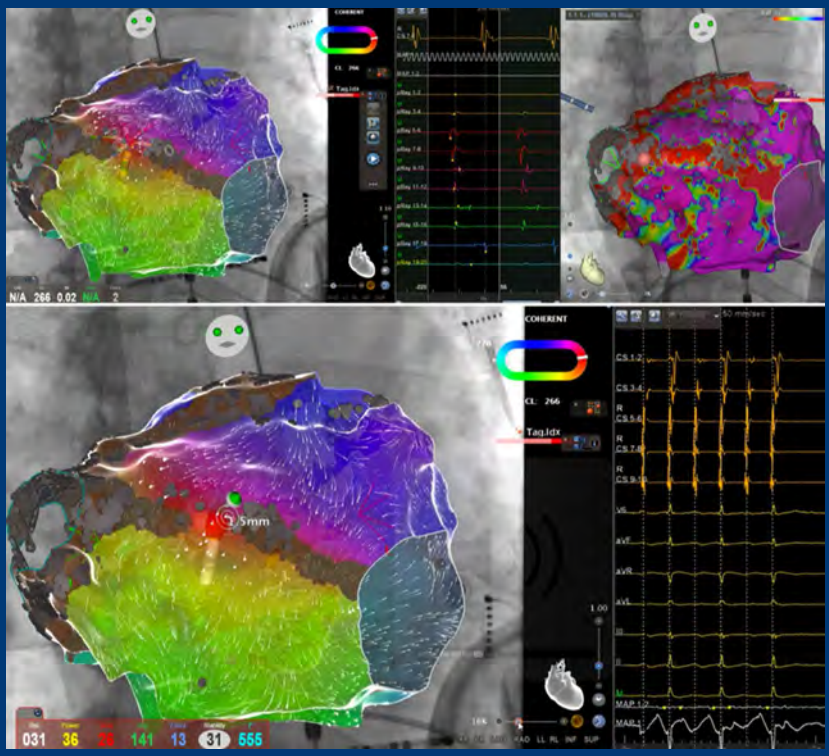
CARDIOLOGY JOURNAL

Impact Factor: 2.737

May 2022, Vol. 29, No. 3, pp. 369–536 www.cardiologyjournal.org



Krzysztof Myrda et al., see figure legend on page 526

ORIGINAL ARTICLES

ISSN 1897–5593
eISSN 1898–018X

VIA MEDICA

CARDIOLOGY JOURNAL

www.cardiologyjournal.org

CARDIOLOGY JOURNAL

www.cardiologyjournal.org

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

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

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

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

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

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

CARDIOLOGY JOURNAL

www.cardiologyjournal.org

May 2022, Vol. 29, No. 3

Table of Contents

VIA MEDICA

REVIEW ARTICLE

Cardiology Journal
2022, Vol. 29, No. 3, 369–380
DOI: 10.5603/CJ.a2021.0130

ISSN 1897–5593
eISSN 1898–018X

Innovative medical technologies in the percutaneous treatment of tricuspid regurgitation in Poland

Adam Witkowski[1], Dariusz Dudek[2, 3], Stanisław Bartuś[2], Wojciech Wojakowski[4], Andrzej Gackowski[5], Marek Grygier[6], Mariusz Kuśmierczyk[7], Miłosz J. Jaguszewski[8], Ewa Kowalik[9], Katarzyna Bondaryk[10], Maciej Niewada[11, 12], Piotr Przygodzki[13], Michał Jakubczyk[12, 14]

[1]Department of Cardiology and Interventional Angiology, National Institute of Cardiology, Warsaw, Poland; [2]Institute of Cardiology, Jagiellonian University Medical College, Krakow, Poland; [3]Maria Cecilia Hospital, GVM Care and Research, Cotignola (RA), Ravenna, Italy; [4]Division of Cardiology and Structural Heart Diseases, SMK in Katowice, Poland; [5]Jagiellonian University, Medical College, Institute of Cardiology, Department of Coronary Disease and Heart Failure, Noninvasive Cardiovascular Laboratory, John Paul II Hospital, Krakow, Poland; [6]First Department of Cardiology, Poznan University of Medical Sciences, Poznan, Poland; [7]Department of Cardiac Surgery and Transplantology, National Institute of Cardiology, Warsaw, Poland; [8]First Department of Cardiology, Medical University of Gdansk, Poland; [9]Department of Congenital Heart Diseases, National Institute of Cardiology, Warsaw, Poland; [10]Law Office Bondaryk, Warsaw, Poland; [11]Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, Poland; [12]HealthQuest, Poland; [13]Abbott Medical sp. z o.o., Health Economics and Reimbursement, Warsaw, Poland; [14]SGH Warsaw School of Economics, Poland

The paper was guest edited by Prof. Dariusz Jagielak

Abstract

Tricuspid regurgitation (TR) usually develops secondarily to left-sided heart diseases, whereas primary lesions to the valve apparatus is less common. Untreated severe TR has a poor prognosis and surgical treatment, i.e., valve repair or replacement, is the only treatment option with class I recommendation. However, cardiac surgical procedures may be associated with a high risk of complications. Recent advances in percutaneous approaches to managing structural heart diseases, especially mitral valve diseases, have enabled the implementation of this therapeutic strategy in the population of patients with TR. This paper presents data on the clinical efficacy, cost-effectiveness and expected population size for one of these procedures, namely the TriClip TTVr System procedure. Its efficacy was assessed in the TRILUMINATE study involving 85 patients with co-morbidities and at high surgical risk. After 1 year of follow-up, the reduction in the TR grade was reported in 71% of patients. Clinical improvement in New York Heart Association functional class, a 6-minute walk test, and the quality of life were also observed. A published analysis comparing percutaneous treatment modalities with a drug therapy based on data from medical registers was utilized, and propensity score matching was also employed. Percutaneous treatment reduced 1-year mortality and rehospitalization risk. The economic analysis showed the use of TriClip TTVr System is cost-effective: the cost of an additional quality-adjusted life year ranged from approximately PLN 85,000 to PLN 100,000, which is below the official threshold in Poland. The potential annual number of candidates for this treatment modality in Poland is estimated at 265.
(Cardiol J 2022; 29, 3: 369–380)

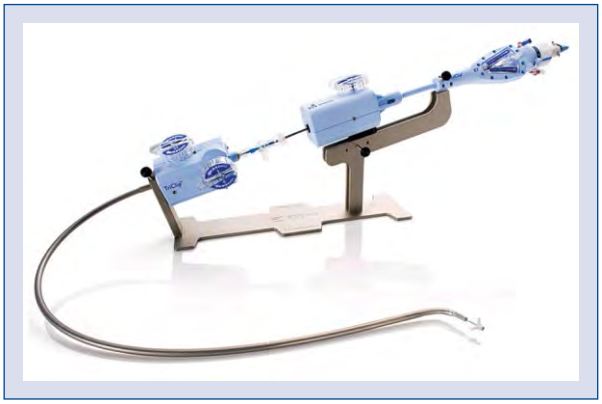
Key words: tricuspid regurgitation, transcatheter tricuspid valve interventions, transcatheter tricuspid valve repair, TriClip TTVr System, MitraClip

Address for correspondence: Dr. Maciej Niewada, Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, ul. Banacha 1b, 02–097 Warszawa, Poland, tel: +48 22 116 61 60, fax: +48 22 116 62 02, e-mail: maciej.niewada@wum.edu.pl

Received: 19.07.2021 Accepted: 6.10.2021 Early publication date: 18.10.2021

Introduction

This paper summarizes the discussion held at meetings of an advisory board comprised of experts in interventional cardiology and cardiac surgery. The meetings took place between May and September 2020. They were attended by 7 clinicians representing 5 centers experienced in treating patients with tricuspid regurgitation (TR). This paper aims to identify a potential place for CE-marked TriClip TTVr System (Abbott, USA; Central illustration) in the treatment of TR in Poland, present clinical evidence of its effectiveness, attempt to determine its cost-effectiveness and estimate the number of potential Polish patients if the technology was available.



Central illustration. TriClip XT Delivery System.

Tricuspid regurgitation: Epidemiology

Tricuspid regurgitation is the most common heart valve pathology. Trace or mild TR is a common finding, reported in over 70% of the population [1]. In a study published in 2020 which included more than 33,000 patients referred for echocardiography, mild TR was detected in 21.9% of patients, moderate — 8%, while severe — 0.8% [2]. OxVALVE registry showed that prevalence of moderate/severe TR in the general population was 2.7% [3].

The incidence of TR increases with age. In a population-based study conducted in Olmsted County (USA), moderate or severe TR was detected in 0.05% of patients aged 18–44 years and in 3.96% of patients aged > 75 years [4]. TR was significantly more frequently diagnosed in females. Similar relationships were presented in an earlier analysis based on the Framingham study: in the 40–49-year age group, at least moderate TR was detected in 0.5% of females and 0.3% of males while in the 70–83-year age group — in 5.6% of females and 1.5% of males [1]. Therefore, it can be assumed that moderate-to-severe TR affects approximately 4% of individuals over 75 years of age. Isolated regurgitation was diagnosed in about 8% of patients, while others had co-existent cardiac and non-cardiac comorbidities.

No reliable data on the incidence of TR in Poland are available. Given the epidemiological data for the United States, it is estimated that some level of TR affects approximately 200,000 individuals in Poland [5].

Etiology and pathogenesis of tricuspid regurgitation

Most TR cases are secondary to right ventricular (RV) overload and dilation. The most common mechanism underlying TR development is the dilation of the valve annulus (at the site of insertion of the anterior and posterior leaflets) with normal leaflet morphology (type I) and/or RV enlargement (which results in papillary muscle displacement with restricted leaflet position) — type IIIb. Secondary TR occurs due to left-sided heart diseases (including left ventricular [LV] dysfunction and mitral valve disease), other forms of pulmonary hypertension, atrial fibrillation, heart tumors or as a result of RV myocardial injury in the course of coronary artery disease or cardiomyopathy.

Injury to valve leaflets or the subvalvular apparatus, which leads to the development of the much less common primary TR (~15%) [4], may be caused by infective endocarditis (especially in cases of intravenous drug abuse), rheumatic heart disease, carcinoid syndrome, myxoid degeneration, endomyocardial fibrosis, congenital defects (Ebstein's anomaly, congenital valve dysplasia), chest trauma or the increasingly common iatrogenic injury (transvenous electrodes, endomyocardial biopsy, ionizing radiation, drug-induced lesions).

Tricuspid regurgitation leads to right atrial and RV volume overload; once the compensatory capacity of the right heart chambers is exhausted, the patient develops systemic venous congestion and severe heart failure.

Clinical presentation and prognosis of patients with tricuspid regurgitation

Clinical manifestations of this defect depend on the severity of the comorbidities and initially tend to be non-specific (fatigue, worsened exercise tolerance, shortness of breath). Patients develop peripheral edema, jugular vein dilatation and hepatomegaly. Persistent, hemodynamically significant TR results in increased venostasis and edema (despite diuretic therapy) as well as hepatic hyperemia, which lead to organ dysfunction and gradual development of cardiac cirrhosis.

The diagnosis of advanced TR worsens the prognosis. A meta-analysis of 70 studies involving over 32,500 patients with a mean follow-up of 3.2 ± 2.1 years showed that moderate/severe TR was associated with a 2-fold increase in the risk of death compared with mild/no regurgitation (relative risk [RR] = 1.95; 95% confidence interval [CI] = 1.75–2.17) [6]. The relationship between TR severity and all-cause mortality remained significant also after adjustment for pulmonary artery systolic pressure (PASP; meta-analysis of 13 studies; RR = 1.85; 95% CI = 1.44–2.39) and RV dysfunction (meta-analysis of 15 studies; RR = 1.78; 95% CI = 1.49–2.13). Moderate/severe TR also increased cardiac mortality (RR = 2.56; 95% CI = 1.84–3.55) and heart failure hospitalization rates (RR = 1.73; 95% CI = 1.14–2.62). A gradual increase in the risk of all-cause mortality was observed (RR = 1.25; 1.61; and 3.44, respectively; $p < 0.001$ for the trend) in patients with mild, moderate and severe regurgitation compared to patients without TR.

The presence of significant TR worsens the prognosis of patients regardless of LV function. A large retrospective study (over 5,200 patients, 4-year follow-up) showed that moderate or higher-grade TR was associated with increased mortality regardless of PASP (hazard ratio [HR] = 1.31; 95% CI = 1.16–1.49 for PASP > 40 mmHg and HR = 1.32, 95% CI = 1.05–1.62 for ≤ 40 mmHg) and regardless of LV ejection fraction (EF) (HR = 1.49; 95% CI = 1.34–1.66 for EF < 50% and HR = 1.54; 95% CI = 1.37–1.71 for EF ≥ 50%) [7]. Compared with the absence of TR, patients with moderate-to-severe defects had worse prognosis also after adjustment for age, systolic function of both ventricles, RV dimension and inferior vena cava dilatation (HR 1.17; 95% CI = 0.96–1.42 for moderate regurgitation and HR = 1.31; 95% CI = 1.05–1.66 for severe regurgitation).

Diagnostic evaluation

Transthoracic echocardiography (and transesophageal echocardiography in selected cases) is the most important diagnostic method in evaluation of TR prior to intervention. It requires advanced skills and high-quality equipment utilizing full range of echocardiographic techniques, including 3-dimensional (3D) imaging. Echocardiography plays a key role in differentiating between primary and secondary valve regurgitation for determining the main mechanism and etiology of the defect and assessing its severity. The evaluation should involve assessment of the morphology of the valve itself, the size of the right heart chambers and tricuspid annulus, dimension and collapsibility of the inferior vena cava and assessment of RV systolic function. Doppler analysis of the regurgitation jet and the assessment of the RV systolic pressure are also crucial elements of comprehensive assessment. Despite the use of new echocardiographic techniques (including 3D imaging), valve assessment is challenging in some patients because of poor echogenicity of leaflets and difficulties in obtaining a good acoustic window. Special skills are required to carry out transesophageal assessment because, in contrast to mitral valve, tricuspid valve is located distally and non-axially to the oesophagus.

Tricuspid regurgitation grading is based on a combined analysis of multiple parameters [8]: qualitative, semi-quantitative and quantitative. Qualitative criteria apply to valve morphology (leaflet thickening/prolapse/restriction/substantial coaptation defect), regurgitation jet assessment in color Doppler (very large central jet or eccentric jet striking the right atrial wall) and assessment of the regurgitation jet by continuous wave Doppler signal (dense/triangular with early peaking [peak velocity of < 2.0 m/s in severe TR]). Semi-quantitative criteria are as follows:

- regurgitation vena contracta width ≥ 7 mm;
- proximal isovelocity surface area radius ≥ 9 mm at Nyquist cutoff value of 0.3 m/s;
- hepatic veins systolic flow reversal;
- tricuspid inflow pattern with E wave dominance ≥ 1.0 m/s.

Echocardiographic quantitative criteria for severe TR include:

- effective regurgitant orifice area (EROA) ≥ 40 mm^2;
- regurgitation jet volume ≥ 45 mL;
- enlargement of the right heart chambers, and dilatation of the inferior vena cava.

It should be noted that so far, no cut-off points for moderate and mild regurgitation have been established for quantitative parameters of TR (EROA, regurgitation jet volume). However, as demonstrated by clinical studies of new percutaneous valve repair techniques, severe TR affects patients with very advanced defects and regurgitation jet quantitative parameters significantly above the cutoffs proposed. To allow for precise grading of TR in this group of patients in the context of enrolment for percutaneous interventions and their outcome monitoring, Hahn and Zamorano [9] presented a new, 5-grade classification of TR. They proposed additional massive regurgitation and torrential regurgitation based on the assessment of vena contracta (14–20 mm for massive regurgitation and ≥ 21 mm for torrential regurgitation) and EROA (60–79 mm^2 for massive regurgitation and ≥ 80 mm^2 for torrential regurgitation). Furthermore, they introduced another echocardiographic assessment criterion, namely 3D vena contracta area with the cutoffs of 75–94 mm^2 for severe regurgitation, 95–114 mm^2 for massive regurgitation, and ≥ 115 mm^2 for torrential regurgitation. This expanded TR classification also has a prognostic value, because the outcomes of patients with massive and torrential TR have incremental risk of mortality in comparison to severe TR.

In turn, Dreyfus et al. [10] proposed classification of functional TR and qualification for surgical treatment based not on regurgitation jet assessment alone but also on the tricuspid annular size (diastolic diameter of > 40 mm is considered a significant dilatation) and tricuspid leaflet coaptation (normal/leaflet restriction/no coaptation).

Current recommendations of scientific societies on the management and treatment of tricuspid regurgitation

Tricuspid regurgitation is a major challenge not only in terms of diagnostics but primarily in terms of treatment. Currently, surgical treatment is the standard of care in severe symptomatic isolated valve regurgitation. In the presence of other left-sided valve defects requiring surgery, indications for tricuspid valve repair include severe TR or moderate TR with coexistent tricuspid annular dilatation.

Several valve repair techniques have been proposed for cardiac surgery for TR [11]. The first method, introduced by Kay et al. [12], involves posterior leaflet plication, which leads to the formation of the bicuspid tricuspid valve. Subsequently, de Vega [13] introduced tricuspid valve annuloplasty with suture placement in the posterior and anterior part of the annulus (bypassing atrioventricular node). Another modification of surgery was annuloplasty using a synthetic ring that restores the normal shape of the valve. Insertion of a semi-open rigid ring is currently the most widely used method of surgical tricuspid valve repair.

In cases of RV enlargement and remodeling with leaflet restriction, annular reduction as the only treatment option may not be effective enough. In such a situation, anterior tricuspid leaflet extension or the clover technique is applied, i.e., suturing valve leaflet edges (similar to the Alfieri technique for mitral valve).

In severe leaflet restriction or organic lesions preventing effective repair, artificial (mechanical or biological) valve implantation is necessary. Biological valves are preferred due to a lower risk of thrombosis and possibly the chances of subsequent percutaneous treatment of its dysfunction (valve-in-valve procedure).

According to the 2017 guidelines of the European Society of Cardiology (ESC) and the European Association for Cardiothoracic Surgery (EACTS) on the treatment of valvular heart defects [14], a surgical procedure is indicated (class I) in patients with severe primary or secondary TR undergoing left heart defect surgery. Surgery should also be considered (class IIa recommendation) in patients with moderate primary TR undergoing left heart surgery, as well as in patients with mild to moderate secondary valve insufficiency with tricuspid annulus dilatation (≥ 40 mm or > 21 mm/m^2, evaluated using 2D echocardiography) undergoing left heart surgery. Surgical treatment may be considered at a time of left heart surgery (class IIb recommendation) in patients with a history of right-sided heart failure and mild-to-moderate secondary TR, even if the tricuspid valve annulus is not dilated.

Indications for surgical treatment of isolated TR include symptomatic disease with severe isolated primary TR without severe RV dysfunction (class I recommendation). Surgery should be considered in asymptomatic patients or patients with mild symptoms with severe primary TR and progressive RV dilatation or worsening RV function (class IIa). After surgery for left heart defects and in the absence of recurrent left valve dysfunction, surgery should be considered in patients with severe secondary tricuspid insufficiency who develop symptoms or progressive RV dilatation/dysfunction, in the absence of severe RV or LV dysfunction and severe pulmonary vascular disease/pulmonary

hypertension (class IIa). Both ESC/EACTS recommendations on the surgical treatment of TR have the level of evidence C, which means that they are based on an agreed expert opinion or data from small retrospective studies or registries.

Similar recommendations on the interventional treatment of TR were provided by the American Heart Association/American College of Cardiology (AHA/ACC) in 2020 [15]. The recommendations concern valve repair primarily in patients undergoing left heart surgery. As for the surgical treatment of symptomatic patients with severe primary TR, a lower class (IIa) recommendation was provided compared to the European guidelines. In addition, special attention is paid to atrial fibrillation in the USA guidelines as the cause of isolated secondary TR resulting primarily from annular dilatation.

Eligibility for surgical treatment should be based on the patient's clinical status, co-morbidities, and perioperative risk. The right moment for the surgery of the defect has not been determined. Similarly, no optimal drug therapy for TR has been defined. According to the AHA's position statement on the diagnosis and treatment of RV insufficiency of 2018, drug therapy for RV insufficiency should be based on diuretics (or renal replacement therapy, if increased diuretics doses failed); afterload-reducing agents are also used (vasodilators for pulmonary circulation), and in extreme cases, mechanical circulatory support [16]. Late-onset symptoms of TR and delayed qualification for surgical treatment of the defect have a negative impact on treatment outcomes [17]. Early and late outcomes of surgical treatment of TR are still unsatisfactory.

In an analysis of nearly 55,000 tricuspid valve surgeries in the USA between 2000 and 2010 (in 85.7% of cases, the procedure on tricuspid valve accompanied other procedures, with 88.9% of valve repairs), the perioperative mortality rate was 10.6% in 2000 and 8.2% 10 years later [18]. Predictors of mortality included: older age, high creatinine level, renal failure requiring dialysis prior to surgery, cardiogenic shock, use of intra-aortic counterpulsation or inotropic agents, presence of significant peripheral or cerebrovascular disease, mitral stenosis, myocardial infarction, tricuspid valve replacement, chronic pulmonary disease, diabetes mellitus, coronary artery disease, urgent surgery, reoperation, congestive heart failure, and all other procedures except for double valve replacement (mitral or aortic).

More recent data (2007–2017) on the outcomes of surgical treatment of isolated TR come from 12 centers in France [19]. Most of the 466 patients who underwent surgery for tricuspid valve alone (8% of all TR surgeries) had an advanced disease (47% New York Heart Association [NYHA] class II/IV; 57% with symptoms of right-ventricular failure). Of these patients, 49% were diagnosed with functional TR (22% after left heart surgery, 27% — isolated TR) and 51% had an organic defect (including 31% with infective endocarditis). Overall, in-hospital mortality following surgery for isolated TR was 10%, including 16% of patients after left heart surgery, 13% of patients with isolated functional TR, 5% of patients with infective endocarditis and 8% of patients with organic TR of another etiology. A multivariate analysis showed that independent risk factors for in-hospital mortality were as follows: NYHA class III/IV (odds ratio [OR] = 2.7; 95% CI = 1.2–6.1; p = 0.01), moderate/severe RV dysfunction (OR = 2.6; 95% CI = 1.2–5.8; p = 0.02) and lower prothrombin time (OR = 0.98; 95% CI = 0.96–0.99; p = 0.008); clinical signs of heart failure fell just short of statistical significance (OR = 2.4; 95% CI = 0.9–6.5; p = 0.06). Overall, the 1-year survival rate following surgery for isolated TR was 86%, while the 5-year survival rate was 75%. Independent predictors of mortality in longer follow-up were as follows: NYHA class III/IV (HR = 1.7; 95% CI = 1.1–2.8; p = 0.04), clinical signs of right heart failure (OR = 1.8; 95% CI = 1.01–3.3; p < 0.05), and lower prothrombin time (OR 0.98; 95% CI = 0.97–0.99; p = 0.04).

New methods of percutaneous tricuspid valve repair

Minimally invasive surgical procedures and percutaneous valve repair have recently been used to treat valvular heart disease. However, due to technical challenges resulting from the tricuspid annulus structure, the tricuspid valve was called a 'forgotten valve' in terms of the percutaneous treatment of heart defects. Only in recent years have attempts been made at the transcatheter treatment of TR, based on percutaneous mitral valve treatment experience [20].

Percutaneous treatment modalities for TR are based on:

1. Reduction in the tricuspid annular dimension (percutaneous annuloplasty):
    a. Cardioband (ValtechCardio) — direct annuloplasty using an anchoring system to fix and then reduce the size of an artificial annulus, technique originally introduced in the percutaneous treatment of mitral regurgitation,

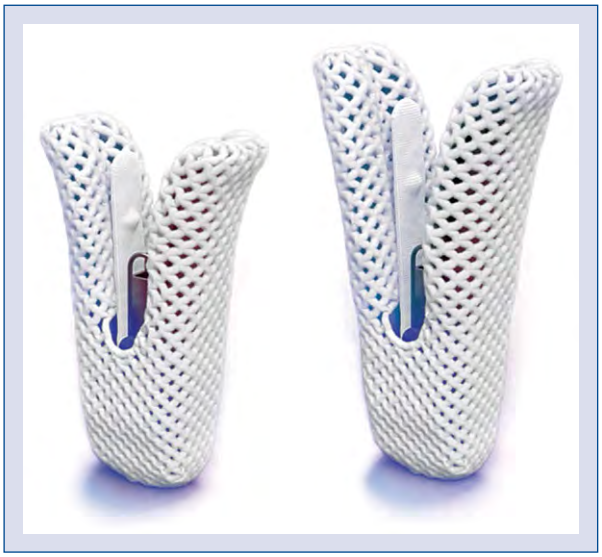


Figure 1. TriClip NT-TriClip XT implant.

   b. The Trialign System (Mitralign, Inc.) — sutures are placed percutaneously in the commissural area; cinching of the sutures results in plication of the posterior cusp and bicuspidisation of the valve,
   c. The TriCinch System (4Tech Cardio) — by placing one end of the system in the anteroposterior commissure area and the other in the inferior vena cava, a change in the tricuspid annular geometry is achieved;
2. Improvement of cusp coaptation:
   a. The Forma System (Edwards Lifesciences) — a polymer balloon is placed in the tricuspid orifice and anchored in the RV apex. The balloon fills up the regurgitant orifice,
   b. The MitraClip System (Abbott Vascular) — a system for percutaneous treatment of mitral valve regurgitation, based on the Alfieri surgical technique (edge-to-edge),
   d. The PASCAL System (Edwards Lifesciences) — involving the approximation of valve leaflets, used for percutaneous mitral valve repair,
   e. The TriClip TTVr System (Abbott Vascular) — based on the MitraClip System in which the control and clip delivery system were re-designed for the anatomy and morphology of the right atrioventricular valve (Fig. 1), soon to be complemented by a new generation TriClip G4 TTVr System;
3. Caval valve implantation (CAVI):
   a. Sapien XT and Sapien 3 valves (Edwards Lifesciences) implanted into the inferior vena cava,
   b. The TricValve System (P+F PRODUCTS + FEATURES GMBH) based on the implantation of biological valves mounted to nitinol stents into the superior and inferior vena cava;
4. Percutaneous tricuspid valve implantation (to replace dysfunctional bioprosthesis implanted in the tricuspid orifice):
   a. The Melody valve (Medtronic),
   b. The NAVIGATE valve (NaviGate Cardiac Structures Inc.),
   c. The Sapien valve (Edwards Lifesciences);
5. Transcatheter percutaneous implantation of a dedicated self-expanding valve:
   a. The Evoque valve (Edwards Lifesciences).

The outcomes of percutaneous treatment of TR were analyzed, among others, using data from the international TRIVALVE registry. The first data concerned 106 patients with severe symptomatic TR undergoing percutaneous interventions at 11 centers in Europe, the USA and Canada between January 2014 and December 2016 [21]. The mean patient age was 76 ± 9 years, 60.4% of patients were females, and the EuroScore (European System for Cardiac Operative Risk Evaluation) II score was 7.6 ± 5.7%. In total, 35% of patients had undergone left heart valve surgery. RV dysfunction (defined as tricuspid annular plane systolic excursion < 17 mm) was observed in 56.3% of patients, 95% were in NYHA class III/IV. In patients who underwent the intervention, functional regurgitation predominated (95.2%); the tricuspid annular diameter was 45.4 ± 11 mm, and pre-intervention PASP was 39.7 ± 13.8 mmHg. The MitraClip System was most frequently used (n = 58); other devices used were: Trialign (n = 17), TriCinch (n = 15), FORMA (n = 7), Cardioband (n = 5), and venae cavae valves (n = 3). Procedure efficacy, defined as successful implantation of the device and TR reduction to grade ≤ 2, was observed in 62% of patients. In the 30-day follow-up period, overall mortality was 3.7% and the incidence of serious cardiovascular and cerebrovascular events was 26%. More than half of the patients (58%) were in NYHA class I/II 30 days after the procedure.

Since most patients with TR underwent the 'edge-to-edge' procedure with the use of the MitraClip System, the authors of the TRIVALVE registry summarized the procedure effectiveness at 1 year of follow-up [22]. The analysis included 249 patients with a mean age of 77 ± 9

(EuroScore II mean score: 6.4%). With the use of two clips on average (standard deviation = 1), the procedure was effective in 77% of patients. At 1 year of follow-up, sustained improvement in the TR grade was observed in 72% of patients, and 69% of patients were in NYHA class I/II. Overall, 1 year mortality was 20%, and the composite endpoint of mortality and unscheduled hospitalizations for heart failure was 35%. Predictors of annual mortality were as follows: ineffective procedure, worsening of renal function and absence of sinus rhythm.

Data from the TRIVALVE registry showed that 'edge-to-edge' procedures are effective in most patients and demonstrated marked clinical improvement in high-risk patients subjected to percutaneous TR repair.

The estimated effectiveness of percutaneous tricuspid regurgitation treatment using the MitraClip TMVr and TriClip TTVr Systems

A systematic review of primary studies of percutaneous TR repair (regardless of the devices used) was conducted. The search strategy allowed for both experimental and observational (including non-comparative) studies and was not limited to specific devices used for valve repair. The review included PubMed, Embase and Cochrane Library data (search cut-off date March 20, 2020).

A total of 58 papers were included in the review-based analysis. One comparative study was found in which TTVr was compared with drug therapy [23], and 1 study concerning TriClip technology — a prospective TRILUMINATE registry [24]. Both studies are discussed below.

Taramasso 2019 study

The study involved 472 patients included in the TriValve registry, from 22 European and North American sites, who underwent transcatheter tricuspid valve intervention (TTVI) between 2016 and 2018. The control group was comprised of patients from two retrospective registries, including patients with TR who received drug therapy and were additionally included in the analysis.

The study was conducted using propensity score matching — a statistical technique aimed at increasing the comparability of two patient groups in non-randomized trials by dividing patients into pairs based on an estimation of their similarity in terms of clinical parameters, to reduce the impact of potential confounding factors, i.e., factors affecting the choice of treatment method and at the same time its outcome, and thereby estimate the causal effect of the technology in question [25]. Propensity score matching is widely used in clinical analyzes in the absence of randomized studies, including studies of cardiac procedures [26–28].

Propensity score matching yielded 268 patient pairs. The primary endpoint was the annual all-cause mortality, heart failure rehospitalization rate, or the composite endpoint of both events.

After matching, patients in the TTVI group, compared with patients receiving drug therapy, had lower 1-year mortality (23 ± 3% vs. 36 ± 3%, $p = 0.001$), a lower risk of rehospitalization (27 ± 3% vs. 47 ± 3%, $p < 0.0001$) and a lower risk of the composite endpoint (32 ± 4% vs. 49 ± 3%, $p = 0.0003$). The survival analysis using the Cox model showed that TTVI was associated with a reduction in the risk of composite endpoint (HR = 0.60; 95% CI = 0.46–0.79; $p = 0.003$), also in the multivariate analysis, after adjustment for gender, NYHA class, RV dysfunction, and atrial fibrillation (HR = 0.39; 95% CI = 0.26–0.59; $p < 0.0001$), and after adjustment for mitral regurgitation grade and the presence of a stimulator/cardioverter defibrillator (HR = 0.35; 95% CI = 0.23–0.54; $p < 0.0001$).

Improved survival was also confirmed in a subset of patients without concomitant left-sided valve defects. The type of valve repair device used (MitraClip vs. other repair systems) did not affect the primary endpoint rate, with MitraClip being the most frequently used device (229 out of 268 patients).

The obvious limitation of the study, in terms of the aim of this paper, is the use of MitraClip rather than TriClip. However, both technologies are based on Alfieri's (edge-to-edge) technique with the identical implants which remains after procedure. Differences between the technologies result from the clip Delivery System and Steering Guide Catheter, reflecting the anatomic challenges of the right side of the heart. Therefore, both technologies can be considered similar enough to allow for the use of the data.

TRILUMINATE study

The TRILUMINATE study aimed to assess the safety and efficacy of the TriClip TTVr System in the treatment of patients with symptomatic, at least moderate, tricuspid valve insufficiency who were receiving drug therapy and for whom TTVr seemed substantiated [24]. This was a prospective,

Table 1. TriClip TTVr System effectiveness in the TRILUMINATE study.

Endpoint	Assessment at 30 days (n = 85)	Assessment at 6 months (n = 85)	Assessment at 1 year (n = 63)
Reduction in TR severity by at least 1 grade within 30 days of the procedure	85.5%	87.1%	87%
NYHA class I/II (25.3% at baseline)	79.7%	86.3%	80%
Mean vena contracta width of TR [cm] (1.7 cm at baseline)	0.99	0.86	NA
Quality of life endpoints			
6MWT [m], mean improvement (277.6, SD: 37.1 at baseline)	NA	54.6 (SD: 111.4)	33.09 (SD: 62.88)
KCCQ, mean improvement vs. baseline, score	14.2 (SD: 16.7)	18.6 (SD: 21.5)	16.81 (SD: 23.4)
SF-36 (MCS), mean improvement (baseline 44.6, SD: 14.0), score	47.6 (SD: 12.3)	50.1 (SD: 10.6)	NA
SF-36 (PCS), mean improvement (35.6, SD: 9.6 at baseline), score	39.5 (SD: 10.0)	42.5 (SD: 9.6)	NA

6MWT — a 6-minute walk test; KCCQ — Kansas City Cardiomyopathy Questionnaire; MCS — Mental Component Summary; NA — not available; NYHA — New York Heart Association; PCS — Physical Component Summary; SF-36 — Short-Form Health Survey; SD — standard deviation; TR — tricuspid regurgitation

single-arm, multicenter (Europe and the USA) study, with the following inclusion criteria:

- age ≥ 18 years and ≤ 90 years at enrolment;
- patients treated according to appropriate standards (including optimal drug therapy) prior to enrolment;
- with moderate-to-severe TR;
- NYHA class II or higher;
- no indications for left-sided heart surgery or mitral valve repair.

Exclusion criteria included:

- PASP above 60 mmHg as estimated by echocardiography;
- prior tricuspid valve procedure or the presence of a cardiac implantable electronic device (e.g., a transvenous stimulation device), which could prevent proper insertion of the TriClip TTVr System device.

The TRILUMINATE study involved 85 patients (66% females) with co-morbidities and a high surgical risk. The mean patient age was 77.8 ± ± 7.9 years and the EuroSCORE II score was 8.7 ± ± 10.7%. Most patients were diagnosed with severe TR (84%), less frequently organic (12%) or mixed 94%. The most common co-morbidities included: atrial fibrillation (92%), hypertension (86%), kidney diseases (46%), diabetes mellitus (22%) and prior myocardial infarction (18%). One-third of the patients had undergone mitral valve intervention and 75% of the patients had NYHA class III/IV disease. The efficacy of device implantation (defined as a reduction in TR by at least one grade on echocardiography before discharge) was 91%. After 1 year of follow-up, the reduction in the TR grade (to moderate at most) was reported in 71% of patients [29]. Clinical improvement in NYHA functional class, a 6-minute walk test, and the quality of life were observed. Overall, post-procedure mortality in 1-year follow-up was 7.1%. Detailed efficacy and safety data for the TriClip TTVr System in the subsequent follow-up period are presented in Tables 1 and 2.

TripClip cost effectiveness

An attempt was made at estimating the cost-effectiveness of the TriClip TTVr System compared to drug therapy for TR, i.e., assessing a mean difference (calculated per patient) in the cost from the public payer's perspective and the effect expressed by life years gained (LYG) and quality-adjusted life years (QALYs). The analysis used the only comparative study available (and discussed above) [23], so the target population for the analysis was consistent with patient characteristics in the study. A 1-year horizon was used in the study, and the estimated Kaplan-Meier curves for survival at 1 year indicated the value of approximately 77% for TTVI and ~64% for drug therapy. Given the difference in survival, benefits from TTVI are also derived in the years following the procedure. To allow for these benefits, the survival curves were

Table 2. TriClip TTVr System safety in the TRILUMINATE study.

Endpoint	Assessment at 30 days (n = 85)	Assessment at 6 months (n = 85)	Assessment at 1 year (n = 50)
Major adverse event	NA	5 (6%)	3 (6%)
CV mortality	2 (2.4%)	3 (3.6%)	3 (6%)
Myocardial infarction	0 (0%)	1 (1.2%)	0 (0%)
Stroke	0 (0%)	0 (0%)	0 (0%)
De novo kidney failure	1 (1.2%)	1 (1.2%)	0 (0%)
Any CV surgery for device-related AE	0 (0%)	0 (0%)	0 (0%)
Major bleeding	6 (7.3%)	10 (11.9%)	7 (14%)
Pulmonary thromboembolism	0 (0%)	0 (0%)	0 (0%)
Newly diagnosed hepatic failure	0 (0%)	0 (0%)	0 (0%)
Newly diagnosed atrial fibrillation	1 (1.2%)	1 (1.2%)	0 (0%)
All-cause mortality	0 (0%)	4 (4.8%)	5 (10%)
Single device insertion	NA	5 (7.2%)	3 (6%)
Embolization	NA	0 (0%)	0 (0%)
Tricuspid valve stenosis	NA	7 (10.8%)	NA
Tricuspid valve surgery	NA	1 (1.2%)	NA

AE — adverse event; CV — cardiovascular; NA — not available

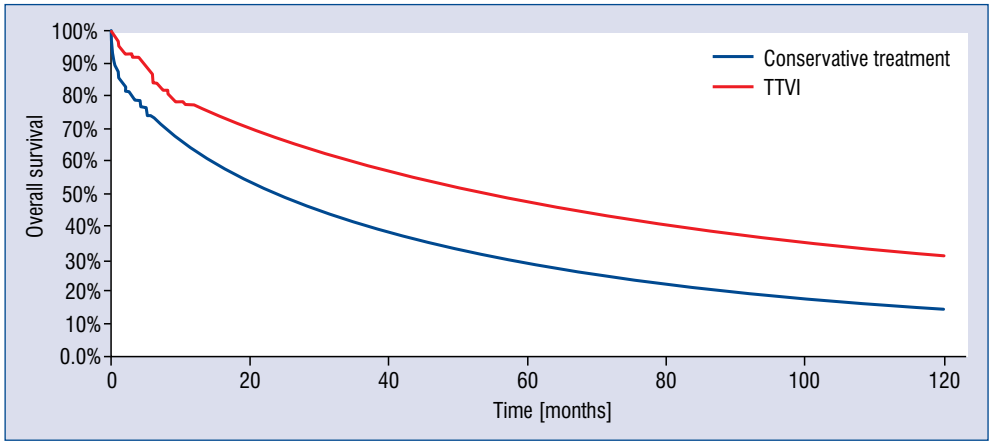


Figure 2. Survival curves for transcatheter tricuspid valve intervention (TTVI) and drug therapy in the 2019 Taramasso study [23], extrapolated using the Weibull model.

extrapolated beyond the horizon of the Taramasso 2019 study to 10 years, using the Weibull model (Fig. 2).

In the analysis of QALYs, information on NYHA class distribution and Kansas City Cardiomyopathy Questionnaire (KCCQ) values at enrolment and at 6 months were used to allow for the technology's impact on health-related quality of life (Table 3). It was assumed that the value of these parameters in patients with the TriClip TTVr System implanted would correspond to those observed 6 months in the study (1-year data were available for an incomplete group of patients). For patients receiving drug therapy, it was assumed that the values would remain at the baseline level. Since only patients on optimal drug therapy at enrolment were included in the TRILUMINATE study, it seems reasonable to assume that NYHA class in the control group should not be subject to significant changes in the short-term horizon. In the long-term horizon, both NYHA and KCCQ may likely worsen in both groups.

Table 3. New York Heart Association (NYHA) class changes in the TRILUMINATE study (the difference from baseline was statistically significant for 30-day, 6-month and 12-month follow-up, $p < 0.0001$).

NYHA class	Assessment at baseline (n = 83)	Assessment at 30 days (n = 84)	Assessment at 6 months (n = 73)	Assessment at 1 year (n = 65)
NYHA I	0%	23%	36%	32%
NYHA II	25%	57%	51%	51%
NYHA III	70%	20%	12%	17%
NYHA IV	5%	0%	1%	0%

However, from the point of view of the economic analysis results, an intergroup difference in the parameters plays a key role. This paper de facto assumes that the difference is maintained in the long-term horizon.

The NYHA and KCCQ values were assigned health-state utilities based on the results of a systematic literature review. As for KCCQ, 1 study was found [30], which showed the following dependence: utility = 0.44 + 0.0035* KCCQ-OS. As for NYHA, several studies were identified and qualified for parameterization, which reported utility values for patients with heart failure in individual NYHA classes [31–36]. Mean utility values for NYHA class I and mean decrements for other groups from the publications found were used. Ultimately, the following utility values were used: 0.858 for NYHA class I, 0.762 for NYHA class II, 0.646 for NYHA class III, and 0.459 for NYHA class IV.

In the analysis, it was assumed that the TTVI cost would amount to approximately PLN 125,000. The costs of rehospitalization were also taken into account, required by 26% of patients who had received the TriClip TTVr System and 47% of patients on drug therapy, according to the 2019 Taramasso study. It was assumed that the cost of rehospitalization would equal the weighted average cost of procedure E50: acute or decompensated heart failure — treatment at Intensive Cardiac Care Unit (PLN 17,000; 80% of patients) and procedure E52: advanced circulatory failure (PLN 5,987; 20% of patients). The analysis included the additional costs of drug therapy used in both patient groups, amounting to approximately PLN 100 per year. Future costs and effects were discounted at the rates of 5% and 3.5%, respectively, as per Polish Health Technology Assessment guidelines.

The incremental cost-effectiveness ratio for the TriClip TTVr System compared to drug therapy for TR was PLN 84,109.79/QALY for the analysis based on the NYHA class and PLN 101,290.90/QALY for the analysis based on KCCQ. In turn, when considering the impact on life expectancy only, the obtained coefficient amounted to PLN 86,422.02/LYG. In all cases, the incremental cost-effectiveness ratio value was clearly below the cost-effectiveness threshold defined in Poland, i.e., PLN 155,514/QALY (or PLN/LYG).

Estimation of the size of the population that may benefit from the TriClip TTVr System

As a rule, TriClip TTVr System should be used in patients with TR and a high cardiac surgical risk in whom drug therapy fails to provide satisfactory outcomes. In an attempt to determine the size and structure of this population, four groups may be distinguished, which should constitute the largest part of the target population:

- high surgical risk or inoperable patients with mitral regurgitation and coexistent TR, with indications for the repair of both valves;
- patients after mitral valve surgery who developed moderate-to-severe TR;
- patients with severe TR in the course of RV insufficiency after the implantation of an LV assist device;
- patients with isolated severe TR who, in the opinion of the Heart Team, are not candidates for surgical valve repair/replacement.

The estimation of the size of the first subpopulation was based on determining the annual population of candidates for percutaneous mitral regurgitation treatment. Data from other countries were used for this purpose, as Poland's actual number of procedures may not include all patients who needed it. By calculating the average number of procedures with respect to the number of citizens, the demand for the edge-to-edge procedure in Poland was estimated at 778 per year (due to data confidentiality, they were not presented in this paper). The estimated proportion of patients with additional TR ranges from 19.4% [37] to 27% [38].

The ultimate size of the first subpopulation can be estimated at approximately 180 patients per year.

According to National Cardiac Surgery Registry data, 896 mitral valve surgeries were performed in Poland in 2019. Assuming that TR develops in 5% of patients after mitral valve surgery, the size of the second subpopulation can be estimated at 45 per year. According to the authors' clinical experience, the size of the third subpopulation should be estimated at approximately 20 patients per year. Assuming that isolated TR occurs in approximately 8% of patients [19], the size of the fourth group was estimated with respect to the size of the first three groups, resulting in approximately 20 patients per year.

In total, the number of patients with likely indications for TriClip TTVr System implantation is approximately 265 per year. It should be noted that in the first years of the system's availability, the actual number of procedures would most likely be lower and would reach the estimated level only after a few years.

Summary

Severe TR leads to heart failure and worsened quality of life and is associated with a poor prognosis. Treatment modalities include drug therapy (of limited effectiveness) and cardiac surgery, associated with a very high risk, especially in patients in a worse clinical condition, with RV dysfunction and co-morbidities. Thanks to the availability of percutaneous treatment of TR, patients may be offered an effective, non-invasive procedure associated with a low risk of complications. The TriClip TTVr System proved safe and effective in the TRILUMINATE study. Based on the Taramasso 2019 study, it may be inferred that transcatheter edge-to-edge tricuspid valve repair is more effective than drug therapy regarding its effect on survival and rehospitalizations but this needs to be confirmed in further studies. In light of the survival benefit, improved quality of life, and anticipated cost, the TriClip TTVr System should be considered cost-effective. A subgroup analysis of patients who could benefit from the technology suggests that the annual number of procedures could be approximately 265 after a few years.

Acknowledgments

The authors would like to thank Abbott Medical sp. z o.o., Health Economics & Reimbursement, Warsaw, Poland, for the organization and financial support for the experts' meetings. We would also like to thank HealthQuest employees (I. Lipka and B. Tabor) for their support in preparing parts of this paper.

Conflict of interest: HealthQuest (including Maciej Niewada and Michał Jakubczyk) received fees for preparing materials for the experts' discussion. HealthQuest collaborates with Abbott and receives fees for the preparation of health technology assessments. Adam Witkowski: Abbott Poland Advisory Board member, presentation fees (Abbott); Wojciech Wojakowski: Abbott Poland Advisory Board member, lecture fees (Abbott); Andrzej Gackowski: ECHO proctor — Abbott, Edwards; Marek Grygier: Abbott Poland Advisory Board member, lecture fees, proctor for structural heart interventions (Abbott); Piotr Przygocki: Employee of Abbott.

References

1. Singh JP, Evans JC, Levy D, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). Am J Cardiol. 1999; 83(6): 897–902, doi: 10.1016/s0002-9149(98)01064-9, indexed in Pubmed: 10190406.
2. Chorin E, Rozenbaum Z, Topilsky Y, et al. Tricuspid regurgitation and long-term clinical outcomes. Eur Heart J Cardiovasc Imaging. 2020; 21(2): 157–165, doi: 10.1093/ehjci/jez216, indexed in Pubmed: 31544933.
3. Lindekleiv H, Løchen ML, Mathiesen EB, et al. Echocardiographic screening of the general population and long-term survival: a randomized clinical study. JAMA Intern Med. 2013; 173(17): 1592–1598, doi: 10.1001/jamainternmed.2013.8412, indexed in Pubmed: 23877591.
4. Topilsky Y, Maltais S, Medina Inojosa J, et al. Burden of tricuspid regurgitation in Patients diagnosed in the community setting. JACC Cardiovasc Imaging. 2019; 12(3): 433–442, doi: 10.1016/j.jcmg.2018.06.014, indexed in Pubmed: 30121261.
5. Brykczyński M, Mokrzycki K, Jędrzejczak T. Chirurgiczne leczenie wtórnej niedomykalności zastawki trójdzielnej. Kardiologia po Dyplomie. 2011; 10(4): 82–85.
6. Wang N, Fulcher J, Abeysuriya N, et al. Tricuspid regurgitation is associated with increased mortality independent of pulmonary pressures and right heart failure: a systematic review and meta-analysis. Eur Heart J. 2019; 40(5): 476–484, doi: 10.1093/eurheartj/ehy641, indexed in Pubmed: 30351406.
7. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. J Am Coll Cardiol. 2004; 43(3): 405–409, doi: 10.1016/j.jacc.2003.09.036, indexed in Pubmed: 15013122.
8. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Scientific Document Committee of the European Association of Cardiovascular Imaging. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2013; 14(7): 611–644, doi: 10.1093/ehjci/jet105, indexed in Pubmed: 23733442.
9. Hahn RT, Zamorano JL. The need for a new tricuspid regurgitation grading scheme. Eur Heart J Cardiovasc Imaging. 2017; 18(12): 1342–1343, doi: 10.1093/ehjci/jex139, indexed in Pubmed: 28977455.

10. Dreyfus GD, Martin RP, Chan KM, et al. Functional tricuspid regurgitation: a need to revise our understanding. J Am Coll Cardiol. 2015; 65(21): 2331–2336, doi: 10.1016/j.jacc.2015.04.011, indexed in Pubmed: 26022823.
11. Van Praet KM, Stamm C, Starck CT, et al. An overview of surgical treatment modalities and emerging transcatheter interventions in the management of tricuspid valve regurgitation. Expert Rev Cardiovasc Ther. 2018; 16(2): 75–89, doi: 10.1080/14779072.2018.1421068, indexed in Pubmed: 29283684.
12. Kay JH, Maselli-Campagna G, Tsuji KK. Surgical treatment of tricuspid insufficiency. Ann Surg. 1965; 162: 53–58, doi: 10.1097/00000658-196507000-00009, indexed in Pubmed: 14313519.
13. De Vega NG. [Selective, adjustable and permanent annuloplasty. An original technic for the treatment of tricuspid insufficiency]. Rev Esp Cardiol. 1972; 25(6): 555–556, indexed in Pubmed: 4658611.
14. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017; 38(36): 2739–2791, doi: 10.1093/eurheartj/ehx391, indexed in Pubmed: 28886619.
15. Otto C, Nishimura R, Bonow R, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021; 143(5), doi: 10.1161/cir.0000000000000923.
16. Konstam MA, Kiernan MS, Bernstein D, et al. Evaluation and management of right-sided heart failure: a scientific statement from the American Heart Association. Circulation. 2018; 137(20): e578–e622, doi: 10.1161/CIR.0000000000000560, indexed in Pubmed: 29650544.
17. Chang CC, Veen KM, Hahn RT, et al. Uncertainties and challenges in surgical and transcatheter tricuspid valve therapy: a state-of-the-art expert review. Eur Heart J. 2020; 41(20): 1932–1940, doi: 10.1093/eurheartj/ehz614, indexed in Pubmed: 31511897.
18. Kilic A, Saha-Chaudhuri P, Rankin JS, et al. Trends and outcomes of tricuspid valve surgery in North America: an analysis of more than 50,000 patients from the Society of Thoracic Surgeons database. Ann Thorac Surg. 2013; 96(5): 1546–52; discussion 1552, doi: 10.1016/j.athoracsur.2013.06.031, indexed in Pubmed: 24070702.
19. Dreyfus J, Flagiello M, Bazire B, et al. Isolated tricuspid valve surgery: impact of aetiology and clinical presentation on outcomes. Eur Heart J. 2020; 41(45): 4304–4317, doi: 10.1093/eurheartj/ehaa643, indexed in Pubmed: 32974668.
20. Oliveira DC, Oliveira CGC. The forgotten, not studied or not valorized tricuspid valve: the transcatheter revolution is coming. Cardiol Res. 2019; 10(4): 199–206, doi: 10.14740/cr874, indexed in Pubmed: 31413775.
21. Taramasso M, Hahn RT, Alessandrini H, et al. The international multicenter trivalve registry: which patients are undergoing transcatheter tricuspid repair? JACC Cardiovasc Interv. 2017; 10(19): 1982–1990, doi: 10.1016/j.jcin.2017.08.011, indexed in Pubmed: 28982563.
22. Mehr M, Taramasso M, Besler C, et al. 1-Year outcomes after edge-to-edge valve repair for symptomatic tricuspid regurgitation: results from the TriValve registry. JACC Cardiovasc Interv. 2019; 12(15): 1451–1461, doi: 10.1016/j.jcin.2019.04.019, indexed in Pubmed: 31395215.
23. Taramasso M, Benfari G, van der Bijl P, et al. Transcatheter versus medical treatment of patients with symptomatic severe tricuspid regurgitation. J Am Coll Cardiol. 2019; 74(24): 2998–3008, doi: 10.1016/j.jacc.2019.09.028, indexed in Pubmed: 31568868.
24. Nickenig G, Weber M, Lurz P, et al. Transcatheter edge-to-edge repair for reduction of tricuspid regurgitation: 6-month outcomes of the TRILUMINATE single-arm study. Lancet. 2019; 394(10213): 2002–2011, doi: 10.1016/S0140-6736(19)32600-5, indexed in Pubmed: 31708188.
25. Rosenbaum P, Rubin D. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983; 70(1): 41–55, doi: 10.1093/biomet/70.1.41.
26. Blackstone EH. Breaking down barriers: helpful breakthrough statistical methods you need to understand better. J Thorac Cardiovasc Surg. 2001; 122(3): 430–439, doi: 10.1067/mtc.2001.117536, indexed in Pubmed: 11547291.
27. Blackstone EH. Comparing apples and oranges. J Thorac Cardiovasc Surg. 2002; 123(1): 8–15, doi: 10.1067/mtc.2002.120329, indexed in Pubmed: 11782750.
28. Brookhart MA, Wyss R, Layton JB, et al. Propensity score methods for confounding control in nonexperimental research. Circ Cardiovasc Qual Outcomes. 2013; 6(5): 604–611, doi: 10.1161/CIRCOUTCOMES.113.000359, indexed in Pubmed: 24021692.
29. Lurz P, Stephan von Bardeleben R, Weber M, et al. Transcatheter edge-to-edge repair for treatment of tricuspid regurgitation. J Am Coll Cardiol. 2021; 77(3): 229–239, doi: 10.1016/j.jacc.2020.11.038, indexed in Pubmed: 33478646.
30. Goates S, Baron SJ, Arnold SV, et al. Estimating health-state utility in patients with heart failure: mapping the kansas city cardiomyopathy questionnaire to SF-6D utility scores. Value in Health. 2019; 22: S124, doi: 10.1016/j.jval.2019.04.466.
31. Alehagen U, Rahmqvist M, Paulsson T, et al. Quality-adjusted life year weights among elderly patients with heart failure. Eur J Heart Fail. 2008; 10(10): 1033–1039, doi: 10.1016/j.ejheart.2008.07.015, indexed in Pubmed: 18760669.
32. Berg J, Lindgren P, Mejhert M, et al. Determinants of utility based on the EuroQol Five-Dimensional Questionnaire in patients with chronic heart failure and their change over time: results from the swedish heart failure registry. Value Health. 2015; 18(4): 439–448, doi: 10.1016/j.jval.2015.02.003, indexed in Pubmed: 26091598.
33. Göhler A, Geisler BP, Manne JM, et al. Utility estimates for decision-analytic modeling in chronic heart failure: health states based on New York Heart Association classes and number of rehospitalizations. Value Health. 2009; 12(1): 185–187, doi: 10.1111/j.1524-4733.2008.00425.x, indexed in Pubmed: 18647251.
34. Griffiths A, Paracha N, Davies A, et al. Analyzing health-related quality of life data to estimate parameters for cost-effectiveness models: an example using longitudinal EQ-5D data from the SHIFT randomized controlled trial. Adv Ther. 2017; 34(3): 753–764, doi: 10.1007/s12325-016-0471-x, indexed in Pubmed: 28205056.
35. Kirsch J, McGuire A. Establishing health state valuations for disease specific states: an example from heart disease. Health Econ. 2000; 9(2): 149–158, doi: 10.1002/(sici)1099-1050(200003)9:2<149::aid-hec501>3.0.co;2-n, indexed in Pubmed: 10721016.
36. Linde C, Mealing S, Hawkins N, et al. REVERSE study group. Cost-effectiveness of cardiac resynchronization therapy in patients with asymptomatic to mild heart failure: insights from the European cohort of the REVERSE (Resynchronization Reverses remodeling in Systolic Left Ventricular Dysfunction). Eur Heart J. 2011; 32(13): 1631–1639, doi: 10.1093/eurheartj/ehq408, indexed in Pubmed: 21112898.
37. Ejiofor JI, Hirji SA, Ramirez-Del Val F, et al. Outcomes of repeat mitral valve replacement in patients with prior mitral surgery: A benchmark for transcatheter approaches. J Thorac Cardiovasc Surg. 2018; 156(2): 619–627.e1, doi: 10.1016/j.jtcvs.2018.03.126, indexed in Pubmed: 29759741.
38. Pręgowski J, Kłapyta A, Chmielak Z, et al. Incidence, clinical correlates, timing, and consequences of acute thrombus formation in patients undergoing the MitraClip procedure. Kardiol Pol. 2020; 78(1): 45–50, doi: 10.33963/KP.15056, indexed in Pubmed: 31719512.

VIA MEDICA

REVIEW ARTICLE

Cardiology Journal
2022, Vol. 29, No. 3, 381–387
DOI: 10.5603/CJ.a2020.0186

ISSN 1897–5593
eISSN 1898–018X

The progress of pulmonary artery denervation

Yonghui Xie[1, 2]*, Na Liu[3]*, Zhenghui Xiao[1], Fang Yang[3], Yunhong Zeng[1, 2], Zhou Yang[1, 2], Yuanxi Xia[1, 2], Zhi Chen[1, 2], Yunbin Xiao[1, 2]

[1]Academy of Pediatrics, University of South China, Changsha, China
[2]Department of Cardiology, Hunan Children's Hospital, Changsha, China
[3]Department of Cardiology, The Second Xiangya Hospital of Central South University, China

Abstract

Pulmonary arterial hypertension (PAH) is a chronic pulmonary vascular disease characterized by increased pulmonary arterial pressure and pulmonary arterioles remodeling. Some studies have discovered the relationship between sympathetic nerves (SNs) and pathogenesis of PAH. This review is aimed to illustrate the location and components of SNs in the pulmonary artery, along with different methods and effects of pulmonary artery denervation (PADN). Studies have shown that the SNs distributed mainly around the main pulmonary artery and pulmonary artery bifurcation. And the SNs could be destroyed by three ways: the chemical way, the surgical way and the catheter-based way. PADN can significantly decrease pulmonary arterial pressure rapidly, improve hemodynamic varieties, and then palliate PAH. PADN has been recognized as a prospective and effective therapy for PAH patients, especially for those with medication-refractory PAH. However, further enlarged clinical studies are needed to confirm accurate distribution of SNs in the pulmonary artery and the efficacy of PADN. (Cardiol J 2022; 29, 3: 381–387)

Key words: pulmonary arterial hypertension, pulmonary artery denervation, sympathetic nerves

Introduction

Pulmonary arterial hypertension (PAH), characterized by mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest, pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg and pulmonary vascular resistance (PVR) > 3 Wood units [1], is a disease induced by a wide range of causes, which makes it difficult to formulate an appropriate therapeutic plan and receive great responses for PAH patients [2]. Up till the present, most patients can only rely on combined targeted medicine, however, not all patients can be relieved [2, 3]. Besides, the 1-year, 3-year and 5-year survival rate of medium to high-risk patients treated by target therapy are 90%, 61%, 43% [4], and side effects of targeted medicine are not tolerable in a considerable number of patients. Thus, these patients are eager to acquire better therapies. Recently, pulmonary artery denervation (PADN), as a novel therapy, has gradually proved beneficial to improve hemodynamic measurements in animal models and in PAH patients through regulating the autonomic nervous system [5]. Previous studies have proved that PADN can significantly decrease pulmonary arterial pressure rapidly, and then palliate the development of PAH through destroying the sympathetic nerves (SNs) of the pulmonary artery (PA) [6].

Address for correspondence: Yunbin Xiao, PhD, MD, Department of Cardiology, Hunan Children's Hospital, No. 86 Ziyuan Road, Yuhua District, Changsha, Hunan, 410007, China, tel: +8673185356800, +8613549658136, fax: (0731)5356666, e-mail: xiaoyunbinrui@126.com

Received: 27.10.2020 Accepted: 6.12.2020 Early publication date: 31.12.2020

**Equal contributors.*

Sympathetic nerves along the pulmonary artery

The autonomic nervous system consists of sympathetic and parasympathetic parts, which are regulated by various neural and endocrine factors [7]. The sympathetic nervous system (SNS) arises from the spinal cord (T1-L2), and postganglionic neurons administrate the pulmonary vascular systems [7, 8]. Studies have proved that the components of SNs around PA include many tyrosine hydroxylase (TH)-positive, neuropeptide-Y (NPY)--positive and a few calcitonin-gene–related peptide (CGRP)-positive nerve fibers in rat models and in humans [9]. Thus, when SNS is activated, the SNs can locally release neurohormones to enhance the vascular tone so that the PA pressure will be quickly elevated. Furthermore, chronic inflammation is known as a critical factor contributing to the progress of PAH [10], and de Juan et al. [11] has investigated that sympathetic nerves of arteries play an important role in inflammation. Therefore, the over-activation of SNS [12] may accelerate the development of PAH via regulating the inflammation.

Rothman et al. [13] deemed that SNs around the main pulmonary artery (MPA) and PA bifurcation were relatively larger than those around the left pulmonary artery (LPA) or right pulmonary artery (RPA). Although there is not enough evidence about the distribution of SNs around PA in humans, most animal studies also represented that SNs distributed mostly around MPA and PA bifurcation [9, 14–16], while diverse races may have a little difference in the distribution site of SNs. Currently, many animals can be used as PAH models, and mainly include two animals. Big animals, including swine [16, 17], dogs [14, 15], sheep [18], rabbits [19] and so on, which are easier to operate on because of their larger vessels, better tolerance to surgical injury, higher degree of the similarity to humans, but the cost in time and money is also much higher. Small animals, such as mice and rats [9, 20], are more suitable for surgical models, because they can recover quickly and a have stronger anti-infection ability, but skilled operators are needed.

Heretofore, some studies have shown the distribution of SNs around the PA in swine, dog and rat models (Fig. 1). Rothman et al. [16] showed that most nerves are located approximately 1 to 3 mm from the luminal aspect in the MPA of swine. Besides, the diameter of SNs is greater than those in the distal PA. In the LPA and RPA, almost all nerves are located less than 1 mm away from intra-artery surface. There are two distal boundaries, including the ostium of left posterior artery and right posterior descending artery. The nerve bundles are located in the posterior and right of MPA and posterior and lateral of the RPA [16]. But in dogs, Zhou et al. [15] reported that PA sympathetic nerve bundles are located in the left of MPA, and most branches were distributed in the posterior wall of MPA and LPA, which is different from the distribution of SNs in swine. Furthermore, Huang et al. [9] investigated that the distribution of nerves was mainly in the adipose and connective tissues in rats, especially located in posterior and right anterior of MPA and PA bifurcation, which was the same with the distribution of SNs in swine. Compared with normal rats, the area of SNs distribution was significantly larger in the PAH rats, and the SNs of PAH rats mainly located in posterior and right anterior of MPA and PA bifurcation.

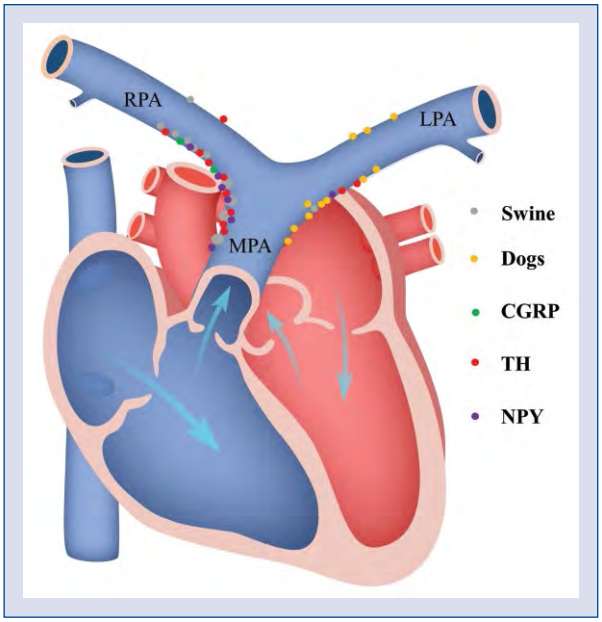
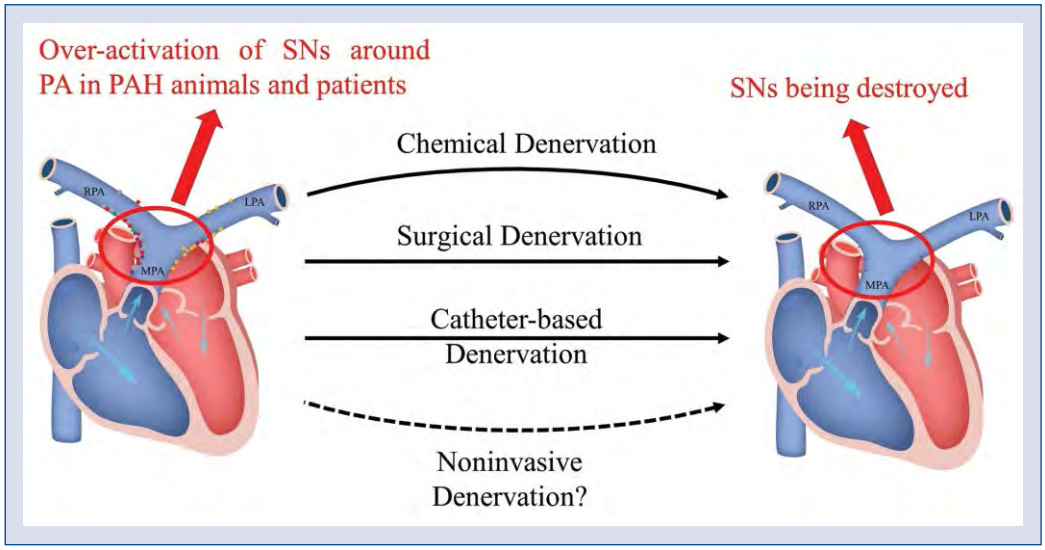


Figure 1. Distribution of sympathetic nerves (SNs) of pulmonary artery (PA) in different races. In dogs, most nerves (yellow spots) are distributed in posterior wall of main pulmonary artery (MPA) and left pulmonary artery (LPA), while in swine (gray spots), the SNs are distributed mostly in posterior and right of MPA. Besides, in PA of rats, the components of SNs around PA include many TH-positive nerve fibers (red spots), NPY-positive nerve fibers (purple spots) and a few CGRP-positive nerve fibers (green spots). TH — tyrosine hydroxylase; NPY — neuropeptide-Y; CGRP — calcitonin-gene–related peptide; RPA — right pulmonary artery.



Central illustration. Schematic diagram summarizing principles and methods of pulmonary artery denervation (PADN). The area of sympathetic nerves (SNs) distribution was significantly larger in the pulmonary arterial hypertension (PAH) animals and patients. PADN can destroy those SNs and then palliate PAH; PA — pulmonary artery.

Pulmonary artery denervation

Pulmonary artery denervation is aimed at destroying the anatomic structures and functions of SNs along the PA by three methods, including chemical denervation, surgical denervation and catheter-based denervation. Since 1980, Juratsch et al. [21] found that elevation of mPAP increased by balloon distension of MPA can be abolished by destroying SNs distributed around PA bifurcation via surgical or chemical measures [21]. From then on, more and continuing studies are conducted to search for the best way to perform PADN (Central illustration).

Chemical denervation

Chemical denervation is performed via using the SNs blocking drugs to damage nerves around PA by intravenous infusion [21] or intraperitoneal injection [22]. To date, there have only been a few animal studies referring to chemical PADN, most of the studies used 6-hydroxydopamine (6-OHDA), a mediator of adrenergic nerves, to destroy the activity of SNs [22]. Juratsch et al. [21] has performed chemical denervation with 8 dogs, and then compared the increments of mPAP post balloon inflation in MPA. After destroying the pulmonary adrenergic nerves, the responses to balloon inflation in MPA was relieved, and increased the value of pulmonary arterial pressure (PAP) and PVR all declined markedly when compared with before denervation in these dogs [21]. There is no doubt that this way is the most convenient, while the side effects cannot be ignored. Jiang et al. [22] has shown that chemical sympathectomy with administration of 6-OHDA caused dysregulation of the cardiac autonomic nervous system and myocardial injury. Moreover, administration of 6-OHDA can produce selective degeneration of adrenergic nerve terminals and blockades or destroying adrenergic receptor sites [23] which consisted of the pathogenesis of diabetes mellitus. Thus, it is necessary to find a new drug, which is only plays a role in SNs around PA, or find a new way to make the drug to only influence PA nerves. Recently, there have been many studies trying to perform denervation with magnetic nanoparticles (MNP) [24]. Yu et al. [25] has done autonomic denervation in four major atrial ganglionated plexi (GP) suppressed atrial fibrillation with MNP. They also successfully ablated GP by external electromagnet pulled Ca-MNP to the targeted GP after an injected Ca-MNP in the coronary artery [26]. Thus, further studies may conduct an active targeting magnetic nanoparticle with 6-OHDA, then using magnetic material in vitro guiding MNP with 6-OHDA in MPA and PA bifurcation. Since aminopeptidase P (APP) has been confirmed specifically distributed in PA endothelium [27], an active targeting drug delivery system can be considered, such as APP antibody-decorated nanoparticles with 6-OHDA loading.

Surgical denervation

With further research being conducted, the distribution of SNs has been clearly depicted that many nerves located in the adipose and connective tissues of PA adventitia [28]. The performance of surgical denervation is mainly via removing adipose and connective tissues of PA adventitia. Juratsch et al. [21] performed surgical denervation in dogs with elevated PAP when the balloon was inflated in the MPA. After denervation, both systolic and diastolic pulmonary artery pressure of these dogs did not significantly change when the balloon inflated. Transthoracic pulmonary artery denervation (TPADN) is more accurate and direct, after thoracotomy in the left third intercostal space, the adipose and connective tissues around the trunk and branches of MPA were exfoliated using microsurgical techniques. The main PA trunk and bifurcation and the proximal regions of the LPA and RPA were the key stripping areas for TPADN. Compared with the sham group, the mPAP of the test group decreased significantly after denervation. Furthermore, they demonstrated that the muscularization rate declined after denervation [9]. Although TPADN was a more effective way to reduce mPAP in monocrotaline PAH rat models, still the largest limitation cannot be ignored that the surgery itself is an invasive way with high risks, especially for those who cannot afford anesthesia, which makes it very difficult to apply for PAH patients, so a less invasive PADN method is needed.

Catheter-based denervation

Catheter-based denervation is already applied to PAH patients for its micro-traumatic, low-risk and quick effect. Many animal studies and clinical studies have proved the curative effect of ablation [29]. After inserting a sheath through femoral vein and advancing to MPA and PA bifurcation after PA angiography, then the PADN catheter was advanced along this long sheath. Letting the circular tip place in the lumen of MPA and PA bifurcation where SNs were mostly distributed [30], then ablation was conducted. For most animals and PAH patients, the mPAP and PVR were decreased immediately to some degree and were declining in the follow-up months after PADN. There was some catheter-based PADN conducted in swine [16] and dogs [15], and these studies found that the SNs injury induced by PADN could remain for a long time, and PADN continually improved hemodynamic parameters and PA remodeling in PAH animal models [15, 16]. To date, catheter-based PADN has been applied in clinical trials. Chen et al. [30] did the first PADN clinical study with low-risk idiopathic pulmonary arterial hypertension (IPAH) patients, and showed that the PADN procedure can improve hemodynamic measurements and clinical presentation quickly and effectively. In this trial, the systolic PAP and mPAP of 12 patients with PADN procedures obviously declined at once and during the subsequent 3 months. Furthermore, during the 3-month follow-up, these IPAH patients who performed PADN procedures showed a significant improvement in cardiac output and 6-min walk distance (6WMD). In the treatment group, just one procedure failed when the patient suddenly experienced intolerable chest pain after the first-place ablation (three ablation places in total), but mPAP still reduced 6 mmHg [30]. Although this study has investigated hemodynamic improvements and functional capacity of IPAH patients after PADN, the conclusion that PADN was an effective therapy for medication-refractory PAH patients was still recognized with controversies in the low-risk type and insufficient quantity of PAH patient individuals for nonrandomized trials, no sham populations and not enough follow-up. To confirm the efficacy of PADN, Chen et al. then performed other studies that enrolled varieties of patients from different centers, in different World Health Organization groups and were induced by different causes [31–33], thereafter they found that performing PADN in the internal surface of PA can still achieve a significant curative effect for those PAH patients who can bear chest pain induced by the PADN procedure after ablation. However, there are still some patients who cannot achieve benefits from this type of PADN. It is probably associated with the limited depth of ablation in the lumen and only a few SNs being destroyed. Moreover, the TIVUS system, a novel ultrasound energy delivery system using a multidirectional ultrasound catheter, is being observed because it can prolong the depth of ablation. Rothman et al. [34] lately conducted related animal and clinical experiments, and manifested that PADN using catheter-based ultrasonic energy can also improve states of pulmonary hypertension (PH) in animal models and PAH patients. In addition, studies showed that many SNs exist in the PA adventitia. And Garcia-Lunar et al. [35] conducted an animal trial using a bipolar radiofrequency system to perform PADN in the PA adventitia after thoracotomy, but hemodynamic parameters of the animal models did not improve significantly after PADN. Recently, Mahfoud et al. [36] reported an innovative alcohol-mediated renal denervation system which could infuse absolute

alcohol through needles being penetrated into the renal artery and safely decrease blood pressure in patients. Similarly, this system also can be used in PADN so that drugs can be injected to destroy the SNs in the whole layer of PA, and then make most SNs around PA inactive aiming to minimize the over-activity of SNS and rein–angiotensin––aldosterone system (RAAS) in a larger extent.

Changes of sympathetic nerves after pulmonary artery denervation

After PADN, the anatomic structure and functions of SNs around PA both have been destroyed to some extent, though PADN itself cannot destroy all SNs. Early preclinical studies have shown that sympathetic nerve conduction velocity (SNCV) immediately changed when PADN was done. In a study with 41 dogs (6 control, 10 with mPAP ≤ 25 mmHg after injected dehydrogenized monocrotaline (DHMCT), 5 with PAH but without PADN, 20 with PADN) was used to examine SNs, the 20 PAH dogs induced by DHMCT underwent PADN at the conjunctional area between the distal MPA and the ostial LPA with the following parameters: a temperature of 45° to 50°, energy ≤ 10 W, and times of 120 s. Compared with the prior-PADN groups, the SNCV of those with mPAP ≥ 25 mmHg was decreased immediately after the PADN procedure. Furthermore, in the follow-up during 3 months, SNCV was continually declining and eventually almost equalled the control animals. Nevertheless, in the study, the axon diameter and myelin thickness of these dogs with mPAP ≥ 25 mmHg was noticeably higher than those with mPAP ≤ 25 mmHg. Compared with the sham group, the axon diameter and myelin thickness had a gradual decline in the PADN group post PADN. The same with SNCV, in the subsequent 3 months, the axon diameter was decreasing, and the myelin sheath was increasingly thinner over time. Eventually, the nerves became almost demyelinated [15]. These findings represented that PADN can induce serious and long-term SNs injury and then decrease the activity of SNS [6]. Furthermore, some studies reported that in the lung tissue, main components of RAAS are decreased in the PADN group [37], such as renin, angiotensin converting enzyme (ACE), angiotensin II (Ang II), Ang II type 2 receptor (AT2 receptor), mineralocorticoid receptor (MR) and Ang II type 1 receptor (AT1 receptor), which illustrated that the activity of RAAS was reduced after SNs were destroyed.

Improvements of hemodynamic measurements after pulmonary artery denervation

Animal studies

Pulmonary artery denervation can almost safely and effectively abolish the increases of mPAP in PAH animals induced by a variety of measures, including using balloon occlusion at the interlobar segment [38], injecting DHMCT [9, 15] and infusing thromboxane A2 [16]. These studies have illustrated that PADN can decrease mPAP immediately and mPAP continued to decline in the following minimum of 3 months. Eventually, the mPAP of these PAH models with PADN procedures may even be similar to the normal animals. Zhou et al. [15] examined the hemodynamic changes of dogs found that compared with the sham group, mPAP, right atrial pressure (RAP), systolic PAP, and PVR were all significantly reduced and cardiac output was improved in PAH dogs after the PADN procedure. Zhang et al. [39] also investigated that PADN is effective in the PAH rat models secondary to heart failure, which is a disease without a useful therapy at present.

Clinical studies

At present, only catheter-based denervation is applied to clinical studies, and has achieved great effect similar to animal studies. PADN has been applied to many types of PAH patients, including IPAH [30], PAH secondary to connective diseases, PAH associated with congenital heart diseases [31], combined pre- and post-capillary PH associated with left heart failure [32] and so on. For most patients, PADN can quickly and significantly improve hemodynamic measurements, clinical symptoms, functional capacity and clinical follow-up. These trials all indicated that PADN is a prospective therapy for PAH patients, but a few patients cannot tolerate PADN procedures for unbearable chest pain and some patients seem to be irresponsive to PADN. Studies reported that there are two key adrenergic receptors (ARs) in PA, namely, β-ARs and α1-ARs. PADN can downregulate the density of α1-ARs and upregulate β-ARs in lung tissues and then improve PA contraction and remodeling [39]. In these patients with little benefit from PADN, perhaps it was related to the capacity of regulating ARs being lost, then the constriction of PA cannot be mediated. Moreover, Tzafriri et al. [40] found that arterial microanatomy could influence effect of catheter-based renal denervation. They

demonstrated that power density did not peak at the arterial lumen interface where the electrode was located, and surrounding tissues, especially in water-rich tissues, like lymph nodes, could change power density diffusing to a certain extent. Furthermore, blood vessels adjacent to electrode could clear power density to a great extent. Similarly, for those patients without benefits from PADN, perhaps this phenomenon was owing to those surrounding tissues and vessels around the electrode, which changes power density diffusing, and then the degree of SNs destruction is insufficient [40]. In addition, Fujisawa et al. [41] performed PADN successfully after determining ablation sites through observing the patient's responses when high-output burst electric stimulation was applied to PA, which made the ablation sites more appropriate and avoided damaging other important nerves at the same time. Thus, to achieve better benefits, PADN should be conducted individually and clinical studies still have a long way to go.

Conclusions

In conclusion, PADN is a prospective and effective medical therapy for PAH patients, especially for those with medication-refractory PAH or PAH patients with limited treatment options, such as combined pre- and post-capillary PH [42]. While the mechanisms of PADN are still equivocal. In addition, there are still many issues which are eager to be resolved: (1) Previous studies have mostly investigated the distribution, components of SNs in animal models, and there are insufficient studies with humans. (2) which layer is more suitable for conducting PADN? The adventitia? The inner surface? Or all the layers? (3) Is TPADN, catheter-based denervation or accurate drug-based ablation the best method? And there already exist newmethods for renal denervation [43], such as alcohol-mediated denervation, ultrasonic energy-based ablation [44] and noninvasive stereotactic body radiotherapy [45], which brings a new direction in performing PADN. (4) The long-term efficacy, the indications and contraindications are still indeterminate. These questions should be answered by further studies.

Funding

This work was supported by Hunan Provincial Key Laboratory of Emergency Medicine for Children (grant 2018TP1028), Project of Hunan Provincial Research on Chinese Medicine (grant 201914), Hunan Provincial Natural Science Youth Foundation of China (grant 2019JJ50881), Hunan Provincial Innovation Foundation For Postgraduate (grant CX20200984) and Hunan Provincial Health Commission project (grant 20200587 and 20200596).

Conflict of interest: None declared

References

1. Galiè N, Humbert M, Vachiery J-L, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2016; 37: 67–119, doi: 10.1093/eurheartj/ehv317, indexed in Pubmed: 26320113.
2. Barberà JA, Román A, Gómez-Sánchez MÁ, et al. Guidelines on the diagnosis and treatment of pulmonary hypertension: summary of recommendations. Arch Bronconeumol. 2018; 54(4): 205–215, doi: 10.1016/j.arbres.2017.11.014, indexed in Pubmed: 29472044.
3. Leopold JA. Catheter-based therapies for patients with medication-refractory pulmonary arterial hypertension. Circ Cardiovasc Interv. 2015; 8(11): e003332, doi: 10.1161/CIRCINTERVENTIONS.115.003332, indexed in Pubmed: 26553702.
4. Hoeper MM, Pittrow D, Opitz C, et al. and Huscher D. Risk assessment in pulmonary arterial hypertension. Eur Respir J. 2018; 51.
5. Le T, Makar C, Morway P, et al. Pulmonary artery denervation: a novel treatment modality for pulmonary hypertension. J Thorac Dis. 2019; 11(4): 1094–1096, doi: 10.21037/jtd.2019.02.93, indexed in Pubmed: 31179049.
6. Kim CW, Aronow WS, Dutta T, et al. Pulmonary artery denervation as an innovative treatment for pulmonary hypertension with and without heart failure. Cardiol Rev. 2020 [Epub ahead of print], doi: 10.1097/CRD.0000000000000299, indexed in Pubmed: 32032132.
7. Vaillancourt M, Chia P, Sarji S, et al. Autonomic nervous system involvement in pulmonary arterial hypertension. Respir Res. 2017; 18(1): 201, doi: 10.1186/s12931-017-0679-6, indexed in Pubmed: 29202826.
8. Maron BA, Leopold JA. Emerging concepts in the molecular basis of pulmonary arterial hypertension: part II: neurohormonal signaling contributes to the pulmonary vascular and right ventricular pathophenotype of pulmonary arterial hypertension. Circulation. 2015; 131(23): 2079–2091, doi: 10.1161/CIRCULATIONAHA.114.006980, indexed in Pubmed: 26056345.
9. Huang Y, Liu YW, Pan HZ, et al. Transthoracic pulmonary artery denervation for pulmonary arterial hypertension. Arterioscler Thromb Vasc Biol. 2019; 39(4): 704–718, doi: 10.1161/ATVBAHA.118.311992, indexed in Pubmed: 30816802.
10. Thenappan T, Ormiston ML, Ryan JJ, et al. Pulmonary arterial hypertension: pathogenesis and clinical management. BMJ. 2018; 360: j5492, doi: 10.1136/bmj.j5492, indexed in Pubmed: 29540357.
11. de Juan A, Ince LM, Pick R, et al. Artery-Associated sympathetic innervation drives rhythmic vascular inflammation of arteries and veins. Circulation. 2019; 140(13): 1100–1114, doi: 10.1161/CIRCULATIONAHA.119.040232, indexed in Pubmed: 31401849.
12. Velez-Roa S, Ciarka A, Najem B, et al. Increased sympathetic nerve activity in pulmonary artery hypertension. Circulation. 2004; 110(10): 1308–1312, doi: 10.1161/01.CIR.0000140724.90898.D3, indexed in Pubmed: 15337703.
13. Rothman A, Jonas M, Castel D, et al. Pulmonary artery denervation using catheter-based ultrasonic energy. EuroIntervention. 2019; 15(8): 722–730, doi: 10.4244/EIJ-D-18-01082, indexed in Pubmed: 31062694.

