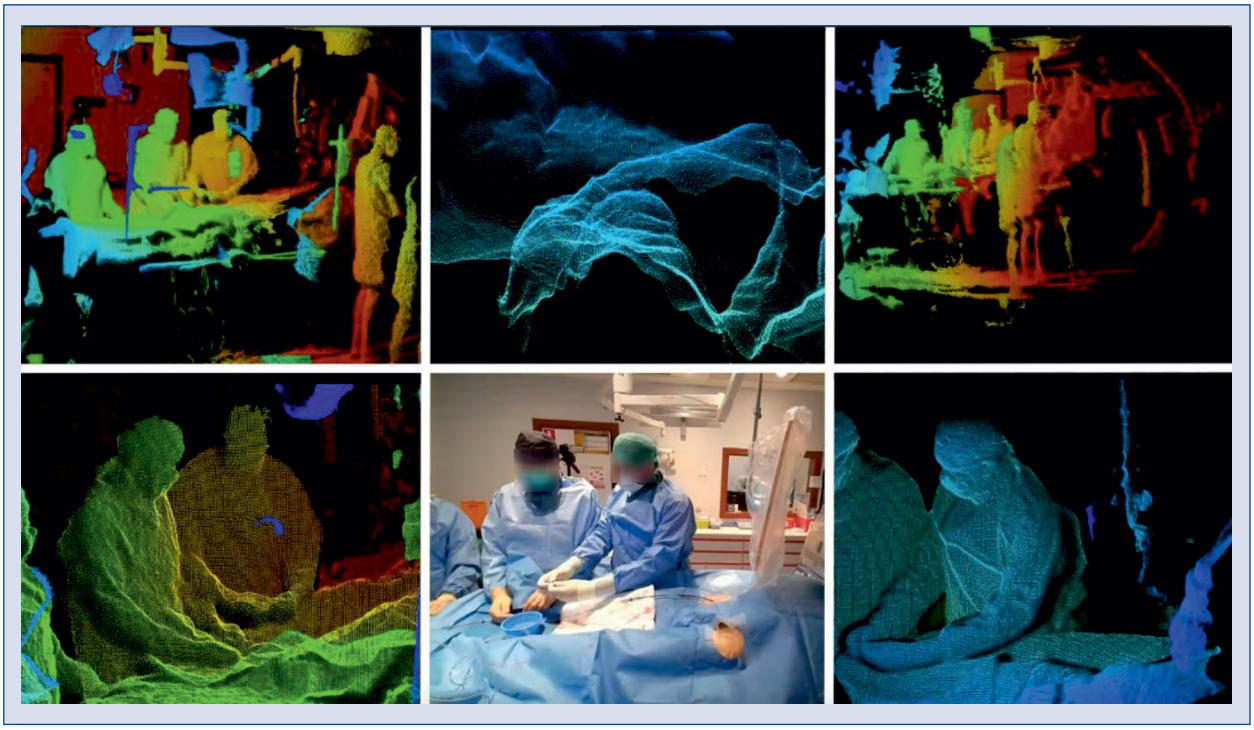

Figure 10. Experimental validation of the HoloView application.

removes almost everything from the doctor's desk. No cables, monitors, or even a mouse or keyboard is needed. Thanks to holographic technology, multiple screens can be used around a doctor's desk. A number of them can be selected in the way that doctors like. One huge screen or maybe four smaller screens with different pieces of information on each of them. Doctors decide exactly what is needed at that moment. It could be an RTG photo, treatment history, or maybe a schedule to plan the next visit. Everything becomes available right in front of the doctor. All information is displayed in front of the doctor to remind them about important facts regarding the subject like a dangerous reaction for anesthetics, heart problems, or HIV, AIDS sickness as when doctors should engage with high caution. Everything becomes available only after the doctor types a password on a virtual keyboard hanging in the air.

The impetus of digital technologies have entered almost every area of life, and so too, are hackers who are looking for innovative ways to obtain personal data. Severe financial penalties imposed on entities responsible for the leakage of personal data of their users or clients, which were introduced in May last year together with the EU regulation on the protection of personal data, which force companies and universities to control the processing of data carefully, especially in pandemic times. Global corporations, but also small enterprises are required to increase their levels of security. It is worth remembering, however, that even GDPR realization is not sufficient in protecting us from potential threats, so it is crucial to be aware of how to care for information available on the Internet and minimize the dangers present on the Internet.

The system proposed has also been validated by doctors under real conditions, i.e., in the operating room (which is shown in Fig. 10). The cardiologists from University Hospital in Krakow carried out the patent for amen ovale structural procedure using HoloView.

General data protection regulation [1] allows for broadening patient confidentiality and medical data protection. Changes in the law, especially in the sector of medical research, are discussed in Rumbold et al. [36]. Simulation on policy effecting the Digital EU Public Health Sector was presented in Yuan et al. [37]. The main advantage of the proposed HoloView solution is that the displayed data is only visible to a person wearing HoloLens goggles. Owing to that, additional confidence is gained as no one else can see restricted data. The patient is recognized using an existing QR/barcode. Access to the application is possible after entering

a password on the virtual keyboard by the doctor. Patient personal and sensitive information like names, addresses, health status is presented only to the eyes of a doctor who wears a head-mounted display. A safe Internet connection is the only further requirement for security

Another critical issue is connected with Global Health Security [38]. This is dependent upon having an adequately prepared and healthy security workforce which is necessary to ensure the safety of medical service during and after the pandemic of COVID-19. Kochanczyk et al. [39] proposed a Susceptible–Infected–Infectious–Excluded model to analyze the influence of contact rate on the dynamics of COVID-19. It turned out that the pandemic can be limited by limiting contact availability. This can be done during a medical consultation using the HoloView application. Augmented technology has also been tested during COVID-19 with teaching and learning, particularly in medical education [40, 41]. The proposed solution protects the doctor by providing a safe distance to the patient. The future remains unknown, but the pandemic can be an enduring transformation in medicine and education with the application of immersive technologies [42].

Conclusions

Changes in European law have had a huge influence on the way in which organizations handle and manage user data and sensitive information. One can expect the requirement to inform users what information about them will be used for and it is essential to protect these data. Even US healthcare units additionally have to abide by the Health Insurance Portability Accountability Act when they want to collaborate with European organizations. The development and implementation of provisions protecting us against cybercrime is a long-term process requiring the involvement of both European and national legislators and dialogue with entities from various sectors of the economy, including health protection organizations. Given the scale and complexity of cybercrime, it is necessary to develop an interdisciplinary system of specialist provisions, covering primary regulatory and personal data protection provisions. The proposed solution based on immersive technologies, such as holography and MR, meet the requirements imposed by GDPR regulations. It removes everything from a doctors' desk and is replaced with MR glasses, which are protected by a password for each doctor. Information about patients are processed and visualized in the Microsoft HoloLens which is placed on the head. Thus, all health data are visible only to the doctor; no other person present in the room has access to this data. Another advantage of the proposed solution is to ensure a safe distance between doctor and patient. The use of the Holoview during the COVID-19 pandemic simplifies documentation. It ensures continued high-quality care in times of a significant increase in the number of patients (including critical patients), where specialists/health care providers or other specialist colleagues can be involved in patient care without actually being present.

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New-onset atrial fibrillation during COVID-19 infection predicts poor prognosis

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Abstract

Background: *Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has led to a paradigm shift in healthcare worldwide. Little is known about the impact on the cardiovascular system, and the incidence and consequences of new onset of atrial fibrillation (AF) in infected patients remain unclear. The aim of this study was to analyze the cardiovascular outcomes of patients with new-onset AF and coronavirus disease 2019 (COVID-19) infection.*

Methods: *This observational study analyzed a sample of 160 consecutive patients hospitalized due to COVID-19. A group with new-onset AF ($n = 12$) was compared with a control group (total: $n = 148$, sinus rhythm: $n = 118$, previous AF: $n = 30$). New-onset AF patients were significantly older and hypertensive, as well as presenting more frequently with a history of acute coronary syndrome and renal dysfunction. This group showed a higher incidence of thromboembolic events (41.7% vs. 4.1%; $p < 0.001$), bleeding (33.3% vs. 4.7%, $p = 0.005$), a combined endpoint of thrombosis and death (58.3% vs. 19.6%, $p = 0.006$) and longer hospital stays (16.4 vs. 8.6 days, $p < 0.001$), with no differences in all-cause mortality.*

Results: *In multivariate analysis, adjusted by potential confounding factors, new-onset AF demonstrated a 14.26 odds ratio for thromboembolism (95% confidence interval 2.86–71.10, $p < 0.001$).*

Conclusions: *New-onset AF in COVID-19 patients presumably has a notable impact on prognosis. The appearance of new-onset AF is related to worse cardiovascular outcomes, considering it as an independent predictor of embolic events. Further studies are needed to identify patients with COVID-19 at high risk of developing "de novo" AF, provide early anticoagulation and minimize the embolic risk of both entities.* (Cardiol J 2021; 28, 1: 34–40)

Key words: new-onset atrial fibrillation, COVID-19 prognostic, SARS-CoV-2, embolism

Introduction

Coronavirus disease 2019 (COVID-19), a viral respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused a pandemic which is overwhelming health care systems worldwide. Affected patients have been reported to have an inflammatory state that may predispose patients to in-hospital cardiovascular complications, such as myocardial damage, atrial fibrillation (AF), and stroke. Furthermore, patients with pre-existing health conditions such as obesity, pulmonary disease, hypertension and heart failure are at higher risk for a more severe infection by SARS-CoV-2. The disease can trigger exacerbated inflammatory responses that can be challenging for patients with heart conditions.

There is a lack of information about the incidence and the consequences of arrhythmias related to the virus. As with any infection, there can be an increase of stress on the body from which arrhythmias can arise [1]. AF is the most common pathologic of arrhythmia, and its incidence is increased in the presence of an infection [2].

The presence of palpitations has been reported as one of the most common initial symptom of the

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disease (7.3%) [3]. In 138 patients from Wuhan who were hospitalized with COVID-19-related infection, arrhythmias were reported in 17% of the general cohort and in 44% of the patients admitted to an intensive care unit [4]. The most common arrhythmia overall in patients with COVID-19 is sinus tachycardia, but the most frequent pathologic arrhythmias include AF, atrial flutter and monomorphic or polymorphic ventricular tachycardia. The prevalence of AF in COVID-19 patients is substantial when combining both pre-existing and new-onset AF. The onset of AF may be related to electrolyte abnormalities, dehydration and hypoxia [5]. Several previous studies have demonstrated that new onset atrial arrhythmias are associated with increased morbidity and mortality [6, 7]. The outcomes in patients with new-onset AF, pre-existing AF, and sinus rhythm remain unclear in patients with COVID-19.

Atrial fibrillation is a common cause of stroke, hospitalization and death, whereas anticoagulation therapy for the prevention of stroke can trigger bleeding events. The management of AF regarding the use of antithrombotic therapies in the setting of COVID-19 disease, in clinical practice, does not differ from the routine management [8]. On the other hand, coagulopathy is a common abnormality in patients with COVID-19 disease and these patients seem to have a higher risk of developing thromboembolic events [9]. The balance between embolic and bleeding risk in these patients is challenging.

The current study aims to evaluate the impact of new-onset AF compared with pre-existing AF and sinus rhythm on long-term mortality, stroke, and bleeding in COVID patients.

Methods

The present observational single-center review consists of consecutive patients hospitalized with COVID-19-related infection in a tertiary hospital and prospective follow-up until discharge. A total of 160 consecutive patients were enrolled.

Patients hospitalized with COVID-19 infection between March and April 2020 were studied. Inclusion criteria were age > 18 years old and diagnosis of COVID-19 confirmed by polymerase chain reaction. For comparison purposes, two groups were established: the new-onset AF group, which constituted consecutive patients with "de novo" AF during the hospitalization; and the control group, formed by patients in sinus rhythm or with previous AF hospitalized with COVID-19 during the same period. In the present study, the groups were defined as new-onset AF and control group (with pre-existing AF or sinus rhythm), to scrutinize the role of new-onset AF.

No explicit exclusion criteria were defined other than valvular AF or mechanic cardiac prostheses to avoid selection bias.

All data were captured using a dedicated electronic case report form. Clinical and therapeutic data were collected. The risk of thromboembolic and bleeding events was assessed by calculating the CHA_2DS_2-VASc and the HAS-BLED scores in all patients, because the international normalized ratio (INR) is not pertinent for the use of heparin (and no patient was in treatment with warfarin), the "labile INR" component from the original HAS-BLED score was not included. Therefore, the maximum points for this cohort for the HAS-BLED score was 8 instead of 9.

The prevalence of new-onset AF was documented by electrocardiograms, rhythm strips, and Holter monitors. Patients were examined and pulse tests were performed daily.

Clinical follow-up was performed during the hospitalization, with special attention to anticoagulation therapy, and the incidence of embolic and bleeding events was monitored.

The primary endpoint was thrombosis, defined as a combination of ischemic stroke, systemic embolism and pulmonary embolism. Ischemic stroke was considered in the case of an abrupt onset of a focal neurological deficit non-attributable to an identifiable nonvascular cause and excluded intracranial bleeding. Systemic embolic event consisted on an abrupt episode of arterial occlusion with clinical or radiologic documentation in the absence of prior instrumentation.

The primary safety outcome for the current study included fatal bleeding, bleeding into a critical organ (intracranial, intraspinal, pericardial, retroperitoneal or intramuscular with compartment syndrome) or relevant bleeding with a hemoglobin drop of ≥ 2 g/dL. The definition of major bleeding events was consistent with the International Society of Thrombosis and Hemostasis (ISTH) criteria [10].

The study protocol complied with the Declaration of Helsinki and it was authorized by the Reference Ethic Committee and the Local Ethic Committees of the hospital. Access to the medical records was granted for retrospective analysis.

There has been no patient and public involvement in this work.

Table 1. Baseline demographics and patient characteristics.

	New onset AF (n = 12)	Control group (n = 148)	P-value (univariate)
Sex (female)	N = 4 (33.3%)	N = 60 (40.5%)	0.43
Age (years), mean ± SD	75.9 ± 9.6	64.9 ± 16.3	0.007
Arterial hypertension	9 (75%)	66 (44.6%)	0.04
Diabetes mellitus	3 (25%)	22 (14.9%)	0.28
Previous myocardial infarction	4 (33.3%)	10 (6.8%)	0.01
Congestive heart failure	2 (16.7%)	11 (7.5%)	0.25
Previous stroke/systemic embolism	0 (0%)	12 (8.1%)	0.38
Previous bleeding	1 (8.3%)	9 (6.1%)	0.40
Abnormal liver function	6 (50%)	43 (29.1%)	0.12
Renal dysfunction	5 (41.7%)	22 (14.9%)	0.03
CHA_2DS_2VASc	1.66±1.51	2.1 ± 1.7	0.39
HAS-BLED	1.19±1.12	1.5 ± 1.3	0.17
Anticoagulation therapy	3 (25%)	33 (22.3%)	0.53
Troponin I [ng/mL]	0.4 ± 1.0	0.5 ± 26.5	0.87
D-dimer [ng/mL]	10833 ± 18959	3642 ± 9936	0.03
Hemoglobin [g/dL]	13.0 ± 0.9	14.2 ± 7.2	0.50

Values are expressed as number (%) unless otherwise indicated; SD — standard deviation; AF — atrial fibrillation; CHA_2DS_2-VASc — Congestive heart failure, Hypertension, Age > 75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category; HAS-BLED — Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol

Statistics analysis

Variables are presented as number (percentage) or mean ± standard deviation (SD), as appropriate. Baseline characteristics between the "de novo" AF and control groups, were compared with the χ^2 test for discrete variables and the Student t-test for continuous variables provided that populations were normally distributed. Multivariable logistic analysis was used to determine independent predictors of embolic events, including variables with statistical significance on univariate analysis and potential confounding factors. Observations with missing data were excluded from the analysis (< 1% from total). Analysis was conducted using SPSS software V.22.0, with a two-tailed significance value of 0.05.

Results

Patient characteristics

A total of 160 consecutive patients with COVID-19 infection were enrolled, 7.5% with new-onset AF (n = 12) and 92.5% in the control group (n = 148). In the control group, 30 patients had previous diagnostic of AF and the rest of the patients (n = 118) were in sinus rhythm.

New-onset AF patients were studied according to their baseline characteristics, in-hospital features and clinical outcomes. The main demographic and clinical characteristics of the study population are shown in Table 1.

New-onset AF was more frequent in older patients (p = 0.007), hypertensive (p = 0.04), history of previous acute coronary syndrome (p = 0.01) and renal dysfunction (p = 0.03). No differences were seen regarding other cardiovascular risk factors or comorbidities. Baseline embolic risk, as assessed by CHA_2DS_2-VASc, and baseline bleeding risk (HAS-BLED) did not show significant differences between groups. The chosen anticoagulation therapy was low molecular weight heparin in a therapeutic dose (1 mg/kg/12 h), with no differences between groups (new-onset AF and control group). For the rest of the patients hospitalized due to COVID-19 infection, low molecular weight heparin in a prophylactic dosage (40 mg once daily and 20 mg for patients with severe renal impairment) was prescribed. Regarding laboratory parameters, higher values of peak D-dimer were recorded in the group with "de novo" AF (p = 0.03). Only 7 patients had been admitted to the intensive care unit in the total sample, 16% (n = 2) in the group

Table 2. Events during hospitalization in patients with COVID-19.

Events	New-onset atrial fibrillation (n = 12)	Control group (n = 148)	P-value (univariate)
Embolic events	5 (41.7%)	6 (4.1%)	< 0.001
Bleeding events	4 (33.3%)	7 (4.7%)	0.005
All-cause mortality	4 (33.3%)	26 (17.6%)	0.16
Death + embolic event	7 (58.3%)	29 (19.6%)	0.006
Days of admission	16.4 ± 13.0	8.6 ± 6.5	< 0.001

of new-onset AF and 3.3% (n = 5) in the control group, p = 0.08 (the Fisher exact test).

Both groups received treatment for COVID-19 according to the hospital protocol at that moment, that included hydroxychloroquine and azithromycin if there were no contraindications, antiviral, dexamethasone if needed and oxygen support, with no differences between groups.

Incidence of major outcomes

New-onset AF was a predictor of embolic events (p < 0.001) during hospital stay. The incidence of bleeding events during hospitalization was also higher in the group with "de novo" AF (p = 0.005). When both embolic events and all-cause mortality were assessed collectively, new-onset AF was related to worse prognosis (p = 0.006). The embolic events in the group with new-onset AF were one stroke, two systemic embolism and one pulmonary embolism, and none of these patients were receiving anticoagulation therapy. Patients with COVID-19 disease and new-onset AF had a higher incidence of bleeding events, and gastrointestinal bleeding was the main source of hemorrhages in both groups. All-cause mortality during the admission showed no differences between the groups. The hospital stay was longer in the group with new-onset AF (p < 0.001). The events in the population are shown in Table 2.

In multivariate analysis, only the new onset of AF remained an independent predictor of embolic events, carrying a risk 14.26 times higher than in the control group (95% confidence interval 2.86–71.10, p < 0.001). The multivariate analysis is shown in Table 3. The characteristics of the group with new-onset AF are shown in Table 4.

Table 3. Independent predictors of embolic events in patients with COVID-19 infection.

Multivariate analysis	Odds ratio	95% CI	P-value
New onset AF	14.26	2.86–71.10	< 0.001
Age	1.00	0.95–1.06	0.65
Arterial hypertension	2.04	0.40–10.29	0.26
Renal dysfunction	0.38	0.04–3.03	0.41
Bleeding events	1.82	0.21–15.66	0.96

AF — atrial fibrillation; CI — confidence interval

Discussion

The present study shows that:

— New-onset of AF during hospital stay in patients with COVID-19 is an independent predictor of in-hospital embolic events;

— New-onset AF is associated with worse clinical features during hospitalization in terms of more bleeding events, and more events in the combined end-point (death + embolic events);

— New-onset AF is associated with a longer hospital stay.

Atrial fibrillation is a common cause of stroke and embolism, especially when it is not treated with anticoagulation therapy when indicated, as prevention of stroke. On the other hand, COVID-19 may predispose patients to thrombotic disease, both in the venous and arterial circulations, due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis [11]. Preliminary reports suggest that hemostatic abnormalities, including disseminated intravascular coagulation, occurs in patients affected by COVID-19 [12]. This makes management challenging because of anticoagulation therapy in patients with both conditions.

It remains unclear whether hemostatic changes are a specific effect of SARS-CoV-2 or are a consequence of cytokine storm that precipitates the onset of systemic inflammatory response syndrome, as observed in other viral diseases [13].

It is already known that thrombogenic phenomenon in AF is not only limited to local factors

Table 4. Characteristics of patients with COVID-19 infection and new-onset atrial fibrillation.

Patient	Age (years-old)	Days of admission	CHA_2DS_2-VASc	Anticoagulation therapy	Embolic events	Bleeding events
1	74	4	1	Low molecular weight heparin (1 mg/kg/24 h)	No events	No events
2	82	6	2	Prophylactic heparin	No events	No events
3	57	15	0	Prophylactic heparin	No events	No events
4	88	7	3	Low molecular weight heparin (1 mg/kg/24 h)	No events	No events
5	82	14	2	Prophylactic heparin	No events	No events
6	82	38	2	Prophylactic heparin	Systemic embolism	No events
7	82	12	2	Prophylactic heparin	Systemic embolism	No events
8	58	8	1	Prophylactic heparin	No events	Gastrointestinal bleeding
9	73	17	1	Prophylactic heparin	Pulmonary embolism	Epistaxis
10	75	28	2	Prophylactic heparin	Stroke	Gastrointestinal bleeding
11	76	40	2	Prophylactic heparin	Stroke	Gastrointestinal bleeding
12	82	8	2	Low molecular weight heparin (1 mg/kg/24 h)	No events	No events

such as stasis or a dysfunctional atrium contraction. A generalized hypercoagulable state has been proposed, too. This may lead to concern that other proinflammatory and procoagulant situations, such as cancer or infections could have a synergic effect on cardiovascular events [14].

New-onset AF was associated with a higher incidence of embolic events, and this was regardless of the use of anticoagulation (there are no significant differences between the groups). However, the rate of bleeding events was also higher, and this points out that the onset of AF probably indicates a more inflammatory scenario, with more severe hypoxia and a more important coagulopathy in patients with "de novo" AF.

The use of anticoagulation with a therapeutic dosage is not recommended in general for all patients with COVID-19, if they do not have AF or other indications. In the present study, bleeding events were more frequent in patients with anticoagulation, with no differences between the groups (new-onset AF and control group). However, the incidence of embolism was higher in patients with new-onset AF (41.7%). All patients with embolic events in our sample were not receiving anticoagulation therapy (with a therapeutic dosage). If we look at the control group, patients with AF were correctly treated with anticoagulation therapy, and no embolic events were observed. All the events in this group corresponded to patients with sinus rhythm and without anticoagulation therapy (4.1%). The majority of patients with new-onset AF were not receiving anticoagulation therapy (75%, 9 patients). This can be explained because the diagnosis of AF was after the embolic event (in 5 patients), and because of high bleeding risk (in 4 patients).

Thus, it would be of interest to identify predictors for the onset of AF, in order to manage the challenging balance between embolic and bleeding risk. A variety of further factors, including congestive heart failure, ischemic heart disease and hypertension have been addressed as potential co-factors for the development of new-onset AF in critically ill patients [15]. In the current study, similar factors like age, arterial hypertension, history of myocardial infarction, renal dysfunction and a higher value of D-dimer, acted as possible co-factors for the new onset of AF in patients with COVID-19. The present data support the hypothesis that these factors might play a major role in the development of AF in COVID-19 patients.

New onset of AF is common in several diseases and, on the other hand, it has been associated

with an increased incidence of other complications including stroke, increased hospital length of stay and increased cost of hospitalization. Prevention of AF has been a reasonable clinical goal, consequently, many randomized trials have evaluated the effectiveness of pharmacological and non-pharmacological interventions in other pathologies, such as cardiac surgery [16–20].

It has been shown that agents with anti-inflammatory and antioxidant properties decreased postoperative AF rates in previous studies. Further studies are needed in order to identify predictors and potential treatments that might be useful for patients with "de novo" AF in the context of COVID disease. The pathophysiological mechanism underlying the development of AF and the incidence of embolic events in COVID-19 patients is not known. However, the systemic inflammatory response per se, could be a trigger for both conditions in COVID-19 patients.

Is the development of the arrhythmia just a marker of the severity of the infection? Does the onset of AF imply per se, a higher incidence of embolic and bleeding events? Little is known about triggers that could modify the coagulation cascade in patients with COVID-19, but hemostatic changes are common during the infection.

Limitations of the study

The number of patients studied with new-onset AF was small, which could limit the number of independent predictors identified and the consistency of the results. However, the statistical difference is such that it allows drawing preliminary conclusions.

Conclusions

Patients with new-onset AF in the context of COVID-19 disease have worse prognosis in terms of higher incidence of embolic events. The onset of AF has implications in patients with COVID-19 that go beyond the simple presence of the arrhythmia, and the outcomes in these patients is worse than in patients with previous AF (and, of course, than patients in sinus rhythm). Patients with "de novo" AF also have a higher incidence of bleeding events, and a longer hospital stay. Further investigations are needed to enable strategies that may predict the new onset of AF, in order to identify high risk patients, provide an early treatment and thus minimize the embolic risk of COVID-19 and AF.

Conflict of interest: None declared

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Coronary artery height differences and their effect on fractional flow reserve

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Abstract

Background: *Fractional flow reserve (FFR) uses pressure-based measurements to assess the severity of a coronary stenosis. Distal pressure (Pd) is often at a different vertical height to that of the proximal aortic pressure (Pa). The difference in pressure between Pd and Pa due to hydrostatic pressure, may impact FFR calculation.*

Methods: *One hundred computed tomography coronary angiographies were used to measure height differences between the coronary ostia and points in the coronary tree. Mean heights were used to calculate the hydrostatic pressure effect in each artery, using a correction factor of 0.8 mmHg/cm. This was tested in a simulation of intermediate coronary stenosis to give the "corrected FFR" (cFFR) and percentage of values, which crossed a threshold of 0.8.*

Results: *The mean height from coronary ostium to distal left anterior descending (LAD) was +5.26 cm, distal circumflex (Cx) –3.35 cm, distal right coronary artery-posterior left ventricular artery (RCA-PLV) –5.74 cm and distal RCA-posterior descending artery (PDA) +1.83 cm. For LAD, correction resulted in a mean change in FFR of +0.042, –0.027 in the Cx, –0.046 in the PLV and +0.015 in the PDA. Using 200 random FFR values between 0.75 and 0.85, the resulting cFFR crossed the clinical treatment threshold of 0.8 in 43% of LAD, 27% of Cx, 47% of PLV and 15% of PDA cases.*

Conclusions: *There are significant vertical height differences between the distal artery (Pd) and its point of normalization (Pa). This is likely to have a modest effect on FFR, and correcting for this results in a proportion of values crossing treatment thresholds. Operators should be mindful of this phenomenon when interpreting FFR values.* (Cardiol J 2021; 28, 1: 41–48)

Key words: hydrostatic pressure, computed tomography coronary angiography, coronary stenosis

Introduction

Fractional flow reserve (FFR) is the gold standard for invasive assessment of flow limitation caused by a coronary stenosis and it has been shown to improve clinical outcomes in randomized clinical trials [1–3]. In practice, FFR is calculated as the ratio of the distal trans-stenotic pressure to the proximal coronary or aortic pressure during pharmacological hyperemia. The hydrostatic consequences of the wire position are one of the recognized pitfalls when FFR measurements are performed. Coronary arteries lie in different vertical planes and height variations are part of

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normal anatomy. Thus, the pressure wire sensor measuring distal pressure (Pd) is seldom at the same level with the coronary ostium where aortic pressure (Pa) is measured and where the Pd and Pa were previously equalized. This effect is present in any pressure based measurement, including the resting indices such as instantaneous wave free ratio (iFR) [4]. Despite strong evidence for its use, FFR remains underutilized [5]. Avoiding confounding factors when using pressure-based indices is crucial in accurate stenosis assessment.

In clinical practice hydrostatic effect produces FFR values higher than 1.00 in a non-diseased vessels, most commonly positioned posteriorly [6]. A recent study documented coronary ostia and distal vessels height differences in an elderly patient cohort with aortic stenosis [7]. Furthermore, the investigators used an *in vitro* model to calculate the impact of their observed height difference in pressure derived physiological indices. The observed changes were small, meaning that it is unlikely to cause a significant change of FFR value in clinical practice. However, when using a binary cut-off for flow limitation for a given coronary stenosis, even a change of 0.02 can change the classification of FFR from ischemic to non-ischemic (FFR from 0.79 to 0.81).

In this study, the aim was to quantify the height differences between distal coronary vessels and corresponding coronary ostia in a supine position in a real-life cohort of patients undergoing investigations for coronary artery disease. Based on these measurements, quantifying the effect of coronary anatomical variations on FFR values around the ischemic cut-off point of 0.80 was sought.

Methods

A retrospective analysis of 100 patients was conducted who were undergoing computed tomography (CT) coronary angiograms from August 2016 to April 2017 for new onset chest pain suspected to be angina. Vertical coronary height measurements were recorded in all coronary arteries and then used to calculate the potential hydrostatic effect on that specific point in the artery. The effect of the calculated pressure difference and hence effect on FFR was applied to a model of 200 randomly generated FFR values. FFR was compared pre- and post-correction for hydrostatic force.

Inclusion and exclusion criteria

All patients were elective outpatients under investigation for angina. Patients with previous bypass grafting or valve surgery were excluded. Scans, which did not show the upper rim of the CT table could not be analyzed (as this was the reference point for measurement). Coronary visualizations with poor contrast penetration, or significant artefact were excluded. Finally, left dominant coronary circulations were not included in the present analysis.

CT coronary angiogram

Computed tomography coronary angiography was performed as per local criteria at the documented institution using a 64-slice CT scanner. A resting heart rate of less than 80 bpm was required. Intravenous metoprolol was administered for heart rate reduction if necessary.

Coronary height analysis

Using an electronic radiology reporting program (Agfa IMPAX™) and a measuring caliper, distance from the upper rim of the CT table to multiple points in the coronary tree were obtained. Arterial measurement points included:

— left coronary ostium;
— right coronary ostium;
— ostial left anterior descending (LAD);
— distal LAD — at its highest point;
— distal circumflex (Cx) — at its lowest point;
— right coronary artery (RCA) bifurcation;
— distal posterior descending artery (PDA) — at its highest point;
— distal posterior left ventricular artery (PLV) — at its lowest point.

Measurements were in millimeters and taken at the furthest point of contrast penetration visible in the vessel.

FFR impact analysis

The difference in height between the coronary ostium and the measurement point in the artery is the calculated height difference. This was multiplied by 0.8 (according to the Pascal Law and adjusting for blood density) to give a positive or negative change in pressure — in mmHg. This is the theoretical effect on Pd. The denominator (Pa) is assumed to be 100 in the following calculation model. The resulting value was factored into 200 random computer generated FFR values between 0.75 and 0.85 to give a corrected FFR (cFFR) using Microsoft Excel™. Corrected FFR was compared with baseline FFR and the percentage of values that crossed the threshold of 0.8 (from positive to negative or vice versa) was calculated.

Statistical analysis

Continuous variables are expressed as mean values plus or minus standard deviation. Categorical variables are described as numbers and percentages. Statistical significance of coronary height variations was calculated using the Student t-test.

Results

Study population

Patient demographics are summarized in Table 1. All patients had a resting heart rate below 80 bpm before scanning.

Coronary height data

Figure 1 shows an example of coronary height measurement. The measuring caliper in green calculates height from the upper rim of the CT table to the corresponding point in the coronary artery. In this particular example the caliper is measuring from the ostial left main stem.

Results are displayed below are of all measurement points within the coronary tree (Fig. 2, Table 2). Height measurement is taken from the upper rim of the CT table.

Table 3 summarizes data points from each coronary artery with regard to their respective coronary ostia. The height difference between the coronary specific coronary ostium (Pa) and the vessel containing the height measurement point (Pd), is the value used to calculate effect on FFR and hence, the cFFR.

Table 1. Demographics of 100 study patients.

Characteristic	Number (also % as n = 100)
Age	55.9%
Female	68
Current smoker	12
Ex-smoker	19
Hypertension	33
Hypercholesterolemia	25
Family history	24
Ejection fraction	54.8%

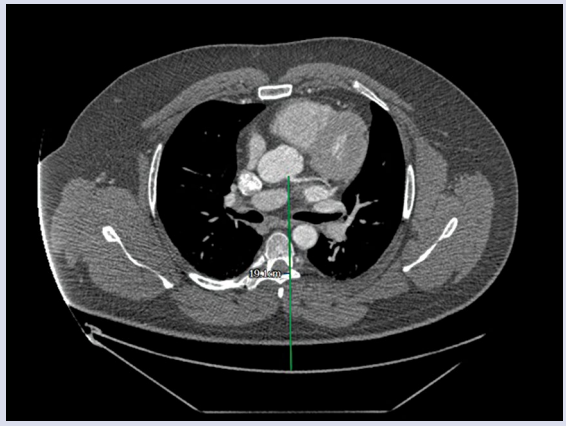

Figure 1. Vessel height measurement illustration on coronary computed tomography. The image demonstrates the measurement caliper from the left main stem ostium, to the upper rim of the computed tomography table.

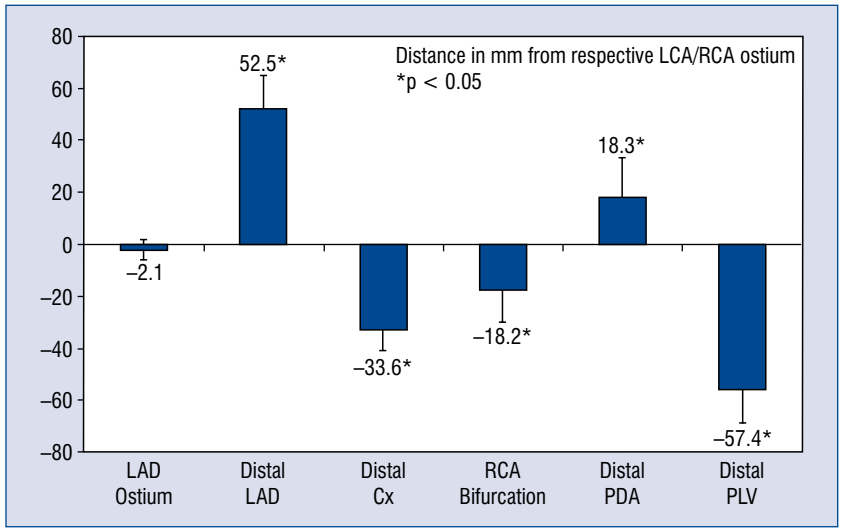

Figure 2. Coronary height variation from their respective ostium. Height variation of the distal vessel from its respective ostium; *These measurements were statistically significant. LAD — left anterior descending; Cx — circumflex; PDA — posterior descending artery; PLV — posterior left ventricular artery; RCA — right coronary artery; LCA — left coronary artery.

Table 2. Computed tomography (CT) height measurements. The vertical height measurements are shown from the upper rim of the CT table. P values are calculated for each point to the respective vessel ostium.

Measurement point	Mean height from upper rim of CT table [mm]	P value compared to vessel ostium
Left coronary circulation		
LCA ostium	170.0 ± 19.6	NA
LAD ostium	167.9 ± 19.6	0.06
Distal LAD	222.5 ± 28.3	< 0.0001
Distal Cx	136.4 ± 20.4	< 0.0001
Right coronary circulation		
RCA ostium	193.8 ± 21.2	NA
RCA bifurcation	175.6 ± 28.3	< 0.0001
Distal PDA	212.1 ± 30.7	< 0.0001
Distal PLV	136.4 ± 26.1	< 0.0001

LAD — left anterior descending; LCA — left coronary artery; Cx — circumflex; PDA — posterior descending artery; PLV — posterior left ventricular artery; RCA — right coronary artery; NA — not available

Table 3. Fractional flow reserve (FFR) effect. The height variations have been converted into pressure effect in mmHg. The impact on FFR with a proximal pressure of 100 is shown in the far-right column.

Measurement point	Height from respective coronary ostium [mm]	Height effect on distal pressure [mmHg]	FFR correction factor
Height from left coronary ostium			
LAD ostium	+2.1	–0.2	+0.002
Distal LAD	+52.5	+4.2	+0.04
Distal Cx	–33.6	–2.7	–0.03
Height from right coronary ostium			
RCA bifurcation	–18.2	–1.5	–0.02
Distal PDA	+18.3	+1.5	+0.02
Distal PLV	–57.4	–4.6	–0.05

LAD — left anterior descending; Cx — circumflex; PDA — posterior descending artery; PLV — posterior left ventricular artery; RCA — right coronary artery

Hydrostatic effect and cFFR

The corresponding hydrostatic effect of distal LAD, distal Cx, distal PDA and distal PLV were factored into the FFR equation to give the cFFR (Table 3). For anterior vessels, the FFR increased, for posterior vessels, it fell. Out of the 200 randomly generated FFR values, 45.5% were below 0.8 and 55.5% above 0.8. After correction and calculation of cFFR, these percentages changed substantially. Those that crossed from positive to negative, or vice versa were calculated. Table 4 summarizes the results.

Clinical case example

An *in vivo* example demonstrating the effect of wire position is presented of a 73-year-old male with a lesion in the mid RCA (Fig. 3). The patient presented with typical stable angina. There was a background history of inflammatory bowel disease, but no typical cardiac risk factors were presented. Ejection fraction was normal. A combined pressure and velocity wire (Combowire, Volcano Corporation™, San Diego, California, USA) was passed through a 6 F guiding catheter. The wire was passed beyond the lesion and FFR was measured firstly in the PDA (as distal as a clear velocity tracing allowed), followed by the PLV (distally as per PDA) and lastly three vessel diameters were placed beyond the stenosis in the main mid RCA. 400 μg of intra-arterial nitrates were administered before FFR measurement. Intravenous adenosine at 140 μg/kg was used to induce a steady state

Table 4. Effect on fractional flow reserve (FFR) measurements between 0.75 and 0.8. The effect on 200 randomly generated FFR measurements is shown for each vessel point. Percent values crossing a threshold of 0.8 is shown in the far-right column.

Vessel point (+change in distal pressure)	% FFR below 0.8	% FFR above 0.8	% cFFR below 0.8	% cFFR above 0.8	% Crossing 0.8
Distal LAD (–0.04)			6	94	42.5
Distal Cx (+0.03)	45.5	54.5	72	28	26.5
Distal PLV (+0.05)			92	8	46.5
Distal PDA (–0.02)			30.5	69.5	15

cFFR — corrected FFR; LAD — left anterior descending; Cx — circumflex; PDA — posterior descending artery; PLV — posterior left ventricular artery

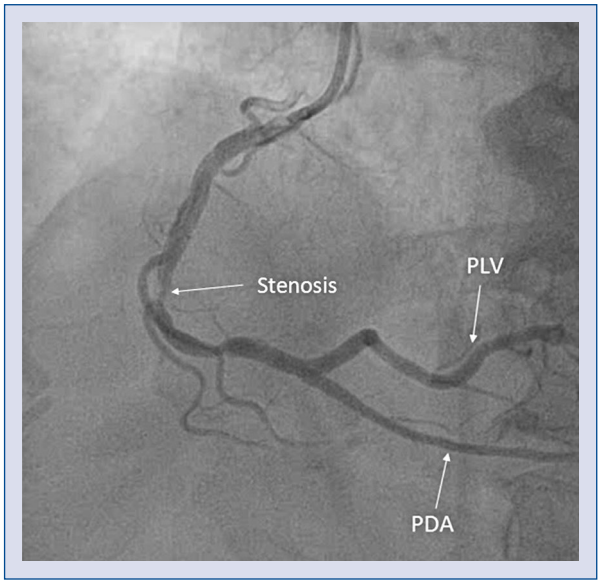

Figure 3. Mid right coronary artery stenosis. The stenosis is shown in the mid right coronary artery, with arrows indicating the posterior left ventricular artery (PLV) and posterior descending artery (PDA).

Table 5. Clinical case data. Fractional flow reserve (FFR) measurement varied by 0.05 between PLV and PDA. Velocity measurements did not vary significantly. This is due to the vertical height differences in both vessels and in turn the hydrostatic effect.

Measurement point	FFR	Flow [cm/s]
PDA	0.75	17.1
PLV	0.8	19.1
Three vessel diameters beyond stenosis (mid RCA)	0.79	18.6

PDA — posterior descending artery; PLV — posterior left ventricular artery; RCA — right coronary artery

of hyperemia. There was no drift with any of the acquired measurements. Invasive measurements are presented in Table 5.

For the same lesion, placement of the wire in the PDA or PLV altered FFR by 0.05. Placing the wire three vessel diameters beyond the stenosis, gave an FFR of 0.79. The small flow variations measured on each occasion were not significantly different, and within normal variations as expected during Doppler measurements [8].

Discussion

In summary, the present findings show that coronary anatomy results in statistically significant height variations between proximal (Pa) and distal vessel (Pd). There is a potential change in FFR of 0.02–0.05, causing a number of 'grey-zone' FFR results to cross a binary cut-off point.

In the current cohort, the most superior points in a supine patient were the distal LAD, followed by distal PDA. The most inferior points were the distal Cx and distal PLV. All measurements were statistically significant when compared to the respective ostium, apart from the ostial LAD. Even though mean height of PLV and Cx were identical with reference to the CT table, when compared to their respective ostium (Pa), the PLV had a larger height difference, owing to the more superior position of the RCA ostium. In turn, the hydrostatic pressure effect was more pronounced in the PLV. More proximal points in a vessel, e.g. ostial LAD or RCA bifurcation had a smaller height variation when compared to their respective coronary artery ostium. In general, there was a gradual change in height from proximal to distal vessel. Note however, that the most distal point in the vessel does not always have the greatest height variation. An example of this is in a 'wrap around' LAD, where

the vessel height falls after reaching the apex. This occurred in over half of patients in one study [9].

Computed tomography coronary angiography can accurately map the course of coronary vessels and their vertical heights. Subsequently, the height of the distal vessel (i.e. the position of the pressure wire, or Pd) may be higher, or lower than its origin (Pa), depending on the course it takes. This may explain observed changes in groups of patients with 'moderate' coronary stenoses in which posterior vessels (those vertically lower when supine — circumflex, posterior left ventricular) have higher mean FFR values than anterior vessels (those that are vertically higher — left anterior descending, posterior descending) [10]. Resting Pd/Pa can also often be seen above 1.0. Studies have identified this phenomenon [6] and it is caused by the distal pressure sensor sitting vertically lower than the aortic pressure sensor (and original point of normalization). For a resting index to be above one, disease in the vessel is usually mild. While often attributed to drift, physical principles can predict this concept. It is useful to note this phenomenon rather than to assume the physiology wire is at fault.

A recent study assessing coronary artery height variations using CT coronary angiograms has been conducted recently in a group composed predominantly of transcutaneous aortic valve implantation patients [5]. Hydrostatic pressure effects were then confirmed using an *in vitro* model. The anatomy of these patients with severe aortic stenosis may slightly alter the anatomy of the coronary arteries themselves due to changes in the aortic root. The present assessment of coronary height variations in a more heterogeneous group of patients presenting with stable cardiac chest pain was thought to be a useful addition to current knowledge. In general, patients studied herein were younger females in keeping with the low to intermediate risk group initially assessed with CT coronary angiography at the time. There were some differences in height measurements from CT scans between this study and Härle et al. [10]. Measurements from ostial left coronary artery to LAD and Cx were similar (5.3 vs. 4.9 cm and 3.4 vs. 3.9 cm, respectively). There were however more pronounced differences in the measurement of PLV and PDA from the right coronary ostium (5.7 vs. 2.6 and 1.8 vs. 3.8). There are potential explanations. Observer variation between two studies may account for some of the change. Contrast penetration into the distal vessel can significantly alter the measurement point within the artery, thus leading to errors in measurement in both studies. Finally, the patient cohort varies between the studies. One anticipates that coronary height measurements may vary between a predominantly older population with aortic stenosis, and a younger cohort without.

Pressure based invasive physiology such as FFR, has been well validated for many years. However, pressure-based measurements are subject to potential effects of hydrostatic pressure. If hydrostatic forces alter distal pressure recordings FFR will in turn change. The change may be small (0.02–0.05) but useful to acknowledge for FFR values circling the cut-off point (0.75–0.85) [11]. In theory, the addition of adenosine should not alter the physical hydrostatic pressure effect in a coronary vessel *in vivo*, as height, fluid density and gravitational effect have not changed. An important consideration is the hypotensive effect and hence reduction in Pa during adenosine infusion. Aortic pressure may fall below 100 mmHg during hyperemia, meaning alterations in Pd have a larger effect on overall Pd/Pa. Hydrostatic effect is constant across resting and hyperemic states. A change in Pd of 5 mmHg is therefore of greater relative importance in resting indices (where a transtenotic gradient of 10 mmHg is considered abnormal) compared to hyperemic indices (where 20 mmHg is considered abnormal).

Whilst the effect of hydrostatic pressure upon FFR is described, it was believed herein, that this novel data demonstrates that depending on the coronary artery in question and its anatomical course the physiological significance of coronary stenosis can be both over or under-estimated. Treatment of intermediate coronary stenoses therefore must not be a binary decision, and the operator must exert clinical judgment when faced with a grey zone physiological values.

The exact position of the pressure sensor of the physiology wire is often not considered. Hydrostatic effect becomes more pronounced as the pressure sensor is positioned more distally. Avoiding an unnecessarily distal wire position will minimize the hydrostatic effect on obtained measurements by reducing the guide to pressure sensor distance.

By changing patient position during angiography, (i.e. turning onto one side), and leaving the wire in exactly the same position in the artery, FFR values have been shown to change [12]. Correcting for the presumed hydrostatic effect due to this position change (by using measured height difference between guide and wire), abolished the

difference between the two FFR recordings, seeming to explain the difference.

Another important observation is the pressure change along the longitudinal length of a coronary artery, which has been attributed to diffuse atherosclerosis [13]. The additive effect of hydrostatic pressure however cannot be excluded, as vertical height also gradually changes along the length of an artery. This along with other confounding factors, such chronic kidney disease [14] may also impact stenosis assessment. Finally, hydrostatic pressure effects may also contribute to measurements that use mean distal pressure, such as the index of microvascular resistance measured using thermodilution.

In the present clinical case example, wire placement altered FFR by 0.05 (PDA vs. PLV placement). Flow within the artery does not change in this case study as coronary autoregulation maintains flow over a wide pressure range when these mechanisms are intact [15]. Using the present coronary CT data, the mean height difference between PLV and PDA was 7.57 cm, equating into a potential distal pressure difference (Pd) of 6.06 mmHg. Therefore, a change in FFR of up to 0.06 is possible on average. This is the mean change, and patient factors such as height, play a role in individual FFR measurements [7]. Although clinical decision-making takes into account multiple factors and is not a binary process revolving around a cut-off point, one should recognize the potential effects of wire position and hydrostatic pressure.

Limitations of the study

The study group consisted of low to intermediate risk patients, hence, the majority were younger females. This is not in keeping with typical demographics of patients who require invasive treatment for coronary artery disease.

The visualization of the coronary artery in question was limited by contrast penetration into the distal vessel. Some vessels were not completely opacified, meaning a potential underestimation of height measurements were present. This seemed especially prominent in the PDA where contrast did not penetrate to the distal vessel in 15% of cases. Measurements for these patients were excluded.

Height was measured at distal sections in the coronary artery, as this was the point of maximal height variation. In clinical practice the wire is often not positioned as far distal as these measurements were taken, meaning there was a potential overestimation of the hydrostatic effect.

With regard to the 200 random FFR results generated, it can be seen that 54.5% of FFR values generated were over 0.8. This was apparently a chance occurrence, but the lack of a more linear 50/50 split of values will affect subsequent analyses.

The hydrostatic effect on FFR in this study takes into account Pa pressure of 100 mmHg. Further data on alterations in Pa and the subsequent impact on FFR may have been a useful addition.

The calculated hydrostatic effect is theoretical, and needs further investigation *in vivo*. Recent trials have upheld anticipated changes in pressure based measurements due to hydrostatic forces [12].

Conclusions

The anatomical path of coronary arteries resulted in a significant vertical height difference between the distal artery (Pd) and its point of normalization (Pa). According to the present hydrostatic pressure model, this is likely to have a modest effect on FFR calculation, which in turn, could result in values crossing the treatment threshold. Operators should be mindful of this phenomenon when interpreting FFR values, particularly in the LAD and RCA-PLV.

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Comparison of long-term radial artery occlusion following trans-radial coronary intervention using 6-french versus 7-french sheaths

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Abstract

Background: *The aim of this study was to explore the impact of 6-Fr and 7-Fr sheaths on the incidence of long-term radial artery occlusion (RAO) after trans-radial coronary intervention (TRI).*

Methods: *From September 2013 to January 2016, patients with ischemic heart disease including acute myocardial infarction and true bifurcation lesions were randomly assigned to 6-Fr group and 7-Fr group immediately after coronary angiography in a 1:1 ratio. The radial artery diameters were observed by ultrasound examination one day prior to TRI as well as at 30 days and 1 year after TRI. The primary endpoint was the incidence of RAO at 1-year after TRI. The secondary endpoints were the incidence of local vascular complications during hospitalization and changes of radial artery diameters within 1-year after TRI between the two groups. Additionally, multivariate logistic regression analysis was used to explore potential factors related to the incidence of long-term RAO after TRI.*

Results: *A total of 214 patients were enrolled and randomly assigned to 6-Fr group ($n = 105$) or 7-Fr group ($n = 109$). There was no significant difference in the incidence of RAO at 1-year after TRI (8.57% vs. 12.84%, $p = 0.313$). Moreover, no significant difference was observed in the incidence of local vascular complications during hospitalization (20% vs. 24.77%, $p = 0.403$). After 1-year follow-up, no significant difference was found in radial artery diameters (2.63 ± 0.31 mm vs. 2.64 ± 0.27 mm, $p = 0.802$). Multivariate logistic analysis revealed that repeated TRI was an independent risk factor of long-term RAO 1 year after TRI (OR = 10.316, 95% CI 2.928–36.351, $p = 0.001$).*

Conclusions: *Compared to 6-Fr sheath, 7-Fr sheath did not increase short-term or long-term incidence of RAO after TRI.* (Cardiol J 2021; 28, 1: 49–57)

Key words: radial artery occlusion, trans-radial coronary intervention, radial artery diameter, artery sheath, local vascular complication

Introduction

With the rapid development of percutaneous coronary intervention (PCI) technique and persistent improvement of dedicated devices, trans-radial coronary intervention (TRI) has drastically advanced over the past two decades [1, 2]. Compared to conventional femoral artery access, TRI has significantly reduced the incidence of local vascular complications. More importantly, it has brought overall therapeutic benefits with lower mortality and fewer major adverse cardiac events (MACE) rates [3, 4]. Nowadays, the vast majority of patients undergoing TRI procedure, 6 french (6-Fr) sheaths and guiding catheters are recommended as the first choice [5]. Usually, it is possible to do most of PCI procedures in regular cases through 6-Fr guiding catheters. However,

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sometimes it is difficult to conduct complex coronary procedures through 6-Fr guiding catheters, such as unprotected left main lesions, true bifurcation lesions treated with a two-stent strategy, severe calcified lesions requiring rotational atherectomy, and chronic total occlusion lesions requiring multiple wires, balloons and specialized devices (e.g., microcatheter, child-mother catheter, 1.75-mm or larger burrs) simultaneously in one guiding catheter. Thus, a large-bore sheath (7-Fr) may be required to allow stronger back-up support and better materials delivery with no impact on hemodynamics monitoring and quality of coronary angiography, making the procedure easier and perhaps better [6]. Therefore, 7-Fr sheath and guiding catheters may be the better choice for complex coronary lesions as mentioned above.

Radial artery occlusion (RAO) is the most common local vascular complication, with a reported incidence of between 0.8% and 30% [7, 8]. A previous study showed that a dis-match between radial artery inner diameter and sheath outer diameter was an independent risk factor for RAO after TRI [5]. In contrast, a previous study revealed that 7-Fr sheath did not increase the incidence of RAO at 30-day follow-up after TRI in comparison to 6-Fr sheath [9]. Furthermore, few studies have focused on the impact of 7-Fr sheath on long-term RAO after TRI with inconsistent conclusions [10–12]. Thus, the aim of this study was to explore the impact of 6-Fr and 7-Fr sheaths on the incidence of long-term RAO after TRI via vascular ultrasound.

Methods

Patient population and study design

This study was a prospective, randomized, controlled trial. From September 2013 to January 2016, patients with angina pectoris or evidence of myocardial ischemia and true bifurcation lesions confirmed by coronary angiography (CAG) in the Cardiology Department of the Second Hospital of Hebei Medical University were enrolled in this study. The true bifurcation lesions were defined as the diameter of side branch of more than 2 mm as well as degree of side branch ostium stenosis beyond 75% [9]. All coronary lesions were suitable for PCI treatment in this study. The exclusion criteria were: a negative Allen test, active inflammation, crossed over to other approaches (trans-femoral or trans-ulnar), repeated CAG or PCI via radial artery observed during the follow-up period, allergy to contrast agent, refusal to participate in the study, and inability to follow the protocol. The study protocol was approved by the ethics committee of the Second Hospital of Hebei Medical University (the IRB No. 2013L-22). Informed consent was obtained from each participant before TRI procedure. The study was conducted in accordance with the Declaration of Helsinki.

The enrolled patients were randomly assigned by computer-generated random numbers to either 6-Fr group or 7-Fr group immediately after CAG in a 1:1 ratio. Patients in 6-Fr group underwent PCI with 6-Fr sheaths (outer diameter: 2.52 mm, Radifocus, Terumo, Japan), while patients in 7-Fr group underwent PCI with 7-Fr sheaths (outer diameter: 2.85 mm, Medtronic, USA). Patients could cross-over to the other group if necessary. Before inserting the 7-Fr sheath, sufficient local subcutaneous anesthesia with lidocaine and intra-arterial nitroglycerin were administrated to avoid radial artery spasm.

Trans-radial catheterization

Coronary procedures were performed according to the standard technique of radial artery approach. The TRI was performed by the same experienced cardiac interventional team at a same center in both groups. The forearm was positioned beside the patient's body and the wrist was hyperextended. After local subcutaneous anesthesia with 1% lidocaine, radial artery puncture was carried out using a 20-gauge needle (Terumo Co) using the Seldinger technique and a 0.025-in straight tip guidewire (Terumo Co) was inserted through the needle. After removing the needle, a 16-cm 6-Fr hydrophilic sheath (Terumo Co) was placed over the guidewire. Subsequently, a bolus of unfractionated heparin (3000 IU) and 200 μg nitroglycerin was administered through the sheath. The CAG was performed with 4-Fr Judkins diagnostic catheters (Terumo Co) or 5-Fr TIG diagnostic catheters (Terumo Co). Moreover, weight-adjusted unfractionated heparin (70–100 IU/kg) was administered to maintain activated clotting time between 250 and 300 s during the PCI procedure. After TRI procedures, the radial arterial sheath was immediately pulled out and hemostasis (TR Band; Terumo Co) was achieved by radial compression. The TR Band was applied by inflating 13 to 15 mL of air at the puncture site. After each subsequent hour, the TR Band was gradually deflated (2–3 mL) until being completely removed. If there was bleeding during the deflation process, 2 mL of air would be injected to stop the bleeding and then was rechecked after 15 min.

Procedural variables among the two groups such as radial artery diameter (RAD) to sheath size ratio (A/S ratio), number of punctures (a needle pushed even just inside the skin was counted as a single attempt, regardless of skin puncture times), number of catheters used, heparin dose, procedure time, compression time, forearm hematomas and volume of contrast media were observed and evaluated.

Ultrasound examination

An experienced vascular sonographer blinded to the patients performed ultrasound examinations using an ultrasound system (Terason T3000, the USA) with a 5.0 to12.0 MHz linear transducer. Ultrasound-Doppler assessment of bilateral RAD, was conducted 1-day before the procedure at point 3 to 5 cm proximal to the styloid process of the radius bone. In addition, the RAD was assessed in 30 days and 1-year post TRI procedure. Moreover, the incidence of RAO in 1 year after TRI was observed, and was considered as the absence of antegrade flow in the radial artery observed by ultrasound.

Study endpoints

The primary endpoint of study was the incidence of RAO at 1 year after TRI between the two groups. On the other hand, the secondary endpoints of the study were the incidence of local vascular complications during hospitalization and RAD changes within 1 year after TRI in comparison to the baseline value before TRI between the two groups. The local vascular access-site complications included radial artery spasm (RAS), pseudoaneurysm, local hematoma, arteriovenous fistula and hand ischemia. The RAS was defined as a severe local pain and discomfort during catheter movement compelling the operator to stop the procedure and was confirmed by radial artery angiography. Local forearm hematomas were graded using the EASY classification [13].

Statistical analysis

Based on earlier studies it was speculated that at 1-year, the incidence of RAO after TRI procedure would be 6% in 6-Fr group and 19% in 7-Fr group [7]. Accordingly, at least 98 patients in each group were needed for a test power set at 0.8 and statistical level (2-sided) at 0.05. Based on a 15% 1-year loss rate, at least 112 patients were needed in each group. All calculations were analyzed with SPSS statistical software (version 17.0; SPSS Inc, Chicago, Illinois). The continuous variables were expressed as means ± standard deviation for normally distributed variables, while as median with interquartile range for non-normally distributed variables. The categorical variables were presented as percentages. Continuous variables were compared using the Student t test for normally distributed values and the Mann-Whitney U test for non-normally distributed values. For proportions, if the expected frequency was < 5, they were compared using the χ^2 test or Fisher exact test. Multivariate logistic regression analysis was used to explore the possible factors associated with the incidence of long-term RAO after TRI. A 2-sided $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics of the patients

A total of 248 patients were enrolled and randomly divided into 6-Fr group (n = 124) and 7-Fr group (n = 124). During PCI procedure, 4 patients in the 6-Fr group were crossed-over to the 7-Fr group owing to their clinical need. All 7-Fr sheaths were successfully inserted. During follow-up, 34 (13.7%) patients were excluded in this study, 15 patients in 6-Fr group (8 patients experienced repeated TRI, 5 patients were lost to follow-up and 2 patients died), and 19 patients in 7-Fr group (10 patients experienced repeated TRI, 7 patients were lost to follow-up and 2 patients died). Finally, a number of 214 patients were enrolled and divided into the 6-Fr group (n = 105) and the 7-Fr group (n = 109) (Fig. 1). There were no significant differences in terms of age, gender, body mass index, risk factors of coronary artery disease, clinical presentation, previous TRI history or follow-up medication between the groups. The baseline clinical characteristics are shown in Table 1.

Procedural characteristics of the patients

No significant differences were found with respect to access artery, the number of puncture attempts, heparin dose, number of catheters used, volume of contrast medium or duration of compression. The ratio of radial artery inner diameter and sheath outer diameter in 6-Fr group was much higher than that in 7-Fr group (1.09 ± 0.11 vs. 0.96 ± 0.13, $p < 0.001$). Besides, the procedural time of 6-Fr group was much longer than that of 7-Fr group (74.27 ± 12.58 min vs. 66.67 ± 14.72 min, $p < 0.001$). The procedural characteristics are shown in Table 2.

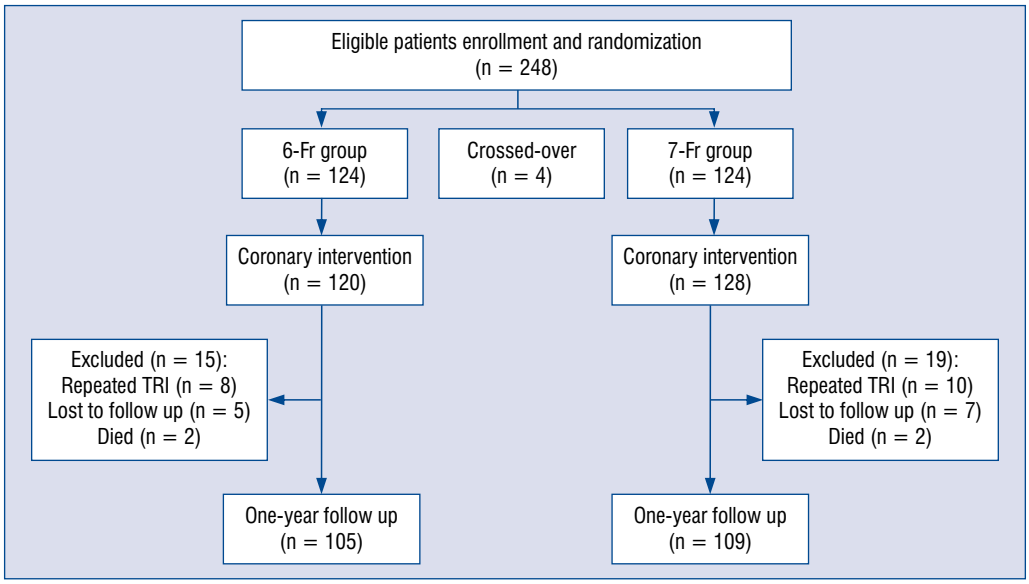

Figure 1. Flow chart of this study; TRI — trans-radial coronary intervention.

Table 1. Baseline clinical characteristics between the two groups.

Variables	6-Fr group (n = 105)	7-Fr group (n = 109)	P
Age [years]	58.08 ± 10.07	59.39 ± 9.31	0.325
Male	75 (71.43%)	82 (75.22%)	0.529
BMI [kg/m^2]	25.39 ± 3.13	25.59 ± 2.42	0.587
Hypertension	54 (51.43%)	59 (54.13%)	0.692
Diabetes	35 (33.33%)	33 (30.28%)	0.631
Hyperlipidemia	41 (39.05%)	43 (39.44%)	0.952
Current smoking	36 (34.28%)	40 (36.69%)	0.712
Clinical presentation:			
Stable angina	4 (3.81%)	3 (2.75%)	0.664
Unstable angina	72 (68.57%)	74 (67.89%)	0.968
NSTEMI	23 (21.90%)	27 (24.77%)	0.738
STEMI	6 (5.72%)	5 (4.59%)	0.948
Previous TRI history	29 (27.62%)	33 (30.28%)	0.668
Follow-up medication:			
ASA	105 (100%)	109 (100%)	NS
Clopidogrel	78 (74.28%)	80 (73.39%)	0.882
Ticagrelor	27 (25.72%)	29 (26.61%)	0.882
Statins	102 (97.14%)	107 (98.17%)	0.621
ACEI/ARB	45 (42.86%)	47 (43.12%)	0.969
Beta-blocker	72 (68.57%)	77 (70.64%)	0.742

ASA — acetylsalicylic acid; ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor blocker; BMI — body mass index; NS — not significant; STEMI — ST-segment elevation myocardial infarction; NSTEMI — non-ST-segment elevation myocardial infarction; TRI — trans-radial coronary intervention

Incidence of RAO at 1 year after TRI

Overall, RAO occurred in 23 (10.75%) of the 214 patients (9 patients in 6-Fr group and 14 patients in 7-Fr group). Besides, all patients were asymptomatic and there was no incidence of acute hand ischemia. There was no significant difference of incidence of RAO in 1 year after TRI between the two groups (8.57% vs. 12.84%, p = 0.313) (Fig. 2).

Table 2. Procedural characteristics between the two groups.