14. Zhang Y, Chen W, Xu Y, et al. Nerve distribution of canine pulmonary arteries and potential clinical implications. Am J Transl Res. 2016; 8: 365–374.
15. Zhou L, Zhang J, Jiang XM, et al. Pulmonary artery denervation attenuates pulmonary arterial remodeling in dogs with pulmonary arterial hypertension induced by dehydrogenized monocrotaline. JACC Cardiovasc Interv. 2015; 8(15): 2013–2023, doi: 10.1016/j.jcin.2015.09.015, indexed in Pubmed: 26738673.
16. Rothman AMK, Arnold ND, Chang W, et al. Pulmonary artery denervation reduces pulmonary artery pressure and induces histological changes in an acute porcine model of pulmonary hypertension. Circ Cardiovasc Interv. 2015; 8(11): e002569, doi: 10.1161/CIRCINTERVENTIONS.115.002569, indexed in Pubmed: 26553697.
17. Watanabe S, Ishikawa K, Plataki M, et al. Safety and long-term efficacy of AAV1.SERCA2a using nebulizer delivery in a pig model of pulmonary hypertension. Pulm Circ. 2018; 8(4): 2045894018799738, doi: 10.1177/2045894018799738, indexed in Pubmed: 30129881.
18. Zhou X, Wang D, Castro CY, et al. A pulmonary hypertension model induced by continuous pulmonary air embolization. J Surg Res. 2011; 170(1): e11–e16, doi: 10.1016/j.jss.2011.04.030, indexed in Pubmed: 21696769.
19. Wang W, Liu R, Cao G, et al. A reliable rabbit model for hyperkinetic pulmonary hypertension. J Thorac Cardiovasc Surg. 2010; 140(2): 395–399, doi: 10.1016/j.jtcvs.2009.04.071, indexed in Pubmed: 20570291.
20. Jungebluth P, Ostertag H, Macchiarini P. An experimental animal model of postobstructive pulmonary hypertension. J Surg Res. 2008; 147(1): 75–78, doi: 10.1016/j.jss.2007.05.042, indexed in Pubmed: 18262548.
21. Juratsch CE, Jengo JA, Castagna J, et al. Experimental pulmonary hypertension produced by surgical and chemical denervation of the pulmonary vasculature. Chest. 1980; 77(4): 525–530, doi: 10.1378/chest.77.4.525, indexed in Pubmed: 7357977.
22. Jiang YH, Jiang P, Yang JL, et al. Cardiac dysregulation and myocardial injury in a 6-hydroxydopamine-induced rat model of sympathetic denervation. PLoS One. 2015; 10(7): e0133971, doi: 10.1371/journal.pone.0133971, indexed in Pubmed: 26230083.
23. Kostrzewa RM, Jacobowitz DM. Pharmacological actions of 6-hydroxydopamine. Pharmacol Rev. 1974; 26(3): 199–288, indexed in Pubmed: 4376244.
24. Kraitchman DL, Bulte JWM. Magnetic nanoparticles and neurotoxins for treating atrial fibrillation: a new way to get burned? Circulation. 2010; 122(25): 2642–2644, doi: 10.1161/CIRCULATIONAHA.110.000166, indexed in Pubmed: 21135362.
25. Yu L, Scherlag BJ, Dormer K, et al. Autonomic denervation with magnetic nanoparticles. Circulation. 2010; 122(25): 2653–2659, doi: 10.1161/CIRCULATIONAHA.110.940288, indexed in Pubmed: 21135360.
26. Yu L, Scherlag BS, Dormer K, et al. Targeted ganglionated plexi denervation using magnetic nanoparticles carrying calcium chloride payload. JACC Clin Electrophysiol. 2018; 4(10): 1347–1358, doi: 10.1016/j.jacep.2018.06.012, indexed in Pubmed: 30336881.
27. Chrastina A, Valadon P, Massey KA, et al. Lung vascular targeting using antibody to aminopeptidase P: CT-SPECT imaging, biodistribution and pharmacokinetic analysis. J Vasc Res. 2010; 47(6): 531–543, doi: 10.1159/000313880, indexed in Pubmed: 20431301.
28. Ogo T. Transthoracic pulmonary artery denervation. Arterioscler Thromb Vasc Biol. 2019; 39(6): 979–981, doi: 10.1161/ATVBAHA.119.312591, indexed in Pubmed: 31116607.
29. Zhang H, Chen SL. Pulmonary artery denervation: update on clinical studies. Curr Cardiol Rep. 2019; 21(10): 124, doi: 10.1007/s11886-019-1203-z, indexed in Pubmed: 31486924.
30. Chen SL, Zhang FF, Xu J, et al. Pulmonary artery denervation to treat pulmonary arterial hypertension. J Am Coll Cardiol. 2013; 62(12): 1092–1100, doi: 10.1016/j.jacc.2013.05.075.
31. Chen SL, Zhang H, Xie DJ, et al. Hemodynamic, functional, and clinical responses to pulmonary artery denervation in patients with pulmonary arterial hypertension of different causes: phase II results from the Pulmonary Artery Denervation-1 study. Circ Cardiovasc Interv. 2015; 8(11): e002837, doi: 10.1161/CIRCINTERVENTIONS.115.002837, indexed in Pubmed: 26553699.
32. Zhang H, Zhang J, Chen M, et al. Pulmonary artery denervation significantly increases 6-min walk distance for patients with combined pre- and post-capillary pulmonary hypertension associated with left heart failure: the PADN-5 study. JACC Cardiovasc Interv. 2019; 12(3): 274–284, doi: 10.1016/j.jcin.2018.09.021, indexed in Pubmed: 30732732.
33. Zhang H, Zhang J, Xie DJ, et al. Pulmonary artery denervation for treatment of a patient with pulmonary hypertension secondary to left heart disease. Pulm Circ. 2016; 6(2): 240–243, doi: 10.1086/685550, indexed in Pubmed: 27252851.
34. Rothman AMK, Vachiery JL, Howard LS, et al. Intravascular Ultrasound Pulmonary Artery Denervation to Treat Pulmonary Arterial Hypertension (TROPHY1): Multicenter, Early Feasibility Study. JACC Cardiovasc Interv. 2020; 13(8): 989–999, doi: 10.1016/j.jcin.2019.12.027, indexed in Pubmed: 32327095.
35. Garcia-Lunar I, Pereda D, Santiago E, et al. Effect of pulmonary artery denervation in postcapillary pulmonary hypertension: results of a randomized controlled translational study. Basic Res Cardiol. 2019; 114(2): 5, doi: 10.1007/s00395-018-0714-x, indexed in Pubmed: 30635778.
36. Mahfoud F, Renkin J, Sievert H, et al. Alcohol-Mediated renal denervation using the peregrine system infusion catheter for treatment of hypertension. JACC Cardiovasc Interv. 2020; 13(4): 471–484, doi: 10.1016/j.jcin.2019.10.048, indexed in Pubmed: 32081241.
37. Liu C, Jiang XM, Zhang J, et al. Pulmonary artery denervation improves pulmonary arterial hypertension induced right ventricular dysfunction by modulating the local renin-angiotensin-aldosterone system. BMC Cardiovasc Disord. 2016; 16(1): 192, doi: 10.1186/s12872-016-0366-4, indexed in Pubmed: 27724864.
38. Chen SL, Zhang YJ, Zhou L, et al. Percutaneous pulmonary artery denervation completely abolishes experimental pulmonary arterial hypertension in vivo. EuroIntervention. 2013; 9(2): 269–276, doi: 10.4244/EIJV9I2A43, indexed in Pubmed: 23466961.
39. Zhang H, Yu W, Zhang J, et al. Pulmonary artery denervation improves hemodynamics and cardiac function in pulmonary hypertension secondary to heart failure. Pulm Circ. 2019; 9(2): 2045894018816297, doi: 10.1177/2045894018816297, indexed in Pubmed: 30421645.
40. Tzafriri AR, Keating JH, Markham PM, et al. Arterial microanatomy determines the success of energy-based renal denervation in controlling hypertension. Sci Transl Med. 2015; 7(285): 285ra65, doi: 10.1126/scitranslmed.aaa3236, indexed in Pubmed: 25925684.
41. Fujisawa T, Kataoka M, Kawakami T, et al. Pulmonary artery denervation by determining targeted ablation sites for treatment of pulmonary arterial hypertension. Circ Cardiovasc Interv. 2017; 10(10): e006244, doi: 10.1161/CIRCINTERVENTIONS.117.005812, indexed in Pubmed: 29042401.
42. Dimopoulos K, Ernst S, McCabe C, et al. Pulmonary artery denervation: a new, long-awaited interventional treatment for combined pre- and post-capillary pulmonary hypertension? JACC Cardiovasc Interv. 2019; 12(3): 285–288, doi: 10.1016/j.jcin.2018.10.045, indexed in Pubmed: 30732733.
43. Bhatt DL, Majithia A. Continued evolution of renal artery denervation for hypertension. JACC Cardiovasc Interv. 2020; 13(4): 485–487, doi: 10.1016/j.jcin.2019.12.002, indexed in Pubmed: 32081242.
44. Kjeldsen SE, Narkiewicz K, Burnier M, et al. Renal denervation achieved by endovascular delivery of ultrasound in RADIANCE-HTN SOLO or by radiofrequency energy in SPYRAL HTN-OFF and SPYRAL-ON lowers blood pressure. Blood Press. 2018; 27(4): 185–187, doi: 10.1080/08037051.2018.1486178, indexed in Pubmed: 29936868.
45. Cai X, Yang Y, Shen Y, et al. Noninvasive stereotactic radiotherapy for renal denervation in a swine model. J Am Coll Cardiol. 2019; 74(13): 1697–1709, doi: 10.1016/j.jacc.2019.07.053, indexed in Pubmed: 31558254.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 3, 388–395
DOI: 10.5603/CJ.a2022.0030

ISSN 1897–5593
eISSN 1898–018X

Agreement between Murray law-based quantitative flow ratio (μQFR) and three--dimensional quantitative flow ratio (3D-QFR) in non-selected angiographic stenosis: A multicenter study

Carlos Cortés[1]*, Lili Liu[2]*, Scarlet Luisa Berdin[3, 4], Pablo M. Fernández-Corredoira[1], Ruiyan Zhang[2], Ulrich Schäfer[5], María López[6], José A. Diarte[1], Shengxian Tu[7], Juan Luis Gutiérrez-Chico[2, 5]

[1]Miguel Servet University Hospital, Zaragoza, Spain
[2]Department of Cardiovascular Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[3]Bundeswehrkrankenhaus (Federal Army Military Hospital), Hamburg, Germany
[4]Asklepios Klinik St. Georg (Asklepios St. Georg Clinic), Hamburg, Germany
[5]Bundeswehrzentralkrankenhaus (Federal Army Central Military Hospital), Koblenz, Germany
[6]Nursing High School, University of Valladolid, Valladolid, Spain
[7]Med-X Research Institute, School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai, China

This paper was guest edited by Prof. Tomasz Roleder

Abstract

Background: *The agreement between single-projection Murray-based quantitative flow ratio (μQFR) and conventional three-dimensional quantitative flow ratio (3D-QFR) has not been reported hitherto.*

Methods: *Patients from a multinational database were randomly selected for the study of agreement, according to sample size calculation. Both conventional 3D-QFR and μQFR were analyzed for all available arteries at a central corelab by independent analysts, blinded to each other's results.*

Results: *Ninety-eight coronary arteries from 35 patients were finally analyzed. Median 3D-QFR was 0.82 (interquartile range 0.78–0.87). The intraclass correlation coefficient for the absolute agreement between 3D-QFR and μQFR was 0.996 (95% confidence interval [CI]: 0.993–0.997); Lin's coefficient 0.996 (95% CI: 0.993–0.997), without constant or proportional bias (intercept = 0 and slope = 1 in orthogonal regression). As dichotomous variable, there was absolute agreement between μQFR and 3D-QFR, resulting in no single false positive or negative. Kappa index was 1 and the diagnostic accuracy 100%.*

Conclusions: *μQFR using a single angiographic projection showed almost perfect agreement with standard 3D-QFR. These results encourage the interchangeable use of μQFR and 3D-QFR, which can be interesting to improve QFR feasibility in retrospective studies, wherein appropriate double angiographic projections might be challenging to obtain.* (Cardiol J 2022; 29, 3: 388–395)

Key words: quantitative flow ratio, μQFR, coronary physiology, resting index, computational physiology, Murray law, coronary heart disease

Address for correspondence: OFA Prof. Juan Luis Gutiérrez-Chico, MD, PhD, FESC, FACC, Head of Interventional Cardiology, Bundeswehrzentralkrankenhaus, Rübenacherstraße 170, 56072 – Koblenz, Germany, tel: +49 26128121610, +34 615 319370, e-mail: juanluis.gutierrezchico@ictra.es

**These authors have equally contributed.*

Received: 17.04.2022 Accepted: 11.05.2022 Early publication date: 17.05.2022

Introduction

Physiology-based decision-making about the need for revascularization in patients with stable coronary heart disease has consistently proven better clinical outcomes than a merely anatomical approach [1–5]. Notwithstanding this compelling evidence, the penetration of physiology in real-world surveys is still scarce [6–10], although modestly increasing over time [11]. Against current guideline recommendations [12], the indication for revascularization in most patients with chronic coronary syndromes still relies on coronary angiography alone, without a proper functional assessment [6–10]. The reasons for this evidence--reality mismatch are multifactorial: the increase in costs and in procedural complexity of wire-based physiology, patient's discomfort during the induction of hyperemia, gaps in the operator training or the inertia of interventional teams to change their traditional *modus operandi* have been advocated to explain this phenomenon [8, 9, 13, 14].

Computational physiology has been developed to overcome the limitations of wire-based physiology and to increase the penetration of invasive functional assessment in coronary stenosis. The basic concept of computational physiology consists of an imaging--based rendering of the coronary anatomy to subsequently apply computational fluid dynamics, with the aim of estimating the pressure drop along the artery [10, 15, 16]. Intense research on this topic has resulted in a substantial simplification of the process, up to the point of circumventing the computational fluid dynamics simulation and substituting it for faster algorithms that allow a remarkably accurate estimation of fractional flow reserve (FFR) in a few seconds [14, 17]. Likewise, specific computational physiology algorithms are currently available for different imaging modalities: coronary angiography [15, 17–19], optical coherence tomography [14], intravascular ultrasound [20] or even non-invasive computed tomography angiography [21].

Quantitative flow ratio (QFR) is the most widespread method of computational physiology based on coronary angiography. Although several studies have proven the outstanding accuracy of QFR to estimate FFR [15, 17–19], the requirement of two good-quality orthogonal/separate projections for the three-dimensional (3D) rendering of the coronary lumen cannot be always accomplished, thus resulting in a proportion around 15% of cases unsuitable for analysis in retrospective studies [19, 22]. Murray law-based QFR (μQFR) is a novel computational method that enables accurate estimation of FFR based on the analysis of a single angiographic projection with adequate quality [23], adjusting both the reference vessel diameter and the outgoing flow through side branches according to fractal geometry [16, 24]. A post-hoc analysis of patients recruited in the FAVOR (Functional Diagnostic Accuracy of Quantitative Flow Ratio in Online Assessment of Coronary Stenosis) II China study (NCT03191708) has reported excellent agreement between μQFR and FFR [23]. Nonetheless, agreement between μQFR and standard QFR based on 3D lumen reconstruction has not been reported hitherto, thus leaving a gap in the evidence about whether both methods could be indistinctly applicable in retrospective studies, depending on the quality of the angiographic projections available.

Methods

Study population

Real-world patients from two different retrospective cohorts, with clinical suspicion of stable coronary heart disease were screened for the current study. Inclusion criteria were: 1) having undergone a coronary angiography between 2015 and 2021; 2) mild to severe stenosis in ≥ 1 major coronary artery. Exclusion criteria were: hemodynamic or electrical instability at the moment of angiography acquisition; the analyzed lesion being the culprit vessel of an acute coronary syndrome in the past 7 days; chronic total occlusion of any coronary artery; bypass graft connected to the target vessel; presence of a stent in the target vessel or impossibility to provide informed consent to the analysis. Patients stemmed from a multicenter national registry of stable coronary heart disease in Spain (NCT05251012, Spanish cohort) and from Ruijin University Hospital in Shanghai (Chinese cohort). In order to shorten the analysis time, a sample of 35 patients, according to sample size calculation, were randomly selected for the study, using a computer-generated sequence of random numbers between 0 and 1, that were consecutively adjudicated to the patients. The patients with the highest adjudicated random score were selected until completing the predefined sample in a 3:2 ratio between the Spanish and Chinese cohorts, respectively, as agreed upon by the investigators.

The study complied with the principles of good clinical practice and with the Declaration of Helsinki for investigations in human beings. The study protocol was approved by the corresponding Ethics Committee and institutional review boards. All patients signed

informed consent to the anonymized use of their personal data for scientific or quality-control purposes.

Angiographic analysis

Angiographic images were recorded at ≥ 15 frames/s by monoplane X-rays systems (Allura Xper FD20, Philips; Artist Q Zeego, Siemens; Innova IGS520, GE). Angiographic projections with minimal overlap and foreshortening at the corresponding target lesions were selected for offline analysis by two experienced and independent operators at an official and regularly audited corelab (Cardiovascular Imaging Core Laboratory of the Shanghai Jiao Tong University School of Medicine, Shanghai, China), using computerized edge-detection quantitative coronary angiography (QCA) software (AngioPlus Core, Pulse Medical Imaging Technology, Shanghai, China). All analysts were blinded to clinical, angiographic and functional data of the patients at all steps.

Three-dimensional quantitative flow ratio (3D-QFR)

Two angiographic projections, acquired > 25° apart, were used for 3D reconstruction of the target arteries. Markers were manually placed at the proximal and distal segments of the target vessel to guide the automatic lumen contour detection. In case of misleading vessel track, additional points markers could be placed along the lumen or the vessel contour could be manually edited. QCA was performed, reporting reference vessel diameters, minimal lumen diameter, minimal lumen area and percent diameter/area stenosis. 3D-QFR was obtained by means of artificial-intelligence (AI)-aided computation software (AngioPlus Core, Pulse Medical Imaging Technology, Shanghai, China), combining the 3D reconstruction of the angiogram with the estimation of coronary flow rendered by AI-analysis of the coronary filling velocity, as previously described [25].

In cases where 3D-QFR could not be obtained due to recording of a single projection of the target vessel, insufficient separation of the second projection, incomplete filming of the target artery, panning or irregular coronary filling, the case was labelled as non-analysable and the causes for it were registered.

Murray-law based quantitate flow ratio (μQFR)

Murray-law based quantitate flow ratio was calculated using AI-aided computation software (AngioPlus Core Pulse Medical Imaging Technology, Shanghai, China), as previously described [23]. Briefly, a single angiographic projection, in which the coronary stenosis was best visualized, minimising foreshortening and vessel overlap, was selected by the operator. The angiographic projection could be part of the pair normally used for 3D-QFR or being a totally different projection, at the operator's discretion. The lumen contour of the main vessel and its side branches with > 1 mm caliber was automatically delineated by artificial intelligence throughout the angiographic loop. The frame in which the lumen contour of the lesion was best depicted was selected by the operator for the computation. μQFR was then calculated, based on this single angiographic projection, but taking into account the outgoing flow through the side branches to calculate both the reference diameters and the pressure drop along the stenotic segment, according to Murray's fractal law [10, 16, 24].

A paradigmatic example of analysis by 3D-QFR and μQFR is presented at Figure 1.

Statistical analysis

Dichotomous and categorical variables were presented as counts (percentages). Continuous variables were presented as mean ± 95% confidence interval (CI). 3D-QFR and μQFR were dichotomised with a cut-off value of 0.80, thus defining ≤ 0.80 as significant and > 0.80 as non-significant. Continuous variables were compared with the t-Student test for unpaired samples, whilst dichotomous and categorical values were compared with the Fisher exact test. A Gaussian distribution of continuous variables was checked by means of the Saphiro-Wilk test.

Due to the difficulty of defining a gold standard for the comparison QFR vs. μQFR, non-parametric Passing-Bablok orthogonal regression was performed to analyze correlation and eventual bias. Constant and proportional bias were evaluated as the deviation of the intercept from 0 and the deviation of the slope from 1 in the orthogonal regression model, respectively. The agreement as continuous variables was analyzed by means of Lin's coefficient, intraclass correlation coefficients for the absolute agreement (ICCa) and the Bland-Altman method. The agreement as dichotomous variables was assessed by means of kappa coefficient.

Pre-specified subgroup analysis was performed at the Spanish and Chinese cohorts, to assess the consistency between these populations.

For sample size calculation, the diagnostic accuracy of μQFR to predict the significance of 3D-QFR as dichotomous variable was assumed

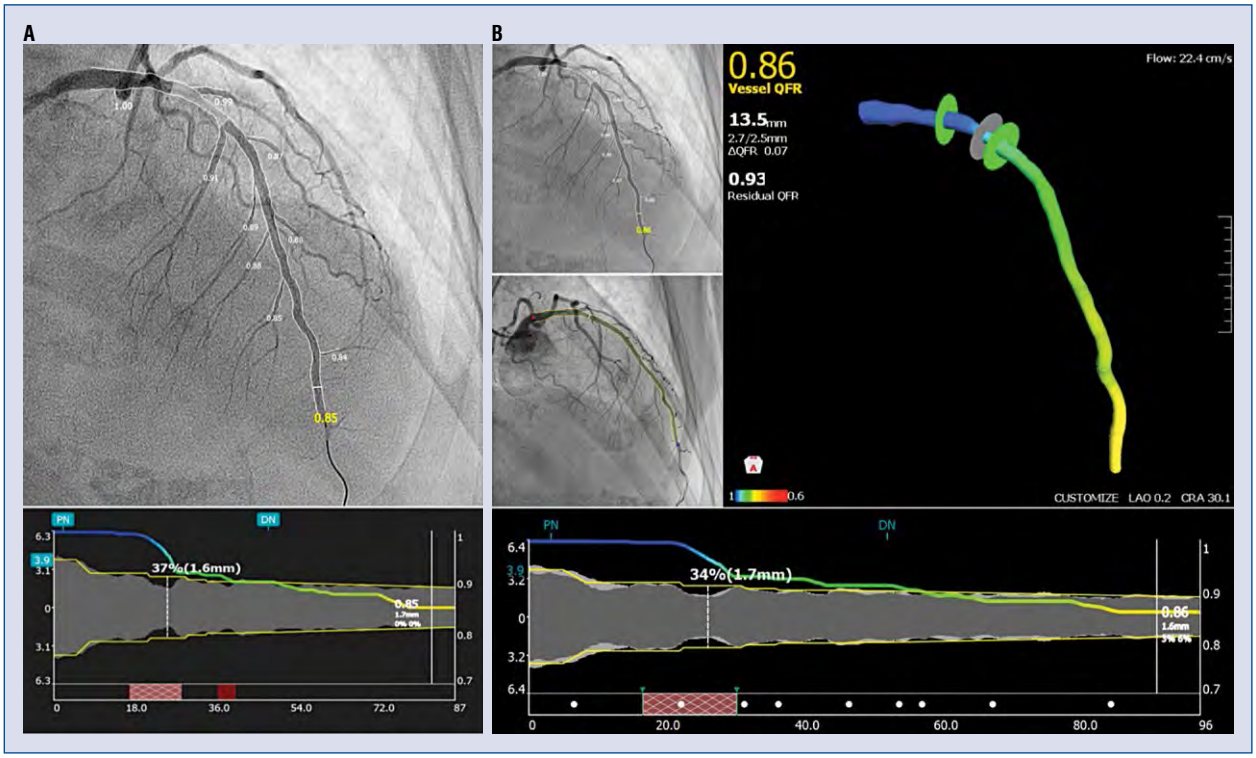


Figure 1. Paradigmatic example of both quantitative flow ratio (QFR) modalities: μQFR (**A**) and three-dimensional quantitative flow ratio (3D-QFR) (**B**).

to be superior to the agreement of the most accurate computational method to date, i.e., optical flow ratio, with a diagnostic accuracy 93% in the pivotal prospective study [14]. Therefore, assuming a diagnostic accuracy ≥ 94%, with a precision of the estimation (ε) of 5% in the interval and a 5% likelihood of α-error, in two-sided calculation, the number of vessels required for a head-to-head comparison would be 87. Considering that 2.5 vessels would be on average analysable per patient, according to previous QFR multivessel studies [26], a sample of 35 patients would be able to provide sufficient statistical power to guarantee the precision of the estimation.

All statistical analysis was performed with Stata (16.1, StataCorp LLC, College Station, TX).

Results

Between 2015 and 2021, 803 patients were included into the Spanish registry, whilst 498 coronary angiographies fulfilling the inclusion criteria were performed at the Ruijin Hospital in March 2021. After screening at the corelab, 102 patients from the Spanish cohort and 107 patients from the Chinese cohort were excluded (Fig. 2), resulting in a total of 1092 potentially eligible patients (2878 coronary arteries), among whom 35 of them were randomly selected for the current analysis.

A total of 98 coronary arteries from 35 patients were finally analyzed: 56 (57.1%) from the Spanish cohort and 42 (42.9%) from the Chinese cohort. Patients' procedural and lesion characteristics, including QCA and computational physiology parameters of 3D-QFR and μQFR, are presented in Table 1. The Chinese cohort had significantly shorter lesions (17.05 vs. 24.30 mm, p = 0.025), with a milder degree of stenosis (31.07% vs. 41.06%, p = 0.008) than the Spanish cohort, thus resulting in a non-significant trend to higher physiology values (3D-QFR: 0.85 vs. 0.80, p = 0.250; μQFR: 0.85 vs. 0.79, p = 0.204). The three coronary territories were equally represented (left anterior descending artery: 34.69%, circumflex artery: 33.67%, right coronary artery: 31.63%).

Agreement between 3D-QFR and μQFR in the global sample

As continuous variables, μ-QFR and 3D-QFR showed excellent agreement: ICCa 0.996 (95% CI: 0.993–0.997); Lin's coefficient 0.996 (95% CI: 0.993–0.997), without constant or proportional

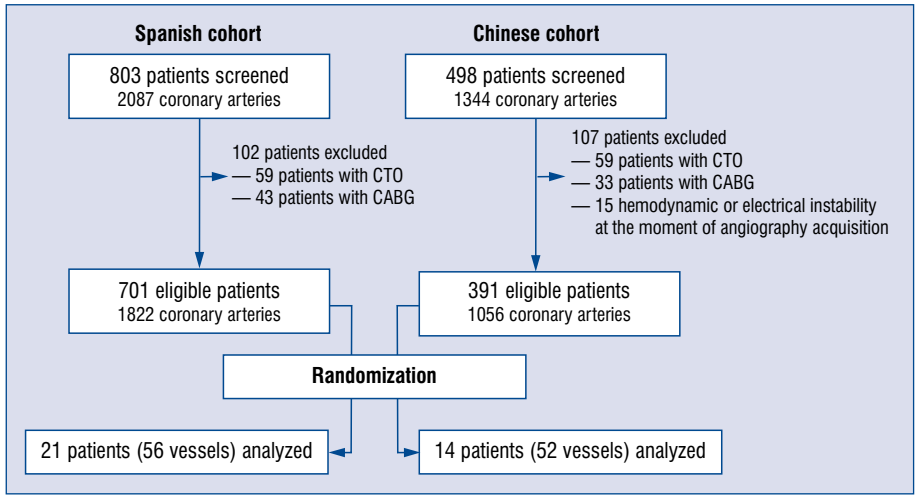


Figure 2. Flow chart; CABG — coronary artery bypass grafting; CTO — chronic total occlusion.

bias (intercept = 0 and slope = 1 in orthogonal regression). The estimation of the orthogonal regression line (Passing and Bablok method) and Bland-Altman graphics are represented in Figure 3.

As dichotomous variable, there was absolute agreement between μQFR and 3D-QFR, resulting in no single false positive or negative. Kappa index was 1 and the diagnostic accuracy 100%, meeting the premise used for sample size calculation (≥ 94%).

Consistency between cohorts

Evaluating each cohort separately, the agreement between both methods showed similar values: ICCa was 0.996 (95% CI: 0.992–0.997) and 0.999 (95% CI: 0.999–0.999) in the Spanish and Chinese cohorts, respectively.

Non-analysable cases by 3D-QFR

All cases in the study could be analyzed by μ-QFR (retrospective feasibility 100%), whilst only 86 coronary arteries were analysable by 3D-QFR (retrospective feasibility of 87.76%). Four (4.08%) cases were unsuitable for 3D-QFR analysis due to lack of adequate second angiographic views of the target vessel for 3D reconstruction and 8 (8.16%) cases due to poor image quality with excessive overlap. The unsuitability for retrospective 3D--QFR analysis tended to be more frequent in the Spanish than in the Chinese cohort (16.1 vs. 7.1%, p = 0.225).

Discussion

The main findings of this study can be summarised as follows: 1) Murray-law based μQFR using a single angiographic projection and standard 3D-QFR using two angiographic projections show practically perfect agreement, both as continuous or as dichotomous variables, with negligible incidence of discordant cases; 2) The retrospective feasibility of standard 3D-QCR is 87.76%, lower than reported in prospective studies, mostly due to the lack of an appropriate second projection, but it can be substantially increased in the case of μQFR, because it only requires a single projection of good quality per target vessel; 3) These results are consistent throughout different cohorts, stemming from different geographic regions or acquired at different times.

These results are consistent with the diagnostic accuracy reported for both methods against FFR in the FAVOR II China cohort (92.7% for 3D-QFR and 93.0% for μQFR) [23]. The superior agreement between both computational methods, as compared to the agreement reported for an invasive gold standard, might be considered as a proof of concept, i.e., that the simplified method, based on a single angiographic projection, preserves the rationale and the accuracy of the original 3D-QFR, whilst sparing extra time and efforts to the operator. Actually, the agreement tends to be close to perfect, with indexes close to 1 and negligible incidence of discordance in the dichotomous classification as significant/non-significant, thus confirming its huge potential for routine clinical applications.

The almost perfect agreement between both methods encourages the interchangeable use of 3D-QFR or μQFR in retrospective studies of computational physiology, whenever a proper 3D reconstruction of the angiography cannot be reli-

Table 1. Descriptive statistics of patients, intervention and lesions.

Patient level	N = 35	Spanish cohort (n = 21)	Chinese cohort (n = 14)	P
Male	25 (71.4%)	14 (66.7%)	11 (78.6%)	0.445
Age [years] (95% CI)	65.8 (61.9–72.9)	65.1 (59.6–70.6)	66.9 (61.0–72.9)	0.639
BMI (95% CI)	25.4 (24.2–26.7)	26.6 (25.0–28.2)	23.7 (22.1–25.4)	0.016
Cardiovascular risk factors:				
Hypertension	28 (80.0%)	18 (85.7%)	10 (71.4%)	0.301
Hypercholesterolemia	16 (45.7%)	16 (76.2%)	8 (57.1%)	0.505
Diabetes mellitus:	10 (28.6%)	8 (38.1%)	2 (14.3%)	0.127
Type 2 on OAD	8 (22.9%)	6 (28.6%)	2 (14.3%)	0.324
Type 2 on insulin	2 (5.7%)	2 (9.5%)	0 (0.0%)	0.234
Smoking:	20 (57.1%)	12 (57.1%)	8 (57.1%)	1.000
Previous smoker	8 (22.9%)	5 (23.8%)	3 (21.4%)	0.869
Current smoker	12 (34.3%)	7 (33.3%)	5 (35.7%)	0.884
Previous MI	7 (20.0%)	5 (23.8%)	2 (14.3%)	0.490
Previous revascularization	7 (20.0%)	4 (19.1%)	3 (21.4%)	0.863
GFR [mL/min] (95% CI)	77.4 (68.5–86.2)	75.1 (60.8–89.4)	80.8 (72.3–89.3)	0.530
Hemoglobin [g/dL] (95% CI)	14.0 (13.5–14.5)	14.3 (13.5–15.0)	13.5 (12.8–14.2)	0.141
LVEF [%] (95% CI)	58.8 (55.2–62.4)	54.7 (49.6–59.8)	64.9 (62.4–67.5)	0.002
Procedural variables				
Syntax score (95% CI)	9.3 (6.9–11.6)	9.3 (6.2–12.4)	9.2 (5.1–13.4)	0.973
Fluoroscopy [min] (95% CI)	12.2 (9.0–15.4)	12.8 (8.7–16.9)	11.3 (5.5–17.1)	0.645
Clinical indication				0.004
Stable disease	29 (82.9%)	21 (100.0%)	8 (57.1%)	
Unstable angina	5 (14.7%)	0 (0.0%)	5 (35.7%)	
Non-ST-elevation MI	1 (2.9%)	0 (0.0%)	1 (7.1%)	
Vessels	**N = 98**	**N = 56**	**N = 42**	0.947
LAD	34 (34.7%)	20 (35.7%)	14 (33.3%)	
LCX	33 (33.7%)	19 (33.9%)	14 (33.3%)	
RCA	31 (31.6%)	17 (30.4%)	14 (33.3%)	
Lesions (3D-QFR ≤ 0.80)	24 (24.5%)	18 (32.1%)	6 (14.3%)	0.057
Calcification:				
None to little	78 (79.6%)	42 (75.0%)	36 (87.7%)	0.216
Moderate to severe	20 (20.4%)	14 (25.0%)	6 (14.3%)	0.216
Lesion length [mm]	20.99 (18.0–24.0)	24.30 (19.5–29.1)	17.05 (13.1–21.0)	0.025
RVD [mm]	2.60 (2.5–2.7)	2.56 (2.4–2.8)	2.70 (2.5–2.9)	0.337
MLD [mm]	1.62 (1.5–1.8)	1.5 (1.3–1.6)	1.8 (1.6–2.1)	0.018
DS [%]	38.37 (34.8–42.0)	41.06 (36.9–45.2)	31.07 (24.7–37.4)	0.008
3D-QFR (95% CI)	0.82 (0.78–0.87)	0.80 (0.74–0.86)	0.85 (0.77–0.94)	0.250
μQFR (95% CI)	0.81 (0.76–0.85)	0.79 (0.73–0.85)	0.85 (0.77–0.94)	0.204

Data presented as counts (percent), mean (standard deviation) or median (P_{25} – P_{75}); 3D-QFR — three-dimensional quantitative flow ratio; BMI — body mass index; CI — confidence interval; DS — diameter stenosis; GFR — glomerular filtration rate by Cockroft-Gault method; LAD — left anterior descending artery; LCX — left circumflex artery; LVEF — left ventricular ejection fraction; MLD — minimal lumen diameter; MI — myocardial infarction; OAD — oral antidiabetics; PCI — percutaneous coronary intervention; RCA — right coronary artery; RVD — reference vessel diameter; μQFR (microQFR) — single angiographic view quantitative flow ratio

ably performed. In the current retrospective study, 12.24% of the arteries were unsuitable for standard 3D-QFR, in line with previous retrospective reports, in which the unfeasibility was around 15% [19, 22]. This retrospective feasibility is sensibly lower than that reported for prospective stud-

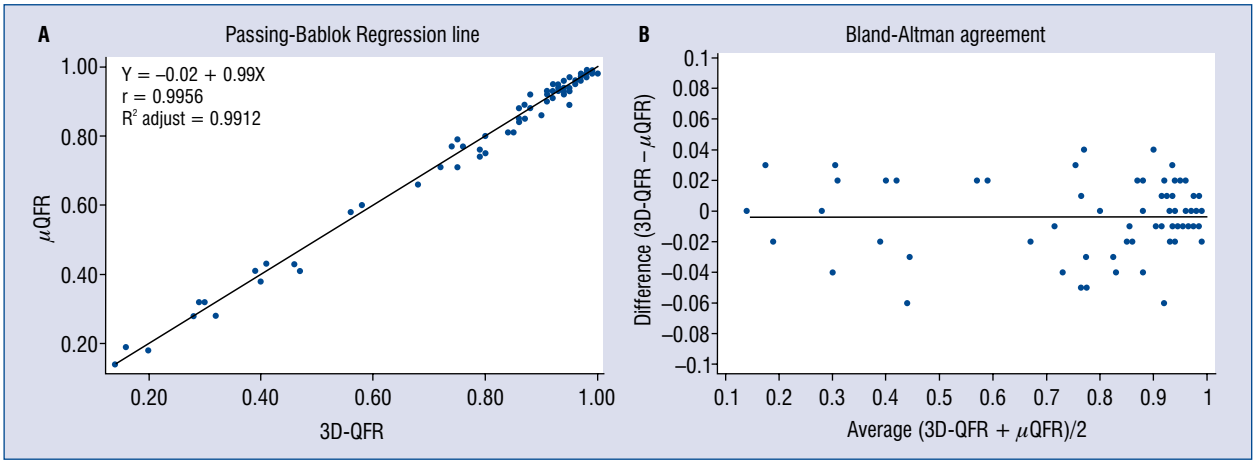


Figure 3. Agreement between three-dimensional quantitative flow ratio (3D-QFR) and single angiographic view quantitative flow ratio (μQFR) estimated by orthogonal regression line in panel **A** (Passing-Bablok method) and Bland-Altman graphics in panel **B**.

ies [15, 17], wherein a dedicated acquisition was upfront pursued to optimize the QFR calculation. This aspect might be important not only for scientific purposes, but also for clinical applications, for instance to avoid staged procedures in non-infarct-related artery lesions after primary percutaneous coronary intervention [26, 27].

Likewise, the excellent agreement of μQFR with standard 3D-QFR methods reassures the results reported in previous studies, in which the novel method proved excellent diagnostic accuracy, as compared with wire-based FFR [23]. This methodologically simplified but still accurate method could help to increase the penetration of physiology in routine clinical practice, which is still suboptimal in real-life [6–10]. Indeed, current evidence can hardly justify the use of plain angiography for decision-making about the need of revascularization in stable coronary heart disease, as physiology-guided revascularization has consistently proven superior clinical outcomes to anatomy-guided revascularization [1–5].

Limitations of the study

The retrospective design of the present study might be regarded as a limitation, as it controls the possibility of selection bias in an imperfect way, notwithstanding the careful methodological design. Nonetheless, the retrospective design was explicitly preferred in this case, because it was the setting in which eventual differences in feasibility was most likely to be unravelled.

The analysis was centrally performed offline by highly expert analysts in a certified corelab. The agreement onsite between both methods, performed by local operators should be appraised in future studies.

The 3D-QFR used in this study (Pulse Medical, Shanghai, China) also takes into account the fractal geometry at the bifurcations. This might have favoured the optimal agreement between the methods, which might be not directly extrapolated to other methods of computational physiology which do not take Murray's law into account.

The accuracy of μQFR could be theoretically jeopardized in highly eccentric lesions, in which the differences in computed QFR between angiographic projections might be exaggerated. In the study sample, this theoretical inaccuracy was not clearly unveiled in any single case. The retrospective design, relying exclusively on angiography, makes the assessment of eccentricity somewhat difficult and subjective in the current study, but it is worthy of specific clarification in future studies.

Conclusions

Murray-law based quantitative flow ratio using a single angiographic projection showed excellent agreement with standard 3D-QFR and improved the feasibility of the latter in retrospective studies. These results encourage the interchangeable use of μQFR whenever a proper 3D-QFR cannot be reliably calculated due to lack of suitable double projections.

Conflict of interest: None declared

References

1. Bech GJ, De Bruyne B, Pijls NH, et al. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. Circulation. 2001; 103(24): 2928–2934, doi: 10.1161/01.cir.103.24.2928, indexed in Pubmed: 11413082.
2. Tonino PAL, De Bruyne B, Pijls NHJ, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009; 360(3): 213–224, doi: 10.1056/NEJMoa0807611, indexed in Pubmed: 19144937.
3. De Bruyne B, Pijls NHJ, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med. 2012; 367(11): 991–1001, doi: 10.1056/NEJMoa1205361, indexed in Pubmed: 22924638.
4. Davies J, Sen S, Dehbi HM, et al. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. N Engl J Med. 2017; 376(19): 1824–1834, doi: 10.1056/nejmoa1700445.
5. Götberg M, Christiansen E, Gudmundsdottir I, et al. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. N Engl J Med. 2017; 376(19): 1813–1823, doi: 10.1056/nejmoa1616540.
6. Toth G, Toth B, Johnson N, et al. Revascularization Decisions in Patients With Stable Angina and Intermediate Lesions. Circ Cardiovasc Interv. 2014; 7(6): 751–759, doi: 10.1161/circinterventions.114.001608.
7. Härle T, Zeymer U, Hochadel M, et al. Real-world use of fractional flow reserve in Germany: results of the prospective ALKK coronary angiography and PCI registry. Clin Res Cardiol. 2017; 106(2): 140–150, doi: 10.1007/s00392-016-1034-5, indexed in Pubmed: 27599974.
8. Lee HS, Lee JM, Nam CW, et al. Consensus document for invasive coronary physiologic assessment in Asia-Pacific countries. Cardiol J. 2019; 26(3): 215–225, doi: 10.5603/CJ.a2019.0054, indexed in Pubmed: 31225632.
9. Gutiérrez-Chico JL, Zhao S, Chatzizisis YS. Vorticity: at the crossroads of coronary biomechanics and physiology. Atherosclerosis. 2018; 273: 115–116, doi: 10.1016/j.atherosclerosis.2018.04.001, indexed in Pubmed: 29665968.
10. Gutiérrez-Chico JL. Planning percutaneous interventions with optical flow ratio: "niu" odds in favour of imaging in the year of the Ox. EuroIntervention. 2021; 17(12): e958–e960, doi: 10.4244/EIJV17I12A160, indexed in Pubmed: 34916180.
11. Ojeda S, Romaguera R, Cruz-González I, et al. [Spanish Cardiac Catheterization and Coronary Intervention Registry. 29th Official Report of the Interventional Cardiology Association of the Spanish Society of Cardiology (1990-2019)]. Rev Esp Cardiol. 2020; 73(11): 927–936, doi: 10.1016/j.recesp.2020.07.024, indexed in Pubmed: 33012949.
12. Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019; 40: 87––165, doi: 10.1093/eurheartj/ehy394, indexed in Pubmed: 30165437.
13. Tebaldi M, Biscaglia S, Fineschi M, et al. Evolving Routine Standards in Invasive Hemodynamic Assessment of Coronary Stenosis: The Nationwide Italian SICI-GISE Cross-Sectional ERIS Study. JACC Cardiovasc Interv. 2018; 11(15): 1482–1491, doi: 10.1016/j.jcin.2018.04.037, indexed in Pubmed: 29803695.
14. Gutiérrez-Chico JL, Chen Y, Yu W, et al. Diagnostic accuracy and reproducibility of optical flow ratio for functional evaluation of coronary stenosis in a prospective series. Cardiol J. 2020; 27(4): 350–361, doi: 10.5603/CJ.a2020.0071, indexed in Pubmed: 32436590.
15. Tu S, Barbato E, Köszegi Z, et al. Fractional flow reserve calculation from 3-dimensional quantitative coronary angiography and TIMI frame count: a fast computer model to quantify the functional significance of moderately obstructed coronary arteries. JACC Cardiovasc Interv. 2014; 7(7): 768–777, doi: 10.1016/j.jcin.2014.03.004, indexed in Pubmed: 25060020.
16. Li Y, Gutiérrez-Chico JL, Holm NR, et al. Impact of side branch modeling on computation of endothelial shear stress in coronary artery disease: coronary tree reconstruction by fusion of 3D angiography and OCT. J Am Coll Cardiol. 2015; 66(2): 125–135, doi: 10.1016/j.jacc.2015.05.008, indexed in Pubmed: 26160628.
17. Tu S, Westra J, Yang J, et al. Diagnostic Accuracy of Fast Computational Approaches to Derive Fractional Flow Reserve From Diagnostic Coronary Angiography: The International Multicenter FAVOR Pilot Study. JACC Cardiovasc Interv. 2016; 9(19): 2024–2035, doi: 10.1016/j.jcin.2016.07.013, indexed in Pubmed: 27712739.
18. Collet C, Onuma Y, Sonck J, et al. Diagnostic performance of angiography-derived fractional flow reserve: a systematic review and Bayesian meta-analysis. Eur Heart J. 2018; 39(35): 3314–3321, doi: 10.1093/eurheartj/ehy445, indexed in Pubmed: 30137305.
19. Cortés C, Carrasco-Moraleja M, Aparisi A, et al. Quantitative flow ratio-meta-analysis and systematic review. Catheter Cardiovasc Interv. 2021; 97(5): 807–814, doi: 10.1002/ccd.28857, indexed in Pubmed: 32196932.
20. Yu W, Tanigaki T, Ding D, et al. Accuracy of intravascular ultrasound-based fractional flow reserve in identifying hemodynamic significance of coronary stenosis. Circ Cardiovasc Interv. 2021; 14(2): e009840, doi: 10.1161/CIRCINTERVENTIONS.120.009840, indexed in Pubmed: 33541105.
21. Li Z, Zhang J, Xu L, et al. Diagnostic accuracy of a fast computational approach to derive fractional flow reserve from coronary CT angiography. JACC Cardiovasc Imaging. 2020; 13(1 Pt 1): 172–175, doi: 10.1016/j.jcmg.2019.08.003, indexed in Pubmed: 31542542.
22. Cortés C, Rivero F, Gutiérrez-Ibañes E, et al. Prospective validation and comparison of new indexes for the assessment of coronary stenosis: resting full-cycle and quantitative flow ratio. Rev Esp Cardiol (Engl Ed). 2021; 74(1): 94–97, doi: 10.1016/j.rec.2020.05.039, indexed in Pubmed: 32792309.
23. Tu S, Ding D, Chang Y, et al. Diagnostic accuracy of quantitative flow ratio for assessment of coronary stenosis significance from a single angiographic view: A novel method based on bifurcation fractal law. Catheter Cardiovasc Interv. 2021; 97 (Suppl 2): 1040––1047, doi: 10.1002/ccd.29592, indexed in Pubmed: 33660921.
24. Murray CD. The physiological principle of minimum work: I. The vascular system and the cost of blood volume. Proc Natl Acad Sci U S A. 1926; 12(3): 207–214, doi: 10.1073/pnas.12.3.207, indexed in Pubmed: 16576980.
25. Zhao Q, Li C, Chu M, et al. Angiography-based coronary flow reserve: The feasibility of automatic computation by artificial intelligence. Cardiol J. 2021 [Epub ahead of print], doi: 10.5603/CJ.a2021.0087, indexed in Pubmed: 34355775.
26. Cortés C, Rodríguez-Gabella T, Gutiérrez H, et al. Quantitative flow ratio in myocardial infarction for the evaluation of non-infarct-related arteries. The QIMERA pilot study. RECICE. 2019, doi: 10.24875/recice.m19000007.
27. Zhang J, Yao M, Jia X, et al. The efficacy and safety of quantitative flow ratio-guided complete revascularization in patients with ST-segment elevation myocardial infarction and multivessel disease: A pilot randomized controlled trial. Cardiol J. 2021 [Epub ahead of print], doi: 10.5603/CJ.a2021.0111, indexed in Pubmed: 34581424.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 3, 396–404
DOI: 10.5603/CJ.a2020.0131

ISSN 1897–5593
eISSN 1898–018X

One-year outcomes of percutaneous coronary intervention in native coronary arteries versus saphenous vein grafts in patients with prior coronary artery bypass graft surgery

Amr Abdelrahman, Maciej Dębski, Ranjit More, Hesham K. Abdelaziz, Tawfiqur Choudhury, Jonas Eichhofer, Billal Patel

Department of Cardiology, Lancashire Cardiac Centre, Blackpool Teaching Hospitals NHS Foundation Trust, Blackpool FY3 8NR, United Kingdom

Abstract

Background: *Patients with prior coronary artery bypass graft (CABG) surgery often require percutaneous coronary intervention (PCI). Data are still limited in regards to the outcomes of native saphenous vein graft (SVG) PCI after CABG.*

Methods: *We performed a retrospective study in a tertiary reference cardiac center of consecutive patients who underwent PCI after CABG. The data were collected for patients who underwent either native or graft PCI from January 2008 to December 2018. Arterial graft PCIs were excluded. Multivariable Cox regression analysis with propensity matching was performed, and major adverse cardiac events (MACE) outcomes including death or myocardial infarction (MI) or revascularization were assessed at 1-year after each index procedure.*

Results: *A total of 435 PCI were performed in 401 patients (209 had native PCI and 192 had graft PCI). Target lesions were classified as following: 235 (54%) native coronary arteries and 200 (46%) SVG. Propensity matching resulted in 167 matched pairs. In multivariable Cox regression graft PCI relative to native PCI was an independent risk factor for MACE (hazard ratio [HR] 1.725, 95% confidence interval [CI] 1.049–2.837) which was primarily driven by increased incidence in revascularization (HR 2.218, 95% CI 1.193–4.122) and MI (HR 2.248, 95% CI 1.220–4.142) and with no significant difference in mortality (HR 1.118, 95% CI 0.435–2.870).*

Conclusions: *Compared with native coronary PCI, bypass graft PCI was significantly associated with higher incidence of MACE at 1-year and this was mainly driven by MI and revascularization.* (Cardiol J 2022; 29, 3: 396–404)

Key words: acute coronary syndrome, coronary artery bypass graft, coronary artery disease, major adverse cardiac event, percutaneous coronary intervention

Introduction

Patients with prior coronary artery bypass graft (CABG) surgery often require repeat revascularization either due to graft failure or a combination of graft failure and progression of coronary atherosclerosis. Thrombosis, intimal hyperplasia and atherosclerosis are the main pathological processes underlying saphenous venous grafts disease [1]. Early thrombosis is the principle cause of vein graft attrition during the first month after bypass surgery, with intimal hyperplasia being an issue

Address for correspondence: Maciej Dębski, MD, PhD, Cardiology Department, Lancashire Cardiac Centre, Blackpool Teaching Hospitals NHS Foundation Trust, Whinney Heys Rd, Blackpool FY3 8NR, United Kingdom, tel: +44 01253 9 57783, e-mail: maciej.debski@nhs.net

Received: 25.02.2020 Accepted: 26.07.2020 Early publication date: 28.09.2020

during the remainder of the first year. Thereafter, atherogenesis predominates. The optimal revascularization strategy of patients with prior CABG and graft failure remains a subject of debate. Redo surgeries are associated with higher morbidity and mortality as well as poorer outcomes compared to initial operations [2]. Furthermore, there is limited evidence on the optimal percutaneous coronary intervention (PCI) option (i.e. native coronary artery or graft PCI) in such population. Present study was conducted to compare 1-year major adverse cardiac events (MACE) of native versus graft PCI.

Methods

This is a retrospective study performed in a tertiary cardiac center of CABG patients who underwent subsequent PCI. The data were collected for consecutive patients who underwent either native or graft PCI from January 2008 to December 2018. Arterial graft PCI patients were excluded from the study. The procedural data for the patients who underwent PCI were collected from our local catheterization laboratory database. If a patient had more than one procedure during the study period, the first PCI was considered as the index procedure and the subsequent procedures were considered as outcomes. If a patient had undergone more than one PCI in the same first procedure during the study time period, all lesions intervened on underwent analysis. However, if those PCI involved both native and saphenous vein graft (SVG) interventions, then the patient was included in the SVG PCI study arm. The primary end point was 1-year MACE defined as a composite of death, myocardial infarction (MI) or target vessel revascularization. Secondary endpoints included angiographic complications (no-reflow, dissection and perforation). Patients' mortality was identified from the hospital clinical system which is updated regularly from the United Kingdom's Office of National Statistics. All outcomes were assessed at 1-year after each index procedure.

Statistical analysis

Continuous variables are presented as means (SD) or medians (IQR). For normally distributed variables, Student's t-test was used, whereas in samples with non-normal distribution Mann–Whitney U test was used. Categorical variables were compared with the use of Fisher's exact tests (2-sided). To best control for the non-random assignment of patients to 1 of 2 PCI approaches, we have used a combination of matching methods: it is matched exactly on the categorical variables (gender, diabetes, chronic kidney disease, hypertension, urgency of procedures and clinical presentation [angina or acute coronary syndrome; ACS]) and used a propensity score on the age variable. So, in each matched pair the age may vary slightly but the other covariates all take exactly the same value. Matching resulted in 167 matched pairs. Kaplan–Meier curves for outcomes and compared with the use of the log-rank test. For multivariable analysis, the Cox regression model was applied. Estimated hazard ratios (HR) and their 95% confident intervals (CI) were calculated. Two-sided statistics were performed with a p-value less than 0.05 determining significance. Statistical analysis was performed using SPSS v.25.0 (IBM Corp., Armonk, New York, United States).

Results

A total of 435 PCI were performed to 401 patients during the study period. They were classified as following: native coronary artery (235 [54%]), SVG (200 [46%]), The native vessel and SVG intervention had comparable baseline characteristics, left ventricular ejection fraction and clinical presentation (angina and ACS) as shown in Table 1. Graft age was greater in patients who underwent graft PCI. Femoral access was used in over half of both groups with no statistical difference between two groups. Most bypass graft target lesions were located at the body of the graft 58.6%. Compared with patients who underwent bypass graft PCI, those who underwent native coronary artery PCI were more likely to undergo PCI of a chronic total occlusion (CTO) or to an in-stent restenosis (ISR). In native vessel PCI, there was a greater likelihood of requiring more than one stent. However, in graft PCI stent diameters were larger. Regarding the length of the stents, there was no statistical difference between the two groups. In comparison to native coronary lesions, graft lesions were more likely to be treated with bare-metal stents (BMS) and drug eluting balloon. Patients in native PCI group were more likely to have post-procedural Thrombolysis in Myocardial Infarction III flow. Statistically, there was no difference in fluoroscopy time and contrast amount between both groups (Table 2). No reflow phenomenon was significantly more frequent in patients undergoing graft PCI compared to patients with native artery PCI (10% vs. 0.4%, $p < 0.001$) (Table 3). Matched groups analysis resulted in a significant difference in age between both groups

Table 1. Baseline characteristics and presentation of patients undergoing native and graft percutaneous coronary intervention, before and after matching.

Parameter	Before matching			After matching		
	Native coronary PCI (209)	SVG PCI (192)	P	Native coronary PCI (167)	SVG PCI (167)	P
Demographics						
Age, median (IQR)	70 [62–76]	70 [65–78]	0.090	71 [63–76]	71 [66–79]	0.023
Female	28 (13%)	29 (15%)	0.669	23 (14%)	23 (14%)	1
Comorbidities						
Diabetes	84 (40%)	77 (40%)	1	67 (40%)	67 (40%)	1
Hypertension	148 (71%)	123 (64%)	0.166	112 (67%)	112 (67%)	1
Hyperlipidemia	99 (47%)	87 (45%)	0.690	78 (47%)	80 (48%)	0.913
Chronic kidney disease	30 (14%)	28 (15%)	1	23 (14%)	23 (14%)	1
Dialysis	3 (1%)	4 (2%)	0.714	3 (2%)	4 (2%)	1
Previous MI	156 (75%)	130 (68%)	0.151	122 (73%)	113 (68%)	0.338
Previous PCI	53 (25%)	47 (25%)	0.908	40 (24%)	40 (24%)	1
Reduced left ventricular systolic function (LVEF ≤ 40%)	60 (29%)	45 (23%)	0.256	50 (30%)	36 (22%)	0.103
Years from CABG, median (IQR)	10 [7–14]	12 [9–15]	0.002	10 [7–14]	12 [9–15]	0.003
Presentation						
Urgent procedure	102 (49%)	116 (60%)	0.021	97 (58%)	97 (58%)	1
Angina	106 (51%)	76 (40%)	0.061	70 (42%)	70 (42%)	0.899
NSTEMI	66 (32%)	80 (42%)		63 (38%)	66 (40%)	
STEMI	37 (18%)	36 (19%)		34 (20%)	31 (19%)	

CABG — coronary artery bypass graft; IQR — interquartile range; LVEF — left ventricular ejection fraction; MI — myocardial infarction; NSTEMI — non-ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention; STEMI — ST-segment elevation myocardial infarction; SVG — saphenous vein graft

Table 2. Lesion characteristics and procedural details, before and after matching.

Parameter	Before matching			After matching		
	Native coronary PCI (235)	SVG PCI (200)	P	Native coronary PCI (189)	SVG PCI (176)	P
Femoral access	121 (52%)	111 (56%)	0.441	93 (49%)	97 (55%)	0.295
Targeted vessel						
LM	28 (12%)	–	–	25 (13%)	–	–
LAD/diagonal	45 (19%)	48 (24%)		37 (20%)	42 (24%)	
LCX/OM	76 (32%)	83 (42%)		59 (31%)	76 (42%)	
RCA/PDA/PLV	86 (37%)	69 (33%)		68 (36%)	58 (33%)	
Lesion characteristic						
In-stent restenosis	26 (11%)	12 (6%)	0.087	18 (10%)	11 (6%)	0.245
True bifurcation	5 (1%)	–	–	5 (3%)	0	–
Graft aortic anastomosis	–	63 (31.5%)	–	–	58 (33%)	–
Graft body	–	119 (59.5%)		–	102 (58%)	–
Graft distal anastomosis	–	18 (9.0%)	–	–	16 (9%)	–

→

Table 2 (cont.). Lesion characteristics and procedural details, before and after matching.

Parameter	Before matching			After matching		
	Native coronary PCI (235)	SVG PCI (200)	P	Native coronary PCI (189)	SVG PCI (176)	P
Stents characteristics and TIMI flow						
Number of stents, median (IQR)	1 [1–2]	1 [1–1]	< 0.001	1 [1–2]	1 [1–1]	< 0.001
Length of stents [mm], median (IQR)	23 [16–32]	22 [16–28]	0.114	23.5 [17–32]	22 [16–28]	0.138
Diameter of stents [mm], median (IQR)	3 [2.75–3.5]	3.5 [3.0–4.0]	< 0.001	3.0 [2.75–3.5]	3.5 [3.0–4.0]	< 0.001
Bare metal stents	22 (10%)	42 (20%)	< 0.001	15 (8%)	37 (21%)	< 0.001
Drug eluting stents	201 (87%)	138 (69%)		164 (88%)	121 (69%)	
Drug eluting balloons	9 (4%)	19 (10%)		7 (4%)	17 (10%)	
Pre-procedural TIMI flow						
TIMI III flow	165 (70%)	135 (68%)	0.136	129 (68%)	120 (68%)	0.154
TIMI II flow	20 (9%)	14 (7%)		18 (10%)	10 (6%)	
TIMI I flow	7 (3%)	16 (8%)		7 (4%)	15 (9%)	
TIMI 0 flow	43 (18%)	35 (18%)		35 (19%)	31 (18%)	
Post-procedural TIMI flow						
TIMI III flow	233 (99%)	179 (90%)	< 0.001	187 (99%)	157 (89%)	< 0.001
TIMI II flow	1 (0.4%)	7 (4%)		1 (0.5%)	7 (4%)	
TIMI I flow	1 (0.4%)	6 (3%)		1 (0.5%)	5 (3%)	
TIMI 0 flow	0	8 (4%)		0	7 (4%)	
Contrast amount, median (IQR) [mL]	230 [170–320]	230 [160–310]	0.643	230 [175–320]	230 [160–300]	0.422
Fluoroscopy time, median (IQR) [min]	16.5 [11–25]	16.5 [11–24.5]	0.824	17.5 [11.5–25.75]	18 [11–26]	0.951

IQR — interquartile range; PCI — percutaneous coronary intervention; SVG — saphenous vein graft; TIMI — Thrombolysis in Myocardial Infarction

Table 3. Peri-procedural complications before and after matching.

Parameter	Before matching			After matching		
	Native coronary PCI (235)	SVG PCI (200)	P	Native coronary PCI (189)	SVG PCI (176)	P
No reflow	1 (0.4%)	19 (10%)	< 0.001	1 (0.5%)	16 (9%)	< 0.001
Dissection	7 (3%)	2 (1%)	0.188	6 (3%)	2 (1%)	0.286
Perforation	3 (1%)	0	–	2 (1%)	0	–
Intra-aortic balloon pump	6 (3%)	3 (2%)	0.337	6 (3%)	3 (2%)	0.505

PCI — percutaneous coronary intervention; SVG — saphenous vein graft

(p = 0.023), however the size of the difference was not large (median age 71 [63–76] vs. 71 [66–79] in native PCI and SVG PCI groups, respectively). On the other hand, after matching the presentation (stable angina or ACS) was equally distributed across the two groups. The lesion characteristics of matched patient groups were comparable to those prior to matching. Patients who underwent graft PCI had a significantly higher incidence of MACE (Fig. 1), principally driven by MI (Fig. 2)

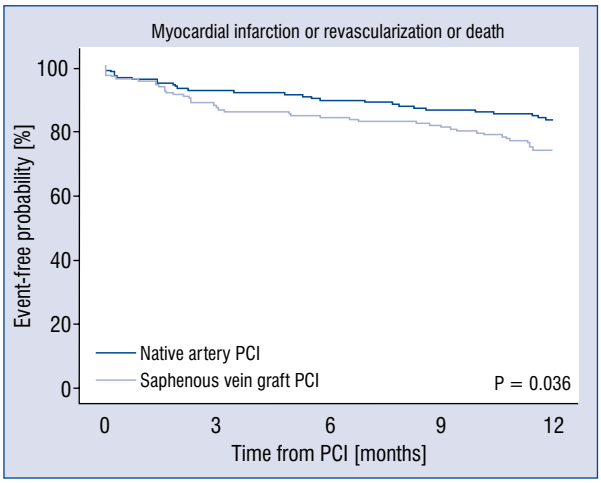


Figure 1. Myocardial infarction or revascularization or death after index percutaneous coronary intervention (PCI) in matched groups.

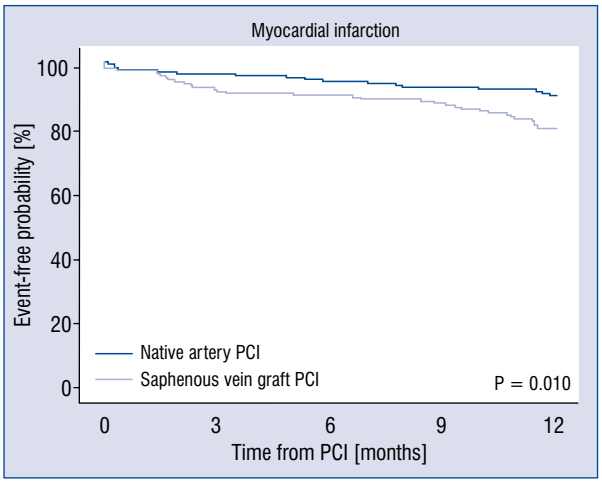


Figure 2. Myocardial infarction after index percutaneous coronary intervention (PCI) in matched groups.

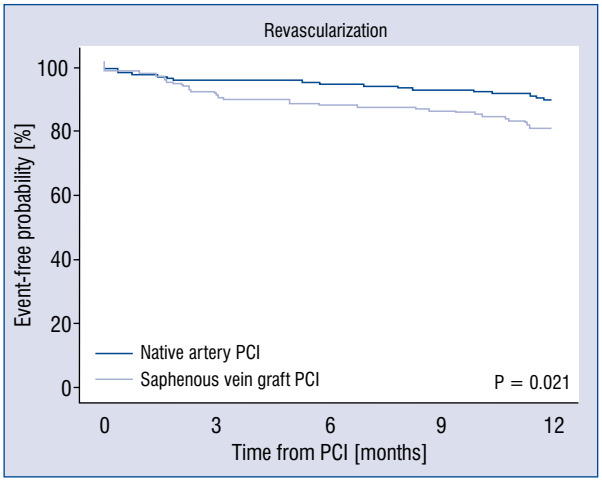


Figure 3. Revascularization after index percutaneous coronary intervention (PCI) in matched groups.

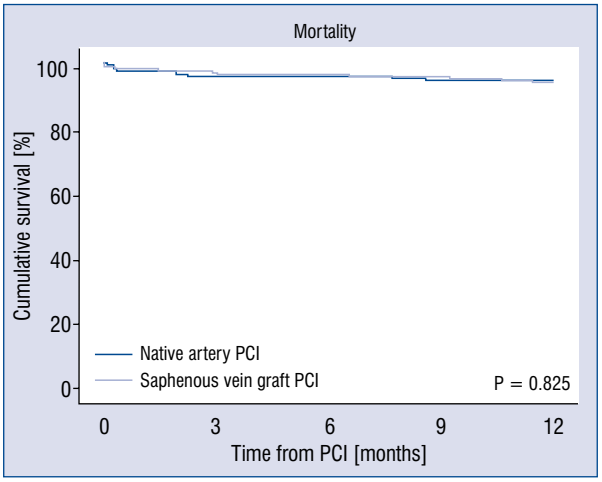


Figure 4. Mortality after index percutaneous coronary intervention (PCI) in matched groups.

and revascularization rate (Fig. 3), while there was no significant difference in mortality (Fig. 4).

In multivariable Cox regression analysis (Table 4) the only factor associated with MACE was graft PCI compared to native PCI (HR 1.725, 95% CI 1.049–2.837, p = 0.032). Age, urgency of the procedure, history of MI, diabetes, hypertension, hyperlipidemia, previous PCI, left ventricular ejection fraction, contrast amount used and fluoroscopy time were not significantly associated with MACE. Detailed Cox regression analyses on mortality, MI and revascularization are presented in Tables 5–7, respectively.

Discussion

This single-center study which compares outcomes of PCI in patients with previous CABG has a number of interesting findings. Although there was no statistical difference in the baseline demographics of the two patient groups (Table 1), SVG PCIs were more likely to be urgent procedures. To reduce selection bias, there was a preponderance of males in the present study (86%). There was an even greater disproportion as reported by Brilakis et al. (99% of males) [3]. This significant underrepresentation of females with prior CABG

Table 4. Multivariate Cox regression with regard to major adverse cardiac events in matched groups.

Parameter	Hazard ratio	95% CI	P
Age [years]	0.990	0.964–1.017	0.467
Type of procedure (urgent vs. elective)	0.913	0.551–1.513	0.724
Graft PCI vs. native PCI	1.725	1.049–2.837	0.032
History of MI	1.444	0.759–2.746	0.263
Previous PCI	1.677	0.966–2.912	0.066
Diabetes	0.972	0.536–1.761	0.925
Hypertension	1.440	0.728–2.847	0.294
Hyperlipidemia	1.240	0.713–2.157	0.446
Chronic kidney disease	1.403	0.741–2.656	0.299
Fluoroscopy time (1 min increase)	0.999	0.983–1.015	0.878
Contrast amount (1 mL increase)	1.001	0.999–1.004	0.254
LVEF (≤ 40%)	0.839	0.465–1.516	0.562

CI — confidence interval; MI — myocardial infarction; LVEF — left ventricular ejection fraction; PCI — percutaneous coronary intervention

Table 5. Multivariate Cox regression with regard to revascularization in matched groups.

Parameter	Hazard ratio	95% CI	P
Age [years]	0.964	0.933–0.995	0.025
Type of procedure (urgent vs. elective)	0.684	0.374–1.252	0.218
Graft PCI vs. native PCI	2.218	1.193–4.122	0.012
History of MI	1.650	0.737–3.691	0.223
Previous PCI	1.824	0.953–3.493	0.070
Diabetes	0.972	0.581–2.487	0.925
Hypertension	1.003	0.453–2.222	0.994
Hyperlipidemia	0.994	0.498–1.983	0.986
Chronic kidney disease	1.257	0.741–2.656	0.582
Fluoroscopy time (1 min increase)	0.998	0.977–1.020	0.867
Contrast amount (1 mL increase)	1.000	0.997–1.004	0.853
LVEF (≤ 40%)	0.953	0.472–1.923	0.893

CI — confidence interval; MI — myocardial infarction; LVEF — left ventricular ejection fraction; PCI — percutaneous coronary intervention

Table 6. Multivariate Cox regression with regard to myocardial infarction in matched groups.

Parameter	Hazard ratio	95% CI	P
Age [years]	0.996	0.964–1.028	0.791
Type of procedure (urgent vs. elective)	1.349	0.715–2.544	0.355
Graft PCI vs. native PCI	2.248	1.220–4.142	0.009
History of MI	1.226	0.600–2.506	0.576
Previous PCI	1.425	0.732–2.772	0.297
Diabetes	0.910	0.455–1.821	0.790
Hypertension	2.112	0.913–4.883	0.081
Hyperlipidemia	0.885	0.472–1.656	0.701
Chronic kidney disease	1.667	0.804–3.454	0.169
Fluoroscopy time (1 min increase)	1.001	0.984–1.018	0.924
Contrast amount (1 mL increase)	1.001	0.998–1.004	0.413
LVEF (≤ 40%)	1.152	0.593–2.238	0.675

CI — confidence interval; MI — myocardial infarction; LVEF — left ventricular ejection fraction; PCI — percutaneous coronary intervention

Table 7. Multivariate Cox regression with regard to mortality in matched groups.

Parameter	Hazard ratio	95% CI	P
Age [years]	1.047	0.990–1.107	0.107
Type of procedure (urgent vs. elective)	0.684	0.537–5.495	0.361
Graft PCI vs. native PCI	1.118	0.435–2.870	0.817
History of MI	1.327	0.403–4.370	0.642
Previous PCI	0.913	0.282–2.954	0.879
Diabetes	0.900	0.303–2.674	0.850
Hypertension	4.859	0.564–4.829	0.150
Hyperlipidemia	1.942	0.660–5.719	0.228
Chronic kidney disease	2.296.	0.809–6.513	0.118
Fluoroscopy time (1 min increase)	1.005	0.983–1.028	0.642
Contrast amount (1 mL increase)	1.004	1.000–1.008	0.060
LVEF (≤ 40%)	0.840	0.262–2.694	0.769

CI — confidence interval; MI — myocardial infarction; LVEF — left ventricular ejection fraction; PCI — percutaneous coronary intervention

in need of subsequent PCI reported in studies to date warrants further prospective assessment. In the current study there was a relatively high percentage of radial approach (47%) in comparison to the other reported studies [4]. RADIAL-CABG Trial [5] was a randomized prospective study which suggested that diagnostic angiography using radial access compared with femoral access was associated with greater contrast use, longer procedure and fluoroscopy time as well as greater patient and operator radiation exposure. However, no significant differences in these parameters were observed among patients undergoing PCI in the present study. Other studies suggested that a radial approach is feasible and is as fast as the femoral approach [6, 7]. It was noted that venous grafts were more likely to be the PCI target vessel with increasing time after CABG, consistent with the accelerated pace of late saphenous venous graft failure [8]. Nearly all target bypass grafts were SVG, a reflection of the excellent outcomes achieved with use of internal mammary arteries [9, 10]. Radial-artery grafts have a lower rate of graft occlusion at 1-year than SVGs [11]. We would thus advocate a randomized study to compare the outcomes of conventional CABG versus a hybrid approach where only arterial grafts would be used, plus PCI for the other vessels. It was found that patients who underwent bypass graft rather than native coronary PCI were more likely to receive BMS. The benefits of drug eluting stents (DES) over BMS in venous graft interventions are still controversial. The DIVA study [12], which is the most recent randomized trial included 597 patients undergoing PCI of de-novo SVG lesions. There was no significant difference in 12-month and long-term (median 2.7 years) incidence of cardiac death, target vessel MI or target vessel revascularization (TVR). DES implantation was associated with improved results in ISAR-CABG trial which randomized 610 patients with diseased SVG to DES or BMS and reported that DES were associated with favorable hard endpoint outcomes (15.4% vs. 22.1%; p = = 0.03) [13]. The stenting of saphenous vein grafts trial (SOS), also demonstrated a significant reduction in MACE rates with paclitaxel-eluting stents compared with BMS, which was mainly driven by lower target lesion revascularization (TLR) rates [14]. Sirolimus-eluting stents were studied in the Reduction of Restenosis In Saphenous Vein Grafts With Cypher Sirolimus-eluting Stent RRISC trial [15], which demonstrated a reduction in TLR and TVR, and late stent loss in the DES group compared with the BMS group at 6 months. Conversely, the DELAYED RRISC study [16] found the TVR benefit was lost at 3-year follow-up and BMS was associated with lower long-term mortality. In the present study, no-reflow was significantly higher in graft PCI compared to native artery PCI (10% vs. 0.4%; p < 0.001). Venous graft PCI was an independent risk factor for the peri-procedural complications including no-reflow [17], especially if the presentation was ST-segment elevation MI [18]. From our real-world data, SVG PCI carried a higher risk of MACE at 1 year when compared with native coronary PCI, that was mainly driven by MI and TVR. All of the efforts need to be taken into consideration to attempt native coronary revascularization. Percutaneous revascularization of CTO continues to gain popularity and accept-

ance despite its risk and complexity. Techniques have improved with the increasing availability of new equipment as previous studies showed favorably high success rates for CTO PCI even in previously bypassed patients [19–21]. SVG can be used to attempt CTO PCI via the retrograde approach as shown in a previous study [22]. Anatomic complexity in patients with previous CABG might adversely impact in the outcome of chronic coronary occlusions PCI [23]. Redo CABG carries a higher mortality rate compared with first-time CABG [24, 25]. In post-CABG patients, PCI was associated with better survival compared to redo CABG [26]. Another study suggested no difference in survival between redo CABG and PCI, however, PCI was associated with a higher revascularization rate [27]. Overall, redo CABG could be considered as an option for revascularization especially if the arterial graft (i.e. left anterior mammary artery; LIMA) was not used during the first CABG.

Limitations of the study

Firstly, it was a retrospective study and not a prospective randomized trial and hence was subject to all the limitations of observational studies. Secondly, the choice of PCI target was dependent on the judgement of the operator. Thirdly, some patient data may have been missed since not all patients were routinely followed up at 12 months post-procedure.

Conclusions

The present study findings would currently support considering PCI in the native vessel rather than the failing venous graft in patients with previous CABG. Further work however is needed and, in this respect, the currently ongoing PROCTOR study, a multi-center, prospective trial is randomizing patients to native vessel versus venous graft PCI [28].

Conflict of interest: None declared

References

1. Motwani JG, Topol EJ. Aortocoronary saphenous vein graft disease: pathogenesis, predisposition, and prevention. Circulation. 1998; 97(9): 916–931, doi: 10.1161/01.cir.97.9.916, indexed in Pubmed: 9521341.
2. Lytle BW, Loop FD, Cosgrove DM, et al. Fifteen hundred coronary reoperations. Results and determinants of early and late survival. J Thorac Cardiovasc Surg. 1987; 93(6): 847–859, indexed in Pubmed: 3494885.
3. Brilakis ES, O'Donnell CI, Penny W, et al. Percutaneous coronary intervention in native coronary arteries versus bypass grafts in patients with prior coronary artery bypass graft surgery: Insights From the veterans affairs clinical assessment, reporting, and tracking program. JACC Cardiovasc Interv. 2016; 9(9): 884–893, doi: 10.1016/j.jcin.2016.01.034, indexed in Pubmed: 27085582.
4. Kinnaird T, Anderson R, Gallagher S, et al. Vascular access site and outcomes in 58,870 patients undergoing percutaneous coronary intervention with a previous history of coronary bypass surgery: results from the british cardiovascular interventions society national database. JACC Cardiovasc Interv. 2018; 11(5): 482–492, doi: 10.1016/j.jcin.2017.12.020, indexed in Pubmed: 29519382.
5. Michael TT, Alomar M, Papayannis A, et al. A randomized comparison of the transradial and transfemoral approaches for coronary artery bypass graft angiography and intervention: the RADIAL-CABG Trial (RADIAL Versus Femoral Access for Coronary Artery Bypass Graft Angiography and Intervention). JACC Cardiovasc Interv. 2013; 6(11): 1138–1144, doi: 10.1016/j.jcin.2013.08.004, indexed in Pubmed: 24139930.
6. Rathore S, Roberts E, Hakeem AR, et al. The feasibility of percutaneous transradial coronary intervention for saphenous vein graft lesions and comparison with transfemoral route. J Interv Cardiol. 2009; 22(4): 336–340, doi: 10.1111/j.1540-8183.2009.00479.x, indexed in Pubmed: 19689657.
7. Bundhoo SS, Earp E, Ivanauskiene T, et al. Saphenous vein graft percutaneous coronary intervention via radial artery access: safe and effective with reduced hospital length of stay. Am Heart J. 2012; 164(4): 468–472, doi: 10.1016/j.ahj.2012.07.029, indexed in Pubmed: 23067903.
8. Fitzgibbon GM, Kafka HP, Leach AJ, et al. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. J Am Coll Cardiol. 1996; 28(3): 616–626, doi: 10.1016/0735-1097(96)00206-9, indexed in Pubmed: 8772748.
9. Goldman S, Zadina K, Moritz T, et al. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery: results from a Department of Veterans Affairs Cooperative Study. J Am Coll Cardiol. 2004; 44(11): 2149–2156, doi: 10.1016/j.jacc.2004.08.064, indexed in Pubmed: 15582312.
10. Tatoulis J, Buxton BF, Fuller JA. Patencies of 2127 arterial to coronary conduits over 15 years. Ann Thorac Surg. 2004; 77(1): 93–101, doi: 10.1016/s0003-4975(03)01331-6, indexed in Pubmed: 14726042.
11. Desai ND, Miwa S, Kodama D, et al. A randomized comparison of radial-artery and saphenous-vein coronary bypass grafts. N Engl J Med. 2004; 351(22): 2302–2309, doi: 10.1056/NEJMoa040982, indexed in Pubmed: 15564545.
12. Brilakis ES, Edson R, Bhatt DL, et al. Drug-eluting stents versus bare-metal stents in saphenous vein grafts: a double-blind, randomised trial. Lancet. 2018; 391(10134): 1997–2007, doi: 10.1016/S0140-6736(18)30801-8, indexed in Pubmed: 29759512.
13. Colleran R, Kufner S, Mehilli J, et al. Efficacy over time with drug-eluting stents in saphenous vein graft lesions. J Am Coll Cardiol. 2018; 71(18): 1973–1982, doi: 10.1016/j.jacc.2018.03.456, indexed in Pubmed: 29724350.
14. Brilakis ES, Lichtenwalter C, Abdel-karim ArR, et al. Continued benefit from paclitaxel-eluting compared with bare-metal stent implantation in saphenous vein graft lesions during long-term follow-up of the SOS (Stenting of Saphenous Vein Grafts) trial.

JACC Cardiovasc Interv. 2011; 4(2): 176–182, doi: 10.1016/j.jcin.2010.10.003, indexed in Pubmed: 21349456.
15. Vermeersch P, Agostoni P, Verheye S, et al. Randomized double-blind comparison of sirolimus-eluting stent versus bare-metal stent implantation in diseased saphenous vein grafts: six-month angiographic, intravascular ultrasound, and clinical follow-up of the RRISC Trial. J Am Coll Cardiol. 2006; 48(12): 2423–2431, doi: 10.1016/j.jacc.2006.09.021, indexed in Pubmed: 17174178.
16. Vermeersch P, Agostoni P, Verheye S, et al. Increased late mortality after sirolimus-eluting stents versus bare-metal stents in diseased saphenous vein grafts: results from the randomized DELAYED RRISC Trial. J Am Coll Cardiol. 2007; 50(3): 261–267, doi: 10.1016/j.jacc.2007.05.010, indexed in Pubmed: 17631219.
17. Januszek RA, Dziewierz A, Siudak Z, et al. Predictors of periprocedural complications in patients undergoing percutaneous coronary interventions within coronary artery bypass grafts. Cardiol J. 2019; 26(6): 633–644, doi: 10.5603/CJ.a2018.0044, indexed in Pubmed: 29671862.
18. Welsh RC, Granger CB, Westerhout CM, et al. Prior coronary artery bypass graft patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. JACC Cardiovasc Interv. 2010; 3(3): 343–351, doi: 10.1016/j.jcin.2009.12.008, indexed in Pubmed: 20298996.
19. Galassi AR, Sianos G, Werner GS, et al. Retrograde Recanalization of Chronic Total Occlusions in Europe: Procedural, In-Hospital, and Long-Term Outcomes From the Multicenter ERCTO Registry. J Am Coll Cardiol. 2015; 65(22): 2388–2400, doi: 10.1016/j.jacc.2015.03.566, indexed in Pubmed: 26046732.
20. Dautov R, Manh Nguyen C, Altisent O, et al. Recanalization of chronic total occlusions in patients with previous coronary bypass surgery and consideration of retrograde access via saphenous vein grafts. Circ Cardiovasc Interv. 2016; 9(7), doi: 10.1161/CIRCINTERVENTIONS.115.003515, indexed in Pubmed: 27418611.
21. Michael TT, Karmpaliotis D, Brilakis ES, et al. Impact of prior coronary artery bypass graft surgery on chronic total occlusion revascularisation: insights from a multicentre US registry. Heart. 2013; 99(20): 1515–1518, doi: 10.1136/heartjnl-2013-303763, indexed in Pubmed: 23598543.
22. Nguyen-Trong PKJ, Alaswad K, Karmpaliotis D, et al. Use of saphenous vein bypass grafts for retrograde recanalization of coronary chronic total occlusions: insights from a multicenter registry. J Invasive Cardiol. 2016; 28(6): 218–224, indexed in Pubmed: 27236005.
23. Teramoto T, Tsuchikane E, Yamamoto M, et al. Successful revascularization improves long-term clinical outcome in patients with chronic coronary total occlusion. Int J Cardiol Heart Vasc. 2017; 14: 28–32, doi: 10.1016/j.ijcha.2016.11.001, indexed in Pubmed: 28616560.
24. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. ESC Scientific Document Group, ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019; 40(2): 87–165, doi: 10.1093/eurheartj/ehy394, indexed in Pubmed: 30165437.
25. Parasca CA, Head SJ, Milojevic M, et al. Incidence, characteristics, predictors, and Outcomes of repeat revascularization after percutaneous coronary intervention and coronary artery bypass grafting: the SYNTAX trial at 5 years. JACC Cardiovasc Interv. 2016; 9(24): 2493–2507, doi: 10.1016/j.jcin.2016.09.044, indexed in Pubmed: 28007201.
26. Morrison DA, Sethi G, Sacks J, et al. Percutaneous coronary intervention versus repeat bypass surgery for patients with medically refractory myocardial ischemia: AWESOME randomized trial and registry experience with post-CABG patients. J Am Coll Cardiol. 2002; 40(11): 1951–1954, doi: 10.1016/s0735-1097(02)02560-3, indexed in Pubmed: 12475454.
27. Harskamp R, Beijk M, Damman P, et al. Clinical outcome after surgical or percutaneous revascularization in coronary bypass graft failure. J Cardiovasc Med. 2013; 14(6): 438–445, doi: 10.2459/jcm.0b013e328356a4fc.
28. https://clinicaltrials.gov/ct2/show/NCT03805048 (last accessed 08.01.2020).

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 3, 405–412
DOI: 10.5603/CJ.a2022.0031

ISSN 1897–5593
eISSN 1898–018X

Use of single pill combinations in the treatment of arterial hypertension in Poland: The current practice and guidelines, the impact on reimbursement spending and patient co-payment

Marcin Czech[1], Stefan Boguslawski[2], Anna Smaga[2], Krzysztof J. Filipiak[3]

[1]Department of Pharmacoeconomics, the Institute of Mother and Child, Warsaw, Poland
[2]Department of Population Health Monitoring and Analysis, the National Institute of Public Health NIH — National Research Institute, Warsaw, Poland
[3]Maria Sklodowska-Curie Medical Academy, Warsaw, Poland

Abstract

Background: *Clinical guidelines recommend using single pill combinations (SPC) when initiating and intensifying the treatment of arterial hypertension (AH), which is not reflected in the Summaries of Product Characteristics (SMPC) for individual preparations. The drug reimbursement system in Poland (with a few exceptions) does not provide for reimbursement outside the indications specified in the SMPC. Therefore, it excludes the use of SPC under reimbursement. In 2020 the share of SPC in the treatment of AH amounted to 12.8% of unit volume and was lower than the 80% based on the guidelines of the Polish Society of Hypertension.*

Methods: *Using the data from a sample of pharmacies in Poland over the period November–December 2020, the potential was assessed of switching from existing AH therapy with monocomponent drugs containing selected combinations of active ingredients to the equivalent SPC.*

Results: *The potential of switching from AH treatment in the analyzed period using monocomponent drugs with the equivalent SPC amounted to 19% of unit volume (a reduction of 212M units), with the highest switch potential (43.9%) for drugs containing amlodipine. The public payer's savings would be EUR 12.3 million and patient savings would amount to EUR 5.0 million.*

Conclusions: *Enabling reimbursement of SPC in Poland in line with the clinical guidelines can significantly increase the share of SPC in the treatment of AH, which will result in better health outcomes and a significant reduction in the payer's drug reimbursement spending and will lower the financial barrier for patients to access this type of treatment.* (Cardiol J 2022; 29, 3: 405–412)

Key words: hypertension, treatment, single pill combination

Introduction

The way single pill combinations (SPC) are reimbursed in Poland affects clinical practice in the treatment of arterial hypertension (AH), thus hindering the implementation of the guidelines of scientific societies. It restricts their introduction into therapy, which according to numerous studies has a negative impact on health outcomes, while unnecessarily increasing the costs incurred by the

Address for correspondence: Dr. Stefan Boguslawski, Department of Population Health Monitoring and Analysis, the National Institute of Public Health NIH — National Research Institute, ul. Chocimska 24, 00–791 Warszawa, Poland, tel/fax: +48 22 5421298, e-mail: sboguslawski@pzh.gov.pl

Received: 26.10.2021 Accepted: 6.05.2022 Early publication date: 13.05.2022

public payer — the National Health Fund (NFZ) and patients [1–6]. The purpose of the analysis was to estimate the size of the hypertension treatment segment in Poland, which according to the current guidelines of scientific societies [7–9] may experience an increase in the share of SPC. A simulation of switching from the already existing therapy comprising two or three monocomponent drugs to SPC was carried out, keeping the equivalence of the used active ingredients and the doses within the range of hypotensive preparations available in the Polish reimbursement system. Additionally, potential economic benefits for patients and the NFZ resulting from the switch were also calculated.

Arterial hypertensoin is one of the most prevalent risk factors for cardiovascular complications in the population [10–15]. The epidemiological situation in the world and in Poland is poor in this regard, with the situation in Poland having deteriorated in recent decades [11–20]. The number and the percentage of AH patients are increasing, while the percentage of patients with well-controlled blood pressure is still low [13, 16, 17]. On the other hand, the appropriate pharmacotherapy reduces the risk of AH-related complications by up to 40% [21, 22]. In particular, using SPC in line with the guidelines has been instrumental in achieving better health outcomes from AH treatment in countries with comprehensive AH programs (Portugal, Spain) [1–5, 23–25].

The guidelines of the European Society of Cardiology/the European Society of Hypertension (ESC/ESH) published in 2018 [7] have changed the rules of hypotensive treatment in Europe recommending that the treatment of the majority of AH patients be initiated with two-component SPC (first step of treatment) and a switch to three-component SPC in the second step of treatment. Initiating treatment with monotherapy has been reserved for rare, strictly defined situations, therefore it can be assumed that practically all patients with AH should be treated with SPC [8].

The basic two-component SPC used to initiate the treatment of AH patients include:

— angiotensin-converting enzyme (ACE) inhibitors with dihydropyridine calcium antagonist;
— ACE inhibitors with a diuretic (optimally thiazide-like diuretic);
— sartans with a diuretic;
— sartans with a calcium antagonist.

The basic three-component SPC are:

— ACE inhibitors with a diuretic and a calcium antagonist;
— sartans with a diuretic and a calcium antagonist.

The value of using SPC at the beginning of AH therapy particularly strongly implies the need to increase the availability of SPC preparations for AH patients in every country and the simplification of therapy intensification with a quick shift to three-component therapy, although Summaries of Product Characteristics (SMPC) of many SPC lack indications for their use in line with guidelines. The guidelines of the Polish Society of Hypertension (PTNT) published in 2019 [8] have also adopted the same algorithms, emphasising that in the case of approximately 60% of AH patients well controlled pressure is achieved with increasing doses of two hypotensive drugs and in the case of 20% of AH patients — with three drugs i.e., a three-component SPC. This means that at least 80% of AH patients should be treated with SPC in the given country. The PTNT guidelines [8] have assumed that almost all AH patients under 65 years of age should start treatment with a two-component SPC.

Therapy initiation with a two-component SPC is also recommended to patients aged 65–80 (stage 2/3 hypertension; some patients with stage 1 hypertension). Its introduction is also recommended in second step of treatment (other patients with stage 1 hypertension). PTNT suggests introducing a two-component SPC at the onset of treatment (stage 3 hypertension) or as a second step treatment (other patients) even for patients in their ninth and later decades of life.

The strengths of using SPC include: a lower number of units taken by the patient, better tolerability of treatment, convenience of use, improved patient compliance, quicker blood pressure control, demonstrated better arterial pressure control in the population [1–3, 23–25]. Compared to those who use the same active ingredients, in the same doses, but in separate units, patients taking SPC show: better adherence, a strong trend towards greater persistence in treatment continuation, a greater arterial pressure reduction, and greater pressure normalization [4, 5].

Despite the educational efforts of PTNT, SPC are still too rarely used in the treatment of AH in Poland. In 2020 6.1 billion units of drugs used in AH were sold in retail pharmacies in Poland, including 0.8 billion SPC units (Table 1). The share of SPC has been steadily increasing — in 2020 it amounted to 12.8% of the sales volume, in units (Table 2).

Paradoxically, the legal changes introduced in Poland by the Reimbursement Act in 2011 have restricted the possibility of using SPC in the treatment of AH. Prior to its entry going into force, when using a drug included in the list of

Table 1. Sale of monocomponent drugs and single-pill combination (million units).

	2016	2017	2018	2019	2020
Monocomponent drugs	4,952.3	4,925.3	4,987.7	5,278.2	5,301.2
Single-pill combination	580.0	620.4	662.8	733.9	775.8
Total	5,532.2	5,545.7	5,650.5	6,012.1	6,077.0

Table 2. Share of monocomponent drugs and single-pill combination in units.

	2016	2017	2018	2019	2020
Monocomponent drugs	89.5%	88.8%	88.3%	87.8%	87.2%
Single-pill combination	10.5%	11.2%	11.7%	12.2%	12.8%

reimbursed drugs a physician could rely on either the indications specified in SMPC, current medical knowledge or scientific evidence. After the Reimbursement Act entered into force the drugs can be reimbursed for the full or limited range of indications registered within the SMPC at the time of the respective reimbursement decision. It can also be reimbursed for a specific indication defined by the clinical condition outside SMPC, as long as this condition is precisely indicated by the reimbursement list. Almost 100% of SPC have substitution indications in their SMPC, which are not in line with Evidence Based Medicine (EBM) or guidelines of scientific societies. Hence, the availability of SPC within the reimbursement system in Poland has gone down, because they can be prescribed with reimbursement in accordance with their SMPC i.e., in the treatment of AH, only in a substitution indication. In practice, following therapy initiation (typically, with one drug), a patient (in the absence of control) gets two monocomponent drugs, which are subsequently, if necessary, replaced by a corresponding SPC.

At the same time, in line with the existing financing rules, the public payer reimburses the drug at the level of monotherapy — just one, the most expensive component of the SPC with two or three active ingredients. Public financing of SPC is limited to the cost of the monotherapy, on which the limit is based, by applying the rule of 1+1=1 or 1+1+1=1, which increases the level of patient co-payment for such drugs, hence reducing their availability. Hence, it is worth noting that when applying the substitution principle, the payer often finances two monocomponent drugs (separate units) instead of paying for one SPC containing the same two components in one unit.

Widening the scope of SPC reimbursement with the indications in line with the current guidelines will significantly increase their use, which will have a positive impact on health outcomes, while reducing the amounts allocated by the NFZ to the reimbursement of drugs used in the treatment of AH and the level of patient co-payments.

Methods

Source of data

The analyses were carried out using data from the pharmacy panel of PEX PharmaSequence, which in the period November–December 2020 included 6,100 retail pharmacies and pharmacy points. The sample is representative for the all-Poland population of retail pharmacies (13,395 pharmacies and pharmacy points as of December 2020), the 16-county coverage varies from 42% to 53%. Its sample structure is controlled in terms of geographical distribution, sales volume, and pharmacy chain affiliation. The raw data are projected to the national level and the difference versus census reimbursement data from NFZ is measured, indicating insignificant volume deviation (< 1% to < 5% depending on the individual product sales volume). Transaction data are automatically and continuously extracted from IT systems. To prepare this analysis, data from receipts issued by pharmacies was used to determine the different combinations co-occurrence rate of active ingredients and doses at the level of the anonymised unique patient and doctor ID. The analysis was based on the data of more than 2 million transactions (single receipts) concluded in the period November–December 2020, within which patients bought at least one hypotensive drug. The transac-

Table 3. Combinations of two active ingredients in single-pill combination used in hypotensive therapy — included in the reimbursement lists and covered by the analysis.

	Amlodipine	Felodipine	Indapamide	Hydrochlorothiazide
Amiloride				(excluded from the analysis)
Indapamide	X			
Ramipril	X	X (excluded felodipine 2.5 mg)		X
Cilazapril				X
Lisinopril	X			X
Perindopril	X		X (excluded indapamide 0.625 mg + perindopril 2.5 mg)	
Candesartan	X			X
Losartan	X			X
Telmisartan	X			X
Valsartan	X			X

tion data also provided information on the number of packs of hypotensive drugs sold split by active ingredient and dose, as well as on the share of sales for packs dispensed within the list of free drugs for persons over 75.

Choice of active ingredients

The analysis was carried out on all SPC included in the reimbursement list in November–December 2020, which contain active ingredients from the group of basic hypotensive therapies listed in the guidelines of the PTNT [8] (drugs with a proven impact on prognosis, recommended in combination therapy and available in the form of SPC, and used in monotherapy in specific situations), i.e., thiazide diuretics, beta-adrenolitics, calcium antagonists, ACE inhibitors, AT_1 receptor antagonists (sartans).

On the basis of the 18 reimbursed combinations of active substances including the above-named drug groups, further analyses were carried out on products containing 12 active ingredients: amlodipine, candesartan, cilazapril, felodipine, hydrochlorothiazide, indapamide, lisinopril, losartan, perindopril, ramipril, telmisartan, and valsartan (Table 3).

Due to the lack of registration for AH monotherapy and the actual market unavailability, amiloride was excluded from the analyses. A combination of small dose indapamide and perindopril (i.e., 0.625 mg and 2.5 mg) was also excluded from the analyses due to the registration indications according to which the combination that can be used for AH therapy initiation — and is therefore not affected by the restriction, which is the subject of this analysis. A combination of felodipine 2.5 mg with other active ingredients was also excluded due to the actual market unavailability of drugs with this dose for use in monotherapy. Moreover, the analysis included a three-component SPC including amlodipine, hydrochlorothiazide, and valsartan.

Method description

The analytical work carried out consisted of the following stages:

1. Determining the rate of using monocomponent drugs, which can be replaced by reimbursed SPC on the basis of items appearing on a single receipt with a single patient code and prescribed by a single physician;
2. Estimating the maximum potential switch from concomitantly purchased monocomponent drugs to SPC by applying an iterative switch algorithm seeking to reflect the SPC sales structure over the observed period in order to avoid arbitrariness in the allocation to a particular SPC. For the purpose of the analysis, it was assumed that all the therapies, which are currently carried out using two or three monocomponent drugs can be switched over to the SPC equivalent in terms of active ingredients and doses. The result of the switch algorithm was the number of units within the molecule-doses of SPC that can replace the current monocomponent therapy;
3. Calculating the cost, for the payer and the patient, of buying monocomponent drugs, which can be replaced or the potential cost of purchasing SPC, which can be used instead;
4. Estimating a reduction in the number of units/packs purchased following the potential switch.