Variables	6-Fr group (n = 105)	7-Fr group (n = 109)	P
Access artery:			0.353
Right radial artery	97 (92.38%)	104 (95.41%)	
Left radial artery	8 (7.62%)	5 (4.59%)	
A/S ratio	1.09 ± 0.11	0.96 ± 0.13	< 0.001
Numbers of puncture:	1.12 ± 0.47	1.11 ± 0.37	0.813
Single puncture	97 (92.38%)	99 (90.82%)	0.479
Anticoagulation drug:			0.658
Heparin	98 (93.33%)	100 (91.74%)	
Bivalirudin	7 (6.67%)	9 (8.26%)	
Heparin dose [IU]	10409.52 ± 1836.83	10389.91 ± 1475.66	0.931
Procedure time [min]	74.27 ± 12.58	66.67 ± 14.72	< 0.001
Number of catheters	2.10 ± 0.33	2.08 ± 0.30	0.616
Compression time [h]	6.93 ± 1.48	6.81 ± 1.42	0.526
Use of GPI	18 (17.14%)	22 (20.18%)	0.196
Volume of CM [mL]	162.24 ± 24.31	159.32 ± 24.77	0.385

A/S — radial artery inner diameter/sheath outer diameter; CM — contrast medium; GPI — platelet glycoprotein IIb/IIIa inhibitor

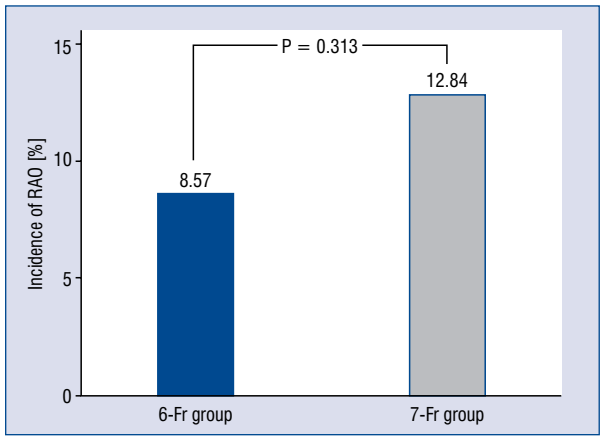

Figure 2. Incidence of radial artery occlusion (RAO) at 1 year after trans-radial coronary intervention.

Peri-procedure local vascular complications

There was no significant difference observed for the incidence of local vascular complications during hospitalization between the two groups (20% vs. 24.77%, p = 0.403). Moreover, there was no difference in RAO during hospitalization between the 6-Fr (5.71%) and 7-Fr groups (7.34%, p = 0.613). Additionally, no obvious difference was found in the incidence of RAS, pseudoaneurysm, local hematoma, arteriovenous fistula and hand ischemia between the two groups (Table 3).

Change of RADs within 1-year after TRI

There was no significant difference of RADs at baseline between the two groups (2.74 ± 0.28 mm vs. 2.73 ± 0.39 mm, p = 0.830) and 30-day follow-up (2.69 ± 0.39 vs. 2.73 ± 0.29 mm, p = 0.396). At 1-year follow-up, RADs in both the 6-Fr and 7-Fr groups were significantly reduced compared with baseline values before TRI (6-Fr group: 2.64 ± 0.27 mm vs. 2.74 ± 0.28 mm, p = 0.009; 7-Fr group: 2.63 ± 0.31 mm vs. 2.73 ± 0.39 mm, p = 0.031). However, no significant difference in RADs was found between the two groups at 1-year follow-up (2.63 ± 0.31 mm vs. 2.64 ± 0.27 mm, p = 0.802). The change of RADs within 1-year after TRI are listed in Table 4 and Figure 3.

Results of multiple logistic regression analysis

Multivariate logistic analysis revealed that repeated TRI was an independent risk factor of long-term RAO in 1-year post TRI (odds ratio [OR] = = 10.316, 95% confidence interval [CI] 2.928–36.351, p = 0.001). However, RAD, the ratio of radial artery inner diameter/sheath and outer diameter, and the sheath size of the artery were not independent predictors of long-term RAO after TRI (Table 5).

Discussion

In this study, it was revealed that 7-Fr sheath did not increase the long-term incidence of RAO

Table 3. Peri-procedure local vascular complications between two groups.

Variables	6-Fr group (n = 105)	7-Fr group (n = 109)	P
Total number of complications	21 (20.00%)	27 (24.77%)	0.403
Radial artery occlusion	6 (5.71%)	8 (7.34%)	0.631
Radial artery spasm	10 (9.52%)	12 (11.01%)	0.721
Forearm hematoma:	9 (8.56%)	13 (11.93%)	0.419
≤ II type	8 (7.61%)	11 (10.09%)	0.525
> II type	1 (0.95%)	2 (1.83%)	0.583
Pseudoaneurysm	1 (0.95%)	0 (0%)	NS
Arteriovenous fistula	0 (0%)	0 (0%)	NS
Hand ischemia	0 (0%)	0 (0%)	NS

Table 4. Change of radial artery diameters between two groups.

Variables	6-Fr group (n = 105)	7-Fr group (n = 109)	P
Baseline [mm]	2.74 ± 0.28	2.73 ± 0.39	0.830
30 days after TRI [mm]	2.73 ± 0.29	2.69 ± 0.39	0.396
1 year after TRI [mm]	2.64 ± 0.27*	2.63 ± 0.31*	0.802

*Compared with baseline, $p < 0.05$; TRI — trans-radial coronary intervention

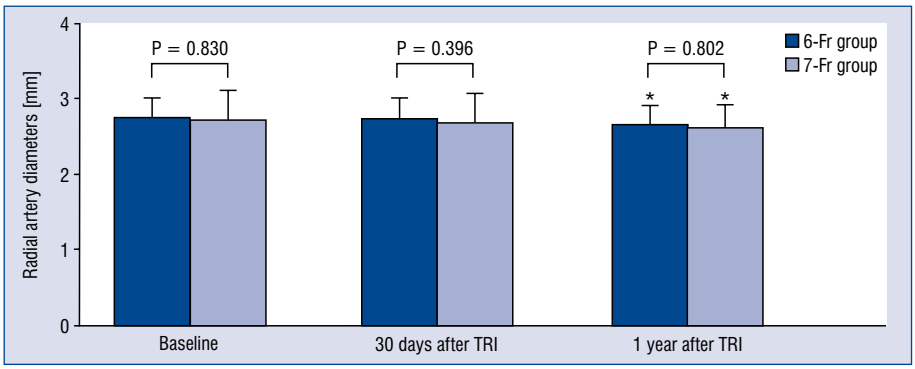

Figure 3. Change of radial artery diameters within 1-year after trans-radial coronary intervention (TRI); *Compared with the baseline value, radial diameters were significantly decreased in both groups, $p < 0.05$.

after TRI compared to the 6-Fr sheath. Additionally, no apparent difference was observed on the RAD between 6-Fr and 7-Fr sheaths in 1 year after TRI, but both of them were significantly reduced compared to the baseline value before TRI. In addition, repeated TRI was an independent risk factor of long-term RAO after TRI but not the RAD, A/S ratio or artery sheath size.

The use of the radial instead of the femoral approach is beneficial not only due to the reduction in the incidence of access-site complications, but also its capacity to reduce mortality and the risk of cardiac complications, especially in high-risk patients [14–16]. Moreover, the radial approach is also associated with more comfort for the patient, shorter hospitalization stays, and lower costs of treatment. However, RAO is one of the major complications of procedures performed via the radial artery [17, 18]. Although with an asymptomatic course, as well as the incidence of hand ischemia caused by RAO is extremely rare, RAO eliminates the ability to use the radial artery as an access for PCI in the future, to use it as a bypass conduit for patients undergoing coronary artery bypass surgery, or to

Table 5. Predictors of radial artery occlusion by multivariate logistic analysis.

Variables	Radial artery occlusion		P
	Odds ratio	95% CI	
Diabetes	0.945	0.269–3.317	0.930
History of TRI	10.316	2.928–36.351	0.001
Compression time	0.790	0.526–1.188	0.258
Baseline radial artery diameter	1.964	0.218–8.413	0.239
Radial artery spasm	1.871	0.444–7.891	0.393
A/S < 1	0.561	0.056–5.640	0.624
Artery sheath size	0.933	0.263–3.309	0.914

A/S — radial artery inner diameter/sheath outer diameter; CI — confidence interval; TRI — trans-radial coronary intervention

use it for dialysis fistula. Previous studies have disclosed that RAO may be associated with the following factors such as female gender, diabetes, history of TRI, low dose of unfractionated heparin, longer hemostasis times, smaller radial artery and A/S ratio < 1 [7]. However, these findings have not been consistent among studies [19–22].

Traditionally, complex PCI has been performed at the femoral but not the radial approach due to the need for large size catheters. The use of 7-Fr sheath is limited mainly via radial artery owing to a risk of RAO after TRI. In a Japanese study using ultrasound evaluation, the A/S ratio < 1 predicted lower blood flow in radial artery after TRI procedure, but the impact on RAO has not been evaluated [5]. Besides, Uhlemann et al. [23] found that among 455 patients randomized to 5-Fr or 6-Fr sheaths, the 6-Fr sheaths were associated with a significant higher incidence in RAO (13.7% vs. 30.5%, p < < 0.001). A previous study however, showed that 7-Fr sheath did not increase the incidence of RAO at 30 days follow-up after TRI compared with 6-Fr sheath (2% vs. 3.9%, p = 0.70). In addition, in a single center registry [11], 175 patients were subjected to TRI via radial artery through a 7-Fr Radifocus® Introducer II (Terumo Corporation, Tokyo, Japan) with a 6-month follow-up, which observed an RAO rate of 6% (95% CI 3–11%) at manual assessment and 7% (95% CI 4–12%) at Doppler evaluation, consistent to those reported in previous studies (ranging from 5% to 38%) using a 6-Fr sheath.

Nevertheless, all studies mentioned above were not randomized with a short-term follow-up, hence a bias in their selection may have occurred. Therefore, this prospective, randomized, controlled trial was conducted, and showed that 7-Fr sheath did not increase the long-term incidence of RAO after TRI compared with the 6-Fr sheath.

The reasons why 7-Fr sheath did not increase the long-term incidence of RAO after TRI may be associated with the following factors. Firstly, as a relatively high-volume TRI center, the operators have a rich experience of using 7-Fr sheath via radial artery access. The high success rate of single puncture (97–99%) may, to some extent, reduce injury to the radial artery. Moreover, the diameter of the radial artery, as measured by vascular ultrasound, is not a constant but a variable parameter. The diameter of radial artery can be reduced by stimuli and increased by intra-arterial administration of vasodilatory drugs such as nitroglycerin and verapamil. In this study, before insertion of 7-Fr sheath, sufficient local subcutaneous anesthesia with lidocaine and intra-arterial nitroglycerin were administrated to decrease RAS and increase the compatibility between radial artery and sheath with a lower vascular resistance. Finally, patent hemostasis and adequate anticoagulation have also played important roles in preventing RAO.

Another interesting finding was that the RAD at 1-year follow-up after TRI was significantly lower than baseline value before TRI in both of 6-Fr and 7-Fr groups, however, no obvious difference was observed between the two groups. Previous studies documented that TRI was related to intimal hyperplasia in the cannulated radial artery, as revealed by vascular imaging modalities such as intravascular ultrasound and optical coherence tomography [24–26]. In addition, recent studies have shown that the TRI procedure may lead to impaired flow-mediated dilation during long-term follow-up, which has been widely used for the non-invasive assessment of endothelium-dependent vasodilation response [27–29]. Therefore, it was assumed that the reduction of RAD may be associated with structural damage and impaired endothelial func-

tion of the cannulated radial artery due to chronic inflammatory and the proliferative process. This could explain why repeated TRI was an independent risk factor of long-term RAO at one year after TRI in the present study.

The current study has several potential limitations. First, it is a relatively small-scale study, conducted in a single center. In addition, optical coherence tomography could have provided more details about structural damage such as intimal tears and medial dissections together with chronic intimal modifications but was not used.

Conclusions

In conclusion, this study showed that 7-Fr sheath did not increase the long-term incidence of RAO after TRI compared with 6-Fr sheath. Therefore, 7-Fr sheath in the radial artery access could be feasible and safe for complex coronary lesions, especially at experienced centers.

Conflict of interest: None declared

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Low dose of ROSuvastatin in combination with EZEtimibe effectively and permanently reduce low density lipoprotein cholesterol concentration independently of timing of administration (ROSEZE): A randomized, crossover study — preliminary results

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Abstract

Background: *In an attempt to improve low density lipoprotein-cholesterol (LDL-C) level control in patients ineffectively treated with statins, we evaluated the effectiveness of a fixed-dose combination (FDC) of 10 mg rosuvastatin and ezetimibe and its relation to the timing of drug administration.*

Methods: *A randomized, open label, single center, crossover study involving 83 patients with coronary artery disease and hypercholesterolemia with baseline LDL-C ≥ 70 mg/dL. In arm I the FDC drug was administered in the morning for 6 weeks, then in the evening for the following 6 weeks and vice versa in arm II. The primary endpoint was the change in LDL-C after 6 and 12 weeks.*

Results: *The median LDL-C concentration at baseline, after 6 and 12 weeks respectively was: 98.10 mg/dL (Q1;Q3: 85.10;116.80), 63.14 mg/dL (50.70;77.10) and 59.40 mg/dL (49.00;73.30); p < 0.001. LDL-C levels were similar regardless of the timing of drug administration (morning 62.50 mg/dL [50.70;76.00] vs. evening 59.70 mg/dL [48.20;73.80]; p = 0.259], in both time points: 6 week: 63.15 mg/dL (50.75;80.65) vs. 63.40 mg/dL (50.60;74.00), p = 0.775; and 12 week: 62.00 mg/dL (50.20;74.40) vs. 59.05 mg/dL (47.65;66.05), p = 0.362. The absolute change in LDL-C concentration for the morning vs. evening drug administration was — 6 week: –34.6 mg/dL (–56.55; –19.85) (–34.87%) vs. –31.10 mg/dL (–44.20; –16.00) (–35.87%) (p not significant); 12. week: –34.20 mg/dL (–47.8; –19.0) (–37.12%) vs. –37.20 mg/dL (–65.55; –23.85) (–40.06%) (p not significant). The therapy was safe and well tolerated.*

Conclusions: *Fixed-dose combination of rosuvastatin and ezetimibe significantly and permanently decreases LDL-C regardless of the timing of drug administration.* (Cardiol J 2021; 28, 1: 58–66)

Key words: hypercholesterolemia, fixed-dose, secondary prevention, timing of administration, adherence, apolipoprotein B, lipoprotein(a)

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Introduction

Coronary artery disease (CAD) remains the most common single cause of death worldwide [1]. Hypercholesterolemia constitutes one of its major risk factors [2]. According to the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) 2016 guidelines for the management of dyslipidemias, the therapeutic target for low density lipoprotein-cholesterol (LDL-C) is < 70 mg/dL (< 1.8 mmol/L) [1, 3]. The first line treatment of hypercholesterolemia is statin therapy [3]. However, when the therapeutic target of LDL-C is not achieved, the addition of cholesterol absorption inhibitor — ezetimibe — to statin therapy is recommended [3, 4]. Unfortunately, lipid-lowering therapy is discontinued in a high percentage of patients with CAD [5]. One year after myocardial infarction (MI) only approximately 50% of patients report persistent use of statins [6, 7]. Furthermore, even when patients follow the recommendations and continue statin therapy, only a minority obtains optimal level of LDL-C [8, 9].

The aim of the present study was to evaluate the effectiveness of hypercholesterolemia treatment with rosuvastatin and ezetimibe in patients ineffectively treated with statin monotherapy. Also under investigation was whether the timing (morning vs. evening) of rosuvastatin and ezetimibe administration affects their efficacy.

Methods

Study design and population

The study was designed as a randomized, open-label, single-center, crossover study. It was conducted in accordance with the principles contained in the Declaration of Helsinki and Good Clinical Practice guidelines and aimed to evaluate: the effectiveness of combined therapy with rosuvastatin and ezetimibe for hypercholesterolemia in patients with inadequate LDL-C control on statins alone, and to determine whether the timing of drug administration influences their efficacy (ClinicalTrials.gov Identifier: NCT02772640). The study was approved by local institutional review board (The Ethics Committee of Nicolaus Copernicus University in Torun, Collegium Medicum in Bydgoszcz, Poland). All participants signed informed consent prior to the performance of any investigational procedures. Key inclusion criteria included: diagnosis of hypercholesterolemia, defined according to the 2016 European guidelines [3], ineffectively treated for at least 6 weeks with statins. Patients eligible for the study had LDL-C ≥ 70 mg/dL. Major exclusion criteria included: active liver disease; unexplained persistent increase in serum transaminases activity (i.e. > 3-fold higher than the upper reference limit [URL]); myopathy; activity of creatine kinase (CK) > 5-fold higher than the URL. The complete list of inclusion and exclusion criteria has been previously published [10].

Patients hospitalized at the Department of Cardiology, Dr. Antoni Jurasz University Hospital No. 1 in Bydgoszcz, Poland, between the years 2016 and 2018 were screened, and if eligible, were enrolled in the study. The diagnosis of hypercholesterolemia was confirmed based on the lipid profile assessed during hospitalization. Patients with LDL-C ≥ 70 mg/dL, despite having a 6-week statin monotherapy, were enrolled. After enrollment, all participants were randomly assigned to one of two study arms using Random Allocation Software 1.0. The study drug was a fixed dose combination (FDC) of rosuvastatin 10 mg and ezetimibe 10 mg formulated as capsules (Rosulip plus by Egis). In arm I, the study drug was administered in the morning (8:00 am) for 6 weeks and then in the evening (8:00 pm) for the next 6 weeks. In arm II, patients were receiving the study drug in the evening (8:00 pm) for the first 6 weeks and then in the morning (8:00 am) for the following 6 weeks. All patients received the study drug free of charge over the entire observational period. The remaining medications were as recommended by the ESC guidelines accordingly to specific comorbidities. Clinical evaluation and blood sampling were performed on the day of randomization and after 6 and 12 weeks of treatment. In a subgroup of patients, blood samples were collected twice a day: 12 and 24 hours after the last dose of study drug during follow-up visits.

Endpoints

The primary outcome was defined as change in LDL-C after 6 and 12 weeks of the investigated therapy, with respect to timing of the study drug administration. The secondary endpoints included: change in total cholesterol (TC) and triglycerides (TG) levels after 6 and 12 weeks (also with respect to timing of the study drug administration), concentration of high-sensitivity C-reactive protein (hs-CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK), apolipoprotein B (apoB) and lipoprotein(a) (Lp(a)) at baseline and after 6 and 12 weeks of the therapy.

Table 1. Baseline characteristics of study patients and comparison between study arms.

Population	N = 83 patients	Group I (40 patients)	Group II (43 patients)	P
Female	20 (24.1%)	7 (17.5%)	13 (30.2%)	0.1753
Age [years]	64.6 ± 8.7	64.6 ± 7.9	64.6 ± 9.4	0.9675
Post myocardial infarction	52 (62.7%)	21 (52.5%)	31 (72.%)	0.0867
Hypertension	58 (69.9%)	24 (60.0%)	34 (70.1%)	0.0814
Heart failure	30 (36.2%)	12 (30.0%)	18 (41.9%)	0.2977
Diabetes mellitus	22 (36.5%)	9 (22.5%)	13 (30.2%)	0.4652

Blood collection and laboratory measurements

A detailed description of blood collection and laboratory measurements has been previously published [10]. Routine laboratory measurements were performed in fresh serum (basic lipid profile [TC, TG, LDL-C], AST, ALT, CK). The remaining serum was aliquoted and stored at –80°C until assayed for hs-CRP, apoB, Lp(a). All measurements (except for CRP) were performed using the Horiba ABX Pentra 400 analyzer (Horiba ABX, Montpellier, France). LDL-C was measured directly. CRP was measured using the Alinity c analyzer (Abbott Laboratories, Chicago, IL, USA) with the Alinity c CRP Vario High Sensitivity assay for the quantitative, immunoturbidimetric determination of CRP with a limit of detection of 0.4 mg/L. Laboratory measurements were performed at the Department of Laboratory Medicine, Nicolaus Copernicus University, Collegium Medicum, Bydgoszcz, Poland.

Statistical analysis

Statistical analysis was carried out using the Statistica 13.0 package (StatSoft, Tulsa, USA). The Shapiro-Wilk test demonstrated that the investigated continuous variables were not normally distributed. Therefore, continuous variables were presented as median and quartiles (lower and upper) and nonparametric tests (the Mann-Whitney unpaired rank sum test, the Wilcoxon signed rank test, and the Friedman ANOVA) were used for statistical analysis. The χ^2 test was used for comparisons of qualitative variables. Differences were considered statistically significant at $p < 0.05$.

Results

Eighty-three patients were enrolled into the study. The mean age was 64.6 ± 8.7 years. The majority of included patients had a documented history of CAD (93.98%) and 62.7% had prior MI. There were no differences between patients in both study arms (Table 1). At the time of enrollment, the majority of patients were treated with atorvastatin (72.29%), 16.87% used rosuvastatin, and the rest were treated with simvastatin.

Primary endpoint

After 6 weeks of therapy with the study drug, there was a significant reduction in LDL-C (median: 98.10 mg/dL; interquartile distribution [Q1;Q3]: 85.10;116.80 vs. 63.14 mg/dL; 50.70;77.10; $p < 0.001$). The decrease was constant over time after 12 weeks (63.14 mg/dL [50.70;77.10] vs. 59.40 mg/dL [49.00;73.30]; $p = 0.077$; Fig. 1). There was no significant difference between LDL-C with respect to the timing of the study drug administration (morning: 62.50 mg/dL [50.70;76.00] vs. evening: 59.70 mg/dL [48.20;73.80]; $p = 0.259$; Fig. 2), in both time points after 6 and 12 weeks, respectively (after 6 weeks: 63.15 mg/dL [50.75;80.65] vs. 63.40 mg/dL [50.60;74.00]; $p = 0.775$); after 12 weeks: 62.00 mg/dL [50.20;74.40] vs. 59.05 mg/dL [47.65;66.05]; $p = 0.362$). After 6 weeks the absolute change in LDL-C was –34.6 (–56.55; –19.85) (–34.87% [–46.83; –22.69]) for the morning administration of the study drug, and –31.10 (–44.20; –16.00) (–35.87% [–47.87; –17.96]) (p not significant) for the evening administration. Twelve weeks after, the absolute change in LDL-C was –34.20 (–47.8; –19.0) (–37.12% [–46.18; –20.62]) for the morning and –37.20 (–65.55; –23.85) (40.06% [–55.24;–23.33]) (p not significant) for the evening administration, respectively.

In a subgroup of 20 patients additional measurements were performed at 12 and 24 hours after the last dose of the study drug. In patients receiving the study drug in the morning, LDL-C measured in the evening (i.e. 12 h after the last dose) were significantly lower than the next morning (i.e. 24 h

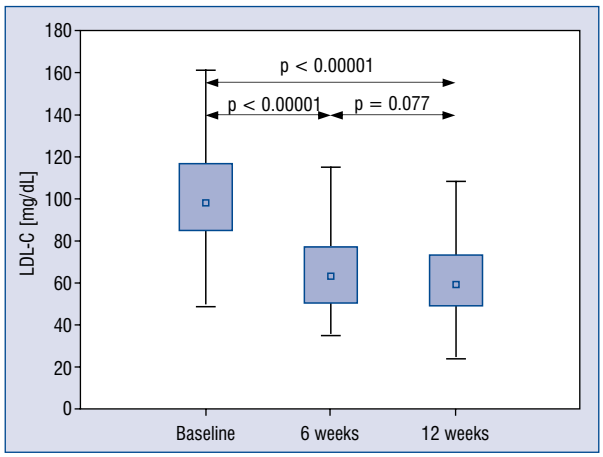

Figure 1. Primary endpoint: Change in low density lipoprotein cholesterol (LDL-C) after 6 and 12 weeks of therapy.

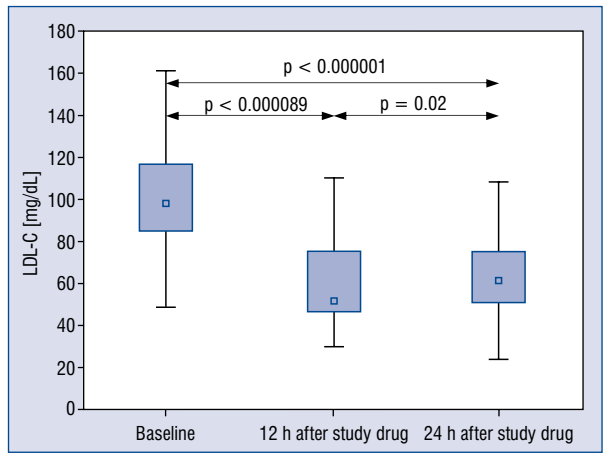

Figure 3. Morning administration of the study drug: change in low density lipoprotein cholesterol (LDL-C) concentration depending of time of testing.

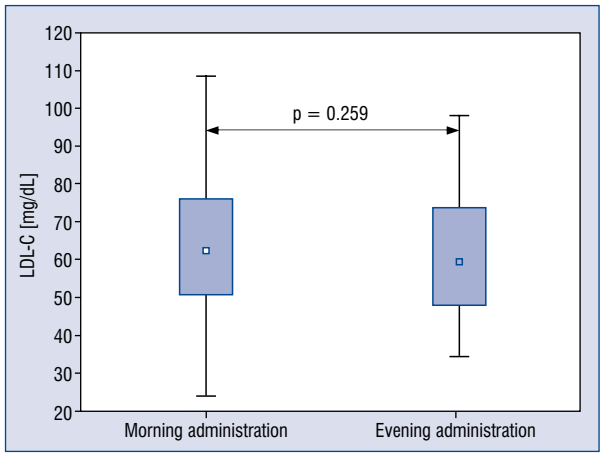

Figure 2. Low density lipoprotein cholesterol (LDL-C) concentration depending on time of day of study drug administration.

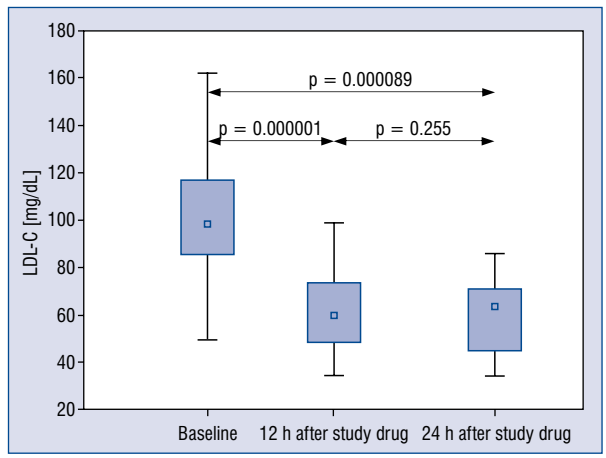

Figure 4. Evening administration of the study drug: change in low density lipoprotein cholesterol (LDL-C) concentration depending of time of testing.

after the last dose of the study drug) [52 mg/dL (46.95;75.85) vs. 64.95 mg/dL (50.35;77.05); p=0.019] (Fig. 3). Nevertheless, both results were significantly lower compared with baseline LDL-C [12 h: 93.5 mg/dL (86.15;113.4) vs. 52 mg/dL (46.95;75.85); p=0.000089; 24 h: 93.5 mg/dL (86.15;113.4) vs. 64.95 mg/dL (50.35;77.05); p<0.000001]. Among patients taking the drug in the evening, LDL-C measured next morning (i.e. 12 h after the last dose of the study drug) was comparable with the LDL-C level measured in the evening the same day (i.e. 24 h after the last dose of the study drug) [61.05 mg/dL (45.85;74.05) vs. 63.35 mg/dL (44.75;71.00); p = 0.255] (Fig. 4).

Secondary endpoints

Total cholesterol was significantly lower after 6 weeks of therapy with the study drug and this effect was stable throughout the observational period (Fig. 5). Moreover, the effect was independent of the timing of study drug administration (Table 2). Similar results were achieved for TG. There was a significant reduction in TG concentration compared with baseline values (Table 2), and the outcome was again independent of the timing of the study drug administration (Table 2).

With regard to apoB, a significant reduction was found in its concentration after 6 weeks of treatment with the study drug (93.00 [77.00;

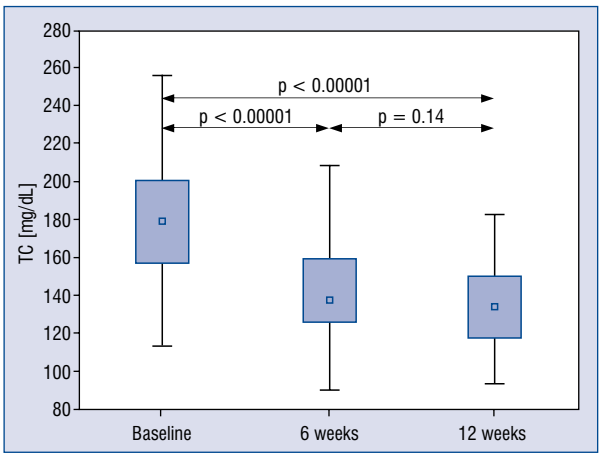

Figure 5. Change in total cholesterol (TC) concentration after 6 and 12 weeks of therapy.

104.00] vs. 68.00 [57.00;83.00]; p < 0.00001). The reduction was persistent throughout the observational period, and was independent of the timing of the study drug administration (Table 2).

Lipoprotein(a) decreased after the study drug administration, however without statistical significance (Table 2).

There was no alteration in AST activity. An increase in ALT activity compared with baseline values was recorded, regardless of the timing of the study drug administration. Nevertheless, the morning and evening measurements showed no significant difference (Table 2). There were no cases of ALT activity increase ≥ 3 × URL.

There was a statistically significant, transient increase in CK activity after initiation of the treatment (Table 2), always < 5 × URL. After 12 weeks of therapy CK activity showed no significant differences compared with baseline levels (73.0 [55.0;108.0] vs. 84.0 [60.0;125.0]; p = 0.245). Similar CK activity was noted regardless of the timing of the study drug administration (morning: 86.0 [56.0;116.0] vs. evening: 80.0 [63.0;128.0]; p = 0.984).

High-sensitivity C-reactive protein concentration was significantly reduced after 6 weeks of treatment (Table 2). The effect was stable throughout the observational period (Table 2).

Discussion

The main finding of the ROSEZE study is confirmation of the effectiveness and safety of combined therapy for hypercholesterolemia using an FDC of low dose rosuvastatin (10 mg)

Table 2. Secondary endpoints.

Secondary endpoints	Baseline [median]	Q1;Q3	After 6 weeks [median]	Q1;Q3	P	After 12 weeks [median]	Q1;Q3	P (6 vs. 12 weeks)	Morning administration [median]	Q1;Q3	Evening administration [median]	Q1;Q3	P
TC [mg/dL]	179.50	156.50; 200.70	137.70	125.4; 159.5	<0.00001	134.3	117.4; 150.4	0.14	138.0	122.80; 160.20	134.3	121.0; 150.0	0.22
HDL [mg/dL]	42.60	8.48–41.00	47.91	13.52–45.2	0.00002	45.35	9.25–42.8	0.114	47.44	13.5–45.3	45.82	9.37–43.9	0.819
TG [mg/dL]	153.90	117.90;214.00	121.65	94.60;164.00	< 0.00001	130.30	92.10;167.00	0.310	121.9	93.5;170.0	131.2	90.4;164.0	0.62
AST [U/L]	22.60	18.80;27.50	23.30	19.40;29.70	0.1279	23.50	19.50;29.70	0.494	23.5	19.8;29.8	23.0	19.2;29.3	0.87
ALT [U/L]	14.90	11.10;21.10	16.10	12.00;28.00	0.0045	17.70	12.00;26.50	0.426	18.0	12.0;27.2	15.8	12.1;27.3	0.467
CK [U/L]	73.00	55.00;108.00	80.00	58.0;115.0	0.011	84.0	60.0;125.0	0.782	86.0	56.0;116.0	80.0	63.0;128.0	0.984
hs-CRP [mg/L]	1.82	0.86;2.87	1.21	0.64;2.39	0.01	1.22	0.64;1.995	0.44	1.26	0.76;2.13	0.93	0.58;2.035	0.461
apo B [mg/dL]	93.00	77.00–104.00	68.00	57.00–83.00	< 0.00001	67.00	58.00–78.00	0.171	69.00	60.00–78.00	66.00	58.00–81.00	0.14
Lp(a) [mg/dL]	14.05	5.10–25.55	10.50	4.60–23.00	0.051	11.0	4.80–24.15	0.512	10.35	4.30–20.90	10.50	4.45–23.50	0.59
apoAI [mg/dL]	147.0	131.00–164.00	150.00	135.00–172.00	0.007	154.00	141.00–172.00	0.5	156.00	135.00–175.00	151.00	137.00–171.00	0.108

Data are shown as median (interquartile distribution (Q1;Q3). TC — total cholesterol; HDL — high density lipoprotein; TG — triglycerides; AST — aspartate aminotransferase; ALT — alanine aminotransferase; CK — creatine kinase; hsCRP — high-sensitivity C-reactive protein; apoB — apolipoprotein B; Lp(a) — lipoprotein(a); apoAI — apolipoprotein AI

and ezetimibe, regardless of the timing of drug administration, in patients unsuccessfully treated with statin monotherapy. According to available research, the current study is the first trial assessing the effectiveness of an FDC of rosuvastatin and ezetimibe in relation to the daily timing of drug administration.

As demonstrated in a meta-analysis of trials assessing statin therapy, each 40 mg/dL drop in LDL-C translates into a significant reduction in all-cause mortality (by 10%) [11] and major cardiovascular events (by 23%) [12]. More powerful statins compared with weaker ones, produce a highly significant 15% (95% confidence interval [CI] 11–18; $p < 0.0001$) further reduction in major vascular events [11]. More intensive LDL-C lowering therapies including potent statins alone or combinations of statins with ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors are associated with a great reduction in risk of total and cardiovascular mortality, especially when the baseline LDL-C level exceeds 100 mg/dL [13].

Surveys and national databases of patients with hypercholesterolemia and CAD demonstrated that the LDL-C target levels recommended by 2016 ESC guidelines were achieved only in a small percentage of patients: 19.3% according to EUROASPIRE IV [5], 19–25% according to a large real-life German registry from the years 2011–2016 [8] and were only 5.8% according to a large Italian database published in 2019 [9]. Other lessons coming from available registries include (i) too low usage of high intensity statins and (ii) frequently premature discontinuation of lipid lowering therapy (LLT).

Several trials demonstrated the superiority of combined treatment of hypercholesterolemia with statins and ezetimibe compared with statin monotherapy, revealing that addition of ezetimibe to statin therapy provides more extensive reduction of LDL-C than doubling the statin dose, and thus allows more patients to achieve the LDL-C goal [14–16]. The IMPROVE-IT trial, demonstrated that adding ezetimibe to low intensity statin (simvastatin 40 mg) carries benefit (24% of additional reduction in LDL-C compared with statin monotherapy and lowering the risk of cardiovascular events compared with statin monotherapy with a 2.0-percentage-point lower rate of primary end point defined as a composite of death from cardiovascular disease, a major coronary event or nonfatal stroke [17]) independent of age [18] and sex [19] with a good safety profile, supporting the use of intensive, combined LLT to optimize cardiovascular outcomes [17–19].

In studies evaluating the effectiveness of more potent regimens, rosuvastatin enabled LDL-C reduction by 44–47% [20–22]. The PULSAR trial revealed that in high-risk patients with hypercholesterolemia, rosuvastatin 10 mg is more efficient at reducing the LDL-C level than the commonly used 20 mg dose of atorvastatin, enabling LDL-C goal achievement and improving other lipid parameters [22]. In the MRS-ROZE study, Kim et al. [23] demonstrated that FDCs of ezetimibe and rosuvastatin provided superior efficacy to rosuvastatin alone in lowering LDL-C, TC and TG levels (reduction by 56–63%, 37–43%, and 19–24%, respectively).

Similarly, the I-ROSETTE trial reported the LDL-C lowering efficacy of each ezetimibe/rosuvastatin combination to be superior to each of the respective doses of rosuvastatin [24]. The mean percent change in LDL-C in all ezetimibe/rosuvastatin combination groups exceeded 50% [24]. Moreover, the number of patients who achieved target LDL-C levels after 8 weeks of an observational period was significantly higher in the combined therapy group than in the rosuvastatin monotherapy group (92.3% vs. 79.9%, $p < 0.001$) [24]. Rosuvastatin alone or in combination with ezetimibe is very effective even in patients with familiar hypercholesterolemia. Mickiewicz et al. [25] demonstrated a reduction in LDL-C concentration by 45.9% and 55.4% depending whether it concerned monogenic or polygenic subjects with familiar hypercholesterolemia [25].

As expected, the present study also demonstrated that an FDC of rosuvastatin 10 mg/ /ezetimibe 10 mg significantly reduces LDL-C and other lipid fractions including TC and TG. The median percentage change in LDL-C after FDC drug in the current study was –35–40%. It allowed achievement of the target LDL-C level < 70 mg/dL in 66.27% and 69.88% in patients receiving the FDC drug in the morning and in the evening, respectively. Nevertheless, this result cannot be regarded as fully satisfactory, considering that according to the newly published 2019 European Guidelines for the Management of Dyslipidemias, the therapeutic goal for LDL-C in very high-risk patients was further lowered to the level of < 55 mg/dL (< 1.4 mmol/L) [4], thus the combination with 10 mg of rosuvastatin might not be sufficient for every single patient.

Apolipoprotein B, which is known to be a more informative marker of adequacy of statin treatment than LDL-C [26], similar to other studies [27–30] it was reduced in the present study by 26.9%, achiev-

ing median values close to those recommended in the recent 2019 guidelines [4].

Nozue et al. [31] showed a potential role of ezetimibe as an Lp(a) lowering drug. The reduction in Lp(a) concentration in the current study did not reach statistical significance. In a meta-analysis of randomized controlled trials, Sahebkar et al. [32] demonstrated that ezetimibe in monotherapy or in combination with statin did not affect plasma Lp(a) levels.

As indicated by the present results, the daily timing of administration of the study drug did not affect its efficacy. So far, statins were commonly administered in the evening due to the peak of hepatic 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductive activity and cholesterol synthesis which occurs at night [33, 34]. Meanwhile, the majority of medications are taken in the morning, thus avoidance of the last pill during the day, which is statin in most cases, is a huge problem. For this reason, we investigated whether the daily timing of intake is relevant for lipid lowering drugs. Although, in our study there was no significant difference between obtained LDL-C levels according to the timing of study drug intake (morning vs. evening), the discrepancies found in LDL-C reduction depending on the time of test performance: 12 or 24 hours after the last dose of the drug studied, are not completely clear and need further exploration. According to a research by Nishida et al. [35], rosuvastatin exposure decreases under the fed condition compared with strict fasting. However, it was only a pharmacokinetics study assessing potential food effect and the bioequivalence between co-administered ezetimibe and rosuvastatin and FDC tablets containing ezetimibe and rosuvastatin in healthy Japanese subjects under fasted and fed conditions [35].

According to available research, the present study is the first one to reveal the influence of the timing of an FDC of rosuvastatin and ezetimibe on the effectiveness of LLT. Observations herein, indicate similar potency of tested therapy, regardless of whether the drug was administered in the evening or in the morning. As a consequence of this, we encourage administration of the FDC of rosuvastatin with ezetimibe in the morning with the majority of other drugs. This timing modification may translate into better adherence to recommended LLT, compared with traditional statin dosing in the evening, which leads to its frequent omission. Simplifying the treatment strategies and reducing the number of tablets by using polypills are one of key factors for better cooperation between health care providers and patients, and better drug adherence [3].

Similar to previous studies in patients with CAD [36, 37], in the present study, the tested therapy provoked a further reduction in hs-CRP concentration, compared with baseline values. Considering the fact that our population of patients had been already treated with statins for secondary prevention prior to the study, it was the addition of ezetimibe that led to a further reduction of the inflammatory process. This finding supports the existence of a pleotropic anti-inflammatory, in addition to hypolipemic, effect of ezetimibe, both of which are responsible for residual atherosclerotic risk [38].

The safety and tolerability of the tested therapy were similar in both arms of the current study. There were no cases of rosuvastatin/ezetimibe-related adverse events including muscular, hepatic and gastrointestinal events.

Limitations of the study

This study has several limitations. The first one is a relatively small sample size. Due to the preliminary nature of the study, the number of patients included in the current analysis is lower than calculated earlier for the sample size. Second, the study was designed to assess changes in LDL-C concentration without addressing the relationship between LDL-C reduction and clinical outcomes. Third, the divergences between LDL-C levels assessed 12 and 24 hours after the last dose of rosuvastatin and ezetimibe may have had a multifactorial origin which is difficult to explain at this point and would likely require an adequate sample size for clarification.

Conclusions

The present study demonstrates that a combination of rosuvastatin and ezetimibe as a polypill is effective and well tolerated, showing similar efficacy whether administered in the morning or in the evening.

Conflict of interest: None declared

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Ischemic and non-ischemic patterns of late gadolinium enhancement in heart failure with reduced ejection fraction

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Abstract

Background: *Late gadolinium enhancement (LGE) by cardiac magnetic resonance (CMR) may reveal myocardial fibrosis which is associated with adverse clinical outcomes in patients undergoing implantable cardioverter-defibrillator (ICD) placement. At the same time, transmural LGE in the posterolateral wall is related to nonresponse to conventional cardiac resynchronization therapy (CRT). Herein, the aim was to assess the presence and determinants of LGE in CMR in heart failure (HF) with reduced ejection fraction.*

Methods: *Sixty-seven patients were included (17.9% female, aged 45 [29–60] years), who underwent LGE-CMR and had left ventricular ejection fraction (LVEF) as determined by echocardiography.*

Results: *In HF patients with LVEF ≤ 35% (n = 29), ischemic and non-ischemic patterns of LGE were observed in 51.7% and 34.5% of patients, respectively. In controls (n = 38), these patterns were noted in 23.7% and 42.1% of patients, respectively. HF patients with LVEF ≤ 35% and transmural LGE in the posterolateral wall (31.0%) were characterized by older age, coronary artery disease (CAD) and previous myocardial infarction (MI) (61 ± 6 vs. 49 ± 16 years, p = 0.008, 100% vs. 40%, p = 0.003 and 78% vs. 25%, p = 0.014, respectively). In patients with LVEF ≤ 35%, LGE of any type, diagnosed in 86.2% of patients, was associated with CAD (68% vs. 0%, p = 0.02), while only trends were observed for its association with older age and previous MI (p = 0.08 and p = 0.12, respectively).*

Conclusions: *Among HF patients with LVEF ≤ 35%, clinical factors including older age, CAD, and previous MI are associated with transmural LGE in the posterolateral wall, while CAD is associated with LGE. This data may have potential implications for planning ICD and CRT placement procedures.* (Cardiol J 2021; 28, 1: 67–76)

Key words: heart failure, late gadolinium enhancement, ischemic, cardiac magnetic resonance, transmural late gadolinium enhancement, cardiac resynchronization therapy, implantable cardioverter-defibrillator

Introduction

Appropriate patient evaluation for the placement of implantable cardioverter-defibrillators (ICD) and cardiac resynchronization therapy (CRT) devices is important in the management of heart failure (HF) patients with reduced ejection fraction (HFrEF). In patients with an ischemic or non-ischemic etiology of HF, left ventricular ejection fraction (LVEF) ≤ 35%, as determined by echocardiography, continues to be used as a major criterion when considering patients for placement of an ICD

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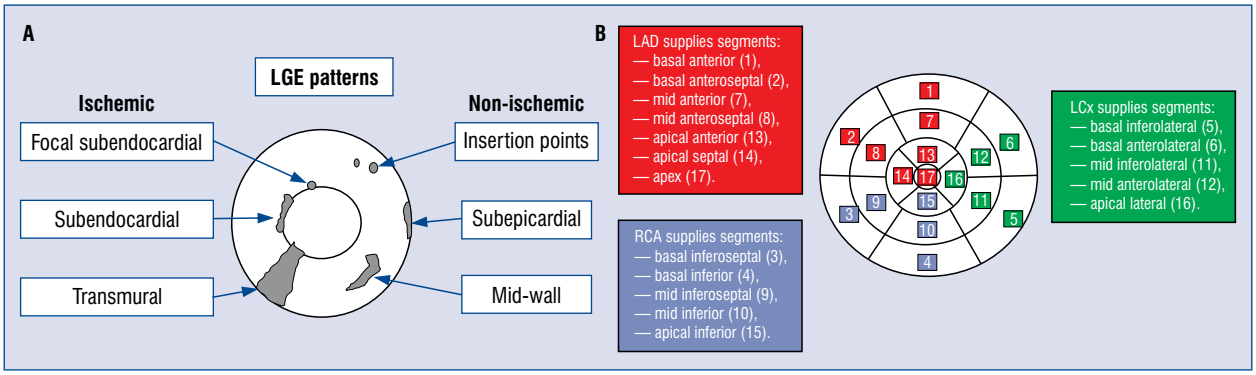

Figure 1. The patterns of late gadolinium enhancement reflecting ischemic and non-ischemic myocardial injury (**A**) and assignment of the 17 myocardial segments to the territories of the coronary arteries (**B**). Based on references [7, 11]; LAD — left anterior descending coronary artery; LCx — left circumflex coronary artery; LGE — late gadolinium enhancement; RCA — right coronary artery.

in primary sudden cardiac death (SCD) prevention and to improve HF through CRT [1]. However, effective SCD risk stratification based solely on HF symptoms and LVEF has a number of limitations. At the same time, about 30% of patients do not respond to CRT [2, 3].

Cardiac magnetic resonance (CMR) imaging, especially with late gadolinium enhancement (LGE), is a valuable clinical tool in diagnostic of patients with HF or left ventricular (LV) dysfunction [4, 5]. Gadolinium-based contrast agents accumulate and demonstrate delayed enhancement within areas of increased extracellular space such as fibrosis, thus enhancing areas of scarring [6]. The patterns of LGE help to differentiate between ischemic and non-ischemic myocardial injury (Fig. 1A). Generally, ischemic myocardial injury tends to cause LGE which is typically subendocardial or transmural [7]. Non-ischemic myocardial injury can be observed at the epicardium, in the midwall, or at insertion points [5, 7, 8]. Moreover, LGE has been found to predict clinical outcomes in selected patients undergoing ICD placement [9]. At the same time, response to conventional CRT is decreased in the presence of transmural scarring in the posterolateral LV segments (the place over which an LV lead is usually placed) [10].

The cardiac LV segmentation model published by the American Heart Association (AHA) divides the heart into 17 segments and is now widely used for the description of disease-affected myocardium [11]. These 17 segments have a reasonably consistent vascular supply from the main coronary arteries (Fig. 1B). As described previously, generally the left anterior descending coronary artery (LAD) supplies myocardial segments 1, 2, 7, 8, 13, 14, and 17, the right coronary artery (RCA) supplies segments 3, 4, 9, 10, and 15, while the left circumflex coronary artery (LCx) supplies the remainder myocardial segments (5, 6, 11, 12, and 16) [11]. However, coronary arteries may be anomalous and their anatomy varies from patient to patient, creating a limitation of the AHA model [12–15].

The main purpose of this study was to assess the presence and determinants of LGE in CMR in patients with HFrEF.

Methods

Study population

The study group included 67 patients (17.9% female, aged 45 [29–60] years) who underwent LGE-CMR at the Department of Diagnostic Imaging, University Hospital in Krakow between 2011 and 2015, and had data available on LVEF as determined by echocardiography. Further data were obtained from a structured medical documentation review (baseline patient demographics and clinical data including chronic diseases). Diagnosis of significant coronary artery disease (CAD) was based on coronary angiography (available in medical records of 36 patients) and was defined as coronary artery diameter stenosis of 50% or more, or previous cardiac revascularization (coronary angioplasty or coronary artery bypass grafting) [16]. Moreover, specifically a group of patients with LVEF ≤ 35%, as determined by echocardiography, was addressed, because they are frequently considered for ICD and CRT placement according

to the European Society of Cardiology guidelines [17]. The study was approved by the local ethics committee.

CMR imaging

Cardiac magnetic resonance imaging was performed using a 1.5 Tesla scanner. Steady-state free precession cine images were acquired in the short-axis and two-, three-, and four-chamber views. LGE images were generally acquired 10–20 min after injection of 0.2 mL/kg gadoteridol (ProHance). Inversion recovery time was individually adapted to maximize contrast between regions of LGE and normal myocardium. The cardiac LV segmentation model published by the AHA was used for the description of disease-affected myocardial segments [11]. The distribution of LGE was also assessed according to territories supplied by coronary arteries as proposed in the AHA model [11]. Posterolateral LV segments were defined as basal inferior (4), basal inferolateral (5), mid inferior (10), and mid inferolateral (11) segments [10]. A transmural scar was defined as a hyperenhancement extending ≥ 51% of LV wall thickness in ≥ 1 of the LV segments [10].

Statistical analysis

Continuous variables are presented as means ± standard deviations or medians (interquartile ranges [IQR]), while categorical variables are shown as numbers and percentages. Associations between categorical variables were assessed using the Pearson chi-squared test or the Fisher's exact test. Continuous variables between two groups were compared using the Student's t-test or Mann-Whitney U test, as appropriate. The Spearman rank test was used to measure the association between two continuous variables (both of the variables tested had a non-normal distribution). Statistical significance was defined as a p value < 0.05. Statistical analyses were performed using IBM SPSS Statistics (version 24, IBM Corp., Armonk, NY, USA).

Results

Study population

Twenty nine patients with HF and LVEF ≤ 35%, and 38 control patients with LVEF > 35%, as determined by echocardiography, were analyzed. Baseline characteristics of patients are shown in Table 1. In the whole group of patients only ischemic or only non-ischemic patterns of LGE were observed in 24 (35.8%) and 26 (38.8%) patients, respectively. Six (9.0%) patients (only in the control group) had features of both ischemic and non-ischemic or a non-specific LGE pattern, while in 11 (16.4%) patients no LGE was observed. LVEF measured by echocardiography correlated with LVEF measured by CMR ($R = 0.825$, $p < 0.001$). Median LVEF measured by echocardiography was 47% (IQR 25–60%), while median LVEF measured by CMR was 44% (IQR 25–54%). Results of coronary angiography were available in medical documentation from the University Hospital for 36 patients. The median time interval between CMR and coronary angiography was 7 days (IQR 3–24 days).

Comparison of HF patients with LVEF of 35% or less and controls with LVEF > 35%

Among patients with HF and LVEF ≤ 35%, as determined by echocardiography, an ischemic pattern of LGE was observed in 15 (51.7%) subjects, non-ischemic in 10 (34.5%) patients, while 4 (13.8%) patients had no LGE. In controls, an ischemic pattern of LGE was observed in 9 (23.7%) subjects, non-ischemic in 16 (42.1%), combined ischemic and non-ischemic or a non-specific pattern in 6 (15.8%), while 7 (18.4%) had no LGE.

There was no significant difference regarding the presence of any LGE between HF patients with LVEF ≤ 35% when compared to controls. However, the ischemic pattern of LGE was more prevalent in HF patients with LVEF ≤ 35% when compared to controls (Table 1). Moreover, in the first group of patients, transmural LGE was observed more frequently when compared with the remainder of the patients (44.8% vs. 13.2%, $p = 0.004$). The presence of LGE of any pattern was observed more frequently in patients with LVEF ≤ 35% than in controls in the mid and apical third (75.9% vs. 44.7%, $p = 0.01$; 51.7% vs. 26.3%, $p = 0.033$; respectively), while there was no difference in observed LGE in the basal third between these two groups (Table 2). Interestingly, in the mid third LGE was observed more commonly in segments 8, 10, and 12, while in the apical third LGE was observed more commonly in segments 13, 15, and 16 in HF patients with LVEF ≤ 35% than in the control group (Table 2).

In patients for whom coronary angiography data were available ($n = 36$) there was a trend towards a higher prevalence of CAD in HF patients with LVEF ≤ 35% than the remainder of the patients (63.6% vs. 35.7%, $p = 0.102$; Table 3). When individual coronary arteries were analyzed, only the LCx was more commonly affected by

Table 1. Baseline characteristics of heart failure (HF) patients with left ventricular ejection fraction (LVEF) ≤ 35% determined by echocardiography and controls with LVEF > 35%.

Parameters	Patients with HF and LVEF ≤ 35% (n = 29)	Control patients (n = 38)	P
Demographics			
Female sex	5 (17.2%)	7 (18.4%)	0.901
Age [years]	57.0 (38.5–62.0)	35.0 (25.8–57.5)	**0.004**
LVEF determined by echocardiography [%]	23.3 ± 7.3	57.1 ± 8.8	**< 0.001**
Diseases and risk factors			
HF	29 (100.0%)	13 (34.2%)	**< 0.001**
Myocardial infarction	12 (41.4%)	9 (23.7%)	0.122
CAD	17 (58.6%)	15 (39.5%)	0.120
Atrial fibrillation	6 (20.7%)	3 (7.9%)	0.160*
Diabetes	6 (20.7%)	4 (10.5%)	0.309*
Hyperlipidemia	13 (44.8%)	12 (31.6%)	0.267
Hypertension	16 (55.2%)	13 (34.2%)	0.086
Smoking	8 (27.6%)	8 (21.1%)	0.534
CMR parameters			
CMR-LVEF [%]	24.7 (19.2–32.4)	51.8 (46.6–61.2)	**< 0.001**
CMR-LVEDV [mL]	271.3 (184.1–368.9)	170.9 (140.9–189.7)	**< 0.001**
CMR-LVESV [mL]	205.5 (121.5–280.3)	73.1 (61.7–93.6)	**< 0.001**
Ischemic LGE pattern only	15 (51.7%)	9 (23.7%)	**0.018**
Any LGE	25 (86.2%)	31 (81.6%)	0.745*
Any LGE in posterolateral LV segment	14 (48.3%)	11 (28.9%)	0.105
Any transmural LGE	13 (44.8%)	5 (13.2%)	**0.004**
Any transmural LGE in posterolateral segment	9 (31.0%)	3 (7.9%)	**0.014**

*The Fisher's exact test (exact significance, 2-sided). Values are presented as mean ± standard deviation or median (interquartile range) or number (percentage). CAD — coronary artery disease; CMR — cardiac magnetic resonance; LGE — late gadolinium enhancement; LVEDV — left ventricular end diastolic volume; LVESV — left ventricular end systolic volume

significant CAD in HF patients with LVEF ≤ 35% when compared to controls (50.0% vs. 7.1%, p = 0.011). At the same time, when LGE was assessed in segments according to coronary artery distribution, there was a trend to more commonly observed LGE in segments supplied by the LAD in HF patients with LVEF ≤ 35% than in controls (68.2% vs. 35.7%, p = 0.056; Table 3).

Assessment of HF patients with LVEF of 35% or less with or without LGE

The vast majority of studied HF patients with LVEF ≤ 35% had observed LGE (n = 25, 86.2%). LGE in HF patients with LVEF ≤ 35% was associated with CAD (68.0% vs. 0.0%, p = 0.02), while only trends were observed for its association with older age and previous myocardial infarction (MI) (54.4 ± 13.4 vs. 41.0 ± 16.2, p = 0.08 and 48.0% vs. 0.0%, p = 0.12, respectively).

Patients with LVEF ≤ 35% and transmural LGE were older than the remainder of HF patients with LVEF ≤ 35% and no transmural LGE (60.1 ± 7.6 vs. 46.5 ± 15.7, p = 0.006; Table 4). CAD, MI, and the ischemic pattern of LGE were observed more commonly in patients with LVEF ≤ 35% and transmural LGE when compared with the remainder of patients with LVEF ≤ 35% and no transmural LGE (92.3% vs. 31.3%, p = 0.001; 84.6% vs. 6.3%, p < 0.001; 100.0% vs. 12.5%, p < 0.001, as in Table 4).

In HF patients with LVEF ≤ 35%, transmural LGE in the posterolateral wall (31%) was associated with older age, CAD, and previous MI (60.6 ± 6.3 vs. 49.0 ± 15.6 years, p = 0.008, 100% vs. 40%, p = 0.003 and 77.8% vs. 25%, p = 0.014, respectively, Table 4). In a group of patients with LVEF ≤ 35% and transmural LGE in the posterolateral LV segments, the presence of an ischemic pattern of LGE was more prevalent when compared with the remaining HF patients with LVEF ≤ 35% and no observed transmural LGE in this region (100% vs. 30%, p = 0.001, Table 4).

Table 2. Comparison of localization of late gadolinium enhancement (LGE) between heart failure (HF) patients with left ventricular ejection fraction (LVEF) ≤ 35% determined by echocardiography and controls with LVEF > 35%.

Segments	Patients with HF and LVEF ≤ 35% (n = 29)	Control patients (n = 38)	P
Any LGE pattern in basal segments	18 (62.1%)	20 (52.6%)	0.440
Basal anterior (1)	7 (24.1%)	5 (13.2%)	0.246
Basal anteroseptal (2)	11 (37.9%)	9 (23.7%)	0.207
Basal inferoseptal (3)	13 (44.8%)	12 (31.6%)	0.267
Basal inferior (4)	10 (34.5%)	7 (18.4%)	0.134
Basal inferolateral (5)	9 (31.0%)	5 (13.2%)	0.075
Basal anterolateral (6)	5 (17.2%)	3 (7.9%)	0.278*
Any LGE pattern in mid segments	22 (75.9%)	17 (44.7%)	**0.01**
Mid anterior (7)	9 (31.0%)	6 (15.8%)	0.138
Mid anteroseptal (8)	11 (37.9%)	6 (15.8%)	**0.039**
Mid inferoseptal (9)	10 (34.5%)	7 (18.4%)	0.134
Mid inferior (10)	11 (37.9%)	5 (13.2%)	**0.018**
Mid inferolateral (11)	10 (34.5%)	7 (18.4%)	0.134
Mid anterolateral (12)	10 (34.5%)	3 (7.9%)	**0.006**
Any LGE pattern in apical segments	15 (51.7%)	10 (26.3%)	**0.033**
Apical anterior (13)	9 (31.0%)	4 (10.5%)	**0.035**
Apical septal (14)	11 (37.9%)	7 (18.4%)	0.074
Apical inferior (15)	11 (37.9%)	5 (13.2%)	**0.018**
Apical lateral (16)	8 (27.6%)	2 (5.3%)	**0.016***
Apex (17)	3 (10.3%)	1 (2.6%)	0.308*

*The Fisher's exact test (exact significance, 2-sided). Values are presented as number (percentage).

Table 3. Comparison in observed coronary artery disease in coronary angiography and segments with observed late gadolinium enhancement (LGE) according to coronary artery distribution between heart failure (HF) patients with left ventricular ejection fraction (LVEF) ≤ 35% as determined by echocardiography and controls with LVEF > 35%.

Significant coronary artery disease and LGE	Patients with HF and LVEF ≤ 35% (n = 22)	Control patients (n = 14)	P
Significant coronary artery disease presence			
Any coronary artery	14 (63.6%)	5 (35.7%)	0.102
Right coronary artery	10 (45.5%)	3 (21.4%)	0.143
Left circumflex coronary artery	11 (50.0%)	1 (7.1%)	**0.011***
Left anterior descending coronary artery	10 (45.5%)	3 (21.4%)	0.143
In one coronary artery	2 (9.1%)	4 (28.6%)	0.181*
In two coronary arteries	6 (27.3%)	0 (0.0%)	0.062*
In three coronary arteries	6 (27.3%)	1 (7.1%)	0.209*
LGE location by coronary arteries territories			
LGE location in left anterior descending coronary artery territory	15 (68.2%)	5 (35.7%)	0.056
LGE location in right coronary artery territory	15 (68.2%)	8 (57.1%)	0.501
LGE location in left circumflex coronary artery territory	12 (54.5%)	4 (28.6%)	0.126
LGE location in one coronary artery territory	5 (22.7%)	4 (28.6%)	0.712*
LGE location in two coronary arteries territories	5 (22.7%)	5 (35.7%)	0.462*
LGE location in three coronary arteries territories	9 (40.9%)	1 (7.1%)	0.054*

*The Fisher's exact test (exact significance, 2-sided). Data on coronary angiography were available for 36 patients. Values are presented as number (percentage).

Table 4. Differences between patients with and without any observed transmural late gadolinium enhancement (LGE) and between patients with and without any observed transmural LGE in posterolateral left ventricular segments, in heart failure (HF) patients with left ventricular ejection fraction (LVEF) ≤ 35% determined by echocardiography.

Parameters	Transmural LGE present (n = 13)	No transmural LGE (n = 16)	P	Transmural LGE in posterolateral LV segments (n = 9)	No transmural LGE in posterolateral LV segments (n = 20)	P
Demographics and other parameters						
Female	3 (23.1%)	2 (12.5%)	0.632*	1 (11.1%)	4 (20.0%)	1*
Age [years]	60.1 ± 7.6	46.5 ± 15.7	**0.006**	60.6 ± 6.3	49.0 ± 15.6	**0.008**
LVEF determined by echocardiography [%]	24.6 ± 6.9	22.3 ± 7.6	0.405	22.6 ± 7.2	23.7 ± 7.4	0.702
Urgent admission to hospital	11 (84.6%)	7 (43.8%)	0.052*	8 (88.9%)	10 (50.0%)	0.096*
Diseases and risk factors						
CAD	12 (92.3%)	5 (31.3%)	**0.001**	9 (100.0%)	8 (40.0%)	**0.003***
Myocardial infarction	11 (84.6%)	1 (6.3%)	**< 0.001**	7 (77.8%)	5 (25.0%)	**0.014***
Diabetes	2 (15.4%)	4 (25.0%)	0.663*	0 (0.0%)	6 (30.0%)	0.137*
Hypertension	8 (61.5%)	8 (50.0%)	0.534	5 (55.6%)	11 (55.0%)	1*
Dyslipidemia	8 (61.5%)	5 (31.3%)	0.103	5 (55.6%)	8 (40.0%)	0.688*
Smoking	3 (23.1%)	5 (31.3%)	0.697*	2 (22.2%)	6 (30.0%)	1*
Atrial fibrillation	3 (23.1%)	3 (18.8%)	1*	3 (33.3%)	3 (15.0%)	0.339*
CMR parameters						
CMR-LVEF [%]	24.0 (18.3–32.4)	24.8 (20.9–36.1)	0.809	22.8 ± 7.9	29.0 ± 10.4	0.120
CMR-LVEDV [mL]	281.9 ± 124.8	284.0 ± 100.7	0.959	332.5 ± 117.7	260.8 ± 101.6	0.105
CMR-LVESV [mL]	212.0 ± 105.8	205.3 ± 99.7	0.863	256.3 ± 97.7	186.7 ± 96.6	0.085
Akinesia	6 (46.2%)	4 (25.0%)	0.270*	4 (44.4%)	6 (30.0%)	0.675*
Dyskinesia	7 (53.8%)	8 (50.0%)	0.837	5 (55.6%)	10 (50.0%)	1*
Hypokinesia	13 (100.0%)	14 (87.5%)	0.488*	9 (100.0%)	18 (90.0%)	1*
Ischemic LGE pattern only	13 (100.0%)	2 (12.5%)	**< 0.001**	9 (100.0%)	6 (30.0%)	**< 0.001***

*The Fisher's exact test (exact significance, 2-sided). Values are presented as number (percentage). For abbreviations — see Table 1

Patients with LVEF ≤ 35% and observed LGE in any LV segment from the posterolateral wall were older than patients with LVEF ≤ 35% and had no observed LGE in this region (61.5 ± 9.3 vs. 44.3 ± 13.2, p < 0.001). Among patients with LVEF ≤ 35% and observed LGE in any LV segment from the posterolateral wall, CAD was more frequently present than in the remaining patients with LVEF ≤ 35% and no observed LGE in this region (85.7% vs. 33.3%, p = 0.004; Table 5). The ischemic pattern of LGE was more common in patients with LGE in the posterolateral LV wall than in the group without LGE in this region (78.6% vs. 26.7%, p = 0.005). Transmural LGE of any type was observed more commonly in HF patients with LGE in the posterolateral LV wall than in those without LGE in this region (71.4% vs. 20.0%, p = 0.005, Table 5).

Comparison of patients with ischemic vs. non-ischemic pattern of LGE

When patients with an ischemic (n = 24) vs. non-ischemic pattern (n = 26) of LGE were compared, CAD, previous MI, and dyslipidemia were more common in those with the ischemic pattern of LGE (Table 5). Patients with an ischemic pattern of LGE were more commonly admitted urgently to the hospital and had observed akinesia more commonly in CMR (79.2% vs. 46.2%, p = 0.016; 41.7% vs. 15.4%, p = 0.039, Table 5) when compared to patients with a non-ischemic LGE pattern. Interestingly, in all patients with an ischemic pattern of LGE (n = 24), LGE was observed more commonly only in apical segments when compared to patients with a non-ischemic pattern (70.8% vs. 30.8%, p = = 0.005). Moreover, LGE of any pattern in the pos-

Table 5. Differences between patients with and without observed any late gadolinium enhancement (LGE) in posterolateral left ventricular segments in heart failure (HF) patients with left ventricular ejection fraction (LVEF) ≤ 35% as determined by echocardiography and comparison of patients with ischemic and non-ischemic pattern of LGE.

Parameters	LGE in post-erolateral wall (n = 14)	No LGE in post-erolateral wall (n = 15)	P	Ischemic LGE pattern only (n = 24)#	Non-ischemic LGE pattern only (n = 26)#	P
Demographics and other parameters						
Female	1 (7.1%)	4 (26.7%)	0.330*	5 (20.8%)	4 (15.4%)	0.721*
Age [years]	61.5 ± 9.3	44.3 ± 13.2	**< 0.001**	60.0 (53.5–68.0)	38.0 (27.8–57.5)	**0.001**
LVEF determined by echocardiography [%]	21.9 ± 7.5	24.7 ± 7.0	0.294	31.0 (20.8–50.0)	50.0 (23.8–61.3)	0.147
Urgent admission to hospital	10 (71.4%)	8 (53.3%)	0.316	19 (79.2%)	12 (46.2%)	**0.016**
Diseases and risk factors						
CAD	12 (85.7%)	5 (33.3%)	**0.004**	21 (87.5%)	9 (34.6%)	**< 0.001**
Myocardial infarction	8 (57.1%)	4 (26.7%)	0.096	18 (75.0%)	1 (3.8%)	**< 0.001**
Diabetes	4 (28.6%)	2 (13.3%)	0.390*	7 (29.2%)	3 (11.5%)	0.164*
Hypertension	10 (71.4%)	6 (40.0%)	0.089	15 (62.5%)	10 (38.5%)	0.089
Dyslipidemia	8 (57.1%)	5 (33.3%)	0.198	15 (62.5%)	6 (23.1%)	**0.005**
Smoking	3 (21.4%)	5 (33.3%)	0.682*	4 (16.7%)	8 (30.8%)	0.243
Atrial fibrillation	4 (28.6%)	2 (13.3%)	0.390	5 (20.8%)	3 (11.5%)	0.456*
CMR parameters						
CMR-LVEF [%]	24.6 ± 8.0	29.5 ± 11.4	0.194	31.8 ± 12.7	45.5 ± 16.3	**0.002**
CMR-LVEDV [mL]	313.4 ± 113.5	254.8 ±102.4	0.155	214.9 (169.1–322.4)	179.7 (153.3–268.9)	0.236
CMR-LVESV [mL]	229.5 ± 106.5	188.6 ± 94.2	0.283	140.3 (114.6–260.1)	80.8 (61.5–169.0)	**0.011**
Akinesia	7 (50.0%)	3 (20.0%)	0.128*	10 (41.7%)	4 (15.4%)	**0.039**
Dyskinesia	8 (57.1%)	7 (46.7%)	0.573	10 (41.7%)	7 (26.9%)	0.272
Hypokinesia	14 (100.0%)	13 (86.7%)	0.483*	21 (87.5%)	18 (69.2%)	0.119
Any transmural LGE	10 (71.4%)	3 (20.0%)	**0.005**	17 (70.8%)	1 (3.8%)	**< 0.001**
Any transmural LGE in posterolateral LV segment	9 (64.3%)	0 (0.0%)	**< 0.001***	11 (45.8%)	1 (3.8%)	**< 0.001**

#Six patients with both ischemic and non-ischemic or non-specific pattern of LGE and 11 patients with no LGE were excluded from these sub-analyses. *Fisher's exact test (exact significance, 2-sided). Values are presented as number (percentage). For abbreviations see Table 1.

terolateral wall was observed more commonly in patients with an ischemic LGE pattern when compared to patients with a non-ischemic LGE pattern (66.7% vs. 34.6%, p = 0.024). Similarly, transmural LGE, including that in the posterolateral wall, was observed more commonly in the first group when compared to the second group (Table 5). Interestingly, only LVEF measured by CMR, but not by echocardiography, differed between patients with an ischemic and non-ischemic pattern of LGE (31.8 ± ± 12.7 vs. 45.5 ± 16.3, p = 0.002; 31.0 [20.8–50.0] vs. 50.0 [23.8–61.3], p = 0.147, Table 5).

Discussion

Cardiac magnetic resonance is currently the most accurate non-invasive method to evaluate myocardial necrosis and fibrosis, which helps in the identification of the underlying cause of LV dysfunction, and may provide important prognostic information [18–21]. Previous studies have shown the usefulness of CMR imaging qualitative assessment in the diagnostics of CAD [21–23]. It has been suggested that LGE may be useful in excluding significant CAD in some patients with new-onset

LV dysfunction in whom there is no data suggestive of ischemic disease [22]. An analysis of LGE distribution is also valuable when differentiating between non-ischemic etiologies of LV dysfunction including dilated cardiomyopathy, cardiac sarcoidosis, myocarditis, hypertrophic cardiomyopathy, cardiac amyloidosis, and Anderson-Fabry disease [6]. However, it should be highlighted that a LGE pattern is not always specific for a particular disease and the inclusion of clinical information is crucial in the diagnostic process.

Patient-specific coronary supply territories may be derived from magnetic resonance angiography, and these territories sometimes differ from those defined by the AHA model of coronary blood supply, which suggests that the 17-segmented model proposed by the AHA may be inaccurate [12, 24]. A greater prevalence of significant CAD in the LCx and a trend towards more frequent LGE in segments supplied by the LAD in HF patients with LVEF ≤ 35%, have been observed. This highlights the potential discrepancies between coronary territories determined by coronary angiography and the presence of LGE on CMR. Moreover, this study suggests that LVEF as measured in CMR, but not in echocardiography, may be associated with patterns of LGE. Previous studies have shown a strong relationship between myocardial fibrosis and worsening of HF [25–27]. In patients with muscular dystrophy, Florian et al. [28] found a correlation between LVEF and LGE extent and a relationship between the LGE pattern and degree of LV systolic dysfunction. However, several studies involving patients with non-ischemic cardiomyopathy showed only a weak or no relationship between the presence of LGE or LGE volume and LV volume and function [29–32].

LGE-CMR imaging could also be useful in the assessment of patients who are bordeline candidates for CRT since absence of LGE is associated with greater CRT response [10]. Previous studies have found a significant correlation between total scar burden and non-response to CRT, and have proposed a dose–response type relationship in these groups, which may predict this outcome [33, 34]. A recent study including patients with dilated cardiomyopathy and CRT found that CRT-defibrillators provided a survival benefit over CRT-pacemakers only in patients with observed LGE [35]. Moreover, implantation of a LV lead over an area with transmural myocardial scarring may result in an ineffective CRT [10]. Thus, clinical determinants of transmural scarring in posterolateral LV segments were also searched for as its identification may lead to a qualification of patients to other forms of physiologic cardiac pacing, including His or para-His pacing, which would avoid potentially adverse outcomes related to right ventricular pacing [36]. Findings herein, suggest that clinical variables (older age, CAD, and previous MI) are associated with transmural posterolateral LGE.

Cardiovascular risk stratification is important and could be improved by the use of biomarkers or data from Holter electrocardiogram recordings [37–39]. Some studies have demonstrated that the presence of LGE predicts poor clinical outcomes such as hospitalization due to HF, fatal ventricular arrhythmias, and SCD, in patients with either an ischemic or non-ischemic etiology of HF [8, 26, 40–44]. Non-ischemic HF etiology is one of the predictors of LVEF recovery [45]. However, a recently adjusted analysis has shown that major non-ischemic fibrosis was related to worse clinical outcomes than MI [8]. The presence of LGE was found to be associated with appropriate ICD therapy. Among patients with dilated cardiomyopathy and LVEF ≤ 35%, ICD implantation was associated with a reduction in mortality only among those with LGE [9]. Thus, the present study is important as it explores the determinants of LGE presence. It was found that CAD is associated with LGE in HF patients with LVEF ≤ 35%, while previous MI and older age have a tendency to be associated with LGE in these patients. This is in line with observations by other researches who have shown that the presence of LGE was significantly higher in patients with CAD. Moreover, they suggested that CMR is useful for classification of patients with new-onset HF and LV systolic dysfunction in relation to the presence or absence of CAD [22, 23]. LGE-CMR imaging may provide independent prognostic information beyond LVEF. Thus, the analysis of LGE presence and distribution may improve patient selection and scheduling for ICD implantation in primary prevention of SCD. The association between LGE and ventricular arrhythmias was observed both in studies on patients with mean LVEF ≤ 35% and in those with mean LVEF > 35% [43]. Importantly, many SCD occur in patients with LVEF > 35% [46]. Therefore, it may be hypothesized that some patients with prevalent LGE, risk factors for SCD and LVEF > 35% could also benefit from primary SCD prevention with ICD placement.

Limitations of the study

There are some limitations in this study. The current study is a retrospective analysis and in-

cludes a relatively small group of patients. There is potential over-representation of non-ischemic HF etiologies in the present cohort due to typical clinical scenarios in which CMR is most commonly used in clinical practice. Information on coronary angiography results was not available for all patients in their medical documentation. Coronary angiography and CMR were not always performed within few days apart. However, the median time interval between these studies was relatively short at 7 days (IQR 3–24 days). Detailed indications for the use of LGE-CMR before potential cardiovascular implantable electronic devices implantation remain to be established in large prospective studies.

Conclusions

Among HF patients with LVEF of 35% or less, clinical factors, including older age, CAD, and previous MI are associated with transmural LGE in the posterolateral wall, while CAD is associated with LGE. This data may have potential implications for planning ICD and CRT placement procedures.

Conflict of interest: None declared

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The non-invasive evaluation of heart function in patients with an acute myocardial infarction: The role of impedance cardiography

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Abstract

Background: *The purpose of this study was to analyze hemodynamic changes in patients treated with percutaneous coronary intervention (PCI) at an early stage of acute myocardial infarction (AMI) and at 1-month follow-up.*

Methods: *Patients with AMI (n = 27) who underwent PCI were analyzed using impedance cardiography (ICG). ICG data were collected continuously (beat by beat) during the whole PCI procedure and thereafter at every 60 s for the next 24 h. Blood pressure was taken every 10 min and stored for analysis. Additionally the following parameters were measured: cardiac index (CI), stroke volume index (SVi), left cardiac work index (LCWi), contractility index (CTi), ventricular ejection time (VET), systemic vascular resistance index (SVRi), thoracic fluid content index (TFCi) and heart rate (HR).*

Results: *In the first 24 h after PCI all the contractility parameters including CI, SVi, LCWi, CTi and VET significantly decreased, whereas HR, SVRi and TFCi increased compared to baseline. All of the parameters examined got normalized at 1 month. The CI, SVi, LCWi, CTi, SVRi did not significantly differ from baseline, however the HR and VET were significantly lower compared to first day after PCI*

Conclusions: *Cardiac performance deteriorates early after PCI and normalizes after 1 month in patients with an AMI. ICG is useful for hemodynamic monitoring of AMI patients during and after invasive therapy.* (Cardiol J 2021; 28, 1: 77–85)

Key words: impedance cardiography, acute myocardial infarction, hemodynamics, percutaneous coronary intervention

Introduction

Although a commonly used early reperfusion treatment in AMI, by using either thrombolysis or primary percutaneous coronary intervention (PCI) significantly limits myocardial damage, the process of reperfusion itself may induce so called ischemic reperfusion injury (IRI) [1–4]. The pathogenesis of this phenomenon is complex and may be related to myocardial stunning [5], microvascular obstruction [6–8], lethal myocardial reperfusion injury [3] or reperfusion-induced ventricular arrhythmias [9].

Despite significant progress in PCI technology and antiplatelet therapy, the IRI remains an important therapeutic target in patients with AMI. Therefore, it is fundamental to stratify the risk at an early stage of AMI and to evaluate heart function in a real-time manner.

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Recently used monitoring of patient's hemodynamic profile is based mainly on electrocardiographic (ECG) analysis, blood pressure (BP) monitoring and bedside transthoracic echocardiography (TTE). The three-dimensional ultrasonography and magnetic resonance imaging are accurate in the evaluation of myocardial function, but they involve high costs, and require qualified personnel. An invasive heart catheterization with Swan-Ganz does not occur in the guidelines because of its complexity and complication risk. Therefore, in patients requiring intensive care after AMI, non-invasive hemodynamic monitors such as impedance cardiography (ICG) might be an interesting option in the treatment strategy.

The ICG is a non-invasive diagnostic method based on the detection of thoracic electrical bioimpedance across the thorax during systole and diastole of the heart. The ICG allows monitoring of hemodynamic parameters, comprising for instance: stroke volume (SV), cardiac output (CO), systemic vascular resistance (SVR), thoracic fluid content (TFC) and many others.

Transthoracic bio-impedance is a technique, which quantifies mechanical activity of the heart instead of its electrical activity. A fundamental principle of transthoracic bio-impedance is that it uses direct measurement of baseline impedance, ventricular ejection time, heart rate, and early diastolic filling ratio. These parameters are measured and used to compute other hemodynamic parameters.

Application of ICG for the determination of hemodynamic parameters is based on the following principle: different tissues, i.e. muscles, bones, fat and blood have specific electrical properties. Among them, the blood is the most conductive body tissue in the thorax. The differences in thoracic electrical impedance are essentially created by changes in the velocity and blood volume in the aorta.

The clinical use of ICG has been described recently.

In patients after off-pump coronary artery bypass grafting, the findings obtained from ICG were correlated with B-type natriuretic peptide (BNP) levels and TTE measurements for the evaluation of cardiac hemodynamic changes during perioperative period [10].

Louvaris et al. [11] compared concurrent CO measurements captured by ICG (COIC) and by the indocyanine green dye dilution method (CO_{DD}) in patients with chronic obstructive pulmonary disease. They found a strong correlation between CO_{IC} and CO_{DD}. Malek et al. [12] analyzed hemodynamic data obtained from ICG, TTE and gas exchange analysis during rest and exercise among wheelchair rugby players. Their analysis showed a good correlation between the methods, however, interestingly, a CO was overestimated by ICG.

Last but not least, an impaired hemodynamic response to exercise in hypertensive females with dyspnea was proved by ICG [13].

Thus, the aim of the present study was to evaluate the dynamic changes in the hemodynamic profile of patients during an early stage of AMI and at 1-month follow-up.

Methods

Herein, 27 AMI patients were included. The ECG of 20 patients revealed on admission persistent ST-segment elevation myocardial infarction (STEMI) and the other 7 were diagnosed with non-ST-segment elevation myocardial infarction (NSTEMI). All patients underwent urgent coronary catheterization with subsequent PCI.

The ICG was performed with PhysioFlow Q-Link (Manatec Biomedical, Paris, France) and TTE examination was obtained by using Aloka Prosound Alpha 6.

Bioimpednace measurements

The PhysioFlow® Q-LinkTM is a noninvasive hemodynamic evaluation system to assess patient cardiovascular state using analyses of transthoracic bio-impedance signals.

PhysioFlow System measures the change in impedance by injecting a high frequency alternating electrical current (66 kHz) of low magnitude (4.5 mA peak to peak) towards the thorax between two electrodes positioned on the neck and another two positioned on the xiphoid process. The use of a high frequency current eliminates the risk of interference with heart and brain bioelectrical activity.

For measurement at rest the electrodes were placed on the thorax as presented in Figure 1.

Impedance cardiography was initiated in the cathlab just before a coronary catheterization. Four ICG and two ECG pre-gelled electrodes were placed accordingly: two (Z1, Z2) on the left side of patient's neck, one (Z3) at the level of the xiphoid and the last one (Z4) just to the right of Z3. The ICG data were collected continuously (beat by beat) during the whole PCI procedure and later, after PCI, the recorded signal was averaged for each 10 s during the next 24 h automatically. BP was taken each 10 min during PCI and stored for analysis. The following parameters were measured beat-to-beat continuously: cardiac index (CI [l/min/m^2]), stroke volume index (SVi [mL/m^2]), left

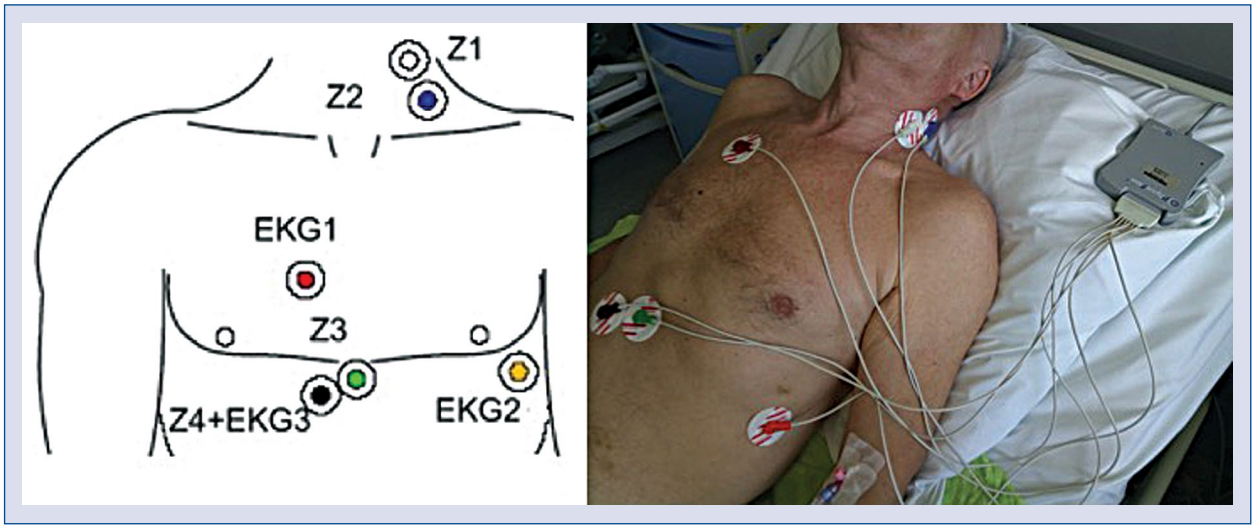

Figure 1. The position current (Z1, Z4) and voltage (Z2, Z3) electrodes on the thorax — scheme and original photo. The electrodes were positioned on the neck, the back at the level of the xiphoid on the left-hand side of the spine, the left-hand side lower ribs and the right clavicle.

Table 1. The clinical and angiographic data of 27 patients with an acute myocardial infarction (MI).

Age [years]	62.3 ± 13.4
Male/female	17/10
BMI [kg/m^2]	27.7 ± 4.8
STEMI/NSTEMI	20/7
Arterial hypertension	14
Diabetes	9
History of previous MI	2
REF-HF	9
History of stroke	4
COPD	4
History of previous PCI	4
LVEF at 1st day	39.4 ± 9.2
LVEF at follow up	52.5 ± 5.4
Infarct related artery:	
LM	2
LAD	11
CX	2
RCA	12
TIMI 3 after PCI	25

BMI — body mass index; STEMI — ST segment elevation myocardial infarction; NSTEMI — non ST segment elevation myocardial infarction; REF-HF — reduced ejection fraction heart failure; COPD — chronic obstructive pulmonary disease; PCI — percutaneous coronary intervention; LVEF — left ventricular ejection fraction; LM — left main coronary artery; LAD — left artery descending artery; CX — circumflex artery; RCA — right coronary artery; TIMI — thrombolysis in myocardial infarction scale

cardiac work index (LCWi [kg·m/m^2]), contractility index (CTi), ventricular ejection time (VET [ms]), systemic vascular resistance index (SVRi [dyn·s/cm^5·m^2]), thoracic fluid content index (TFCi [1/kΩ·m^2]) and heart rate (HR [1/min]). Specific calculations conducted as part of a further analysis were based on the values obtained in the supine position. The quality of all measurements was high, and no relevant errors were noted.

Echocardiographic measurements

The measurements were taken in 24 h after AMI and at the follow-up visit. The examinations were taken as recommended by the European Society of Cardiology and American Heart Association. Patients were imaged in the left lateral decubitus position. Images were obtained in parasternal and apical projections. A left ventricular ejection fraction (LVEF) was determined by using the Simpson method for biplane assessment. All examinations were performed by the same investigator.

Every patient has been scheduled for a followup visit after 30 days in order to perform TTE, clinical examination and ICG hemodynamics was continuous for a 20 min measurement.

Statistical analysis

To test the validity of the data a series of statistical tests were prepared including: the Shapiro-Wilk test and ANOVA statistic. All statistical analysis presented was conducted using Python programming language (v. 3.6.1) and a selection of supporting mathematical packages: NumPy and Pandas for basic mathematical operations,

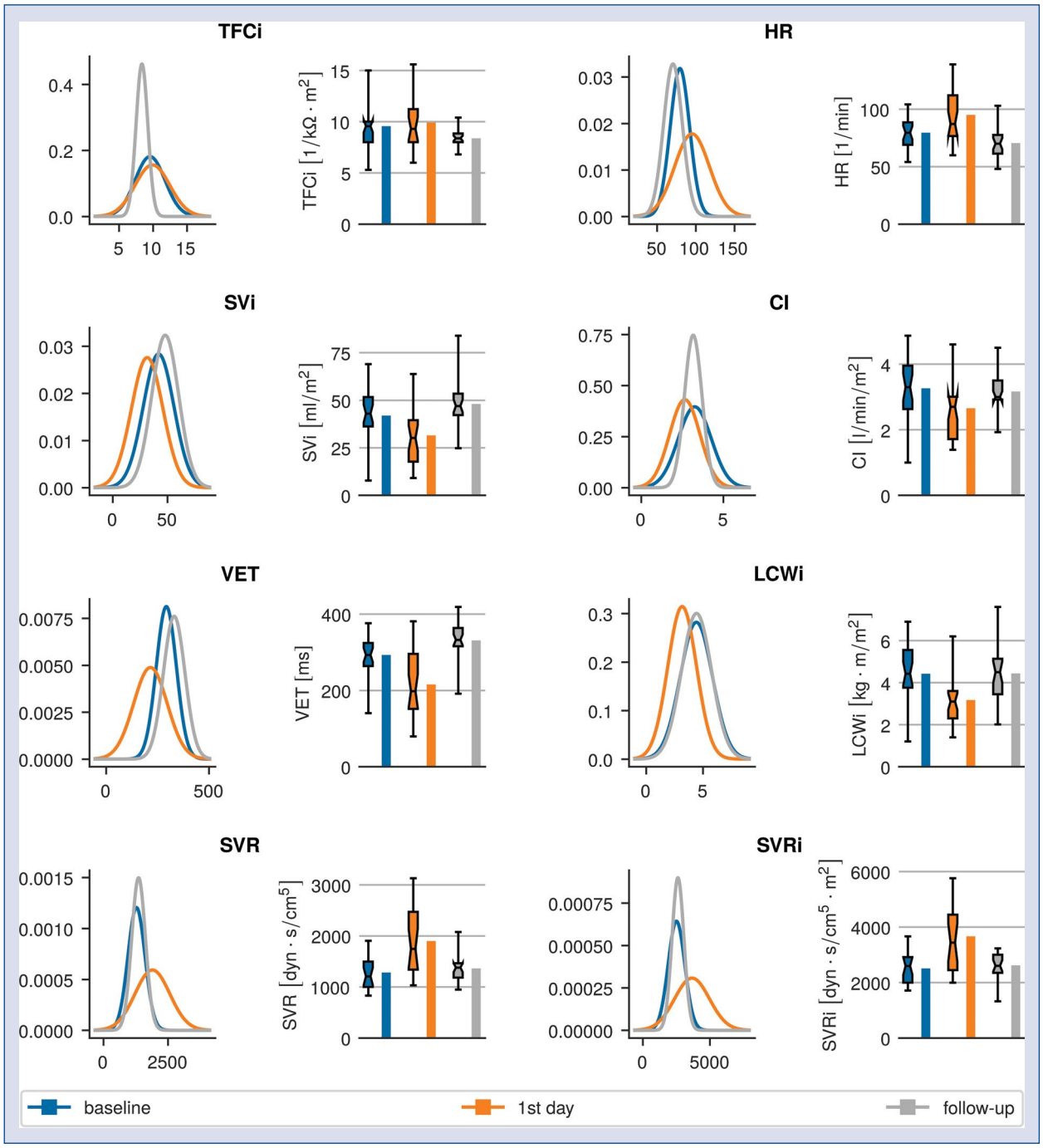

Figure 2. Comparison of hemodynamic parameters in 27 patients with myocardial infarction recorded before percutaneous coronary intervention (PCI) and at 1 and 30 days after PCI; abbreviations — see text.

and SciPy for all relevant statistical computations. Plots were generated using Python programming language (v. 3.6.1) and the Matplotlib package.

Results

In the group observed there were more males than females (Table 1). The majority of patients were hospitalized with STEMI and the most common culprit lesions were right coronary artery or left anterior descending branch. All patients underwent PCI. A good angiographic result (TIMI 3) was achieved in all but two subjects.

The results are presented in Figure 2 and Table 2. On the first day after PCI, a significant decrease in hemodynamic parameters describing heart contractility was observed: CI, LCWi, CTi and VET. The contractility index reflects an amplitude

Table 2. Hemodynamic profile during the early stage of acute myocardial infarction and at the 1-month follow-up in 27 patients.

Parameter	Measurement day	Mean ± SD	P
TFCi [1/kΩ·m^2]	1/ Just before PCI	9.6 ± 2.2	1 vs. 2: p = 0.62
	2/ 1st day after PCI	9.9 ± 2.6	1 vs. 3: p = 0.01
	3/ 30 days after PCI	8.4 ± 0.9	2 vs. 3: p = 0.006
HR [1/min]	1/ Just before PCI	79.5 ± 12.5	1 vs. 2: p = 0.003
	2/ 1st day after PCI	95.1 ± 22.5	1 vs. 3: p = 0.01
	3/ 30 days after PCI	70.5 ± 12.2	2 vs. 3: p = 6.94E-06
SVi [mL/m^2]	1/ Just before PCI	42.0 ± 14.1	1 vs. 2: p = 0.01
	2/ 1st day after PCI	31.5 ± 14.5	1 vs. 3: p = 0.098
	3/ 30 days after PCI	48.0 ± 12.3	2 vs. 3: p =3.75E-05
CI [l/min/m^2]	1/ Just before PCI	3.3 ± 1.0	1 vs. 2: p = 0.025
	2/ 1st day after PCI	2.7 ± 0.9	1 vs. 3: p = 0.669
	3/ 30 days after PCI	3.2 ± 0.5	2 vs. 3: p = 0.016
VET [ms]	1/ Just before PCI	292.9 ± 49.1	1 vs. 2: p = 9.93E-05
	2/ 1st day after PCI	215.6 ± 81.7	1 vs. 3: p = 0.008
	3/ 30 days after PCI	331.0 ± 52.4	2 vs. 3: p = 1.01E-07
LCWi [kg·m/m^2]	1/ Just before PCI	4.4 ± 1.4	1 vs. 2: p = 0.001
	2/ 1st day after PCI	3.2 ± 1.3	1 vs. 3: p = 0.969
	3/ 30 days after PCI	4.4 ± 1.3	2 vs. 3: p = 0.0008
SVRi [dyn·s/cm^5·m^2]	1/ Just before PCI	2506.3 ± 620.4	1 vs. 2: p = 0.02
	2/ 1st day after PCI	3663.7 ± 1296.5	1 vs. 3: p = 0.03
	3/ 30 days after PCI	2616.2 ± 443.8	2 vs. 3: p = 0.02
SVR [dyn·s/cm^5]	1/ Just before PCI	1282.2 ± 331.0	1 vs. 2: p = 0.02
	2/ 1st day after PCI	1899.0 ± 673.8	1 vs. 3: p = 0.03
	3/ 30 days after PCI	1482.8 ± 534.5	2 vs. 3: p = 0.02
SABP [mmHg	1/ Just before PCI	132.5 ± 25.7	1 vs. 2: p = 0.41
	2/ 1st day after PCI	127.0 ± 21.4	1 vs. 3: p = 0.19
	3/ 30 days after PCI	141.7 ± 24.0	2 vs. 3: p = 0.02
DABP [mmHg]	1/ Just before PCI	78.0 ± 14.9	1 vs. 2: p = 0.18
	2/ 1st day after PCI	73.1 ± 10.7	1 vs. 3: p = 0.96
	3/ 30 days after PCI	77.8 ± 10.5	2 vs. 3: p = 0.12
MABP [mmHg]	1/ Just before PCI	101.5 ± 18.6	1 vs. 2: p = 0.24
	2/ 1st day after PCI	96.1 ± 14.0	1 vs. 3: p = 0.48
	3/ 30 days after PCI	104.9 ± 14.6	2 vs. 3: p = 0.03

Hemodynamic parameters measured by impedance cardiography. The p-values are based on the AVOVA test. CI — cardiac index [l/min/m^2]; CO — cardiac output [l/min]; SVRi — systemic vascular resistance index [dyn·s/cm5·m2]; SVR — systemic vascular resistance [dyn·s/cm5]; HR — heart rate [1/min]; SVi — stroke volume index [mL/m2]; LCWi — cardiac work index [kg·m/m2]; VET — ventricular ejection time [ms]; TFCi — thoracic fluid content index [1/kΩ·m2], SABP — systolic arterial blood pressure [mmHg], DABP — diastolic arterial blood pressure [mmHg]; MABP — mean arterial blood pressure [mmHg]

of the first derivative dz/dt was significantly decreased during first day after PCI ($p < 0.002$) and had increased at the time of follow-up ($p < 0.004$).

In contrast, during the same period, an increase in HR and SVRi was noticed during the first day after PCI compared to baseline, but decreased after 1 month (Fig. 1).

At follow-up CI, SVi, LCWi, CTi, SVRi did not differ from baseline. Heart rate decreased and ventricular ejection time was significantly longer compared to the first day after PCI.

The LVEF was significantly higher compared to 24 h after PCI and at follow-up (39.4% ± 9 vs. 52.6% ± 5, $p < 0.01$).

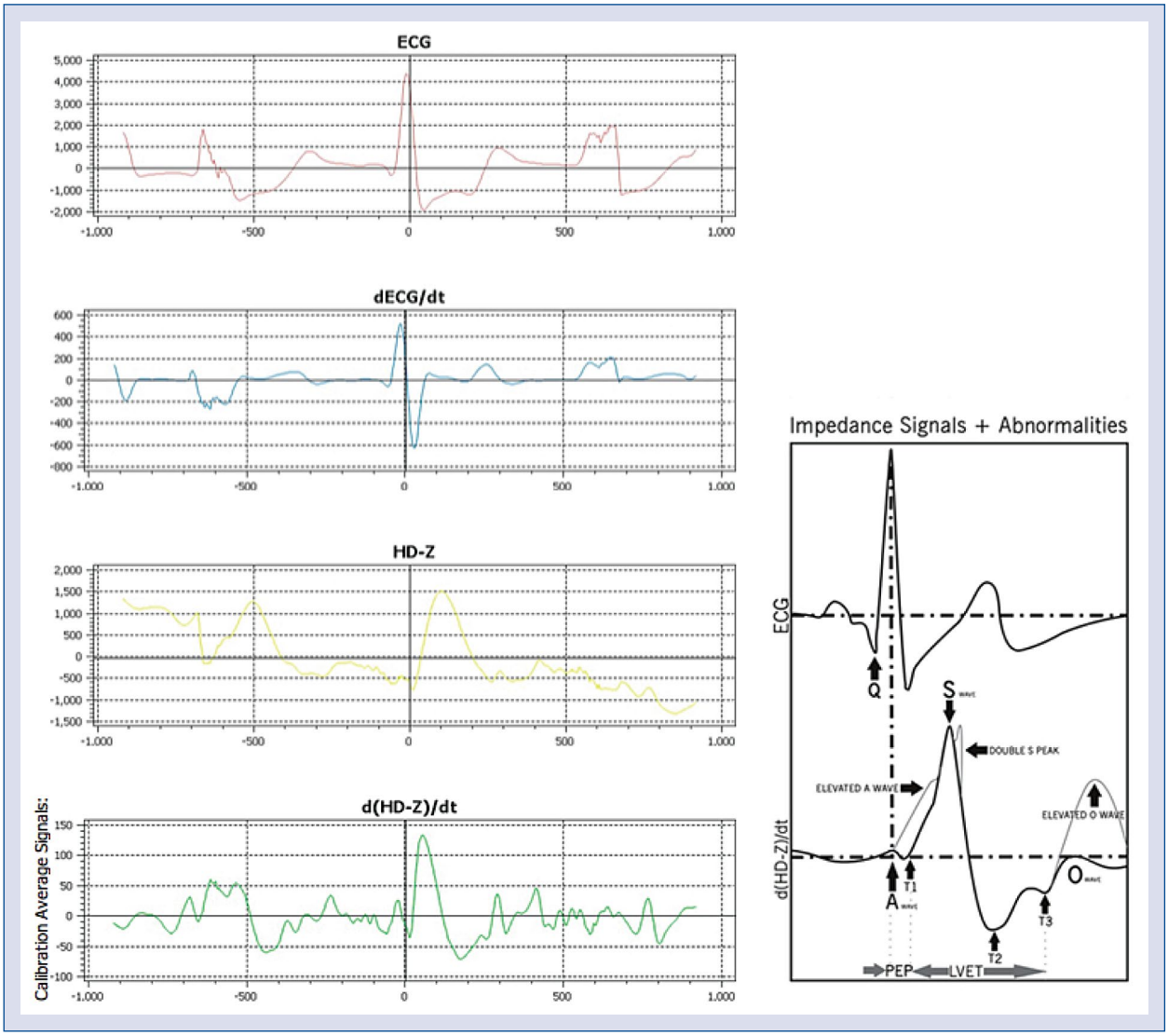

Figure 3. Averaged electrocardiogram and impedance signal in a patient during percutaneous coronary intervention.

The examples of averaged electrocardiogram and impedance signals are presented in Figures 3, 4 and 5.

Discussion

In this single-center study changes were analyzed in the hemodynamic profile of AMI patients by using ICG. Although a good correlation between impedance diagnostics and invasive assessment of cardiac output and systemic vascular resistance has been reported [10, 11], thus far, data is mostly limited to heart failure [12–19] and with only a few AMI subsets examined [20–22].

Herewith, despite an early and successful primary PCI this study presents that, a contractility of a myocardium did not improve immediately and, interestingly, it became worse during the first day. This observation was followed by an increase in systemic vascular resistance and HR, which could be explained as a compensatory reaction for maintaining cardiac output in consideration of decreased cardiac contractility. Chen et al. [23] observed that HR and BP significantly decreased 7 days after primary PCI, whereas other ICG parameters remained unchanged in an AMI setting. In contrast to the present findings, that were focused on the very early stage of AMI, including the first hours after PCI — in a study by Chen et al. [23], the authors might have overlooked the early changes.

The observed transient hemodynamic deterioration may appear as a consequence of "myocar-

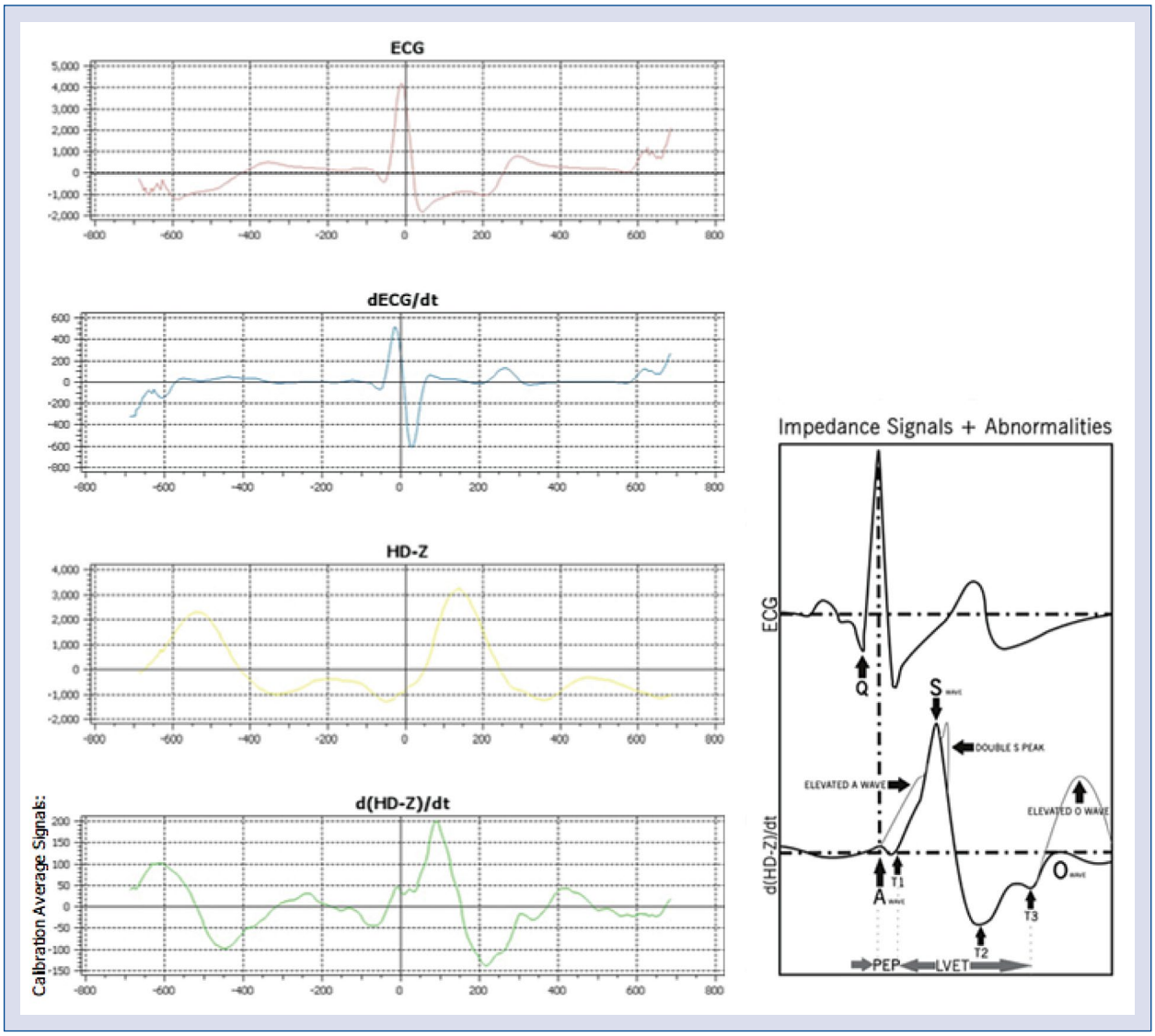

Figure 4. Averaged electrocardiogram and impedance signal in a patient after percutaneous coronary intervention.

dial stunning". This phenomenon is described as a reversible post-ischemic contractile dysfunction, one of the forms of IRI. All parameters that characterized myocardial contractility returned to a normal range after 1 month, which corresponds to the reversible nature of myocardial stunning.

Decreased HR at follow up vs. baseline could be explained either by contractility improvement, or as well as by beta-blockers routinely included in treatment.

The TFCi that reflects thoracic fluid content, significantly decreased at follow-up in comparison to baseline. The transient elevation of this parameter observed on the first day, post PCI, may be related to common in-hospital fluid overload: contrast agent, intravenous saline etc. Malfatto et al. [24] showed good correlation between the TFC and an increased pulmonary capillary wedge pressure. The higher TFCi may also reflect an exacerbation of left ventricle failure. In another analysis, Sadauskas et al. [16] found a moderately strong relationship between BNP and TFCI.

The pathogenesis of IRI is still not completely understood. Several mechanisms have been proposed: Ca2+ overload, oxidative stress or inflammatory response [1, 23].

As IRI is a serious clinical problem among AMI patients, it requires detailed monitoring of the hemodynamics during hospitalization on intensive coronary care units (ICCU). ICG seems to be an easy and useful method for precise monitoring of patients with AMI on ICCU. Herewith, is reported a detailed pattern of changes in ICG hemodynamic

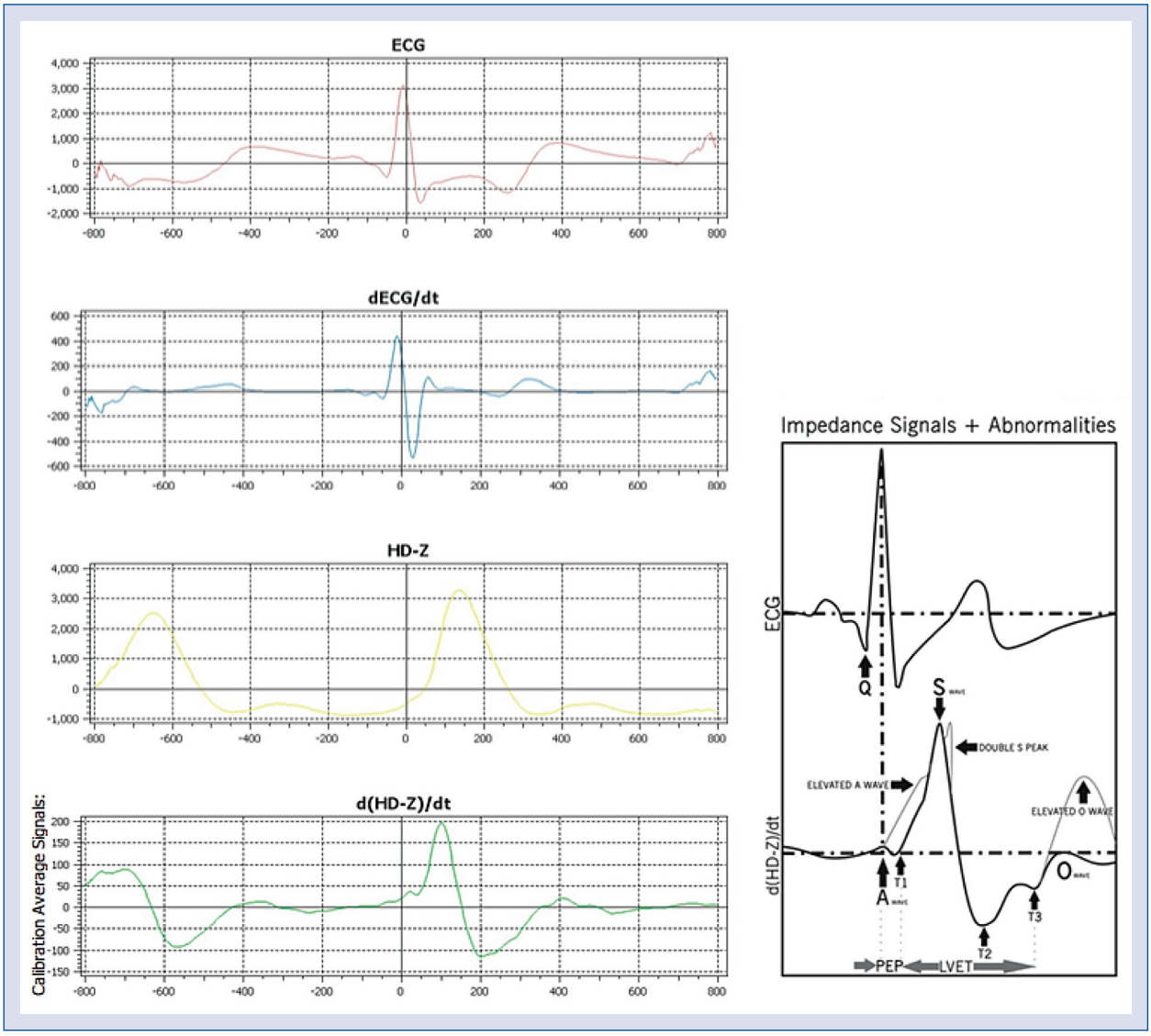

Figure 5. Averaged electrocardiogram and impedance signal in a patient 30 days after percutaneous coronary intervention.

profile of patients early after PCI and at 30 day follow-up. This method is potentially helpful in modifying intensive therapy with fluids or inotropes in clinical routine.

Conclusions

Despite a successful PCI, cardiac contractility deteriorates early after PCI and normalizes after one month in AMI patients.

Impedance cardiography is useful for non-invasive hemodynamic monitoring in ICCU patients, providing an optimal hemodynamic profile and a better understanding of myocardial stunning processes.

Conflict of interest: None declared

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Short and long-term results of endoscopic atraumatic coronary artery off-pump bypass grafting in patients with left anterior descending artery stenosis

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Abstract

Background: *To perform a retrospective analysis of patients who underwent endoscopic atraumatic coronary artery off-pump bypass grafting (EACAB) in a single center over a period of 11 years.*

Methods: *Data was acquired from the hospital registry and patient medical records. In order to determine changes in clinical profile, patients were subdivided into three groups regarding year of surgery: 1998–2002 (group 1), 2003–2005 (group 2), 2006–2009 (group 3). In-hospital analysis up to 30 days and long-term observation were conducted.*

Results: *The study cohort consisted of 714 patients (581 male). Procedural success accounted for 99% of all patients. No mortality was observed up to 30 days. Complications in the early period included pleural effusion (7.6%), cardiac arrhythmias (3.6%), bleeding related revision (2.7%) and wound infection (1.6%). Mean follow-up was 6 years (2132 ± 1313 days; median: 1918.5). Nineteen (2.7%) patients died, of which 52.6% (10 patients) were due to heart related conditions. Overall frequency of major adverse cerebral and cardiovascular events (MACCE) was 10.8% (77 patients). The Kaplan-Meyer analysis defined survival rate and event-free survival in long-term observation of 96.1% and 85.3%, respectively. Ejection fraction (EF) < 50% was the only independent factor of mortality (OR: 3.35). Regarding cumulative MACCE, older age (OR: 1.72), lower EF (OR: 3.03), the history of percutaneous coronary intervention (OR: 2.13) and higher New York Heart Association class (OR: 2.63) influenced the incidence rate.*

Conclusions: *The presented short and very long-term results confirm that EACAB is an efficient alternative for patients requiring revascularization of the left anterior descending artery. The elimination of cardiopulmonary bypass significantly reduces the number of complications.* (Cardiol J 2021; 28, 1: 86–94)

Key words: endoscopic atraumatic coronary artery off-pump bypass grafting (EACAB), minimally invasive surgery, left anterior descending coronary artery stenosis, minimally invasive direct coronary artery bypass grafting (MIDCAB)

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Introduction

Percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are widely used revascularization techniques [1]. In a selected group of patients, minimally invasive direct coronary artery bypass grafting (MIDCAB) may be used as an alternative treatment. MIDCAB comprises high efficacy of surgical revascularization combined with a minimal traumatic approach due to the use of anterolateral thoracotomy or endoscopy (endoscopic atraumatic coronary artery bypass grafting [EACAB]) for left internal mammary artery (LITA) harvest and anterolateral thoracotomy for suturing the anastomosis. It results in the avoidance of sternotomy, reduction of wound diameter, improved healing and faster recovery [2, 3]. Current guidelines for the use of MIDCAB are limited. The procedure is most widely applied in the single vessel disease of the left anterior descending coronary artery (LAD), as a hybrid procedure (along with stenting of other vessels in patients treated for multi-vessel disease), in patients unable to undergo the complete CABG revascularization and as a palliative therapy in patients with in-stent restenosis [3, 4]. Studies have proven the efficacy and safety of the MIDCAB procedure in comparison to both CABG and PCI [5–8]. It is estimated that MIDCAB may be indicated in 2–8% of patients primarily qualified for CABG. This highlights the need for further investigation in order to increase usage of this method. Most available studies addressing MIDCAB lack long-term observation conducted on a large study cohort. Therefore, a retrospective analysis was performed on patients who underwent the procedure in the documented clinic over a period of 11 years. The aim was to collect for the longest possible follow-up and to determine changes in a surgically treated population whose characteristics were revealed over time.

Methods

Study population

The study cohort consisted of patients who underwent MIDCAB (EACAB) surgery in First Cardiac Surgery Clinic of Medical University of Silesia from April 1998 through December 2009. To determine the changes in clinical profiles, patients were subdivided into three groups depending on their year of surgery: 1998–2002 (group 1), 2003––2005 (group 2), 2006–2009 (group 3). Retrospective analysis was performed with the use of data acquired from hospital registry and patient medical records. Pre-admission data, such as age, gender, Canadian Cardiovascular Society (CCS) class, New York Heart Association (NYHA) class, body mass index and others were used to calculate the additive EuroSCORE (ES) and logistic EuroSCORE (LES). Arrhythmias and conduction disorders were diagnosed on the basis of an electrocardiogram (ECG).

The surgical technique

General anesthesia was induced. The double-lumen endotracheal tube was introduced to ensure single lung ventilation throughout the procedure. The harmonic blade and endoscopic manipulators were used for the LITA harvest. When the harvest was completed, heparin was given in a dose adequate to the patient's weight. The incision was made in the fourth or fifth intercostal space and LITA-LAD anastomosis was sutured in a standard technique on the beating heart, with the use of cardiac stabilizer. The protamine sulphate was administered after completion of the anastomosis.

The primary and secondary endpoints

The primary endpoint was major adverse cerebral and cardio-vascular event (MACCE) incidence throughout the observation period. The MACCE was defined as: death, myocardial infarction (MI), repeat cardiac revascularization (both surgical or percutaneous), stroke or transient ischemic attack (TIA). The secondary endpoint consisted of post-operative renal insufficiency, hemorrhage and prolonged hospitalization. The MI was diagnosed in accordance to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, based on ECG changes, the levels of cardiac enzymes and the evaluation of the cardiac contractility with transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE). Neurological disorders were diagnosed with the use of imaging modalities (computed tomography scan) and physical examination conducted by a qualified neurologist.

Peri-procedural observation

In-hospital analysis consisted of peri-procedural parameters assessment, observation focused on both primary and secondary endpoints, as well as the incidence of other possible complications at the time of surgery and throughout the subsequent 30 days.

Long-term observation

Long-term observation encompassed an evaluation of post hospital mortality and occurrence

of MACCE. Patients with incomplete in-hospital data were excluded from analysis. Follow up was gathered via telephone survey by qualified study coordinators. When telephone contact was not possible, mail was sent to the patients' address with a request to mail back a questionnaire to be filled in and, if available, printed history cards from other hospitalizations. Information regarding mortality was confirmed owing to access to the Polish central population registry database called PESEL.

Statistical analysis

Statistical analysis was performed using Statistica 7.1 software by a qualified statistician. Differences between groups were assessed with the Student t-test and variation analysis for quantitative variables and with an χ^2 or the Fisher test for qualitative variables. The cumulative survival rate was described using the Kaplan-Meier estimator plot. Factors influencing MACCE incidence were typed using log-rank analysis. For the proper interpretation of differences and correlations, statistical significance parameter was $p < 0.05$.

Results

Study population

The study cohort consisted of 714 patients (581 male, 133 female). There were 238 patients in group 1 (33.3%), 229 patients in group 2 (32.1%) and 247 patients in group 3 (34.6%). Detailed study cohort characterizations are shown in Table 1. The majority of patients presented with good left ventricular ejection fraction (LVEF) > 50% within average of 55%, had mild angina (CCS II: 86.1%) and preserved heart function (NYHA I: 91.8%). Therefore, they remained in a group of low surgical risk, which was reflected both in additive and logistic EuroSCORE (values of ES < 3 points in 68.7% of patients and values of LES: 2.0 ± 1.9%).

Peri-procedural observation

Ninety-nine percent of patients successfully underwent MIDCAB (EACAB) procedure. In 1% of cases (7 procedures) the conversion to OPCAB (4 patients) or CABG (3 patients) were required. Only 9.5% of surgeries were urgent (due to exacerbation of angina symptoms or critical LAD stenosis), the remaining were planned. All patients underwent LAD grafting. Most of them (99.5%) received left internal thoracic artery graft. In 0.5% of cases the use of LITA was impossible due to damage made to the vessel. Incomplete revascularization (patients requiring further percutaneous

Table 1. Study cohort characterization.

Variable	Value
Age [years]	57.9 ± 9.7 (57.0; 51–65)
Body weight [kg]	74.6 ± 16.1 (75.5; 64.5–85)
Height [m]	1.70 ± 0.08 (1.71; 1.64–1.76)
BMI [kg/m²] — Mean	27.6 ± 3.8 (27.6; 25.5–29.4)
BMI ≥ 25 kg/m²	75.2%
CCS class — Mean	2.0 ± 0.37 (2.0; 2–2)
1	6.8%
2	86.1%
3/4	7.1%
NYHA class — Mean	1.1 ± 0.27 (1.0; 1–1)
I	91.8%
II	8.2%
III/IV	–
Arterial hypertension	51.5%
Diabetes	13.9%
MI in history	39.8%
PCI in history	24.6%
Dyslipidemia	57.4%
Nicotinism	79%
Renal insufficiency	1%
Peptic ulcer disease in history	1.5%
Peripheral artery disease	2%
Stroke/TIA in history	0.8%
Thyroid disease	1.8%
COPD	2.8%
EuroSCORE [points] — Mean	1.88 ± 1.87 (2.0; 0–3)
0–2	68.7%
3–5	28.6%
> 5	2.7%
Logistic EuroSCORE [%]	2.0 ±1.9 (1.33; 0.88–2.36)
Ejection fraction [%] — Mean	54.7 ± 7.4 (55; 50–60)
> 50%	74.2%
30–50%	25.6%
< 30%	0.2%
Valvular disease	
MVI +/++	3%
TVI +/++	0.3%

BMI — body mass index; CCS — Canadian Cardiovascular Society; COPD — chronic obstructive pulmonary disease; MI — myocardial infarction; MVI — mitral valve insufficiency; NYHA — New York Heart Association; PCI — percutaneous coronary intervention; TIA — transient ischemic attack; TVI — tricuspid valve insufficiency

treatment) was observed in 1% of patients. The complete post-op drainage amounted 593.2 ± ± 509.5 mL on average (median [Mdn]: 425, interquartile range [IQR]: 260–720).

No deaths were observed for up to 30 days after the surgery. Complications in the early post-operative period were rare and included pleural effusion (7.0%), cardiac arrhythmias (3.6%), bleeding related revision (2.7%) and wound infection (1.6%). Transfusion of red cell concentrate, frozen plasma and platelet concentrate was required in 5%, 4,7% and 0.6% of patients, respectively. The average stay in the post-operative ward was 2 ± 0.7 days (Mdn: 2, IQR: 2–2) with an overall hospital stay of 7 ± ± 1.2 days (Mdn: 7, IQR: 6–8). Detailed information about observed complications is listed in Table 2.

Clinical profile changes

Similar to the trend observed in cardiac surgery in general, patients undergoing the procedure in subsequent years were increasingly older and suffered from more concomitant diseases (Table 3). The reported difference in age was 3 and 6 years between groups 1 vs. 2 and 1 vs. 3, respectively ($p < 0.01$). Other statistically significant differences included body weight (with peak value reported in group 2; $p < 0.01$), presence of arterial hypertension ($p < 0.01$), diabetes ($p < 0.01$), peptic ulcer disease ($p < 0.01$), past episodes of MI ($p = 0.03$), history of stroke/TIA ($p = 0.02$), history of PCI ($p < 0.01$) and renal insufficiency ($p = 0.03$). Patients qualified for the surgery were also more frequently diagnosed as having mitral ($p < 0.01$) or tricuspid valve regurgitation ($p < 0.04$) concomitantly. What was understandable, all of this translated into a rise in EuroSCORE value, both additive (from 1.11 ± 1.12 in group 1 to 2.11 ± ± 1.95 in group 3) and logistic (1.12 ± 0.75 to 2.26 ± 2 24). Despite visible changes, this difference appeared to be statistically insignificant, reaching $p = 0.06$. Interestingly, no variations were reported in the LVEF. In following years, the median LVEF was stable and amounted to 55% ($p = 0.13$).

The urgency of procedures evolved over time. In group 1 all patients were admitted for planned surgery, whereas in group 2 and 3 the amount diminished to 95.8% and 78.5%, respectively, giving rise to ones conducted due to urgent causes. What is more, the analysis of in-hospital complications showed that MI ($p < 0.01$) and sudden cardiac arrest ($p = 0.01$) were more likely to happen in early years. No other variations were reported in frequency of complications, as well as in hospital stay duration (Table 4).

Table 2. Periprocedural complications (up to 30 days).

Type of complication	Frequency
Death	0%
Left ventricular insufficiency	0.1%
Sudden cardiac arrest	0.6%
Myocardial infarction	1.5%
IABP	0.4%
Inotropic support:	
Aggregate	1.3%
Epinephrine	0.3%
Norepinephrine	1.0%
Dopamine	1.0%
Arrhythmias (AF/SVT)	3.6%
Conduction disorders	0%
Stroke/TIA	0.2%
Acute kidney injury	0%
Acute lower limb ischemia	0%
Prolonged ventilation (> 48 h)	0.1%
Reintubation	0.1%
Gastrointestinal bleeding	0.1%
Delirium	0.6%
Multi organ failure	0.1%
Systemic infection	0%
Wound infection	1.6%
Pleural effusion	7.0%
Chest revision surgery	2.7%

AF — atrial fibrillation; IABP — intra-aortic balloon pump; SVT — supraventricular tachycardia; TIA — transient ischemic attack

Long-term observation

The average follow-up time was almost 6 years (2132 ± 1313 days; Mdn: 1918.5) with the longest spanning up to 13 years (4661 days). Nineteen (2.7%) patients died during observation period, of whom 52.6% (10 patients) due to heart related conditions. Overall frequency of MACCE was 10.8% (77 patients). The most frequent complication was the need for repeat revascularization in 50 (7%) patients with angioplasty of LIMA-LAD graft being responsible for 38% of cases (19/50). It was followed by MI in 2.4% (17 patients) of cases and stroke or TIA in 1% (7) of patients. The Kaplan-Meyer analysis defined survival rate and event-free survival in long-term observation of 96.1% and 85.3%, respectively (Figs. 1, 2). Detailed analysis revealed that LVEF < 50% was the only independent factor of mortality (odds ratio [OR]: 3.35). Age > 57, history of PCI and higher NYHA class were on

Table 3. Clinical profile changes.

Variable	Group 1 (1998–2002)	Group 2 (2003–2005)	Group 3 (2006–2009)	P
Male sex	84.9%	74.5%	79.8%	0.15
Age [years]	55.1 ± 9.6	58.5 ± 9.6	59.9 ± 9.2	0.001
Body weight [kg]	71.9 ± 16.4	81.6 ± 14.1	79.8 ± 13.3	0.001
Height [m]	1.72 ± 8.2	1.71 ± 8.4	1.7 ± 7.4	0.68
BMI [kg/m^2]	25.1 ± 4.1	27.8 ± 3.6	27.5 ± 4.1	0.51
≥ 25 kg/m^2	58%	79%	78%	0.42
CCS class:	1.98 ± 0.33	2.01 ± 0.41	2.02 ± 0.39	0.59
1	6.5%	7.5%	6.5%	0.57
2	88.8%	84.1%	85%	
3/4	4.7%	8.4%	8.5%	
NYHA class:	1.04 ± 0.19	1.13 ± 0.34	1.08 ± 0.28	0.11
I	96.2%	86.9%	91.6%	0.05
II	3.8%	13.1%	8.4%	
EuroSCORE [points]:	1.11 ± 1.12	1.51 ± 1.69	2.11 ± 1.95	0.06
0–2	72.5%	68.7%	64.2%	0.03
3–5	26%	28.5%	32.5%	
> 5	1.5%	2.8%	3.3%	
Logistic EuroSCORE [%]	1.12 ± 0.75	1.53 ± 0.89	2.26 ± 2.24	0.06
Ejection fraction [%]:	55.8 ± 8.0	54.2 ± 6.6	54.2 ± 7.2	0.13
> 50%	76.2%	73.8%	75.1%	0.61
30–50%	23.7%	26%	24.7%	
< 30%	0.1%	0.2%	0.2%	
Valvular disease:				
MVI +/++	0	4.2%	5.8%	0.001
TVI +/++	0	0	1.3%	0.04
Arterial hypertension	45.2%	49.5%	69%	0.001
Diabetes	9.5%	14%	18.9%	0.005
MI in history	35.3%	38.9%	44.9%	0.03
PCI in history	11%	29.7%	33.1%	0.001
Dyslipidemia	53%	62%	57.4%	0.32
Nicotinism	75%	80%	78%	0.56
Renal insufficiency	0.4%	0	2.4%	0.03
Peptic ulcer disease in history	0	1.4%	3.4%	0.004
Peripheral artery disease	2.2%	0	3.8%	0.24
Stroke/TIA in history	0	0.4%	1.9%	0.02
Thyroid disease	0.8%	1.4%	3.3%	0.05
Chronic obstructive pulmonary disease	1.3%	4.2%	2.8%	0.21

BMI — body mass index; CCS — Canadian Cardiovascular Society; MI — myocardial infarction; MVI — mitral valve insufficiency; NYHA — New York Heart Association; PCI — percutaneous coronary intervention; TIA — transient ischemic attack; TVI — tricuspid valve insufficiency

the edge of statistical significance. Regarding cumulative MACCE, older age (OR: 1.72), lower LVEF (OR: 3.03), the history of PCI (OR: 2.13) and higher NYHA class (OR: 2.63) influenced the incidence rate. The risk of MI rose with the presence of lower LVEF (OR: 3.56) and incomplete revascularization (OR: 6.58), whereas risk of stroke/TIA was greater when the patient was over 57 years old (OR: 6.30). Other important, but not statistically significant, factors were the presence of arterial hypertension and male sex. Detailed information is shown in Table 5.

Table 4. Periprocedural complications (up to 30 days) with subgroup analysis.