Table 4. Potential of switching from monocomponent drugs to single-pill combination (SPC) (per year).

Active ingredient	Number of units per year (+000)	Potential of the switch to SPC — units (+000)	Potential of the switch (%)	Potential of the switch to SPC — packs* (+000)
Amlodipine	381,591.4	167,503.5	43.9%	5,583.5
Candesartan	55,706.0	4,504.3	8.1%	150.1
Cilazapril	5,828.7	43.6	0.7%	1.5
Felodipine	847.7	44.7	5.3%	1.5
Hydrochlorothiazide	22,742.1	4,133.6	18.2%	137.8
Indapamide	404,952.9	63,919.3	15.8%	2,130.6
Lisinopril	46,561.5	4,940.5	10.6%	164.7
Losartan	71,635.5	7,236.5	10.1%	241.2
Perindopril	161,070.7	36,339.8	22.6%	1,211.3
Ramipril	600,772.4	66,335.5	11.0%	2,211.2
Telmisartan	207,786.2	18,445.9	8.9%	614.9
Valsartan	123,238.3	12,990.9	10.5%	433.0
Total	2,082,733.4	386,438.1	18.6%	12,881.3

*30-tab pack equivalents estimated on the basis of the number of units

The financial impact of the switch for the public payer and the patient was determined using retail prices/co-payment by NFZ and patients per unit, taking into account the weights resulting from the volume of individual reimbursed packs in the period November–December 2020. The reimbursement list in Poland changes every 2 months in terms of the composition and the patient co-payment level, impacting the individual products share within the reference price groups. Therefore, the period of 2 months was chosen for the analysis, as the individual products share stayed stable during this period. An estimate of the approximate impact of the switch on a 12-month basis was obtained by multiplying the data obtained by 6. It was possible as the bimonthly SPC volume share (within AH products group) variation to the 2020 average did not exceed 1.2%.

Results

Potential of the switch

The estimated switch potential for the analysed active ingredients amounts to 18.6% of monocomponent units. The highest, in terms of the share and the number of units, potential switch exists for amlodipine — 43.9% of the currently sold units, 167.5 million units, which accounts for 5.6 million 30-unit packs. In terms of the volume of the potential switch, the next active ingredients are ramipril, indapamide, and perindopril (Table 4).

Assuming the switch potential is realized, the unit sales volume for the SPC included in the analysis would increase by 31.3%. The highest increase in the number of units sold would be for amlodipine and ramipril SPC and amlodipine and indapamide SPC (together 55.8% of the potential increase in the number of packs sold) (Table 5).

The impact of the switch on patients' and the public payer's spending and the number of units bought

Replacing the existing politherapies using monocomponent drugs with equivalent SPC available within the reimbursement system would reduce the total annual cost of hypotensive treatment in Poland by EUR 12.3 million (PLN 55.3 million) from the public payer's perspective and by EUR 5.0 million (PLN 22.6 million) from patients' perspective. The NFZ savings would amount to EUR 8.4 million (PLN 37.9 million) and the savings for the Ministry of Health — EUR 3.9 million (PLN 17.4 million) within the budget dedicated to financing free drugs for people aged 75+ (Table 6). At the same time, due to therapy switch to SPC patients would buy almost 212 million units less per year, which might have a positive impact on compliance, thus generating improved health outcomes and reducing the cost concerning the treatment of AH-related complications. Realising the estimated scope of the switch would increase the share of SPC from 12.8% in 2020, to 17%.

Table 5. Potential change in the level of single-pill combination (SPC) purchases (per year).

Active ingredient	Number of units per year (+000)	Potential of the switch to SPC — units (+000)	Potential of the switch (%)	Potential of the switch to SPC — packs* (+000)
Amlodipine, candesartan	6,272.2	4,296.5	68.5%	143.2
Amlodipine, hydrochlorothiazide, valsartan	3,852.1	6.9	0.2%	0.2
Amlodipine, indapamide	21,847.5	42,378.6	194.0%	1,412.6
Amlodipine, lisinopril	15,244.9	4,629.6	30.4%	154.3
Amlodipine, losartan	1,791.4	6,897,3	385.0%	229.9
Amlodipine, perindopril	87,891.7	14,799.1	16.8%	493.3
Amlodipine, ramipril	70,411.3	65,439.6	92.9%	2,181.3
Amlodipine, telmisartan	11,543.8	17,446.9	151.1%	581.6
Amlodipine, valsartan	13,702.8	11,608.9	84.7%	387.0
Candesartan, hydrochlorothiazide	31,576.9	207.8	0.7%	6.9
Cilazapril, hydrochlorothiazide	170.4	43.6	25.6%	1.5
Felodipine, ramipril	1,378.6	44.7	3.2%	1.5
Hydrochlorothiazide, lisinopril	18,824.7	310.9	1.7%	10.4
Hydrochlorothiazide, losartan	43,835.7	339.1	0.8%	11.3
Hydrochlorothiazide, ramipril	8,919.9	851.1	9.5%	28.4
Hydrochlorothiazide, telmisartan	102,025.2	999.0	1.0%	33.3
Hydrochlorothiazide, valsartan	87,710.7	1,375.1	1.6%	45.8
Indapamide, perindopril	91,056.2.	21,540.7	23.7%	718.0
Total	618,055.9	193,215.6	31.3%	6,440.5

*30-tab pack equivalents estimated on the basis of the number of units

Table 6. Estimated annual savings connected with a polytherapy change in hypotensive treatment.

	Change in spending when switching to SPC million Euro (million PLN)
Public payer's spending, included:	–12.3 (–55.3)
reimbursement	–8.4 (–37.9)
subsidy for people aged 75+	–3.9 (–17.4)
Patients' spending	–5.0 (–22.6)

SPC — single-pill combination

Discussion

The analysis only takes into account the switches from the existing, currently carried out, therapies using several (two or three) active ingredients and does not take into account potential switches from monocomponent drugs to SPC containing different active ingredients. Therefore, the presented analytical approach can be deemed conservative. It is worth noting that once an incentive for wider use of SPC is offered by broadening reimbursed indications beyond possible switching covered by this analysis, additional uses of SPC will appear, which will result in a further reduction in the number of units taken by patients and savings for the payer and patients. In particular, this concerns:

— use of SPC instead of monotherapy for hypotensive therapy initiation; or
— use of SPC instead of monotherapy for therapy intensification (increasing a dose or the need to add another active ingredient).

Either of these situations will generate additional financial savings due to the mechanism where the financing limit is based on one molecule only.

The analysis only takes into account the direct cost of drug purchase. Apart from the immediate financial effect presented in this document, broadening indications for SPC reimbursement should also be expected to significantly influence the patient's compliance and persistence, and consequently to influence AH monitoring indicators, the incidence of AH-related complications and pre-mature deaths, as well as the related costs, including indirect costs. As shown by the results of the analysis carried out in 2015 concerning the appropriateness, under Polish conditions, of treating AH patients with an indapamide and amlodipine SPC compared to polytherapy, SPC therapy means additional 7.6 days of life in full health and extra 2.9 days of survival [4]. Despite the relatively low clinical effects per patient, if the total population of AH patients is considered clinical benefits can be significant.

Therefore, in Poland AH therapy using SPC is financed under the drug reimbursement system contrary to the latest medical knowledge, the guidelines, against the welfare of the patient (if there is an indication for polytherapy), and the financial interests of the payer.

Conclusions

The current SPC reimbursement status causes a significant dissonance between the recognized medical knowledge, which is in line with EBM principles in the field of hypertension and the resulting guidelines from national and international medical societies, and the regulations governing drug reimbursement. As a result, the treatment of AH patients is often inconsistent with the guidelines of scientific societies, thus compromising the health outcomes and leading to a sub-optimal allocation of scarce resources available in the reimbursement budget.

Conflict of interest: Marcin Czech — lecture fees, participation in satellite sessions, in Polish and European advisory groups, research grants and clinical trials sponsored by: AstraZeneca, Berlin Chemie Menarini, Sanofi, Servier; Stefan Boguslawski — consultancy projects for: Merck, Sanofi, Servier; Anna Smaga — consultancy projects for: Adamed, Merck, Sanofi, Servier; Krzysztof J. Filipiak — lecture fees, participation in satellite sessions, in Polish and European advisory groups, research grants and clinical trials sponsored by: Adamed, Alfasigma, Amgen, AstraZeneca, Bausch Health, Bayer, Berlin Chemie Menarini, Boehringer Ingelheim, Egis, Krka, Merck, Mylan, Sandoz, Sanofi, Servier, Zentiva.

References

1. Tsioufis K, Kreutz R, Sykara G, et al. Impact of single-pill combination therapy on adherence, blood pressure control, and clinical outcomes: a rapid evidence assessment of recent literature. J Hypertens. 2020; 38(6): 1016–1028, doi: 10.1097/HJH.0000000000002381, indexed in Pubmed: 32371789.
2. Weisser B, Predel HG, Gillessen A, et al. Single pill regimen leads to better adherence and clinical outcome in daily practice in patients suffering from hypertension and/or dyslipidemia: results of a meta-analysis. High Blood Press Cardiovasc Prev. 2020; 27(2): 157–164, doi: 10.1007/s40292-020-00370-5, indexed in Pubmed: 32219670.
3. Sicras Mainar A, Galera Llorca J, Muñoz Ortí G, et al. [Influence of compliance on the incidence of cardiovascular events and health costs when using single-pill fixed-dose combinations for the treatment of hypertension]. Med Clin (Barc). 2011; 136(5): 183–191, doi: 10.1016/j.medcli.2010.01.038, indexed in Pubmed: 21106209.
4. Kawalec P, Holko P, Stawowczyk E, et al. Economic evaluation of single-pill combination of indapamide and amlodipine in the treatment of arterial hypertension in the Polish setting. Kardiol Pol. 2015; 73(9): 768–780, doi: 10.5603/KP.a2015.0089, indexed in Pubmed: 25987296.
5. Baser O, Andrews LM, Wang Li, et al. Comparison of real-world adherence, healthcare resource utilization and costs for newly initiated valsartan/amlodipine single-pill combination versus angiotensin receptor blocker/calcium channel blocker free-combination therapy. J Med Econ. 2011; 14(5): 576–583, doi: 10.3111/13696998.2011.596873, indexed in Pubmed: 21728914.
6. Wierzejska E, Giernaś B, Lipiak A, et al. A global perspective on the costs of hypertension: a systematic review. Arch Med Sci. 2020; 16(5): 1078–1091, doi: 10.5114/aoms.2020.92689, indexed in Pubmed: 32863997.
7. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018; 39(33): 3021–3104, doi: 10.1093/eurheartj/ehy339, indexed in Pubmed: 30165516.
8. Tykarski A, Filipiak KJ, Januszewicz A, et al. Zasady postępowania w nadciśnieniu tętniczym — 2019 rok Wytyczne Polskiego Towarzystwa Nadciśnienia Tętniczego. Nadciśnienie Tętnicze w Praktyce. 2019; 5(1): 1–86.
9. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure In Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018; 71(6): e13–e115, doi: 10.1161/HYP.0000000000000065, indexed in Pubmed: 29133356.
10. Yusuf S, Joseph P, Rangarajan S, et al. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. Lancet. 2020; 395(10226): 795–808, doi: 10.1016/S0140-6736(19)32008-2, indexed in Pubmed: 31492503.
11. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 2020; 75(6): 1334–1357, doi: 10.1161/HYPERTENSIONAHA.120.15026, indexed in Pubmed: 32370572.

12. Waśkiewicz A, Zujko ME, Szcześniewska D, et al. Polyphenols and dietary antioxidant potential, and their relationship with arterial hypertension: A cross-sectional study of the adult population in Poland (WOBASZ II). Adv Clin Exp Med. 2019; 28(6): 797–806, doi: 10.17219/acem/91487, indexed in Pubmed: 30968608.
13. Hering D, Szymański FM. Comparison of hypertension epidemiology and treatment in Poland and Australia. Kardiol Pol. 2018; 76(3): 520–528, doi: 10.5603/KP.a2018.0002, indexed in Pubmed: 29313567.
14. Yang Q, Cogswell ME, Flanders WD, et al. Trends in cardiovascular health metrics and associations with all-cause and CVD mortality among US adults. JAMA. 2012; 307(12): 1273–1283, doi: 10.1001/jama.2012.339, indexed in Pubmed: 22427615.
15. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet. 2016; 387(10017): 435–443, doi: 10.1016/S0140-6736(15)00805-3, indexed in Pubmed: 26559744.
16. Niklas A, Flotyńska A, Puch-Walczak A, et al. Prevalence, awareness, treatment and control of hypertension in the adult Polish population - Multi-center National Population Health Examination Surveys - WOBASZ studies. Arch Med Sci. 2018; 14(5): 951–961, doi: 10.5114/aoms.2017.72423, indexed in Pubmed: 30154875.
17. Filipiak KJ, Tomaniak M, Płatek AE, et al. Negative predictors of treatment success in outpatient therapy of arterial hypertension in Poland. Results of the CONTROL NT observational registry. Kardiol Pol. 2018; 76(2): 353–361, doi: 10.5603/KP.a2017.0211, indexed in Pubmed: 29131289.
18. Rossier BC, Bochud M, Devuyst O. The hypertension pandemic: an evolutionary perspective. Physiology (Bethesda). 2017; 32(2): 112–125, doi: 10.1152/physiol.00026.2016, indexed in Pubmed: 28202622.
19. Mills KT, Bundy JD, Kelly TN, et al. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. Circulation. 2016; 134(6): 441–450, doi: 10.1161/CIRCULATIONAHA.115.018912, indexed in Pubmed: 27502908.
20. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nat Rev Nephrol. 2020; 16(4): 223–237, doi: 10.1038/s41581-019-0244-2, indexed in Pubmed: 32024986.
21. Mancia G. Hypertension: Does antihypertensive treatment have long-term benefits? Nat Rev Cardiol. 2012; 9(3): 130–132, doi: 10.1038/nrcardio.2012.11, indexed in Pubmed: 22310709.
22. Staessen JA, Thijisq L, Fagard R, et al. Effects of immediate versus delayed antihypertensive therapy on outcome in the Systolic Hypertension in Europe Trial. J Hypertens. 2004; 22(4): 847–857, doi: 10.1097/00004872-200404000-00029, indexed in Pubmed: 15126928.
23. Düsing R, Waeber B, Destro M, et al. Triple-combination therapy in the treatment of hypertension: a review of the evidence. J Hum Hypertens. 2017; 31(8): 501–510, doi: 10.1038/jhh.2017.5, indexed in Pubmed: 28230062.
24. Parati G, Kjeldsen S, Coca A, et al. Adherence to single-pill versus free-equivalent combination therapy in hypertension: a systematic review and meta-analysis. Hypertension. 2021; 77(2): 692–705, doi: 10.1161/HYPERTENSIONAHA.120.15781, indexed in Pubmed: 33390044.
25. Chrysant SG. Single-pill triple-combination therapy: an alternative to multiple-drug treatment of hypertension. Postgrad Med. 2011; 123(6): 21–31, doi: 10.3810/pgm.2011.11.2492, indexed in Pubmed: 22104451.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 3, 413–422
DOI: 10.5603/CJ.a2022.0012

ISSN 1897–5593
eISSN 1898–018X

Predictors of left atrial fibrosis in patients with atrial fibrillation referred for catheter ablation

Valentina A. Rossi[1]*, Iva Krizanovic-Grgic[1]*, Jan Steffel[1], Daniel Hofer[1], Thomas Wolber[1], Corinna B. Brunckhorst[1], Frank Ruschitzka[1], Firat Duru[1, 2], Alexander Breitenstein[1], Ardan M. Saguner[1]

[1]Department of Cardiology, University Heart Center, University Hospital Zurich, Switzerland
[2]Center for Integrative Human Physiology, University of Zurich, Switzerland

Abstract

Background: *Left atrial (LA) fibrosis in patients with atrial fibrillation (AF) is associated with an increased risk of AF recurrence after catheter ablation. Therefore, we searched for clinical risk factors that confer an increased risk of LA fibrosis, which can influence the treatment strategy.*

Methods: *We included 94 patients undergoing 3-dimensional electroanatomical voltage mapping-guided catheter ablation of AF. LA low-voltage areas during sinus rhythm as a surrogate parameter of fibrosis were measured with the CARTO3 mapping system and adjusted for LA volumes obtained by computed tomography. Blood tests including N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) and echocardiographic parameters of left ventricular function were also analyzed.*

Results: *Patients were 62.5 ± 11.4 years old, and 29% were female. LA fibrosis was present in 65%, with 50% having a fibrotic area > 5% (≥ Utah-Stage 1). Mean left ventricular ejection fraction (LVEF) was 53.9 ± 10.5%. Patients with LA fibrosis had higher NT-proBNP levels (869 ± 1056 vs. 552 ± ± 859 ng/L, p = 0.001) and larger LA volumes (body surface area-corrected 63.3 ± 19.3 vs. 80 ± ± 27.1 mL/m², p = 0.003). In univariable analyses, LA fibrosis was significantly associated with female gender, older age, increased LA volumes, hypertension, statin therapy, higher NT-proBNP values, and echocardiographic E/e'. In bivariable analyses, higher NT-proBNP, echocardiographic parameters of diastolic dysfunction, female gender, older age, and higher DR-FLASH scores remained as independent predictors of LA fibrosis.*

Conclusions: *In this single-center longitudinal study, surrogate parameters of elevated left-sided cardiac filling pressures such as higher NT-proBNP levels and higher echocardiographic E/e' values as well as female gender independently predicted the prevalence of LA fibrosis in patients referred for catheter ablation of AF.* (Cardiol J 2022; 29, 3: 413–422)

Key words: atrial fibrillation, heart failure with preserved ejection fraction, diastolic dysfunction, gender medicine, atrial fibrosis

Introduction

Atrial fibrillation (AF) is a common rhythm disorder affecting about 3% of adults [1]. Because left atrial (LA) fibrosis has been associated with an increased incidence of stroke and AF recurrence after catheter ablation, it is important to identify potentially modifiable risk factors for LA fibrosis, and to identify patients who may benefit less from catheter ablation of AF [2]. Recent studies have

Address for correspondence: PD Dr. med. Ardan M. Saguner, MD, Department of Cardiology, University Heart Center, Rämistrasse 100, 8091 Zurich, Switzerland, tel: +41-44-2552111, fax: +41-44-2554007, e-mail: ardansaguner@yahoo.de

Received: 9.11.2021 Accepted: 2.02.2022 Early publication date: 4.03.2022

**Valentina Rossi and Iva Krizanovic-Grgic contributed equally to this work.*

suggested an approximately 2-fold higher amount of LA fibrosis in women as compared to men, but it is unclear whether this finding is an independent gender-dependent effect or linked to other risk factors. Recently, the APPLE-score, which does not include female gender, has been suggested as a potential tool to predict LA fibrosis prior to catheter ablation of AF [3].

In previous studies, LA fibrosis was mainly assessed by cardiac magnetic resonance imaging (CMR) with late gadolinium enhancement. CMR uses a different non-invasive method to assess LA fibrosis as compared to invasive 3-dimensional (3D) electroanatomical voltage mapping (EAM) with assessment of bipolar low-voltage areas (LVA), which can be used as a surrogate parameter for myocardial fibrosis [4–7]. Furthermore, there is previous evidence of the usefulness of targeting LVA to successfully treat AF [8]. Therefore, we sought to identify clinical risk factors of LA fibrosis by using EAM in a cohort of patients referred for catheter ablation of AF.

Methods

Study population

In this longitudinal single-center study, out of a total of 634 patients receiving AF ablation at our center, 94 patients were included in this analysis. The remaining patients were excluded for the following reasons: 1) Only LA maps obtained during sinus rhythm were included; 2) Some AF ablations were performed using cryoballoon technology; 3) Some LA maps were created using the "point by point" method with insufficient LA mapping points; 4) For methodological reasons we included only patients in whom radiofrequency (RF) ablation was performed by three operators, because those three had the same mapping/ablation approach; 5) Patients with incomplete electroanatomical LA maps were excluded; 6) At the beginning of 2019, we had a system crash of our EAM Software and the backup of several months (including maps) was lost. Therefore, 94 consecutive patients undergoing a catheter ablation procedure for AF during sinus rhythm (SR) were enrolled between 2016 and 2021. All patients underwent pulmonary vein (PV) isolation (PVI) using endocardial RF ablation guided by 3D EAM of the LA. Different types of AF were defined according to current European guidelines [1]. The APPLE and DR-FLASH score were calculated as previously described [7, 9]. The CHA_2DS_2-VASc score was adjusted for gender (–1 point in females). Subjects with a reduced left ventricular ejection fraction (LVEF) < 40% or a known myocardial disease were assumed to have a diastolic dysfunction at least grade I in the absence of further documentation according to current guidelines [10]. This retrospective study was approved by the Ethics Committee of the Canton of Zurich (KEK-ZH-Nr.2016-00116).

Cardiac computed tomography

Cardiac computed tomography (cCT) was performed within < 48 h prior to the procedure to exclude LA thrombi and measure the LA volume. PV, left atrial appendage (LAA), and mitral valve were excluded from the volume analysis. Aortic dimensions (sinus portion and diameter of the ascending aorta) were assessed. Measurements were performed using Advanced Workstation GE software (v11.3, GE Healthcare, USA).

Catheter ablation

All ablation procedures were conducted under general anesthesia. Diagnostic multipolar catheters were positioned in the coronary sinus and at the His-bundle. Access to the LA was performed by single or double trans-septal puncture [11]. 3D-LA anatomy was reconstructed during SR (Fig. 1) in the 3D-EAM CARTO3 system (Biosense Webster, Diamond Bar, California, USA). Only patients in whom conversion to SR was possible and in whom voltage maps were created during SR were included. After 3D reconstruction of the LA with the 20-polar Lasso Nav catheter or multipolar PentaRay catheter (Biosense Webster), the ostium of each PV was tagged to guide wide-area circumferential ablation. The goal was to achieve electrical isolation of the PV (entrance block) after a waiting period of 20 minutes, as previously described [12].

Measurement of left atrial fibrosis

Prior to catheter ablation, an invasive endocardial 3D-EAM of the LA including the PV, mitral anulus (delineated with the ablation catheter by visualizing a large ventricular and much smaller atrial signal, and after matching with the 3D-CT--derived LA map), and LAA (separate map) was created during SR after gating for respiration. Bipolar low-voltage areas (< 0.5 mV) as a surrogate parameter of LA fibrosis were determined by using the area measurement tool (in cm^2), and fibrosis was suspected if at least three adjacent points in an area covering 1 cm^2 had a bipolar voltage < 0.5 mV, as previously described [13]. The interpolation and color threshold of the voltage maps was set to 15 mm [2]. At least 100 points were acquired in

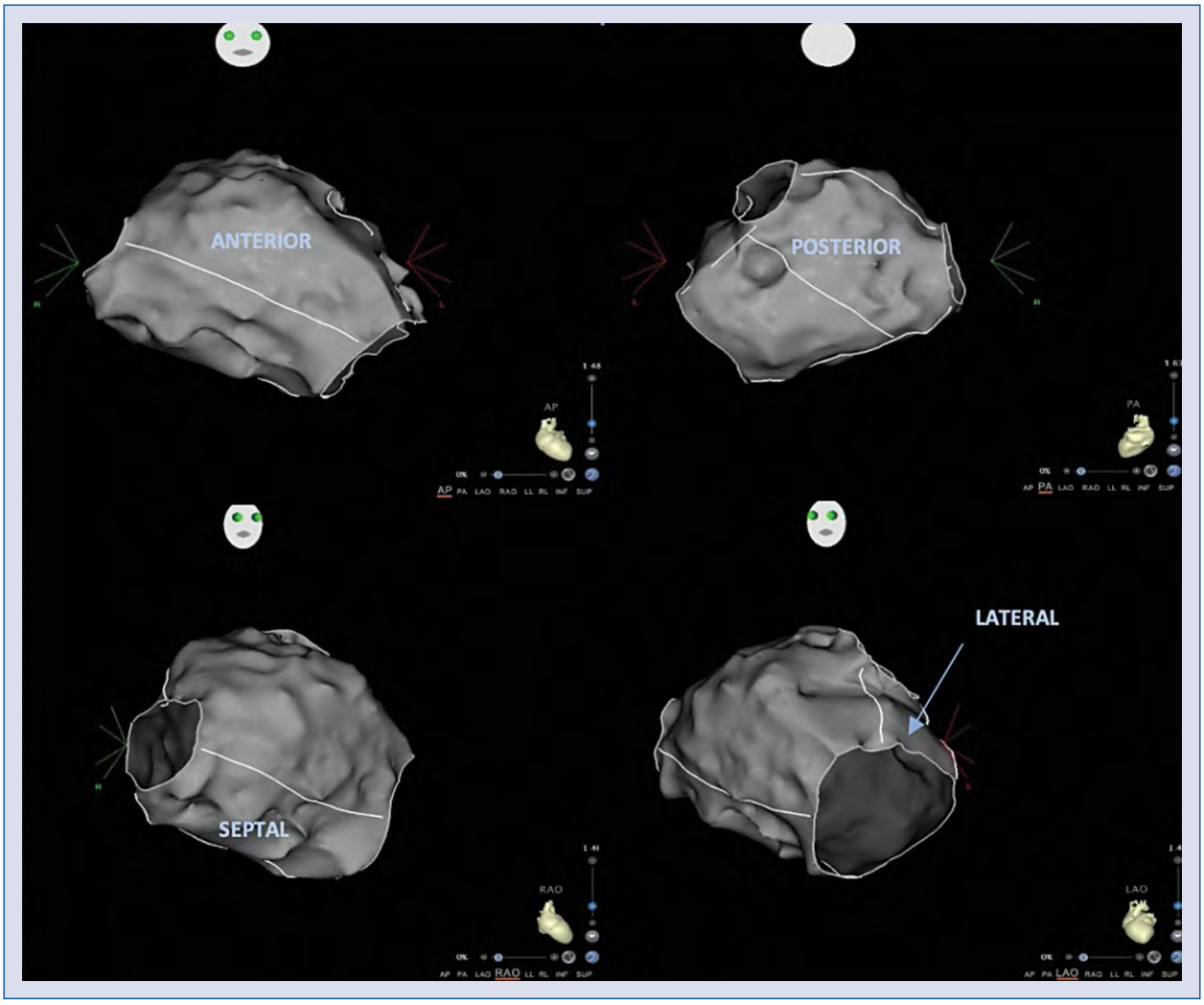


Figure 1. Left atrium divided into four segments in the CARTO3 software. Left upper (anterior-posterior view): anterior segment; right upper (posterior-anterior view): posterior segment; left bottom (right anterior oblique view): septal segment; right bottom (left anterior oblique): lateral segment. The pulmonary veins are not shown in this illustration

the LA. To assess the localization of LVA, the LA was subdivided into four areas (anterior, posterior, lateral, and septal; Fig. 1). The LAA was excluded because it almost never shows LVA and is often a very small structure. The ratio between LVA and total LA surface area (in %) and LVA to LA volume ratio assessed by cCT were calculated [4].

Blood samples

Venous blood samples were collected prior to ablation (Vacutainer TM, USA) and were immediately processed. The electro-chemiluminescence immunoassays and the Cobas 8000 (Roche Diagnostics, Switzerland) were used for detection of the N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) [14].

Statistical analysis

Continuous variables are presented as mean (± standard deviation) for normal distribution and median (interquartile range) for skewed distribution. Categorical variables are expressed as percentages, unless otherwise stated. Differences in baseline characteristics between the groups were assessed by independent Student's t-test or ANOVA for parameters with parametric distribution, while the Mann-Whitney U-test or Kruskal-Wallis test were used for parameters with a non-normal distribution. The χ^2 test was calculated for dichotomic variables. Univariable analysis for relevant clinical covariates was performed by Pearson or Spearman's test, as appropriate. To adjust for confounders, bivariable regression was performed

with a stepwise approach, and the strength of relationships was tested with F-test ANOVA. To avoid overfitting, multiple models restricted to a maximum of two clinical variables each were run. A two-sided p-value of < 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves were calculated to assess the area under the curve (AUC), and sensitivity and specificity of different NT-proBNP serum levels. According to the Utah stages, a cut-off of 5% for LA fibrosis and a cut-off of 20% for relevant LA fibrosis burden were considered for calculation of ROC curves [6, 15]. All statistical analyses were performed with SPSS software (v25, SPSS Inc., USA).

Results

Baseline characteristics and 3D electroanatomical mapping

Baseline characteristics of the study population are shown in Table 1. The mean patient age was 62.5 ± 11.4 years. Twenty-nine percent of patients were female, and 33% had persistent AF. The average number of points collected during the ablation procedure was 1362 ± 1067. Endocardial bipolar LVA as a surrogate parameter of LA fibrosis was present in 65% of patients, with 50% having a fibrotic area > 5% (at least Utah Stage 1) [15]. Fibrosis was most prevalent in the anterior (91.5% of patients with > 5% fibrosis) and posterior area (83% of patients with > 5% fibrosis). Fibrosis was less commonly observed in the septal and lateral LA area (63.3% and 48.9%, respectively). AF patients with any amount of LA fibrosis had higher NT-proBNP values (869 ± 1056 vs. 552 ± ± 859 ng/L, p = 0.001) and larger LA volumes after correction for body surface area (BSA; 63.3 ± 19.3 vs. 80 ± 27.1 mL/m^2, p = 0.003) as compared to those without. A positive correlation between the ascending aorta diameters (corrected for BSA) and the amount of fibrosis in the anterior LA was found (Pearson correlation 0.301, p = 0.005).

Atrial fibrillation patients with a higher burden of LA fibrosis presented with higher APPLE scores (2.2 ± 1.3 vs. 1.5 ± 1, p = 0.007) and higher DR-FLASH scores (3.6 ± 1.4 vs. 2.4 ± 1.5, p < 0.001).

Gender differences

Most of the study population was male (71% vs. 29%). Although females did not present with significantly higher NT-proBNP values as compared to males (960 ± 1327 vs. 622 ± 786 ng/L, p = 0.195), and they were more likely to have fibrosis in the anterior, septal, and lateral LA (Fig. 2).

Table 1. Baseline clinical characteristics.

Patient characteristic	All patients (n = 94)
Age	62.5 (11.4)
Female	28.7%
BMI [kg/m^2]	26.9 (4.6)
Adjusted (for gender) CHA_2DS_2-VASc score	1.5 (1–3)
APPLE score	1.8 (1.2)
DR-FLASH score	3 (1.6)
EHRA score (n = 73)	2.2 (0.73)
Days since AF diagnosis	1044 (224–2116)
Total LA fibrosis [cm^2]	5.2 (0–26.6)
LVA in % based on 3D mapping	3.7 (0–17.1)
LA fibrosis corrected for LA volume from CT scan [%]	4.8 (0–18.3)
Smoking	20.2
Hypertension	54.3
Diabetes	10.6
Stroke	7.4
Vascular disease	4.3
Sleep apnea	10.6
NOACs	86.2
Beta-blockers	67
Amiodarone	19.1
Diuretics	28.7
Aldosterone-antagonists	8.5
ACE-I/ATII-ag	48.9
Statins	34
Leucocytes [G/L]	6.8 (2)
NT-proBNP [ng/L]	280 (151–927)
CRP [mg/L]	3.8 (8.9)
eGFR [mL/min/m^2]	73 (18.4)
TSH [mU/L]	1.9 (1.1)
Aorta sinus portion/BSA [mm]	17.1 (2.2)
Ascending aorta/BSA [mm]	17.1 (2.7)
LA volume/BSA	69.2 (52.7–84)
LVEF [%]	56 (51–61)
E/e′	9 (7–13.3)

Values are means (standard deviation), median (interquartile range) or numbers (percentages). BMI — body mass index; AF — atrial fibrillation; LA — left atrial; LVA — low voltage area; 3D — three dimensional; CT — computed tomography; NOACs — non-vitamin K oral anticoagulants; ACE-I/ATII — angiotensin-converting enzyme inhibitor/angiotensin-receptor blockers; NT-proBNP — N-terminal pro B-type natriuretic peptide; CRP — C-reactive protein; eGFR — estimated glomerular filtration rate according to CKD-EPI; TSH — thyroid stimulating hormone; BSA — body surface area; LVEF — left ventricular ejection fraction

Compared to males, females had larger diameters of the ascending aorta (corrected for BSA) (18.6 ± ± 3.1 vs. 16.5 ± 2.3 mm/m^2, p = 0.001) and higher

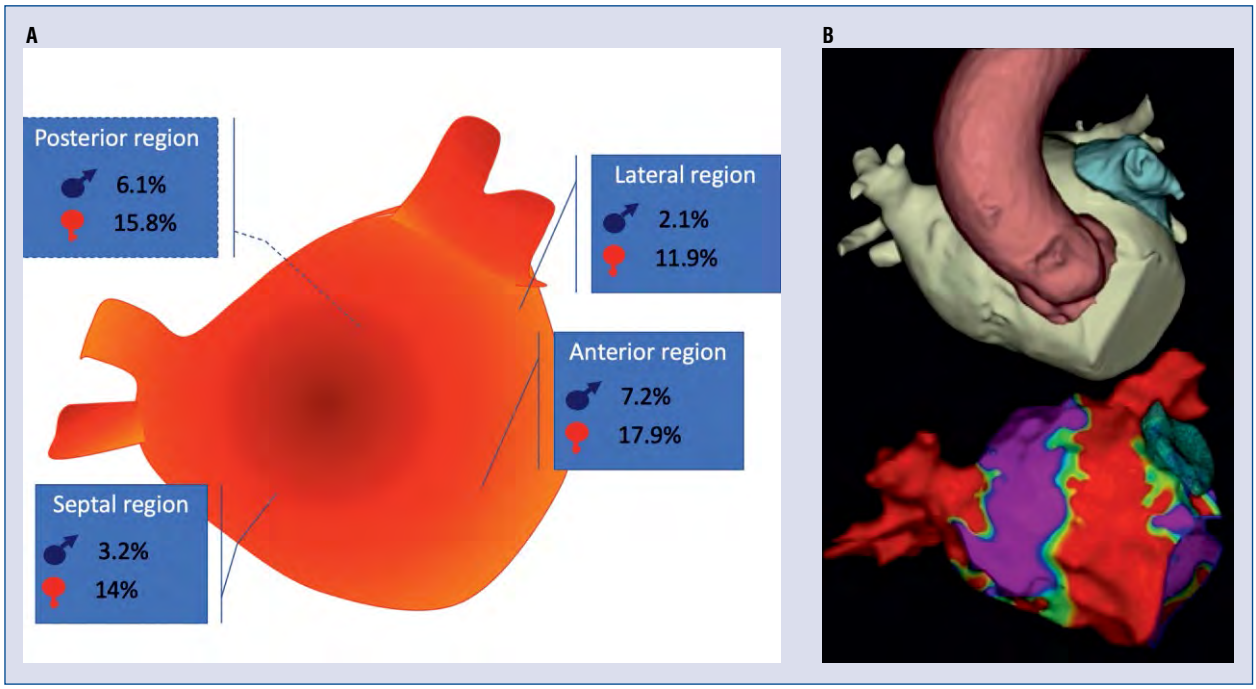


Figure 2. A. Mean distribution of left atrial fibrosis in subjects with > 5% fibrosis divided for male (blue) and female (red). **B.** Three-dimensional reconstruction of the left atrium and aortic position by voltage mapping and corresponding computed tomography-scan.

E/e' values (13.5 ± 6.7 vs. 9.4 ± 4.2, p = 0.002) as a measure of diastolic dysfunction.

Predictors of fibrosis

In univariable analysis, LA fibrosis was associated with female gender, older age, increased LA volumes (corrected for BSA), hypertension, higher NT-proBNP values, higher E/e' values, higher APPLE, DR-FLASH, and adjusted CHA_2DS_2-VASc scores. In bivariable analyses, incorporating relevant clinical variables from univariable analysis, the APPLE score did not independently predict LA fibrosis, while female gender independently predicted LA fibrosis. Furthermore, in other bivariable models, higher NT-proBNP levels, higher E/e' values, older age, and higher DR-FLASH scores also independently predicted LA fibrosis (Table 2).

The optimal NT-proBNP value for predicting LA fibrosis was found for a NT-proBNP of > 190 ng/L (for LA fibrosis > 5%: sensitivity 82% and specificity of 55%, Youden-index 0.37; for LA fibrosis > 20%: sensitivity 95% and specificity of 47%, Youden-index 0.42). To reduce the number of false positives, we individuated a NT-proBNP cut-off of > 400 ng/L, which yielded a sensitivity of 55% and specificity of 73% for predicting a LA fibrosis burden of ≥ 5%, and a sensitivity of 59% with a specificity of 65% for predicting a LA fibrosis burden of ≥ 20% (Fig. 3; **Suppl. Fig. 1**).

Ablation procedure

Acute procedural success was obtained in all patients. The mean procedural duration was 82.4 ± ± 72.5 min, and mean fluoroscopy times and area dose products were 7 ± 7 min and 813 ± ± 977 μGym^2, respectively. There were no gender-related differences with regard to procedural duration (84.3 ± 76 vs. 77.9 ± 64.3 min, p = 0.708), fluoroscopy times (7 ± 7.3 vs. 6.8 ± ± 6 min, p = 0.902), and dose area products (919 ± 1110 vs. 552 ± 437 μGym^2, p = 0.107). No periprocedural complications occurred.

Discussion

In this single-center longitudinal study, higher NT-proBNP and higher E/e' — both markers of increased left-sided cardiac filling pressures — as well as older age, higher DR-FLASH scores, and female gender were independently associated with LA fibrosis in patients referred for catheter ablation of AF. LA fibrosis was most prevalent in the anterior followed by the posterior LA wall. A positive correlation between the ascending aorta

Table 2. Variables associated with bipolar endocardial low-voltage areas as a surrogate parameter of left atrial fibrosis.

Variable	Univariable analysis		Bivariable analysis		
	Pearson correlation	P	Standardized B	B (95% CI)	P
Gender	0.285	0.005	0.234 to 0.397	9.7 (2–17.4) to 14.9 (6.6–23.1)	0.001
Age	0.245	0.018	0.252	0.421 (0.08–0.76)	0.016
BMI [kg/m^2]	–0.087	0.404			
LA volume/BSA [mL/m^2]	0.204	0.048	0.086	0.065 (–0.105–0.236)	0.449
Hypertension	0.232	0.025			
Statin use	0.258	0.012	0.164	6.7 (–1.9–15.3)	0.126
eGFR [mL/min/m^2]	–0.095	0.364			
Serum NT-proBNP [ng/L]	0.299	0.006	0.232 to 0.298	0.005 (0.0–0.009) to 0.006 (0.002–0.01)	0.005 to 0.049
E/e'	0.482	< 0.001	0.339 to 0.394	1.1 (0.39–1.8) to 1.3 (0.5–2)	0.002
Adjusted CHA_2DS_2-VASc score	0.379	< 0.001			
APPLE score	0.282	0.006	0.155	2.57 (–1.28–6.42)	0.188
DR-FLASH score	0.401	< 0.001	0.316 to 0.286	3.92 (1.27–6.57) to 4.42 (2.2–6.6)	< 0.001
LVEF	–0.169	0.104	–0.018	–0.033 (–0.45/–0.39)	0.877

Left atrial fibrosis was calculated as a continuous variable as a ratio between low-voltage area and total LA surface area (in %). BMI — body mass index; LA — left atrial; BSA — body surface area; GFR — glomerular fraction rate according to CKD-EPI; NT-proBNP — N-terminal pro B-type natriuretic peptide. P-values were calculated by Pearson correlation (univariable analyses) and regression analyses (bivariable analyses). Following models were calculated (*p < 0.05): 1) NT-proBNP*, gender*; 2) NT-proBNP*, age*; 3) NT-proBNP*, LA volume/BSA, mL/m^2 (p = 0.449); 4) NT-proBNP*, APPLE score (p = 0.188); 5) DR-FLASH*, gender*; 6) NT-proBNP*, LVEF (p = 0.877); 7) NT-proBNP*, E/e'*; 8) E/e'*, gender*; 9) E/e'**, age*; 10) NT-proBNP*, statins, age

diameters and the amount of fibrosis in the anterior LA was found. Females were more likely to have fibrosis in the anterior, septal, and lateral LA as compared to males.

Predictors of left atrial fibrosis

Left atrial fibrosis may represent the anatomical substrate altering electromechanical cellular coupling, favoring reentry, and thus predisposing to the onset and maintenance of AF. As such, myocardial fibrosis has been widely reported in AF patients both in histological and in autoptic studies [16, 17]. Based upon previous studies and clinical experience that fibrotic tissue yields a low voltage signal, besides histological studies, invasive 3D--EAM voltage mapping is a standard method to assess and stage the extent of atrial fibrosis [18, 19].

In bivariable analyses, we found that elevated NT-proBNP, higher E/e' values — both surrogate parameters of increased left-sided cardiac filling pressures — independently predicted LA fibrosis after correction for confounding factors. Moreover, a NT-proBNP cut-off of > 400 ng/L showed a good specificity to predict significant LA fibrosis in our population. Both NT-proBNP levels and LA volumes are frequently elevated in the setting of heart failure with reduced, but also preserved, ejection fraction (HFpEF), which is related to high LA filling pressures [20]. In AF patients, an expanded myocardial extracellular volume has been associated with adverse LA remodeling, and LA enlargement is a typical finding in diastolic dysfunction and in patients with increased left-sided filling pressures [20, 21]. An independent association between LVA, higher LA volumes, and persistent AF has previously been described [5, 6]. Our findings are in line with previous studies and extend previous knowledge revealing that parameters of diastolic dysfunction and higher cardiac filling pressures (NT-proBNP and echocardiographic E/e') constitute important predictors of LA fibrosis. LA fibrosis itself may promote AF and synergistically increase left-sided filling pressures leading to a vicious cycle.

NT-proBNP levels reflect not only an increased myocardial wall stress, but it may also be related to

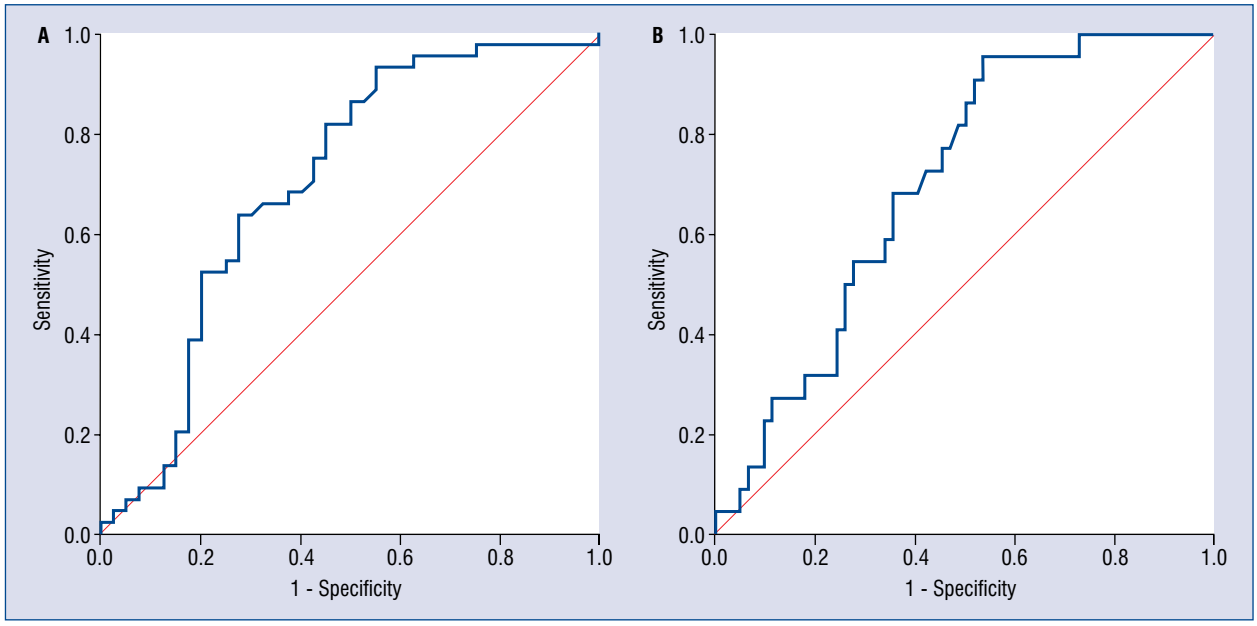


Figure 3. A. Receiver operating charasteristic curves for serum N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) levels as a predictor of left atrial (LA) fibrosis (cut-off: ≥ 5%); area under the curve (AUC) 70%, p = 0.001, NT-proBNP cut-off 400 ng/L: sensitivity 55%, specificity 73%; **B.** Receiver operating characteristic curves for serum NT-proBNP levels as a predictor of relevant LA fibrosis (cut-off: ≥ 20%); AUC 70%, p = 0.005, NT-proBNP cut-off 400 ng/L: sensitivity 59%, specificity 65%.

intrinsic myocardial disease [22]. Similarly to our study, the SwedeHF register found an association between NT-proBNP and AF in HFpEF patients, suggesting a direct pathological linkage between higher filling pressures and development of AF. In this study, patients with AF and HFpEF were older, more likely to be male, and associated with a worse 1-year survival, even when compared to patients with a reduced ejection fraction [23]. The association between increased NT-proBNP values and LA fibrosis has been described by Kornej et al. [24], although this parameter did not independently predict LA fibrosis in their study.

Other biomarkers such as galectin-3, pro-collagen type III N-terminal pro-peptide (PIIINP), type I collagen C-telopeptide (ICTP), and fibroblast growth-factor 23 (FGF-23) have recently been suggested as biomarkers of fibrosis and might be helpful in identifying patients who are more likely to benefit from AF catheter ablation [25–28]. Although promising, these biomarkers are not yet clinically available, and NT-proBNP remains the most established and clinically available parameter.

Hypertension is an established risk factor for AF development and its perpetuation [1]. Interestingly, we found that approximately half of our population were hypertensive. This is possibly due to the fact that our patients were relatively young and the majority of them were referred for AF ablation of paroxysmal AF.

The APPLE score has recently been suggested as a powerful predictor of both LA fibrosis and AF recurrence after catheter ablation, and it has been externally validated [7, 24, 29]. Similarly, the DR-FLASH score proved to be effective in predicting the presence of LVA in more than 900 patients with AF [9]. Our study confirms these findings, as we found higher scores in subjects with a higher burden of LA fibrosis as well as a positive correlation between the two variables. The DR-FLASH score independently predicted LVA after adjustment for gender, while the APPLE score was not an independent predictor for LVA in bivariable analyses. Interestingly, persistent AF was not predictive of relevant fibrosis. Thus, AF duration may not represent per se a criterion to more intense ablation approaches.

These findings are clinically relevant when choosing the appropriate treatment strategy in these patients (e.g., more aggressive risk factor management) because increased LA fibrosis is as-

sociated with lower AF-free survival after catheter ablation and adverse events [30].

Gender differences

In line with previous studies, female gender was an independent predictor of LA fibrosis [5, 6]. This finding seems to be related to a direct gender-dependent effect based on differences in the effect of sex hormones on adverse LA remodeling and fibrosis [14]. Although the presence of higher left-sided filling pressures likely plays a crucial role as a predictor of LA fibrosis, in our cohort diuretic treatment was not significantly more frequent in females and NT-proBNP values were not significantly different between males and females. On the other hand, both E/e' as an indicator of diastolic dysfunction and higher left-sided filling pressures were higher in females as compared to males, indicating that females with AF tend to present with higher left-sided filling pressures, thereby promoting LA fibrosis. However, in bivariable analyses, female gender per se remained an independent predictor of LA fibrosis, indicating that female gender is associated with LA fibrosis independently of higher left-sided filling pressures. We were able to confirm previous findings by invasively assessing LA fibrosis via EAM, which is considered to be an alternative method for detection of fibrosis as compared to late-gadolinium enhancement CMR [31]. CMR-based assessment of LA fibrosis is a well-established method in some experienced centers, but it requires great expertise in interpretation, and for some centers assessment of LA fibrosis during AF ablation by 3D-EAM may be more feasible. Most previous studies showing an association between female gender and LA fibrosis have performed their analyses based on absolute values without indexing LA volumes for BSA. We confirmed these findings in patients with paroxysmal and persistent AF and, in line with another study, after correcting LA volumes for BSA [32]. Regarding this, females had bigger LA volumes indexed for BSA compared to males. Furthermore, no differences in age were found between females and males, although females had lower body mass index.

Epidemiologically, the incidence and prevalence of AF is age-related [20]. However, it is still debated whether age is a risk factor per se or if it is mainly related to other co-morbidities [16]. In our study, we found older age to be related to higher amounts of LA fibrosis and to be an independent predictor of LA fibrosis [6, 33]. Similarly to previous studies, women receiving catheter ablation for AF were older than the men in our study, suggesting that women develop AF at an older age as compared to men [6, 33]. However, as shown in the recent EAM study from Ammar-Busch et al. [31], fibrosis may be rather related to increased filling pressures than older age per se.

Compared to most previous studies, we found a relatively high incidence of LA fibrosis in a predominantly male population with paroxysmal AF. This is possibly due to the different method of detecting fibrosis by invasive EAM mapping as compared to MRI-LGE [5].

Localization of left atrial fibrosis

Left atrial fibrosis was most prevalent in the anterior followed by the posterior LA wall. The septal and lateral LA wall showed less fibrosis, which may be related to the thickness of atrial tissue. With regard to this, a positive correlation between the ascending aorta diameters and the amount of fibrosis in the anterior LA was found. It has been previously reported that dilatation of the ascending aorta, e.g., by hypertension, can lead to chronic pressure on the anterior LA wall due to its anatomic proximity, thereby promoting fibrotic remodeling of this area [34, 35]. Females were more likely to have fibrosis in the anterior, septal, and lateral LA, which is in line with the observation that they presented with higher ascending aorta dimensions when adjusted for BSA. Moreover, an independent gender-specific effect may also play a role for LA fibrotic remodeling, which certainly needs further investigation.

Limitations of the study

This was a small single-center study performed in patients with AF referred for catheter ablation, and only 29% of the population were female. Moreover, assessment of LA fibrosis by CMR is currently not performed in our center. The 20-polar Pentaray mapping catheter creating high-density maps with > 1000 of points has a much higher resolution to detect LVA, but is not routinely used for PVI in our center. Antiarrhythmic drugs and/or beta-blockers were recommended to be discontinued 3–5 half-lives prior to the ablation procedure (2 weeks for amiodarone), but due to symptoms this was not possible in all patients. These limitations may have influenced the data accuracy for EAM. Therefore, our data may not be generalizable to the overall AF population, and larger prospective studies including more women and MR data should be carried out in the future. Moreover, we cannot rule out that the accuracy of EAM might have

been influenced by functional voltage reduction related to electrical stunning rather than fibrosis in patients with longer episodes of persistent AF and electrical cardioversion.

Conclusions

In this single-center longitudinal study, surrogate parameters of elevated left-sided cardiac filling pressures such as higher serum NT-proBNP levels and higher echocardiographic E/e' values as well as female gender independently predicted the prevalence of LA fibrosis in patients referred for catheter ablation of AF.

Conflict of interest: Dr. Jan Steffel has received consultant and/or speaker fees from Abbott, Amgen, AstraZeneca, Atricure, Bayer, Biosense Webster, Biotronik, Boehringer-Ingelheim, Boston Scientific, Bristol-Myers Squibb, Daiichi Sankyo, Medscape, Medtronic, Merck/MSD, Novartis, Pfizer, Sanofi-Aventis, WebMD, and Zoll. He reports ownership of CorXL. Dr. Steffel has received grant support through his institution from Abbott, Bayer Healthcare, Biosense Webster, Biotronik, Boston Scientific, Daiichi Sankyo, and Medtronic; Dr. Daniel Hofer reports educational grants, speaker fees, or fellowship support from Abbott, Medtronic, Biotronik, Boston Scientific, Biosense Webster, Novartis, Bayer; Dr. Alexander Breitenstein has received consultant and/or speaker fees from Abbott, Bayer Healthcare, Biosense Webster, Biotronik, Boston Scientific, Bristol-Myers Squibb, Cook Medical, Daiichi Sankyo, Medtronic, Pfizer, and Spectranetics/Philipps; Dr. Ardan M. Saguner reports educational grant support through his institution from Abbott and Biosense Webster, and speaker fees from Bayer, BMS-Pfizer and Daiichi Sankyo. All other authors have no conflict of interest to declare.

References

1. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016; 37(38): 2893–2962, doi: 10.1093/eurheartj/ehw210, indexed in Pubmed: 27567408.
2. Daccarett M, Badger TJ, Akoum N, et al. Association of left atrial fibrosis detected by delayed-enhancement magnetic resonance imaging and the risk of stroke in patients with atrial fibrillation. J Am Coll Cardiol. 2011; 57(7): 831–838, doi: 10.1016/j.jacc.2010.09.049, indexed in Pubmed: 21310320.
3. Seewöster T, Kosich F, Sommer P, et al. Prediction of low-voltage areas using modified APPLE score. Europace. 2021; 23(4): 575–580, doi: 10.1093/europace/euaa311, indexed in Pubmed: 33279992.
4. Asvestas D, Vlachos K, Bazoukis G, et al. Left atrial voltage mapping using a new impedance-based algorithm in patients with paroxysmal atrial fibrillation. Pacing Clin Electrophysiol. 2018; 41(11): 1447–1453, doi: 10.1111/pace.13501, indexed in Pubmed: 30225845.
5. Huo Y, Gaspar T, Pohl M, et al. Prevalence and predictors of low voltage zones in the left atrium in patients with atrial fibrillation. Europace. 2018; 20(6): 956–962, doi: 10.1093/europace/eux082, indexed in Pubmed: 28605524.
6. Akoum N, Mahnkopf C, Kholmovski EG, et al. Age and sex differences in atrial fibrosis among patients with atrial fibrillation. Europace. 2018; 20(7): 1086–1092, doi: 10.1093/europace/eux260, indexed in Pubmed: 29016990.
7. Kornej J, Schumacher K, Dinov B, et al. Prediction of electro-anatomical substrate and arrhythmia recurrences using APPLE, DR-FLASH and MB-LATER scores in patients with atrial fibrillation undergoing catheter ablation. Sci Rep. 2018; 8(1): 12686, doi: 10.1038/s41598-018-31133-x, indexed in Pubmed: 30139967.
8. Rolf S, Kircher S, Arya A, et al. Tailored atrial substrate modification based on low-voltage areas in catheter ablation of atrial fibrillation. Circ Arrhythm Electrophysiol. 2014; 7(5): 825–833, doi: 10.1161/CIRCEP.113.001251, indexed in Pubmed: 25151631.
9. Kosiuk J, Dinov B, Kornej J, et al. Prospective, multicenter validation of a clinical risk score for left atrial arrhythmogenic substrate based on voltage analysis: DR-FLASH score. Heart Rhythm. 2015; 12(11): 2207–2212, doi: 10.1016/j.hrthm.2015.07.003, indexed in Pubmed: 26144350.
10. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016; 17(12): 1321–1360, doi: 10.1093/ehjci/jew082, indexed in Pubmed: 27422899.
11. Stegmann C, Jahnke C, Paetsch I, et al. Association of left ventricular late gadolinium enhancement with left atrial low voltage areas in patients with atrial fibrillation. Europace. 2018; 20(10): 1606–1611, doi: 10.1093/europace/euy013, indexed in Pubmed: 29420707.
12. Saguner AM, Maurer T, Wissner E, et al. Catheter ablation of atrial fibrillation in very young adults: a 5-year follow-up study. Europace. 2018; 20(1): 58–64, doi: 10.1093/europace/euw378, indexed in Pubmed: 28017937.
13. Verma A, Wazni OM, Marrouche NF, et al. Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. J Am Coll Cardiol. 2005; 45(2): 285–292, doi: 10.1016/j.jacc.2004.10.035, indexed in Pubmed: 15653029.
14. Akdis D, Saguner AM, Shah K, et al. Sex hormones affect outcome in arrhythmogenic right ventricular cardiomyopathy/dysplasia: from a stem cell derived cardiomyocyte-based model to clinical biomarkers of disease outcome. Eur Heart J. 2017; 38(19): 1498–1508, doi: 10.1093/eurheartj/ehx011, indexed in Pubmed: 28329361.
15. Marrouche NF, Wilber D, Hindricks G, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. JAMA. 2014; 311(5): 498–506, doi: 10.1001/jama.2014.3, indexed in Pubmed: 24496537.
16. Platonov PG, Mitrofanova LB, Orshanskaya V, et al. Structural abnormalities in atrial walls are associated with presence and

persistency of atrial fibrillation but not with age. J Am Coll Cardiol. 2011; 58(21): 2225–2232, doi: 10.1016/j.jacc.2011.05.061, indexed in Pubmed: 22078429.
17. Spach MS, Boineau JP. Microfibrosis produces electrical load variations due to loss of side-to-side cell connections: a major mechanism of structural heart disease arrhythmias. Pacing Clin Electrophysiol. 1997; 20(2 Pt 2): 397–413, doi: 10.1111/j.1540-8159.1997.tb06199.x, indexed in Pubmed: 9058844.
18. Kottkamp H. Human atrial fibrillation substrate: towards a specific fibrotic atrial cardiomyopathy. Eur Heart J. 2013; 34(35): 2731–2738, doi: 10.1093/eurheartj/eht194, indexed in Pubmed: 23761394.
19. Siebermair J, Kholmovski EG, Marrouche N. Assessment of left atrial fibrosis by late gadolinium enhancement magnetic resonance imaging: methodology and clinical implications. JACC Clin Electrophysiol. 2017; 3(8): 791–802, doi: 10.1016/j.jacep.2017.07.004, indexed in Pubmed: 29759774.
20. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016; 37(27): 2129–2200, doi: 10.1093/eurheartj/ehw128, indexed in Pubmed: 27206819.
21. Neilan TG, Mongeon FP, Shah RV, et al. Myocardial extracellular volume expansion and the risk of recurrent atrial fibrillation after pulmonary vein isolation. JACC Cardiovasc Imaging. 2014; 7(1): 1–11, doi: 10.1016/j.jcmg.2013.08.013, indexed in Pubmed: 24290570.
22. Hussein AA, Saliba WI, Martin DO, et al. Plasma B-type natriuretic peptide levels and recurrent arrhythmia after successful ablation of lone atrial fibrillation. Circulation. 2011; 123(19): 2077–2082, doi: 10.1161/CIRCULATIONAHA.110.007252, indexed in Pubmed: 21536999.
23. Sartipy U, Dahlström U, Fu M, et al. Atrial fibrillation in heart failure with preserved, mid-range, and reduced ejection fraction. JACC Heart Fail. 2017; 5(8): 565–574, doi: 10.1016/j.jchf.2017.05.001, indexed in Pubmed: 28711451.
24. Kornej J, Büttner P, Sommer P, et al. Prediction of electro-anatomical substrate using APPLE score and biomarkers. Europace. 2019; 21(1): 54–59, doi: 10.1093/europace/euy120, indexed in Pubmed: 29893827.
25. Wu XY, Li SN, Wen SN, et al. Plasma galectin-3 predicts clinical outcomes after catheter ablation in persistent atrial fibrillation patients without structural heart disease. Europace. 2015; 17(10): 1541–1547, doi: 10.1093/europace/euv045, indexed in Pubmed: 25921557.
26. Begg GA, Karim R, Oesterlein T, et al. Intra-cardiac and peripheral levels of biochemical markers of fibrosis in patients undergoing catheter ablation for atrial fibrillation. Europace. 2017; 19(12): 1944–1950, doi: 10.1093/europace/euw315, indexed in Pubmed: 28339804.
27. Takemoto Y, Ramirez RJ, Yokokawa M, et al. Galectin-3 regulates atrial fibrillation remodeling and predicts catheter ablation outcomes. JACC Basic Transl Sci. 2016; 1(3): 143–154, doi: 10.1016/j.jacbts.2016.03.003, indexed in Pubmed: 27525318.
28. Clementy N, Garcia B, André C, et al. Galectin-3 level predicts response to ablation and outcomes in patients with persistent atrial fibrillation and systolic heart failure. PLoS One. 2018; 13(8): e0201517, doi: 10.1371/journal.pone.0201517, indexed in Pubmed: 30067817.
29. Kornej J, Hindricks G, Shoemaker MB, et al. The APPLE score: a novel and simple score for the prediction of rhythm outcomes after catheter ablation of atrial fibrillation. Clin Res Cardiol. 2015; 104(10): 871–876, doi: 10.1007/s00392-015-0856-x, indexed in Pubmed: 25876528.
30. Ballesteros G, Ravassa S, Bragard J, et al. Association of left atrium voltage amplitude and distribution with the risk of atrial fibrillation recurrence and evolution after pulmonary vein isolation: An ultrahigh-density mapping study. J Cardiovasc Electrophysiol. 2019; 30(8): 1231–1240, doi: 10.1111/jce.13972, indexed in Pubmed: 31077505.
31. Ammar-Busch S, Buiatti A, Tatzber A, et al. Predictors of low voltage areas in persistent atrial fibrillation: is it really a matter of time? J Interv Card Electrophysiol. 2020; 57(3): 345–352, doi: 10.1007/s10840-018-0471-7, indexed in Pubmed: 30374659.
32. Kiedrowicz RM, Wielusinski M, Wojtarowicz A, et al. Predictors of the voltage derived left atrial fibrosis in patients with long-standing persistent atrial fibrillation. Cardiol J. 2020 [Epub ahead of print], doi: 10.5603/CJ.a2020.0069, indexed in Pubmed: 32419127.
33. Kaufman ES, Zimmermann PA, Wang T, et al. Risk of proarrhythmic events in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study: a multivariate analysis. J Am Coll Cardiol. 2004; 44(6): 1276–1282, doi: 10.1016/j.jacc.2004.06.052, indexed in Pubmed: 15364332.
34. Maeda S, Yamauchi Y, Tao S, et al. Small reentrant atrial tachycardia adjacent to left aortic sinus of valsalva. Circ J. 2013; 77(12): 3054–3055, doi: 10.1253/circj.cj-13-0437, indexed in Pubmed: 23934389.
35. Hori Y, Nakahara S, Kamijima T, et al. Influence of left atrium anatomical contact area in persistent atrial fibrillation-relationship between low-voltage area and fractionated electrogram. Circ J. 2014; 78(8): 1851–1857, doi: 10.1253/circj.cj-14-0440, indexed in Pubmed: 25008487.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 3, 423–431
DOI: 10.5603/CJ.a2021.0151

ISSN 1897–5593
eISSN 1898–018X

The number of circulating CD34-positive cells is an independent predictor of coronary artery calcification progression: Sub-analysis of a prospective multicenter study

Keishi Ichikawa[1], Toru Miyoshi[1], Kazuhiro Osawa[2], Takashi Miki[1], Kunihisa Kohno[1], Kazufumi Nakamura[1], Yasushi Koyama[3], Hiroshi Ito[1]

[1]Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Density and Pharmaceutical Sciences, Okayama, Japan
[2]Department of Cardiovascular Medicine, Japanese Red Cross Okayama Hospital, Okayama, Japan
[3]Department of Cardiology, Sakurabashi Watanabe Hospital, Osaka, Japan

Abstract

Background: *Decreases in circulating CD34-positive cells are associated with increases in cardiovascular events. We investigated the association between the number of CD34-positive cells and the progression of coronary artery calcification (CAC), a marker of atherosclerosis, in patients with hypercholesteremia under statin therapy in a sub-analysis of a multicenter study.*

Methods: *In the principal study, patients with CAC scores of 1–999 were treated with pitavastatin. Measurement of CAC by non-enhanced computed tomography and a blood test were performed at baseline and at 1-year follow-up. Patients were divided into two groups: CAC progression (change in CAC score > 0) and non-progression. The number of circulating CD34-positive cells was counted using flow cytometry.*

Results: *A total of 156 patients (mean age 67 years, 55% men) were included in this sub-analysis. CD34 positive cell numbers at baseline as a continuous variable was inversely correlated with annual change in the log-transformed CAC score ($r = –0.19$, $p = 0.02$). When patients were divided into high and low CD34 groups based on the median value of 0.8 cells/μL, the adjusted change in CAC score in the low-CD34 group was significantly greater than that in the high-CD34 group (54.2% vs. 20.8%, respectively, $p = 0.04$). In multiple logistic analysis, a low CD34-positive cell number was an independent predictor of CAC progression, with an odds ratio of 2.88 (95% confidence interval 1.28–6.49, $p = 0.01$).*

Conclusions: *Low numbers of CD34-positive cells are associated with CAC progression in patients with hypercholesterolemia under statin therapy. The number of CD34-positive cells may help to identify patients at increased cardiovascular risk.* (Cardiol J 2022; 29, 3: 423–431)

Key words: coronary artery calcification, computed tomography, endothelial progenitor cells, hypercholesterolemia

Address for correspondence: Toru Miyoshi, MD, PhD, Department of Cardiovascular Medicine, Okayama University, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan, tel: +81-86-235-7351, fax: +81-86-235-7353, e-mail: miyoshit@cc.okayama-u.ac.jp

Received: 30.10.2020 Accepted: 24.10.2021 Early publication date: 15.11.2021

Introduction

Endothelial progenitor cells are mononuclear cells largely derived from bone marrow. They can be quantified in peripheral blood using flow cytometry. CD34-positive mononuclear cells have the potential to differentiate into several lineages and contribute to vascular repair and regeneration [1, 2]. Low counts of CD34-positive cells indicate reduced endothelial repair activity, with previous studies demonstrating a direct correlation between endothelial progenitor cell numbers and endothelial dysfunction [2]. Moreover, a previous report has demonstrated that a decrease in circulating progenitor cells is a predictor of cardiovascular events [3]. However, the mechanism underlying the association between CD34-positive cells and cardiovascular events has not been fully elucidated.

The coronary artery calcification (CAC) score determined by non-enhanced computed tomography (CT) reflects the presence and extent of coronary atherosclerosis and predicts future cardiovascular events in multiple populations [4, 5]. A previous study has shown the association between CAC progression and adverse cardiovascular outcomes [6]. We have previously reported the results of a prospective multicenter study that examined the effects of intensive and standard pitavastatin treatment with or without eicosapentaenoic acid on the progression of CAC [7]. The study found that the progression of CAC in each patient group was not affected by any of the treatments. Therefore, it is of interest to find other factors involved in CAC progression.

In this study, we investigated the association between baseline circulating CD34-positive cell number and CAC progression in patients with hypercholesterolemia undergoing statin therapy.

Methods

Study design

This study was designed as a sub-analysis of a prospective, multicenter, randomized trial [7]. The main trial was conducted at 27 centers from May 2010 to August 2011. The design and results of the main study have already been published [7]. Briefly, the trial investigated the effects of intensive and standard statin therapy with or without eicosapentaenoic acid on the progression of CAC score over 1 year. After taking 2 mg/day pitavastatin for 2 months to check for tolerance, all participants were randomly allocated to the 2 mg/day pitavastatin (PIT2), 4 mg/day pitavastatin (PIT4), or 2 mg/day pitavastatin + 1800 mg/day eicosapentaenoic acid (PIT2 + EPA) groups. Baseline blood test data and non-enhanced cardiac CT images were obtained immediately before starting the allocated treatment and repeated at 1-year follow-up. The data presented in this manuscript are a sub-analysis of the collected data. This study was conducted according to the principles of the Declaration of Helsinki and approved by the ethics committees of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences and other hospitals. The main study is registered at UMIN Clinical Trial Registry (UMIN000003171). All study participants gave written informed consent.

Study population

Eligible participants were patients > 20 years old, with an Agatston score of 1–999, hypercholesterolemia, and no history of cardiovascular disease. We excluded patients with a history of coronary revascularization (including percutaneous coronary intervention and coronary artery bypass surgery), Agatston score 0 or > 1000, familial hypercholesterolemia, use of cyclosporine, and use of lipid-lowering agents excluding statins. A flow diagram of the study is shown in Figure 1. Among the 157 patients analyzed in the principal study, 1 patient was excluded because there were no data for CD34-positive cell number. Thus, 156 patients were included in this sub-analysis.

CAC analysis and definition of CAC progression

Non-enhanced CT imaging was performed at baseline and 1-year follow-up in a standardized fashion as previously described [7]. CT images were documented in a Digital Imaging and Communications in Medicine format, which was sent to the core laboratory at L&L Company (Osaka, Japan) for blinded analysis. CAC score was calculated using the Agatston method [8]. To minimize the effect of interscan variability [9], two definitions of CAC progression were used; the percentage changes in CAC score > 0% and > 20% were applied in the analyses. The percentage change in CAC score was calculated as (CAC [follow up] – CAC [baseline]) / / CAC [baseline]) × 100.

Measurement of circulating CD34-positive cells

Peripheral blood was collected and incubated with fluorochrome-labeled monoclonal anti-human mouse antibodies to identify surface markers expressed on mononuclear cells. The number of

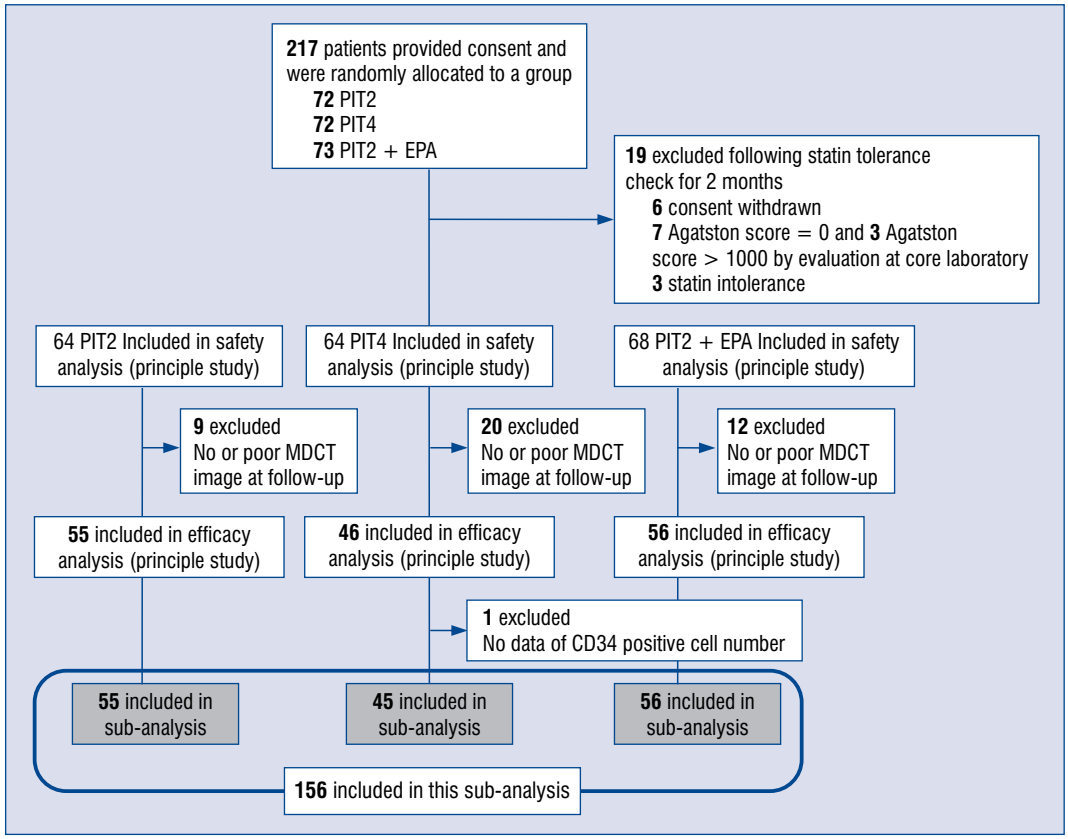


Figure 1. Flowchart showing enrollment of patients in the study. PIT2 — 2 mg/day pitavastatin; PIT4 — 4 mg/day pitavastatin; EPA — 1800 mg/day eicosapentaenoic acid; MDCT — multidetector row computed tomography.

circulating CD34-positive cells was counted by flow cytometry at an independent central study laboratory (SRL, Tokyo, Japan). The membrane expression of CD34 was studied in the lymphomonocyte gate. Results are expressed as the number of CD34-positive cells per μL blood, taking into account the number of leukocytes of each subject.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range), as appropriate. Patients were classified into two groups based on median values of circulating CD34--positive cells, with a cut-off value of 0.8 cells/μL. Differences in continuous variables between the two groups were analyzed by Student's t-test or Mann-Whitney U-test, as appropriate. Categorical variables are presented as frequency and proportion (%), and were compared by χ^2 analysis. In subsequent analysis, triglyceride, high-sensitivity C-reactive protein (hsCRP), and CAC score were log transformed because they did not exhibit a normal distribution. Associations of variables were assessed by Pearson's correlation analysis. The annual change in log-transformed CAC score was calculated as follows: log transformed (CAC score at follow-up) — log transformed (CAC score at baseline). The mean change in CAC score and 95% confidence intervals (CI) adjusted for age, gender, and smoking status were estimated using multivariate linear models. Univariate logistic regression analysis was performed to identify potential predictive factors for CAC progression. Multivariate logistic regression analysis was performed using the variables with p-value < 0.05 in the univariate analysis. All statistical tests were two-sided, and p-value < 0.05 was considered significant. All statistical analyses were performed using SPSS 27.0 for Windows (IBM, Armonk, NY, USA).

Results

In total, 156 patients were enrolled in this study sub-analysis. The baseline patient characteristics are shown in Table 1. The mean age was 67 years, and 55% of patients were men. 82% of patients had hypertension and 27% had diabetes mellitus. The median (interquartile rage) CAC

Table 1. Baseline patient characteristics.

Variables	N = 156
Age [years]	67 ± 9
Male gender	85 (55)
Body mass index [kg/m^2]	25.1 ± 4.0
Hypertension	127 (81)
Diabetes mellitus	42 (27)
Current smoker	26 (17)
Warfarin use	7 (4)
Creatinine [mg/dL]	0.87 ± 1.01
AST [IU/L]	27 ± 13
ALT [IU/L]	28 ± 22
Total cholesterol [mg/dL]	175 ± 31
LDL-C [mg/dL]	93 ± 24
HDL-C [mg/dL]	55 ± 14
Triglyceride [mg/dL]	115 (89–163)
HbA1c [%]	5.7 ± 0.7
hsCRP [mg/L]	537 (327–1058)
CAC score	97 (26–237)
PIT2/PIT4/PIT2 + EPA	55 (35)/45 (29)/56 (36)
CD34-positive cell number [/μL]	1.0 ± 0.7

Data are presented as mean ± standard deviation, number (%), or median (interquartile range). AST — aspartate aminotransferase; ALT — alanine aminotransferase; LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; HbA1c — glycated hemoglobin A1c; hsCRP — high-sensitivity C-reactive protein; CAC score — coronary artery calcium score; PIT2 — 2 mg/day pitavastatin; PIT4 — 4 mg/day pitavastatin; EPA — 1800 mg/day eicosapentaenoic acid

score was 97 (26–237) and the mean (standard deviation) serum CD34-positive cell number was 1.0 (0.7) cells/μL.

Simple correlation coefficients for the association between CD34-positive cell number and other variables are shown in Table 2. The baseline number of CD34-positive cells was significantly positively associated with male gender ($r = 0.38$, $p < 0.01$) and smoking status ($r = 0.30$, $p < 0.01$), and was significantly inversely associated with age ($r = –0.26$, $p < 0.01$). Meanwhile, there were no significant correlations between the baseline number of CD34-positive cells and CAC score.

Next, we evaluated the association between the baseline number of CD34-positive cells and the annual change in CAC score. At 1-year follow-up, 117 (75%) patients had an increase in CAC score compared with baseline. The percentage change in CAC score in all patients was 36.6%. There was no significant difference in percentage change in CAC score between the PIT2, PIT4, and PIT1 + EPA groups (31.1%, 38.9%, and 40.2%, respectively, $p = 0.86$). Table 3 presents the results of the simple correlation analysis showing

Table 2. Correlations between number of CD34-positive cells and other variables.

Variables	r	p
Age	–0.26	< 0.01
Male gender	0.38	< 0.01
Hypertension	–0.02	0.81
Diabetes mellitus	0.12	0.14
Smoker	0.30	< 0.01
Warfarin use	–0.01	0.90
Creatinine	–0.03	0.68
Total cholesterol	0.05	0.57
LDL-C	0.16	0.05
HDL-C	–0.14	0.09
Triglyceride*	0.09	0.27
hsCRP*	0.13	0.12
CAC score*	–0.06	0.43

*Triglyceride, hsCRP, and CAC score were log-transformed in this analysis. LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; hsCRP — high-sensitivity C-reactive protein; CAC score — coronary artery calcium score

Table 3. Correlations between annual change in coronary artery calcium (CAC) score and other variables

Variables	r	p
Age	0.02	0.80
Male gender	0.05	0.57
Hypertension	–0.08	0.33
Diabetes	0.02	0.78
Smoker	–0.11	0.19
Warfarin use	–0.06	0.47
Creatinine	0.13	0.12
Total cholesterol	–0.07	0.40
LDL-C	–0.15	0.07
HDL-C	0.02	0.78
Triglyceride*	0.08	0.34
hsCRP*	–0.03	0.67
CD34 positive cell number	–0.19	0.02

*Triglyceride and hsCRP were log-transformed in this analysis. LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; hsCRP — high-sensitivity C-reactive protein

the association between change in CAC score and baseline variables. Age, sex, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride, and hsCRP at baseline were not significantly correlated with annual change in log-transformed CAC score. Meanwhile, CD34-positive cell numbers at baseline as a continuous

Table 4. Comparison of baseline characteristics between the high- and low-CD34 groups.

	High-CD34 group	Low-CD34 group	P
N	82	74	
Age [years]	65 ± 10	69 ± 9	< 0.01
Male gender	60 (73)	25 (34)	< 0.01
Body mass index [kg/m^2]	25.6 ± 4.1	24.6 ± 3.8	0.13
Hypertension	65 (79)	62 (84)	0.47
Diabetes mellitus	23 (28)	19 (26)	0.74
Current smoker	21 (26)	5 (7)	< 0.01
Warfarin use	5 (6)	2 (3)	0.45
Creatinine [mg/dL]	0.81 ± 0.22	0.93 ± 1.45	0.47
AST [IU/L]	28 ± 14	26 ± 13	0.50
ALT [IU/L]	31 ± 21	25 ± 22	0.11
Total cholesterol [mg/dL]	177 ± 30	174 ± 33	0.59
LDL-C [mg/dL]	96 ± 23	90 ± 25	0.16
HDL-C [mg/dL]	54 ± 12	57 ± 15	0.17
Triglyceride [mg/dL]	123 (95–167)	106 (77–155)	0.06
HbA1c [%]	5.8 ± 0.9	5.7 ± 0.5	0.62
hsCRP [mg/L]	545 (338–1110)	530 (305–945)	0.71
CAC score	90 (24–242)	101 (33–225)	0.74
PIT2/PIT4/PIT2 + EPA	29 (35)/24 (29)/29 (35)	26 (35)/21 (28)/27 (37)	0.99
CD34-positive cell number [/μL]	1.5 ± 0.6	0.5 ± 0.2	< 0.01

Data are presented as mean ± standard deviation, number (%), or median (interquartile range). AST — aspartate aminotransferase; ALT — alanine aminotransferase; LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; HbA1c — glycated hemoglobin A1c; hsCRP — high-sensitivity C-reactive protein; CAC score — coronary artery calcium score; PIT2 — 2 mg/day pitavastatin; PIT4 — 4 mg/day pitavastatin; EPA — 1800 mg/day eicosapentaenoic acid

variable was inversely correlated with annual change in log-transformed CAC score (r = –0.19, p = 0.02).

Furthermore, patients were classified into two groups based on the median number of circulating CD34-positive cells (0.8 cells/μL) and defined as high- and low-CD34 groups. Baseline characteristics were compared between the high-CD34 and low-CD34 patients (Table 4). The low-CD34 group was older and had a lower prevalence of smokers and male patients compared with the high-CD34 group. No significant differences were observed between the two groups in any of the blood test variables. In addition, baseline CAC score was not significantly different between the two groups. The change in CAC score was compared between the high- and low-CD34 groups after adjusting for age, gender, and smoking status, which were significantly different between the two groups. The adjusted change in CAC score in the low-CD34 group was significantly greater than that in the high-CD34 group (53.9% [95% CI 31.3–76.5] vs. 21.1% [95% CI –0.3–42.5], respectively, p = 0.04; Fig. 2).

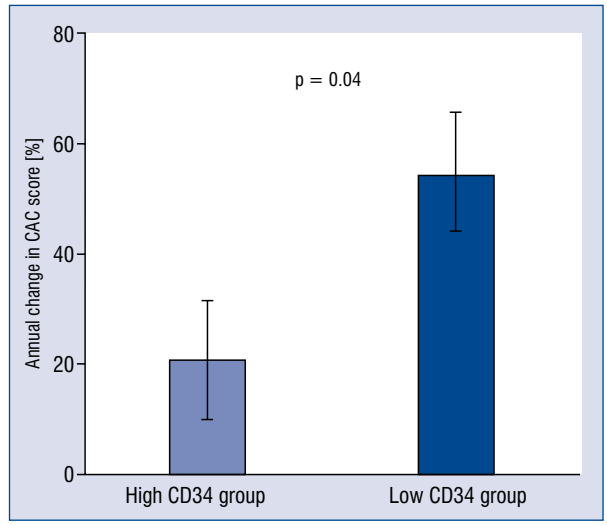


Figure 2. Comparison of the adjusted percentage change in coronary artery calcium (CAC) score between high- and low-CD34 groups. CAC scores were adjusted for age and gender. Bars represent mean ± 95% confidential interval.

Table 5. Univariate and multivariate predictors of coronary artery calcium (CAC) progression.

Variables	Univariable			Multivariable		
	Odds ratio	95% CI	P	Odds ratio	95% CI	P
Age (≥ 65 years)	1.08	0.50–2.34	0.84			
Male gender	1.04	0.50–2.14	0.93			
Hypertension	0.95	0.37–2.42	0.91			
Diabetes mellitus	1.59	0.66–3.80	0.30			
Current smoker	0.71	0.279–1.777	0.46			
Warfarin use	0.43	0.09–1.99	0.28			
Creatinine	1.17	0.56–2.34	0.66			
LDL-C	0.98	0.97–1.00	0.02	0.99	0.97–1.00	0.08
HDL-C	1.01	0.98–1.04	0.47			
HbA1c	1.17	0.63–2.16	0.63			
CAC score*	1.95	1.15–3.23	0.01	1.82	1.05–3.17	0.03
Low CD34 group	2.97	1.35–6.52	< 0.01	2.88	1.28–6.49	0.01
PIT2	0.63	0.39–1.76	0.83			
PIT4	1.24	0.55–2.81	0.61			
PIT2 + EPA	1.00	0.47–2.13	1.00			

*CAC score was log-transformed in this analysis. CI — confidence interval; LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; HbA1c — glycated hemoglobin A1c; PIT2 — 2 mg/day pitavastatin; PIT4 — 4 mg/day pitavastatin; EPA — 1800 mg/day eicosapentaenoic acid

Table 5 shows the unadjusted and adjusted odds ratio (OR) for the association between clinical variables and CAC progression. In univariate logistic regression analysis, low CD34-positive cell numbers (< 0.8 cells/μL), high CAC score, and high LDL-C were significantly associated with CAC progression. In multivariate logistic regression analysis, low CD34-positive cell numbers and high CAC score remained independent predictors of CAC progression, with ORs of 2.88 (95% CI: 1.28–6.49, p = 0.01) and 1.82 (95% CI: 1.05–3.17, p = 0.03), respectively. To validate the association between number of CD34-positive cells and CAC progression further, CAC progression was redefined as a change in CAC score > 20%. In line with previous analysis, univariate logistic regression analysis showed that low CD34-positive cell number was a significant independent predictor of percentage change in CAC score > 20% with an OR of 1.96 (95% CI: 1.04–3.70, p = 0.04).

Finally, the association between annual change in CD34-positive cells and CAC progression was analyzed. At 1-year follow-up, 85 (54.5%) patients had an increase in CD34-positive cell numbers compared with baseline. The percentage change in the number of CD34-positive cells in all patients was 27.3%. There was no significant difference in the percentage change in CD34-positive cell numbers between the PIT2, PIT4, and PIT1 + EPA groups (39.1%, 23.7%, and 19.0%, respectively, p = 0.40). Meanwhile, at 1-year follow-up, 117 (75%) patients had an increase in CAC score compared with baseline. The percentage change in CAC score in all patients was 36.6%. There was also no significant difference in the percentage change in CAC score between the PIT2, PIT4, and PIT1 + EPA groups (31.1%, 38.9%, and 40.2%, respectively, p = 0.86). No significant association between the change in CD34-positive cell numbers and the change in CAC score was observed when all patients were combined (r = 0.10, p = 0.24).

Discussion

The major finding of the present study is that low numbers of circulating CD34-positive cells are independently associated with CAC progression in patients with hypercholesterolemia under statin therapy. To the best of our knowledge, this is the first study to investigate the association between the number of CD34-positive cells and CAC progression. Our finding further characterizes the association between low CD34-positive cell numbers and the development of cardiovascular events. The measurement of circulating CD34-positive

cells may help identify patients at higher risk of atherosclerotic disease.

Endothelial progenitor cells that express CD34 on their cell surface play an important role in maintaining and repairing the vascular endothelium [10]. A decrease in the number of CD34-positive cells suggests a reduction in endothelial repair activity, which may result in insufficient repair. Previous studies have confirmed a direct correlation between endothelial progenitor cell numbers and endothelial dysfunction, measured as brachial artery flow-mediated dilation [2]. Moreover, a report has demonstrated that reduced baseline CD34-positive cell numbers is a predictor of mortality among patients with coronary artery disease risk factors [11–13]. Although CD34-positive cell numbers are reduced by conventional cardiovascular risk factors [14–16], the direct contribution of CD34-positive cells to cardiovascular events remains unclear. Our result may simply denote that patients with low CD34-positive cell numbers have more cardiovascular risk factors than patients with high CD34-positive cell numbers. However, taken together with data from other groups, the measurement of CD34-positive cell numbers may be useful to evaluate the risk of cardiovascular disease.

The CAC score reflects the presence and extent of coronary atherosclerosis and is a useful tool for risk stratification of adverse events [4, 5]. In a population-based study of 6722 participants, the CAC score was shown to predict cardiovascular events independently of traditional risk factors [17]. Meanwhile, statins lower the risk of cardiovascular events [18]. Considering the procalcific effects of statins on coronary arteries, there is a possibility that statins reduce the absolute risk of cardiovascular events in patients on statin therapy. A previous study — the Multi-Ethnic Study of Atherosclerosis — demonstrated that CAC > 0 was associated with a nearly twofold higher risk of incident cardiovascular events regardless of baseline statin or incident statin use [19]. CAC can therefore risk stratify individuals already taking statins. Moreover, serial CAC score assessment has also been proposed as a useful tool for monitoring disease progression, and CAC progression is an independent predictor for adverse cardiovascular outcomes [6]. In previous short-term and long-term studies, standard coronary risk factors have been related to CAC progression [20, 21]. In this study, two definitions of CAC progression were used: annual percentage change in CAC score > 0% and > 20% were applied to exclude interscan variability, and confirmed independent association between number of CD34-positive cells and CAC progression.

Our study demonstrated the association between the baseline number of CD34-positive cells and CAC progression; however, whether CD34-positive cells are directly involved in CAC progression remains unclear for several reasons. First, CD34-positive cells as markers of endothelial dysfunction (the earliest sign of atherosclerosis) and CAC, which is found in advanced atherosclerotic lesions, reflect different stages of atherosclerosis [2, 22, 23]. Second, previous experimental studies have suggested that osteopontin-mediated vascular calcification may originate from osteoprogenitor cells and occurs in the adventitia independently of endothelial injury [24]. However, other studies of the relationship between endothelial dysfunction and CAC have shown conflicting results [25, 26]. Further study is needed to clarify the role of CD34-positive cells in vascular calcification.

Our study did not find a significant association between the change in CD34-positive cell number and CAC progression. One explanation could be the effect of statins and eicosapentaenoic acid on these measures. Previous studies have demonstrated that both statin monotherapy and statin plus omega-3 fatty acids increase CD34-positive cell numbers [27, 28]. Additionally, intensive lipid-lowering by statins has been reported to increase CAC [29, 30]. Thus, the increase in both CD34-positive cells and CAC by statins could affect the association between the change in CD34-positive cells and CAC progression. Another explanation is that the follow-up duration of this study was too short to assess the association between them. A long-term follow-up may be needed to clarify the association between the change in CD34-positive cell numbers and CAC progression.