Type of complication	Group 1 (1998–2002)	Group 2 (2003–2005)	Group 3 (2006–2009)	P*	Mean aggregate
Death	0	0	0	–	**0%**
Left ventricular insufficiency	0.4%	0	0	0.21	**0.1%**
Sudden cardiac arrest	1.7%	0	0	0.01	**0.6%**
Myocardial infarction	4.2%	0.4%	0	0.001	**1.5%**
IABP	0.4%	0	0	0.47	**0.4%**
Inotropic support:					
1.5%	0.8%	0.6%	0.11	0.11	**1.3%**
0.4%	0	0	0.21	0.21	**0.3%**
1.8%	0	0.8%	0.14	0.14	**1.0%**
1.5%	1%	0	0.21	0.21	**1.0%**
Arrhythmias (AF/SVT)	4.2%	3.1%	3.6%	0.74	**3.6%**
Conduction disorders	0	0	0	–	**0%**
Stroke/TIA	0	0	0.8%	0.09	**0.2%**
Acute kidney injury	0	0	0	–	**0%**
Acute lower limb ischemia	0	0	0	–	**0%**
Prolonged ventilation (> 48 h)	0.4%	0	0	0.21	**0.1%**
Reintubation	0	0	0.4%	0.21	**0.1%**
Gastrointestinal bleeding	0.4%	0	0	0.21	**0.1%**
Delirium	0.4%	0.9%	0.4%	0.97	**0.6%**
Multi organ failure	0	0	0.4%	0.21	**0.1%**
Systemic infection	0	0	0	–	**0%**
Wound infection	1.7%	1.7%	1.2%	0.31	**1.6%**
Pleural effusion	5.8%	7.5%	6%	0.94	**7.0%**
Chest revision surgery	3.4%	3.5%	1.2%	0.14	**2.7%**

*Statistical significance defined as $p < 0.05$; AF — atrial fibrillation; IABP — intra-aortic balloon pump; SVT — supraventricular tachycardia TIA — transient ischemic attack

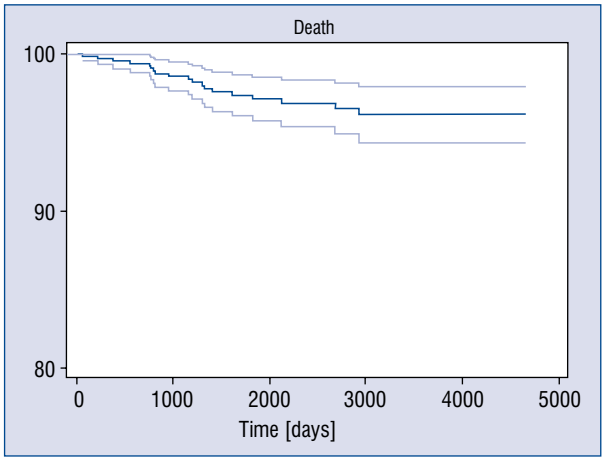

Figure 1. Kaplan-Mayer survival rate of 96.1%.

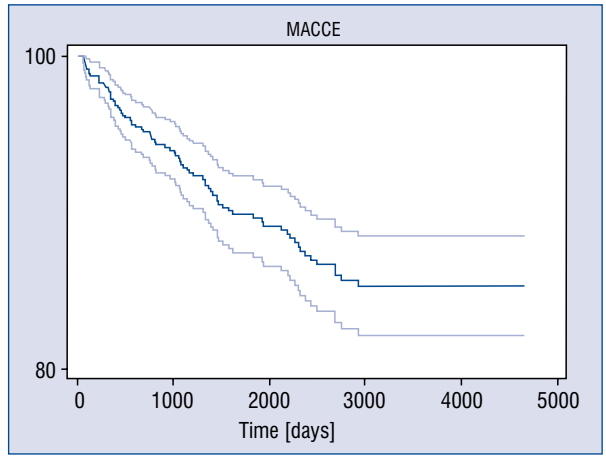

Figure 2. Major adverse cerebral and cardiovascular events (MACCE) — free survival of 85.3%.

Table 5. Major adverse cerebral and cardiovascular events (MACCE) risk factors analysis in very long-term observation.

	MACCE	Death	MI	RE-PCI	Stroke/TIA
Male sex	1.17 (0.62–2.16) p = 0.72	0 (0–1.13) p = 0.15	1.35 (0.37–4.55) p = 0.83	1.42 (0.68–2.91) p = 0.41	**3.33** (0.58–17.81) p = 0.24
Age > 57 years	**1.72 (1.03–2.86) p = 0.02**	**2.29** (0.88–6.83) p = 0.08	0.92 (0.32–2.62) p = 0.94	1.47 (0.79–2.73) p = 0.25	**6.30 (0.75–139) p = 0.05**
EF < 50%	**3.03 (1.49–6.25) p = 0.001**	**3.55 (1.03–11.59 p = 0.03**	**3.56 (1.49–20.6) p = 0.005**	0.49 (0.19–1.31) p = 0.18	**3.76** (0.47–24.55) p = 0.10
Diabetes	1.45 (0.72–2.88) p = 0.34	1.98 (0.53–6.72) p = 0.40	1.49 (0.33–5.70) p = 0.79	1.32 (0.55–3.07) p = 0.64	1.0 (0.98–1.03) p = 0.69
Arterial hypertension	1.05 (0.63–1.77) p = 0.95	1.02 (0.36–2.95) p = 0.84	1.31 (0.45–3.86) p = 0.76	0.79 (0.42–1.48) p = 0.52	**4.60** (0.52–104) p = 0.12
Incomplete revascularization	**3.30** (0.44–19.64) p = 0.37	0 (0–32.03) p = 0.44	**6.58 (1–109.1) p = 0.05**	2.18 (0.80–3.47) p = 0.46	0 (0–107.67) p = 0.79
PCI in history	**2.13 (1.28–3.54) p = 0.002**	**2.15** (0.79–5.82) p = 0.09	**2.70** (0.94–7.80) p = 0.06	**2.11 (1.14–3.91) p = 0.01**	1.76 (0.31–9.38) p = 0.73
MI in history	0.89 (0.52–1.53) p = 0.76	1.12 (0.38–3.25) p = 0.98	1.83 (0.64–5.28) p = 0.32	0.73 (0.37–1.44) p = 0.42	0.32 (0.01–2.79) p = 0.49
CCS class 3–4 vs. 1–2	1.02 (0.34–2.83) p = 0.97	1.0 (0.95–1.05) p = 0.87	1.0 (0.95–1.05) p = 0.87	0.92 (0.22–3.28) p = 0.86	0 (0–13.14) p = 0.88
NYHA class II vs. I	**2.63 (1.15–5.93) p = 0.01**	**3.12** (0.88–12.33) p = 0.08	**3.12** (0.88–12.33) p = 0.08	1.32 (0.38–4.12) p = 0.83	0 (0–13.38) p = 0.87
Urgent surgery	0.47 (0.11–1.60) p = 0.28	1.45 (0–6.82) p = 0.95	0.99 (0.96–1.03) p = 0.84	0 (0–2.13) p = 0.27	0 (0–9.78) p = 0.96

CCS — Canadian Cardiovascular Society; EF — ejection fraction; MI — myocardial infarction; NYHA — New York Heart Association; PCI — percutaneous coronary intervention; TIA — transient ischemic attack

Discussion

The MIDCAB surgery, along with all of its variations, is a well-established procedure in many cardiothoracic centers. Although PCI procedures have become increasingly effective over the last decades, both AHA/ACC and the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) guidelines underline the role of surgical revascularization in patients with stable angina and single vessel coronary heart disease with proximal LAD stenosis (IIA/B indication in AHA/ACC guidelines and IA indication in ESC/EACTS guidelines) [4, 9–10]. Furthermore, in a recent (2017) ACC report regarding the appropriate use of revascularization criteria, there was no discussion about possible changes in indications for surgical treatment in these cases [10].

The main purpose of the present research was to evaluate the short and long-term results of minimally invasive direct coronary artery bypass performed in patients operated on in the documented clinic in years between 1998 and 2009. Moreover, changes in the clinical profiles of the treated population happening over these years were analyzed.

The research showed that clinical characteristics of patients deteriorated, making treatment more challenging. Simultaneously, the frequency of complications was significantly reduced. This potential paradox can work as a confirmation of analysis which is well-described in the literature, a learning curve phenomenon, and meaning reduction in the number of complications due to excelling of surgical techniques and operator skills.

Research presented herein displays one of the biggest and longest observed groups of patients undergoing MIDCAB surgery. Mean follow-up amounted to 2132 ± 1313 days (Mdn: 1918.5, longest follow-up 4661 days). In the assessed time interval, frequency of MACCE was 10.8%, with a death rate of 2.7% and a need for revascularization of 7%. Bearing in mind the evaluated cumulative survival rate and event free survival of 96.9% and 85.3%, respectively, indicates an optimal therapeutic effect.

As mentioned before, there are few studies regarding long-term observation after MIDCAB surgery. Holzhey et al. [11] reported long-term

follow-up of more than 1300 patients with a death rate of 10.6% and cumulative MACCE 16.7% in 7-year observation. Hoffman et al. [12] presented his observation in an octogenarian group with a median survival rate of 6.7 years, which correlates well with the mean survival after CABG [13, 14] and with an age-adjusted general population. This study clearly demonstrated that the method provides satisfactory long-term outcomes, regardless of patient age group.

Blazek et al. [15] compared sirolimus-eluting stenting with minimally invasive bypass surgery for stenosis of the LAD. Although the groups were relatively small (65 patients each), the authors described excellent survival at median follow-up time of 7.3 years (17% death rate in the MIDCAB group) and a clear superiority of surgical revascularization in terms of repeat target vessel revascularization (20% vs. 1.5%, $p < 0.01$). Similarly, Benedetto et al. [6] made a propensity score analysis of 303 MIDCAB and 730 DES-PCI patients. They proved, that at 10 years DES-PCI was associated with a 2.19--fold increased risk of late death [6]. The survival rate after the MIDCAB procedure was 95.4 ± 1.3 and 94.8 ± 1.3 at 5 and at 10 years, respectively. Deppe et al. [16] performed meta-analysis of 2885 patients included in 12 studies. In all analyzed reports, patients were assigned to either PCI or MIDCAB group. The authors point out that MIDCAB reduces repeat target vessel revascularization of the LAD and cumulative MACCE in long-term observation. It is noted that the incidence of MACCEs after PCI had almost doubled for the entire population after 6 months, which suggests that MIDCAB is an excellent strategy when long-term clinical outcome is required.

Finally, in the retrospective analysis performed, this study compared exclusive use of DES with MIDCAB in 463 consecutive patients. After adjustment at 5-year follow-up there were no differences in survival, MACCE free survival and MI survival between PCI and MIDCAB, respectively. However, there was a significantly higher freedom from repeated revascularization in patients who underwent MIDCAB [17].

It was considered essential to underline that this report is different from most studies as it refers to long-term follow up after minimally invasive surgical revascularization. The majority of large-group observations, including the Holzhey analysis of more than 1300 patients, which represented mainly or exclusively cases of direct vision LITA harvest. This makes the present observation quite unique and results seem to be even more valuable. The direct vision LITA harvesting may be associated with the risk of kinking, not to mention the necessity of costal resection or tough chest wall retraction. Furthermore, the endoscopy allows a complete dissection of the LITA from the subclavian artery to the sixth intercostal branches with transection of all collateral branches originating from LITA. This result is difficult to acquire under direct vision. In consequence, mastering the endoscopic LITA harvest ensures the avoidance of possible coronary steal syndrome [18, 19]. Sabashnikov et al. [20] reported results of a team experienced in performing minimally invasive surgical revascularization in its various dimensions. They concluded that the endoscopic approach (EACAB) for LITA harvest is free from the disadvantages of longer operation duration observed in robotically assisted direct coronary artery bypass grafting (RADCAB) or higher incidence of angina and shorter freedom from MACEs observed in both MIDCAB and RADCAB groups [20]. This fact clearly demonstrates that both high quality anastomosis and perfect LITA harvest remain essential for satisfactory clinical outcome.

Limitations of the study

An inability to collect follow-up from approximately 25% of patients is a significant limitation of this research. However, the data obtained from the national registry database PESEL was crucial to the current study, as it allowed gathering of 100% follow-up regarding overall mortality. Additionally, the utilized method of data collection does not provide absolute certainty on whether renewed revascularization targeted the previously treated vessel or one of other coronary arteries. This information is vital for the proper evaluation of MIDCAB efficacy and can only be achieved through thorough evaluation of follow-up angiograms.

Conclusions

The presented short and long-term results confirm that MIDCAB (EACAB) is an efficacious alternative for patients requiring revascularization of the left anterior descending artery. The method is highly beneficial for the patient as it eliminates the use of cardiopulmonary bypass and avoids the sternotomy, which are both related to a number of complications widely described in the literature. The frequency of MACCE is low and acceptable, similar to a general population. However, it is to be remembered that the proper selection of patients in terms of both surgical risk and anatomical set-

ting of presented coronary artery lesions remains essential.

Conflict of interest: None declared

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Predicting survival in out-of-hospital cardiac arrest patients undergoing targeted temperature management: The Polish Hypothermia Registry Risk Score

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Abstract

Background: *Prompt reperfusion and post-resuscitation care, including targeted temperature management (TTM), improve survival in out-of-hospital cardiac arrest (OHCA) patients. To predict in-hospital mortality in OHCA patients treated with TTM, the Polish Hypothermia Registry Risk Score (PHR-RS) was developed. The use of dedicated risk stratification tools may support treatment decisions.*

Methods: *Three hundred seventy-six OHCA patients who underwent TTM between 2012 and 2016 were retrospectively analysed and whose data were collected in the Polish Hypothermia Registry. A multivariate logistic regression model identified a set of predictors of in-hospital mortality that were used to develop a dedicated risk prediction model, which was tested for accuracy.*

Results: *The mean age of the studied population was 59.2 ± 12.9 years. 80% of patients were male, 73.8% had shockable rhythms, and mean time from cardiac arrest (CA) to cardiopulmonary resuscitation (CPR) was 7.2 ± 8.6 min. The inputs for PHR-RS were patient age and score according to the Mild Therapeutic Hypothermia (MTH) Scale. Criteria for the MTH score consisted of time from CA to CPR above 10 min, time from CA to the return of spontaneous circulation above 20 min, in-hospital CA, unwitnessed CA, and non-shockable rhythm, each counted as 1 point. The predictive value of PHR-RS was expressed as an area under the curve of 0.74.*

Conclusions: *PHR-RS is one of the simplest and easiest models to use and enables a reliable prediction of in-hospital mortality in OHCA patients treated with TTM.* (Cardiol J 2021; 28, 1: 95–100)

Key words: targeted temperature management, temperature control, post-resuscitation care, risk prediction model

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Introduction

It is estimated that each year one in 3000 individuals will suffer from out-of-hospital cardiac arrest (OHCA). Despite the implementation of an emergency system with rapid ambulance dispatch, standardization of resuscitation, advanced life support, access to prompt invasive reperfusion techniques and post-resuscitation care including targeted temperature management (TTM), the discharge survival rate among OHCA patients is barely 24% [1]. Besides TTM, other time- and resource-consuming techniques, which have shown survival benefit in selected patients, can be implemented during an intensive care unit (ICU) stay. This increasing number of treatment options with preventive potential, together with limited resources, force physicians to make choices based on subjective judgments and available general ICU risk estimation tools. Although there are several scoring tools to evaluate in-hospital mortality risk of post-cardiac arrest (CA) patients admitted to ICU, were developed before TTM became widely used. Thus, their predictive value in actively cooled OHCA patients is limited [2, 3]. In order to support physicians and optimize treatment decisions in this cohort of patients, a dedicated risk score is needed. Therefore, the aim of this research project was to develop a risk prediction model for the in-hospital mortality of post-CA patients treated with TTM.

Methods

Study design and study population

The clinical data of 376 patients who underwent TTM between 2012 and 2016 and were collected in the Polish Hypothermia Registry were retrospectively analysed. The Polish Hypothermia Registry is a project initiated by the Polish Society of Cardiology and coordinated by the Medical University of Warsaw, Poland. The study was approved by the local Bioethics Committee. The nature of the registry required all centers to enter clinical data of patients prospectively and anonymously, using a web-based secured panel connected to a central database. There were no specific exclusion criteria, and all patients who received TTM (n = 376) were included in the analysis. The collected data included demographic information and peri-event information, including time to cardiopulmonary resuscitation (CPR), time to return of spontaneous circulation (ROSC), presence of witnesses, comorbidities, Glasgow Coma Scale (GCS) score, index diagnosis, need for percutaneous coronary intervention (PCI), use of early cooling, type of stationary cooling technique, incidence of shock at each time-point throughout the in-hospital course, duration of cooling, complications, early outcome, duration of hospital stay, and clinical and neurological outcome at discharge.

Definitions and standard care procedures

All participating centres used a dedicated TTM protocol (**Suppl. Appendix 1**). Any patient admitted due to OHCA who met the inclusion criteria (ROSC, GCS below 8 points, time from CPR below 4 h) was qualified for TTM. The survivors were assessed using the Mild Therapeutic Hypothermia (MTH) Scale which was developed to identify patients at increased risk of TTM-associated adverse events. It consists of 5 elements, each counted as 1 point (Table 1). To exclude intracerebral bleeding if suspected, a brain computed tomography (CT) scan was performed. All patients in whom a cardiac cause of CA was suspected underwent a coronary angiogram followed by PCI if indicated. The first cooling phase was initiated simultaneously with PCI using intravenous cool fluids and continued with stationary cooling systems (surface or endovascular) in the ICU. The targeted temperature of 32–36°C was maintained for 24–36 h. After rewarming and extubating, patients who remained hemodynamically stable were transferred to the general ward.

Statistical analysis and identification of predictors

The statistical analysis was conducted with IBM SPSS Statistics 24. Continuous variables with a normal distribution are expressed as the mean ± standard deviation (SD) and those with a skewed distribution as the median with interquartile range (IQR). Categorical variables are presented as absolute values and percentages. The Wilcoxon signed-rank test was used to compare pairs of related samples, and the Pearson correlation coefficient was used for continuous variables. The adequacy of the analysed variables was assessed by fitting corresponding models and investigating the area under the receiver operating characteristic (ROC) curve (AUC). All tests were 2-sided, and the level of significance was set at 0.05.

Results

Group characteristics

Three hundred seventy-six post-CA patients treated with TTM were included in the study. Most

Table 1. Mild Therapeutic Hypothermia score.

Variable	Value
Cardiac arrest to CPR above 10 min	+ 1 point
Time from cardiac arrest to ROSC above 20 min	+ 1 point
In-hospital cardiac arrest	+ 1 point
Unwitnessed cardiac arrest	+ 1 point
Non-shockable rhythm	+ 1 point

CPR — cardiopulmonary resuscitation; ROSC — return of spontaneous circulation

of them were men (n = 301; 80.1%; p < 0.001). The mean age of the studied population was 59.2 ± 12.9 years. One out of 5 patients had a history of myocardial infarction (n = 78; 20.7%), and almost half of the group suffered from hypertension (n = 166; 44.1%; p < 0.05). Other comorbidities are listed in Table 2.

Characteristics of OHCA

Most of the CAs were witnessed (n = 268; 77.7%; p < 0.001). The initial rhythm in most of the patients was ventricular fibrillation or pulseless ventricular tachycardia (73.8%). In more than half of the CA patients, CPR was initiated by paramedics (60.7%; p < 0.05). The mean time from CA to CPR was 7.2 ± 8.6 min and from CA to ROSC 30.2 ± 57.3 min. Almost half of the CA survivors had a Glasgow Coma Scale (GCS) of 3 after the ROSC (n = 147; 49.5%) and at the time of admission to hospital (n = = 161; 47.4%). Twenty-one percent of survivors were in cardiogenic shock. The pre-cooling body temperature was 36.3 ± 0.7°C. In almost half of the patients, the time from CA to ROSC was greater than 20 min (44.9%; p < 0.05), and in 26.5% the CA to CPR time was greater than 10 min. CA was not witnessed in 22.3% of patients. Non-shockable rhythm was initially registered in 20.8% of patients. One in 10 (11.4%) patients experienced in-hospital CA.

Almost half of the patients scored 1 point in the MTH Scale (p < 0.001). Only 1 patient scored 5 points (0.4%). Details are shown in Table 3.

Mortality

In-hospital mortality was 18.6% (70 patients). Most deaths occurred after completion of the TTM procedure (53 out of 70 patients; 75.7%), mainly due to multiorgan failure secondary to cardiac shock. The average time between admission and death was 15 days (range: 1–156 days).

Table 2. Clinical characteristics on admission (n = 376).

Variable	Number (%)
Gender (male)	301 (80.1%)
Hypertension	166 (44.1%)
Past MI	78 (20.1%)
Diabetes mellitus	64 (17.0%)
Renal failure	22 (5.9%)
History of stroke	13 (3.5%)
Anemia	8 (2.3%)
First rhythm of SCA:	
VF/VT	277 (73.8%)
Asystole	74 (19.6%)
PEA	25 (6.5%)
Time to CPR [min]	7.2
Time to ROSC [min]	30.2
Diagnosis on admission:	
STEMI	167 (47.2)
NSTEMI	96 (25.5)
CAD	12 (3.3)
DCM	90 (24.0)
HCM	11 (3.0)
GSC scale:	
3 points	179 (47.4)
4–6 points	156 (41.6)
7–8 points	41 (11.0)
Temperature on admission [°C]	35.9
Cardiogenic shock	79 (21.0%)
Primary PCI	303 (80.6%)
Brain CT scan	168 (44.7%)
Precooling with cold saline	287 (76.2%)
Volume of cold saline for precooling [mL]:	
< 1000	13 (4.6%)
1000	88 (30.5%)
1500	90 (31.4%)
2000	71 (24.7%)
> 2500	25 (8.8%)
Time form ROSC do precooling [min]	124.3
Cooling technique:	
Intravascular	88 (23.4%)
Surface cooling	288 (76.6%)

CAD — coronary artery disease; CPR — cardiopulmonary resuscitation; CT — computed tomography; DCM — dilated cardiomyopathy; GCS — Glasgow Coma Scale; HCM — hypertrophic cardiomyopathy; MI — myocardial infarction; NSTEMI — non-ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention; PEA — pulseless electrical activity; ROSC — return of spontaneous circulation; SCA — sudden cardiac arrest; STEMI — ST-segment elevation myocardial infarction; VF — ventricular fibrillation; VT — ventricular tachycardia

Table 3. Distribution of Mild Therapeutic Hypothermia (MTH) score in the registry.

MTH Scale score	N	Percent
1	120	45.6%
2	103	39.2%
3	34	12.9%
4	4	1.9%
5	1	0.4%

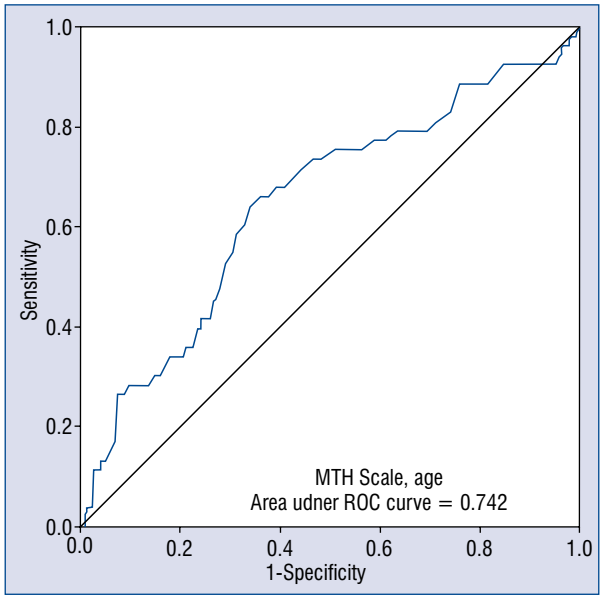

Figure 1. Predictive value of the Polish Hypothermia Registry Risk Score for prognosis of in-hospital mortality in post-cardiac arrest patients treated with targeted temperature management, expressed by the receiver operating characteristic (ROC) curve; MTH — Mild Therapeutic Hypothermia.

Predictive value of the Polish Hypothermia Registry Risk Score

Based on the results of the multivariate logistic regression model, a set of potential predictors of in-hospital mortality was identified. The greatest predictive values were confirmed for age and MTH scale score. To simplify the use of these predictors, a dedicated risk score was constructed and named the Polish Hypothermia Registry Risk Score (PHR-RS). The PHR-RS was calculated with the following equation: [(age [years] × 0.003) + (score in MTH Scale × 0.11) – 0.25] × 100%.

The predictive value of PHR-RS was expressed by an AUC of 0.74, and it was the same after adding sex to the equation (Fig. 1).

Discussion

In this study, we described a simple model predicting a high probability of in-hospital death in patients after OHCA treated with TTM. The inputs of our model were the patient's age and MTH scale score, which includes time to CPR, time to ROSC, in-hospital localization of CA, whether the CA was witnessed or not, and whether the first rhythm was shockable. To the best of our knowledge, this is the first study to propose a scale enabling the prediction of the probability of in-hospital mortality in patients after OHCA with sufficient strength. Its use does not require any biochemical data or data from patient medical history and is based mainly on information from OHCA and CPR. There is a need for prognostic tools in this very demanding group of patients to help in decision-making about an escalation of medical treatment. PHR-RS may provide reliable data about patient in-hospital mortality risk, which would be useful when providing the information to patient family members.

Most studies on prediction factors in OHCA survivors date back to an era before the common use of TTM. In a meta-analysis of 79 studies involving 142, 740 patients after OHCA, the pooled survival rate to hospital discharge was 7.6% and failed to improve significantly despite technological advances. This meta-analysis included studies carried out between 1950 and 2008, when TTM was not commonly used. The influence of TTM was not evaluated, but the authors reported that patients with witnessed OHCA, ventricular fibrillation/ventricular tachycardia (VF/VT), and in whom ROSC was achieved, had a greater chance of being discharged from the hospital [4]. Early CPR/defibrillation performed by a by-stander or members of a medical team, CA occurrence outside the home, the presence of initial shockable rhythms, and quick ROSC were shown to be better prognostic factors in several other studies [5–8]. Wibrandt et al. [6] reported that VT/VF as initial rhythm, the cardiac etiology of OHCA and time to ROSC < 20 min were strong predictors of both survival and favourable neurological outcomes. In a recent Polish study on pre-hospital death predictors in OHCA victims, Gach et al. [9] reported that univariate analysis indicated 6 predictors of death: OHCA without witnesses, OHCA in a public place, no bystander CPR, no bystander cardiac massage, initial diagnosis of non-shockable cardiac rhythm and the amount of drugs used for CPR. However, logistic regression confirmed that only the lack of bystander cardiac massage and non-shockable

rhythm were independent determinants of prehospital death [9]. Among other recent reports, Aldhoon et al. [10] examined the factors affecting 1-month outcomes in 46 OHCA survivors treated with hypothermia. In this study, patients eventually discharged in good neurological condition were younger and had lower lactate level on admission. In addition, the underlying cause of CA was acute myocardial infarction [10].

The data on the influence of sex on survival are conflicting, with some studies reporting better survival in women [5, 11], another in men [12], and in some no difference between the sexes was observed [13, 14]. The literature is lacking in studies evaluating how comorbidities influence survival. Only Fabbri et al. [15] reported that no history of hypertension, diabetes, myocardial infarction, or congestive heart failure were positive outcome predictors after OHCA. It is known that lactate level [10] and pH [8] are important in terms of survival prognosis after OHCA. Whittaker et al. [8] used a multivariate logistic regression analysis to demonstrate that an initial pH ≤ 7.1, among other factors, was a predictor of in-hospital mortality after OHCA. Aldhoon et al. [10] showed that OHCA survivors who underwent TTM with a favourable outcome had lower lactate levels on admission and after 24 h of hospital treatment. The level of acidosis is often interpreted as a measurement of the length and adequacy of CPR, increasingly more studies emphasize the importance of this parameter [16]. The present model did not include biochemical parameters because the aim was to create a quick and easy to use scale that could be calculated in the emergency room even prior to obtaining blood test results. The main limitation of the present study is a lack of external validation of the proposed risk score. An international registry would allow for the confirmation of the predictive value in a multinational patient population treated according to various local protocols. Also, bias related to the relative weight of each center and the unbalanced distribution of the TTM procedure could not excluded. However, all centers used one standardised TTM protocol. Furthermore, there was a relatively small group of patients included in the study. Finally, the MTH score was assigned based on expert opinions and has never been validated by any clinical data set.

Krawczyk et al. [17] emphasised the need for discussion and education when they reported that the TTM procedure in Polish ICUs is underused. The most common limitations include a lack of dedicated devices, logistical issues and a misunderstanding or misinterpretation of published evidence. Herein, is hypothesized that the PHR-RS, as a simple predictive model, may help in TTM implementation.

Another issue is the neurological prognostication in post-CA survivors. The SPAME trial revealed that most large university hospitals in Europe had a standard operating protocol for TTM. However, only a minority used a standard operating protocol for neurological prognostication, giving electroencephalography and brain CT scans the highest priority [18]. PHR-RS was not evaluated as a neurological prognostication tool.

Conclusions

The PHR-RS is a simple tool that may be useful in the prediction of the in-hospital mortality in OHCA patients treated with TTM. The PHR-RS was created based on the multicenter register and includes age and MTH score.

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Usefulness of transesophageal echocardiography before cardioversion in atrial arrhythmias

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Abstract

Background: *Although many thromboembolism risk factors are well defined, formation of thrombus or dense spontaneous contrast (sludge) in the left atrium remains enigmatic and confounding. Exclusion of the thrombus is extremely important with respect to planned reversal of sinus rhythm. Data regarding the routine transesophagal echocardiography (TEE) before cardioversion are inconclusive. The authors focused on analyzing the usefulness of TEE before cardioversion by assessment of factors influencing the risk of thrombus and/or dense spontaneous echo contrast with the intention of extending indications for TEE in the group with a high risk of thrombus or to forgo TEE in the low risk group.*

Methods: *Two hundred sixty-nine consecutive patients with persistent (> 48 h) atrial fibrillation or atrial flutter, in whom a direct current cardioversion was planned, were undergoing TEE for the detection of the left atrial thrombus or dense spontaneous echo contrast. Additional clinical and echocardiographic data were collected. The relationship between both thrombus and dense spontaneous echo contrast and covariates was analyzed with the use of binary logistic regression.*

Results: *Left atrium (LA) appendage (LAA) thrombus and/or sludge were detected in 79 (29%) patients. Signs of dementia in mini-mental state examination (hazard ratio [HR]: 1.16; p = 0.005), low velocities in LAA (HR: 3.38; p = 0.032); presence of spontaneous echo contrast in LA (HR: 3.38; p = 0,003) consecutive episode of AF (HR: 2.27; p = 0,046); longer duration of atrial fibrillation (HR: 1.009; p = 0.022); were significant predictors of thrombus and/or dense spontaneous echo contrast. None of the patients with a CHA_2DS_2VASc score ≤ 1 had thrombus or sludge in the LAA. Among patients with a CHA_2DS_2VASc score > 1, the prevalence of thrombus or sludge in LAA was independent of the CHA_2DS_2VASc score value.*

Conclusions: *Amongst many factors, including an established as risk for thromboembolism only a few of them increased the risk for the presence of thrombus in LAA: low velocities in LAA, presence of spontaneous echo contrast, longer duration of arrhythmia, consecutive (not first) arrhythmia episode and signs of dementia from a mini-mental state examination questionnaire. It was believed that there could be a need for an extension of indications of TEE in vast majority of the patients with atrial arrhythmias, due most often to an unpredictable occurrence of thrombus and potentially disastrous thromboembolism. The only exception could have been the group of the patients with a CHA_2DS_2VASc score ≤ 1.* (Cardiol J 2021; 28, 1: 101–109)

Key words: left atrial appendage thrombus, sludge, atrial fibrillation, atrial flutter, cardioversion, transesophagal echocardiography

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Introduction

Cerebral stroke and other thromboembolic events caused by thrombus with the source in the left atrial appendage (LAA) in patients with atrial fibrillation (AF) and atrial flutter (AFl) might be the most serious complications after cardioversion. In subjects with AF, the thrombus in LAA has been recognized as a robust independent risk factor for stroke [1–3] and stands as an absolute contraindication to cardioversion. The presence of dense spontaneous echo contrast, commonly called sludge, has also been proved to be associated with high embolic risk [4, 5] and all-cause mortality [4]. For this reason, thrombus and sludge were recognized as equally dangerous.

An established way to prevent severe outcomes of cardioversion is the administration of anticoagulants for at least 3 weeks prior to the procedure [6–10].

Nevertheless, there are many patients diagnosed with presence of thrombus or sludge in the LAA despite proper anticoagulation [11, 12]. Transesophageal echocardiography (TEE) has been stated as an imaging technique for exclusion or confirmation thrombus and/or dense spontaneous echo contrast in the LAA [1, 2, 13, 14]. In the group of patients planned for cardioversion it was recommended as a guide, especially in inadequately anticoagulated patients [1, 2, 9, 10]. An unstable state of patients with inappropriate anticoagulation is also a stated indication for TEE before cardioversion in AF or AFl [8, 15]. Except for the above-mentioned clinical conditions, guidelines do not commit the present operators to perform TEE routinely before cardioversion, the decision for this is usually made on the assumption that the expected risk of thromboembolic complications was higher. Therefore, an unresolved issue still remains in question: to do, or not to do TEE routinely before cardioversion?

Methods

Two hundred sixty-nine consecutive patients from two medical centers (St. Vincent Hospital in Gdynia, Poland and First Department of Cardiology, Medical University of Gdansk, Poland) were prospectively enrolled from January 2016 to June 2017. In this group of patients direct current cardioversion was planned due to persistent AF or AFl. Exclusion criteria for the study were: arrhythmia shorter than 48 h, contraindications to TEE and lack of consent. All patients included underwent TEE and transthoracic echocardiography (TTE). Ultrasound scanners (GE, Vivid S70, Horten, Norway) equipped with a 1.5–4.6 MHz transducer and a 3–8 MHz omniplane phase probe were used. The detailed questionnaire regarding state of health was also performed and laboratory blood samples were collected at the day of TEE. The Bioethics Committee of Medical University of Gdansk approved the study.

In cases which confirm both LAA thrombus and sludge, a decision against reversal of sinus rhythm are stated. Further procedures for these patients were made individually, depending on the clinical state of the patient and previous treatment.

Clinical, demographic, echocardiographic and social data were collected: sex, age, body mass index (BMI), CHA_2DS_2VASc score, co-morbidities, mini-mental state examination (MMSE) questionnaire, information regarding type and durance of anticoagulation, data of arrhythmia episode, medical history including smoking, healthcare quality, level of activity and self-reliance; laboratory tests including hematology, creatinine, international normalized ratio (INR), activated partial thromboplastin time (aPTT), TTE with automated 2-dimensional measurements of left ventricular ejection fraction (LVEF), presence or absence of increased filling pressure according the recommendation of European Association of Cardiovascular Imaging: $E/e' > 11$, mitral deceleration time < 150 ms, isovolumetric relaxation time < 65 ms, tricuspid regurgitation with $Vmax > 2.8$ m/s, left atrial size measurements. In the TEE there was precise scanning of LAA at angles: 30/60/90/120 degrees and transgastric 2-chamber 90 degrees with careful adjustment of gain and frequency in search of thrombus and dense spontaneous echo contrast (sludge) [16]. The LAA early diastolic emptying velocity was also measured. Sludge was defined, as already described in the literature, as an intracavitary echodensity with viscid gelatinous qualities giving the impression of impending precipitation but without a discrete organized mass [17]. There were also other TEE assessments: significant valvular pathology, presence of any spontaneous echo contrast (recognized as dynamic, swirling, smoke-like echoes), analysis of LAA velocities and aortic plaque [3, 18]. Both TEE and TTE were performed and analyzed by two certified echocardiographers (K.K. and M.F.).

Statistical analysis

Univariate analysis revealed differences between groups of patients with or with-

out thrombus or/and dense spontaneous echo contrast in LAA and enabled for identification of appropriate covariates for inclusion in a binary logistic regression model. Continuous variables like CHA_2DS_2VASc and MMSE questionnaire results or duration of arrhythmia were analyzed for normality and compared using the Student t test. Evaluation of the categorical variables was performed using the χ^2 test. Pearson correlation coefficients were used to reveal correlations.

A priori alfa level was 0.05 and values resulting in $p < 0.05$ were statistically significant.

A multivariate logistic regression analysis was performed (with the backward likelihood ratio method and p for stepwise removal > 0.10). A p value of less than 0.05 was considered significant. Computations were performed using the Statistica version 13.1.

On the basis of results of the univariate analysis, the following variables were entered into the multivariate model: arrhythmia duration, first vs. consecutive episode, left atrium enlargement, spontaneous echo contrast, LAA velocities, non-vitamin K oral anticoagulants (NOACs) therapy, anticoagulation interruption, MMSE scoring, symptoms of heart failure, mitral stenosis, CHA_2DS_2VASc scoring.

Results

The clinical and echocardiographic characteristics of patients with and without LAA thrombi/ /sludge are shown in Table 1. Patients with LAA thrombi were more often experienced in AF/AFl (not first episode), had longer duration of arrhythmia, larger left atrium, presence of spontaneous echo contrast, lower LAA early diastolic emptying velocity, increased left ventricle filling pressures, were treated less often with non-NOACs but more often with vitamin-K antagonists (VKA), had declared inappropriate anticoagulation. Analyzing the MMSE score, they more often had a result typical of dementia, more often had symptoms of heart failure and higher scores in CHA_2DS_2VASc than those without LAA thrombi.

Thrombus and/or sludge resulting in withdrawal from cardioversion was diagnosed in 79 of 269 (29%) patients (Fig. 1).

243 patients of the whole study group (90%) were treated with anticoagulant. The risk of the LAA thrombus and/or dense spontaneous echo contrast in patients treated with VKA (with good therapeutic-time-ratio) was higher: 37% patients on VKA therapy had had thrombus vs. 25% in the group of patients treated with other anticoagulants; hazard ratio [HR]: 1.62. NOAC therapy in a corresponding analysis was superior to other forms of treatment (HR: 0.52), but the result was not confirmed in multivariate analysis. CHA_2DS_2VASc was significantly higher in the group of patients with thrombus and/or dense spontaneous echo contrast (mean 5 vs. 4) in univariate analysis but surprisingly in multivariate analysis, this factor was not significant. Of note, none of the 16 patients with CHA_2DS_2VASc 0 or 1 had thrombus or sludge in LAA (Fig. 2).

Another startling finding was that thrombus occurred less often in a group of untreated patients or patients treated for shorter than 3 weeks. Thrombus or/and dense spontaneous echo contrast was diagnosed in 8 (14%) patients from the group of untreated/short-term treated patients vs. 50 (26%) among patients treated adequately but the difference was not clinically significant in both uni- and multivariate analysis.

Patients with thrombus and/or dense spontaneous echo contrast were older but the difference was not significant (median 76 vs. 73; $p = 0.383$). In women, the presence of thrombus and/or dense spontaneous echo contrast was also more frequent (53% patients with thrombus were female vs. 43% patients without thrombus were female), but the difference did not approach statistical significance ($p = 0.134$).

Obesity was equally often in both groups of the patients with persistent AF (37% vs. 36%; $p = 0.918$).

No individual points of the CHA_2DS_2VASc score revealed statistical difference: diabetes and hypertension, previous stroke or thromboembolism, vascular disease and congestive heart failure were not correlated with higher incidence of thrombus and/or dense spontaneous echo contrast.

Laboratory parameters analyzed (creatinine, hematocrit, platelets, INR, aPTT), were not correlated with higher or lower thrombus risk and/or dense spontaneous echo contrast.

In the group of echocardiographic parameters presence of moderate or severe mitral stenosis were correlated significantly (3.8% in group with thrombus vs. 0.53% in group without thrombus; $p = 0.043$) but the result was not confirmed in multivariate analysis. Similarly, increased left ventricle filling pressures in univariate analysis correlated with higher risk of thrombus (61% in the group of thrombus vs. 44% in group without thrombus; $p = 0.018$), but the factor did not turn out to be an independent risk factor in binary regression. None

Table 1. Characteristics of patients with and without left atrial appendage thrombi.

	Thrombus or sludge (+)	Thrombus or sludge (–)	P
Clinical			
Age	75.76 ± 8.26	73.01 ± 10.19	0.383
Female sex	42 (53.16)	82 (43.16)	0.134
CHA_2DS_2VASc	5.00 (4.00–6.00)	4.00 (3.00–5.00)	0.071
$CHA_2DS_2VASc > 3$	61 (77.22)	138 (72.63)	0.376
First episode of AF/AFl	24 (30.38)	92 (48.42)	0.013
AFl	12 (15.19)	41 (21.58)	0.311
Arrhythmia episode duration in weeks	52.75 ± 106.90	22.53 ± 40.99	0.012
BMI [kg/m^2]	28.97 ±5.30	29.11 ±4.94	0.840
Overweight	33 (41.77)	79 (41.58)	0.939
Obesity	29 (36.71)	69 (36.32)	0.918
Arterial hypertension	64 (81.01)	147 (77.37)	0.435
Diabetes	35 (44.30)	68 (35.79)	0.175
Previous stroke/TIA	17 (21.52)	42 (22.11)	0.939
Vascular disease	51 (64.56)	100 (52.63)	0.061
Congestive heart failure	40 (50.63)	72 (37.89)	0.051
Active cancer	2 (2.53)	7 (3.68)	1.000
Cancer in medical history	6 (7.59)	16 (8.42)	1.00
Smoking	5 (6.33)	7 (3.68)	0.520
Active inflammation	6 (7.59)	14 (7.37)	1.000
Infection in last 3 months	16 (20.25)	33 (17.37)	0.729
Surgery in last 3 months	4 (5.06)	12 (6.32)	0.783
Echocardiography			
LVEF	43.17 ± 12.73	46.24 ± 11.72	0.073
LA surface	30.02 ± 10.22	27.05 ± 5.22	0.033
Presence of spontaneous echo contrast	58 (73.42)	62 (32.63)	< 0.001
Low LAA velocities	70 (88.61)	113 (59.47)	0.024
Aortic stenosis moderate-to-severe	4 (5.06)	13 (6.84)	0.785
Aortic regurgitation moderate-to-severe	2 (2.53)	6 (3.16)	1.000
Mitral stenosis moderate-to-severe	3 (3.80)	1 (0.53)	0.077
Mitral regurgitation moderate-to-severe	19 (24.05)	50 (26.32)	0.761
Aortic prosthesis	4 (5.06)	8 (4.21)	0.752
Mitral prosthesis	4 (5.06)	5 (2.63)	0.456
Laboratory			
Creatinine [mg/dL]	0.99 ± 0.38	1.01 ± 0.41	0.479
Hematocrit [%]	40.49 ± 4.57	40.63 ± 4.68	0.931
Platelets [G/L]	214.03 ± 55.20	220.07 ± 82.79	0.965
INR	1.88 ± 0.88	1.73 ± 0.72	0.229
aPTT ratio	1.35 ± 0.39	1.30 ± 0.33	0.617
Anticoagulation			
Proper anticoagulation	75 (94.94)	168 (88.42)	0.061
Anticoagulation duration in weeks	108.96 ± 199.69	123.05 ± 235.11	0.536
Anticoagulation > 4 weeks	67 (84.81)	159 (83.68)	0.819
NOAC	38 (48.10)	122 (64.21)	0.014
VKA with TTR > 85%	29 (36.71)	43 (22.63)	0.018
No anticoagulation or shorter than 3 weeks or warfarin with TTR < 80% or LMWH in prophylactic dose	8 (14.04)	20 (12.35)	0.818

→

Table 1 (cont.). Characteristics of patients with and without left atrial appendage thrombi.

	Thrombus or sludge (+)	Thrombus or sludge (–)	P
Anticoagulation interruption in last 3 months	12 (15.19)	11 (5.79)	0.028
Cardiologist-controlled anticoagulation	55/59 (93.22)	126/134 (94.02)	0.830
Mini-mental state examination (MMSE)			
MMSE score	24.67 ± 4.51	26.62 ± 3.38	0.001
Mild impairment of cognitive function	16 (20.25)	30 (15.79)	0.378
Dementia	7 (8.86)	2 (1.05)	0.003

Data are shown as mean ± standard deviation and the number of patients (percentage). AF — atrial fibrillation; atrial flutter; LA — left atrium; LAA — left atrium appendage; aPTT — activated partial thromboplastin time; BMI — body mass index; INR — international normalized ratio; LVEF — left ventricular ejection fraction; LMWH — low molecular weight heparin; NOACs — non-vitamin K oral anticoagulant; TIA — transient ischemic attack; TTR — therapeutic time ratio; VKA — vitamin K antagonists

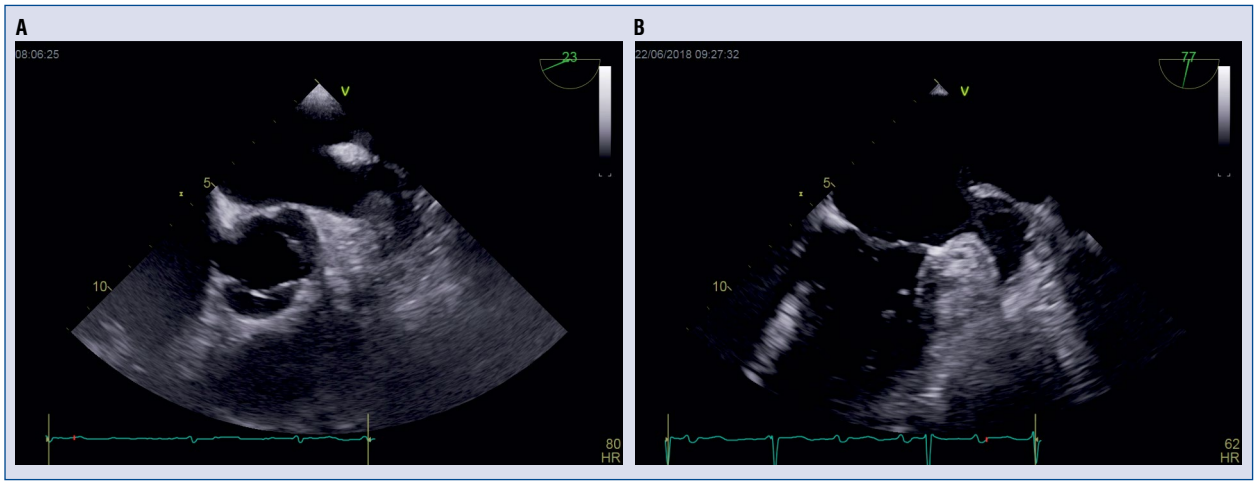

Figure 1. Examples of the left atrium appendage thrombi (**A**) and LAA sludge (**B**).

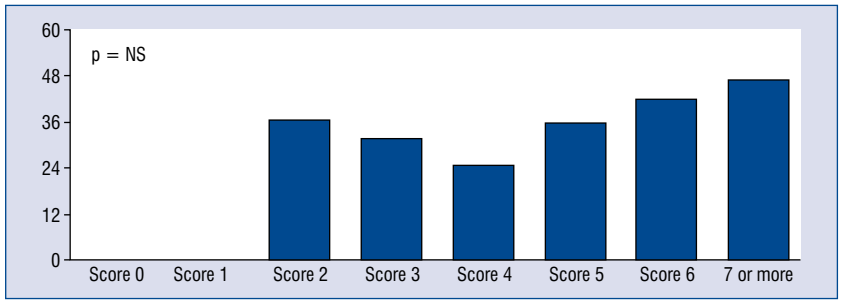

Figure 2. Percentage of patients with left atrium appendage thrombus/sludge by CHA_2DS_2VASc score.

of the other echocardiographic factors, including LVEF, significant mitral regurgitation and LAA enlargement were correlated with higher or lower risk of LAA thrombus.

Other clinical features i.e. cancer, smoking, inflammation, recent surgery, kind of arrhythmia (AF vs. AFl) were not correlated with higher risk of thrombus and/or sludge.

Multivariate analysis revealed only 5 of 53 parameters analyzed as independent risk factors for thrombus/dense spontaneous echo contrast: low LAA early diastolic emptying velocities (p = 0.032; HR: 3.38; 95% confidence interval [CI] 1.11–10.33), presence of spontaneous echo contrast (p = 0.003; HR: 3.38; 95% CI 1.49–7.67), sequent atrial arrhythmia episode (p = 0.046; HR: 0.44; 95% CI 0.19–0.99),

Table 2. Results of the multivariable analysis: independent predictors of left atrial thrombi.

	Univariate logistic regression	Multivariate logistic regression		
	p	p	HR	95% CI
CHA_2DS_2VASc	0.049	0.988	1.002	0.74–1.36
Vascular disease	0.061	0.646	1.213	0.53–2.76
Mitral stenosis	0.043	0.999	2.65	1.54–4.09
Spontaneous echo contrast	< 0.001	0.003	3.38	1.49–7.67
Low LAA velocities	< 0.001	0.032	3.38	1.11–10.33
Increased filling pressure	0.018	0.669	1.19	0.54–2.63
Congestive heart failure	0.051	0.432	1.39	0.61–3.15
Dementia in MMSE	< 0.001	0.005	0.86	0.78–0.96
NOAC	0.014	0.381	0.69	0.31–1.58
Anticoagulation interruption	0.013	0.242	2.13	0.60–7.55
First arrhythmia episode	0.030	0.046	0.44	0.19–0.99
Arrhythmia episode duration	0.002	0.022	1.009	1.01–1.02

CI — confidence interval; HR — hazard ratio; LAA — left atrium appendage; MMSE — mini-mental state examination; NOAC — non-vitamin K oral anticoagulant

low result in MMSE (p = 0.005; HR: 0.86; 95% CI 0.78–0.96) and longer duration of arrhythmia (p = 0.022; HR: 1.009; 95% CI 1.01–1.02) (Table 2).

Discussion

First of the important findings of the present study is high prevalence of thrombus or sludge formations in patients with AF and AFl, diagnosed by TEE (29%). Second valuable and interesting finding is that none of the patients with CHA_2DS_2VASc score ≤ 1 had thrombus or sludge in LAA but when patients CHA_2DS_2VASc score ≤ 1 are excluded, thrombus occurrence do not correlate with of CHA_2DS_2VASc scores. Third, unique finding is that we have discovered only one independent risk factor for thrombus formation before TEE performance; cognitive impairment diagnosed in MMSE. There are two other independent risk factors; low early diastolic emptying velocities in LAA and the presence of spontaneous echo contrast, but they were diagnosed during TEE, therefore cannot reveal whether to do or not to do TEE before cardioversion.

It was decided to put into the analysis both cases of thrombus and dense spontaneous echo contrast (sludge). Differentiation between those two entities is difficult especially before a decision of reversal of sinus rhythm [14]. It has been demonstrated that the presence of sludge is strongly associated with thrombus, embolic events and poor prognosis [4, 5]. In retrospective analysis of Lowe et al. [3] the presence of sludge correlated with similar risk of death but higher risk of thromboembolism than thrombus appearance.

The general incidence of thrombus/sludge in the present study was high. This fact might have been caused by prospective nature of the study, especially by a further decision for cardioversion which compelled recognition in uncertain cases as LAA thrombus. Nonetheless, in several similar studies the incidence is equal or even higher [3, 19, 20].

In this prospective study of 269 consecutive patients with AF and AFl undergoing TEE, before attempting cardioversion, many clinical, echocardiographic and social factors were taken into account which might have influenced thrombus formation. Among the multiple factors only low LAA early diastolic emptying velocities, presence of spontaneous echo contrast, sequent episode of AF/AFl, dementia in MMSE, longer episodes of arrhythmia were independent risk factors for thrombus formation. Converse to other studies, no significant difference was noted in age, sex, LVEF, renal function, lower or higher CHA_2DS_2VASc score [21–24], however, in the group with a risk score 0 or 1 no thrombi or dense spontaneous echo contrast in LAA was diagnosed. In the group scoring higher (two or more) there was no statistical difference between the number of points in CHA_2DS_2VASc score and risk of thrombus.

The present results may underlie creating hypotheses with potential implications for clinical decision-making. Regarding contemporary recom-

mendations, in cases of anticoagulation 3 weeks prior cardioversion can be performed without the need of any other diagnostic tests. Nevertheless, the thrombus or sludge was diagnosed in 25% of patients with declared proper anticoagulation. This fact might be a source for beginning a discussion over extending indications for TEE before cardioversion, similar to the current discussion over necessity of TEE before AF ablation — most ablation centers perform TEE routinely despite the general low risk of thrombus/slugde [25, 26]. This procedure could be supported by important clinical outcomes although the evidence given in guiding this decision is limited [27]. The extension of TEE indications is additionally favored if the results of the ACUTE trial take into account, especially lower risk of hemorrhage and higher success rate in sinus rhythm reversal in TEE guided patients [7]. Despite the fact, that there are reports on the usefulness of other echocardiographic techniques for the prediction of thrombus in LAA, TEE before cardioversion still remains the gold standard. Kupczynska et al. [28] have demonstrated the value of speckle-tracking analysis of the LA wall to identify patients with higher risk of thrombus. Additionally, both LVEF and global longitudinal turned out to be an independent risk factor for thrombus and provided additional diagnostic value for discriminating between patients with and without left atrial thrombus [29].

One of the most relevant and clinically important findings of the study is the relationship between cognitive dysfunction and thrombus (Figs. 3, 4). Cognitive disorders are very common in patients with chronic AF and low anticoagulation compliance was observed in this group [19]. Those patients should be advised that they would be subjected to TEE before cardioversion independently of a declared period of treatment. According to available research this is the first study that suggests cognitive disorders as an independent LAA thrombus or sludge risk factor.

The CHA_2DS_2VASc score has clinical prediction rules for estimating the risk of stroke in patients with non-rheumatic AF associated with thromboembolic stroke. Such a score is used to determine whether or not treatment is required with anticoagulation therapy or antiplatelet therapy and gives a better stratification of low-risk patients. Indeed, in the present study not a single case of thrombus occurred in the group with very low thromboembolic risk ($CHA_2DS_2VASc \leq 1$). The fact that reflects the accuracy of CHA_2DS_2VASc score may help to identify patients in forgoing

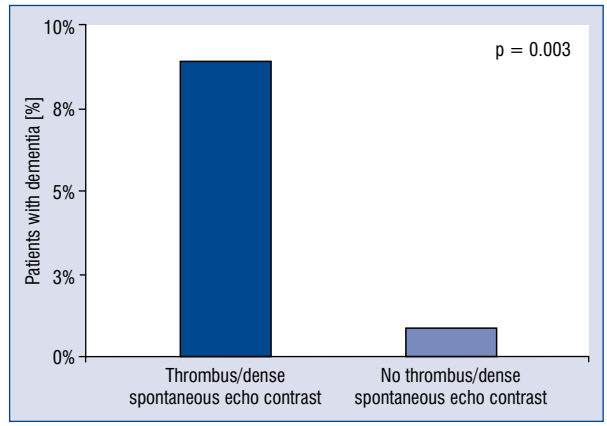

Figure 3. Percentage of patients with dementia and the presence of left atrium appendage thrombus/sludge.

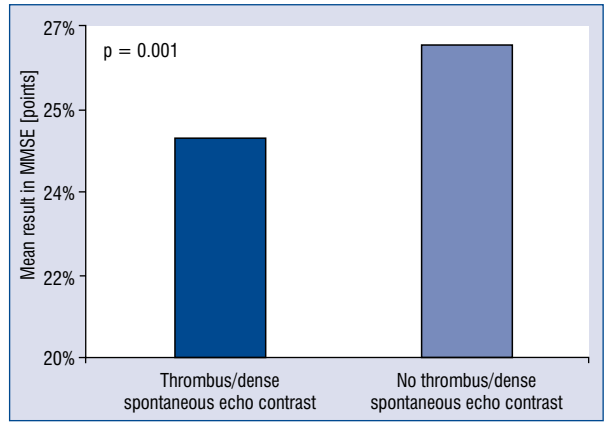

Figure 4. Results of mini-mental state examination (MMSE) questionnaire test and the presence of left atrium appendage thrombus/sludge.

TEE before cardioversion, but these results should be confirmed in larger studies [30]. Additionally, although CHA_2DS_2VASc score correlates directly with annual stroke risk, among patients in this study with $CHA_2DS_2VASc > 1$ the prevalence of thrombus or sludge in LAA was independent of CHA_2DS_2VASc score values that could suggest additional risk factors of stroke in patients with a higher score like atherosclerosis and arterial hypertension. Usefulness of dichotomous scoring of CHA_2DS_2VASc values (≤ 1 and > 1) could simplify clinical every day routine but requires further evaluation.

Limitations of the study

The most important limitation is the uncertain cases that were recognized as suspected thrombus

and were included in the analysis. In both of the documented centers there was a possibility to perform differentiation with the use of echocardiographic contrast or computed tomography but the decision reached was not to use any of those methods to adjust to clinical conditions in all wards performing direct current cardioversion due to the high cost and lack of widespread availability for these methods.

Data regarding anticoagulation were based on questionnaires, with the exception of VKA-treated patients (INR performed once a week for 3 weeks before direct current cardioversion). Additionally, the focus was not on the important issue of whether and when TEE should be repeated to check if the thrombus has been dissolved in anticoagulant therapy.

Cost-effective analysis goes beyond this study but might be a valuable complement.

Conclusions

It is believed herein, that there could be a need for an extension of indications to TEE in a vast majority of patients with atrial fibrillation and atrial flutter.

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Paramedic versus physician-staffed ambulances and prehospital delays in the management of patients with ST-segment elevation myocardial infarction

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Abstract

Background: *Time delays to reperfusion therapy in ST-segment elevation myocardial infarction (STEMI) still remain a considerable drawback in many healthcare systems. Emergency medical service (EMS) has a critical role in the early management of STEMI. Under investigation herein, was whether the use of physician-staffed ambulances leads to shorter pre-hospital delays in STEMI patients.*

Methods: *This was an observational and retrospective study, using data from the registry of the Silesian regional EMS system in Katowice, Poland and the Polish Registry on Acute Coronary Syndromes (PL-ACS) for a study period of January 1, 2013 to December 31, 2016. The study population (n = 717) was divided into two groups: group 1 (n = 546 patients) — physician-staffed ambulances and group 2 (n = 171 patients) — paramedic-staffed ambulances.*

Results: *Responses during the day and night shifts were similar. Paramedic-led ambulances more often transmitted 12-lead electrocardiogram (ECG) to the percutaneous coronary intervention centers. All EMS time intervals were similar in both groups. The type of EMS dispatched to patients (physician-staffed vs. paramedic/nurse-only staffed ambulance) was adjusted for ECG transmission, sex had no impact on in-hospital mortality (odds ratio [OR] 1.41; 95% confidence interval [CI] 0.79–1.95; p = 0.4). However, service time exceeding 42 min was an independent predictor of in-hospital mortality (OR 4.19; 95% CI 1.27–13.89; p = 0.019). In-hospital mortality rate was higher in the two upper quartiles of service time in the entire study population.*

Conclusions: *These findings suggest that both physician-led and paramedic-led ambulances meet the criteria set out by the Polish and European authorities. All EMS time intervals are similar regardless of the type of EMS unit dispatched. A physician being present on board did not have a prognostic impact on outcomes.* (Cardiol J 2021; 28, 1: 110–117)

Key words: acute myocardial infarction, paramedic-only staffed ambulances, physician-staffed ambulances, time delays

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Introduction

Acute myocardial infarction (AMI) is the leading cause of morbidity and mortality worldwide. In Europe, the incidence varies from 43 to 144 per 100,000 per year [1]. Timely institution of reperfusion therapy is linked to substantial survival benefits. A study by De Luca et al. [2] showed that every 30 min prolongation in treatment delay was associated with a 7.5% greater relative risk of 1-year mortality. Despite the introduction of novel interventional techniques and progress in antithrombotic treatment, mortality remains substantial in ST-elevation myocardial infarction (STEMI) patients and varies between 4% and 12% in European countries [3].

STEMI management starts from the point of first medical contact when the working diagnosis of STEMI is made (so called "STEMI diagnosis"). Although there have been dramatic changes in the management of STEMI patients over the past several decades, time delays to reperfusion therapy remain a considerable drawback in many healthcare services. Meanwhile, treatment delays are the most easily audited index of quality of care in STEMI [4].

The significance of emergency medical service (EMS) system in the early phases of STEMI is critical, as it is not only a means of transportation, but also enables prompt initiation of proper treatment [4]. European Society of Cardiology (ESC) experts suggests that all ambulances should be equipped with electrocardiogram (ECG) recorders, defibrillators, and at least one person that is certified in advanced life support techniques [4]. The experts believe that the quality of the care is strongly dependent on the training of EMS personnel. The majority of ambulance services worldwide have highly specialized and trained EMS paramedics or nurses on board. However, physician-based EMS systems are present in most European countries [5].

Not every emergent situation requires the presence of a physician on scene. In fact, most EMS interventions do not require the skills of a physician, nor could they be performed at a distance via teleconsultation (phone-assisted medical advice) [6]. Notwithstanding, the use of many advanced life support measures and medications on scene in the pre-hospital setting may require the assistance of a physician or at least a highly specialized EMS paramedic [5]. However, in some situations, e.g. STEMI or respiratory distress, health care systems that provide physician-led ambulances may reduce time delays in diagnosis and treatment of acutely ill patients, and this, in turn, may improve outcomes. Studies show that the presence of a physician in pre-hospital settings improves survival in patients with acute cardio-respiratory emergencies [7, 8]. Accordingly, Acute Cardiovascular Care Association (ACCA) of the ESC recommends that physician-based EMS organization, have the availability of emergency physicians in cases of chest pain or acute dyspnea of suspected cardiac origin [5].

The evidence for the beneficial effect of a physician's presence on board an ambulance in pre-hospital settings in STEMI patients is lacking. Therefore, this study set out to determine whether the use of physician-staffed ambulances leads to shorter pre-hospital delays which in turn could result in survival benefits for STEMI patients.

Methods

This study conforms to the Declaration of Helsinki. Informed consent for data analysis was obtained from patients according to Polish law on patient rights regarding data registration. Approval for analyzing recorded data was waived by the institutional review board on human research at the Medical University of Silesia, given the retrospective nature of the study (SUM KNW/0022/KB/12/18).

The present study was observational and retrospective in nature, using data from the registry of the Silesian regional EMS system (Voivodeship Rescue Service [VRS]) in Katowice, Poland and the Polish Registry on Acute Coronary Syndromes (PL-ACS) for the study period of January 1, 2013 to December 31, 2016. VRS in Katowice operates in the majority of Silesian regions and covers an area of 3883 km^2 (1.2% of the area of Poland) with approximately 2,700,000 inhabitants (7% of the population of Poland) which represents a population density of 695 inhabitants per 1 km^2. VRS in Katowice is the biggest public EMS provider in Poland. It operates 88 EMS ambulances including 59 ambulances consisting of 2 paramedics or nurses, and 29 ambulances consisting of 2 paramedics or nurses and 1 physician. Annual call volume is approximately 625,000 with the number of EMS responses of VRS in Katowice being 250,000 per year on average. VRS in Katowice employs highly sophisticated Computer Aided Dispatch hardware and software programs. This fully digitalized system allows for accurate (free of human error) registering of various time intervals essential for the analyses of response times. EMS teams were

dispatched based on caller complaints and chest pain complaints received priority for the dispatch of physician-staffed EMS. In the event of a lack of available physician-staffed ambulances the first available EMS team (paramedic-staffed) was dispatched to avoid system delays.

The PL-ACS registry is an ongoing, nationwide, multicenter, prospective, observational study of patients hospitalized with ACS. The registry is a joint initiative of the Silesian Center for Heart Disease and the Polish Ministry of Health. A detailed protocol with inclusion and exclusion criteria, methods and definitions has been previously published [9]. The definition of STEMI was based on a widely accepted universal definition of AMI [10].

Based on these two data sources, 870 patients with STEMI were identified. Because inter-hospital transfers form non-percutaneous coronary intervention (PCI) centers to PCI centers has an important impact on outcomes [11] 153 patients were excluded who were transported to non-PCI centers by EMS in order to obtain a homogenous population of patients that would allow analysis of the type of EMS dispatched on the outcomes in patients with STEMI. The study population (n = 717) was divided into two groups based on the type of ambulance that was dispatched: group 1 (n = 546 patients) — physician-staffed ambulance and group 2 (n = 171 patients) — paramedic/nurse only-staffed ambulance.