Limitations of the study

Our study has some limitations that should be addressed. First, our study includes only Japanese patients with hypercholesterolemia. The prevalence and development of CAC score have significant differences by race or ethnicity [31]. In addition, patients with hypercholesterolemia are known to exhibit lower numbers of CD34-positive cells than the general population [10]. Therefore, our result may not reflect the general population and other ethnic groups. Second, all patients enrolled in our study were taking statin therapies. CAC progression might be affected by statin use due to its procalcific effects [32]. Third, we defined CAC progression as an endpoint in this study, not

cardiovascular events. The prognostic significance of our study should be confirmed in larger studies with long follow-up periods.

Conclusions

In conclusion, our study demonstrates the association between low CD34-positive cell numbers and CAC progression in patients with hypercholesterolemia, which may explain the association between the number of CD34-positive cells and cardiovascular events. The quantification of circulating CD34-positive cells may help identify patients at higher risk of atherosclerotic disease.

Acknowledgments

This research was funded by the Japan Heart Foundation (No. 12090021).

We thank Hirohiko Asonuma, MD, Satoru Sakuragi, MD, Makoto Nakahama, MD, Yusuke Kawai, MD, Tadahisa Uesugi, MD, Takefumi Oka, MD, Mitsuru Munemasa, MD, Natsuki Takahashi, MD, Naoki Mukohara, MD, Seiji Habara, MD, Yusuke Katayama, MD, Ritsuko Terasaka, MD, Atsushi Mima, MD, Hitoshi Matsubara, MD, Shingo Hosogi, MD, Masayuki Doi, MD, Masayuki Ueeda, MD, Norio Urabe, MD, Kazufumi Takeuchi, MD, Yasuharu Namba, MD, Tetsuya Sato, MD, Nobuyuki Yamada, MD, Masahito Taniguchi, MD, Yutaka Kajikawa, MD, Kouki Watanabe, MD, Kenichi Hisamatsu, MD, Hiroo Kobayashi, MD, and Kiyoaki Maekawa, MD, who were the PEACH Investigators. We thank Kaoru Akazawa, Miyuki Fujiwara, and Masayo Ohmori for their technical assistance.

Conflict of interest: None declared

References

1. Asahara T, Murohara T, Sullivan A, et al. Isolation of putative progenitor endothelial cells for angiogenesis. Science. 1997; 275(5302): 964–967, doi: 10.1126/science.275.5302.964, indexed in Pubmed: 9020076.
2. Hill JM, Zalos G, Halcox JPJ, et al. Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. N Engl J Med. 2003; 348(7): 593–600, doi: 10.1056/NEJMoa022287, indexed in Pubmed: 12584367.
3. Werner N, Kosiol S, Schiegl T, et al. Circulating endothelial progenitor cells and cardiovascular outcomes. N Engl J Med. 2005; 353(10): 999–1007, doi: 10.1056/NEJMoa043814, indexed in Pubmed: 16148285.
4. Wexler L, Brundage B, Crouse J, et al. Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications. A statement for health professionals from the American Heart Association. Writing Group. Circulation. 1996; 94(5): 1175–1192, doi: 10.1161/01.cir.94.5.1175, indexed in Pubmed: 8790070.
5. Greenland P, LaBree L, Azen SP, et al. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA. 2004; 291(2): 210–215, doi: 10.1001/jama.291.2.210, indexed in Pubmed: 14722147.
6. Budoff MJ, Hokanson JE, Nasir K, et al. Progression of coronary artery calcium predicts all-cause mortality. JACC Cardiovasc Imaging. 2010; 3(12): 1229–1236, doi: 10.1016/j.jcmg.2010.08.018, indexed in Pubmed: 21163451.
7. Miyoshi T, Kohno K, Asonuma H, et al. Effect of intensive and standard pitavastatin treatment with or without eicosapentaenoic acid on progression of coronary artery calcification over 12 months: prospective multicenter study. Circ J. 2018; 82(2): 532–540, doi: 10.1253/circj.CJ-17-0419, indexed in Pubmed: 28867681.
8. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990; 15(4): 827–832, doi: 10.1016/0735-1097(90)90282-t, indexed in Pubmed: 2407762.
9. Hokanson JE, MacKenzie T, Kinney G, et al. Evaluating changes in coronary artery calcium: an analytic method that accounts for interscan variability. AJR Am J Roentgenol. 2004; 182(5): 1327–1332, doi: 10.2214/ajr.182.5.1821327, indexed in Pubmed: 15100140.
10. Fadini GP, Losordo D, Dimmeler S. Critical reevaluation of endothelial progenitor cell phenotypes for therapeutic and diagnostic use. Circ Res. 2012; 110(4): 624–637, doi: 10.1161/CIRCRESAHA.111.243386, indexed in Pubmed: 22343557.
11. Fadini GP, de Kreutzenberg S, Agostini C, et al. Low CD34+ cell count and metabolic syndrome synergistically increase the risk of adverse outcomes. Atherosclerosis. 2009; 207(1): 213–219, doi: 10.1016/j.atherosclerosis.2009.03.040, indexed in Pubmed: 19406403.
12. Samman Tahhan A, Hammadah M, Raad M, et al. Progenitor cells and clinical outcomes in patients with acute coronary syndromes. Circ Res. 2018; 122(11): 1565–1575, doi: 10.1161/CIRCRESAHA.118.312821, indexed in Pubmed: 29514830.
13. Patel RS, Li Q, Ghasemzadeh N, et al. Circulating CD34+ progenitor cells and risk of mortality in a population with coronary artery disease. Circ Res. 2015; 116(2): 289–297, doi: 10.1161/CIRCRESAHA.116.304187, indexed in Pubmed: 25323857.
14. Di Stefano R, Barsotti MC, Felice F, et al. Smoking and endothelial progenitor cells: a revision of literature. Curr Pharm Des. 2010; 16(23): 2559–2566, doi: 10.2174/138161210792062939, indexed in Pubmed: 20550506.
15. Umemura T, Soga J, Hidaka T, et al. Aging and hypertension are independent risk factors for reduced number of circulating endothelial progenitor cells. Am J Hypertens. 2008; 21(11): 1203–1209, doi: 10.1038/ajh.2008.278, indexed in Pubmed: 18787520.
16. Fadini GP, Miorin M, Facco M, et al. Circulating endothelial progenitor cells are reduced in peripheral vascular complications of type 2 diabetes mellitus. J Am Coll Cardiol. 2005; 45(9): 1449–1457, doi: 10.1016/j.jacc.2004.11.067, indexed in Pubmed: 15862417.
17. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med. 2008; 358(13): 1336–1345, doi: 10.1056/NEJMoa072100, indexed in Pubmed: 18367736.
18. Kimura T, Iimuro S, Taguchi I, et al. High-dose versus low-dose pitavastatin in japanese patients with stable coronary artery

disease (REAL-CAD): a randomized superiority trial. Circulation. 2018; 137(19): 1997–2009, doi: 10.1161/CIRCULATIONAHA.117.032615, indexed in Pubmed: 29735587.
19. Rifai MAl, Blaha MJ, Patel J, et al. Coronary artery calcification, statin use and long-term risk of atherosclerotic cardiovascular disease events (from the multi-ethnic study of atherosclerosis). Am J Cardiol. 2020; 125(6): 835–839, doi: 10.1016/j.amjcard.2019.12.031, indexed in Pubmed: 31980142.
20. Kronmal RA, McClelland RL, Detrano R, et al. Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation. 2007; 115(21): 2722–2730, doi: 10.1161/CIRCULATIONAHA.106.674143, indexed in Pubmed: 17502571.
21. Gassett AJ, Sheppard L, McClelland RL, et al. Risk factors for long-term coronary artery calcium progression in the multi-ethnic study of atherosclerosis. J Am Heart Assoc. 2015; 4(8): e001726, doi: 10.1161/JAHA.114.001726, indexed in Pubmed: 26251281.
22. Nakahara T, Dweck MR, Narula N, et al. Coronary Artery Calcification: From Mechanism to Molecular Imaging. JACC Cardiovasc Imaging. 2017; 10(5): 582–593, doi: 10.1016/j.jcmg.2017.03.005, indexed in Pubmed: 28473100.
23. Gutiérrez E, Flammer AJ, Lerman LO, et al. Endothelial dysfunction over the course of coronary artery disease. Eur Heart J. 2013; 34(41): 3175–3181, doi: 10.1093/eurheartj/eht351, indexed in Pubmed: 24014385.
24. Towler DA, Bidder M, Latifi T, et al. Diet-induced diabetes activates an osteogenic gene regulatory program in the aortas of low density lipoprotein receptor-deficient mice. J Biol Chem. 1998; 273(46): 30427–30434, doi: 10.1074/jbc.273.46.30427, indexed in Pubmed: 9804809.
25. Ramadan MM, Mahfouz EM, Gomaa GF, et al. Evaluation of coronary calcium score by multidetector computed tomography in relation to endothelial function and inflammatory markers in asymptomatic individuals. Circ J. 2008; 72(5): 778–785, doi: 10.1253/circj.72.778, indexed in Pubmed: 18441459.
26. Han SH, Gerber TC, Suwaidi JAl, et al. Relationship between coronary endothelial function and coronary calcification in early atherosclerosis. Atherosclerosis. 2010; 209(1): 197–200, doi: 10.1016/j.atherosclerosis.2009.08.027, indexed in Pubmed: 19962702.
27. Pirro M, Schillaci G, Romagno PF, et al. Influence of short-term rosuvastatin therapy on endothelial progenitor cells and endothelial function. J Cardiovasc Pharmacol Ther. 2009; 14(1): 14–21, doi: 10.1177/1074248408331021, indexed in Pubmed: 19158317.
28. Chantzichristos VG, Agouridis AP, Moutzouri E, et al. Effect of rosuvastatin or its combination with omega-3 fatty acids on circulating CD34(+) progenitor cells and on endothelial colony formation in patients with mixed dyslipidaemia. Atherosclerosis. 2016; 251: 240–247, doi: 10.1016/j.atherosclerosis.2016.06.047, indexed in Pubmed: 27415612.
29. Smit JM, van Rosendael AR, El Mahdiui M, et al. Impact of clinical characteristics and statins on coronary plaque progression by serial computed tomography angiography. Circ Cardiovasc Imaging. 2020; 13(3): e009750, doi: 10.1161/CIRCIMAGING.119.009750, indexed in Pubmed: 32160786.
30. Lee SE, Sung JiM, Andreini D, et al. Effects of statins on coronary atherosclerotic plaques: the PARADIGM study. JACC Cardiovasc Imaging. 2018; 11(10): 1475–1484, doi: 10.1016/j.jcmg.2018.04.015, indexed in Pubmed: 29909109.
31. Orimoloye OA, Budoff MJ, Dardari ZA, et al. Race/Ethnicity and the prognostic implications of coronary artery calcium for all-cause and cardiovascular disease mortality: the coronary artery calcium consortium. J Am Heart Assoc. 2018; 7(20): e010471, doi: 10.1161/JAHA.118.010471, indexed in Pubmed: 30371271.
32. Puri R, Nicholls SJ, Shao M, et al. Impact of statins on serial coronary calcification during atheroma progression and regression. J Am Coll Cardiol. 2015; 65(13): 1273–1282, doi: 10.1016/j.jacc.2015.01.036, indexed in Pubmed: 25835438.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 3, 432–440
DOI: 10.5603/CJ.a2020.0040

ISSN 1897–5593
eISSN 1898–018X

Oral NAloxone to overcome the moRphine effect in acute COronary syndrome patients treated with TICagrelor — NARCOTIC trial

Piotr Niezgoda[1]*, Malwina A. Barańska[1]*, Joanna Sikora[2], Przemysław Sobczak[2], Katarzyna Buszko[3], Adam Sikora[4], Michał P. Marszałł[4], Eliano P. Navarese[1, 5, 6], Bernd Jilma[7], Jacek Kubica[1]

[1]Department of Cardiology and Internal Medicine, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland
[2]Department of Pharmacology and Therapy, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland
[3]Department of Theoretical Foundations of Biomedical Science and Medical Informatics, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland
[4]Department of Medicinal Chemistry, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland
[5]Interventional Cardiology and Cardiovascular Medicine Research, Mater Dei Hospital, Bari, Italy
[6]Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Alberta, Canada
[7]Department of Clinical Pharmacology, Medical University of Vienna, Austria

Abstract

Background: *Numerous worldwide clinical trials have proven the indisputably negative influence of morphine on the pharmacokinetics and pharmacodynamics of $P2Y_{12}$ receptor inhibitors in patients presenting with acute coronary syndromes. The aim of this trial was to evaluate whether oral co-administration of an anti-opioid agent, naloxone, can be considered a successful approach to overcome 'the morphine effect'.*

Methods: *Consecutive unstable angina patients receiving ticagrelor and morphine with or without orally administered naloxone underwent assessment of platelet reactivity using Multiplate analyzer as well as evaluation of the pharmacokinetic profile of ticagrelor and its active metabolite, AR-C124910XX, at 9 pre-defined time points within the first 6 hours following oral intake of the ticagrelor loading dose.*

Results: *The trial shows no significant differences regarding the pharmacokinetics of ticagrelor between both study arms throughout the study period. AR-C124910XX plasma concentration was significantly higher 120 min after the ticagrelor loading dose administration ($p = 0.0417$). However, the evaluation of pharmacodynamics did not show any statistically significant differences between the study arms.*

Conclusions: *To conclude, this trial shows that naloxone co-administration in ticagrelor-treated acute coronary syndrome patients on concomitant treatment with morphine shows no definite superiority in terms of ticagrelor pharmacokinetic and pharmacodynamic profile.* (Cardiol J 2022; 29, 3: 432–440)

Key words: acute coronary syndrome, unstable angina, ticagrelor, morphine, naloxone

Address for correspondence: Piotr Niezgoda, MD, Department of Cardiology and Internal Medicine, Collegium Medicum, Nicolaus Copernicus University, ul. Skłodowskiej 9, 85–094 Bydgoszcz, Poland, tel: +48 52 585 40 23, e-mail: piotr.niezgoda1986@gmail.com

Received: 24.09.2019 Accepted: 25.02.2020 Early publication date: 18.03.2020

**Equal contributors.*

Introduction

The development of contemporary treatment of acute coronary syndromes (ACS) has forced the establishment of methods of rapid platelet inhibition. The results of the PLATO trial proved the superiority of ticagrelor over well-known and widely used clopidogrel in terms of its effectiveness, mainly demonstrated by the reduction of the composite endpoint including cardiovascular death, myocardial infarction or stroke with no significant increase of the risk of clinically significant bleeding [1]. Based on those findings ticagrelor has become the treatment of choice in patients presenting with ACS according to currently available guidelines [2–6].

Numerous ACS patients, especially those presenting with ST-segment elevation myocardial infarction (STEMI), require strong and effective analgesia. The most commonly used analgesic medication nowadays is morphine [2]. Morphine administration used to be considered beneficial for ACS patients as it was thought to be associated not only with pain alleviation, but also with a positive tranquilizing effect on treated individuals. Several international studies however, have revealed a negative interaction between morphine and $P2Y_{12}$ receptor inhibitors leading to decrease of the plasma concentrations of those platelet inhibitors and their metabolites as well as delay and attenuation of their antiplatelet activity [7–11]. The discovery of the negative influence of morphine on the pharmacokinetic/pharmacodynamics (PK/PD) profile of ticagrelor in ACS patients resulted in a decrease of class of recommendation for morphine use to class IIa for STEMI based on the latest guidelines [2]. Morphine has been found to negatively influence gastric emptying, impair intestinal motility, reduce intestinal secretion and induce nausea or vomiting [12]. The phenomenon presented above can be called 'the morphine effect'.

Naloxone, a selective opioid receptor antagonist, is widely used to diminish negative effects of opioid drugs. Its utility is most pronounced in opioid substitution therapy in cases of opioid addiction or reversal of opioid action in opioid intoxication. Typically, in such clinical situations, naloxone is administered parenterally. However, if administered orally, it has been proven to successfully reduce the negative impact on gastrointestinal tract by relieving opioid-related constipation in oncological patients requiring regular opioid administration. This approach allows the elimination of intestinal motility impairment without risking attenuation of the analgesic activity of an opioid, as naloxone administered orally is associated with a strong first-pass effect making its serum concentration barely detectable. The final bioavailability of the drug after oral administration ranges from 2% to 3% [13–16].

On the basis of the aforementioned findings it was hypothesized that co-administration of naloxone may prove beneficial as a potential method of overcoming 'the morphine effect' in ACS patients treated with ticagrelor who received morphine.

Methods

Study design and population

A pharmacokinetic/pharmacodynamic, phase IV, single center, investigator-initiated, randomized, open-label, active-controlled trial was designed and it was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki guidelines. The previously published study protocol [17] was approved by The Ethics Committee of The Nicolaus Copernicus University in Torun, Collegium Medicum in Bydgoszcz (approval number KB 540/2015). Any study-related procedures were undertaken only after obtainment of informed consent to participate in the trial from each study participant. Males and non-pregnant females, aged 18–80 years, admitted to the Department of Cardiology, A. Jurasz University Hospital in Bydgoszcz, Poland due to unstable angina and qualified for coronary angiography, underwent eligibility screening. The complete list of inclusion and exclusion criteria is presented in Table 1.

Patients admitted to the Department of Cardiology, due to unstable angina received orally a 300 mg loading dose (LD) of plain acetylsalicylic acid (Polpharma SA, Starogard Gdanski, Poland) and underwent eligibility screening for participation in the study. Having consented to participate in the trial, eligible patients were randomized in a 1:1 ratio into two study arms as follows — the active study arm including patients receiving: 1) crushed tablets of 180 mg ticagrelor in 10 mL suspension in tap water administered orally; 2) 5 mg of morphine administered intravenously; 3) 1 mg of naloxone administered orally; and the control group treated with: 1) crushed tablets of 180 mg ticagrelor in 10 mL suspension in tap water administered orally; and 2) 5 mg of morphine administered intravenously. The Random Allocation Software version 1.0. was used for the process of randomization.

Based on the results of studies previously conducted in the present department, oral ad-

Table 1. A complete list of inclusion/exclusion criteria for the study.

Inclusion criteria (all criteria must be met)
Provision of informed consent prior to any study specific procedures
Diagnosis of unstable angina
Male or non-pregnant female, aged 18–80 years
Provision of informed consent for angiography and percutaneous coronary intervention
GRACE score < 140 patients
Exclusion criteria (none of the criteria can be met)
Treatment with ticlopidine, clopidogrel, prasugrel or ticagrelor within 14 days before study enrollment
Current treatment with morphine or any opioid "mi" receptor agonist
Hypersensitivity to ticagrelor
Current treatment with oral anticoagulant or chronic therapy with low-molecular-weight heparin
Active bleeding
History of intracranial hemorrhage
Recent gastrointestinal bleeding (within 30 days)
History of coagulation disorders
Platelet count less than 100×10^3/mcl
Hemoglobin concentration less than 10.0 g/dL
History of moderate or severe hepatic impairment
History of major surgery or severe trauma (within 3 months)
Risk of bradycardic events as judged by the investigator
Second- or third-degree atrioventricular block during screening for eligibility
History of asthma or severe chronic obstructive pulmonary disease
Kidney disease requiring dialysis
Manifest infection or inflammatory state
Killip class III or IV during screening for eligibility
Respiratory failure
History of severe chronic heart failure (NYHA class III or IV)
Concomitant therapy with strong CYP3A inhibitors (ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin, nefazadone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir) or strong CYP3A inducers (rifampicin, phenytoin, carbamazepine, dexamethasone, phenobarbital) within 14 days and during study treatment
Body weight below 50 kg

ministration of crushed ticagrelor was chosen as it was associated with the optimal pharmacokinetic and pharmacodynamic profile in unstable angina patients [18]. Only patients with low and intermediate risk of in-hospital mortality as assessed with the GRACE scale were enrolled in the study, which allowed completion of the whole blood sampling schedule before coronary angiography, avoiding the risk of its unpredictable impact on platelet function. Taking into account that morphine negatively affects the absorption of ticagrelor from the gastrointestinal tract, we assumed that addition of an opioid antagonist, naloxone administered orally, would contribute to the optimization of the PK/PD profile of ticagrelor and its active metabolite. As assessed in previous studies, a group of 15 patients for each study arm was considered to be sufficient for statistical analysis.

Blood sample collection

According to the study protocol, following obtainment of informed consent for participation in the study and randomization into the study arms, collection of blood samples for the pharmacokinetic and pharmacodynamic assessment was done. Nine predefined time points of blood sampling were as follows: before the administration of ticagrelor LD and 15 min, 30 min, 45 min, 1 h, 2 h, 3 h, 4 h, 6 h after its administration.

Table 2. Complete list of study outcomes.

Study primary outcome
Time to maximum concentration (t_{max}) for ticagrelor and AR-C124900XX
Study secondary outcomes
Maximum ticagrelor and AR-C124900XX concentration
Area under the plasma concentration-time curve for ticagrelor (AUC 0–6 h)
Area under the plasma concentration-time curve for AR-C124900XX (AUC 0–6 h)
Platelet reactivity assessed by multiple electrode aggregometry

Pharmacokinetics

Pharmacokinetic assessment was performed for each study participant at all predefined time points. Plasma concentrations of ticagrelor and its active metabolite were evaluated in The Department of Medicinal Chemistry, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz using liquid chromatography and mass spectrometry. Measurements were performed using Shimadzu UPLC Nexera X2 system and Shimadzu 8030 ESI-Triple Quadrupole mass spectrometer. The limits of quantification for ticagrelor and its active metabolite were defined as 4.69 ng/mL.

Pharmacodynamics

The evaluation of pharmacodynamics was performed using the Multiplate analyzer (ADPtest, Roche Diagnostics, Switzerland). The measurements of platelet reactivity were conducted with multiple electrode aggregometry (MEA) at all time points as mentioned above. Area under the aggregation curve (AUC) as a parameter reflecting the overall exposure to both ticagrelor and AR-C124900XX, was assessed on the assumption that AUC > 46 units (U) was defined as high platelet reactivity (HPR).

Study outcomes

According to the protocol, the primary endpoint of this PK/PD study was the time required to reach the maximum plasma concentration of ticagrelor and AR-C124900XX following ticagrelor loading dose intake. Secondary endpoints included maximum concentration of ticagrelor and its metabolite, area under the plasma concentration-time curve (AUC_{CT}) for ticagrelor and AR-C124900XX and platelet reactivity assessed by MEA in the aforementioned time points. The complete list of study outcomes is presented in Table 2.

Statistical analysis

Statistical analysis was performed using Matlab R2014 Software (Mathworks, Natick, MA, USA), the Statistica 12.5 package (StatSoft, Tulsa, OK, USA) and R version 3.5.0 (R: library lme). $P < 0.05$ were considered statistically significant. AUC was calculated using the trapezoidal rule. Comparative analysis of pharmacokinetic parameters between the study arms and time points were conducted using mixed models with random effects with the maximum likelihood method applied for estimating variance parameters. Comparison of pharmacodynamic parameters between the study arms was performed with the Fisher exact test.

Results

Population baseline characteristics

Between October 2016 and December 2018, a total of 30 unstable angina (UA) patients were enrolled in the study. Baseline serum troponin evaluation required ruling out an acute myocardial infarction was performed for each study participant showing no case of elevation above the reference level of 34.5 ng/L and 15.6 ng/L for men and women, respectively. The study population was generally well balanced, except for the prevalence of prior coronary artery disease and consequently prior percutaneous coronary intervention, which were noticeably higher in the study arm (66.7% vs. 28.6%, $p = 0.04$ and 53.3% vs. 14.3%, $p = 0.03$, respectively). The study population baseline characteristics are presented in Table 3.

Safety and tolerability evaluation

The safety evaluation did not reveal any case of serious adverse events such as death, myocardial infarction, stent thrombosis, stroke or thromboembolic events throughout the study. Minor symptoms including weakness and headache were reported by 2 patients in the active arm. On the other hand, adverse effects in the control group of participants included mild bradycardia (50–55 bpm), nausea (2 patients) and excessive sweating associated with feeling unwell (1 patient). Due to

Table 3. Study population baseline characteristics.

	Study group (%) (n = 15)	Control group (%) (n = 14)	P
Age [years]	66.87*	60.21*	0.56
Male	12 (80)	7 (50)	0.089
Body weight [kg]	88.73*	77.48*	0.25
Body mass index [kg/m^2]	29.05*	27.24*	0.89
Prior CAD	10 (66.7)	4 (28.6)	0.04
Prior AMI	8 (53.3)	3 (21.4)	0.08
Prior PCI	8 (53.3)	2 (14.3)	0.03
Prior CABG	3 (20.0)	3 (21.4)	0.95
Arterial hypertension	12 (80.0)	9 (64.3)	0.34
Prior peptic ulcer disease	3 (20.0)	1 (7.1)	0.31
Prior gastrointestinal bleeding	1 (6.7)	1 (7.1)	0.96
Prior stroke/TIA	2 (13.3)	1 (7.1)	0.59
CKD	0	1 (7.1)	0.29
Hyperlipidemia	13 (86.7)	12 (85.7)	0.94
Current smoker	1 (6.7)	3 (21.4)	0.23
History of smoking	8 (53.3)	4 (28.6)	0.18
Family history of CAD	5 (33.3)	9 (64.3)	0.09
Diabetes mellitus	3 (20.0)	4 (28.6)	0.59
Insulin therapy	0	3 (21.4)	0.06
COPD	0	1 (7.1)	0.30
Peripheral atherosclerosis	3 (20.0)	2 (14.3)	0.68

*Data are shown as mean. AMI — acute myocardial infarction; CABG — coronary artery bypass grafting; CKD — chronic kidney disease; COPD — chronic obstructive pulmonary disease; CAD — coronary artery disease; PCI — percutaneous coronary intervention; TIA — transient ischemic attack

vomiting that required immediate administration of metoclopramide, a prokinetic drug, 1 patient's participation in the trial was terminated, which resulted in exclusion of the initially obtained results of pharmacokinetics and pharmacodynamics of this participant from statistical analysis.

Pharmacokinetics

Pharmacokinetic assessment was performed for each study participant. Statistical analysis of all results showed only a trend toward a better PK profile in the naloxone arm. Mixed models with random effects showed no significant differences between the study arms in terms of ticagrelor--related parameters. However, the difference between plasma concentrations of AR-C124910XX obtained at 120 min following ticagrelor LD reached statistical significance (p=0.0417). PK parameters obtained throughout the study are presented in Table 4. Mean concentration of ticagrelor and its active metabolite is presented in Figures 1 and 2.

Pharmacodynamics

The PD evaluation was performed for each patient, revealing no significant differences between the study arms. The superiority of the naloxone arm in terms of percentage of HPR patients at particular time points patients was only numerical. The most pronounced difference was observed at 30 min following ticagrelor LD (7 vs. 10 patients) for the naloxone and control arm respectively (p = 0.18; Fig. 3).

Discussion

The recent discovery of the so-called 'morphine effect' brought new challenges into contemporary ACS treatment strategies. As mentioned before, co-administration of morphine in the course of ACS is no longer a first-line approach due to its negative impact on $P2Y_{12}$ receptor inhibitors PK/PD profile. Inevitably, some patients, especially presenting with STEMI, will require strong anal-

Table 4. Pharmacokinetic parameters of ticagrelor and AR-C124910XX in mixed model with random effects.

	Value	Standard error	P-value
Ticagrelor			
Intercept	–274.1965	184.04303	0.1377
Time 15 vs. time 0	14.0322	223.66104	0.9500
Time 30 vs. time 0	145.4685	223.66104	0.5161
Time 45 vs. time 0	451.1968	223.66104	0.0449
Time 60 vs. time 0	762.1987	223.66104	0.0008
Time 120 vs. time 0	694.5401	223.66104	0.0022
Time 180 vs. time 0	880.6841	223.66104	0.0001
Time 240 vs. time 0	832.2042	223.66104	0.0003
Time 360 vs. time 0	589.4043	223.66104	0.0090
Group I vs. group II	79.2077	45.08410	0.0803
Time 15 group	5.8586	58.01639	0.9197
Time 30 group	30.3315	58.01639	0.6016
Time 45 group	40.3730	58.01639	0.4872
Time 60 group	31.6464	58.01639	0.5860
Time 120 group	82.9364	58.01639	0.1543
Time 180 group	–7.0878	58.01639	0.9029
Time 240 group	-4.6060	58.01639	0.9368
Time 360 group	24.9611	58.01639	0.6674
Metabolite			
Intercept	–48.18294	39.93862	0.2290
Time 15 vs. time 0	0.00000	49.98636	1.0000
Time 30 vs. time 0	–3.58612	49.98636	0.9429
Time 45 vs. time 0	17.25228	49.98636	0.7303
Time 60 vs. time 0	66.51414	49.98636	0.1847
Time 120 vs. time 0	160.11218	49.98636	0.0016
Time 180 vs. time 0	229.63223	49.98636	0.0000
Time 240 vs. time 0	258.55988	49.98636	0.0000
Time 360 vs. time 0	177.13110	49.98636	0.0005
Group I vs. group II	13.79099	9.97219	0.1681
Time 15 group	0.00000	12.96617	1.0000
Time 30 group	4.96449	12.96617	0.7022
Time 45 group	14.83565	12.96617	0.2538
Time 60 group	19.00707	12.96617	0.1441
Time 120 group	26.55748	12.96617	0.0417
Time 180 group	6.51674	12.96617	0.6158
Time 240 group	–4.16173	12.96617	0.7485
Time 360 group	8.45659	12.96617	0.5150

gesic agents to relieve unbearable pain associated with the infarction. Until now, several approaches to reduce 'the morphine effect' have been described in the literature.

The present study is the first one aiming to assess the influence of oral naloxone on ticagrelor and AR-C124900XX in ACS patients who received morphine. The results show no definite benefit in terms of the PK and PD profile of ticagrelor in the naloxone arm, however a trend toward improvement of analyzed parameters could be observed.

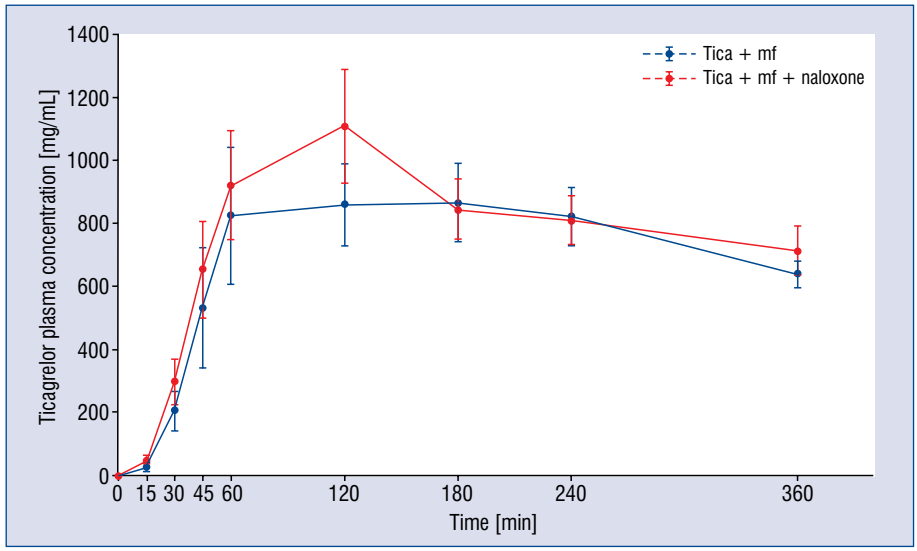


Figure 1. Mean ticagrelor plasma concentration throughout the study; tica — ticagrelor; mf — morphine.

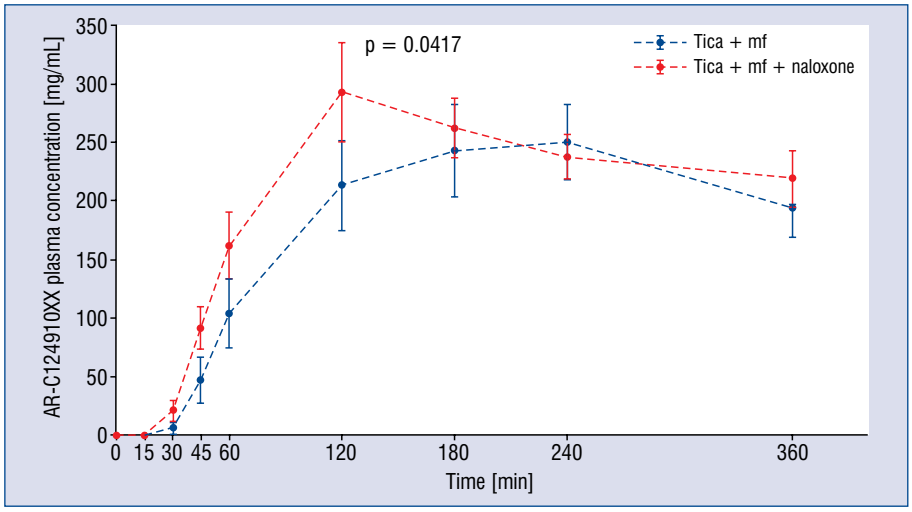


Figure 2. Mean concentration of the active metabolite, AR-C124910XX throughout the study; tica — ticagrelor; mf — morphine.

In our previous study it was proved that co-administration of an anti-emetic agent, metoclopramide, leads to higher plasma concentrations of ticagrelor and its active metabolite and reduction of time required to reach maximum plasma concentrations of ticagrelor and its metabolite (123 min vs. 168 min for control arm, p = 0.015) [19].

The PK/PD profile of currently used $P2Y_{12}$ receptor inhibitors has also been found to be noticeably dependent on the administration strategy of the drug. No inconsistencies can be found in terms of the administration of crushed tablets of $P2Y_{12}$ inhibitors. Zafar et al. [20] proved that the administration of clopidogrel in healthy volunteers was associated with faster and greater bioavailability if the drug was given as a crushed form via a nasogastric tube. According to a study by Rollini et al. [21], administration of crushed prasugrel in STEMI patients led to faster absorption of this agent. Also, it was associated with higher plasma concentrations of its metabolite and reduction of platelet reactivity 30 min after the LD of prasugrel.

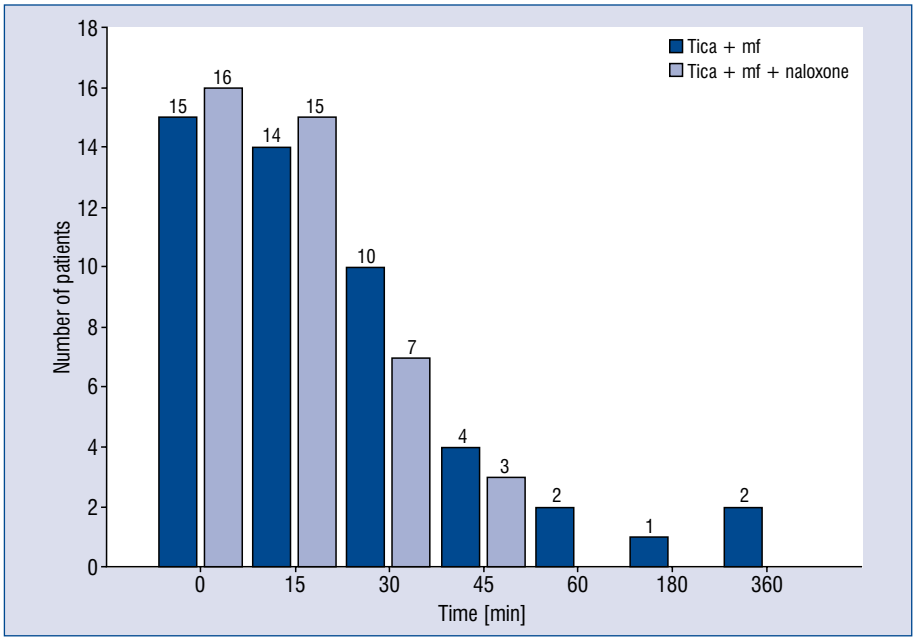


Figure 3. Proportion of patients with high platelet reactivity in study time points.

In the MOHITO study, Parodi et al. [22] reported that the time required to achieve platelet inhibition in STEMI patients was significantly shorter if they received crushed ticagrelor instead of standard integral tablets. Oral administration of crushed ticagrelor was also associated with the best PK/PD profile of ticagrelor and its active metabolite in our previous study evaluating the influence of ticagrelor administration strategy in patients presenting with UA. Moreover, the above-mentioned study demonstrated this strategy to be superior over sublingual administration of crushed ticagrelor [18].

The results of the latest studies aiming to evaluate the impact of ticagrelor administration strategy on its PK/PD profile show superiority of chewed ticagrelor in terms of platelet reactivity units (PRU) measured with VerifyNow in non-STEMI patients at 1 h where it was found to be significantly lower [23]. In a study by Venetsanos et al. [24] PRU were also significantly lower in patients presenting with stable angina pectoris in the chewed-ticagrelor arm in comparison with integral ticagrelor arm.

Limitations of the study

The study population comprised only UA patients, thus baseline platelet reactivity does not fully reflect characteristics of STEMI patients. A limited number of study participants might have negatively influenced the statistical analysis as only a trend toward improvement of the PK profile could be observed in the naloxone arm. Although the prevalence of prior coronary artery disease in the naloxone group was higher than in the control group, it did not affect baseline platelet reactivity.

Conclusions

According to available research, this study is the first one to evaluate the impact of an anti-opioid drug, naloxone, on PK and PD of ticagrelor and its active metabolite. Even though a trend toward improvement of the PK/PD profile of ticagrelor in ACS patients pre-treated with morphine followed by oral naloxone is perceptible, further research is required to determine optimal approaches to overcome the 'morphine effect'.

Conflict of interest: Malwina Barańska received honoraria for lectures from AstraZeneca. Bernd Jilma has served as a consultant to and in advisory boards of AstraZeneca. Jacek Kubica delivered a lecture for AstraZeneca. All of the other authors declare no potential conflict of interests regarding publication of this paper.

References

1. Cannon C, Harrington R, James S, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. The Lancet. 2010; 375(9711): 283–293, doi: 10.1016/s0140-6736(09)62191-7.
2. Ibanez B, James S, Agewall S, et al. ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018; 39(2): 119–177, doi: 10.1093/eurheartj/ehx393, indexed in Pubmed: 28886621.
3. Roffi M, Patrono C, Collet JP, et al. ESC Scientific Document Group . 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016; 37(3): 267–315, doi: 10.1093/eurheartj/ehv320, indexed in Pubmed: 26320110.
4. Jneid H, Anderson JL, Wright RS, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/Non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2012; 60: 645–81.
5. O'Gara PT, Kushner FG, Ascheim DD, et al. American College of Cardiology Foundation, American Heart Association Task Force on Practice Guidelines, American College of Emergency Physicians, Society for Cardiovascular Angiography and Interventions. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the American College of Emergency Physicians and Society for Cardiovascular Angiography and Interventions. Catheter Cardiovasc Interv. 2013; 82(1): E1–27, doi: 10.1002/ccd.24776, indexed in Pubmed: 23299937.
6. Kubica J, Adamski P, Paciorek P, et al. Treatment of patients with acute coronary syndrome: Recommendations for medical emergency teams: Focus on antiplatelet therapies. Updated experts' standpoint. Cardiol J. 2018; 25(3): 291–300, doi: 10.5603/CJ.a2018.0042, indexed in Pubmed: 29671864.
7. Meine TJ, Roe MT, Chen AY, et al. CRUSADE Investigators. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. Am Heart J. 2005; 149(6): 1043–1049, doi: 10.1016/j.ahj.2005.02.010, indexed in Pubmed: 15976786.
8. Kubica J, Adamski P, Ostrowska M, et al. Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial. Eur Heart J. 2016; 37(3): 245–252, doi: 10.1093/eurheartj/ehv547.
9. Parodi G, Bellandi B, Xanthopoulou I, et al. Morphine is associated with a delayed activity of oral antiplatelet agents in patients with ST-elevation acute myocardial infarction undergoing primary percutaneous coronary intervention. Circ Cardiovasc Interv. 2015; 8(1), doi: 10.1161/CIRCINTERVENTIONS.114.001593, indexed in Pubmed: 25552565.
10. Hobl EL, Stimpfl T, Ebner J, et al. Morphine decreases clopidogrel concentrations and effects: a randomized, double-blind, placebo-controlled trial. J Am Coll Cardiol. 2014; 63(7): 630–635, doi: 10.1016/j.jacc.2013.10.068, indexed in Pubmed: 24315907.
11. Hobl EL, Reiter B, Schoergenhofer C, et al. Morphine decreases ticagrelor concentrations but not its antiplatelet effects: a randomized trial in healthy volunteers. Eur J Clin Invest. 2015; 46(1): 7–14, doi: 10.1111/eci.12550.
12. Kubica J, Kubica A, Jilma B, et al. Impact of morphine on antiplatelet effects of oral P2Y12 receptor inhibitors. Int J Cardiol. 2016; 215: 201–208, doi: 10.1016/j.ijcard.2016.04.077, indexed in Pubmed: 27128531.
13. Greenwood-Van Meerveld B, Gardner CJ, Little PJ, et al. Preclinical studies of opioids and opioid antagonists on gastrointestinal function. Neurogastroenterol Motil. 2004; 16 Suppl 2: 46–53, doi: 10.1111/j.1743-3150.2004.00555.x, indexed in Pubmed: 15357851.
14. Smith K, Hopp M, Mundin G, et al. Low absolute bioavailability of oral naloxone in healthy subjects. Int J Clin Pharmacol Ther. 2012; 50(5): 360–367, doi: 10.5414/cp201646, indexed in Pubmed: 22541841.
15. Choi YS, Billings JA. Opioid antagonists: a review of their role in palliative care, focusing on use in opioid-related constipation. J Pain Symptom Manage. 2002; 24(1): 71–90, doi: 10.1016/s0885-3924(02)00424-4, indexed in Pubmed: 12183097.
16. Sykes NP. An investigation of the ability of oral naloxone to correct opioid-related constipation in patients with advanced cancer. Palliat Med. 1996; 10(2): 135–144, doi: 10.1177/026921639601000208, indexed in Pubmed: 8800821.
17. Barańska M, Niezgoda P, Kubica J. The influence of naloxone on pharmacokinetics and pharmacodynamics of ticagrelor in patients with unstable angina pectoris receiving concomitant treatment with morphine — a protocol of a randomized trial. Med Res J. 2018, doi: 10.5603/mrj.a2018.0035.
18. Niezgoda P, Sikora J, Barańska M, et al. Crushed sublingual versus oral ticagrelor administration strategies in patients with unstable angina. A pharmacokinetic/pharmacodynamic study. Thromb Haemost. 2017; 117(4): 718–726, doi: 10.1160/TH16-08-0670, indexed in Pubmed: 28203684.
19. Sikora J, Niezgoda P, Barańska M, et al. METoclopramide Administration as a Strategy to Overcome MORPHine-ticagrelOr Interaction in PatientS with Unstable Angina PectorIS — The METAMORPHOSIS Trial. Thromb Haemost. 2018; 118(12): 2126–2133, doi: 10.1055/s-0038-1675605, indexed in Pubmed: 30453344.
20. Zafar MU, Farkouh ME, Fuster V, et al. Crushed clopidogrel administered via nasogastric tube has faster and greater absorption than oral whole tablets. J Interv Cardiol. 2009; 22(4): 385–389, doi: 10.1111/j.1540-8183.2009.00475.x, indexed in Pubmed: 19496900.
21. Rollini F, Franchi F, Angiolillo DJ, et al. Crushed prasugrel tablets in patients with STEMI undergoing primary percutaneous coronary intervention: the CRUSH study. J Am Coll Cardiol. 2016; 67(17): 1994–2004, doi: 10.1016/j.jacc.2016.02.045, indexed in Pubmed: 27012781.
22. Parodi G, Xanthopoulou I, Bellandi B, et al. Ticagrelor crushed tablets administration in STEMI patients: the MOJITO study. J Am Coll Cardiol. 2015; 65(5): 511–512, doi: 10.1016/j.jacc.2014.08.056, indexed in Pubmed: 25660931.
23. Asher E, Frydman S, Katz M, et al. Chewing versus swallowing ticagrelor to accelerate platelet inhibition in acute coronary syndrome - the CHEERS study. For the PLATIS (platelets and thrombosis in sheba) study group. Thromb Haemost. 2017; 117(4): 727–733, doi: 10.1160/TH16-09-0728, indexed in Pubmed: 28150850.
24. Venetsanos D, Sederholm Lawesson S, Swahn E, et al. Chewed ticagrelor tablets provide faster platelet inhibition compared to integral tablets: The inhibition of platelet aggregation after administration of three different ticagrelor formulations (IPAAD-Tica) study, a randomised controlled trial. Thromb Res. 2017; 149: 88–94, doi: 10.1016/j.thromres.2016.10.013, indexed in Pubmed: 27773347.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 3, 441–453
DOI: 10.5603/CJ.a2020.0088

ISSN 1897–5593
eISSN 1898–018X

Prevalence and prognostic relevance of myocardial inflammation and cardiotropic viruses in non-ischemic dilated cardiomyopathy

Ieva Kažukauskienė[1], Vaida Baltrūnienė[1], Artūras Jakubauskas[2], Edvardas Žurauskas[1], Vytė Valerija Maneikienė[3], Dainius Daunoravičius[4], Jelena Čelutkienė[3], Kęstutis Ručinskas[3], Virginija Grabauskienė[1, 3]

[1]Department of Pathology, Forensic Medicine and Pharmacology, Faculty of Medicine, Vilnius University, Vilnius, Lithuania
[2]Hematology, Oncology and Transfusion Medicine Center, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania
[3]Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania
[4]Clinicus Vilnius, Lithuania

Abstract

Background: *Non-ischemic dilated cardiomyopathy (DCM) is a heterogeneous disease with a spectrum of etiological factors. However, subsets of the disease are not well-characterized with respect to these factors. The aim of this study was to evaluate the prevalence of myocardial inflammation and cardiotropic viruses in DCM patients and their impact on clinical outcome.*

Methods: *Fifty-seven patients with DCM underwent endomyocardial biopsy between 2010 and 2013. Biopsies were analyzed by polymerase chain reaction (PCR) for the presence of cardiotropic viruses, and inflammatory cell infiltration was assessed by immunohistochemistry. During a 5-year follow-up, 27 (47%) patients reached the composite outcome measure: heart transplantation, left ventricle assist device implantation or cardiovascular-related death.*

Results: *Thirty-one (54%) patients had myocardial inflammation and cardiotropic viruses were detected in 29 (52%). The most frequent viruses were parvovirus B19 and human herpesvirus type-6. Four specific sub-groups were distinguished by PCR and immunohistochemistry: virus-positive (chronic) myocarditis, autoreactive inflammatory DCM, viral DCM, non-inflammatory DCM. The presence of a viral genome in myocardium or diagnosis of inflammatory DCM did not predict the outcome of composite outcome measures ($p > 0.05$). However, univariate Cox regression and survival function estimation revealed an association between inflammation by a high number of T-cells and poor prognosis.*

Conclusions: *This study has shown that two markers — cardiotropic viruses and myocardial inflammation — are prevalent among DCM patients. They are also helpful in identifying sub-groups of DCM. An increased number of T-lymphocytes in the myocardium is a predictor of poor mid-term and long-term prognosis.* (Cardiol J 2022; 29, 3: 441–453)

Key words: dilated cardiomyopathy, chronic heart failure, myocardial inflammation, viruses, prognosis

Address for correspondence: Ieva Kažukauskienė, MD, Department of Pathology, Forensic Medicine and Pharmacology, Faculty of Medicine, Vilnius University, M. K. Ciurlionio 21, LT-03101 Vilnius, Lithuania, tel: +37052398728, e-mail: ieva.zasytyte@gmail.com

Received: 1.11.2019 Accepted: 11.05.2020 Early publication date: 17.06.2020

Introduction

Non-ischemic dilated cardiomyopathy (DCM) is a chronic heart disease. It presents with left ventricle (LV) dilatation and impaired ventricle function (left or both ventricles), which is not caused by coronary artery disease or abnormal loading conditions [1]. DCM is a heterogeneous disease with a spectrum of etiologic factors such as infectious agents, genetic abnormalities, autoimmune mechanisms, drugs, and toxins [2]. DCM causes heart failure, leading to heart transplantation or death [3].

Over the past few decades, the definition of DCM has developed [1, 4–6]. Endomyocardial biopsy, analyzed by immunohistochemistry and viral polymerase chain reaction (PCR), became an essential procedure for diagnosing the cause of DCM [1, 7, 8]. Consequently, cardiotropic viruses are recognized as a crucial etiologic factor of heart failure and are found in the myocardium of up to 67% of DCM patients [10, 11]. The data concerning the impact of the presence of cardiotropic viruses on clinical significance and prognosis remains under debate [12, 13].

Diagnostic criteria for inflammation in the myocardium were updated several times [1, 4, 5, 9]. Myocardial inflammation, confirmed by endomyocardial biopsy, is also known as a significant causal factor, and is responsible for progression of LV dilatation [14–17]. However, the prognostic role of myocardial inflammation on clinical outcome varies in different studies due to diverse diagnostic criteria [12, 18–21]. The latest definition of myocardial inflammation was endorsed by the European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Diseases [1]. However, there is a shortage of data, which demonstrate the prognostic relevance of myocardial inflammation defined by this criterion. In addition, immunohistochemistry and viral PCR are used to characterize etiopathogenetic subsets of DCM patients, but prospective data are lacking for these subsets. Thus, the clinical value of research of etiopathogenetic factors may be of paramount importance to prognosis assessment and may help to further the development of treatment strategies.

The aim of this study was to use immunohistochemistry and PCR — to evaluate the prevalence of myocardial inflammation and cardiotropic viruses — in DCM patients. Further, to investigate their impact on the clinical outcome; and to clarify the impact of different myocardial inflammatory cells on mid-term and long-term prognosis.

Methods

Study population. Inclusion and exclusion criteria

A prospective cohort study was done in our center between January 2010 and December 2013. 57 patients admitted to this institution with heart failure and reduced LV ejection fraction (LVEF) (with unknown etiology of LV dilatation) for diagnostic evaluation were enrolled. Inclusion criteria were clinical signs and symptoms of heart failure, accompanied by echocardiographic evidence of LV dilatation (LV end-diastolic diameter [LVEDD] > 117% of the predicted value, corrected for age and body surface area [> 2 standard deviations] of the predicted normal limit +5%) and reduced (< 45%) LVEF [22, 23].

Exclusion criteria were: 1) Significant coronary artery disease, defined as at least 50% proximal stenosis of a coronary artery or a history of myocardial infarction; 2) Known causes of heart failure, such as primary valvular or heart muscle disease, hypertensive heart disease, endocrine disease, advanced renal insufficiency, drug or alcohol abuse; 3) Acute myocarditis (new-onset symptoms during the past 3 months) or acute myocardial infarction suspected by clinical presentation or in diagnostic testing.

All patients provided written informed consent. Ethical approval was obtained from the local Lithuanian Bioethics Committee (license numbers 158200-09-382-103; 158200-382-PP1-23; and 158200-17-891-413).

All patients were treated according to the ESC guidelines [24, 25]. At the time of inclusion, none of the patients were treated with inotropic agents. Specific etiology-directed treatment was not administered.

Medical examinations

All patients underwent a medical interview, physical examination, and routine laboratory studies. Additionally, the proinflammatory serum cytokine interleukin-6 (IL-6) was tested as described elsewhere [26].

Echocardiography was performed for all patients to obtain conventional echocardiographic parameters. Cardiac magnetic resonance with late gadolinium enhancement was performed for 33 patients.

Mandatory investigations included coronary angiography to exclude coronary artery disease, right heart catheterization for hemodynamic evaluation. During the same procedures, right ventricle

endomyocardial biopsy was performed for the immunohistochemical evaluation and the detection of viruses by PCR. Three endomyocardial biopsy procedures were discontinued because of complications (arrhythmias or right ventricular perforation). Due to the lack of biopsy samples, PCR was performed for two of the above-mentioned patients and immunohistochemical analysis for one.

Histological and immunohistochemical assessment

Storage of the endomyocardial biopsy samples, and histological and immunohistochemical analyses were performed as described previously [26]. In brief, we detected antibodies (Santa Cruz Biotechnology, Inc.) against: T-lymphocyte CD3 (DAKO A0452 Rabbit 1, Hamburg, Germany), active-memory T-lymphocyte CD45Ro (DAKO Hamburg), macrophage CD68 (DAKO M0876 Mouse 1, Hamburg), T-helper cell CD4 (DAKO Hamburg, Germany), intracellular adhesion molecule-1 (ICAM-1) CD54 (NovocastraTM Lyophilized Mouse Monoclonal Antibody CD54 Clone 23G12), and MHC class II cell surface receptor HLA-DR (DAKO Hamburg, Germany). Positive cells were registered by an experienced pathologist and expressed as the number of cells per mm^2. Myocardial inflammation was diagnosed according to the criterion established by the ESC Working Group on Myocardial and Pericardial Diseases. This criterion is immunohistochemical detection of significant focal or diffuse cellular infiltration in the endomyocardial biopsy (≥ 14 leucocytes/mm^2, including up to 4 monocytes/mm^2 with the presence of CD3 positive T-lymphocytes ≥ 7 cells/mm^2) [1]. Inflammatory endothelial activation was diagnosed if immunohistochemical analysis revealed ≥ 3 cells expressing adhesion molecules, i.e., ICAM-1 (CD54) and/or HLA-DR [27].

Detection of viral genomes

Genomic DNA and total RNA were extracted simultaneously using the ZR-Duet DNA/RNA Miniprep kit (Zymo Research, Irvine, CA, USA). RNA (1 μg) was reverse transcribed in 20 μL reaction volumes using random hexamers and the First Strand cDNA Synthesis Kit (Thermo Fisher Scientific, Vilnius, Lithuania) according to the vendor's recommendations and diluted up to 100 μL with deionized water after the reaction.

Nested PCR primers for the detection of adenovirus [28], herpes simplex viruses 1 and 2, varicella-zoster virus (VZV), cytomegalovirus (CMV), parvovirus B19 (B19V), Epstein-Barr virus (EBV), hepatitis C virus (HCV), enterovirus (EV), and rubella virus [29] are described elsewhere. Primer sequences for the nested PCR of human herpes virus 6 (HHV-6, GenBank accession no. NC001664.2 and NC000898.1); Kirsten rat sarcoma viral oncogene homolog (KRAS, GenBank accession no. NM033360); and ubiquitin C (UBC, GenBank accession no. NM021009) are presented in Table 1. Forward primers for the second PCR step (N2Fw) were labeled with 6-carboxyfluorescein at the 5' end. All primers were synthesized by the Metabion Company (Martinsried, Germany).

Table 1. Primers for detection of human herpes virus 6 (HHV6), Kirsten rat sarcoma viral oncogene homolog (KRAS) and ubiquitin C (UBC).

Primer	Sequence (5'–3')
HHV6-N1 Forward	ACCCGAGAGATGATTTTGCGTG
HHV6-N1 Reverse	GCAGAAGACAGCAGCGAGATAG
HHV6-N2 Forward	CATAGCAACCTTTTCTAGCTTTGAC
HHV6-N2 Reverse	TCTATAACATAAATGACCCCTGGGA
UBC-N1 Forward	TTCTTTCCAGAGAGCCGAAC
UBC-N1 Reverse	CCCATCTTCCAGCTGTTTTC
UBC-N2 Forward	TGGGTCGCAGTTCTTGTTTG
UBC-N2 Reverse	CCTTCCTTATCTTGGATCTTTGCC
KRAS-N1 Forward	CTTTGGAGCAGGAACAATGTCT
KRAS-N2 Forward	AATCCAGACTGTGTTTCTCCCT
KRAS-N1/N2 Reverse	TACACAAAGAAAGCCCTCCCC

All PCRs were run on a TProfessional Standard thermocycler (Biometra, Göttingen, Germany), as described by Allard et al. [28]. KRAS and UBC detection was used to validate the extraction of nucleic acids and was performed in parallel according to the conditions for viral DNA and RNR, respectively. Final PCR products were diluted 10-fold and sized by capillary electrophoresis on a Genetic Analyzer 3130*xl,* using GeneScan 600 LIZ™ Size Standard and Gene Mapper Software v4.1 (Applied Biosystems, Foster City, CA, USA). For positive results, the genomic DNA or RNR

specimens from peripheral blood samples were also tested to exclude contamination.

Follow-up

All patients were followed-up for 5 years after the endomyocardial biopsy. The composite outcome measures were composite and combined three outcomes: cardiovascular death, LV assist device implantation, or heart transplantation. The time of the first event was included in the analysis. Follow-up events were confirmed by medical records or telephone interview with the patients' families.

Statistical analysis

Data management and analysis were performed using the R studio package (3.5.1 version) at a 5% significance level. Continuous variables were tested by the Shapiro-Wilk statistic for normal distribution. Normally distributed continuous variables were expressed as the mean ± standard deviation. Other continuous variables were expressed as the median (interquartile range), and categorical data as counts and percentages. Continuous variables were compared by the Student independent t-test when normally distributed, or by the Mann-Whitney-U test when non-normally distributed. Comparisons of categorical variables between the groups were made using the χ^2 test or the Fisher Exact test if expected values were < 5.

Univariate Cox proportional hazards regression analysis was performed to evaluate which inflammatory cells or clinical parameters were associated with poor mid-term and long-term composite outcome measures after 2-year and 5-year follow-up. The optimal cut-off point was determined using the receiver operating characteristic (ROC) curve. The Kaplan-Meier analysis was used to compare cumulative survival rates between different subgroups of DCM patients after a 2-year and 5-year follow-up. The log-rank statistic was used to evaluate the statistical significance of differences between the curves.

Results

Baseline patients' characteristics

Fifty-seven DCM patients (mean age 47.3 ± ± 10.9 years; 45 [79%] males) with chronic heart failure participated in the study. The average LVEDD was 6.8 ± 0.9 cm, average LVEF — 26.1 ± 9.5%, and average pulmonary artery wedge pressure — 22 ± 9 mmHg. Of these patients, 41 (72%) were in New York Heart Association (NYHA) III functional class and 10 (17%) were NYHA IV functional class. The median (interquartile range) heart failure duration was 12 (55) months. Baseline characteristics are shown in Table 2.

Of the 57 patients, 27 (47%) reached the composite outcome measure during the 5-year follow-up period: 10 (18%) patients died, 9 (16%) underwent heart transplantation, and 8 (14%) LV assist device implantation. Other patients remained on conventional medical heart-failure therapy. The 5-year cumulative survival rate was 53%. In univariate Cox regression models, most hemodynamic parameters, echocardiographic parameters and IL-6 were associated with poor clinical outcomes (Table 2).

The prevalence of cardiac inflammation

Immunohistochemical analysis was performed on 55 endomyocardial biopsies. Myocardial inflammation was detected in 31 of the 55 (54%) DCM patients. Patients were divided into two groups: inflammatory DCM (iDCM) and non-inflammatory DCM (non-iDCM). No difference was observed in baseline characteristics of the two groups ($p > 0.05$; Table 2), except for lower systolic blood pressure and higher level of B-type natriuretic peptide (BNP) in the iDCM group ($p \leq 0.05$).

Kaplan-Meier analysis showed no difference between survival curves of patients with iDCM and non-iDCM ($p > 0.05$; Fig. 1).

However, univariate Cox regression analysis revealed an association between a higher CD45ro+ cell count in the myocardium and poor mid-term prognosis. Higher CD3+ cell count in the myocardium was associated with poor mid-term and long-term prognosis. This was not the case for CD68+ inflammatory infiltrative cells (Table 3). ROC curves determined the cut-off values for CD3+ and CD45ro+ cells (Fig. 2). The cohort was divided into two groups according to whether their CD3+ and CD45ro+ cell counts were above or below the cut-off value (13 cells/mm^2 and 11.5 cells/mm^2, respectively). Univariate Cox regression analysis showed that cell counts above cut-off values were associated with worse mid-term and long-term clinical outcome (Table 3). Estimation of survival curves demonstrated that patients with CD3+ and CD45ro+ cell counts above the cut-off values had lower survival rates (Fig. 3). Lower p-values in survival analysis and higher hazard ratio (95% confidence interval) in Cox regression analysis revealed that inflammatory cells predict better mid-term than long-term outcomes.

Inflammatory endothelial activation (increased expression of HLA-DR and ICAM [≥ 3 cells/ /mm^2]) was detected by immunohistochemistry in

Table 2. Baseline characteristics for the study population. A comparison of baseline characteristics of non-inflammatory dilated cardiomyopathy (non-iDCM) and inflammatory dilated cardiomyopathy (iDCM) patients, and patients with and without the viral genome. Univariate Cox analysis showing the association between the various clinical parameters and poor long-term clinical outcome.

Variable	All patients (n = 57)	Non-iDCM (n = 24)	iDCM (n = 31)	P	Virus--negative (n = 27)	Virus--positive (n = 29)	P	HR (95% CI)	P
Clinical characteristics									
Age, years	47.3 ± 10.9	48.3 ± 13	46.6 ± 9,6	0.58	48.44 ± 12.68	46.07 ± 9.28	0.43	0.98 (0.95–1.01)	0.26
Male gender	45 (79%)	17 (71%)	26 (82%)	0.25	23 (85%)	21 (72%)	0.23	1.41 (0.53–3.73)	0.49
BMI [kg/m^2]	26.84 (8.13%)	27.3 (8.2%)	25.7 (8%)	0.45	28.1 (7.2%)	25.2 (8.7%)	0.24	0.98 (0.91–1.05)	0.54
Systolic BP [mmHg]	116 ± 20	123 ± 20	110 ± 17	**0.01**	115 ± 20	118 ± 22	0.63	**0.97 (0.95–0.99)**	**0.002**
Diastolic BP [mmHg]	80 (10%)	78 (13%)	80 (10%)	0.43	80 (10%)	80 (10%)	0.76	**0.96 (0.92–0.99)**	**0.02**
Heart rate [bpm]	77 (27%)	73 (22%)	86 (32%)	0.18	79 (23%)	76 (34%)	0.83	1.01 (0.99–1.03)	0.35
Atrial fibrillation	11 (19%)	3 (13%)	8 (26%)	0.31	6 (22%)	5 (17%)	0.64	0.95 (0.36–2.52)	0.92
LBBB	14 (25%)	6 (25%)	8 (26%)	0.99	10 (37%)	4 (14%)	0.15	1.66 (0.72–3.79)	0.23
NYHA III–IV class	51 (90%)	20 (83%)	29 (94%)	0.64	24 (89%)	26 (90%)	1	4 (0.54–29.53)	0.17
Follow-up time [months]	60 (37%)	60 (32%)	60 (47%)	0.4	48 (46%)	60 (15%)	0.14		
Biomarkers/blood testing									
Hemoglobin [g/L]	142 ± 16	137.7 ± 13.7	144.7 ± 14.7	0.08	142.7 ±16.6	141.3 ±14.6	0.73	1 (0.98–1.02)	0.72
eGFR [mL/min/1.73 m^2]	87 ± 24	83 ± 27	91 ± 22	0.2	86 ± 22	88 ± 26	0.73	1 (0.99–1.02)	0.43
BNP [ng/L]	728 (1797%)	214 (1445%)	1017 (2432%)	0.05	916 (2571%)	228 (1329%)	**0.04**	1 (1–1)	0.12
CRP [mg/L]	4.6 (14.2%)	5.2 (6.6%)	4.5 (15.3%)	0.74	6.6 (13.5%)	2.4 (10.3%)	0.12	1.01 (0.99–1.02)	0.39
IL-6 [pg/mL]	2.5 (4.7%)	2.2 (3.1%)	2.9 (7.4%)	0.21	4.62 (6.3%)	2.01 (2.6%)	**0.04**	**1.04 (1.01–1.06)**	**0.004**
Echocardiographic parameters									
LVEF [%]	26.08 ± 9.5	25.6 ±11.8	26.7 ±7.1	0.69	26.9 ± 9.2	26.7 ± 9.9	0.94	**0.93 (0.89–0.98)**	**0.004**
LVEDD [cm]	6.8 ± 0.9	6.8 ± 0.9	6.9 ± 0.9	0.57	7.0 ± 0.9	6.7 ± 0.8	0.12	1.49 (0.94–2.36)	0.09
LV diastolic function (n = 54):									
Grade I	14 (26%)	7 (30%)	7 (23%)	0.79	6 (22%)	9 (33%)	0.61		
Grade II	16 (30%)	6 (26%)	10 (33%)		8 (30%)	8 (30%)		1.32 (0.44–3.93)	0.62
Grade III	23 (43%)	10 (44%)	13 (43%)		13 (48%)	10 (37%)		2.4 (1.15–6.07)	0.02
Functional MR ≥ moderate*	32 (56%)	13 (54%)	19 (61%)	0.6	17 (63%)	14 (48%)	0.27	**2.4 (1.08–5.33)**	**0.03**
RV end-diastolic diameter [cm]	3.3 ± 0.6	3.2 ± 0.8	3.4 ± 0.5	0.3	3.4 ± 0.6	3.3 ± 0.6	0.63	**2.75 (1.56–4.84)**	**< 0.001**

→

Table 2. (cont.) Baseline characteristics for the study population. A comparison of baseline characteristics of non-inflammatory dilated cardiomyopathy (non-iDCM) and inflammatory dilated cardiomyopathy (iDCM) patients, and patients with and without the viral genome. Univariate Cox analysis showing the association between the various clinical parameters and poor long-term clinical outcome.

Variable	All patients (n = 57)	Non-iDCM (n = 24)	iDCM (n = 31)	P	Virus--negative (n = 27)	Virus--positive (n = 29)	P	HR (95% CI)	P
RV systolic function:*									
Normal	21 (37%)	11 (46%)	9 (29%)	0.11	6 (22%)	15 (52%)	0.13		
Mildly impaired	9 (16%)	4 (17%)	5 (16%)		5 (19%)	4 (14%)		2.04 (0.6–6.41)	0.23
Moderately impaired	11 (19%)	1 (4%)	9 (29%)		6 (22%)	5 (17%)		1.72 (0.55–5.4)	0.35
Severely impaired	16 (28%)	8 (33%)	8 (26%)		10 (37%)	5 (17%)		**3.67 (1.42–9.53)**	**0.008**
TAPSE (n = 33)	15 (6.3%)	15 (5.5%)	13 (5.5%)	0.64	15 (4.5%)	16 (5.5%)	0.83	**0.7 (0.56–0.87)**	**0.001**
Functional TR ≥ moderate*	20 (35%)	9 (38%)	11 (36%)	0.88	11 (41%)	9 (31%)	0.45	**2.98 (1.41–6.3)**	**0.004**
Cardiac magnetic resonance									
Mid-wall late gadolinium enhancement (n = 33)	22 (73%)	7 (54%)	14 (78%)	0.25	10 (72%)	11 (61%)	0.71	1.59 (0.44–5.78)	0.48
Hemodynamic measurements (n = 54)									
PAWP [mmHg]	21.8 ± 8.9	21.5 ± 9.6	22.6 ± 8.8	0.65	25 ± 9	19 ± 8	**0.02**	**1.07 (1.02–1.12)**	**0.004**
Mean RAP [mmHg]	11 (6.5%)	10 (6%)	11 (10%)	0.96	12 (8%)	8 (8%)	0.09	**1.07 (1.02–1.13)**	**0.007**
Mean PAP [mmHg]	29 ± 18	31 ± 12	32 ± 11	0.67	35 ± 11	28 ± 9	**0.02**	**1.05 (1.02–1.09)**	**0.005**
PVR [mmHg]	2 (2%)	1.5 (1.6%)	2.3 (1.6%)	0.08	2.4 (2.7%)	1.6 (1.4%)	**0.04**	**1.22 (1–1.49)**	**0.05**
Pulmonary hypertension	36 (68%)	14 (60%)	21 (75%)	0.28	18 (72%)	17 (63%)	0.49	**3.37 (1.15–9.9)**	**0.03**
Concomitant cardiac medication									
ACEI/ARB	41 (72%)	19 (79%)	20 (65%)	0.24	16 (59%)	24 (83%)	0.06	0.83 (0.38–1.84)	0.65
Beta-blocker	54 (95%)	24 (100%)	28 (90%)	0.25	24 (89%)	29 (100%)	0.11	0.42 (0.1–1.79)	0.24
MRA	51 (90%)	20 (83%)	30 (97%)	0.16	26 (96%)	24 (83%)	0.2		0.99
Diuretics	53 (93%)	21 (88%)	30 (97%)	0.31	25 (93%)	27 (93%)	1	2.46 (0.33–18)	0.38
Virus-positive endomyocardial biopsies									
Total		15 (63%)	14 (47%)	0.25	0	29 (52%)		0.64 (0.3–1.39)	0.26
B19V		13 (54%)	12 (40%)	0.3	0	25 (45%)			
EBV		0 (0%)	1 (3%)	1	0	1 (2%)			
EV		0 (0%)	1 (3%)	1	0	1 (2%)			
HHV-6		2 (8%)	3 (10%)	1	0	5 (9%)			
VZV		1 (4%)	0 (0%)	0.44	0	1 (2%)			
HCV		0 (0%)	1 (3%)	1	0	1 (2%)			

→

Table 2. (cont.) Baseline characteristics for the study population. A comparison of baseline characteristics of non-inflammatory dilated cardiomyopathy (non-iDCM) and inflammatory dilated cardiomyopathy (iDCM) patients, and patients with and without the viral genome. Univariate Cox analysis showing the association between the various clinical parameters and poor long-term clinical outcome.

Variable	All patients (n = 57)	Non-iDCM (n = 24)	iDCM (n = 31)	P	Virus-negative (n = 27)	Virus-positive (n = 29)	P	HR (95% CI)	P
Immunohistological markers of endothelial activation (n = 55)									
ICAM-1/CD54+ [cells/mm^2]	0 (1%)	0 (1%)	0 (1.5%)	0.45	0 (2%)	0 (1%)	0.26		
HLA DR [cells/mm^2]	5 (2%)	4.5 (2%)	5.0 (2%)	0.1	5 (1%)	5 (2%)	0.23		
CD3+ [cells/mm^2]	10 (9%)	7 (2%)	15 (8%)	**< 0.001**	10 (9%)	9 (5%)	0.66		
CD45+ [cells/mm^2]	7 (5%)	5 (2%)	10 (6%)	**< 0.001**	7 (5%)	6 (3%)	0.42		
CD68+ [cells/mm^2]	4 (2%)	3 (2%)	5 (4%)	**< 0.001**	5 (3%)	3 (3%)	**0.01**		

*Evaluated visually. Values are expressed as: median (interquartile range), mean ± standard deviation or number (%); hazard ratio (HR) and 95% confidence interval (CI). Significant at the p-value of < 0.05 (bold value). (bold value). ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin II receptor blocker; BP — blood pressure; BMI — body mass index; BNP — B-type natriuretic peptide; B19V — parvovirus B19; CRP — C-reactive protein; eGFR — estimated glomerular filtration rate; EBV — Epstein-Barr virus; EV — enterovirus; HCV — hepatitis C virus; HHV-6 — human herpes virus 6; VZV — varicella zoster virus; IL-6 — interleukin 6; LBBB — left bundle branch block; LV — left ventricle; LVEF — left ventricular ejection fraction; LVEDD — left ventricular end-diastolic diameter; MRA — mineralocorticoid receptor antagonist; MR — mitral regurgitation; RV — right ventricle; NYHA — New York Heart Association; PAWP — pulmonary capillary wedge pressure; RAP — right atrial pressure; PAP — pulmonary arterial pressure; PVR — pulmonary vascular resistance; TAPSE — tricuspid annular plane systolic excursion; TR — tricuspid regurgitation

50 (91%) patients. The expression did not, however, differ between the iDCM and non-iDCM groups ($p > 0.05$). However, it should be interpreted with caution, while these proteins are not only markers for endothelial activation, but are also found on the surface of immune cells.

Prevalence of cardiotropic viruses

Polymerase chain reaction analysis was performed on 56 endomyocardial biopsies. Viral genomes were detected in the myocardium of 29 (52%) of the 56 DCM patients. Of these 29 patients, 25 (86%) had the B19V genome, and other 5 (17%) had HHV6 genome. Other viruses (VZV, CMV, EBV, HCV, EV), were detected in single cases (n = 1 [3%] of each type). Three (10%) of virus-positive patients had a double infection and one of them (3%) a triple infection. Co-detection of B19V and HHV6 prevailed (n = 3 [10%]).

The remaining 27 (48%) patients were virus-negative. There were no differences in most baseline parameters between the virus-positive and virus-negative groups ($p > 0.05$), except for higher BNP and IL-6 levels, worse hemodynamic parameters (Table 2), and a higher number of infiltrative CD68+ cells in the virus-negative group (Fig. 4).

Kaplan-Meier survival curves demonstrated no difference in survival rates of patients in virus-positive and virus-negative groups ($p > 0.05$; Fig. 5).

Sub-groups of idiopathic DCM

Both PCR analysis and immunohistochemical evaluation were performed on 54 DCM patients. Based on the detection of viral genome — in combination with positive or negative immunohistochemistry — four specific sub-groups of patients were distinguished:

- Virus-positive (chronic) myocarditis (15 [28%] patients): both cardiotropic virus and myocardial inflammation was present;
- Autoreactive iDCM (16 [30%] patients): no cardiotropic virus was detected but myocardial inflammation was present;
- Viral DCM (14 [26%] patients): viral genome was detected but no signs of myocardial inflammation;
- Non-inflammatory DCM (9 [17%] patients): neither viral genome nor inflammation was detected.

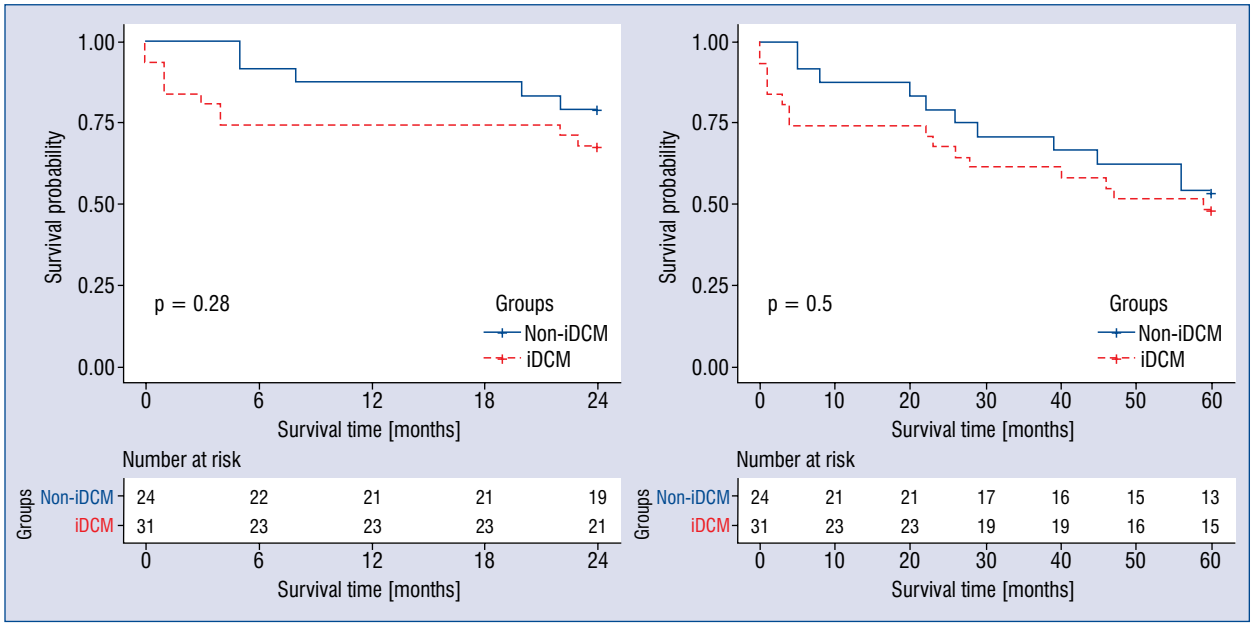


Figure 1. Kaplan-Meier analysis of the inflammatory dilated cardiomyopathy (iDCM) and non-inflammatory dilated cardiomyopathy (non-iDCM) groups.

Table 3. Univariate Cox analysis showing the association between the number of myocardial inflammatory infiltrates and poor clinical outcome after 2-year and 5-year follow-up.

Cardiac inflammatory infiltration and endothelial activation markers [cells/mm^2]	HR (95% CI)			
	2-year follow-up	P	5-year follow-up	P
CD3+	**1.085 (1.04–1.132)**	**< 0.001**	**1.061 (1.02–1.103)**	**0.003**
CD45ro+	**1.079 (1.025–1.136)**	**0.004**	1.048 (0.998–1.101)	0.06
CD68+	1.075 (0.862–1.34)	0.523	1.029 (0.867–1.223)	0.74
CD4+-	1.01 (0.91–1.13)	0.82	1.013 (0.908–0.13)	0.82
CD54+	0.82 (0.53–1.25)	0.35	0.816 (0.532–1.254)	0.35
HLA-DR+	1.02 (0.91–1.14)	0.7	1.022 (0.915–1.143)	0.7
CD3+ ≥ 13 cells/mm^2	**4.481 (1.588–12.64)**	**0.005**	**2.181 (1.009–4.711)**	**0.047**
CD45ro+ ≥ 11.5 cells/mm^2	**5.261 (1.854–14.93)**	**0.002**	**2.892 (1.217–6.871)**	**0.016**

Values are expressed as hazard ratio (HR) and 95% confidence interval (CI). Significant at the p-value of < 0.05 (bold value).

Discussion

This prospective study summarizes an experience identifying etiopathogenetic markers of idiopathic DCM for diagnosis of distinct disease sub-entities, and evaluates their prognostic value. In this study, the criterion defined by the ESC Working Group on Myocardial and Pericardial Diseases [1] for diagnosing iDCM was used. iDCM was diagnosed in 54% of the patients by immunohistochemistry. The rate of the iDCM was similar when compared to the study by Palecek et al. [30]. The prognostic value of myocardial inflammation and different inflammatory cells varies in different studies, possibly due to the diversity of diagnostic protocols [31]. Though, according to available research, we found no study which evaluated the prognostic value of iDCM diagnosed by ESC criterion. In the present cohort, iDCM had no impact on clinical outcomes. However, a higher count of CD3+ and CD45ro+ cells were associated with a poor clinical outcome.

The current study found a high prevalence of cardiotropic viruses (52% of patients), of which

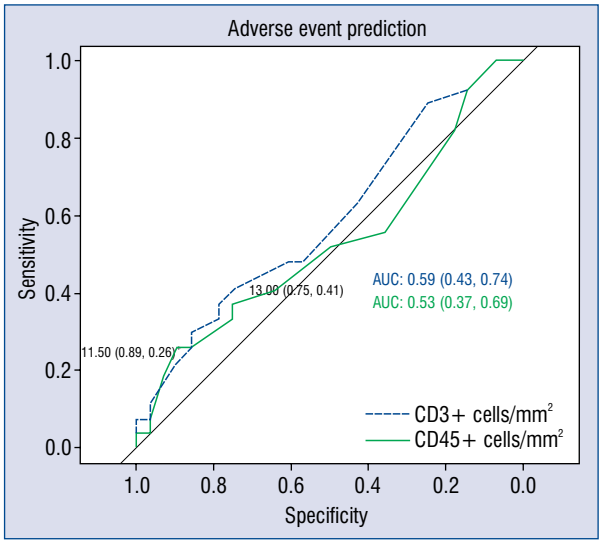


Figure 2. Receiver operating characteristic curve analysis of CD3+ and CD45ro+ cells for predicting composite endpoint. The best cut-off values were 13 CD3+ cells/ /mm^2 (sensitivity, 41%; specificity, 75%) and 11.5 CD45ro+ cells/mm^2 (sensitivity, 26%; specificity, 89%).

the most frequently detected were B19V and HHV6. Three (10%) patients were co-infected with B19V and HHV6. These findings support previous studies, in which B19V and HHV6 were the most frequent viruses [10, 32, 33]. Furthermore, the high prevalence of B19V suggests that chronic DCM might have developed from the previous B19V-associated myocarditis [34]. However, there is conflicting evidence about the viral genome's impact on the long-term prognosis. Several studies revealed that viral genomes were associated with worsening LV function, the need for heart transplantation, and death [10, 35]. While other studies report that the existence of viral genomes *per se* is not associated with poor clinical outcome [12, 36–38]. In the present cohort, detection of a virus had no impact on clinical outcome.

However, half of the virus-positive patients had no myocardial inflammation. This finding is also reported by Kühl et al. [10], in whose study DCM patients had symptoms of heart failure and viral genome, but no evidence of inflammation. Kindermann et al. [12] have also reported that the frequency of inflammation is independent of any evidence of the virus genome. Several studies detected B19V in healthy people's hearts with no evidence of inflammation [38–40].

In contrast, half of the current iDCM patients had no viral genome, and cause of inflammation remains unknown. This finding supports the idea that myocardial inflammation could be maintained by an autoimmune process leading to the deterioration of LV function [41]. Contrarily, this high prevalence of cardiac inflammation might be due to the advanced DCM phenotype. The question remains whether this inflammation is a consequence of this advanced stadium or if it acts as a causal factor.

Interestingly, the macrophage count was higher in the virus-negative group. It could be hypothesized that CD68+ macrophages have an impact on DCM pathogenesis because of their pro-inflammatory activity. As known from previous studies, macrophages can cause or maintain persistent LV systolic dysfunction and LV remodeling [42]. While recent studies have noted the importance of macrophage profiles and their function in heart diseases, much is still unknown about their impact on DCM pathogenesis [43].

Virus-negative patients had worse hemodynamic parameters and higher BNP levels than the virus-positive patients, although echocardiographic parameters did not differ between the two groups. Worse hemodynamic status might be explained by chronic immune activation and myocardial inflammation, given that higher numbers of macrophages and higher levels of IL-6 were detected in this virus-negative group. Macrophages secrete IL-6 [44], which might increase the severity of pulmonary hypertension [45].

Although heart failure treatment has become more effective, there are still many refractory DCM patients who do not respond to any available treatment. Therefore, developing alternative therapies is essential. Four etiopathogenetic groups were distinguished, for whom the specific therapeutic strategy selected could be suitable [1, 6, 46] or novel treatment options established [13]. Treatment strategies based on the etiopathogenetic approach to the disease might improve LV function, prevent progression of heart failure, and, in some cases, exclude patients from the heart transplant list.

Limitations of the study

First, small sample size did not allow for differentiation of patients based on the type of infectious agent. Second, the study had no control group, due to a shortage of healthy donor hearts which were not suitable for transplantation. Third, as a result of financial considerations, neither virus replication nor the viral load for distinguishing active from incidental infection were investigated [47], nor was autoantibody testing performed or genetic screening for pathogenic DCM mutations. Fourth, due to limited-experience in specific DCM treatment and

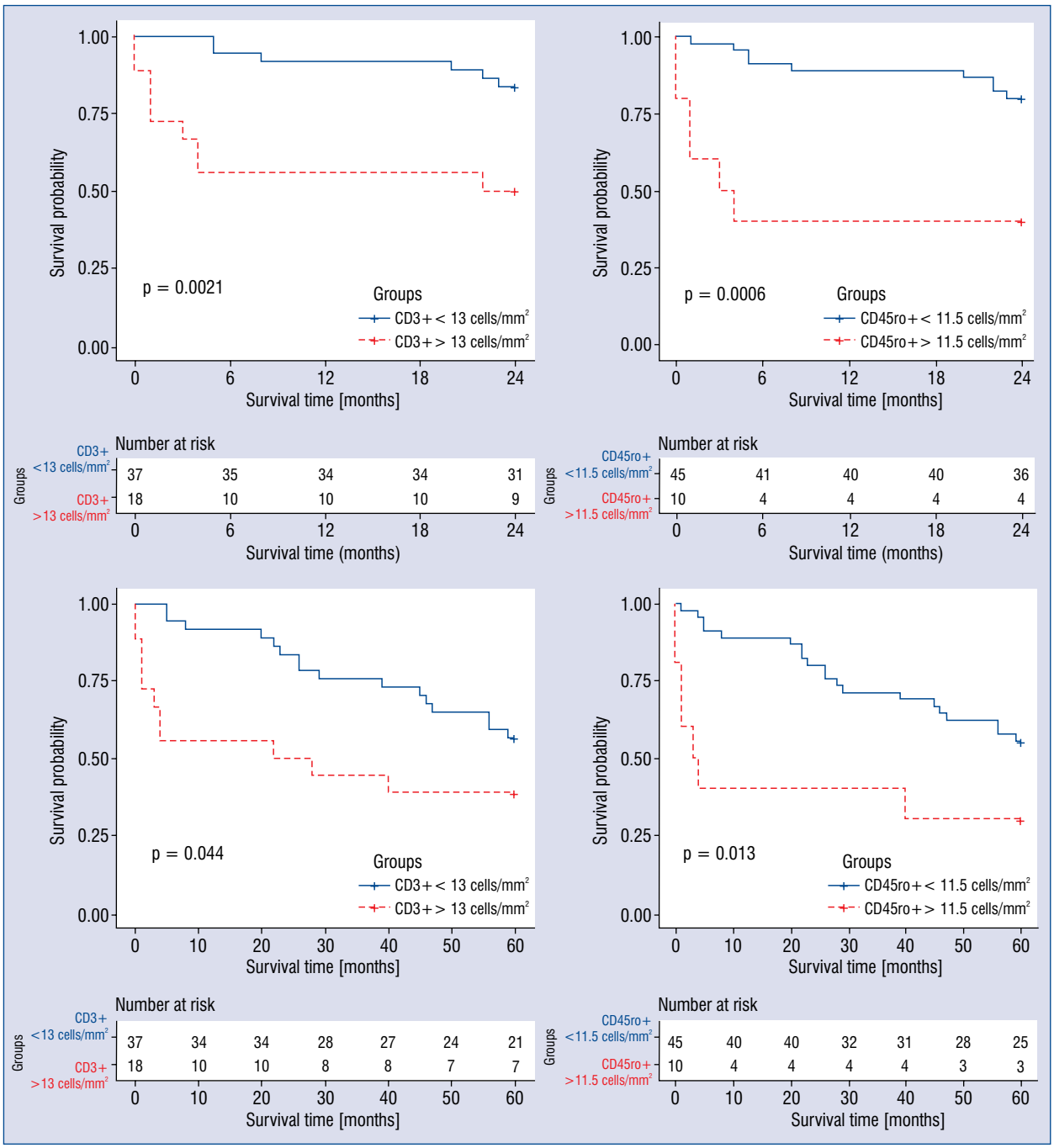


Figure 3. Survival curves according to the count of CD3+ and CD45ro+ cells. Patient groups with a higher number of infiltrative cells (CD3+ > 13 cells/mm² and CD45ro+ > 11.5 cells/mm²) had a significantly lower survival rate than groups with lower cell counts.

the treatment costs, none of the patients received etiology-directed treatment. Finally, the study was held at a time when right ventricle was a "forgotten" ventricle, therefore it was limitedly assessed. In spite of its limitations, the study certainly provides a basis for a more extensive diagnostic and treatment studies — based on etiopathogenetic sub-entities which include a control group.

Conclusions

This study has shown that two markers, cardiotropic viruses and myocardial inflammation, are prevalent among DCM patients and are helpful in identifying sub-groups of DCMs. An increased number of T-lymphocytes in the myocardium is a predictor of poor mid-term and long-term

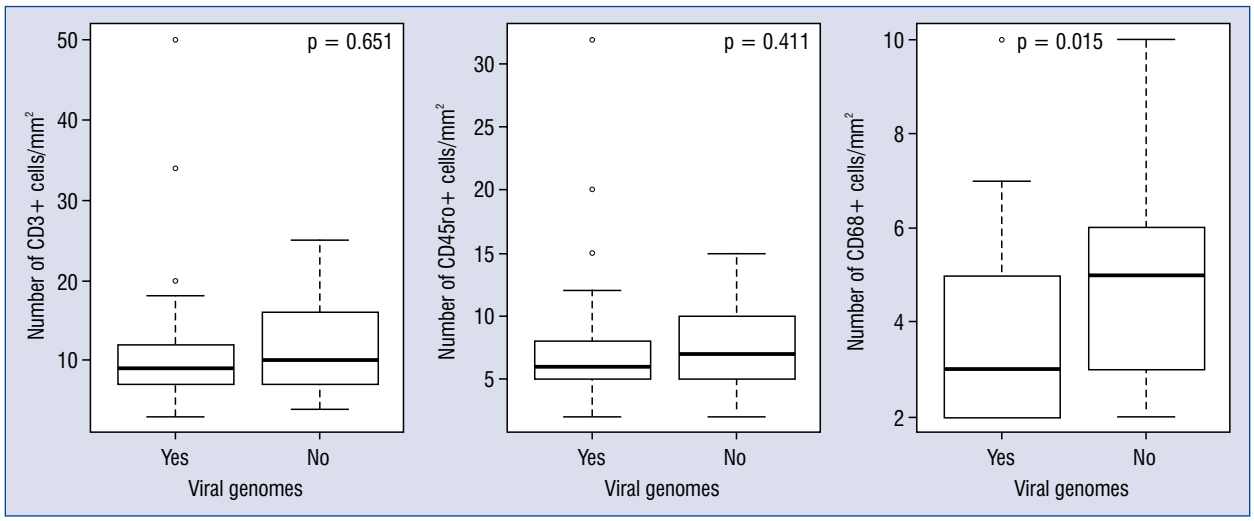


Figure 4. Comparison of inflammatory cell (CD3+, CD45ro+, and CD68+) counts in the virus-negative and virus--positive biopsies.

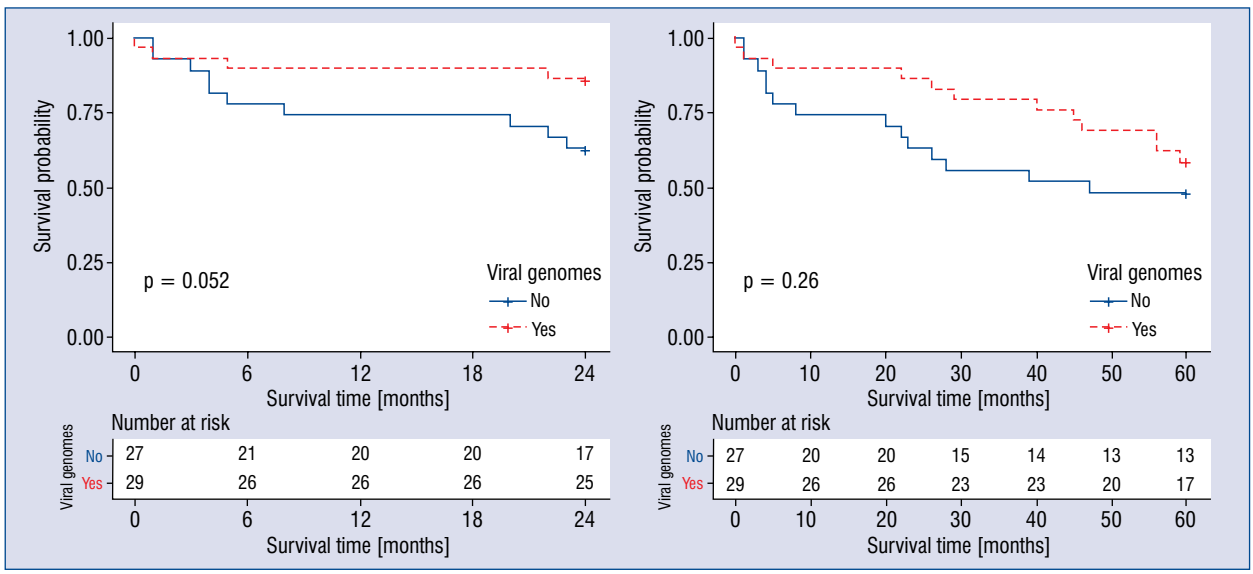


Figure 5. The Kaplan-Meier curves for virus-positive and virus-negative groups.

prognosis. The finding of specific inflammatory cells as a prognostic marker could be of value in determining new definitions of cardiac inflammation. A natural continuation of this work would be further analysis of specific etiologic DCM subgroups and a search for etiology-directed treatment strategies.

Acknowledgments

The study was supported by the Research Council of Lithuania (Grants no. MIP-086/2012 and MIP-011/2014), the European Union, EU-FP7, SARCOSI Project (no. 291834).

Conflict of interest: Jelena Čelutkiné — personal fees from: Novartis, Roche Diagnostics, Servier, AstraZeneca, outside the submitted work.

References

1. Caforio ALP, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of

myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2013; 34(33): 2636–2648, doi: 10.1093/eurheartj/eht210, indexed in Pubmed: 23824828.
2. Elliott P, Andersson B, Arbustini E, et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2008; 29(2): 270–276, doi: 10.1093/eurheartj/ehm342, indexed in Pubmed: 17916581.
3. Chambers DC, Cherikh WS, Goldfarb SB, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-fifth adult lung and heart-lung transplant report-2018; Focus theme: Multiorgan Transplantation. J Heart Lung Transplant. 2018; 37(10): 1169–1183, doi: 10.1016/j.healun.2018.07.020, indexed in Pubmed: 30293613.
4. Richardson P, McKenna W, Bristow M, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of cardiomyopathies. Circulation. 1996; 93(5): 841–842, doi: 10.1161/01.cir.93.5.841, indexed in Pubmed: 8598070.
5. Maisch B, Portig I, Ristic A, et al. Definition of inflammatory cardiomyopathy (myocarditis): on the way to consensus. A status report. Herz. 2000; 25(3): 200–209, doi: 10.1007/s000590050007, indexed in Pubmed: 10904839.
6. Pinto YM, Elliott PM, Arbustini E, et al. Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases. Eur Heart J. 2016; 37(23): 1850–1858, doi: 10.1093/eurheartj/ehv727, indexed in Pubmed: 26792875.
7. Cooper L, Baughman K, Feldman A, et al. The Role of Endomyocardial Biopsy in the Management of Cardiovascular Disease. J Am Coll Cardiol. 2007; 50(19): 1914–1931, doi: 10.1016/j.jacc.2007.09.008.
8. Caforio ALP, Calabrese F, Angelini A, et al. A prospective study of biopsy-proven myocarditis: prognostic relevance of clinical and aetiopathogenetic features at diagnosis. Eur Heart J. 2007; 28(11): 1326–1333, doi: 10.1093/eurheartj/ehm076, indexed in Pubmed: 17493945.
9. Aretz HT, Billingham ME, Edwards WD, et al. Myocarditis. A histopathologic definition and classification. Am J Cardiovasc Pathol. 1987; 1(1): 3–14, indexed in Pubmed: 3455232.
10. Kühl U, Pauschinger M, Noutsias M, et al. High prevalence of viral genomes and multiple viral infections in the myocardium of adults with "idiopathic" left ventricular dysfunction. Circulation. 2005; 111(7): 887–893, doi: 10.1161/01.CIR.0000155616.07901.35, indexed in Pubmed: 15699250.
11. Mahrholdt H, Wagner A, Deluigi CC, et al. Presentation, patterns of myocardial damage, and clinical course of viral myocarditis. Circulation. 2006; 114(15): 1581–1590, doi: 10.1161/CIRCULATIONAHA.105.606509, indexed in Pubmed: 17015795.
12. Kindermann I, Kindermann M, Kandolf R, et al. Predictors of outcome in patients with suspected myocarditis. Circulation. 2008; 118(6): 639–648, doi: 10.1161/CIRCULATIONAHA.108.769489, indexed in Pubmed: 18645053.
13. Van Linthout S, Tschöpe C. Viral myocarditis: a prime example for endomyocardial biopsy-guided diagnosis and therapy. Curr Opin Cardiol. 2018; 33(3): 325–333, doi: 10.1097/HCO.0000000000000515, indexed in Pubmed: 29528906.
14. Cooper L. Myocarditis. N Engl J Med. 2009; 360(15): 1526–1538, doi: 10.1056/nejmra0800028.
15. D'Ambrosio A, Patti G, Manzoli A, et al. The fate of acute myocarditis between spontaneous improvement and evolution to dilated cardiomyopathy: a review. Heart. 2001; 85(5): 499–504, doi: 10.1136/heart.85.5.499, indexed in Pubmed: 11302994.
16. Kühl U, Noutsias M, Seeberg B, et al. Immunohistological evidence for a chronic intramyocardial inflammatory process in dilated cardiomyopathy. Heart. 1996; 75(3): 295–300, doi: 10.1136/hrt.75.3.295, indexed in Pubmed: 8800996.
17. Hunt S, Baker D, Chin M, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. J Am Coll Cardiol. 2001; 38(7): 2101–2113, doi: 10.1016/s0735-1097(01)01683-7.
18. Mueller KAL, Patzelt J, Sauter M, et al. Myocardial expression of the anaphylatoxin receptor C3aR is associated with cardiac inflammation and prognosis in patients with non-ischaemic heart failure. ESC Heart Fail. 2018; 5(5): 846–857, doi: 10.1002/ehf2.12298, indexed in Pubmed: 30168657.
19. Nakayama T, Sugano Y, Yokokawa T, et al. Clinical impact of the presence of macrophages in endomyocardial biopsies of patients with dilated cardiomyopathy. Eur J Heart Fail. 2017; 19(4): 490–498, doi: 10.1002/ejhf.767, indexed in Pubmed: 28217949.
20. Escher F, Kühl U, Lassner D, et al. Presence of perforin in endomyocardial biopsies of patients with inflammatory cardiomyopathy predicts poor outcome. Eur J Heart Fail. 2014; 16(10): 1066–1072, doi: 10.1002/ejhf.148, indexed in Pubmed: 25163698.
21. Katzmann JL, Schlattmann P, Rigopoulos AG, et al. Meta-analysis on the immunohistological detection of inflammatory cardiomyopathy in endomyocardial biopsies. Heart Fail Rev. 2020; 25(2): 277–294, doi: 10.1007/s10741-019-09835-9, indexed in Pubmed: 31396762.
22. Henry WL, Gardin JM, Ware JH. Echocardiographic measurements in normal subjects from infancy to old age. Circulation. 1980; 62(5): 1054–1061, doi: 10.1161/01.cir.62.5.1054, indexed in Pubmed: 7418156.
23. Mestroni L, Maisch B, McKenna WJ, et al. Guidelines for the study of familial dilated cardiomyopathies. Collaborative Research Group of the European Human and Capital Mobility Project on Familial Dilated Cardiomyopathy. Eur Heart J. 1999; 20(2): 93–102, doi: 10.1053/euhj.1998.1145, indexed in Pubmed: 10099905.
24. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail. 2008; 10(10): 933–989, doi: 10.1016/j.ejheart.2008.08.005, indexed in Pubmed: 18826876.
25. McMurray JJV, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012; 33(14): 1787–1847, doi: 10.1093/eurheartj/ehs104, indexed in Pubmed: 22611136.
26. Baltrūnienė V, Bironaitė D, Kažukauskienė I, et al. The role of serum adiponectin for outcome prediction in patients with dilated cardiomyopathy and advanced heart failure. Biomed Res Int. 2017; 2017: 3818292, doi: 10.1155/2017/3818292, indexed in Pubmed: 29318144.
27. Noutsias M, Seeberg B, Schultheiss HP, et al. Expression of cell adhesion molecules in dilated cardiomyopathy: evidence for en-

dothelial activation in inflammatory cardiomyopathy. Circulation. 1999; 99(16): 2124–2131, doi: 10.1161/01.cir.99.16.2124, indexed in Pubmed: 10217652.
28. Allard A, Albinsson B, Wadell G. Rapid typing of human adenoviruses by a general PCR combined with restriction endonuclease analysis. J Clin Microbiol. 2001; 39(2): 498–505, doi: 10.1128/JCM.39.2.498-505.2001, indexed in Pubmed: 11158096.
29. McIver CJ, Jacques CFH, Chow SSW, et al. Development of multiplex PCRs for detection of common viral pathogens and agents of congenital infections. J Clin Microbiol. 2005; 43(10): 5102–5110, doi: 10.1128/JCM.43.10.5102-5110.2005, indexed in Pubmed: 16207970.
30. Palecek T, Kuchynka P, Hulinska D, et al. Presence of Borrelia burgdorferi in endomyocardial biopsies in patients with new-onset unexplained dilated cardiomyopathy. Med Microbiol Immunol. 2010; 199(2): 139–143, doi: 10.1007/s00430-009-0141-6, indexed in Pubmed: 20052487.
31. Katzmann JL, Schlattmann P, Rigopoulos AG, et al. Meta-analysis on the immunohistological detection of inflammatory cardiomyopathy in endomyocardial biopsies. Heart Fail Rev. 2020; 25(2): 277–294, doi: 10.1007/s10741-019-09835-9, indexed in Pubmed: 31396762.
32. Pankuweit S, Portig I, Eckhardt H, et al. Prevalence of viral genome in endomyocardial biopsies from patients with inflammatory heart muscle disease. Herz. 2000; 25(3): 221–226, doi: 10.1007/s000590050010, indexed in Pubmed: 10904842.
33. Verdonschot J, Hazebroek M, Merken J, et al. Relevance of cardiac parvovirus B19 in myocarditis and dilated cardiomyopathy: review of the literature. Eur J Heart Fail. 2016; 18(12): 1430–1441, doi: 10.1002/ejhf.665, indexed in Pubmed: 27748022.
34. Maisch B, Richter A, Sandmöller A, et al. BMBF-Heart Failure Network. Inflammatory dilated cardiomyopathy (DCMI). Herz. 2005; 30(6): 535–544, doi: 10.1007/s00059-005-2730-5, indexed in Pubmed: 16170686.
35. Kühl U, Pauschinger M, Seeberg B, et al. Viral persistence in the myocardium is associated with progressive cardiac dysfunction. Circulation. 2005; 112(13): 1965–1970, doi: 10.1161/CIRCULATIONAHA.105.548156, indexed in Pubmed: 16172268.
36. Nowalany-Kozielska E, Kozieł M, Domal-Kwiatkowska D, et al. Clinical significance of viral genome persistence in the myocardium of patients with dilated cardiomyopathy. Intervirology. 2015; 58(6): 350–356, doi: 10.1159/000443375, indexed in Pubmed: 26845221.
37. Kuethe F, Sigusch HH, Hilbig K, et al. Detection of viral genome in the myocardium: lack of prognostic and functional relevance in patients with acute dilated cardiomyopathy. Am Heart J. 2007; 153(5): 850–858, doi: 10.1016/j.ahj.2007.02.013, indexed in Pubmed: 17452164.
38. Lotze U, Egerer R, Glück B, et al. Low level myocardial parvovirus B19 persistence is a frequent finding in patients with heart disease but unrelated to ongoing myocardial injury. J Med Virol. 2010; 82(8): 1449–1457, doi: 10.1002/jmv.21821, indexed in Pubmed: 20572082.
39. Schenk T, Enders M, Pollak S, et al. High prevalence of human parvovirus B19 DNA in myocardial autopsy samples from subjects without myocarditis or dilative cardiomyopathy. J Clin Microbiol. 2009; 47(1): 106–110, doi: 10.1128/JCM.01672-08, indexed in Pubmed: 19005147.
40. Corcioli F, Zakrzewska K, Rinieri A, et al. Tissue persistence of parvovirus B19 genotypes in asymptomatic persons. J Med Virol. 2008; 80(11): 2005–2011, doi: 10.1002/jmv.21289, indexed in Pubmed: 18814251.
41. Kawai C. From myocarditis to cardiomyopathy: mechanisms of inflammation and cell death: learning from the past for the future. Circulation. 1999; 99(8): 1091–1100, doi: 10.1161/01.cir.99.8.1091, indexed in Pubmed: 10051305.
42. Bajpai G, Schneider C, Wong N, et al. The human heart contains distinct macrophage subsets with divergent origins and functions. Nat Med. 2018; 24(8): 1234–1245, doi: 10.1038/s41591-018-0059-x, indexed in Pubmed: 29892064.
43. Lavine KJ, Pinto AR, Epelman S, et al. The Macrophage in Cardiac Homeostasis and Disease: JACC Macrophage in CVD Series (Part 4). J Am Coll Cardiol. 2018; 72(18): 2213–2230, doi: 10.1016/j.jacc.2018.08.2149, indexed in Pubmed: 30360829.
44. Hilgendorf I, Gerhardt LMS, Tan TC, et al. Ly-6Chigh monocytes depend on Nr4a1 to balance both inflammatory and reparative phases in the infarcted myocardium. Circ Res. 2014; 114(10): 1611–1622, doi: 10.1161/CIRCRESAHA.114.303204, indexed in Pubmed: 24625784.
45. Steiner MK, Syrkina OL, Kolliputi N, et al. Interleukin-6 overexpression induces pulmonary hypertension. Circ Res. 2009; 104(2): 236–244, doi: 10.1161/CIRCRESAHA.108.182014, indexed in Pubmed: 19074475.
46. Tschöpe C, Elsanhoury A, Schlieker S, et al. Immunosuppression in inflammatory cardiomyopathy and parvovirus B19 persistence. Eur J Heart Fail. 2019; 21(11): 1468–1469, doi: 10.1002/ejhf.1560, indexed in Pubmed: 31476088.
47. Bock CT, Klingel K, Kandolf R. Human parvovirus B19-associated myocarditis. N Engl J Med. 2010; 362(13): 1248–1249, doi: 10.1056/NEJMc0911362, indexed in Pubmed: 20357294.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 3, 454–462
DOI: 10.5603/CJ.a2020.0095

ISSN 1897–5593
eISSN 1898–018X

Right ventricular involvement in left ventricular non-compaction cardiomyopathy

Simon F. Stämpfli[1, 2, *], Alexander Gotschy[1, 3, *], Pascal Kiarostami[1], Tardu Özkartal[1], Christiane Gruner[1], Markus Niemann[1, 4], Robert Manka[1, 5], Felix C. Tanner[1]

[1]Department of Cardiology, University Heart Center Zurich, Switzerland
[2]Department of Cardiology, Heart Center Lucerne, Luzerner Kantonsspital, Lucerne, Switzerland
[3]Institute for Biomedical Engineering, University and ETH Zurich, Switzerland
[4]Faculty Mechanical and Medical Engineering, Furtwangen University, Germany
[5]Institute of Diagnostic and Interventional Radiology, University Hospital Zurich, Switzerland

Abstract

Background: *Left ventricular non-compaction cardiomyopathy (LVNC) features extensive trabeculations. Involvement of the right ventricle (RV) has been reported; however, distinction from normal RV trabeculation is difficult. This study aimed at assessing RV morphology and function in LVNC by cardiac magnetic resonance (CMR) and transthoracic echocardiography (TTE).*

Methods: *Dimensional and functional parameters were assessed according to guidelines. Novel CMR parameters were RV end-diastolic (ED) trabeculated area, RV ED trabeculated volume, and RV ED non-compacted to compacted (NC/N) ratio in short axis (SAX) as well as in four-chamber view (4CH).*

Results: *Twenty patients with LVNC and 20 controls were included. RV size and function were comparable in LVNC and controls and exhibited a good correlation between TTE and CMR. Although RV trabeculated area, RV trabeculated volume, and RV ED NC/C ratio in SAX as well as in 4CH were larger in LVNC, there was a major overlap with values in controls. RV ED NC/C ratio in SAX correlated with LV ED NC/C ratio (not in 4CH). Quantitative assessment of RV non-compaction was not feasible in TTE.*

Conclusions: *Right ventricle size and function in LVNC can be measured by CMR and TTE, while RV trabeculation can only be quantified by CMR. RV myocardium displays more trabeculations in LVNC; however, overlap with normal individuals is extensive, not allowing separation of patients with LVNC from controls.* (Cardiol J 2022; 29, 3: 454–462)

Key words: trabeculation, cardiac magnetic resonance imaging, echocardiography, left ventricular non-compaction cardiomyopathy

Introduction

Left ventricular non-compaction cardiomyopathy (LVNC) is characterized by a two-layered myocardium involving a thin, compacted, outer layer and a thick, non-compacted, inner layer with deep recesses between prominent trabeculations [1]. During recent years, the awareness of LVNC has increased [2–6], with wider recognition of the disease and systematic family screening, the number of symptomatic and asymptomatic patients diagnosed with LVNC is growing [7–14].

While most studies have focused on the left ventricle (LV) [15–17], prominent trabeculation has also been reported in the right ventricle (RV) of patients with LVNC [5, 18, 19]. In addition, RV

Address for correspondence: Felix C. Tanner, MD, Department of Cardiology, University Heart Center Zurich, Rämistrasse 100, CH-8091 Zurich, Switzerland, tel: +41 44 255 87 00, fax +41 44 255 87 01, e-mail: felix.tanner@usz.ch

Received: 20.03.2020 Accepted: 29.06.2020 Early publication date: 10.07.2020

**Simon F. Stämpfli and Alexander Gotschy share first authorship.*

systolic function was decreased in patients with advanced LVNC and seemed to be associated with impaired outcome [20–22]. However, the extent and incidence of RV involvement remains unclear. Cardiac magnetic resonance (CMR) performed in 56 LVNC patients revealed in only 6 patients RV non-compaction as defined somewhat arbitrarily by the presence of recesses within the inflow area of the RV involving at least 75% of the RV thickness [21]. RV apical trabecular thickness assessed by CMR correlated with the extent of LV involvement in LVNC, whereas RV end-diastolic (ED) non-compacted to compacted (NC/C) ratio in four-chamber view (4CH) did not differ from normal ventricles [22]. RV systolic function was decreased in patients with advanced LVNC and seemed to be associated with enhanced RV trabeculation and impaired outcome [20–23].

Due to its complex shape, comprehensive evaluation of the RV is difficult by transthoracic two-dimensional echocardiography (TTE) [20]. In addition, the RV exhibits a substantially higher number of trabeculations than the LV even in healthy individuals, wherefore it is challenging to differentiate between normal and pathologic anatomy in patients with suspected LVNC [22]. CMR provides a full volume three-dimensional (3D) dataset independent of acoustic windows and is regarded as the reference method for assessing the RV in various cardiac diseases [24]. It is of great value for diagnosis and morphological description of LVNC in the LV and indeed has become one of the standard modalities for assessing LVNC patients [25–28]. On the other hand, due to its wide availability and high versatility, echocardiography is still the standard tool for assessment of LV and RV in patients with cardiomyopathies.

Neither the optimal imaging modality nor standardized measurements for RV assessment in LVNC patients have been defined. This study aims at assessing RV morphology in LVNC patients versus controls by introducing novel CMR parameters such as trabeculated area, trabeculated volume, and NC/C ratio in short axis (SAX) and at comparing the suitability of CMR and TTE for diagnosing RV involvement in LVNC patients.

Methods

Twenty patients with LVNC (fulfilling both TTE [15] and CMR criteria [27]) and 20 healthy controls (age and gender matched) underwent TTE and CMR at the University Hospital Zurich between 2011 and 2016. Measurements were performed in a blinded manner. Patient records were reviewed for baseline characteristics, New York Heart Association (NYHA) functional class, body height, body weight, blood pressure, heart rate, and medication. The study was approved by the local ethical committee.

All CMR exams were performed on a clinical 1.5 T scanner (Achieva, Philips Healthcare, Best, The Netherlands) using a 5-channel cardiac coil array. Steady-state free precession cine images (echo time/repetition time 1.6/3.3 ms, flip angle 60°) were acquired in three long-axis views (2-, 3-, and 4-chamber view) and a stack of short-axis slices covering the whole LV and RV. A single reader performed all CMR analysis in a blinded manner using GTVolume software (GyroTools LLC, Zurich, Switzerland). Commonly measured dimensional and functional parameters were assessed according to current guidelines and recommendations [29, 30]. As novel CMR parameters RV ED trabeculated area in 4CH view, RV ED trabeculated volume, and RV ED NC/N ratio in short axis (SAX) and long axis (LAX) were introduced (Fig. 1A–E). RV ED trabeculated area was quantified by manually contouring the trabeculation in 4CH view, while RV ED trabeculated volume was assessed by summation of the trabeculated area in all RV short axes multiplied by the slice thickness. RV ED NC/C values in long and short axis are reported as the maximal ratio of the thickness of NC to C layer measured at a single location perpendicular to the compacted wall.

Echocardiographic studies were performed on commercially available echocardiography units (GE E95 and E9, GE Healthcare, Horten, Norway and Philips iE33 and Epic, Philips Medical Systems, Erlangen, Germany) equipped with multi-frequency transducers (1.5–4 MHz). All examinations were performed by experienced sonographers and stored on a digital workstation for subsequent off-line analysis (Xcelera R4.1, Philips Medical Systems, Erlangen, Germany). A modified apical 4CH view focusing on the RV was used to measure RV area and fractional area change (FAC) by tracing the endocardial surface of the RV compacted myocardial layer both in systole and diastole [31]. Commonly measured dimensional and functional parameters were assessed according to current guidelines and recommendations [32].

Statistical analysis

Statistical analysis was performed using GraphPad Prism (Version 5.04, La Jolla, USA). Normal distribution of data was confirmed using the

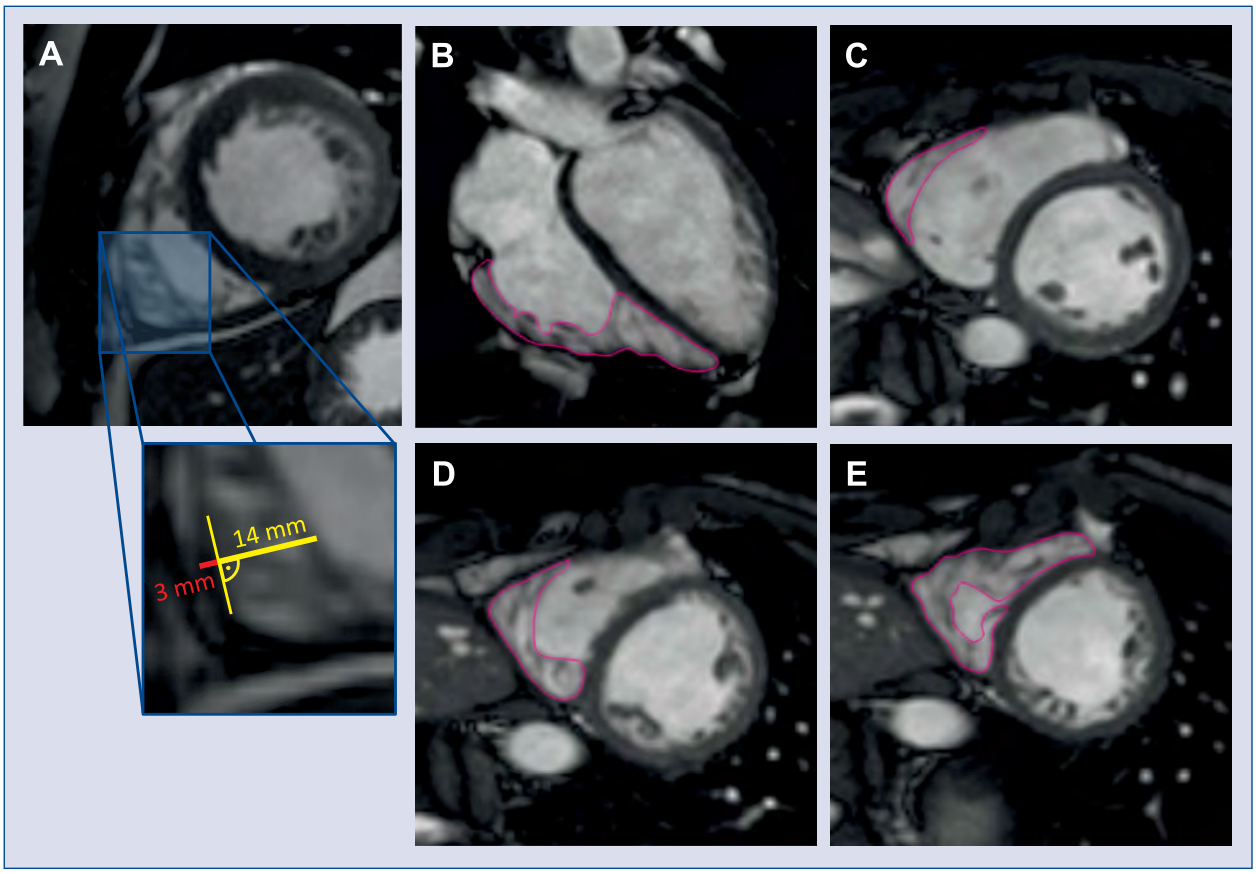


Figure 1. Example of right ventricular end-diastolic non-compacted to compacted ratio as assessed in short axis view (**A**), right ventricular end-diastolic trabeculated area assessed in four-chamber view (**B**), and right ventricular end-diastolic trabeculated volume as assessed in short-axis views on a basal (**C**), midventricular (**D**) and apical level (**E**).

Shapiro-Wilk test. Normally distributed continuous values are depicted as mean ± standard deviation (SD), non-normally distributed continuous data as median and interquartile range (IQR). Categorical data is displayed as number (percentage). To determine the statistical significance between LVNC and control group, the unpaired Student t-test was used. The agreement between CMR and echocardiography measurements was assessed with the Spearman rank correlation. A p-value < 0.05 was considered statistically significant.

Results

Twenty patients (9 females, 45%) with confirmed LVNC and 20 healthy subjects (7 females, 35%) were included in the study. The median age of patients with LVNC at the time of CMR was 46 (IQR 33–57) years, that of controls was 54 (IQR 43–57) years ($p = 0.16$). In 29 subjects, TTE and CMR took place on the same day; in the remaining 11 subjects, the median time between the two examinations was 11 (4–40) days. CMR-based LV ejection fraction (LVEF) was lower in LVNC patients as compared to controls (52% vs. 62%, $p < 0.0001$). However, median LVEF in LVNC patients was only mildly impaired (median 53%, IQR 48–57%); 8 (40%) patients had a normal LVEF (≥ 55%). Heart rate was slightly higher and systolic blood pressure lower in LVNC patients as compared to controls. Table 1 summarizes baseline characteristics.

Right ventricular end-diastolic area exhibited good correlation between TTE and CMR (Fig. 2, absolute values Table 2) in LVNC ($r = 0.66, \beta = 0.85$, $p = 0.0016$) and in controls ($r = 0.88$, $\beta = 0.80$, $p < 0.0001$). RV ED area was higher in CMR as compared to TTE for LVNC (agreement of ΔCMR-TTE = $= 7.5\ cm^2$, 95% limits of agreement 0.007–15.1) and for controls (agreement of ΔCMR-TTE = $7.8\ cm^2$, 95% limits of agreement 1.8–13.7). Similarly, RV ED basal diameter was higher in CMR as compared to TTE for both groups (LVNC: agreement of ΔCMR-TTE = 7.9 mm, 95% limits of agreement

Table 1. Patient characteristics.

Characteristic	LVNC (n = 20)	Controls (n = 20)	P
Age [years]	46 (33–57)	54 (43–57)	0.16
Female sex	9 (45%)	7 (35%)	0.52
Body mass index [kg/m^2]	24.3 ± 4.0	26.2 ± 4.6	0.09
Heart rate [bpm]	65.5 ± 11.6	64.8 ± 13.1	0.6
Systolic blood pressure [mmHg]	117 ± 13.4	131 ± 9.7	**0.03**
Diastolic blood pressure [mmHg]	71.0 ± 8.5	78.6 ± 8.8	0.07
NYHA class:			
Class I	17 (85%)	20 (100%)	
Class II	3 (15%)	0 (0%)	
Left ventricular ejection fraction (CMR) [%]	51.6 ± 8.6	62.0 ± 4.3	**< 0.0001**
Medication:			
Acetylsalicylic acid	1 (5%)	0 (0%)	
Phenprocoumon	3 (15%)	0 (0%)	
Beta-blocker	5 (25%)	0 (0%)	
ACEI or ARB	8 (40%)	0 (0%)	
Diuretics	6 (30%)	0 (0%)	

Data are shown as mean ± standard deviation or median (interquartile range) or number (percentage). ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin-receptor blocker; CMR — cardiac magnetic resonance imaging; LVNC — left ventricular non-compaction cardiomyopathy; NYHA — New York Heart Association

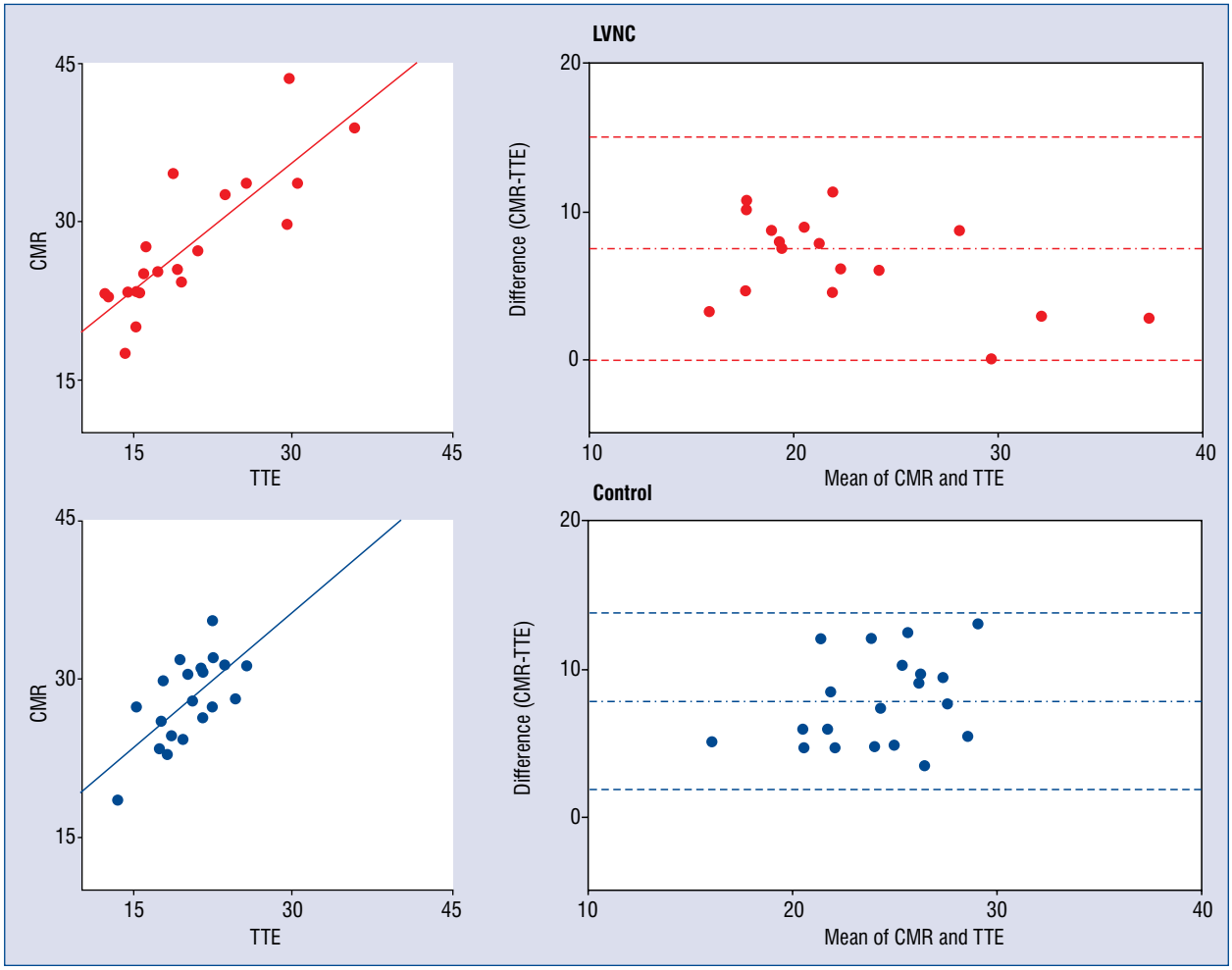


Figure 2. Right ventricular end-diastolic area as measured in transthoracic echocardiography (TTE) and cardiac magnetic resonance (CMR) exhibits good correlation between the two methods in both left ventricular non-compaction cardiomyopathy (LVNC) patients and controls. Scatter plot correlation graph (left), Bland-Altman plot (right).

Table 2. Structural and functional right ventricular parameters in transthoracic echocardiography (TTE) and cardiac magnetic resonance imaging (CMR).

Parameter	LVNC (n = 20)	Controls (n = 20)	P
RV ED area [cm^2]			
CMR	25.3 (23.2–33.3)	28.0 (25.0–31.2)	0.86
TTE	18.1 (15.3–25.2)	20.4 (17.9–22.5)	0.96
RV ED basal diameter [mm]:			
CMR	36 (30–41)	41 (37–44)	0.18
TTE	28 (25–32)	30 (27–32)	0.4
FAC [%]:			
CMR	46.3 ± 11.8	42.8 ± 6.2	0.25
TTE	43.0 ± 9.6	41.8 ± 5.0	0.62

Data are shown as mean ± standard deviation or median (interquartile range). ED — end-diastolic; FAC — fractional area change; LVNC — left ventricular non-compaction cardiomyopathy; RV — right ventricle

Table 3. Quantitative assessment of right ventricle (RV) non-compaction in cardiac magnetic resonance imaging (CMR).

Parameter	LVNC (n = 20)	Controls (n = 20)	P
RV ED trabeculated area [cm^2]	9.15 ± 3.69	6.47 ± 2.97	0.048
RV ED trabeculated volume [mL]	35.2 (25.6–61.3)	27.0 (19.5–35.2)	0.028
RV ED NC/C ratio in SAX	3.93 (3.39–5.18)	2.96 (2.48–3.69)	0.001
RV ED NC/C ratio in 4CH	3.3 (2.94–4.13)	2.73 (2.00–3.10)	0.019

Data are shown as mean ± standard deviation or median (interquartile range). ED — end-diastolic; LVNC — left ventricular non-compaction cardiomyopathy; NC/C — non-compacted to compacted; SAX — short axis; 4CH — four-chamber view

–2.5–18.4; controls: agreement of ΔCMR-TTE = = 9.7 mm, 95% limits of agreement –0.9–20.1).

Fractional area change was assessed as a functional parameter and exhibited good correlation between the two imaging modalities in LVNC ($r = 0.72$, $\beta = 0.92$, $p = 0.0004$) and in controls ($r = 0.56$, $\beta = 0.65$, $p = 0.011$). The bias between the two methods was minimal in LVNC (agreement of ΔCMR-TTE = 3.3%, 95% limits of agreement –12.1–18.7) and in controls (agreement of ΔCMR-TTE = 1.1%, 95% limits of agreement –9.79–11.93).

In TTE, quantitative assessment of RV non-compaction was not feasible. In particular, the decline of lateral resolution with imaging depth hampered a reliable quantification of RV trabeculated area and RV NC/C ratio along the whole RV free wall. In addition, reverberation artifacts as well as near field artifacts accounted for an inadequate quantification of RV trabeculation.

The data comparing RV parameters in LVNC and controls are summarized in Tables 2 and 3. RV size was assessed by RV ED area and RV ED basal diameter, while RV systolic function was determined by FAC. All these parameters were comparable in LVNC and controls, and this finding was observed with both imaging modalities (Fig. 2). In contrast, RV ED trabeculated area in 4CH view and RV ED trabeculated volume were significantly higher in LVNC as compared to controls (Table 3, Fig. 3A, B). There was a major overlap of values obtained in patients and controls. Only 6 (30%) patients displayed values above the upper limit of normal for both parameters (mean+2SD; 12.4 cm^2 for area; 50.9 mL for volume). Similarly, RV ED NC/C ratio in SAX and RV ED NC/C ratio in 4CH were significantly higher in LVNC than in controls (Table 3, Fig. 4A, B), but with a major overlap between the two groups. Six (30%) patients displayed values above the upper limit of normal for NC/C in SAX (4.74), and only 4 (20%) patients displayed values above the upper limit of normal for NC/C in 4CH (4.22). RV ED NC/C ratio in SAX as well as RV ED NC/C ratio in 4CH correlated with LV ED NC/C ratio in long axis (SAX: $r = 0.61$, $\beta = 0.60$, $p = 0.0044$, Fig. 4C; 4CH: $r = 0.77$,

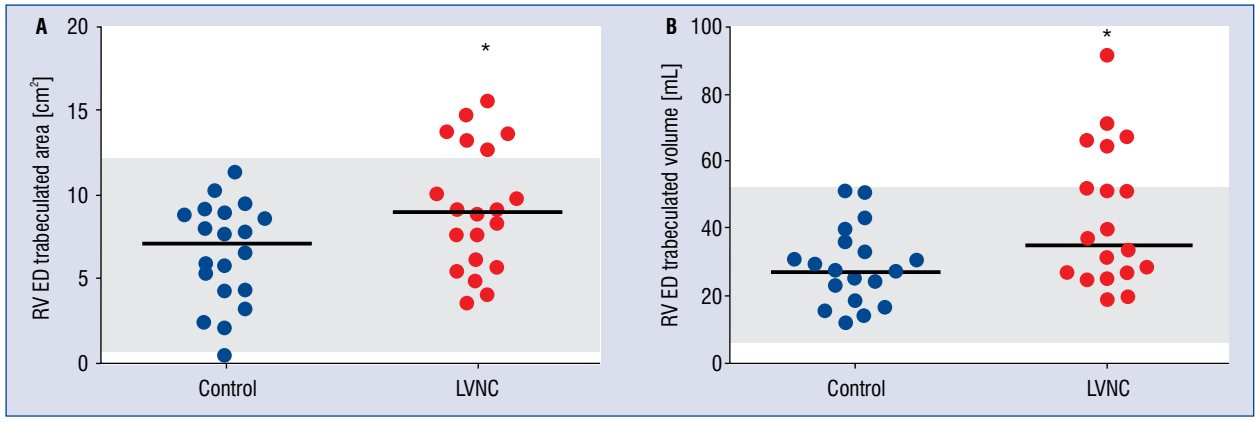


Figure 3. End-diastolic (ED) trabeculated area (**A**) and end-diastolic (ED) trabeculated volume (**B**) as assessed in cardiac magnetic resonance (CMR) in left ventricular non-compaction cardiomyopathy (LVNC) patients as compared to controls. Lines represent median values. Upper and lower limit of normal (gray): 6 (30%) patients are above the upper limit for both parameters; RV — right ventricle; *p < 0.05.

β = 0.70, p = 0.0001, Fig. 4D). No significant correlation was observed for RVEF and RV ED NC/C ratio, neither in 4CH nor in SAX (r = –0.104, β = 0.21, p = 0.66).

Discussion

This study assessed RV morphology, size, and function in LVNC patients and controls using two different imaging modalities (CMR and TTE). RV size and function were comparable in LVNC patients and controls by use of both modalities. Parameters indicating right ventricular involvement in LVNC such as RV ED trabeculated area and volume measured by CMR were significantly higher in the LVNC group although there was a major overlap between RV trabeculation of LVNC patients and controls hampering diagnosis of RV involvement in LVNC.

While several studies have compared CMR and TTE in LVNC patients regarding the LV [25, 26], this is the first study to do so for RV parameters. Assessment of RV size exhibited good correlation between the two imaging modalities. Dimensional parameters such as RV ED area and RV ED basal diameter exhibited higher values in CMR as compared to TTE. This is in line with the current guidelines reporting higher values for these parameters in CMR [33, 34] as compared to TTE [32]. RV systolic function assessed by FAC exhibited good correlation between the two imaging modalities. In contrast to the afore-mentioned dimensional parameters, the values for FAC were very similar with both methods presumably because dimensional parameters are considered in a relative manner when a fraction such as FAC is calculated.

To assess the extent of non-compaction in the RV myocardium, different parameters were measured such as trabeculated area, trabeculated volume, and NC/C ratio in long and short axis. While RV ED NC/C ratio in long axis has been measured in a previous study [22], the other parameters have not been investigated yet in LVNC patients. In contrast to CMR, it was not feasible to assess the extent of non-compaction in the RV myocardium by TTE for different reasons. First, there is no controllable echocardiographic equivalent to the CMR short axis with whole heart coverage to calculate RV trabeculated volume. In theory, this is feasible in a 3D echocardiography data set; however, current technology does not provide sufficient spatial solution to reliably assess NC/C ratio. Second, the decline of lateral resolution with imaging depth, reverberations, and near field artifacts in combination with suboptimal acoustic windows in a subset of patients hampered the accurate quantification of RV trabeculated area and RV ED NC/C ratio.

Cardiac magnetic resonance imaging and TTE displayed similar RV size and function in LVNC as compared to controls. This seems to be in contrast to a previous study describing impaired RV function in LVNC [22]. In the cited study, however, LVNC patients were at a later stage of the disease as indicted by higher age, lower LVEF, and higher rate of heart failure. In line with this, studies examining RV function in LVNC patients revealed an associa-

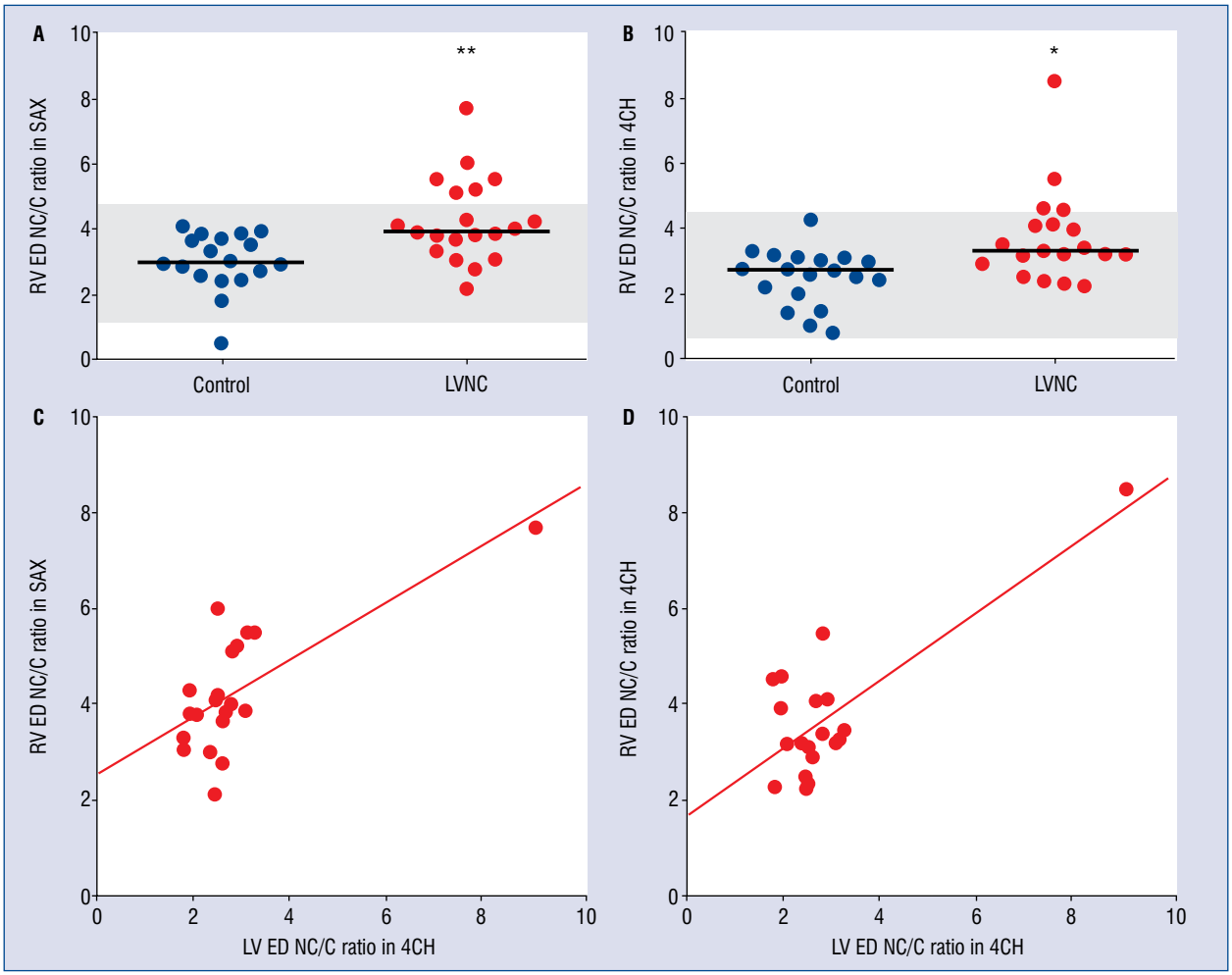


Figure 4. Right ventricular end-diastolic non-compacted to compacted (RV ED NC/C) ratio as assessed in cardiac magnetic resonance (CMR) short axis (SAX) view (**A**) and in CMR four-chamber (4CH) view (**B**) in left ventricular non-compaction cardiomyopathy (LVNC) patients as compared to controls. Lines represent median values. Upper and lower limit of normal (gray): 6 (30%) patients are above the upper limit of non-compacted to compacted (NC/C) ratio in SAX, 4 (20%) patients above the upper limit of NC/C ratio in 4CH. RV ED NC/C ratio as assessed in CMR SAX (**C**) as well as when assessed in CMR 4CH (**D**) exhibits significant correlation with conventional left ventricular end-diastolic (LV ED) NC/C ratio as assessed in CMR 4CH; *$p < 0.05$; **$p < 0.01$.

tion of RV dysfunction with LV dysfunction as well as with heart failure symptoms [20, 21].

To assess RV non-compaction in LVNC, the afore-mentioned novel parameters were determined. RV ED trabeculated area and RV ED trabeculated volume were higher in LVNC as compared to controls. Similarly, RV ED NC/C ratio in both long and short axis was increased in LVNC as compared to controls. However, it is questionable whether these differences represent an RV involvement since there was a major overlap with 70% of LVNC patients within the normal range. This is partially in line with another cohort of LVNC patients, where RV ED NC/C ratio in long axis was not increased as compared to a control group [22].

RV ED NC/C ratio in SAX and 4CH correlated significantly with the extent of LV non-compaction as assessed by a standardized protocol [27]. Similar to these results, another study described that apical trabecular thickness in the RV correlates with LV end-systolic NC/C ratio [22]. To exclude that the correlation was only due to the 1 patient with much higher NC/C ratios, the analysis was repeated without this patient. In the latter analysis, the correlation was still significant when RV ED NC/C ratio was measured in SAX while it was not significant thereafter when measured in 4CH. The reason for the more robust correlation with the SAX method may be related to the observation that RV NC/C SAX displays the maximal NC/C ratio of

all RV segments (as CMR SAX covers the whole RV). In contrast, RV NC/C in 4CH only covers a small part of the RV free wall, which may not be representative for the whole RV.

The present findings suggest that (1) the RV may be affected in some patients with LVNC and that (2) RV ED NC/C ratio measured in short axis is a more reliable parameter for evaluating RV involvement than RV ED NC/C ratio measured in long axis. However, for all parameters of RV non-compaction determined in this study, there is a major overlap between LVNC and controls, which seems to be related to the prominent trabeculation of the RV in normal individuals, and which renders the diagnosis of RV involvement in LVNC patients very difficult. It is almost impossible to define a diagnostic cutoff value for RV trabeculation with only 30% of LVNC patients above the upper limit of normal.

Interestingly, also for LV morphology, a recent study on the current CMR criteria for the diagnosis of LVNC describes a high variability and their prognostic value seems questionable [14]. This and the present findings suggest that a more comprehensive approach including LV and RV morphology as well as genetic and functional parameters may increase diagnostic accuracy. Further studies will be needed to examine this hypothesis.

Cardiac magnetic resonance imaging and TTE provide similar quantitative data on RV size and function in LVNC patients suggesting that these parameters can be assessed by TTE in clinical routine, resulting in lower cost and avoiding problems related to implantable cardioverter-defibrillator and claustrophobia. In contrast, CMR is the method of choice for morphological assessment of RV trabeculations.

A limitation of this study is that LVNC is a very rare disease, accounting for the small number of patients. In addition, referral bias may have affected the results.

Conclusions

Some patients with LVNC may exhibit non-compaction of the RV myocardium with higher values for RV trabeculated area, RV trabeculated volume, and RV NC/C ratio as compared to control individuals. Consistent with this, the NC/C ratio exhibited a fair correlation between RV and LV. Nevertheless, there is substantial overlap with RV trabeculation in healthy individuals. Thus, quantification of RV trabeculation does not allow separation of LVNC form healthy individuals. Even though measurement of RV trabeculation may not serve as an independent diagnostic tool, it was thought, herein, that it improves the evaluation of LVNC patients. In the future it may serve as an additional parameter in comprehensive diagnostic and prognostic approaches possibly including LV and RV morphology as well as genetic and functional parameters.

Acknowledgments

The study was supported by the Swiss Heart Foundation.

Conflict of interest: None declared

References

1. Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation. 2006; 113(14): 1807–1816, doi: 10.1161/CIRCULATIONAHA.106.174287, indexed in Pubmed: 16567565.
2. Finsterer J, Stöllberger C, Towbin JA. Left ventricular noncompaction cardiomyopathy: cardiac, neuromuscular, and genetic factors. Nat Rev Cardiol. 2017; 14(4): 224–237, doi: 10.1038/nrcardio.2016.207, indexed in Pubmed: 28079110.
3. Stöllberger C, Finsterer J. Left ventricular hypertrabeculation/noncompaction. J Am Soc Echocardiogr. 2004; 17(1): 91–100, doi: 10.1016/s0894-7317(03)00514-5.
4. Engberding R, Bender F. Identification of a rare congenital anomaly of the myocardium by two-dimensional echocardiography: persistence of isolated myocardial sinusoids. Am J Cardiol. 1984; 53(11): 1733–1734, doi: 10.1016/0002-9149(84)90618-0, indexed in Pubmed: 6731322.
5. Jenni R, Goebel N, Tartini R, et al. Persisting myocardial sinusoids of both ventricles as an isolated anomaly: echocardiographic, angiographic, and pathologic anatomical findings. Cardiovasc Intervent Radiol. 1986; 9(3): 127–131, doi: 10.1007/BF02577920, indexed in Pubmed: 3089618.
6. Oechslin E, Jenni R. Left ventricular non-compaction revisited: a distinct phenotype with genetic heterogeneity? Eur Heart J. 2011; 32(12): 1446–1456, doi: 10.1093/eurheartj/ehq508, indexed in Pubmed: 21285074.
7. Oechslin EN, Attenhofer Jost CH, Rojas JR, et al. Long-term follow-up of 34 adults with isolated left ventricular noncompaction: a distinct cardiomyopathy with poor prognosis. J Am Coll Cardiol. 2000; 36(2): 493–500, doi: 10.1016/s0735-1097(00)00755-5, indexed in Pubmed: 10933363.
8. Stämpfli SF, Erhart L, Hagenbuch N, et al. Prognostic power of NT-proBNP in left ventricular non-compaction cardiomyopathy. Int J Cardiol. 2017; 236: 321–327, doi: 10.1016/j.ijcard.2017.02.064, indexed in Pubmed: 28268080.
9. Chin TK, Perloff JK, Williams RG, et al. Isolated noncompaction of left ventricular myocardium. A study of eight cases. Circula-

tion. 1990; 82(2): 507–513, doi: 10.1161/01.cir.82.2.507, indexed in Pubmed: 2372897.
10. Murphy RT, Thaman R, Blanes JG, et al. Natural history and familial characteristics of isolated left ventricular non-compaction. Eur Heart J. 2005; 26(2): 187–192, doi: 10.1093/eurheartj/ehi025, indexed in Pubmed: 15618076.
11. Lofiego C, Biagini E, Pasquale F, et al. Wide spectrum of presentation and variable outcomes of isolated left ventricular non-compaction. Heart. 2007; 93(1): 65–71, doi: 10.1136/hrt.2006.088229, indexed in Pubmed: 16644854.
12. Aras D, Tufekcioglu O, Ergun K, et al. Clinical features of isolated ventricular noncompaction in adults long-term clinical course, echocardiographic properties, and predictors of left ventricular failure. J Card Fail. 2006; 12(9): 726–733, doi: 10.1016/j.cardfail.2006.08.002, indexed in Pubmed: 17174235.
13. Lilje C, Rázek V, Joyce JJ, et al. Complications of non-compaction of the left ventricular myocardium in a paediatric population: a prospective study. Eur Heart J. 2006; 27(15): 1855–1860, doi: 10.1093/eurheartj/ehl112, indexed in Pubmed: 16818458.
14. Ivanov A, Dabiesingh DS, Bhumireddy GP, et al. Prevalence and Prognostic Significance of Left Ventricular Noncompaction in Patients Referred for Cardiac Magnetic Resonance Imaging. Circ Cardiovasc Imaging. 2017; 10(9), doi: 10.1161/CIRCIMAGING.117.006174, indexed in Pubmed: 28899950.
15. Ritter M, Oechslin E, Sütsch G, et al. Isolated noncompaction of the myocardium in adults. Mayo Clin Proc. 1997; 72(1): 26–31, doi: 10.4065/72.1.26, indexed in Pubmed: 9005281.
16. Bleyl SB, Mumford BR, Brown-Harrison MC, et al. Xq28-linked noncompaction of the left ventricular myocardium: prenatal diagnosis and pathologic analysis of affected individuals. Am J Med Genet. 1997; 72(3): 257–265, indexed in Pubmed: 9332651.
17. Gebhard C, Stähli BE, Greutmann M, et al. Reduced left ventricular compacta thickness: a novel echocardiographic criterion for non-compaction cardiomyopathy. J Am Soc Echocardiogr. 2012; 25(10): 1050–1057, doi: 10.1016/j.echo.2012.07.003, indexed in Pubmed: 22883316.
18. Chiribiri A, Leuzzi S, Salvetti I, et al. Isolated noncompaction of the right ventricular myocardium in the adulthood? Int J Cardiol. 2009; 134(1): e17–e19, doi: 10.1016/j.ijcard.2008.02.001, indexed in Pubmed: 18378024.
19. Ichida F, Hamamichi Y, Miyawaki T, et al. Clinical features of isolated noncompaction of the ventricular myocardium: long-term clinical course, hemodynamic properties, and genetic background. J Am Coll Cardiol. 1999; 34(1): 233–240, doi: 10.1016/s0735-1097(99)00170-9, indexed in Pubmed: 10400016.
20. Leung SW, Elayi CS, Charnigo RJ, et al. Clinical significance of right ventricular dysfunction in left ventricular non-compaction cardiomyopathy. Int J Cardiovasc Imaging. 2012; 28(5): 1123––1131, doi: 10.1007/s10554-011-9925-z, indexed in Pubmed: 21792620.
21. Nucifora G, Aquaro GD, Masci PG, et al. Magnetic resonance assessment of prevalence and correlates of right ventricular abnormalities in isolated left ventricular noncompaction. Am J Cardiol. 2014; 113(1): 142–146, doi: 10.1016/j.amjcard.2013.08.049, indexed in Pubmed: 24176065.
22. Stacey RB, Andersen M, Haag J, et al. Right ventricular morphology and systolic function in left ventricular noncompaction cardiomyopathy. Am J Cardiol. 2014; 113(6): 1018–1023, doi: 10.1016/j.amjcard.2013.12.008, indexed in Pubmed: 24462071.
23. Stämpfli SF, Donati TG, Hellermann J, et al. Right ventricle and outcome in left ventricular non-compaction cardiomyopathy. J Cardiol. 2020; 75(1): 20–26, doi: 10.1016/j.jjcc.2019.09.003, indexed in Pubmed: 31587941.
24. Bleeker GB, Steendijk P, Holman ER, et al. Assessing right ventricular function: the role of echocardiography and complementary technologies. Heart. 2006; 92 Suppl 1: i19–i26, doi: 10.1136/hrt.2005.082503, indexed in Pubmed: 16543597.
25. Alhabshan F, Smallhorn JF, Golding F, et al. Extent of myocardial non-compaction: comparison between MRI and echocardiographic evaluation. Pediatr Radiol. 2005; 35(11): 1147–1151, doi: 10.1007/s00247-005-1551-2, indexed in Pubmed: 16086159.
26. Thuny F, Jacquier A, Jop B, et al. Assessment of left ventricular non-compaction in adults: side-by-side comparison of cardiac magnetic resonance imaging with echocardiography. Arch Cardiovasc Dis. 2010; 103(3): 150–159, doi: 10.1016/j.acvd.2010.01.002, indexed in Pubmed: 20417446.
27. Petersen SE, Selvanayagam JB, Wiesmann F, et al. Left ventricular non-compaction: insights from cardiovascular magnetic resonance imaging. J Am Coll Cardiol. 2005; 46(1): 101–105, doi: 10.1016/j.jacc.2005.03.045, indexed in Pubmed: 15992642.
28. Jacquier A, Thuny F, Jop B, et al. Measurement of trabeculated left ventricular mass using cardiac magnetic resonance imaging in the diagnosis of left ventricular non-compaction. Eur Heart J. 2010; 31(9): 1098–1104, doi: 10.1093/eurheartj/ehp595, indexed in Pubmed: 20089517.
29. Kramer CM, Barkhausen J, Flamm SD, et al. Standardized cardiovascular magnetic resonance imaging (CMR) protocols, society for cardiovascular magnetic resonance: board of trustees task force on standardized protocols. J Cardiovasc Magn Reson. 2008; 10: 35, doi: 10.1186/1532-429X-10-35, indexed in Pubmed: 18605997.
30. Kramer CM, Barkhausen J, Flamm SD, et al. Standardized cardiovascular magnetic resonance (CMR) protocols 2013 update. J Cardiovasc Magn Reson. 2013; 15: 91, doi: 10.1186/1532-429X-15-91, indexed in Pubmed: 24103764.
31. Rudski L, Lai W, Afilalo J, et al. Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: A Report from the American Society of Echocardiography. J Am Soc Echocardiogr. 2010; 23(7): 685–713, doi: 10.1016/j.echo.2010.05.010.
32. Lang R, Badano L, Mor-Avi V, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015; 16(3): 233–271, doi: 10.1093/ehjci/jev014.
33. Maceira AM, Prasad SK, Khan M, et al. Reference right ventricular systolic and diastolic function normalized to age, gender and body surface area from steady-state free precession cardiovascular magnetic resonance. Eur Heart J. 2006; 27(23): 2879–2888, doi: 10.1093/eurheartj/ehl336, indexed in Pubmed: 17088316.
34. Le Ven F, Bibeau K, De Larochellière É, et al. Cardiac morphology and function reference values derived from a large subset of healthy young Caucasian adults by magnetic resonance imaging. Eur Heart J Cardiovasc Imaging. 2016; 17(9): 981–990, doi: 10.1093/ehjci/jev217, indexed in Pubmed: 26354980.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 3, 463–471
DOI: 10.5603/CJ.a2020.0096

ISSN 1897–5593
eISSN 1898–018X

Effectiveness and safety of hypotension fluid resuscitation in traumatic hemorrhagic shock: A systematic review and meta-analysis of randomized controlled trials

Kamil Safiejko[1], Jacek Smereka[2, 3], Krzysztof J. Filipiak[4], Agnieszka Szarpak[5], Marek Dabrowski[6], Jerzy R. Ladny[3, 7], Milosz J. Jaguszewski[8], Lukasz Szarpak[3, 9]

[1]Comprehensive Cancer Center in Bialystok, Poland
[2]Department of Emergency Medical Service, Wroclaw Medical University, Wroclaw, Poland
[3]Polish Society of Disaster Medicine, Warsaw, Poland
[4]First Chair and Department of Cardiology, Medical University of Warsaw, Poland
[5]Maria Skłodowska-Curie Medical Academy in Warsaw, Poland
[6]Chair and Department of Medical Education, Poznan University of Medical Sciences, Poznan, Poland
[7]Clinic of Emergency Medicine, Medical University of Bialystok, Poland
[8]First Department of Cardiology, Medical University of Gdansk, Poland
[9]Bialystok Oncology Center, Bialystok, Poland

This paper was guest edited by Prof. Togay Evrin

Abstract

Background: *Although the resuscitation of an adult trauma patient has been researched and written about for the past century, the ideal fluid strategy to infuse during the initial resuscitation period remains unresolved. This work was aimed at assessing the effect of hypotensive versus conventional resuscitation strategies in traumatic hemorrhagic shock patients on mortality, and the need for blood transfusions including adverse events.*

Methods: *This systematic review and meta-analysis were performed following the PRISMA guidelines. Electronic databases were searched for randomized controlled trials (RCT) comparing the effect of hypotension versus conventional fluid resuscitation for traumatic hemorrhagic shock patients. Two reviewers independently performed the screening, data extraction, and bias assessment. The data analysis was completed using the Cochrane Collaboration's software RevMan 5.4.*

Results: *Data from 28 RCTs on 4503 patients were included in the final meta-analysis. Patients receiving hypotension fluid resuscitation compared with conventional fluid resuscitation experienced less mortality (12.5% vs. 21.4%; RR = 0.58; 95% CI: 0.51–0.66; $p < 0.001$), fewer adverse events (10.8% vs. 13.4%; RR = 0.70; 95% CI: 0.59–0.83; $p < 0.001$), including fever acute respiratory distress syndrome (7.8% vs. 16.8%) or multiple organ dysfunction syndrome (8.6% vs. 21.6%).*

Conclusions: *This meta-analysis showed that hypotensive fluid resuscitation significantly reduced the mortality of hypovolemic shock patients. Findings are low in certainty and should be interpreted with caution. Therefore, there is an urgent need for larger, multicenter, randomized trials to confirm these findings.* (Cardiol J 2022; 29, 3: 463–471)

Key words: fluid resuscitation, restricted fluid resuscitation, hemorrhagic shock, hemorrhage, meta-analysis, systematic review

Address for correspondence: Lukasz Szarpak, Assoc. Prof. PhD, Bialystok Oncology Center, ul. Ogrodowa 12, 15–027 Białystok, Poland, tel: +48 500186225, e-mail: lukasz.szarpak@gmail.com

Received: 25.06.2020 Accepted: 6.07.2020 Early publication date: 10.07.2020

Introduction

Trauma injury remains the leading cause of death among people aged less than 35 years, with 40% of trauma deaths imputable to uncontrolled hemorrhagic shock or its consequences [1, 2].

Currently, fluid resuscitation is the first step in the hemodynamic management of traumatic hemorrhagic shock [3]. The rapid vascular access and stabilization of the cardiovascular system can protect the patient from the severe consequences of hypovolemic shock. The origins of fluid resuscitation can be traced back to the thirties of the nineteenth century, when Thomas Latta performed an attempt of intravenous fluid resuscitation for the first time [4]. In the period 1879–1881 Kroneecker and Landerer stated that in cases of blood loss the most valuable thing is to rapidly restore the vascular bed volume. For this purpose, they proposed using a normal saline solution with the addition of sugar [5, 6]. The development of fluid therapy was in the 1920s, when Alfred Blalock experimented with incremental hemorrhage to induce shock in dogs [7, 8]. In his research, Blalock used blood pressure (BP), cardiac output as well as blood oxygen content from left and right ventricles to evaluate the effect of three types of treatment: saline, transfusion and pharmacological treatment.

Applying an appropriate fluid therapy strategy may restore tissue perfusion and consequently oxygenation of the body. Fluid resuscitation can be carried out based on changes in hemodynamics, diuresis, serum lactate levels or alkaline deficit. However, excessive fluid resuscitation could contribute to the development of coagulopathy of trauma [3, 9] as well as tissue edema [10], which can lead to alterations of tissue perfusion and complications such as abdominal compartment syndrome or adult respiratory distress syndrome [11, 12]. The optimal level of BP during resuscitation of hemorrhagic shock patients is still debated.

The present work aimed to assess the effect of hypotensive versus conventional resuscitation strategies in traumatic hemorrhagic shock patients on mortality, need for blood transfusion and adverse events (specifically: acute myocardial or renal failure or acute respiratory distress syndrome).

Methods

This systematic review and meta-analysis adhere to the reporting guidelines of the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) statement (**Suppl. Table 1**).

Search strategy

Available literature databases including EMBASE, MEDLINE, Google Scholar, Cochrane Central Register of Controlled Trials (CENTRAL) were searched from the inception of the databases until 18 June 2020. Searches were conducted independently by two persons (K.S. and L.S.). The papers were restricted to those with the English language. Reference lists of eligible articles were reviewed and content experts were consulted with (K.J.F. and M.J.J.) to identify additional published reports. Incomplete data were dealt with by contacting the principal authors, when possible, to ask for missing or unclear information.

The search strategy was comprised of MESH terms and keywords such as: "shock"OR, "hemorrhagic" OR, "trauma" OR, "injury" OR, "hypotensive resuscitation" OR, "limited resuscitation" OR, "fluid resuscitation" OR, "limited fluid". To identify in-progress or terminated studies, clinicaltrials.gov registry was also searched.

Study selection

This study included randomized controlled trials (RCTs) and quasi-randomized trials. Observational studies, case reports, studies not based on original research and studies not involving patients, conference papers as well as letters to the editor were excluded from the present study.

Data extraction

Using a standardized data extraction sheet, two authors (K.S. and L.S.) independently extracted data from each report included. Any discrepancies were resolved by consensus with the third author (J.S.). When necessary for data or article clarification, personal communication was made with select study authors. Baseline patient characteristics were extracted as well as data about each trial's intervention, inclusion and exclusion criteria, mortality and adverse events. For all clinical outcomes, the number of events that occurred in each arm of each trial were tabulated.

Quality assessment

Two reviewers (J.S. and A.S.) independently assessed the methodological quality of each eligible article using the "risk of bias" assessment tool of the Cochrane Handbook [13]. The following domains were evaluated for RCTs: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete

outcome data (attrition bias), selective reporting (reporting bias) and other bias [12]. Each was graded "yes", "no", or "unclear", which reflected a high risk of bias, low risk of bias, and uncertain bias, respectively (**Suppl. Fig. S1**). The review authors' judgments about each risk of bias item are provided in **Supplementary Figure S2**. The overall risk of bias for the study was rated 'low' if 7 or more domains were rated low, 'moderate' if 4 to 6 domains were rated low, and 'high' if 1 to 3 domains were rated low.

Statistical analysis

Statistical analysis was done by two authors (A.S. and L.S.) independently and was cross-validated. For continuous outcomes, mean difference (MD), and for dichotomous outcomes were used, and risk ratios (RR), were calculated. All continuous data with either means with standard deviations (SD) or medians with interquartile ranges (IQR) as reported in the primary study are presented. When the continuous outcome was reported in a study as median, range, and IQR, means and SD using the formula described by Hozo et al. [14] were estimated. For descriptive purposes, absolute and relative frequencies are reported for categoric variates.

Statistical heterogeneity and inconsistency were measured by using the Cochran Q test and I^2, respectively [14]. Odds ratios (OR) with 95% confidence intervals (CI) were calculated as summary statistics. The pooled OR was calculated with the Mantel-Haenszel method. Weighted mean differences and 95% CIs were computed for continuous variables, again using a fixed-effect method in cases of low statistical inconsistency ($I^2 \leq 50\%$) and using a random-effect method in cases of moderate or high statistical inconsistency ($I^2 > 50\%$) [15]. Results were considered statistically significant at $p < 0.05$. Statistical analyses were performed with the Review Manager (version 5.4; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Results

Eligible studies and their characteristics

The flowchart of the literature search is presented in Figure 1. The initial search returned 432 records from all the databases. Two more studies were identified from the references of the relevant articles. Two hundred and ninety-six records were further screened by titles and abstracts and 138 duplicate articles were removed. Unrelated articles, comments, reviews, letters, and duplicate articles were excluded. Then 47 articles were assessed by accessing the full-text. Nineteen studies were excluded because of unavailable data, duplicates, and unrelated topics. Finally, 28 studies were included in the analysis [16–43].

Assessment of quality

The quality assessment is represented in **Supplementary Figures S1 and S2**. The method of random sequence generation was perfect in all the studies. There were high risks of attrition bias, lack of intention-to-treat analysis, and selective reporting. The detailed information about blinding and allocation concealment was insufficient in most studies. None of the trials included was at low risk of bias across all domains.

Mortality

Twenty-eight studies reported overall mortality [16–23]. Mortality with hypotension fluid resuscitation was 12.5% and was statistically significant, being smaller than with the conventional fluid resuscitation group – 21.4% (RR = 0.58; 95% CI: 0.51–0.66; $I^2 = 37\%$; $p < 0.001$; Fig. 2). In contrast, only one study by Morrison et al. [28] indicated mortality rates during the first 24 hours. According to this study, mortality for hypotension versus conventional fluid resuscitation varied and amounted to 13.6% vs. 21.7% respectively (RR = 0.63; 95% CI: 0.25–1.58; p = 0.32).

Adverse events

The polled analysis showed that hypotension fluid resuscitation compared to conventional fluid resuscitation was associated with a lower risk of adverse events (10.8% vs. 13.4%, respectively; RR = 0.70; 95% CI: 0.59–0.83; $I^2 = 52\%$; $p < 0.001$).

The use of hypotension versus conventional fluid resuscitation showed a higher incidence of anemia (74.3% vs. 68.6%), thrombocytopenia (33.6% vs. 29.4%) and acute renal failure (8.8% vs. 8.1%). In other types of adverse events the relationship was reversed, and the use of hypotension fluid resuscitation was associated with a lower risk of complications (Table 1).

Fluid balance and transfusion requirements

Additional analysis showed that patients who were treated with hypotension fluid resuscitation required smaller volumes of fluids than the conventional fluid resuscitation group (MD = –1.02; 95% CI: –1.33 to –0.71; $I^2 = 99\%$; $p < 0.001$; Fig. 3).

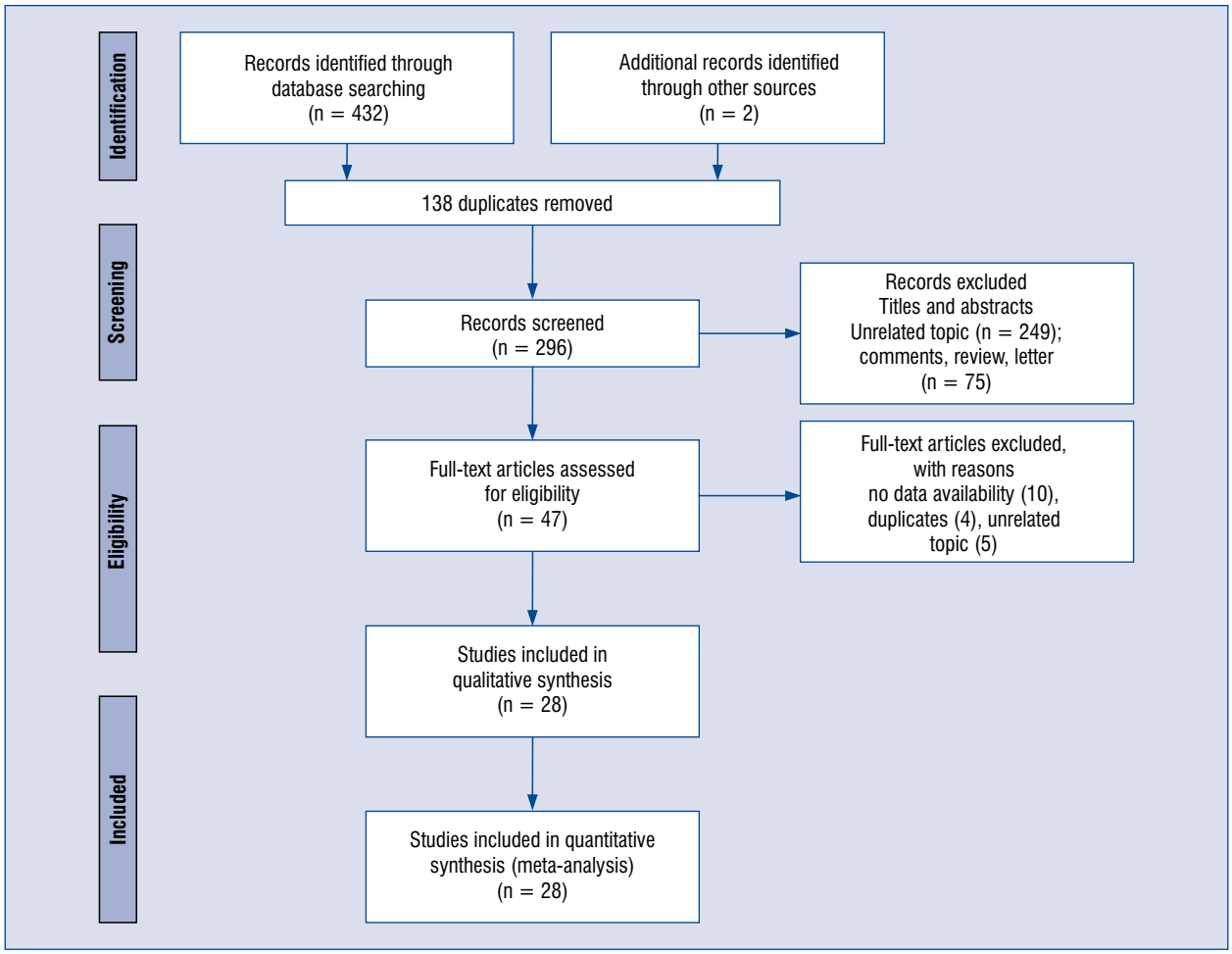


Figure 1. Flow diagram showing stages of database searching and study selection as per PRISMA guidelines.

Length of stay ICU/hospital

The length of stay in the intensive care unit (ICU) was reported by two studies [16, 32]. The polled analysis did not show significant differences in the length of stay in ICU between the groups (MD = 0.38; 95% CI: –1.83–2.59; I^2 = 73%; p = = 0.74; **Suppl. Fig. S3**). Three studies indicated length of stay in hospital [16, 29, 32]. The difference between therapeutic groups was not statistically significant (MD = –0.82; 95% CI: –2.43–0.78; I^2 = 0%; p = 0.32; **Suppl. Fig. S4**).

Discussion

The purpose of this research was to compare the effects of hypovolemic and conventional fluid resuscitation on the mortality rate among patients with traumatic hemorrhagic shock. Meta-analysis for overall mortality showed that hypovolemic fluid resuscitation offered benefit in comparison with conventional fluid resuscitation for patients with traumatic hemorrhagic shock at the final follow-up ($p < 0.001$).

Obtaining intravascular access in hypovolemic patients (especially trauma patients) should be done as soon as possible. In patients with hemorrhage, the most important part of the procedure is to stop the hemorrhage. In such a patient's hospital setting, transfusion of blood substitutes should be limited in favor of the transfusion of blood components. It is recommended to transfuse the red blood cell concentrate in a volume that maintains the hemoglobin concentration at 7–9 g/dL. Fresh frozen plasma should be transfused immediately at a dose of 10–15 mL/kg b.w. and further replenishment of fresh frozen plasma should depend on the volume of red blood cells transfused and the coagulogram. In the case of platelets, they should be transfused in sufficient quantities to maintain a concentration of 50,000/mL. To mitigate the effects of hypovolemic shock caused by the injury, transfusion of cryoprecipitate or fibrinogen concentrate may also be considered.

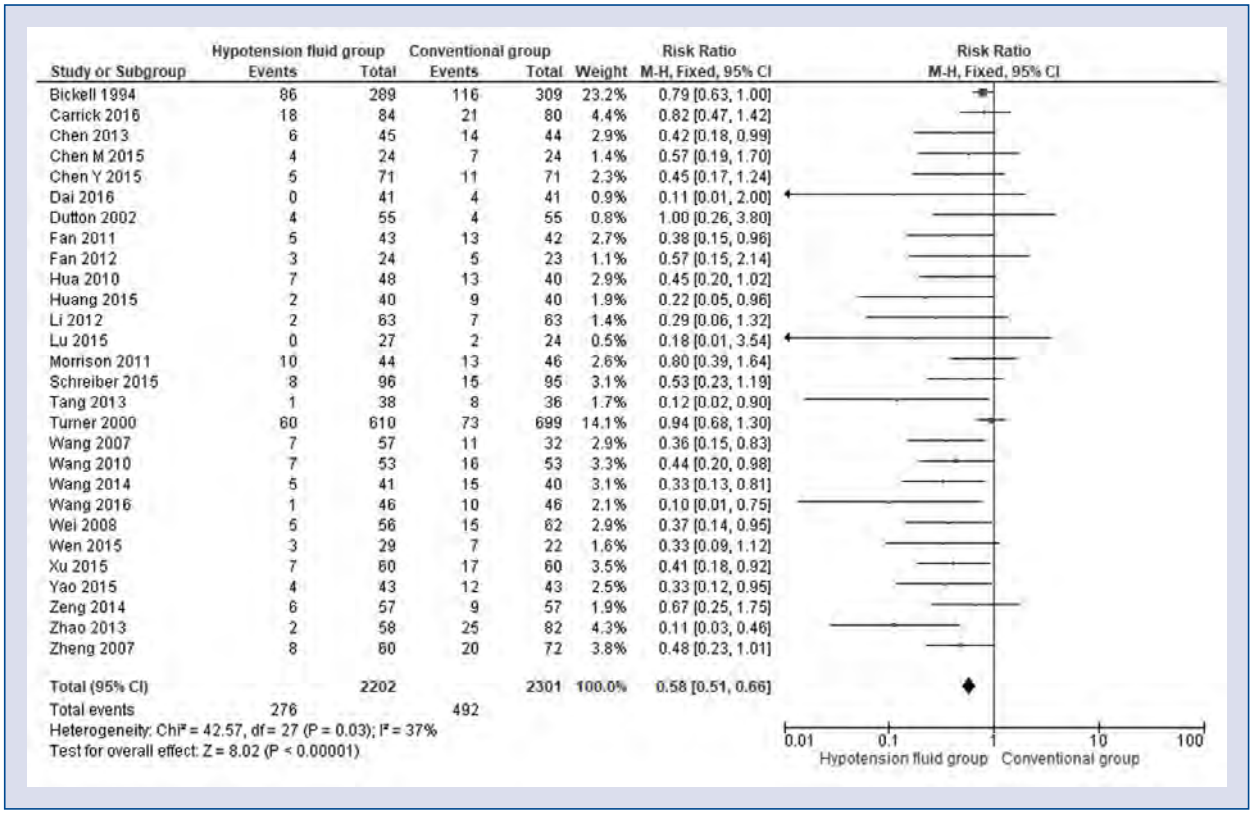


Figure 2. Forest plot of hypotension versus. conventional fluid resuscitation, relative to mortality. The center of each square represents the relative risk for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results.

Table 1. Comparison of hypotension and conventional fluid resuscitation relative to adverse events.

	Number of trials	Hypotension fluid resuscitation	Conventional fluid resuscitation	RR or MD (95% CI)	P value	I^2 statistic, %
ARDS	13	7.8%	16.8%	0.44 [0.34–0.58]	< 0.001	0%
Acute myocardial infarction	1	1.3%	1.5%	0.88 [0.06–13.79]	0.93	–
Stroke	1	0%	3.0%	0.18 [0.01–3.61]	0.26	–
Sepsis syndrome	2	3.5%	3.9%	0.91 [0.42–1.98]	0.82	0%
MODS	10	8.6%	21.6%	0.42 [0.30–0.60]	< 0.001	0%
Any renal failure	1	14.7%	12.1%	1.21 [0.52–2.83]	0.66	–
Acute renal failure	8	8.8%	8.1%	0.99 [0.53–1.86]	0.98	61%
Anemia	2	74.3%	68.6%	1.11 [0.96–1.28]	0.16	2%
Hypotension	1	13.3%	16.7%	0.80 [0.36–1.76]	0.58	–
Coagulopathy	3	15.7%	15.8%	0.95 [0.73–1.24]	0.73	0%
Thrombocytopenia	2	33.6%	29.4%	1.21 [0.64–2.28]	0.56	54%
Pneumonia	1	7.6%	9.1%	0.84 [0.49–1.43]	0.52	–
Deterioration in T-RTS	1	7.4%	7.9%	0.93 [0.50–1.71]	0.81	–
Complications not specified	1	7.5%	8.6%	0.88 [0.61–1.27]	0.49	–

ARDS — acute respiratory distress syndrome; MORS — multiple organ dysfunction syndrome; MD — mean difference; RR — risk ratio

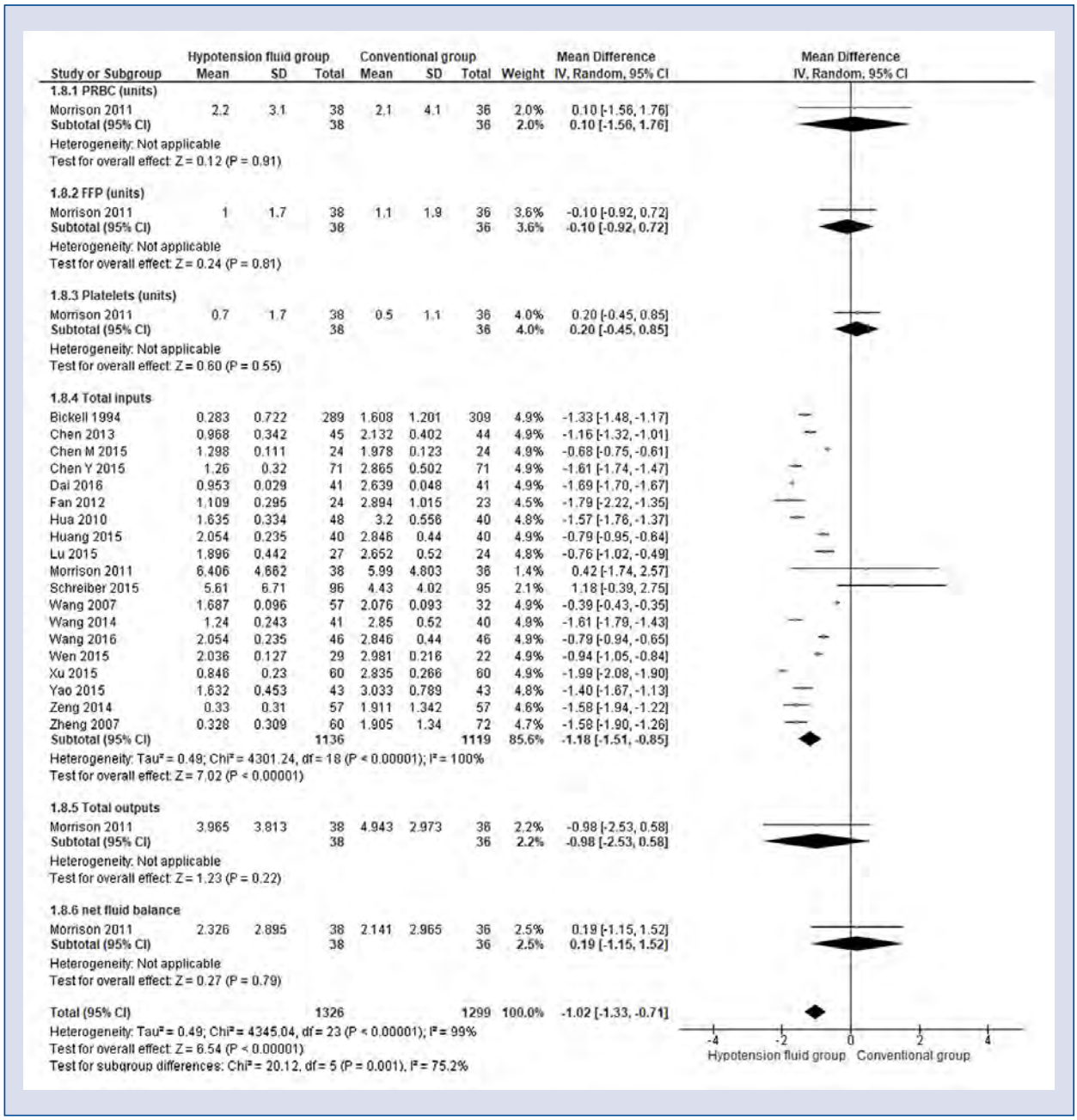


Figure 3. Forest plot of hypotension versus conventional fluid resuscitation, relative to fluid balance and transfusion requirements. The center of each square represents the mean difference for individual trials, and the corresponding horizontal line stands for 95% confidence interval (CI). The diamonds represent pooled results.

Fluid therapy aims not only to maintain and restore the intravascular volume but also, by optimizing the preload, to increase cardiac output and improve tissue perfusion. Discussions are still ongoing as to whether crystalloids (i.e. 0.9% saline or Ringer's Lactate) or colloidal solutions (i.e. dextran's, gelatins, HAES) should be used in the initial phase of fluid resuscitation. De Crescenzo et al. [44] indicates no beneficial effect of hypertonic saline with or without dextran in general trauma patients. In turn, Martin et al. [45] in his meta-analysis indicated that crystalloids were less efficient than colloids at stabilizing resuscitation endpoints. The application of an appropriate fluid resuscitation strategy is, therefore, more important than the type of fluid administered. Malbrain et al. [46] showed that a positive cumulative fluid balance is associated with intra-abdominal

hypertension and worse outcomes. Hypotensive fluid resuscitation as shown by numerous studies may offer a survival benefit over conventional fluid resuscitation for trauma patients. It can also further reduce blood loss and thus blood product utilization. It can, therefore, be concluded that fluid resuscitation in trauma patients should be based on a specific compromise between too small a volume leading to hypoperfusion and too much hydration in patients, which may result in increased bleeding due to increased BP. The use of too large a volume of fluid can lead to "dilutive" hemorrhagic bleeding.

As indicated by numerous randomized studies — as also confirmed by this meta-analysis — hypovolemic fluid resuscitation can bring benefits in the management of the trauma patient [28, 29, 47]. However, it should be remembered that the hypotension should not last longer than 1 hour [22, 28]. It should be kept in mind that the rules of fluid resuscitation in trauma patients with concomitant craniocerebral trauma are different. Thereafter, as recommended by the National Institute for Health and Clinical Excellence (NICE), it is important to increase BP (systolic BP 110–120 mmHg) as quickly as possible to secure proper brain perfusion and prevent secondary brain changes.