In order to accurately analyze EMS response time, the following time intervals were recorded:

— Time to emergency call being answered — the time of the incoming emergency call to be answered by the emergency medical dispatcher (EMD);
— Dispatcher call-processing time — the time interval of the duration of the emergency call and needed for the information captured by an EMD to be entered into the Computer Aided Dispatch;
— Delay time — the time interval between the emergency call received and the ambulance dispatched;
— Response time — the time interval between the ambulance dispatched and ambulance arrival at the scene;
— Field time — the time interval between the emergency call received and the ambulance arrival at the scene (the sum of delay time and response time);
— Service time — the time interval between the ambulance arrival at the scene and ambulance arrival at the hospital;
— Total run time — call time, delay time, response time, response time, and service time amount to the total run time.

Statistical analysis

Quantitative variables are presented as means and standard deviations or medians and interquartile ranges (lower and upper quartiles) where appropriate. Qualitative variables are presented as frequencies. The Shapiro-Wilk test was used to determine whether random samples came from a normal distribution. The χ^2 test with the Yates correction was used to compare categorical variables. The unpaired t-test was used to compare normally-distributed continuous variables between groups. The Mann-Whitney U-test was used to compare continuous variables with a distribution other than normal. In-hospital survival was estimated with the Kaplan-Meier method and compared with the log-rank test. A receiver operating characteristic (ROC) analysis was planned to identify possible cut-offs to predict in-hospital death. All variables with a "p" value of less than 0.05 in the univariate analysis entered into the multivariate logistic regression model using the Wald statistic backward stepwise selection. Multivariate logistic regression analysis was employed to evaluate odds ratios (OR) and 95% confidence intervals (95% CI) to identify independent pre-hospital prognostic factors with respect to in-hospital death. A value of $p < 0.05$ was considered significant.

Results

During the study period call volume reached 2,500,000 with 915,345 dispatched EMS units. 870 patients were diagnosed and recorded as STEMI in the pre-hospital setting. 153 (17.6%) patients were transported to non-PCI centers and were excluded from the study in order to obtain a homogenous population. Of 153 patients, 134 were transported by physician-staffed ambulances and 19 were transported by paramedic/nurse-only ambulances. The final study population consisted of 717 patients. The distribution of each component of EMS time intervals for the entire cohort is depicted in Figure 1. The median delay time was 2 min 30 s, the median response time was 5 min and 30 s, the median service time 41 min and 18 s, and the total run time was 50 min and 42 s. Baseline clinical characteristics are presented in Table 1. Physician-led ambulances responded more often to male callers. Responses during the day and night shifts were similar. Paramedic-led

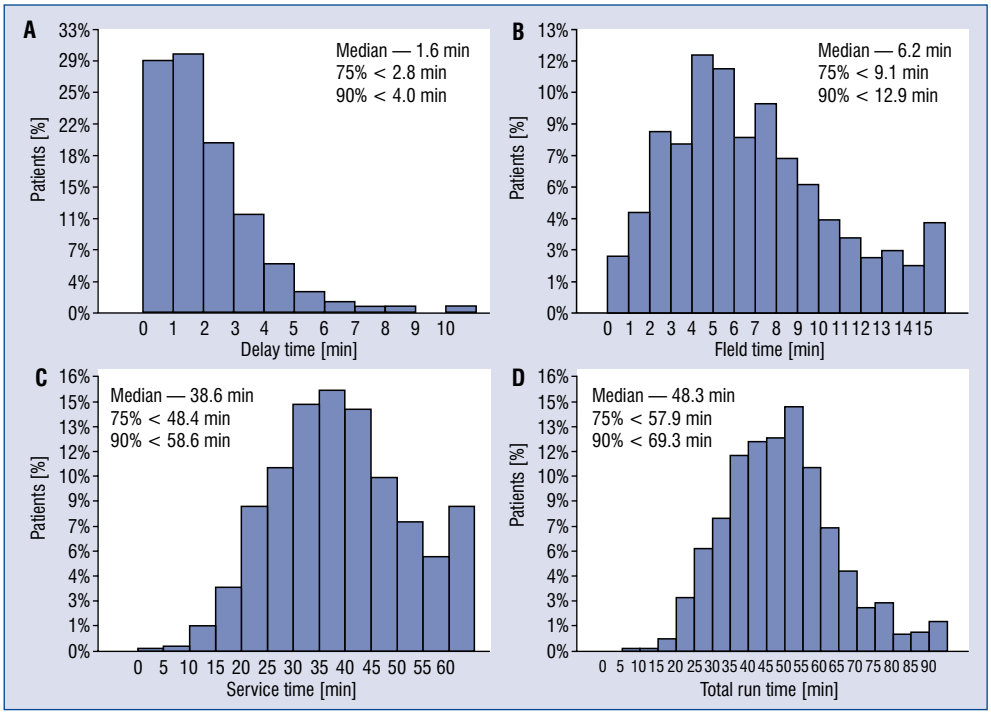

Figure 1. The distribution of each component of the emergency medical service time intervals for the entire cohort; **A.** Delay time; **B.** Field time; **C.** Service time; **D.** Total run time.

ambulances more often transmitted 12-lead ECG to the PCI center in comparison to physician-led ambulances. Delay times and response times were similar in both study groups. Service time was numerically shorter for physician-led ambulances (40.0 min vs. 43.3 min; p = 0.1) however it did not reach statistical significance. In-hospital and long-term mortality was similar in both groups (Table 1, Fig. 2). In the entire cohort, service time of more than 42 min had a weak value in predicting in-hospital death in ROC analysis (area under curve [AUC] 61; 95% CI 0.53–0.68; p = 0.009). The type of EMS dispatched to the patient (physician-staffed vs. paramedic/nurse-only staffed ambulance) adjusted for ECG transmission and sex had no impact on in-hospital mortality (OR 1.41; 95% CI 0.79–1.95; p = 0.4). However, service time exceeding 42 min was an independent predictor of in-hospital mortality (OR 4.19; 95% CI 1.27–13.89; p = 0.019). The in-hospital mortality rate was higher in the two upper quartiles of service time in the entire study population (Fig. 3).

Discussion

This study set out to determine whether the presence of the physician in EMS teams responding in STEMI patients has an effect on prehospital delay. Moreover, the aim was to analyze whether the presence of physician-staffed ambulances in an EMS system translates into survival benefits in STEMI patients. There are four key findings of the present study. First and foremost, dispatcher call-processing time, delay time, and the response time are similar irrespective of the presence of a physician on board suggesting that this fact has no bearing on the activation of the EMS system. Moreover, service time was similar in both types of ambulances. More importantly, service time (irrespective of the presence of physician on board) did influence in-hospital mortality and finally, the type of ambulance dispatched to STEMI patients did not have an effect on early or late survival.

Prolonged total ischemic time has been associated with poor outcomes following AMI [2]. It is comprised of both patient delay and system delay. EMS plays a key role in system delays as it may minimize or prolong the time to STEMI diagnosis [4]. Of note, ambulances and EMS are not only the means of transportation to the hospital, but more importantly they enhance prompt diagnosis and management of STEMI patients. Moreover, most patients with signs and symptoms of AMI still demonstrate a considerable delay in seeking treatment, which adds to the overall ischemic time [11].

Table 1. Baseline clinical characteristics.

	Group 1 (n = 546)	Group 2 (n = 171)	P
Sex, men	388 (71.1%)	97 (56.7%)	0.001
Age [years]	64 ± 11	64 ± 11	0.8
STEMI location:			0.5
Anterior	197 (36.1%)	68 (39.8%)	
Inferior	314 (57.5%)	90 (52.6%)	
Other	35 (6.4%)	13 (7.6%)	
NYHA class:			
I	348 (65.8%)	101 (59.4%)	0.16
II	153 (28.9%)	56 (32.9%)	0.4
III	5 (0.9%)	4 (2.4%)	0.3
IV	23 (4.3%)	9 (5.3%)	0.7
Kilip class:			
1	471 (86.3%)	142 (83.0%)	0.3
2	67 (12.3%)	27 (15.8%)	0.3
≥ 3	8 (1.5%)	2 (1.2%)	0.9
Hypertension	370 (67.8%)	129 (75.4%)	0.07
Hypercholesterolemia	261 (47.8%)	97 (56.7%)	0.051
Obesity	93 (17.0%)	30 (17.5%)	0.9
Type 2 diabetes mellitus	123 (22.5%)	38 (22.2%)	0.9
Smoking (current or history of)	327 (59.9%)	104 (60.8%)	0.8
Dispatch time of day, 7 AM – 7 PM	337 (61.7%)	114 (66.6%)	0.17
Dispatch code, C1	369 (67.6%)	107 (62.6%)	0.19
Cardiac arrest	7 (1.3%)	0 (0%)	0.2
ECG transmission	213 (39.0%)	102 (59.6%)	< 0.0001
Body mass index	27.5 ± 4.7	28.3 ± 4.9	0.2
Systolic BP [mmHg]	134 ± 25	135 ± 28	0.7
Diastolic BP [mmHg]	81 ± 14	80 ± 14	0.7
In-hospital death	29 (5.3%)	12 (7.0%)	0.5

BP — blood presuure; ECG — electrocardiogram; STEMI — ST-segment elevation myocardial infarction

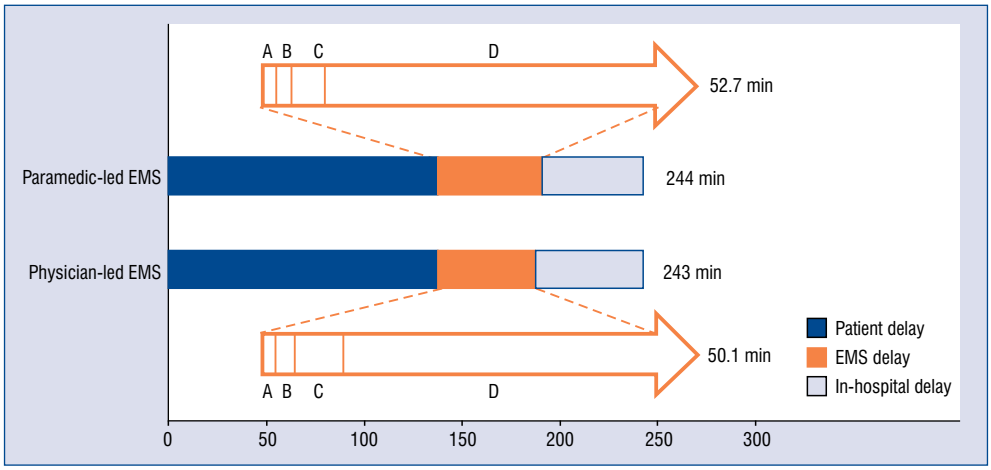

Figure 2. Median total ischemic time in the studied population. Time intervals of the emergency medical service (EMS) delay; A — dispatcher call-processing time; B — delay time; C — response time; d — service time.

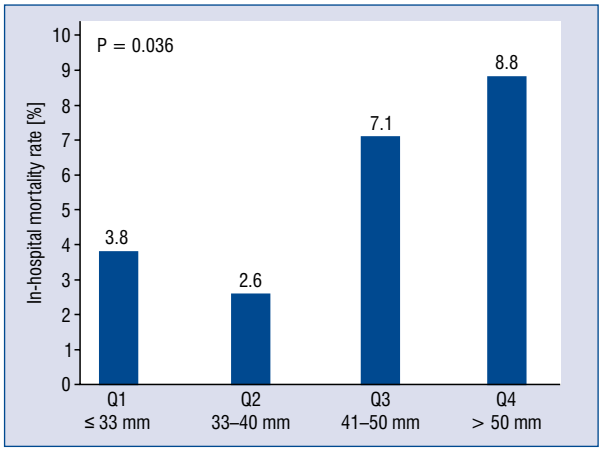

Figure 3. In-hospital mortality rates for quartiles of service time in the entire study population.

Given the STEMI setting may require the presence of emergency physician on-scene in the pre-hospital setting, the ACCA defined delays for diagnosis and treatment in the pre-hospital setting in STEMI patients. And these time intervals are universal for both physician-based and paramedic-based EMS heath care systems [5]. The time between an EMS call and team on scene (the so-called 'Field time') should be no longer than 20 min, but this time limit may differ based on geographic and logistic variations [5]. Results herein, indicate that field time for both physician-led and paramedic-led ambulances are well within recommended time intervals. Notwithstanding, Polish law sets other criteria for ideal time of pre-hospital EMS management of STEMI patients. These times include (a) a median of less than 8 min for field time delays in cities with more than 10,000 inhabitants; (b) a 75th percentile (Q3) of less than 12 min for field time delays in cities with more than 10,000 inhabitants; and c) a maximal field time delay limit is 15 min in cities with more than 10,000 inhabitants. Although both physician-led and paramedic-led ambulances meet the criteria set out for median and Q3 delays, however maximal field time delays exceeded the proposed timelines in both groups (Table 2).

Several strategies have been proposed for field activation of STEMI networks. These include, among others, transmission of ECG to PCI centers or having physicians involved as part of the ambulance team. These strategies have been linked to better short-term and long-term prognosis [12]. Recording of pre-hospital ECG and notification of PCI center result in a substantial reduction in reperfusion time which in turn leads to survival benefit [13–15]. O'Donnell et al. [16] reported that the availability of prior ECG recordings improved paramedic accuracy in recognizing ST-elevation pattern and diagnosing STEMI. In the present study it was found that only 38.4% of physician-led ambulances and 60% of paramedic-led ambulances transmitted ECG recording to a PCI center ($p < < 0.0001$). Studies show similar rates of pre-hospital ECG triage with telemedicine varying between 30% and 50% of cases [17–19]. A meta-analysis of non-randomized studies on pre-hospital ECG transmission demonstrated reduction of absolute time to reperfusion by 19 to 114 min which represented a 19% to 56% relative time reductions (95% CI from –33% to –48%; $p < 0.001$) [17]. Kleinrok et al. [20] showed that during an 8-year period more than 7000 ECG transmissions resulted in admission of nearly 1500 STEMI patients. Zimoch et al. [19] pointed out that pre-hospital ECG transmission results in a higher rate of patients transferred directly to a PCI center (88% vs. 63%; $p = 0.002$). Similarly, it was noticed that the rate

Table 2. Time intervals of emergency medical service responses.

	Group 1 (n = 546)			Group 2 (n = 171)			P
	Median	75%	90%	Median	75%	90%	
Symptom onset -to-emergency call [h]	2.3	6.6	22.9	2.3	6.5	23.3	0.7
Time to emergency call being answered [s]	6	7	7	6	7	7	1.0
Dispatcher call-processing time [min]	1.75	2.85	3.63	1.73	2.80	2.63	0.9
Delay time [min]	2.5	3.5	4.63	2.3	3.3	4.0	0.3
Response time [min]	5.6	8.8	12.0	5.0	8.4	12.5	0.5
Field time [min]	7.9	12.0	15.2	7.3	11.2	16.1	0.3
Service time [min]	40.0	50.0	59.5	43.3	52.0	62.0	0.1
Total run time [min]	50.1	59.9	69.3	52.7	61.7	74.3	0.18

of direct transfers to PCI centers in the present screening cohort was higher in paramedic-led ambulances (171/190 [90.0%] vs. 546/680 [80.3%]; p = 0.003) which could have resulted from ECG transmission and direct contact with interventional cardiologists. Although, in-hospital mortality rates in the current study were similar in both groups, it was known that service times were predictive of in-hospital mortality in the entire cohort. Studies implicated inter-hospital transfers (from non-PCI centers to PCI centers) resulted in substantial delays in receiving reperfusion therapy, thereby causing subsequent larger myocardial damage [21–24]. Kawecki et al. [21] indicated that direct admission to a PCI center resulted in a shorter median symptoms-to-admission time (by 44 min; p < 0.001) and a lower 12-month mortality (9.6% vs. 10.4%; p < 0.001). However, results are inconsistent and other studies did not confirm these findings [25–27]. Notwithstanding, comparing to previous studies, rates of direct transfers to PCI centers in the present study were much higher for both physician-led and paramedic-led ambulances.

Limitations of the study

The study should be viewed with regard to its limitations. This is a single-region, retrospective, observational study. The studied region is densely populated with a high number of EMS stations and PCI centers (STEMI networks). Thus, current results may be region-specific and may differ from other geographic regions. Unfortunately, medical treatment in the pre-hospital setting was not recorded and, thus, not reported. It would be interesting to see whether there are any differences in the therapeutic approach to STEMI patients (antithrombotic strategies in particular) for physician-led and paramedic-led ambulances. EMS teams were dispatched based on the caller complaints, but sometimes the first available EMS team was dispatched.

Conclusions

Taken together, these findings suggest that both physician-led and paramedic-led ambulances meet the time criteria set out by the Polish and European authorities and scientific organizations. All time intervals associated with EMS management of STEMI patients are similar regardless of the type of EMS unit dispatched to the scene. The presence or absence of a physician on board did not have a prognostic impact on outcomes.

Notwithstanding, this study has identified a few areas of management that require further improvement for all ambulances. There is an urgent need for more frequent pre-hospital ECG transmission and triage, in physician-led ambulances in particular. This could increase the number of patients transferred directly to PCI centers. This, in turn, could result in prominent reductions in ischemic time.

Conflict of interest: None declared

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Pretreatment with antiplatelet drugs improves the cardiac function after myocardial infarction without reperfusion in a mouse model

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Abstract

Background: *Reperfusion therapy is known to improve prognosis and limit myocardial damage after myocardial infarction (MI). The administration of antiplatelet drugs prior to percutaneous coronary intervention also proves beneficial to patients with acute MI (AMI). However, a good number of AMI patients do not receive reperfusion therapy, and it is not clear if they would benefit from antiplatelet pre-treatment.*

Methods: *Experimental C57BL/6 mice were randomly allocated to five groups: the sham group, control, post-treatment, pre-treatment, and pre- and post-treatment groups. Acetylsalicylic acid (15 mg/kg), clopidogrel (11 mg/kg), ticagrelor (27 mg/kg), and prasugrel (1.5 mg/kg) were intragastrically administered in the treatment groups. On day 7 post MI, cardiac function and cardiac fibrosis were evaluated using echocardiography and Masson's trichrome staining, respectively. Histopathological examinations were performed on tissue sections to grade inflammatory cell infiltration. Platelet inhibition was monitored by measuring thrombin-induced platelet aggregation.*

Results: *Left ventricular ejection fraction and fractional shortening improved significantly ($p < 0.01$) in the pre-treatment groups when compared to the post-treatment and control groups. A significant ($p < 0.01$) decrease in cardiac fibrosis was observed in the pre-treatment group, compared with the post-treatment and control groups. Inflammatory cell infiltration significantly decreased in the pre-treatment group compared with the control group ($p < 0.05$). Thrombin-induced platelet aggregation was significantly inhibited by antiplatelet drugs, but increased with the exposure to H_2O_2.*

Conclusions: *In the absence of reperfusion therapy, pre-treatment with antiplatelet drugs successfully improved cardiac function, reduced cardiac fibrosis and inflammatory cell infiltration, and inhibited oxidative stress-induced platelet aggregation after MI in the mouse model.* (Cardiol J 2021; 28, 1: 118–128)

Key words: antiplatelet drugs, pre-treatment, myocardial infarction, cardiac function, reperfusion therapy

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Introduction

Acute myocardial infarction (AMI) is the most severe manifestation of coronary artery disease [1]. Prompt recanalization of the culprit vessel and restoration of blood flow to the myocardium are the main therapeutic goals in AMI. Currently, percutaneous coronary intervention (PCI) and thrombolytic therapy are used for effective reperfusion, improving blood flow and preventing recurrent ischemia [2, 3]. Nevertheless, studies have suggested that there is a great variation in the provision of reperfusion therapy [4]. Although the rate of early reperfusion therapy for myocardial infarction (MI) has reached a fairly high level in many developed countries. In developing countries, such as China, during the decade 2001–2011, outcomes of in-hospital treatment for ST-segment elevation MI (STEMI) patients have not improved significantly: the proportion of patients receiving reperfusion therapy has not increased. The treatment of STEMI patients is still significantly delayed, and more than half of STEMI patients miss the opportunity of reperfusion therapy due to delayed consultation [5].

Antiplatelet drugs have been the cornerstone of secondary prevention in patients with coronary heart disease, and these agents have significantly reduced the mortality and have improved the prognosis. Double antiplatelet therapy (DAPT) is a pivotal treatment strategy for patients with AMI and has been recommended in many guidelines [2, 3, 6]. In recent years, assessment of the most appropriate timing for initiating the administration of antiplatelet drugs has been focused upon on with great interest. Many studies [7, 8] have shown the administration of antiplatelet drugs prior to PCI to be beneficial in patients with MI. Brener et al. [8] suggested that acetylsalicylic acid (ASA) pretreatment reduced the mortality at 30 days, especially in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS). However, the benefits of pretreatment with antiplatelet drugs in patients with MI who do not receive reperfusion therapy are not clear. The aim of this study was to evaluate the effects of pretreatment with antiplatelet drugs on cardiac function after MI in a mouse MI model.

Methods

Reagents and materials

Apyrase and prostaglandin E1 were purchased from Sigma-Aldrich Corporation (St. Louis, MO, USA). Thrombin was obtained from Enzyme Research Laboratories (South Bend, IN, USA). CD45 antibody was obtained from Bio-Rad (Hercules, CA, USA). Biotinylated goat anti-rat antibody was obtained from Vector (Burlingame, CA, USA). ASA was obtained from Bayer Health Care (Leverkusen, Germany), ticagrelor was obtained from AstraZeneca PLC (Shanghai, China), clopidogrel was purchased from Sanofi Winthrop Industrie (Shanghai, China), and prasugrel was purchased from Bio tool (Houston, TX, USA). Prasugrel and clopidogrel active metabolites were purchased from Shanghai Race Chemical Co., Ltd. (Shanghai, China). The Masson Stain Kit was obtained from Shanghai Yeasen Biological Technology Co., Ltd. (Shanghai, China).

Animals

C57BL/6 male mice (8 weeks old) were purchased from the Shanghai Slack Laboratory Company (Shanghai, China). The mice were anesthetized by intraperitoneal injection of pentobarbital sodium (50 mg/kg) and were then exsanguinated to retrieve blood and heart. Pentobarbital sodium (200 mg/kg, intraperitoneally) was used to euthanize the mice at the end of the experiments. The Shanghai Jiao Tong University School of Medicine Animal Care and Use Committee approved the animal research protocol. All animal procedures conformed to NIH guidelines (Guide for the Care and Use of Laboratory Animals).

Experimental design

The mice were randomly divided into five groups: (1) sham operation group — a suture was passed under the left anterior descending (LAD) coronary artery without ligation; (2) control group — MI was induced using the model described below, and the same vehicle was administered intragastrically; (3) post-treatment group — after MI induction, mice were given ASA (15 mg/kg), clopidogrel (11 mg/kg), ticagrelor (27 mg/kg), or prasugrel (1.5 mg/kg) by intragastric administration for 7 days; (4) pre-treatment group — before MI induction, ASA (15 mg/kg), clopidogrel (11 mg/ /kg), ticagrelor (27 mg/kg), or prasugrel (1.5 mg/ kg) was orally administered to the mice for 7 days; (5) pre- and post-treatment group — for 7 days prior to and for 7 days after MI induction, ASA (15 mg/ /kg), clopidogrel (11 mg/kg), ticagrelor (27 mg/kg), or prasugrel (1.5 mg/kg) was orally administered to the mice. In each group, 10 mice were treated with each of the drugs. The drugs were dissolved in normal saline. For each drug, the dose selec-

tion was based on the human clinical dosage: ASA (100 mg/60 kg), clopidogrel (75 mg/60 kg), ticagrelor (90 mg/60 kg), or prasugrel (10 mg/60 kg).

Myocardial infarction model

The mice were housed in a temperature--controlled environment with 12-h light/12-h dark cycles. MI was induced by permanent ligation of the LAD coronary artery, as described previously [9]. Eight-week-old mice were anesthetized by isoflurane inhalation. A rodent ventilator (Model 683, Harvard Apparatus, Inc., Holliston, MA, USA) was used with 65% oxygen during the surgical procedure. The animals were kept warm using heat lamps and heating pads. A left thoracotomy was performed in the fourth intercostal space. The heart of the mouse was exposed, and the LAD coronary artery was ligated, 2 mm from its ostial origin, with a 7-0 silk suture. Regional ischemia was confirmed by changes in the electrocardiogram (ST-segment elevation). A sham operation involved the same procedure, but a suture was passed under the LAD coronary artery without ligation.

Echocardiography

Echocardiography was performed using a Vevo 770 high-resolution imaging system at day 7 after MI induction as described previously [9]. The animals were anesthetized with isoflurane inhalation and placed in the supine position. The chest was shaved, and parasternal short- and long-axis views were used to obtain two-dimensional and M-mode images by echocardiography. At least 10 independent cardiac cycles were obtained for each measurement.

Masson's trichrome staining

The hearts were harvested at the end of the study and were perfused and fixed in formalin. Parasternal short-axis sections were cut before staining with Masson trichrome reagent. The slides were analyzed and photographed with an AXIO ScopeA1 microscope (ZEISS Group, Jena, Germany). The area of cardiac fibrosis (blue collagen staining for scar tissue) was expressed as a percentage of the left ventricular (LV) surface area by using ImageJ software (National Institutes of Health, Bethesda, MD, USA).

Platelet preparation and aggregation

The washed platelets from wild-type mice were prepared as previously described [10]. These were adjusted to a density of 3×10^8 platelets/mL. The platelets were evaluated for aggregation with reactive oxygen species (ROS)-induced stress with thrombin. They were incubated with H_2O_2 (200 μmol/mL) for 3 min and then with ASA, the clopidogrel active metabolite, ticagrelor, or the prasugrel active metabolite for 3 min, and platelet aggregation was induced by thrombin.

Immunohistochemistry

Myocardial tissue was fixed in formalin for 24 h and then embedded in paraffin. The parasternal short-axis sections were cut into 4 μm-thick slices. To quench the endogenous peroxidase activity the sections were deparaffinized and incubated with 3% hydrogen peroxide for 10 min at room temperature. The sections were layered with the anti-CD45 polyclonal antibody (1:500) at 4°C overnight and were subsequently washed 3 times with phosphate buffered saline (PBS) for 5 min each. The sections were incubated with secondary goat anti-rat antibody labeled with biotin for 30 min at 37°C and then visualized with diaminobenzidine using an AXIO ScopeA1 microscope (ZEISS Group, Jena, Germany). The CD45-positive cells were counted in 5 to 10 myocardial views per section with ImageJ software.

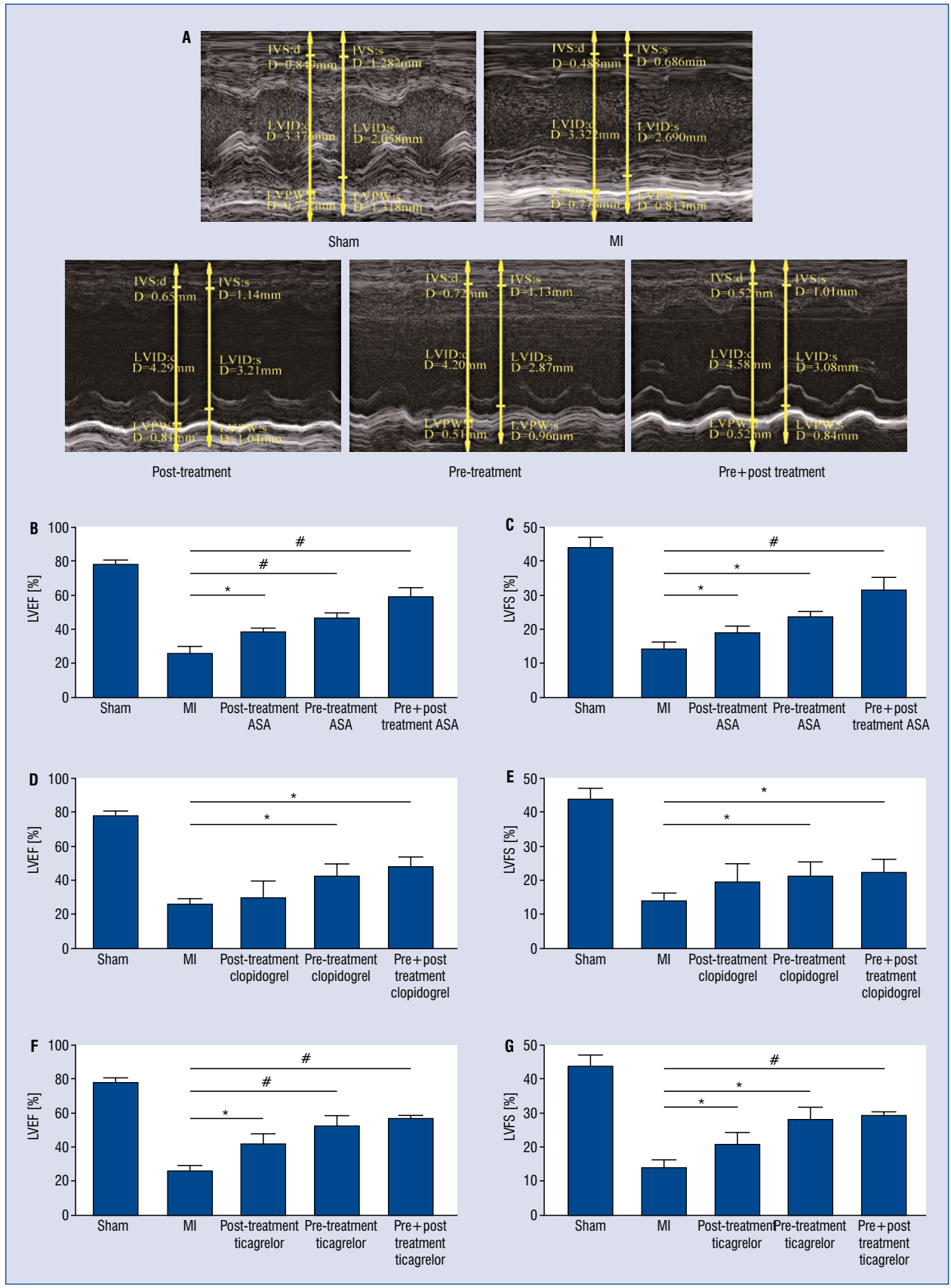
Statistical analysis

Data are presented as means ± standard error. The statistical significance of multiple treatments was determined using the GraphPad Prism Software Version 5.9 (San Diego, CA, USA) by the Student *t*-test or ANOVA (one-way and two-way), followed by either a Newman-Keuls or Bonferroni post hoc test, when appropriate. The values of $p < 0.05$ were considered statistically significant.

Results

ASA, clopidogrel, ticagrelor, and prasugrel pretreatment improves cardiac function after MI

The representative M-mode echocardiograms, performed on day 7 after MI, from each group are shown in Figure 1A. Compared with the control group, significant changes in left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS) were observed in the pre-treatment, pre- and post-treatment, and post-treatment groups. In the groups that were pretreated with ASA, clopidogrel, ticagrelor, or prasugrel, the cardiac function was significantly preserved compared to that in the post-treatment and control groups (Fig. 1B–I). The differences between the control and pre-treatment groups were statistically significant ($p < 0.01$). Among the 4 drugs, clopidogrel


A
Sham
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C
LVFS [%]
D
LVEF [%]
Post-treatment clopidogrel
Pre-treatment clopidogrel
Pre+post treatment clopidogrel
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LVFS [%]
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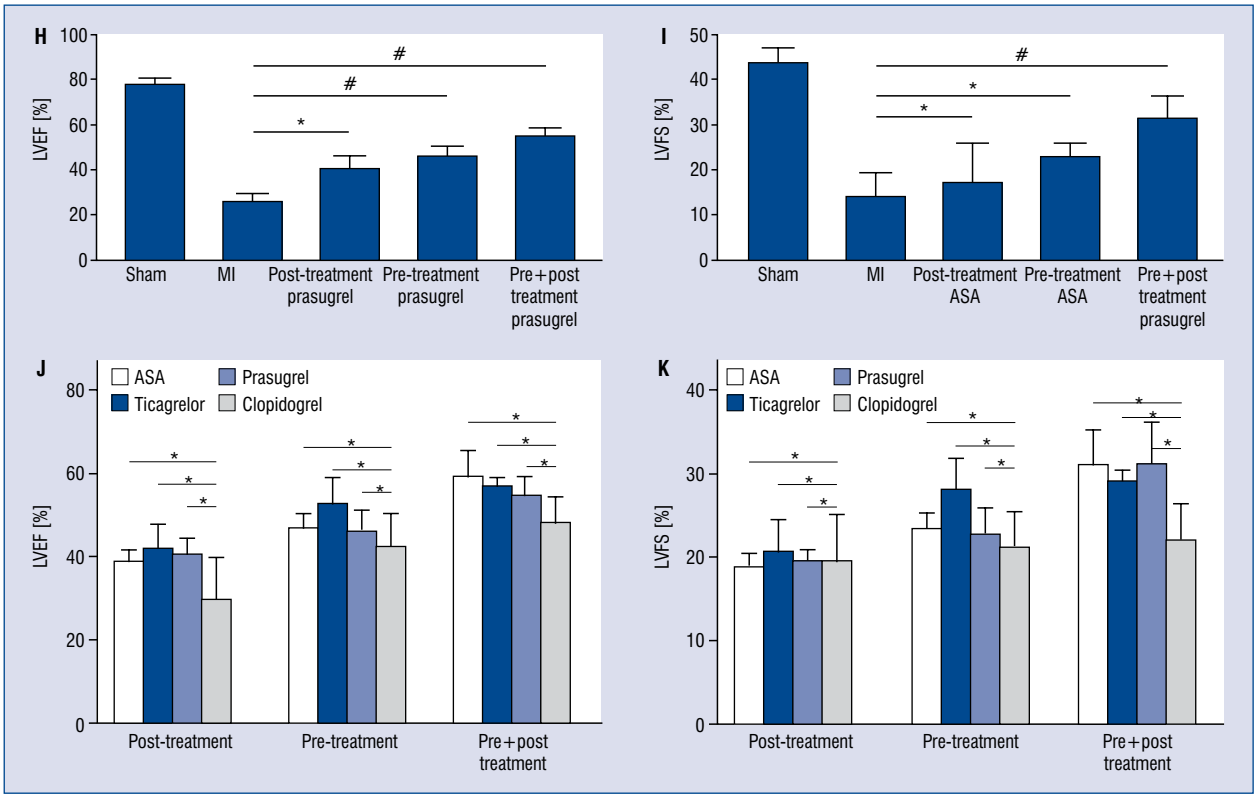

Figure 1. Acetylsalicylic acid (ASA), clopidogrel, ticagrelor, and prasugrel pretreatment preserved cardiac function after myocardial infarction (MI) in vivo; **A.** Representative M-mode echocardiograms for wild type, post-treatment, pre-treatment, and pre + post treatment mice on day 7 post MI; **B–I.** Echocardiographic quantification of left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS). Compared with the control group, the ASA, clopidogrel, ticagrelor, and prasugrel pretreated mice demonstrated improved LVEF and LVFS; **J, K.** Comparisons of the four different antiplatelet drugs; clopidogrel was less effective in improving mice cardiac LVEF and LVFS, when compared to ASA, ticagrelor, and prasugrel (mean ± standard error, n = 10, *p < 0.05, #p < 0.01 vs. control, t test for statistical analyses).

was less effective in improving the mouse cardiac LVEF and LVFS compared with ASA, ticagrelor, and prasugrel in the pre-treatment, pre- and post-treatment, and post-treatment groups (Fig. 1J, K); significant differences ($p < 0.05$) were observed in these cases.

ASA, clopidogrel, ticagrelor and prasugrel pretreatment decreases cardiac fibrosis after MI

After MI, the initial reparative fibrosis is crucial in preventing the rupture of the ventricular wall, but an exaggerated fibrotic response is detrimental and results in progressive impairment of cardiac function [11]. Cardiac fibrosis with the Masson trichrome staining on day 7 after MI was evaluated. Representative images of fibrotic areas in the different groups are shown in Figure 2A. Compared with the control group, treatment with ASA, clopidogrel, ticagrelor, and prasugrel decreased cardiac fibrosis. It was more significantly reduced in the group pretreated with antiplatelet drugs than in the posttreatment and control groups (Fig. 2B–E). The differences in cardiac fibrosis between the control and drug treatment groups were statistically significant ($p < 0.05$). In a comparison of different antiplatelet drugs, the clopidogrel group had a larger fibrotic area after MI compared with that in the ASA, ticagrelor or prasugrel group (Fig. 2F, $p < 0.05$); these differences were statistically significant.

ASA, clopidogrel, ticagrelor, and prasugrel pretreatment reduces infiltration of inflammatory cells in the myocardium

Inflammatory processes are known to result in myocardial injury and impair cardiac function after an MI. A histopathological examination was conducted of the tissue sections to evaluate the

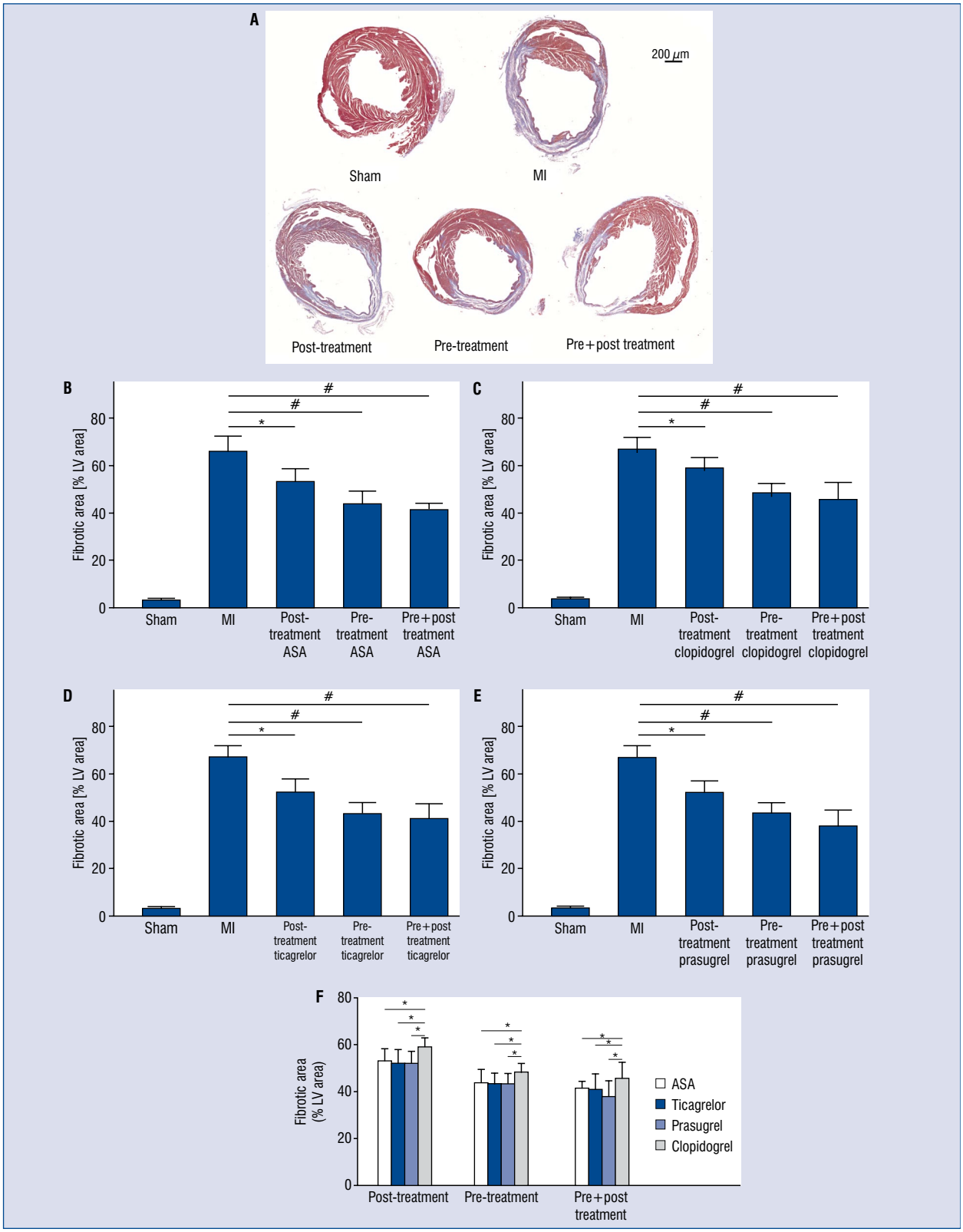

Figure 2. Pretreatment with acetylsalicylic acid (ASA), clopidogrel, ticagrelor, and prasugrel decreased cardiac fibrosis; **A.** Representative images of fibrotic area in different study groups stained with the Masson trichrome stain on day 7 post myocardial infarction (MI). Red represents viable myocardium and blue represents fibrosis; **B–E.** Quantification of Masson trichrome positive staining; **F.** Comparison of different antiplatelet drugs, clopidogrel had a larger fibrotic area after MI compared with ASA, ticagrelor and prasugrel (mean % of left ventricular [LV] area, n = 10/group, *$p \leq 0.05$, #$p < 0.01$ vs. control, t test for statistical analyses).

extent of infiltration of inflammatory cells. The representative images of CD45+ staining in the different study groups are presented in Figure 3A. A decreased infiltration of inflammatory cells was observed in ASA, clopidogrel, ticagrelor, and prasugrel groups compared with that in the control group (Fig. 3B–E). The groups pretreated with antiplatelet drugs demonstrated lesser infiltration of inflammatory cells than post-treatment and control groups. Differences in the infiltration of inflammatory cells in the control and experimental groups were statistically significant ($p < 0.05$). The number of CD45+ positive cells in the clopidogrel group was higher compared with that in the ASA, ticagrelor and prasugrel groups, and there were significant differences among the 4 drugs (Fig. 3F, $p < 0.05$).

ASA, clopidogrel, ticagrelor, and prasugrel inhibit platelet aggregation in response to oxidative stress

Platelets are activated soon after an MI, and their activation depends on the duration of coronary occlusion and the extent of myocardial injury. Platelet aggregation was measured using washed mouse platelets stimulated with thrombin. In the control group, thrombin-induced platelet aggregation was increased with exposure to H_2O_2. Thrombin-induced platelet aggregation in the presence of H_2O_2 was significantly inhibited by ASA, clopidogrel, ticagrelor, and prasugrel (Fig. 4). Ticagrelor and prasugrel were used at lower doses than ASA and clopidogrel; nonetheless, they demonstrated similar inhibitory effects on thrombin-induced platelet aggregation (Fig. 4).

Discussion

The main findings of the present study were that ASA, clopidogrel, ticagrelor, and prasugrel pre-treatment improved cardiac function, reduced cardiac fibrosis, decreased infiltration of inflammatory cells into the myocardium after MI, in cases where reperfusion therapy was not performed, and inhibited platelet aggregation under oxidative stress.

In China, morbidity and mortality from AMI are increasing year by year. In the past two decades, the death rate of coronary heart disease in China has doubled to 1 million per year [12]. However, the provision of coronary reperfusion therapy varies greatly in patients with AMI. The China PEACE-Retrospective Acute Myocardial Infarction Study [13] showed that the proportion of patients who did not receive reperfusion was 44.8% in 2001 and 45.0% in 2011. The China AMI (CAMI) registry [14] showed that among patients with non-STEMI, 9.3% received an early invasive approach. Among patients with STEMI, only 43.0% were treated with primary PCI; besides, 9.9% received thrombolytic therapy. In many other developing countries this phenomenon may even be less optimistic. Recanalization with PCI and thrombolytic therapy are not always available, and other approaches have been taken to limit damage caused by MI. The clinical benefits of ASA, clopidogrel, ticagrelor, and prasugrel in STEMI patients undergoing reperfusion therapy have been previously confirmed in clinical trials [6, 15, 16]. Brener et al. [8] showed that pretreatment with ASA for 5–7 days reduced mortality at 30 days among patients with acute coronary syndromes; all patients accepted revascularization within 72 h. Nanhwan et al. [17] recently reported that pretreatment with ticagrelor protected against ischemia-reperfusion injury and limited the infarct size in rats. At present, primary prevention by ASA is highly controversial. Sanmuganathan et al. [18] showed that ASA treatment for primary prevention is safe and worthwhile at coronary event risk ≥ 1.5%/year, safe but of limited value at coronary risk 1%/year, and unsafe at coronary event risk 0.5%/year. Raju et al. [19] suggested that ASA prevents death, MI, and ischemic stroke. Moreover, it would help reduce hemorrhagic stroke as well as major bleeding when used in the primary prevention of cardiovascular disease. However, as shown in a recent research, Aspirin in Reducing Events in the Elderly (ASPREE) trial [20–22], the use of ASA in healthy elderly people who did not have known cardiovascular disease failed to prolong disability-free survival but led to a higher rate of major hemorrhage than placebo, which suggests that the use of ASA is not reasonable for primary prevention. In conjunction with the results of the present study, it was believed that primary prevention with antiplatelet drugs may bring significant clinical benefits for people with high risk factors of MI as well as for those who are not able to receive reperfusion therapy in time. In particular, the use of ASA will let the economically underdeveloped countries become key beneficiaries, as ASA does have a cost advantage and is easy to obtain.

In the current study, the cardiac function after an MI was significantly preserved on antiplatelet pre-treatment compared with that in the post-treatment and control groups. These results suggest a mechanism for reduction in 30-day mortality reported in previous studies [8]. Clopidogrel was

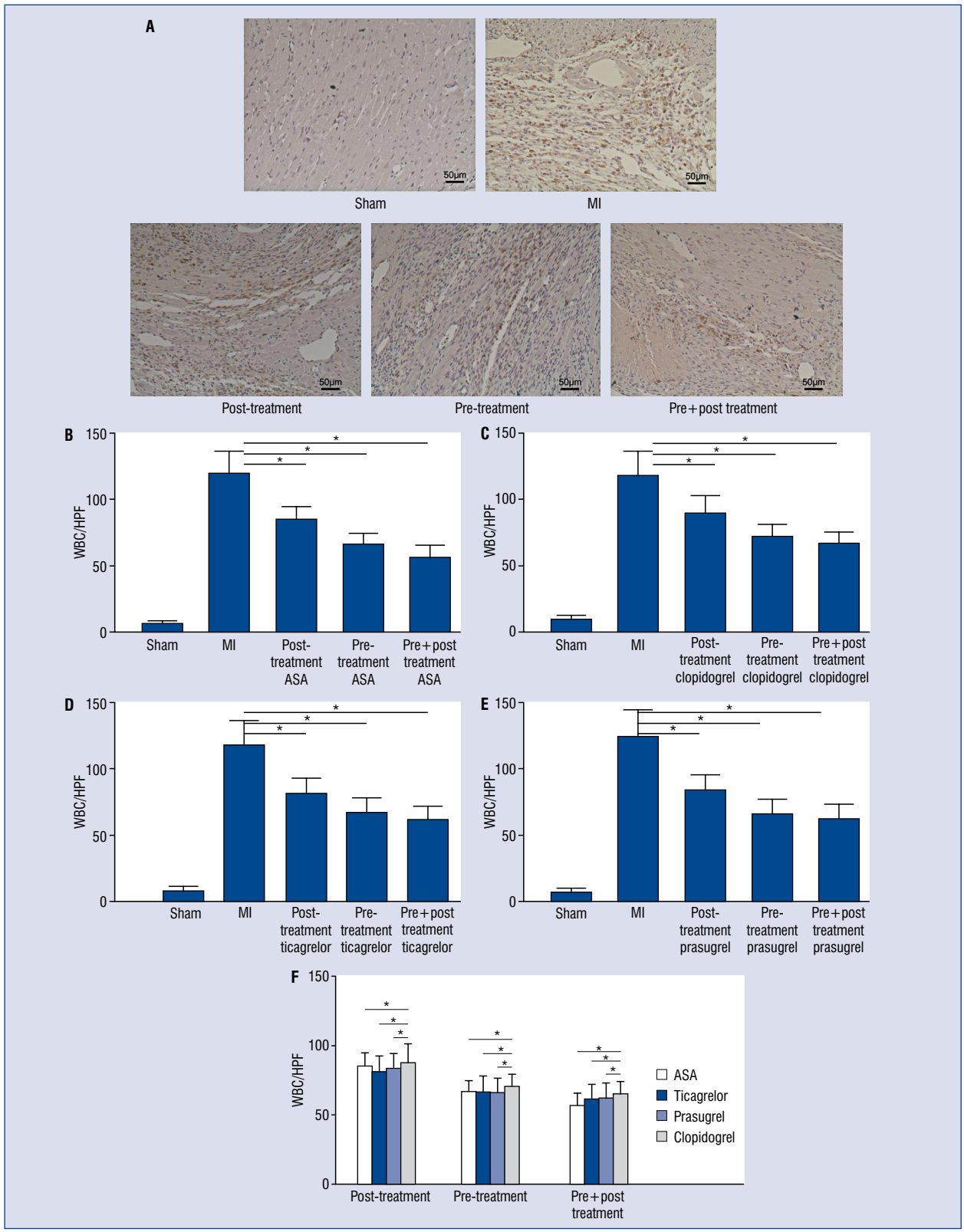

Figure 3. Myocardial white blood cell (WBC) infiltration. CD45+ staining on day 7 post myocardial infarction (MI) in the mouse model; **A.** Representative images of CD45+ positive staining in different groups; **B–E.** Quantification of CD45+ positive cells in the different study groups; **F.** Comparison of different antiplatelet drugs, CD45+ positive cells were more in the clopidogrel group compared with acetylsalicylic acid (ASA), ticagrelor and prasugrel. Immunohistochemical staining was quantitatively analyzed using ImageJ (magnification × 200). Data are shown as the mean white blood cell count per high powered field (mean ± standard error, n = 6; *p < 0.05, t test for statistical analyses); HPF — high power field.

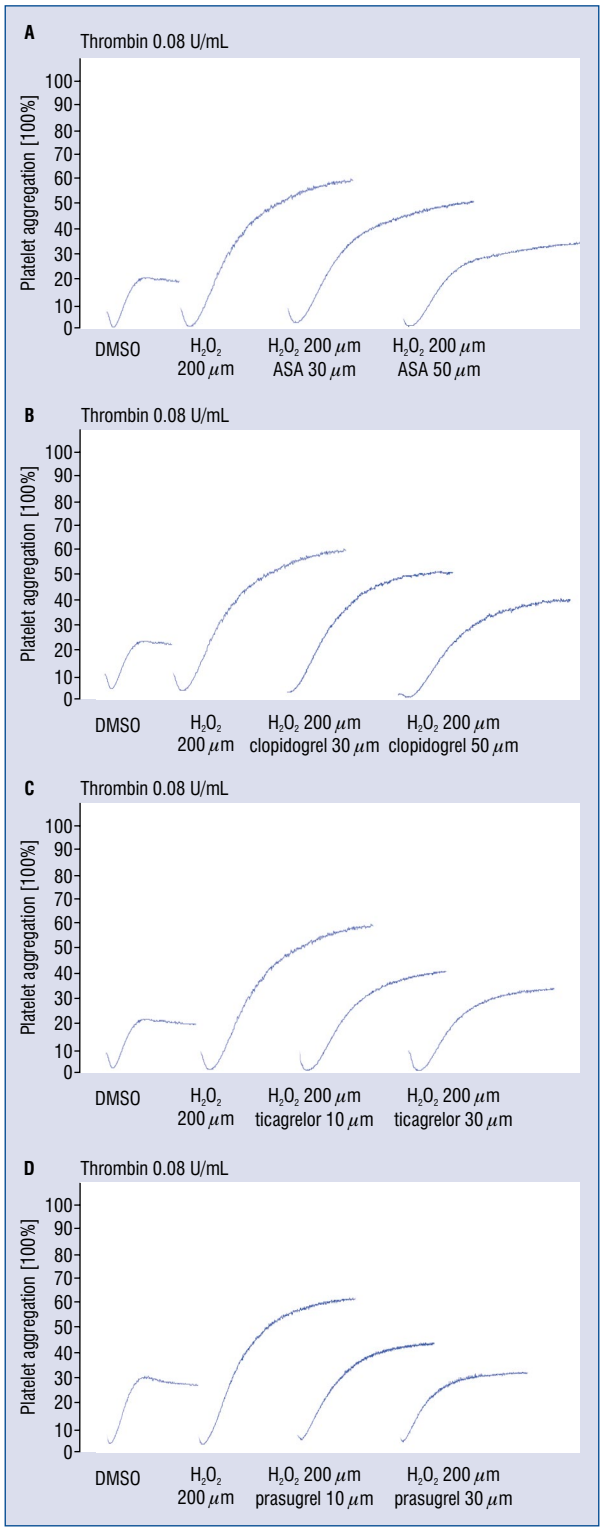

Figure 4. Acetylsalicylic acid (ASA), clopidogrel, ticagrelor, and prasugrel inhibited mouse platelet aggregation with oxidative stress; **A–D.** Washed mouse platelets were stimulated with H_2O_2 (200 μmol/L) for 3 min. Thrombin induced aggregation of mouse platelets was diminished by ASA, clopidogrel, ticagrelor, and prasugrel in a dose-dependent manner. At least five independent experiments were performed; DMSO — dimethyl sulfoxide.

less effective than ASA, ticagrelor, and prasugrel with regard to improving the LVEF and LVFS in mice in each of the treated groups. The dosage of each drug was based on human clinical dosage. Because different medications showed similar platelet inhibition, differences in the improvement of cardiac function with the use of the 4 drugs suggests that the protective effects might occur through mechanisms other than platelet inhibition. Vilahuret et al. [23] suggested that ticagrelor, but not clopidogrel, exerted cardioprotective effects via adenosine-dependent mechanisms.

The adult cardiomyocyte has a limited capacity to regenerate after injury, and the reparative scarring process after MI is critical for maintaining the structural integrity of the ventricular wall. Reparative scarring is followed by remodeling of the surrounding myocardium and eventually leads to impaired cardiac function [11]. It was reported [24] that activated platelets participate in the recruitment and activation of white blood cells in injured areas, release a large number of cytokines and tissue repair factors, and promote the occurrence of inflammatory response in injured areas, while the latter promotes the process of myocardial fibrosis. Antiplatelet drugs can effectively inhibit activation or aggregation of platelets, thus reducing the degree of myocardial fibrosis after MI. Some studies [25, 26] demonstrated that inhibition of platelet activation by clopidogrel prevented cardiac inflammation and fibrosis in response to angiotensin II-induced hypertension. In this study, compared with the control group, mice treated with ASA, clopidogrel, ticagrelor, or prasugrel demonstrated decreased cardiac fibrosis. This might be related to platelet inhibition as suggested in previous studies, and these findings are consistent with the effects of antiplatelet pretreatment on cardiac function after an MI.

An intense inflammatory response is triggered after MI, which has been implicated in the pathogenesis of post-infarction remodeling and heart failure [27]. The activated platelets not only bind to different subsets of leukocytes, but also secrete mediators that induce transendothelial migration [28]. In the present study, decreased infiltration of inflammatory cells was observed after MI in the ASA, clopidogrel, ticagrelor, and prasugrel treatment groups compared with that in the control group, especially in those mice pretreated with antiplatelet drugs.

When MI occurs, ROS are acutely produced in an ischemic microenvironment [29] and are major mediators of distal embolization, microvascular

obstruction, and inflammatory response [30]. It was reported [31] that H_2O_2 alone does not affect platelet aggregation. H_2O_2 dose-dependently promotes low-level thrombin-induced human platelet aggregation. To simulate oxidative stress after MI, platelets were incubated with H_2O_2. The effects of ASA, clopidogrel, ticagrelor, and prasugrel on platelet aggregation under oxidative stress was investigated in this study. Results herein showed that platelet aggregation, stimulated with H_2O_2, was inhibited significantly by these 4 drugs. These results suggest that inhibition of platelet activity was associated with limiting myocardial fibrosis and reducing inflammatory cell infiltration, thereby improving cardiac function.

Limitations of the study

There are several limitations of the present study. Firstly, the cardiac function was evaluated on the 7th day after MI, and therefore, there is a need for evaluating long-term effects of pretreatment with these drugs. Secondly, the European Society of Cardiology states that assessment in large animal models is an obligatory step before initiating human trials; thus, results of the current study should be verified in other animal models. Finally, the elucidation of mechanisms responsible for the improvement in cardiac function using these drugs need further investigations.

Conclusions

Pretreatment with ASA, clopidogrel, ticagrelor, and prasugrel can improve the cardiac function after MI. Pretreatment with these agents may reduce harm caused by MI in patients not receiving reperfusion therapy.

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Conflict of interest: None declared

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ST2 in patients with severe aortic stenosis and heart failure

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Abstract

Background: *ST2 is a circulating biomarker that is well established for predicting outcome in heart failure (HF). This is the first study to look at ST2 concentrations in optimally treated patients with stable but significant left ventricular systolic dysfunction (LVSD) compared to patients with severe aortic stenosis (AS).*

Methods: *Two cohorts were retrospectively studied: 94 patients undergoing transcatheter aortic valve implantation for severe AS (63 with normal ejection fraction [EF] and 31 with reduced EF), and 50 patients with severe LVSD from non-valvular causes. ST2 pre-procedural samples were taken, and repeated again at 3 and 6 months. Patients were followed-up for 2 years. Data was analyzed using SPSS software.*

Results: *Baseline concentrations of soluble ST2 did not differ significantly between the HF group and AS group with normal EF (EF ≥ 50%). However, in the AS group with a low EF (EF < 50%) ST2 concentrations were significantly higher that the HF group (p = 0.009). New York Heart Association class IV HF, baseline N-terminal pro-B-type natriuretic peptide and gender were all independent predictors of soluble ST2 (sST2) baseline concentrations.*

Conclusions: *Raised ST2 concentrations in the context of severe AS may be a marker for subclinical or clinical left ventricular dysfunction. More research is required to assess its use for assessment of prognosis and response to treatment.* (Cardiol J 2021; 28, 1: 129–135)

Key words: ST2, biomarkers, aortic stenosis, transcatheter aortic valve implantation, heart failure

Introduction

ST2 is a circulating biomarker of the interleukin (IL) 1 gene family that binds with the IL-33 ligand. This exists either in a transmembrane receptor (ST2L) which binds to circulating IL-33 and reduces tissue fibrosis, or a soluble receptor (sST2) which blocks this beneficial effect by binding itself to IL-33. Elevated plasma concentrations of ST2 are powerful predictors of death, pump failure and arrhythmias [1]. It is now a well validated biomarker for predicting outcome in heart failure (HF) [2–4]. It may also be useful in the serial monitoring of patients with HF [5].

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ST2 is thought to be produced in the peripheral vasculature [6] in response to increased biomechanical stress on the myocardium [7]. ST2 may also be involved with remodeling in left ventricular hypertrophy (LVH), and it is thought to be a marker of cardiac fibrosis. However, its precise pathophysiological roles in HF and LVH remain unclear. Since severe aortic stenosis (AS) and established HF are associated with biomechanical stress on the myocardium and patients with severe AS additionally have microvascular ischemia, under examination was whether the ST2 concentrations in patients with severe AS were similar to those in patients with established HF who were on optimal medical therapy.

Methods

Ethical approval of the protocol and for collection of samples to measure and analyze biomarker concentrations were obtained from the London (Dulwich) and East Midlands National Research Ethics Service Committee.

A total of 144 patients were retrospectively studied, comprising 50 patients with severe left ventricular (LV) systolic dysfunction (LVSD) due to non-valvular causes and 94 patients undergoing transcatheter aortic valve implantation (TAVI) for severe AS. Between October 2011 and October 2012, 50 patients were recruited with chronic HF in the New York Heart Association (NYHA) classes I–III and LV ejection fraction (EF) ≤ 40% from the HF clinics at Kings College Hospital, London. All patients were on optimum tolerated HF medications, comprising of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, mineralocorticoid receptor antagonists and diuretics. The target doses were determined according to current guidelines [8]. Exclusion criteria included a cardiovascular admission or change in HF medication within 4 weeks of recruitment, a planned cardiovascular admission, significant renal impairment (estimated glomerular filtration rate [eGFR] < 20 mL/min/1.73 m^2), or the inability or unwillingness to consent. This HF cohort has been described previously [5].

Additionally, 97 patients were studied who had undergone TAVI from March 2009 to May 2012 for severe AS. 3 patients were excluded for not having blood samples taken for biomarker analysis; therefore, 94 patients comprised the AS group. Patients who had TAVI for "valve in valve" replacement for aortic regurgitation were also excluded. The details of investigations and outcomes were obtained from electronic databases and patient records. ST2 samples were drawn prior to the interventional procedure.

The blood samples were obtained by venepuncture after the patients had rested for 20 min in a semi-recumbent position and collected in tubes containing ethylenediaminetraacetic acid. The serum ST2 was measured by enzyme linked immunosorbent assay (R&D Systems Europe, Ltd, Abingdon, UK). The ST2 assay contains an NS0-expressed recombinant human ST2 and has been shown to accurately quantify the recombinant factor. The intra-assay precision was 5.6%, 4.4% and 4.5% and the inter-assay precision was 7.1%, 5.4% and 6.3% at 5.4, 12.6 and 20.6 μg/L, respectively. The limit of detection was 0.005 μg/L and the reference range is 6.74–20.4 μg/L [9].

The LV dimensions, function and mass were derived from the transthoracic echocardiographic evaluations. The TAVI procedures were performed by experienced cardiologists using Sapien 3 and Sapien XT valves (Edwards Life Sciences, Irvine, CA, USA). Serial ST2 concentrations were measured between 3 and 6 months from baseline. At the end of a 2 year follow-up, the primary end-point was all-cause mortality.

Statistical analysis

Statistical analyses were performed using the IBM® SPSS® package version 22 (IBM Corporation, Armonk, NY, USA). Normally distributed data were expressed as mean and standard deviation and the groups were compared using the Student t-test. Non-normally distributed data were expressed as medians plus interquartile range and were compared using the Kruskall-Wallis and Mann-Whitney-U tests. Categorical data were summarized using numbers and percentages and the groups were compared with respect to these data using the χ^2 test. Stepwise multiple linear regression was used to identify the predictors of baseline sST2 concentration using a probability (F) of 0.05 for entry into and 0.10 for removal from the model. Survival analysis was performed on all-cause mortality and survival curves were plotted using the Kaplan-Meier method and compared using the log-rank test. A value of $p < 0.05$ considered statistically significant.

Results

The baseline characteristics of patients are shown in Table 1. A total of 144 patients with an average age of 78 years were included in the analysis, of whom 89 were male and 55 were female. Of these

Table 1. Baseline characteristics of study population.