In this meta-analysis, hypovolemic fluid resuscitation was associated with a higher incidence of thrombocytopenia, renal failure or anemia in comparison with conventional management. The above symptoms are closely related. Thrombocytopenia is the most frequently diagnosed hemorrhagic flaw and may lead to anemia. As many authors indicate, acute kidney injury is a common feature in patients with thrombocytopenia-associated multiple organ failure with incidences as high as 42% in disseminated intravascular coagulation, 58% in thrombocytopenic purpura and 100% in hemolytic uremic syndromes [48–50]. On the other hand, in the case of conventional fluid resuscitation, a statistically significantly higher incidence of acute respiratory distress syndrome (ARDS) or multiple organ dysfunction syndrome (MODS) was observed. Jiang et al. [51] indicate that hypovolemic/restricted fluid resuscitation can effectively eliminate inflammatory factors, improve immune function, maintain the stability of blood components, and reduce the incidences of ARDS and MODS. In the case of hypotension fluid resuscitation, there was also a higher incidence of acute myocardial infarction, which may be caused by lower myocardial overload.

Limitations of the study

The present study has some limitations. First, only in several articles study groups are appropriate, in other articles the sample size is relatively small, which led to a wide 95% CI. Second, two studies referred to mean arterial pressure, the others to systolic blood pressure.

Conclusions

The present study findings show significant associations between hypotensive fluid resuscitation and a decreased risk of adverse events and cardiovascular mortality in hypovolemic shock trauma patients. There is an urgent need for a large multicenter randomized trial to confirm these findings.

Acknowledgments

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

Conflict of interest: None declared

References

1. Alberdi F, García I, Atutxa L, et al. Trauma and Neurointensive Care Work Group of the SEMICYUC. Epidemiology of severe trauma. Med Intensiva. 2014; 38(9): 580–588, doi: 10.1016/j.medin.2014.06.012, indexed in Pubmed: 25241267.
2. Alexandrescu R, O'Brien SJ, Lecky FE. A review of injury epidemiology in the UK and Europe: some methodological considerations in constructing rates. BMC Public Health. 2009; 9: 226–231, doi: 10.1186/1471-2458-9-226, indexed in Pubmed: 19591670.
3. Krzych ŁJ, Czempik PF. Effect of fluid resuscitation with balanced solutions on platelets: In vitro simulation of 20% volume substitution. Cardiol J. 2018; 25(2): 254–259, doi: 10.5603/CJ.a2017.0054, indexed in Pubmed: 28497841.
4. Baskett T. William O'Shaughnessy, Thomas Latta and the origins of intravenous saline. Resuscitation. 2002; 55(3): 231–234, doi: 10.1016/s0300-9572(02)00294-0, indexed in Pubmed: 12458058.
5. Milano R. Fluid resuscitation of the adult trauma patient: where have we been and where are we going? Nurs Clin North Am. 2017; 52(2): 237–247, doi: 10.1016/j.cnur.2017.01.001, indexed in Pubmed: 28478872.
6. Kalkwarf KJ, Cotton BA. Resuscitation for hypovolemic shock. Surg Clin North Am. 2017; 97(6): 1307–1321, doi: 10.1016/j.suc.2017.07.011, indexed in Pubmed: 29132511.
7. Beaty CA, George TJ, Conte JV. Historical perspectives of The American Association for Thoracic Surgery: Alfred Blalock (1899-1964). J Thorac Cardiovasc Surg. 2012; 143(2): 260–263, doi: 10.1016/j.jtcvs.2011.10.071, indexed in Pubmed: 22248679.
8. Ravitch MM. The contributions of Alfred Blalock to the science and practice of surgery. Johns Hopkins Med J. 1977; 140(2): 57–67, indexed in Pubmed: 319290.

9. Srivastava A. Fluid resuscitation: principles of therapy and. Adv Chronic Kidney Dis. 2017; 24(4): 205–212, doi: 10.1053/j.ackd.2017.05.002, indexed in Pubmed: 28778359.
10. Solomonov E, Hirsh M, Yahiya A, et al. The effect of vigorous fluid resuscitation in uncontrolled hemorrhagic shock after massive splenic injury. Crit Care Med. 2000; 28(3): 749–754, doi: 10.1097/00003246-200003000-00024, indexed in Pubmed: 10752825.
11. Varela JE, Cohn SM, Diaz I, et al. Splanchnic perfusion during delayed, hypotensive, or aggressive fluid resuscitation from uncontrolled hemorrhage. Shock. 2003; 20(5): 476–480, doi: 10.1097/01.SHK.0000094036.09886.9b, indexed in Pubmed: 14560114.
12. Muttath A, Annayappa Venkatesh L, Jose J, et al. Adverse outcomes due to aggressive fluid resuscitation in children: a prospective observational study. J Pediatr Intensive Care. 2019; 8(2): 64–70, doi: 10.1055/s-0038-1667009, indexed in Pubmed: 31093457.
13. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. Version 5.1 [updated March 2011]. The Cochrane Collaboration. http://handbook-5-1.cochrane.org/ (Accessed 10 June 2020).
14. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005; 5: 13, doi: 10.1186/1471-2288-5-13, indexed in Pubmed: 15840177.
15. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003; 327(7414): 557–560, doi: 10.1136/bmj.327.7414.557, indexed in Pubmed: 12958120.
16. Bickell WH, Wall MJ, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. N Engl J Med. 1994; 331(17): 1105–1109, doi: 10.1056/NEJM199410273311701, indexed in Pubmed: 7935634.
17. Carrick MM, Morrison CA, Tapia NM, et al. Intraoperative hypotensive resuscitation for patients undergoing laparotomy or thoracotomy for trauma: Early termination of a randomized prospective clinical trial. J Trauma Acute Care Surg. 2016; 80(6): 886–896, doi: 10.1097/TA.0000000000001044, indexed in Pubmed: 27015578.
18. Chen M, Zhong W, Hu Y. The study on limited fluid resuscitation patients with traumatic shock. Sichuan Med J. 2013; 34: 1–10.
19. Chen M. Analysis on the efficacy of limited fluid resuscitation of traumatic hemorrhagic shock. China Academic J. 2015; 22: 3–6.
20. Chen I, Bin L, Ai-guo Z, et al. The application of limited fluid resuscitation in first aid of hemorrhagic traumatic shock. J Hunan Normal Univ. 2015; 12: 1–5.
21. Dai Y. Effect of limited fluid resuscitation on prognosis of patients with severe closed traumatic hemorrhagic shock. J Liaoning Medical University. 2016; 37: 1–5.
22. Dutton RP, Mackenzie CF, Scalea TM. Hypotensive resuscitation during active hemorrhage: impact on in-hospital mortality. J Trauma. 2002; 52(6): 1141–1146, doi: 10.1097/00005373-200206000-00020, indexed in Pubmed: 12045644.
23. Fun H, Yue M, Wu Y, et al. Early therapeutic effects of limited fluid resuscitation on severe pelvic fracture combined with hemorrhagic shock. J Traumatic Surg. 2011; 13(5): 1–4.
24. Fan H, Wu Y, Yue M. Early therapeutic effects of limited fluid resuscitation on severe hepatic and spleen injury combined with hemorrhagic shock. J Trauma Surg. 2012; 14: 10–16.
25. Hua LD, Tu YY, Fu JF, et al. Application of limited fluid resuscitation in patients with severe multiple trauma hemorrhagic shock. Progress in Modern Biomedicine. 2010; 10(13): 2462–2464.
26. Li W, Lin H, Deng X. Clinical discussion of limited fluid resuscitation on hemorrhagic traumatic shock without controlling bleeding. J Clini Med Engineering. 2012; 19: 1–9.
27. Lu Bo, Li MQ, Li JQ. The use of limited fluid resuscitation and blood pressure-controlling drugs in the treatment of acute upper gastrointestinal hemorrhage concomitant with hemorrhagic shock. Cell Biochem Biophys. 2015; 72(2): 461–463, doi: 10.1007/s12013-014-0487-2, indexed in Pubmed: 25567656.
28. Morrison CA, Carrick MM, Norman MA, et al. Hypotensive resuscitation strategy reduces transfusion requirements and severe postoperative coagulopathy in trauma patients with hemorrhagic shock: preliminary results of a randomized controlled trial. J Trauma. 2011; 70(3): 652–663, doi: 10.1097/TA.0b013e31820e77ea, indexed in Pubmed: 21610356.
29. Schreiber MA, Meier EN, Tisherman SA, et al. A controlled resuscitation strategy is feasible and safe in hypotensive trauma patients: results of a prospective randomized pilot trial. J Trauma Acute Care Surg. 2015; 78(4): 687–95; discussion 695, doi: 10.1097/TA.0000000000000600, indexed in Pubmed: 25807399.
30. Huang T, Zhang Y. Analysis of the therapeutic effect of limited fluid resuscitation in hemorrhagic shock patients. China Modern Doctor. 2015; 53: 11–15.
31. Tang T, Li WP. The curative effect analysis of limited fluid resuscitation to esophageal variceal bleeding combined with hemorrhagic shock. Modern Practical Medicine. 2013; 25: 3–8.
32. Turner J, Nicholl J, Webber I, et al. A randomised controlled trial of prehospital intravenous fluid replacement therapy in serious trauma. Health Technology Assessment. 2000; 4(31), doi: 10.3310/hta4310.
33. Wang A, Gao J, Li X, et al. The significance of APACHE II and IL-6 in patients with traumatic hemorrhagic shock by limited fluids resuscitation. Tianjin Med J. 2010; 38(11): 1–6.
34. Wang Mt, Mei b, He J, et al. Effect of preoperative limited fluid resuscitation to the patients with traumatic shock. J Medi Coll PLA. 2007; 22(4): 226–229, doi: 10.1016/s1000-1948(07)60045-8.
35. Wang X, L Z, Wei L. Diagnosis and treatment of traumatic hemorrhagic shock caused by rupture of the liver and spleen on early fluid resuscitation. J Hepatobiliary Surg. 2014; 22: 4–7.
36. Wang F. Efficacy of limited fluid resuscitation in the early treatment of patients with active hemorrhagic shock. Henan Med Res. 2016; 25: 3–9.
37. Wei SK, He Y, Huang YQ, et al. Clinical analysis of 56 hemorrhagic patients with limited fluid resuscitation. J Youjiang National Med Coll. 2008; 1(2): 9.
38. Wen Z, Liu J, Chen J. Comparison of application effects by hypertonic saline fluid resuscitation, limited fluid resuscitation and conventional fluid resuscitation in traumatic hemorrhagic shock. China Prac Med. 2015; 10: 15–18.
39. Xu G. Clinical observation on limited fluid resuscitation in the treatment of uncontrolled hemorrhagic shock. Chinese J Disaster Med. 2015; 3: 5–9.
40. Yao J, Lu J. A comparative study on the clinical effect of limited fluid resuscitation and active fluid resuscitation in the treatment of patients with multiple trauma and hemorrhagic shock. Chinese J Frontier Med. 2015; 7: 6–10.
41. Zeng F, Deng Z, Hu M, et al. Clinical observation of limited fluid resuscitation on preoperative uncontrolled hemorrhagic shock. J Chin Pract Diagn Ther. 2014; 28: 1–5.
42. Zhao Y. The clinical effect analysis of limited fluids resuscitation in treatment of hemorrhagic shock. Medical Innovation of China. 2013; 10: 36–40.

43. Zheng W, Wang X, Xu H. Effects of limited fluid resuscitation in treatment of hemorrhagic traumatic shock. China J Emergency Resuscitation Disaster Med. 2007; 2: 9.
44. De Crescenzo C, Gorouhi F, Salcedo ES, et al. Prehospital hypertonic fluid resuscitation for trauma patients: A systematic review and meta-analysis. J Trauma Acute Care Surg. 2017; 82(5): 956–962, doi: 10.1097/TA.0000000000001409, indexed in Pubmed: 28257392.
45. Martin GS, Bassett P. Crystalloids vs. colloids for fluid resuscitation in the Intensive Care Unit: A systematic review and meta-analysis. J Crit Care. 2019; 50: 144–154, doi: 10.1016/j.jcrc.2018.11.031, indexed in Pubmed: 30540968.
46. Malbrain ML, Marik PE, Witters I, et al. Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice. Anaesthesiol Intensive Ther. 2014; 46(5): 361–380, doi: 10.5603/AIT.2014.0060, indexed in Pubmed: 25432556.
47. Hjortrup PB, Haase N, Bundgaard H, et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. Intensive Care Med. 2016; 42(11): 1695–1705, doi: 10.1007/s00134-016-4500-7, indexed in Pubmed: 27686349.
48. Zafrani L, Mariotte E, Darmon M, et al. Acute renal failure is prevalent in patients with thrombotic thrombocytopenic purpura associated with low plasma ADAMTS13 activity. J Thrombosis Haemostasis. 2015; 13(3): 380–389, doi: 10.1111/jth.12826.
49. In JiW, Kim JE, Jeong JS, et al. Diagnostic and prognostic significance of neutrophil gelatinase-associated lipocalin in disseminated intravascular coagulation. Clin Chim Acta. 2014; 430: 145–149, doi: 10.1016/j.cca.2014.01.022, indexed in Pubmed: 24508993.
50. Levi M, van der Poll T. Disseminated intravascular coagulation: a review for the internist. Intern Emerg Med. 2013; 8(1): 23–32, doi: 10.1007/s11739-012-0859-9, indexed in Pubmed: 23015284.
51. Jiang LM, He J, Xi XY, et al. Effect of early restrictive fluid resuscitation on inflammatory and immune factors in patients with severe pelvic fracture. Chin J Traumatol. 2019; 22(6): 311–315, doi: 10.1016/j.cjtee.2019.07.008, indexed in Pubmed: 31685356.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 3, 472–480
DOI: 10.5603/CJ.a2020.0103

ISSN 1897–5593
eISSN 1898–018X

Impact of successful restoration of sinus rhythm in patients with atrial fibrillation and acute heart failure: Results from the Korean Acute Heart Failure registry

Youngjin Cho[1], Il-Young Oh[1], Jin Joo Park[1], Byung-Hee Oh[2], Eun-Seok Jeon[3], Jae-Joong Kim[4], Kyung-Kuk Hwang[5], Myeong-Chan Cho[5], Shung Chull Chae[6], Sang Hong Baek[7], Seok-Min Kang[8], Byung-Su Yoo[9], Youngkeun Ahn[10], Dong-Ju Choi[1]

[1]Department of Internal Medicine, Seoul National University Bundang Hospital, Korea
[2]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea
[3]Department of Internal Medicine, Sungkyunkwan University College of Medicine, Seoul, Korea
[4]Department of Internal Medicine, University of Ulsan College of Medicine, Seoul, Korea
[5]Department of Internal Medicine, Chungbuk National University College of Medicine, Cheongju, Korea
[6]Department of Internal Medicine, Kyungpook National University College of Medicine, Daegu, Korea
[7]Department of Internal Medicine, The Catholic University of Korea, Seoul, Korea
[8]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea
[9]Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea
[10]Department of Internal Medicine, Heart Research Center of Chonnam National University, Gwangju, Korea

Abstract

Background: *Restoring and maintaining sinus rhythm (SR) in patients with atrial fibrillation (AF) failed to show superior outcomes over rate control strategies in prior randomized trials. However, there is sparse data on their outcomes in patients with acute heart failure (AHF).*

Methods: *From December 2010 to February 2014, 5,625 patients with AHF from 10 tertiary hospitals were enrolled in the Korean Acute Heart Failure registry, including 1,961 patients whose initial electrocardiogram showed AF. Clinical outcomes of patients who restored SR by pharmacological or electrical cardioversion (SR conversion group, n = 212) were compared to those of patients who showed a persistent AF rhythm (AF persistent group, n = 1,662).*

Results: *All-cause mortality both in-hospital and during the follow-up (median 2.5 years) were significantly lower in the SR conversion group than in the AF persistent group after adjustment for risk factors (adjusted hazard ratio [HR]; 95% confidence interval [CI] = 0.26 [0.08–0.88], p = 0.031 and 0.59 [0.43–0.82], p = 0.002, for mortality in-hospital and during follow-up, respectively). After 1:3 propensity score matching (SR conversion group = 167, AF persistent group = 501), successful restoration of SR was associated with lower all-cause mortality (HR [95% CI] = 0.68 [0.49–0.93], p = 0.015), heart failure rehospitalization (HR [95% CI] = 0.66 [0.45–0.97], p = 0.032), and composite of death and heart failure rehospitalization (HR [95% CI] = 0.66 [0.51–0.86], p = 0.002).*

Conclusions: *Patients with AHF and AF had significantly lower mortality in-hospital and during follow-up if rhythm treatment for AF was successful, underscoring the importance of restoring SR in patients with AHF.* (Cardiol J 2022; 29, 3: 472–480)

Key words: atrial fibrillation, acute heart failure, cardioversion

Address for correspondence: Dong-Ju Choi, MD, PhD, Professor, Department of Internal Medicine, Division of Cardiology, Cardiovascular Center, Seoul National University Bundang Hospital, 300 Gumi-dong, Bundang-gu, Seongnam city, Gyeonggi-do, 13620, South Korea, tel: 82-31-787-7007, e-mail: djchoi@snubh.org

Received: 12.05.2020 Accepted: 23.07.2020 Early publication date: 11.08.2020

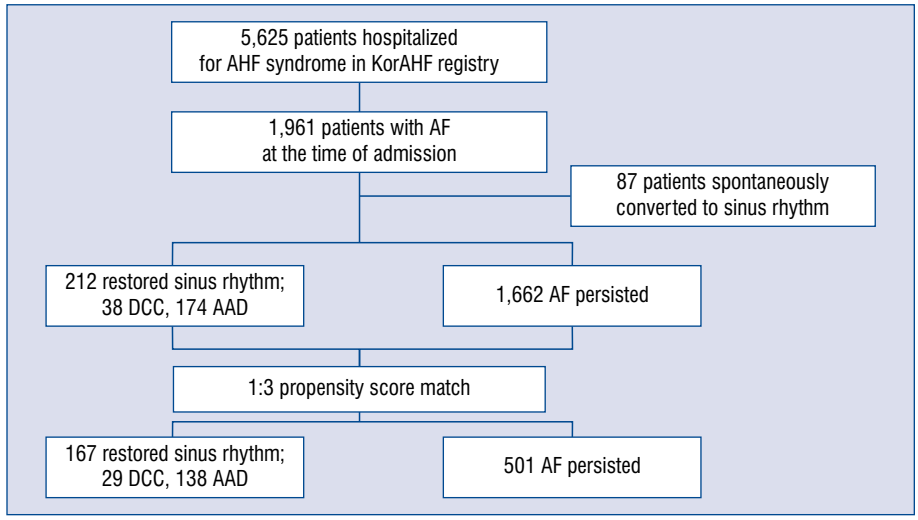


Figure 1. Flowchart of the study population; AAD — anti-arrhythmic drug; AF — atrial fibrillation; AHF — acute heart failure; DCC — direct current cardioversion; KorAHF — The Korean Acute Heart Failure registry.

Introduction

Atrial fibrillation (AF) and heart failure (HF) are very prevalent cardiovascular diseases resulting in enormous healthcare expenditures and patient suffering. They share risk factors, often coexist, and affect each other's outcomes [1–3]. Therefore, the importance for the proper management of AF in patients with HF is growing. Rhythm control strategies for AF management — restoring and maintaining sinus rhythm (SR) — failed to show superior outcomes in terms of mortality in prior randomized trials. In the AFFIRM trial, around 4,000 patients with AF and risk factors for stroke or death were randomized and treated either with rhythm control or rate control strategies, and it was suggested that rate control strategies might be potentially advantageous because of their lower risk of adverse drug effects. However, it was also suggested that rhythm control strategies might be beneficial in higher risk patients with AF [4]. In the AF-CHF trial, patients with both AF and chronic HF were enrolled, and it also failed to show a superior impact of rhythm control strategies over rate control strategies [5]. However, there are limited data on the impact of conversion to SR from AF in patients with acute heart failure (AHF). The aim of this study was to investigate the outcomes after rhythm treatment in patients with AHF and AF.

Methods

Study population and Korean Acute Heart Failure registry

The Korean Acute Heart Failure (KorAHF) registry is a prospective multicenter cohort study that is currently ongoing. Patients are consecutively enrolled upon initial hospital admission for AHF syndrome and are followed up accordingly. The registry is accumulating data on individual patients, not individual hospitalizations. Information on the objectives of the study design and study population is provided in the clinical trial registration (ClinicalTrial.gov NCT01389843), and the design and the purpose of the KorAHF registry have been published elsewhere [6, 7]. Among a total of 5,625 patients with AHF enrolled in this registry, the initial electrocardiograms of 1,933 patients showed AF. Excluding 87 patients who spontaneously converted to SR without any rhythm treatment, herein, 212 patients were compared who had restoration of SR and its maintenance until discharge (SR conversion group) with 1,662 patients who showed a persistent AF rhythm (AF persistent group). The study population flow diagram is presented in Figure 1. The study protocol was approved by the ethics committee or institutional review board at each hospital (IRB No. B-1104-125-014). The need for written informed consent was waived by the institutional review board. The study complied with the Declaration of Helsinki.

Rhythm treatment for atrial fibrillation

Restoration of SR as well as the modality of rhythm treatment in patients with AHF and AF were left to the individual physician's choice. Both electrical (n = 38) and pharmacological cardioversion (n = 174) were included as adequate rhythm treatment. When AF spontaneously converted to SR, the patient was excluded from the analysis.

Clinical follow-up and endpoints

The attending physician completed a web-based case report form in the Clinical Data Management System (iCReaT) from the Korea National Institute of Health (NIH) with the assistance of a clinical research coordinator. The latest information on patient clinical manifestation, biochemistry, and medication was collected at the first follow-up visit at 30 days and again at follow-up visits at 3, 6, 12, 24, 36, 48, and 60 months. The follow-up data were collected from the patients by the attending physician and stored in the web-based case report form. The outcome data on subjects who were not followed-up were ascertained by telephone interview. In addition, the outcome data on patients lost to follow-up were collected from the National Death Records. The primary endpoint of this study was the all-cause mortality rate. The in-hospital outcomes, especially in-hospital mortality were also evaluated. All deaths were considered cardiac unless a definite non-cardiac cause could be established. All outcome data reported from the participating centers were reviewed by an independent clinical event adjudicating committee.

Statistical analysis

The Student t-test and χ^2 or the Fisher exact test were used to compare means and proportions of baseline clinical characteristics between the two groups. To address potential sources of bias and confounding factors in this retrospective study, propensity analysis was performed. Baseline clinical characteristics were incorporated into a non-parsimonious logistic regression model to compute the propensity score for AF rhythm treatment. The included covariates were age, sex, diabetes, hypertension, ischemic heart disease, cerebrovascular disease, chronic kidney disease, malignancy, serum hemoglobin and creatinine levels, high B-type natriuretic peptide (BNP, > 500 pg/mL) or N-terminal pro-BNP (NT-proBNP, > 1000 pg/mL), left ventricular ejection fraction (LVEF), type of HF (de novo vs. acute decompensated), tachycardia as an etiology of AHF, new-onset AF, admission to the intensive care unit (ICU), and mechanical ventilation support (C-statistics = 0.739). 1:3 propensity score-matching iteration were then performed from the fifth digit to the first digit and 167 patients with restoration of SR were matched to 501 patients with persistent AF. Baseline characteristics of the two groups were compared again in this matched population. The Cox proportional hazard model was used to estimate the hazard ratio (HR) and 95% confidence interval (95% CI) for the clinical outcomes of the two groups. All of the statistical analyses were performed using R version 3.6.0, and $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Baseline clinical characteristics of the overall study population and propensity score-matched population are shown in Table 1. An SR was more frequently restored in relatively younger patients with lower CHA_2DS_2-VASc scores. Hypertension and chronic kidney disease tended to be more prevalent in the AF persistent group. The proportion of new-onset AF, de novo HF, and elevated BNP (or NT-proBNP) was higher in the SR conversion group. The SR conversion group included more patients who were admitted to ICU or had mechanical ventilator support. The LVEF was significantly lower and the left atrium dimension was smaller in the SR conversion group. These parameters were all comparable between the groups after propensity score matching.

In-hospital outcomes

The median duration of hospitalization was 8 days (interquartile range [IQR], 5–13), and overall in-hospital mortality was 4.2% in patients with AHF presenting with AF. The median duration of hospitalization was 11 days (IQR, 7–19) in the SR conversion group and 7 days (IQR, 5–13) when AF persisted. Comparisons of in-hospital outcomes between the SR conversion and AF persistent groups are presented in Table 2. In-hospital all-cause mortality was 4.2% in both groups (unadjusted odds ratio [OR], 95% confidence interval [95% CI] = 1.01 [0.44–2.07], p = 0.982), but after adjustment for age, sex, comorbidities, type of HF, new-onset AF, laboratory tests, echocardiographic parameters, ICU admission, and mechanical ventilation, all-cause mortality was significantly lower in the SR conversion group than in the AF persistent group (adjusted OR [95% CI] = 0.26 [0.08–0.88], p = 0.031). Cardiovascular mortality and cerebral vascular events were not different between the two groups, regardless of the adjustments. After propensity score matching, the overall mortality was 2.4% in SR restored patients and 5.9% in AF persisted patients (OR [95% CI] = 0.39 [0.10–1.00], p = 0.050). Cardiovascular mortality and the incidence of cerebral vascular accident were not significantly different between the SR conversion and AF persistent groups.

Table 1. Baseline characteristics.

	Overall AF patients			Matched population		
	SR restored (n = 212)	AF (n = 1,662)	P	SR restored (n = 167)	AF (n = 501)	P
Age [years]	67 ± 14	71 ± 12	< 0.001	68 ± 13	68 ± 14	0.840
Male	104 (49.1)	866 (52.1)	0.403	83 (49.7)	274 (54.7)	0.303
Hypertension	114 (53.8)	999 (60.1)	0.077	91 (57.7)	226 (54.5)	0.528
Diabetes mellitus	57 (26.9)	483 (29.1)	0.510	46 (27.5)	147 (29.3)	0.730
CAD	37 (17.5)	346 (20.8)	0.262	32 (19.2)	116 (23.2)	0.333
Valvular heart disease	41 (19.3)	393 (23.6)	0.162	32 (19.2)	77 (15.4)	0.304
Cerebrovascular disease	32 (15.1)	325 (19.6)	0.119	22 (13.2)	62 (12.4)	0.893
CKD	17 (8.0)	197 (11.9)	0.098	14 (8.4)	43 (8.6)	1.00
De novo heart failure	115 (54.2)	705 (42.4)	0.001	90 (53.9)	271 (54.1)	1.00
Lung congestion	164 (77.4)	1303 (78.4)	0.729	112 (76.6)	410 (81.8)	0.176
Previous HF admission	65 (30.7)	652 (39.3)	0.019	52 (31.1)	147 (29.3)	0.732
New onset AF	108 (51.9)	499 (30.4)	< 0.001	85 (50.9)	261 (52.1)	0.858
Tachycardia induced HF	105 (49.5)	729 (43.9)	0.118	88 (52.7)	251 (50.1)	0.623
CHA_2DS_2-VASc score	4.4 ± 1.7	4.8 ± 1.7	0.001	4.4 ± 1.7	4.4 ± 1.5	0.766
Malignancy	21 (9.9)	132 (7.9)	0.326	16 (9.6)	39 (7.8)	0.569
ICU admission	134 (63.2)	642 (38.6)	< 0.001	99 (59.3)	297 (59.3)	1.00
Mechanical ventilation	54 (25.5)	172 (10.3)	< 0.001	33 (19.8)	98 (19.6)	1.00
Hemoglobin [g/dL]	12.7 ± 2.2	12.7 ± 2.2	0.903	12.8 ± 2.2	12.8 ± 2.1	0.693
Creatinine [mg/dL]	1.3 ± 1.4	1.3 ± 1.0	0.939	1.2 ± 0.9	1.3 ± 0.8	0.604
High BNP or NT-proBNP	162 (88.0)	1220 (81.4)	0.034	128 (88.9)	424 (91.0)	0.557
LVEF [%]	37 ± 16	41 ± 16	< 0.001	37 ± 17	36 ± 16	0.550
LA dimension [mm]	49 ± 10	54 ± 10	< 0.001	50 ± 10	50 ± 8	0.882
Discharge medication:						
ACEI or ARB	123 (58.0)	1062 (63.9)	0.110	102 (61.1)	323 (64.5)	0.486
Beta-blocker	99 (46.7)	802 (48.3)	0.723	78 (46.7)	270 (53.9)	0.128

Data are expressed as number (%) or mean ± standard deviation. ACEI — angiotensin-converting enzyme inhibitor; AF — atrial fibrillation; ARB — angiotensin receptor blocker; BNP — B-type natriuretic peptide; CAD — coronary artery disease; CKD — chronic kidney disease; HF — heart failure; ICU — intensive care unit; LA — left atrium; LVEF — left ventricular ejection fraction; NT-proBNP — N-terminal-pro B-type natriuretic peptide; SR — sinus rhythm

Mortality and HF rehospitalization during follow-up

The overall mortality rates at 1, 2, and 3-year follow-up were 18.9%, 23.6%, and 27.2% when SR was successfully restored, and 22.9%, 31.3%, and 38.2% when AF persisted, respectively. The median follow-up duration was 2.5 years. Univariate survival analysis indicated that old age and various co-morbidities significantly increased the risk of death after AHF. Type of AHF (de novo vs. acute decompensated HF), timing of AF onset (newly diagnosed vs. previously diagnosed), laboratory tests, and discharge medications were also significantly correlated with mortality (Table 3). The SR conversion group showed significantly lower mortality than the AF persistent group in both the unadjusted (unadjusted HR [95% CI] = = 0.70 [0.54–0.91], p = 0.007) and adjusted analysis (adjusted HR [95% CI] = 0.59 [0.43–0.82], p = 0.002). HF rehospitalization rate tended to be lower in the SR conversion group (unadjusted HR [95% CI] = 0.60 [0.47–0.77], p = 0.001; adjusted HR [95% CI] = 0.72 [0.49–1.05], p = 0.084). The composite of death and HF rehospitalization rate was lower in the SR conversion group than in the AF persistent group (unadjusted HR [95% CI] = 0.60 [0.47–0.77], p = 0.001; adjusted HR [95% CI] = 0.65 [0.49–0.85], p = 0.002). Kaplan-Meier curves for cumulative incidences of outcome events are presented in Figure 2.

After propensity score matching, all-cause mortality was still significantly lower in the SR

Table 2. In-hospital outcomes.

	Overall population				Matched population			
	SR (n = 212)	AF (n = 1,662)	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P	SR (n = 167)	AF (n = 501)	Unadjusted OR (95% CI)	P
All-cause mortality	9 (4.2%)	70 (4.2%)	1.01 (0.44–2.07)	0.982	0.26 (0.08–0.88)	0.031	5 (3.0%)	37 (7.4%)	0.39 (0.15–1.00)	0.050
Cardiovascular death	8 (3.8%)	50 (3.0%)	1.26 (0.51–2.74)	0.545	0.40 (0.11–1.40)	0.151	5 (3.0%)	27 (5.4%)	0.54 (0.21–1.43)	0.216
Cerebral vascular accident	2 (0.9%)	27 (1.6%)	0.58 (0.07–2.32)	0.449	0.56 (0.12–2.65)	0.465	2 (1.2%)	7 (1.4%)	0.86 (0.18–4.16)	0.847

Odds ratios (OR) for in-hospital clinical outcomes of the sinus rhythm (SR) conversion group compared to the atrial fibrillation (AF) persistent group; CI — confidence interval

Table 3. Predictors for all-cause mortality at follow-up in an overall population.

	Unadjusted HR (95% CI)	P
Conversion to SR	0.70 (0.54–0.91)	0.007
Age (per 1 year)	1.05 (1.04–1.05)	< 0.001
Male	1.05 (0.91–1.22)	0.481
Hypertension	1.36 (1.17–1.59)	< 0.001
Diabetes	1.52 (1.31–1.77)	< 0.001
Ischemic heart disease	1.51 (1.28–1.79)	< 0.001
Valvular heart disease	1.34 (1.14–1.58)	< 0.001
Cerebrovascular disease	1.48 (1.25–1.76)	< 0.001
CKD	2.36 (1.96–2.85)	< 0.001
ADHF (vs. de novo)	1.77 (1.51–2.06)	< 0.001
Lung congestion	1.27 (1.06–1.54)	0.011
Previous HF admission	1.80 (1.55–2.10)	< 0.001
New onset AF	0.80 (0.68–0.94)	0.007
Tachycardia-induced HF	0.61 (0.52–0.71)	< 0.001
Malignancy	1.36 (1.07–1.73)	0.013
ICU admission	1.27 (1.10–1.48)	0.001
Mechanical ventilation	1.75 (1.43–2.14)	< 0.001
Hemoglobin (per 1 g/dL)	0.81 (0.79–0.84)	< 0.001
Creatinine (per 1 mg/dL)	1.17 (1.13–1.21)	< 0.001
High BNP or NT-proBNP	1.36 (1.09–1.68)	0.006
LVEF > 40%	1.03 (0.88–1.20)	0.745
LA (per 1 mm)	1.01 (1.00–1.01)	0.134
ACEI or ARB at discharge	0.57 (0.49–0.65)	< 0.001
Beta-blocker at discharge	0.59 (0.51–0.68)	< 0.001

ADHF — acute decompensated heart failure; CI — confidence interval; HR — hazard ratio; other abbreviations as for Table 1

conversion group (HR [95% CI] = 0.68 [0.49–0.93], p = 0.015). HF rehospitalization and the composite of mortality and HF rehospitalization were also lower in the SR group than in the AF persistent group (HF rehospitalization: HR [95% CI] = 0.66 [0.45–0.97], p = 0.032, composite of mortality/HF rehospitalization: HR [95% CI] = 0.66 [0.51–0.86], p = 0.002) (Fig. 3).

In subgroup analysis, successful SR conversion was significantly associated with lower mortal-

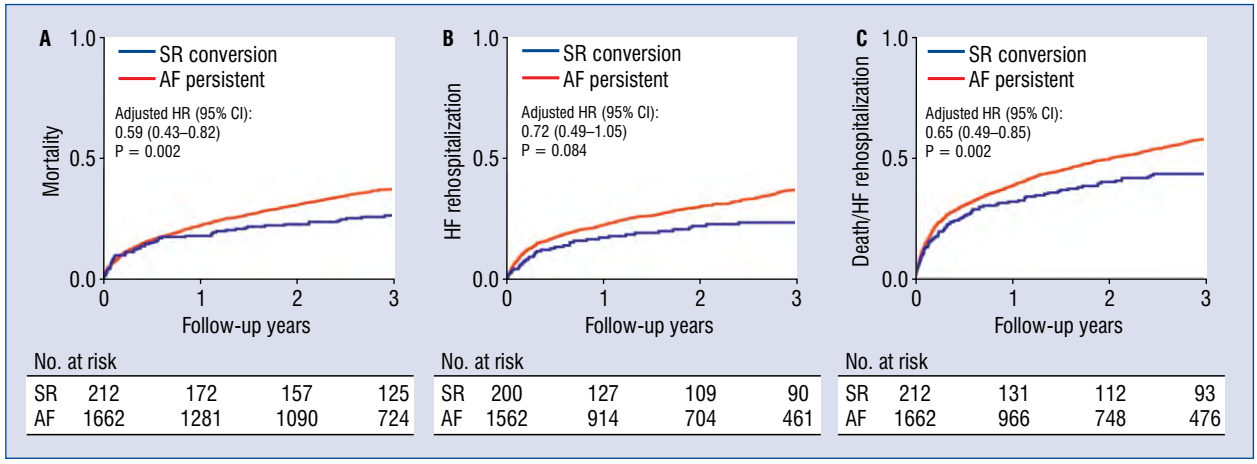


Figure 2. Clinical outcomes in overall study population; **A.** Mortality; **B.** Heart failure (HF) rehospitalization; **C.** Composite of mortality and HF rehospitalization; AF — atrial fibrillation; CI — confidence interval; HR — hazard ratio; SR — sinus rhythm.

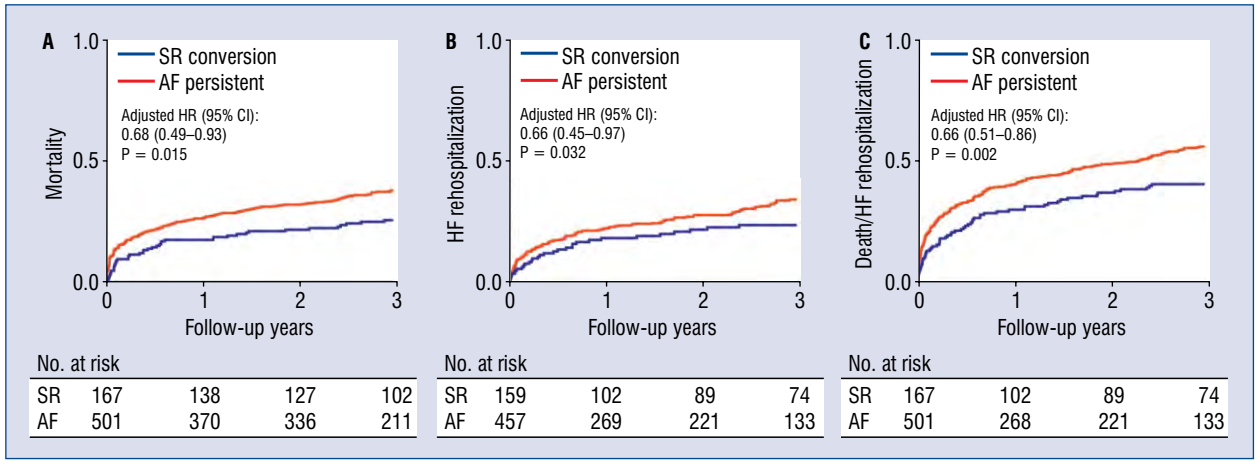


Figure 3. Clinical outcomes in a propensity-score matched population; **A** Mortality; **B.** Heart failure (HF) rehospitalization; **C.** Composite of mortality and HF rehospitalization; abbreviations as for Figure 2.

ity rate in patients with hypertension, in contrast to patients without hypertension, where there was no difference in mortality between the SR conversion and AF persistent group (interaction p = 0.021). Other than hypertension, the beneficial effect of successful SR conversion for patients with AHF and AF did not, in terms of mortality, significantly differ according to age, sex, diabetes mellitus, onset of AF, and the type or aetiology of HF (Table 4).

Cerebrovascular events during follow-up

Cerebrovascular accident rates at the 3-year follow-up were 3.1% when SR was restored and 2.3% when AF persisted (HR [95% CI] = 1.28 [0.50–3.28], p = 0.614) in the crude study population. After propensity score matching, cerebrovascular event rates were 3.3% and 3.1% (HR [95% CI] = 1.28 [0.44–3.67], p = 0.652), respectively.

Discussion

The benefit of rhythm control over rate control strategies in patients with AF has been controversial thus far in terms of mortality [4, 5, 8, 9]. Therefore, the current guidelines recommend restoration and maintenance of SR mainly in patients with symptomatic AF [10]. However, very high-risk patients with AF, such as the patients with AHF in the present study, have not been adequately evaluated. The data showed a significantly

Table 4. Subgroup analysis for mortality in a matched population.

	No. of patients	Adjusted HR (95% CI)	P	Interaction P
Age:				
≥ 65 years	429	0.43 (0.28–0.64)	< 0.001	0. 283
< 65 years	239	0.78 (0.35–1.73)	0.549	
Gender:				
Male	357	0.38 (0.23–0.65)	< 0.001	0. 139
Female	311	0.63 (0.39–1.04)	0.068	
Diabetes mellitus:				
Yes	193	0.64 (0.33–1.24)	0.184	0.511
No	475	0.48 (0.31–0.74)	0.001	
Hypertension:				
Yes	380	0.34 (0.21–0.54)	<0.001	0.021
No	288	0.89 (0.51–1.57)	0.703	
New-onset AF:				
Yes	346	0.34 (0.19–0.60)	< 0.001	0. 216
No	322	0.56 (0.34–0.91)	0.019	
Type of HF:				
De novo	361	0.35 (0.19–0.65)	< 0.001	0.101
ADHF	307	0.62 (0.39–0.99)	0.043	
Etiology of HF:				
Ischemic	148	0.40 (0.18–0.86)	0.019	0.229
Non-ischemic	520	0.55 (0.36–0.83)	0.005	

Abbreviations as for Tables 1 and 3.

lower in-hospital mortality rate when initial AF was successfully converted to SR either by drugs or electrical cardioversion in patients with AHF after adjustments for various covariates. And interestingly, this beneficial effect on mortality persisted during the long-term follow-up. The HF readmission rate was also lower in the SR conversion group in the matched population. There was no significant difference in terms of cerebrovascular events, both in-hospital and during follow-up.

Atrial fibrillation and HF are two very prevalent cardiovascular diseases, often considered to be epidemic [1, 11]. These two cardiovascular diseases share many risk factors, such as ageing, hypertension, diabetes mellitus, and underlying ischemic/valvular heart disease. Moreover, AF and HF can aggravate each other. There are several suggested mechanisms by which AF facilitates the development of HF. First, AF decreases cardiac output not only because of the consequences of poor ventricular rate control but also those of irregular ventricular filling and loss of atrial contraction. Decreased cardiac output augments neuro-hormonal activation observed in HF. Functional mitral annular enlargement is another possible explanation for HF development in patients with AF. On the other hand, HF can also cause AF development through atrial enlargement, vasoconstrictive neuro-hormonal milieu, and atrial fibrosis [1, 12]. These interconnections between AF and HF lead to a high prevalence of AF in patients with HF [13], which was 27% in this KorAHF registry.

Beyond its high prevalence, there is evidence that AF involves increased adverse events in patients with congestive HF. In participants of the Framingham Heart Study, AF and HF showed a temporal association, and concomitant AF and HF resulted in a lower survival rate [14]. Retrospective post-hoc analysis of the SOLVD (Studies of Left Ventricular Dysfunction) Prevention and Treatment trials demonstrated that the presence of AF increased the risk of all-cause mortality in patients with left ventricular systolic dysfunction [15]. A recent meta-analysis of randomized trials concluded that AF increased adverse events in patients with chronic HF after adjusting for other clinical risk factors (adjusted OR 1.40) [16]. Regarding the timing of AF and HF diagnosis, a community-based study

suggested that the negative effect of AF on patients with HF was greater with incident AF than with prevalent AF [17]. The Framingham cohort [14] and MADIT II (Multicenter Automatic Defibrillator Trial II) trial demonstrated supporting results [18].

On the other hand, the impact of concomitant AF in patients presenting with AHF syndrome appears less clear. In contrast to the results from patients with chronic HF, data from the ATTEND registry showed no difference in 30-day all-cause mortality between patients with (3.04%) or without AF (3.88%) [13]. Additionally, in the KorAHF registry, the in-hospital all-cause mortality of the AF population (4.2%) was not different from that of the overall population (5.3%). These results might suggest that AF is not a worse etiology or more aggravating factor for AHF syndrome than other etiologic factors, although AF is a significant risk factor for adverse outcomes in patients with chronic HF.

Despite the increase in adverse events by the presence of AF in patients with congestive HF, large randomized trials such as the AF-CHF (Atrial Fibrillation and Congestive Heart Failure) study [5] and DIAMOND-CHF trial (Danish Investigations of Arrhythmia and Mortality on Dofetilide in Congestive Heart Failure) [19] demonstrated no benefit of a rhythm control strategy in those patients. However, this result was often accounted for by the adverse effects of anti-arrhythmic drugs, especially in AF patients with left ventricular dysfunction, and the benefit of maintaining SR itself was not completely denied. Maintaining SR using catheter ablation has been reported to improve functional capacity and LVEF compared with the rate control strategy [20–22], and more recent trials demonstrated a survival benefit of catheter ablation in patients with AF and chronic HF, emphasising the importance of maintaining SR itself [23–25]. Data herein, also suggest the importance of attempts to maintain SR in AF patients with an acute setting of HF.

In the setting of AHF with AF, benefits of the restoration of SR have not been adequately evaluated, perhaps because of difficulties in conducting large randomized clinical trials in this population. In the KorAHF registry, all-cause mortality was significantly lower when initial AF was converted to SR either by drug (amiodarone) or electrical cardioversion in patients with AHF. Despite emerging evidence for the benefit of catheter ablation in patients with AF and congestive HF, performing catheter ablation is not widely accepted in the setting of AHF syndrome. Therefore, the present study data may reflect the clinical outcomes of rhythm control strategies in a daily practice setting. In this study, there was no difference in in-hospital mortality irrespective of whether AF persisted or successful conversion to SR was acquired in the overall population. However, after adjustments for various clinical predictors for mortality, in-hospital mortality was significantly better in the SR conversion group. Interestingly, the beneficial effect of conversion to SR in patients with AHF and AF was still significant after discharge from the index HF admission, suggesting the importance of adequate treatment of the index HF admission. Restoring SR and maintaining it during index HF admission appeared to affect not only the in-hospital outcomes but also the long-term outcomes over several years.

Limitations of the study

There were several limitations to this study. This was a non-randomized, registry-based study and might have been affected by unmeasured confounding factors. Since the attending physician's intension regarding AF treatment strategy (rhythm control vs. rate control) was not collected in this registry, the definition of the present study groups is different from that of the rhythm and rate control strategy groups in previous randomized trials. The KorAHF registry did not collect data on the rhythm status during follow-up, thus further analysis according to the recurrence of AF during follow-up was not available. Further studies are warranted to confirm the effect of rhythm control strategies for AF in these high-risk patients with AHF.

Conclusions

In this large multicenter KorAHF registry, patients with AHF and AF had significantly lower future mortality rates when rhythm treatments for AF were successfully applied. These results underscore the importance of restoring SR in patients presenting with AHF.

Acknowledgments

This work was supported by the Research of Korea Centers for Disease Control and Prevention [2010-E63003-00, 2011-E63002-00, 2012-E63005-00, 2013-E63003-00, 2013-E63003-01, 2013-E63003-02, and 2016-ER6303-00] and by the SNUBH Research Fund [Grant no. 14-2015-029, 16-2017-003].

Conflict of interest: None declared

References

1. Verma A, Kalman JM, Callans DJ. Treatment of patients with atrial fibrillation and heart failure with reduced ejection fraction. Circulation. 2017; 135(16): 1547–1563, doi: 10.1161/CIRCULATIONAHA.116.026054, indexed in Pubmed: 28416525.
2. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. J Am Coll Cardiol. 2019; 74(1): 104–32.
3. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014; 64(21): e1–76.
4. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002; 347(23): 1825–1833, doi: 10.1056/NEJMoa021328, indexed in Pubmed: 12466506.
5. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med. 2008; 358(25): 2667–2677, doi: 10.1056/NEJMoa0708789, indexed in Pubmed: 18565859.
6. Lee SE, Cho HJ, Lee HY, et al. A multicentre cohort study of acute heart failure syndromes in Korea: rationale, design, and interim observations of the Korean Acute Heart Failure (KorAHF) registry. Eur J Heart Fail. 2014; 16(6): 700–708, doi: 10.1002/ejhf.91, indexed in Pubmed: 24797348.
7. Lim NK, Lee SE, Lee HY, et al. Clinical Characteristics and Outcome of Acute Heart Failure in Korea: Results from the Korean Acute Heart Failure Registry (KorAHF). Korean Circ J. 2017; 47(3): 341–353, doi: 10.4070/kcj.2016.0419, indexed in Pubmed: 28567084.
8. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med. 2002; 347(23): 1834–1840, doi: 10.1056/NEJMoa021375, indexed in Pubmed: 12466507.
9. Flaker GC, Blackshear JL, McBride R, et al. Antiarrhythmic drug therapy and cardiac mortality in atrial fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators. J Am Coll Cardiol. 1992; 20(3): 527–532, doi: 10.1016/0735-1097(92)90003-6, indexed in Pubmed: 1512329.
10. Wann LS, Curtis AB, January CT, et al. 2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Updating the 2006 Guideline). A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2011; 57(2): 223–242.
11. Braunwald E. Cardiovascular Medicine at the Turn of the Millennium: Triumphs, Concerns, and Opportunities. N Engl J Med. 1997; 337(19): 1360–1369, doi: 10.1056/nejm199711063371906.
12. Anter E, Jessup M, Callans DJ. Atrial fibrillation and heart failure: treatment considerations for a dual epidemic. Circulation. 2009; 119(18): 2516–2525, doi: 10.1161/CIRCULATIONAHA.108.821306, indexed in Pubmed: 19433768.
13. Kajimoto K, Sato N, Takano T, et al. investigators of the Acute Decompensated Heart Failure Syndromes (ATTEND) registry. Relationship of renal insufficiency and clinical features or comorbidities with clinical outcome in patients hospitalised for acute heart failure syndromes. Eur Heart J Acute Cardiovasc Care. 2016; 6(8): 697–708, doi: 10.1177/2048872616658586, indexed in Pubmed: 27363422.
14. Santhanakrishnan R, Wang Na, Larson MG, et al. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. Circulation. 2016; 133(5): 484–492, doi: 10.1161/CIRCULATIONAHA.115.018614, indexed in Pubmed: 26746177.
15. Dries D, Exner D, Gersh B, et al. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. J Am Coll Cardiol. 1998; 32(3): 695–703, doi: 10.1016/s0735-1097(98)00297-6.
16. Mamas MA, Caldwell JC, Chacko S, et al. A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. Eur J Heart Fail. 2009; 11(7): 676–683, doi: 10.1093/eurjhf/hfp085, indexed in Pubmed: 19553398.
17. Chamberlain AM, Redfield MM, Alonso A, et al. Atrial fibrillation and mortality in heart failure: a community study. Circ Heart Fail. 2011; 4(6): 740–746, doi: 10.1161/CIRCHEARTFAILURE.111.962688, indexed in Pubmed: 21920917.
18. Zareba W, Steinberg J, McNitt S, et al. Implantable cardioverter-defibrillator therapy and risk of congestive heart failure or death in MADIT II patients with atrial fibrillation. Heart Rhythm. 2006; 3(6): 631–637, doi: 10.1016/j.hrthm.2006.02.012.
19. Torp-Pedersen C, Møller M, Bloch-Thomsen P, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. N Engl J Med. 1999; 341(12): 857–865, doi: 10.1056/nejm199909163411201.
20. Anselmino M, Matta M, Castagno D, et al. Catheter ablation of atrial fibrillation in chronic heart failure: state-of-the-art and future perspectives. Europace. 2016; 18(5): 638–647, doi: 10.1093/europace/euv368, indexed in Pubmed: 26857188.
21. Hunter RJ, Berriman TJ, Diab I, et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). Circ Arrhythm Electrophysiol. 2014; 7(1): 31–38, doi: 10.1161/CIRCEP.113.000806, indexed in Pubmed: 24382410.
22. Jones DG, Haldar SK, Hussain W, et al. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. J Am Coll Cardiol. 2013; 61(18): 1894–1903, doi: 10.1016/j.jacc.2013.01.069, indexed in Pubmed: 23500267.
23. Di Biase L, Mohanty P, Mohanty S, et al. Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device: Results From the AATAC Multicenter Randomized Trial. Circulation. 2016; 133(17): 1637–1644, doi: 10.1161/CIRCULATIONAHA.115.019406, indexed in Pubmed: 27029350.
24. Ullah W, Ling LH, Prabhu S, et al. Catheter ablation of atrial fibrillation in patients with heart failure: impact of maintaining sinus rhythm on heart failure status and long-term rates of stroke and death. Europace. 2016; 18(5): 679–686, doi: 10.1093/europace/euv440, indexed in Pubmed: 26843584.
25. Marrouche N, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med. 2018; 378(5): 417–427, doi: 10.1056/nejmoa1707855.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 3, 481–488
DOI: 10.5603/CJ.a2020.0106

ISSN 1897–5593
eISSN 1898–018X

ILEEM-survey on the Heart Team approach and team training for lead extraction procedures

Christoph T. Starck[1, 2, 3], Frank Bracke[4], Peter-Paul Delnoy[5], Roger A. Freedman[6], Andrzej Kutarski[7], Mark Gallagher[8], Morio Shoda[9, 10], Robert Peyton[11], Manav Sohal[8], Frederik Gadler[12], Kamil Sedlacek[13], Juha Hartikainen[14], Patrizio Mazzone[15], Alexander Breitenstein[16], Nigel Lever[17]

[1]German Heart Center Berlin, Department of Cardiothoracic and Vascular Surgery, Berlin, Germany; [2]German Center of Cardiovascular Research (DZHK), partner site Berlin, Berlin, Germany; [3]Steinbeis University Berlin, Institute (STI) of Cardiovascular Perfusion, Berlin, Germany; [4]Department of Cardiology, Catharina Hospital, Eindhoven, The Netherlands; [5]Department of Cardiology, Isala Hospital, Zwolle, The Netherlands; [6]University of Utah Sciences Center, Salt Lake City, Utah, United States; [7]Department of Cardiology, Medical University of Lublin, Poland; [8]Cardiology Clinical Academic Group, St. George's University Hospitals NHS Foundation Trust, London, United Kingdom; [9]Department of Cardiology, Tokyo Women's Medical University, Tokyo, Japan; [10]Department of Cardiovascular Medicine, Shinshu University School of Medicine, Matsumoto, Japan; [11]UNC REX Healthcare, Cardiac Surgical Specialists, Raleigh, North Carolina, United States; [12]Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden; [13]Department for Cardiology, Institute for Clinical and Experimental Medicine (IKEM), Prague, Czech Republic; [14]Heart Center, Kuopio University Hospital and University of Eastern Finland, Kuopio, Finland; [15]Department of Arrhythmology and Cardiac Pacing Unit, IRCCS Ospedale San Raffaele, Milan, Italy; [16]Division of Electrophysiology and Pacing, Department of Cardiology, University Heart Center Zurich, Switzerland; [17]Green Lane Cardiovascular Service, Auckland City Hospital, and University of Auckland, New Zealand

Abstract

Background: *The Heart Team approach has become an integral part of modern cardiovascular medicine. To evaluate current opinions and real-world practice among lead extraction practitioners, an online survey was created and distributed among a pool of lead extraction specialists participating in the International Lead Extraction Expert Meeting (ILEEM) 2018.*

Methods: *The online survey consisted of 10 questions and was performed using an online survey tool (www.surveymonkey.com). The collector link was sent to 48 lead extraction experts via email.*

Results: *A total of 43 answers were collected (89% return rate) from lead extraction experts in 16 different countries. A great majority (83.7%) of the respondents performed more than 30 lead extraction procedures per year. The most common procedural environment in this survey was the hybrid operating room (67.4%). Most procedures were performed by electrophysiologists and cardiologists (80.9%). Important additional members of the current lead extraction teams were cardiac surgeons (79.1%), anesthesiologists (95.3%) and operating room scrub nurses (76.7%). An extended Heart Team is regarded beneficial for patient care by 86.0%, with potential further members being infectious diseases specialists, intensivists and radiologists. Team training activities are performed in 48.8% of participating centers.*

Conclusions: *This survey supports the importance of establishing lead extraction Heart Teams in specialized lead extraction centers to potentially improve patient outcomes. The concept of a core and an extended Heart Team approach in lead extraction procedures is introduced.* (Cardiol J 2022; 29, 3: 481–488)

Key words: lead extraction, Heart Team, team training, pacemaker, ICD

Address for correspondence: Prof. Dr. Christoph T. Starck, MD, FEHRA, Department of Cardiothoracic and Vascular Surgery, German Heart Center Berlin, Augustenburger Platz 1, 13353 Berlin, Germany, tel: +49 30 4593 2055, e-mail: starck@dhzb.de

Received: 29.10.2019 Accepted: 21.07.2020 Early publication date: 14.08.2020

Introduction

The Heart Team approach plays an important role in modern cardiovascular medicine. The main purpose of the Heart Team is to determine the best available therapy in an individual patient using a multidisciplinary team approach, balancing the risks and benefits of different therapeutic strategies. The implementation of a multidisciplinary team approach has been recommended in multiple European Society of Cardiology guidelines (e.g. management of valvular disease, myocardial revascularization, management of atrial fibrillation, heart failure and infective endocarditis) [1–5].

For transvenous lead extraction (TLE) procedures the multidisciplinary team approach is noted in section 11.1 ("Personnel") of the current 2017 Heart Rhythm Society expert consensus statement. As members of this multidisciplinary team, cardiologists, electrophysiologists, cardiothoracic surgeons (in centers where the primary operator is not a surgeon), interventional radiologists, vascular surgeons are suggested. For centers that perform lead extractions in children or young adults, pediatric cardiologists as well as pediatric electrophysiologists should also be included. In section 8.1 ("Cardiovascular Implantable Electronic Device Infection") an evaluation by physicians with specific expertise in cardiovascular implantable electronic devices (CIED) infection and lead extraction is recommended for patients with documented (class I recommendation, level of evidence C) and suspected (class IIa recommendation, level of evidence C) CIED infection [6]. Putting the given information together with the assumption that in most cases, worldwide, the primary operator is an electrophysiologist or cardiologist [7], the suggested Heart Team for lead extraction procedures is represented by the following specialists: electrophysiologist or cardiologist, cardiothoracic surgeon, interventional radiologist, vascular surgeon, infectious disease specialist (in CIED infection cases) and pediatric cardiologist/electrophysiologist (in children/young adults).

In order to evaluate current opinions and real-world practice among lead extraction experts a short online survey was created and distributed among a pool of lead extraction specialists who were participants of the International Lead Extraction Expert Meeting (ILEEM) 2018.

Methods

A short survey was created by formulating 10 questions: 9 closed-ended questions (2 dichotomous question [22.2%], 7 multiple choice questions [77.8%]) and 1 open-ended question (question on country of work) (Table 1). 7 of the 9 (77.8%) closed-ended questions had the additional option to enter details on not available answer items ("other"). The goal was to generate relevant questions that could be answered in less than 5 min, in order to get a maximum response rate. The invitation to participate was sent out by email amongst lead extraction specialists who were recruited from the participant pool of the ILEEM, which is held annually in Berlin, Germany. The recipients were encouraged to forward the invitation to other lead extraction practitioners.

The survey was performed by using an online tool called SurveyMonkey (www.surveymonkey.com; SurveyMonkey Inc., San Mateo, California, USA).

Statistics

Answers were analyzed with the tool provided by SurveyMonkey (www.surveymonkey.com; SurveyMonkey Inc., San Mateo, California, USA). Categorical variables are presented as numbers and percentages.

Results

The invitation to participate was sent to 48 lead extraction specialists by email with a collector link to an internet-based survey at the end of October 2018. The survey was closed at the end of November 2018 and 43 answers to the survey were recorded, a return rate of 89%. The average time spent for completing the survey was 2 min 38 s.

Participant countries

Forty one participants of this survey were located in 16 different countries with the following distributions of answers: Austria (3), Czech Republic (1), Denmark (1), Finland (1), Germany (2), Italy (2), Japan (3), Netherlands (1), New Zealand (1), Poland (11), Spain (2), Sweden (1), Switzerland (4), Thailand (1), United Kingdom (3), United States (4). Two respondents did not answer country of origin.

Annual volume of TLE procedures

This question was answered by all participants. The detailed answers are shown in Figure 1. More than 30 procedures per year, being a common definition of high-volume centers, were performed in 83.7% of centers.

Table 1. Questions of the online International Lead Extraction Expert Meeting (ILEEM) survey on the Heart Team approach in lead extraction procedures.

Questions of ILEEM survey on Heart Team approach in lead extraction procedures	Question type
1. In which country are you working?	Open-ended
2. How many TLE procedures are performed in your clinic per year?	Closed-ended (multiple choice)
3. Where are TLE procedures performed in your hospital?	Closed-ended (multiple choice)
4. Who is predominantly performing TLE procedures in your hospital?	Closed-ended (multiple choice)
5. Who is part of your team performing TLE procedures?	closed-ended (multiple choice)
6. Who is performing TEE during TLE procedures in your hospital?	Closed-ended (multiple choice)
7. How is cardiac surgical backup for TLE procedures organized in your hospital?	Closed-ended (multiple choice)
8. Would you consider an "Extended Heart Team Approach" as beneficial for the treatment quality of patients requiring TLE procedures?	Closed-ended (dichotomous question)
9. In your opinion who should be the members of an "Extended Heart Team" for TLE procedures?	Closed-ended (multiple choice)
10. Do you perform team trainings with your TLE team?	Closed-ended (dichotomous question)

All closed-ended multiple choice questions had the additional option to enter details on not available answer items ("other"). TLE — transvenous lead extraction; TEE — transesophageal echocardiography

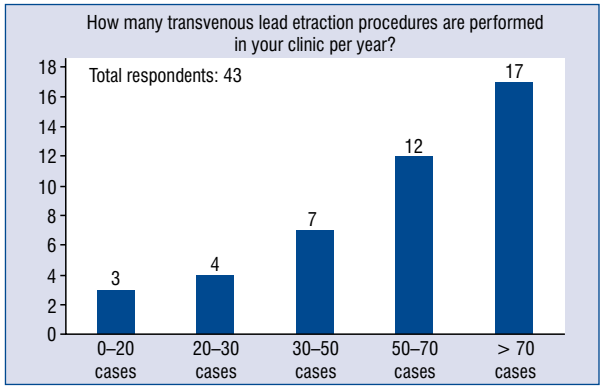


Figure 1. Annual center volume of transvenous lead extraction procedures amongst survey participants.

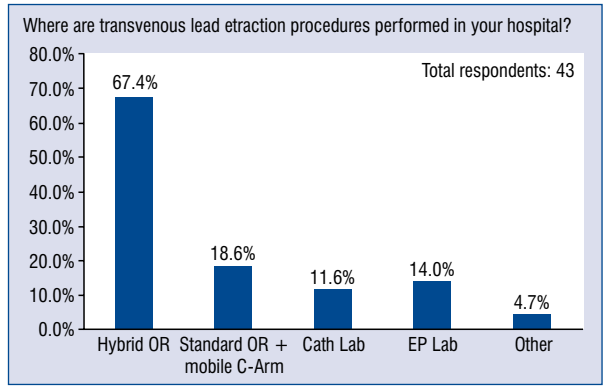


Figure 2. Procedural environment of transvenous lead extraction procedures. (Multiple responses were allowed. Percentages calculated in relation to the total number of respondents); OR — operating room.

Procedural environment

The answer rate on this question was 100%. The detailed answers are shown in Figure 2. Eighty-six percent of all participants performed lead extraction procedures in an operating room (OR), with most procedures done in a hybrid OR. Two answers were "other" and specified as OR and a mixture of OR and hybrid OR.

Primary operator in lead extraction procedures

This answer was completed by 42 participants. The primary operator is an electrophysiologist in 24 (57.1%) centers, a cardiologist in 10 (23.8%) centers and a cardiac surgeon in 8 (19.1%) centers. Five additional comments were given mainly stressing the presence of a cardiac surgeon when the procedure is performed by an electrophysiologist or cardiologist.

Current team composition in lead extraction procedures

All participants answered this question. The detailed answers are shown in Figure 3. Given answers were physicians (cardiologist, electrophysiologist, cardiac surgeon, anesthesiologist) as

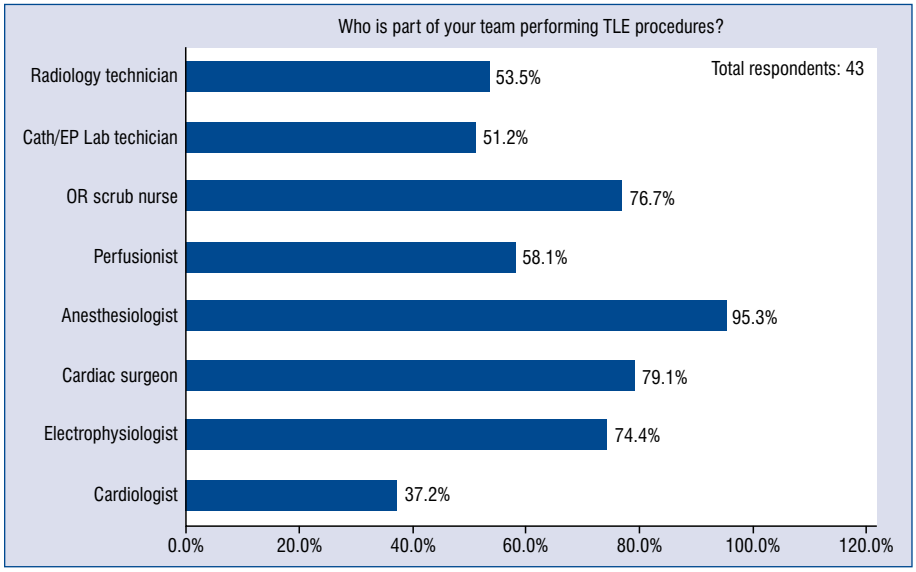


Figure 3. Current team members of lead extraction teams. (Multiple responses were allowed. Percentages calculated in relation to the total number of respondents); OR — operating room; TLE — transvenous lead extraction.

well as non-physician members (perfusionist, OR scrub nurse, Cath/EP Lab technician, radiology technician).

Performance of TEE during lead extraction procedures

This answer was completed by 42 participants. In most cases transesophageal echocardiography (TEE) is performed by an anesthesiologist (n = 25; 59.5%). In 17 (40.5%) centers TEE was performed by a cardiologist. Two (4.8%) centers have a specific echocardiography technician for this task. In almost 10% (4 centers; 9.5%) TEE was not routinely performed during TLE procedures. In 1 (2.4%) center, intracardiac echocardiography (ICE) was used as an ultrasound monitoring tool during TLE procedures.

Cardiac surgical backup

Forty-one participants answered this question. In all of the responses, participating centers had cardiac surgical backup available and present but with differing access and extent. Detailed results are shown in Table 2.

Extended Heart Team approach in TLE procedures

To collect the opinions of participants on an "extended heart team approach" in TLE procedures, the following question was posed: "Would you consider an "Extended Heart Team Approach" as beneficial to the quality of treatment of patients requiring TLE procedures?". This question was answered by 100% of participants.

Thirty-seven participants in the survey (86.0%) considered the extended Heart Team approach as beneficial, whereas for 6 (14.0%) answered that it was not considered as beneficial.

Table 2. Cardiac surgical backup during transvenous lead extraction procedures (participants: 43, answered: 41, skipped: 2).

Cardiac surgical backup	Responses
Cardiac surgeon scrubbed and present during the procedure	17 (41.5%)
Cardiac surgeon in the operating room — not scrubbed	13 (31.7%)
Cardiac surgeon in the hospital	11 (26.8%)
No cardiac surgeon available	0 (0%)

Members of an "Extended Heart Team" for TLE procedures

This answer was completed by 41 participants. Besides the electrophysiologist (80.5%) and the cardiologist (48.8%), the cardiac surgeon (95.1%), the anesthesiologist (90.2%) and the infectious disease specialist (78.0%) were considered important members of an extended lead extraction heart team. Detailed results are shown in Figure 4.

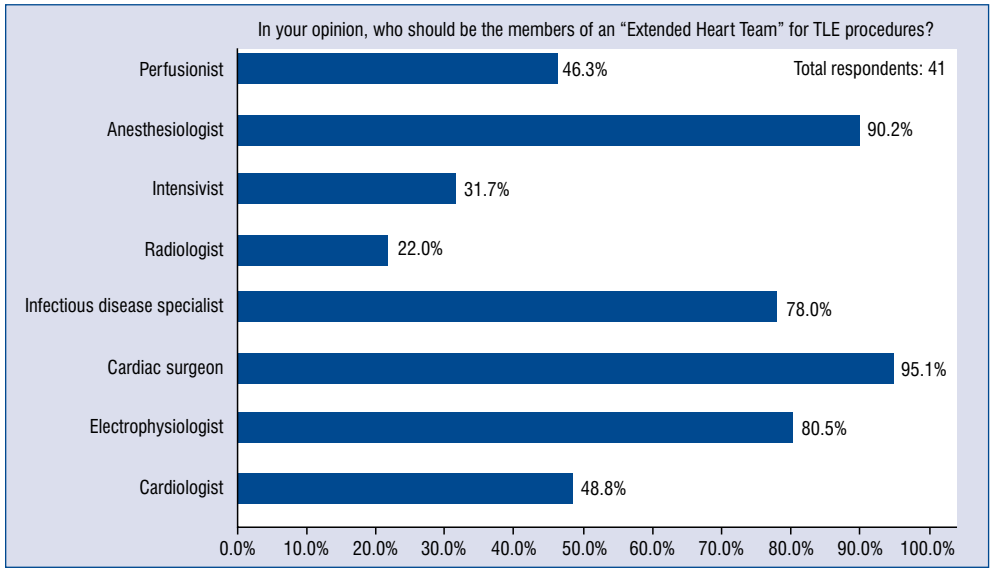


Figure 4. Opinion of the survey participants on the composition of an extended Heart Team in transvenous lead extraction (TLE) procedures. (Multiple responses were allowed. Percentages calculated in relation to the total number of respondents).

One respondent was uncertain about the terminology of an "Extended Heart Team", highlighting the potential for a broad team definition or composition. Additional potential members such as an echocardiography specialist were suggested. The quality, experience and skill mix of the team membership was also considered to be important.

Training TLE teams

This question was answered by 100% of the survey participants. 48.8% (21) of the centers perform specific team training with their TLE team, whereas 51.2% currently do not perform team training.

Additional information was supplied by 15 respondents. These comments included reporting the frequency of trainings as monthly, quarterly, twice annually or when a new member enters the team. Format of training was comprised of: workshops, seminars, clinical conferences, emergency procedure training, review of techniques, external trainings and simulation.

Discussion

A multidisciplinary team approach is now considered an integral part of current methods for providing patient-centered therapy under many cardiovascular conditions. In patients with complex coronary artery disease, it was shown that the decision-making process in a Heart Team is reproducible and that outcomes are successfully implemented in a majority of cases [8, 9].

The 2017 European Society of Cardiology guidelines on the management of valvular diseases recommended the concepts of a Heart Team approach and establishment of heart valve centers. Requirements of a heart valve center include a multidisciplinary team which meet on a regular basis, work with standard operating procedures (SOP), have the availability of multiple high-quality imaging techniques, conduct regular consultations with extracardiac departments and other hospitals, have the availability of back-up services and implement data reviews [1].

Given the results of this survey on the current composition of Heart Teams in lead extraction procedures and that a majority of participants regard the extended Heart Team approach to be beneficial to the quality of treatment of patients, the requirements for a Heart Team approach in lead extraction procedures can be summarized as similar to those for valvular heart disease: regular meetings, SOP-based approaches, availability of imaging specialists, infectious disease specialists as well as intensivists, close contact with referring non-extraction centers and implementation of data reviews for quality assurance purposes (Table 3).

The composition of the Heart Team is an important aspect. Based on the results of this survey, physicians of different specialties

Table 3. Requirements for a Heart Team approach in lead extraction procedures.

Requirements for a lead extraction Heart Team approach
Regular meetings
Standard operating procedures-based approaches
Availability of specialists:
• imaging specialists/radiologists
• infectious disease specialists
• intensivists
Close contact to referring non-extraction centers
Implementation of data review for quality assurance purposes

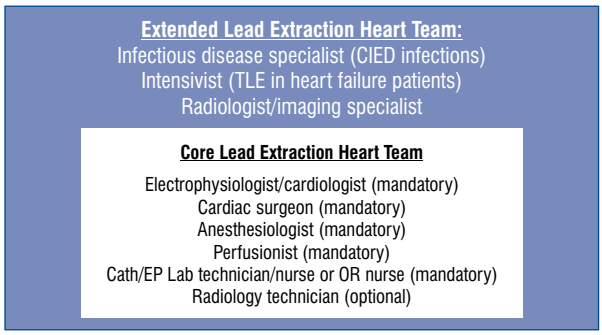


Figure 5. Concept of a core and an extended lead extraction Heart Team approach.

as well as non-physician members should be members of a lead extraction Heart Team. The definition or composition was deliberately not defined in the survey, in order to draw comment and not to influence answers. Based on the results of this survey we propose the concept of a combined core and extended Heart Team in TLE procedures (Fig. 5). The core lead extraction Heart Team should consist of all professionals involved in the actual lead extraction procedure: electrophysiologist/cardiologist (mandatory), cardiac surgeon (mandatory), anesthesiologist (mandatory), perfusionist (mandatory), Cath/EP Lab technician/nurse or OR scrub nurse (mandatory) and radiology technician (optional). The extended Heart Team in TLE procedures additionally consists of the following professionals: Infectious diseases specialist (in cases with documented or suspected CIED infection), intensive care specialists (especially in TLE procedures in heart failure patients or when sepsis or multiorgan support is required), radiologist/imaging specialist (when special imaging modalities are required pre-operatively). A wider membership is important when considering the pre- and post-procedure management and does not exclude the need for consultation outside of the group. The role of the group should not be restricted to the performance of the procedure alone, but to be involved in pre-, peri- and post-procedure management.

The composition of the core TLE Heart Team is already well accepted in most centers. The concept of an extended lead extraction Heart Team still needs to be established and defined amongst the wider clinical cardiology community. It is a fact that performing lead extraction procedures at specialized lead extraction centers leads to higher procedure volume and better patient outcomes, with a well-documented volume-outcome relationship for lead extraction procedures [7, 10]. The two most common causes of non-procedure related in-hospital mortality in the ELECTRa registry were sepsis and heart failure. In this registry, amongst others, predictors of increased all-cause mortality during hospitalization were found to be systemic infection (odds ratio 4.93, 95% confidence interval 2.72–8.93) and New York Heart Association class III/IV (odds ratio 4.08, 95% confidence interval 2.24–7.43) [7]. Consequently, regular involvement of specialist physicians for the treatment of septic complications or heart failure makes good clinical sense in order to improve outcomes for these subgroups of lead extraction patients. This makes the infectious disease specialist service of particular importance for patients with CIED infections (especially systemic infections). For heart failure patients, especially for those having cardiac resynchronization systems extracted, the intensivists and/or heart failure teams have important roles in helping manage and improve post-procedure survival. Furthermore, the availability of extracorporeal life support and short-term mechanical circulatory support may be beneficial for selected heart failure patients. In certain patients special imaging techniques may be required to confirm a suspected diagnosis (e.g. FDG/PET CT scan for suspected pocket infection), to assess special anatomical situations (e.g. CT angiography for venous occlusion or CT scan to confirm inadvertently placed leads in the left ventricle) or to assess lead course in relation to critical anatomical structures (e.g. superior vena cava, tricuspid valve) [11, 12]. The vast majority (86%) of the survey participants considered an extended Heart Team approach as beneficial for improving the quality of TLE procedural planning and performance.

Last but not least, this survey revealed that approximately half of the centers contacted (48.8%) undertook team training. Furthermore, the responses show a large heterogeneity in terms of the frequency and format of such team training. This is probably due to the fact that training teams specifically in lead extraction procedures remains in its infancy. There is considerable surgical team training predominantly for the non-technical skill sets that have been adopted in many centers which is applicable and transferable. Since many TLE procedures are performed in hybrid surgical environments, team training routines already exist for the more generic tasks. Specific team training for TLE work should be considered since the volume of procedures for all team members may be small in comparison to other work performed (other cardiac surgical procedures, electrophysiology procedures). Possible targets for team trainings are rehearsals of uncomplicated lead extraction procedures to improve familiarization and situational awareness with such work as well as crisis management for peri-procedural complications and management of postoperative care. With regard to procedural task training (performance of the procedure and management of complications) the use of virtual reality (VR) or augmented reality (AR) techniques may be beneficial but are as yet unproven and not specifically available for TLE procedures. Besides being used in training scenarios these VR and AR technologies may also be used as an adjunct for optimizing procedure planning and rehearsal prior to the case. These are important areas for future development.

Limitations of the study

This survey provides a consensus group opinion from a select group of clinicians who are or have been participants of the ILEEM in Berlin, Germany (www.ileem.com). Therefore, the survey participants do not represent an average group of physicians in real world practice, especially with regard to low and medium volume extraction centers. All participants perform TLE procedures using a variety of tools and techniques with 83.7% of all participants undertaking more than 30 TLE procedures annually, a common definition for a high-volume center [7]. Almost 40% of the contacted centers performed more than 70 procedures per year, highlighting the expertise amongst respondents to this survey. Only lead extraction experts involved with ILEEM provided opinions which may not reflect the experience and opinions of others, e.g. in low volume centers or views in other geographical regions. The survey was designed to gain an understanding of current opinions about the importance of a team approach to TLE procedures and provoke further discussion within the community.

The impact on clinical outcomes of such an extended Heart Team approach has to be investigated in future studies as a verification of this current expert opinion on the benefits of this approach backed by solid data.

Conclusions

This survey supports the importance of establishing lead extraction Heart Teams in specialized lead extraction centers to potentially improve patient outcomes. The concept of a core and an extended Heart Team approach in lead extraction procedures was introduced. The clinical benefits have to be proven in future studies.

Conflict of interest: None declared

References

1. Baumgartner H, Falk V, Bax JJ, et al. ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017; 38(36): 2739–2791, doi: 10.1093/eurheartj/ehx391, indexed in Pubmed: 28886619.
2. Neumann FJ, Ahlsson A, Alfonso F, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2018; 34(10): 2449–2496, doi: 10.1093/eurheartj/ehy394/5079120.
3. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur J Cardiothorac Surg. 2016; 50(5): e1–e88, doi: 10.1093/ejcts/ezw313, indexed in Pubmed: 27663299.
4. Ponikowski P, Voors AA, Anker SD, et al. ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016; 37(27): 2129–2200, doi: 10.1093/eurheartj/ehw128, indexed in Pubmed: 27206819.
5. Habib G, Lancellotti P, Antunes M, et al. 2015 ESC Guidelines for the management of infective endocarditis. Eur Heart J. 2015; 36(44): 3075–3128, doi: 10.1093/eurheartj/ehv319.
6. Kusumoto FM, Schoenfeld MH, Wilkoff BL, et al. 2017 HRS expert consensus statement on cardiovascular implantable electronic device lead management and extraction. Heart Rhythm. 2017; 14(12): e503–e551, doi: 10.1016/j.hrthm.2017.09.001, indexed in Pubmed: 28919379.
7. Bongiorni MG, Kennergren C, Butter C, et al. ELECTRa Investigators. The European Lead Extraction ConTRolled (ELECTRa) study: a European Heart Rhythm Association (EHRA) Registry of Transvenous Lead Extraction Outcomes. Eur Heart J. 2017; 38(40): 2995–3005, doi: 10.1093/eurheartj/ehx080, indexed in Pubmed: 28369414.

8. Pavlidis AN, Perera D, Karamasis GV, et al. Implementation and consistency of Heart Team decision-making in complex coronary revascularisation. Int J Cardiol. 2016; 206: 37–41, doi: 10.1016/j.ijcard.2016.01.041, indexed in Pubmed: 26774827.
9. Sanchez CE, Dota A, Badhwar V, et al. Revascularization heart team recommendations as an adjunct to appropriate use criteria for coronary revascularization in patients with complex coronary artery disease. Catheter Cardiovasc Interv. 2016; 88(4): E103–E112, doi: 10.1002/ccd.26276, indexed in Pubmed: 26527352.
10. Deshmukh A, Patel N, Noseworthy PA, et al. Trends in Use and Adverse Outcomes Associated with Transvenous Lead Removal in the United States. Circulation. 2015; 132(25): 2363–2371, doi: 10.1161/CIRCULATIONAHA.114.013801, indexed in Pubmed: 26534954.
11. Vatterott P, Syed I, Khan A. Lead extraction imaging. Cardiac Electrophysiol Clin. 2018; 10(4): 625–636, doi: 10.1016/j.ccep.2018.07.007.
12. Ahmed FZ, James J, Cunnington C, et al. Early diagnosis of cardiac implantable electronic device generator pocket infection using ^{18}F-FDG-PET/CT. Eur Heart J Cardiovasc Imaging. 2015; 16(5): 521–530, doi: 10.1093/ehjci/jeu295, indexed in Pubmed: 25651856.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 3, 489–498
DOI: 10.5603/CJ.a2020.0125

ISSN 1897–5593
eISSN 1898–018X

Contrast-enhanced transesophageal echocardiography predicts neo-intimal coverage of device post-left atrial appendage closure

Xiaoxia Wu[1], Dali Fan[2], Wei Huang[3], Yuezhi Meng[1], Tao Wan[4], Ezra A. Amsterdam[2], Yejia Shen[1], Yilong Chen[5, 6], Dongxing Ma[1]

[1]Department of Cardiology, the Third Medical Center, Chinese PLA (People's Liberation Army) General Hospital, Beijing, China
[2]Department of Medicine, Division of Cardiology, University of California (Davis) Medical Center, Sacramento, California, USA
[3]Department of Mechanical and Aerospace Engineering, Hong Kong University of Science and Technology, Hong Kong SAR, China
[4]Department of Hepatobiliary Surgery, the First Medical Center, Chinese PLA (People's Liberation Army) General Hospital, Beijing, China
[5]ShenZhen KYD Biomedical Technology Co. Ltd., China
[6]ShenZhen Cardiovascular Engineering Laboratory of Drug and Device Development, China

Abstract

Background: *Left atrial appendage (LAA) closure (LAAC) is a viable alternative to anticoagulation for stroke prevention in non-valvular atrial fibrillation. However, device-associated thrombosis (DAT) is known as a complication of LAAC as observed within the first few weeks after implantation. A noninvasive method is needed to predict the progress for endothelialization surveillance. The aim of the study was to develop a noninvasive visual contrast-enhanced transesophageal echocardiography (cTEE) method for monitoring the communication between left atrium (LA) and LAA post-LAAC by cTEE-score evaluating the contrast enhancement in LAA.*

Methods: *A total of 29 healthy dogs were studied by LAAC at < 24 h and 1, 2, 3 and 6-months. The LAAC procedure was assessed by TEE with color Doppler flow imaging (CDFI) and contrast imaging. The cTEE score was calculated based on the differential contrast opacification of LA and LAA cavities, the CDFI on the width of peri-device color flow, and that of histology on the level of occluder surface endothelialization in postmortem histological examination. Spearman's correlation analysis was used to correlate these scores.*

Results: *The correlation between cTEE and histology scores was superior to that between CDFI and histology scores. The trend of average cTEE score was tracked with that of histology, while that of CDFI was far from that of histology. The correlation coefficient of CDFI and histology scores was not significant ($p > 0.05$).*

Conclusions: *The noninvasive visual cTEE is feasible and reliable to monitor communication between the LA and LAA post-LAAC. cTEE is superior to CDFI as a tool in predicting the progress for endothelialization surveillance.* (Cardiol J 2022; 29, 3: 489–498)

Key words: left atrial appendage closure, endothelialization, contrast echocardiography, histology, noninvasive surveillance

Address for correspondence: Dr. Dongxing Ma, Department of Cardiology, the Third Medical Center, Chinese PLA (People's Liberation Army) General Hospital, 69 Yongding Road, Hai Dian District, Beijing 100039, China, tel: +86 13911119501, fax: +8610-57712528, e-mail: madongxing2004@126.com

Received: 10.04.2020 Accepted: 2.09.2020 Early publication date: 21.09.2020

Introduction

Left atrial appendage closure (LAAC) is an important alternative to life-long oral anticoagulation (OAC) in patients with high stroke risk and contraindication for OAC [1]. The Watchman device (Boston Scientific Inc., USA) and Amplatzer Cardiac Plug (ACP) device (St. Jude Medical Inc., USA) are the most commonly used devices [1–3]. Clinical trials with the Watchman device suggested that LAAC was similar to warfarin therapy for stroke prevention in non-valvular atrial fibrillation patients [4, 5]. The 5-year outcomes of the PREVAIL and the PROTECTAF trials demonstrated that LAAC by the Watchman device prevented stroke in non-valvular atrial fibrillation as compared to warfarin with fewer hemorrhagic strokes and mortalities [6, 7].

Interestingly, if the foreign material of LAAC devices is not fully covered by endothelial cells, thrombus develops on the left atrial surface of the device, followed by thromboembolization [8]. Reportedly, device-associated thrombosis (DAT) is a complication that occurs after LAAC with an incidence of 0–17.6% [1, 8–13]. Typically, the incidence of thrombus formation is frequent in the first few weeks after LAAC, followed by a decline with complete endothelialization of the device surface [10]. DAT and the peri-device leak showed a correlation with late thromboembolic events after technically successful LAAC [12]. Therefore, the optimal regimen of post-procedural anticoagulation or platelet inhibition after LAAC is recommended for both the Watchman and ACP devices [11].

However, the correlation between endothelialization of the left atrial appendage (LAA) occluder surface during healing and the blood flow between the left atrium (LA) and LAA is yet to be elucidated. The communication flow between LA and LAA, including central-device flow and peri-device flow (residual flow), may be associated with incomplete endothelialization of occluder surface and the risk of DAT formation. Both color Doppler flow imaging (CDFI) and contrast-enhanced transesophageal echocardiography (cTEE) is used to monitor the blood flow [14]. CDFI has been used to identify the residue flow by measuring the width of peri-device flow in PROTECTAF, PREVAIL, and EVOLUTION trials [4, 5]. However, the use of cTEE for post-LAAC follow-up examination has not yet been explored despite it being a valuable tool for differentiating between spontaneous contrast and thrombus in LAA [14].

Herein, we sought to monitor the communication between LA and LAA by applying cTEE after LAAC and found complete closure of LAA and endothelialization of the surface of the device in the absence of contrast agent within the LAA. However, the LAA opacification indicated the presence of communication between LA and LAA, although it could not be quantified. Furthermore, the correlation between CDFI, cTEE, and endothelialization is unclear.

Because complete cessation of flow by CDFI is the current "gold standard" for discontinuation of anticoagulation post-LAAC clinically, we focused on the correlation between cTEE, CDFI, and the histological evidence of complete endothelialization. In this study, we proposed that cTEE is a noninvasive method to evaluate not only the LAAC effectiveness but also the degree of endothelialization (related to histological analysis) and that it is a superior tool to CDFI for endothelialization surveillance.

Methods

Animal preparation

A total of 29 healthy dogs (7 females, 28.0 ± ± 3.7 kg) were divided into five groups randomly and euthanized at < 24 h, 1-, 2-, 3-, and 6-months after LAA device implantation. The study protocol was approved by the Committee on Animal Research of Beijing Pinggu District Hospital's Animal Experimental Center (Beijing, China). For the LAAC procedure and follow-up transesophageal echocardiography (TEE) examinations, the animals were under general anesthesia with xylazine hydrochloride (0.1 mg/kg) and propofol intramuscularly after 12 h of fasting.

TEE and cTEE examinations

A GE Vivid E9 with XD clear ultrasound system (GE Vingmed Ultrasound AS, Norway) containing a 6VT-D TEE transducer (3–8 MHz) was used. The TEE probe was inserted at a depth of 50–60 cm from the incisors. At 0, 45–60, 80–90, and 120–135°, the following were recorded: the LAA lobes, orifice diameter and depth, and the distance between left superior pulmonary vein and mitral annulus. The peri-device flow post-LAAC was assessed by CDFI with > 10 frames/s.

By adjusting in the left ventricular contrast mode, the mechanical index was set between 0.3 and 0.4, while the soft tissue thermal index was 0.2. After focusing the LAA and placing the

sample volume on the LAA orifice, 1.0–1.5 mL contrast agent (SonoVue™, Bracco Diagnostics, Princeton, NJ, USA) was injected intravenously in the femoral vein by bolus application, followed by a flush of saline. The images were acquired in 3–5 cardiac cycles after microbubbles was gradually flushed into the LAA. The time intensity curves of micobubble concentrations were acquired from the sample points (2.0-mm high and 2.0-mm wide). The curves were fitted using Time Intensity Curve Manual (Ultrasound Lab, 2005) and: *Fitting Curve* $= A\,[1 - exp(-kt)] + B$, where A is the difference between B and the maximum intensity at t is infinity, B is the intercept intensity at $t = 0$, k is a constant, $1 - exp(-kt)$ is the increasing function for wash-in.

The definition of cTEE score is three scores: 2, 1, and 0. The cTEE score of 2 is defined as microbubbles in both LA and LAA simultaneously with in 3 heart beats that fully fill the LAA, and 1 as microbubbles that slowly appear in LAA, following 3–5 heartbeats after LA is fully or partially filled. The final filling of LAA may be partial or complete. The cTEE score of 0 is defined as non-visible microbubbles in LAA, in which, there is no communication between LA and LAA. The cTEE scores 2 and 1 represent at least partial blood flow between LA and LAA.

The CDFI scores are based on the width of the residual flow into LAA. The CDFI score of 2 is defined as the width of peri-device flow > 5 mm, 1 as the width of peri-device flow ≤ 5 mm, and 0 as non-detectable peri-device flow.