Variable	HF (n = 50)	AS, EF > 50% (n = 63)	AS, EF < 50% (n = 31)	Total (n = 144)	P
Age [years]*	68.5 (21)	85.0 (8)	86.0 (7)	81.00 (15)	< 0.001
Male	82.0%	54.0%	45.2%	61.8%	0.001
Diabetes mellitus	16.0%	22.2%	25.8%	20.8%	0.536
Hypertension	50.0%	52.4%	51.6%	51.4%	0.968
Dyslipidemia	56.0%	28.6%	16.1%	35.4%	< 0.001
NYHA class:					< 0.001
I	10.0%	1.6%	0.0%	4.2%	
II	70.0%	25.4%	12.9%	38.2%	
III	20.0%	71.4%	74.2%	54.2%	
IV	0.0%	1.6%	12.9%	3.5%	
Systolic BP [mmHg]**	116.88 (19.4)	132.89 (22.1)	125.90 (25.2)	125.83 (22.9)	0.001
Diastolic BP [mmHg]**	68.12 (10.7)	68.73 (11.9)	68.61 (14.5)	68.49 (12.0)	0.963
Heart rate [bpm]*	66.00 (18)	74.00 (17)	71.00 (16)	70.00 (20)	0.026
ICD (not CRT-D)	14.0	0.0	0.0	4.9	0.001
PPM	8.0	14.3	12.9	11.8	0.576
CRT	28.0	0.0	6.5	11.1	< 0.001
Sinus rhythm	76.0	65.1	54.8	66.7	0.039
Baseline QRS [ms]*	118.50 (68)	96.00 (35)	119.00 (52)	110.00 (49)	< 0.001
eGFR [mL/min/1.73 m^2]*	62.0 (26)	64.0 (26)	51.0 (33)	61.50 (28)	0.253
Hemoglobin [g/L]**	137.2 (14.2)	122.38 (16.0)	124.32 (16.2)	127.94 (16.8)	< 0.001
LV mass [g]*	248.5 (93.0)	253.3 (76.9)	280.6 (103.0)	198.76 (147)	0.03
Baseline EF [%]*	31.50 (11)	59.00 (8)	42.00 (12)	45.00 (23)	< 0.001
Baseline NT-proBNP [ng/L]*	300.00 (1201)	1756.00 (3353)	5263.00 (11907)	1446.00 (3862)	< 0.001
Na+ [mmol/L]*	138.50 (5)	138.0 (4)	137.00 (5)	138.00 (4)	0.099

The data presented are the medians and the interquartile ranges (*) or the means and standard deviations (**). AS — aortic stenosis; BP — blood pressure; CRT — cardiac resynchronization therapy; CRT-D — cardiac resynchronization therapy-defibrillator; eGFR — estimated glomerular filtration rate; HF — heart failure; EF — ejection fraction; ICD — implantable cardioverter defibrillator; LV — left ventricular; Na — sodium; NT-proBNP — N-terminal pro-B-type natriuretic peptide; NYHA — New York Heart Association; PPM — permanent pacemaker

patients, 113 (78.4%) had an LVEF ≥ 50%, and 31 (21.6%) had an LVEF < 50%. When 40% was used as the cut-off value for EF, 132 (91.7%) patients had an EF ≥ 40% and 12 (8.3%) had an EF < 40%. Using 40% as the cut off for EF had little impact on the final statistical analysis (data not shown). Twenty-four out of 144 (16.7%) patients had renal dysfunction, which was defined as an eGFR < 45 mL/min/1.73 m^2. Of the 50 patients who comprised the HF group, 24 had ischemic cardiomyopathy and 26 had non-ischemic cardiomyopathy.

Baseline concentrations of sST2 did not differ significantly between the HF group and those in the AS group who had EFs ≥ 50%. The baseline concentrations of sST2 were significantly higher for patients in the AS group who had low EFs (< 50%) compared with those in the HF group (p = 0.009) (Fig. 1), a finding that did not change appreciably when the analysis was repeated using an EF cut-off value of 40% (Fig. 2). The latter analysis was performed in an attempt to standardize the definition of LV systolic function, because the HF cohort had an EF cut-off value of 40%.

A multivariate linear regression analysis was performed to determine the factors that predict the baseline sST2 concentration using a stepwise method and the following variables: baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration, cohort (AS with EF < 50% and AS with EF > 50%), age, eGFR, gender, hypertension, diabetes, hypercholesterolemia, baseline QRS, LV mass, baseline EF, baseline end-diastolic volume, left atrial volume, and NYHA class (I–IV). NYHA class IV HF, baseline NT-proBNP level, and gender were identified as independent predictors of baseline sST2 concentrations (Table 2).

Figure 3 presents the Kaplan-Meier survival curves. The log-rank test did not determine

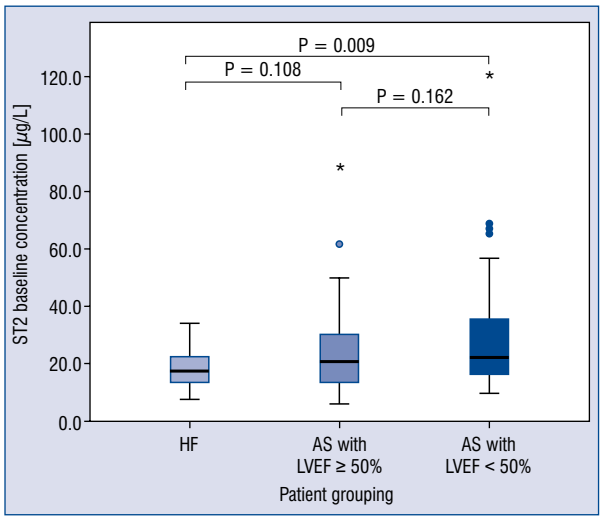

Figure 1. Box plots of the cohort median ST2 concentrations using a left ventricular ejection fraction (LVEF) cut-off value of < 50%. The Kruskal-Wallis test indicated that the difference between the patients with heart failure (HF) and those with aortic stenosis (AS) and a low ejection fraction with respect to ST2 concentration was significant (*p = 0.009).

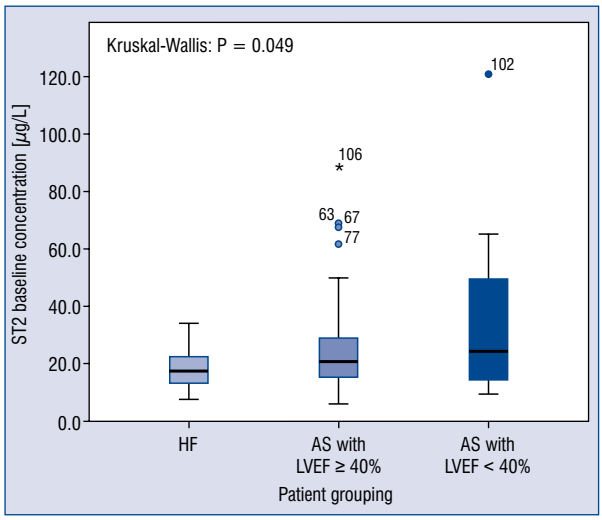

Figure 2. Box plots of the cohort baseline ST2 concentrations using a left ventricular systolic dysfunction (LVSD) cut-off value of < 40%. The Kruskal-Wallis test indicated that the difference between the patients with heart failure (HF) and those with aortic stenosis (AS) and LVSD with respect to the ST2 concentration was significant (p = 0.049); LVEF — left ventricular ejection fraction; *p = 0.049.

Table 2. Stepwise multivariate linear regression analysis of the baseline sST2 concentration.

	Non-standardized coefficient		Standardized coefficient	T-statistic	P value
	Beta	SE[A1]	Beta		
NYHA IV	34.6	8.3	0.41	4.12	< 0.001
Male gender	11.7	3.7	0.31	3.13	0.003
NT-proBNP [ng/L]	0.001	0.0	0.40	4.01	< 0.001

NT-proBNP — N-terminal pro–B-type natriuretic peptide; NYHA — New York Heart Association; SE — standard error

a significant difference between the cohorts that had baseline ST2 concentrations that were either above or below the median concentration (p = 0.463) (Fig. 3).

Significant differences were evident between the HF group and the AS subgroup with an EF > 50% and between the HF group and the AS subgroup with EF < 50% with respect to all-cause mortality (log-rank test: p < 0.001) (Fig. 4). These differences persisted when EF was changed to a cut-off value of 40% and when 30-day mortality was excluded from the analysis (data not shown). This is consistent with current knowledge from previous studies [10].

A comparison of survival according to the baseline NT-proBNP levels that were dichotomized at the median concentration, showed a significant difference with respect to prediction of death (log-rank; p = 0.002) (Fig. 5).

The receiver operating curve analysis revealed an area under the curve (AUC) of 0.580 for all-cause mortality at 2 years. The serial ST2 concentrations determined from 3 to 6 months from baseline showed a change of +0.88 µg/L in the HF group and a change of +0.47 µg/L in patients with AS who had undergone TAVI, a difference that was not significant. The AUC for all-cause mortality at 2 years improved to 0.602 when the analysis included the 3–6-month ST2 concentrations.

Discussion

ST2 has been extensively studied and validated as a biomarker for HF [4, 11] but it is much

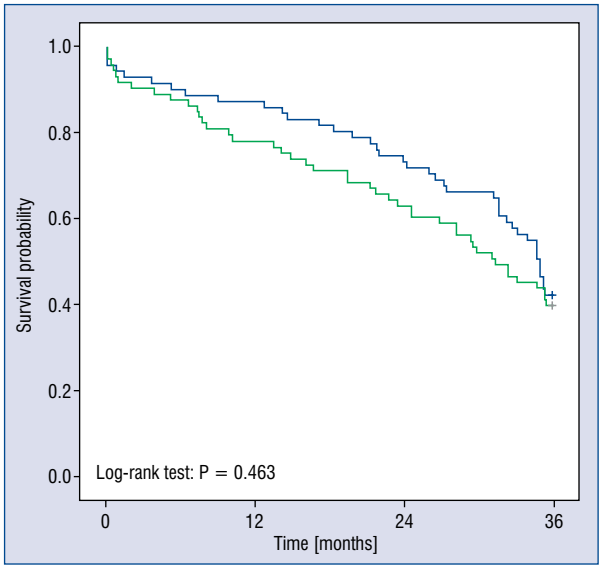

Figure 3. Kaplan-Meier plots for the cohorts split at the median ST2 concentration. The green line is the high ST2 concentration, and the blue line is the low ST2 concentration.

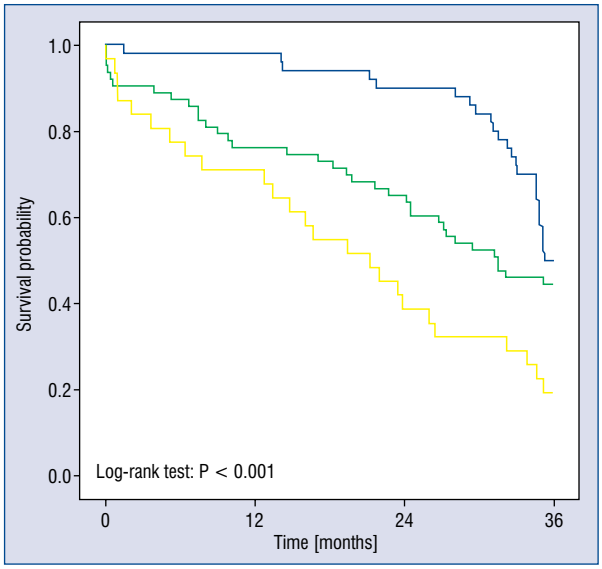

Figure 4. Kaplan-Meier plots of survival probability of the cohorts using a left ventricular systolic dysfunction (LVSD) cut-off value of left ventricular ejection fraction (LVEF) < 50%. The blue line represents the heart failure group, the green line represents the aortic stenosis (AS) group without LVSD, and the yellow line represents the AS group with LVSD. The scale of the x-axis is in days up to 3 years.

less well described in association with severe AS. Bartunek et al. [6] demonstrated that ST2 concentrations in the coronary sinus in AS were

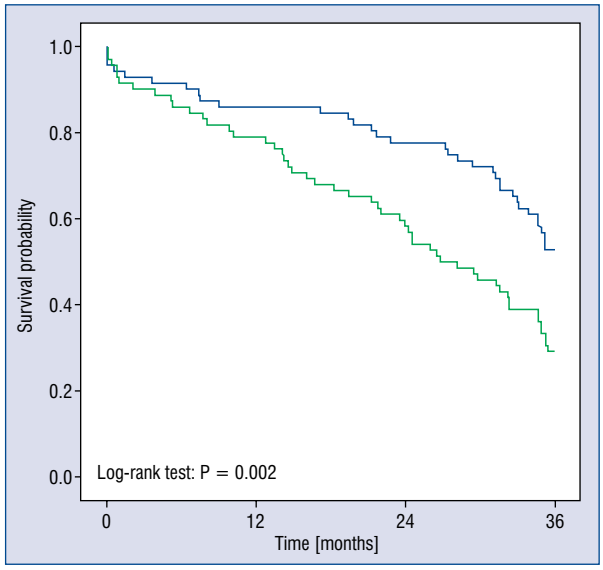

Figure 5. Kaplan-Meier plots of the survival probability of the patient population according to baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP). This was split at the NT-proBNP median concentration, up to the time at which the data were censored, which was 3 years. The blue line represents patients with NT-proBNP concentration above median and the green line represent the patients with NT-proBNP concentration below median.

non-significantly different to controls. Therefore, ST2 production is likely to be extra-cardiac, even though its actions directly affect the myocardium. The presence of biomechanical stress is believed to initiate production of ST2 in the vascular endothelium, which in turn binds to IL-33 receptors to inhibit or promote fibrogenesis [6, 7].

Findings from one small study found elevated ST2 concentrations in stenotic but non-regurgitant aortic valve leaflet tissue [12]. This may reflect the difference in pathological changes that the aortic valve undergoes. Although, it is unlikely that the degree of ST2 expression within valve tissue would affect serum concentrations significantly, this has yet to be formally tested.

The findings from the present study indicate that the ST2 concentrations were similarly elevated in patients with HF and in those with severe AS. However, the ST2 concentrations were significantly higher in patients with severe AS and LVSD, which concurs with a poorer prognosis in this group of patients [13]. This result was unexpected, because LVH from severe AS is not usually associated with the same levels of myocardial fibrosis as those seen in patients with severe LVSD.

The presence of raised ST2 concentrations may be an early warning sign for subclinical LVSD or decompensated AS in patients with AS. While it is yet to be determined whether measuring ST2 concentrations could help clinicians decide when to intervene, the findings from one study have demonstrated that raised ST2 concentrations may predict a poorer prognosis in asymptomatic patients with severe AS [14].

ST2 has emerged as marker of inflammation, fibrosis, cardiac stress and remodeling. In many studies ST2 has been shown to be a BNP independent predictor of cardiac and all-cause mortality. ST2 reflects the dynamic changes in a failing heart and thus parallel the myocardial remodeling and risk of cardiac events. Its value is potentially more significant in patients with normal systolic LV function but with LVH.

Sample size in the current study was small and not sufficiently powered to determine whether ST2 concentration would be a good predictor of mortality in AS. However, 3-year outcomes for patients in the HF cohort and AS with an LVEF > 50% were similar. ST2 concentrations were also similar. The 3-year outcome was significantly worse for AS patients with impaired LV systolic function, and the baseline ST2 concentrations were significantly higher. A repeat of the analysis using a cut-off value of 40% for the LVSD generated similar results. The ST2 concentrations appeared to be independent of LV mass, which was an echocardiographically derived value, and were independent of diabetes, eGFR, QRS duration, EF and age.

ST2 is thought to be a marker of fibrosis, but not hypertrophy; hence, ST2 may be a useful marker for fibrotic disease or the lack of response to aortic valve intervention in AS and HF [5]. This should be investigated in a future prospective study as levels of fibrosis were not measured in this study. Raised ST2 concentrations, however, did not appear to predict group outcomes in the current study. This was surprising and may reflect the relatively small sample size in this study. In the future, there may be a role for combining ST2 and NT-proBNP levels to provide clinicians with additional information for the management of cardiovascular disease [15].

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Undertaking serial measurements of the ST2 concentrations did not appear to show significant differences in concentrations, but analysis of the data revealed that ST2 concentration changed from –99 to 29 μg/L in patients who had undergone TAVI, which indicates a large variation within a small population. While the results may have been influenced by statistical outliers, many patients did not show significant changes in their ST2 concentrations post-TAVI.

Limitations of the study

One limitation of the current study was the small sample size of the HF cohort, which was a consequence of strict inclusion criteria for the study. Furthermore, this study was an observational cohort study and its results are, therefore, subject to undetermined confounding factors; and hence, should be interpreted with caution. It is acknowledged that average ages of the HF and AS cohorts were very different. However, since TAVI is a life-extending and, sometimes, life-saving procedure, it was believed that a 3-year follow-up duration was a reasonable life expectancy post-TAVI for patients selected to undergo the procedure. It was also recognized that this study did not include a healthy control group. However, these data are hypothesis generating and they will support a much larger prospective study that is designed to determine the effects of changing ST2 levels on the outcomes in this population.

Conclusions

The serum ST2 concentrations are elevated to similar levels in patients with severe LVSD and in the population of patients with severe AS who underwent TAVI. The concentrations were highest in patients with severe LVSD and severe AS. This is the first study to compare ST2 concentrations in optimally treated patients with stable but significant LV dysfunction with those in patients with severe AS. Raised ST2 concentrations from increased biomechanical stress on the myocardium in the context of severe AS may be a marker for subclinical or clinical LV dysfunction.

Ongoing biomarker research in this area should not focus solely on replacing NT-proBNP or even troponin, but rather on investigating early pathophysiological changes in the myocardium, which may lead to future therapeutic targets. It is tempting to speculate that early detection

of disease progression using novel biomarkers or significant changes in interval testing may be of future clinical relevance, but larger prospective studies will be required to address these gaps in knowledge.

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Conflict of interest: None declared

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Drug-coated balloon treatment in coronary artery disease: Recommendations from an Asia-Pacific Consensus Group

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Abstract

Coronary artery disease (CAD) is currently the leading cause of death globally, and the prevalence of this disease is growing more rapidly in the Asia-Pacific region than in Western countries. Although the use of metal coronary stents has rapidly increased thanks to the advancement of safety and efficacy of newer generation drug eluting stent (DES), patients are still negatively affected by some the inherent limitations of this type of treatment, such as stent thrombosis or restenosis, including neoatherosclerosis, and the obligatory use of dual antiplatelet therapy (DAPT) with unknown optimal duration.

Drug-coated balloon (DCB) treatment is based on a leave-nothing-behind concept and therefore it is not limited by stent thrombosis and long-term DAPT; it directly delivers an anti-proliferative drug which is coated on a balloon after improving coronary blood flow. At present, DCB treatment is recommended as the first-line treatment option in metal stent-related restenosis linked to DES and bare metal stent. For de novo coronary lesions, the application of DCB treatment is extended further, for conditions such as small vessel disease, bifurcation lesions, and chronic total occlusion lesions, and others. Recently, several reports have suggested that fractional flow reserve guided DCB application was safe for larger coronary artery lesions and showed good long-term outcomes. Therefore, the aim of these recommendations of the consensus group was to provide adequate guidelines for patients with CAD based on objective evidence, and to extend the application of DCB to a wider variety of coronary diseases and guide their most effective and correct use in actual clinical practice. (Cardiol J 2021; 28, 1: 136–149)

Key words: drug-coated balloon, Asia-Pacific, coronary artery disease, de novo lesion, in-stent restenosis

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Introduction

Non-stent based local drug delivery using a drug-coated balloon (DCB) has emerged as a new treatment modality for coronary artery disease (CAD) [1]. The proposed advantages of DCB include homogeneous drug delivery to the vessel wall, immediate drug release without the use of a polymer, the potential of reducing the intensity and duration of antiplatelet therapy, and the absence of residual foreign material in the vessel [2]. Current DCB treatment has an established indication in the lesion of in-stent restenosis (ISR) and small vessel disease, but there is a need for more data regarding other variable disease subsets. Although several published data from registries and randomized trials provided the empirical basis for the current European and German guidelines [2, 3], the demographics and patterns of disease are different in patients of the Asia-Pacific region when compared to those in Europe. Asia-Pacific patients have relatively smaller coronary arteries but longer lesion length as observed by coronary angiography, when compared to Western patients [4]. This coronary phenotype of "small and diffuse CAD" could be a reflection of the higher rate of diabetes mellitus in Asia-Pacific patients. Small vessel CAD carries a worse prognosis than large vessel CAD in terms of restenosis as it is less capable of accommodating neointimal growth after stenting [5]. Another difference is that, in the contemporary trials of antithrombotic treatment, Asia-Pacific patients have a higher risk for bleeding (especially, gastrointestinal bleeding and hemorrhagic stroke) [6–8]. Therefore, the aim of these recommendations of the consensus group is to provide adequate guidelines for Asia-Pacific patients with CAD based on the objective evidence and extend the application of DCB to a wider variety of coronary diseases and guide their most effective and correct use in real clinical practice.

Drug-coated balloon application for coronary artery disease

In-stent restenosis

Historically, there have been many questions concerning whether the plain old balloon angioplasty (BA) or stent-in-stent approach is the best option for the treatment of ISR. Previous trials reported that treatment using bare metal stent (BMS)-ISR and drug-eluting stent (DES)-ISR with BA or first-generation DES still resulted in high revascularization rates and long-term stent thrombosis rates compared to DCB [9–12]. Even in the era of newer generation DES with enhanced performance, ISR is still clinically challenging. In this regard, the use of DCB has been proven to be very effective in patients with both BMS-ISR and DES-ISR.

Bare-metal stent restenosis. The Paccocath ISR-I trial of BMS-ISR demonstrated, for the first time, that DCB was superior to BA alone [13]. The angiographic results and the rate of major adverse cardiovascular events (MACE) were significantly improved in the DCB group at follow-up. The larger randomized PEPCAD II trial compared DCB to paclitaxel-DES treatment in BMS-ISR [14]. At 6-month follow-up, DCB significantly reduced the primary endpoint of the study (late lumen loss [LLL]: 0.17 ± 0.42 mm in DCB vs. 0.38 ± 0.61 mm in DES, $p = 0.03$). These results showed that DCB was at least as efficacious and as well tolerated as first-generation DES in BMS-ISR lesions. The RIBS V trial compared DCB with second-generation DES in patients with BMS-ISR [15]. This trial showed better late angiographic findings in the DES group (minimal lumen diameter [MLD]: 2.01 ± 0.60 mm in DCB vs. 2.36 ± 0.60 mm in DES, $p < 0.001$), but showed similar rates of restenosis and clinical outcomes. Therefore, the overall non-inferior outcomes of DCB treatment when compared with the outcomes of DES implantation support the use of DCB for the treatment of BMS-ISR lesions.

Drug-eluting stent restenosis. An initial small randomized study demonstrated that DCB provided superior clinical and angiographic results compared with BA alone in patients with DES-ISR at 6-month follow-up [16]. Thereafter, the efficacy of DCB compared to BA in DES-ISR was confirmed in a multicenter, randomized PEPCAD-DES trial including patients with any type (either — limus- or paclitaxel-eluting stents) of DES-ISR [17]. Another controlled PEPCAD China ISR study suggested that DCB is equivalent to paclitaxel-DES in patients with DES-ISR at 9-month follow-up [18]. The larger randomized ISAR-DESIRE 3 trial investigated the efficacy of DCB versus paclitaxel-DES versus BA alone in patients with DES-ISR [19]. The results showed that DCB was non-inferior to paclitaxel-DES and that both DCB and DES were superior to BA alone at 6 to 8-month follow-up. In summary, the data from the meta-analyses of available randomized clinical trials suggested that DCB is superior to BA alone and is similar to first-generation DES in terms of clinical outcomes in patients with DES-ISR [20–22].

In the RIBS IV trial, which compared second-generation DES to DCB for treatment of DES-ISR, both angiographic and clinical outcomes favored second-generation DES over DCB at 6–9-month follow-up [23]. However, in a recent DARE trial, DCB treatment was comparable to second-generation DES in terms of 6-month MLD (6-month MLD: 1.71 ± 0.51 mm in DCB vs. 1.74 ± 0.61 mm in DES, p for non-inferiority < 0.0001) and target vessel revascularization (TVR) up to 1 year (8.8% in DCB vs. 7.1% in DES, p = 0.65) in patients with any type of ISR [24]. Therefore, in the future, consideration should be given to ensure randomization when either DCB or DES treatment is possible after BA. In recurrent DES-ISR, DCB and second-generation DES yielded similar clinical outcomes (target lesion revascularization [TLR], MACE) at 12–24 months [25]. In a recently published ISAR DESIRE 4 randomized trial, the efficacy of DCB was further improved by optimal lesion preparation by scoring/cutting the balloon [26]. Compared with conventional treatment, scoring balloon predilation was shown to have significantly lowered the primary endpoint rates (diameter stenosis [DS]: 35.0 ± 16.8% vs. 40.4 ± 21.4%, p = 0.047) and binary angiographic restenosis rates (18.5% vs. 32.0%, p = 0.026). The latest European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) Guidelines on myocardial revascularization recommend the use of DCB for the treatment of both BMS-ISR and DES-ISR lesions that are class I (level of evidence A) [3]. The previous clinical trials are summarized in Table 1.

Therefore, it is recommended that DES-ISR lesions be treated with DCB if the angiographic results are good after BA, and if otherwise, they should be treated with newer generation DES.

De novo lesion

Although the combination of DCB with routine BMS implantation resulted in improved outcomes when compared to BA, previous randomized trials using DCB with the routine BMS strategy did not show improvement over a BMS-only approach and was inferior to DES [27, 28]. The randomized DEB-AMI trial, which enrolled patients treated with DCB plus BMS versus BMS-only versus DES for ST-segment elevation myocardial infarction (STEMI) demonstrated that DCB plus routine BMS was not superior to BMS-only and was inferior to DES [27]. The PEPCAD-III trial also showed that the combination of DCB and BMS failed to prove non-inferiority to sirolimus DES with higher ISR rates (19% in DCB plus BMS vs. 11% in DES, p < 0.01) [28]. Therefore, the non-inferiority of routine combination of DCB and BMS in de novo coronary disease is in doubt and recent clinical trials performed a DCB-only approach, reserving stenting for cases in which a suboptimal result was achieved with the DCB-only approach.

Small vessel disease. The DCB-only approach may have an important role in settings such as small vessel disease, because lumen loss after stent implantation comprises a larger percentage of the total lumen diameter in small vessels than in large vessels. Although published evidence for the DCB treatment for small vessel disease is limited, some larger registry data and randomized trial data suggested low MACE rates with DCB use for small vessel disease (diameter of 2 mm to less than 3 mm) (Table 2) [29–33]. In the initial PICCOLETO study comparing DCB with first-generation DES for small vessel disease, DCB was inferior to DES showing a higher percentage of DS than DES at 6-month follow-up [29]. In the PEPCAD I study, 120 patients with small coronary vessels (2.25–2.8 mm) were treated with the DCB [32]. The patients treated with DCB only had an LLL of 0.18 ± 0.38 mm. However, when DCB was combined with bail-out BMS, the LLL increased significantly to 0.73 ± ± 0.74 mm, p < 0.001. At 12–36 months follow-up, both the MACE rates and TLR rates increased in the DCB plus BMS group. These results were attributed to the "geographic mismatch phenomenon". In addition, the results suggested the importance of covering the whole dilated segment with the DCB to avoid geographic mismatch. Based on this evidence, the routine use of the combination of DCB and BMS in de novo coronary disease is not recommended. Exceptionally, if the DCB-only approach shows a suboptimal result such as flow-limiting dissection or acute recoil, bail-out BMS implantation should be considered to avoid geographical mismatch. However, recent data has shown that bail-out stenting with DES for suboptimal DCB results is a feasible and safe strategy and is comparable to bail-out BMS [34, 35]. For this issue, further large-scaled, randomized controlled trials are needed. Recently, a large randomized BASKET-SMALL 2 trial compared DCB with second-generation DES in small CAD using a 12-month composite clinical endpoint of MACE in an all-comer population [33]. A total of 758 patients with de novo lesion (< 3 mm in diameter) were randomly enrolled. After 12 months, the rates of MACE were similar in both groups (7.5% in DCB vs. 7.3% in DES; hazard ratio [HR]: 0.97; 95% confidence interval [CI] 0.58–1.64, p = 0.918). Rates of

Table 1. Clinical trials of DCB on treatment of ISR.

Author/trial	Previous stent	Treatment	N	Angiographic follow-up	Clinical follow-up
Paccocath ISR-I [13]	BMS	DCB vs. BA	52	LLL: 0.03 ± 0.48 mm (DCB) vs. 0.74 ± 0.86 mm (BA), p = 0.002 at 6 months	MACE: 4% (DCB) vs. 31% (BA), p = 0.01 at 12 months
PEPCAD II [14]	BMS	DCB vs. DES-P	131	LLL: 0.17 ± 0.42 mm (DCB) vs. 0.38 ± 0.61 mm (DES), p = 0.03 Binary restenosis rate: 7% (DCB) vs. 20% (DES), p = 0.06 at 6 months	MACE: 9% (DCB) vs. 22% (DES), p = 0.08 at 12 months
RIBS V [15]	BMS	DCB vs. DES-E	189	MLD: 2.01 ± 0.60 mm (DCB) vs. 2.36 ± 0.60 mm (DES), p < 0.001 at 9 months	MACE: 8% (DCB) vs. 6% (DES), HR: 0.76, p = 0.60 at 12 months
Habara et al. [16]	DES-S	DCB vs. BA	50	LLL: 0.18 ± 0.45 mm (DCB) vs. 0.72 ± 0.55 mm (BA), p = 0.001 Binary restenosis rate: 8.7% (DCB) vs. 62.5% (BA), p < 0.001 at 6 months	MACE: 4% (DCB) vs. 40% (BA), p = 0.005 at 12 months
PEPCAD-DES [17]	DES	DCB vs. BA	110	LLL: 0.43 ± 0.61 mm (DCB) vs. 1.03 ± 0.77 mm (DES), p < 0.001 Binary restenosis rate: 17.2% (DCB) vs. 58.1% (BA), p < 0.001 at 6 months	MACE: 17% (DCB) vs. 50% (BA), p < 0.001 at 12 months
PEPCAD China ISR [18]	DES	DCB vs. DES-P	220	LLL: 0.46 ± 0.51 mm (DCB) vs. 0.55 ± 0.61 mm (DES), p for noninferiority < 0.001 at 9 months	TLF: 17% (DCB) vs. 16% (DES), p = 0.52 at 12 months
ISAR-DESIRE 3 [19]	DES	DCB vs. DES-P vs. BA	402	DS: 38.0 ± 21.5% (DCB) vs. 37.4 ± 21.7% (DES) vs. 54.1 ± 25.0% (BA), p for non-inferiority = 0.007 (DCB vs. DES), p for superiority < 0.001 (other vs. BA) at 6–8 months	MACE: 24% (DCB) vs. 19% (DES) vs. 46% (BA)
RIBS IV [23]	DES	DCB vs. DES-E	309	MLD: 1.80 ± 0.60 mm (DCB) vs. 2.03 ± 0.70 mm (DES), p < 0.01 at 6–9 months	MACE: 18% (DCB) vs. 10% (DES), HR: 0.58, p = 0.04 at 12 months
DARE [24]	DES and BMS	DCB vs. DES-E	278	MLD: 1.71 ± 0.51 mm (DCB) vs. 1.74 ± 0.61 mm (DES), p for noninferiority < 0.0001 at 6 months	TVR: 9% (DCB) vs. 7% (DES), p = 0.65 at 12 months

BMS — bare-metal stents; DCB — drug-coated balloons; DES — drug-eluting stents; DES-P — paclitaxel drug-eluting stents; DES-E — everolimus drug-eluting stents; DES-S — sirolimus drug-eluting stents; DS — diameter stenosis; HR — hazard ratio; ISR — in-stent restenosis; MACE — major adverse cardiac events; N — number; LLL — late lumen loss; MLD — minimal lumen diameter; BA — balloon angioplasty; TLF — target lesion failure; TVR — target vessel revascularization

Table 2. Clinical trials of DCB on treatment of de novo small vessel disease.

Author/trial	Treatment	N	Angiographic follow-up	Clinical follow-up
PICCOLETO [29]	DCB (Dior) vs. DES (Taxus)	57	Percent DS: 43.5 ± 27.4% (DCB) vs. 24.3 ± 25.1% (DES), p for superiority = 0.029 at 6 months	MACE: 35.7% (DCB) vs. 13.8% (DES), p = 0.054 at 9 months
BELLO [30]	DCB (Inpact Falcon) ± BMS vs. DES (Taxus)	182	LLL: 0.08 ± 0.38 mm (DCB) vs. 0.29 ± 0.44 mm (DES), p for noninferiority < 0.001, p for superiority = 0.001 at 6 months Binary restenosis rate: 10% (DCB) vs. 15% (DES), p = 0.35 at 6 months	TLR: 4% (DCB) vs. 8% (DES), p = 0.37 MACE: 10% (DCB) vs. 16% (DES), p = 0.21 at 6 months
Zeymer et al. [31] (Registry)	DCB (Sequent Please)	479	Clinically driven TLR: 3.6% at 9 months	Bail-out stenting with BMS: 6% MACE: 4.6%
PEPCAD I [32]	DCB (Sequent Please) ± BMS	120	LLL: 0.18 ± 0.38 mm (DCB only) vs. 0.73 ± 0.74 mm (DCB + BMS), p < 0.001 at 6 months	TLR: 4.9% (DCB only) vs. 28.1% (DCB + BMS), p < 0.001 MACE: 6.1% (DCB only) vs. 37.5% (DCB + BMS), p < 0.001 at 12–36 months
BASKET SAMLL-2 (Randomized trial) [33]	DCB (Sequent Please) vs. DES (Xience or Taxus Element)	758	–	Cardiac death: 3.1% (DCB) vs. 1.3% (DES), p = 0.113 Non-fatal MI: 1.6% (DCB) vs. 3.5% (DES), p = 0.112 TVR: 3.4% (DCB) vs. 4.5% (DES), p = 0.438 MACE: 7.5% (DCB) vs. 7.3% (DES), p = 0.918 at 12 months

DCB — drug-coated balloons; DES — drug-eluting stents; DS — diameter stenosis; MACE — major adverse cardiac events; BMS — bare metal stents; LLL — late lumen loss; N — number; TLR — target lesion revascularization; MI — myocardial infarction; TVR — target vessel revascularization

cardiac death, non-fatal myocardial infarction [MI], and TVR did not differ between the groups. The results showed that in small CAD, DCB was non-inferior to DES regarding MACE up to 12 months with similar event rates for both groups. A recent multicenter randomized trial in China also showed that DCB was non-inferior to DES for 9-month in-segment DS for small vessel disease [36].

Therefore, when compared with DES implantation, the overall non-inferior outcomes of DCB treatment support the use of DCB for the treatment of de novo small vessel disease (diameter of 2 mm to less than 3 mm).

Large vessel disease. For large de novo coronary vessels, although the evidence is limited, recently published data demonstrated that fractional flow reserve (FFR) guided DCB treatment was safe and effective for de novo large coronary vessels including acute coronary syndrome with good anatomical and physiological patency at 9-month follow-up [37]. All cases used DCB of 2.5 mm or more in size and DCB of 3.0 mm or more in 70% cases. In this trial, if FFR after BA was favorable (≥ 0.85), DCB was applied and if FFR after BA was < 0.85, DES implantation was preferred. LLL with DCB was superior to DES (0.05 ± 0.27 mm in DCB vs. 0.40 ± 0.54 mm in DES, p = 0.015), and the FFR at 9-month follow-up did not differ between the two groups. In addition, using intravascular ultrasound (IVUS) and optical coherence tomography (OCT), the investigators suggested that DCB restores coronary blood flow by means of plaque modification, causing an increment in the minimal lumen area [38, 39]. Recent European data also showed that the FFR-guided DCB-only approach of de novo lesions (cutoff value of FFR: 0.80) was feasible and safe in stable CAD, showing positive remodeling without lumen loss by OCT at 6 months [40]. Another study showed that the safety and efficacy of DCB was comparable with DES when the cut-off value of FFR was 0.75 after balloon angioplasty [41]. Recent Chinese data showed that DCB for de novo coronary lesions with diameters greater than 2.8 mm was safe and effective as for small vessel lesions [42]. The follow-up MLD was significantly increased compared with immediate BA in both the large vessel group (2.26 ± 0.66 mm vs. 2.09 ± 0.40 mm, p = 0.067) and the small vessel group (1.75 ± 0.48 mm vs. 1.58 ± 0.31 mm, p = 0.008). These data suggested that DCB was also safe and effective in large de novo lesions. Nevertheless, a large multicenter trial is needed to demonstrate the safety and efficacy of DCB treatment of the lesions of large vessels.

Others: Bifurcation, chronic total occlusion, diffuse long lesion, atherothrombotic lesion, calcified lesion etc. In bifurcation coronary diseases, current knowledge and experience suggest that treating lesions of the main vessel with a DES produces reasonable results but only suboptimal results in adjacent side-branches [43, 44]. Main vessel stenting in bifurcation lesion is associated with some disadvantages, such as overstretching of the distal vessel and straightening of the vessel, both leading to a carina shift into the side-branch [2, 45]. Therefore, because DCB has an advantage of the absence of residual foreign material in the vessel, DCB treatment may be applied efficiently in bifurcation lesions. However, the randomized DEBIUT bifurcation trial comparing a DCB (Dior™) with BMS and DES failed to show angiographic and clinical superiority over BMS and DES using a provisional T-stenting technique [46]. Simply, DCB treatment was demonstrated to be safe with no thrombotic events, despite the shorter, 3-months duration of dual antiplatelet therapy (DAPT). The observational PEPCAD V study using DCB for both the main vessel and the side-branch resulted in a low LLL in the main vessel and the side-branch with a procedural success rate of 100% [47]. However, when the DCB was combined with BMS in the main vessel, late and very late stent thrombosis occurred in 3 (7.5%) patients. The randomized BABILON trial included 108 patients with sequential main vessel/side-branch dilatation with DCB; provisional T-stenting with BMS in the main vessel was performed in the DCB group and performed with everolimus DES in the DES group [48]. Although the DCB plus provisional BMS strategy resulted in greater LLL and increased MACE compared to the DES group due to higher main vessel restenosis, both strategies showed similar results in the side-branch: LLL in the side-branch was –0.04 ± 0.76 mm in the case of BMS in the main vessel and –0.03 ± 0.51 mm in the case of DES in the main vessel (p = 0.983). The recent randomized PEPCAD-BIF trial comparing the DCB-only approach with BA in the side-branch showed that the restenosis rate was 6% in the DCB group and 26% in the BA group (p = 0.045) [49]. The Korean OCT study using the DCB-only approach applied only to the main vessel suggested that the DCB treatment was safe in bifurcation lesion and there was an increase in the side-branch ostium lumen enlargement despite the absence of treatment of the side-branch [45]. The mean side-branch ostial lumen area increased at 9-month follow-up. Although the optimal strategy and the role

of DCB treatment in bifurcation diseases are not yet confirmed, DCB treatment may be an alternative option for bifurcation lesions. Approximately, these recommendations are similar to that of the German consensus [2]. The first-step is the pre-dilatation of the main branch and/or the side-branch using conventional balloons with a balloon-to-vessel ratio of 0.8–1.0 and an inflation pressure higher than nominal. If the flow-limiting dissection is absent and residual stenosis is < 30% in the main vessel and < 75% in the side-branch with thrombolysis in myocardial infarction (TIMI) flow 3, DCB can be applied to the side-branch extending 4–5 mm into main vessel and distally 2–3 mm beyond the pre-dilated area with a balloon-to-vessel ratio of 0.8–1.0 at least for 60 s. Then the DCB can be applied to the main vessel in the same way, extending the balloon covered length 2–3 mm on both sides, respectively beyond the pre-dilated area. If the result is not satisfactory, the DES can be applied to the main vessel and the provisional stenting can be applied to the side-branch. In other words, the application of a DES in the main vessel and a DCB-only approach in the side-branch may be reasonable and has been shown to be effective according to previous evidence, despite the need of further scientific evaluations. Practically, the DCB application on the side-branch is recommended before stenting the main vessel, rather than after stenting the main vessel, because the drug on the DCB may get lost when crossing the stent strut. If a final kissing balloon angioplasty needs to be performed, it is recommended to use conventional balloons.

Chronic total occlusion (CTO) poses significant technical challenges in percutaneous coronary intervention (PCI), and the results on long term efficacy and safety are still limited. In PEPCAD CTO, BMS was performed on patients followed by DCB to the stented segment as well as beyond the stent edges after successful CTO recanalization in a native coronary artery [50]. Angiographic results and clinical endpoints in the BMS plus DCB group were no different from those of matched patients treated with a paclitaxel-eluting stent. Another recent study showed that a DCB-only strategy without stenting was a feasible and well-tolerated treatment method for CTO if the predilatation result was good [51]. CTO lesions have negative remodeled distal vessels because they have not had flow for a long time. After BA, antegrade flow increases and vessels become larger, requiring several weeks to several months. Therefore, stent sizing immediately after BA is easy to underestimate and could cause late stent malapposition. However, once treated with DCB, it is possible that the vessels will return to their original size over time, which is one of the greatest advantages of DCB treatment in CTO lesions.

For diffuse long lesions, the implantation of long metal devices in coronary vessels may impair the restoration of vasomotion in the stented segment, associated with ISR, stent thrombosis, and neoatherosclerosis, and limit access for coronary artery bypass graft [52–54]. In a retrospective study, patients treated with DCB either alone or in combination with DES were compared with those obtained from a cohort of patients with similar characteristics treated with DES alone [55]. The outcome rates for DCB ± DES were comparable to those with DES alone at 2-year follow-up (MACE: 20.8% vs. 22.7%, p = 0.74; TVR: 14.8% vs. 11.5%, p = 0.44; TLR: 9.6% vs. 9.3%, p = 0.84). Thus, DCB treatment may be an alternative and useful approach in diffuse de novo long lesions, either alone or in combination with DES.

ST-segment elevation myocardial infarction is the most representative disease of atherothrombotic lesions. Although stent implantation has significantly reduced repeat revascularization for STEMI, even DES did not result in lower rates of recurrent MI or death, when compared with balloon angioplasty alone or BMS [56–61]. An important limitation of stent implantation in patients with STEMI is the persistent risk of stent thrombosis or ISR [62–64]. In the majority of STEMI patients, rapid restoration of coronary flow is the main purpose of treatment, and this can be achieved by a combined approach of pharmacologic (antiplatelet and antithrombotic agents) and interventional (thrombus aspiration, balloon dilatation) treatments before stenting. Therefore, DCB treatment may be an optional therapeutic strategy in STEMI if coronary flow is restored and no significant residual stenosis persists after thrombus aspiration and balloon dilatation. A previous study showed that the DCB-only approach is safe and feasible in the setting of STEMI comparing newer generation DES (Biomime™ Sirolimus-Eluting Coronary Stent) and showed good clinical and angiographic outcomes in a 6-month follow-up period [65]. Late lumen loss in the DES group was 0.10 ± 0.19 mm and –0.09 ± ± 0.09 mm in the DCB group (p < 0.05), and MACE were reported in 5.4% of patients in the DES group and none in the DCB group (risk ratio [RR] 5.13, 95% CI: 0.25–103.42, p = 0.29). Other recent registry data showed that DCB-only strategy with provisional stenting is a safe and efficient in de novo coronary lesions in acute coronary syndrome (ACS)

[66]. Therefore, although there remains a need for larger randomized data confirming this issue, the DCB approach may be considered in STEMI if good angiographic results are obtained after thrombus aspiration and balloon dilatation.

Heavily calcified lesions are associated with poorer clinical outcomes due to incomplete stent expansion and malapposition because of the difficulty of adequately deploying the stent into the lesion. Ito et al. [67] demonstrated that DCB treatment shows acceptable MACE and TLR rates at 6-month follow-up for calcified lesions. The rates for TLR and MACE at 2 years were comparable between the calcified group and the non-calcified group. These favorable results may be explained by the exclusion of patients with significant residual stenosis and dissection following the preparation of lesions with rotational atherectomy and a non-compliant balloon as well as the use of IVUS and OCT. Therefore, in calcified lesions with DCB treatment, it is thought that rotational atherectomy and non-compliant balloons used prior to DCB treatment reduces the calcific burden, thus enhancing penetration of the drug into the vessel wall.

Optimal lesion preparation

The successful PCI for treatment of CAD is not just the resolution of epicardial coronary artery stenosis but the acquisition of adequate coronary blood flow. Optimal lesion preparation is of the utmost importance to obtain proper flow in the subtended myocardium and this is performed by BA. A previous study demonstrated that after BA percent stenosis, intimal tear or dissection and pressure gradient of 20 mmHg or more are risk factors for acute closure [68]. Other studies reported that coronary dissection with a TIMI flow grade of 3 or uncomplicated and non-flow-limiting dissections are associated with favorable outcomes and predict a low restenosis rate [69, 70]. Although DCB is similar in construction to conventional angioplasty, DCB is designed to deliver an anti-proliferative drug, not to relieve stenosis as BA does. Therefore, the key to successful DCB treatment depends on whether lesion preparation is appropriately performed before applying DCB. Optimal lesion preparation by pre-treating the lesion with conventional BA is considered the mandatory first step to obtain optimal results from DCB treatment. The main goals of pre-treatment are to improve blood flow by inducing dissection and to facilitate homogeneous drug delivery [71]. Although optimal lesion preparation is a very important factor for successful DCB treatment, there is a fear that major dissection may occur at a high rate. In this case, if flow-limiting dissection is developed, treatment ought to be performed with DES, and if flow is normal, it is safe to decide which device (DCB or DES) to select for treatment using FFR.

In-stent restenosis (Fig. 1)

Data recently published in Korea suggested that the independent predictors of target lesion failure (TLF) in patients with DES-ISR treated with DCB were residual DS after lesion preparation, DCB-to-stent size ratio, and DCB inflation time, whose best cutoff values were 20%, 0.91, and 60 s, respectively [72]. TLF rates were significantly higher in groups with residual DS ≥ 20% (34.7% vs. 12.5%; HR: 2.15; 95% CI: 1.86–2.48, $p < 0.001$), DCB-to-stent size ratio ≤ 0.91 (46.4% vs. 21.9%; HR: 2.02; 95% CI: 1.75–2.34, $p < 0.001$), and DCB inflation time ≤ 60 s (26.2% vs. 14.0%; HR: 1.82; 95% CI: 1.36–2.45, $p < 0.001$). When ISR lesions were classified by the combination of procedure-related factors, TLF occurred in 8.3% in the fully optimized procedure group (residual DS < 20%, DCB-to-stent size ratio > 0.91, and inflation time > 60 s) and 66.7% in the non-optimized group ($p < 0.001$). Unlike DES, the efficacy of DCB is proportional to the amount of the drug delivered to the target lesion. In this regard, the DCB delivery time (time delay from vascular access to the lesion) would correlate with the amount of drug loss into the bloodstream, and the lesion preparation status would affect distribution and absorption of the drug [73]. Therefore, fully optimized DCB treatment with optimal lesion preparation, fast delivery, and prolonged inflation time may play an important role in reducing TLF after DCB treatment.

The originally recommended form of lesion preparation is conventional angioplasty with a non- or semi-compliant balloon with a balloon-to-stent ratio of 0.9 and an inflation pressure higher than nominal [74]. Especially, the use of a non-compliant balloon is preferred over a semi-compliant balloon because a non-compliant balloon helps to improve the previous stent expansion. If the result from the use of a non- or semi-compliant balloon is not satisfactory, using a high-pressure non-compliant balloon or scoring/cutting the balloon may be recommended to facilitate a complete expansion of the restenosed previous stent, neointimal modification, and homogeneous drug delivery, which improves the antirestenotic efficacy of DCB therapy [26].

Based on scientific evidence, additional intravascular imaging such as IVUS and OCT is recommended

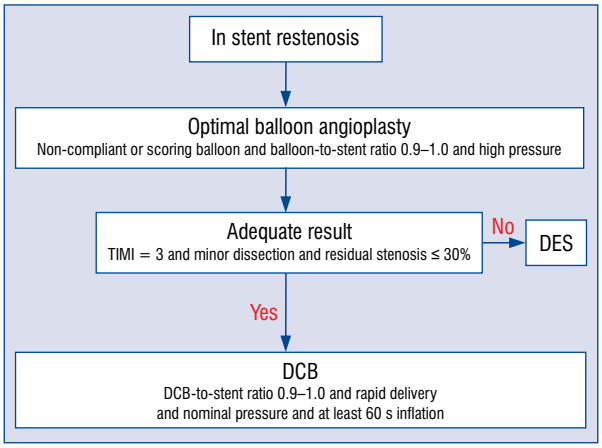

Figure 1. Treatment recommendations for in-stent restenosis. This flow chart shows the recommendations of drug-coated balloon (DCB) treatment for in-stent restenosis. If a non-compliant or scoring balloon or cutting balloon does not pass into the lesion, balloon angioplasty with a smaller sized semi-compliant balloon can be applied; DES — drug eluting stent.

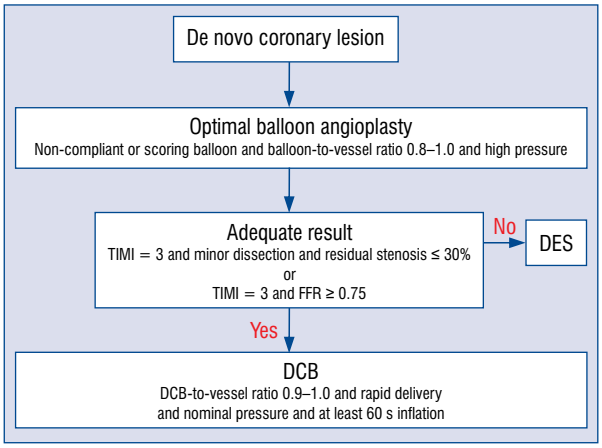

Figure 2. Treatment recommendations for de novo lesions. This flow chart shows the recommendations of drug-coated balloon (DCB) treatment for de novo lesion. If a non-compliant or scoring balloon or cutting balloon does not pass into the lesion, balloon angioplasty with a smaller sized semi-compliant balloon can be applied; DES — drug eluting stent.

to identify the morphological causes of the ISR and achieve optimal lesion preparation, satisfactory angiographic results and successful drug delivery.

De novo lesion (Fig. 2)

Lesion preparation is considered the mandatory first step for successful DCB treatment [74]. The simplest form of lesion preparation is conventional angioplasty with a semi-compliant balloon with a balloon-to-vessel ratio of 0.8–1.0 and an inflation pressure higher than nominal. In more complex lesions, the use of non-compliant high-pressure balloons, scoring or cutting balloons, even rotablation might be considered as well as additional intravascular imaging (IVUS, OCT) or functional measurements (FFR) [2]. To determine whether it is appropriate to perform DCB treatment, all of the following three criteria have to be met after balloon angioplasty; no dissection or type A/B dissection, TIMI grade 3 flow, and residual stenosis ≤ 30%. For larger vessels, when FFR was applied after BA it can determine whether treatment of this lesion with DCB or DES is appropriate. In the FFR--guided DCB approach, if the FFR value after BA is good enough to treat with DCB, DCB treatment is safe and effective with good anatomical and physiological patency at follow-up [37]. In this study, if FFR after BA was ≥ 0.85, DCB was applied and if FFR after BA was < 0.85, stent implantation was preferred over DCB. Additionally, when the same criteria of lesion preparation using FFR were applied, DCB treatment showed persistent anatomical and physiological patency with plaque redistribution and vessel remodeling without chronic elastic recoil or plaque compositional change during follow-up [38]. Similarly, recent European data showed that if it was determined that there was sufficient lesion preparation with residual stenosis < 40%, FFR > 0.80 and no severe dissection, DCB treatment was feasible and safe with a trend toward positive vessel remodeling without lumen loss at 6 months [40].

If the angiographic results are acceptable, DCB may be applied. It should extend beyond the predilated area by 2–3 mm on each side to avoid geographic mismatch. The diameter of the DCB should match with the diameter of the target vessel and the reference ratio of balloon to vessel is between 0.8 and 1.0. The DCB should be inflated for at least 60 s (30 s may be acceptable if the patient is intolerable to longer inflation time) at nominal pressure (about 7–8 atm) to avoid further dissection. It is important to remember that the DCB is a tool for drug delivery and not intended for resolving vessel stenosis like BA. Basically, DCB exists only for drug delivery and is not for angioplasty. Although a product company recommends that the DCB delivery time to the lesion should be within 2 min, the faster, the better.

Optimal medical treatment

Previous trials showed a broad range of duration of DAPT, ranging from 1 to 12 months after

DCB treatment. Although recent ESC guidelines recommend that DAPT should be considered for 6 months after DCB treatment in stable CAD [3], this recommendation did not reflect the results of recent trials for DCB treatment. Importantly, in the recent studies using relatively shorter duration of DAPT such as 1–3 months after DCB, there appeared to be no significant increase in MACE compared to cases with a longer duration of DAPT [29, 30, 32, 46]. In a large randomized BASKET-SMALL 2 trial comparing DCB with second-generation DES in small native CAD, DCB was non-inferior to DES regarding 12-month composite clinical endpoint of MACE despite the shorter duration of 1-month DAPT after DCB treatment [33]. The advantages of shorter duration of DAPT after DCB treatment may be applicable to patients with high bleeding risk, an urgent surgical indication. According to the ESC guidelines for myocardial revascularization, all patients scheduled for DCB treatment should be considered for pre-treatment with acetylsalicylic acid (ASA) and clopidogrel [3]. To ensure full antiplatelet therapy, ASA with a loading dose of 150–300 mg and clopidogrel with a loading dose of 300 mg should be initiated at least 6–16 hours prior to the procedure [2]. If this is not possible, a loading dose of 600 mg of clopidogrel should be applied at least 2 hours before the procedure. For ACS, the loading dose of the adenosine diphosphate (ADP)-receptor blocker (clopidogrel 600 mg or prasugrel 60 mg or ticagrelor 180 mg) should be administered as soon as possible. The duration of DAPT after DCB treatment varies depending on the indications of DCB. For treatment of BMS-ISR and DES-ISR, patients should maintain a lifelong therapy with ASA 100 mg and take clopidogrel 75 mg for at least 1–3 months. For treatment of de novo coronary disease except ACS with DCB only, patients should receive ASA 100 mg lifelong and clopidogrel 75 mg for at least 1 month. In addition, for the cases of de novo stable coronary disease with DCB plus bail-out BMS, DAPT is recommended for at least 3–6 months. For patients with ACS, DAPT is recommended for at least 12 months regardless of the use of BMS or DCB or DES. For the treatment of bifurcation disease, if the DCB-only method without stenting is used, the duration of DAPT should be the same as in the case of other de novo coronary diseases. For cases using DCB plus stenting, the recommended duration of DAPT is at least 6–12 months because of the higher risk of stent thrombosis.

Furthermore, the effect of high-dose statin therapy can be extended after DCB application. In regards to the effects of statin therapy, a previous study demonstrated that a clear reduction of lipid core was observed only for the thin-cap fibroatheroma plaque type, suggesting that changes in plaque composition following statin therapy might occur earlier in vulnerable plaque than in stable plaque [75]. Recent Korean data showed that DCB treatment with high dose statin caused persistent patency with plaque redistribution without chronic elastic recoil and restored coronary blood flow resulting in increased lumen areas at follow-up [38]. In other words, it can be expected that there will be regression of plaque after DCB treatment through high dose statin therapy because balloon angioplasty replaces stable plaque with iatrogenic vulnerable plaque. Therefore, the high intensity of statin therapy can reinforce the efficacy of DCB treatment.

Perspectives

Most recent researches have focused on different coatings and drug delivery technologies. Although zotarolimus- and sirolimus-DCB have shown promising results in preclinical studies, it remains to be determined whether they will result in relevant clinical effects [76–78]. In comparison to zotarolimus-eluting stents, zotarolimus-coated balloons demonstrated similar reductions in neointimal proliferation with a reduction in inflammation scores [77]. A trial of sirolimus-DCB showed similar angiographic outcomes in the treatment of DES-ISR compared with a clinically proven paclitaxel-DCB [79]. Another study of a novel phospholipid-encapsulated sirolimus nanocarrier, used as a coating, showed the most appropriate identification of the best nanoparticle structure associated with an extremely efficient transfer of the drug to all layers of the vessel wall, achieving high tissue concentrations that persisted days after the application with low systemic drug leaks [78]. Furthermore, a recent preclinical study suggested that the vascular effects of sirolimus nanoparticles delivered through a porous angioplasty balloon in a porcine model achieved therapeutic long-term intra-arterial drug concentrations without significant systemic residual exposure [80]. These different types of DCB are unique (i.e., drug type, drug dose, crystallinity, and excipient) with different clinical outcomes. Further research with head-to-head comparison between different DCBs in patients with CAD is needed to determine which DCBs are most effective.

Conclusions

Drug-coated balloons treatment is an attractive therapeutic option and may have several ben-

efits over stent-based strategies in various subsets of coronary diseases. DCB treatment is vastly superior to BA for both ISR and de novo coronary disease. At present, DCB and second-generation DES are recommended in both BMS-ISR and DES-ISR. Although DES has shown the best angiographic and clinical outcomes, DCB may be an alternative option for ISR lesion due to favorable outcomes similar to those of DES, without adding a new stent layer. For de novo coronary disease, although DCB treatment remains controversial in various settings, a provisional DCB approach after optimal BA may have advantages over a direct DCB approach. For successful DCB treatment, the first and most important step is optimal lesion preparation using conventional BA, preferably with the use of a non-compliant balloon or scoring balloon. If the result is no flow-limiting dissection and acceptable residual DS and normal flow, a DCB-only approach without any vascular scaffold like a stent is recommended. In addition, for more complex lesions such as bifurcation disease and larger de novo coronary lesions, further intravascular imaging or functional measurements are more useful than a simple angiography-guided strategy. There is insufficient data about the ideal duration of DAPT in DCB treatment but it is certain that a relatively shorter duration of DAPT than that required in DES would be reasonable. In terms of prognosis, high-dose statin therapy is expected to improve the efficacy of DCB treatment. Finally, if its applications are carefully and adequately performed with a good technique, DCB may have an important role in the treatment of ISR and in various de novo coronary lesions.

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Multimodality cardiovascular imaging in pulmonary embolism

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Abstract

Acute pulmonary embolism (APE) is one of the leading causes of cardiovascular (CV) morbidity and mortality. To select appropriate therapeutic strategy and/or to minimize the mortality and morbidity, rapid and correct identification of life-threatening APE is very important. Also, right ventricular (RV) failure usually precedes acute hemodynamic compromise or death, and thus the identification of RV failure is another important step in risk stratification or treatment of APE. With advances in diagnosis and treatment, the prognosis of APE has been dramatically improving in most cases, but inadequate therapy or recurrent episodes of pulmonary embolism (PE) may result in negative outcomes or, so called, chronic thromboembolic pulmonary hypertension (CTEPH). CTEPH is a condition characterized by remaining chronic thromboembolic material in the pulmonary vasculature and subsequent chronic pulmonary hypertension.

Various imaging modalities include chest computed tomography pulmonary angiography (CTPA), echocardiography, magnetic resonance imaging, and nuclear imaging and each are used for the assessment of varying status of PE. Assessment of thromboembolic burden by chest CTPA is the first step in the diagnosis of PE. Hemodynamic assessment can be achieved by echocardiography and also by chest CTPA. Nuclear imaging is useful in discriminating CTEPH from APE.

Better perspectives on diagnosis, risk stratification and decision making in PE can be provided by combining multimodality CV imaging. Here, the advantages or pitfalls of each imaging modality in diagnosis, risk stratification, or management of PE will be discussed. (Cardiol J 2021; 28, 1: 150–160)

Key words: pulmonary embolism, imaging

Introduction

Acute pulmonary embolism (APE) refers to a condition in which the pulmonary vasculatures are abruptly occluded by abnormal thrombi or emboli, usually originating from deep veins of the lower extremities. Because APE may result in right ventricular (RV) dysfunction and hemodynamic compromise, APE is one of the major causes of mortality worldwide [1, 2]. The rapid and correct diagnosis of APE is essential in selecting an appropriate therapeutic strategy and to reduce mortality from APE. In this regard, multi-modality cardiovascular (CV) imaging, including chest computed tomography (CT), computed tomography pulmonary angiography (CTPA) and echocardiography are useful not only in the diagnosis of APE, but also in the evaluation of hemodynamic significance of APE

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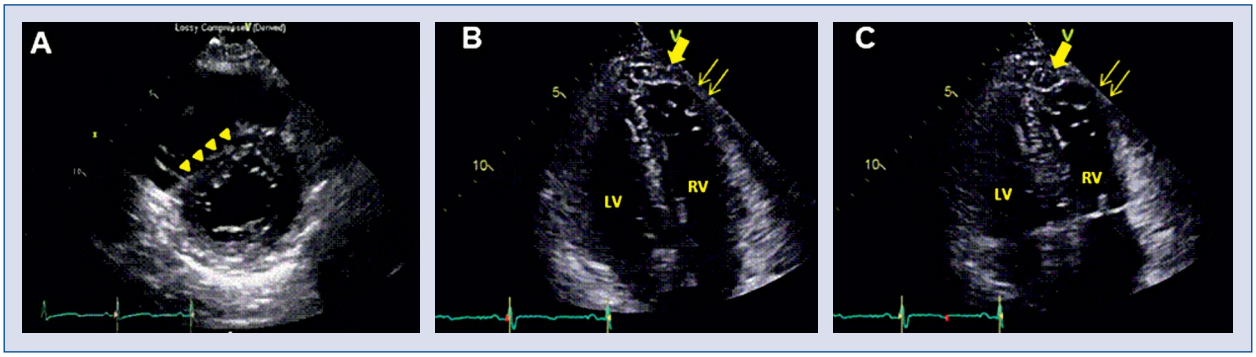

Figure 1. Transthoracic echocardiography demonstrating right ventricular (RV) dysfunction. D-shaped left ventricle (LV) (arrowheads) on parasternal short axis view represents RV pressure overload (**A**). RV enlargement and free wall hypokinesia with sparing of apical wall motion (McConnell's sign) on apical four-chamber view (**B.** At diastole; **C.** At systole).

and thus clinical decision making and therapeutic strategy [3]. The evaluation of therapeutic efficacy is another important role of CV imaging in APE.

With the advances in diagnosis, treatment and prognosis of APE has been dramatically improved in most of cases. Inadequate therapy or recurrent episodes of pulmonary embolism (PE) may result in a serious negative outcomes, including so called chronic thromboembolic pulmonary hypertension (CTEPH). Although the pathogenesis of CTEPH is not completely understood, unresolved organized fibrotic thrombi or emboli, subsequent endothelial dysfunction and abnormal vascular remodeling seem to be involved in the development of pulmonary hypertension (PH). In case of CTEPH, RV can initially adapt to the increased afterload by PH through the process of RV dilatation and hypertrophy, but a progressive or sustained significant increase of pulmonary artery pressure results in RV failure and death [4]. Contrary to the evanescent role of nuclear imaging in APE, ventilation/perfusion (V/Q) scan is an imaging of choice in the detection of CTEPH [5].

In this review, the advantages and pitfalls of each imaging modality in diagnosis, risk stratification, and/or management of PE will be discussed.

Role of TTE

Although transthoracic echocardiography (TTE) is the most widely used CV imaging modality in the assessment of cardiac function and structure, it plays a limited role in the diagnosis of APE because TTE cannot directly visualize the location or extent of pulmonary arterial thrombi or emboli in many cases. However, TTE has a critical role in evaluating hemodynamic significance of APE, including RV dysfunction, and thus TTE is the most useful CV imaging modality in risk stratification, clinical decision making of therapeutic strategy, or evaluating the prognosis of APE [6]. Furthermore, TTE can provide the first indications for diagnosing APE frequently, because it is the most widely used CV imaging modality in patients with dyspnea or chest pain.

The presence of RV dysfunction in APE is a hallmark of higher risk patients and an independent predictor of adverse clinical outcomes, and sometimes it can advocate emergency reperfusion treatment for APE. Therefore, the echocardiographic evaluation of RV function is an important step in the evaluation of APE [7]. Echocardiographic findings suggesting RV dysfunction include RV dilatation, hypokinesia or akinesia of the RV free wall and relative sparing of RV apical wall motion (Mc Connell's sign), decreased tricuspid annulus plan systolic excursion (TAPSE) or fractional area change (FAC), and diminished RV longitudinal strain (Fig. 1) [8–13]. In addition, an increased RV systolic pressure assessed by measuring the peak velocity of tricuspid regurgitation (TR) jet or the increased size of the inferior vena cava or the change of an inferior vena cava size of less than 50% with inspiration can be a supportive sign of RV dysfunction [14]. Despite RV hypokinesia and PH, RV hypertrophy is not a finding of APE because of the acute nature of the illness. Contrary to APE, RV hypertrophy with moderate to severe PH is a common finding in CTEPH as a consequence of adaptation of RV to an elevated afterload. Accordingly, RV hypertrophy on TTE is a simple qualitative clue for chronic PE [15].

In summary, the role of TTE in PE can be summarized as follows; 1) TTE is an imaging of choice

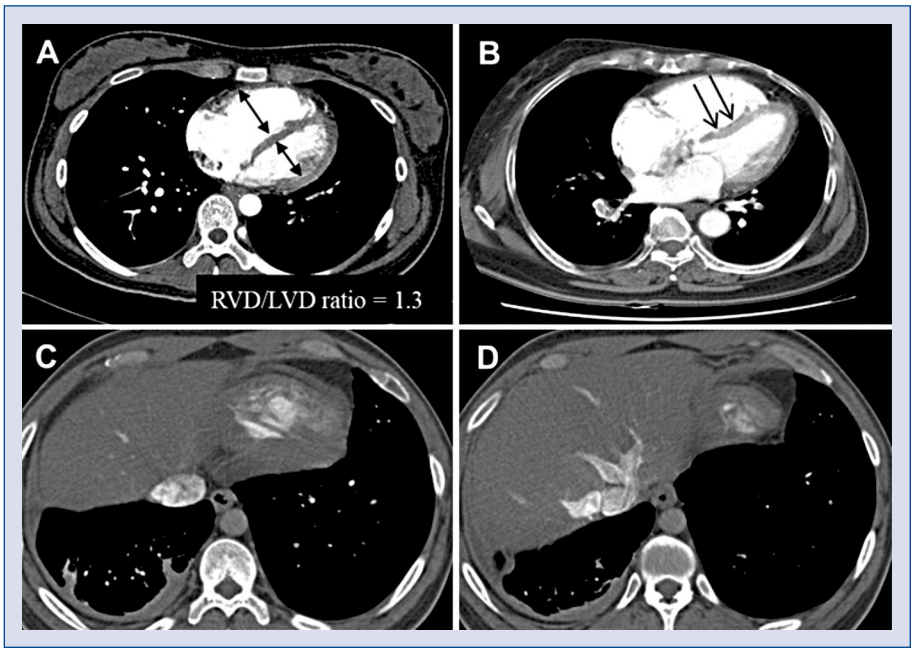

Figure 2. Chest computed tomography angiography suggesting right ventricular (RV) dysfunction. RV dimension is greater than left ventricular dimension (**A**). Leftward ventricular septal bowing (**B**). Contrast reflux (arrows) to the inferior vena cava (**C**) and hepatic veins (**D**).

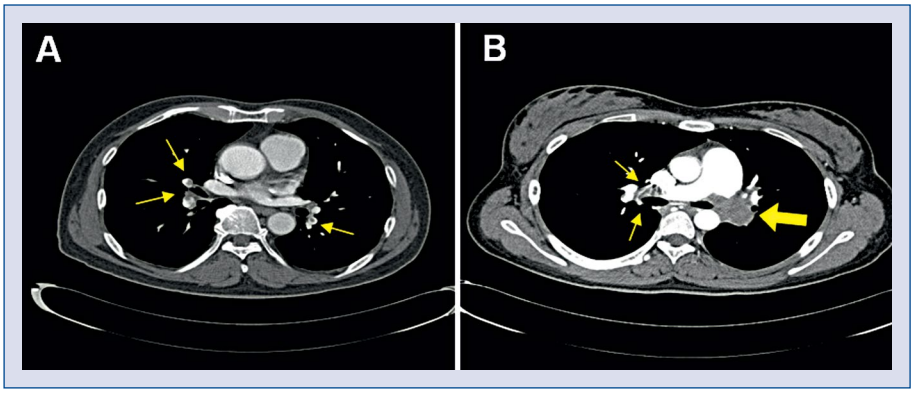

Figure 3. Chest computed tomography angiography shows multifocal small filling defects in both pulmonary arteries (arrows) (**A**) and large filling defects resulting in near total occlusion of the left pulmonary artery (wide arrow) and filling defect in right pulmonary artery (narrow arrow) (**B**).

in the evaluation of hemodynamic significance including RV dysfunction and thus risk stratification or clinical decision making of therapeutic strategy of known APE; 2) TTE can provide the first indication for suspecting APE in some patients; 3) RV hypertrophy with PH in patients with known PE may suggest a finding of CTEPH.

Chest CTPA

Rapid availability and reliability in diagnosis, has made chest CTPA the gold standard CV imaging for the evaluation of suspected APE, and actually it replaced the role of the V/Q scan in the diagnosis of APE. According to the PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) II trial, CTPA appeared to have high negative predictive value (96%) in patients with low clinical probability for APE and also has a high positive predictive value (96%) in patients with high clinical probability for APE [16]. Hence, current guidelines recommend performing CTPA in patients highly suspected for APE or even in patients with low to intermedi-

ate clinical probability for APE when they have hypotension or shock.

Besides the role in diagnosing APE, chest CTPA can provide information about hemodynamic significance of APE. Previous studies have shown that RV enlargement of chest CTPA is a marker for RV dysfunction in patients with APE (Fig. 2A) [17, 18]. RV enlargement can be evaluated by measuring right ventricular dimension to left ventricular dimension (RVD/LVD) ratio in a 4-chamber view of the chest CTPA, and RVD/LVD ratio greater than 1.0 is suggested as a reliable marker for RV dysfunction in a meta-analysis [19]. RVD/LVD ratio greater than 0.9 on chest CTPA was used as a marker for RV dysfunction in another prospective cohort study [20]. In a previous study, the optimal cut-off value of RVD/LVD ratio on CTPA for predicting RV dysfunction was 1.12 [21]. Leftward ventricular septal bowing and contrast reflux to the inferior vena cava on CTPA are also considered as suggestive findings of RV dysfunction in APE (Fig. 2B–D), but the diagnostic sensitivity and/or specificity of these findings are lower than those of RVD/LVD ratio. For these reasons, the measurement of RVD/LVD ratio has proved to be the most reliable predictor of mortality in patients with APE among CTPA measurements [21–23].

Chest CTPA also enables assessment of the presence, location, and degree of thrombi burden in APE (Fig. 3). Several scoring systems have been developed to evaluate the severity of a current episode of APE by measuring PA clot loads (Table 1) [24–28]. Qanadli index is a scoring system that evaluates the embolic burden by combining the total number of involved pulmonary vascular segments and degree of embolic obstruction [25]. Some studies demonstrated that the Qanadli index was a good predictor of RV dysfunction or mortality in APE, but it was not a predictor of RV dysfunction or mortality from APE in other studies [29–32]. Therefore, the clinical significance of these pulmonary artery clot load scoring systems for the prediction of RV dysfunction or mortality in patients with APE should be clarified through further and larger studies.

With recent advances in processing of CT images, dual energy CT (DECT) has become available for the assessment of pulmonary parenchyma perfusion, by using iodine-subtraction techniques [33]. Perfusion defect or hypo-perfused region corresponding to the vascular obstruction is indicative of PE (Fig. 4). Thus, DECT can be useful in the assessment of PE without evidence of overt thrombus on CTPA. However, the diagnostic or prognostic role of DECT in APE remains poorly defined. Further research should be conducted to investigate the role of quantitative DECT on clinical outcomes in patients with APE.

Table 1. Various scoring systems assessing pulmonary arterial clot load

Pulmonary Artery Clot Load Scores
Miller score [24, 28]
n — number of obstructed arterial segments
1 point for filling defects on any one of segmental branches
Max.16 points: according to the involved lobal region
— right: max. 9 points (upper 3, middle 2, lower 4)
— left: max. 7 points (upper 2, middle 2, lower 3)
Walsh score [27, 28]
n — number of obstructed arterial segments
1 point for segmental filling defect or obstruction
Max. 18 points: according to the involved lobal region
— max. 9 points for each lobe (upper 3, middle or lingular 2, lower 4)
— max. 3 points for single central region
Qanadli score [25]
Qanadli index = Σ (n × d) / 40 × 100 (CT obstruction index)
n — number of obstructed arterial segments
— 1: presence of embolus in a segmental artery
d — degree of vascular obstruction
— 0: no occlusion
— 1: partial occlusion
— 2: total occlusion
Max. 40 points: 10 segmental arteries for each lobe
Mastora score [26]
n — number of obstructed arterial segments
d — degree of vascular obstruction
— 1: < 25% obstruction
— 2: 25~49% obstruction
— 3: 50~74% obstruction
— 4: 75~99% obstruction
— 5: 100% obstruction
Scoring in each location level
— central score (5 mediastinal and 6 lobar)
— peripheral score (20 segmental)
— global score (central and peripheral)
Max. 155 points

Max — maximal; CT — computed tomography

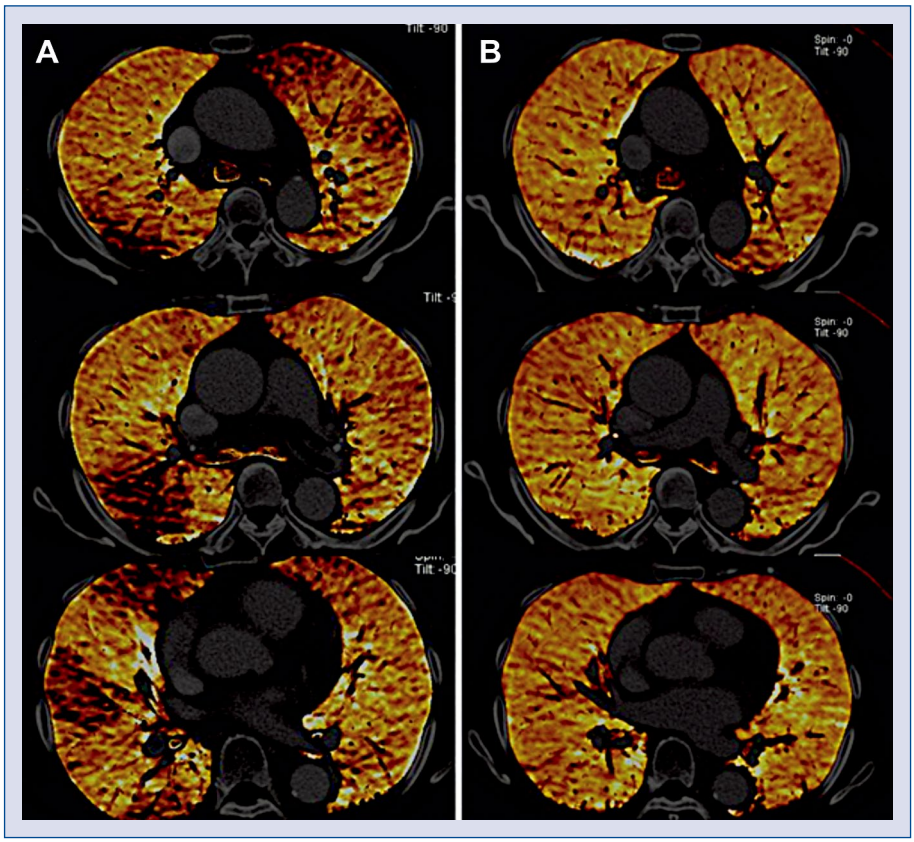

Figure 4. Dual energy computed tomography (DECT) in a 55-year-old female with acute pulmonary embolism. Pre-treatment DECT shows multi-focal hypoperfused regions (dark-brown color) corresponding to the location of vascular obstruction (**A**). Follow up DECT shows the disappearance of hypoperfused regions after 6-months of anticoagulation (**B**).

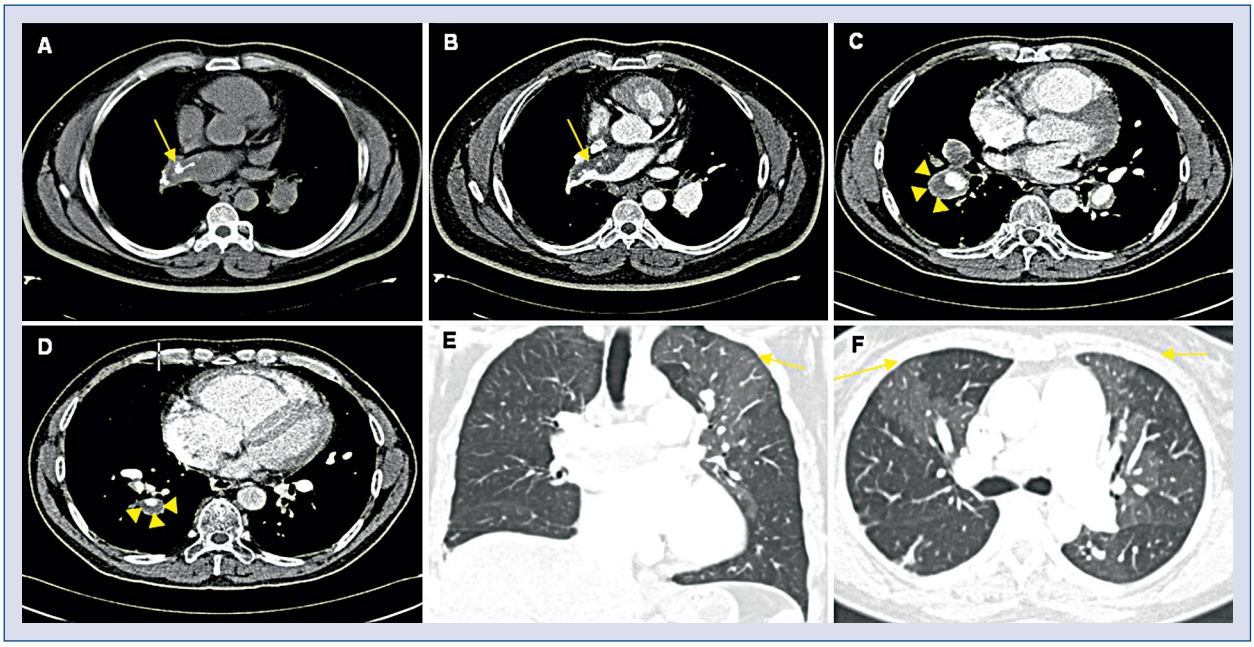

Figure 5. Chest computed tomography angiography (CTPA) suggesting chronic thromboembolic pulmonary hypertension. Calcific thrombi (arrows) in right pulmonary artery on pre-enhance (**A**), post-enhance CTPA (**B**), eccentric (crescentic shape) thrombi (arrow heads; **C**, **D**), and nonuniform arterial perfusion pattern and mosaic pattern of lung attenuation (**E**, **F**).

Chest CTPA is an imaging of choice for the diagnosis of APE, but CTPA alone cannot exclude or confirm CTEPH completely. In the current guidelines, V/Q lung scan still remains the first-line imaging modality for the detection of CTEPH because V/Q scans demonstrate better sensitivity and specificity for the diagnosis of CTEPH as compared to those of chest CTPA [3, 34]. Nevertheless, several findings of chest CTPA can be useful in differentiating CTEPH from APE and CTEPH. The eccentric wall-adherent or mural thrombi, which are often calcified, is a relatively specific finding of CTEPH on CTPA (Fig. 5A, B). Complete vessel cutoff with convex margin due to organized thrombi is another specific feature of CTEPH, which is different from the concave margin of acute PE with a tapering of thrombus (Fig. 5C, D). An additional finding of CTEPH is the abrupt narrowing of the vessel distal to complete obstruction, due to contraction of the thrombus in chronic PE. Intraluminal webs or band and intimal irregularities by organized thrombi are not pathognomic but suggestive that findings with CTPA are consistent with CTEPH as well. In the chronic type of PE, development of collateral systemic circulation such as bronchial artery dilatation is frequently observed [35–37]. In addition, a non-uniform arterial perfusion pattern and mosaic pattern of lung attenuation can be observed on CTPA in CTEPH (Fig. 5E, F). When chest CTPA revealed these findings, the possibility of CTEPH should be carefully monitored even in patients who were first diagnosed as PE.

In summary, the role of chest CTPA in PE can be summarized as follows; 1) chest CTPA is a gold standard CV imaging for the evaluation of suspected APE, and it has replaced the role of V/Q scan in the diagnosis of APE; 2) chest CTPA is useful in the evaluation of RV dysfunction in APE and thus risk stratification or clinical decision making of therapeutic strategy, especially before performing TTE or when TTE is not available; 3) chest CTPA enables a quantitative assessment of pulmonary artery clot loads by using a scoring system and DECT allows an assessment of pulmonary parenchyma perfusion, but the significance of these techniques should be validated through larger, future studies; 4) several findings of CTPA can be useful in differentiating CTEPH from APE, even though a V/Q scan is an imaging of choice in the diagnosis of CTEPH.

Nuclear imaging: Ventilation/ /perfusion scintigraphy

V/Q scan is an established diagnostic test for suspected PE. The main finding of V/Q scans in PE is that of perfusion (Q) defect without corresponding ventilation (V) defect, which is recognized as a V/Q mismatch (Fig. 6). Interpretation of the V/Q scan is important, considering the fact that there are other medical conditions that might cause a V/Q mismatch, such as veno-occlusive disorder, vasculitis, congenital pulmonary vascular abnormalities, pulmonary artery sarcoma, fibrosing mediastinitis, malignancy and mediastinal lymphadenopathy. Currently, the modified PIOPED II and prospective investigative study of acute pulmonary embolism diagnosis (PISAPED) criteria are most commonly used in the interpretation, with a sensitivity of 85% vs. 80% and specificity of 93% vs. 97%, respectively [38, 39].

These systems classify studies as high probability, very low probability, normal and non-diagnostic. Current guideline recommends excluding PE when the study has been classified as normal, and to confirm PE when the study has been classified as high probability [3].

Presently, the V/Q scan is one of the most useful imaging modalities in screening CTEPH in patients with PH in the absence or disappearance of PE. In CTEPH, V/Q scans reveal at least one segmental perfusion defect despite normal ventilation. According to the current guidelines, V/Q scan is recommended as a first-line imaging modality for CTEPH, with 96–97% sensitivity and 90–95% specificity for diagnosis [3].

Recently, the introduction of single photon emission computed tomography (SPECT) into V/Q scintigraphy has emerged, which enables defining the size and location of perfusion defects more accurately, using a three-dimensional imaging technique [40]. Accordingly, the diagnostic performance of SPECT V/Q has been increasing with higher reproducibility and lower indeterminate rate compared to V/Q scanning [41–43].

In summary, the role of the V/Q scan can be summarized as follows; 1) V/Q scan has high diagnostic accuracy in the evaluation of PE; 2) V/Q scan is useful in the discrimination of CTEPH from APE, and is recommended as a first-line diagnostic tool for CTEPH.

Magnetic resonance pulmonary angiography

Magnetic resonance pulmonary angiography (MRPA) is another non-invasive imaging modality that can provide information about not only morphological assessment, but also functional assessment in patients with PE.

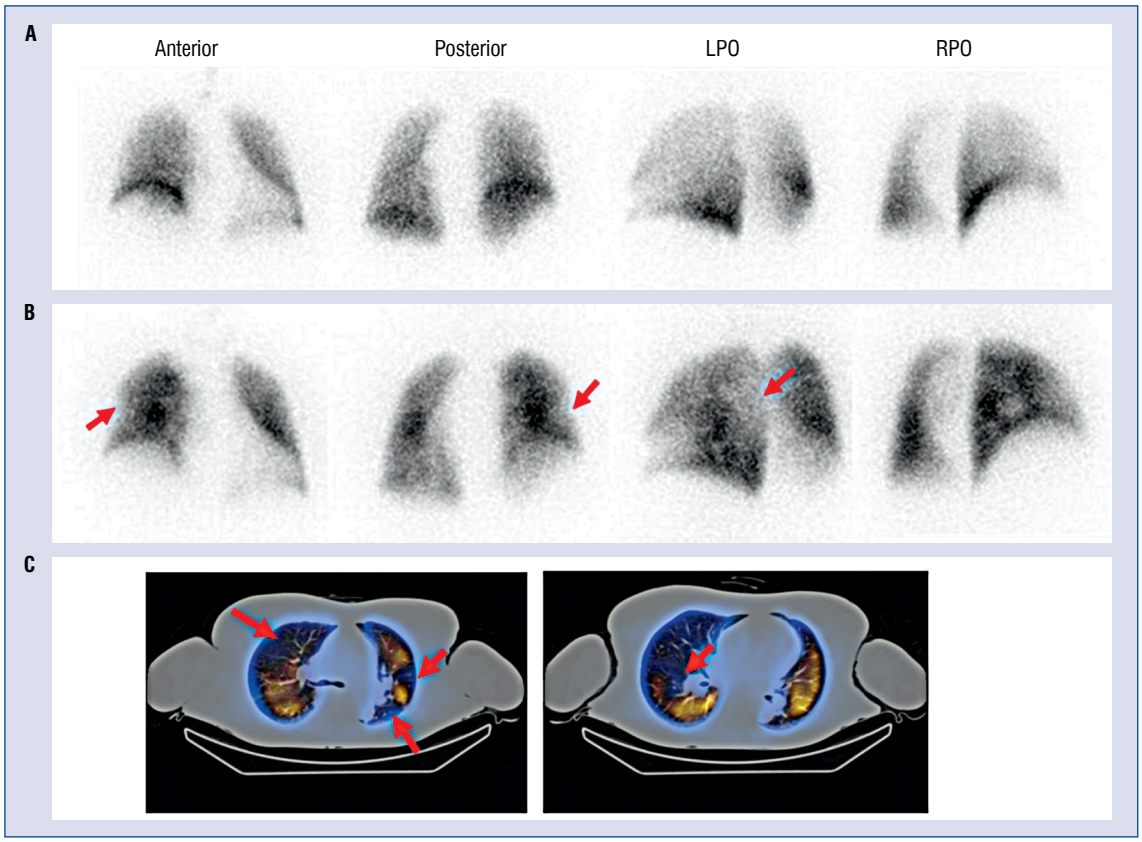

Figure 6. Ventilation/perfusion (V/Q) scans demonstrating pulmonary embolism. Moderate to large mismatch on V/Q scan: normal ventilation scan (**A**) and moderate-sized perfusion defect in right middle lung and large-sized perfusion defect in left upper lung on perfusion scan (**B**). A large-sized perfusion defect in right upper lung, and two, small-sized perfusion defects in left upper lung and a missed perfusion defect in anterior basal segment of right lower lung on perfusion planar image in perfusion single photon emission computed tomography-computed tomography (SPECT-CT; **C**); LPO — left posterior oblique; RPO — right posterior oblique.

With MRPA, vascular deformities such as vascular filling defects, complete absence of vessel enhancement, post-stenotic dilatation, and dilatation of a main pulmonary artery can be detected [44]. As with CTPA, irregular luminal filling defects, intraluminal webs and bands, vessel cutoffs and organized thrombi are indicative findings of CTEPH [45].

Recent research have shown that pulmonary artery flow can be assessed using phase contrast magnetic resonance [46]. Three- and four-dimensional phase contrast magnetic resonance imaging (MRI) provides visualization of vortex flow changes in pulmonary arteries [46, 47].

However, MRPA has lower sensitivity of PE compared to CTPA, especially in peripheral involvements [48]. The main advantages of MRPA are that it is free of ionizing radiation and can provide information on structure and flow mechanics [49–51].

Nevertheless, MRPA is not recommended for routine investigation of PE, because of its limited availability, technically inadequate studies, reduced robustness and higher cost [3]. MRPA is anticipated as a promising imaging tool in the diagnosis of PE, however further studies are warranted for the clinical use of MRI in the diagnosis of PE.

Role of conventional pulmonary angiography

Pulmonary angiography provides direct visualization of obstructed vasculature or thrombi and also hemodynamic measurements [52]. It offers better visualization of peripheral pulmonary vessels, which can go undetected with other non-invasive imaging modalities, such as CTPA or MRPA. Filling defect or loss of pulmonary arterial branch is an indicative sign of PE. Currently, pulmonary angiography is more useful in patients suspected

Table 2. Comparisons of various cardiovascular imaging modalities in the assessment of pulmonary embolism

Modality	Advantages	Disadvantages
Transthoracic echocardiography (TTE)	1. Bedside evaluation is possible 2. Useful in the evaluation of treatment efficacy by serial exam 3. Allows assessment of hemodynamics 4. Relatively inexpensive cost 5. Widely available equipment 6. No radiation	1. Operator-dependent 2. Cannot identify the thrombus extent 3. High sensitivity, low specificity 4. Suboptimal in patients with poor imaging windows
Computed tomography pulmonary angiography (CTPA)	1. High diagnostic accuracy 2. Diagnostic modality of choice 3. Directly visualize the extent and burden of the thrombus 4. Visualize thromboembolic resolution after treatment 5. Allows assessment of other cardiac structures	1. Radiation exposure 2. Contrast administration precludes use in patients with advanced renal disease
Ventilation/perfusion (V/Q) scan	1. High diagnostic accuracy 2. Helps to distinguish CTEPH from acute pulmonary embolism	1. Limited availability 2. High cost 3. Radiation exposure
Magnetic resonance imaging (MRI)	1. Free from ionizing radiation 2. Can provide information on structure and flow mechanics	1. Limited availability 2. Gadolinium administration precludes use in patient with advanced renal disease 3. High cost

CTEPH — chronic thromboembolic pulmonary hypertension

for CTEPH. Similar to CTPA findings, complete vessel cutoff with convex contour of thrombi, abrupt vessel narrowing, luminal irregularity and intravascular bands or webs are indicative signs of CTEPH rather than APE [36].

In patients with APE with shock or hypotension, prompt catheter-directed thrombolysis or thrombectomy can be performed after diagnosis of APE. Otherwise in patients with PH with suspected CTEPH, pulmonary balloon angioplasty followed by diagnostic pulmonary angiography can be performed for PH relief [3, 34, 53, 54].

Role of venous compression ultrasonography

The role of lower extremity venous compression ultrasonography (CUS) in the routine diagnostic strategy is limited because of its low sensitivity for PE [3, 55].

With the advancements in technology, CTPA has shown better diagnostic performance in detecting PE compared to CUS [56]. However, it is useful to perform a CUS in diagnosing PE, in cases where it is difficult to obtain CTPA, such as pregnant women, patients with chronic kidney disease or with an allergy to contrast media [57, 58].

Imaging modalities in special cases

Pregnancy

The imaging modality of choice in the diagnosis of deep vein thrombosis (DVT) of the lower limb in pregnancy is CUS. Abnormal D-dimer and proximal DVT founded by lower extremity compressive venous sonography warrants anticoagulation therapy and makes thoracic imaging unnecessary.

Guidelines recommend performing a V/Q scan over CTPA in the diagnosis of PE in pregnant women. The V/Q scan protocol can be adjusted to

lower fetal and maternal radiation exposure. A low dose perfusion scan can be performed with a half dose of routine radiopharmaceutical agents. It is not fully established, but V/Q scan may offer less maternal radiation exposure and higher diagnostic accuracy compared to that of CTPA [3, 59, 60].

Impaired renal function

Computed tomography pulmonary angiography is not a good option for the diagnosis of PE in patients with high risk for radio-contrast induced nephropathy. Magnetic resonance angiography carries a better renal safety profile and no radiation exposure [61]. However, gadolinium-related nephrogenic systemic fibrosis could occur [62]. V/Q scan is preferred over CTPA in patients with impaired renal function and suspicions of PE to avoid contrast mediated injury of the kidneys [63].

Conclusions

Despite many advances in medical technology, there is still uncertainty about decisions in the diagnosis and prognosis of PE and treatment plans in clinical practice. A high index of clinical suspicion and selection and use of optimal CV imaging are essential in the diagnosis of PE. Physicians, therefore, should be familiar with the major advantages or pitfalls of various CV imaging modalities used in the evaluation of PE (Table 2). The optimal use of multimodality CV imaging enables the comprehensive assessment of anatomical and functional severity of PE and the prediction of prognosis as well as the decision for choosing therapeutic strategy.

Conflict of interest: None declared

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TECHNOLOGY NOTE

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First-in-human radiofrequency ablation of ventricular tachycardia performed through an Atrial Flow Regulator device

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Despite substantial progress in electrotherapy, sustained ventricular tachycardia (VT) and electrical storm remain the frequent causes of death among patients with end-stage heart failure (HF). A radiofrequency (RF) ablation (RFA) is a well-recognized treatment option for patients with electrical storm who suffer from resistant VT [1].

Recently we published the clinical and hemodynamic results of a 66-year-old patient with HF, left ventricular ejection fraction 20%, who underwent a novel therapy based on atrial septostomy followed by implantation of the Atrial Flow Regulator (AFR, Occlutech, Helsingborg, Sweden) [2]. Six weeks after AFR implantation, the patient was hospitalized because of recurrent VT with multiple appropriate cardioverter-defibrillator (ICD) shocks. On admission, the patient was conscious and hemodynamically stable. He was taking beta-blocker and amiodarone for an extended period before recent hospitalization. During the patient's stay in the intensive care unit, a basic pacing rhythm was increased to 100/min, and continuous infusion of lignocaine up to 120 mg per hour was started. The patient received sedation, however, sustained VT recurred during the following couple of days. Therefore, a decision was made to perform an electrophysiological study followed by RFA.

The procedure was done on 4th of March 2020.

Under local anesthesia and sedation with remifentanil and midazolam, right femoral vein access was obtained. A 0.032 guidewire was placed into the left atrium through the 8 mm fenestration in the AFR device in the first step. Steerable sheath (Agilis NxT large curve) was introduced into the left atrium using the 8 mm hole (Fig. 1). The procedure was performed using the Ensite Precision three-dimensional mapping system (Abbott Cardiovascular). Substrate mapping and ablation of conductive channels within the scar approach was planned. During right ventricle pacing from implanted ICD, a potential bipolar map was obtained with an HDGrid catheter. An extensive scar of the anterior wall, including the anterior part of the septum and apex, was mapped. Also, low and late potentials were found, especially in the apex and mid anterior wall (Fig. 1). During catheter manipulation, clinical arrhythmia was easily induced. Because of acceptable tolerance, an activation map during VT was also obtained, revealing the exit of the VT loop in the mid-region of the anterior wall. Pacing within the scar of this site resulted in S-QRS 150 ms with 90% QRS morphology concordance. HDGrid mapping catheter was exchanged to TactiCath SE F-J ablation catheter, and RF applications in this region (50 W 30 s) was applied. Rapid ventricular

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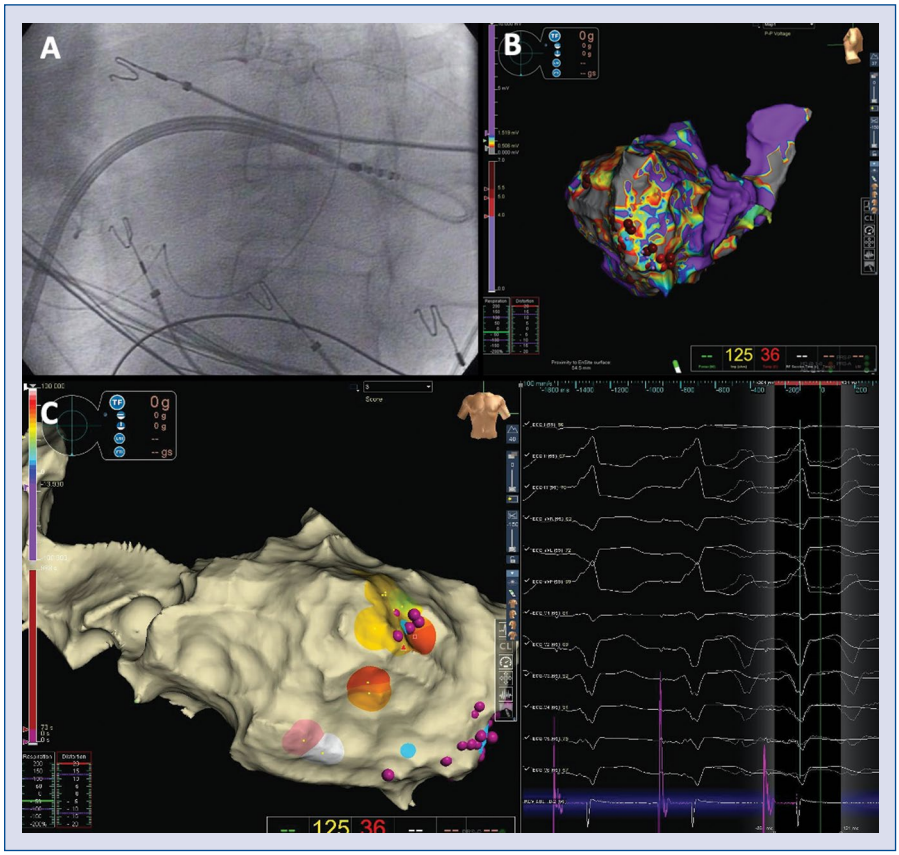

Figure 1. A. Left anterior oblique 30 view of the steerable sheath with the ablation electrode introduced through Atrial Flow Regulator device; **B.** Bipolar map of the extensive anterior wall, septum, and apical scar with patchy areas in apex and late potentials recorded in this region; **C.** Long S-QRS interval during anterior part of septum stimulation (capture of conducting channel in a scar) with similar to ventricular tachycardia paced QRS morphology.

stimulation-induced another VT with a loop exiting scar in the apical region. RF applications (55 W 30 s) resulted in the abolition of late potentials in this area and the arrhythmia's non-inducibility.

The patient was discharged home on the third day after the procedure. He remained free of ventricular arrhythmia during 3 months follow-up.

The AFR is a self-expandable double-disc nitinol wire mesh construction allowing communication across the interatrial septum through an 8 mm fenestration. This communication enables the decompression of the left atrium and may improve patients' symptoms [3].

We have successfully implanted ten AFR devices thus far in patients with severe HF. These procedures were done as part of an ongoing PROLONGER trial (Pomeranian atRial flOw reguLatOr iN conGestive hEart failuRe; No. NCT04334694 at clinicaltrials.gov). According to available research, this is the first published data on performing an RFA in a patient with an electrical storm using a fenestration in AFR.

Conflict of interest: None declared

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RESEARCH LETTER

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Hyperemic contrast velocity assessment improves accuracy of the image-based fractional flow reserve calculation

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Collet et al. [1] published a meta-analysis about the diagnostic performance of angiography-derived (image-based) fractional flow reserve (FFR). They concluded that the angiography-derived FFR was suitable for detecting hemodynamically significant lesions with good accuracy compared with pressure wire measured FFR as a reference. Thirteen studies were included in this systematic review; hyperemia was induced in three studies [2–4] and the comparison of the results of FFR values from hyperemic and baseline velocity data was published only in the FAVOR pilot study (FAVOR1) [3].

In our previous study, on a less invasive FFR measurement, we proposed a new simplified model developed for the estimation of FFR [2]. It was found that this method was suitable for characterizing every single intermediate stenosis with an especially good positive predictive value; furthermore, the calculations only require a simple MS Excel sheet for the input of the hyperemic flow velocity values and the data of the three-dimensional coronary reconstruction. During this previous study, real patient specific flow information was applied in every case using the hyperemic frame count data during i.c. adenosine challenge. The translesional pressure gradients were calculated according to simple fluid dynamic equations as published in an earlier paper by our group [5].

The purpose of this present study was to perform a retrospective analysis on the cases of the previous study [2] to assess the accuracy of FFR calculations using the fixed hyperemic contrast flow, the resting frame count, and the hyperemic frame count data.

Fifty patients with intermediate severity epicardial coronary artery disease (40–70% diameter stenosis) were re-evaluated. The details of the measurements were published in Tu et al. [4]. Diagnostic angiographic images were recorded at 15 frame/sec both in resting and hyperemic conditions. Low- or iso-osmolar contrast material (CM) (iopamidol [Scanlux] or iodixanol [Visipaque]) was injected in 5 mL fractions with a speed of 3 mL/s using a dedicated contrast pump (Fig. 1).

The calculations were performed using three different velocity values:

— **fixed** FFR_{sim}: calculated from the fixed hyperemic velocity (35 cm/s);
— **rest** FFR_{sim}: calculated using the non-hyperemic frame count data to extrapolate the hyperemic velocity. For extrapolation the quadratic relation between the baseline contrast flow velocity (CFV) and the hyperemic flow velo-

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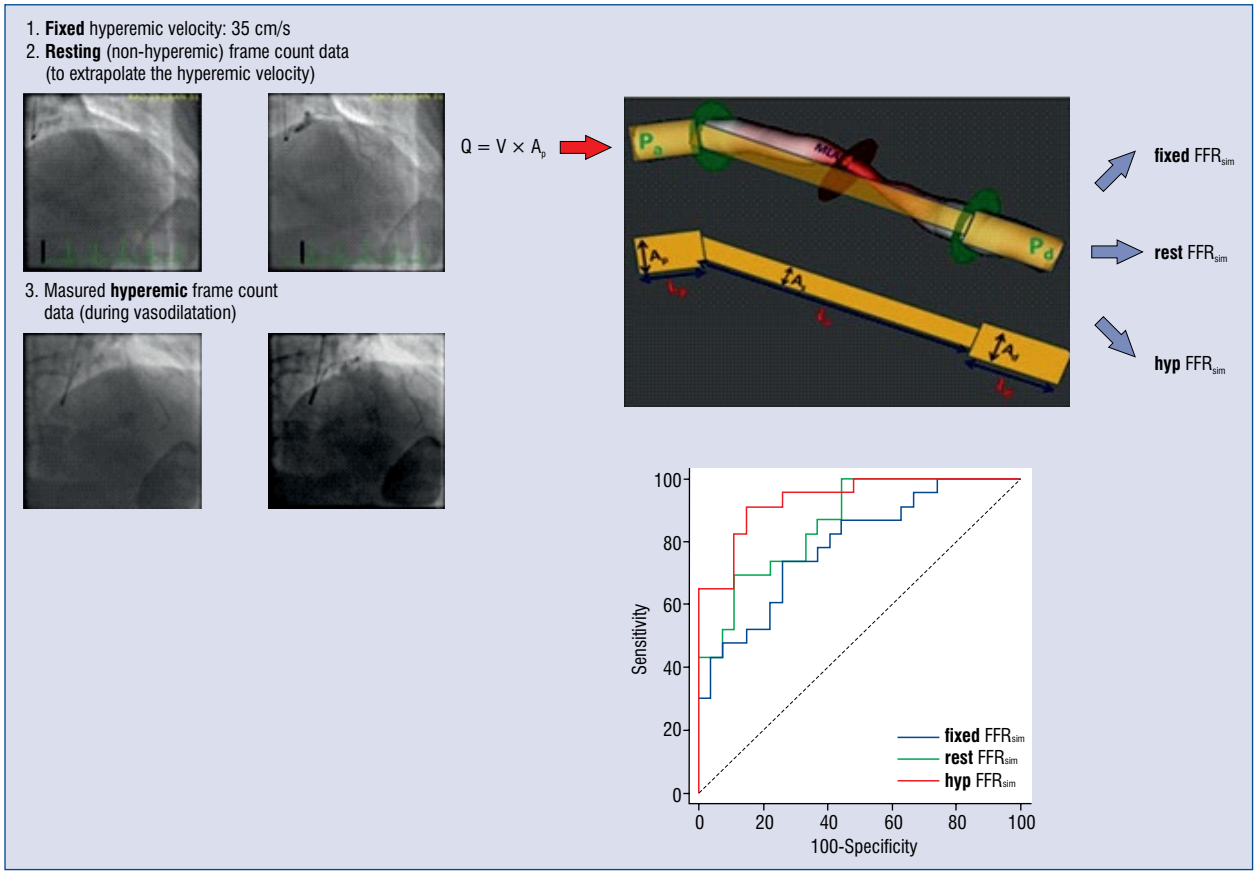

Figure 1. Different calculations of the FFR_{sim} and the comparison of receiver operating characteristic (ROC) curves. Flow velocities for pressure drop calculations were applied: 1. **Fixed** hyperemic velocity: 35 cm/s; 2. **Resting** (non-hyperemic) frame count data to extrapolate the hyperemic velocity according to a database: $HFV = a_0 + a_1xCFV + a_2xCFV^2$ ($a_0 = 0.10$; $a_1 = 1.55$; $a_2 = -0.93$), where HFV is hyperemic flow velocity, CFV is a resting contrast flow velocity) [5]; 3. Measured **hyperemic** frame count data (during vasodilatation). Comparison of ROC curves: The **hyp** FFR_{sim} showed the strongest prediction of the measured FFR values. The area under the curve (AUC) for **hyp** FFR_{sim}: 0.936 (95% CI 0.828–0.985), for rest FFR_{sim} 0.862 (95% CI 0.734–0.943) and for fixed FFR_{sim}: 0.791 (95% CI 0.652–0.893); p = 0.011 between **hyp** FFR_{sim} and **rest** FFR_{sim}; p = 0.005 between **hyp** FFR_{sim} and **fixed** FFR_{sim}.

city (HFV) was applied and was published in the FAVOR1 study [5]: $HFV = a0 + a1xCFV + a2xCFV^2$, where a0 = 0.10, a1 = 1.55 and a2 = –0.93;

— **hyp** FFR_{sim}: values from hyperemic frame count assessment [4].

The area under the curve (AUC) by receiver operating characteristic (ROC) analysis was used to assess the diagnostic power of FFR_{sim}.

The diagnostic powers of different computations of the FFR_{sim} was assessed comparing the results to standard invasive FFR measurements (FFR_{meas}). Based on ROC curve analysis for predicting the abnormal FFR of ≤ 0.80 the AUC were significantly higher for the hyperemia-based parameters than for those calculated with the resting frame counts: 0.936 (95% confidence interval [CI] 0.828–0.985) for **hyp** FFR_{sim}, 0.862 (95% CI 0.734–0.943) for **rest** FFR_{sim}, and 0.791 (95% CI 0.652–0.893) for **fixed** FFR_{sim} (p = 0.011 between **hyp** FFR_{sim} and **rest** FFR_{sim}; p = 0.005 between **hyp** FFR_{sim} and **fixed** FFR_{sim}; Fig. 1).

Despite the potential confounding factors of the Thrombolysis in Myocardial Infarction (TIMI) frame count measurement, it was proven that its reproducibility is acceptable for clinical purposes [6]. However, the heart rate and the phase of the cardiac cycle in which the dye is injected have been reported to exert significant effects on the TIMI frame count determination [7].

The effect of timing of the injection on the produced contrast speed in the different phases of the cardiac cycle is evident: there are significantly different coronary flow velocities during the

phases of the heart cycle — the diastolic velocity is usually twice as high as the systolic velocity in the left coronary artery. Theoretically it would be possible to correct the assessed frame count to the assumed average blood flow by relating the determined frame count to the measuring interval of the cardiac cycle by an appropriate algorithm to be developed in the future.

In contrast to the FAVOR1 study [3], the work herein, demonstrates that the hyperemic velocity assessment is superior for patient specific calculation of the hyperemic pressure gradient i.e. the FFR. The diagnostic performance of hyperemic frame count determination is significantly higher according to the ROC analysis than the resting frame count-based calculations. The differing results of the FAVOR1 study can be explained by the different patient populations in the two studies. While in the FAVOR1 study only 31.5% of the patients had prior myocardial infarction, in the present patient population prior myocardial infarction had occurred in 51.6% of patients [3, 4]. This implies that in our population, the distal microvasculature could be damaged more frequently with consequent impairment of the vasodilator capacity [8].

In our opinion, the calculation of the extrapolated image based FFR without vasodilation could only be acceptable if the results are unequivocal — either below 0.70 or above 0.90. However, in the range of FFR 0.70–0.90, vasodilator challenge is highly reasonable, especially if the presence of microvascular disease is suspected. Currently there is no other viable approach to increase the accuracy of image-based FFR without assessing patient specific hyperemic velocity.

Although image-based FFR calculation without hyperemia seemed to be accurate enough for clinical purposes, the vasodilator challenge is highly reasonable for personalized accuracy of the investigation, especially when the presence of microvascular disease is suspected. An exact heart cycle correction for the hyperemic velocity assessment could further improve the accuracy of image-based FFR determination.

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QRS duration and cardiovascular mortality in Asian patients with heart failure and preserved and reduced ejection fraction

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The QRS duration has been well established as a predictor of mortality in patients with heart failure with reduced ejection fraction (HFrEF) [1]. In patients with heart failure with preserved ejection fraction (HFpEF), some studies have shown that prolonged QRS duration has been associated with increased morbidity and mortality [2, 3]. However, these studies were based mainly on Western cohorts with scarce data from Asia, where normal ranges for QRS duration may differ [4, 5]. The aim of this study was to examine the association between QRS duration and mortality in an Asian heart failure cohort.

Consecutive patients who were admitted with heart failure as the primary diagnosis from two institutions from 1 January 2008 to 31 December 2009 were included. Those with paced rhythms were excluded. The QRS interval was measured by trained staff on a 12-lead electrocardiogram upon admission. HFpEF was defined as heart failure patients with ejection fraction (EF) ≥ 50% and ≥ grade 1 diastolic dysfunction on the echocardiogram or N-terminal-pro-B-type natriuretic peptide (NT-proBNP) level > 220 pg/mL heart failure with non-preserved EF (HFnpEF) was defined as EF < 50%. The outcomes were obtained from national registries. All patients were followed-up till December 2014. The primary outcomes were all-cause mortality and cardiovascular mortality. Ethics approval was obtained from the institutional review board.

Cox proportional hazard modelling was used to identify predictors of all-cause and cardiovascular mortality. Variables significant on univariate analysis ($p < 0.05$) were selected for the multivariate models. Multivariate Cox proportional hazard models were then performed for each heart failure cohort to calculate hazard ratios (HR) and associated 95% confidence intervals (CI) for mortality. QRS duration was analyzed both as a continuous and categorical variable. The optimal QRS cut-off was assessed by area under receiver operating characteristics (AUROC) curve. Data was analyzed using the Statistical Package for the Social Sciences (SPSS®, version 23.0). A p value of < 0.05 was taken to be statistically significant.

A total of 666 HFpEF (mean age 73.1 ± 10.5, 36.3% male, mean LVEF 61 ± 8%) and 1032 HFnpEF (mean age 66.3 ± 12.4 years, 64.3% male, mean LVEF 29 ± 13%) were included. The clinical characteristics are summarized in Table 1.

In patients with HFpEF, 5-year overall and cardiovascular mortality was 57% (n = 381) and 28% (n = 189) respectively. QRS duration as a continuous variable was a significant predictor of cardiovascular (adjusted HR 1.010; 95% CI 1.002–1.018; p = 0.011) but not overall mortality (p = 0.190). A cut-off of 100 ms was found to provide the optimal discriminatory AUC compared to other cut-offs including 90 ms, 110 ms and 120 ms. A QRS ≥ 100 ms was a significant predictor of cardiovascular mortality (adjusted HR 1.468; 95% CI 1.014–2.126; p = 0.042) but not overall mortality (adjusted HR 1.287; 95% CI 0.993–1.668; p = 0.056).

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Table 1. Clinical characteristics of the study population.

	Preserved ejection fraction (n = 666)			Reduced ejection fraction (n = 1032)		
	< 100 ms (n = 482)	≥ 100 ms (n = 184)	P	< 100 ms (n = 484)	≥ 100 ms (n = 548)	P
Demographics						
Mean age (SD)	73.0 (10.5)	72.6 (11.0)	0.634	65.9 (12.8)	66.8 (12.1)	0.239
Male	141 (29.3%)	101 (54.9%)	< 0.001	272 (56.2%)	394 (71.9%)	< 0.001
Race:						
Chinese	360 (74.7%)	136 (73.9%)	0.452	328 (67.8%)	372 (67.9%)	0.545
Malay	55 (11.4%)	24 (13.0%)		95 (19.6%)	94 (17.2%)	
Indian	59 (12.2%)	18 (9.8%)		51 (10.5%)	71 (13.0%)	
Others	8 (1.7%)	6 (3.3%)		10 (2.1%)	11 (2.0%)	
Clinical characteristics						
Prior CAD	204 (42.3%)	69 (37.5%)	0.258	193 (39.9%)	298 (54.4%)	< 0.001
Prior MI	80 (16.6%)	34 (18.5%)	0.564	179 (37.0%)	210 (38.3%)	0.658
Atrial fibrillation	164 (34.0%)	73 (39.7%)	0.173	94 (19.4%)	127 (23.2%)	0.142
Diabetes mellitus	225 (46.7%)	86 (46.7%)	0.989	304 (62.8%)	277 (50.5%)	< 0.001
Hypertension	388 (80.5%)	139 (75.5%)	0.159	324 (66.9%)	386 (70.4%)	0.226
Hyperlipidemia	297 (61.6%)	96 (52.2%)	0.027	306 (63.2%)	355 (64.8%)	0.603
Stroke	86 (17.8%)	36 (19.6%)	0.607	66 (13.6%)	78 (14.2%)	0.782
PVD	24 (5.0%)	12 (6.5%)	0.431	35 (7.2%)	38 (6.9%)	0.853
COPD	61 (12.7%)	30 (16.3%)	0.220	48 (9.9%)	74 (13.5%)	0.075
Ever smoker	116 (24.1%)	67 (36.4%)	0.001	202 (41.7%)	279 (50.9%)	0.003
Systolic BP (SD) [mmHg]	143.1 (29.1)	140.3 (31.3)	0.266	139.8 (30.5)	133.6 (29.2)	0.001
Diastolic BP (SD) [mmHg]	73.2 (16.5)	72.4 (17.5)	0.608	80.6 (19.3)	75.6 (18.3)	< 0.001
Heart rate (SD)	84.4 (22.9)	78.8 (22.9)	0.005	92.8 (21.0)	84.4 (18.3)	< 0.001
QRS duration (SD)	85.1 (8.1)	115.7 (17.5)	< 0.001	87.9 (7.6)	123.9 (24.2)	< 0.001
NT-proBNP (SD) [pg/mL]	5079.9 (7141.8)	8282.3 (11909.7)	0.061	11741.1 (14600.0)	12389.6 (15358.1)	0.537
Creatinine (SD) [μmol/L]	121.4 (84.8)	145.9 (125.3)	0.015	133.4 (98.4)	141.2 (92.7)	0.186
Sodium (SD) [mmol/L]	136.4 (4.9)	136.2 (5.2)	0.706	136.0 (7.3)	135.8 (8.7)	0.713
Potassium (SD) [mmol/L]	4.2 (0.8)	4.2 (0.8)	0.451	4.3 (0.8)	4.3 (1.8)	0.895
Hemoglobin (SD) [g/dL]	11.7 (2.0)	12.0 (2.1)	0.085	12.4 (2.1)	12.6 (2.0)	0.046
Discharge medications						
ACEI/ARB	284 (58.9%)	114 (62.0%)	0.475	360 (74.4%)	415 (75.7%)	0.617
Beta-blocker	240 (49.8%)	98 (53.3%)	0.423	314 (64.9%)	369 (67.3%)	0.405
Spironolactone/Aldosterone antagonist	35 (7.3%)	17 (9.2%)	0.395	90 (18.6%)	145 (26.5%)	0.003
Nitrate	192 (39.8%)	84 (45.7%)	0.173	245 (50.6%)	312 (56.9%)	0.042
Diuretic	365 (75.7%)	148 (80.4%)	0.176	424 (87.6%)	476 (86.9%)	0.722
Digoxin	88 (18.3%)	37 (20.1%)	0.584	130 (26.9%)	158 (28.8%)	0.481
ASA	196 (40.7%)	87 (47.3%)	0.122	282 (58.3%)	331 (60.4%)	0.485
Clopidogrel	63 (13.1%)	16 (8.7%)	0.118	89 (18.4%)	90 (16.4%)	0.405
Warfarin	86 (17.8%)	33 (17.9%)	0.978	52 (10.7%)	70 (12.8%)	0.313
Lipid-lowering	301 (62.4%)	112 (60.9%)	0.707	357 (73.8%)	395 (72.1%)	0.545

CAD — coronary artery disease; MI — myocardial infarction; PVD — peripheral vascular disease; COPD — chronic obstructive pulmonary disease; BP — blood pressure; NT-proBNP — N-terminal-pro-B-type natriuretic peptide; ACEI/ARB — angiotensin converting enzyme/angiotensin receptor blocker; ASA — acetylsalicylic acid

In patients with HFnpEF, 5-year overall and cardiovascular mortality was 65% (n = 673) and 43.0% (n = 444). QRS duration as a continuous variable was a significant predictor of both overall (adjusted HR 1.005; 95% CI 1.001–1.008; p = 0.004) and cardiovascular mortality (adjusted HR 1.006; 95% CI 1.002–1.010; p = 0.003). A cut-off of 100 ms was found to provide the optimal discriminatory AUC compared to other cut-offs including 90 ms, 110 ms and 120 ms. QRS ≥ 100 ms was a significant predictor of both overall (adjusted HR 1.262; 95% CI 1.047–1.522; p = 0.015) and cardiovascular mortality (adjusted HR 1.336; 95% CI 1.058–1.688; p = 0.015; Table 2).

In this Asian HFnpEF cohort, it was found that QRS prolongation predicted both overall and cardiovascular mortality. This is in-line with current literature [1] and lends further evidence to the detrimental impact of QRS prolongation across different ethnicities.

Of greater interest are the results from the HFpEF cohort. In two non-Asian studies, QRS prolongation in HFpEF impacted upon overall mortality [2, 3]. In one of the few Asian studies to-date, Gisberts found a significant association of QRS duration on overall mortality in HFrEF patients, but not in HFpEF patients [4]; cardiovascular mortality was not assessed. The neutral all-cause mortality finding was similar to that of our HFpEF cohort. However, a significant relationship with cardiovascular mortality was additionally found in the HFpEF patients of the current study. This is pathophysiologically plausible with QRS prolongation indicative of cardiac abnormalities [6]. Of note, the cut-offs in the above two non-Asian studies was found to be 120 ms [2, 3]; a cut-off of 100 ms to was found have greater discriminatory value in the Asian cohort. This may be a result of body size or ethnicity [4, 5]. It was found that the average QRS duration in a healthy community-based cohort of Chinese, Malays and Indians was 89 ms in males and 83 ms in female [5]. In the Framingham heart study, the average QRS duration in a healthy Caucasian male was 97 ms and 87 ms in females [7]. Several studies have shown that increasing body size results in increasing QRS duration [5] and this may account for the lower QRS cut-offs as seen in the present study with known smaller body sizes of Asians. The differences in findings between the current HFpEF and HFnpEF cohort are likely the result of both conditions being separate disease entities. Multiple studies have previously shown distinct clinical and prognostic differences between these groups [8].

Table 2. QRS duration, all-cause and cardiovascular (CV) mortality.

	Unadjusted overall mortality		Unadjusted CV mortality		Adjusted overall mortality		Adjusted CV mortality	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Preserved ejection fraction								
QRS duration (continuous)	1.007 (1.002–1.013)	0.012	1.013 (1.006–1.020)	< 0.001	1.004 (0.998–1.011)	0.190*	1.010 (1.002–1.018)	0.011**
QRS duration (categorical)								
< 100 ms								
≥ 100 ms	1.347 (1.086–1.671)	0.007	1.674 (1.246–2.250)	0.001	1.287 (0.993–1.668)	0.056*	1.468 (1.014–2.126)	0.042**
Reduced ejection fraction								
QRS duration (continuous)	1.005 (1.002–1.007)	0.001	1.007 (1.004–1.010)	< 0.001	1.005 (1.001–1.008)	0.004^	1.006 (1.002–1.010)	0.003^^
QRS duration (categorical)								
< 100 ms								
≥ 100 ms	1.249 (1.072–1.454)	0.004	1.488 (1.230–1.800)	< 0.001	1.262 (1.047–1.522)	0.015^	1.336 (1.058–1.688)	0.015^^

HR — hazard ratio; CI — confidence interval; other abbreviations — see Table 1. *Adjusted for age, gender, left ventricular hypertrophy, prior MI, atrial fibrillation, stroke, PVD, smoker, diastolic BP, NT-proBNP, creatinine, sodium, potassium, hemoglobin, ACEI/ARB, beta-blocker, warfarin; **Adjusted for age, ethnicity, left bundle branch block, left ventricular hypertrophy, prior MI, hyperlipidemia, stroke, PVD, systolic BP, NT-proBNP, creatinine, potassium, haemoglobin, warfarin; ^ Adjusted for age, heart rate, coronary artery disease, prior MI, atrial fibrillation, diabetes mellitus, hypertension, hyperlipidaemia, stroke, PVD, systolic BP, diastolic BP, NT-proBNP, creatinine, hemoglobin, ACEI/ARB use, beta-blocker use, nitrates use, ASA use; ^ ^ Adjusted for age, heart rate, right ventricular hypertrophy, CAD, prior MI, atrial fibrillation, diabetes mellitus, hyperlipidemia, stroke, PVD, systolic BP, diastolic BP, NT-proBNP, creatinine, hemoglobin, ACEI/ARB, aldosterone antagonist

HFpEF remains a difficult clinical condition to manage due to its limited therapeutic options. Risk stratification is challenging and has fewer established prognostic markers [9]. An electrocardiogram is readily available and thus QRS duration could potentially be used as a simple risk stratification tool for clinicians. QRS prolongation has been linked to mechanical desynchrony in HFpEF [10]. In appropriate HFrEF patients, the use of cardiac resynchronization therapy has been shown to provide mortality and symptomatic benefit, but how this eventually translates to therapeutic options for HFpEF is less clear. Regardless, HFpEF patients with prolonged QRS duration identifies a subset at higher risk of adverse outcomes; greater efforts must be taken to optimize the holistic care of these patients including control of cardiovascular risk factors.

Limitations of the present study include primary use of hospitalized patients with heart failure; more stable patients in an outpatient/community setting may have been different. Secondly, the current cohort consisted of patients who were mainly of Chinese, Malay and Indian ethnicity which reflects the population distribution in Singapore; the data should be validated in other Asian ethnicities. Thirdly, the uptake of guideline directed medical therapy in the present cohort reflects real-world practice and this cohort was recruited from 2008 to 2009; the potential impact of heart failure therapies, especially the more contemporary medications, will be the work of future studies. Lastly, the QRS duration was only available from the admission electrocardiogram. Changes in QRS duration over time was not captured.

In the present Asian heart failure cohort, QRS duration is a significant predictor of cardiovascular mortality in both HFpEF and HFnpEF patients. QRS duration also significantly predicted overall mortality in HFnpEF patients.

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Perioperative D-dimer levels after transcatheter aortic valve replacement: Comparison of patients with and without anticoagulant therapy

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Transcatheter aortic valve replacement (TAVR) has become an established treatment option for severe aortic valve stenosis. Given this situation, leaflet thrombosis of prosthesis after TAVR has been raised as a persisting concern, as it might cause systemic embolism or valve failure [1]. A prior report showed the relationship between leaflet thrombosis on enhanced computed tomography and elevated D-dimer level [2], which is a product of fibrinolysis and is used as a sensitive marker of intravascular thrombus [3]. An antiplatelet agent is used in the current standard antithrombotic regimen after TAVR; however, some recent reports suggest that patients treated with anticoagulant therapy after TAVR were at lower risk of leaflet thrombosis than those treated without anticoagulant therapy [4, 5]. The purpose of this study was to compare the D-dimer levels during the perioperative period of TAVR between patients with and without anticoagulant therapy.

From among 114 consecutive patients who received TAVR between April 2016 and June 2019 at Nagoya University Hospital, subjects were identified with available perioperative D-dimer levels (more than once within 7 days after TAVR). Patients were excluded if their postoperative D-dimer levels were not available (n = 19), anticoagulant therapy was changed to antiplatelet therapy or vice versa within 7 days (n = 2), antithrombotic therapy was not started within 5 days of TAVR (n = 5), or the baseline D-dimer level before TAVR was extremely high (D-dimer level > 10 IU/mL; n = 1). Finally, 87 patients were analyzed in this study. The highest D-dimer levels were defined within 7 days after TAVR as "peak D-dimer" and the D-dimer level before TAVR as "baseline D-dimer". ΔD-dimer was also calculated with peak and baseline D-dimer levels.

Categorical variables are presented as numbers and percentages, and continuous variables are presented as mean ± standard deviation or median (interquartile range). To compare the categorical variables, χ^2 or the Fisher exact test was used. Continuous variables were compared using a t test or the Mann-Whitney test. P values < 0.05 were considered to indicate statistical significance. All statistical analyses were performed using SPSS version 26.0 (SPSS, Chicago, Illinois).

Patient characteristics are shown in Table 1. Of the 87 patients, 21 received anticoagulants (2 received warfarin; 12, direct oral anticoagulants [DOAC]; and 7, both DOAC and single antiplatelet agents). Seventeen patients received anticoagulants for atrial fibrillation at baseline, and the other 4 patients started taking anticoagulants after TAVR. Sixty-six patients received only antiplatelet agents without anticoagulants (11 received dual and 55 received single antiplatelet therapy). The patients treated with anticoagulant therapy had atrial fibrillation more frequently.

The perioperative D-dimer levels are shown in Table 1. The peak D-dimer level was significantly lower in the patients treated with anticoagulants than in those treated without anticoagulants (2.38

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Table 1. Baseline characteristics and perioperative D-dimer levels.

	Anticoagulant (n = 21)	Non-anticoagulant (n = 66)	P
Baseline characteristics			
Age [years]	84 ± 4	84 ± 5	0.51
Male	7 (33%)	22 (33%)	1.00
Height [cm]	148 (146–160)	147 (143–153)	0.20
Body weight [kg]	48 (42–54)	48 (41–61)	0.68
Body mass index	21.8 (19.2–26.6)	22.5 (18.9–26.7)	0.17
Hypertension	16 (76%)	50 (76%)	0.97
Dyslipidemia	14 (67%)	38 (58%)	0.46
Diabetes mellitus	7 (33%)	23 (35%)	0.90
eGFR < 60 mL/min/1.73 m^2	12 (57%)	48 (73%)	0.18
Atrial fibrillation	17 (81%)	2 (3%)	< 0.001
Extracardiac arteriopathy	4 (19%)	9 (14%)	0.38
Active cancer	2 (10%)	0 (0%)	0.06
Previous cardiac surgery	3 (15%)	4 (6%)	0.22
STS score	5.9 (5.0–8.9)	5.6 (4.4–7.6)	0.41
Echocardiography			
Left ventricular ejection fraction [%]	66.5 (62.0–75.0)	64.5 (59.0–71.9)	0.34
Mean pressure gradient [mmHg]	43.3 (38.7–51.2)	43.5 (36.0–62.1)	0.78
Aortic valve area [cm^2]	0.57 ± 0.15	0.60 ± 0.18	0.38
Computed tomography			
Annulus area [cm^2]	420.9 ± 63.9	410.7 ± 76.8	0.59
Annulus perimeter [mm]	73.9 ± 5.6	73.0 ± 6.2	0.62
Mean sinus of Valsalva diameter [mm]	29.6 ± 3.1	29.5 ± 3.1	0.95
Procedural characteristics			
Approach site:			0.55
Transfemoral	20 (95%)	61 (92%)	
Non-transfemoral	1 (5%)	5 (8%)	
Prosthesis type:			0.79
SAPIEN XT/3	14 (67%)	46 (70%)	
Evolut R/Pro	7 (33%)	20 (30%)	
Antithrombotic therapy:			
Warfarin only	2	0	
DOAC only	12	0	
DOAC + SAPT	7	0	
DAPT	0	11	
SAPT	0	55	
Perioperative D-dimer levels			
Baseline D-dimer level [IU/mL]	0.50 (0.50–0.65)*	1.10 (0.64–1.95)*	0.003
Peak D-dimer level [IU/mL]	2.38 (1.74–4.29)	5.15 (2.64–8.51)	0.001
ΔD-dimer	1.56 (0.83–2.48)*	5.05 (2.10–7.76)*	< 0.001

eGFR — estimated glomerular filtration rate; STS — Society of Thoracic Surgeons; DOAC — direct oral anticoagulant; DAPT — dual antiplatelet therapy; SAPT — single antiplatelet therapy; ΔD-dimer — peak minus baseline D-dimer levels; *Baseline D-dimer levels were available in 16 patients with anticoagulant and 46 patients without anticoagulant, therefore, ΔD-dimer was calculated in those patients

IU/mL [1.74–4.29 IU/mL] vs. 5.15 IU/mL [2.64––8.51 IU/mL]; p = 0.001). The baseline D-dimer (0.50 IU/mL [0.50–0.65 IU/mL] vs. 1.10 IU/mL [0.64–1.95 IU/mL]; p = 0.003) and Δ-dimer levels (1.56 IU/mL [0.83–2.48 IU/mL] vs. 5.05 IU/mL [2.10–7.76 IU/mL]; p < 0.001) were significantly

lower in the patients with, than in those without anticoagulant therapy.