LAA occlusion

The procedure was performed through a femoral vein under fluoroscopic and angiographic guidance. Based on the measurements by angiography and TEE, a self-expanding device (LAMax™ LAAC occluder, ShenZhen KYD Biomedical Technology Co., Ltd, China) was chosen, which comprises a proximal cover-disc to seal the ostium of the LAA and a distal embedded-hook anchor to be positioned within the LAA; a short central waist was connected with the two parts. Both the disc and the anchor were constructed from nitinol mesh and incorporate with fabric. Prior to the device release, five signs (acronym COVER) should be observed: 1) Concavity of the cover-disc to ensure adequate sealing; 2) Oversizing, i.e., the diameter of the anchor is 20–50% larger than the measured zone; 3) Verifying the position and impingement on the surrounding structures; 4) Ensuring stability for tug test; and 5) Residual flow assessed to be < 5 mm.

Follow-up gross and microscopic examinations

After postoperative TEEs, the dogs were euthanized with an overdose of intravenous injection of pentobarbital (86 mg/kg). The chest and pericardial cavities were inspected. The heart was opened from the right atrial. The device migration, DAT, the surface of the cover-disc, and the correlation with left superior pulmonary vein and mitral annulus were analyzed. The anchor of the device was inspected by cutting through the LAA. A histology score of 2 is defined as no neo-intimal coverage on the atrial surface of the cover-disc, 1 as partial neo-intimal coverage on the atrial surface or full neo-intimal coverage but gaps are present between the periphery of the cover-disc and the LA tissue, indicating incomplete LAAC, and 0 as full neo-intimal coverage on the surface of the cover-disc without any gap between the periphery of the cover-disc and the LA tissue, indicating complete LAA occlusion.

Subsequently, the device and the surrounding tissue underwent dehydration, followed by infiltration and were embedded in methyl methacrylate. The device was cut along the long axis of the appendage with an EXAKT 300CP diamond band saw, polished with an EXAKT 400CS grinding system (EXAKT, Norderstedt, Germany), stained with toluidine blue, and analyzed under light microscopy.

Statistical methods

Data were analyzed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). Values were displayed as mean ± standard deviation (SD). Spearman's correlation coefficients were computed among the cTEE, CDFI, and histology scores. $P < 0.05$ was considered statistically significant. The total scores were computed as the sum of the scores of all accountable dogs at that time point. The average score was computed by using total score divided by the animal count in a group. Plots were created with Microsoft Excel.

Results

Transesophageal echocardiography was performed in 29 dogs before LAAC. At 3–5 s after the intravenous injection of contrast agent, microbubbles could be seen filling the LAA (Fig. 1). No contrast filling defect was detected in any of them. The success of device implantation was 100%. There was no evidence of infarction in the major organs, as assessed by gross examinations.

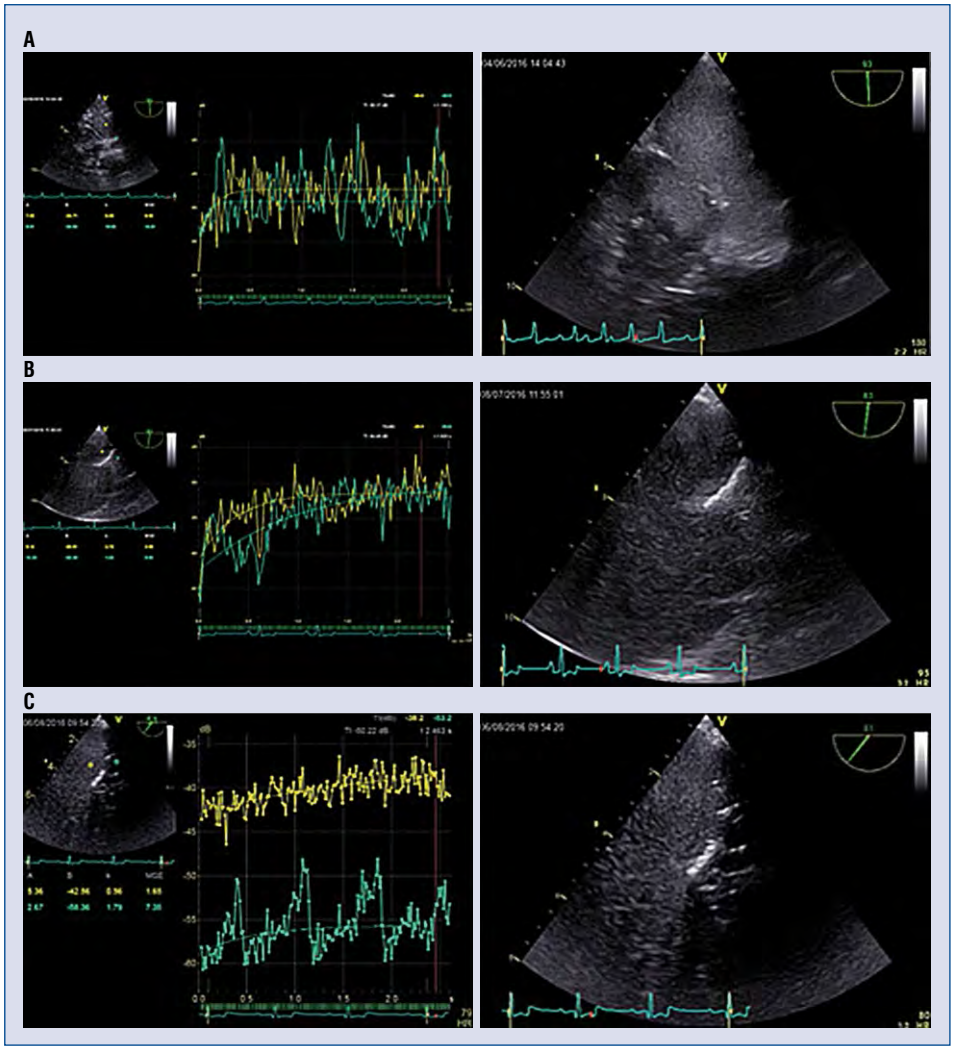


Figure 1. Representative contrast-enhanced transesophageal echocardiography (cTEE) graphs of different score gradings; **A.** cTEE-score 2: Microbubbles appeared in both left atrium (LA) and left atrial appendage (LAA) simultaneously within 3 heart beats, and fully filled in LAA; both time intensity curves (TIC) for the concentrations in LA (yellow TIC) and LAA (green TIC) were mingled and reached their plateaus at the same time; **B.** cTEE-score 1: Microbubbles appear slowly in LAA by 3 heart beats after the LA was fully filled with microbubbles; the rising speed of TIC in LAA (green) was slower than the one in LA (yellow), and finally both TICs mixed together although the yellow TIC reached its plateau earlier; **C.** cTEE-score 0: None visible microbubble in LAA, both TICs were separated with the TIC in LAA lower than that in LA.

At the follow-up visit, all animals had TEEs. The post-mortem pathology showed the LAA orifices were occluded by the cover-disc, and no thrombi were detected at any of these stages. Beginning from 1-month post LAAC, the atrial surface of the cover-discs started to be covered by a glistening white neo-endocardial layer. Bytheendof 6-month, the neo-endocardialization was 100% (Table 1). The neo-intima covered the device-left atrial interfaces, thereby sealing the LAA orifices completely. The claws of the anchor were well opposed to the LAA walls, without any evidence of tissue necrosis.

Figures 2 and 3 present examples of cTEE scores 0, and 2, respectively. As shown in Figure 4, the local atrial tissue tolerated the device well, as shown histologically.

Table 1 summarizes the results of cTEE-score, peri-device flow detected by CDFI, and histology score. In Table 2, at the < 24 h time point, only 17 dogs exhibited cTEE scores; the average cTEE score was 1.41. The average CDFI-score of 29 dogs

Table 1. Results of contrast-enhanced transesophageal echocardiography (cTEE)-score, peri-device flow detected by color Doppler flow imaging (CDFI)-score, and histology score.

Group	Case No.	cTEE-score					Peri-device flow detected by CDFI score					Histology score
		< 24 h	1 m	2 m	3 m	6 m	< 24 h	1 m	2 m	3 m	6 m	
< 24 h	1	2	–	–	–	–	0	–	–	–	–	2
	2	1	–	–	–	–	0	–	–	–	–	2
	3	1	–	–	–	–	0	–	–	–	–	2
	4	1	–	–	–	–	0	–	–	–	–	2
	5	2	–	–	–	–	0	–	–	–	–	2
	6	2	–	–	–	–	0	–	–	–	–	2
1–month	7		0	–	–	–	0	0	–	–	–	0
	8		1	–	–	–	0	0	–	–	–	1
	9		1	–	–	–	0	0	–	–	–	1
	10		0	–	–	–	0	0	–	–	–	0
	11		1	–	–	–	2	0	–	–	–	1
	12		0	–	–	–	0	0	–	–	–	0
2–months	13	1	0	0	–	–	0	0	0	–	–	0
	14	2	1	1	–	–	1	0	0	–	–	1
	15	2	1	0	–	–	0	0	0	–	–	0
	16	1	1	0	–	–	0	0	0	–	–	0
	17	1	1	0	–	–	0	0	0	–	–	0
3–months	18		1	0	0	–	0	0	0	0	–	0
	19		1	1	1	–	0	0	0	0	–	1
	20		1	0	0	–	0	0	0	0	–	0
	21	2	2	2	2	–	1	1	1	1	–	1
	22	1	0	0	0	–	0	0	0	0	–	0
	23	1	1	1	1	–	1	1	0	0	–	1
	24	2	2	2	1	–	1	1	1	1	–	1
6–months	25		x	0	0	0	0	0	0	0	0	0
	26		0	0	0	0	0	0	0	0	0	0
	27		0	0	0	0	0	0	0	0	0	0
	28	1	0	0	0	0	0	0	0	0	0	0
	29	1	x	0	0	0	0	0	0	0	0	0

–: the animal was euthanized; x: no CDFI or cTEE measurement; h — hour; m — month

was 0.17. Six dogs were sacrificed for autopsy. The average cTEE, CDFI and histology scores of these 6 dogs were 1.5, 0, and 2, respectively.

At the 1-month time point, the 6 dogs were sacrificed. The average cTEE, CDFI and histology scores of these dogs were 0.5, 0 and 0.5, respectively. One device malposition was found with a histology score of 1 (Case No. 11, Table 3). At the 2-month time point, no device migration was found.

At the 3-month time point, 7 dogs were sacrificed. Their average cTEE, CDFI and histology scores were 0.71, 0.29 and 0.57, respectively. There was peri-device flow in 2 cases (Case No. 21 and 24) with a width of 2-mm detected by a CDFI and cTEE score of 2 or 1 at post-LAAC. CDFI demonstrated that 3/7 animals had peri-device flow at both < 24 h and 1-month post-LAAC time points. Among these 3 animals, a peri-device flow was no longer apparent at 2 months, as assessed by CDFI but was detected by cTEE (Table 1). At the 6-month time point, the cTEE, CDFI, and histology scores of the remaining dogs were 0. The LSPV was partially obstructed and the MA was compressed by the cover-disc of the same device.

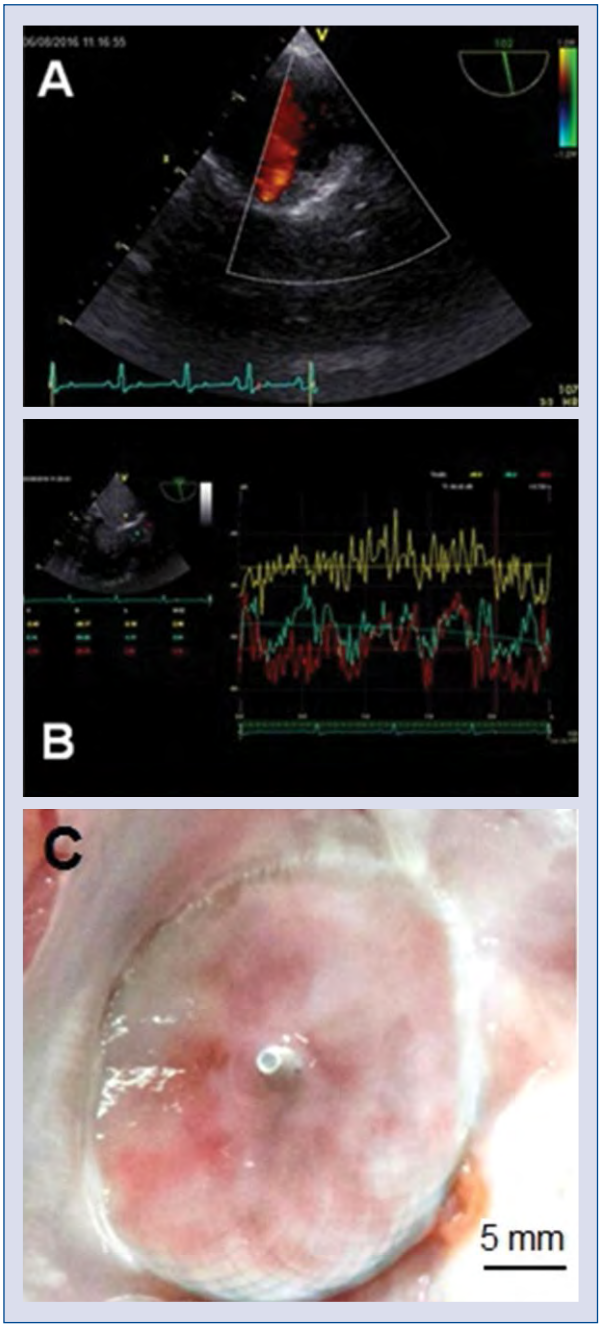


Figure 2. Example of contrast-enhanced transesophageal echocardiography (cTEE)-score 0 (2-months post--left atrial appendage closure); **A.** Color Doppler flow imaging (CDFI): none peri-device flow into left atrial appendage (LAA); **B.** cTEE and time intensity curves (TIC): none visible microbubble in LAA, two mixed TICs (red, green) in two different locations of LAA were much lower than that in left atrium (yellow); **C.** Gross examination: fully endothelialization of LAA occluder's atrial-surface, and the occluder was well coupled with the surrounding tissue.

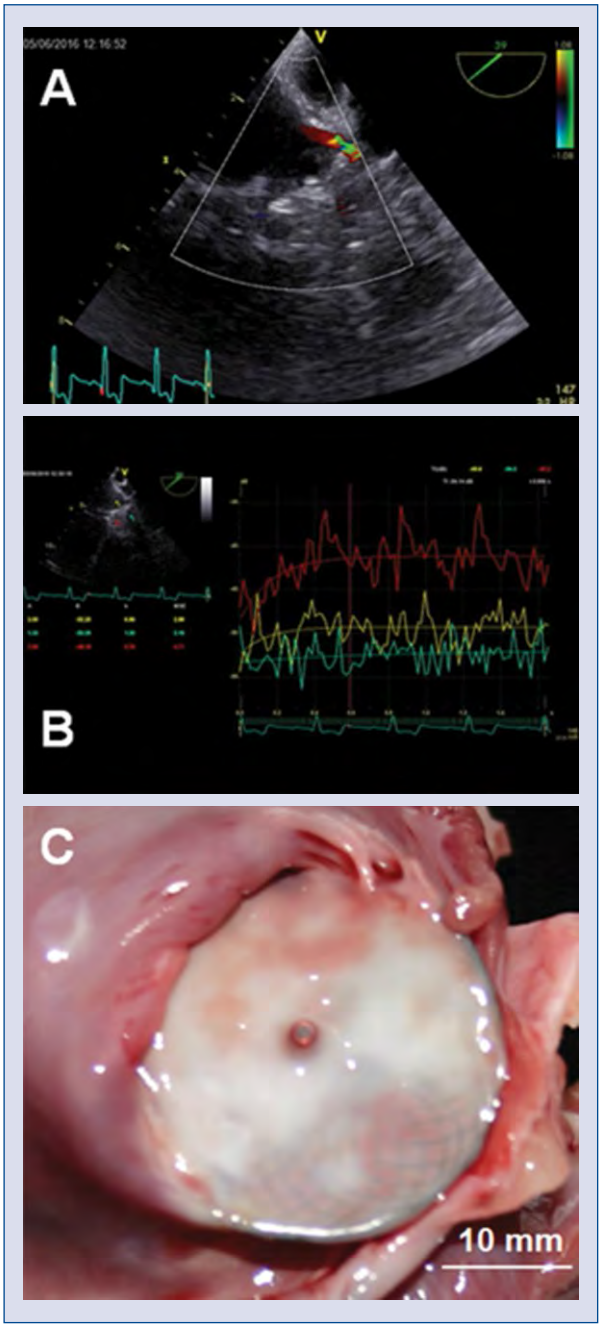


Figure 3. Example of contrast-enhanced transesophageal echocardiography (cTEE)-score 2 (3-months post--left atrial appendage closure [LAAC]); **A.** Color Doppler flow imaging (CDFI): a width of 2 mm peri-device flow into left atrial appendage (LAA); **B.** cTEE and time intensity curves (TIC): microbubbles got into LAA through a communication channel quickly from left atrium (LA) to LAA after LAAC, the TIC in LAA (red) was higher than the one in LA (yellow) due to the effect of an echo by the cover-plate; **C.** Gross examination: fully neo-intimal coverage of occluder's atrial-surface, the left edge of cover-plate was inside LAA, and an irregular fissure along the cover-plate's edge was found and passed with a 18-gauge hypodermic needle from LA to LAA.

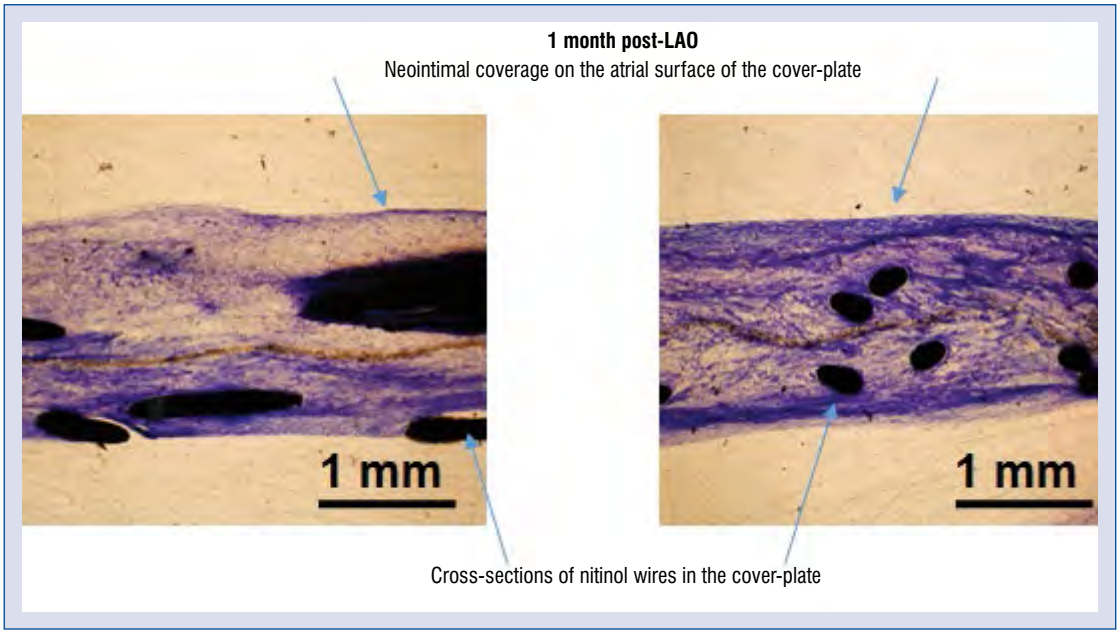


Figure 4. Histological section of the left atrial appendage closure (LAAC) device's cover-plate. Sagittal section through the center of the left atrial appendage and device in a dog (1-month post-LAAC). Microscopic views showed neointimal coverage over the atrial surface of the cover-plate.

Table 2. Summary of total score, average score for the contrast-enhanced transesophageal echocardiography (cTEE)-score, color Doppler flow imaging (CDFI)-score, histology-score at < 24 h, 1-month, 2-months, 3-months, and 6-months post-left atrial appendage closure (LAAC).

	< 24 hours	1-month	2-months	3-month	6-months
cTEE-score:					
Total	24 (17*)	15 (21)	7 (17)	5 (12)	0 (5)
Average	1.41**	0.71	0.41	0.42	0
CDFI-score:					
Total	5 (29)	3 (23)	2 (17)	2 (12)	0 (5)
Average	0.17	0.13	0.12	0.17	0
Histology-score:					
Total	12 (6)	3 (6)	1 (5)	4 (7)	0 (5)
Average	2	0.5	0.2	0.57	0

*Animal count; **1.41 = 24/7

Table 3. Three special cases.

Case	Description
No. 11	In case no. 11 (1-month post-LAAC), although the LAAC orifice was blocked by the anchor of the device while the cover-disc was in the left atrium (LA) but not attached to the orifice at all; the atrial surface of the device, including the central screw, was well covered by the neo-intimal tissue, while the incomplete neo-intimal coverage was found on the LAA surface of the cover--plate and the short central waist; no communication between LA and LAA was detected.
No. 21 and 24	In case no. 21 (3-months post-LAAC) and case no. 24 (3-months post-LAAC), the gross examination showed that in both animals, the left edge of the cover-plate was inside the LAA and there was a fissure along the cover-plate's edge; an 18-gauge hypodermic needle was used to examine the hole and could be passed from LA to LAA.

LA — left atrium; LAA — left atrial appendage; LAAC — left atrial appendage closure

Table 4. The correlation coefficients among contrast-enhanced transesophageal echocardiography (cTEE)-score, color Doppler flow imaging (CDFI)-score, and histology score.

	cTEE score (n)	CDFI score (n)	Histology score (n)
cTEE score	1.00 (72)	0.55* (72)	0.95* (29)
CDFI score	0.55* (72)	1.00 (72)	0.16 (29)
Histology score	0.95* (29)	0.16 (29)	1.00 (29)

*Correlation is significant at the 0.01 level (2-tailed).

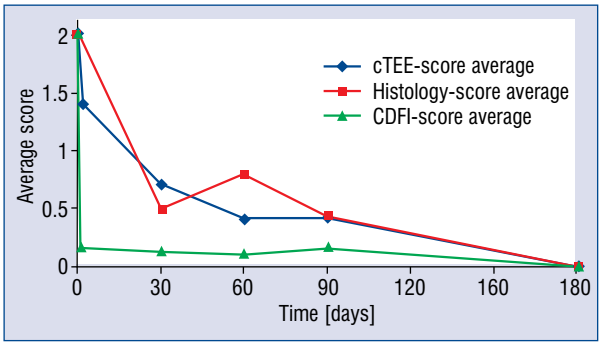


Figure 5. The trends of the average score number of contrast-enhanced transesophageal echocardiography (cTEE)-score, histology-score, color Doppler flow imaging (CDFI)-score, respectively, from the time before left atrial appendage closure (LAAC) (i.e., the time was 0) to 1-, 30-, 60-, 90-, 180-days post-LAAC.

Table 4 shows the Spearman's correlations of the cTEE, CDFI, and histology scores at time points < 24 h, and 30, 60, 90, and 180 days post-LAAC, respectively. The correlation between cTEE and histology scores was superior to that between CDFI and histology scores. In Figure 5, shows the trend of the average cTEE score tracks with that of the histology score at different time points, but the curve of the average CDFI score declines sharply after device implantation immediately, which is distal from that of the histology score.

Discussion

This study introduced a noninvasive visual cTEE score method to monitor the communication between LA and LAA and predict the progression of the LAAC endothelialization process. By comparing with the conventional CDFI method, as well as correlating with the post-mortem anatomical and histological examinations, we found that cTEE is superior to CDFI as a tool for endothelialization surveillance.

The post-LAAC healing reactions are similar between canine and human, and the canine model is suitable for pre-clinical evaluation of LAA occlusion devices [2]. Usually, the LAAC devices consist of nitinol frame and polyester fabric membrane. If not fully endothelialized, the left atrial surface of the devices have the potential to promote subsequent thrombosis [8]. In a systematic review of DAT after LAAC, the overall incidence of DAT was 3.9%. The median time from procedure to diagnosis of DAT was 1.5 months. These early cases of DAT are related to delayed device surface endothelialization, and the late cases could be secondary to mechanical factors or systemic patient factors [5, 10, 15]. Thus, the endothelialization of the LAA occluder's atrial surface is clinically critical in DAT prevention postoperatively in patients. Therefore, in the clinical trials, human subjects were given warfarin by Watchman devices for 45 days after LAAC. If the 45-day TEE documented either complete closure of the LAA or if peri-device flow was < 5 mm in width and there was no visible large thrombus on the device, warfarin was discontinued [4, 5]. Interestingly, the conformation of LAA surrounding structures exhibited variable healing responses among different LAAC devices, which might affect the progress of endothelialization [2]. In this study, LAMax™ LAAC occluder was applied, and the shape of the cover-disc was similar to the disc of ACP.

The following questions remain unanswered: Can the device endothelialization process be effectively monitored *in vivo*? Is the device endothelialization process associated with the communicated flow between LA and LAA? Intriguingly, TEE has been applied widely to guide LAAC implantation and follow-up anticoagulation. Routine device surveillance by TEE at intermediate follow-up provides the opportunity to assess DAT, peri-device leak, device positioning, surrounding structures. However, CDFI and cTEE monitor the blood flow by different mechanisms [14]. Echo contrast agents are lipid-encapsulated microbubbles, which are 1–7 μm in diameter and similar in size to red blood cells. The microbubbles are injected intravenously and remain within the blood pool to circulate in a manner similar to the red blood cells for a short interval. The use of cTEE has been described for delineation of an LAA thrombus and distinction between spontaneous contrast and thrombus [16].

In this study, cTEE was found to be superior to CDFI with respect to communication between LA

and LAA post-LAAC as well as the progression of device endothelialization *in vivo*. The CDFI score decreased precipitously immediately post-implantation in > 83% of the cases. This phenomenon indicated that in most cases, the communication between the LA and LAA reduces to the level below the detection of CDFI after successful device deportment. However, the CDFI score of 0 does not mean total cessation of the flow as seen in this cohort. There were 28/57 cases with a CDFI score of 0 zero, but their cTEE scores were 1 or 2, indicating at least partial flow between the LA and the LAA. Moreover, the positive predictive value was 100% with 12 CDFI score-positive (1 or 2) studies, which also had positive cTEE scores (1 or 2). Furthermore, in the set of < 24 h post-LAAC group with no neo-intimal coverage on the surface of cover-plate, all 6 dogs had a CDFI score of 0 and the cTEE score was 1 or 2. This indicated that cTEE can detect the communicated flow between LA and LAA post-LAAC beyond the resolution of CDFI.

Left atrial appendage closure device surface endothelialization is a slow process. It was shown that at the end of 1 month, 50% (3/6) of the dogs had complete device endothelialization, and by the end of 6 months, 100% of the devices' cover-discs were completely covered, and the neoendocardial covering was continuous from the left atrial wall to the device. At different time points, the histology scores of 15 dogs were 0; also, their cTEE and CDFI scores were uniformly 0, with a positive predictive value of 100%. However, when the endothelial process occurred partially with a histology score of 1, the cTEE score was superior to the CDFI score. In the 8 dogs with the histology score of 1, 7/8 had cTEE score of 1, and one had a score of 2, while 2/8 dogs had a CDFI score of 1, and the remaining had a score of 0. Overall, the cTEE-score was correlated to the histology score with a coefficient of 0.95. It is shown that a trend of the average cTEE score tracked with that of the histology score, but the trend of the average CDFI score was far from that of the histology score. This finding indicates that cTEE has a better temporal resolution than CDFI in monitoring the device endothelialization process *in vivo*.

The present study also showed that the effective healing response after implantation of LAAC devices was related to the achievement of concavity of the cover-plate and less peri-device flow. Especially, in 3-months post-LAAC group, both the average cTEE and histology scores were higher than that of the 2-month post-LAAC group. This is due to a higher number of cases with immediate post-LAAC peri-device flow present in this group. Therefore, it is important to avoid the incidence of residual flow during the LAAC procedure; if the residual flow is unavoidable, it may be necessary to monitor the healing progress by cTEE before terminating the use of anticoagulants.

Despite a satisfactory correlation with the histology score, the clinical significance of cTEE score is yet uncertain. Thus, a large-scale clinical study with DAT as the endpoint is imperative. For clinical application, it is better to have cTEE assessment before 1 month after LAAC. If cTEE score remains not 0, cTEE should be done again before terminating the OAC. If the residual flow is found by CDFI, cTEE could be avoided. Nevertheless, we speculated that cTEE could be used as a noninvasive tool for endothelialization surveillance after LAAC for the future.

Limitations of the study

The number of animals studied is relatively small. Since LAA occlusion devices are usually tested in canines before clinical application, the present study has extended these methods to healthy adult dogs as the animal model. However, clinical trials are required for further evaluation.

Conclusions

The noninvasive visual cTEE is feasible and reliable to monitor the communication between LA and LAA post-LAAC. The cTEE is superior to the currently used CDFI to predict the progress of neo-intimal coverage on the atrial surface of the LAAC device in dogs.

Acknowledgments

We would like to thank GE Healthcare for generously lending us the TEE system that made this study possible.

Conflict of interest: Dr. Yilong Chen is an employee of ShenZhen KYD Biomedical Technology Co. Ltd., China.

References

1. Main ML, Fan D, Reddy VY, et al. Assessment of Device-Related Thrombus and Associated Clinical Outcomes With the WATCHMAN Left Atrial Appendage Closure Device for Embolic Protection in Patients With Atrial Fibrillation (from the PROTECT-AF Trial). Am J Cardiol. 2016; 117(7): 1127–1134, doi: 10.1016/j.amjcard.2016.01.039, indexed in Pubmed: 26993976.

2. Kar S, Hou D, Jones R, et al. Impact of Watchman and Amplatzer devices on left atrial appendage adjacent structures and healing response in a canine model. JACC Cardiovasc Interv. 2014; 7(7): 801–809, doi: 10.1016/j.jcin.2014.03.003, indexed in Pubmed: 25060026.
3. Landmesser U, Schmidt B, Nielsen-Kudsk JE, et al. Left atrial appendage occlusion with the AMPLATZER Amulet device: periprocedural and early clinical/echocardiographic data from a global prospective observational study. EuroIntervention. 2017; 13(7): 867–876, doi: 10.4244/EIJ-D-17-00493, indexed in Pubmed: 28649053.
4. Boersma LVA, Schmidt B, Betts TR, et al. Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. Eur Heart J. 2016; 37(31): 2465–2474, doi: 10.1093/eurheartj/ehv730, indexed in Pubmed: 26822918.
5. Holmes DR, Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. J Am Coll Cardiol. 2014; 64(1): 1–12, doi: 10.1016/j.jacc.2014.04.029, indexed in Pubmed: 24998121.
6. Hobohm L, von Bardeleben RS, Ostad MA, et al. 5-year experience of in-hospital outcomes after percutaneous left atrial appendage closure in germany. JACC Cardiovasc Interv. 2019; 12(11): 1044–1052, doi: 10.1016/j.jcin.2019.04.002, indexed in Pubmed: 31171280.
7. Reddy VY, Doshi SK, Kar S, et al. 5-Year outcomes after left atrial appendage closure: from the PREVAIL and PROTECT AF trials. J Am Coll Cardiol. 2017; 70(24): 2964–2975, doi: 10.1016/j.jacc.2017.10.021, indexed in Pubmed: 29103847.
8. Dukkipati SR, Kar S, Holmes DR, et al. Device-Related thrombus after left atrial appendage closure: incidence, predictors, and outcomes. Circulation. 2018; 138(9): 874–885, doi: 10.1161/CIRCULATIONAHA.118.035090, indexed in Pubmed: 29752398.
9. Aminian A, Lalmand J, Tzikas A, et al. Embolization of left atrial appendage closure devices: A systematic review of cases reported with the watchman device and the amplatzer cardiac plug. Catheter Cardiovasc Interv. 2015; 86(1): 128–135, doi: 10.1002/ccd.25891, indexed in Pubmed: 25676316.
10. Lempereur M, Aminian A, Freixa X, et al. Device-associated thrombus formation after left atrial appendage occlusion: a systematic review of events reported with the Watchman, the Amplatzer Cardiac Plug and the Amulet. Catheter Cardiovasc Interv. 2017; 90(5): E111–E121, doi: 10.1002/ccd.26903, indexed in Pubmed: 28145040.
11. Tzikas A, Bergmann MW. Left atrial appendage closure: patient, device and post-procedure drug selection. EuroIntervention. 2016; 12 (Suppl X): X48–X54, doi: 10.4244/EIJV12SXA10, indexed in Pubmed: 27174112.
12. Saw J, Tzikas A, Shakir S, et al. Incidence and clinical impact of device-associated thrombus and Peri-Device leak following left atrial appendage closure with the Amplatzer cardiac plug. JACC Cardiovasc Interv. 2017; 10(4): 391–399, doi: 10.1016/j.jcin.2016.11.029, indexed in Pubmed: 28231907.
13. Bergmann MW, Ince H, Kische S, et al. Real-world safety and efficacy of WATCHMAN LAA closure at one year in patients on dual antiplatelet therapy: results of the DAPT subgroup from the EWOLUTION all-comers study. EuroIntervention. 2018; 13(17): 2003–2011, doi: 10.4244/EIJ-D-17-00672, indexed in Pubmed: 29313819.
14. Porter TR, Abdelmoneim S, Belcik JT, et al. Guidelines for the cardiac sonographer in the performance of contrast echocardiography: a focused update from the American Society of Echocardiography. J Am Soc Echocardiogr. 2014; 27(8): 797–810, doi: 10.1016/j.echo.2014.05.011, indexed in Pubmed: 25085408.
15. Lam SC, Bertog S, Sievert H. Incomplete left atrial appendage occlusion and thrombus formation after Watchman implantation treated with anticoagulation followed by further transcatheter closure with a second-generation Amplatzer Cardiac Plug (Amulet device). Catheter Cardiovasc Interv. 2015; 85(2): 321–327, doi: 10.1002/ccd.25456, indexed in Pubmed: 24550125.
16. Porter TR, Mulvagh SL, Abdelmoneim SS, et al. Clinical Applications of Ultrasonic Enhancing Agents in Echocardiography: 2018 American Society of Echocardiography Guidelines Update. J Am Soc Echocardiogr. 2018; 31(3): 241–274, doi: 10.1016/j.echo.2017.11.013, indexed in Pubmed: 29502588.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 3, 499–508
DOI: 10.5603/CJ.a2020.0140

ISSN 1897–5593
eISSN 1898–018X

Cardiovascular outcomes with glucagon-like peptide 1 agonists and sodium-glucose cotransporter 2 inhibitors in patients with type 2 diabetes: A meta-analysis

Yeong-Min Lee, Soon-Hee Lee, Tae-Hee Kim, Eun-Ji Park, Young-Ah Park, Jae-Sik Jang

Department of Internal Medicine, Busan Paik Hospital, Inje University College of Medicine, Busan, Korea

Abstract

Background: *According to available research, there have been no head-to-head studies comparing the effect of glucagon-like peptide 1 (GLP-1) agonists and sodium-glucose cotransporter 2 (SGLT-2) inhibitors on cardiovascular outcomes among patients with type 2 diabetes not reaching glycemic goal with metformin.*

Methods: *Relevant studies were identified through electronic searches of PubMed and EMBASE published up to January 15, 2020. Efficacy outcomes of interest included the composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke, its individual components, all-cause death, and hospitalization for heart failure (HF). Safety outcomes included all suggested side effects of both agents previously reported.*

Results: *Eleven studies, including 94,727 patients were used for the analysis. The risk of composite end point was significantly lower in both groups compared to the control group (hazard ratio [HR] 0.88, 95% confidence interval [CI] 0.85–0.92, $p < 0.001$). The risk of hospitalization for HF was significantly lower in both groups but the magnitude of the effect was more pronounced in the SGLT-2 inhibitors group (HR 0.68, 95% CI 0.60–0.76, $p < 0.001$) than the GLP-1 agonists group (HR 0.92, 95% CI 0.84–0.99, $p = 0.03$). Patients treated with GLP-1 agonists discontinued trial medications more frequently compared to conventionally treated patients because of serious side effects.*

Conclusions: *Both GLP-1 agonists and SGLT-2 inhibitors showed comparable cardiovascular outcomes in patients with type 2 diabetes. However, the SGLT-2 inhibitors were associated with more pronounced reduction of hospitalization for HF and lower risk of treatment discontinuation than GLP-1 agonists.* (Cardiol J 2022; 29, 3: 499–508)

Key words: diabetes mellitus, sodium-glucose transporter 2 inhibitors, glucagon-like peptide 1 receptor, cardiovascular disease

Introduction

Use of appropriate antidiabetic drugs has become an important issue in diabetic patients with atherosclerotic cardiovascular disease (CVD) and those with multiple risk factors [1, 2]. Although metformin is generally recommended and widely used as a first-line therapy due to its cardioprotective effects, selection of a subsequent antidiabetic agent among type 2 diabetic patients who failed to reach their glycemic goal has been debated [3, 4].

Address for correspondence: Jae-Sik Jang, MD, PhD, Department of Internal Medicine, Busan Paik Hospital, University of Inje College of Medicine, 75, Bokji-ro, Busanjin-gu, Busan 47392, Korea, tel: +82-51-890-6418, fax: +82-51-890-6341, e-mail: jsjang71@gmail.com

Received: 21.03.2020 Accepted: 12.10.2020 Early publication date: 26.10.2020

**The first two authors (Drs. Y.M. Lee and S.H. Lee) contributed equally to this article.*

Several classes of antidiabetic agents have been effective in glycemic control when added to metformin and these include the incretin-based dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide 1 (GLP-1) agonists [5], and sodium-glucose cotransporter 2 (SGLT-2) inhibitors. Current guidelines recommend addition of either SGLT-2 inhibitors or GLP-1 agonists in type 2 diabetes patients who failed to achieve their glycemic goal with metformin monotherapy or even as a first-line therapy for patients with atherosclerotic CVD [4, 6, 7].

Contrary to recent trials of DPP-4 inhibitors that did not show benefits or harms, several GLP-1 agonists and SGLT-2 inhibitors were effective in terms of cardiovascular outcomes [8–17]. Understanding cardiovascular outcomes of second-line antidiabetic agents in high-risk diabetic patients could help physicians to select treatment strategy after failure of metformin-based antidiabetic management. However, there were no head-to-head studies comparing the efficacy of both classes of antidiabetic agents. The purpose of this study was to investigate the effectiveness of GLP-1 agonists and SGLT-2 inhibitors and their safety profiles.

Methods

Data sources

Relevant studies were identified through electronic searches of PubMed and EMBASE published up to January 15, 2020. Medical subject headings and keyword searches included the terms 'empagliflozin', 'canagliflozin', 'dapagliflozin', 'ertugliflozin', 'lixisenatide', 'exenatide', 'liraglutide', 'semaglutide', 'albiglutide', 'dulaglutide', 'heart infarction', 'myocardial infarction', 'cerebrovascular accident', 'stroke', 'death', 'major adverse cardiac event', 'mace', 'major adverse cardiovascular event', 'heart failure', 'controlled study', 'random', and 'placebo'. Reference lists of selected articles were systematically reviewed for other potentially relevant citations. No language restriction was enforced.

Study selection

Two investigators (S.-H.L. and J.-S.J.) independently conducted the literature search, data extraction, and quality assessment by using a standardized approach. Selected publications were reviewed by the same investigators to assess if studies met the inclusion criteria: (1) randomized allocation; (2) all participants with type 2 diabetes mellitus; (3) comparison of GLP-1 agonist or SGLT-2 inhibitor with a control group; (4) follow-up of more than 1 year.

Data extraction

Two reviewers (Y.-M.L. and J.-S.J.) extracted relevant information from the articles including study treatment, study period, patient characteristics (mean age, gender distribution, duration of diabetes, history of atherosclerotic CVD and heart failure [HF]), sample size, estimated glomerular filtration rates. Reviewers were not blinded to the articles, publication sites, and affiliation of authors.

End points

Efficacy end points of this study were the composite of cardiovascular death, non-fatal myocardial infarction (MI), or non-fatal stroke, its individual components, all-cause death, and hospitalization for HF. Safety end points of interest included pancreatitis, pancreatic cancer, retinopathy, genital and urinary tract infection, diabetic ketoacidosis, lower limb amputations, fractures, acute kidney injury, any malignancy, severe hypoglycemia, and discontinuation of study medications.

Data synthesis and analysis

Hazard ratios (HRs) were pooled with 95% confidence intervals (CIs) for the effect of randomizing treatment allocation on the outcomes across trials and the adjusted risk estimates were pooled after logarithmic transformation according to fixed-effects models with the generic inverse variance method. For safety outcomes, random--effects models producing across-study summary risk ratios (RRs) with 95% CIs were used. All p values were 2-tailed, with statistical significance set at 0.05. Included studies were well performed and the Cochrane tool for the assessment of risk bias in randomized clinical trials revealed low risk of bias in all studies [18]. Statistical heterogeneity between trials was assessed with I^2 statistic, which is derived from the Cochran's Q and the degree of freedom [$100 \times (Q - df)/Q$]] [19]. I^2 values lesser than 25%, greater than 25%, 50%, and 75% were considered as evidence of no, low, moderate, and severe statistical heterogeneity, respectively. If significant heterogeneity was noted across the studies, we then performed sensitivity analyses, serially excluding studies to determine the source of heterogeneity. Additionally, sensitivity analysis based on the different backbone across GLP-1 agonist studies were conducted to examine the heterogeneity between exendin-4 analogues and human GLP-1 analogues. Publication bias was examined by visual inspection of constructed funnel plots. All statistical analyses were performed using the Review Manager version 5.2 (The Nordic

Cochrane Center, Copenhagen, Denmark). Meta-analysis was performed according the statement of Preferred Reporting Items for Systematic reviews and meta-analysis [20].

Results

The search strategy identified 309 potential articles, of which 32 were read in full text and 11 clinical studies were included into the final analysis. Among them, 7 studies were phase 3, double-blind, placebo-controlled trials comparing GLP-1 agonists and standard treatment [9–11, 13, 21–23], while 4 trials were phase 3, double-blind, placebo-controlled trials comparing SGLT-2 inhibitors and control group [12, 17, 24, 25]. Table 1 summarizes characteristics of the included studies. Of the 94,727 patients, 27,977 patients received GLP-1 agonists, 21,266 patients received SGLT-2 inhibitors and 45,484 patients were managed with conventional treatment. To compare different studies, regimen of study treatment, duration of diabetes, glycated hemoglobin level, proportion of patients with atherosclerotic CVD and HF, and glomerular filtration rates were extracted (Table 1). Of the 7 GLP-1 agonists studies, only one of the latest studies [23] used oral regimen, instead of subcutaneous injection. Human GLP-1 analogues were used in 5 GLP-1 agonist studies [10, 11, 21–23] while exendin-4 analogues were used in 2 studies [9, 13]. Primary end point of the included studies was composite of cardiovascular mortality, MI, or non-fatal stroke except for one study [24] reporting composite of renal outcomes and mortality.

Efficacy outcomes

Composite of cardiovascular death, non-fatal MI, or non-fatal stroke

Eleven studies including 94,727 patients were used for the analysis of composite end point. The risk for the composite end point of cardiovascular death, non-fatal MI, or non-fatal stroke was significantly lower in both GLP-1 agonists group and SGLT-2 inhibitors group compared to the control group (HR 0.88, 95% CI 0.85–0.92, $p < 0.001$, Fig. 1). There was evidence of low statistical heterogeneity among the included studies (heterogeneity $\chi^2 = 13.13$, $I^2 = 24\%$, $p = 0.22$).

Mortality, non-fatal MI, non-fatal stroke

Pooled effects of cardiovascular mortality showed significantly lower rates in the GLP-1 agonists and SGLT-2 inhibitors group compared to conventional treatment (HR 0.86, 95% CI 0.81–0.92, $p < 0.001$, Fig. 2A). Low statistical heterogeneity was found among the included studies (heterogeneity $\chi^2 = 18.14$, $I^2 = 45\%$, $p = 0.05$). All-cause death was also significantly lower in patients treated with both GLP-1 agonists and SGLT-2 inhibitors compared with the control group (HR 0.87, 95% CI 0.83– 0.91, $p < 0.001$). Both GLP-1 agonists and SGLT-2 inhibitors were associated with significantly lower rates of non-fatal MI (HR 0.90, 95% CI 0.85–0.96, $p < 0.001$, Fig. 2B). Risk of non-fatal stroke was significantly lower with the use of GLP-1 agonists (HR 0.91, 95% CI 0.83–0.99, $p = 0.02$) but not with the SGLT-2 inhibitors (HR 1.02, 95% CI 0.89–1.16, $p = 0.81$, Fig. 2C).

Hospitalization for heart failure

There was a substantial disparity between GLP-1 agonists and SGLT-2 inhibitors in the risk of hospitalization for HF. The risk of hospitalization for HF was significantly lower in both GLP-1 agonists group and SGLT-2 inhibitors group as compared to the control group (HR 0.83, 95% CI 0.78–0.89, $p < 0.001$, Fig. 3), but the magnitude of effect was more pronounced in the SGLT-2 inhibitors group (HR 0.68, 95% CI 0.60–0.76, $p < 0.001$) compared with the GLP-1 agonists group (HR 0.92, 95% CI 0.84–0.99, $p = 0.03$). There was no evidence of statistical heterogeneity among the included studies (GLP-1 agonists; heterogeneity $\chi^2 = 2.00$, $I^2 = 0\%$, $p = 0.92$, SGLT-2 inhibitors; heterogeneity $\chi^2 = 1.32$, $I^2 = 0\%$, $p = 0.72$).

Safety outcomes

In the analysis of safety outcomes, use of GLP-1 agonists was associated with a significantly increased risk of gastrointestinal events (RR 1.47, 95% CI 1.06–2.02, $p = 0.02$), but did not influence the rates of pancreatitis (RR 0.72, 95% CI 0.37––1.43, $p = 0.35$), pancreatic cancer (RR 1.17, 95% CI 0.74–1.85, $p = 0.51$) and retinopathy (RR 1.07, 95% CI 0.88–1.29, $p = 0.50$) (**Suppl. Fig. S1**). Patients treated with SGLT-2 inhibitors showed a significantly increased risk of genital infection compared with the patients on conventional treatment (RR 4.50, 95% CI 3.32–6.10, $p < 0.001$), but showed a similar risk of urinary tract infection (RR 1.03, 95% CI 0.96–1.10, $p = 0.38$). Use of SGLT-2 inhibitors tended to increase the risk of amputation (RR 1.31, 95% CI 1.00–1.70, $p = 0.05$), but the exclusion of studies with canagliflozin demonstrated a similar risk of amputation between the canagliflozin and the conventional treatment group (RR 1.08, 95% CI 0.90–1.28, $p = 0.41$) (**Suppl. Fig. S2**). The SGLT-2 inhibitors decreased the risk of acute

Table 1. Characteristics of included studies.

Study	Study treatment	Year	Randomization period	Patients	Median follow-up [years]	Age [years]	Women (%)	Diabetes duration [years]	HbA_{1c} [%]	ASCVD [%]	Heart failure [%]	eGFR [mL/min/ /1.73 m^2]	eGFR < 60 mL/ /min/1.73 m^2
GLP-1 agonists													
ELIXA	Lixisenatide (up to 20 μg sc daily)	2015	2010–2013	3034/3034	2.1	60/61	30/31	9.3 / 9.5	7.7/7.6	100/100	23/22	77/75	22/25
LEADER	Liraglutide (up to 1.8 mg sc daily)	2016	2010–2012	4668/4672	3.5	64/64	35/36	13/13	8.7/8.7	82/81	18/18	–	24/22
SUSTAIN-6	Semaglutide (0.5 mg/1.0 mg sc weekly)	2016	2013	1648/1649	2.1	65/65	39/40	14/14	8.7/8.7	60/61	23/24	–	28/29
EXSCEL	Extended–release exenatide (2 mg sc weekly)	2017	2010–2015	7356/7396	3.2	62/62	38/38	12/12	8.0/0.0	73/73	16/17	77/76	21/22
Harmony Outcomes	Albiglutide (30–50 mg sc weekly)	2018	2015–2016	4731/4732	1.6	64/64	30/31	14/14	8.8/8.7	–	20/20	79/79	11/11
REWIND	Dulaglutide (1.5 mg sc weekly)	2019	2011–2013	4949/4952	5.4	66/66	47/46	11/11	7.3/7.4	32/31	9/9	75/75	22/23
PIONEER 6	Semaglutide (14 mg po daily)	2019	2017	1591/1592	1.3	66/66	32/31	15/15	8.2/8.2	85/85	12/13	74/74	27/27
SGLT-2 inhibitors													
EMPA-REG OUTCOME	Empagliflozin (10 mg/25 mg po daily)	2015	2010–2013	4687/2333	3.1	63/63	29/28	–	8.1/8.1	100/100	10/11	74/74	26/26
CANVAS Program	Canagliflozin (100–300 mg po daily)	2017	2009–2017	5795/4347	2.4	63/63	35/37	14/14	8.2/8.2	71/74	14/15	77/76	–
DECLARE-TIMI 58	Dapagliflozin (10 mg po daily)	2018	2013–2015	8582/8578	4.2	64/64	37/38	11/10	8.3/8.3	41/41	10/10	85/85	7/8
CREDENCE	Canagliflozin (100 mg po daily)	2019	2014–2017	2202/2199	2.6	63/63	35/33	16/16	8.3/8.3	51/50	15/15	56/56	59/59

Data are presented as second line agents/control. HbA1c — glycated hemoglobin; ASCVD — atherosclerotic cardiovascular disease; eGFR — estimated glomerular filtration rate; GLP-1 — glucagon-like peptide 1; ELIXA — evaluation of lixisenatide in acute coronary syndrome; LEADER — liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results; SUSTAIN-6 — trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes; EXSCEL — exenatide study of cardiovascular event lowering study group; REWIND — researching cardiovascular events with a weekly incretin in diabetes; SGLT-2 — sodium glucose cotransporter 2; CANVAS — canagliflozin cardiovascular assessment study; DECLARE-TIMI 58 — dapagliflozin effect on cardiovascular events–thrombolysis in myocardial infarction 58; CREDENCE — canagliflozin and renal events in diabetes with established nephropathy clinical evaluation

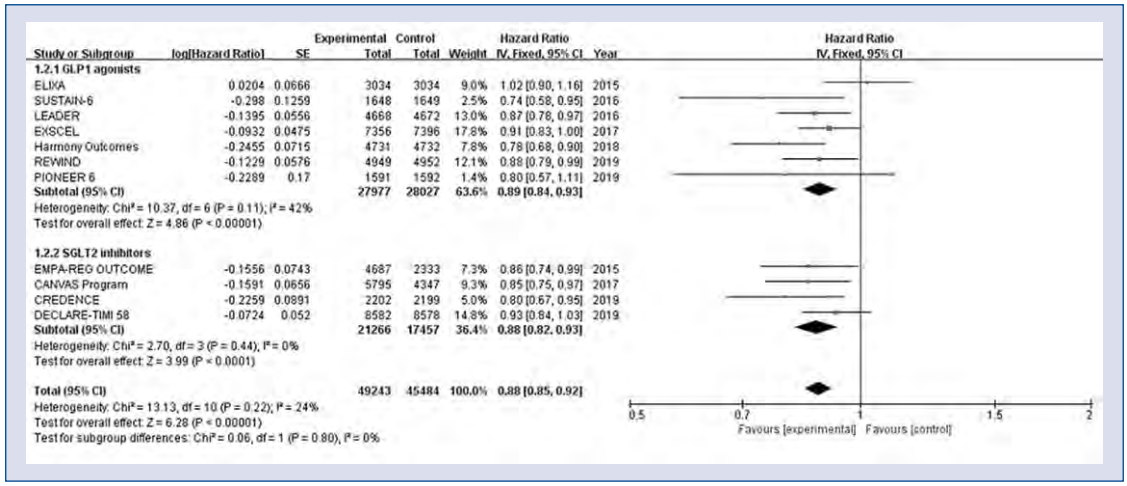


Figure 1. Hazard ratios for composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke stratified by classes of anti-diabetic agent; CI — confidence interval.

kidney injury compared with the conventional treatment (RR 0.75, 95% CI 0.62–0.89, p = 0.001).

Patients treated with GLP-1 agonists discontinued trial medication more frequently compared to conventionally treated patients because of serious side effects (RR 1.50, 95% CI 1.24–1.81, p < 0.001, Fig. 4), but SGLT-2 inhibitors did not increase the rates of withdrawal (RR 1.10, 95% CI 0.86–1.41, p = 0.44, Fig. 4).

Sensitivity analysis of different GLP-1 agonist studies

Stratified analysis according to the different GLP-1 agonists demonstrated significantly lower rates of the composite end point of cardiovascular death, non-fatal MI, or non-fatal stroke compared to the control group in the studies of human GLP-1 analogues (HR 0.84, 95% CI 0.79–0.90, p < 0.001), but not in studies using exendin-4 analogues (HR 0.95, 95% CI 0.88–1.02, p = 0.16, **Suppl. Fig. S3**). Human GLP-1 analogue was associated with significantly lower rates of non-fatal MI (HR 0.85, 95% CI 0.77–0.94, p = 0.001) and non-fatal stroke (HR 0.80, 95% CI 0.70–0.91, p < 0.001) than conventional regimen, whereas no significant differences were found in exendin-4 analogues group. Moreover, the risk of hospitalization for HF was significantly lower in the human GLP-1 analogues group as compared to the control group (HR 0.90, 95% CI 0.81–1.00, p = 0.005), but not in the exendin-4 analogues group (HR 0.94, 95% CI 0.82–1.07, p = 0.35).

Publication bias

Assessment of publication bias using RR of composite end point of cardiovascular death, non-fatal MI, or non-fatal stroke of the included studies showed a symmetric funnel plot with little evidence of publication bias.

Discussion

In this systematic review and meta-analysis of the 11 trials enrolling 94,727 patients with type 2 diabetes, both GLP-1 agonists and SGLT-2 inhibitors showed comparable efficacy in the reduction of composite end point of cardiovascular death, non-fatal MI, or non-fatal stroke as compared with the conventional antidiabetic treatment. There was also a comparably significant reduction in the respective risk of all-cause death, cardiovascular death and non-fatal MI in both groups. Also found was significantly lower risk of hospitalization for HF in both classes of experimental medications, especially more pronounced effect with SGLT-2 inhibitors than GLP-1 agonists. Regarding safety outcomes, it was found that the GLP-1 agonists did not increase risk of pancreatitis, pancreatic cancer, or retinopathy. The SGLT-2 inhibitors showed a tendency toward increased risk of genital infection, but did not increase urinary tract infection compared with control group. Risk of non-fatal stroke was significantly lower with the use of GLP-1 agonists, but not with the use of SGLT-2 inhibitors. However, discontinuation of trial medication due to serious side effects was more frequently observed in patients receiving GLP-1 agonists treatment.

There have been no randomized clinical trials that directly compared the efficacy of GLP-1 agonists and SGLT-2 inhibitors to improve cardiovascular outcomes. Despite limitations of observation-

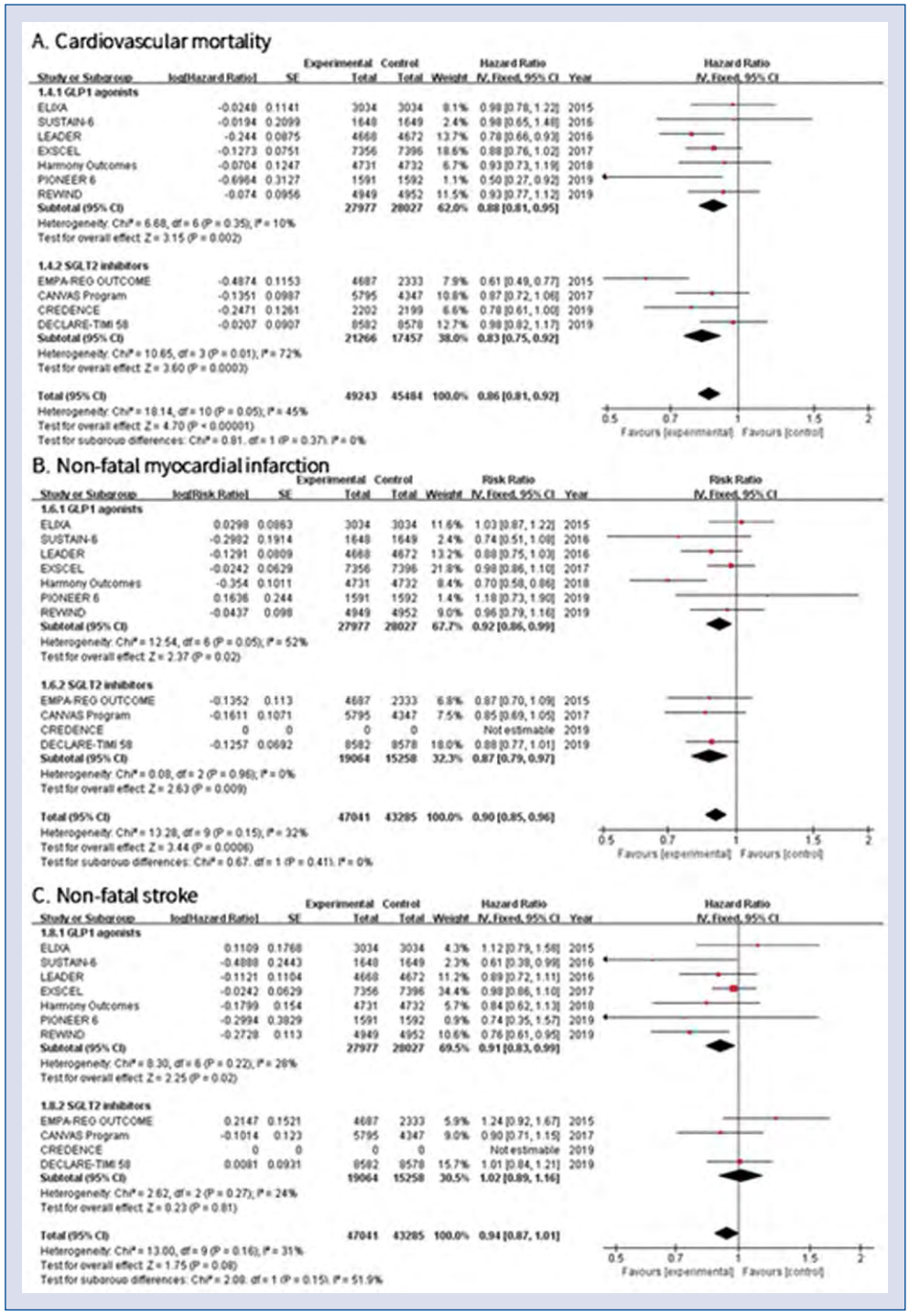


Figure 2. Hazard ratios stratified by classes of anti-diabetic agent; **A.** Cardiovascular mortality; **B.** Non-fatal myocardial infarction; **C.** Non-fatal stroke; CI — confidence interval.

al studies, the CVD-REAL study demonstrated that use of SGLT-2 inhibitors lowered all-cause mortality compared with other medications [26, 27]. In the EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) trial, which is a randomized, double-blind, placebo-controlled trial of 7,020 patients with type 2 diabetes, composite risk of MI, stroke, and cardiovascular death was significantly reduced with empagliflozin (HR 0.86, 95% CI 0.74–0.99) over a median follow-up of 3.1 years [17]. Cardiovascular death (HR 0.62, 95% CI 0.49–0.77)

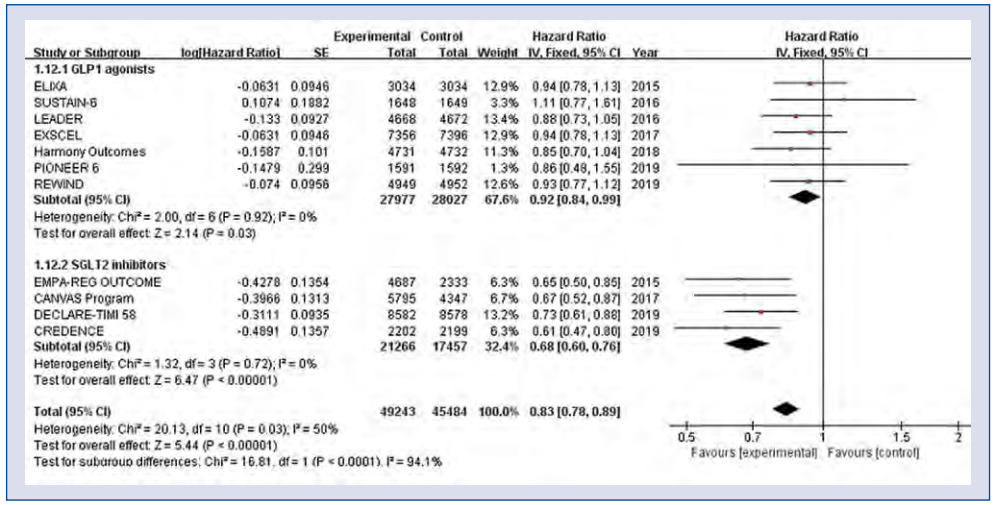


Figure 3. Hazard ratios for hospitalization for heart failure stratified by classes of anti-diabetic agent; CI — confidence interval.

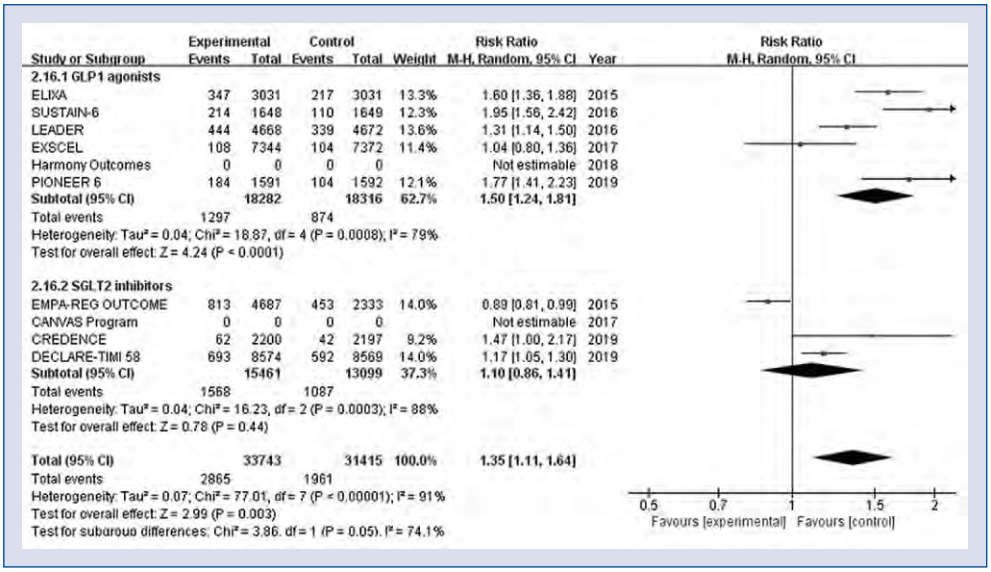


Figure 4. Hazard ratios for adverse events leading to discontinuation of study medication stratified by classes of anti-diabetic agent; CI — confidence interval.

and all-cause death were reduced in a similar magnitude (HR 0.68, 95% CI 0.57–0.82) and there was also significant reduction in hospitalization for HF in the empagliflozin group (HR 0.65, 95% CI 0.50–0.85). However, a reduction in hospitalizations for HF and cardiovascular death in the empagliflozin group was observed consistently across patients who have HF or did not have HF at baseline [28].

The mechanism of beneficial effects for HF of SGLT-2 inhibitors has not been definitely defined [29]. Recent studies of SGLT-2 inhibitors for prevention of cardiovascular and renal outcomes suggest that the renoprotective effects related with the natriuresis comprise a part of the reasons for the improvement in hospitalization for HF [30, 31]. The natriuresis induced by SGLT-2 inhibition is a stimulating factor for tubuloglomerular feedback, which, in turn causes afferent renal arteriolar vasoconstriction. After the vasoconstriction of afferent arterioles of the kidney, resultant intraglomerular pressure reduction is caused and reduced intraglomerular pressure provides a renoprotective effect [32]. Furthermore, renoprotective effects and

natriuresis are especially beneficial in patients with impaired renal function at baseline who have substantial risk for hospitalization for HF [29]. A 32% reduction in the risk of hospitalization for HF and a 25% reduction in the rates of acute kidney injury in the present study might explain the reduced risk of cardiovascular death. Ongoing trials are assessing cardioprotective effects of SGLT-2 inhibitors on hospitalization for HF in non-diabetic patients with HF as well as diabetic patients with HF [33].

In the present study, the SGLT-2 inhibitors were relatively well tolerated with lower incidence of serious adverse events compared with the GLP-1 agonists that were associated with higher risk of adverse events leading to withdrawal of the study drug. As previously reported [34], gastrointestinal side effects were reported as the main side effect by GLP-1 agonists leading to participant withdrawal of study drug in our analysis. We think that SGLT-2 inhibitors have an advantage over GLP-1 agonists in terms of lower rates of treatment discontinuation and this might help physicians to make a better treatment plan for diabetic patients who have failed to achieve their glycemic target with metformin monotherapy.

Two studies with exendin-4 analogues (exenatide and lixisenatide) did not reveal superiority over control regimen with respect to clinical outcomes [9, 13]. In our analysis, human GLP-1 analogues showed a greater effect on the composite end point of cardiovascular death, non-fatal MI, or non-fatal stroke compared to the control group but exendin-4 analogues did not. Differences in structure of GLP-1 agonists and subsequent different immunogenicity might be responsible for the better clinical outcomes in studies using human GLP-1 analogues than exendin-4 analogues [35]. Further studies are needed to elucidate how different molecular structure could affect diverse cardiovascular outcomes [36].

Limitations of the study

There are several limitations in this study. First, aggregated study-level data for meta-analysis was used instead of patient-level data. Therefore, a further subgroup-level study and quantified cumulative follow-up time for end point events and safety events could not be investigated. Second, all of the trial did not use exactly the same definition of events, inclusion and exclusion criteria. But most of the definitions of events are very similar to each other, there would not have been a significant difference in event discrimination and there was no significant statistical heterogeneity among the included studies for analyses. Third, most of the included studies showed median follow-up duration shorter than 4 years. Because risk factors for CVD is chronic diseases and some of side effects may occur later over time, there is a strong need for long-term follow-up. Fourth, this study lacks evidence for diabetic patients with low cardiovascular risk. Most of the included study targeted diabetic patients with established CVD or high-risk patients. Until now there is no definite treatment option about second-line antidiabetic agents improving cardiovascular outcomes for diabetic patients with low cardiovascular risk. Finally, this study is not a direct head-to-head study but compared SGLT-2 inhibitors with GLP-1 agonists indirectly. Despite being an indirectly comparative study, consistent results of efficacy and safety outcomes were found across most of the included studies. Furthermore, the results of this study add to a growing body of evidence in the literature aggregating individual studies that compared SGLT-2 inhibitors and GLP-1 agonist as second-line antidiabetic agents with conventional therapy.

Conclusions

Both GLP-1 agonists and SGLT-2 inhibitors showed comparable efficacy in reducing composite cardiovascular outcomes, mortality, and MI as compared to conventional antidiabetic medications in patients with type 2 diabetes. Safety analyses of the included studies revealed increased risk of genital infections by SGLT-2 inhibitors, and use of GLP-1 agonists were associated with a higher risk of adverse events leading to medication withdrawal.

Funding

This work was supported by 2019 Inje University Busan Paik Hospital research grant.

Conflict of interest: None declared

References

1. Campbell PT, Newton CC, Patel AV, et al. Diabetes and cause-specific mortality in a prospective cohort of one million U.S. adults. Diabetes Care. 2012; 35(9): 1835–1844, doi: 10.2337/dc12-0002, indexed in Pubmed: 22699290.
2. American Diabetes Association. 8. Pharmacologic Approaches to Glycemic Treatment:. Diabetes Care. 2018; 41(Suppl 1): S73–S85, doi: 10.2337/dc18-S008, indexed in Pubmed: 29222379.
3. Nesti L, Natali A. Metformin effects on the heart and the cardiovascular system: A review of experimental and clinical data. Nutr Metab Cardiovasc Dis. 2017; 27(8): 657–669, doi: 10.1016/j.numecd.2017.04.009, indexed in Pubmed: 28709719.

4. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm — 2018 Executive Summary. Endocr Pract. 2018; 24(1): 91–120, doi: 10.4158/CS-2017-0153, indexed in Pubmed: 29368965.
5. Liu J, Li L, Deng Ke, et al. Incretin based treatments and mortality in patients with type 2 diabetes: systematic review and meta-analysis. BMJ. 2017; 357: j2499, doi: 10.1136/bmj.j2499, indexed in Pubmed: 28596247.
6. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment:. Diabetes Care. 2019; 42(Suppl 1): S90––S102, doi: 10.2337/dc19-S009, indexed in Pubmed: 30559235.
7. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020; 41(2): 255–323, doi: 10.1093/eurheartj/ehz486, indexed in Pubmed: 31497854.
8. Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med. 2015; 373(1): 11–22, doi: 10.1056/NEJMoa1411892, indexed in Pubmed: 26132939.
9. Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2017; 377(13): 1228–1239, doi: 10.1056/NEJMoa1612917, indexed in Pubmed: 28910237.
10. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016; 375(19): 1834–1844, doi: 10.1056/NEJMoa1607141, indexed in Pubmed: 27633186.
11. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016; 375(4): 311–322, doi: 10.1056/NEJMoa1603827, indexed in Pubmed: 27295427.
12. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017; 377(7): 644–657, doi: 10.1056/NEJMoa1611925, indexed in Pubmed: 28605608.
13. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med. 2015; 373(23): 2247–2257, doi: 10.1056/NEJMoa1509225, indexed in Pubmed: 26630143.
14. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013; 369(14): 1317–1326, doi: 10.1056/NEJMoa1307684, indexed in Pubmed: 23992601.
15. White W, Kupfer S, Zannad F, et al. Cardiovascular mortality in patients with type 2 diabetes and recent acute coronary syndromes from the EXAMINE trial. Diabetes Care. 2016; 39(7): 1267–1273, doi: 10.2337/dc16-0303.
16. Zheng SL, Roddick AJ, Aghar-Jaffar R, et al. Association between use of sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with all-cause mortality in patients with type 2 diabetes: a systematic review and meta-analysis. JAMA. 2018; 319(15): 1580–1591, doi: 10.1001/jama.2018.3024, indexed in Pubmed: 29677303.
17. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015; 373(22): 2117–2128, doi: 10.1056/NEJMoa1504720, indexed in Pubmed: 26378978.
18. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011; 343: d5928, doi: 10.1136/bmj.d5928, indexed in Pubmed: 22008217.
19. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003; 327(7414): 557–560, doi: 10.1136/bmj.327.7414.557, indexed in Pubmed: 12958120.
20. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009; 339: b2700, doi: 10.1136/bmj.b2700, indexed in Pubmed: 19622552.
21. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019; 394(10193): 121–130, doi: 10.1016/S0140-6736(19)31149-3, indexed in Pubmed: 31189511.
22. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet. 2018; 392(10157): 1519–29.
23. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2019; 381(9): 841–851, doi: 10.1056/NEJMoa1901118, indexed in Pubmed: 31185157.
24. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019; 380(24): 2295–2306, doi: 10.1056/NEJMoa1811744, indexed in Pubmed: 30990260.
25. Wiviott S, Raz I, Bonaca M, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019; 380(4): 347–357, doi: 10.1056/nejmoa1812389.
26. Birkeland KI, Jørgensen ME, Carstensen B, et al. Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL Nordic): a multinational observational analysis. Lancet Diabetes Endocrinol. 2017; 5(9): 709–717, doi: 10.1016/S2213-8587(17)30258-9, indexed in Pubmed: 28781064.
27. Kosiborod M, Cavender MA, Fu AZ, et al. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study (comparative effectiveness of cardiovascular outcomes in new users of sodium-glucose cotransporter-2 inhibitors). Circulation. 2017; 136(3): 249–259, doi: 10.1161/CIRCULATIONAHA.117.029190, indexed in Pubmed: 28522450.
28. Fitchett D, Butler J, van de Borne P, et al. Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME® trial. Eur Heart J. 2018; 39(5): 363–370, doi: 10.1093/eurheartj/ehx511, indexed in Pubmed: 29020355.
29. Zelniker TA, Braunwald E. Cardiac and renal effects of sodium-glucose co-transporter 2 inhibitors in diabetes: JACC state-of-the-art review. J Am Coll Cardiol. 2018; 72(15): 1845–1855, doi: 10.1016/j.jacc.2018.06.040, indexed in Pubmed: 30075873.
30. Heerspink HJL, Perkins BA, Fitchett DH, et al. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. Circulation. 2016; 134(10): 752–772, doi:

10.1161/CIRCULATIONAHA.116.021887, indexed in Pubmed: 27470878.

31. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019; 393(10166): 31–39, doi: 10.1016/S0140-6736(18)32590-X, indexed in Pubmed: 30424892.
32. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia. 2018; 61(10): 2108–2117, doi: 10.1007/s00125-018-4670-7, indexed in Pubmed: 30132036.
33. Butler J, Hamo CE, Filippatos G, et al. The potential role and rationale for treatment of heart failure with sodium-glucose co-transporter 2 inhibitors. Eur J Heart Fail. 2017; 19(11): 1390–1400, doi: 10.1002/ejhf.933, indexed in Pubmed: 28836359.
34. Shyangdan DS, Royle P, Clar C, et al. Glucagon-like peptide analogues for type 2 diabetes mellitus: systematic review and meta-analysis. BMC Endocr Disord. 2010; 10(10): 20, doi: 10.1186/1472-6823-10-20, indexed in Pubmed: 21143938.
35. Madsbad S. Review of head-to-head comparisons of glucagon-like peptide-1 receptor agonists. Diabetes Obes Metab. 2016; 18(4): 317–332, doi: 10.1111/dom.12596, indexed in Pubmed: 26511102.
36. Uccellatore A, Genovese S, Dicembrini I, et al. Comparison review of short-acting and long-acting glucagon-like peptide-1 receptor agonists. Diabetes Ther. 2015; 6(3): 239–256, doi: 10.1007/s13300-015-0127-x, indexed in Pubmed: 26271795.

VIA MEDICA

RESEARCH LETTER

Cardiology Journal
2022, Vol. 29, No. 3, 509–510
DOI: 10.5603/CJ.a2021.0127

ISSN 1897–5593
eISSN 1898–018X

Peripartum cardiomyopathy incidence and mortality in Sweden

Gustav Mattsson[1], Peter Magnusson[1, 2, 3]

[1]Center for Research and Development, Uppsala University/Region Gävleborg, Gävle, Sweden
[2]Cardiology Research Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden
[3]Faculty of Health and Occupational Studies, Department of Caring Sciences, University of Gävle, Gävle, Sweden

Peripartum cardiomyopathy (PPCM) is a form of dilated cardiomyopathy with reduced ejection fraction that affects women late in pregnancy or the months following delivery [1]. It is a global disease with various geographical incidence and previously reported mortality across selected European centers was 4% at 6-month follow-up and higher in other continents [2, 3]. In the Danish population, the incidence of PPCM was 1:10 149 and at 1 year 3.3% had died [4]. The aim of this study was to examine long-term all-cause mortality in a Swedish nationwide cohort of patients with a history of PPCM.

This retrospective observational study included all patients who received the diagnosis of PPCM, International Classification of Diseases, tenth revision, (ICD-10) code O90.3, in The Swedish National Patient Register for both inpatient and outpatient specialist care episodes between 1997 and 2014 [5]. This was merged with data from the Swedish Cause of Death Register for the same time period. Data were described as frequencies, percentages, and means including standard deviations (±). The Kaplan-Meier estimator was used to describe survival. The cumulative incidence of death was calculated using time to death as the censoring event; otherwise, total time of follow-up was used for patients who were still alive. The software program SPSS version 25 (IBM, Armonk, NY) was used for analyses.

The sample consisted of 150 patients with the diagnosis of PPCM. The mean age at diagnosis was 34.6 ± 6.3 years and mean follow-up time 5.3 ± ± 4.29 years. Median year at the time of the diagnosis was 2010, with an interquartile range of 5 years. During the study period 5 (3.3%) patients died from any cause. Kaplan-Meier estimated cumulative incidence of death was at 1-year 2.1%, 3-years 3.2%, 5-years 3.2%, and at 10-years 5.5%. Figure 1 shows a Kaplan-Meier plot of estimated cumulative survival. Out of the 5 deaths, the main cause of death was cardiovascular disease in 4 cases and infectious disease in 1 case.

The National Board of Health and Welfare of Sweden provides data regarding the number of deliveries for the year 1997 up until 2014 [6]. Using these data the incidence of PPCM could be calculated for each year (Fig. 2). There was an increasing incidence of PPCM per 100,000 deliveries during the study period, ranging from 1.2 in 1997 up to 22.5 in 2012, likely in part due to improved diagnostics and use of the ICD-10 code. In the Danish registry-based study the incidence was 1 in every 10,149 deliveries during the period 2005–2014 [4], the incidence in Sweden for the same period was 1 in every 11,014 deliveries.

The long-term prognosis of PPCM in the Swedish setting is good. Nevertheless, PPCM is a potentially life-threatening condition that requires careful attention in each individual case.

Conflict of interest: Gustav Mattsson has received speaker fee from Alnylam, Internetmedicin, and MSD; Peter Magnusson received speaker fees or grants from Abbott, Alnylam, Amicus Therapeutics, Bayer, AstraZeneca, BMS, Boehringer-Ingelheim, Coala Life, Internetmedicin, Lilly, MSD, Novo Nordisk, Octopus Medical, Pfizer, Vifor Pharma, and Zoll. No external financial support or funding was received for this study.

Address for correspondence: Gustav Mattsson, MD, Center for Research and Development, Uppsala University/Region Gävleborg, Gävle, SE-801 87, Sweden, tel: +46(0)703122296, e-mail: gustav.mattsson@regiongavleborg.se

Received: 20.04.2021 Accepted: 29.05.2021 Early publication date: 8.10.2021

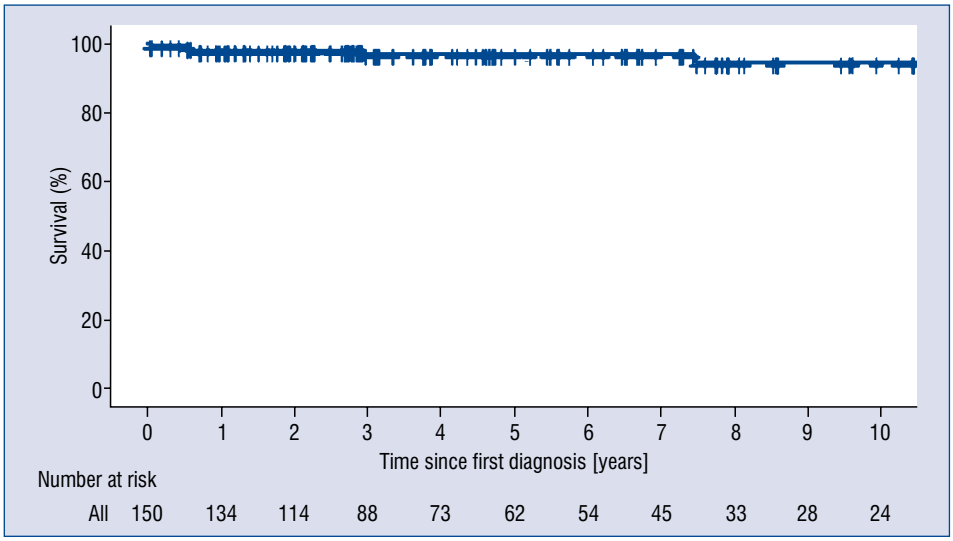


Figure 1. Kaplan-Meier estimate of cumulative survival for 150 patients with peripartum cardiomyopathy.

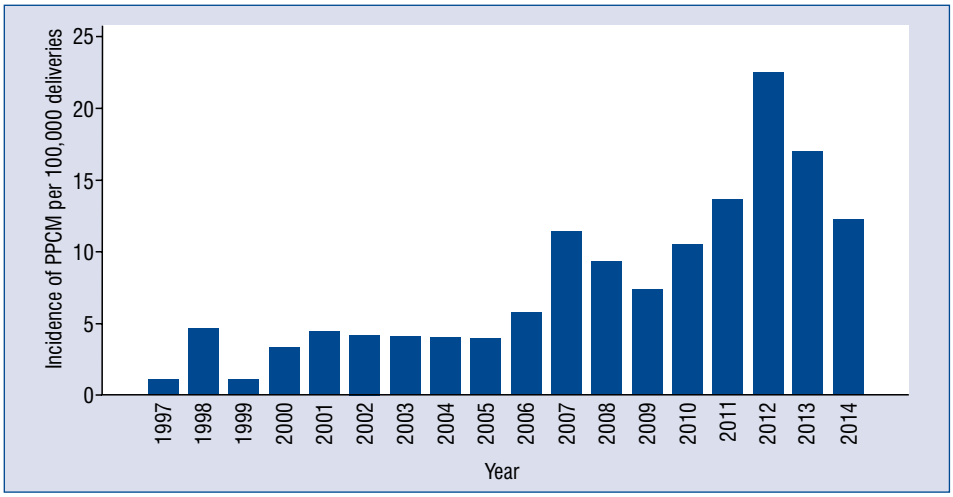


Figure 2. Incidence of peripartum cardiomyopathy (PPCM) diagnosis per 100,000 deliveries in Sweden for the years 1997–2014.

References

1. Bauersachs J, König T, van der Meer P, et al. Pathophysiology, diagnosis and management of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Study Group on peripartum cardiomyopathy. Eur J Heart Fail. 2019; 21(7): 827–843, doi: 10.1002/ejhf.1493, indexed in Pubmed: 31243866.
2. Van Veldhuisen DJ, McMurray JJV, Bauersachs J. Clinical presentation, management, and 6-month outcomes in women with peripartum cardiomyopathy: an ESC EORP registry. Eur Heart J. 2020; 41(39): 3787–3797, doi: 10.1093/eurheartj/ehaa455, indexed in Pubmed: 32840318.
3. Sliwa K, Petrie MC, Hilfiker-Kleiner D, et al. Long-term prognosis, subsequent pregnancy, contraception and overall management of peripartum cardiomyopathy: practical guidance paper from the Heart Failure Association of the European Society of Cardiology Study Group on Peripartum Cardiomyopathy. Eur J Heart Fail. 2018; 20(6): 951–962, doi: 10.1002/ejhf.1178, indexed in Pubmed: 29578284.
4. Ersbøll AS, Johansen M, Damm P, et al. Peripartum cardiomyopathy in Denmark: a retrospective, population-based study of incidence, management and outcome. Eur J Heart Fail. 2017; 19(12): 1712–1720, doi: 10.1002/ejhf.882, indexed in Pubmed: 28597481.
5. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011; 11: 450, doi: 10.1186/1471-2458-11-450, indexed in Pubmed: 21658213.
6. The National Board of Health and Welfare. Retrieved on the 26 of May 2021. https://www.socialstyrelsen.se/statistik-och-data/statistik/statistikdatabasen/.

VIA MEDICA

RESEARCH LETTER

Cardiology Journal
2022, Vol. 29, No. 3, 511–513
DOI: 10.5603/CJ.a2021.0153

ISSN 1897–5593
eISSN 1898–018X

Infective endocarditis on transcatheter aortic prosthesis: Are there differences with endocarditis on surgically implanted aortic bioprosthesis?

Consuelo Fernández-Avilés[1], Juan C. Castillo[1, 2], Gloria Heredia[1], Adriana Resúa[1], Rafael González, Manuel Pan[1, 2], Manuel Anguita[1, 2]

[1]Department of Cardiology, University Hospital Reina Sofía, Córdoba, Spain
[2]Biomedical Investigation Maimónides Institute (IMIBIC), University of Córdoba, Córdoba, Spain

Transcatheter aortic valve implantation (TAVI) has been a major advance in the treatment of aortic stenosis in elderly patients or those at very high surgical risk, and its indication has been extended to cases of high or even intermediate risk. For this reason, its use has increased notably in the past years [1]. One of the problems associated with TAVI is bioprosthesis infection [2]. The development of infective endocarditis (IE) on TAVI (IETAVI) is a serious complication, with the added problem that in many cases open-heart surgery is necessary to manage it. In patients at high baseline surgical risk, surgery may be contraindicated, or, in any case, the presence of the supporting stent makes the surgical procedure more complex. Some studies have analyzed the incidence of IETAVI, both in Spain [2, 3] and in other countries [4–6]. They all agree on an annual incidence of approximately 1.4–1.6% and high mortality, ranging from 41.8% in the Swedish registry of Bjursten et al. [6] to 47.2% in the Spanish multicenter study by Amat-Santos et al. [3]. They also agree with regard to a high mean age of around 80 years, greater comorbidity (higher incidence of renal failure, previous cancer, higher Charlson index, etc.), and the finding of *enterococci*, *Staphylococcus aureus* and coagulase-negative *staphylococci* as the most frequent microorganisms involved [2–6].

An aspect that has not been well studied yet is the possible difference between IETAVI and IE on surgical aortic valve replacement (IESAVR). Three multicenter registries carried out in different countries (USA, France and Sweden) [4–6] found a similar incidence of IE in both groups, but there is a lack of studies that had compared clinical features, treatment and mortality between these two types of IE. Only 1 French study, using an administrative database, has compared mortality between IETAVI and IESAVR, but without differentiating between biological and mechanical prostheses [5], finding no differences between them. Therefore, given the scarcity of data on this subject, the objective herein, was to evaluate the incidence and characteristics of IE on TAVI, as well as its comparison with biological IESAVR in our hospital, a center of reference for cardiac surgery and invasive cardiology in Spain. For this purpose, two cohorts of patients were analyzed, including all cases of TAVI (n = 520) and biological SAVR (n = 652) consecutively implanted in our center between 2012 and 2020, and the incidence of IE is compared in both cohorts, their clinical characteristics, treatment and early in-hospital mortality. Non-parametric tests were used for comparisons (the Pearson exact test for dichotomous variables and the Mann-Whitney test for continuous variables). Continuous variables were expressed as median (interquartile range).

The incidence of IE in the TAVI group (n = 9) and in the SAVR group (n = 11) was similar (1.56% in the TAVI group and 1.68% in the surgical group). Age showed a trend to be higher in the IETAVI group: 81 (78–82) vs. 72 (70–79) years (p = 0.18).

Address for correspondence: Dr. Manuel Anguita, Menéndez Pidal Av, 1. 14004 Córdoba, Spain, tel/fax: 669635412, e-mail: manuelanguita@secardiologia.es

Received: 27.09.2021 Accepted: 28.10.2021 Early publication date: 15.11.2021

Table 1. Characteristics, treatment and early mortality of infective endocarditis in the overall series and in the two cohorts of patients.

	Overall series (n = 20)	IETAVI (n = 9)	IESAVR (n = 11)	P
Age [years]*	78 (72–81)	81 (78–82)	72 (70–79)	0.17
Female gender	6 (30%)	4 (44.4%)	2 (18.2%)	0.33
Early infective endocarditis	10 (55%)	6 (75%)	5 (45.5%)	0.18
Causal microorganism:				0.65
Staphylococcus aureus	1 (5%)	1 (11.1%)	0 (0%)	
Coagulase-negative Staphylococcus	6 (30%)	3 (33.3%)	3 (27.3%)	
Enterococcus	7 (35%)	2 (22.2%)	5 (45.5%)	
Streptococcus viridans	3 (15%)	1 (22.2%)	2 (18.2%)	
Not identified	3 (15%)	2 (22.2%)	1 (9.1%)	
Comorbidity and frailty indexes:				
Charlson index*	4 (2–7)	6 (4–7)	3 (2–5)	0.04
Frail index*	3 (2–4)	3 (3–4)	2 (2–3)	0.28
Complications:				
Any severe complication	19 (95%)	9 (100%)	10 (90.9%)	1
Heart failure	14 (70%)	6 (66.6%)	8 (72.7%)	1
Renal failure	7 (35%)	4 (44.4%)	3 (27.3%)	0.64
Persistent infection	13 (65%)	6 (66.6%)	7 (63.6%)	1
Prosthetic dysfunction	9 (45%)	3 (33.3%)	6 (54.5%)	0.64
Surgical indication:	13 (65%)	5 (55.5%)	8 (72.7%)	0.64
Operated	8 (62.5%)	2 (40%)	6 (75%)	0.23
Not operated	5 (38.5%)	3 (60%)	2 (25%)	
Type of surgery (on operated cases):				0.37
Emergent/urgent	3 (37.5%)	1 (50%)	2 (33.3%)	
Elective	5 (62.5%)	1 (50%)	4 (66.6%)	
In-hospital death	8 (40%)	4 (44.4%)	4 (36.4%)	1

*Median (interquartile range); IETAVI — infective endocarditis on transaortic valve implantation; IESAVR — infective endocarditis on surgical aortic valve replacement

Frailty, measured by the Frail scale, was similar in both groups: 3 (3–4) vs. 2 (2–3) (p = 0.28). Comorbidity, measured by the Charlson index, was significantly higher in the EITAVI group: 6 (4–7) vs. 3 (2–5) (p = 0.04). There was a slight predominance of women and of early prosthetic IE in the TAVI group (Table 1). There were no differences between the two groups regarding causal microorganisms (Table 1), being the most frequent coagulase-negative *staphylococci* in IETAVI, 37.8% of the total, and *enterococci* in IESAVR, 45.5% (p = 0.65). The incidence of severe complications was very high, although similar in both groups (TAVI 88.9%, SAVR 90.9%), as was the incidence of the different specific complications, as shown in Table 1. Regarding treatment, there was an indication for surgery, in accordance with the clinical practice guidelines of the European Society of Cardiology, in the same proportion of patients: 62.5% of the IETAVI group and 72.7% of the IESAVR group (p = 0.64). However, 5 of the 13 patients (38.5%) with an indication for surgery did not undergo surgery due to contraindications or very high surgical risk, and this proportion of patients who did not undergo surgery was numerically higher in the IETAVI group, 60% vs. 25% of the IESAVRs (p = 0.234). In operated cases, the proportion of emergent/urgent and elective indications was similar in both groups (Table 1). Early in-hospital mortality within the active phase of the disease was high (40% in the overall series), but was similar in both groups (44.4% in IETAVI and 36.4% in IESAVR; Table 1). All deaths were related to endocarditis, except 1 of the 4 in the TAVI group, that was due to pneumonia.