Preliminary data showed that the baseline, peak, and D-dimer levels were significantly lower in patients with anticoagulant therapy. Recent reports suggest the effectiveness of anticoagulant therapy for prevention and treatment of leaflet thrombosis after TAVR [4, 5], and the present data may support these results. D-dimer levels could be affected by various factors, and suppression of the increase in D-dimer level might not directly demonstrate the effectiveness of anticoagulant therapy. Prior reports have shown that D-dimer levels decreased in patients with atrial fibrillation after initiation of DOAC therapy [6], and anticoagulant therapy might suppress the coagulation reaction and formation of leaflet thrombosis of prosthesis after TAVR. However, the effectiveness of a prevention for leaflet thrombosis does not mean it is the optimal therapy for patients undergoing TAVR [7, 8] because the balance between safety and efficacy for the various issues should be considered in clinical practice. Further investigations are required to address the optimal antithrombotic regimen in patients undergoing TAVR.

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VIA MEDICA

RESEARCH LETTER

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Familial dilated cardiomyopathy associated with a novel heterozygous *RYR2* early truncating variant

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Dilated cardiomyopathy (DCM), characterized by dilation and dysfunction of one or both ventricles [1], is the most prevalent form of cardiomyopathy. 30–50% of DCM cases are genetically determined [2, 3]. Genetic variants over a number of proteins that affect cardiomyocyte function are an important cause of DCM. Up until recently, mutations in the Ryanodine receptor 2 (*RYR2*) gene have been shown to be involved, especially in catecholaminergic polymorphic ventricular tachycardia (CPVT) [4], and arrhythmogenic cardiomyopathy [3]. Herein, is reported on a family with a novel early truncation in *RYR2* associated with an autosomal-dominant form of DCM.

A 51-year-old woman of Caucasian descent (Case 1) was admitted to the documented hospital for decompensated heart failure (New York Heart Association [NYHA] stage IV). Her 12-lead electrocardiogram (ECG) showed sinus rhythm with T-wave inversions (TWI) in leads II, III, aVF and V3–V6 (Fig. 1A). The transthoracic echocardiography (TTE) showed a heavily dilated left ventricle (LV) (LV end diastolic volume index [LVEDVi] 129 mL/m^2) with a decreased LV ejection fraction (LVEF) of < 15%, in the presence of diffuse hypokinesia without evidence of an LV thrombus (Fig. 1B). The left atrium (LA) was moderately dilated (LA volume index [LAVI] 45 mL/m^2). Magnetic resonance imaging (MRI) showed no evidence of fibrosis or fatty infiltration, but confirmed DCM (Fig. 1C) with normal right ventricle (RV) dimensions and function. Medical therapy for heart failure was started and optimized including lisinopril (5 mg bid), later changed to valsartan (50 mg tid), bisoprolol (5 mg bid), spironolactone (25 mg qd), and torasemide (10 mg qd). 48 h Holter-ECG only showed a very low premature ventricular complex (PVC) burden (0.3%) and no tachyarrhythmia, while two exercise stress tests revealed no PVCs or other forms of ventricular tachyarrhythmia. Nevertheless, despite being on optimal guideline-directed medical therapy at 4 month follow-up, a markedly decreased LVEF on TTE (22%) necessitated the implantation of a subcutaneous implantable cardioverter-defibrillator (ICD) for primary prevention. The family history indicated a familial autosomal-dominant form of DCM: the mother of the index case was transplanted for heart failure due to DCM at the age of 45 years, while the mother's brother died of heart failure due to DCM at the age of 70. No genetic tests or tissue were available. During cascade screening, one of the daughters (Case 2) of the index patient, a 26-year-old woman, was found to have a slightly dilated LV (LVEDVi 66 mL/m^2) with a normal LVEF (57%). Her 12-lead ECG showed normal sinus rhythm and normal de-/repolarization. A 48 h Holter-ECG showed a low PVC burden (0.06%) and no tachyarrhythmia. Further investigations revealed late gadolinium enhancement (LGE) on cardiac MRI, specifically in the LV apical and septal areas, as well as a transmural scar in the inferior LV.

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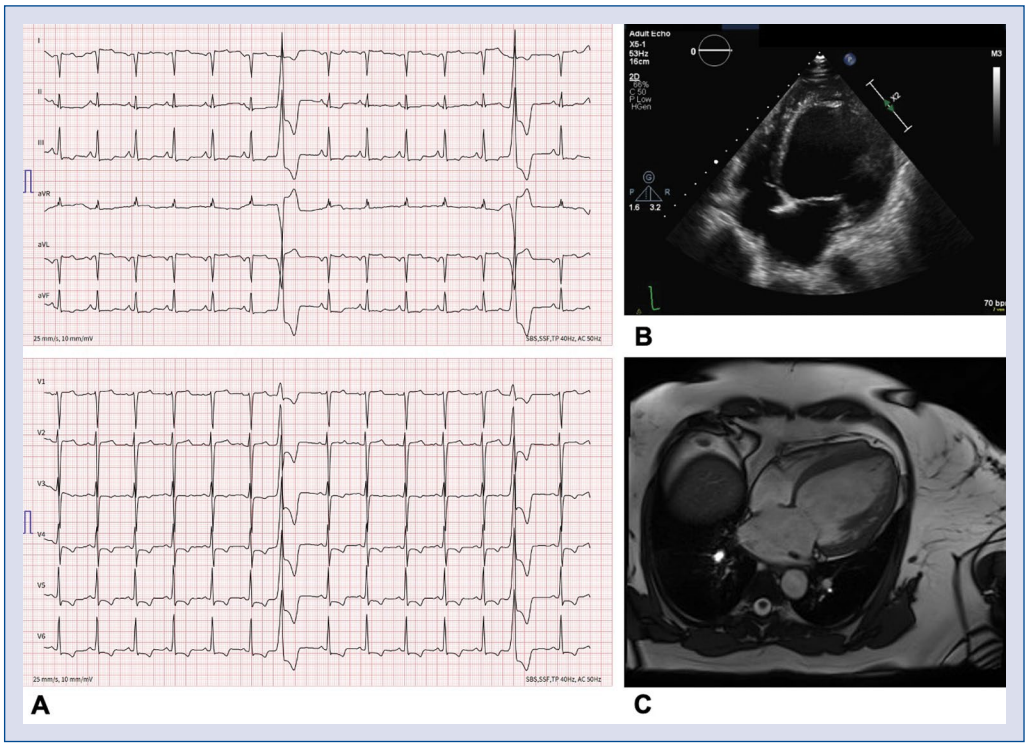

Figure 1. Diagnostic work-up in the index patient. **A.** 12-lead electrocardiogram showing sinus rhythm with T wave inversions in II, III, aVF and V3–V6, and two premature ventricular complexes originating from the anterobasal left ventricle (LV); **B.** Transthoracic echocardiogram showing a heavily dilated LV (LV end-diastolic volume index: 129 mL/m^2); **C.** Cardiac magnetic resonance imaging, confirming dilated cardiomyopathy without fibrosis or fatty infiltration.

The genetic test performed in the index patient (Case 1; performed using next generation sequencing technology — Illumina's Trusight Cardio sequencing panel, covering 176 genes) resulted in a previously unreported variant in Exon 4 of the RYR2 gene (heterozygous c.294G>A; p.Trp98Ter), which is considered likely pathogenic (class IV) following the 2015 American College of Medical Genetics criteria [5], since it is an early truncating variant and leads to a significantly shortened and dysfunctional protein product. The same variant was identified through Sanger Sequencing in the phenotypically affected daughter (Case 2), while it was not identified in the two other healthy siblings. Recently, evidence has been emerging about genes encoding sarcoplasmatic reticulum (SR) proteins as putative for DCM [3].

The cardiac RYR2 is an important calcium (Ca^{2+}) release channel of the SR and plays an essential role in excitation-contraction coupling in cardiomyocytes [6]. RYR2 dysfunction causes an abnormal Ca^{2+} leakage from the SR, which can generate delayed afterdepolarizations, which in turn can lead to ventricular arrhythmias [7]. *RYR2* variants altering the termination of Ca^{2+} release seem to lead to a cardiomyopathic phenotype, which is usually associated with mutations in sarcomeric proteins. Specifically, DCM-associated sarcomeric variants tend to decrease the myofilament Ca^{2+} sensitivity and thus increase cytosolic Ca^{2+} transients. The abnormal cytosolic Ca^{2+} transient resulting from altered myofilament Ca^{2+} sensitivity is thought to trigger cardiac remodeling (via Ca^{2+}/calmodulin-dependent signaling pathways, the calcineurin/NFAT pathways, or apoptotic signaling) that can lead to DCM [8]. Moreover, in dystrophic cardiomyopathy, the RYR hypersensitivity for Ca^{2+} due to redox modifications is not only responsible for excessive stress responses, but also changes the signal transduction linking L-type Ca^{2+} channels to RYRs during excitation-contraction coupling [9]. This connection between abnormal RYR function and dystrophic cardiomyopathy further underlines a putative role for abnormal RYR function not only in arrhythmogenesis, but also in cardiomyopathies.

Genetic variants in the *RYR2* gene are frequently autosomal dominant and usually associated with CPVT, but radical variants such as truncating variants, have also been described in the setting of DCM. There are various studies, where RYR2

variants have been recognized as causative in a small number of patients with DCM. In 2007, Bhuiyan et al. [10] reported two families with a deletion in exon 3 of the RYR2 gene, displaying a phenotype of CPVT in some family members and a DCM phenotype with LV dysfunction in other family members. Ohno et al. [6] linked large deletions in exon 3 of the RYR2 gene to LV non-compaction cardiomyopathy in two unrelated probands and their affected family members. This is in line with the present findings: the variant in this family leads to a stop codon which generates an early truncation (exon 4 out of 105 exons), leading to a dysfunctional protein product. Together with the, albeit limited, co-segregation shown in the reported family, this confirms a putative pathogenic role of the current reported truncating heterozygous *RYR2* genetic variant (c.294 294G>A; p.Trp98Ter) in the setting of familial DCM.

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VIA MEDICA

BRIEF COMMUNICATION

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Effects of intracoronary antithrombotics on ventricular function: A comparison of tenecteplase versus abciximab during primary percutaneous intervention in myocardial infarction

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Adjunctive medical therapy during primary percutaneous coronary intervention (PPCI) is based on anticoagulation and antiplatelet drugs. Additionally, the glycoprotein IIb/IIIa inhibitor (GPI) abciximab has been shown to reduce infarct size in some clinical trials [1]. However, the role of intracoronary fibrinolysis has not been well established during PPCI. We sought to explore the hypothesis that a locally administered fibrinolytic could be more effective in dissolving coronary thrombus at the macro and microvasculature than adding a third antiplatelet drug in patients already receiving double antiplatelet therapy, and therefore improve myocardial perfusion and left ventricular function.

The present study involved conducting a phase-III, single-center, prospective, randomized controlled trial, in which patients with acute anterior ST-segment elevation myocardial infarction (STEMI) and a coronary flow-limiting lesion (Thombolysis In Myocardial Infarction [TIMI] flow grade 0–2) in the left anterior descending coronary artery were randomized to receive either intracoronary tenecteplase (one fifth of the usual systemic dose according to weight) or abciximab (an intracoronary dose of 0.25 mg/kg followed by an intravenous infusion of 0.125 mcg/kg/min for 12 h). After crossing the culprit lesion with a guidewire, the study medication was infused through the guiding catheter for 3 min. All patients had received oral acetylsalicylic acid (300 mg), clopidogrel (600 mg) and an intravenous bolus of 70 UI/kg of unfractionated heparin before the procedure. In both groups, PPCI was then performed as usual with implantation of coronary stents as needed. The complete study protocol was described in a previous publication [2].

All patients were scheduled for a contrast echocardiogram before discharge and at 6 months (contrast agent Sonovue, Bracco, The Netherlands), all of them performed with a GE Vivid 7 ultrasound system by the same experienced cardiologist, who was blinded to the study medication, assessing the usual systolic and diastolic ventricular function parameters according to the American Society of Echocardiography. Additionally, all patients were scheduled for a 4-month cardiac-magnetic resonance imaging (MRI) at an external radiological center, for a blinded analysis of infarct size, left ventricular volumes and ejection fraction, as previously described [2]. The study protocol was approved by the local and regional ethics committees. The trial was registered in Eudra CT (https://www.clinicaltrialregister.eu, identifier 2010-022725-16). All patients gave written informed consent to participate in the study.

From August 2012 to April 2016, 102 patients with acute anterior STEMI were screened for enrolment in the study, 26 of which were later excluded due to not meeting the listed criteria. Consequently, 76 patients with acute anterior STEMI were randomized to receive either intracoronary tenecteplase (n = 38) or abciximab (n = 38) dur-

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Table 1. Echocardiogram and cardiac-magnetic resonance imaging (MRI) results.

	i.c. Tenecteplase	i.c. Abciximab	P
48-hour echocardiogram	**N = 38**	**N = 38**	
LVEDV index [mL/m^2]	54.2 [44.2–71.7]	51.5 [47.5–62.1]	0.69
LVESV index [mL/m^2]	23.8 [14.9–35.5]	26.1 [18.1–36.7]	0.91
LVEF [%]	54.0 [40.2–66.7]	50.5 [43.0–60.7]	0.79
LAV index [mL/m^2]	27.4 [22.6–37.4]	29.7 [23.6–33.2]	0.71
Average e' wave [cm/s]	6.2 [5.0–7.7]	6.0 [4.7–7.0]	0.60
Average E/e' ratio	11.4 [9.4–14.9]	14.3 [11.2–17.6]	0.04
Average E/e' ratio ≥ 13	12 (33.3%)	21 (55.3%)	0.05
4-month angio-MRI	**N = 26**	**N = 28**	
LVEDV index [mL/m^2]	85.4 [71.7–99.9]	88.5 [72.9–104.4]	0.94
LVESV index [ml/m^2]	38.9 [25.0–54.0]	40.1 [31.2–55.8]	0.63
LVEF [%]	54.0 [44.0–62.0]	53.0 [44.5–59.5]	0.58
6-month echocardiogram	**N = 28**	**N = 35**	
LVEDV index [mL/m^2]	54.8 [45.4–69.2]	55.4 [42.9–67.1]	0.82
LVESV index [mL/m^2]	22.1 [13.5–33.9]	23.0 [13.3–31.9]	0.87
LVEF [%]	59.0 [47.0–73.0]	57.5 [43.0–60.7]	0.74
LV remodeling > 20%	6 (21.4%)	9 (26.5%)	0.65
LAV index [mL/m^2]	28.3 [22.2–40.0]	28.8 [24.1–37.1]	0.75
Average e' wave [cm/s]	6.5 [5.0–8.0]	6.0 [4.0–7.0]	0.23
E/e' ratio	10.3 [8.1–14.6]	13.2 [10.7–15.5]	0.03
E/e' ratio ≥ 13	8 (28.6%)	18 (51.4%)	0.05

Variables are expressed as median [interquartile range] or as n (%); LVEDV — left ventricular end-diastolic volume; LVESV — left ventricular end-systolic volume; LVEF — left ventricular ejection fraction; LAV — left atrial volume; Average e' wave — average of the values from the septal and lateral mitral annulus; Average E/e' ratio — ratio of the transmitral Doppler E wave velocity and the composite mean of e'; LV — left ventricular

ing PPCI. Both groups were comparable in demographic, clinical, angiographic and periprocedural characteristics, and there were no significant differences in major cardiovascular or bleeding events between study groups, as published elsewhere [2].

Echocardiogram and cardio-MRI results are displayed in Table 1. Left ventricular volumes and ejection fraction did not significantly differ between the study groups at 6 months, and adverse ventricular remodeling was similar. Only diastolic function, as assessed by the E/e' ratio at 6 months, was significantly better in the tenecteplase group (median 10.3 [interquartile range 8.1––14.6]) in comparison to the abciximab group (median 13.2 [interquartile range 10.7–15.5, respectively, $p = 0.04$]). An E/e' ratio ≥ 13 was observed in 26.6% of the patients in the tenecteplase group versus 51.4% in the abciximab group ($p = 0.05$) and final infarction size (expressed as weight of infarct mass in grams) had a significant correlation to e' wave value ($r = –0.49$, $p < 0.01$) and E/e' ratio ($r = 0.45$, $p = 0.04$).

Primary PCI is the strategy of choice in STEMI, and one of its main goals is saving as much myocardium as possible, since impaired ventricular function after STEMI is an unfavorable prognostic predictor [3]. Adjunctive treatment with GPI during PPCI has shown to improve myocardial perfusion and reduce infarct size in some studies [1]. According to available research, the present study constitutes the first randomized trial comparing intracoronary administration of a fibrinolytic drug and a GPI in patients with STEMI undergoing PPCI. In a recent publication, it was communicated that there were no significant differences in infarct size between both drugs in the study population [2]. In the present manuscript, it is also reported that there were no significant differences in systolic ventricular function as well. There was only a mild trend to a better preservation of diastolic function in the tenecteplase group that could be considered as marginal.

Previous [2] and the present results agree with those previously reported in the recent T-TIME

study [4], in which intracoronary alteplase worsened the microvascular obstruction and increased intramyocardial hemorrhage when compared to the placebo, essentially in case of prolonged ischemia. Furthermore, these worse results on myocardial reperfusion are not necessarily related to final infarct size, since edema and intramyocardial hemorrhage are usually solved when the 4-month monitoring MRI is performed. This could explain the absence of significant differences in infarct size between the two therapy groups. Additionally, as in the current study, in the T-TIME trial no significant benefits on ventricular function were found [4].

The sample size in this pilot study was arbitrary and was not previously calculated. The relatively small size of infarcted myocardium in the whole study population could have limited the ability to detect significant differences in most systolic and diastolic function parameters. Additionally, comparing tenecteplase to an antiplatelet drug rather than a placebo may have diminished its capacity of showing positive results on the study endpoints. The choice of tenecteplase dose was selected from previous case reports and observational studies, although it could have been insufficient to achieve the desirable antithrombotic effect. Finally, more recent P2Y12 inhibitors (such as ticagrelor or prasugrel) were not used in the present study since their administration is not recommended in addition to a fibrinolytic drug.

In this first clinical randomized trial comparing intracoronary fibrinolysis with a GPI drug during PPCI, and when combining present results with those recently reported [2], no benefits were found on ventricular function nor infarct size after myocardial infarction when intracoronary fibrinolysis was performed. Therefore, and lacking results from larger studies, the results do not support a systematic use of intracoronary fibrinolysis as adjunctive therapy during PPCI.

Conflict of interest: None declared

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Left main revascularization with intracoronary lithotripsy guided by optical coherence tomography

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A 75-year-old male previously disqualified from coronary artery bypass grafting was referred to the documented clinic for percutaneous treatment of heavily calcified distal left main (LM) and proximal left anterior descending artery (LAD) lesions. Baseline angiography revealed heavily calcified significant lesion in the distal LM and calcifications in the proximal LAD (Fig. 1A). Due to the large diameter of the coronaries, use of rotational atherectomy was excluded and the patient was qualified for intracoronary lithotripsy (ICL). A transfemoral approach using a 7 F extra back up guiding catheter was chosen. Pre-procedural optical coherence tomography (OCT) confirmed thick calcifications in the distal LM (minimal lumen diameter [MLD] 3.5 mm) and in the proximal LAD (MLD 2.5 mm) (Fig. 1B). Subsequently, an ICL catheter (4.0 × 12 mm, Shockwave C2, Shockwave Medical Inc.) was successfully delivered to the lesion. Eighty applications (at 4 atm) in the LM/LAD were performed, achieving full dilation of the ICL balloon at 6 atm. The OCT images obtained after ICL revealed the presence of calcium cracks in the distal LM and proximal LAD (Fig. 1C). Two drug-eluting stents (Orsiro, Biotronik) were then implanted, 4.0 × 15 mm in the LM/LAD and overlapping 3.0 × 15 mm in the proximal LAD. Subsequently the proximal optimization technique was performed in the LM using non-compliant balloons (4.5 followed by 5.0 mm at 20 atm.). Angiography revealed good angiographic results of the procedure (Fig. 1D). Final OCT confirmed the luminal gain (final MLD: LM 4.8 mm, LAD 3.0 mm) with proper stent strut apposition (Fig. 1E). No periprocedural complications were observed and the patient was discharged 24 hours after the procedure.

Conflict of interest: None declared

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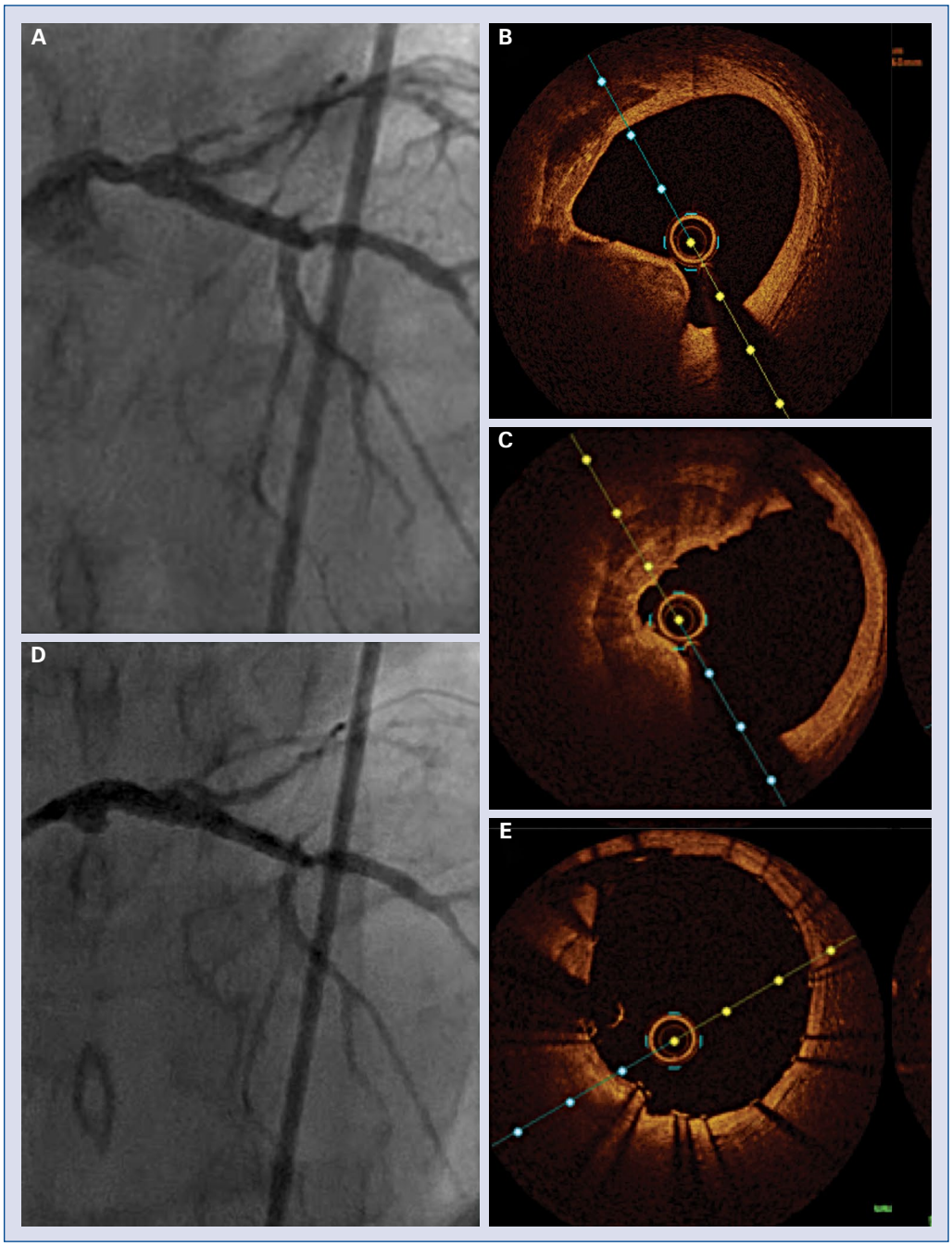

Figure 1. Baseline angiography revealed significant calcified stenosis in the distal left main (LM) and proximal left anterior descending artery (LAD) (**A**). Pre-procedural optical coherence tomography (OCT) revealed a thick calcium presence (**B**). OCT after lithotripsy demonstrated cracks in the calcified plaque (**C**). Angiography after stent implantation showed a good angiographic outcome (**D**). Final OCT confirmed the luminal gain with proper stent strut apposition (**E**).

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Synergistic application of high-speed rotational atherectomy and intravascular lithotripsy for a severely calcified undilatable proximal left anterior descending coronary artery bifurcation lesion: Case of rotalithoplasty-facilitated DK-CRUSH

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Coronary calcified plaques may affect both procedural and long-term outcomes of coronary stenting, resulting in impaired device deliverability, disruption of stent coatings, and poor stent expansion and apposition. A novel intravascular lithotripsy (IVL) method was introduced and recently tested in catheterization laboratories (ShockWave). A 62-year-old male presented with severely calcified proximal left anterior descending artery/diagonal true bifurcation stenosis (Medina 1,1,1) (Fig. 1A, B). The operator's strategy was to perform IVL after small balloon pre-dilation (NC Emerge 2.0 × 12 mm, Boston Scientific Co.), but advancement of the ShockWave (ShockWave Medical Co.) balloon was unsuccessful due to the unfavorable location of the calcium. After several pre-dilations with non-compliant balloons (2.0 mm, 2.5 mm, and 3.0 mm; NC Emerge, Boston Scientific Co.) inflated to 20 atm, the artery was not fully opened and IVL advancement failed. At this stage, the operators decided to perform high-speed rotational atherectomy with 1.5 burr. Subsequently, due to residual large calcific plaque burden after rotablation, the IVL balloon (3.5 × 12 mm) was placed within the lesion and 80 seconds of wave was applied to modify the plaque (Fig. 1C, D). Finally, the diagonal branch was protected with the wire and regular angioplasty was performed. The well-known classic double-kissing crush technique was implemented for the patient. Operators deployed Orsiro 2.5 × 22 mm (15 atm) (Biotronik) in the diagonal branch followed by another Orsiro stent 3.5 × 22 mm (14 atm) (Biotronik) in the left anterior descending artery. The final proximal optimalization technique with 3.5 × 8 mm (16 atm) (NC Emerge; Boston Scientific Co.) was used and achieved an excellent angiographic result (Fig. 1E, F).

Conflict of interest: None declared

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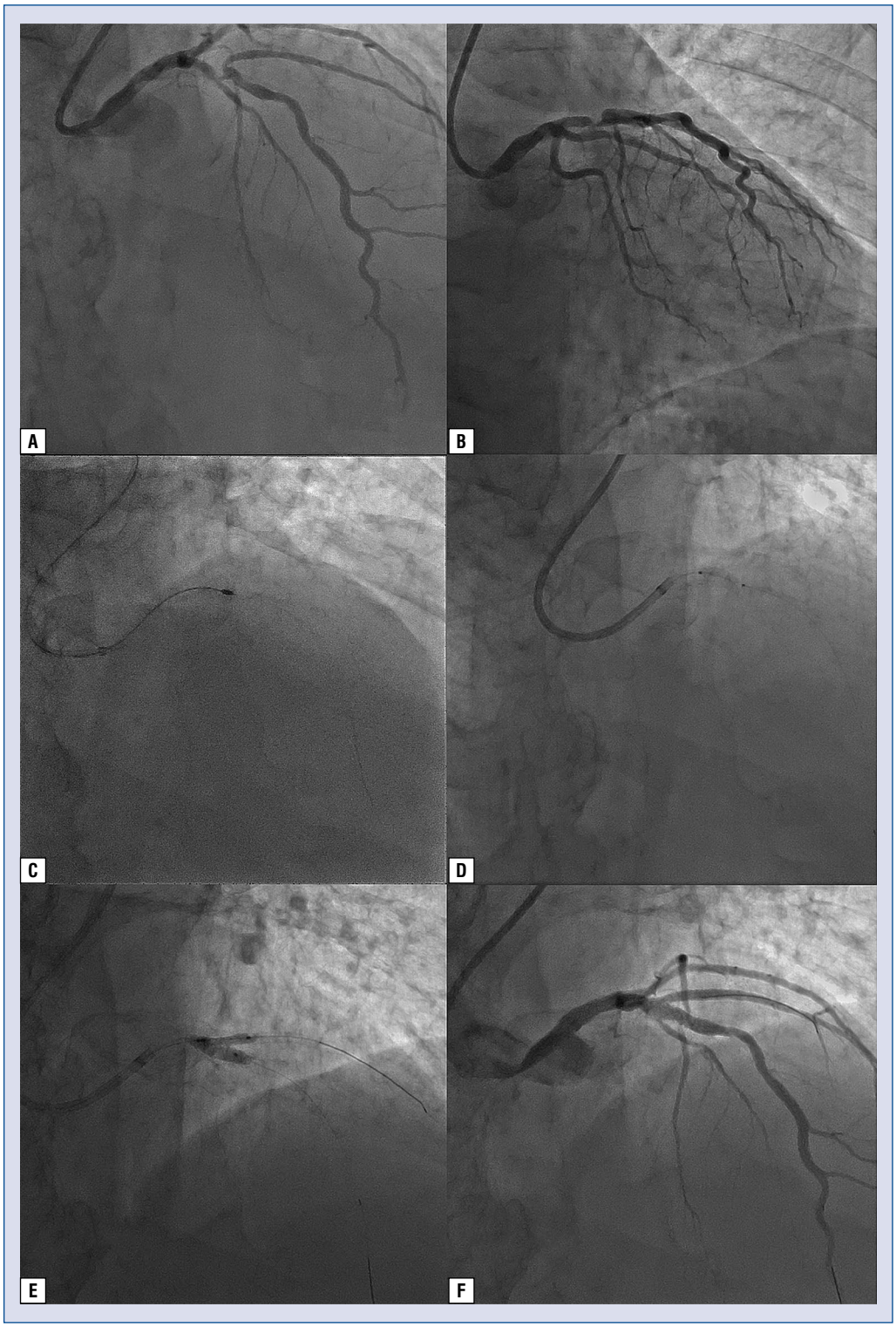

Figure 1. Coronary angioplasty of the left anterior descending artery using RotaShock strategy; **A, B.** Initial visualization of the lesion in the two orthogonal views; **C.** Rotablation with a 1.5-mm burr; **D.** A 3.5 × 12-mm ShockWave balloon; **E, F.** The kissing technique and the final angiographic result. Final kissing inflation was achieved with both non-compliant balloons (NC Emerge, Boston Scientific Co., Marlborough, USA) of 2.5 × 12 mm (14 atm) for the diagonal branch and 3.5 × 12 mm (14 atm) for the main vessel.

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Chimney stent deployment to overcome an acute right coronary occlusion due to a small right coronary sinus during transcatheter aortic valve implantation procedure

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An 84-year-old woman with degenerative aortic stenosis was admitted for planned transcatheter aortic valve replacement procedure. The baseline tomography showed the following measurements: aortic annulus (maximum, minimum, and mean diameters of 22.5, 17.8, and 20.2 mm, respectively, perimeter 64.8 mm, area 322 mm^2), the Agatston score was 1300, sinuses of Valsalva (left 27.7 mm, right 23.8 mm, noncoronary 28.1 mm) (Fig. 1A). Likewise, an unusual takeoff of the right coronary artery (RCA) was encountered, without a clear definition within a small right coronary sinus (Fig. 1B); the height of left coronary ostia was normal (Fig. 1C). Based on previous measurements, a 23 mm Portico bioprosthesis was selected. After predilatation using an 18 mm true dilatation balloon, the patency of RCA was checked with the balloon inflated. Subsequently, the prosthesis was deployed and the patient started with signs of hemodynamic instability. Then, an RCA occlusion was found in a control angiography (Fig. 1D). Therefore, it was decided to remove the prosthesis, reassess the RCA patency (Fig. 1E) and position an undeployed 4 × 30 mm Onyx stent at the RCA (Fig. 1F). Straightaway, the prosthesis was released and simultaneously the stent at the RCA was successfully deployed according to the "chimney stent" technique [1] (Fig. 1G). Finally, the proper position and expansion of the prosthesis, the absence of periprosthetic leak and the patency of the RCA were verified (Fig. 1H). Ultimately, the correct expansion of the stent was confirmed using intravascular ultrasound (Fig. 1I).

Conflict of interest: None declared

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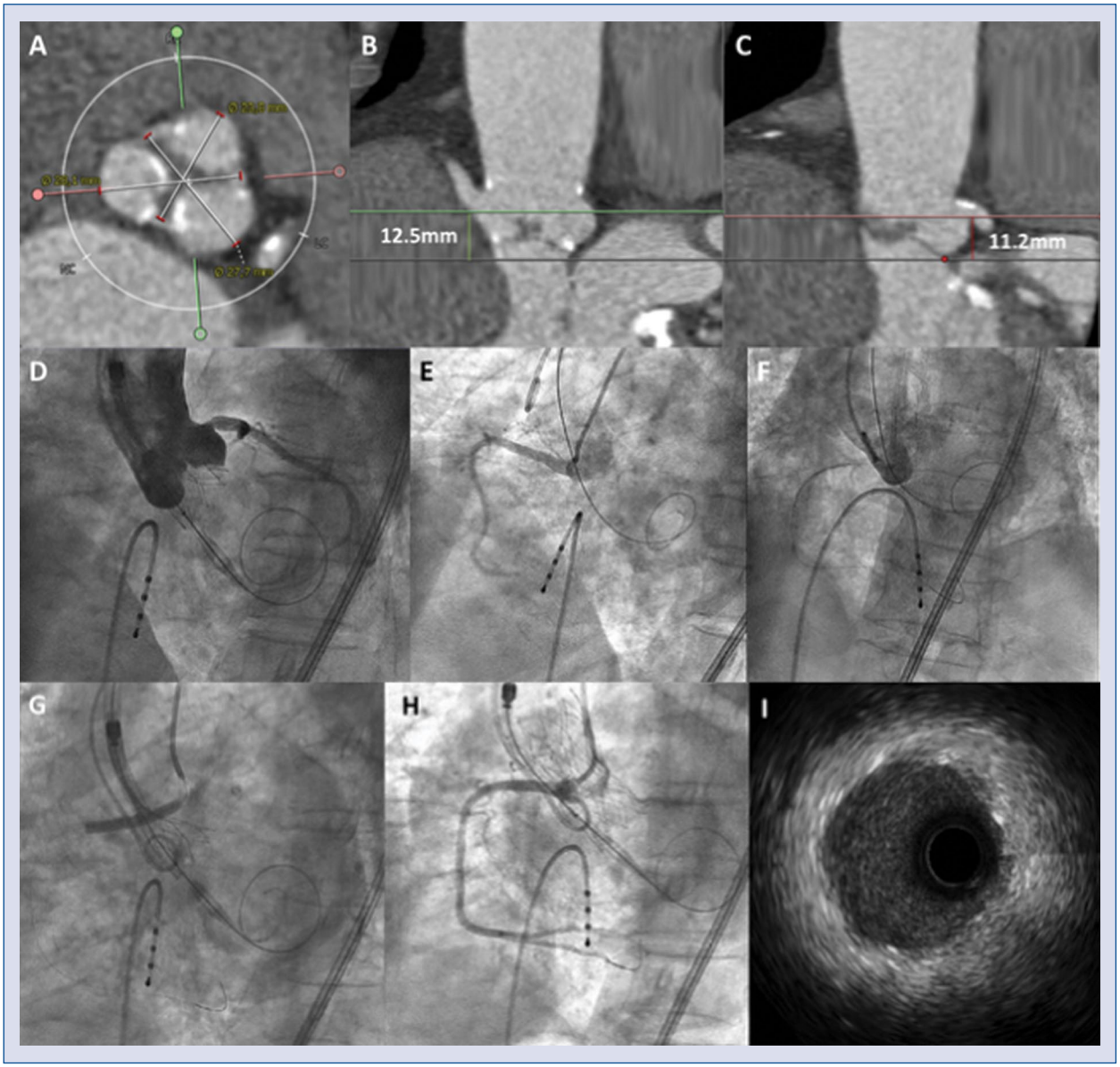

Figure 1. A. Tomographic image at the level of sinuses of Valsalva showing its measurements (left 27.7 mm, right 23.8 mm, noncoronary 28.1 mm); **B.** Tomographic image showing lack of a clear definition of the origin of the right coronary artery (RCA) within a small right coronary sinus; **C.** Tomographic image showing a normal origin of the left main coronary artery; **D.** Angiographic image performed after deployment of the prosthesis showing acute occlusion of the RCA; **E.** Angiographic image performed after the prosthesis was recaptured showing patency of the RCA; **F.** Angiographic image showing the guidewire and progress of a stent in the RCA; **G.** Angiographic image showing the release of the prosthesis and implantation of the stent with the "chimney stent" technique in the RCA; **H.** Final aortography showing the proper position and expansion of the prosthesis, absence of periprosthetic leak and patency of the RCA; **I.** Intracoronary imaging using intravascular ultrasound showing correct expansion of the stent implanted in the RCA.

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Successful percutaneous mechanical thrombectomy of an Impella CP-related femoral artery thrombosis

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A 77-year-old female was admitted for non-ST-segment elevation myocardial infarction. Electrocardiogram demonstrated 2 mm ST depression from V2–V6. High sensitivity troponins were elevated (53 → 120 ng/L [treshold for positivity: 14 ng/L]). Coronary angiogram showed bitroncular coronary artery disease with a severe lesion of the proximal to distal left anterior descending (LAD) coronary artery, treated by angioplasty with 4 drug eluting stents. Percutaneous revascularization was complicated by no reflow in the LAD leading to cardiogenic shock. Impella CP was inserted for hemodynamic support using a left femoral artery approach and a 14 French sheath. Following stabilization of patient's hemodynamics, retrieval of the Impella CP was performed subsequently on day 3. Hemostasis of the left common femoral artery was obtained via pre-positioned percutaneous sutures. Injection of the left femoral artery through contralateral access demonstrated a thrombosis extending on the entire length of the common femoral artery as well as the distal external iliac artery (Fig. 1A), with subocclusion of the vessel. Mechanical thrombectomy using Rotarex, (Fig. 1B) was performed through a 6 French cross-over sheath placed in the right femoral artery, allowing immediate antegrade blood flow restoration in the left common femoral artery (Fig. 1C) and absence of distal embolization (Fig. 1D).

Percutaneous mechanical support devices, inserted through large bore sheaths, are used increasingly in the catheterization laboratory for hemodynamic support. Vascular complications are rare, notwithstanding they may limit patient outcomes. Comprehensive assessment of femoral access upon retrieval of the devices/sheaths, commonly using a contralateral femoral access, allows for prompt recognition and treatment of vascular complications.

Conflict of interest: None declared

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Work was performed at Geneva University Hospital.

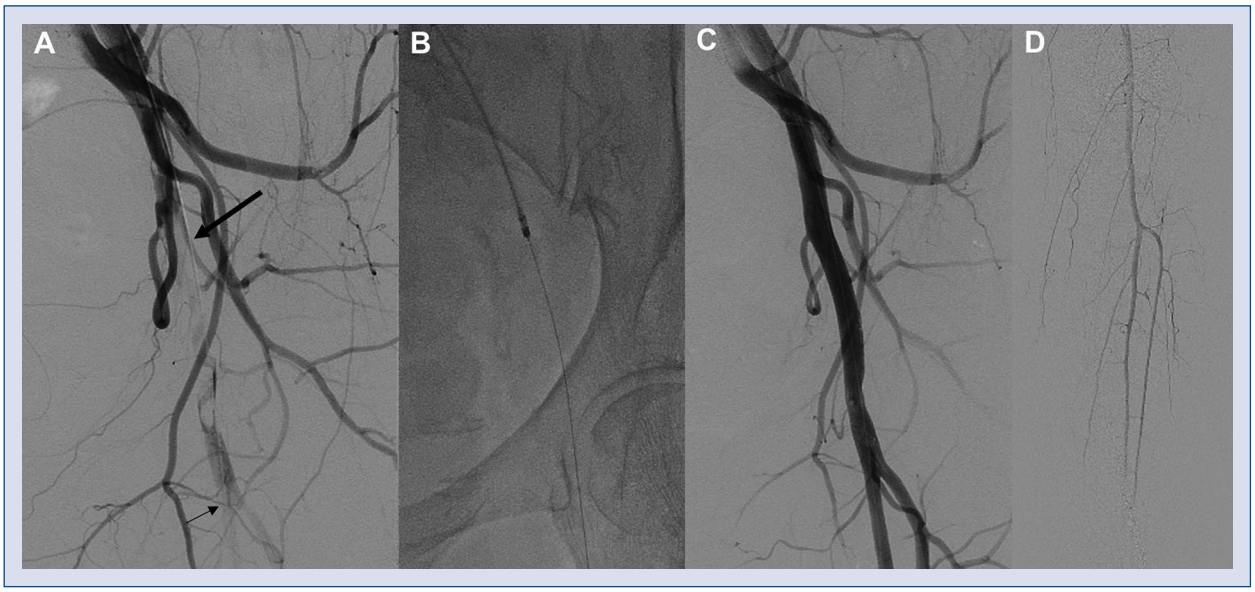

Figure 1. A. Subocclusive thrombosis extending on the entire length of the common femoral artery as well as the distal external iliac artery (large arrow). The small arrow denotes the faint opacification at the level of the femoral bifurcation; **B.** Mechanical thrombectomy using Rotarex, through a 6 French cross-over sheath placed in the right femoral artery; **C.** Restoration of antegrade blood flow in the left common femoral artery, absence of residual thrombosis; **D.** Below-the-knee angiography showing three patent vessels in the absence of distal embolization.

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Emergency assessment of proximal left anterior descending coronary stent permeability using transthoracic echocardiography

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A 44-year-old man with acute anterior ST elevation myocardial infarction underwent emergency percutaneous coronary intervention and stenting of an occluded ostial left anterior descending artery (LAD). Initial echocardiographic assessment showed anterior septal and apical akinesis. Thirty-six hours later, he developed a crushing chest pain that radiated to the back and the abdomen. Serial 12-lead electrocardiograms showed persistence of ST segment elevation that had not resolved since admission to the coronary unit. An emergency echocardiogram was performed. Using the left parasternal acoustic window, a short axis view at the level of the aortic valve was obtained and slightly modified by superiorly tilting the probe. Color Doppler flow mapping with the Nyquist limit lowered at 14 cm/s allowed identification of the mid-LAD and its bifurcation with a large septal branch (Fig. 1A, **Suppl. Video**). Antegrade LAD flow was also demonstrated by the red color Doppler flow into the anterior interventricular groove (Fig. 1B) and using pulsed wave Doppler with the sampling volume placed inside the LAD (Fig. 1C). As the electrocardiogram was not contributing, these echocardiographic findings allowed the demonstration of at least partial permeability of the ostial LAD, excluding a complete occlusion of the stent, and provided time to obtain serial troponin samples. A decreasing troponin trend and further clinical evaluation-oriented investigations to the upper abdominal region and an acute cholecystitis was finally diagnosed by means of a thoraco-abdominal computed tomography scan.

Direct visualization of antegrade blood flow in the coronary arteries is feasible and can directly influence clinical decision making.

Conflict of interest: None declared

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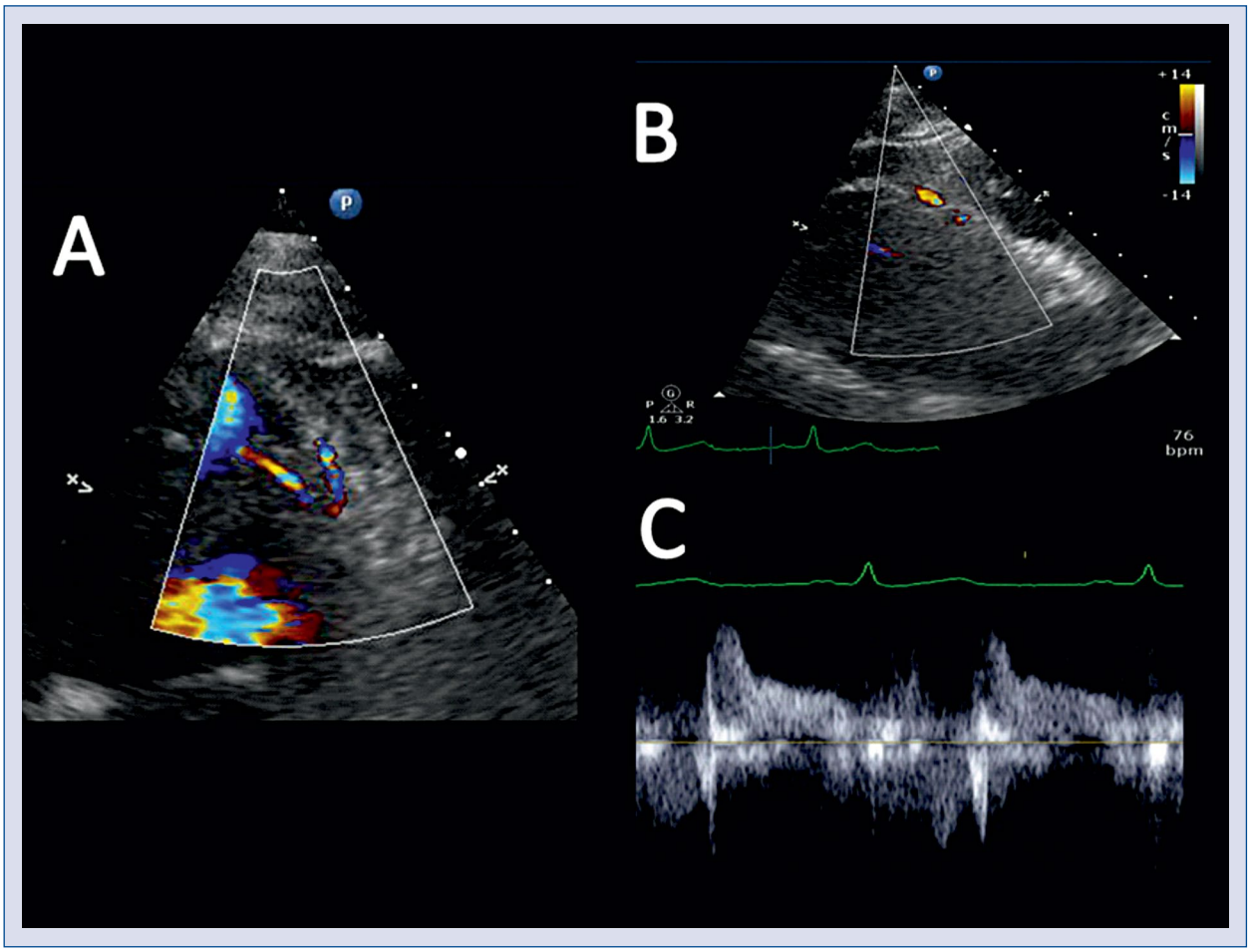

Figure 1. A. Modified parasternal short axis view. Color Doppler flow mapping in mid-diastole showing the bifurcation of left anterior descending artery (LAD) (to the right) with a large septal branch (to the left); **B.** Modified parasternal long axis view showing an antegrade (red) diastolic color Doppler flow in the anterior interventricular sulcus corresponding to the distal portion of the LAD; **C.** Pulsed wave Doppler with the sample volume positioned on the color Doppler signal of the LAD showing a predominately diastolic antegrade flow.

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Intermittent wide QRS complex sinus bradycardia in a 72-year-old woman

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A 72-year-old woman without previous medical history was admitted to the emergency department for episodes of dizziness and blurred vision without syncope. The performed electrocardiogram (ECG) showed sinus bradycardia at 45 bpm with pauses measuring two times the preceding P-P cycle, compatible with a type 2 second-degree sinoatrial block (Fig. 1). There was also a widening of QRS complexes coinciding with sinoatrial block pauses were also noticeable (Fig. 1). In this phenomenon, known as bradycardia-dependent aberrancy, conduction delay occurs when the heart rate drops below a critical level due to depolarization of Purkinje fibres during phase 4 of the action potential, remaining hypopolarized (also named 'spontaneous diastolic depolarization'). Thus, the next impulse coming through the atrioventricular pathway results in an aberrant conduction. Due to shorter critical cycle lengths, phase 4 block occurs more frequently in the left bundle branch (as it was seen in this case) than in the right one, coexisting in both morphologies in few cases. After detecting pauses longer than 8 seconds in continuous ECG monitoring, a dual chamber pacemaker was implanted in the patient.

Conflict of interest: None declared

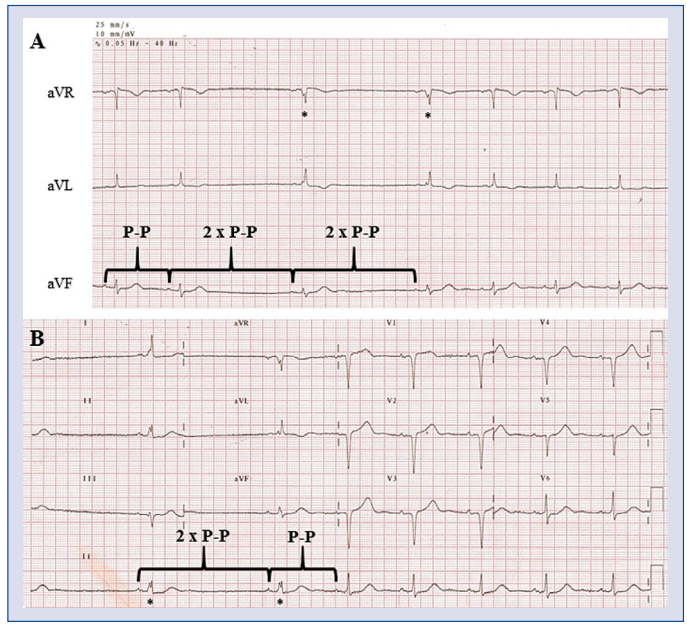

Figure 1. Electrocardiograms at admission showing sinus bradycardia. Pauses have a duration which is double the previous P-P cycle (**A**). An asterisk points out the widening of QRS complexes concurrently with the pause (**A**, **B**).

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Multiple heart beats: A unique presentation of cardiac rhabdomyoma

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A male infant was born via vaginal delivery from non-consanguineous and healthy parents. His birth weight and gestational age were 2,947 g and 39 weeks, respectively. Based on fetal echocardiography findings, it was suspected that he had cardiac tumors. After birth, transthoracic echocardiography revealed multiple "heart-shaped" tumors in the right ventricle (Fig. 1A, B, **Suppl. Video 1**). There was no obstruction to ventricular inflow or outflow. The systolic and diastolic function of both ventricles were preserved. Twelve-lead electrocardiogram showed normal sinus rhythm with ST-T segment abnormality. Brain magnetic resonance imaging revealed cortical tubers and subependymal nodules (Fig. 1C). He was subsequently diagnosed as having tuberous sclerosis complex. The cardiac tumors were classified as rhabdomyomas based on the findings of cardiac computed tomography and magnetic resonance imaging. Holter electrocardiography on day 23 showed a few isolated premature ventricular contractions. The infant was uneventfully discharged from our hospital on day 35. His parents and elder sister were unlikely to have tuberous sclerosis complex according to the clinical diagnostic criteria.

Tuberous sclerosis complex is a multisystem genetic disorder with a highly variable phenotype that may affect several organ systems. At least 50% of newborns with tuberous sclerosis complex have cardiac rhabdomyomas. These lesions typically regress within the first 3 years of life. However, they may obstruct inflow or outflow leading to heart failure or arrhythmia depending on size, location, and number. Recently, the utility of mammalian target of rapamycin inhibitors for treating life-threatening cardiac rhabdomyomas has been reported. Cardiologists should be aware of this potentially life-threatening presentation of tuberous sclerosis complex and management options.

Conflict of interest: None declared

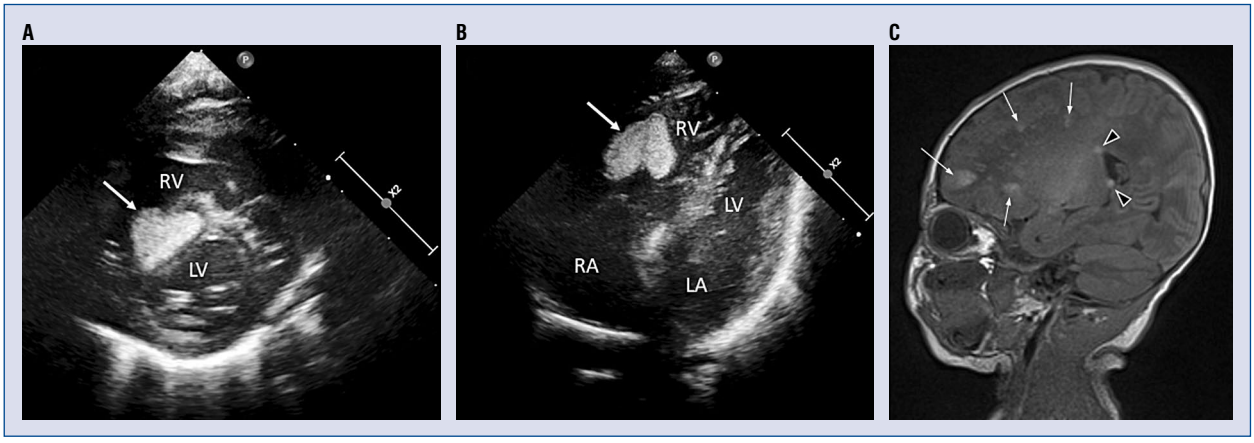

Figure 1. A. B. Transthoracic echocardiography of the patient; **C.** Brain magnetic resonance imaging of the patient. Arrows and arrow heads denote cortical tubers and subependymal nodules, respectively; LA — left atrium; LV — left ventricle; RA — right atrium; RV — right ventricle.

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Silent journey of a late lead pacemaker perforation

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An 83-year-old male with frailty and ischemic cardiomyopathy underwent uncomplicated pacemaker implantation with passive fixation atrial lead and active fixation ventricular lead (VL) (Fig. 1A), for paroxysmal high-degree atrioventricular block. Follow-up ensued with normal pacemaker function at 3 months, but intermittent loss of ventricular capture was perceived 1 year later. Echocardiography excluded pericardial effusion. On fluoroscopy-guided surgical review, VL appeared dislocated and surrounded by fibrous adhesions, so it was abandoned and a new VL was implanted (Fig. 1B). Two years after surgical review, cardiac computed tomography (CT) was performed due to unrelated motive and disclosed lead perforation (Fig. 1C; **Suppl. Video 1**). Precise perforation time was hard to determine. Late lead perforation (LLP) was retrospectively assumed on the basis of VL malfunctioning at 1 year plus active fixation and elderly as predisposing factors. Conservative treatment was chosen based on the absence of symptoms or pericardial effusion, stable condition, and incidental finding as a silent perforation. One year after CT diagnosis, at the age of 87, the patient remained asymptomatic but ultimately died from medical complications during hospitalization for a right femur fracture.

Late lead perforation occurs in 0.1% of implantations when a lead exceeds cardiac contour 1 month after implantation. Incidental LLP has a 6% prevalence in CT studies and should be considered, even many years after implantation. The imbalance and complex interaction of forces determines LLP when lead tip prevails over myocardium counterforce. Lead positioning in a vulnerable region, thinner and less compliant leads, bipolar leads, and excessive loop or tension are other predisposing factors. Treatment depends on the timing of perforation, presence of symptoms, pericardial effusion or extracardiac damage. Measuring risk and benefit, asymptomatic and stable patients with prohibitive surgical risk can be managed conservatively.

Conflict of interest: None declared

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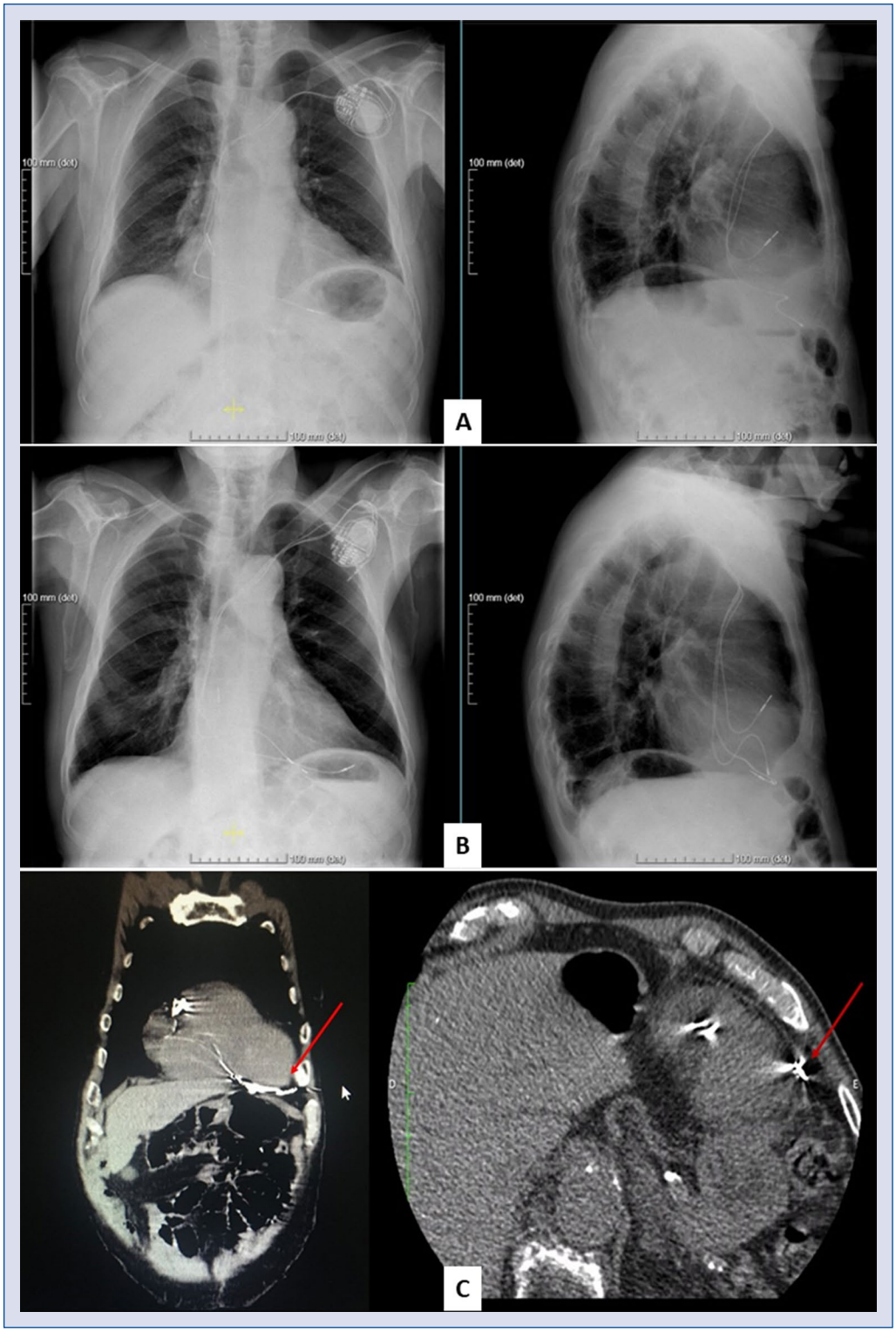

Figure 1. A. First implantation; on discharge date: thorax X-ray showing normal positioning of atrial and ventricular leads and absence of pleural complications; **B.** After surgical review, a new ventricular lead is implanted; on discharge date: thorax X-ray showing a new lead in normal position, and the old one displaced within the cardiac silhouette; **C.** Cardiac computed tomography: showing right ventricular apex perforation by a ventricular lead located beneath the left ventricle's inferior wall and apex (arrows).

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In memoriam Emil Płowiecki

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Allow me to recall in these lines a man whose passing I have deeply lamented, a man with an impeccable sense of duty, and whose friendship I have cultivated with immense pleasure. I had the privilege of visiting him on multiple occasions, wherein I always observed him taking care of the smallest details regarding the development of his products, paying attention to his company and the people who, in one way or another, worked in or collaborated with it. He was the first to arrive and the last to leave the factory. He was an otherwise discreet man, generously open to innovation, who succeeded, in many senses, in becoming a leader in the field of biomedical engineering. In summary, one of the kindest people I have ever met, whose friendship I have always deeply appreciated: Mr. Emil Płowiecki (1951–2020).

Mr. Emil Płowiecki, Founder and President of Balton Sp., was the recipient of many prestigious awards in the field of business and innovation. The Polish Government bestowed on him the Golden Cross of Merit for achievements in promoting Polish technical and technological development. He was also awarded the Golden Laurel in the field of Medicine and Biomedical Engineering.

While visiting Balton facilities in Warsaw I can recall a feeling of harmony, pervading every corner, like a calm sea of order and efficiency. When he received guests in his office, he made them feel part of the company, which he conceived as a great family. I vividly remember how he offered his guests honey from a small pot that he kept on his table to sweeten the coffee, instead of sugar, and how he took as much time as needed to listen to his guests' proposals or to explain his new designs and products, while drinking his coffee.

He created a company with its own research and development facilities which encompassed microbiological, chemical and mechanical laboratories that implement the latest designs and advances. He always knew how to attract and encourage the collaboration of scientists and end users.

Mr. Emil Płowiecki and Dr. Luis Íñigo in Balton in 2016.

Herein is a brief look back on some of Mr. Emil Płowiecki's milestones here. After founding Balton in 1980, he commenced his activity producing stainless steel guide wires for introducers. Soon after, he expanded to epidural catheters, needles for hemodialysis and, in 1987, catheters for angiography. He continued to incorporate numerous devices into the manufacturing process to make Balton an innovative design and medical production company. In 2005, Balton created the World's first paclitaxel eluting stent coated with a biodegradable polymer and, in 2010, introduced the coronary bifurcation stent system. Today,

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Balton produces medical equipment for cardiology, radiology, anesthesiology, surgery, dialysis, urology and gynecology. The company cooperates with many scientific centers and clinics in Poland and Europe as well as with companies from France, the United States, Germany, Russia and Japan.

Mr. Emil Płowiecki achieved great success worldwide and his products continue to save human lives in hospitals and clinics around the world. Balton company uses the latest materials, technology, production and control equipment which are used in the most sophisticated hi-tech plants in the world.

Apart from being active in the medical industry, he was also involved in charitable activities and promoted young artists and athletes.

Emil Płowiecki, a noble, kind man with a big heart, a wonderful, invaluable friend, accept these words of remembrance from the heart, as a testament in your memory, and rest in peace.

Conflict of interest: None declared