From the data in the present series, with the limitation of a small sample size, inherent to the low frequency of this type of IE and the single-center nature of the study, it can be concluded that the incidence of IE on TAVI is infrequent and similar to that of surgical bioprosthetic IE, and that, despite a worse risk profile (older age, comorbidity, earlier prosthetic IE, and less surgery performed in indicated cases), the incidence of serious complications and their mortality are similar. This reinforces using TAVI as an aortic valve substitution therapy in elderly or high-risk patients.

Conflict of interest: None declared

References

1. Leon MB, Smith CR, Mack MJ. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Eng J Med. 2016; 374(17): 1609–1620, doi: 10.1056/NEJMoa1514616, indexed in Pubmed: 27040324.
2. Martínez-Sellés M, Bouza E, Díez-Villanueva P, et al. GAMES study group. Incidence and clinical impact of infective endocarditis after transcatheter aortic valve implantation. EuroIntervention. 2016; 11(10): 1180–1187, doi: 10.4244/EIJY15M02_05, indexed in Pubmed: 25671426.
3. Amat-Santos IJ, Messika-Zeitoun D, Eltchaninoff H, et al. Infective endocarditis after transcatheter aortic valve implantation: results from a large multicenter registry. Circulation. 2015; 131(18): 1566–1574, doi: 10.1161/CIRCULATIONAHA.114.014089, indexed in Pubmed: 25753535.
4. Butt JH, Ihlemann N, De Backer O, et al. Long-Term risk of infective endocarditis after transcatheter aortic valve replacement. J Am Coll Cardiol. 2019; 73(13): 1646–1655, doi: 10.1016/j.jacc.2018.12.078, indexed in Pubmed: 30947917.
5. Fauchier L, Bisson A, Herbert J, et al. Incidence and outcomes of infective endocarditis after transcatheter aortic valve implantation versus surgical aortic valve replacement. Clin Microbiol Infect. 2020; 26(10): 1368–1374, doi: 10.1016/j.cmi.2020.01.036, indexed in Pubmed: 32036047.
6. Bjursten H, Rasmussen M, Nozohoor S, et al. Infective endocarditis after transcatheter aortic valve implantation: a nationwide study. Eur Heart J. 2019; 40(39): 3263–3269, doi: 10.1093/eurheartj/ehz588, indexed in Pubmed: 31433472.

VIA MEDICA

RESEARCH LETTER

Cardiology Journal
2022, Vol. 29, No. 3, 514–516
DOI: 10.5603/CJ.a2021.0157

ISSN 1897–5593
eISSN 1898–018X

The novel *TRPM4* c.448G>T variant is associated with familial conduction disorders, cardiomyopathy, and sudden cardiac death

Boldizsar Kovacs[1]*, Stephan Winnik[1]*, Argelia Medeiros-Domingo[2], Sarah Costa[1], Guan Fu[1], Saskia Biskup[3], Frank Ruschitzka[1], Andreas J. Flammer[1], Felix C. Tanner[1], Firat Duru[1, 4], Ardan M. Saguner[1]

[1]Department of Cardiology, University Heart Center, University Hospital Zurich, Switzerland
[2]Swiss DNAlysis, Dubendorf, Switzerland
[3]Praxis für Humangenetik, Tübingen, Germany & CeGaT GmbH, Tübingen, Germany
[4]Center for Integrative Human Physiology, University of Zurich, Switzerland

Dilated cardiomyopathy (DCM) is a common cause of heart failure, which may be associated with electrical conduction disturbances and life-threatening arrhythmias. Its etiology is reported to be genetic in up to 65% of cases. Transient receptor melastatin 4 channel (*TRPM4*) is a Ca^{2+}-activated transmembrane non-selective cation channel. *TRPM4* contributes to the depolarization of excitable cells in the myocardium by changing the frequency and duration of action potentials by influencing the Ca^{2+} influx [1]. Genetic variants in *TRPM4* have been linked to inheritable conduction diseases (congenital atrioventricular node block and right bundle branch block) and Brugada syndrome, suggesting that this ion-channel may play a role in electrical propagation [2]. Furthermore, an association with systemic arterial hypertension and left ventricular hypertrophy has been described in animal models [3, 4]. A recent study has also reported a *TRPM4* variant to be associated with DCM [5].

We herein describe a family with a novel, likely pathogenic, heterozygous variant (class IV) in the *TRPM4* gene presenting with conduction disorders, DCM, and sudden cardiac death (SCD).

A 40-year-old Caucasian male was admitted to our department due to progressive malaise and exertional dyspnea. He was diagnosed to have congestive heart failure (New York Heart Association [NYHA] III). Twelve-lead electrocardiogram (ECG) showed a complete left bundle branch block (LBBB) (Fig. 1, upper left panel), and transthoracic echocardiography revealed a severely dilated left ventricular (LV) end-diastolic volume index of 110 mL/m^2, normal LV wall thickness (7 mm), and severely reduced LV ejection fraction (17%). Cardiac magnetic-resonance (CMR) imaging excluded ischemic heart disease but revealed septal edema (T2-weighted imaging showing hyperintensity; Fig. 1, upper middle panel). Serum high-sensitivity troponin assays and C-reactive protein levels were normal. Cardiac 18-FDG PET-CT scanning excluded active myocarditis and cardiac sarcoidosis. Further work-up was unremarkable, and the diagnosis of DCM was established.

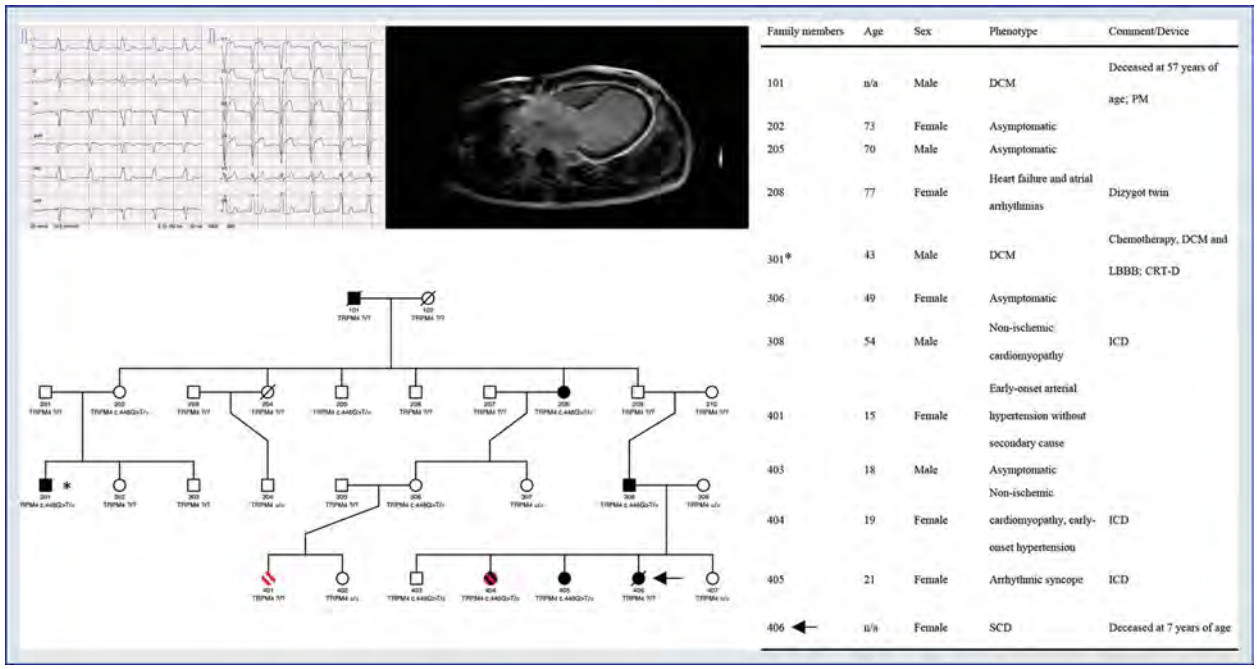
The patient had a past medical history of Hodgkin's lymphoma, for which he received 6 cycles of chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine 7 months prior. Cumulative dose of doxorubicin was 600 mg (300 mg/m^2). A 12-lead ECG prior to initiation of chemotherapy had already shown a complete LBBB, but the patient reported no signs of congestive heart failure.

The family history was remarkable. The daughter of a first-degree male cousin had suffered SCD at the age of 7 years. Autopsy findings revealed

Address for correspondence: PD Dr. Ardan M. Saguner, Department of Cardiology, University Heart Center Zurich, Rämistrasse 100, CH-8091, Zurich, Switzerland, tel: +41 44 2551111, e-mail: ardansaguner@yahoo.de

Received: 29.04.2021 Accepted: 20.11.2021 Early publication date: 1.12.2021

**Shared authorship*



Family members	Age	Sex	Phenotype	Comment/Device
101	n/a	Male	DCM	Deceased at 57 years of age; PM
202	73	Female	Asymptomatic	
205	70	Male	Asymptomatic	
208	77	Female	Heart failure and atrial arrhythmias	Dizygot twin
301*	43	Male	DCM	Chemotherapy, DCM and LBBB; CRT-D
306	49	Female	Asymptomatic	
308	54	Male	Non-ischemic cardiomyopathy	ICD
401	15	Female	Early-onset arterial hypertension without secondary cause	
403	18	Male	Asymptomatic	
404	19	Female	Non-ischemic cardiomyopathy, early-onset hypertension	ICD
405	21	Female	Arrhythmic syncope	ICD
406 ←	n/a	Female	SCD	Deceased at 7 years of age

Figure 1. Top left panel showing electrocardiogram of presented patient with a left bundle-branch block (LBBB). Top central panel showing a cardiac magnetic resonance imaging and a four-chamber view with a dilated left ventricle. Bottom left panel showing the family tree of the presented patients. Asterisk marks the presented patient; arrow marks the index patient. Black filled circles and boxes present patients with a cardiac phenotype; red diagonal lines in circles present patients with early-onset hypertension. Genotype is shown below the respective circles and boxes. Equal sign indicating wild type. Right panel showing description of genotypically positive family members; DCM — dilated cardiomyopathy; CRT-D — cardiac resynchronization therapy plus defibrillator; ICD — implantable cardioverter-defibrillator; PM — pacemaker; SCD — sudden cardiac death.

the presence of DCM. Molecular autopsy was refused by her parents. Genetic testing was performed in her sister at the age of 17 years following a syncopal episode and suspected hypertrophic cardiomyopathy. Next-generation sequencing, which covered a cardiomyopathy panel of 31 genes using the HiSeq2500 Illumina system (ACTC1, ACTN2, ANKRD1, CALR3, CAV3, CSRP3, FHL1, GLA, JPH2, LAMP2, LDB3, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYLK2, MYOZ2, MYPN, NEXN, PLN, PRKAG2, TCAP, TNNC1, TNNI3, TNNT2, TPM1, TTN, TTR, VCL, and TRPM4), revealed a novel heterozygous variant in the *TRPM4* gene (c.448G>T; p.Gly150* — transcript: NM_017636.3), classified as likely pathogenic (class IV) according to the 2015 American College of Medical Genetics Criteria [6]. Although most of the variants in the *TRPM4* gene lead to channel gain of function, there are some loss of function missense variants reported that are associated with cardiovascular disease [7, 8]. This nonsense mutation leads to a premature stop codon, but the variant affects the last nucleotide in exon 4 and is predicted to cause the loss of the neighboring splice donor site (SpliceAI score 0.878) [9]. Both aberrant splicing and the stop mutation likely lead to nonsense-mediated mRNA-decay. Cascade screening revealed several relatives with conduction disease, atrial arrhythmias, or SCD in this family (Fig. 1, lower left and right panels), and this *TRPM4* variant co-segregated with the phenotype in this family, suggesting a Mendelian autosomal-dominant inheritance with variable penetrance. Based on these criteria, the pathogenicity of this variant is likely. Of note, a variable phenotypic expression and incomplete penetrance is a well-known entity in inherited cardiomyopathies, which likely explains the findings in this family.

The same heterozygous variant in *TRPM4* was confirmed in our patient by genetic cascade screening. We must consider that chemotherapy for lymphoma may have contributed to the DCM phenotype in this patient. Doxorubicin therapy may frequently lead to toxic cardiomyopathy in a dose-dependent manner. Nevertheless, this patient had a preexisting LBBB, suggesting the

presence of a prior heart condition. Unfortunately, cardiac imaging had not been performed prior to initiation of chemotherapy.

It is possible that cardiotoxic chemotherapy could act as a second hit in our patient, who has a genetic predisposition for DCM. Garcia-Pavia et al. [10] investigated a patient cohort with a history of chemotherapy-induced cardiomyopathy. After genotyping 213 patients who underwent chemotherapy predominantly with anthracyclines, they found a significantly higher rate of titin (*TTN*) truncating variants in patients with cardiomyopathy as compared to those without cardiomyopathy. This finding may suggest a genetic predisposition to develop chemotherapy-induced cardiomyopathy.

A limitation to our finding is the lack of functional studies that would support the pathogenicity of the described variant.

In conclusion, we describe a novel, likely pathogenic, heterozygous variant in the *TRPM4* gene affecting a family over 4 generations being associated with a phenotype of conduction disease, atrial arrhythmias, DCM, and SCD.

Acknowledgments

We would like to thank Robert Manka from the Department of Radiology, University Hospital Zurich, Switzerland for providing the cardiac magnetic resonance images of the described patient.

Conflict of interest: Stephan Winnik reports educational grant support and/or travel support and/or consulting/speaker fees from Servier, Daichi-Sankyo, Boehringer-Ingelheim, Abbott, Bayer, Fehling Instruments, Cardinal Health, and Boston-Scientific, all not relevant to this article. Andreas J. Flammer reports fees from Alnylam, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Fresenius, Medtronic, MSD, Mundipharma, Novartis, Pfizer, Pierre Fabre, Roche, Vifor, and Zoll, all not relevant to this article. Firat Duru and Ardan M. Saguner received educational grants through their institution from Abbott, Bayer Healthcare, Biosense Webster, Biotronik, Boston Scientific, BMS/Pfizer, Zoll, and Medtronic. Ardan M. Saguner received speaker fees from Bayer Healthcare, BMS/Pfizer, and Daichi-Sankyo. He received educational grants through his institution from Abbott, Biosense Webster, Biotronik, Boston Scientific, and Medtronic. Boldizsar Kovacs, Sarah Costa, Saskia Biskup, Guan Fu, Felix C. Tanner, Argelia Medeiros-Domingo, and Frank Ruschitzka: None declared.

References

1. Launay P, Fleig A, Perraud AL, et al. TRPM4 is a Ca2+-activated nonselective cation channel mediating cell membrane depolarization. Cell. 2002; 109(3): 397–407, doi: 10.1016/s0092-8674(02)00719-5, indexed in Pubmed: 12015988.
2. Stallmeyer B, Zumhagen S, Denjoy I, et al. Mutational spectrum in the Ca(2+)-activated cation channel gene TRPM4 in patients with cardiac conductance disturbances. Hum Mutat. 2012; 33(1): 109–117, doi: 10.1002/humu.21599, indexed in Pubmed: 21887725.
3. Mathar I, Vennekens R, Meissner M, et al. Increased catecholamine secretion contributes to hypertension in TRPM4-deficient mice. J Clin Invest. 2010; 120(9): 3267–3279, doi: 10.1172/JCI41348, indexed in Pubmed: 20679729.
4. Demion M, Thireau J, Gueffier M, et al. Trpm4 gene invalidation leads to cardiac hypertrophy and electrophysiological alterations. PLoS One. 2014; 9(12): e115256, doi: 10.1371/journal.pone.0115256, indexed in Pubmed: 25531103.
5. Forleo C, D'Erchia AM, Sorrentino S, et al. Targeted next-generation sequencing detects novel gene-phenotype associations and expands the mutational spectrum in cardiomyopathies. PLoS One. 2017; 12(7): e0181842, doi: 10.1371/journal.pone.0181842, indexed in Pubmed: 28750076.
6. Richards S, Aziz N, Bale S, et al. ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015; 17(5): 405–424, doi: 10.1038/gim.2015.30, indexed in Pubmed: 25741868.
7. Syam N, Chatel S, Ozhathil LC, et al. Variants of transient receptor potential melastatin member 4 in childhood atrioventricular block. J Am Heart Assoc. 2016; 5(5), doi: 10.1161/JAHA.114.001625, indexed in Pubmed: 27207958.
8. Xian W, Hui X, Tian Q, et al. Aberrant deactivation-induced gain of function in TRPM4 mutant is associated with human cardiac conduction block. Cell Rep. 2018; 24(3): 724–731, doi: 10.1016/j.celrep.2018.06.034, indexed in Pubmed: 30021168.
9. Jaganathan K, Kyriazopoulou Panagiotopoulou S, McRae JF, et al. Predicting splicing from primary sequence with deep learning. Cell. 2019; 176(3): 535–548.e24, doi: 10.1016/j.cell.2018.12.015, indexed in Pubmed: 30661751.
10. Garcia-Pavia P, Kim Y, Restrepo-Cordoba MA, et al. Genetic variants associated with cancer therapy-induced cardiomyopathy. Circulation. 2019; 140(1): 31–41, doi: 10.1161/CIRCULATIONAHA.118.037934, indexed in Pubmed: 30987448.

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

Cardiology Journal
2022, Vol. 29, No. 3, 517–518
DOI: 10.5603/CJ.2022.0037

ISSN 1897–5593
eISSN 1898–018X

Left atrial dissection due to massive atrioventricular separation following a redo mitral valve replacement

Ziming Zhang[1, 2]*, Yuman Li[1, 2]*, Li Zhang[1, 2], Mingxing Xie[1, 2]

[1]Department of Ultrasound Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[2]Hubei Province Key Laboratory of Molecular Imaging, Wuhan, China

A 55-year-old man with severe mitral valve regurgitation was admitted to our hospital and was scheduled for mitral valve replacement (MVR). He had undergone a Bentall surgery 3 years earlier due to aortic dissection. MVR with mechanical prosthetic valve was performed. Three days after surgery, hemoglobinuria was noticed. Bedside transthoracic echocardiography (TTE) showed a severe peri-prosthetic mitral leak and an emergency surgery of a redo MVR with mechanical prosthetic valve was performed. Post-bypass transesophageal echocardiography confirmed prosthetic valve with normal function. On postoperative day 5, acute hemodynamic deterioration occurred. His oxygen saturation was 88%, blood pressure was 85/43 mmHg. Bedside TTE revealed a severe atrioventricular disruption causing left atrial (LA) dissection (Fig. 1A, **Suppl. Video 1**). There was a markedly rocking motion of the mechanical mitral valve. Color flow Doppler imaging showed that the dissected cavity directly communicated with left ventricle via a massive atrioventricular separation, through which it received blood during left ventricular systole. In addition, the dissected cavity also communicated with the true left atrium through a 9-mm defect (Fig. 1B). With the use of a three-dimensional TTE, the dissected LA wall was displayed intuitively and the extent of atrioventricular separation was more readily appreciated (Fig. 1C, D). Patient died due to low cardiac output on the 6th day after surgery.

Left atrial dissection is an extremely rare complication after mitral valve surgery with an incidence of 0.84%. We report a rare case of LA dissection due to severe atrioventricular separation after a redo MVR.

Funding: The study was supported by National Key R&D Program of China (Grant Nos. 2018YFC0-114600) and the National Natural Science Foundation of China (Grant Nos. 81727805, 81922033, 81401432), the Key Research and Development Program of Hubei (Grant Nos. 2020DCD015, 2021BCA138).

Conflict of interest: None declared

Address for correspondence: Mingxing Xie, MD, PhD, Department of Ultrasound Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Avenue, Wuhan 430022, China, tel: 86-27-85726430, fax: 86-27-85726386, e-mail: xiemx@hust.edu.cn

Received: 12.07.2021 Accepted: 8.08.2021

**These authors contributed equally to this manuscript.*

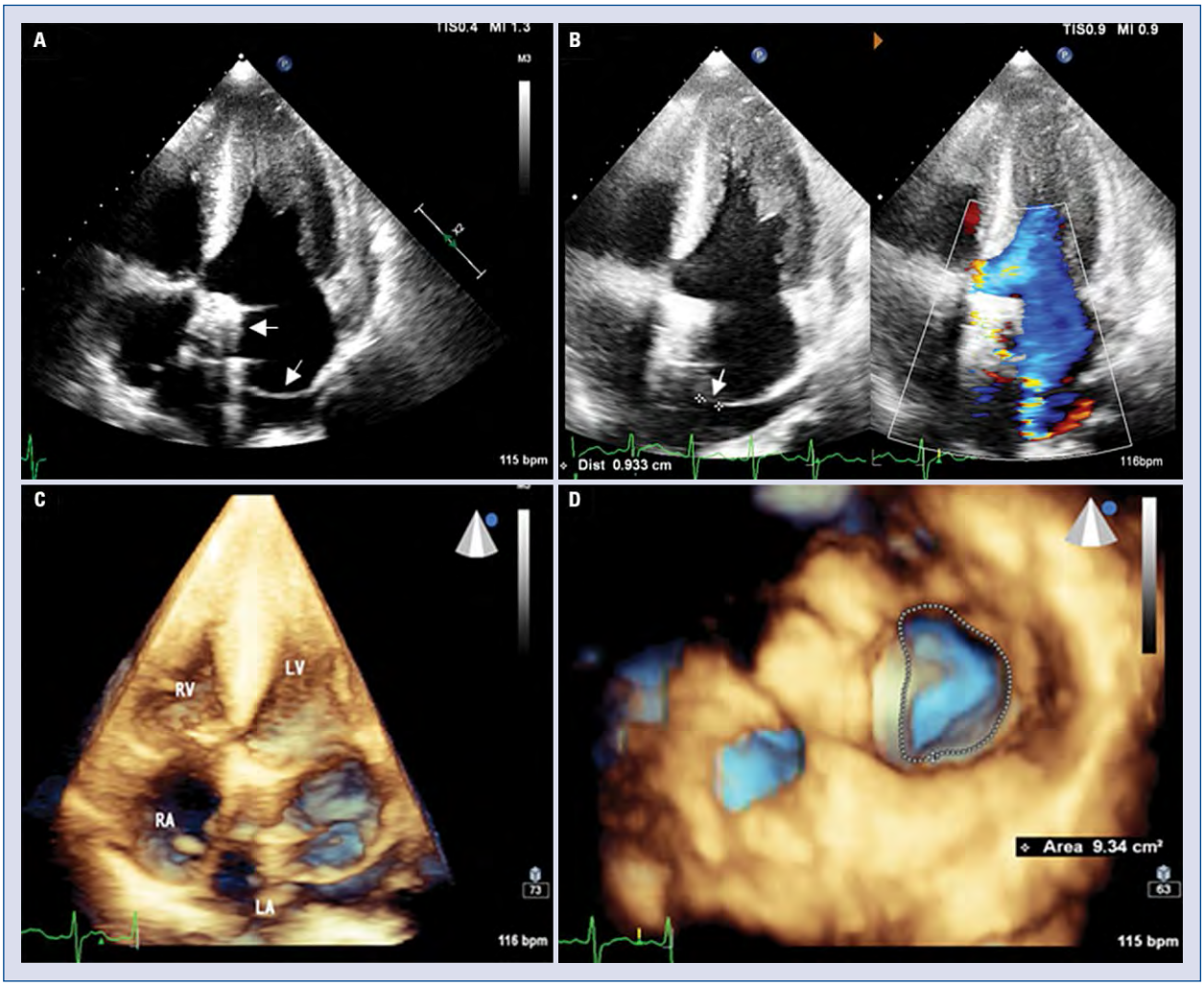


Figure 1. A. Bedside transthoracic echocardiography (TTE) revealing a severe atrioventricular disruption and left atrial dissection (arrows) in the apical 4-chamber view; **B.** Color Doppler imaging shows that the dissected cavity directly communicated with left ventricle via a massive atrioventricular separation. The dissected cavity also communicated with true left atrium through a 9-mm defect (arrow); **C.** Three-dimensional TTE intuitively displaying the dissected left atrium wall; **D.** Three-dimensional TTE from the left ventricular perspective showing the extent of atrioventricular separation (9.3 cm^2); LA — left atrium; LV — left ventricle; RA — right atrium; RV — right ventricle.

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

Cardiology Journal
2022, Vol. 29, No. 3, 519–520
DOI: 10.5603/CJ.2022.0038

ISSN 1897–5593
eISSN 1898–018X

Surgical electrocautery and balloon atrial septostomy facilitated MitraClip in ring

Alexandru I. Patrascu[1], Donat Binder[1], Marco Goldbach[2], Ilka Ott[1]

[1]Department of Cardiology, Helios Klinikum, Pforzheim, Germany
[2]Abbott Medical, Wiesbaden, Germany

An 81-year-old patient, who had undergone mitral valve annuloplasty 1 year prior, was admitted with pulmonary edema, attributed to residual high-grade mitral valve regurgitation (MR) (Fig. 1A, B). Due to high surgical risk and hemodynamic instability the Heart Team decided on percutaneous repair ("Clip-in-Ring" treatment).

The MitraClip® G4 system was preferred but periprocedural difficulties were expected: mean valve gradient of 4 mmHg, short posterior leaflet of 7 mm and especially past history of double-layer pericardial patch implantation for atrial septal defect II closure (Synovis Peri-Gourd®).

After obtaining access to the right atrium, the Brockenbrough needle caused typical tenting at the level of the fossa ovalis, now covered by the pericardial patch. Successful puncture was possible only after connecting the needle to a surgical electrocautery. After placing a stiff wire in the left upper pulmonary vein (Fig. 1C) the MitraClip delivery system (25F) could not pass through the interatrial septum (IAS). An unconventional septostomy of the IAS was performed by angioplasty using conventional peripheral balloons (Fig. 1D) with incremental diameters up to 9.0 mm.

Upon system advancement, placement of a NTW Clip was finally possible (Fig. 1E). Transmitral mean gradient did not rise and adequate leaflet tissue grasping was confirmed. A significant reduction to mild MR was obtained (Fig. 1F) and merely a trivial left-to-right shunt of IAS was noticed. Extubation was performed in the cath lab and discharge occurred 3 days later.

This case highlights the need for thorough procedural planning of percutaneous MR repair. Electrocautery of IAS and septostomy are bail-out techniques that can be used to gain access to the left atrium (**Suppl. Video 1**).

Conflict of interest: None declared

Address for correspondence: Alexandru I. Patrascu, MD, Department of Cardiology, Helios Klinikum Pforzheim, Kanzlerstrasse 2-6, 75175 Pforzheim, Germany, e-mail: alexbasket23@yahoo.com

Received: 6.10.2021 Accepted: 1.11.2021

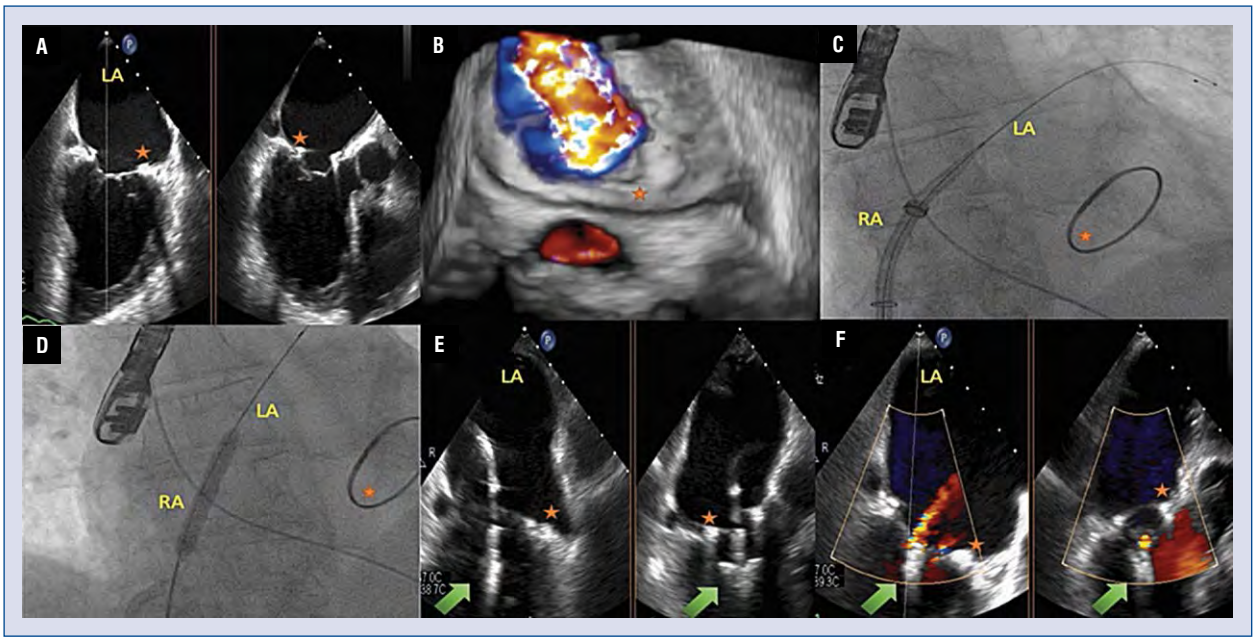


Figure 1. Electrocautery and septostomy facilitated MitraClip in ring; **A.** Baseline transesophageal echocardiography (TEE) bi-plane view depicting mitral valve (MV) ring position and leaflet tethering; **B.** Baseline three-dimensional TEE anatomical MV view demonstrating high-grade mitral regurgitation (MR); **C.** Fluoroscopy showing successful crossing of the fossa ovalis and positioning of a 0.035" wire in the left upper pulmonary vein; **D.** Balloon atrial septostomy facilitating advancement of the MitraClip delivery system; **E.** Positioning of the NTW Clip between P2/A2 scallops; **F.** Final result showing only trivial MR; LA — left atrium; RA — right atrium; Green arrow indicates the Clip; Orange star depicts MV ring position.

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

Cardiology Journal
2022, Vol. 29, No. 3, 521–522
DOI: 10.5603/CJ.2022.0039

ISSN 1897–5593
eISSN 1898–018X

Shockwave intracoronary lithotripsy for the treatment of calcium-mediated undilatable in-stent restenosis

Michał Kuzemczak[1, 2], Tomasz Pawłowski[1], Robert Gil[1]

[1]Department of Invasive Cardiology, Central Clinical Hospital of the Ministry of Interior and Administration, Warsaw, Poland
[2]Chair of Emergency Medicine, Department of Medical Rescue, Poznan University of Medical Sciences, Poznan, Poland

Stent underexpansion due to calcifications is a predictor of stent failure and adverse clinical outcomes. Intravasular lithotripsy (IVL) has proved to be effective in dilating calcified de novo coronary lesions, but indications for the technique are expanding.

A 56-year-old man was scheduled for percutaneous coronary intervention due to severely calcified in-stent restenosis (ISR) in a bifurcation dedicated drug-eluting stent (DES) BiossLimC 3.5/4.25/24 mm which had been implanted 2 years prior into the left main/left anterior descending artery (LM/LAD) with a suboptimal result (residual stenosis of 50% in the proxLAD due to calcificatitons). As confimed during the present admission, the lesion progressed (90% calcified ISR) (Fig. 1A) and was unsuccessfully dilated with non-compliant balloon (NCB) inflations (Fig. 1B). Advancement of intavascular ultrasound catheter to interrogate the lesion was unsuccessful. Considering the presence of severe calcifications, calcium deposits covered by the previously implanted stent and angiographically visible calcifications in the outer layers of the vessel, we elected to use IVL. IVL balloon (Shockwave 3.5/12 mm) was positioned and inflated within the lesion in the proxLAD (4 atm). Then, 80 shockwave pulses were delivered with a subsequent pressure increase (6 atm). The "dog-boning" effect (Fig. 1B) which had been observed during NCB inflations dissapeared (Fig. 1C) and the lesion was re-dilated with NCBs (NC Emerge 3.5/12 mm, Pantera Leo 3.75/12 mm). Subsequently, DES (Orsiro 3.5/13 mm) was implanted (Fig. 1D) and post-dilated with a NCB (Pantera Leo 3.75/12 mm). A satisfactory angiographic result was achieved (Fig. 1E) with good expansion/apposition of the stent, and achievement of Kang's criteria (Fig. 1F).

The present case implies that IVL is an effective modality for undilatable ISR caused by stent underexpansion secondary to calcifications.

Conflict of interest: None declared

Address for correspondence: Michał Kuzemczak, MD, PhD, MSc, Department of Invasive Cardiology, Central Clinical Hospital of the Ministry of Interior and Administration, ul. Wołoska 137, 02–507 Warszawa, Poland, tel: +48 698 020 284, e-mail: michal.kuzemczak@gmail.com

Received: 27.09.2021 Accepted: 6.02.2022

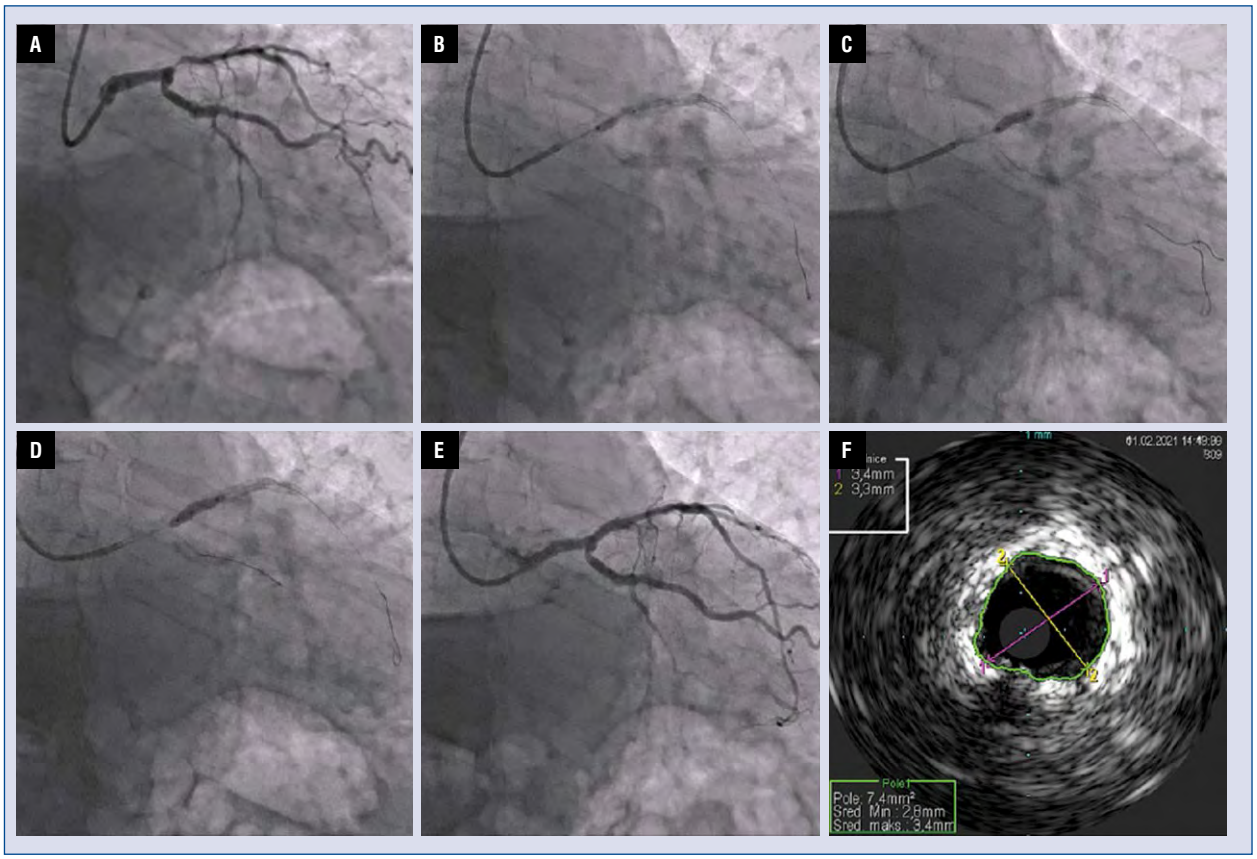


Figure 1. Procedural steps of the procedure; **A.** A baseline left coronary angiograpy demonstrating calcified in-stent restenosis in the ostium of the left anterior descending artery (LAD); **B.** Predilatation of the target lesion with a non--compliant balloon with a "dog-boning" effect; **C.** An inflated intravasular lithotripsy balloon demonstrating lack of "dog-boning" effect following 80 shockwave pulses; **D.** Stent implantation in the proxLAD; **E.** Final angiographic result; **F.** Final intavascular ultrasound assessment (lumen area 7.4 mm^2).

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

Cardiology Journal
2022, Vol. 29, No. 3, 523–524
DOI: 10.5603/CJ.2022.0040

ISSN 1897–5593
eISSN 1898–018X

Fish bone or calcification of arterial ligament?

Meng Zhao, Jingxin Zhou, Yihu Tang, Xiang Liu, Yanhu Wu

Department of Cardiovascular Surgery, Nanjing Medical University First Affiliated Hospital, Nanjing, Jiangsu, China

A 34-year-old woman was admitted to the documented hospital for backache. She had swallowed a fishbone 3 days prior, and nothing could be found by gastroscopy in a local hospital. After admission, a computed tomography (CT) was performed, a high-density shadow could be seen beneath the arcus aortae (Fig. 1A). The "fishbone" was so close to the aorta and pulmonary artery that an emergency operation was performed to prevent the possibility of rupture.

After surgery, the patient felt the backache disappear. Before discharge, a CT was performed again and the high-density shadow had disappeared when compared with the previous picture (Fig. 1B). Five days later, a pathological examination showed calcification of cartilage. But, strangely, as a foreign body, inflammatory cells could not be found around the "fishbone" (Fig. 1C). Considering the position and pathological result of the "fishbone", another possibility came to mind: calcification of arterial ligament (CAL). For further conformation, a blood sample and pathological section was sent to the Academy of Forensic Science for DNA sequencing after acquiring permission from the patient. 16 loci (D3S1358, D1S1656, D6S1043, D13S317, D16S539, D18S51, D2S1338, TH01, vWA, D7S820, D5S818, TP0X, D8S1179, D12S391, D19S433, Amelogenin) were exactly the same in 2 samples and 5 loci (Penta E, CSF1P0, Penta D, D21S11, and FGA) could not be detected in the pathological section (**Suppl. Fig. 1**).

In conclusion, an eye should be kept on CAL when handling an emergency esophageal foreign body based on the lesson learned from this case.

Funding

This work was financially supported by projects of the National Scientific Foundation of China (NSFC, Grant Nos. 81700340).

Conflict of interest: None declared

Address for correspondence: Dr. Xiang Liu, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, China, 210029, tel: +86 13770912266, fax: +86 25 83724440, e-mail: 13770912266@139.com; Dr. Yanhu Wu, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, China, 210029, tel: +86 13951945999, fax: +86 25 83724440, e-mail: wuyanhu@njmu.edu.cn

Received: 5.04.2021 Accepted: 3.07.2021

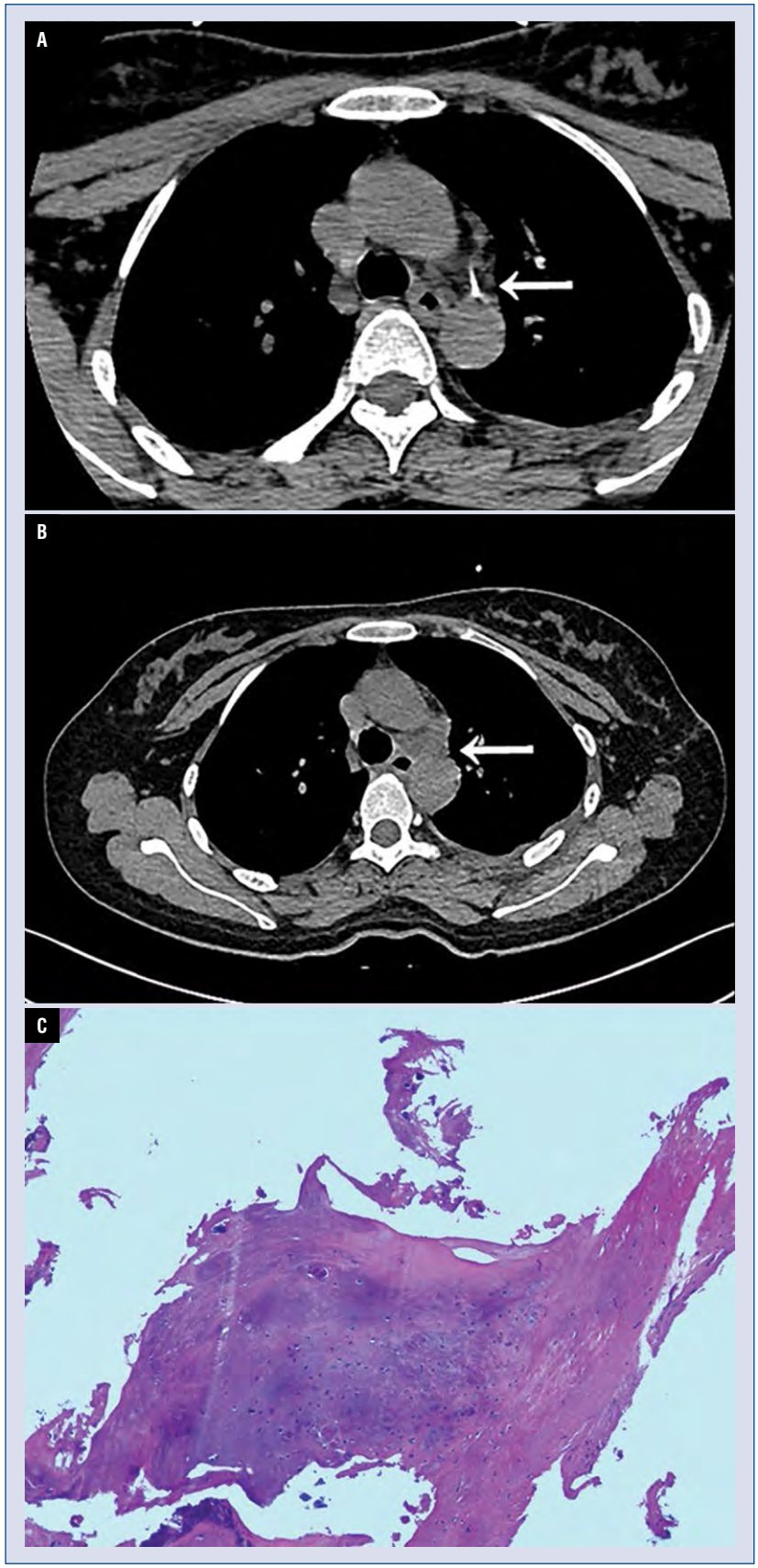


Figure 1. A. A high-density shadow could be seen before surgery; **B.** The high-density shadow disappeared after surgery; **C.** Pathology showed calcification of cartilage.

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

Cardiology Journal
2022, Vol. 29, No. 3, 525–526
DOI: 10.5603/CJ.2022.0041

ISSN 1897–5593
eISSN 1898–018X

The coherent module use for mapping of atypical atrial flutter

Krzysztof Myrda[1], Aleksandra Błachut[1], Mariusz Gąsior[1, 2]

[1]3rd Department of Cardiology, Silesian Center for Heart Diseases, Zabrze, Poland
[2]Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland

In 2018, a 75-year-old woman after circumferential pulmonary vein isolation with radiofrequency (RF) substrate modification and cavotricuspid isthmus ablation was referred for catheter re-ablation due to persistent atrial flutter (AFl). Because of electrophysiological study results, including entrainment pacing, activation mapping of atypical AFl with cycle length of 260 ms was performed in the left atrium as a first. Usage of multielectrode high-density mapping catheter (PentaRay; Biosense Webster Inc., CA, USA) and the new CARTO PRIME coherent mapping module (CARTO3 version 7, Biosense Webster Inc., CA, USA) revealed a critical isthmus on a previously performed septal line (Fig. 1A). First RF applications (30–35 W) delivered by 3.5-mm irrigated tip ablation catheter (SmartTouch SF, Biosense Webster Inc., CA, USA), terminated AFl successfully (Fig. 1B, **Suppl. Video 1**). Achieving of the bidirectional block of the septal line was confirmed by site pacing maneuvers. No further atrial arrhythmia was inducible. The patient had no symptoms during 3-month follow-up.

The coherent activation mapping seems to be valuable tool in daily practice and may simplify the acquisition of electro-anatomical mapping of complex arrhythmia and also reduce the ablation time required for arrhythmia termination.

Conflict of interest: None declared

Address for correspondence: Krzysztof Myrda, MD, PhD, 3rd Department of Cardiology, Silesian Center for Heart Diseases, ul. M. Skłodowskiej-Curie 9, 41–800 Zabrze, Poland, tel: +48 506 603 277, e-mail: k_myrda@interia.pl

Received: 28.03.2021 Accepted: 22.08.2021

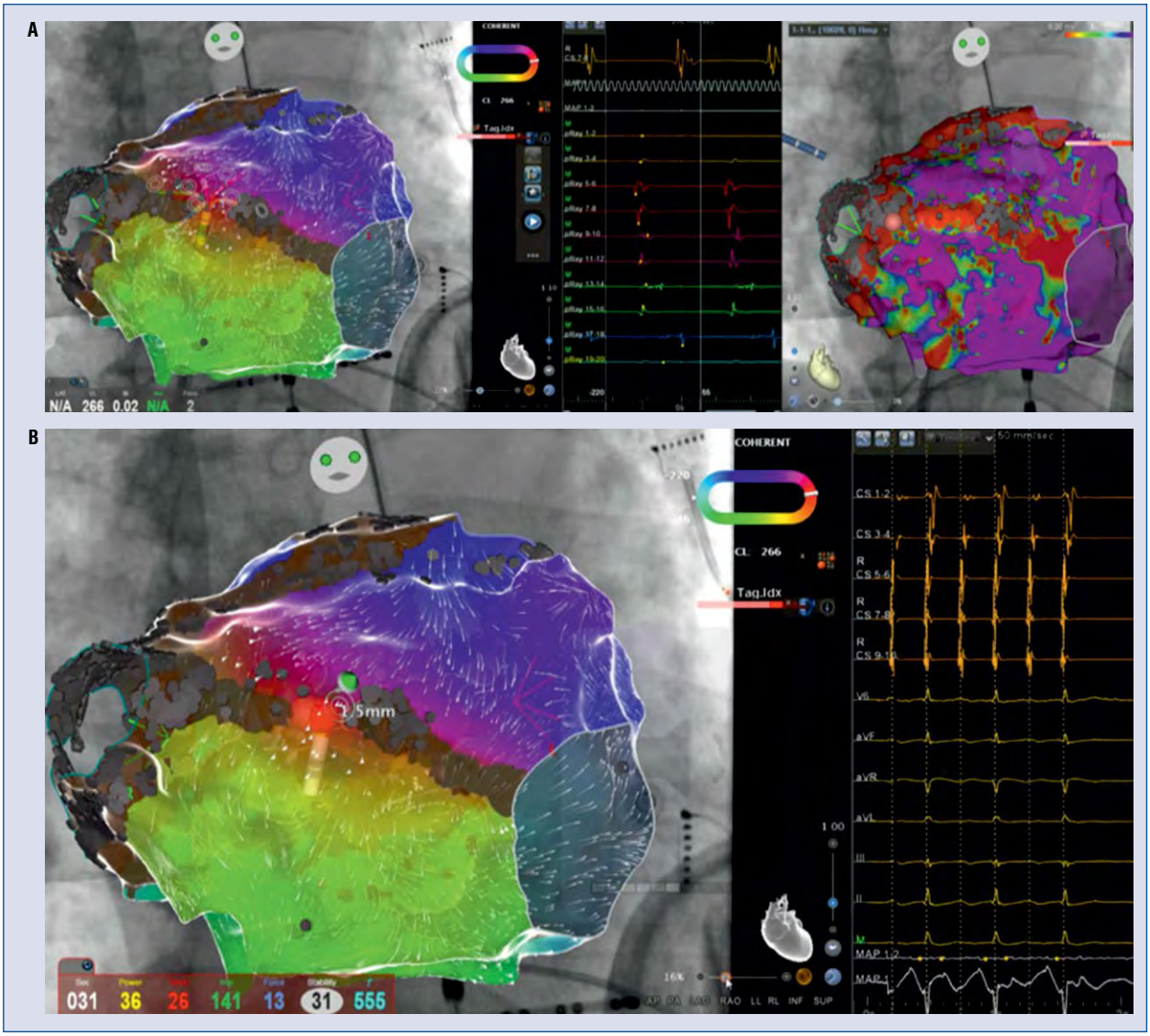


Figure 1. Coherent activation mapping of left atrium; **A.** Mapping catheter revealed critical isthmus on previously performed septal line (left side), bipolar voltage mapping (right side); **B.** Completed septal line and termination of the arrhythmia.

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

Cardiology Journal
2022, Vol. 29, No. 3, 527–528
DOI: 10.5603/CJ.2022.0042

ISSN 1897–5593
eISSN 1898–018X

Apical left ventricular pseudoaneurysm: Diagnosis by multimodal cardiac imaging

María Anguita-Gámez[1], Martín Negreira-Caamaño[2], Iván Nuñez[1], Pedro Marcos-Alberca[1], María Vidal[3], Paula Hernández[3], David Vivas[1], José A. De Agustín[1]

[1]Cardiovascular Institute, San Carlos Clinic Hospital, Madrid, Spain
[2]Cardiology Department, Universitary General Hospital, Ciudad Real, Spain
[3]Radiology Department, San Carlos Clinic Hospital, Madrid, Spain

A 63-year-old woman with a history of permanent atrial fibrillation and mitral valve replacement with a mechanical prosthesis underwent outpatient cardiac catheterization due to repeated atypical chest pain. Coronary angiography showed no coronary stenosis, but ventriculography showed focal dilatation of the ventricular wall at the apical level (Fig. 1, A: Systole, B: Diastole), not described in previous imaging studies. Transthoracic echocardiography showed a short-necked, non-contractile saccular image, located at the apex of the left ventricle (Fig. 1C, D). No wall motion abnormalities were observed. The observed wide neck suggested the diagnosis of aneurysm, but a cardiac magnetic resonance showed a lack of continuity in the muscular layer, and a late gadolinium uptake circumscribed to the adjacent epicardial region (Fig. 1E, F). Thus, a diagnosis of ventricular pseudoaneurysm was established, confirmed by the findings of a cardiac computed tomography (Fig. 1G, H).

The interest of this case lies on the differentiation between true ventricular aneurysm and pseudoaneurysm, and about their etiology. Among the causes of pseudoaneurysm, the most frequent is a contained cardiac rupture in acute myocardial infarction.This was ruled out in the present case by the absence of coronary artery disease or myocardial contractility defects. Other more uncommon causes are infective endocarditis, thoracic trauma, congenital diverticula, cardiac surgery (for instance, the use of a transapical dilator for mitral valve commissurotomy) or an embolic myocardial infarction involving the most apical segments of left anterior descendent artery. The latter being a plausible hypothesis in a patient with a mechanical mitral prosthesis.

Conflict of interest: None declared

Address for correspondence: Dr. María Anguita-Gámez, Servicio de Cardiología, Hospital Clínico San Carlos, Calle Profesor Martín Lagos, s/n. 28040, Madrid, Spain, tel: 913303000, e-mail: maria.anguita95@gmail.com

Received: 29.09.2021 Accepted: 28.10.2021

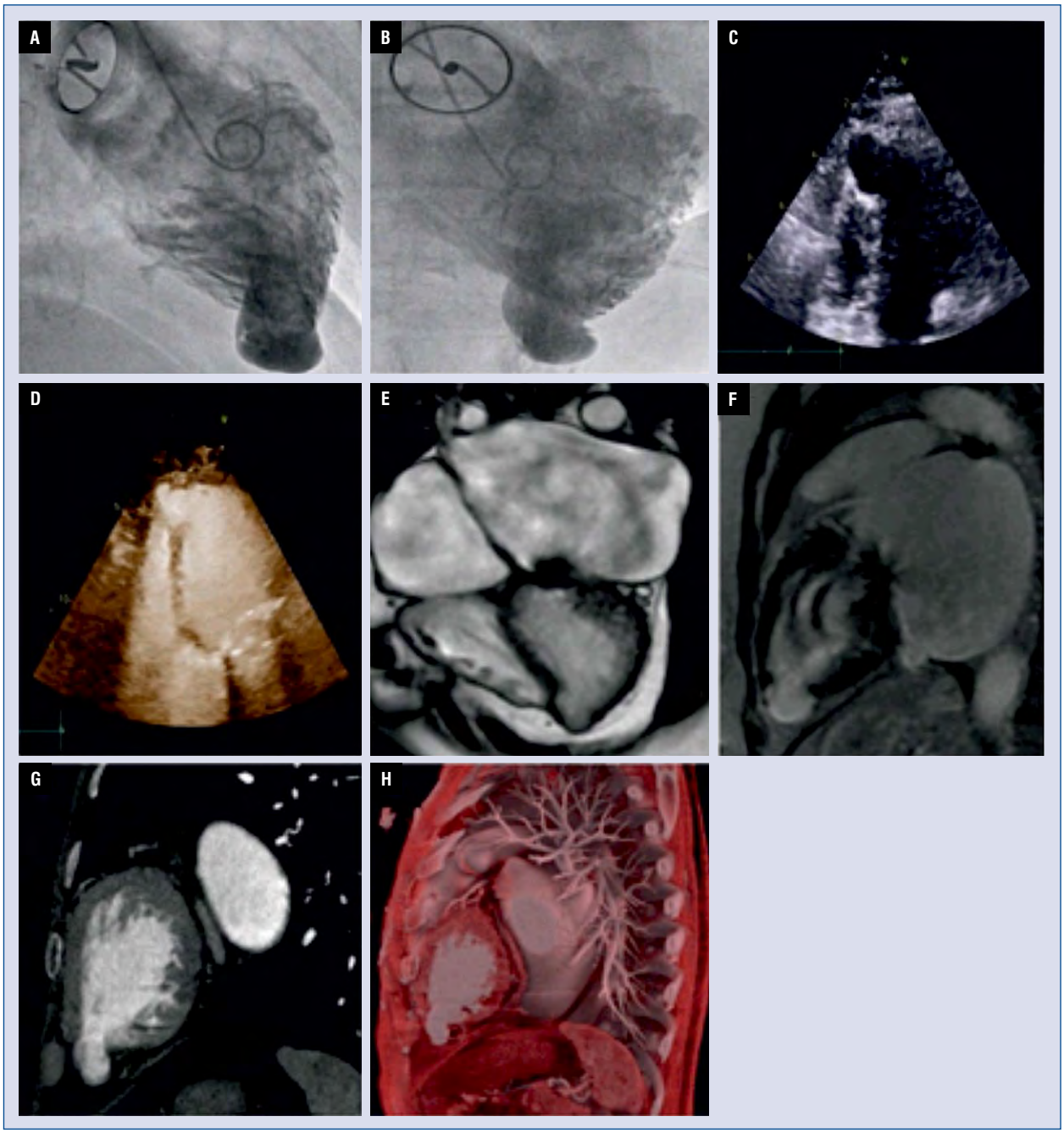


Figure 1. Multimodality cardiovascular imaging showing apical left ventricular pseudoaneurysm in the patient; **A, B.** Contrast invasive ventriculography: left (**A**) and right (**B**) anterior oblique views, revealing a small protrusion in the apical segment of myocardial wall. Mitral prosthetic valve was also noticed; **C, D.** Two-dimensional transthoracic echocardiogram without (**C**) and with contrast (**D**) showing the apical protrusion; **E, F.** Cardiac magnetic resonance: massive left atrial dilatation with a ventricular wall-defect at the apex of the left ventricle (**E**), and epicardial late gadolinium enhancement (**F**); **G, H.** Gated computed cardiac tomography in sagittal view (**G**) and after three-dimensional reconstruction (**H**) showing the same findings.

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

Cardiology Journal
2022, Vol. 29, No. 3, 529–530
DOI: 10.5603/CJ.2022.0043

ISSN 1897–5593
eISSN 1898–018X

Early detection of cardiac involvement of desminopathy by cardiovascular magnetic resonance

Martyna Faber[1], Teresa Trenkwalder[2], Federica Montagnese[3], Heiko Stern[4], Christian Meierhofer[4]

[1]Department of Radiology, German Heart Center Munich, Technical Universitiy of Munich, Germany
[2]Department of Cardiology, German Heart Center Munich, Technical Universitiy of Munich, Germany
[3]Department of Myopathology, Friedrich-Baur-Institute, Department of Neurology, LMU Klinikum Munich, Germany
[4]Department of Congenital Heart Disease and Pediatric Cardiology, German Heart Center Munich, Technical Universitiy of Munich, Germany

A 42-year-old man presented with loss of muscle strength and aching in the calves. Skeletal muscle biopsy of anterior tibial muscle showed a myofibrillar myopathy with increased endo- and perimysial connective tissue, centralized myonuclei, and intracellular rimmed vacuoles (Fig. 1C, D). Molecular genetic analysis detected classic R350P-desmin gene mutation, causing an autosomal-dominant desminopathy.

Cardiac examinations were performed. Transthoracic echocardiogram was unremarkable with normal biventricular function, electrocardiogram revealed a slightly prolonged PQ-time but no pronounced arrhythmia.

Cardiovascular magnetic resonance showed no late-gadolinium-enhancement. Pre- and postcontrast T1-mapping was performed using modified look-locker-inversion-sequence (MOLLI, Myomaps, Siemens healthineers). T1-relaxation-times were located in the upper normal range with values between 940 and 1000 ms. Extracellular volume fraction (ECV) was calculated by using T1-map pre and post contrast. The patient's hematocrit was measured on the examination day. ECV-maps (Fig. 1A) and polarmaps (Fig. 1B) were generated to visualize ECV results in left ventricular myocardial segments. ECV ranged between 25.1% and 34.7% (normal up to 29%) in the different cardiac segments, with higher values in the apical myocardium. As these findings are compatible with the myopathological changes of increased deposit of connective tissue in the endo- and perimysium, these are suspicions for early stage of cardiac involvement in desminopathy. Cardiac magnetic resonance proved to be a sensitive diagnostic tool for early cardiac involvement in desminopathy, which have not yet been revealed by other non-invasive methods.

Desminopathies belong to a genetically heterogeneous group of disorders named myofibrillar myopathies, which might be caused by mutations in the desmin gene, but may also affect other adjacent genes.

Conflict of interest: None declared

Address for correspondence: Martyna Faber, MD, Department of Radiology, German Heart Center Munich, Technical Universitiy of Munich, Lazarettstrasse 36, 80636 Munich, Germany, e-mail: martyna.faber89@gmail.com

Received: 25.05.2021 Accepted: 20.07.2021

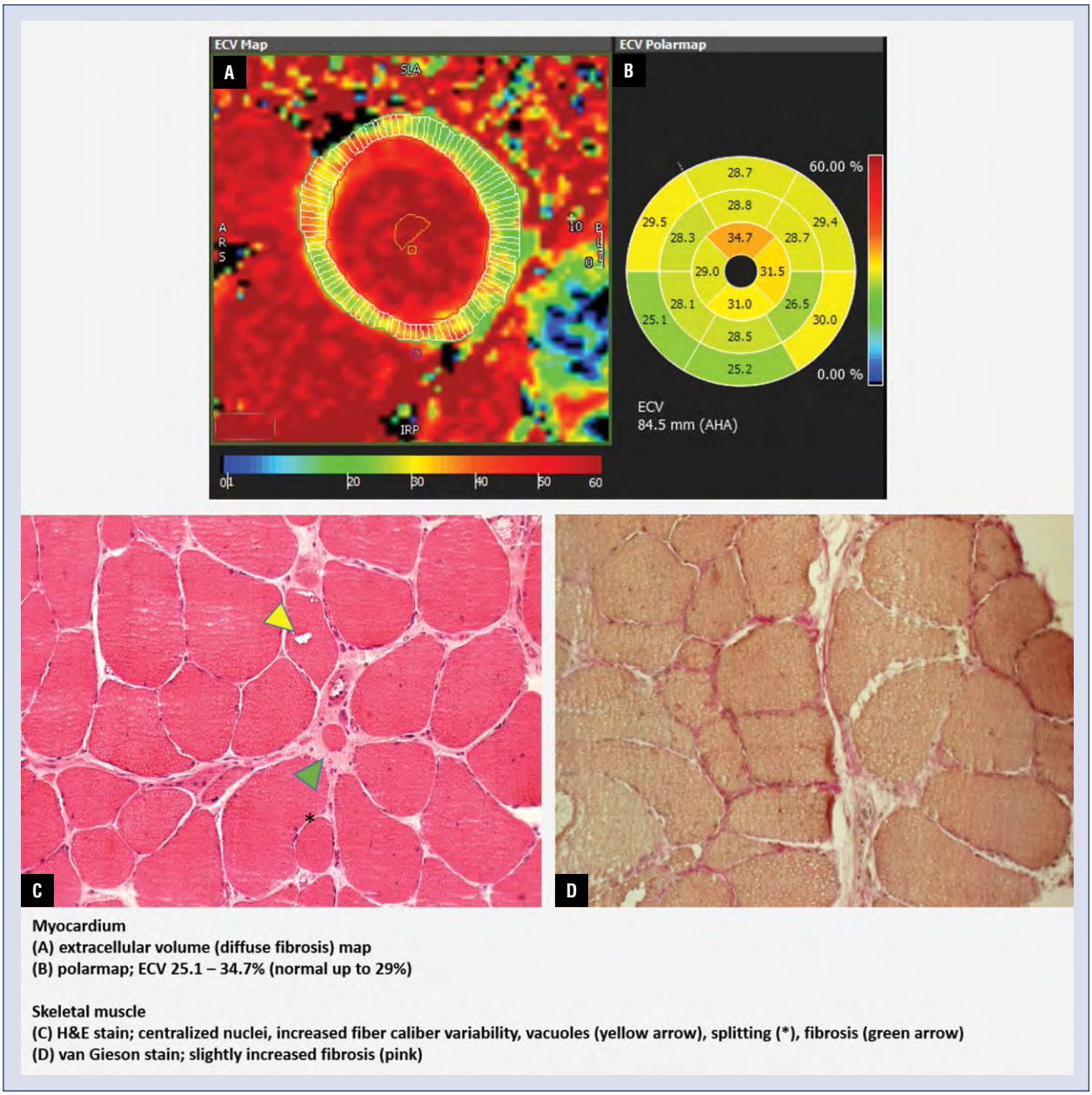


Figure 1. Cardiac and skeletal muscle involvement in autosomal-dominant desminopathy. Cardiac magnetic resonance imaging: Extracellular volume map (**A**); polarmap (**B**). Skeletal muscle biopsy: hematoxylin and eosin stain (**C**) and van Gieson stain (**D**).

VIA MEDICA

LETTER TO THE EDITOR

Cardiology Journal
2022, Vol. 29, No. 3, 531–532
DOI: 10.5603/CJ.a2022.0021

ISSN 1897–5593
eISSN 1898–018X

Post-COVID-19 postural orthostatic tachycardia syndrome

Ivan Volodymyrovych Savytskyi[1], Michal Pruc[2], Marek Malysz[2], Anatoliy Maslyukov[1, 3], Lukasz Szarpak[4]

[1]School of Medicine, International European University, Kyiv, Ukraine
[2]Research Unit, Polish Society of Disaster Medicine, Warsaw, Poland
[3]Department of Biomedical Sciences, Odessa International Medical University, Odessa, Ukraine
[4]Henry JN Taub Department of Emergency Medicine, Baylor College of Medicine, Houston, TX, United States

Since the beginning of the pandemic, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has faced a significant threat healthcare systems and medical professionals [1]. Despite the current pandemic and recent considerable increases in the incidence and hospitalizations linked with the Omnicron BA.2, patients with a history of coronavirus disease 2019 (COVID-19) who suffer post-COVID-19 complications should be given additional attention. It is known that as a result of post-COVID-19 syndrome, patients struggle with a number of cardiac complications, such as myocarditis and progressive damage to the heart muscle [2]. People recovering from the COVID-19 sometimes show symptoms of a condition called postural orthostatic tachycardia syndrome (POTS). Typical arrhythmias occur in COVID-19 and long-term COVID-19 has been linked to tachycardia, with 25–50% of patients at a tertiary post-COVID-19 multidisciplinary team clinic experiencing persistent tachycardia or palpitations [3, 4]. It is unknown how many people worldwide suffer with long-COVID-19. However, according to one research roughly 43% of patients who tested positive for COVID-19, and more than half of those who got inpatient care for this condition, developed long-COVID-19 [5]. However, POTS is not a direct cardiac condition, but a neurological disorder that affects a component of the nervous system that controls heart rate and blood flow. POTS can cause the heart to beat rapidly when standing from a reclining position, causing symptoms such as brain fog, fatigue, palpitations, dizziness, shortness of breath and other issues. A range of diseases, including viral or bacterial infections, can cause POTS. Because an increasing number of patients who recovered from COVID-19 are now reporting POTS-like symptoms including brain fog, tachycardia and severe chronic fatigue, some experts believe coronavirus may be a trigger for POTS. More and more studies provide us with information on POTS patients with long-COVID-19 [6]. According to studies, the prevalence of orthostatic hypotension with long-COVID-19 might range from 10% to 41% [7, 8]. The mechanism of POTS is unknown, although research is continuing to find the most likely reasons. People with POTS have platelet storage pool shortage, according to Gunning et al. [9], which is connected to symptoms including nosebleeds, dysmenorrhea, easy bruising, and anemia. It was also shown that persons with POTS have higher inflammatory biomarkers, all of which might indicate a chronic inflammatory condition. The presented conditions, especially inflammatory markers, could be associated with a cytokine storm during COVID-19 [9]. POTS affected an estimated 1–3 million persons in the United States, well before the pandemic, according to data published by the group Dysautonomia International. Although it is unknown how many more patients are seeking care as a result of COVID-19 than they were before the pandemic,

Address for correspondence: Lukasz Szarpak, PhD, DPH, DBA, MBA, LLM, Henry JN Taub Department of Emergency Medicine, Baylor College of Medicine, One Baylor Plaza, Houston, Texas 77030, United States, tel: +48 500186225, e-mail: lukasz.szarpak@bcm.edu

Received: 27.03.2022 Accepted: 31.03.2022 Early publication date: 19.04.2022

American Autonomic Society statement reports suggest a sharp rise in instances, the majority of which are linked to long-COVID-19 [10]. These data suggest that POTS may be significantly related to COVID-19. POTS is an incurable condition, thus understanding its link with COVID-19 is critical if we are to protect people against it. At the moment, the sole treatment for POTS is conservative treatment, which includes exercise programs, avoiding triggers, high fluid and salt intake, wearing compression stockings, and engaging in cognitive behavioral therapy. At present, the only goal of pharmacological interventions is to correct physiological parameters. Further research is needed on the pathomechanism of POTS and the relationship between POTS and COVID-19 and long-COVID-19 in order to protect patients against the disease. In clinical practice, special attention should also be paid to post-COVID-19 patients in order to detect possible POTS, which, as reported during the COVID-19 pandemic, is becoming more frequent.

Acknowledgments

The study was supported by the Polish Society of Disaster Medicine.

Conflict of interest: None declared

References

1. Dzieciatkowski T, Szarpak L, Filipiak KJ, et al. COVID-19 challenge for modern medicine. Cardiol J. 2020; 27(2): 175–183, doi: 10.5603/CJ.a2020.0055, indexed in Pubmed: 32286679.
2. Szarpak L, Pruc M, Filipiak KJ, et al. Myocarditis: a complication of COVID-19 and long-COVID-19 syndrome as a serious threat in modern cardiology. Cardiol J. 2022; 29(1): 178–179, doi: 10.5603/CJ.a2021.0155, indexed in Pubmed: 34811716.
3. Szarpak L, Filipiak KJ, Skwarek A, et al. Outcomes and mortality associated with atrial arrhythmias among patients hospitalized with COVID-19: a systematic review and meta-analysis. Cardiol J. 2022; 29(1): 33–43, doi: 10.5603/CJ.a2021.0167, indexed in Pubmed: 34897631.
4. Ståhlberg M, Reistam U, Fedorowski A, et al. Post-COVID-19 tachycardia syndrome: a distinct phenotype of post-acute COVID-19 syndrome. Am J Med. 2021; 134(12): 1451–1456, doi: 10.1016/j.amjmed.2021.07.004, indexed in Pubmed: 34390682.
5. Chen C, Haupert S, Zimmermann L, et al. Global prevalence of post-acute sequelae of COVID-19 (PASC) or long COVID: a meta-analysis and systematic review. medRxiv. 2021, doi: 10.1101/2021.11.15.21266377.
6. Dani M, Dirksen A, Taraborrelli P, et al. Autonomic dysfunction in ‚long COVID': rationale, physiology and management strategies. Clin Med (Lond). 2021; 21(1): e63–e67, doi: 10.7861/clinmed.2020-0896, indexed in Pubmed: 33243837.
7. Buoite Stella A, Furlanis G, Frezza NA, et al. Autonomic dysfunction in post-COVID patients with and witfhout neurological symptoms: a prospective multidomain observational study. J Neurol. 2022; 269(2): 587–596, doi: 10.1007/s00415-021-10735-y, indexed in Pubmed: 34386903.
8. Shah B, Kunal S, Bansal A, et al. Heart rate variability as a marker of cardiovascular dysautonomia in post-COVID-19 syndrome using artificial intelligence. Indian Pacing Electrophysiol J. 2022; 22(2): 70–76, doi: 10.1016/j.ipej.2022.01.004, indexed in Pubmed: 35101582.
9. Gunning WT, Kramer PM, Cichocki JA, et al. Platelet storage pool deficiency and elevated inflammatory biomarkers are prevalent in postural orthostatic tachycardia syndrome. Cells. 2022; 11(5), doi: 10.3390/cells11050774, indexed in Pubmed: 35269395.
10. Raj SR, Arnold AC, Barboi A, et al. Long-COVID postural tachycardia syndrome: an American Autonomic Society statement. Clin Auton Res. 2021; 31(3): 365–368, doi: 10.1007/s10286-021-00798-2, indexed in Pubmed: 33740207.

VIA MEDICA

LETTER TO THE EDITOR

Cardiology Journal
2022, Vol. 29, No. 3, 533–534
DOI: 10.5603/CJ.a2022.0022

ISSN 1897–5593
eISSN 1898–018X

Treatment prospects for post-COVID-19 cardiac patients

Michal Pruc[1], Yaroslaw Merza[2], Krzysztof J. Filipiak[3], Ihor Navolokin[2], Lukasz Szarpak[4, 5]

[1]Research Unit, Polish Society of Disaster Medicine, Warsaw, Poland
[2]School of Medicine, International European University, Kyiv, Ukraine
[3]Institute of Clinical Medicine, Maria Sklodowska-Curie Medical Academy, Warsaw, Poland
[4]Institute of Outcomes Research, Maria Sklodowska-Curie Medical Academy, Warsaw, Poland
[5]Henry JN Taub Department of Emergency Medicine, Baylor College of Medicine, Houston, TX, United States

Since the beginning of the pandemic, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has posed a serious threat to the health care system and medical personnel, but the fight against the pandemic itself will not end our struggle with complications that will arise in patients struggling with long-COVID-19 and the post-COVID-19 syndrome [1]. Research among people hospitalized for COVID-19 shows that 32.6% to 87.4% of patients still reported at least one symptom that persists after several months [2]. COVID-19 can cause difficulties even with a mild or moderate course. Long-COVID-19 occurs in non-hospitalized individuals roughly 6–9 months after infection, according to Hamburg Doctors' observations. The alterations are obvious in multiple physiological systems, with the heart, blood vessels, lungs, and kidneys being the most affected. There was a trend toward greater localized cardiac fibrosis in the circulatory system, but no edema was seen. The ventricles of the heart showed more severe alterations. In the left ventricle, a slightly reduced ejection fraction, accompanied by a higher concentration of cardiac biomarkers, reflecting little myocardial involvement. On the other hand, in the right ventricle, the systolic fraction was assessed as significantly reduced. In the long run, even a little deterioration in left ventricular function and a rise in N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration increases the risk of mortality in the general population. To minimize untreated cardiac impairment, NT-proBNP testing following recovery from COVID-19 may be advised, followed by echocardiographic surveillance if increased levels are seen. In the case of blood vessels, "incompressible" femoral veins were found, suggesting a significantly higher incidence of deep vein thrombosis in study participants after SARS-CoV-2 infection. Changes in the kidneys were also seen, as demonstrated by higher creatinine and cystatin C levels, as well as lower sodium and potassium levels. An initial phase of chronic kidney disease, which raises the risk of cardiovascular disease and mortality, may be indicated by abnormalities in the composition of the eyes and the picture of the kidneys [3]. Following COVID-19 infection, patients may have a variety of cardiovascular consequences, including an increased risk of cardiovascular disorders, arrhythmias, ischemic heart disease, pericarditis, and myocarditis, as well as heart failure and thrombosis. Even among patients who were not hospitalized in the acute phase of illness, these risks and burdens were obvious, and they gradually increased depending on the settings of treatment. COVID-19 survivors face a considerable risk and yearly burden of cardiovascular disease, according to studies [4, 5]. Long-COVID-19 patients report a wide range of symptoms, ranging from moderate to highly debilitating. The origins of this illness have been hypothesized by scientists, ranging from

Address for correspondence: Lukasz Szarpak, PhD, DPH, DBA, MBA, LLM, Henry JN Taub Department of Emergency Medicine, Baylor College of Medicine, One Baylor Plaza, Houston, Texas 77030, United States, tel: +48 500186225, e-mail: lukasz.szarpak@bcm.edu

Received: 3.04.2022 Accepted: 7.04.2022 Early publication date: 7.04.2022

chronic viral reservoirs and autoimmune to tiny blood clots. A mixture of these things, according to many, is to blame. Vaccines are the most effective strategy to prevent long-COVID-19 so far. COVID-19 vaccinations minimize the risk of SARS--CoV-2 infection and may lessen the likelihood of long-COVID-19 infection after a breakthrough illness in a vaccinated individual. In a group of almost 3,000 double-vaccinated persons who later were infected with SARS-CoV-2, the study indicated that vaccination decreased the probability of acquiring long-COVID-19 symptoms by about 41% [6]. Aside from immunization, it is unknown whether any existing COVID-19 medication has had an impact on the likelihood of long-term illness. A medicine that lessens the severity of the condition might theoretically reduce the probability of this occurring. However, long-COVID-19 is not usually linked to a severe acute illness; many patients with this syndrome have had asymptomatic or minor illness. Clinics for persons with long-COVID-19 are being established in several countries. Because persons with long-COVID-19 must rest for months at a period and require help during that time, much of the difficulty will be social and political [7]. Nonetheless, several researchers will investigate the effects of long-COVID-19 therapy. The hunt for a treatment that can minimize the risk of long--COVID-19 is still continuing. Heal-COVID, a big United Kingdom trial, is looking into two drugs that target the cardiovascular system in COVID-19 patients. Apixaban, an anticoagulant, and atorvastatin, a cholesterol-lowering drug that also helps to reduce inflammation in the blood vessels. PANORAMIC is a clinical experiment that aims to see if the antiviral molnupiravir affects the severity of COVID-19. While this is not the study's primary goal, researchers will gather data from individuals 3 and 6 months after treatment to see if the medicine has an effect on long-COVID-19 risk. Similarly, participants in the two Paxlovid studies will be followed for 6 months. These antiviral drugs are primarily used to treat COVID-19 patients who have just minor symptoms. Ayodeji Adegunsoye of the University of Chicago discovered an increase in the deposition of scar tissue in the lungs, known as fibrosis, long after acute infection in persons hospitalized with COVID-19 and requiring supplementary oxygen. He is presently studying an immunosuppressive medicine called sirolimus on these folks, which is commonly given to organ transplant recipients in the hopes of preventing fibrotic cell migration in the lungs [8]. Currently, methods of treating post--COVID-19 ailments are not known and they are treated in accordance with the drugs appropriate to the given disease entities. Special medication can arranged based on the outcomes of morphological studies and more extensive diagnostics focusing on certain diseases. Each phase of the diagnosis of a post-COVID-19 complication results from a different disease. For example, when cardiac function is tested, BNP is the recommended test, and when it is elevated, consider echocardiography. Biochemical tests play a very important role in this diagnosis. An example of this is the diagnosis of changes in the venous system, where even with the slightest suspicion of deep vein thrombosis, basic tests such as D-dimers should be performed, and then Doppler ultrasound should be performed at elevated levels. There are no effective therapies against long-COVID-19, despite the high effectiveness of vaccinations, therefore, in the face of the growing number of COVID-19 cases associated with the Omnicron BA.2 variant, use personal protective equipment should continue and extensive self-testing implemented to reduce the spread of COVID-19 in the population [9, 10].

Acknowledgments

The study was supported by the Polish Society of Disaster Medicine.

Conflict of interest: None declared

References

1. Dzieciatkowski T, Szarpak L, Filipiak KJ, et al. COVID-19 challenge for modern medicine. Cardiol J. 2020; 27(2): 175–183, doi: 10.5603/CJ.a2020.0055, indexed in Pubmed: 32286679.
2. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. Nat Med. 2021; 27(4): 601–615, doi: 10.1038/s41591-021-01283-z, indexed in Pubmed: 33753937.
3. Petersen EL, Goßling A, Adam G, et al. Multi-organ assessment in mainly non-hospitalized individuals after SARS-CoV-2 infection: The Hamburg City Health Study COVID programme. Eur Heart J. 2022; 43(11): 1124–1137, doi: 10.1093/eurheartj/ehab914, indexed in Pubmed: 34999762.
4. Gasecka A, Pruc M, Kukula K, et al. Post-COVID-19 heart syndrome. Cardiol J. 2021; 28(2): 353–354, doi: 10.5603/CJ.a2021.0028, indexed in Pubmed: 33645626.
5. Xie Y, Xu E, Bowe B, et al. Long-term cardiovascular outcomes of COVID-19. Nat Med. 2022; 28(3): 583–590, doi: 10.1038/s41591-022-01689-3, indexed in Pubmed: 35132265.
6. Ayoubkhani D, Bosworth M, King S, et al. Risk of Long Covid in people infected with SARS-CoV-2 after two doses of a COVID-19 vaccine: community-based, matched cohort study. medRxiv. 2022, doi: 10.1101/2022.02.23.22271388.
7. Nucera G, Chirico F, Rafique Z, et al. Need to update cardiological guidelines to prevent COVID-19 related myocardial infarction and ischemic stroke. Cardiol J. 2022; 29(1): 174–175, doi: 10.5603/CJ.a2021.0120, indexed in Pubmed: 34642925.
8. https://www.reuters.com/business/healthcare-pharmaceuticals/drugmakers-scientists-begin-hunt-long-covid-treatments-2022-03-25/. (Access: 30.03.2022).
9. Evrin T, Szarpak L, Pruc M. Self-testing as a method of reducing COVID-19 infections. Disaster Emerg Med J. 2021; 6(2): 94–95, doi: 10.5603/demj.a2021.0011.
10. Smereka J, Szarpak L, Filipiak K. Modern medicine in COVID-19 era. Disaster Emerg Med J. 2020, doi: 10.5603/demj.a2020.0012.

VIA MEDICA

LETTER TO THE EDITOR

Cardiology Journal
2022, Vol. 29, No. 3, 535–536
DOI: 10.5603/CJ.a2022.0028

ISSN 1897–5593
eISSN 1898–018X

Genesis of arrhythmia in the course of COVID-19

Lukasz Szarpak[1, 2], Michal Pruc[3], Anatoliy Maslyukov[4, 5], Mihajlo T. Glamcevski[4, 6], Natasza Gilis-Malinowska[7], Milosz J. Jaguszewski[7]

[1]Henry JN Taub Department of Emergency Medicine, Baylor College of Medicine, Houston, TX, United States
[2]Institute of Outcomes Research, Maria Sklodowska-Curie Medical Academy, Warsaw, Poland
[3]Research Unit, Polish Society of Disaster Medicine, Warsaw, Poland
[4]School of Medicine, International European University, Kyiv, Ukraine
[5]Department of Biomedical Sciences, Odessa International Medical University, Odessa, Ukraine
[6]Royal University of Phnom Penh, Penh, Cambodia
[7]1st Department of Cardiology, Medical University of Gdansk, Poland

The paper was guest edited by Prof. Togay Evrin

Coronavirus disease 2019 (COVID-19) is associated with severe acute respiratory syndrome (SARS) this connection and effect has been exacerbated by the new strain of coronavirus (SARS--CoV-2) which has rapidly spread across the globe, posing a significant medical challenge [1, 2]. An analysis of various national health records demonstrates that many COVID-19 patients develop cardiac arrhythmias as the disease progresses. Several studies have found that these aberrant rhythms worsen the medical outcome of patients with COVID-19. However, the current medical science is unclear as to how SARS-CoV-2 infection might generate such arrhythmias [3].

The arrhythmia in COVID-19 may occur due to a large range of causes such as damage to the heart muscle, myocardial ischemia as well as in the case of myocarditis [4]. Arrhythmia can also occur in patients who have hypoxia, septic or cardiogenic shock, indications of broad systemic inflammation, or electrolyte problems such as hypokalemia. In addition, in the case of treatment of remdesivir for COVID-19, some cardiac arrhythmias have been documented [5]. Arrhythmias in the course of COVID-19 are a serious problem that occurs both in hospitalized patients and in convalescents who have already had the disease.

Tachycardia is a common symptom reported in COVID-19 patients, from their electrocardiogram results. However, recent reports have demonstrated that bradycardia is prevalent in up to 56% of hospitalized COVID-19 patients with a fever [6]. There is growing evidence and medical investigations suggesting that SARS-CoV-2 is able to infect the specialized cardiac cells known as pacemaker cells.

In healthy individuals, the primary pacemaker of the heart is the sinus node; as part of the heart's conductive system, the node is one of the main electrical regulators of cardiac rate and rhythm. Disruption to the sinus node's structure can cause bradycardia. Researchers have used animal models combined with human stem cell-derived pacemaker cells to further understand this condition and set of effects.

Researchers using a type of pluripotent stem cell (hPSC) called human embryonic stem cells (hESC), have found that SARS-CoV-2 can readily infect pacemaker cells and induce a process known as ferroptosis [7]. Apoptosis, necrosis, autophagy, and other kinds of cell death are all distinct from ferroptosis, which is an iron-dependent cell death. The buildup of fatal lipid species resulting from lipid peroxidation defines the process of ferroptotic

Address for correspondence: Dr. Michal Pruc, Polish Society of Disaster Medicine, P.O. Box 78, 05–090 Raszyn, Poland, tel: +48 695483564, e-mail: m.pruc@ptmk.org

Received: 15.04.2022 Accepted: 23.04.2022 Early publication date: 4.05.2022

cell death, which can be avoided by iron chelators — deferiprone, deferoxamine and tiny lipophilic antioxidants — ferrostatin and liproxstatin [8]. Researchers discovered that during the process of ferroptosis the human pacemaker cells produce angiotensin-converting enzyme 2 receptors and other complimentary components that facilitates and improves SARS-CoV-2 ability and frequency to enter cells, thus increasing infected cell rates by SARS-CoV-2 in human cells. These same SARS--CoV-2 infected cells also showed a significant rise in inflammatory immune gene activity. It is hypothesized that pacemaker cells infected with SARS-CoV-2 commence a self-destructive process of ferroptosis, an iron-dependent cell death and that commences early in COVID-19 patients within the sinus node, which explains the high incidence of bradycardia in patients.

Researchers have also investigated whether the damaging consequences of ferroptosis might be reversed by utilizing chelating agents; chemical molecules that closely attach to metal ions. The researchers examined the impact of chelating agents on the elimination of iron from the circulation and thus prevent the ferroptosis process. The chelating agents deferoxamine and imatinib were shown to prevent SARS-CoV-2-induced ferroptosis in the heart's pacemaker cells [7].

From these research findings, it indicated that patients with COVID-19 could theoretically be treated with ferroptosis inhibitors to protect the sinoatrial (sinus node) cells, antiviral drugs that block the effects of SARS-CoV-2 infection in all cell types would be a preferred course of treatment. Although there is a worldwide medical push to protect all organs in both the severe course and the post-COVID-19 syndrome, other treatments do need to be considered.

The development of arrhythmias in the course of COVID-19 can have many reasons, but there is mounting research evidence demonstrating the involvement of pacemaker cells. This highlights the complexity of COVID-19 in the context of the cardiovascular system. Future research will need to be conducted into whether this phenomenon plays an important role among convalescents and patients struggling with the long-COVID-19 syndrome [9]. There is a need for further clinical and cellular research to clearly understand the mechanisms and the implementation of appropriate treatment strategies for the cardiac and other organs, both protective and symptomatic [10].

Acknowledgments

The study was supported by the Polish Society of Disaster Medicine.

Conflict of interest: None declared

References

1. Dzieciatkowski T, Szarpak L, Filipiak KJ, et al. COVID-19 challenge for modern medicine. Cardiol J. 2020; 27(2): 175–183, doi: 10.5603/CJ.a2020.0055, indexed in Pubmed: 32286679.
2. Saban M, Shachar T. The silent effect of COVID-19 on emergency departments: How to avoid complacency? Disaster Emerg Med J. 2020, doi: 10.5603/demj.a2020.0035.
3. Szarpak L, Filipiak KJ, Skwarek A, et al. Outcomes and mortality associated with atrial arrhythmias among patients hospitalized with COVID-19: A systematic review and meta-analysis. Cardiol J. 2022; 29(1): 33–43, doi: 10.5603/CJ.a2021.0167, indexed in Pubmed: 34897631.
4. Nucera G, Chirico F, Rafique Z, et al. Need to update cardiological guidelines to prevent COVID-19 related myocardial infarction and ischemic stroke. Cardiol J. 2022; 29(1): 174–175, doi: 10.5603/CJ.a2021.0120, indexed in Pubmed: 34642925.
5. Touafchia A, Bagheri H, Carrié D, et al. Serious bradycardia and remdesivir for coronavirus 2019 (COVID-19): a new safety concerns. Clin Microbiol Infect. 2021 [Epub ahead of print], doi: 10.1016/j.cmi.2021.02.013, indexed in Pubmed: 33647441.
6. Long B, Brady WJ, Bridwell RE, et al. Electrocardiographic manifestations of COVID-19. Am J Emerg Med. 2021; 41: 96–103, doi: 10.1016/j.ajem.2020.12.060, indexed in Pubmed: 33412365.
7. Han Y, Zhu J, Yang L, et al. SARS-CoV-2 infection induces ferroptosis of sinoatrial node pacemaker cells. Circ Res. 2022; 130(7): 963–977, doi: 10.1161/CIRCRESAHA.121.320518, indexed in Pubmed: 35255712.
8. Yan HF, Zou T, Tuo QZ, et al. Ferroptosis: mechanisms and links with diseases. Signal Transduct Target Ther. 2021; 6(1): 49, doi: 10.1038/s41392-020-00428-9, indexed in Pubmed: 33536413.
9. Szarpak L, Pruc M, Filipiak KJ, et al. Myocarditis: A complication of COVID-19 and long-COVID-19 syndrome as a serious threat in modern cardiology. Cardiol J. 2022; 29(1): 178–179, doi: 10.5603/CJ.a2021.0155, indexed in Pubmed: 34811716.
10. Smereka J, Szarpak L, Filipiak K. Modern medicine in COVID-19 era. Disaster Emerg Med J. 2020, doi: 10.5603/demj.a2020.0012.